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Volume 41

ASCO®
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

American Society of Clinical Oncology Educational Book

Equity: Every Patient. Every Day. Everywhere.

Volume 41

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ASCO®

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

MAKING A WORLD OF DIFFERENCE IN CANCER CARE

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DESCRIPTION

The *ASCO Educational Book* is an NLM-indexed, peer-reviewed collection of articles written by ASCO Annual Meeting faculty and invited experts in oncology. Published annually, each volume highlights the most compelling research and developments across the multidisciplinary fields of oncology with the goal of improving patient value and care.

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The Expert Panel is a group of well-recognized international physicians and researchers in oncology and related fields who serve as peer reviewers of the *ASCO Educational Book*. Each article is reviewed for clarity, accuracy, and balance.

To view the members of the expert panel who graciously lend their time and expertise to ensure the integrity of the content in the *ASCO Educational Book*, please visit: https://ascopubs.org/edbk/expert-panel.html.

Letter From the Editor in Chief

On behalf of my associate editors, Nathan Pennell, MD, PhD, FASCO, and Hope S. Rugo, MD, FASCO, I am privileged to present the 41st volume of the NLM-indexed *ASCO Educational Book*.

Even as we hopefully see the light at the end of the COVID-19 tunnel finally revealing itself, most of the world is still reeling from the unimaginable loss experienced since this pandemic began. As members of the oncology care community, we have worked on the frontlines of the pandemic, adapted to providing our patients with virtual care, and united to ensure we identified and addressed the unique needs of patients with COVID-19 and cancer. So much has changed, but now we face our future, and I join our entire community in looking forward with cautious hope.

This year, the 2020-2021 ASCO President Lori J. Pierce, MD, FASTRO, FASCO, chose a presidential theme that focuses on doing right by the patients for whom we care. "Equity: Every Patient. Every Day. Everywhere" means that we will confront and address complex forces and systems that have created disparities in cancer care, treatment, and research. It is my sincerest belief that this year's Ed Book plays a critical role in sharing how inequality has affected our patients and how to disrupt the systems that stand in the way of delivering equitable cancer care.

The insight found within Ed Book's pages comes from a diverse set of the brightest minds in oncology who have been chosen to serve as Annual Meeting Education Program faculty. Most articles represent a collaboration between session speakers and their invited co-authors, many of whom are junior faculty and fellows. It takes tremendous effort and time to document the knowledge of many into one scholarly review, especially on the heels of a pandemic that have left many of us exhausted. I cannot thank the faculty enough for the generosity of their contributions to this year's edition. It is a gift to current and future oncology care team members.

I would also like to recognize the expert panel members who selflessly dedicated their time to perform thorough and thoughtful peer reviews. Finally, a well-deserved message of appreciation to both Nate Pennell and Hope Rugo for their contributions.

The 2021 *ASCO Educational Book* articles, as well as articles from past volumes, are available online for free public access and download at www.asco.org/edbook. We welcome your feedback and suggestions on how we can improve the content, so please contact us at edbook@asco.org with your comments.

Sincerely,

Don S. Dizon, MD, FACP, FASCO
ASCO Educational Book Editor in Chief

INVITED ARTICLES

This year's Invited Articles represent the 2021 ASCO Annual Meeting theme, "Equity: Every Patient. Every Day. Everywhere." These important contributions to the 41st volume of the *ASCO Educational Book* focus on how research findings can be translated into improving care for all patients, so everyone, everywhere, has equal access to high-quality cancer care. Authors were nominated by the *ASCO Educational Book* Editors and 2021 Annual Meeting leadership.

ARTICLES

invited article

overview

An Arm and a Leg: The Rising Cost of Cancer Drugs and Impact on Access

Natasha B. Leighl, MD[1]; Sharon Nirmalakumar, BSc[1]; Doreen A. Ezeife, MD[2]; and Bishal Gyawali, MD, PhD[3]

Increasing cancer drug prices present global challenges to treatment access and cancer outcomes. Substantial variability exists in drug pricing across countries. In countries without universal health care, patients are responsible for treatment costs. Low- or middle-income countries are heavily impacted, with limited patient access to novel cancer treatments. Financial toxicity is seen across cancer types, countries, and health care systems. Those at highest risk include younger patients, new immigrants, visible minority groups, and those without private health coverage. Currently, cancer drug pricing does not correlate with value or clinical benefit. Value-based pricing of oncology drugs may incentivize development of higher-value medicines and eliminate excess spending on drugs that yield little benefit. Generics and biosimilars in oncology can also improve affordability and patient access, offering dramatic reductions in drug spending while maintaining patient benefit. Oncologists can promote value-based care by following evidence-based clinical guidelines that avoid low-value treatments. Researchers can also engage in value-based research that critically explores optimal cancer drug dosing, schedules, and treatment duration and defines patient populations most likely to benefit (e.g., through biomarker selection). Cancer Groundshot proposes that we improve outcomes for today's patients with cancer, including broader global access for high-value treatments, promotion of affordable cancer control strategies, and reduction of cancer morbidity and mortality through low-cost prevention and screening initiatives. Moving forward, major oncology societies recommend promoting uniform global access to essential cancer medicines and avoiding financial harm for patients as key principles in addressing the affordability of cancer drugs.

THE CHALLENGE

Since 1995, there has been a marked increase in the price of new cancer drugs corresponding to the uptake of biologics in oncology. Most agents launched between 2009 and 2014 cost more than $100,000 USD per year. More recently developed agents, such as CAR T-cell therapy, may cost up to almost $500,000 USD per year.[1] The monthly cost of many anticancer drugs greatly exceeds most household incomes, including in the United States.[2]

The price of cancer drugs varies across countries and may not correlate directly with the country's gross domestic product (Fig. 1). A substantial variability in drug prices has been reported, with up to a 13-fold difference between countries in Europe and Oceania.[3-5] Cancer drug prices are highest in the United States; they are more than two-fold higher than in Europe and are two to six times higher than the rest of the world.[2,6] Goldstein and colleagues explored this concept in more detail and compared monthly drug acquisition costs as well as the regional affordability of eight patented anticancer agents in seven countries.[7] The countries were India, China, South Africa, Israel, the United Kingdom, Australia, and the United States. Although the monthly dollar amount for cancer drug acquisition was highest in the United States, the relative cost or affordability, expressed as a fraction of monthly per capita gross domestic product, was the highest in India, followed by China and South Africa (Fig. 2). Patients in the United Kingdom and Australia, which both have managed care systems, paid the least. Although drug acquisition costs were the highest in the United States, cancer drugs were more affordable than in the lower-income countries after data were adjusted for per capita gross domestic product.

Other factors are also essential for patient access and affordability. Some countries negotiate drug prices on behalf of public payer systems, whereas other countries do not have universal health coverage, so drug costs are borne entirely by patients. This approach is highly prevalent in low- or middle-income countries (LMICs). Some countries have less purchasing power than others, leading to support for differential pricing by national gross domestic product by several groups as well as support for coalitions to increase purchasing power and negotiate greater access for patients.

Author affiliations and support information (if applicable) appear at the end of this article.

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PRACTICAL APPLICATIONS

- Globally, rising cancer drug prices result in variable access and outcomes, with low- or middle-income countries being most heavily affected.
- Financial toxicity impacts patients with cancer, particularly younger patients, new immigrants, and those without private health coverage.
- The use of value frameworks to determine cancer drug pricing and to tie prices to regional gross domestic product or affordability is being supported by many oncology groups as a way to improve global access to important cancer medicines.
- Cancer care providers are called upon to follow evidence-based guidelines, choose wisely, prioritize higher-value treatments, and discuss financial toxicity with patients.
- Cancer researchers can contribute to value-based research by defining the optimal dose, schedule, and duration of novel therapies and by defining the patient populations most likely to benefit (e.g., through biomarker discovery and selection).

Market entry of novel cancer medicines in LMICs takes more than a year after approval by the European Medicines Agency or the U.S. Food and Drug Administration (FDA).[22] Even after market entry, most patients in LMICs cannot afford to pay for these therapies out of pocket. The FDA and other regulators are working to harmonize regulatory review across high-income countries through Project Orbis. However, these efforts are limited to high-income countries, and accelerating access in LMICs remains a major challenge.

In the 2015 European Society for Medical Oncology International Consortium Study, the availability and accessibility of novel anticancer therapies were significantly restricted in LMICs in Asia.[23,24] Many of the essential cancer medications included in the study—such as trastuzumab and EGFR, ALK, and VEGF inhibitors—were not subsidized or even available in many regions. Key barriers to access included lack of approval by local regulatory agencies and high out-of-pocket costs for patients. Other barriers included lack of access to quality-assured generics or biosimilars and a general lack of commercial motivation to promote access to essential cancer medicines in LMICs.

Across Europe, there are large variations in access to novel cancer medicines, with less developed countries in Eastern Europe reporting the greatest limitations.[25] Most medications included in the World Health Organization (WHO) Model List of Essential Medicines were available in Europe, but other factors, such as prolonged time for preapproval, limited real access in several countries. The availability of cancer medicines, as expected, was least in those countries with the lowest gross domestic product per capita. Access to expensive targeted agents was the most variable, whereas access to established curative medications, such as chemotherapy for testis cancer, was the most prevalent. The investigators also identified that lower-cost anticancer medications, such as tamoxifen and cisplatin, were not always available because of manufacturing and distribution challenges. This problem has been seen with drug shortages of generics and other essential cancer medicines around the world that are related to quality and production issues, regulatory challenges, and lack of financial incentives to maintain the needed supply.[3,26-28]

THE IMPACT ON PATIENTS WITH CANCER

The main impacts of high cancer drug prices are the lack of access for patients and the lack of ensuing benefits of novel therapies. This is widely true for novel therapies in LMICs and in jurisdictions with managed care and major budgetary restraints, such as New Zealand. Chemotherapy, by contrast, is more affordable and widely accessible. Thus, it is still used even though targeted therapies and immunotherapy are often more effective and less toxic.[29] This approach results in inferior outcomes and greater toxicity, because access to concurrent supportive care to manage chemotherapy side effects is also more challenging in LMICs. Many of the patients who could benefit most from innovations in precision oncology are among those who are least likely to afford them.

A diagnosis of cancer in any country can lead to financial catastrophe. Approximately one-quarter of patients with cancer in Thailand and three-quarters of patients in India report extreme out-of-pocket expenses and are required to sell assets and borrow funds to pay for cancer therapy.[24] Another study demonstrated an association between patients in the United States filing for bankruptcy and increased cancer mortality.[30] Whether cancer outcomes were worse because patients could not afford to continue therapy is unknown. Another study of patients with colorectal cancer or lung cancer in the United States found that more than one-third had severely limited financial reserve.[31] Those with limited reserve had significantly higher symptom burdens and worse quality of life and were less able to afford cancer therapy.

In recent years, financial toxicity has emerged as an important patient-reported outcome.[32] Studies have demonstrated that financial toxicity in patients with cancer is prevalent and is seen across cancer types, countries, and health care systems. The Comprehensive Score for Financial Toxicity was developed to assess the burden of the

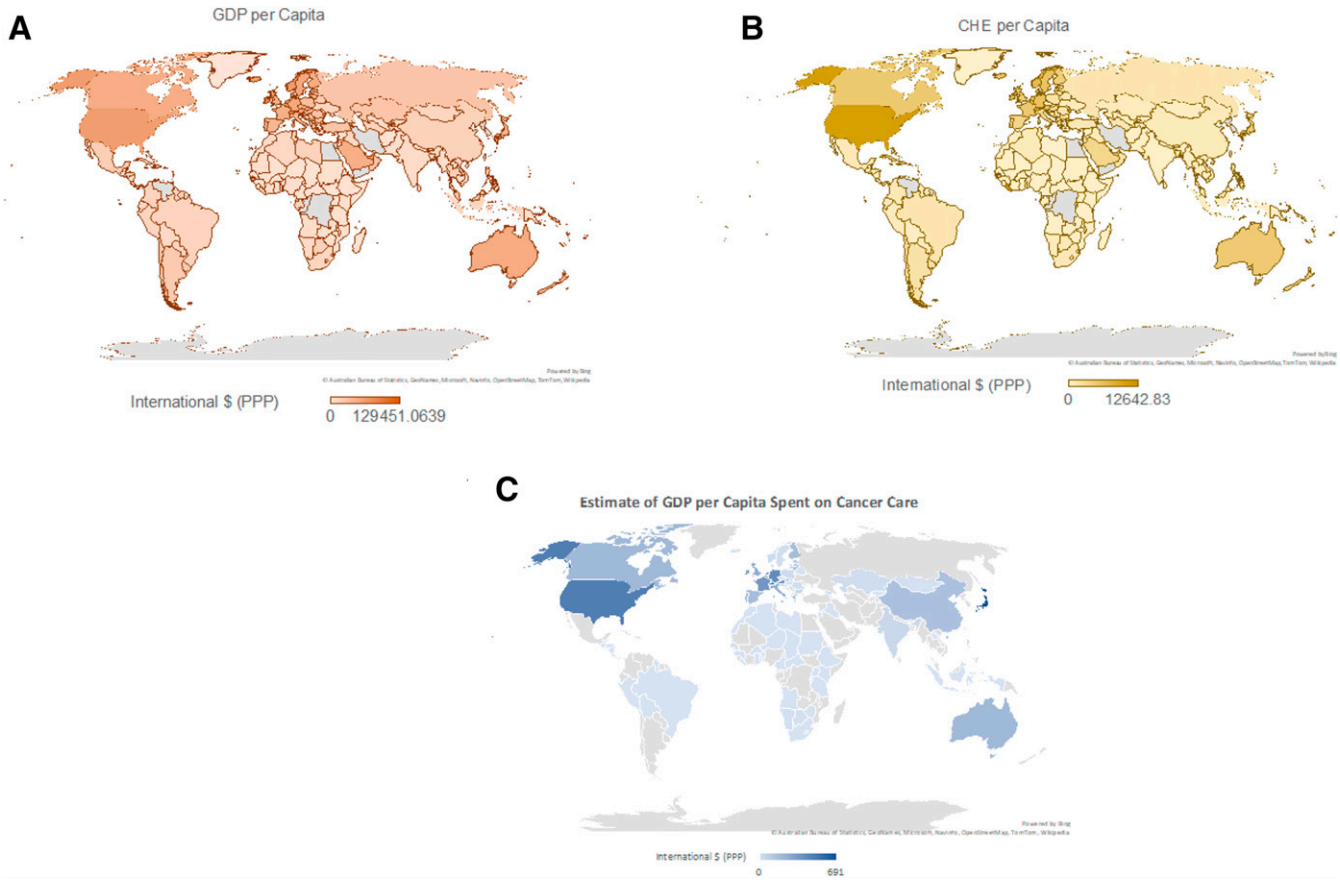

FIGURE 1. Global Price Differences for Cancer Drugs

(A) Gross domestic product (GDP) differences per capita; (B) current health expenditure per capita; and (C) estimated GDP per capita spent on cancer care.[8-11]

Gray shading indicates that data for the past 5 years are not available.

Abbreviation: PPP, purchasing power parity.

costs of cancer care on patients in the United States.[33] Studies of patients with cancer around the world show similar findings, with a high prevalence of financial toxicity and a greater impact on younger patients and those from low-income households. Groups at highest risk include new immigrants, visible minorities, those without private health coverage, or those on sick leave.[34-38] In several studies, higher out-of-pocket costs correlated with financial toxicity and decreased treatment adherence. For example, patients with chronic myeloid leukemia in the United States who had higher prescription copayments were almost twice as likely to stop expensive life-prolonging therapy compared with those who had lower copayments, leading to worse outcomes.[39]

CANCER DRUG PRICING

The pricing of cancer drugs involves several factors. The most important factor is what drug manufacturers believe the market will bear and will bring the most profitable returns. Free market forces have had minimal impacts on cancer drug pricing. For cancer treatments, there is greater demand and willingness to pay because of the lethality, morbidity, and public fear of the disease. A key barrier to lower costs has been historic legislation in the United States that prevented Medicare from negotiating drug prices (Medicare Modernization Act of 2003). However, newer legislation may change this in the future, if opposition from drug manufacturers and the public can be addressed.[40,41] Because most cancer agents launch first in the United States, the initial list prices are high, setting an unattainable bar for pricing around the globe. Production costs remain a minor component of the overall drug price. For example, it is estimated that production costs for generic small molecule inhibitors are 0.2% to 2.9% of the list price in the United States.[42] Drug manufacturers cite the cost of research and development as the key factor leading to high

drug prices. However, several drug manufacturers spend less on research and development than they spend on other areas, such as marketing, or than they generate in profit.[2] Revenue from cancer medicine sales continues to exceed research and development costs (Fig. 3).[43]

The failure of market forces to impact cancer drug prices has been demonstrated in several studies. Although one might expect to pay higher prices for first-in-class agents and lower prices for second-in-class or "me too" drugs, the opposite has been reported for oncology agents. Second-in-class agents are often priced similarly or even higher than first-in-class cancer drugs.[44] Although one might expect oncology drug prices to decrease over time after market entry, the price of some anticancer agents has, paradoxically, increased. A study of 24 patented injectable cancer agents in the United States demonstrated that prices increased by 25% (range, −14% to +96%) in the years after launch.[45] These increases in cost were not offset by supplemental FDA approvals, new competitors, or new off-label indications. Even with the introduction of generics, the cost of cancer therapy has not always decreased. Some generic agents have been priced similarly to patented agents[46] or with only modest price reductions. Furthermore, market entry of generics is often delayed, whereas more expensive, newer-generation agents overtake the older and now affordable agents.[47]

VALUE-BASED PRICING

In 2014, the ASCO Cancer Research Committee challenged researchers and patients to raise the bar on expectations from novel therapies to "significantly advance cancer care."[48] They reminded us that demonstrating a statistical significance for small differences does not lead to meaningful benefit for patients and that some treatments are of low value to patients and progress against cancer.[49] Since that time, many groups have developed frameworks to evaluate the value of anticancer drugs for patients, including assessment of the magnitude of benefit and patient endpoints. The European Society for Medical Oncology Magnitude of Clinical Benefit Scale is among the most widely used; it assesses treatment efficacy in the curative and palliative settings.[50] Other frameworks, including the ASCO Value Framework, also explicitly discuss cost, among other outcomes.[51-54] A Canadian drug assessment framework, developed to promote transparency and consistency in oncology drug–funding decisions, also includes valuation of unmet need, equity, and disease severity as part of structured decision-making.[55]

Despite the establishment of value frameworks, multiple studies confirm that cancer drug prices do not correlate with value or clinical benefit.[6,44,56,57] Drugs that provide less value to patients are often higher priced than those that provide greater value. A recent study reported that, although new cancer drug prices in France increased by more than 50% between 2004 and 2017, there was no increase in the net clinical benefit of these agents.[58] Because of these observations, there has been a call for increased focus on value-based pricing using value frameworks.

Using real-world performance of novel agents to set market prices has been a strategy applied by several countries.[59] In Italy, market entry pricing is based on the performance of a novel agent in a real-world setting. In Germany, although a manufacturer can set drug prices in the first year of market entry, this price is revisited on the basis of real-world outcomes and comparison with the reference standard. Prices are then adjusted according to population outcomes and the reference standard price. Challenges with this approach include the ability to gather high-quality, real-world evidence rapidly and the ability to incorporate these data into drug-pricing decisions in a timely manner. Other caveats include a potentially overpriced reference standard, perpetuating high drug costs, and the lack of a mandate to revisit prices over time.

GENERICS AND BIOSIMILARS

The WHO and other groups, including the European Society for Medical Oncology, ASCO, and the FDA, have advocated for the stimulation of market competition through the development and approval of biosimilars and generic formulations of important cancer medicines.[3,25-27,60,61] The development of generic medicines is easier and cheaper, because these have identical chemical compositions to the original synthetic drugs and can be substituted readily for the original agents after regulatory approval. This approach has led to major improvements in affordability and patient access. Biosimilars are not identical to the original patented biologic agent but are highly similar, with similar clinical outcomes. Their development is more expensive, because it requires additional clinical studies to demonstrate efficacy and gain regulatory approval. Although cost savings with biosimilars are less than with generics, both can dramatically decrease cancer drug expenditures without sacrificing outcomes. The reduction in drug costs over time with the use of generics can improve cost effectiveness, change reimbursement decisions, and increase the number of treatment options accessible to patients.[62,63]

However, generics often experience delayed entry into the market, challenged by drug manufacturer patents and regulatory hurdles. For example, trade secrets and data exclusivity provisions demanded by drug manufacturers may lead to restricted development and approval of biosimilars and generic agents. Some generic medicines are still highly priced, limiting patient access. By contrast, some generic medicines are priced too competitively, and shortages of essential cancer medicines have occurred. Manufacturers have stopped production or declared bankruptcy,

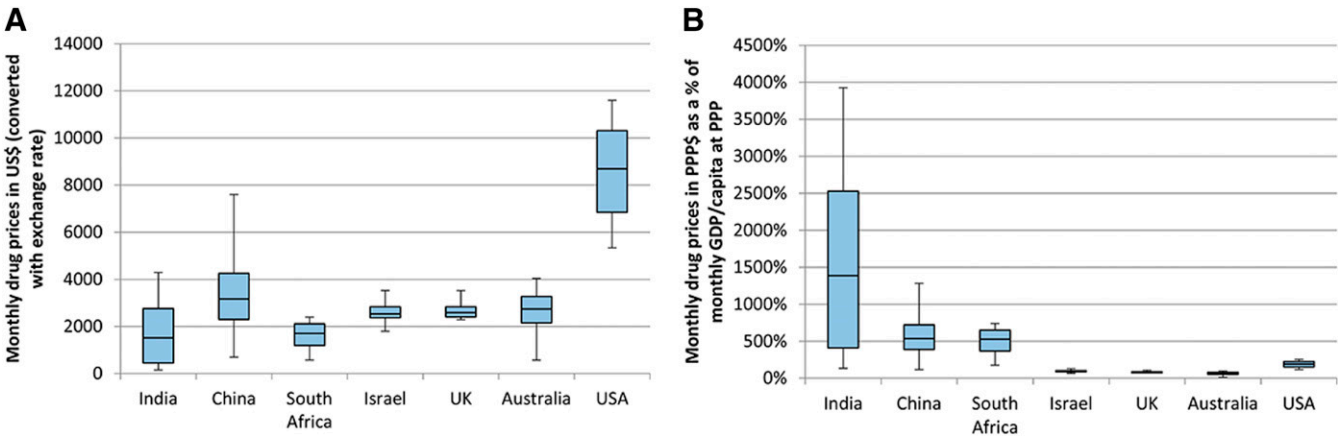

FIGURE 2. Cost and Affordability of Eight Patented Cancer Drugs in Seven Countries[12-21]

(A) Prices were converted from local currency to USD (exchange rates, January 1, 2016) and expressed as box and whisker plots. (B) Monthly prices at purchasing power parity (PPP) were divided by the country's monthly gross domestic product (GDP) per capita.[12-21]

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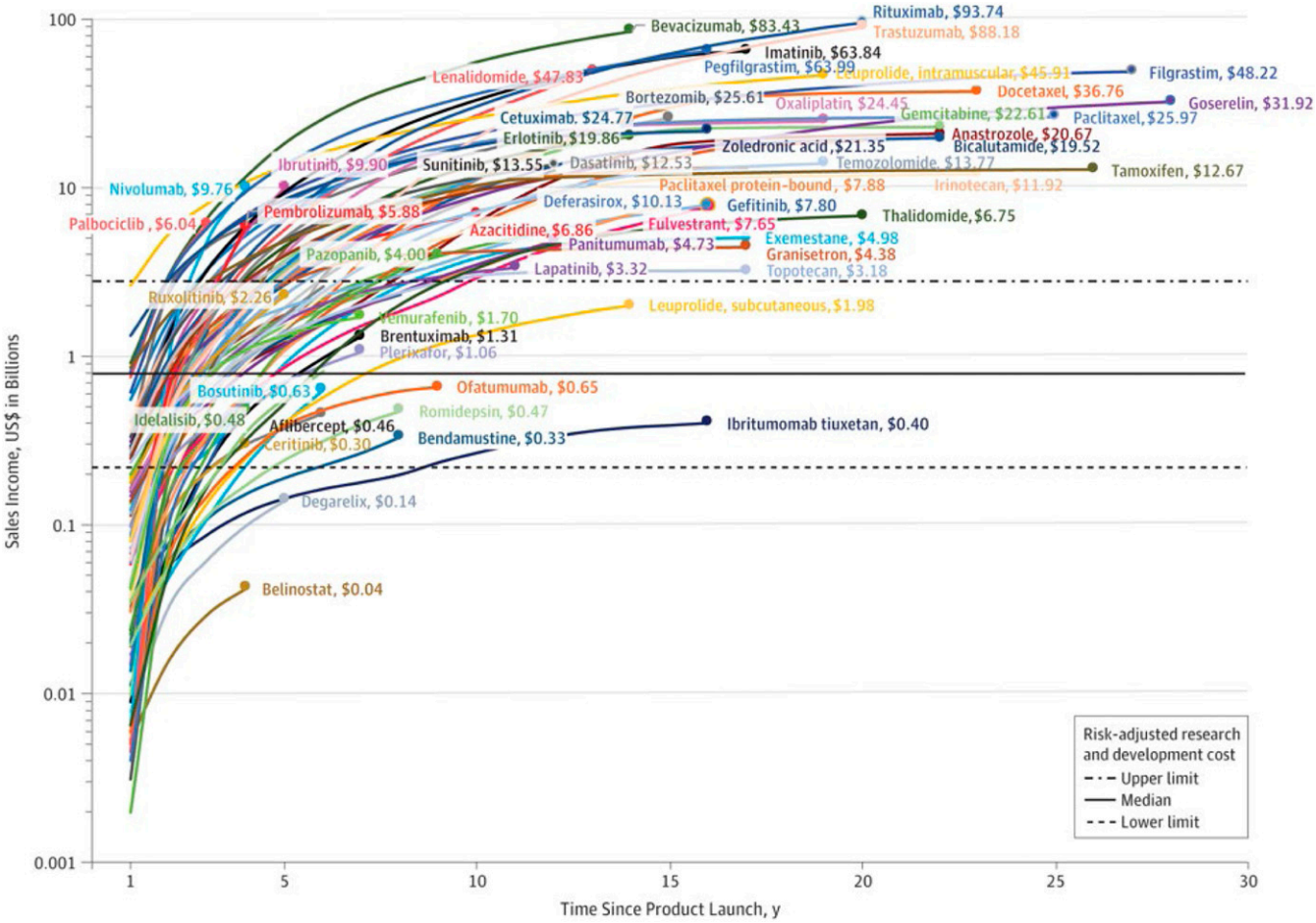

FIGURE 3. Cumulative Sales of Cancer Drugs in 2017 USD, by Drug and Time Since Product Launch

Drug sales revenues are represented in billions of USD.

Reprinted from Tay-Teo et al,[43] with permission from the publisher.

resulting in these shortages. Thus, it is important that the pricing of generic medicines and biosimilars remains sufficient to maintain production and access for patients.

VALUE-BASED TREATMENT

Prescribers of cancer medicine play a key role in promoting value-based care. A team of U.S. community oncologists previously demonstrated that treating patients according to clinical guidelines decreased treatment costs by 35%, primarily through avoiding low-value treatments, with no decrease in survival compared with patients treated off guidelines.[64] Selecting treatments with the greatest value for patients, following evidence-based clinical practice guidelines, and minimizing futile investigations and futile therapy all help improve outcomes for patients without increasing costs of care. Initiatives like Choosing Wisely can be expanded beyond North America, including to LMICs. Oncologists in India developed a consensus document to improve value in the delivery of cancer care, adapting Choosing Wisely recommendations from North America to the local context.[65]

Some systems have greater challenges in the provision of value-based care. Some provide incentives, such as institutional markups from drug sales or sales quotas, to prescribers for administering more intravenous chemotherapy and/or more expensive therapy. Patients and prescribers should be protected from these influences, and the provision of value-based care should be incentivized instead. Other systems, such as those in Brazil, suffer from the introduction of price mark-ups from multiple parties along the supply chain. Simplifying the drug-acquisition process, or removing the middlemen, could decrease final prices.

Even simple concepts like minimizing drug wastage may decrease the costs of cancer drug therapy. The use of weight-based dosing of pembrolizumab compared with flat dosing reduced drug acquisition costs by 24%.[66] Advocating for smaller vial sizes or packaging of cancer medications may also decrease wastage. For example, pembrolizumab is only available in 100-mg vials from the manufacturer. The production of smaller vials would permit less wastage and save money in the case of weight-based dosing.

A key value proposition for patients is precision oncology. Identifying those patients who are most likely to benefit from a treatment using biomarker selection has markedly improved patient outcomes in breast, lung, and other cancers. For example, immunotherapy treatment of patients with advanced lung cancer with tumor PD-L1 expression significantly improves treatment efficacy and reduces cost.[67,68] Similarly, selection of patients for targeted therapy by identification of tumor genomic drivers has become standard, with the recognition that targeted therapy in patients without genomic tumor aberrations leads to poor outcomes.[69] Biomarker selection helps identify those who will benefit the most and minimizes the risk of futile therapy, associated toxicity, and cost for those unlikely to benefit.

Biomarker testing, such as molecular testing in lung cancer, has become prevalent in high-income countries. Guidelines recommend broad-panel genomic testing rather than single-gene testing to expedite results and treatment initiation, increase patient access to targeted therapies instead of chemotherapy, and decrease the need for repeat biopsies for testing. Although this approach is potentially cost saving in the United States, other investigators have demonstrated great challenges in affording genomic sequencing.[70,71] For example, despite advantages in identifying targetable aberrations, broad-spectrum genomic testing was not cost effective in the Brazilian public system. Thus, several jurisdictions continue to rely on highly selected single-gene testing, if testing is performed at all. In LMICs, prescribers also must consider subsequent access to targeted therapies. If patients are unable to access targeted treatment according to testing results, paying out of pocket for genomic testing is of little to no value.

VALUE-BASED RESEARCH

As a research community, we have a role to play in ensuring that clinical research remains of high value for patients. We must advocate for a high bar of what we expect from novel treatments and ensure that meaningful endpoints for patients, including survival and quality of life, are used in trials. We should also reconsider our support of trials that will not add value or benefit for patients.

Defining the optimal dose, schedule, and duration of novel therapies is an example of an area in which the oncology community can contribute to value-based research. With cytotoxic chemotherapy, dosing has been determined by toxicity or the maximum targeted dose. The optimal biologic dose of targeted therapies and biologics has been more challenging, because most trials continue to use dose-limiting toxicity as their guide. Many immunotherapy agents and small molecule inhibitors have had limited study of optimal dosing and schedules. The rational determination of treatment duration has also been a challenge in the setting of checkpoint inhibitors, as well as some adjuvant and consolidation treatments. An excellent example of value-based research is the optimization of the dose of ceritinib, a potent ALK inhibitor. In 2014, on the basis of randomized trial results, ceritinib was approved for use at a dose of 750 mg daily, taken in a fasted state; frequent dose reductions were required for gastrointestinal toxicity.[72] ASCEND-8 was a phase I study in which patients were randomly selected to receive different dose levels of ceritinib to be taken either fed or fasting. The investigators demonstrated that a lower dose of ceritinib, 450 mg taken with food, had similar bioavailability, less toxicity, and similar

activity as the previously recommended 750-mg dose in fasted patients.[73,74] Ceritinib is available in 150-mg tablets, and the new recommended dose of 450 mg with food allows patients to reduce costs and pill burden by 40% and decreases toxicity while maintaining similar efficacy.

Alectinib, another ALK inhibitor, is prescribed at a dose of 300 mg twice a day in Japan and several Asian countries, but it is prescribed at 600 mg twice a day outside of Asia according to different doses used in registration trials in Japan, China, and the rest of the world.[75-77] Although both doses are highly active, the higher dose is associated with more toxicity, fatal adverse events, dose reductions, and drug discontinuation. A phase I/II study in North America revealed that the 300-mg twice-a-day dose yielded lower drug exposure levels than in the Japanese phase I study, and higher doses were required to yield higher alectinib exposure in the North American population.[78] However, additional work to determine optimal dosing (e.g., by body weight) has not been pursued and might lead to lower pill burden, cost, and toxicity for a larger group of patients.

Duration of therapy has been a key area of interest for biologics, including immune checkpoint inhibitors. When adjuvant trastuzumab was first established as standard of care in patients with resected HER2-positive breast cancer, duration of therapy was actively investigated through several trials.[79,80] Immunotherapy is another area in which trials can contribute additional value by exploring different dosing schedules and treatment durations. The CheckMate-153 trial compared stopping nivolumab therapy at 1 year versus continuing in previously treated patients with advanced non–small cell lung cancer that had not progressed by that point.[81] The study identified that treatment beyond 12 months was associated with better outcomes in this population. Several drug manufacturers recommend 24 months of treatment as standard, although the evidence underpinning this recommendation remains unclear. Also, it is unknown whether treatment must be given every 2 to 4 weeks continuously versus a period of induction followed by less frequent maintenance dosing to activate T cells and maintain antitumor activity. The STOP-GAP study in melanoma (NCT02821013), developed by the Canadian Cancer Trials Group, offered patients with advanced disease standard immunotherapy treatment until maximum tumor response occurred. Patients were randomly selected to continue or stop therapy, with the option to resume immunotherapy in case of disease progression. The primary endpoint of the trial was overall survival; secondary outcomes included quality of life and cost utility. The development and conduct of trials that challenge current dosing paradigms and define value should not be the responsibility of cooperative groups alone. Regulatory bodies, such as the FDA and the European Medicines Agency, may be able to encourage optimization of value-based treatment as part of regulatory review of drug manufacturer–planned trials and submissions.

THINKING BEYOND CANCER MOONSHOT TO CANCER GROUNDSHOT

The U.S. National Cancer Institute Cancer Moonshot initiative is a major investment in progress against cancer, including the acceleration of scientific discovery, translational research, and data sharing. It is expected that technologic advances from this and similar initiatives in high-income countries will yield better outcomes for some patients but will be costly and are likely to remain inaccessible to many around the world.[82] An example might be the use of liquid biopsies and cell-free genomic or multimodal assays to monitor or inform treatment planning. Patients not experiencing a response to expensive therapies could be identified earlier and switched to alternate treatments. Patients cured with primary treatment could also be identified early and spared the toxicity and cost of additional adjuvant, consolidation, or maintenance therapies. However, only jurisdictions and health care systems that can afford innovative technologies and novel treatments would be able to benefit.

As our research community reaches for the moon, we are reminded of the growing disparities in cancer control globally. Cancer Groundshot has been proposed as a complementary initiative to improve the lives of today's patients with cancer.[82] The focus includes implementing existing high-value treatments in more jurisdictions, incentivizing research on cost-effective and affordable strategies for cancer control, and implementing global strategies to reduce cancer morbidity and mortality—especially cancer-prevention, low-cost screening, and early-detection initiatives. Other strategies for Cancer Groundshot dovetail with the important work of the WHO and other organizations to improve the burden of cancer around the globe. These strategies include rapid implementation of cost-effective cancer prevention, such as HPV vaccination programs. Codevelopment of novel agents or strategies across high-income countries and LMICs could include repurposing of existing drugs, as in the case of arsenic in acute promyelocytic leukemia or propranolol in angiosarcoma. This method could extend to other agents, especially in the area of cancer prevention. Greater collaboration between the academic community and nonprofit organizations may also lead to more funding opportunities in this area. Working toward greater uniform access to high-value treatments remains key. Investment in improving health care delivery systems, including improvements to essential diagnostic and curative treatment services, is required in many countries. Greater activism and investment will also be required to ensure that patients with advanced cancer have access to pain relief and other essential supportive medicines.

MOVING FORWARD

The WHO, supported by the European Society for Medical Oncology, ASCO, and other organizations, has undertaken a comprehensive assessment and developed recommendations for how to address the high cost of cancer drugs.[3,60,61,83-85] Promoting uniform global access to the WHO's list of essential cancer medicines is key. Ensuring that this list includes newer, high-value, transformative cancer medicines is also important to help advance cancer outcomes for patients around the world. The establishment of value-based pricing—for example, using the European Society for Medical Oncology Magnitude of Clinical Benefit Scale to determine pricing—remains a major focus of several groups. Health technology assessment of novel treatments can help promote affordability, and results could be shared across jurisdictions, recognizing that each country would have different system costs and thresholds for affordability. For agents with uncertain cost effectiveness, managed entry or risk-sharing agreements have been used to facilitate assessment of the real-world impact of a novel treatment and inform pricing. Pricing based on regional gross domestic product, cancer burden, and current health care expenditures should also be encouraged, again to promote greater access to life-prolonging therapies for patients around the world.

Stimulation of market competition through the development of high-quality generics and biosimilars remains important, even in jurisdictions like the United States. Harmonization of regulatory requirements for biosimilars can promote high quality and competitive pricing. However, it is important to maintain sufficient pricing to prevent shortages and streamline management of supply in such cases. Reducing the cost of drug development may also support greater access to novel agents (e.g., collaborating with cooperative groups). The FDA and other regulators have established pathways for accelerated approval of novel agents that are designed to bring novel treatments to market faster and potentially decrease the costs of development. In a study examining 10 approved cancer drugs, the median cost of development of a single agent was $648.0 million (2017 USD). Half of the agents studied received accelerated approval from the FDA, and the lower median drug-development cost was $328.1 million USD compared with $817.6 million USD for those that did not receive accelerated approval ($p = .08$).[86] Interestingly, second-in-class agents cost more to develop than first-in-class agents do. Another potential area for improvement is the decreased development of "me too" or second-in-class agents. Fojo and Mailankody determined that 74% of the oncology agents in development by 10 pharmaceutical agents had overlapping mechanisms of action, and only 24% had unique, nonoverlapping mechanisms of action.[87] If the development of second-in-class agents led to competition and a reduction in market prices, this redundancy might be in the public interest; however, given the trend toward increased prices for such agents, the value for the consumer appears to be limited.

The negotiation of initial list prices for novel agents at market entry has led to a wider uptake of these medicines outside of the United States. Manufacturers are incentivized to launch novel agents in high-income countries first and defer market entry in LMICs so that the international reference price will not be affected.[5] Many of the final prices negotiated are confidential; thus, those countries that use external price referencing based on published list prices are at risk for paying higher prices than others. By the same token, countries paying lower prices may experience delays in novel agents entering the market or even nonavailability. In Canada, for a drug to enter the market, its list price must be accepted by the Patented Medicine Prices Review Board. Excessively priced drugs are rejected on the basis of a review of the current price in the relevant market, the price of agents in the same therapeutic class both in and out of Canada, and the Consumer Price Index (measure of purchasing power and inflation). Drug efficacy and safety undergo review and approval by Health Canada, similar to the FDA or the European Medicines Agency. Manufacturers seeking public reimbursement also make submissions to the pan-Canadian Oncology Drug Review and l'Institut National d'Excellence en Santé et Services Sociaux to assess their overall net clinical benefit, alignment with patient values, cost effectiveness, and feasibility of adoption into the health system. Drug manufacturers then negotiate with individual provincial (state) health care payers or the pan-Canadian Pharmaceutical Alliance, which can combine negotiating power across provinces; however, the price of affordable cancer therapy in the Canadian system includes delayed regulatory submissions, prolonged price negotiations, and delayed patient access.[88,89] Although compassionate access programs and clinical trials may help bridge the gap, the impact on patients remains substantial.

Additional considerations highlighted by the WHO and other organizations include price caps, tiered pricing over time, increasing transparency of external and internal reference pricing, cost-based pricing (including acceptable profit levels), pooling procurement efforts to negotiate greater price reductions, and maximum reimbursement rates. Although these actions may reduce prices, the challenge of limiting reimbursement rates is the potential for cost shifting to patient out-of-pocket expenses. Reducing the number of intermediaries in the drug-acquisition process may also decrease prices; for example, in Brazil, multiple parties involved in drug purchasing and distribution lead to increased mark-ups and overall costs. Innovative financing strategies for cancer care, including public-private partnerships, sin tax, or other levies, have also been proposed. It is also important to find innovative ways to reward social giving by drug manufacturers, enabling patients in LMICs to access novel medications at no cost or a heavily subsidized cost.

As oncology care providers, we need to continue efforts to provide high-value care to patients. These efforts include evidence-based care, choosing wisely, prioritizing treatments with high value over low value, and increasing awareness of our patients' risk for financial toxicity. We must have heightened awareness that, despite our best intentions, treatment recommendations and prescribing choices may have financial implications and result in potential harm to patients. We must also work to enhance system efficiency in our practice and research programs.

In the ASCO Position Statement addressing the affordability of cancer drugs, key principles include (1) ensuring patient access to life-prolonging and life-improving treatments, (2) avoiding financial harm to patients, (3) not limiting patient and provider access to appropriate care, and (4) rewarding innovation that results in meaningful improvements in patient outcomes, ensuring ongoing investment in high-risk, high-reward science to advance patient care.[61]

LIMITATIONS AND CAVEATS

We have focused on cancer drug costs and not on overall cancer control in this article. As oncologists and care providers, we must remember that it is better to prevent a cancer than to allow it to develop, and it is better to detect cancer early and cure rather than palliate. Preventive measures must be aggressively pursued, including greater tobacco control and greater uptake of cancer-preventing vaccines (e.g., HPV and hepatitis B). We must also invest and focus on screening and early detection of curable cancers (e.g., cervical cancer). Prevention remains less costly than diagnosis and treatment, and screening interventions yield greater benefit and cost effectiveness than palliative measures. In addition, the importance of supportive care globally remains paramount.

The delivery of cancer care will never be the same in high-income countries and LMICs or across all jurisdictions. But we must continue to strive to improve basic cancer care for all. It is estimated that, by 2040, two-thirds of cancer cases will occur in LMICs.[60] We are reminded by the WHO that cancer prevention and cancer control are broad responsibilities that are shouldered by all citizens, and they extend beyond the health care sector and medicines into pollution control, education, recreation, and society as a whole.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. President's Cancer Panel. Promoting Value, Affordability, and Innovation in Cancer Drug Treatment. https://prescancerpanel.cancer.gov/report/drugvalue/. Accessed March 15, 2021.
2. Prasad V, De Jesús K, Mailankody S. The high price of anticancer drugs: origins, implications, barriers, solutions. Nat Rev Clin Oncol. 2017;14:381-390.
3. World Health Organization. Technical report: pricing of cancer medicines and its impacts: a comprehensive technical report for the World Health Assembly Resolution 70.12: operative paragraph 2.9 on pricing approaches and their impacts on availability and affordability of medicines for the prevention and treatment of cancer. https://apps.who.int/iris/handle/10665/277190. Accessed March 15, 2021.
4. van Harten WH, Wind A, de Paoli P, et al. Actual costs of cancer drugs in 15 European countries. Lancet Oncol. 2016;17:18-20.
5. Vogler S, Vitry A, Babar ZU. Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study. Lancet Oncol. 2016; 17:39-47.
6. Vokinger KN, Hwang TJ, Grischott T, et al. Prices and clinical benefit of cancer drugs in the USA and Europe: a cost-benefit analysis. Lancet Oncol. 2020; 21:664-670.
7. Goldstein DA, Clark J, Tu Y, et al. A global comparison of the cost of patented cancer drugs in relation to global differences in wealth. Oncotarget. 2017; 8:71548-71555.
8. The World Bank. Data Bank: World Development Indicators. https://databank.worldbank.org/reports.aspx?source=2&series=NY.GDP.PCAP.PP.CD&country=. Accessed February 1, 2021.
9. World Health Organization. Global Health Observatory Data Repository. https://apps.who.int/gho/data/node.main.SDGCHEPERCAPITA?lang=en. Accessed February 2, 2021.

10. Organisation for Economic Co-operation and Development: Conversion Rates: Purchasing Power Parities (PPP). https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm. Accessed February 10, 2021.
11. The World Bank. Data Bank: World Development Indicators. https://databank.worldbank.org/reports.aspx?source=2&series=SP.POP.TOTL&country. Accessed March 3, 2021.
12. Cuomo RE, Seidman RL, Mackey TK. Country and regional variations in purchase prices for essential cancer medications. BMC Cancer. 2017;17:566.
13. Hofmarcher T, Lindgren P, Wilking N, et al. The cost of cancer in Europe 2018. Eur J Cancer. 2020;129:41-49.
14. De Oliveira C, Weir S, Rangrej J, et al. The economic burden of cancer care in Canada: a population-based cost study. CMAJ Open. 2018;6:e1-e10.
15. Pramesh CS, Badwe RA, Borthakur BB, et al. Delivery of affordable and equitable cancer care in India. Lancet Oncol. 2014;15.
16. Cai Y, Xue M, Chen W, et al. Expenditure of hospital care on cancer in China, from 2011 to 2015. Chin J Cancer Res. 2017;29:253-262.
17. O'Carroll S. Cancer Cost Ireland €1.447 Billion in 2009. www.thejournal.ie/cancer-in-ireland-1123519-Oct2013/. Accessed March 15, 2021.
18. Koinuma N, Wilking NE, Jonsson B, et al. The burden of cancer in Japan, the United States, France, Germany, Italy, Spain, Sweden, and the United Kingdom. J Clin Oncol. 2011;29 (suppl; abstr 1569).
19. Price AJ, Ndom P, Atenguena E, et al. Cancer care challenges in developing countries. Cancer. 2012;118:3627-3635.
20. Datta NR, Heuser M, Bodis S. A roadmap and cost implications of establishing comprehensive cancer care using a teleradiotherapy network in a group of sub-Saharan African countries with no access to radiation therapy. Int J Radiat Oncol Biol Phy. 2016;95:1334-1343.
21. Elias F, Bou-Orm IR, Adib SM, et al. Cost of oncology drugs in the Middle-Eastern country of Lebanon: an update (2014-2016). J Glob Oncol. 2018;4:1-7.
22. Ruff P, Al-Sukhun S, Blanchard C, et al. Access to cancer therapeutics in low- and middle-income countries. Am Soc Clin Oncol Educ Book. 2016;35:58-65.
23. Cherny NI, Sullivan R, Torode J, et al. ESMO international consortium study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in countries outside of Europe. Ann Oncol. 2017;28:2633-2647.
24. Eniu A, Cherny NI, Bertram M, et al. Cancer medicines in Asia and Asia-Pacific: what is available, and is it effective enough? ESMO Open. 2019;4:e000483.
25. Cherny N, Sullivan R, Torode J, et al. ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe [published correction appears in Ann Oncol. 2020;31:1589]. Ann Oncol. 2016;27:1423-1443.
26. The Economist Intelligence Unit. Cancer Medicines Shortages in Europe: Policy Recommendations To Prevent and Manage Shortages. www.eiu.com/graphics/marketing/pdf/ESMO-Cancer-medicines-shortages.pdf. Accessed March 10, 2021.
27. World Health Organization. Medicines shortages: global approaches to addressing shortages of essential medicines in health systems. WHO Drug Information. 2016;30:180-185.
28. Pauwels K, Huys I, Casteels M, et al. Drug shortages in European countries: a trade-off between market attractiveness and cost containment? BMC Health Serv Res. 2014;14:438.
29. Ezeife DA, Leighl NB. Personalized medicine for non–small cell lung cancer: where are we now and where can we go? Expert Rev Respir Med. 2018;12:81-82.
30. Ramsey SD, Bansal A, Fedorenko CR, et al. Financial insolvency as a risk factor for early mortality among patients with cancer. J Clin Oncol. 2016;34:980-986.
31. Lathan CS, Cronin A, Tucker-Seeley R, et al. Association of financial strain with symptom burden and quality of life for patients with lung or colorectal cancer. J Clin Oncol. 2016;34:1732-1740.
32. Khera N. Reporting and grading financial toxicity. J Clin Oncol. 2014;32:3337-3338.
33. de Souza JA, Yap BJ, Hlubocky FJ, et al. The development of a financial toxicity patient-reported outcome in cancer: the COST measure. Cancer. 2014;120:3245-3253.
34. Ezeife DA, Morganstein BJ, Lau S, et al. Financial burden among patients with lung cancer in a publically funded health care system. Clin Lung Cancer. 2019;20:231-236.
35. Yap SL, Wong SS, Chew KS, et al. Assessing the relationship between socio-demographic, clinical profile and financial toxicity: evidence from cancer survivors in Sarawak. Asian Pac J Cancer Prev. 2020;21:3077-3083.
36. Barbaret C, Brosse C, Rhondali W, et al. Financial distress in patients with advanced cancer. PLoS One. 2017;12:e0176470.
37. Bouberhan S, Shea M, Kennedy A, et al. Financial toxicity in gynecologic oncology. Gynecol Oncol. 2019;154:8-12.
38. Politi MC, Yen RW, Elwyn G, et al. Women who are young, non-white, and with lower socioeconomic status report higher financial toxicity up to 1 year after breast cancer surgery: a mixed-effects regression analysis. Oncologist. 2021;26:e142-e152.
39. Dusetzina SB, Winn AN, Abel GA, et al. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. J Clin Oncol. 2014;32:306-311.
40. Gross CP, Gluck AR. Soaring cost of cancer treatment: moving beyond sticker shock. J Clin Oncol. 2018;36:305-307.
41. Will cancer drugs get cheaper in 2020? Nat Rev Clin Oncol. 2020;17:127.
42. Hill A, Gotham D, Fortunak J, et al. Target prices for mass production of tyrosine kinase inhibitors for global cancer treatment. BMJ Open. 2016;6:e009586.
43. Tay-Teo K, Ilbawi A, Hill SR. Comparison of sales income and research and development costs for FDA-approved cancer drugs sold by originator drug companies. JAMA Netw Open. 2019;2:e186875.
44. Mailankody S, Prasad V. Five years of cancer drug approvals: innovation, efficacy and costs. JAMA Oncol. 2015;1:539-540.

45. Gordon N, Stemmer SM, Greenberg D, et al. Trajectories of injectable cancer drug costs after launch in the United States. J Clin Oncol. 2018;36:319-325.
46. Cohen J. The Curious Case of Gleevec Pricing. www.forbes.com/sites/joshuacohen/2018/09/12/the-curious-case-of-gleevec-pricing. Accessed February 6, 2021.
47. Gyawali B, Sullivan R. Economics of cancer medicines: for whose benefit? New Bioeth. 2017;23:95-104.
48. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes [published correction appears in J Clin Oncol. 2015;33:3523]. J Clin Oncol. 2014;32:1277-1280.
49. Sacher AG, Le LW, Leighl NB. Shifting patterns in the interpretation of phase III clinical trial outcomes in advanced non–small cell lung cancer: the bar is dropping. J Clin Oncol. 2014;32:1407-1411.
50. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol. 2015;26:1547-1573.
51. Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology Value Framework: revisions and reflections in response to comments received. J Clin Oncol. 2016;34:2925-2934.
52. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer.org/wp-content/uploads/2021/03/ICER_2020_2023_VAF_013120-4-2.pdf. Accessed March 16, 2021.
53. Memorial Sloan Kettering Cancer Center. Drug Abacus Tool. http://abacus.realendpoints.com. Accessed March 16, 2021.
54. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) With NCCN Evidence Blocks. www.nccn.org/evidenceblocks. Accessed March 16, 2021.
55. Ezeife DA, Dionne F, Fares AF, et al. Value assessment of oncology drugs using a weighted criterion-based approach. Cancer. 2020;126:1530-1540.
56. Del Paggio JC, Sullivan R, Schrag D, et al. Delivery of meaningful cancer care: a retrospective cohort study assessing cost and benefit with the ASCO and ESMO frameworks. Lancet Oncol. 2017;18:887-894.
57. Hwang TJ, Kesselheim AS, Gyawali B. Affordability and price increases of new cancer drugs in clinical guidelines, 2007-2016. JNCI Cancer Spectr. 2018;2:pky016.
58. Rodwin MA, Mancini J, Duran S, et al. The use of 'added benefit' to determine the price of new anti-cancer drugs in France, 2004-2017. Eur J Cancer. 2021;145:11-18.
59. Goldstein DA, Sarfaty M. Cancer drug pricing and reimbursement: lessons for the United States from around the world. Oncologist. 2016;21:907-909.
60. World Health Organization. WHO Report on Cancer: Setting Priorities, Investing Wisely and Providing Care For All. http://apps.who.int/iris. Accessed February 16, 2021.
61. American Society of Clinical Oncology. American Society of Clinical Oncology position statement on addressing the affordability of cancer drugs. J Oncol Pract. 2018;14:187-192.
62. Reaume MN, Leighl NB, Mittmann N, et al. Economic analysis of a randomized phase III trial of gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus vinorelbine or cisplatin plus gemicitabine for advanced non–small cell lung cancer (Italian GEMVIN3/NCIC CTG BR14 trial). Lung Cancer. 2013;82:115-120.
63. Cheung WY, Kornelsen EA, Mittmann N, et al. The economic impact of the transition from branded to generic oncology drugs. Curr Oncol. 2019;26:89-93.
64. Neubauer MA, Hoverman JR, Kolodziej M, et al. Cost effectiveness of evidence-based treatment guidelines for the treatment of non–small cell lung cancer in the community setting. J Oncol Pract. 2010;6:12-18.
65. Pramesh CS, Chaturvedi H, Reddy VA, et al; National Cancer Grid. Choosing Wisely India: ten low-value or harmful practices that should be avoided in cancer care. Lancet Oncol. 2019;20:e218-e223.
66. Goldstein DA, Gordon N, Davidescu M, et al. A pharmacoeconomic analysis of personalized dosing vs fixed dosing of pembrolizumab in firstline PD-L1-positive non–small cell lung cancer. J Natl Cancer Inst. 2017;109.
67. Aguiar PN Jr., Perry LA, Penny-Dimri J, et al. The effect of PD-L1 testing on the cost-effectiveness and economic impact of immune checkpoint inhibitors for the second-line treatment of NSCLC. Ann Oncol. 2017;28:2256-2263.
68. Ferreira CG, Nicolini A, Dalurzo L, et al. The value of biomarkers in optimizing the use of immuno-oncologic therapy. Curr Drug Targets. 2019;20:81-86.
69. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947-957.
70. Pennell NA, Zhou J, Hobbs B, et al. A model comparing the value of broad next-gen sequencing (NGS)-based testing to single-gene testing (SGT) in patients with nonsquamous non–small cell lung cancer (NSCLC) in the United States. J Clin Oncol. 2020;38 (suppl; abstr 9529).
71. Schluckebier L, Caetano R, Garay OU, et al. Cost-effectiveness analysis comparing companion diagnostic tests for EGFR, ALK, and ROS1 versus next-generation sequencing (NGS) in advanced adenocarcinoma lung cancer patients. BMC Cancer. 2020;20:875.
72. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non–small cell lung cancer. N Engl J Med. 2014;370:1189-1197.
73. Cho BC, Kim DW, Bearz A, et al. ASCEND-8: a randomized phase 1 study of ceritinib, 450 mg or 600 mg, taken with a low-fat meal versus 750 mg in fasted state in patients with anaplastic lymphoma kinase (ALK)-rearranged metastatic non–small cell lung cancer (NSCLC). J Thorac Oncol. 2017;12:1357-1367.
74. Cho BC, Obermannova R, Bearz A, et al. Efficacy and safety of ceritinib (450 mg/d or 600 mg/d) with food versus 750-mg/d fasted in patients with ALK receptor tyrosine kinase (ALK)-positive NSCLC: primary efficacy results from the ASCEND-8 Study. J Thorac Oncol. 2019;14:1255-1265.

75. Peters S, Camidge DR, Shaw AT, et al; ALEX Trial Investigators. Alectinib versus crizotinib in untreated ALK-positive non–small cell lung cancer. N Engl J Med. 2017;377:829-838.

76. Zhou C, Kim SW, Reungwetwattana T, et al. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non–small cell lung cancer (ALESIA): a randomised phase 3 study. Lancet Respir Med. 2019;7:437-446.

77. Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non–small cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet. 2017;390:29-39.

78. Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non–small cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol. 2014;15:1119-1128.

79. Joensuu H, Kellokumpu-Lehtinen P-L, Bono P, et al; FinHer Study Investigators. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354:809-820.

80. Pivot X, Romieu G, Debled M, et al; PHARE trial investigators. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Lancet Oncol. 2013;14:741-748.

81. Waterhouse DM, Garon EB, Chandler J, et al. Continuous versus 1-year fixed-duration nivolumab in previously treated advanced non–small cell lung cancer: Checkmate 153. j clin oncol. 2020;38:3863-3873.

82. Gyawali B, Sullivan R, Booth CM. Cancer Groundshot: going global before going to the moon. Lancet Oncol. 2018;19:288-290.

83. World Health Organization. WHO Model List of Essential Medicines: 21st List, 2019. www.who.int/publications/i/item/WHOMVPEMPIAU2019.06. Accessed February 1, 2021.

84. Cortes J, Perez-García JM, Llombart-Cussac A, et al. Enhancing global access to cancer medicines. CA Cancer J Clin. 2020;70:105-124.

85. Gyawali B. Causes, Consequences and Control of High Cancer Drug Prices. In Bernicker EH, (ed). Cancer and Society. Cham, Switzerland: Springer Nature Switzerland AG; 2019;39-57.

86. Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. JAMA Intern Med. 2017; 177:1569-1575.

87. Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics: the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity—the John Conley Lecture. JAMA Otolaryngol Head Neck Surg. 2014;140:1225-1236.

88. Ezeife DA, Truong TH, Heng DYC, et al. Comparison of oncology drug approval between Health Canada and the U.S. Food and Drug Administration. Cancer. 2015;121:1688-1693.

89. Gotfrit J, Shin JJW, Mallick R, et al. Potential life-years lots: the impact of the cancer drug regulatory and funding process in Canada. Oncologist. 2020; 25:e130-e137.

invited article

overview

The Ethical Imperative of Equity in Oncology: Lessons Learned From 2020 and a Path Forward

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The COVID-19 pandemic and the simultaneous increased focus on structural racism and racial/ethnic disparities across the United States have shed light on glaring inequities in U.S. health care, both in oncology and more generally. In this article, we describe how, through the lens of fundamental ethical principles, an ethical imperative exists for the oncology community to overcome these inequities in cancer care, research, and the oncology workforce. We first explain why this is an ethical imperative, centering the discussion on lessons learned during 2020. We continue by describing ongoing equity-focused efforts by ASCO and other related professional medical organizations. We end with a call to action—all members of the oncology community have an ethical responsibility to take steps to address inequities in their clinical and academic work—and with guidance to practicing oncologists looking to optimize equity in their research and clinical practice.

INTRODUCTION

Last year was punctuated by two overlapping health crises. First, from March 2020 to March 2021, more than 500,000 people in the United States died of COVID-19, the disease caused by the novel SARS-COV-2. Although no single American life was left unaffected by the pandemic, its negative impact was significantly greater among Black, Latinx, and Indigenous persons of color, both in children and adults.[1-4] Second, although not new in 2020, the Black Lives Matter movement highlighted the far-too-long overlooked reality of structural racism, specifically anti-Black racism. Defined as a "system in which public policies, institutional practices, cultural representations, and other norms work in various, often reinforcing ways to perpetuate racial group inequity,"[5] structural racism is finally being recognized as a root cause of health inequities in the United States.[6]

Patients with cancer have served as an all-too-perfect illustration of these crises. Despite improvements in cancer survival in the United States, it is well-established that Black patients fare much worse for most cancers compared with all other racial/ethnic groups.[7] In 2020, Hispanic and Black patients with cancer had greater odds of contracting COVID-19 compared with White patients,[8] and, when infected, Hispanic patients also experienced greater odds of treatment delays.[8] Furthermore, among those with active or prior histories of cancer, Black and Hispanic patients experienced substantially higher COVID-19 symptom severity and higher rates of mortality compared with White patients, even after controlling for sex, age, and clinically relevant covariables.[9] These differences were not due to biology but rather to long-standing and persistent systemic racism in medicine.[10]

It is time to stop talking about disparities in oncology as unfortunate circumstances and, instead, it is time to act and correct them. In this article, we use a common framework for ethical analysis in health care to demonstrate that (1) clinical oncology care and research are not equitable and (2) if we believe that these ethical principles are the foundation of appropriate medical care, then correcting those inequities is an ethical imperative. We then introduce some promising first steps presently being taken throughout the oncology community. Finally, we provide guidance to practicing oncologists to optimize equity in their practices.

EQUITY THROUGH THE LENS OF FUNDAMENTAL ETHICAL PRINCIPLES

A common approach to ethics in health care is to consider fundamental ethical principles.[11] Many clinicians are familiar with the four principles of respect for autonomy, beneficence, nonmaleficence, and justice. Popularized by Beauchamp and Childress[11] and now central tenets in the ethics education of many medical trainees, these principles provide a practical approach to ethically informed medical decision-making. Although other principles beyond these four may be relevant for a given case (e.g., truth-telling), we focus here on these four for the sake of brevity and simplicity. Importantly, these and other ethical principles do not necessarily tell us the "right" thing to do

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PRACTICAL APPLICATIONS

- The COVID-19 pandemic has shed light on substantial inequities in U.S. health care, both in oncology and more generally.
- Fundamental ethical principles, including respect for autonomy, beneficence, nonmaleficence, and justice, demonstrate the ethical imperative for oncology professionals to work to overcome inequities in cancer care, cancer research, and the oncology workforce.
- ASCO and other professional medical organizations have begun various equity-focused efforts, and much more work remains to be done.
- As members of the oncology community, we each have an ethical responsibility to take steps to address inequities in our clinical and academic work. These steps include addressing interpersonal racism experienced by health care professionals and patients/families; examining our own implicit and explicit biases; and providing anti-racist training for all oncology clinicians, staff, trainees, and leaders.

(i.e., we cannot choose between treatment A and treatment B simply by hearkening to the principle of beneficence); rather, considering these principles together helps guide us toward an ethically supportable action.

Respect for Autonomy

In Western health care, we place particular emphasis on the importance of respecting a competent adult's autonomous choice to accept (or refuse) a given intervention in the absence of coercion or undue pressure. A competent adult may make a decision that their clinician believes not to be in their best interests, assuming they comprehend the risks/benefits and other relevant features of the decision.[12,13] In oncology, a paradigmatic example of respect for autonomy is when offering enrollment in a clinical trial; patient participation first requires informed (autonomous) consent to receive the proposed treatment. We respect the choice made by the patient and proceed with their care accordingly. The problem with this example is that it assumes equitable access to treatment choices, when the wealth of evidence suggests that patients of minoritized racial and ethnic backgrounds lack access to clinical trials and are persistently under-represented in clinical research, despite a similar willingness to participate as White patients.[14-16] Thus, can we really claim a universal and equitable respect for autonomy? Are we really giving all individuals the same opportunities to exercise their autonomy and make informed choices? This problem is only compounded more when we consider the mistreatment and exploitation of Black patients by health care professionals and health care research systems (e.g., the infamous Tuskegee experiments and many other atrocities). If we truly value the ethical principle of respecting the autonomy of our patients with cancer, then we must strive first to ensure equal access to care and relevant care decisions for all patients with cancer. Similarly, to gain the trust of all our patients, we must first demonstrate to them that we are worthy of that trust.

Beneficence

A second relevant principle is that of beneficence, supporting a patient's best interests. Put simply, beneficence supports promoting the "good" of an individual. In oncology, we should consider this principle in nearly all care decisions, whether collaborating with a patient to choose the treatment that is expected to maximally extend their survival, optimize their quality of life, or otherwise support their goals and values. However, truly promoting the good for all patients, equitably, assumes that all patients have equal access to standard oncology care. This is not the case. First, following the example of clinical research to its conclusion, the considerable under-representation of patients of color in genomic databases and precision oncology trials means that inequitable access to targeted therapies is likely to continue.[17] Second, consider another example of medical insurance. Oncology care is extremely expensive, and few patients can afford it without insurance. Because Black, Latinx, and Indigenous persons of color are less likely than White people to have medical insurance, at a population level, they are also less likely to benefit from the full breadth of oncology treatments.[18-21] Indeed, recent work suggests that Medicaid expansion under the Affordable Care Act reduces health care inequities and improves outcomes for patients of color simply by improving access.[22] It follows that practicing beneficence equitably requires all patients to have equal access to care as well as equal ability to pay.

Nonmaleficence

Nonmaleficence is often considered alongside beneficence as flip sides of the same coin, as patients and clinicians together consider how best to balance the benefits and harms of health care decisions. The Hippocratic Oath is often colloquially distilled down to "do no harm," which ultimately is a statement of nonmaleficence. We see the focus on this principle in various aspects of cancer care and research. When a new drug is being developed, for example, even before its efficacy (beneficence) is examined, early-phase trials first focus on its safety, to minimize the harm it causes to patients, before moving on to larger trials aimed at determining the drug's benefit. Without equity in the research and clinical settings, how can we claim to be minimizing harm to our patients? As described above, without adequate and equitable representation in the clinical trials

that inform drug approvals and without equitable access to standard oncology care, we cannot reliably assess the safety and potential toxicities of new treatments for our patients. In fact, we may actually be causing harm in not providing those options.

Justice

The fourth and final principle we examine in this article is justice, which can be simultaneously described as the concept that (1) all persons should be treated alike and (2) benefits and harms should be distributed equally among individuals.[11] Unfortunately, when we consider equity through the lens of justice in oncology, we are faced with the reality that we are falling alarmingly short of our goal of providing just care to all patients with cancer. Improvements in oncology care in recent decades have come as a result of rigorous study and standardization of treatment regimens, in part through development and use of treatment guidelines. However, recent work has shown that Black and Hispanic patients and those with Medicaid insurance receive guideline-concordant care less frequently than do White patients and those with other insurance types.[23] When considering this fact in tandem with the concerns raised above about inequitable access to new cancer therapies experienced by minoritized patient populations, we must acknowledge startling injustices inherent in modern cancer care. As we as the oncology community consider how best to care for our patients now and in the future, it is imperative that we make sure that this care is just across all patient populations.

STRUCTURAL RACISM IN CLINICAL ONCOLOGY PRACTICE

Black people in the United States persistently experience the highest incidence of certain cancers and have the highest cancer mortality rates compared with all other racial and ethnic groups in the United States.[7] At the core of these disparities is structural racism related not only to access to care but also to differential treatment of minoritized populations by health care providers in oncology as well as other areas of medicine.[24-27] Importantly, in tandem with and as a result of this structural racism, minoritized populations also encounter various other factors that might contribute to disparities in health care outcomes (in oncology and more generally), including residential segregation, police violence, and incarceration;[28] less access to healthy foods and grocery stores;[29] and greater exposure to pollution and environmental hazards.[30]

And that is not all. Structural racism also impacts Black health care trainees and professionals. Systemic exclusion of Black students from medical schools as a result of racial disparities in access to high-quality educational opportunities and the financial burden imposed on disadvantaged students applying to medical school are deterrents to entering the medical profession.[31] In fact, although the absolute number of Black, Latinx, and Native American U.S. medical school matriculants has increased over time, it has done so at a slower rate than their growth in the U.S. population, meaning that disparities in representation in medical school only continue to worsen.[32] The downstream effect of this lack of diversity in medical education—and, ultimately, in the medical workforce—is a pervasive and persistent sense of nonbelonging for both patients and clinicians.

ONGOING ASCO EQUITY INITIATIVES

It is both our responsibility and our ethical obligation as individual oncologists and as a professional society to operationalize respect for autonomy, beneficence, nonmaleficence, and justice for patients with cancer of all races and ethnicities. Several scholars and medical organizations, including ASCO, have provided guidance on how to begin.[33] We highlight a few of these initiatives here, with the understanding that this work is constantly changing and requires intentional, ongoing efforts.

First, ASCO has created the Social Determinants of Health Education Series.[34] This series of podcasts highlights several themes, including the importance of understanding how social determinants of health impact cancer care and cancer outcomes; what ASCO as an organization is doing to promote equity; implantation of the social history with best practices for connecting patients to services to address their social needs; and acknowledging and addressing the impact of financial toxicity on quality of care, access to care, and cancer outcomes as a result of the increasing cost of cancer care. Together, this series is designed to inform the ASCO community about social determinants of health in oncology and, in turn, to promote practice changes leading to more equitable care.

Second, the steering committees of ASCO and the Association of Community Cancer Centers are collaborating in work aimed at prioritizing the participation of Black and Latinx persons in clinical trials.[35] This initiative endeavors to engage the oncology community in addressing the longstanding and worsening racial and ethnic disparities in cancer clinical trial participation,[14-16] ultimately aiming to improve equitable access to cancer clinical trials. Included in this effort is an open call to members for novel strategies and practical solutions that address this incredibly important shortcoming of the oncology clinical trial infrastructure.

Third, in the wake of the vast changes to oncology clinical care and research required because of the COVID-19 pandemic, ASCO recently published the report of its "Road to Recovery" task force, which engaged leaders in clinical care and research from across the oncology community to examine how patient care and clinical research can be improved in the wake of our experiences with COVID-19.[36] Included in the recommendations offered in the report are calls for renewed efforts to promote equitable access to cancer

TABLE 1. Recent Statements by Professional Medical Organizations About Racism and Health Equity

Organization	Statement	Link to Statement	Notable Statement Features
National Institutes of Health	"NIH stands against structural racism in biomedical research"	https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-stands-against-structural-racism-biomedical-research	Focuses on ending structural racism and racial inequities in research Introduces UNITE initiative
National Cancer Institute	"NCI statement on ending structural racism in biomedical research"	https://www.cancer.gov/news-events/press-releases/2021/nci-statement-unite-end-structural-racism	Supports NIH statement and efforts through UNITE initiative Additional focus on diversity of cancer research workforce
American Medical Association	"How the AMA is reshaping its path toward racial equity"	https://www.ama-assn.org/delivering-care/health-equity/how-ama-reshaping-its-path-toward-racial-equity	Launching of AMA Center for Health Equity and hiring of chief health equity officer Describes AMA efforts and partnerships to advance health equity in practice
Association of American Medical Colleges	"Addressing and eliminating racism at the AAMC and beyond"	https://www.aamc.org/addressing-and-eliminating-racism-aamc-and-beyond	Highlights four-pillar plan for promoting diversity, equity, and inclusion at AAMC and in academic medicine Focuses on community collaborations in academic medicine with equity aims

Abbreviations: NIH, National Institutes of Health; NCI, National Cancer Institute; AMA, American Medical Association; AAMC, Association of American Medical Colleges.

care and research, including rigorous collection of sociodemographic data in all trials and registries and intensified efforts to eliminate barriers to high-quality cancer care for all.

Finally, the need to address workforce diversity is also being recognized, including how individuals and organizations should support, train, recruit, and retain diverse providers who mirror the demographics of the patients they serve. Although approximately 13% of the U.S. population is African American and 18% is Hispanic, only 2.3% and 5.8% of the oncology workforce self-identify as African American and Hispanic, respectively.[37] ASCO's 3-year (2017–2020) strategic plan for increasing racial and ethnic diversity in the oncology workforce outlines three short-term goals already underway within the organization to establish pathways for medical trainees to enter the oncology workforce (including mentorship and policy solutions), expand diversity in ASCO leadership, and integrate diversity across all ASCO programs and initiatives.[38] It is also important to note that ASCO provides ongoing support to promote workforce diversity through initiatives such as the Medical Student Rotation (https://www.asco.org/research-guidelines/grants-awards/funding-opportunities/medical-student-rotation-underrepresented-populations) and the Resident Travel Award (https://www.asco.org/research-guidelines/grants-awards/funding-opportunities/resident-travel-award-underrepresented-populations) for trainees from populations under-represented in the field of oncology.

A CALL TO ACTION

With this context in mind, it is an ethical imperative that we, as members of the oncology community, take steps to address the inequities we see in oncology. This includes inequities both in and experienced by the oncology workforce as well as those experienced by our patients.

First, it is incumbent upon us to address the unjust and unequal treatment of people of color in our work environment. Interpersonal racism experienced by providers of color is not uncommon. It is an ethical imperative to use our positions as health care leaders (physicians, nurses, managers, etc.) to recognize and address racism and discrimination of all kinds in our day-to-day practices.[39,40] As oncologists, we must take on the responsibility of identifying and responding to racism during medical encounters. We must have policies that allow, if not require, us to report repeated offenders of discriminatory and/or unjust acts and ensure a culture of inclusivity in the workplace. Additionally, our institutions have a responsibility to clinicians, staff, and trainees of color that should include high-quality anti-racism training, particularly for leaders to identify and respond to racism in the workplace,[41] including in medical documentation, which has been shown to demonstrate both implicit and explicit racial biases.[42] Adopting anti-racist skills, procedures, policies, and documentation practices can form the basis for evidence-based practices on how to address racism in the workplace, whether it affects clinicians, trainees, staff, and/or patients.

Furthermore, as members of the oncology workforce, our ethical responsibility also includes examining our own implicit and explicit biases, because both impact how we evaluate our patients, make assessments, provide recommendations, and ultimately deliver care. Increased awareness of our own biases will challenge the practices that perpetuate disparities and inequities in cancer care and outcomes.[43]

Centering our patients' voices during the medical history; spending sufficient time with our patients; and practicing cultural humility, respect, and beneficence will promote better communication and engender trust. Guidance on how we can adopt practices within our medical education system to educate our trainees on racial justice in the care of our patients is available and should also be a core component in our continuing education for professional development.[44]

Importantly, ASCO is not the only organization actively addressing these important issues, so we as individuals should not feel that we are starting from scratch in identifying how best to respond to the ethical imperative of tackling racial inequities in cancer care. Table 1 presents a nonexhaustive list of recent public-facing statements about racism and health care inequities from organizations relevant to the oncology community, which may be considered alongside the ASCO statements referenced earlier. We do not intend to voice support for any particular organization or its statement (or to imply disagreement with any statement not included here). Rather, we hope that these statements and the concepts and resources they reference can serve as a starting point for individuals and institutions in the oncology community looking to build equity initiatives and/or enhance equity in their clinical and research practices. Achieving equity in oncology is indeed an ethical imperative, and this is not an effort that any of us must undertake alone.

CONCLUSION

Last year changed the way we live and interact in U.S. society. It is unclear if and how those changes will endure. One thing is certain, however: we will never forget. Let us use the hard-learned lessons of 2020 to change oncology practice for good. Let us reconsider the principles of respect for autonomy, beneficence, nonmaleficence, and justice through the lens of structural racism and inequity. Let us come together as individuals and as a clinical oncology community to create positive change, reduce disparities, and ultimately provide better care for all our patients, now and in the future.

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REFERENCES

1. Azar KMJ, Shen Z, Romanelli RJ, et al. Disparities in outcomes among COVID-19 patients in a large health care system in California. Health Aff (Millwood). 2020;39:1253-1262.
2. Bassett MT, Chen JT, Krieger N. Variation in racial/ethnic disparities in COVID-19 mortality by age in the United States: a cross-sectional study [published correction appears in *PLoS Med*. 2021;18:e1003541]. PLoS Med. 2020;17:e1003402.
3. Sabatello M, Jackson Scroggins M, Goto G, et al. Structural racism in the COVID-19 pandemic: moving forward. Am J Bioeth. 2021;21:56-74.
4. Marron JM. Structural racism in the COVID-19 pandemic: don't forget about the children!. Am J Bioeth. 2021;21:94-97.
5. Lawrence K, Sutton S, Kubisch A, et al. Structural Racism and Community Building, Aspen Institute Roundtable on Community Change. Washington, DC: The Aspen Institute; 2004. Available at: https://www.aspeninstitute.org/wp-content/uploads/files/content/docs/rcc/aspen_structural_racism2.pdf.
6. Bailey ZD, Krieger N, Agénor M, et al. Structural racism and health inequities in the USA: evidence and interventions. Lancet. 2017;389:1453-1463.
7. American Cancer Society. Cancer Facts & Figures for African Americans, 2019-2021. American Cancer Society, 2019. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-facts-and-figures-for-african-americans/cancer-facts-and-figures-for-african-americans-2019-2021.pdf. Accessed May 13, 2021.
8. Schmidt AL, Bakouny Z, Bhalla S, et al. Cancer care disparities during the COVID-19 pandemic: COVID-19 and cancer outcomes study. Cancer Cell. 2020;38:769-770.

9. Grivas P, Khaki A R, Wise-Draper T M, et al. Association of clinical factors and recent anticancer therapy with COVID-19 severity among patients with cancer: a report from the COVID-19 and Cancer Consortium. Ann Oncol. 2021;32:787-800.
10. Evans MK, Rosenbaum L, Malina D, et al. Diagnosing and treating systemic racism. N Engl J Med. 2020;383:274-276.
11. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. New York: Oxford University Press; 2009.
12. Appelbaum PS. Clinical practice. Assessment of patients' competence to consent to treatment. N Engl J Med. 2007;357:1834-1840.
13. Marron JM, Kyi K, Appelbaum PS, et al. Medical decision-making in oncology for patients lacking capacity. Am Soc Clin Oncol Educ Book. 2020;40:1-11.
14. Al Hadidi S, Mims M, Miller-Chism CN, et al. Participation of African American persons in clinical trials supporting U.S. Food and Drug Administration approval of cancer drugs. Ann Intern Med. 2020;173:320-322.
15. Nazha B, Mishra M, Pentz R, et al. Enrollment of racial minorities in clinical trials: old problem assumes new urgency in the age of immunotherapy. Am Soc Clin Oncol Educ Book. 2019;39:3-10.
16. Duma N, Vera Aguilera J, Paludo J, et al. Representation of minorities and women in oncology clinical trials: review of the past 14 years. J Oncol Pract. 2018; 14:e1-e10.
17. Marron JM, Joffe S. Ethical considerations in genomic testing for hematologic disorders. Blood. 2017;130:460-465.
18. Ko NY, Hong S, Winn RA, et al. Association of insurance status and racial disparities with the detection of early-stage breast cancer. JAMA Oncol. 2020; 6:385-392.
19. Young CL. There are Clear, Race-Based Inequalities in Health Insurance and Health Outcomes. Brookings Institution, 2020. https://www.brookings.edu/blog/usc-brookings-schaeffer-on-health-policy/2020/02/19/there-are-clear-race-based-inequalities-in-health-insurance-and-health-outcomes/. Accessed May 13, 2021.
20. Carlson RW. Treatment Barriers Create Racial Disparities in Cancer Care. They Need to Come Down. STAT News, June 24, 2020. https://www.statnews.com/2020/06/24/cancer-care-racial-disparities-dismantle-barriers/. Accessed May 13, 2021.
21. Zheng D, Li A, Ma C, et al. Socioeconomic disparities in survival after high-risk neuroblastoma treatment with modern therapy. Ped Blood Cancer. In press.
22. Adamson BJS, Cohen AB, Estevez M, et al. Affordable Care Act (ACA) Medicaid expansion impact on racial disparities in time to cancer treatment. J Clin Oncol. 2019;37(18_suppl):LBA1.
23. Clair K, Chang J, Ziogas A, et al. Disparities by race, socioeconomic status, and insurance type in the receipt of NCCN guideline concordant care for select cancer types in California. J Clin Oncol. 2020;38(15_suppl):7031.
24. Penner LA, Dovidio JF, Gonzalez R, et al. The effects of oncologist implicit racial bias in racially discordant oncology interactions. J Clin Oncol. 2016; 34:2874-2880.
25. Niranjan SJ, Martin MY, Fouad MN, et al. Bias and stereotyping among research and clinical professionals: Perspectives on minority recruitment for oncology clinical trials. Cancer. 2020;126:1958-1968.
26. Hall WJ, Chapman MV, Lee KM, et al. Implicit racial/ethnic bias among health care professionals and its influence on health care outcomes: a systematic review. Am J Public Health. 2015;105:e60-e76.
27. Institute of Medicine. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC: The National Academies Press; 2003.
28. Bailey ZD, Feldman JM, Bassett MT, et al. How structural racism works: racist policies as a root cause of U.S. racial health inequities. New Engl J Med. 2021; 384:768-773.
29. Hilmers A, Hilmers DC, Dave J, et al. Neighborhood disparities in access to healthy foods and their effects on environmental justice. Am J Public Health. 2012; 102:1644-1654.
30. Ash M, Boyce JK. Racial disparities in pollution exposure and employment at US industrial facilities. Proc Natl Acad Sci. 2018;115:10636-10641.
31. Chapman CH, Gabeau D, Pinnix CC, et al. Why racial justice matters in radiation oncology. Adv Radiat Oncol. 2020;5:783-790.
32. Lett LA, Murdock HM, Orji WU, et al. Trends in racial/ethnic representation among U.S. medical students. JAMA Netw Open. 2019;2:e1910490.
33. Patel MI, Lopez AM, Blackstock W, et al. Cancer disparities and health equity: a policy statement from the American Society of Clinical Oncology [published correction appears in *J Clin Oncol.* 2020;38:3976]. J Clin Oncol. 2020;38:3439-3448.
34. ASCO in Action. What are Social Determinants of Health and How Can Oncologists Address Their Impact on Patients? February 17, 2021. https://www.asco.org/practice-policy/policy-issues-statements/asco-in-action/what-are-social-determinants-health-and-how. Accessed May 13, 2021.
35. ASCO in Action. ASCO & ACCC Join Forces to Increase Participation of Racial and Ethnic Minority Populations in Cancer Treatment Trials, Initiative Calls on Cancer Community to Share Novel Strategies, Practical Solutions to Address Longstanding Barriers. July 21, 2020. https://www.asco.org/practice-policy/policy-issues-statements/asco-in-action/asco-accc-join-forces-increase-participation. Accessed May 13, 2021.
36. Pennell NA, Dillmon M, Levit LA, et al. American Society of Clinical Oncology Road to Recovery Report: learning from the COVID-19 experience to improve clinical research and cancer care. J Clin Oncol. 2021;39:155-169.
37. American Society of Clinical Oncology. Facts & Figures: Diversity in Oncology. https://www.asco.org/practice-policy/cancer-care-initiatives/diversity-oncology-initiative/facts-figures-diversity. Accessed May 13, 2021.
38. Winkfield KM, Flowers CR, Patel JD, et al. American Society of Clinical Oncology strategic plan for increasing racial and ethnic diversity in the oncology workforce. J Clin Oncol. 2017;35:2576-2579.
39. Charlot M. Power in our hands: addressing racism in the workplace. J Clin Oncol. 2020;38:4118-4119.

40. Issaka RB. Good for us all. JAMA. 2020;324:556-557.

41. Doll KM, Thomas CR Jr. Structural solutions for the rarest of the rare: underrepresented-minority faculty in medical subspecialties. N Engl J Med. 2020; 383:283-285.

42. Balderston JR, Gertz ZM, Seedat R, et al. Differential documentation of race in the first line of the history of present illness. JAMA Int Med. 2021;181:386-388.

43. Gaddy J. Challenge Your Biases: Understanding Your Patient Is Key to Providing High-Quality, Empathetic Care. ASCO Connection, January 12, 2021. https://connection.asco.org/blogs/challenge-your-biases-understanding-your-patient-key-providing-high-quality-empathetic-care. Accessed May 13, 2021.

44. Krishnan A, Rabinowitz M, Ziminsky A, et al. Addressing race, culture, and structural inequality in medical education: a guide for revising teaching cases. Acad Med. 2019;94:550-555.

invited article

overview

Navigating a Path to Equity in Cancer Care: The Role of Patient Navigation

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Notable barriers exist in the delivery of equitable care for all patients with cancers. Social determinants of health at distal, intermediate, and proximal levels impact cancer care. Patient navigation is a patient-centered intervention that functions across these overlapping determinants to increase access to cancer services throughout the cancer care continuum. There is a need to standardize patient navigation training while remaining responsive to local contexts of care and a need to implement patient navigation programs with a health equity lens to address cancer care inequities.

Barriers to equitable access and appropriate care coordination stand in the way of achieving equity in cancer care and delivering high-quality care to all patients with cancer. Notable advances in cancer prevention, cancer screening, and the development of effective cancer treatments have contributed to improvements in outcomes for patients with cancer.[1] However, the benefits of these advances are not shared equally, and great disparities persist in cancer outcomes by race/ethnicity, socioeconomic status, sex, and geography.[1] It is well documented that Black women experience higher rates of mortality from breast cancer,[2] Black men experience higher rates of incidence and mortality from prostate cancer,[3] and Hispanic and Latinx women are more likely to be diagnosed with later-stage breast cancer and experience delays in diagnosis and treatment.[4] Despite wider implementation of colorectal cancer screening, rates remain low in racial and ethnic minority patients, low socioeconomic status populations, women, and patients who speak a primary language other than English.[5,6] In addition to systemic racism, socioeconomic status, insurance, geographic location, language, and immigration status are important determinants of cancer outcomes.[7-12] The differences in cancer survival are related to structural barriers to accessing care and overt documented differences in the delivery of evidence-based care.[13-15]

Patient navigation is a patient-centered intervention designed to improve patient experiences and the delivery of cancer care. Patient navigation is defined as a "community-based service delivery intervention designed to promote access to timely diagnosis and treatment of cancer and other chronic diseases by eliminating barriers to care."[16] Dr. Harold Freeman created the first patient navigation program in Harlem in 1990 to expand access to cancer screening and follow-up after abnormal results for African American women living in the area and successfully improved survival for women with breast cancer.[17,18] Thus, patient navigation in its origin is rooted in health equity and responsiveness to entrenched barriers to care for underserved patients with cancer. Recognizing the role of patient navigation in addressing disparities, the U.S. Congress passed the Patient Navigation Outreach and Chronic Disease Prevention act in 2005 and created a funding mechanism designed to support research on the impacts of patient navigation.[19] In 2010, the Patient Protection and Affordable Care Act specifically identified patient navigation as a strategy to facilitate insurance access.[20] Navigators funded through federal grants assisted consumers seeking health insurance coverage in confirming their eligibility and enrolling in coverage through marketplaces.[21] This important intervention sought to address the association of a lack of insurance with worse cancer outcomes[11] and the financial toxicity associated with cancer treatments.[22] Since then, several policy initiatives have supported implementation of patient navigation programs. For example, in 2012, the American College of Surgeons Commission on Cancer required all Commission on Cancer–accredited organizations to have a patient navigation program for cancer care.

In this review, we examine the impact of patient navigation in addressing health inequities across the cancer continuum and explore future directions in patient navigation to provide equitable care.

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PRACTICAL APPLICATIONS

- Advances in cancer treatments have not benefited racial/ethnic minority patients and patients with low socioeconomic status equally.
- Patient navigation is an important intervention that addresses cancer disparities throughout the cancer care continuum.
- There are several models of patient navigation that can be tailored to the needs of patients and health care systems.
- Future implementation of patient navigation informed by current challenges in cancer care is needed to achieve cancer care equity and improve cancer disparities.

HOW PATIENT NAVIGATION ADDRESSES CANCER DISPARITIES

Causes of health disparities can be divided into three overlapping and intersecting levels of determinants, which are described as population, social context, and individual/interpersonal levels.[23] Distal determinants that occur at the population level include policies that impact socioeconomic status, accessibility, availability and quality of health services, and housing status.[23] The intermediate level, social context, includes communities, neighborhoods, and health systems. Determinants at this level include housing segregation, persistent poverty, and educational access/experiences. The third level includes individual socioeconomic status, race/ethnicity, sex, health literacy, and capacity to address health care needs.[23] Health behaviors, although considered individual determinants, are shaped by the intermediate and distal contexts. For example, negative effects of neighborhood determinants can be improved with social connectedness by increasing social relationships, networks, and engagement,[23] and these networks and social capital can then play important roles in individual health behaviors.[24] As a relational intervention that builds on interpersonal trust and, often, cultural consonance, patient navigation is likely to have strong impacts on individual-level factors, such as quality and clarity of communication between patients and providers, including limited knowledge and cultural beliefs, access to culturally and linguistically consonant information, and timely and appropriate care.[25] Furthermore, patient navigation addresses the three overlapping levels of determinants and works across them, assisting patients and families throughout the cancer care continuum (Fig. 1).[26]

Several studies have reported multilevel barriers to cancer care, including transportation problems, inability to speak English, lack of insurance, financial concerns, lack of social support, lack of information about patient care resources, and poor patient-provider communication.[27] The U.S. health care system is very complex, consisting of a patchwork of government insurance, private insurance, and the uninsured, with a range of health care structures, from small rural practices and low-resource public clinics and hospitals to heavily subscribed urban public hospitals and large academic medical centers and comprehensive cancer centers. Patients with cancer must navigate this fragmented patchwork of health care entities to receive care while traversing other seemingly insurmountable challenges, including the confusing complexity of interdisciplinary cancer treatment. The advantage that well-educated and affluent health care consumers possess, besides the ability to absorb and integrate a certain proportion of complex medical information and to advocate for themselves, is knowledge of and access to formal and informal health care networks. These health care networks are largely invisible to racial and ethnic minority patients, those with low educational attainment, and those with limited English language proficiency. Patient navigators act as a relational bridge,[25] connecting disenfranchised patients to complex networks and processes of cancer care systems. Moreover, they are trusted intermediaries who also educate patients about the diagnostic and treatment processes and support health-related decisions across the continuum of care, from screening, diagnosis, and treatment to cancer survivorship. The services that the patient navigators may provide include assistance with transportation, interpretation, applying for insurance, filling out medical forms, scheduling and coordinating appointments, providing emotional and psychosocial support (especially during uncertainties of diagnostic procedures and treatment), providing education about treatment and follow-up, and community-based resources (Table 1).[28] The provision of these services addresses inherent inequities in access to cancer care and may influence disparities in cancer outcomes.

ROLE OF PATIENT NAVIGATION IN THE CONTINUUM OF CANCER CARE

The goal of patient navigation is to increase access to timely and appropriate cancer care. The most important and earliest data come from Dr. Harold Freeman, who piloted the first patient navigation program in Harlem. By increasing access to and reducing delays in follow-up care, his pilot demonstrated an improvement in 5-year survival for Black women from 39% before the program to 70% during the pilot.[29] Subsequently, several studies have reported that patient navigation increases screening for breast cancer and gynecologic cancers.[30,31] Based on this encouraging data, the effectiveness and scope of patient navigation were studied in relation to cancer screening, diagnosis, treatment, survivorship, and palliative care. The Patient Navigation Research Program, a multisite, randomized controlled trial conducted in

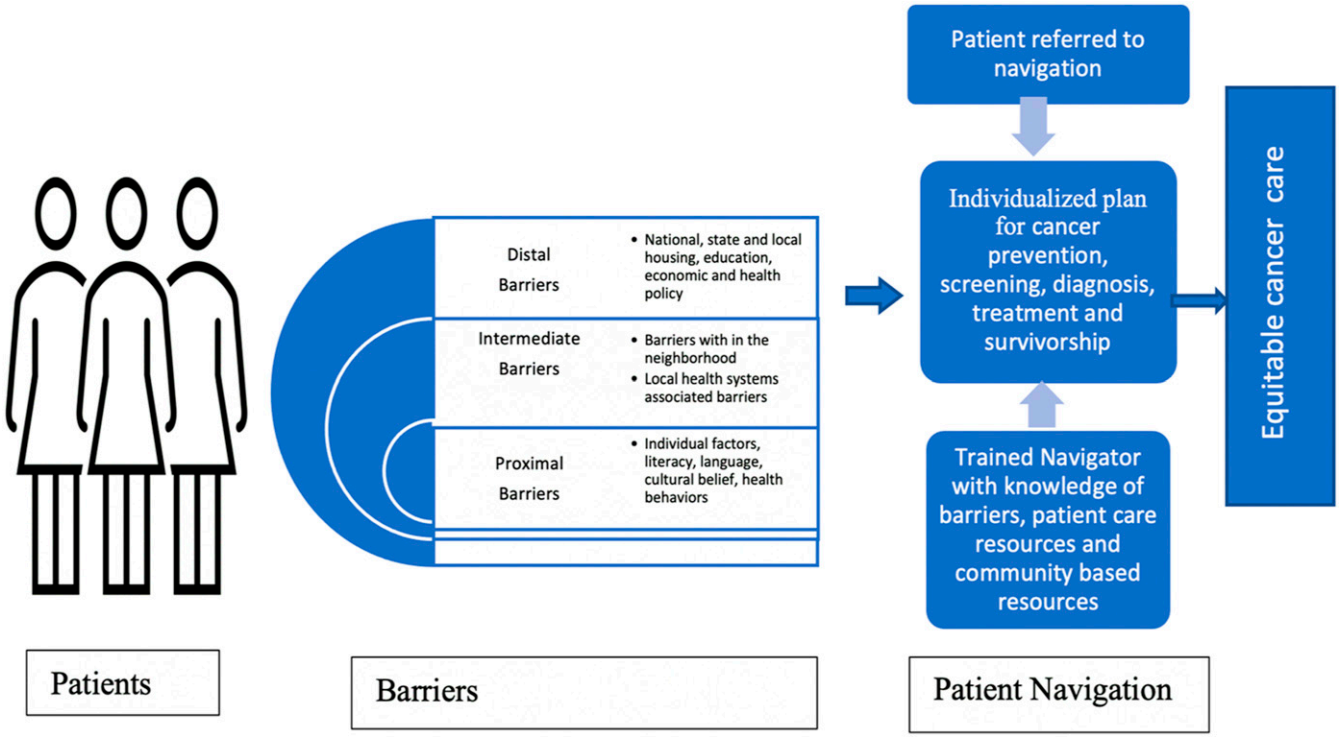

FIGURE 1. Role of Patient Navigation in Health Equity

heterogeneous settings, compared patient navigation to usual care with outcomes that included time to diagnosis and treatment, patient satisfaction, and cost effectiveness.[32] Participants in this study were predominantly from racial/ethnic minority groups (73%); 40% were publicly insured, and 31% were uninsured. The study showed that navigation was beneficial for both diagnostic resolution and treatment initiation.[33,34] The greatest benefit of patient navigation was seen in centers that had the greatest delays in care.[35] Cancer Prevention and Treatment Demonstration, another multisite study, showed similar benefits from navigation for African American women, with the strongest effect seen in women who were not up-to-date with mammography screening.[36] These data suggest that patient navigation can be specifically targeted to a high-risk population and can play a pivotal role in increasing access to care in the public health care systems that disproportionately care for patients with many barriers.[37]

A randomized controlled trial that identified patients at risk for nonadherence from a population-based health information technology algorithm used in primary care clinics and community health centers, and that assigned participants to receive either patient navigator support (intervention) or usual care (control) also found higher screening rates for breast, colon, and cervical cancers in the intervention arm than in the control arm.[38] Although the analysis of pooled data from the Patient Navigation Research Program sites did not show any difference in quality of life, a smaller randomized trial showed that women who received a nurse navigator intervention after diagnosis had significantly greater satisfaction and rehabilitation and experienced lower levels of distress, anxiety, and depression.[39] Several studies have sought to examine the effect of patient navigation on receipt of treatment after diagnosis. Although these data have been mixed, Ramirez et al[40] reported that a significantly higher percentage of Hispanic and Latinx women assigned to a culturally tailored navigation intervention initiated treatment within 30 days (69.0% vs. 46.3%; $p < .05$) and 60 days (97.6% vs. 73.1%; $p < .001$) and experienced a significantly reduced time to treatment (mean, 22.2 days vs. 48.3 days) compared with controls.[41]

Patient navigation can be especially helpful in support for education and lifestyle changes in survivorship care and improved health-related quality of life.[39] Gabitova et al[25] showed, in a northern California safety net hospital, that patient navigation increased collaboration between patients and providers and facilitated better understanding of their care process. The implementation of a culturally tailored intervention to improve palliative care for Spanish-speaking patients in a study by Fink et al[42] had lay patient navigators address the concerns of patients and their families and reduce barriers to palliative care. Patel et al[43] conducted a randomized study of a lay health worker intervention designed to document goals of care. The intervention not

TABLE 1. Barriers Addressed by Patient Navigation

Barrier	Description of Barriers	Example of Navigation Strategies
1.	Insurance: uninsured, underinsured, copays, inability to get procedures or medications	Help identifying resources for insurance coverage, help filling out forms for insurance
2.	Language and cultural barriers	Interpretation and addressing fears and beliefs about cancer treatments
3.	Communication	Making sure that patients understand the recommendation and that providers are aware of patient preferences and values
4.	Care coordination	Making sure appointments are scheduled and multidisciplinary care is coordinated, facilitating primary care referral
5.	Transportation	Assistance with transportation
6.	Financial problems	Referral for housing and food assistance services
7.	Symptoms burden and survivorship care needs	Facilitate communication with provider, referral to community-based resources
8.	Lack of social support	Provide additional layer of support and referral to support groups and community resources

only increased the documentation of goals of care but also reduced health care use and cost of care at the end of life.[43] Real-world examples of patient navigation suggest that it not only improves care and reduces care delays but may also reduce costs by decreasing unnecessary resource utilization, such as emergency visits, and may increase revenue by improving patient and provider retention.[44] Despite documented, positive patient outcomes data and despite documentation of the patient navigator role in addressing inequities and improving access to care, most patient navigation programs remain reliant on philanthropic funding, with limited funding from state and federal governments and from insurers.

MODELS OF PATIENT NAVIGATION

Patient navigation is modeled on case management or care management principles and consists of four components: (1) case identification to identify individuals most at risk; (2) barrier identification; (3) individual care plan development; and (4) case tracking to ensure completion of care.[32] Patient navigation may differ according to the phase of cancer treatment to be navigated and the patient navigation provider themselves. Patient navigation may be provided by health care professionals (nurses and social workers), by lay health workers, by multidisciplinary navigation teams consisting of lay health workers and health professionals, and/or by cancer survivors.[45-47] Navigators in the Patient Navigation Research Program, for example, were required to have a high school diploma or general education diploma, but the education level varied from high school to Masters of Social Work and Public Health.[32] A multidisciplinary team model, including both nurses and lay patient navigators, functioned in some of the Patient Navigation Research Program sites. Several patient navigators in the Patient Navigation Research Program also had other health care–related training as medical assistants and radiation technologists. Napoles et al[48] reported the impact of community-based peer support intervention on breast cancer–related quality of life, wherein trained breast cancer survivors provided stress management support to patients undergoing breast cancer treatment. One option is to consider a longitudinal patient navigation matrix model that is a multidisciplinary model across the cancer continuum, incorporating different personnel according to the patient needs at key time points and connecting through the electronic medical records.[49] The state of the science currently does not support one model over another, and the decision to implement one model versus another should take into account the local context, including the phase of cancer continuum, resource constraints, and the need for bilingual and culturally competent navigators. For example, at Zuckerberg San Francisco General Hospital, a public hospital providing care to low-income residents of San Francisco, the cancer navigation program consists of lay patient navigators, including bilingual Spanish/English and trilingual Cantonese/Mandarin/English speakers, and is funded by the San Francisco Department of Public Health. The patient navigators are assigned according to language concordance, and they provide case management and assist patients who are diagnosed with cancer from diagnosis and treatment to survivorship, navigating patients to different cancer care services that are provided across more than one health care institution.[25]

PATIENT NAVIGATION TRAINING

There is much variability in both the training of patient navigators and the performance of navigation by an individual or a team. A review of 59 studies of patient navigation found that there is no consistent patient navigation training.[50] Although patient navigator training is mentioned as

a requirement in all accreditation standards—for example, in the Commission on Cancer and in health care legislation—there currently is no recognized standard or certification for patient navigation training. Recently, some universities have begun to offer training for patient navigation. However, it remains unclear what components this training should include. It is important that patient navigation training specifically addresses barriers to care, range of appropriate services, and where and how patient navigation intersects with (but does not duplicate) services provided by social workers. Patient navigation training may be informed by the field work conducted within the Patient Navigation Research Program and other studies that describe the type of services that navigators provide.[25,51]

There are two established programs for patient navigation training: the Harold P. Freeman Patient Navigation Institute and the Colorado Patient Navigator Program. In addition, the Patient Navigation Research Program developed their own program-specific training curriculum.[28,52] Braun et al[53] reported on their community-based research methods to design a patient navigation training curriculum for outreach to Native Hawaiians.[53] The content of the training in published studies such as these has focused on topics related to patient care. These topics include care coordination, barriers to care, and skills development (e.g., cultural competency, communication, and maintaining professional boundaries). To our knowledge, there are no data on a specific type of training and composition of training and its impact on patient outcomes. Formalizing some training components and incorporating local context, including knowledge of disparities, barriers, and strategies to overcome these barriers, is needed.

FUTURE DIRECTIONS IN PATIENT NAVIGATION AND THE ADVENT OF TELEHEALTH

The COVID-19 pandemic has laid bare the disparities that have existed and are rooted in social injustice and systemic racism. These disparities are evident in the neighborhood-based inequities that underlie the cancer outcomes in the United States, giving new urgency to the phrase "zip code, not genetic code."[54] Unfortunately, the pandemic has had notable impacts on cancer care. Racial and ethnic disparities in cancer outcomes are being exacerbated by disruptions and delays in screening, diagnosis, and cancer treatment as staff and institutional resources are reallocated to pandemic care. Survivorship needs have been deprioritized as resources shift to meet the demands of COVID-19. It is time to systematically address these disparities with tools such as patient navigation. The data thus far have shown that patient navigation is an important tool for improving patient care and is most impactful for patients who experience many barriers. Patient navigation can and should be used in outreach to patients who have delayed screening and diagnostic procedures because of the pandemic and to help expedite treatment of patients diagnosed with cancer.

Wide adoption of telehealth in cancer care and primary care may also amplify existing disparities. Many patients lack access to the internet or devices such as laptops or tablets and may not feel as connected with their health care team in the current virtual telehealth model. It is likely that telehealth will remain an important aspect of health care for the foreseeable future, providing us with an opportunity to reimagine patient navigator training and update training protocols to integrate patient navigation into the telehealth model of care. Patient navigation may serve as an empowerment tool to provide training for patients to engage with their health care team, not only in telehealth clinical encounters but also in accessing and using their electronic medical records to actively participate in their care. As in the physical clinic, underserved patients and patients with low English proficiency who are diagnosed with cancer will benefit from virtual or telehealth patient navigation to facilitate their engagement with and understanding of their care processes.

An unexplored research area is the use of electronic medical records data to target patient navigation. Although it is ideal for every patient to have access to navigation, limited resources make this impractical. Patient navigation may be better directed by using electronic medical records data on social determinants of health to target the patients who face the most barriers to care, thus making this intervention most financially feasible and impactful. Moreover, patient navigation can also be a catalyst to increase cancer clinical trial participation, because patient navigation can address linguistic and literacy barriers,[55] particularly in therapeutic clinical trials, in which the enrollment of patients with low socioeconomic status, patients from racial and ethnic minority groups, and patients who do not speak English remains a major goal.[56] Patient navigation has the potential to extend clinical trial opportunities to patients outside of large academic cancer centers by increasing knowledge about clinical research while providing practical and social support.[55] An additional layer of support to clinical trial participants is also likely to encourage investigators and research teams to include patients outside the traditional realm of cancer pharmaceutical research.

Another unexplored area for patient navigation is as an adjunct to patient-reported outcomes and electronic patient-reported outcomes for symptom monitoring in patients receiving treatment to improve the patient experience and the delivery of supportive care. Care guided by patient-reported outcomes and electronic patient-reported outcomes has been shown to improve patient outcomes, but not all cancer centers establish these interventions to direct care.[57] Trained patient navigators can provide a human element and high-touch support to patients who are identified as in need of

additional services through patient-reported outcomes/electronic patient-reported outcomes assessment and can alert medical teams to particular patient needs, thus reducing the burden on clinicians while providing additional support to patients.

Other existing gaps in research include the paucity of research on the impacts of patient navigation training on health care–related outcomes and agreement on outcome measures that should be used to define success. Though some limited data exist on the cost effectiveness of increasing patient and physician retention and reducing health care utilization, more robust research on cost effectiveness is needed.[43,44] We recommend focus on implementation-based research in patient navigation, which should include quantitative metrics—such as impact on number of screenings, adherence to diagnostic procedures and treatment, number of missed appointments, as well as patient satisfaction with care, mortality, costs, and return on investments—delivery of evidence-based guidelines concordant care, and the perspectives of stakeholders (patients, providers, and navigators). Most navigation programs have focused on breast, cervical, colon, and (to a smaller extent) prostate cancers, and there is a paucity of research addressing patient navigation in a wider spectrum of cancers, particularly in lung cancer, for which cancer screening is now recommended.

ESTABLISHING A PATIENT NAVIGATION PROGRAM WITH A HEALTH EQUITY LENS

Although every patient with cancer can benefit from navigation and the additional support it provides, financial considerations limit the widespread implementation of patient navigation for cancer. If patient navigation implementation fails to take into account existing disparities, assessment of barriers, and a consistent plan to address the inequities in care, it has the potential to exacerbate the existing disparities. We recommend the following steps to implement a navigation program with a health equity lens:

1. Comprehensive assessment to establish baseline metrics of local inequities at the institutional and city/county level and gaps in care;
2. Documentation of Patient Navigation Research Program–identified barriers in the electronic medical records and implementation of social risk factor screeners to direct patient navigation;
3. Establishment of locally informed patient navigation programs with structures responsive to the patient population (e.g., appropriate language capacities), barriers (e.g., links with housing and food security resources, transportation support), and institutional constraints (e.g., interdisciplinary care structure);
4. Creation of a competency-based[56] patient navigation training program, including communication training, overview of cancer care, local context, and resources within the health care systems and community-based resources and partnerships; and
5. Ongoing evaluations specifically addressing implementation to understand how well the intervention works for the intended population, how effective it is in addressing social needs and improving treatment adherence/completion, and what barriers and facilitators exist to patient navigation.

Finally, patient navigation is an important tool in achieving health equity and delivering outstanding cancer care to every patient, every day, everywhere.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
2. American Cancer Society. Breast Cancer Facts and Figures. https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html. Accessed December 19, 2020.

3. Siegel DA, O'Neil ME, Richards TB, et al. Prostate cancer incidence and survival, by stage and race/ethnicity: United States, 2001-2017. MMWR Morb Mortal Wkly Rep. 2020;69:1473-1480.
4. Champion CD, Thomas SM, Plichta JK, et al. Disparities at the intersection of race and ethnicity: examining trends and outcomes in Hispanic women with breast cancer. JCO Oncol Pract. 2020:OP2000381.
5. Guerrero-Preston R, Chan C, Vlahov D, et al. Previous cancer screening behavior as predictor of endoscopic colon cancer screening among women aged 50 and over, in NYC 2002. J Community Health. 2008;33:10-21.
6. Liss DT, Baker DW. Understanding current racial/ethnic disparities in colorectal cancer screening in the United States: the contribution of socioeconomic status and access to care. Am J Prev Med. 2014;46:228-236.
7. Williams DR, Mohammed SA, Shields AE. Understanding and effectively addressing breast cancer in African American women: unpacking the social context. Cancer. 2016;122:2138-2149.
8. Chandak A, Nayar P, Lin G. Rural-urban disparities in access to breast cancer screening: a spatial clustering analysis. J Rural Health. 2019;35:229-235.
9. Bergin RJ, Emery J, Bollard RC, et al. Rural-urban disparities in time to diagnosis and treatment for colorectal and breast cancer. Cancer Epidemiol Biomarkers Prev. 2018;27:1036-1046.
10. Silber JH, Rosenbaum PR, Ross RN, et al. Disparities in breast cancer survival by socioeconomic status despite Medicare and Medicaid insurance. Milbank Q. 2018;96:706-754.
11. Pulte D, Jansen L, Brenner H. Disparities in colon cancer survival by insurance type: a population-based analysis. Dis Colon Rectum. 2018;61:538-546.
12. Gomez SL, Clarke CA, Shema SJ, et al. Disparities in breast cancer survival among Asian women by ethnicity and immigrant status: a population-based study. Am J Public Health. 2010;100:861-869.
13. Farrow NE, An SJ, Speicher PJ, et al. Disparities in guideline-concordant treatment for node-positive, non–small cell lung cancer following surgery. J Thorac Cardiovasc Surg. 2020;160:261-271.e1.
14. Blom EF, Ten Haaf K, Arenberg DA, et al. Disparities in receiving guideline-concordant treatment for lung cancer in the United States. Ann Am Thorac Soc. 2020; 17:186-194.
15. Visser BC, Ma Y, Zak Y, et al. Failure to comply with NCCN guidelines for the management of pancreatic cancer compromises outcomes. HPB (Oxford). 2012; 14:539-547.
16. Freeman HP, Rodriguez RL. History and principles of patient navigation. Cancer. 2011;117:3539-3542.
17. Oluwole SF, Ali AO, Adu A, et al. Impact of a cancer screening program on breast cancer stage at diagnosis in a medically underserved urban community. J Am Coll Surg. 2003;196:180-188.
18. Freeman HP. Patient navigation: a community based strategy to reduce cancer disparities. J Urban Health. 2006;83:139-141.
19. Patient Navigator Outreach and Chronic Disease Prevention Act of 2005. SEC. 2. Patient Navigator Grants, 2005. https://www.congress.gov/109/plaws/publ18/PLAW-109publ18.pdf. Accessed December 19, 2020.
20. Centers for Medicare & Medicaid Services. In-person assistance in the health insurance marketplaces. https://www.cms.gov/CCIIO/Programs-and-Initiatives/Health-Insurance-Marketplaces/assistance. Accessed December 19, 2020.
21. Moy B, Chabner BA. Patient navigator programs, cancer disparities, and the patient protection and affordable care act. Oncologist. 2011;16:926-929.
22. Chebli P, Lemus J, Avila C, et al. Multilevel determinants of financial toxicity in breast cancer care: perspectives of healthcare professionals and Latina survivors. Support Care Cancer. 2020;28:3179-3188.
23. Warnecke RB, Oh A, Breen N, et al. Approaching health disparities from a population perspective: the National Institutes of Health Centers for Population Health and Health Disparities. Am J Public Health. 2008;98:1608-1615.
24. Ge G, Burke N, Somkin CP, et al. Considering culture in physician–patient communication during colorectal cancer screening. Qual Health Res. 2009; 19:778-789.
25. Gabitova G, Burke NJ. Improving healthcare empowerment through breast cancer patient navigation: a mixed methods evaluation in a safety-net setting. BMC Health Serv Res. 2014;14:407.
26. Cantril C, Haylock PJ. Patient navigation in the oncology care setting. Semin Oncol Nurs. 2013;29:76-90.
27. Rojas M, Mandelblatt J, Cagney K, et al; Cancer Control Center of Harlem. Barriers to follow-up of abnormal screening mammograms among low-income minority women. Ethn Health. 1996;1:221-228.
28. Hendren S, Griggs JJ, Epstein RM, et al. Study protocol: a randomized controlled trial of patient navigation-activation to reduce cancer health disparities. BMC Cancer. 2010;10:551.
29. Freeman HP. The origin, evolution, and principles of patient navigation. Cancer Epidemiol Biomarkers Prev. 2012;21:1614-1617.
30. Freeman HP. Patient navigation: a community centered approach to reducing cancer mortality. J Cancer Educ. 2006;21:S11-S14.
31. Freeman HP, Wasfie TJ. Cancer of the breast in poor black women. Cancer. 1989;63:2562-2569.
32. Freund KM, Battaglia TA, Calhoun E, et al; Patient Navigation Research Program Group. National Cancer Institute Patient Navigation Research Program: methods, protocol, and measures. Cancer. 2008;113:3391-3399.
33. Battaglia TA, Bak SM, Heeren T, et al. Boston Patient Navigation Research Program: the impact of navigation on time to diagnostic resolution after abnormal cancer screening. Cancer Epidemiol Biomarkers Prev. 2012;21:1645-1654.

34. Ko NY, Darnell JS, Calhoun E, et al. Can patient navigation improve receipt of recommended breast cancer care? Evidence from the National Patient Navigation Research Program. J Clin Oncol. 2014;32:2758-2764.
35. DeSalvo JM, Young GS, Krok-Schoen JL, et al. Characterizing time to diagnostic resolution after an abnormal cancer screening exam in older adult participants in the Ohio patient navigation research program. J Aging Health. 2018;30:1284-1304.
36. Marshall JK, Mbah OM, Ford JG, et al. Effect of patient navigation on breast cancer screening among African American Medicare beneficiaries: a randomized controlled trial. J Gen Intern Med. 2016;31:68-76.
37. Raich PC, Whitley EM, Thorland W, et al; Denver Patient Navigation Research Program. Patient navigation improves cancer diagnostic resolution: an individually randomized clinical trial in an underserved population. Cancer Epidemiol Biomarkers Prev. 2012;21:1629-1638.
38. Percac-Lima S, Ashburner JM, Zai AH, et al. Patient navigation for comprehensive cancer screening in high-risk patients using a population-based health information technology system: a randomized clinical trial. JAMA Intern Med. 2016;176:930-937.
39. Ramirez AG, Muñoz E, Long Parma D, et al. Quality of life outcomes from a randomized controlled trial of patient navigation in Latina breast cancer survivors. Cancer Med. 2020;9:7837-7848.
40. Ramirez AG, Pérez-Stable EJ, Talavera GA, et al. Time to definitive diagnosis of breast cancer in Latina and non-Hispanic white women: the six cities study. Springerplus. 2013;2:84.
41. Dudley DJ, Drake J, Quinlan J, et al. Beneficial effects of a combined navigator/promotora approach for Hispanic women diagnosed with breast abnormalities. Cancer Epidemiol Biomarkers Prev. 2012;21:1639-1644.
42. Fink RM, Kline DM, Siler S, et al. Apoyo con Cariño: a qualitative analysis of a palliative care-focused lay patient navigation intervention for Hispanics with advanced cancer. J Hosp Palliat Nurs. 2020;22:335-346.
43. Patel MI, Sundaram V, Desai M, et al. Effect of a lay health worker intervention on goals-of-care documentation and on health care use, costs, and satisfaction among patients with cancer: a randomized clinical trial. JAMA Oncol. 2018;4:1359-1366.
44. Kline RM, Rocque GB, Rohan EA, et al. Patient navigation in cancer: the business case to support clinical needs. J Oncol Pract. 2019;15:585-590.
45. Battaglia TA, Darnell JS, Ko N, et al. The impact of patient navigation on the delivery of diagnostic breast cancer care in the National Patient Navigation Research Program: a prospective meta-analysis. Breast Cancer Res Treat. 2016;158:523-534.
46. Gervès-Pinquié C, Daumas-Yatim F, Lalloué B, et al. Impacts of a navigation program based on health information technology for patients receiving oral anticancer therapy: the CAPRI randomized controlled trial. BMC Health Serv Res. 2017;17:133.
47. Patlak M, Trang C, Nass SJ; National Cancer Policy Forum. Establishing Effective Patient Navigation Programs in Oncology: Proceedings of a Workshop. Washington, DC: National Academies Press; 2018.
48. Nápoles AM, Santoyo-Olsson J, Stewart AL, et al. Evaluating the implementation of a translational peer-delivered stress management program for Spanish-speaking Latina breast cancer survivors. J Cancer Educ. 2018;33:875-884.
49. Corbett CM, Somers TJ, Nuñez CM. Evolution of a longitudinal, multidisciplinary, and scalable patient navigation matrix model. Cancer Med. 2020;9:3202-3210.
50. Ustjanauskas AE, Bredice M, Nuhaily S, et al. Training in patient navigation: a review of the research literature. Health Promot Pract. 2016;17:373-381.
51. Gunn CM, Clark JA, Battaglia TA, et al. An assessment of patient navigator activities in breast cancer patient navigation programs using a nine-principle framework. Health Serv Res. 2014;49:1555-1577.
52. Roetzheim RG, Freund KM, Corle DK, et al; PNRP Design and Analysis Committee for the Patient Navigation Research Program Investigators. Analysis of combined data from heterogeneous study designs: an applied example from the patient navigation research program. Clin Trials. 2012;9:176-187.
53. Braun KL, Allison A, Tsark JU. Using community-based research methods to design cancer patient navigation training. Prog Community Health Partnersh. 2008; 2:329-340.
54. Guan A, Lichtensztajn D, Oh D, et al; San Francisco Cancer Initiative Breast Cancer Task Force. Breast cancer in San Francisco: disentangling disparities at the neighborhood level. Cancer Epidemiol Biomarkers Prev. 2019;28:1968-1976.
55. Nickell A, Stewart SL, Burke NJ, et al. Engaging limited English proficient and ethnically diverse low-income women in health research: a randomized trial of a patient navigator intervention. Patient Educ Couns. 2019;102:1313-1323.
56. Napoles A, Cook E, Ginossar T, et al. Applying a conceptual framework to maximize the participation of diverse populations in cancer clinical trials. Adv Cancer Res. 2017;133:77-94.
57. Basch E, Deal AM, Dueck AC, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA. 2017;318:197-198.

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overview

Providing Appropriate Pancreatic Cancer Care for People Experiencing Homelessness: A Surgical Perspective

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People experiencing homelessness are particularly vulnerable when diagnosed with pancreatic cancer. Patients with lower socioeconomic status have worse outcomes from pancreatic cancer as the result of disparities in access to treatment and barriers to navigation of the health care system. Patients with lower socioeconomic status, or who are vulnerably housed, are less likely to receive surgical treatment even when it is recommended by National Comprehensive Cancer Network guidelines. This disparity in access to surgical care explains much of the gap in pancreatic cancer outcomes. There are many factors that contribute to this disparity in surgical management of pancreatic cancer in people experiencing homelessness. These include a lack of reliable transportation, feeling unwelcome in the medical setting, a lack of primary care and health insurance, and implicit biases of health care providers, including racial bias. Solutions that focus on rectifying these problems include utilizing patient navigators, addressing implicit biases of all health care providers and staff, creating an environment that caters to the needs of patients experiencing homelessness, and improving their access to insurance and regional support networks. Implementing these potential solutions all the way from the individual provider to national safety nets could improve outcomes for patients with pancreatic cancer who are experiencing homelessness.

THE BURDEN OF PANCREATIC CANCER IN PEOPLE EXPERIENCING HOMELESSNESS

Upwards of 3.5 million people experience homelessness annually in the United States alone. A person experiencing homelessness is defined as someone who lacks a fixed, regular, and adequate nighttime residence and who lives in a shelter or place not designated for human habitation (i.e., street-side, abandoned buildings); someone at imminent risk for housing loss within the next 2 weeks; and someone fleeing from domestic violence with inadequate resources to obtain other permanent housing.[1] People experiencing homelessness have markedly poorer health outcomes, and are three to four times more likely to die than the general population.[2] When compared with other fields, such as infectious disease and malnutrition, the epidemiology of cancer has been understudied in this population despite the potential for adverse cancer outcomes. People experiencing homelessness have a higher burden of behavioral, environmental, and biologic risk factors that predispose them to developing cancer, including cigarette smoking (68%–80% of people experiencing homelessness) and alcohol abuse (30%–63% of people experiencing homelessness).[2] At the same time, access to cancer screening in this population is suboptimal at best. Competing priorities of managing day-to-day subsistence needs may detract from the perceived importance of cancer prevention and screening. People who are homeless also experience barriers to diagnosis and treatment. Many lack insurance (70% of Health Care for the Homeless clients do not have health insurance) and thus forego necessary medical care.[2] Inadequate health insurance is itself a cause of homelessness.[2] Lack of knowledge may also contribute to not seeking timely medical care among individuals who are homeless, as seen in instances where reduction in structural barriers to cancer screening is not met with an upswing in utilization of provided screening tests. There are many possible explanations for this discrepancy, including anticipated discomfort, misperceptions about cancer risk, lack of knowledge regarding site of screening or treatment, and lack of transportation.[3] Provider-specific factors may also play a role. Implicit bias of a provider can have an explicit impact on health care provided to a patient with cancer experiencing homelessness.[4]

Metrics used to assess cancer burden in this population are based on extrapolation of risk factors and demographics. In combination with the aforementioned behavioral risk factors (i.e., cigarette smoking, alcohol abuse), age may most effectively capture the burden of cancer, particularly pancreatic cancer, in

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PRACTICAL APPLICATIONS

- Disparities in the care of people experiencing homelessness who have cancer are influenced by patient factors (such as the increased burden of behavioral and environmental risk factors), health care provider and staff biases, and systemic and regional factors.
- Lower socioeconomic status and the logistic and financial barriers of homelessness can make it difficult for patients to access medical treatment. When these patients have pancreatic cancer, they are less likely to receive appropriate surgical treatment, which is associated with disparities in survival.
- Utilizing patient navigators helps patients who are homeless navigate the health care system and overcome potential barriers to care, such as transportation issues, unstable housing, medical insurance, and care coordination.
- Providers and staff can foster patient-provider trust and relationships by recognizing implicit biases, creating a welcoming environment for patients, and practicing self-awareness, perspective-taking, individuation, and better communication to minimize the effect of their biases on patient care and health outcomes.
- Implementing system-wide and regional strategies such as effective street-medicine programs, engagement with nonprofit and faith-based social safety nets, and increased access to health insurance will improve health care delivery to people experiencing homelessness who have pancreatic cancer, which may flatten disparities in patient outcomes.

this population. The population of single adults experiencing homelessness is aging. Baby boomers, those born between 1954 and 1967, are disproportionately likely to experience homelessness in the United States.[5] Cancer, particularly pancreatic cancer, disproportionately affects older adults. Two-thirds of those at risk for developing pancreatic cancer are older than age 65, with the average age at diagnosis being 70. Almost all patients at risk for developing pancreatic cancer are over age 45.[6]

Homelessness is also associated with multiple behavioral determinants of health that increase the risk for pancreatic cancer. People who smoke have double the rate of pancreatic cancer, with persistent increased risk for at least 10 years after smoking cessation.[7] Heavy alcohol consumption also increases the risk of pancreatic cancer, particularly in people who smoke.[7] Adults who are homeless are six times as likely to endorse current alcohol abuse as the domiciled population, and 40% have a history of alcohol abuse.[8] A large-scale study of 30,000 Massachusetts adults experiencing homelessness found alcohol-attributable mortality to be six times that of the general population, and smoking-attributable mortality to be three times that of the general population.[9] Almost 80% of people who are homeless smoke, which is more than double the rate of other low-income populations, and contributes to their high rates of smoking-related cancers.[10] These behavioral factors play a role in the increased cancer disease burden in patients who are homeless.[11]

There is, therefore, a need for more strategies to improve cancer care for individuals who are homeless. The impetus for exploring strategies to improve diagnosis and treatment of cancer in patients who are homeless stems from affirming access to medical care as a human right.[12] This review aims to (1) illustrate the disparities in pancreatic cancer care and outcomes in the people experiencing homelessness relative to the general population, (2) review relevant factors at play (patient-specific, provider-specific, structural and systemic), and (3) propose solutions (personal, systemic, and regional).

DISPARITIES IN PANCREATIC CANCER OUTCOMES AND ACCESS TO TREATMENT FOR PATIENTS EXPERIENCING HOMELESSNESS: SURGERY IS KEY

There are significant socioeconomic disparities in the management and mortality of pancreatic cancer. Lower socioeconomic status, as well as the logistic and financial barriers of homelessness, can make it difficult for patients to travel for medical treatments. This is particularly important in pancreatic cancer, where treatment at high-volume centers is associated with better surgical outcomes and survival.[13] On average, patients treated at academic centers have to travel 50 miles further than those treated at community programs.[14] Socioeconomically disadvantaged patients are less likely to travel to high-volume centers.[15] When these disadvantaged patients are treated at high-volume cancer centers, their socioeconomic status is no longer predictive of survival,[16] indicating that improving access to treatment can address socioeconomic disparities in outcome.

These disparities amount to significant differences in treatment and survival for low-income patients with pancreatic cancer. Patients with lower socioeconomic status have been found to be less likely to get treatment compliant with National Comprehensive Cancer Network guidelines, with associated increases in mortality.[17] They are also less likely to participate in clinical trials, missing out on the potential survival advantages of these trials.[18] One large study revealed a strong correlation between increasing socioeconomic status and increasing overall survival from 14 months in the lowest socioeconomic status group to

20 months among those with the highest socioeconomic status.[19] This indicates that meticulously and deliberately modulating the treatment of lower-socioeconomic-status patients with pancreatic cancer, in an effort to match care provided to patients of high socioeconomic status, could provide significant improvements in overall survival for low-income patients and those experiencing homelessness.

Although management of pancreatic cancer is multimodal, often involving chemotherapy, radiation, and operative resection, the economic divide is particularly stark in the surgical treatment of patients with pancreatic cancer. In an analysis of 56,000 patients with stage I/II pancreatic cancer using the National Cancer Database, lower socioeconomic status and being uninsured were independent negative predictors of receiving surgical resection.[20] A large Florida cancer center registry showed that patients with lower socioeconomic status are less likely to receive surgical treatment even when matched for disease state and tumor grade.[21] These socioeconomic inequalities in rates of pancreatic cancer resection were present even in countries with universal health insurance.[22] Although all low-income patients are less likely to receive operative intervention, increasing levels of residential instability further predicted a decreased likelihood of undergoing surgical resection.[23] This shows that patients of lower socioeconomic status, and particularly the vulnerably housed among them, are not receiving pancreatic cancer resections at rates consistent with economically privileged groups.

The disparity in operative intervention for pancreatic cancer explains the poor outcomes of patients with lower socioeconomic status. More deprived areas with lower access to surgical resection had worse outcomes, even in studies that found no difference in access to chemotherapy.[24] Although generally there is a strong correlation between low socioeconomic status and worse overall survival, the correlation between socioeconomic status and survival disappears after surgical resection.[22] When more marginalized patients are able to receive an operation, there is no association between housing instability or material deprivation and overall survival or receipt of adjuvant therapy.[23] Given that only half of patients with stage I/II pancreatic ductal carcinoma received an operation, addressing disparities to surgical access could affect the outcomes for many patients with pancreatic cancer.[20] Access to resection is key for reducing survival inequalities in pancreatic cancer.

PATIENT, PROVIDER, AND SYSTEMIC FACTORS THAT CONTRIBUTE TO DISPARITIES IN THE CARE OF PATIENTS WITH PANCREATIC CANCER EXPERIENCING HOMELESSNESS

There are many factors that contribute to the disparities in the care of patients with pancreatic cancer experiencing homelessness, ranging in scope from individual patient and provider factors to structural and systemic contributions. Patients who are experiencing homelessness are more likely to present with more complex and challenging needs compared with the general population as the result of a disproportionate burden of acute and chronic medical comorbidities compounded by mental illness and substance use.[25-27] This is further exacerbated by social determinants that affect the health of this population, including race/ethnicity (disproportionately from disadvantaged minority groups), lack of reliable transportation (with many relying on walking and public transportation), lower health literacy levels, and lack of a consistent address or residing in places that are not conducive for recovery.[27-30] All of these factors may pose as additional barriers to health care services access, including cancer screening, appropriate discharge disposition, communication with the health care team, consistent follow-up, and ability to effectively navigate the often-convoluted maze of the health care system. Limited financial resources; lack of access to screening, counseling, guidance, and opportunities; fear of invasive screening and screening results; embarrassment about the screening procedure; fatalistic views of cancer; and a lack of trust in health care professionals have all been identified as barriers to cancer screening among individuals experiencing homelessness.[31]

One study postulated that the patient's perceptions of "welcomeness" and "unwelcomeness"—whether they felt heard, empowered, and valued as a person during their health care encounter—are a critical dimension in understanding and influencing trust or distrust of health care providers among patients experiencing homelessness.[32] Actions that resulted in perceptions of unwelcomeness were not only due to physician behavior but were also influenced by the actions of other health care staff at the facilities. Most patients in this study ascribed these actions to discrimination in reaction to low socioeconomic status and homelessness.[32] This highlights the potential deleterious impact of providers' and health care staff's biases on disparate health outcomes in this patient population compared with housed individuals.

Implicit biases (or unconscious prejudices) have been demonstrated in both children and adults,[33,34] and multiple studies have also demonstrated that the implicit biases of health care professionals adversely affect clinical decision-making and patient care.[4] Unrecognized bias against members of any social group may affect communication or the care offered to members of that group.[35] This may perpetuate ongoing health disparities as well as patient mortality and morbidity. Self-awareness, individuation, and perspective-taking while providing care have been recommended as helpful strategies in mitigating the adverse impact of implicit bias.[4] Given that individuals who are homeless are also more likely to be members of

disadvantaged racial/ethnic minority groups that are also victims of other implicit biases,[30] the role of implicit bias in perpetuating health disparities against this patient population becomes easily compounded.

It is impossible to discuss vulnerable populations without explicitly discussing the compounding effects of race. Black patients have been found to have a higher incidence of pancreatic cancer but are also less likely to have specialist consultations compared with White patients. Murphy et al[36] found that Black race negatively predicted consultation with a medical oncologist, radiation oncologist, and surgeon. This disparity in consultations directly reduces the extent of oncologic treatment that is provided to patients upon diagnosis. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results database showed that even when Black and White patients present with similar stages of pancreatic cancer and are recommended for surgery at similar rates, Black patients receive fewer resections.[37] In addition, Black race has been found to be an independent predictor of shorter survival in patients who receive curative-intent operations.[37,38] Equalizing access to surgical resection regardless of socioeconomic status may also address much of the racial disparities in pancreatic cancer outcomes. Black patients have an increased risk of death from pancreatic cancer, but after adjusting for socioeconomic status and receipt of treatment, they have the same risk of death as White patients.[39] In a population with equal access to surgical resection and treatments, race was not predictive of overall survival.[40] Underutilization of surgical treatment explains much of the racial survival gap.[37] Improving access to surgical resection could eliminate disparities in pancreatic cancer outcomes for ethnic minority populations and patients experiencing homelessness.

Additionally, other barriers to receiving treatment for medical diseases such as pancreatic cancer include lack of access to primary care for coordination and challenges in adhering to medication or prescribed treatment plans.[41-43] In a qualitative study of street pastors, spiritual caregivers, homeless outreach workers, and people who were formerly homeless in the Netherlands, care avoidance was found to be the result of an interplay between individual and system-related factors, including a therapeutic relationship that focuses on the humanity and dignity of the patient, and clear information provided by the provider.[44]

Structural and systemic factors also contribute to the disparities in the care of patients with cancer who are homeless. Although pancreatic cancer is the third most common cause of cancer death in the United States, and its diagnosis is associated with a high mortality, the U.S. Preventive Services Task Force currently recommends against screening for it in asymptomatic adults because the harms of screening exceed potential benefits.[45] Unfortunately, this lack of appropriate screening tools is associated with a higher rate of patients diagnosed later in their disease process. Currently, 75% to 80% of patients who present with advanced disease at diagnosis do not qualify for an operation.[46] A literature review on cancer screening in people experiencing homelessness demonstrates an overall higher incidence of cancer, a more advanced stage at diagnosis, and higher mortality rates.[31]

The timing of presentation and diagnosis of pancreatic cancer is further exacerbated by systemic factors related to accessibility of medical and surgical care. Studies have demonstrated that people who are homeless experience poor access to health care because of inabilities to afford care and a lack of health insurance coverage.[47] The Affordable Care Act included an expansion of Medicaid coverage and increased federal funding for community health centers in 2014, which led directly to increased coverage for low-income individuals.[48,49] In spite of insurance coverage, the cost of treatment and care remains high. In a retrospective cohort study of patients with pancreatic cancer with Medicare, mean total direct costs were $65,500, with total costs higher for resectable locoregional disease at $134,700 and lowest for distant disease at $49,000. Costs for unresectable locoregional disease were $65,300.[50] These estimates are lower than prior studies[51-53] but do not reflect the out-of-pocket costs for uninsured patients or for Medicaid beneficiaries after Medicaid reimbursement.

PRACTICAL SUGGESTIONS TO IMPROVE ACCESS TO CARE FOR PATIENTS EXPERIENCING HOMELESSNESS

There are many ways to ensure patients get the treatment that they need and, specifically, surgical interventions when indicated. The aforementioned barriers to medical care for patients experiencing homelessness may prevent them from advocating for treatment and care to the extent of higher-status socioeconomic groups. These barriers must be specifically addressed to ultimately help patients who are homeless to receive surgical treatment in equitable numbers. Potential solutions to these problems can be divided into personal, systemic, and regional interventions.

Strategies for Individual Providers to Improve the Equity of Care Delivery

Several strategies can be implemented to bridge the gap between the patient and provider. Creating a welcoming environment for the patient begins with the provider's office. Training of personnel in the office in sensitivity, communication, and interpersonal skills can eliminate the first barrier of the patient feeling uncomfortable when entering the seemingly hostile setting of a hospital/medical office. Chapman et al[4] propose training personnel in individuating and perspective-taking to decrease racial bias, but these are applicable to any bias. Individuating is described as making

a "conscious effort to focus on specific information about an individual, making it more salient in decision-making than that person's social category information."[4] This is pertinent for staff dealing with patients experiencing homelessness. Instead of lumping these patients into the familiar stereotype of homelessness, staff and physicians make an effort to learn about the patient and use these characteristics to try to eliminate this implicit bias.

Perspective-taking, described by Galinsky and Moskowitz,[54] is putting yourself in the shoes of the patient. Although a simple training method, it was demonstrated by Drwecki et al[55] that when nurses employed perspective-taking in assessing how much analgesic patients needed, they were more likely to suggest the same amount regardless of race than when asked to use their best judgment. Thus, these two methods can be used in employee training in the office by all staff to increase sensitivity and communication with patients who are homeless. These patients will have one less barrier to overcome when accessing health care.

Medical intake forms, which usually ask for the patient's home address, are an example of a seemingly innocuous office accoutrement that can intimidate a patient experiencing homelessness. Practical solutions can include editing intake forms with checkboxes that indicate that the patient does not have a residence. This solution is adopted from changes done in many medical offices for nonbinary gender individuals.[56] Changing checkboxes on intake forms from male/female for gender to include "nonbinary" is an example that could be used for the form when asked for a place of residence. Adding a checkbox saying "no permanent address" is a way of indicating to the patient that it is not out of the ordinary to have a patient in the office who is experiencing homelessness. As has been done with transgender patients, identifying patients who are homeless through intake forms can ease the execution of quality improvement and research projects designed to further decrease the health care disparities encountered by patients experiencing homelessness.[56]

Patient Navigators and Other Systemic Tools to Address Barriers to Care

The complexity of the medical system and barriers to care often cause delays in cancer treatment for patients who are homeless.[57] Having personnel who specifically help patients experiencing homelessness navigate the complicated medical process of cancer treatment is a solution already implemented at some hospitals, including Rhode Island Hospital. The Harold Freeman navigation model is used to train designated personnel as patient navigators. This navigation model was developed after testimonies from patients during the American Cancer Society National Hearings on Cancer in the Poor, which outlined how patients from lower socioeconomic classes often do not seek care because of financial, communication, trust, and knowledge barriers.[58] Freeman and Rodriguez[58] describe the role of patient navigators as promoting the timely movement of patients through the complex health care continuum and eliminating barriers to the timely care of these individuals.

Patient navigators at Rhode Island Hospital meet with patients in a team to distribute organized information about their care in a way that is easy to follow. The patient is then added to a spreadsheet where they can be flagged as a high-risk patient with potential barriers to treatment completion. The patient navigator signs into the electronic medical record as part of the patient care team so that they can be alerted whenever the patient is admitted for any problem. Tracking these patients during these admissions allows the navigator to provide better care by seeing the patient during their admission and anticipating any contributing problems when they arrive for their next visit. All patients who will be seen in the office are discussed at a weekly multidisciplinary meeting and extra attention is given to patients who are homeless and high-risk. Additionally, patient navigators contact those patients early, to ensure these patients are able to keep their appointments.

Inability to seek care because of financial instability was also identified by patients during the American Cancer Society National Hearings on Cancer in the Poor as a health barrier.[58] Patient navigators work with social workers on Medicare/Medicaid applications to ensure that patients receive benefits. At Rhode Island Hospital, funds are set aside to assist patients with copays, getting rides to appointments, cell phones, and food stipends. Patient navigators, social workers, and shelters work in concert to provide places for patients to stay during treatment.

The utilization of the services of patient navigators has been found to increase screening rates for cancers from 10.8% to 17.1% and adherence to diagnostic follow-up care from 21.0% to 29.2%, compared with a control group.[59] Adding patient navigators to help patients who are homeless has the added benefit of being more cost-effective. Donaldson et al[60] found that "the cost-effectiveness ratio ranged from $511 to $2,080 per breast cancer diagnostic resolution achieved and from $1,192 to $9,708 per colorectal cancer diagnostic resolution achieved." This shows that not only can patient navigators help patients experiencing homelessness achieve recommended health treatments, but also that this intervention is cost-efficient and could be effective in helping patients with pancreatic cancer get the operations and other treatments they need.

Community and Regional Interventions for Patients Experiencing Homelessness

On a regional level, there are various notable solutions already at play, such as the Boston Health Care for the

Homeless Program. From 2008 to 2013, the Boston Health Care for the Homeless Program has increased cervical cancer screening from 19% to 50% among women experiencing homelessness.[61] One section of the six-part program is focused on multidisciplinary screening. This section emphasized a health care team that not only includes the traditional members of the health care team (such as nurses and physicians), but also other staff members such as receptionists, secretaries, and security. It is essential to recognize that health care begins the moment a patient walks into the facility. From the reception at the front desk, to the waiting experience, and the patient's interaction with each member of the health care team, every encounter can be formative in the patient's experience; they are opportunities to emphasize inclusion and evoke feelings of welcomeness. Hence, it is important to train the health care team to consistently respond in a multidisciplinary patient-centered manner.

As discussed, many patients experiencing homelessness have difficulty traveling to medical facilities to receive care. Implementing an alternative health care structure to bring health care to people who are homeless may allow for better participation in care. Many health centers have instituted "street-medicine" programs, where the health care team is deployed via a mobile clinic to bring care to marginalized populations.[62] Although the challenge of ensuring continuity of care when delivered through these approaches would be particularly fraught with complex medical problems such as pancreatic cancer, these mobile clinics can still serve as a first step to introduce the homeless population to the health care system in a more accessible way. Patients experiencing homelessness often have other concerns besides health care, such as housing, transportation, and childcare.[63,64] Programs that address barriers to care, such as transport vouchers, and provide access to basic needs, such as food, shelter, and safety, can allow patients to direct more of their time and energy toward their health care needs.

Nonprofit and faith-based social safety nets can also play a vital role in health care delivery, even when they do not directly provide health services. Patients who are homeless have more fragmented social support networks;[65] hence, the support provided by these community programs is particularly valuable. People experiencing homelessness who have better social support networks are more likely to use health services.[66] A patient's social safety net can also directly impact their postoperative outcomes, with a poor social support network increasing the likelihood of a prolonged hospital stay.[67] Pancreatic operations risk significant complications and have a major short-term impact on functionality. In an analysis of patients undergoing pancreatic operations, physical and functional quality of life were often below preoperative levels for weeks to months after their operation.[68] Physicians assess patients' personal networks and those judgments can shape clinical decision-making.[69] This may make them less likely to recommend operations for patients with pancreatic cancer experiencing homelessness out of concern about postoperative complications. For patients who are homeless and have limited organic support networks, some of those social needs could instead be met through nonprofit and faith-based social services. Integration of those social services into the care system disproportionately benefits the most vulnerable populations and allows for more effective and economic care.[70] A robust safety net can reassure surgeons that a patient's postoperative needs will be met, encouraging surgeons to offer operations to people experiencing homelessness when indicated, instead of deviating from the standard of care for these patients.

Access to health insurance is both a regional and systemic issue. The implementation of the Affordable Care Act caused the U.S. uninsured rate to decline by 43%, to an overall level of 9.1% in 2015.[71] However, the expansion of health insurance through the Affordable Care Act is just one step in ensuring that most Americans have access to health insurance and ultimately health care. Access to health care is a basic human right.[72] Although expanded medical services through the Affordable Care Act have some initiatives in place for people experiencing homelessness, the particular barriers faced by this population are still apparent. The process of applying for health insurance is complex and cumbersome, and may outstrip the resources of marginalized populations.[73] The system of patient navigators discussed earlier can facilitate the acquisition of health insurance as well as navigation of the health care system.

CONCLUSION

Pancreatic cancer can be devastating even in ideal circumstances, and the many challenges faced by patients experiencing homelessness can further complicate care. When medically appropriate, surgical management of pancreatic cancer has a major impact on outcomes, yet patients who are homeless are less likely to receive surgical treatment that is consistent with National Comprehensive Cancer Network guidelines. There are many factors that contribute to the disparities in pancreatic cancer care for patients experiencing homelessness. Patient-level factors such as lack of transportation and underutilization of primary care can delay treatments. Providers can unintentionally act as a barrier through implicit bias or an unwelcoming office environment. Insurance and financial barriers can provide more systemic roadblocks. Addressing the specific needs of patients experiencing homelessness can require solutions at individual, regional, and systemic levels. Solutions can include training staff in communication and perspective-taking, employing patient navigators to

help patients access assistance programs, and expansion of the social and governmental safety net. Applying these solutions may improve outcomes for people experiencing homelessness who have pancreatic cancer by ensuring that they receive the appropriate surgical and medical treatments.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Legal Information Institute. 42 U.S. Code § 11302 - General definition of homeless individual. https://www.law.cornell.edu/uscode/text/42/11302. Accessed February 26, 2021.
2. National Coalition for the Homeless. Health care and homelessness. https://www.nationalhomeless.org/factsheets/health.html. Accessed March 1, 2021.
3. Institute of Medicine (US) Committee on Health Care for Homeless People. Access to Health Care Services for Homeless People: Homelessness, Health, and Human Needs. Washington, DC: National Academies Press (US); 1988.
4. Chapman EN, Kaatz A, Carnes M. Physicians and implicit bias: how doctors may unwittingly perpetuate health care disparities. J Gen Intern Med. 2013;28:1504-1510.
5. Culhane DP, Metraux S, Byrne T, et al. The age structure of contemporary homelessness: evidence and implications for public policy. Anal Soc Issues Public Policy. 2013;13:228-244.
6. American Cancer Society. Pancreatic cancer risk factors. https://www.cancer.org/cancer/pancreatic-cancer/causes-risks-prevention/risk-factors.html. Accessed February 25, 2021.
7. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World J Oncol. 2019;10:10-27.
8. Neisler J, Shree S, Reitzel LR, et al. Characterizing alcohol use behaviors among homeless men and women. Am J Health Behav. 2019;43:37-49.
9. Baggett TP, Chang Y, Singer DE, et al. Tobacco-, alcohol-, and drug-attributable deaths and their contribution to mortality disparities in a cohort of homeless adults in Boston. Am J Public Health. 2015;105:1189-1197.
10. Fazel S, Geddes JR, Kushel M. The health of homeless people in high-income countries: descriptive epidemiology, health consequences, and clinical and policy recommendations. Lancet. 2014;384:1529-1540.
11. Holowatyj AN, Heath EI, Pappas LM, et al. The epidemiology of cancer among homeless adults in metropolitan Detroit. JNCI Cancer Spectr. 2019;3:pkz006.
12. UN Committee on Economic, Social and Cultural Rights. 25th session—2001: Substantive issues arising in the implementation of the International Covenant on Economic, Social and Cultural Rights: poverty and the International Covenant on Economic, Social and Cultural Rights: statement adopted by the Committee on Economic, Social and Cultural Rights on 4 May 2001. Geneva, Switzerland: United Nations; 2001.
13. Lidsky ME, Sun Z, Nussbaum DP, et al. Going the extra mile: improved survival for pancreatic cancer patients traveling to high-volume centers. Ann Surg. 2017;266:333-338.
14. Makar M, Worple E, Dove J, et al. Disparities in care: impact of socioeconomic factors on pancreatic surgery: exploring the National Cancer Database. Am Surg. 2019;85:327-334.
15. Wasif N, Etzioni D, Habermann EB, et al. Racial and socioeconomic differences in the use of high-volume commission on cancer-accredited hospitals for cancer surgery in the United States. Ann Surg Oncol. 2018;25:1116-1125.
16. Powers BD, Fulp W, Dhahri A, et al. The impact of socioeconomic deprivation on clinical outcomes for pancreatic adenocarcinoma at a high-volume cancer center: a retrospective cohort analysis. Ann Surg. Epub 2019 Dec 5.
17. Visser BC, Ma Y, Zak Y, et al. Failure to comply with NCCN guidelines for the management of pancreatic cancer compromises outcomes. HPB (Oxford). 2012;14:539-547.
18. El-Rayes BF, Jasti P, Severson RK, et al. Impact of race, age, and socioeconomic status on participation in pancreatic cancer clinical trials. Pancreas. 2010;39:967-971.
19. Swords DS, Mulvihill SJ, Brooke BS, et al. Disparities in utilization of treatment for clinical stage I-II pancreatic adenocarcinoma by area socioeconomic status and race/ethnicity. Surgery. 2019;165:751-759.

20. Lutfi W, Zenati MS, Zureikat AH, et al. Health disparities impact expected treatment of pancreatic ductal adenocarcinoma nationally. Ann Surg Oncol. 2018; 25:1860-1867.
21. Cheung MC, Yang R, Byrne MM, et al. Are patients of low socioeconomic status receiving suboptimal management for pancreatic adenocarcinoma? Cancer. 2010;116:723-733.
22. van Roest MHG, van der Aa MA, van der Geest LGM, et al. The impact of socioeconomic status, surgical resection and type of hospital on survival in patients with pancreatic cancer: a population-based study in the Netherlands. PLoS One. 2016;11:e0166449.
23. Kagedan DJ, Abraham L, Goyert N, et al. Beyond the dollar: influence of sociodemographic marginalization on surgical resection, adjuvant therapy, and survival in patients with pancreatic cancer. Cancer. 2016;122:3175-3182.
24. Thobie A, Mulliri A, Dolet N, et al. Socioeconomic status impacts survival and access to resection in pancreatic adenocarcinoma: a high-resolution population-based cancer registry study. Surg Oncol. 2018;27:759-766.
25. Maness DL, Khan M. Care of the homeless: an overview. Am Fam Physician. 2014;89:634-640.
26. Substance Abuse and Mental Health Services Administration. Current statistics on the prevalence and characteristics of people experiencing homelessness in the United States. https://www.samhsa.gov/sites/default/files/programs_campaigns/homelessness_programs_resources/hrc-factsheet-current-statistics-prevalence-characteristics-homelessness.pdf. Accessed March 3, 2021.
27. Zlotnick C, Zerger S. Survey findings on characteristics and health status of clients treated by the federally funded (US) Health Care for the Homeless Programs. Health Soc Care Community. 2009;17:18-26.
28. Murphy ER. Transportation and homelessness: a systematic review. J Soc Distress Homeless. 2019;28:96-105.
29. Ramsay N, Hossain R, Moore M, et al. Health care while homeless: barriers, facilitators, and the lived experiences of homeless individuals accessing health care in a Canadian regional municipality. Qual Health Res. 2019;29:1839-1849.
30. US Department of Housing and Urban Development. The 2019 Annual Homeless Assessment Report (AHAR) to Congress, part 1: point-in-time estimates of homelessness. Washington, DC: US Department of Housing and Urban Development; 2019.
31. Asgary R. Cancer screening in the homeless population. Lancet Oncol. 2018;19:e344-e350.
32. Wen CK, Hudak PL, Hwang SW. Homeless people's perceptions of welcomeness and unwelcomeness in healthcare encounters. J Gen Intern Med. 2007; 22:1011-1017.
33. Baron AS, Banaji MR. The development of implicit attitudes: evidence of race evaluations from ages 6 and 10 and adulthood. Psychol Sci. 2006;17:53-58.
34. Newheiser A-K, Olson KR. White and Black American children's implicit intergroup bias. J Exp Soc Psychol. 2012;48:264-270.
35. Institute of Medicine (US) Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC: National Academies Press (US); 2003.
36. Murphy MM, Simons JP, Ng SC, et al. Racial differences in cancer specialist consultation, treatment, and outcomes for locoregional pancreatic adenocarcinoma. Ann Surg Oncol. 2009;16:2968-2977.
37. Murphy MM, Simons JP, Hill JS, et al. Pancreatic resection: a key component to reducing racial disparities in pancreatic adenocarcinoma. Cancer. 2009; 115:3979-3990.
38. Shaib Y, Davila J, Naumann C, et al. The impact of curative intent surgery on the survival of pancreatic cancer patients: a U.S. Population-based study. Am J Gastroenterol. 2007;102:1377-1382.
39. Zell JA, Rhee JM, Ziogas A, et al. Race, socioeconomic status, treatment, and survival time among pancreatic cancer cases in California. Cancer Epidemiol Biomarkers Prev. 2007;16:546-552.
40. Lee S, Reha JL, Tzeng CW, et al. Race does not impact pancreatic cancer treatment and survival in an equal access federal health care system. Ann Surg Oncol. 2013;20:4073-4079.
41. Kraus CK. Invited Editorial: dedicated homeless clinics and emergency department utilization: a new horizon? J Am Coll Emerg Physicians Open. 2020; 1:837-838.
42. White BM, Newman SD. Access to primary care services among the homeless: a synthesis of the literature using the equity of access to medical care framework. J Prim Care Community Health. 2015;6:77-87.
43. Fitzpatrick-Lewis D, Ganann R, Krishnaratne S, et al. Effectiveness of interventions to improve the health and housing status of homeless people: a rapid systematic review. BMC Public Health. 2011;11:638.
44. Klop HT, Evenblij K, Gootjes JRG, et al. Care avoidance among homeless people and access to care: an interview study among spiritual caregivers, street pastors, homeless outreach workers and formerly homeless people. BMC Public Health. 2018;18:1095.
45. Owens DK, Davidson KW, Krist AH, et al; US Preventive Services Task Force. Screening for pancreatic cancer: US Preventive Services Task Force Reaffirmation Recommendation Statement. JAMA. 2019;322:438-444.
46. Tramontano AC, Chen Y, Watson TR, et al. Pancreatic cancer treatment costs, including patient liability, by phase of care and treatment modality, 2000-2013. Medicine (Baltimore). 2019;98:e18082.
47. Baggett TP, O'Connell JJ, Singer DE, et al. The unmet health care needs of homeless adults: a national study. Am J Public Health. 2010;100:1326-1333.
48. Sommers BD, Gawande AA, Baicker K. Health insurance coverage and health - what the recent evidence tells us. N Engl J Med. 2017;377:586-593.

49. Lyon SM, Douglas IS, Cooke CR. Medicaid expansion under the Affordable Care Act: implications for insurance-related disparities in pulmonary, critical care, and sleep. Ann Am Thorac Soc. 2014;11:661-667.
50. O'Neill CB, Atoria CL, O'Reilly EM, et al. Costs and trends in pancreatic cancer treatment. Cancer. 2012;118:5132-5139.
51. Chang S, Long SR, Kutikova L, et al. Burden of pancreatic cancer and disease progression: economic analysis in the US. Oncology. 2006;70:71-80.
52. Du W, Touchette D, Vaitkevicius VK, et al. Cost analysis of pancreatic carcinoma treatment. Cancer. 2000;89:1917-1924.
53. Wilson LS, Lightwood JM. Pancreatic cancer: total costs and utilization of health services. J Surg Oncol. 1999;71:171-181.
54. Galinsky AD, Moskowitz GB. Perspective-taking: decreasing stereotype expression, stereotype accessibility, and in-group favoritism. J Pers Soc Psychol. 2000; 78:708-724.
55. Drwecki BB, Moore CF, Ward SE, et al. Reducing racial disparities in pain treatment: the role of empathy and perspective-taking. Pain. 2011;152:1001-1006.
56. Deutsch MB, Buchholz D. Electronic health records and transgender patients--practical recommendations for the collection of gender identity data. J Gen Intern Med. 2015;30:843-847.
57. Festa K, Hirsch AE, Cassidy MR, et al. Breast cancer treatment delays at an urban safety net hospital among women experiencing homelessness. J Community Health. 2020;45:452-457.
58. Freeman HP, Rodriguez RL. History and principles of patient navigation. Cancer. 2011;117(suppl 15):3539-3542.
59. Wells KJ, Battaglia TA, Dudley DJ, et al; Patient Navigation Research Program. Patient navigation: state of the art or is it science? Cancer. 2008;113:1999-2010.
60. Donaldson EA, Holtgrave DR, Duffin RA, et al. Patient navigation for breast and colorectal cancer in 3 community hospital settings: an economic evaluation. Cancer. 2012;118:4851-4859.
61. Bharel M, Santiago ER, Forgione SN, et al. Eliminating health disparities: innovative methods to improve cervical cancer screening in a medically underserved population. Am J Public Health. 2015;105(suppl S3):S438-S442.
62. Moss NJ, Gallaread A, Siller J, et al. "Street medicine": Collaborating with a faith-based organization to screen at-risk youths for sexually transmitted diseases. Am J Public Health. 2004;94:1081-1084.
63. Wittenberg E, Bharel M, Bridges JFP, et al. Using best-worst scaling to understand patient priorities: a case example of Papanicolaou tests for homeless women. Ann Fam Med. 2016;14:359-364.
64. Phillips S, Raskin SE, Harrington CB, et al. "You have to keep a roof over your head": a qualitative study of housing needs among patients with cancer in New York City. J Oncol Pract. 2019;15:e677-e689.
65. Green HD Jr., Tucker JS, Golinelli D, et al. Social networks, time homeless, and social support: a study of men on Skid Row. Netw Sci (Camb Univ Press). 2013; 1:305-320.
66. Nyamathi A, Leake B, Keenan C, et al. Type of social support among homeless women: its impact on psychosocial resources, health and health behaviors, and use of health services. Nurs Res. 2000;49:318-326.
67. Mitchinson AR, Kim HM, Geisser M, et al. Social connectedness and patient recovery after major operations. J Am Coll Surg. 2008;206:292-300.
68. Torphy RJ, Chapman BC, Friedman C, et al. Quality of life following major laparoscopic or open pancreatic resection. Ann Surg Oncol. 2019;26:2985-2993.
69. Gage-Bouchard EA. Social support, flexible resources, and health care navigation. Soc Sci Med. 2017;190:111-118.
70. Browne G, Roberts J, Gafni A, et al. Economic evaluations of community-based care: lessons from twelve studies in Ontario. J Eval Clin Pract. 1999;5:367-385.
71. Abbasi J. Under Affordable Care Act, uninsured rates fell across demographic groups. JAMA. 2016;316:2077.
72. Office of the High Commissioner for Human Rights. OHCHR and the right to health. https://www.ohchr.org/EN/Issues/ESCR/Pages/Health.aspx. Accessed February 27, 2021.
73. Nardin R, Zallman L, Sayah A, et al. Experiences applying for and understanding health insurance under Massachusetts health care reform. Int J Equity Health. 2016;15:110.

BREAST CANCER

Challenges in Adjuvant Therapy for Premenopausal Women Diagnosed With Luminal Breast Cancers

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Overview

More than 90% of women with newly diagnosed breast cancer present with stage I to III disease and, with optimal multidisciplinary therapy, are likely to survive their disease. Of these patients, 70% are hormone receptor–positive and candidates for adjuvant endocrine therapy. The adoption of cumulatively better adjuvant treatments contributed to improved outcomes in patients with hormone receptor–positive, early-stage breast cancer. Premenopausal women with hormone receptor–positive breast cancer often present with complex disease and have inferior survival outcomes compared with their postmenopausal counterparts. Risk stratification strategies, including classic clinicopathologic features and newer gene expression assays, can assist in treatment decisions, including adjuvant chemotherapy use and type or duration of endocrine therapy. Gene expression assays may help identify patients who can safely forgo chemotherapy, although to a lesser extent among premenopausal patients, in whom they may play a role only in node-negative disease. Patients at lower risk of recurrence can be adequately treated with tamoxifen alone, whereas higher-risk patients benefit from ovarian function suppression with tamoxifen or an aromatase inhibitor. The role of adding newer therapies such as CDK4/6 inhibitors to adjuvant endocrine therapy is not yet clear. Breast cancer treatments are associated with several side effects, with major impact on patients' quality of life and treatment adherence, particularly in premenopausal women for whom these side effects may be more prominent as the result of the abrupt decrease in estrogen concentrations. Personalized management of treatment side effects, addressing patients' concerns, and health promotion should be an integral part of the care of premenopausal women diagnosed with luminal breast cancers.

Breast cancer is a highly heterogeneous disease that encompasses several subtypes with different natural histories, responses to treatment, and clinical outcomes.[1,2] Gene expression assays offer the most precise identification of intrinsic breast cancer subtypes;[3-5] however, immunohistochemistry assessments of hormone receptors (estrogen receptor and progesterone receptor), Ki-67, and HER2 provide a clinically relevant surrogate definition of breast cancer subtypes.[6] The majority of women diagnosed with breast cancer have hormone receptor–disease, or luminal-like subtypes, either Luminal A–like (estrogen receptor–positive and progesterone receptor–positive, HER2-negative, Ki-67–low) or Luminal B-like (Luminal B–like/HER2-negative: estrogen receptor–positive, HER2-negative, and at least one of Ki-67–high or progesterone receptor–negative or low; Luminal B–like/HER2-positive: estrogen receptor–positive, HER2-positive; because of interlaboratory variation, a Ki-67 of at least 20% may be considered indicative of high Ki-67 status, but some experts would use a lower cut point or use multigene-expression assay results, if available; similarly, a progesterone receptor cut point lower than 20% seemed to best define a low progesterone receptor value and to correspond to Luminal B subtypes).[6] The adoption of multidisciplinary therapy, including adjuvant treatment strategies, contributed to the improvement of survival outcomes in patients with hormone receptor–positive, early-stage breast cancer. Although the prevalence of breast cancer is lower in premenopausal women, their tumors are less frequently luminal and more likely to require multiple treatment modalities. Despite multidisciplinary therapy, their overall survival rate is lower compared with their postmenopausal counterparts, particularly in very young women.[7] At the same time, some women may be overtreated. Almost every woman with hormone receptor–positive, early-stage breast cancer is a candidate for adjuvant endocrine therapy. New tools are available to help quantify the benefit from chemotherapy in addition to endocrine therapy (chemo-ET).

Breast cancer treatments are associated with frequent bothersome side effects with major negative impact on patients' quality of life and treatment adherence. This is particularly relevant for premenopausal women with

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PRACTICAL APPLICATIONS

- Among premenopausal women with hormone receptor–positive breast cancer, risk stratification strategies can help determine prognosis and tailor optimal chemotherapy and endocrine therapy decisions.
- These women should be recommended endocrine therapy for 5 to 10 years. Tamoxifen alone can be considered for women with low-risk disease for whom chemotherapy is not recommended. Women at high risk for recurrence should be considered for ovarian function suppression with tamoxifen or an aromatase inhibitor.
- There is no evidence that continuing ovarian function suppression beyond 5 years provides additional benefit.
- Early initiation of ovarian function suppression prior to chemotherapy is appropriate for patients who have not completed childbearing. When childbearing is completed, it is reasonable to commence ovarian function suppression after chemotherapy.
- Substantial side effects of endocrine therapy include vasomotor, musculoskeletal, and vulvovaginal symptoms, fatigue, and emotional distress. Symptom burden can be associated with nonadherence to treatment. Both pharmacologic and nonpharmacologic approaches to mitigate these side effects are available.

early-stage breast cancer, for whom the side effects may be more prominent, as the result of the abrupt decrease in estrogen concentrations with adjuvant systemic therapies.

ADDRESSING STANDARD OF CARE IN ADJUVANT THERAPY FOR PREMENOPAUSAL WOMEN

With few exceptions, premenopausal women with early-stage, hormone receptor–positive, HER2-negative breast cancer should be considered for 5 to 10 years of endocrine therapy. Many are also candidates for adjuvant chemotherapy.

Risk Stratification for Breast Cancer Recurrence

Recent tools are available to clinicians to inform treatment recommendations for their patients.

Online calculators Large data sets such as The Early Breast Cancer Trialists' Collaborative Group meta-analyses or individual large, randomized clinical trials have been used to develop online risk calculators to estimate individual patients' risk of breast cancer recurrence and death, and the expected benefit from endocrine therapy versus chemo-ET. Common tools include the National Health Service Predict tool, based on a U.K. cancer registry database,[8] and CancerMath, derived from the Surveillance, Epidemiology, and End Results Program.[9,10]

Composite scores Composite scores that consist of data from several individual biomarkers may be used to estimate benefit from endocrine therapy versus chemo-ET. Immunohistochemistry 4 is based on standard laboratory evaluations of estrogen receptor, progesterone receptor, HER2, and Ki-67.[11,12] This score is prognostic for outcome, but not predictive for the choice of endocrine therapy. One concern that limits the use of this score is that Ki-67 is not always used in clinical practice.[13,14]

Clinical Treatment Score post-5 years incorporates routine clinical and pathologic information, including patient age and tumor grade, size, and nodal status, and was originally developed and validated in postmenopausal women,[15] in whom it is a prognostic biomarker that predicts the risk of late distant recurrence after 5 years of endocrine therapy. A recent preliminary report evaluating Clinical Treatment Score post-5 years in TAILORx demonstrated that this marker was prognostic in patients older than age 50 with intermediate or high recurrence score (RS), predicting late distant recurrence, but was not prognostic in patients with a low RS.[16] Furthermore, although smaller studies suggested possible prognostic value in premenopausal women,[17,18] Clinical Treatment Score post-5 years' role was more limited in women age 50 or younger versus older than age 50 in TAILORx.[16] Further validation is needed before considering Clinical Treatment Score post-5 years for premenopausal women.

Multiparameter gene expression assays Multiparameter gene expression assays have revolutionized adjuvant therapy decision-making for women with early-stage, hormone receptor–positive breast cancer and are summarized in Table 1. The Oncotype DX assay RS can be used to predict the likelihood of distant recurrence and assist decisions regarding use of chemotherapy in addition to endocrine therapy among patients with hormone receptor–positive, HER2-negative, node-negative disease.[19-22] In TAILORx, women with hormone receptor–positive HER2-negative, lymph node–negative breast cancer with an RS less than 11 received endocrine therapy alone, those with an RS greater than 25 were recommended to receive chemo-ET, and those with an RS of 11 to 25 were randomly assigned to receive endocrine therapy or chemo-ET. Although endocrine therapy was found to be noninferior to chemo-ET for invasive disease-free survival and overall survival in patients with an RS between 11 to 25, in an exploratory analysis, the investigators reported that chemotherapy benefit was observed in women age 50 or younger with an RS between 16 to 25.[23] Integration of clinical risk with RS is also prognostic of distant disease and may predict which premenopausal

TABLE 1. Risk Stratification by Multigene Assay for Adjuvant Treatment Decisions for Women Age 50 or Younger With Early-Stage, Hormone Receptor–Positive, HER2-Negative Breast Cancer

	Setting	Multiparameter Gene Expression Assays
Low Risk: No benefit from the addition of chemotherapy to ET	T ≤ 2.0 cm, node-negative, grade 1 T ≤ 1.0 cm, node-negative, grade 2 T ≤ 0.5 cm, node-negative, grade 3	NA
	Other node-negative	Oncotype Recurrence Score ≤ 15
	T = 2.1–3.0 cm, node-negative, grade 1 T = 1.1–2.0 cm, node-negative, grade 2 T = 0.6–1.0 cm, node-negative, grade 3	MammaPrint Low Score
High Risk: Addition of chemotherapy to ET is recommended	Node-negative	Oncotype Recurrence Score > 15*
	1–3 positive nodes	Any Oncotype Recurrence Score *or* MammaPrint Score**
	≥ 4 positive nodes	Assay is not recommended

Abbreviations: ET, endocrine therapy; HR, hormone receptor; T, tumor size; N, lymph node; NA, not applicable.

*For patients with negative nodes and Oncotype Recurrence Score > 25, benefit from the addition of chemotherapy to endocrine therapy unequivocal; for patients with negative nodes and Recurrence Score 16–25, benefit from the addition of chemotherapy to endocrine therapy unclear if the result of chemotherapy-induced ovarian suppression.

**For patients with 1–3 positive nodes and Oncotype Recurrence Score ≤ 25 or MammaPrint Low Score, benefit from the addition of chemotherapy to endocrine therapy unclear if the result of chemotherapy-induced ovarian suppression.

Note: If multiparameter gene assay is not available, endocrine therapy without chemotherapy may be chosen when all clinicopathologic features are favorable: pT1pN0 grade 1–2 tumor with both estrogen receptor and progesterone receptor positive in at least 50% cells and Ki-67 < 20% and age > 40.

women may benefit most from chemo-ET.[24,25] In the RxPONDER trial, investigators evaluated the benefit of chemotherapy in women with hormone receptor–positive, node-positive breast cancer. Initial results indicate that postmenopausal women with hormone receptor–positive, HER2-negative breast cancer with one to three positive nodes and an RS of 25 or lower did not derive benefit from chemo-ET compared with endocrine therapy alone. In contrast, premenopausal women in this trial experienced a 45% relative risk reduction in invasive disease–free survival events with the addition of chemotherapy to endocrine therapy.[26] In premenopausal women, the RS result might vary according to timing of tumor acquisition in the menstrual cycle, as can other biomarkers.[27,28]

The MammaPrint assay, which provides prognostic information in early-stage breast cancer,[29-31] was evaluated in the MINDACT trial.[32] Participants with breast cancer and zero to three positive lymph nodes were assigned a clinical risk using Adjuvant! Online[33,34] and a genomic risk using Mamma Print. Those with low clinical and low genomic risk were not recommended chemotherapy; those with high clinical and high genomic risk received chemotherapy. Patients with hormone receptor–positive disease and discordant risk results were randomly assigned to endocrine therapy or chemo-ET. Updated results from the MINDACT trial, with a median follow-up of 8.7 years, show that women with high clinical but low genomic risk for recurrence and who did not receive chemotherapy have a 5-year distant metastasis–free survival of 95.1%, suggesting that MammaPrint may be used to identify patients with zero to three positive lymph nodes and high clinical risk in whom the risk of distant recurrence is likely to be low with endocrine therapy alone. However, an exploratory subgroup analysis in MINDACT by age suggested that premenopausal women with high clinical and low genomic risk tumors may benefit from the addition of chemotherapy to endocrine therapy.[32,35] This exploratory analysis looked at outcomes with chemotherapy versus without in women with hormone receptor–positive and HER2-negative tumors by age. Women age 50 or younger with high clinical but low genomic risk who received chemotherapy derived an absolute difference of 5% in distant metastasis–free survival at 8 years (93.6% [95% CI, 89.3–96.3] with chemotherapy versus 88.6% [95% CI, 83.5–92.3] without chemotherapy, resulting in an adjusted hazard ratio (HR) of 0.54 [95% CI, 0.30–0.98] in the intention-to-treat population and consistent findings in the per-protocol analysis). Analogously, in women age 50 or younger with hormone receptor–positive, HER2-negative tumors and clinical high risk/genomic low risk, the absolute difference in overall survival at 10 years among patients receiving versus not receiving chemotherapy was 5.4% in the intention-to-treat population and 7.7% in the per-protocol analysis.[32] The Breast Cancer Index Risk of Recurrence & Extended Endocrine Benefit Test can be considered for women with early-stage, invasive breast cancer, who are distant recurrence–free, are hormone

TABLE 2. Options for Adjuvant Chemotherapy in Luminal HER2-Negative Tumors

Regimen		Considerations
Anthracycline/taxane-based	3–4 cycles epirubicin-cyclophosphamide or 4 cycles doxorubicin-cyclophosphamide followed by 3–4 cycles 3-weekly docetaxel or 12-weekly paclitaxel or dose-dense paclitaxel	
	Dose-dense doxorubicin-cyclophosphamide followed by weekly or dose-dense paclitaxel	
Taxane-based	6 cycles docetaxel-cyclophosphamide*	Node-positive disease with anthracycline contraindication
	4 cycles docetaxel-cyclophosphamide	Node-negative or limited node-positive disease

*As in the Anthracyclines in Early Breast Cancer Trials: The ABC Trials (USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49).[41]

receptor–positive, and have zero to three positive lymph nodes. Among others, data from the aTTom trial and IDEAL trial demonstrate that the Breast Cancer Index is predictive of endocrine response and can identify a subset of patients with hormone receptor–positive tumors who may derive significant benefit from extended endocrine therapy. Of note, the Breast Cancer Index was evaluated in patients with node-positive breast cancer in the aTTom trial, and the proportion of patients with node-positive disease in IDEAL was 73%.[36,37]

Other available genomic assays include the Prosigna Breast Cancer Prognostic Gene Signature Assay (formerly called PAM50), and the 12-gene EndoPredict.[5,38,39] The results of some of these tools may vary by menopausal status and should be interpreted with caution in premenopausal women as they may have been calibrated mostly from trials in postmenopausal women.

Treatment Decisions With Adjuvant Chemotherapy

Once a decision is made to recommend chemotherapy, several multiagent combinations are available for premenopausal women with early-stage, hormone receptor–positive, HER2-negative breast cancer. The Early Breast Cancer Trialists' Collaborative Group investigators have demonstrated that overall the risk of disease recurrence, breast cancer mortality, and overall mortality was reduced in those receiving anthracycline/taxane-based regimens compared with anthracycline-based regimens, irrespective of hormone receptor status.[40] In the ABC trials, investigators compared adjuvant taxane-based regimens to anthracycline/taxane-based regimens in women with early-stage, HER2-negative, node-positive or high-risk, node-negative breast cancer. Overall, anthracycline/taxane-based regimens are associated with improved disease-free survival compared with taxane-based regimens. However, exploratory subgroup analyses suggested that the majority of the anthracycline/taxane-based regimens benefit is seen in patients with hormone receptor–negative tumors, and in those with hormone receptor–positive, lymph node–positive disease, particularly with at least four positive nodes.[41] Options for adjuvant chemotherapy regimens in luminal HER2-negative tumors are summarized in Table 2.

Treatment Decisions With Adjuvant Endocrine Therapy

Five years of adjuvant tamoxifen is associated not only with significant reduction in local, contralateral, and distant breast cancer recurrence, but also in breast cancer–related mortality.[40,42,43] Newer data reported in the last decade have further demonstrated that, compared with 5 years of adjuvant tamoxifen, premenopausal women derive additional benefit from 10 years of tamoxifen, or from 5 years of ovarian function suppression (OFS) with either tamoxifen or an aromatase inhibitor.

Two International Breast Cancer Study Group–led studies, SOFT and TEXT, provide the largest experience evaluating adjuvant endocrine therapy options in premenopausal women with hormone receptor–positive, early-stage breast cancer.[44] In SOFT, women received 5 years of tamoxifen, or tamoxifen plus OFS, or exemestane plus OFS, whereas in TEXT, women received tamoxifen plus OFS or exemestane plus OFS. The addition of OFS to tamoxifen improved both disease-free survival and overall survival compared with tamoxifen alone.[44-48] Furthermore, in a combined analysis of the two studies, exemestane plus OFS was associated with improvement in freedom from distant recurrence compared with tamoxifen plus OFS. The benefit from intensifying adjuvant endocrine therapy was especially significant in patients at high risk of recurrence, including those with high-risk clinicopathologic features and young age, and those treated with chemotherapy.[46] Of note, only 12% of all patients in the combined SOFT/TEXT studies were younger than age 35. In a recent analysis of the SOFT/TEXT HER2-negative population, the investigators reported that the overall rate of 8-year freedom from distant recurrence was 91.1%, with a range from 100% to 63% based on categories across composite risks (lowest to highest).[49] Clinicians may use an online tool developed to assist clinicians with risk/benefit calculations using SOFT/TEXT data.[50]

For appropriately selected women, clinicians can consider surgical OFS via bilateral salpingo-oophorectomy. This method is irreversible and may be considered for women with increased risk of ovarian cancer or those desiring permanent OFS. Pharmacologic methods are reversible and include gonadotropin-releasing hormone (GnRH) agonists (GnRHa) such as goserelin and leuprolide to suppress luteinizing

hormone and follicle-stimulating hormone and subsequent reduction of estrogen production from the ovaries.

Because women with early-stage, hormone receptor–positive breast cancer may develop late recurrences despite 5 years of tamoxifen, several studies have examined extended adjuvant endocrine therapy. In the ATLAS trial, more than 12,000 women who completed 5 years of tamoxifen were randomly assigned to stop the medication or to continue tamoxifen for 5 additional years.[51] In the aTTom study, about 7,000 patients who completed 5 years of tamoxifen were randomly assigned to stop tamoxifen or to continue the drug for 10 years.[52] Both studies demonstrated that 10 years of tamoxifen resulted in significant reductions in the risk of breast cancer recurrence, breast cancer mortality, and overall mortality compared with 5 years. Of note, although in ATLAS there was no significant heterogeneity of the proportional recurrence risk reduction according to menopausal status at diagnosis, with an event rate of 24% in the group allocated to stop tamoxifen and 20% among that continuing to 10 years, only 9% and 10% of women with hormone receptor–positive breast cancer were premenopausal in each group, respectively.[51]

If a woman underwent an oophorectomy and is at a high risk of recurrence, the benefits and risks of 10 years of endocrine therapy should be weighed carefully against possible long-term effects of estrogen deprivation. Fig. 1 summarizes a suggested adjuvant endocrine therapy approach for women who are premenopausal at diagnosis.

Other Considerations

Prior to initiating adjuvant systemic therapy, premenopausal women with early-stage breast cancer should receive genetic testing and counseling and, when appropriate, be offered fertility preservation. These women should avoid hormonal methods of contraception, although among women receiving tamoxifen monotherapy, hormonal intrauterine devices might be safe.[53] Careful monitoring of bone health should include a baseline bone density scan among postmenopausal survivors of breast cancer and a repeat bone density scan every 2 years among postmenopausal women treated with an aromatase inhibitor, premenopausal women receiving tamoxifen or OFS, and women who have menopause prematurely induced by chemotherapy.[54]

The use of bone-modifying agents should be considered in accordance with guidelines.[55] All patients should also be encouraged to maintain ideal body weight and be physically active.[54]

QUESTIONS THAT REMAIN UNANSWERED IN ADJUVANT ENDOCRINE THERAPY

Timing of Initiating Ovarian Function Suppression in Relation to Chemotherapy: Before, After, or Wait to Assess Ovarian Function?

There are no premenopausal hormone receptor–positive, early-stage breast cancer trials that have randomized the timing of initiation of OFS in relation to chemotherapy, with cancer outcomes as the primary endpoint. However, some indirect information on this question is available. In SOFT, patients assigned to OFS commenced OFS after chemotherapy completion, if chemotherapy was given, whereas in TEXT, all patients received OFS and it was initiated early following random assignment and given concurrent with chemotherapy, if chemotherapy was given. In an analysis of 1,872 patients who received OFS by GnRHa triptorelin concurrent with chemotherapy in TEXT (1,242 patients) or sequentially after chemotherapy in SOFT (630 patients), concurrent use of OFS with chemotherapy was not associated with a significant difference in post-landmark invasive breast cancer–free interval compared with sequential OFS after chemotherapy, either overall in this analysis or in the subgroup age 40 or younger.[56]

In a meta-analysis of trials studying prevention of premature ovarian sufficiency that compared GnRHa concurrent with chemotherapy versus chemotherapy without concurrent GnRHa, there was no evidence of a significant difference in disease-free survival or overall survival at 5 years in the subgroup with hormone receptor–positive cancers (approximately 300 patients) according to GnRHa use.[57] Therefore, concurrent use of OFS and chemotherapy appears safe in premenopausal hormone receptor–positive early-stage breast cancer, provided this is delivered in the context of continuation of OFS in the adjuvant setting. For patients with hormone receptor–positive cancers who have not completed childbearing, early initiation of OFS, at least 1 week prior to chemotherapy, is appropriate, in addition to offering other preceding fertility preservation measures.[58-60] For patients with hormone receptor–positive cancers who have completed childbearing, it is reasonable to commence OFS after chemotherapy.

In premenopausal women with early-stage, hormone receptor–positive breast cancer who receive chemotherapy, results from two trials demonstrate survival benefit from the addition of OFS to tamoxifen in women with residual ovarian function.[46,61] Of note, women with only 1% to 9% of cells with hormone receptor staining were not eligible for these trials.[62] The SOFT trial enrolled patients who had a premenopausal estradiol level within 8 months of completing chemotherapy and assigned OFS was for 5 years. The role of adding OFS to tamoxifen in young women with hormone receptor–positive breast cancer who remain premenopausal or regain menstruation after chemotherapy was evaluated in ASTRRA. The trial allowed random assignment up to 2 years following chemotherapy, with 6-monthly assessments of follicle-stimulating hormone or menses to assess eligibility, and assigned OFS was for 2 years. The effect of adding OFS was more pronounced for those randomly assigned at the 6-month post-chemotherapy time-point than later.[45] In SOFT, recurrence was reduced with addition of OFS to tamoxifen, and further reduced with the combination of OFS plus exemestane.[31,32]

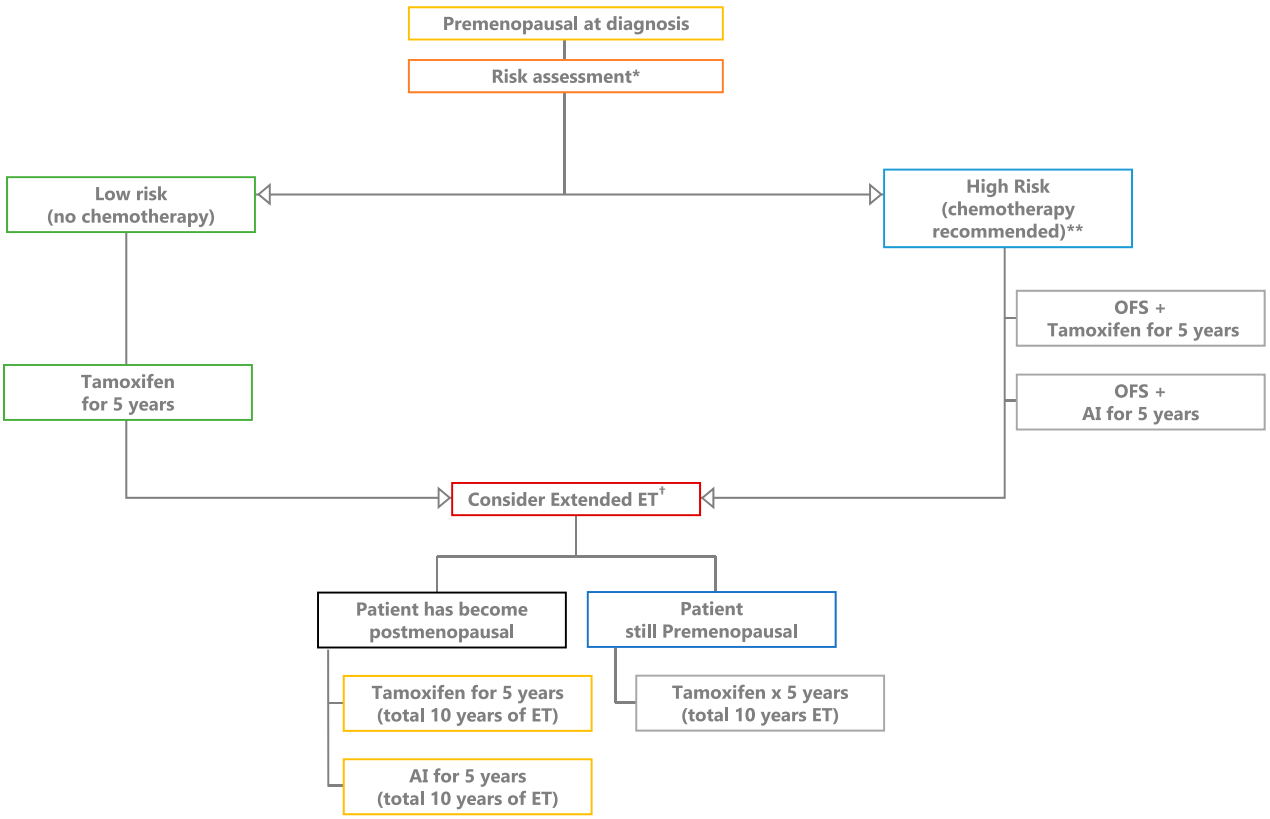

FIGURE 1. Suggested Adjuvant Endocrine Therapy Approach for Women Who Are Premenopausal at Diagnosis

Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy; OFS, ovarian function suppression.

*Risk stratification defined in Table 1.

**For some patients, including those with node-negative disease and Oncotype Recurrence Score 16–25 and some patients with node-positive disease and Oncotype Recurrence Score < 25, it is unclear whether the benefit of adding chemotherapy to ET is due to chemotherapy-induced ovarian suppression. In this setting, it may be appropriate to engage in personalized discussions on withholding chemotherapy and offering ovarian function suppression and oral endocrine therapy.

†There are tools that can guide the decision to extend endocrine therapy based on long-term risk of recurrence, including the Clinical Treatment Score post-5 years and the Breast Cancer Index (see Risk Stratification for Breast Cancer Recurrence). There are currently no available data regarding the use of extended ovarian function suppression beyond 5 years in patients who are deemed candidates for extended endocrine therapy.

If OFS were to be planned to be given with adjuvant tamoxifen, then there is the option to commence tamoxifen and wait and monitor for ovarian function recovery after chemotherapy, before commencing OFS, unless the woman is young and ovarian recovery is expected. However, in a premenopausal woman who has completed childbearing, if it would be preferred to give an aromatase inhibitor after completing chemotherapy, then it may be safer to commence OFS directly after chemotherapy, rather than aiming to assess for possible ovarian recovery. This is because premenopausal women with chemotherapy-induced amenorrhea have a significant likelihood of ovarian recovery following commencement of an aromatase inhibitor, even in the context of prolonged amenorrhea and/or serum hormone levels consistent with menopause.[63] The likelihood of post-chemotherapy ovarian recovery following commencement/switch to an aromatase inhibitor is age-dependent, with 50% of women younger than age 48 experiencing ovarian recovery, as compared with 12% of women older than age 50 in a prospective study.[64] The likelihood of ovarian recovery after chemotherapy is also regimen-dependent, with highest likelihood of recovery with 12-week chemotherapy regimens. Post-chemotherapy ovarian function recovery with an aromatase inhibitor in the absence of OFS creates a risk of ineffective adjuvant endocrine therapy, particularly for women younger than age 50 and/or those who have received a short cytotoxic regimen. Unexpected pregnancy is another potential risk in this context.[63] For women who are within approximately 5 years of the age of natural menopause, a laparoscopic surgical bilateral oophorectomy may be a cost-effective method of OFS that also facilitates compliance.

Duration and Interruption and Type of Adjuvant Ovarian Function Suppression in Premenopausal Patients

In randomized oral endocrine therapy trials, longer durations are somewhat more effective than shorter durations. However, for premenopausal women who receive 5 years of oral endocrine therapy, the optimal duration of adjuvant OFS has not been adequately studied. SOFT randomly assigned women who remained/regained premenopausal status to OFS for 5 years, whereas ASTRRA randomly assigned patients to OFS for 2 years, and both trials have demonstrated efficacy of adding OFS to oral endocrine therapy.[30,45] SOFT also permitted the option of a permanent OFS method, such as bilateral oophorectomy, although this was chosen by a minority of patients. If planning to give an aromatase inhibitor for 5 years after chemotherapy to an initially premenopausal woman, then a commensurate duration of ovarian dormancy/suppression is required. One underpowered randomized trial (222 patients) compared tamoxifen for 5 years plus either OFS for 2 years or OFS for at least 3 years and showed no overall difference in disease-free survival, but subgroup analysis suggested better disease-free survival with longer OFS in higher-risk patients.[65]

There is no evidence that continuing OFS by GnRHa beyond 5 years in premenopausal women provides additional benefit, although this has not been studied. In postmenopausal trials, continuing adjuvant estrogen-lowering therapy with an aromatase inhibitor beyond 5 years provides limited additional reduction in distant recurrences, plus some protection against new breast primaries, which is of relevance in patients with remaining breast(s). However, many patients in those postmenopausal trials were not at particularly high baseline risk of distant recurrence. In premenopausal women who have completed 5 years of OFS with oral endocrine therapy, there is also no evidence about the efficacy of extended oral adjuvant endocrine therapy with tamoxifen, after either an initial 5 years of tamoxifen plus OFS or aromatase inhibitor plus OFS. However, clinicians may consider a switch to tamoxifen monotherapy after 5 years of OFS plus oral endocrine therapy, despite an absence of data, for women who were very young at diagnosis and/or with high-risk features, based on the known risk of late relapse in luminal breast cancer.[66]

Young women with luminal breast cancer may wish to interrupt a proposed 5 to 10 year period of adjuvant endocrine therapy to attempt pregnancy. There is no evidence that a pregnancy after luminal breast cancer increases the risk of cancer recurrence.[67-69] There is no clear duration of adjuvant endocrine therapy that is considered appropriate, before interruption to attempt pregnancy. This decision may also depend upon patient age, patient preference, prior fertility preservation procedures, and baseline risk of breast cancer recurrence. Interrupted endocrine therapy can be resumed after delivery or after lactation is completed. Clinically significant levels of tamoxifen and its metabolites were found to accumulate in human milk over time; therefore, exposure to tamoxifen should be avoided during breastfeeding.[70] Enrollment is now complete to POSITIVE, a prospective cohort study in women with hormone receptor–positive, early-stage breast cancer desiring pregnancy after an initial 18 to 30 months of adjuvant endocrine therapy, for whom a break in therapy for up to 2 years to attempt pregnancy/delivery/lactation is allowed, with a plan for subsequent resumption of adjuvant endocrine therapy. Although not randomly assigned, outcomes in women in POSITIVE will be assessed, and there are outcomes for women with comparable age/tumors/treatments in SOFT/TEXT who did not interrupt therapy for pregnancy attempt.[71]

Currently reversible OFS is recommended by administration of GnRHa injections. It is recommended that these be administered every 4 weeks if concurrent aromatase inhibitor therapy is given, as there are not currently data for use of 3-monthly GnRHa with adjuvant aromatase inhibitor in premenopausal women. In the case of concurrent tamoxifen, there is less concern about possible incomplete suppression with the 3-monthly schedule. A randomized phase II neoadjuvant trial in premenopausal luminal breast cancer compared GnRHa triptorelin plus letrozole versus a GnRH *antagonist* degarelix with letrozole. Ovarian function suppression was achieved more quickly and maintained more effectively with the GnRH antagonist degaralix.[72] However, there has been no comparison of GnRHa versus GnRH antagonist in young patients in the adjuvant setting with respect to breast cancer outcomes or ability to protect against premature ovarian insufficiency.

Is Adjuvant Tamoxifen Monotherapy Sufficient for Very Young Women, If Other Pathologic Features Are Favorable?

Hormone receptor–positive breast cancer diagnosed at a young age is associated with inferior breast cancer outcomes as compared with diagnosis at an older premenopausal age. Historically this has been observed in trials of adjuvant chemotherapy, endocrine therapy, and chemo-ET.[73-75]

Very young patients are more likely to have aggressive breast tumor phenotypes, with a higher ratio of Luminal B–like versus Luminal A–like tumors in women diagnosed at a young age than at an older age. However, even among premenopausal women with Luminal A–like tumors, young age (40 or younger) is associated with an increased risk of breast cancer mortality.[7] In an analysis from the SOFT/TEXT trials, the 5-year breast cancer–free interval in women younger than age 35 with hormone receptor–positive, HER2-negative cancers assigned to receive OFS combined with oral endocrine therapy was

83.6% in those who had Luminal A–like tumors (vs. 96.2% for age 35 or older) and 79.2% in Luminal B–like tumors (vs. 86.4% for age 35 or older). Guidelines suggest considering OFS in women diagnosed with invasive hormone receptor–positive breast cancer who are younger than age 35, with the exception of very small node-negative cancers 1 cm or less without other adverse features.[76,77]

Should We Recommend the Addition of CDK4/6 Inhibitors to Adjuvant Endocrine Therapy in Premenopausal Women With Hormone Receptor–Positive, HER2-Negative Disease?

Premenopausal women with advanced breast cancer can derive significant improvement in overall survival from the addition of a CDK4/6 inhibitor to first-line endocrine therapy.[78] The monarchE adjuvant trial tested adding the CDK4/6 inhibitor abemaciclib for 2 years to adjuvant endocrine therapy in patients with early-stage, hormone receptor–positive, HER2-negative cancer with high-risk features. Recently, with 15.5 months median follow-up, monarchE reported a significant improvement in 2-year invasive disease–free survival with abemaciclib, and this effect appeared robust in the premenopausal subgroup. However, it appears that only approximately half of the trial participants received OFS.[79] Moreover, in the overall trial population, almost one-third of patients received tamoxifen as their initial oral endocrine therapy, calling into question if these patients with higher-risk tumor features received optimal endocrine therapy. Results from the PENELOPE-B trial, which tested the addition of 1 year of CDK-4/6 inhibitor palbociclib to adjuvant endocrine therapy in patients with significant residual tumor after neoadjuvant therapy, showed that adjuvant palbociclib did not result in significant invasive disease–free survival improvement, with a small absolute invasive disease–free survival improvement at 2 years, which subsequently dissipated. This suggests that longer follow-up in monarchE will be important to ascertain if the invasive disease–free survival improvement is sustained and if an overall survival benefit is achieved. In addition, it would be relevant to consider the efficacy in the premenopausal subgroup receiving optimal adjuvant endocrine therapy before we recommend adjuvant abemaciclib for premenopausal women with higher-risk early luminal cancers.

BALANCING ADHERENCE AND PRESERVING QUALITY OF LIFE WHILE TAKING ENDOCRINE THERAPY

Impact of Endocrine Therapy–Related Symptom Burden on Quality of Life

The overwhelming majority of patients receiving endocrine therapy experience a wide range of burdensome and persistent side effects, which may determine a meaningful deterioration of quality of life and lead to significant reductions in adherence rates.[80] Table 3 summarizes main side effects of adjuvant endocrine therapy. This symptom's burden can dramatically deteriorate patient-reported quality of life, affecting numerous aspects of daily living. In a recent analysis using data from CANTO (NCT01993498; multicenter real-world prospective cohort of 12,012 women with stage I–III breast cancer), investigators evaluated a composite score measure of quality of life, the European Organization for Research and Treatment of Cancer C30 Summary Score, and found that adjuvant endocrine therapy has a detrimental impact persisting for over 2 years after diagnosis, which involved multiple functional and symptom domains. Furthermore, there were suggestions that endocrine therapy may attenuate recovery in domains that typically improve after end of primary treatment, including emotional function and future perspectives.[81]

TABLE 3. Type, Prevalence, and Associated Risk Factors of the Main Side Effects of Adjuvant Endocrine Therapy Among Patients With Early-Stage Breast Cancer

Side Effect	Prevalence	Associated Risk Factors	Class of ET
Musculoskeletal symptoms	> 50%	Body mass index < 25, previous treatment with taxanes	Tamoxifen and AI (*)
Vasomotor symptoms (hot flashes)	≈ 40%	Weight gain	Tamoxifen and AI (**)
Sexual dysfunction	26%–45%	Anxiety, hot flashes, body image perception	Tamoxifen and AI (**)
Vulvovaginal symptoms (vaginal dryness, dyspareunia)	8%–26%	Age, psychological distress, prior sexual issues	Tamoxifen and AI (**)
Fatigue	30%	Inactivity, psychological distress, pain	Tamoxifen and AI
Insomnia	20%–70%	Hot flashes	Tamoxifen and AI (**)
Weight gain	20%–30%	Premenopausal women, musculoskeletal symptoms	Tamoxifen and AI
Cognitive impairment	35%	Age, chemotherapy	Tamoxifen and AI
Venous thromboembolic events	< 2%	Age > 55, current smoker, family history of coronaropathy, obesity, hypertension, hypercholesterolemia	Tamoxifen (*)
Endometrial cancer	< 1%	Age, treatment duration	Tamoxifen (*)

Abbreviations: ET, endocrine therapy; AI, aromatase inhibitor.
*Indicates that the event is more typical of the spectrum of a specific type of therapy.
**Adding ovarian function suppression particularly increases frequency and severity of side effects.

Patient-reported outcome data from a subgroup of 579 women in TAILORx suggest that not only women who are receiving chemotherapy, but also those receiving endocrine therapy may experience clinically meaningful quality of life changes, including cognitive impairment.[82]

Extension of endocrine therapy beyond 5 years implies not only a higher risk and prolonged duration of more common side effects such as vasomotor, gynecologic, and musculoskeletal symptoms, but also an increased risk of rarer but serious side effects. In the MA.17R trial, there was a significantly higher incidence of fracture in the extended 10-year letrozole arm (14%) compared with the 5-year arm (9%). Similarly, ATLAS reported that the risk of pulmonary embolism and endometrial cancer was also significantly higher in the extended 10-year tamoxifen arm (0.9% and 3.1%, respectively) compared with the 5-year arm (0.5% and 1.6%, respectively). Similar results were found in the aTTom trial of extended therapy.[51,52,83] However, ATLAS enrolled predominantly postmenopausal women, who are at higher risk for these problems than women who remain premenopausal.

An increased risk of symptoms is also observed with the intensification of endocrine therapy by adding OFS. The SOFT trial showed that patients receiving OFS plus tamoxifen experienced more vasomotor symptoms (hot flashes, 93.4%; night sweats, 61.8%) and vulvovaginal symptoms (vaginal dryness, 49.8%; dyspareunia, 26.1%), when compared with patients receiving tamoxifen monotherapy (hot flashes, 79.8%; night sweats, 48.3%; vaginal dryness, 41.8%; dyspareunia 23.7%).[80]

Adherence to Endocrine Therapy Among Women With Early-Stage Breast Cancer

Prevalence of nonadherence to endocrine therapy Among patients with breast cancer, indirect methods of adherence assessment suggested a range of nonadherence to adjuvant endocrine therapy from 25% to 50% over 5 years.[84] In a large claims-based cohort of 2,378 patients with early-stage breast cancer in the United States, investigators used indirect methods such as insurance/commercial pharmacy medication refills to evaluate adherence to tamoxifen. Findings included that the mean percentage of days with a filled prescription available was 87% during year 1 of treatment with tamoxifen, whereas this proportion decreased to 50% during the remaining 4 years of treatment in a subset of 492 patients with long-term data.[85] Recently, through an objective and direct method to measure adherence (tamoxifen serum assessment), researchers suggested that as early as 1 year after initiating therapy, 16% of the 1,177 premenopausal women who were enrolled in the French CANTO cohort were not adherent to therapy and 55% of them self-declared to be adherent to adjuvant tamoxifen.[86] Data from the ATLAS trial reported that the proportion of patients still receiving treatment at year 2 after study entry was 84% among those allocated to 10 years of tamoxifen treatment.[51] Adherence to aromatase inhibitors was closely comparable, or only sometimes superior, ranging from 82% to 88%, and decreasing to 78% to 86% among patients with at least 3 years of follow-up on therapy.[87] In the combined analysis of the SOFT/TEXT trials, 4,690 patients were assigned to OFS plus exemestane versus OFS plus tamoxifen, and rates of discontinuation of assigned endocrine therapy were 16.1% and 11.2%, respectively.[48]

Symptom burden and adherence to endocrine therapy The substantial symptom burden and deterioration in quality of life that are often associated with endocrine therapy negatively impact adherence, often leading to early treatment discontinuation. Among all barriers to adherence, poor drug tolerability and uncontrolled adverse effects from the medication appear to be the primary reasons for discontinuation.[88-91] Particularly, musculoskeletal symptoms (adjusted odds ratio, 1.58; 95% CI, 1.06–2.37) and severe fatigue (adjusted odds ratio, 1.65; 95% CI, 1.07–2.5) increased the risk of biochemical nonadherence.[86]

Among 500 eligible patients enrolled in the ELPh clinical trial, 32.6% discontinued therapy because of adverse effects, with a median time to treatment discontinuation as a result of development of symptoms of 6.1 months.[90] Musculoskeletal symptoms were the primary patient-reported reasons for treatment discontinuation, reported in 24.4% of the entire study population.

Data also suggest that weight concerns were associated with decreased odds of adherence, as were cognitive and gynecologic symptoms, and severe sleep disturbances.[92-94]

Downstream impact of nonadherence to endocrine therapy on breast cancer clinical outcomes A retrospective cohort study of 1,633 patients receiving tamoxifen had demonstrated that adherence rates lower than 80% were associated with a significant negative impact on survival, with a HR for all-cause mortality of 1.10 (95% CI, 1.0–1.2) at a median duration of tamoxifen use of 2.4 years.[95] In the Breast International Group 1-98 clinical trial, low adherence (defined both as early cessation of letrozole and a compliance score of $< 90\%$) was associated with reduced disease-free survival (multivariable model HR, 1.45; 95% CI, 1.09–1.93; and 1.61; 95% CI, 1.08–2.38, respectively).[96] Among 8,769 women with hormone-sensitive stage I to III breast cancer enrolled in Kaiser Permanente of Northern California, automated pharmacy records identified prescriptions and dates of refill of endocrine therapy. There were 28% of women who were nonadherent (medication possession ratio $< 80\%$) in this study, and survival at 10 years was 81.7% and 77.8% in women who adhered and nonadhered, respectively. Nonadherence represented an independent predictor of mortality after adjustment for relevant clinical and demographic variables (HR, 1.49; 95% CI, 1.23–1.81).[97] More recent prospective evidence

suggests that women with tamoxifen serum concentrations under the adherence threshold have a significantly shorter distant disease–free survival (adjusted HR of distant recurrence or death, 2.31; 95% CI, 1.05–5.06; p = .036), with 89.5% of patients alive without distant recurrence at 3 years among nonadherent versus 95.4% among adherent women.[86]

Implementing effective interventions to improve adherence to endocrine therapy: current barriers and perspectives

Multidisciplinary personalized supportive strategies demonstrated some efficacy in improving adherence in chronic diseases.[98-101] Nevertheless, most approaches in the setting of adjuvant endocrine therapy mostly relied solely upon provision of educational material, which included general information about endocrine therapy and breast cancer, and about strategies to enhance medication adherence. These approaches, although proving to improve patients' awareness about benefits and side effects of endocrine therapy, did not significantly improve adherence.[98,99,102,103] A large survey addressed to 3,196 health care professionals, including medical doctors, nurses, and pharmacists across Europe, showed that only half of the participating health care professionals ask patients with chronic conditions

TABLE 4. Summary of Select Pharmacologic and Nonpharmacologic Strategies to Mitigate Some of the Most Prevalent and Disturbing Side Effects of Endocrine Therapy

	Management Strategy	
Side Effect	**Pharmacologic**	**Nonpharmacologic**
Musculoskeletal symptoms	Switching strategy duloxetine	Physical activity
		Acupuncture
Vasomotor symptoms (hot flashes)	Antidepressants	Cognitive behavioral therapy
	SSRIs (citalopram, escitalopram, sertraline)	Hypnosis
	SNRIs (venlafaxine)	
	Anticonvulsants (gabapentin and pregabalin)	
	Oxybutynin	
Sexual dysfunction (other than vulvovaginal symptoms)	Switch from AI + OFS to tamoxifen ± OFS	Cognitive behavioral therapy
	Switch from tamoxifen + OFS to tamoxifen alone	
	If patient is on antidepressants that can affect sexual function (e.g., SSRI and SNRI), switch to antidepressants that may be less likely to cause sexual side effects (e.g., mirtazapine)	
Vulvovaginal symptoms (vaginal dryness/ dyspareunia)	Moisturizers	Laser therapy**
	Lubricants	
	Lidocaine	
	Switch from AI + OFS to tamoxifen + OFS or tamoxifen alone	
	Vaginal low-dose estrogen (estradiol)*	
Fatigue	—	Physical activity
		Cognitive behavioral therapy
Weight gain	—	Physical activity
		Diet
		Cognitive behavioral therapy

Abbreviations: AI, aromatase inhibitor; OFS, ovarian function suppression; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

*Use of vaginal low-dose estrogen is not universally endorsed. Although data on efficacy on vulvovaginal symptoms are available, there are suggestions of increased levels of serum concentration of estrogen of unknown clinical significance, and there is no robust evidence of safety, particularly among women treated with AI. Therefore, their use should be thoroughly discussed on a case-by-case basis, including considering the risk of recurrence and gravity of symptoms. Vaginal estrogens should be reserved for women who are unresponsive to nonhormonal treatment. If estrogen-based treatment is warranted, duration should be limited in time. There are limited data that suggest minimal systemic absorption with rings and suppositories, which should be preferred over creams for survivors of hormonally sensitive tumors. Of note, use of other types of hormones such as testosterone and dehydroepiandrosterone should also be considered with caution in patients with hormonally sensitive tumors.[53,106]

**More efficacy/safety data required.

Adapted from Condorelli and Vaz-Luis[107]; Franzoi et al.[108]

about treatment adherence on a regular basis, and few of them reported the routine use of technology and/or other resources to maintain patients in treatment.[104] Finally, interventions to overcome barriers to adherence through mitigation of endocrine therapy side effects, which represent one of the primary cause of treatment discontinuation, are not sufficiently implemented.

Mitigating Side Effects of Endocrine Therapy to Preserve Quality of Life and Improve Adherence

One of the first randomized controlled trials of standard versus personalized care included personalized assessment, education, counseling, and interventions directed at severe menopausal symptoms. Results of this trial showed that the experimental arm was more effective in treating symptoms, suggesting that individualizing treatment options can be effective in managing side effects associated with endocrine therapy.[105] Over the following decades, several other randomized controlled trials have validated a number of pharmacologic and nonpharmacologic strategies to manage adverse side effects linked to endocrine therapy, confirming the importance of implementing individualized treatment options to address symptom burden related to endocrine therapy and impact on quality of life in clinical care.

Providing proactive management of side effects of endocrine therapy and assuring balance between quality of life preservation and treatment adherence are now considered core needs in survivorship care. Table 4 summarizes select pharmacologic and nonpharmacologic strategies to mitigate some of the most prevalent and disturbing side effects of endocrine therapy.

CONCLUSION

Improvements in risk stratification strategies and in adjuvant systemic therapy options in recent decades contributed to significant reductions in breast cancer recurrence and death. Premenopausal women with hormone receptor–positive, early-stage breast cancer often present with complex disease, require multimodality therapy, and overall suffer inferior survival outcomes compared with their postmenopausal counterparts. New tools to more precisely predict risk will allow clinicians to further individualize treatments, including the need for chemotherapy, type and duration of endocrine therapy, and to identify those who may need novel strategies. Personalized management of treatment-emergent side effects is also urgently needed to address patients' concerns and to improve quality of life, treatment adherence, and overall wellness.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000;406:747-752.
2. Hugh J, Hanson J, Cheang MCU, et al. Breast cancer subtypes and response to docetaxel in node-positive breast cancer: use of an immunohistochemical definition in the BCIRG 001 trial. J Clin Oncol. 2009;27:1168-1176.
3. Wallden B, Storhoff J, Nielsen T, et al. Development and verification of the PAM50-based Prosigna breast cancer gene signature assay. BMC Med Genomics. 2015;8:54.
4. Gnant M, Filipits M, Greil R, et al; Austrian Breast and Colorectal Cancer Study Group. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. Ann Oncol. 2014;25:339-345.
5. Jensen MB, Lænkholm AV, Nielsen TO, et al. The Prosigna gene expression assay and responsiveness to adjuvant cyclophosphamide-based chemotherapy in premenopausal high-risk patients with breast cancer. Breast Cancer Res. 2018;20:79.
6. Goldhirsch A, Winer EP, Coates AS, et al; Panel members. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013;24:2206-2223.

7. Partridge AH, Hughes ME, Warner ET, et al. Subtype-dependent relationship between young age at diagnosis and breast cancer survival. J Clin Oncol. 2016; 34:3308-3314.
8. Wishart GC, Bajdik CD, Dicks E, et al. PREDICT Plus: development and validation of a prognostic model for early breast cancer that includes HER2. Br J Cancer. 2012;107:800-807.
9. Michaelson JS, Chen LL, Bush D, et al. Improved web-based calculators for predicting breast carcinoma outcomes. Breast Cancer Res Treat. 2011; 128:827-835.
10. Karapanagiotis S, Pharoah PDP, Jackson CH, et al. Development and external validation of prediction models for 10-year survival of invasive breast cancer. Comparison with PREDICT and CancerMath. Clin Cancer Res. 2018;24:2110-2115.
11. Cuzick J, Dowsett M, Pineda S, et al. Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. J Clin Oncol. 2011;29:4273-4278.
12. Cuzick J, Dowsett M, Wale C, et al. Prognostic value of a combined ER, PgR, Ki67, HER2 Immunohistochemical (IHC4) score and comparison with the GHI recurrence score – results from TransATAC. Cancer Res. 2009;69:74.
13. Denkert C, Budczies J, von Minckwitz G, et al. Strategies for developing Ki67 as a useful biomarker in breast cancer. Breast. 2015;24(suppl 2):S67-S72.
14. Brown JR, DiGiovanna MP, Killelea B, et al. Quantitative assessment Ki-67 score for prediction of response to neoadjuvant chemotherapy in breast cancer. Lab Invest. 2014;94:98-106.
15. Dowsett M, Sestak I, Regan MM, et al. Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen receptor-positive breast cancer treated with 5 years of endocrine therapy: CTS5. J Clin Oncol. 2018;36:1941-1948.
16. Sestak I, Crager M, Cuzick J, et al. Validation of the clinical treatment score post 5 years (CTS5) in women with hormone receptor positive, HER2-negative, node-negative disease from the TAILORx study. Cancer Res. 2020;80 (suppl; abstr GS4-03).
17. Richman J, Ring A, Dowsett M, et al. Clinical validity of clinical treatment score 5 (CTS5) for estimating risk of late recurrence in unselected, non-trial patients with early oestrogen receptor-positive breast cancer. Breast Cancer Res Treat. 2021;186:115-123.
18. Lee J, Ahn SG, Cha C, et al. Validation of CTS5 in premenopausal breast cancer patients and the role of Ki67 among risk-stratification groups. Cancer Res. 2020; 80 (suppl; abstr P5-06-22).
19. Gradishar WJ, Anderson BO, Abraham J, et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020; 18:452-478.
20. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004;351:2817-2826.
21. Tang G, Shak S, Paik S, et al. Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: results from NSABP B-14 and NSABP B-20. Breast Cancer Res Treat. 2011;127:133-142.
22. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006;24:3726-3734.
23. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med. 2018;379:111-121.
24. Sparano JA, Gray RJ, Ravdin PM, et al. Clinical and genomic risk to guide the use of adjuvant therapy for breast cancer. N Engl J Med. 2019;380:2395-2405.
25. Sparano JA, Crager MR, Tang G, et al. Development and validation of a tool integrating the 21-gene recurrence score and clinical-pathological features to individualize prognosis and prediction of chemotherapy benefit in early breast cancer. J Clin Oncol. 2021;39:557-564.
26. Kalinsky K, Barlow WE, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/– chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25: SWOG S1007 (RxPonder). Cancer Res. 2021;81 (suppl; abstr GS3-00).
27. Bernhardt SM, Dasari P, Wrin J, et al. Discordance in 21-gene recurrence scores between paired breast cancer samples is inversely associated with patient age. Breast Cancer Res. 2020;22:90.
28. Bernhardt SM, Dasari P, Walsh D, et al. The menstrual cycle is an under-appreciated factor in premenopausal breast cancer diagnosis and treatment. Curr Opin Endocr Metab Res. 2020;15:37-42.
29. van 't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature. 2002;415:530-536.
30. van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med. 2002;347:1999-2009.
31. Buyse M, Loi S, van't Veer L, et al; TRANSBIG Consortium. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J Natl Cancer Inst. 2006;98:1183-1192.
32. Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol. 2021;22:476-488.
33. Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol. 2001;19:980-991.
34. Olivotto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. J Clin Oncol. 2005; 23:2716-2725.
35. Cardoso F, van 't Veer L, Poncet C, et al. MINDACT: Long-term results of the large prospective trial testing the 70-gene signature MammaPrint as guidance for adjuvant chemotherapy in breast cancer patients. J Clin Oncol. 2020;38(suppl 15):506.

36. Bartlett JMS, Sgroi DC, Treuner K, et al. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. Ann Oncol. 2019;30:1776-1783.

37. Noordhoek I, Treuner K, Putter H, et al. Breast cancer index predicts extended endocrine benefit to individualize selection of patients with HR+ early-stage breast cancer for 10 years of endocrine therapy. Clin Cancer Res. 2021;27:311-319.

38. Harris LN, Ismaila N, McShane LM, et al; American Society of Clinical Oncology. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2016;34:1134-1150.

39. Goetz MP, Gradishar WJ, Anderson BO, et al. Breast cancer, version 3.2018 featured updates to the NCCN guidelines. J Natl Compr Cancer Netw. 2019; 17:118-126.

40. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365:1687-1717.

41. Blum JL, Flynn PJ, Yothers G, et al. Anthracyclines in early breast Cancer: The ABC Trials—USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). J Clin Oncol. 2017;35:2647-2655.

42. Peto R, Davies C, Godwin J, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet. 2012;379:432-444.

43. Davies C, Godwin J, Gray R, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011;378:771-784.

44. Regan MM, Pagani O, Fleming GF, et al; GroupSOFT and TEXT Investigators. Adjuvant treatment of premenopausal women with endocrine-responsive early breast cancer: design of the TEXT and SOFT trials. Breast. 2013;22:1094-1100.

45. Francis PA, Regan MM, Fleming GF, et al; International Breast Cancer Study Group. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med. 2015;372:436-446.

46. Francis PA, Pagani O, Fleming GF, et al; SOFT and TEXT Investigators and the International Breast Cancer Study Group. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. N Engl J Med. 2018;379:122-137.

47. Pagani O, Regan MM, Francis PA. Are SOFT and TEXT results practice changing and how? Breast. 2016;27:122-125.

48. Pagani O, Regan MM, Walley BA, et al; International Breast Cancer Study Group. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med. 2014;371:107-118.

49. Pagani O, Francis PA, Fleming GF, et al; SOFT and TEXT Investigators and International Breast Cancer Study Group. Absolute improvements in freedom from distant recurrence to tailor adjuvant endocrine therapies for premenopausal women: results from TExT and Soft. J Clin Oncol. 2020;38:1293-1303.

50. Tailoring adjuvant endocrine therapy for premenopausal women: absolute improvements in freedom from distant recurrence with adjuvant endocrine therapies for premenopausal women with HR+/HER2- breast cancer, as investigated in the TEXT and SOFT clinical trials, according to composite risk. https://rconnect.dfci.harvard.edu/CompositeRiskSTEPP/. Accessed March 11, 2021.

51. Davies C, Pan H, Godwin J, et al; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013;381:805-816.

52. Gray RG, Rea D, Handley K, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. J Clin Oncol. 2013;31(suppl 15):5.

53. Vaz-Luis I, Partridge AH. Exogenous reproductive hormone use in breast cancer survivors and previvors. Nat Rev Clin Oncol. 2018;15:249-261.

54. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. J Clin Oncol. 2016;34:611-635.

55. Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2017;35:2062-2081.

56. Regan MM, Walley BA, Francis PA, et al. Concurrent and sequential initiation of ovarian function suppression with chemotherapy in premenopausal women with endocrine-responsive early breast cancer: an exploratory analysis of TEXT and SOFT. Ann Oncol. 2017;28:2225-2232.

57. Lambertini M, Moore HCF, Leonard RCF, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. J Clin Oncol. 2018;36:1981-1990.

58. Moore HCF, Unger JM, Phillips K-A, et al; POEMS/S0230 Investigators. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med. 2015;372:923-932.

59. Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36:1994-2001.

60. Lambertini M, Peccatori FA, Demeestere I, et al; ESMO Guidelines Committee. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2020;31:1664-1678.

61. Kim HA, Lee JW, Nam SJ, et al. Adding ovarian suppression to tamoxifen for premenopausal breast cancer: a randomized phase III trial. J Clin Oncol. 2020; 38:434-443.

62. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. J Clin Oncol. 2020; 38:1346-1366.

63. Smith IE, Dowsett M, Yap YS, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol. 2006;24:2444-2447.

64. Guerrero A, Gavilá J, Folkerd E, et al. Incidence and predictors of ovarian function recovery (OFR) in breast cancer (BC) patients with chemotherapy-induced amenorrhea (CIA) who switched from tamoxifen to exemestane. Ann Oncol. 2013;24:674-679.

65. Kurebayashi J, Shiba E, Toyama T, et al. A follow-up study of a randomized controlled study evaluating safety and efficacy of leuprorelin acetate every-3-month depot for 2 versus 3 or more years with tamoxifen for 5 years as adjuvant treatment in premenopausal patients with endocrine-responsive breast cancer. Breast Cancer. Epub 2021 Feb 27.

66. Pan H, Gray R, Braybrooke J, et al; EBCTCG. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med. 2017; 377:1836-1846.

67. Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Res Treat. 2016;160:347-360.

68. Lambertini M, Kroman N, Ameye L, et al. Long-term safety of pregnancy following breast cancer according to estrogen receptor status. J Natl Cancer Inst. 2018; 110:426-429.

69. Lambertini M, Ameye L, Hamy ASMP, et al. Pregnancy after breast cancer in patients with germline BRCA mutations. J Clin Oncol. 2020;38:3012-3023.

70. Poggio F, Tagliamento M, Pirrone C, et al. Update on the management of breast cancer during pregnancy. Cancers (Basel). 2020;12:3616.

71. Sun Z, Niman SM, Pagani O, et al; POSITIVE Steering Committee. Estimation of historical control rate for a single arm de-escalation study—application to the POSITIVE trial. Breast. 2020;53:1-7.

72. Dellapasqua S, Gray KP, Munzone E, et al; International Breast Cancer Study Group. Neoadjuvant degarelix versus triptorelin in premenopausal patients who receive letrozole for locally advanced endocrine-responsive breast cancer: a randomized phase II trial. J Clin Oncol. 2019;37:386-395.

73. Goldhirsch A, Gelber RD, Yothers G, et al. Adjuvant therapy for very young women with breast cancer: need for tailored treatments. J Natl Cancer Inst Monogr. 2001;2001:44-51.

74. Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). J Clin Oncol. 2005;23:5973-5982.

75. Ahn SH, Son BH, Kim SW, et al; Korean Breast Cancer Society. Poor outcome of hormone receptor-positive breast cancer at very young age is due to tamoxifen resistance: nationwide survival data in Korea—a report from the Korean Breast Cancer Society. J Clin Oncol. 2007;25:2360-2368.

76. Cardoso F, Kyriakides S, Ohno S, et al. Erratum: Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019; 30:1674.

77. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol. 2019;37:423-438.

78. Im S-A, Lu Y-S, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. N Engl J Med. 2019;381:307-316.

79. Johnston SRD, Harbeck N, Hegg R, et al; monarchE Committee Members and Investigators. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol. 2020;38:3987-3998.

80. Ribi K, Luo W, Bernhard J, et al. Adjuvant tamoxifen plus ovarian function suppression versus tamoxifen alone in premenopausal women with early breast cancer: patient-reported outcomes in the Suppression of Ovarian Function trial. J Clin Oncol. 2016;34:1601-1610.

81. Ferreira AR, Di Meglio A, Pistilli B, et al. Differential impact of endocrine therapy (ET) and chemotherapy (CT) on quality of life (QoL) of 4,262 breast cancer (BC) survivors: a prospective patient-reported outcomes (PRO) analysis. J Clin Oncol. 2019;37(suppl 15):512.

82. Wagner LI, Gray RJ, Sparano JA, et al. Patient-reported cognitive impairment among women with early breast cancer randomly assigned to endocrine therapy alone versus chemoendocrine therapy: results from TAILORx. J Clin Oncol. 2020;38:1875-1886.

83. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med. 2016;375:209-219.

84. Chlebowski RT, Kim J, Haque R. Adherence to endocrine therapy in breast cancer adjuvant and prevention settings. Cancer Prev Res (Phila). 2014;7:378-387.

85. Partridge AH, Wang PS, Winer EP, et al. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol. 2003;21:602-606.

86. Pistilli B, Paci A, Ferreira AR, et al. Serum detection of nonadherence to adjuvant tamoxifen and breast cancer recurrence risk. J Clin Oncol. 2020; 38:2762-2772.

87. Partridge AH, LaFountain A, Mayer E, et al. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. J Clin Oncol. 2008; 26:556-562.

88. Accordino MK, Hershman DL. Disparities and challenges in adherence to oral antineoplastic agents. Am Soc Clin Oncol Educ Book. 2013;271-276.

89. Chim K, Xie SX, Stricker CT, et al. Joint pain severity predicts premature discontinuation of aromatase inhibitors in breast cancer survivors. BMC Cancer. 2013; 13:401.

90. Henry NL, Azzouz F, Desta Z, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. J Clin Oncol. 2012;30:936-942.

91. Crew KD, Capodice JL, Greenlee H, et al. Pilot study of acupuncture for the treatment of joint symptoms related to adjuvant aromatase inhibitor therapy in postmenopausal breast cancer patients. J Cancer Surviv. 2007;1:283-291.

92. Bender CM, Gentry AL, Brufsky AM, et al. Influence of patient and treatment factors on adherence to adjuvant endocrine therapy in breast cancer. Oncol Nurs Forum. 2014;41:274-285.

93. Wickersham KE, Sereika SM, Bender CM. Pretreatment predictors of short-term nonadherence to oral hormonal therapy for women with breast cancer. Nurs Res. 2013;62:243-251.

94. Schover LR, Baum GP, Fuson LA, et al. Sexual problems during the first 2 years of adjuvant treatment with aromatase inhibitors. J Sex Med. 2014; 11:3102-3111.

95. McCowan C, Shearer J, Donnan PT, et al. Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. Br J Cancer. 2008;99:1763-1768.

96. Chirgwin JH, Giobbie-Hurder A, Coates AS, et al. Treatment adherence and its impact on disease-free survival in the Breast International Group 1-98 trial of tamoxifen and letrozole, alone and in sequence. J Clin Oncol. 2016;34:2452-2459.

97. Hershman DL, Shao T, Kushi LH, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat. 2011;126:529-537.

98. Hadji P, Blettner M, Harbeck N, et al. The Patient's Anastrozole Compliance to Therapy (PACT) Program: a randomized, in-practice study on the impact of a standardized information program on persistence and compliance to adjuvant endocrine therapy in postmenopausal women with early breast cancer. Ann Oncol. 2013;24:1505-1512.

99. Hershman DL, Unger JM, Hillyer GC, et al. Randomized trial of text messaging to reduce early discontinuation of adjuvant aromatase inhibitor therapy in women with early-stage breast cancer: SWOG S1105. J Clin Oncol. 2020;38:2122-2129.

100. Hurtado-de-Mendoza A, Cabling ML, Lobo T, et al. Behavioral interventions to enhance adherence to hormone therapy in breast cancer survivors: a systematic literature review. Clin Breast Cancer. 2016;16:247-255.e3.

101. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014; (11):CD000011.

102. Neven P, Markopoulos C, Tanner M, et al. The impact of educational materials on compliance and persistence rates with adjuvant aromatase inhibitor treatment: first-year results from the compliance of aromatase inhibitors assessment in daily practice through educational approach (CARIATIDE) study. Breast. 2014;23:393-399.

103. Rosenberg SM, Petrie KJ, Stanton AL, et al. Interventions to enhance adherence to oral antineoplastic agents: a scoping review. J Natl Cancer Inst. 2020; 112:443-465.

104. Clyne W, Mshelia C, McLachlan S, et al. A multinational cross-sectional survey of the management of patient medication adherence by European healthcare professionals. BMJ Open. 2016;6:e009610.

105. Ganz PA, Greendale GA, Petersen L, et al. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. J Natl Cancer Inst. 2000;92:1054-1064.

106. ACOG Committee Opinion No. 659: the use of vaginal estrogen in women with a history of estrogen-dependent breast cancer. Obstet Gynecol. 2016; 127:e93-e96.

107. Condorelli R, Vaz-Luis I. Managing side effects in adjuvant endocrine therapy for breast cancer. Expert Rev Anticancer Ther. 2018;18:1101-1112.

108. Franzoi MA, Agostinetto E, Perachino M, et al. Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer. Lancet Oncol. Epub 2021 Apr 20.

BREAST CANCER

Harnessing Nutrition and Physical Activity for Breast Cancer Prevention and Control to Reduce Racial/Ethnic Cancer Health Disparities

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Overview

There are well-known racial/ethnic disparities in the prevalence of obesity and physical inactivity, as well as breast cancer risk and survival. However, most of the current scientific evidence that serves as a foundation for nutrition and physical activity guidelines is based on studies conducted in predominantly non-Hispanic White populations. Similarly, exercise, diet, or lifestyle intervention trials for breast cancer prevention and survivorship are scarce in racial/ethnic minority populations. We review the current evidence for racial/ethnic disparities in obesity and breast cancer risk and survival (we are focusing on obesity, because this is considered an ASCO priority, and studies conducted in the United States), discuss the evolution of nutrition/physical activity guidelines for cancer prevention and control, and provide an overview of lifestyle interventions, including barriers and facilitators in implementation and dissemination science among minority populations underrepresented in research. There is a critical need to include racially/ethnically diverse populations in cancer prevention and control research or to specifically target minority populations in which disparities are known to exist to achieve much needed health equity.

INTRODUCTION

Worldwide, female breast cancer has now surpassed lung cancer as the leading cause of cancer incidence and mortality among females, representing 24.5% of all cancer cases and 15.5% of all cancer deaths.[1] Incidence rates are higher in countries with greater socioeconomic development, reflecting the higher prevalence of hormonal, reproductive, and lifestyle risk factors for breast cancer, as well as more access to mammographic screening.[1] Because lifestyle factors are potentially modifiable, they are particularly important in cancer prevention and control.

Obesity, defined as body mass index (BMI) of at least 30 kg/m^2, has a major impact across the breast cancer continuum, because it has been associated with an increased risk for postmenopausal breast cancer, delays in diagnosis, more complications related to surgery and radiation, possible reduction in chemotherapy dosing, and reduction in efficacy of chemotherapy and endocrine therapy in obese patients with breast cancer, as well as worse survival.[2,3] Among the growing population of breast cancer survivors, obesity has also been shown to have a negative impact on patient-reported outcomes, including health-related quality of life, fatigue, and lymphedema.[3,4] As such, ASCO's 2020 *Annual Report on Progress Against Cancer* identified, as a research priority area, the role of obesity in cancer incidence and outcomes, including improving our understanding of its role in cancer development and progression and underlying biologic mechanisms, as well as identifying effective interventions in people at risk and who are living with cancer.[5]

In addition to obesity, higher levels of physical activity have been shown to reduce breast cancer risk[6,7] and improve survival after a breast cancer diagnosis[8] in pre- and postmenopausal women. Maintaining a healthy weight and an active lifestyle are part of the current nutrition and physical activity recommendations for cancer prevention, which also include avoiding alcohol and sugary drinks and eating a healthy diet that emphasizes whole grains, vegetables, fruit, and beans and minimizes red and processed meat, fast foods, and other processed foods high in fat, starches, or sugars.[9] Adherence to these guidelines has been shown to be associated with a reduction in breast cancer risk.[10] It is generally recommended that cancer survivors follow nutrition and physical activity guidelines for cancer prevention after consulting with their health care providers.[11,12] However, these guidelines are based on the currently available scientific evidence, which comes from studies conducted predominantly in non-Hispanic White populations.

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PRACTICAL APPLICATIONS

- Obesity, unhealthy dietary patterns, and physical inactivity, which disproportionately affect minority populations, have been shown to have a major impact on outcomes across the breast cancer continuum.
- Efforts to promote a healthy lifestyle by following the current nutrition and physical activity guidelines, including maintaining a healthy weight, regular exercise, and a healthy diet, are likely to have a major impact in cancer prevention, as well as result in better quality of life and survival after a breast cancer diagnosis.
- Exercise, diet, or lifestyle intervention trials for breast cancer prevention and survivorship are scarce in racial/ethnic minority populations, and potential barriers and facilitators to intervention delivery and participation have been identified.
- Culturally tailored energy balance interventions must seek to promote healthy lifestyle behaviors among minority populations to improve treatment and health outcomes.

Here, we review the current evidence for racial/ethnic disparities in obesity and breast cancer risk and survival (we are focusing on obesity because this is considered an ASCO priority), discuss the evolution of nutrition/physical activity guidelines for cancer prevention and control, and provide an overview of lifestyle interventions, including barriers and facilitators in implementation and dissemination science among minority populations underrepresented in research. Specifically, we focus our review on studies in African American/Black women (referred to hereafter as Black women), Hispanic women, and Asian women in the United States, with the caveat that these are heterogeneous groups; Pacific Islanders, American Indians, and Alaska natives are not included given the limited research in these populations.

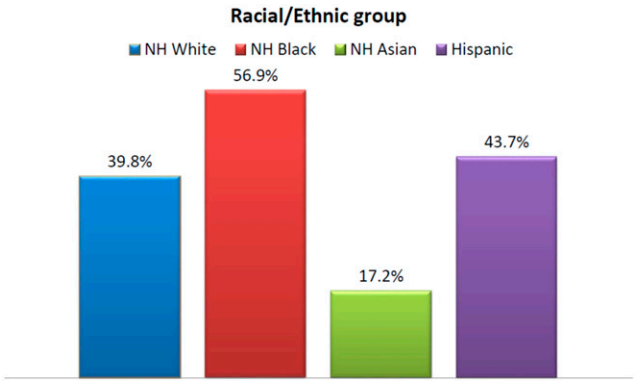

FIGURE 1. Age-Adjusted Prevalence of Obesity Among U.S. Females Age 20 and Older, by Race and Hispanic Origin (2017–2018)[15]
Estimates were age adjusted by the direct method to the 2000 U.S. Census population using the age groups 20 to 39, 40 to 59, and 60 and older.
Abbreviation: NH, non-Hispanic.

RACIAL/ETHNIC DISPARITIES IN OBESITY AND BREAST CANCER RISK AND SURVIVAL

In the United States, there are known racial/ethnic disparities in breast cancer incidence and mortality.[13] Although incidence rates are similar for non-Hispanic White women and Black women, death rates are higher for Black women compared with all other racial/ethnic groups; the lowest incidence and death rates are seen for Asian/Pacific Islander women.[14] Five-year survival rates are lowest for Black women compared with all other racial/ethnic groups, regardless of stage of diagnosis or hormone receptor subtype.[14] The causes for higher death rates in Black women after a diagnosis of breast cancer are likely multifactorial and include being diagnosed with more advanced and aggressive tumors, less access to care, and a higher prevalence of obesity and related comorbidities.[14] Since 2004, the overall incidence of breast cancer has been increasing for estrogen receptor $(ER)^+$ breast cancer, whereas rates for ER^- breast cancer have been decreasing; this has been attributed to increases in obesity rates and decreases in fertility.[14]

The high prevalence of obesity is a major public health concern, and it disproportionately affects non-Hispanic Black women (57%) and Hispanic women (44%; Fig. 1).[15] Body mass index is widely used, and its high correlation with adiposity makes it a useful public health tool, but it has limitations because it cannot capture body fat distribution or body composition.[16,17] Waist circumference and waist-to-hip ratio are commonly collected in epidemiologic studies, along with BMI, as measures of central adiposity and proxy of visceral fat, which is more strongly associated with insulin resistance and metabolic syndrome.[17] Central obesity (waist circumference $>$ 88 cm) is also highest in non-Hispanic Black (74%) and Hispanic (75%) women, with a marked increasing trend in prevalence among Hispanic women.[18] Complex interrelated factors explain the obesity epidemic, including policy, environmental factors (e.g., food supply and marketing, built environment), behavioral patterns (poor diets, sedentary lifestyles), and genetic predisposition,[17] and these vary across populations. Such racial/ethnic disparities in obesity burden were also observed among women with a history of cancer, with breast cancer survivors specifically having a faster increase in obesity prevalence compared with adults without a history of cancer.[19]

Current epidemiologic evidence for the impact of obesity on breast cancer risk and survival in minority and underrepresented populations is discussed in the following sections.

Obesity and Female Breast Cancer Risk: Current Evidence

There is strong evidence that higher BMI, greater central adiposity (waist circumference and waist-to-hip ratio), and weight gain during adulthood increase the risk of postmenopausal breast cancer.[20-22] Based on evidence from 75 cohort studies identified in the World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project, a 5-kg/m^2 increase in BMI and a 10-cm increase in waist circumference was associated with a 12% and 11% increased risk after menopause, respectively.[6] For premenopausal breast cancer, greater BMI is associated with a lower risk,[6,23] whereas waist circumference and waist-to-hip ratio are positively associated with risk when adjusting for BMI.[6] However, the evidence for pre- and postmenopausal breast cancer risk has largely come from studies among non-Hispanic White women. Considering the racial and ethnic differences in body fat distribution and body composition,[24] breast cancer subtypes,[13] and risk factor profiles,[25,26] it is critical to understand the impact of obesity on breast cancer risk by racial/ethnic groups and tumor subtypes.

Obesity and breast cancer risk among U.S. Black women
Among studies reporting on the association with postmenopausal breast cancer risk among Black women,[27-32] the majority did not find notable associations with obesity.[28-31] However, there is some suggestion of a positive association between recent BMI (approximately 1–5 years prior to diagnosis) and ER$^+$ or ER$^+$ and progesterone receptor$^+$ postmenopausal breast cancer risk,[28,30] as well as a suggestion of an inverse association with ER$^-$ or ER$^-$/progesterone receptor$^-$[28-30,33] and triple-negative breast cancer after menopause,[28] based on individual studies and the African American Breast Cancer Epidemiology and Risk consortium,[28] which pooled data from four studies.[29,31,33,34] In that consortium, the risk of postmenopausal ER$^+$ breast cancer was greatest among women with a recent high BMI but who were lean as young adults, and it was positively associated with greater waist-to-hip ratio.[28] The risks of postmenopausal ER$^-$ and triple-negative breast cancer were also elevated among women with greater waist-to-hip ratio.[28]

Different from the finding among predominantly non-Hispanic White women, studies among Black women found mostly null associations between adult BMI and premenopausal breast cancer risk[28-30,32,33,35,36] and across tumor subtypes.[28-30,33,36,37] Although the statistical power became limited for subtype analysis, most studies supported a positive association between waist-to-hip ratio and breast cancer risks for hormone receptor$^+$ and hormone receptor$^-$ tumors, including triple-negative breast cancer, among premenopausal women.[28,29,33,36]

Obesity and breast cancer risk among U.S. Hispanic women
Few studies have evaluated the impact of obesity on breast cancer risk among Hispanic women.[38] For postmenopausal breast cancer, although there were no associations detected with BMI and obesity among U.S. Hispanic women,[39,40] one study found an elevated risk in U.S.-born, but not foreign-born, Hispanic women.[27] To our knowledge, the Breast Cancer Health Disparities Study,[41,42] which pooled data from two case-control studies,[35,39] is the only study that evaluated the associations by hormone receptor status and reported null associations with ER$^+$/progesterone receptor$^+$ and ER$^-$/progesterone receptor$^-$ breast cancer when comparing non-Hispanic White and Hispanic women.[42] No study has evaluated the association with the risk of triple-negative breast cancer among U.S. Hispanic women; this subtype is more common among them compared with non-Hispanic White women.[13,43] The Breast Cancer Health Disparities Study also evaluated the associations by hormone receptor status with weight gain during adult life and central adiposity and reported a positive association between weight gain and ER$^+$/progesterone receptor$^+$ tumors among women not using menopausal hormone therapy.[42]

Based on the limited evidence available among U.S. Hispanic women, adult BMI is associated with a lower risk for ER$^-$/progesterone receptor$^-$ and/or ER$^-$/progesterone receptor$^-$ premenopausal breast cancer,[35,41] but greater waist circumference and waist-to-hip ratio increased the premenopausal tumor risk after controlling for BMI.[41] Weight gain is not associated with risk before menopause in most studies.[35,39-41]

Obesity and breast cancer risk among U.S. Asian women
Increases in body weight after immigration and acculturation are thought to contribute to the higher incidence of breast cancer among Asian women living in the United States versus those living in Asia.[44-46] For postmenopausal breast cancer, greater BMI is associated with a higher risk among Asian Americans,[34,47,48] but no study evaluated subtype-specific associations. In the Multiethnic Cohort Study, being obese and experiencing weight gain during adulthood had a more pronounced risk in Japanese Americans compared with other racial/ethnic groups.[27,34] Only one study has evaluated the relationship between postmenopausal breast cancer and waist-to-hip ratio among Asian Americans; it found a positive association.[47]

For premenopausal breast cancer, the evidence with BMI has been inconsistent among Asian Americans.[47,48] A meta-analysis, including nine studies in Asian countries and one study of Asian Americans, suggested that adult BMI was associated with a higher risk before menopause, which is

different from the inverse association observed among non-Hispanic White women.[49] Greater waist-to-hip ratio was also reported to increase the risk of premenopausal breast cancer.[49]

Obesity and Breast Cancer Survival

Fewer studies have evaluated the impact of obesity on breast cancer prognosis, but there is growing evidence that higher BMI before and after diagnosis is associated with higher breast cancer–specific and overall mortality in pre- and postmenopausal women.[50] Only a handful of studies have evaluated associations by hormone receptor subtype and most have limited statistical power, particularly for ER^- and triple-negative breast cancer. Although the evidence tends to be stronger for hormone receptor $^+$ breast cancer, a recent meta-analysis found that obesity was associated with worse disease-free survival and overall survival for all subtypes, including $HER2^+$ and triple-negative breast cancer.[51] The effect of central adiposity, measured as waist-to-hip ratio or waist circumference, on breast cancer mortality has received little attention, but a meta-analysis based on four studies found elevated mortality for those with high waist-to-hip ratio.[11] Weight changes after diagnosis are particularly important among survivors. Weight gain, particularly 10% or greater,[52] and weight loss (5% or greater) after a breast cancer diagnosis have been associated with worse survival. Unintentional weight loss is particularly important to assess, because it may reflect cancer cachexia associated with advanced disease or sarcopenia/muscle wasting[3]; however, these data have rarely been collected in epidemiologic studies.

Few studies have evaluated the association of obesity and/or central obesity by race/ethnicity. In the Multiethnic Cohort study, analyses including all women showed higher cancer-specific and overall mortality for obese women, but analyses stratified by race/ethnicity did not show a noteworthy interaction, although power for these analyses was very limited.[53] The CARE Study compared the impact of prediagnosis BMI on breast cancer survival in non-Hispanic White and Black women; higher disease-specific mortality and overall mortality were found only for non-Hispanic White women.[54] To our knowledge, the California Breast Cancer Survivorship Consortium is the only study evaluating the impact of BMI and waist-to-hip ratio by race/ethnicity, pooling data from six studies.[55] For overall survival, a BMI of at least 40 kg/m^2 was associated with worse survival among non-Hispanic White and Latina women, whereas a higher waist-to-hip ratio (comparing fourth vs. first quartile) was associated with worse survival in Black and Asian American women. Overall, these findings seem to suggest differential effects by race/ethnicity that could be due to differences in body composition that is not captured by BMI.

Summary

In summary, excess body fat increases the risk of breast cancer, at least in postmenopausal women, and it has detrimental effects on prognosis in pre- and postmenopausal women. Whether these associations vary by race/ethnicity after controlling for all relevant factors, such as socioeconomic status, access to care, and tumor clinicopathologic characteristics, remains unclear and warrants further investigation.

INTERNATIONAL GUIDELINES FOR EXERCISE, DIET, AND ALCOHOL FOR CANCER PREVENTION AND SURVIVORSHIP

To improve exercise and dietary behaviors that can prevent cancer and improve survivorship, international attention has been given to using the evidence base to create clinical guidelines that can facilitate healthy behavior change. Depending on the focus of the organization creating the guidelines, they can be patient facing or clinician facing. These guidelines have been evolving over time as the evidence base matures. With rare exceptions, guidelines are written for cancer prevention or cancer survivorship across cancer types. Below, we articulate the current state of international guidelines of which we are aware for exercise and for diet and alcohol consumption as related to cancer prevention and cancer surviorship. We also highlight how these guidelines have evolved over time and provide some examples of new research that suggests how guidelines will change in the future. We focused our search and our discussion on official publications from organizations that make such guidelines (Tables 1 and 2); we did not include the many other examples of guidance/recommendations that exist on various organization websites or in the literature that are not formal guidelines. As mentioned earlier, these guidelines are based on the currently available scientific evidence, which is largely from studies conducted in non-Hispanic White populations. It is unknown whether more tailored guidelines that are specific to the needs of racial/ethnic subgroups are needed. However, implementation may vary according to cultural preferences and food/exercise access.

Guidelines for Cancer Prevention

Physical activity and cancer prevention Current guidelines for physical activity as related to the prevention of cancer in the United States (Table 1) mirror the broader recommendations for healthy adults outlined in the *Physical Activity Guidelines for Americans, 2nd edition*.[57] These guidelines, updated in 2018, reflect a growing body of evidence supporting the health benefits of physical activity to reduce the risk of chronic diseases, including cancer. They consist of a combination of aerobic exercise (150–300 minutes of moderate physical activity per week, or 75 to 150 minutes of vigorous activity per week, or an equivalent combination of both), together with at least 2 days of muscle-strengthening activities, also known as resistance exercise. International guidelines from the World Cancer Research Fund/American Institute for Cancer Research are

TABLE 1. Physical Activity Guidelines for Cancer Prevention and Survivorship

Organization	Aerobic Exercise	Resistance Exercise	Endorsing Organization
Prevention			
American Cancer Society (2020)[56]	• 150-300 minutes of moderate-intensity exercise per week, or 75–150 minutes of vigorous-intensity exercise per week, or an equivalent combination • More than 300 minutes is optimal	• Not included	
U.S. Department of Health and Human Services (2018)[57]*	• At least 150–300 minutes of moderate-intensity exercise per week, or 75–150 minutes of vigorous-intensity exercise per week, or an equivalent combination	• At least 2 days per week of muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups	• Centers for Disease Control and Prevention[58] • National Cancer Institute[59]
World Cancer Research Fund/American Institute for Cancer Research (2018)[9]	• Be physically active; walk more and sit less • At least 150 minutes of moderate-intensity exercise per week, or 75–150 minutes of vigorous-intensity exercise per week, or an equivalent combination	• Not included	
Survivorship			
American College of Sports Medicine (2019)[60]	• 150 minutes of moderate-intensity exercise per week, or 75 minutes of vigorous-intensity exercise per week, or an equivalent combination • Specific guidelines for various health-related outcomes are available	• 2 or 3 weekly sessions that include exercises for major muscle groups • Specific guidelines for various health-related outcomes are available	• 15 organizations worldwide**
American Heart Association (2019)[61]	• Individualized exercise prescription in addition to diet and cardiovascular risk assessment, based on cardiovascular risk-based algorithm	• Individualized resistance exercise prescription	• American Cancer Society
Exercise and Sports Science Australia (2019)[62]	• At least moderate-intensity exercise involving large muscle groups lasting a minimum of 20 minutes • Exercise should be spread across the week, avoiding 2 consecutive days with no planned exercise • Allowing for variation in intensity	• Moderate- to high-intensity exercise with higher-volume load at least 2 days per week • Incorporating dynamic exercises using machines, free weights, body weight, or resistance bands	
World Cancer Research Fund/American Institute for Cancer Research (2018)[9]	• Be physically active; walk more and sit less • At least 150 minutes of moderate-intensity exercise per week, or 75–150 minutes of vigorous-intensity exercise per week, or an equivalent combination	• Not included	
American Cancer Society (2012)[12]	• Avoid inactivity and return to normal daily activities as soon as possible following diagnosis • At least 150 minutes per week	• At least 2 days per week	• ASCO (breast cancer survivorship)[63]

*Generic guidelines for adults and adults with chronic conditions, including cancer.

**American College of Sports Medicine, American Cancer Society, American Academy of Physical Medicine and Rehabilitation and Foundation for Physical Medicine and Rehabilitation, American Physical Therapy Association and Academy of Oncologic Physical Therapy of the American Physical Therapy Association, American College of Lifestyle Medicine, Canadian Society for Exercise Physiology, Centers for Disease Control and Prevention, Commission on Accreditation of Rehabilitation Facilities, Exercise and Sports Science Australia, German Union for Health Exercise and Exercise Therapy, MacMillan Cancer Support, National Comprehensive Cancer Network, Royal Dutch Society for Physical Therapy, Society for Behavioral Medicine, and Sunflower Wellness.

TABLE 2. Diet and Alcohol Guidelines for Cancer Prevention and Survivorship

	Diet			
Organization	**Encouraged**	**Discouraged**	**Alcohol**	**Endorsing Organization**
Prevention				
American Cancer Society (2020)[56]	• Foods that are high in nutrients in amounts that help you get to and stay at a healthy body weight • Variety of vegetables: dark green, red, and orange; fiber-rich legumes; and others • Fruits, especially whole fruits in a variety of colors • Whole grains	• Red and processed meats • Sugar-sweetened beverages • Highly processed foods and refined grain products	• Best not to drink • No more than one drink per day for women or two drinks per day for men	
U.S. Department of Agriculture and Health and Human Services (2020)[64],*	• Vegetables of all types: dark green, red and orange; beans, peas, and lentils; starchy; and other vegetables • Fruits, especially whole fruit • Grains, at least half of which are whole grain • Dairy, including fat-free or low-fat milk, yogurt, and cheese, and/or lactose-free versions and fortified soy beverages and yogurt as alternatives • Protein foods, including lean meats, poultry, and eggs; seafood; beans, peas, and lentils; and nuts, seeds, and soy products • Oils, including vegetable oils and oils in food, such as seafood and nuts	• Added sugars: < 10% of calories per day • Saturated fat: < 10% of calories per day • Sodium: < 2,300 mg per day	• Best not to drink or drink in moderation • Limiting intake to two drinks or less in a day for men and one drink or less in a day for women	• Centers for Disease Control and Prevention[65]
Survivorship				
World Cancer Research Fund/American Institute for Cancer Research (2018)[9]	• Diet rich in whole grains, vegetables, fruit, and beans • Whole grains, vegetables, fruit, and pulses (legumes) as a major part of usual day's diet	• Fast foods and processed foods high in fat, starches, and sugars • Red and processed meats • Sugar-sweetened drinks	• Best not to drink	
European Society for Clinical Nutrition and Metabolism (2017)[66]	• Diet based on vegetables, fruits, and whole grains	• Saturated fat • Red meat	• Low alcohol consumption	
American Cancer Society (2012)[12]	• Foods from plant sources, fruits, and whole grains	• Processed and red meats		• National Comprehensive Cancer Network[67] • ASCO (breast cancer survivorship)[63]

*Generic guidelines for adults and adults with chronic conditions, including cancer, endorsed by cancer organizations.

similar to those in the United States, but they do not include resistance exercise.[9]

American Cancer Society guidelines for cancer prevention, updated in 2020, differ slightly from the broader recommendations.[56] As had been the case with the American Cancer Society guidelines from 2012, aerobic exercise is the key target of its guidelines, but with a new directive that achieving or exceeding the upper limit of 300 minutes of moderate-to-vigorous physical activity is ideal. This is based on emerging research showing a relationship between higher levels of moderate-to-vigorous physical activity and a lower risk for cancer.[57] A further distinction from the general guidelines is that the American Cancer Society does not include resistance training in its recommendations, stating insufficient evidence on its direct role in cancer prevention to warrant inclusion.

Limiting sedentary behavior is noted across guidelines as relevant to cancer prevention, but quantitative evidence on this relationship is still limited.[68,69] Future guidelines are expected to include specific details on the association between sedentary bouts and overall sedentary time and cancer risk. Most guidelines include the important reminder that any physical activity above usual activity, no matter the individual's current activity level, is likely to have health benefits.[9,56,57]

Diet, alcohol, and cancer prevention A notable evolution in guidelines on diet and cancer prevention is the continued shift away from a "nutrient-centric" approach to one that focuses on dietary patterns (Table 2). Current American Cancer Society recommendations advocate adhering to a "healthy eating pattern" at all ages.[56] This entails a diet that includes nutrient-rich foods, such as fruit and vegetables (in a variety of colors), legumes, and whole grains, while limiting or completely avoiding processed and red meats, highly processed foods, and sugar-sweetened beverages. The *Dietary Guidelines for Americans, 2020-2025*,[64] while also endorsing this movement toward dietary patterns, still include specific recommendations for sugar, salt, and saturated fat intake (e.g., keep saturated fat less than 10% of overall calories). It is recommended that alcohol be avoided completely to minimize cancer risk; however, in those who decide to drink, a limit of one drink per day for women and two drinks per day for men is advised.

Another emerging trend in guidelines is to consider diet and exercise in the context of weight control. Relating to physical activity and dietary behaviors, the World Cancer Research Fund/American Institute for Cancer Research and American Cancer Society guidelines recommend the maintenance of a healthy body weight throughout life to reduce the risk of cancer.[56]

Guidelines for Cancer Survivorship

Exercise and cancer survivorship Cancer survivors face diverse issues that affect their need for and ability to participate in exercise. This heterogeneity differs by cancer and treatment type and by timing during versus postcancer treatment. Guidelines for exercise among cancer survivors have not been tailored to address this heterogeneity in the past. As shown in Table 1, guidelines from the American Cancer Society (2012)[12] and others have largely followed the public health guidance to avoid inactivity and engage in 150 minutes of aerobic activity per week and at least 2 days of strength training per week. More recent guidelines from the World Cancer Research Fund/American Institute for Cancer Research (2018),[9] Exercise and Sports Science Australia (2019),[62] and the American College of Sports Medicine (2019)[60] have refined the prescription of exercise to account for individual preferences for intensity (e.g., the aerobic component may be met through 150 minutes of moderate-intensity exercise or 75 or more minutes of vigorous exercise weekly), and Exercise and Sports Science Australia and the American College of Sports Medicine provide more specificity on strength training volume. The Exercise and Sports Science Australia guidelines also provide detailed considerations for tailoring exercise prescriptions for patients with certain toxicities and ongoing issues. The American College of Sports Medicine guidelines in 2019 was a major evolution in tailoring these guidelines for specific survivors and has been officially endorsed by 15 organizations across the globe. For the first time, these guidelines include specific evidence-based guidance for exercise prescription based on different health-related outcomes (e.g., fatigue, physical function, bone health), for different survivor populations (e.g., older adults, those with an ostomy, those who received stem cell transplantation), and the most effective setting for the exercise (supervised, home based). Personalizing exercise prescription is the focus of many ongoing studies, so these guidelines are expected to become more tailored in the future. There is increasing interest in differentiating survivors who need exercise delivered by cancer rehabilitation clinicians versus in other supervised, community, or home settings.[70] Current research is also focusing on exercise delivered prior to treatment (e.g., prehabilitation),[71] on other types of exercise such as yoga and Pilates, and on exercise delivered along with dietary modification for weight control (e.g., the National Cancer Institute–funded BWEL trial).[72] New guidelines from the American Heart Association provide a more personalized prescription for cancer survivors at high risk for cardiac dysfunction.[61] These guidelines recommend varied exercise prescription plus nutritional counseling and cardiovascular risk factor assessment according to a risk-based algorithm.[61]

Diet, alcohol, and survivorship Dietary intake during cancer treatment may need adjustment to deal with individual patient issues, such as oral mucositis, nausea, or other toxicities; recipe books and other guidance exist from the

National Cancer Institute,[73] the American Cancer Society,[74] and many others globally to help patients experiment with what works for them. As shown in Table 2, we are aware of only three guidelines that specifically focus on dietary intake for survivors, including recent guidelines from the World Cancer Research Fund/American Institute for Cancer Research (2018)[9] and the European Society for Clinical Nutrition and Metabolism (2017),[66] as well as older guidelines from the American Cancer Society (2012)[12]; updated American Cancer Society guidelines are expected to be released in 2021. These guidelines follow the same guidance as for the general population and highlight the importance of a healthy dietary pattern rather than focusing on individual nutrients. They emphasize eating a diet rich in plants (vegetables, fruits, whole grains, and legumes) and low in processed foods, red and processed meats, and sugar-sweetened beverages. Guidelines have always suggested limiting alcohol consumption; the most recent World Cancer Research Fund/American Institute for Cancer Research guidelines recommend that it is "best not to drink."[54] The importance of limiting alcohol has recently been highlighted in a statement by ASCO[75] that also underscores the need to address alcohol use in minority populations who have increasing rates of alcohol abuse. The effects of specific diets (e.g., intermittent fasting, protein supplementation, ketogenic, heavy macronutrient) on the gut microbiome and on cancer treatment efficacy, recovery, and long-term health are areas of active research. Future guidelines may address these issues, as the data in those topics continue to grow.

LIFESTYLE INTERVENTIONS FOR UNDERSERVED MINORITY WOMEN BEFORE AND AFTER A DIAGNOSIS OF BREAST CANCER

In recent years, energy balance research[76] has evolved to address efficacy of interventions on physical, physiologic, and psychosocial health outcomes in women before and after breast cancer diagnosis, whereby exercise oncology research has expanded to include novel exercise approaches, prognostic outcomes, and targeting of rare diseases. Nonetheless, a substantial void exists in the inclusion and focus on diverse populations, because most studies have included primarily non-Hispanic White populations. Overall, racial and ethnic minority women are less physically active, and, especially, the Black and Hispanic populations have higher rates of comorbid conditions and poorer cancer survivorship compared with their non-Hispanic White counterparts.[77-85] Similarly, although Asian Americans are the fastest growing racial group in the United States and their risk for developing breast cancer has been increasing, they are the least likely to exercise compared with other racial/ethnic groups, and their traditionally fruit- and vegetable-rich diet is replaced with a "Westernized" diet that is associated with obesity-related cancers.[46,86-88] Therefore, these populations could benefit substantially from structured nutrition and exercise programs.

Exercise Interventions

Cancer prevention exercise trials among racially/ethnically diverse populations, although sparse, have primarily focused on Black women at high risk for breast cancer. Dash et al reported marked improvements in metabolic syndrome following a 6-month home-based or supervised aerobic exercise program for postmenopausal obese and metabolically unhealthy Black women between age 45 and 65.[89] Adequately powered randomized controlled trials are lacking to assess whether exercise interventions reduce the risk of breast cancer among underserved minority women.

Similar to cancer prevention trials, few studies have evaluated the effect of exercise on health outcomes in minority cancer survivors. Most research has focused on physical fitness and psychosocial health, with reported improvements in weekly physical activity levels, cardiorespiratory fitness, muscle strength measures, functional movement, total quality of life, and fatigue in Black breast cancer survivors after completion of exercise, most often aerobic exercise.[90] For instance, a walking-based aerobic exercise intervention among Black breast cancer survivors achieved 92% adherence while improving total daily step count.[91] Influential factors that may have contributed to this success include the utilization of community- and church-based centers to conduct exercise, as well as curriculum describing benefits and barriers to exercise, the relationship among health and cancer risk and exercise, and personal assessments and problem-solving sessions for motivation. Hispanic breast cancer survivors are severely underrepresented in aerobic exercise trials, with no known studies to date having targeted this population. Also, high-intensity interval training was deemed feasible among patients with breast cancer receiving anthracycline chemotherapy, which included 73% patients who self-identified as Hispanic.[92] There were no cultural or behavioral aspects to supplement this study; however, adherence rates remained positive at 82.3%, reflecting all participants.[92] Notably, no exercise trials in Asian American women exist, other than one study examining a culturally tailored lifestyle intervention (e.g., physical activity and diet) in Chinese American cancer survivors.[85]

In relation to exercise modality, no trial to date has focused solely on resistance exercise among minority women, despite the well-documented physical, psychosocial, and physiologic benefits. One exercise strategy, which is often referred to as combination exercise, has been the subject of additional investigations. Combination exercise utilizes resistance and aerobic exercise and has been well received among cancer survivors across numerous studies, with a myriad of beneficial results, including improvements in

quality of life and physical fitness in breast cancer survivors[93] and patients with cancer presurgery,[94] increased bone health in female cancer survivors,[95] and improvements in postoperative outcomes in patients with cancer.[94] Combined exercise for Black breast cancer survivors included partnership with urban community centers for delivery of the intervention at home.[90,96] Supplementation to exercise occurred in the form of motivational,[90] cultural,[90] educational,[96] and social[96] components. Both studies elicited greater than 70% adherence, along with increased functional endurance,[96] cardiopulmonary fitness,[90] muscle strength,[91] and functional movement.[90] Combined exercise interventions focused on Hispanic cancer survivors' recorded outcomes such as minutes of physical activity.[97] Cultural tailoring included use of phone calls and newsletters in the native language. Mama et al used cultural intervention in the form of phone calls and newsletters to support home-based exercise; attendance of exercise sessions was 57.5%.[97] In addition, a 16-week supervised combined exercise intervention delivered in a clinical exercise research laboratory improved metabolic syndrome in a sample of 100 breast cancer survivors, of whom 57% self-identified as Hispanic. Despite the relatively large time commitment and lack of cultural tailoring, overall adherence was extremely high at 95%,[98] and Hispanic participants improved their relative metabolic profile more than did non-Hispanic participants.[99]

In summary, aerobic exercise prescription, with or without supplementation of behavioral and/or cultural tailoring, remains undefined for minority breast cancer survivors. Black women tend to adhere well to walking interventions, whereas Hispanic women have yet to be specifically targeted with aerobic exercise modalities. Resistance exercise remains grossly underexplored among minority breast cancer survivors; therefore, strict implementation of this exercise modality is an important area of focus for future studies. A combination of resistance and aerobic exercise is the most common type of exercise intervention among minority breast cancer survivors. The efficacy of exercise interventions that were previously investigated mostly in non-Hispanic White women might be similar or even greater in minority populations as a result of their lower physical activity levels and more prevalent comorbid conditions. Furthermore, culturally tailored interventions incorporating group- or team-based and community- or church-based approaches appear to improve the acceptability and effectiveness, which can be taken into account in future studies. Given the mixed results of adherence and retention, future studies may benefit from focusing on recruitment and retention strategies to bolster adherence and should broaden their targeted population to include Hispanics. Finally, exploration of clinical outcomes and implementation of long-term physical activity interventions are necessary among minority breast cancer survivors.

Dietary interventions The feasibility and impact of dietary interventions have been widely studied across the breast cancer continuum.[10,100] Overall, although still inconclusive, evidence shows that healthy dietary interventions are well accepted before and after breast cancer diagnosis and have the potential to reduce breast cancer risk and mortality. However, there are limited data on racially/ethnically diverse populations: only a few dietary intervention studies exist for breast cancer prevention and survivorship in Black and Hispanic women, and none have been performed in Asian American women.[101-105] In terms of breast cancer prevention, a large-scale multicenter trial in 48,835 postmenopausal women (the Women's Health Initiative) found that a low-fat diet was feasible and resulted in a noteworthy weight loss by 2.2 kg of the between-group difference after 1 year and a modest reduction in breast cancer risk; however, the majority of the study participants were non-Hispanic White women (81%).[106] Although the Women's Health Initiative Study posed a feasibility of a low-fat diet intervention resulting in weight loss, this finding is not generalizable to other ethnic groups, such as Black or Hispanic women, because of the racial imbalance of the participants. Future studies are warranted that focus on various underrepresented groups and explore different dietary options that are applicable before diagnosis and are effective for breast cancer prevention.

Regarding breast cancer survivorship, a small number of studies have investigated the effects of dietary programs; these are limited to pilot studies or subanalyses of large trials.[107] For instance, one pilot study developed a culturally tailored dietary program for Black breast cancer survivors that was well received and effective in reducing fat consumption.[101] Similarly, the ¡Cocinar Para Su Salud! Trial, using a theory-driven procedural model, developed a dietary change intervention that was systematically tailored for Hispanic breast cancer survivors[102]; it led to a substantial improvement in diet- and breast cancer–related biomarkers.[103,104] A secondary analysis in 118 Black and 165 Hispanic breast cancer survivors from a larger dietary trial (the Women's Healthy Eating and Living Study[108]) showed that Black and Hispanic breast cancer survivors had poorer dietary patterns compared with their non-Hispanic White counterparts at baseline, and the positive changes in their dietary patterns after the intervention were smaller.[105]

In summary, despite the growing body of evidence, the feasibility and effectiveness of dietary interventions before and after a breast cancer diagnosis in racially and ethnically diverse populations are unclear. Nevertheless, given the higher prevalence of obesity and poorer dietary patterns in the Black and Hispanic populations, the impact of a dietary intervention that focuses on reducing fat intake and body weight seems promising in minority populations.

Intervention programs (e.g., group coaching sessions, intensive telephone follow-ups, web-based approaches, and recruitment of mother-daughter dyads) that are culturally tailored and sustainable in particular ethnic groups appear to improve adherence and retention but must be explored further. More attention is required for early dietary intervention in Black and Hispanic women to examine whether diet modification reduces the risks of breast cancer development and mortality.

Multimodal approaches Several studies that used multimodal approaches, such as combined diet and physical activity interventions, have primarily focused on Black breast cancer survivors.[109-115] Overall, such interventions yielded modest adherence rates (> 70%) and marked reductions in sedentary behavior, fat intake, and body weight.[107] For example, the Moving Forward Trial instituted a comprehensive community-based lifestyle program, including diet and physical activity, that was developed for Black breast cancer survivors; it resulted in a greater than 3% weight loss and improved health outcomes.[110] For Asian American women, a single-arm pilot study introduced a culturally tailored (e.g., language, community-based, and culturally appropriate contents) lifestyle intervention in 50 Chinese American cancer survivors and found a substantial increase in vegetable consumption and physical activity levels.[116] Overall, although efforts have been made to develop intervention programs that are culturally tailored for specific racial/ethnic groups, studies have been relatively small and lack long-term follow-up to identify the effects of the intervention on cancer outcomes. For example, a few ongoing larger trials can help to narrow the research gap, including a lifestyle weight loss study in 100 overweight/obese Black breast cancer survivors (NCT04741802) and a diet plus exercise intervention trial in 652 cancer survivors that is focusing on patients in rural areas and with minority status (NCT04000880).

Overall, diet-only and multimodal interventions with a focus on weight loss have been studied in Black breast cancer survivors, whereas studies targeting Hispanic breast cancer survivors are scarce. Future studies should target specific underrepresented and vulnerable populations to develop and examine tailored programs; ultimately, larger phase II or III trials are needed to determine the effects of dietary/multimodal interventions on long-term clinical outcomes in minority breast cancer survivors.

Barriers and Facilitators to Intervention Delivery and Participation Among Racially/Ethnically Diverse Women

Unique barriers and facilitators exist in the development and conduct of intervention trials among minority women before and after breast cancer diagnosis (Table 3). For researchers, the geographical location of the research institute can limit participant recruitment. Individuals residing in rural areas are likely to be excluded, because participants are often required to visit the research facility for assessment and intervention. Also, the uneven distribution of minority populations across the country can be a challenge, because certain populations may reside in specific areas (e.g., Hispanic women in the southwest and Black women in the southeast). Variations in study design can help to address these geographical challenges, such as using a more accessible remote-based intervention and a multicenter study design involving various geographical locations that can ensure the recruitment of representative participants. However, for technology-based interventions, researchers should consider potential digital divide and limited access (e.g., secure funding to provide participants with appropriate devices). Furthermore, there is a lack of information surrounding study recruitment and retention in underrepresented populations. For example, to design an effective intervention that is culturally tailored to specific ethnic groups, it is crucial to comprehend the potential reasons for declining to participate in the study, dropping out from the study, or not adhering to the intervention. Collection and reporting of data on recruitment and adherence of minority and underrepresented women would be highly beneficial.

On the other hand, challenges exist from the participants' perspective that are often complex and multifaceted.[117] First, a lack of accessible exercise and dietary resources may exist. Examples include the lack of access to safe space, exercise equipment, or affordable facilities for exercise studies,[118-120] as well as limited access to healthy and affordable food options for diet studies. Second, transportation can be a challenge: those who live in suburban or rural areas might have to spend extended time traveling to the research facility or bear the extra expenses of gas and parking. Third, some ethnic groups may have considerable family needs (e.g., multigenerational families), making it challenging to commit additional time for exercise or diet modification. Lastly, poor patient-provider communication may be an issue.[121,122] For example, referring minority patients to a study without understanding the potential constraints of the intervention (e.g., use of technology device) or without established support systems (e.g., language barriers) can be detrimental in recruiting participants from underrepresented populations.

CONCLUSION AND FUTURE CONSIDERATIONS

There is a clear need for studies of the impact of obesity and associated lifestyle behaviors in diverse populations, specifically including or targeting groups with persistent health disparities. This literature would inform the development of clinical practice guidelines that are appropriate for racially and ethnically diverse populations. Given the complex association of obesity with breast cancer, with opposing effect

TABLE 3. Barriers and Potential Facilitators to Intervention Delivery and Participation Among Minority Women

Barriers	Potential Facilitators
Researchers	
• Urban locations of most research institutes limit participation of women residing in suburban/rural areas • Uneven distribution of minority populations across the United States (e.g., Hispanic population in the southwest and Black population in the southeast) • Lack of understanding about reasons for decline of study participation and nonadherence to intervention	• Multicenter design from various geographic locations • Survey/focus group studies to comprehend unique barriers and preferences for intervention • More accessible intervention design, such as remote-based delivery (e.g., telephone, online format)
Participants	
• Limited accessible resources (e.g., spaces/facilities for exercise and costs for healthy food) • Extended transportation time traveling to the research facility or added costs (e.g., gas and parking) • High family needs (e.g., multigenerational families) • Referred to a study that requiresinaccessible or unfamiliar intervention modalities (e.g., use of technology device) or has a lack of support systems (e.g., language barriers)	• Culturally tailored intervention methods, including use of local community (e.g., YMCA, churches) and engagement of family members (e.g., mother-daughter dyads)

by age and menopausal status, as well as by windows of susceptibility and possibly by race/ethnicity, large epidemiologic studies are needed to allow sufficient statistical power for meaningful analyses. Such studies should recruit adequate samples from diverse populations using standardized methodology for recruitment and data collection, including measurements and complete and accurate tumor subtype information so that results can be compared directly across racial/ethnic groups. Data on immigration, acculturation, discrimination, genetic ancestry, and environment (including ethnic enclaves, built environment) are crucial in these analyses. Special attention should be given to measures of adiposity, because body composition and body fat distribution may vary across populations. For example, for a given BMI, Black women tend to have higher lean body mass with lower visceral fat compared with non-Hispanic White women, whereas Asian women tend to have lower lean body mass and higher visceral fat.[17] CT has been used in some studies that took advantage of existing electronic medical records, showing promising results about the importance of muscle mass on prognosis.[123] However, the use of CT scans in large population-based epidemiologic studies is not always feasible given the cost and lack of portability. Other methods to measure body composition, such as bioelectrical impedance analysis using portable scales, as currently used in other studies,[124] may be more practical in large prospective longitudinal studies. Biospecimen collection to ascertain biologic mechanisms is likely to provide critical insights into any possible racial/ethnic disparities in the relationship between obesity and breast cancer. However, any racial/ethnic differences should be interpreted with caution, because they may reflect other social determinants of health, such as socioeconomic status, racial discrimination, or the social environments in which they live, which influence their lifestyle behaviors and access to care.

Similar to the limited epidemiologic studies evaluating the impact of racial/ethnic differences on obesity-related factors, the sparse landscape with regard to energy balance interventions for minority breast cancer survivors provides an opportunity to discuss and explore tangible and pragmatic approaches that seek to improve health outcomes. Major areas on which to focus research efforts include cancer prevention interventions, intervention approaches, clinical and treatment-related endpoints, and cultural tailoring across the research trajectory from study conception to completion. To date, energy balance interventions have fallen short on focusing on minority populations for cancer prevention. Questions remain surrounding the timing of an intervention; a greater emphasis on early interventions during adolescence or even earlier on during in utero may be needed, because previous interventions have targeted middle-aged and older individuals.[125,126] Nonetheless, given the long-term beneficial impact of healthy lifestyle interventions, a clear message to convey to clinicians and the general public is to promote these behaviors by following current nutrition and physical activity guidelines, even if they are not specifically tailored to specific racial/ethnic groups, because they are based on the best available scientific evidence.

Novel intervention approaches that can support accessibility of intervention delivery are warranted. In light of the explosion of remote and virtual delivery of exercise and diet intervention, there is an opportunity to disseminate energy balance interventions to a diverse patient population that otherwise would not have the opportunity to partake in said trials. This includes, but is not limited to, continued and expanded partnerships with social support systems for

minority populations, such as civic organizations, recreation centers, and churches, which have also expanded their outreach with a virtual enterprise. Application of technology-based intervention delivery will support the rigor that is often needed to ensure adequate exercise prescription of personalized dietary approaches whereby supervision is possible through video chat mechanisms. An additional supportive approach to enhance delivery that has gained recent attention in cancer and energy balance interventions is the use of dyads.[127,128] This approach may enhance the family and social support that is highly valued by Black and Hispanic communities.[129,130] Application of novel diet and exercise approaches warrants further examination to ensure enjoyment and accessibility among an otherwise understudied population. In fact, observational and qualitative studies should seek to identify perceived barriers, preferences, and overall lifestyle patterns among a large cohort of minority breast cancer survivors. With this knowledge in hand, researchers and clinicians alike can investigate methods to promote healthy lifestyle behaviors.

The current state of energy balance interventions can be further advanced by challenging the timing of intervention delivery, novel endpoints, and integration of culturally tailored study designs. Targeting energy balance behaviors early on in the presurgical period or during the treatment phase may enhance treatment efficacy, reduce surgical complications and hospital stays, and mitigate treatment-related side effects.[131,132] Of note, there is a lack of long-term interventions and sustainability investigations that include diet and/or exercise beyond a limited number of weeks or months. Although study duration is often driven by funding availability, examination of the sustainability of healthy energy balance behaviors is critical for long-term impact.

Endpoints beyond feasibility and psychosocial health that seek to target treatment, clinical, or physiologic endpoints would aid in eliminating cancer health disparities if effective. With both diet and exercise, careful detailed planning and implementation of cultural tailoring are necessary to enhance the trial design and likelihood of intervention acceptability and efficacy while meeting the needs of a given patient population. This may include health education materials specific for minorities that facilitate awareness of the importance of lifestyle modifications.

The current research climate has resulted in clinical practice guidelines that stem from scientific evidence from predominantly non-Hispanic White study populations.[99,133] The need to include racially/ethnically diverse populations in research and to specifically target minority populations in which disparities are known to exist have never been timelier to achieve health equity.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. Epub 2021 Feb 4.
2. Lee K, Kruper L, Dieli-Conwright CM, et al. The impact of obesity on breast cancer diagnosis and treatment. Curr Oncol Rep. 2019;21:41.
3. Schmitz KH, Neuhouser ML, Agurs-Collins T, et al. Impact of obesity on cancer survivorship and the potential relevance of race and ethnicity. J Natl Cancer Inst. 2013;105:1344-1354.
4. Sheng JY, Sharma D, Jerome G, et al. Obese breast cancer patients and survivors: management considerations. Oncology (Williston Park). 2018;32:410-417.
5. Markham MJ, Wachter K, Agarwal N, et al. Clinical Cancer Advances 2020: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology. J Clin Oncol. 2020;38:1081.
6. Chan DSM, Abar L, Cariolou M, et al. World Cancer Research Fund International: Continuous Update Project-systematic literature review and meta-analysis of observational cohort studies on physical activity, sedentary behavior, adiposity, and weight change and breast cancer risk. Cancer Causes Control. 2019;30:1183-1200.

7. McTiernan A, Friedenreich CM, Katzmarzyk PT, et al; 2018 Physical Activity Guidelines Advisory Committee. Physical activity in cancer prevention and survival: a systematic review. Med Sci Sports Exerc. 2019;51:1252-1261.
8. Friedenreich CM, Stone CR, Cheung WY, et al. Physical activity and mortality in cancer survivors: a systematic review and meta-analysis. JNCI Cancer Spectr. 2019;4:pkz080.
9. World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. The Third Expert Report. www.wrcf.org/dietandcancer. Accessed March 26, 2021.
10. Ligibel JA, Basen-Engquist K, Bea JW. Weight management and physical activity for breast cancer prevention and control. Am Soc Clin Oncol Educ Book. 2019; 39:e22-e33.
11. World Cancer Research Fund. Continuous Update Project Report: Diet, Nutrition, Physical Activity and Breast Cancer Survivors. https://www.wcrf.org/dietandcancer/breast-cancer-survivors. Accessed April 28, 2021.
12. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin. 2012;62:243-274.
13. American Cancer Society. Breast Cancer Facts & Figures 2019-2020. www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf. Accessed March 26, 2021.
14. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. CA Cancer J Clin. 2019;69:438-451.
15. Hales C, Carroll M, Fryar C, et al. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017–2018. NCHS Data Brief, no 360. www.cdc.gov/nchs/data/databriefs/db360-h.pdf. Accessed March 26, 2021.
16. Bandera EV, Fay SH, Giovannucci E, et al; World Cancer Research Fund International Continuous Update Project Panel. The use and interpretation of anthropometric measures in cancer epidemiology: A perspective from the world cancer research fund international continuous update project. Int J Cancer. 2016;139:2391-2397.
17. Sung H, Siegel RL, Torre LA, et al. Global patterns in excess body weight and the associated cancer burden. CA Cancer J Clin. 2019;69:88-112.
18. Zhang Y, Yang J, Hou W, et al. Obesity Trends and associations with types of physical activity and sedentary behavior in US adults: National Health and Nutrition Examination Survey, 2007-2016. Obesity (Silver Spring). 2021;29:240-250.
19. Greenlee H, Shi Z, Sardo Molmenti CL, et al. Trends in obesity prevalence in adults with a history of cancer: results from the US National Health Interview Survey, 1997 to 2014. J Clin Oncol. 2016;34:3133-3140.
20. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, Nutrition, Physical Activity and Breast Cancer. www.dietandcancerreport.org. Accessed March 26, 2021.
21. Lauby-Secretan B, Scoccianti C, Loomis D, et al; International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer--viewpoint of the IARC Working Group. N Engl J Med. 2016;375:794-798.
22. Hidayat K, Yang CM, Shi BM. Body fatness at a young age, body fatness gain and risk of breast cancer: systematic review and meta-analysis of cohort studies. Obes Rev. 2018;19:254-268.
23. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371:569-578.
24. Heymsfield SB, Peterson CM, Thomas DM, et al. Why are there race/ethnic differences in adult body mass index-adiposity relationships? A quantitative critical review. Obes Rev. 2016;17:262-275.
25. Bernstein L, Teal CR, Joslyn S, et al. Ethnicity-related variation in breast cancer risk factors. Cancer. 2003;97(1 suppl):222-229.
26. Williams DR, Mohammed SA, Shields AE. Understanding and effectively addressing breast cancer in African American women: unpacking the social context. Cancer. 2016;122:2138-2149.
27. Maskarinec G, Jacobs S, Park SY, et al. Type II diabetes, obesity, and breast cancer risk: The Multiethnic Cohort. Cancer Epidemiol Biomarkers Prev. 2017; 26:854-861.
28. Bandera EV, Chandran U, Hong CC, et al. Obesity, body fat distribution, and risk of breast cancer subtypes in African American women participating in the AMBER Consortium. Breast Cancer Res Treat. 2015;150:655-666.
29. Bandera EV, Chandran U, Zirpoli G, et al. Body fatness and breast cancer risk in women of African ancestry. BMC Cancer. 2013;13:475.
30. Berstad P, Coates RJ, Bernstein L, et al. A case-control study of body mass index and breast cancer risk in white and African-American women. Cancer Epidemiol Biomarkers Prev. 2010;19:1532-1544.
31. Palmer JR, Adams-Campbell LL, Boggs DA, et al. A prospective study of body size and breast cancer in black women. Cancer Epidemiol Biomarkers Prev. 2007; 16:1795-1802.
32. Zhu K, Caulfield J, Hunter S, et al. Body mass index and breast cancer risk in African American women. Ann Epidemiol. 2005;15:123-128.
33. Robinson WR, Tse CK, Olshan AF, et al. Body size across the life course and risk of premenopausal and postmenopausal breast cancer in Black women, the Carolina Breast Cancer Study, 1993-2001. Cancer Causes Control. 2014;25:1101-1117.
34. White KK, Park SY, Kolonel LN, et al. Body size and breast cancer risk: the Multiethnic Cohort. Int J Cancer. 2012;131:E705-E716.
35. John EM, Sangaramoorthy M, Phipps AI, et al. Adult body size, hormone receptor status, and premenopausal breast cancer risk in a multiethnic population: the San Francisco Bay Area breast cancer study. Am J Epidemiol. 2011;173:201-216.

36. Bertrand KA, Bethea TN, Adams-Campbell LL, et al. Differential patterns of risk factors for early-onset breast cancer by ER status in African American women. Cancer Epidemiol Biomarkers Prev. 2017;26:270-277.

37. Millikan RC, Newman B, Tse CK, et al. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat. 2008;109:123-139.

38. Bandera EV, Maskarinec G, Romieu I, et al. Racial and ethnic disparities in the impact of obesity on breast cancer risk and survival: a global perspective. Adv Nutr. 2015;6:803-819.

39. Slattery ML, Sweeney C, Edwards S, et al. Body size, weight change, fat distribution and breast cancer risk in Hispanic and non-Hispanic white women. Breast Cancer Res Treat. 2007;102:85-101.

40. Wenten M, Gilliland FD, Baumgartner K, et al. Associations of weight, weight change, and body mass with breast cancer risk in Hispanic and non-Hispanic white women. Ann Epidemiol. 2002;12:435-444.

41. John EM, Sangaramoorthy M, Hines LM, et al. Overall and abdominal adiposity and premenopausal breast cancer risk among hispanic women: the breast cancer health disparities study. Cancer Epidemiol Biomarkers Prev. 2015;24:138-147.

42. John EM, Sangaramoorthy M, Hines LM, et al. Body size throughout adult life influences postmenopausal breast cancer risk among hispanic women: the breast cancer health disparities study. Cancer Epidemiol Biomarkers Prev. 2015;24:128-137.

43. Rey-Vargas L, Sanabria-Salas MC, Fejerman L, et al. Risk factors for triple-negative breast cancer among Latina women. Cancer Epidemiol Biomarkers Prev. 2019;28:1771-1783.

44. Torre LA, Sauer AM, Chen MS Jr., et al. Cancer statistics for Asian Americans, Native Hawaiians, and Pacific Islanders, 2016: Converging incidence in males and females. CA Cancer J Clin. 2016;66:182-202.

45. Wu AH, Lee E, Stram DO. Breast Cancer among Asian Americans. In Wu AH, Stram DO, (eds). Cancer Epidemiology Among Asian Americans. Basel, Switzerland: Springer International Publishing; 2016;187-218.

46. Gomez SL, Quach T, Horn-Ross PL, et al. Hidden breast cancer disparities in Asian women: disaggregating incidence rates by ethnicity and migrant status. Am J Public Health. 2010;100(suppl 1):S125-S131.

47. Wu AH, Yu MC, Tseng CC, et al. Body size, hormone therapy and risk of breast cancer in Asian-American women. Int J Cancer. 2007;120:844-852.

48. Ziegler RG, Hoover RN, Nomura AM, et al. Relative weight, weight change, height, and breast cancer risk in Asian-American women. J Natl Cancer Inst. 1996; 88:650-660.

49. Amadou A, Ferrari P, Muwonge R, et al. Overweight, obesity and risk of premenopausal breast cancer according to ethnicity: a systematic review and dose-response meta-analysis. Obes Rev. 2013;14:665-678.

50. Chan DSM, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol. 2014;25:1901-1914.

51. Lohmann AE, Soldera SV, Pimentel I, et al. Association of obesity with breast cancer outcome in relation to cancer subtypes: a meta-analysis. J Natl Cancer Inst. 2021;djab023.

52. Playdon MC, Bracken MB, Sanft TB, et al. Weight gain after breast cancer diagnosis and all-cause mortality: systematic review and meta-analysis. J Natl Cancer Inst. 2015;107:djv275.

53. Conroy SM, Maskarinec G, Wilkens LR, et al. Obesity and breast cancer survival in ethnically diverse postmenopausal women: the Multiethnic Cohort Study. Breast Cancer Res Treat. 2011;129:565-574.

54. Lu Y, Ma H, Malone KE, et al. Obesity and survival among black women and white women 35 to 64 years of age at diagnosis with invasive breast cancer. J Clin Oncol. 2011;29:3358-3365.

55. Kwan ML, John EM, Caan BJ, et al. Obesity and mortality after breast cancer by race/ethnicity: The California Breast Cancer Survivorship Consortium. Am J Epidemiol. 2014;179:95-111.

56. Rock CL, Thomson C, Gansler T, et al. American Cancer Society guideline for diet and physical activity for cancer prevention. CA Cancer J Clin. 2020; 70:245-271.

57. U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans, 2nd Ed., https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf. Accessed March 26, 2021.

58. Centers for Disease Control and Prevention. Physical Activity and Cancer. www.cdc.gov/physicalactivity/basics/pa-health/physical-activity-and-cancer.html. Accessed March 26, 2021.

59. National Cancer Institute. Physical Activity and Cancer. www.cancer.gov/about-cancer/causes-prevention/risk/obesity/physical-activity-fact-sheet. Accessed March 26, 2021.

60. Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise guidelines for cancer survivors: consensus statement from International Multidisciplinary Roundtable. Med Sci Sports Exerc. 2019;51:2375-2390.

61. Gilchrist SC, Barac A, Ades PA, et al; American Heart Association Exercise, Cardiac Rehabilitation, and Secondary Prevention Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and Council on Peripheral Vascular Disease. Cardio-oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: a scientific statement From the American Heart Association. Circulation. 2019;139:e997-e1012.

62. Hayes SC, Newton RU, Spence RR, et al. The Exercise and Sports Science Australia position statement: exercise medicine in cancer management. J Sci Med Sport. 2019;22:1175-1199.

63. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol. 2016;34:611-635.

64. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary guidelines for Americans, 2020-2025 (9th ed). www.dietaryguidelines.gov/sites/default/files/2020-12/Dietary_Guidelines_for_Americans_2020-2025.pdf. Accessed March 26, 2021.

65. Centers for Disease Control and Prevention. Nutrition: Strategies & Guidelines. www.cdc.gov/nutrition/strategies-guidelines/index.html. Accessed March 26, 2021.

66. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36:11-48.

67. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Survivorship. www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf. Accessed March 26, 2021.

68. Jochem C, Wallmann-Sperlich B, Leitzmann MF. The influence of sedentary behavior on cancer risk: epidemiologic evidence and potential molecular mechanisms. Curr Nutr Rep. 2019;8:167-174.

69. Patel AV, Friedenreich CM, Moore SC, et al. American College of Sports Medicine Roundtable Report on physical activity, sedentary behavior, and cancer prevention and control. Med Sci Sports Exerc. 2019;51:2391-2402.

70. Stout NL, Brown JC, Schwartz AL, et al. An exercise oncology clinical pathway: screening and referral for personalized interventions. Cancer. 2020;126:2750-2758.

71. Santa Mina D, van Rooijen SJ, Minnella EM, et al. Multiphasic prehabilitation across the cancer continuum: a narrative review and conceptual framework. Front Oncol. 2021;10:598425.

72. Ligibel JA, Barry WT, Alfano C, et al. Randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese women with early breast cancer (Alliance A011401): study design. NPJ Breast Cancer. 2017;3:37.

73. National Cancer Institute. Eating Hints: Before, During, and After Cancer Treatment. www.cancer.gov/publications/patient-education/eating-hints. Accessed March 26, 2021.

74. American Cancer Society. Nutrition for the Person With Cancer During Treatment: A Guide for Patients and Families. www.cancer.org/content/dam/cancer-org/cancer-control/en/booklets-flyers/nutrition-for-the-patient-with-cancer-during-treatment.pdf. Accessed March 26, 2021.

75. LoConte Noelle K, Gershenwald Jeffrey E, Thomson Cynthia A, et al. Lifestyle Modifications and Policy Implications for Primary and Secondary Cancer Prevention: Diet, Exercise, Sun Safety, and Alcohol Reduction. Am Soc Clin Oncol Educ Book. 2018;38:88-100.

76. Hill JO, Wyatt HR, Peters JC. The importance of energy balance. Eur Endocrinol. 2013;9:111-115.

77. Pekmezi D, Ainsworth C, Joseph R, et al. Rationale, design, and baseline findings from HIPP: A randomized controlled trial testing a home-based, individually-tailored physical activity print intervention for African American women in the Deep South. Contemp Clin Trials. 2016;47:340-348.

78. McCollum AD, Catalano PJ, Haller DG, et al. Outcomes and toxicity in African-American and Caucasian patients in a randomized adjuvant chemotherapy trial for colon cancer. J Natl Cancer Inst. 2002;94:1160-1167.

79. Wilbur J, McDevitt JH, Wang E, et al. Outcomes of a home-based walking program for African-American women. Am J Health Promot. 2008;22:307-317.

80. Newton RL Jr., Perri MG. A randomized pilot trial of exercise promotion in sedentary African-American adults. Ethn Dis. 2004;14:548-557.

81. Bautista L, Reininger B, Gay JL, et al. Perceived barriers to exercise in Hispanic adults by level of activity. J Phys Act Health. 2011;8:916-925.

82. Li CI, Malone KE, Daling JR. Differences in breast cancer stage, treatment, and survival by race and ethnicity. Arch Intern Med. 2003;163:49-56.

83. Hoffman RM, Gilliland FD, Eley JW, et al. Racial and ethnic differences in advanced-stage prostate cancer: the Prostate Cancer Outcomes Study. J Natl Cancer Inst. 2001;93:388-395.

84. Clegg LX, Li FP, Hankey BF, et al. Cancer survival among US whites and minorities: a SEER (Surveillance, Epidemiology, and End Results) Program population-based study. Arch Intern Med. 2002;162:1985-1993.

85. Kao D, Carvalho Gulati A, Lee RE. Physical activity among Asian American adults in Houston, Texas: data from the Health of Houston Survey 2010. J Immigr Minor Health. 2016;18:1470-1481.

86. Chen MS, Jr. Cancer health disparities among Asian Americans: what we do and what we need to do. Cancer. 2005;104(12, suppl)2895-2902.

87. Lee RJ, Madan RA, Kim J, et al. Disparities in cancer care and the Asian American population. Oncologist. Epub 2021 Mar 8.

88. Ziegler RG, Hoover RN, Pike MC, et al. Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst. 1993;85:1819-1827.

89. Dash C, Taylor TR, Makambi KH, et al. Effect of exercise on metabolic syndrome in black women by family history and predicted risk of breast cancer: The FIERCE Study. Cancer. 2018;124:3355-3363.

90. Spector D, Deal AM, Amos KD, et al. A pilot study of a home-based motivational exercise program for African American breast cancer survivors: clinical and quality-of-life outcomes. Integr Cancer Ther. 2014;13:121-132.

91. Wilson DB, Porter JS, Parker G, et al. Anthropometric changes using a walking intervention in African American breast cancer survivors: a pilot study. Prev Chronic Dis. 2005;2:A16.

92. Lee K, Kang I, Mack WJ, et al. Feasibility of high intensity interval training in patients with breast Cancer undergoing anthracycline chemotherapy: a randomized pilot trial. BMC Cancer. 2019;19:653.

93. Herrero F, San Juan AF, Fleck SJ, et al. Combined aerobic and resistance training in breast cancer survivors: A randomized, controlled pilot trial. Int J Sports Med. 2006;27:573-580.

94. Piraux E, Caty G, Reychler G. Effects of preoperative combined aerobic and resistance exercise training in cancer patients undergoing tumour resection surgery: a systematic review of randomised trials. Surg Oncol. 2018;27:584-594.

95. Almstedt HC, Grote S, Korte JR, et al. Combined aerobic and resistance training improves bone health of female cancer survivors. Bone Rep. 2016;5:274-279.

96. Piacentine LB, Robinson KM, Waltke LJ, et al. Promoting team-based exercise among African American breast cancer survivors. West J Nurs Res. 2018; 40:1885-1902.

97. Mama SK, Song J, Ortiz A, et al. Longitudinal social cognitive influences on physical activity and sedentary time in Hispanic breast cancer survivors. Psychooncology. 2017;26:214-221.

98. Dieli-Conwright CM, Courneya KS, Demark-Wahnefried W, et al. Effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: a randomized controlled trial. J Clin Oncol. 2018;36:875-883.

99. Dieli-Conwright CM, Sweeney FC, Courneya KS, et al. Hispanic ethnicity as a moderator of the effects of aerobic and resistance exercise in survivors of breast cancer. Cancer. 2019;125:910-920.

100. Brown JC, Ligibel JA. Lifestyle interventions for breast cancer prevention. Curr Breast Cancer Rep. 2018;10:202-208.

101. Griffith KA, Royak-Schaler R, Nesbitt K, et al. A culturally specific dietary plan to manage weight gain among African American breast cancer survivors: a feasibility study. Nutr Health. 2012;21:97-105.

102. Aycinena AC, Jennings KA, Gaffney AO, et al. ¡Cocinar Para Su Salud! Development of a culturally based nutrition education curriculum for Hispanic breast cancer survivors using a theory-driven procedural model. Health Educ Behav. 2017;44:13-22.

103. Greenlee H, Ogden Gaffney A, Aycinena AC, et al. Long-term diet and biomarker changes after a short-term intervention among Hispanic breast cancer survivors: The ¡Cocinar Para Su Salud! Randomized Controlled Trial. Cancer Epidemiol Biomarkers Prev. 2016;25:1491-1502.

104. Greenlee H, Gaffney AO, Aycinena AC, et al. ¡Cocinar Para Su Salud!: randomized controlled trial of a culturally based dietary intervention among Hispanic breast cancer survivors. J Acad Nutr Diet. 2015;115:709-729.e3.

105. Paxton RJ, Jones LA, Chang S, et al. Was race a factor in the outcomes of the Women's Health Eating and Living Study? Cancer. 2011;117:3805-3813.

106. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA. 2006;295:629-642.

107. Paxton RJ, Garner W, Dean LT, et al. Health behaviors and lifestyle interventions in African American breast cancer survivors: a review. Front Oncol. 2019;9:3.

108. Pierce JP, Natarajan L, Caan BJ, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA. 2007;298:289-298.

109. Stolley M, Sheean P, Gerber B, et al. Efficacy of a weight loss intervention for African American breast cancer survivors. J Clin Oncol. 2017;35:2820-2828.

110. Stolley MR, Sharp LK, Oh A, et al. A weight loss intervention for African American breast cancer survivors, 2006. Prev Chronic Dis. 2009;6:A22.

111. Sheppard VB, Hicks J, Makambi K, et al. The feasibility and acceptability of a diet and exercise trial in overweight and obese black breast cancer survivors: The Stepping STONE study. Contemp Clin Trials. 2016;46:106-113.

112. Chung S, Zhu S, Friedmann E, et al. Weight loss with mindful eating in African American women following treatment for breast cancer: a longitudinal study. Support Care Cancer. 2016;24:1875-1881.

113. Delgado-Cruzata L, Zhang W, McDonald JA, et al. Dietary modifications, weight loss, and changes in metabolic markers affect global DNA methylation in Hispanic, African American, and Afro-Caribbean breast cancer survivors. J Nutr. 2015;145:783-790.

114. Greenlee HA, Crew KD, Mata JM, et al. A pilot randomized controlled trial of a commercial diet and exercise weight loss program in minority breast cancer survivors. Obesity (Silver Spring). 2013;21:65-76.

115. Djuric Z, Mirasolo J, Kimbrough L, et al. A pilot trial of spirituality counseling for weight loss maintenance in African American breast cancer survivors. J Natl Med Assoc. 2009;101:552-564.

116. Deng F, Chen D, Swartz MC, et al. A pilot study of a culturally tailored lifestyle intervention for Chinese American cancer survivors. Cancer Contr. 2019; 26:1073274819895489.

117. Hamel LM, Penner LA, Albrecht TL, et al. Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. Cancer Contr. 2016;23:327-337.

118. Spector D, Battaglini C, Groff D. Perceived exercise barriers and facilitators among ethnically diverse breast cancer survivors. Oncol Nurs Forum. 2013; 40:472-480.

119. Jones A, Paxton RJ. Neighborhood disadvantage, physical activity barriers, and physical activity among African American breast cancer survivors. Prev Med Rep. 2015;2:622-627.

120. Oyekanmi G, Paxton RJ. Barriers to physical activity among African American breast cancer survivors. Psychooncology. 2014;23:1314-1317.

121. Christian AH, O'Malley D, Barac A, et al. Cardiovascular risk and communication among early stage breast cancer survivors. Patient Educ Couns. 2017; 100:1360-1366.

122. Palmer NRA, Kent EE, Forsythe LP, et al. Racial and ethnic disparities in patient-provider communication, quality-of-care ratings, and patient activation among long-term cancer survivors. J Clin Oncol. 2014;32:4087-4094.

123. Caan BJ, Cespedes Feliciano EM, Prado CM, et al. Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. JAMA Oncol. 2018;4:798-804.

124. Bandera EV, Demissie K, Qin B, et al. The Women's Circle of Health Follow-Up Study: a population-based longitudinal study of Black breast cancer survivors in New Jersey. J Cancer Surviv. 2020;14:331-346.

125. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials. 1998;19:61-109.

126. Pierce JP, Faerber S, Wright FA, et al; Women's Healthy Eating and Living (WHEL) study group. A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. Control Clin Trials. 2002;23:728-756.

127. Hallward L, Chemtob K, Lambert SD, et al. Prostate cancer survivors' and caregivers' experiences using behavior change techniques during a web-based self-management and physical activity program: a qualitative study. J Clin Med. 2020;9:9.

128. Crane TE, Badger TA, O'Connor P, et al. Lifestyle intervention for Latina cancer survivors and caregivers: the Nuestra Salud randomized pilot trial. J Cancer Surviv. Epub 2020 Nov 10.

129. Davila YR, Reifsnider E, Pecina I. Familismo: influence on Hispanic health behaviors. Appl Nurs Res. 2011;24:e67-e72.

130. Smith EP, Witherspoon DP, Bhargava S, et al. Cultural values and behavior among African American and European American children. J Child Fam Stud. 2019; 28:1236-1249.

131. Ahn KY, Hur H, Kim DH, et al. The effects of inpatient exercise therapy on the length of hospital stay in stages I-III colon cancer patients: randomized controlled trial. Int J Colorectal Dis. 2013;28:643-651.

132. Kleckner IR, Dunne RF, Asare M, et al. Exercise for toxicity management in cancer-a narrative review. Oncol Hematol Rev. 2018;14:28-37.

133. Cao Y, Baumgartner KB, Visvanathan K, et al. Ethnic and biological differences in the association between physical activity and survival after breast cancer. NPJ Breast Cancer. 2020;6:51.

BREAST CANCER

The Way of the Future: Personalizing Treatment Plans Through Technology

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overview

Advances in tissue analysis methods, image analysis, high-throughput molecular profiling, and computational tools increasingly allow us to capture and quantify patient-to-patient variations that impact cancer risk, prognosis, and treatment response. Statistical models that integrate patient-specific information from multiple sources (e.g., family history, demographics, germline variants, imaging features) can provide individualized cancer risk predictions that can guide screening and prevention strategies. The precision, quality, and standardization of diagnostic imaging are improving through computer-aided solutions, and multigene prognostic and predictive tests improved predictions of prognosis and treatment response in various cancer types. A common theme across many of these advances is that individually moderately informative variables are combined into more accurate multivariable prediction models. Advances in machine learning and the availability of large data sets fuel rapid progress in this field. Molecular dissection of the cancer genome has become a reality in the clinic, and molecular target profiling is now routinely used to select patients for various targeted therapies. These technology-driven increasingly more precise and quantitative estimates of benefit versus risk from a given intervention empower patients and physicians to tailor treatment strategies that match patient values and expectations.

INTRODUCTION

Individualization of patient care has long been the goal of medicine. The Ebers Papyrus written in Egypt in 1500 B.C. provides the following personalized treatment recommendations "…for a person who suffers from abdominal obstruction and you find [on physical examination] that it goes-and-comes under your fingers like oil-in-tube, then prepare for him fruit-of-the-dompalm, dissolve in semen, crush and cook in oil and honey…," on the other hand if a person suffers from abdominal obstruction "…and his stomach is swollen and his chest asthmatic, then make for him wormwood, elderberries, sebesten, sesa chips, crush and cook in beer."[1] One could argue that the history of medicine is the history of increasingly more sophisticated personalization of treatment that involves progressively narrower definitions of disease and selective treatments based on understanding of biology. Most of our current disease terminologies date back to the 19th century and are based on anatomic and microscopic observations paired with clinical descriptions of symptoms. However, dramatic advances in molecular and cell biology, medical imaging, and computer science, as well as increasingly rigorous standards for clinical research, are fundamentally changing how we think about cancer and formulate treatment strategies for our patients. Oncology has reached an inflection point; many of the classic disease definitions started to lose practical value, and for good reason. Generic disease terms like "breast cancer" became so vague and imprecise in the context of contemporary knowledge and diagnostic technologies that it has almost lost its value in determining how to act on this diagnosis. Contemporary state-of-the-art diagnoses increasingly capture the large patient-to-patient variations that impact cancer risk, prognosis, and treatment response. This article briefly reviews advances in imaging technologies and the use of molecular tests to guide treatment selection; focusing on breast cancer as an example, we also discuss the rapidly emerging field of artificial intelligence (AI) to aid diagnosis and reduce undesirable interobserver variance in clinical activities.

OPTIMIZING ADAPTIVE IMAGING IN THE CLINICAL MANAGEMENT OF BREAST CANCER

Imaging is a standard diagnostic procedure in the clinical management of breast cancer; however, its application to personalized treatment is rapidly evolving and requires reassessment of how imaging is performed and how information is derived. The growing field of quantitative imaging biomarkers recognizes the need for standards that address each of the stages of imaging technology, including the imaging device itself ("scanner"), the image reconstruction process, and the method of image quantification.[2-4] Each of

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PRACTICAL APPLICATIONS

- The most accurate cancer risk and prognostic risk models integrate variables from multiple sources. Do not guesstimate; use a validated multivariable model if available.
- Molecular variables and anatomic tumor (T, N) stage tend to provide independent information about clinical outcome and, therefore, complement each other. Use all information that is available to provide the most accurate outcome estimates.
- Quantitative estimates of probable clinical outcome and predicted benefit from a given intervention are now available for many clinical situations. These tools enable patients to tailor treatment strategies to their own risk/benefit tolerance level.

these elements contributes to the overall performance of the imaging biomarker and has to be considered in the optimization process. In breast cancer care, much is being learned in the neoadjuvant treatment setting where the status of the tumor can be monitored during systemic treatment. MRI has evolved as an effective imaging method for assessing tumor response during neoadjuvant treatment and is used here as an example of the benefits and challenges of adaptive imaging. This application highlights several overarching considerations for optimizing imaging markers for use in personalized treatment strategies, including the need to balance potentially competing requirements for clinical assessment and biomarker performance and the need for subtype-specific optimization of imaging markers.

Image-Acquisition Considerations

A challenge to the adoption of imaging markers in clinical practice is the need to control for variabilities at the time of image acquisition that can compromise quantitative measurements, even if they do not adversely impact diagnostic accuracy. This is particularly critical if repeated measures are used to assess change over time. Imaging technologies for breast cancer are designed primarily for cancer screening. MRI image acquisition methods for screening have been engineered to emphasize anatomic clarity and speed. This can often involve the use of image enhancements and filters to improve contrast-to-noise and improve lesion conspicuity; however, these strategies can introduce errors and site-to-site variability to the measured signal. Scan time reduction strategies are used to improve efficiency in the clinic, often at the expense of measurement fidelity. In the clinical setting it is commonplace to adjust image acquisition protocols on a patient-by-patient basis to accommodate differences in body habitus or anatomy. Intelligent software systems on many scanners will often accommodate these adjustments by automatically modifying other image acquisition parameters. These measures improve diagnostic efficiency, but biomarker imaging requires that acquisition techniques also prioritize quantitative accuracy. Controllable errors must be minimized, and this can often come at the expense of spatial resolution and scan time. Inter- and intrapatient variability are minimized using more restrictive protocols, controlled introduction of software and hardware upgrades, and limited allowances for patient-specific adjustments. These requirements are often at odds with the strategies used to optimize clinical imaging and can add steps to the clinical workflow. These conflicting incentives hinder the ability to ensure high-fidelity data for imaging biomarker development and testing.[2,5] A retrospective study performed in the I-SPY breast cancer neoadjuvant trial examined the influence of protocol adherence on the ability of functional tumor volume, a biomarker derived from breast MRI, to predict pathologic complete response (pCR). Functional tumor volume is used as part of the response-adaptive design of the I-SPY2 trial to adjust randomization in favor of arms showing early benefit over control.[6] Multicenter MRI data used in the study followed a prescribed protocol and met acceptance criteria. Protocol adherence was rated for seven technical and quality factors, including acquisition duration, early phase timing, field of view, spatial resolution, contralateral image quality, patient motion, and contrast administration. The area under the receiver operating characteristic curve was used to measure the performance of functional tumor volume change in predicting pCR. Functional tumor volume changes with adherent image quality in all factors had higher estimated area under the receiver operating characteristic curve than did those with nonadherent image quality, although the differences did not reach statistical significance. The study highlighted the impact of protocol adherence and data quality on predictive performance.[7]

MRI of Neoadjuvant Response

Of breast imaging methods, MRI is particularly effective for visualizing the effects of neoadjuvant treatment on breast tumors. MRI signals reflect spatial and functional properties of tissue and provide noninvasive information about tumor burden and biologic heterogeneity, giving it great potential to serve as a biomarker. In the neoadjuvant setting, breast MRI has been evaluated in numerous studies for its ability to detect residual disease and to predict response. Accurate detection and delineation of residual disease has the potential to improve surgical outcomes and perhaps remove the need for surgery for women achieving pCR. There is growing interest in this goal as more effective treatments have led to higher rates of pCR. MRI has been found to be more effective than clinical examination and other routine

imaging modalities (mammography and ultrasound) for residual disease detection.[8,9] Studies examining agreement between MRI and residual disease size on histopathology have found it to vary by subtype, with higher agreement reported among HER2+ and triple-negative breast cancer (TNBC) tumors.[10] Initial studies reported lower agreement in hormone receptor–positive tumors, which often have more diffuse residual disease that is undetectable by MRI. However, a recent literature review on subtype-specific MRI performance in detecting pCR concluded that MRI accuracy in detecting pCR is not as clearly associated with subtype as individual studies initially suggested.[11]

It is well understood that the intrinsic resolving power of MRI limits its ability to detect microscopic residual disease and, thus, its ability to discern between true pCR and minimal residual disease. This limits the use of MRI as a definitive imaging surrogate for surgical exploration to confirm pCR, although several studies are investigating approaches combining imaging and biopsy to explore the potential to avoid surgery.[12-14]

Perhaps more relevant to the personalization of treatment is the ability of imaging to predict treatment outcome when measured early in the course of treatment. Early noninvasive indicators of treatment effectiveness could provide a basis for modifying treatment plans, making de-escalation possible for patients showing excellent response and a recommended change in therapy for those with minimal response. Although MRI has limited accuracy for verifying pCR, it is very effective at determining the extent of disease for large breast tumors and at measuring changes with treatment. Studies examining the early predictive ability of MRI have found greater accuracy compared with other imaging methods in predictive performance across breast cancer subtypes.[15] For early response prediction, functional characteristics can add information to measurements of tumor dimensions alone. A multitude of measurement methods, including radiomics approaches, can be used to quantify tumor properties. Timing of early assessment is an additional variable. Two systematic reviews of the literature that examined the accuracy of MRI for early prediction of subsequent pathologic response to neoadjuvant therapy found that the large heterogeneity of methodologic approaches made comparison of results difficult and precluded definitive conclusions.[16,17] It is likely that machine learning and AI technologies will be an integral part of the development and maturation of imaging markers and their integration into treatment response prediction models.[18]

The marked variability in neoadjuvant chemotherapy response among different molecular subtypes of breast cancer is well established. Biomarker development, including imaging biomarkers, requires optimization by tumor subtype to maximize their usefulness.[19] Subtype-optimized models developed in the I-SPY2 trial have been used to design a de-escalation strategy that combines subtype-specific MRI predictive probabilities with midtreatment percutaneous core biopsy pathology to select candidates who can be safely offered the option to skip the doxorubicin-cyclophosphamide component of their treatment, because the probability of achieving pCR after the initial 12 weeks of taxane-based chemotherapy is very high. The combined rule was found to result in a 91% positive predictive value and 61% sensitivity for pCR and is being evaluated in the I-SPY2 trial.[20]

To fully realize the potential of response-adaptive treatment strategies to truly personalize treatment, information from multiple sources, including clinical risk variables, imaging, genomic profiles, histopathology, and circulating tumor markers, will have to be combined and adjusted for the relative subtype dependencies of these variables. As with each variable in the model, imaging needs to provide measurements that are reliable, timely, cost effective, and independently informative. New standards for quantitative imaging are being developed along with new data-analytics techniques that will enable construction of clinically relevant tools to individualize treatment plans.

UTILIZING MOLECULAR TESTS TO ASSESS RESPONSE TO THERAPY

Breast cancer is a clinically and molecularly heterogeneous disease; prognosis and treatment options vary widely between different subtypes and stages of disease. Hormone receptor and HER2 status are well-known markers for beneficial hormonal and HER2-targeted treatments. Yet, a substantial subset of patients experiences over- or undertreatment using only these markers for treatment selection. To improve outcomes, better patient selection is essential, which motivates the development of improved and new predictive markers to enable personalized treatment. Successful predictive biomarkers reflect a relevant biologic process, are accurate and reproducible, and enable identification of two or more patient subgroups with a differential outcome to a specific treatment.[21] These concepts of analytical validity, clinical validity, and clinical utility, which are applicable to all diagnostic, prognostic, and predictive markers, are summarized in Fig. 1. In this section, we briefly discuss predictive biomarkers in the context of breast cancer management; these illustrate the substantial progress and challenges that characterize molecular biomarker development in general.

HER2-Targeting Treatment

HER2 protein overexpression and gene amplification are predictive markers for HER2-targeting therapies.[22] Combining multiple HER2-targeting drugs has increased response rates, but there remains a subgroup of patients that does not benefit from these drugs despite HER2

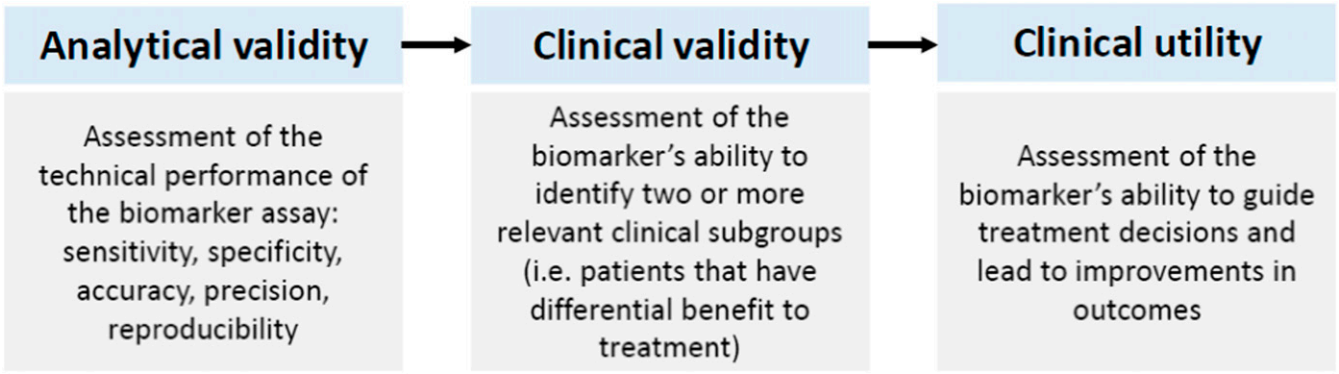

FIGURE 1. Criteria for the Evaluation of Biomarkers

amplification. Identifying these patients may spare them from unsuccessful treatment, and understanding the mechanisms of resistance could lead to more effective new drugs. Novel markers that might refine the predictive values of HER2 protein expression/gene amplification include HER2 messenger RNA expression level, HER2-enriched molecular subtype, and various immune-related markers that are each associated with higher pCR rates and better survival following HER2-targeted therapies.[23,24] A multigene model using messenger RNA expression data from patients with HER2$^+$ inflammatory breast cancer who were randomly selected to receive paclitaxel and trastuzumab, with or without lapatinib, was predictive of pCR, with an impressive area under the receiver operating characteristic curve of 0.76 in the CALGB 40601 trial.[25] However, standardization and independent validation of this and other gene signatures are yet to be accomplished. How to predict the need for, and benefit from, individual components of multidrug HER2-targeted regimens also remains unsolved. In the NeoALTTO trial, a substantial interaction was found between immune and stromal gene expression signatures and pCR with trastuzumab plus lapatinib combined with paclitaxel versus one HER2-targeted drug and paclitaxel; however, this interaction was not seen for survival outcomes.[24] In the NeoSphere study, patients with HER2 membrane protein expression above the median had a marked benefit from the addition of pertuzumab to docetaxel and trastuzumab, whereas there was no benefit for patients with expression that was below the median.[26] These are select examples of intriguing findings that will require independent validation.

Sensitivity to HER2-targeting agents does not completely rely on HER2 overexpression; activating mutations in the *HER2* gene can confer sensitivity to single-agent neratinib (HER2 kinase inhibitor), and neratinib may even have activity in the absence of *HER2* mutation or gene amplification. In the I-SPY2 trial, high *STMN1* gene expression was associated with response to neratinib (concurrent with paclitaxel) in 48 patients with HER2$^-$ tumors.[27] Further validation of this biomarker is necessary before implementation in the clinic.

Immune Checkpoint Inhibition

Immune checkpoint inhibition emerged as a promising new treatment modality, particularly for TNBC (reviewed in Radosa et al[28]). However, overall response rates to single-agent therapy are low, indicating a pressing need for a predictive marker. In the metastatic TNBC setting, PD-L1 protein expression emerged as a U.S. Food and Drug Administration–approved predictive marker to select patients with TNBC for immune checkpoint therapy. In the randomized IMpassion130 trial, only PD-L1 immune cell–positive cancers (with SP142, 22C3, or SP263 assays) showed improved progression-free survival when atezolizumab was added to nab-paclitaxel. In the KEYNOTE-119 trial, objective response rates and progression-free survival with single-agent pembrolizumab increased almost linearly as PD-L1 positivity (22C3 assay) increased. The KEYNOTE-355 trial that compared pembrolizumab plus chemotherapy with chemotherapy plus placebo for metastatic TNBC also demonstrated improvement in progression-free survival in the pembrolizumab arm, but only in PD-L1$^+$ cancers (combined positive score $\geq$ 10 with 22C3 assay). The SAFIR02 trial randomly assigned patients with metastatic breast cancer who had response or stable disease after six to eight cycles of chemotherapy and did not have any actionable mutations to receive maintenance single-agent durvalumab or continuation of chemotherapy. Maintenance durvalumab had inferior progression-free survival in the entire trial population but resulted in improved overall survival in the PD-L1$^+$ (SP142 assay) subset of cancers. In contrast to the metastatic setting, it has not been possible to identify predictive biomarkers that identify stage II to III TNBC that selectively benefits from inclusion of immune checkpoint therapy with neoadjuvant chemotherapy. High tumor-infiltrating lymphocyte count, high expression of PD-L1 protein, and a broad range of immune-related genes all

predict for a higher pCR rate with chemotherapy alone, as well as with chemotherapy plus immune checkpoint therapy. Unlike in metastatic TNBC, PD-L1 protein expression does not define the population that selectively benefits from neoadjuvant immune checkpoint therapy. The biologic reasons behind the distinct predictive functions of PD-L1 in metastatic versus early-stage TNBC are unclear. However, overall, metastatic lesions have a more immune-attenuated tissue microenvironment, even when immune cells are present, compared with primary tumors.[29]

It is important to note that the performance of PD-L1 as a predictive biomarker for response to anti–PD-1/PD-L1 therapy shows low predictive accuracy with an area under the receiver operating characteristic curve of 0.65, even in metastatic disease. This can be explained by the fact that PD-L1 status is difficult to assess because of the very low thresholds applied (1% immune cell positivity with the SP142 assay or a combined positive score > 10 with the 22C3 assay), intratumor heterogeneity in expression, variable assay sensitivity, and large interobserver variability.[30] Tumor mutational burden has emerged as a complementary assay to define patients, regardless of cancer type, who might benefit from pembrolizumab immune checkpoint therapy. The FoundationOne next-generation sequencing assay is approved by the U.S. Food and Drug Administration for this purpose. Immune gene signatures, multiplex immunohistochemistry, and various spatial features of immune cell infiltration are also actively being investigated as potential complementary predictive markers for immunotherapy.[31]

Homologous Recombination Deficiency and Systemic Therapy

Homologous recombination is the primary pathway that is responsible for high-fidelity repair of double-strand DNA breaks. Patients with TNBC and homologous recombination deficiency due to a biallelic BRCA loss of function (usually through a combination of germline and somatic events) respond well to agents that cause double-strand DNA breaks, such as platinum or anthracycline-containing chemotherapies. Consequently, it was hypothesized that patients without BRCA mutations but with genomic "scars" or gene expression features resembling BRCA-mutant tumors may also have a defect in homologous recombination and, therefore, might be sensitive to these agents.[32] Subsequently, studies in metastatic breast cancer showed that patients with TNBC that harbor homologous recombination deficiency (i.e., germline BRCA mutation or homologous recombination deficiency assay positive) have greater benefit from platinum chemotherapy than from a microtubule inhibitor, whereas patients with nonhomologous recombination deficiency have no such differential sensitivity.[33] However, this relationship is not seen in neoadjuvant trials.[34]

Clinical trials also demonstrated substantial single-agent activity of PARP-1 inhibitors in breast cancers that harbor germline BRCA1, BCRA2, or PALB2 mutations or somatic BRCA mutations.[35,36] Several methods exist for detection of homologous recombination deficiency, such as analysis of sporadic or germline homologous recombination mutations, copy number signatures, single-nucleotide polymorphism–based assays, and transcriptional signatures.[32,35] Currently, only germline and somatic BRCA sequencing assays and the Myriad homologous recombination deficiency assay are used in the clinic in the United States to select patients for PARP-1 inhibitor therapy.

Rare Actionable Mutations

Next-generation sequencing assays of a few dozen to a few hundred potential therapeutic target genes are being used increasingly in the clinic to identify patients with metastatic cancer for targeted therapies. In estrogen receptor$^+$ metastatic breast cancer, detection of PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) mutations became important after the SOLAR-1 trial demonstrated a benefit from adding the PIK3CA inhibitor alpelisib to endocrine therapy with fulvestrant, but only in cancers with somatic mutations in the *PIK3CA* gene (median progression-free survival, 11.0 months vs. 5.7 months).[37] Other rare, but potentially actionable, mutations in breast cancer that are supported by clinical trial data include somatic BRCA mutations (for PARP inhibitors), HER2-activating mutations (for neratinib), and *NTRK1* (tropomyosin receptor kinase A) fusion genes (for larotrectinib). Mutations in the *ESR1* (estrogen receptor 1) gene are also commonly encountered in estrogen receptor$^+$ metastatic breast cancer, particularly after prior therapy with aromatase inhibitors. However, the clinical relevance of this finding is limited to recommending fulvestrant over exemestane.

Liquid Biopsy Biomarkers

Circulating biomarkers may better reflect intratumor heterogeneity than do tissue-based biomarkers and are amenable to repeated assessment during treatment. Analyses of mutations in circulating tumor DNA in the MONALEESA-2 trial suggested that patients with an alteration in receptor tyrosine kinase genes in breast cancer have less benefit from letrozole plus ribociclib compared with wild-type cancers.[38] In the PALOMA-3 trial, the ratio of baseline/cycle 5 circulating mutated *PIK3CA* gene copies was predictive of progression-free survival benefit with palbociclib.[39] In a phase I study of elacestrant, patients with estrogen receptor mutations in circulating tumor DNA had a much higher objective response rate than those who did not.[40] In the CirCe T-DM1 trial, patients with HER2$^-$ primary tumors, but HER2-amplified circulating tumor cells, were treated

with trastuzumab emtansine; unfortunately, only one of 11 patients achieved a partial response.[41] These studies highlight that there may be a lot of potential for liquid biopsies in response prediction, but major challenges must be overcome.

Challenges and Future Outlooks

Finding clinically useful predictive biomarkers is highly challenging because of a number of issues, including inter- and intratumor heterogeneity, variability between assays, lack of robustness, and insufficient discriminatory accuracy. Many biomarkers show associations with response to broad classes of therapeutic agents (e.g., chemotherapy, endocrine therapy, HER2-targeted agents, immunotherapy), but it has been very difficult to find drug-specific biomarkers. Furthermore, existing biomarkers are better at identifying who will not have a response to treatment (i.e., high negative predictive values) than predicting actual response to treatment (i.e., modest positive predictive value). With the increasing availability of genomic, transcriptomic, and proteomic data and the integration of these, we hope to come closer to developing clinically useful biomarkers.

OPPORTUNITIES AND CHALLENGES TO IMPLEMENTING ARTIFICIAL INTELLIGENCE IN HEALTH CARE

The past few years have seen an explosion of technologies powered by AI in health care, from triage and early detection to diagnosis to therapy.[42] Artificial intelligence–powered imaging and laboratory devices, medical robots, and mobile services, to mention just a few, almost certainly will improve the reach of high-quality health care across medical offices and countries, accelerate precision medicine, and help patients to proactively manage their health (Fig. 2). This section introduces promising developments in AI, followed by an overview of the challenges that still must be addressed in this field before reaching widespread use.

Decreasing Reader Variability While Improving Workflow Efficiency Through Artificial Intelligence

Medical imaging plays an important role in cancer diagnosis, treatment, and monitoring, but it is highly dependent on the interpretation of readers and their levels of expertise. The requirement of interpreting large amounts of complex data has exceeded the capacity of available specialists and brings new challenges to health care providers, especially in low- and middle-income countries. Recent advances in AI algorithms have resulted in substantial strides in the assessment of radiographic characteristics in medical images,[9] offering considerable promise for improving the efficacy and quality of clinical care. Deep learning is one form of AI that achieves great success in automated learning of imaging features when large, well-annotated databases are available to train the algorithms.[43]

Artificial intelligence–based computer-aided diagnosis and detection systems have shown promising results in the early screening of multiple diseases, including lung cancer, breast cancer, and prostate cancer, when evaluated against human operators.[42-44] This creates an opportunity to reduce the variability in screening quality by introducing AI systems as decision support for radiologists at various levels of training and experience. Artificial intelligence systems are also being developed to assist the image reading workflow. For instance, an AI-based software has been introduced to automatically process multiparametric MRI scans of the prostate, allowing radiologists to identify lesions and facilitate targeted biopsies more easily.[44] Radiation oncology is also greatly benefiting from AI.[45] Delineation of organs at risk is one of the most time-consuming manual tasks performed by radiation oncologists. Artificial intelligence has demonstrated promise in providing comparable autosegmentation of organs at risk to that of human experts. Additionally, dose

FIGURE 2. Hierarchy of Artificial Intelligence Systems in Health Care

distribution can be potentially optimized by AI approaches via integrating patient anatomy information and treatment machine parameters.

From Outcome Prediction to Patient-Specific Digital Twins

The RECIST criteria are widely used in oncology to assess treatment response. However, these size-based metrics are questioned because they oversimplify the complex imaging features of tumors.[46] Radiomics analysis was introduced to comprehensively characterize and compare tumor geometric and textural appearance in images.[46] High-dimensional hand-crafted features can be automatically computed from images to predict the overall survival of patients with non–small cell lung cancer in response to radiotherapy, chemotherapy, or immunotherapy.[46,47] Recently, a deep-learning method, DeepProfiler, was introduced to automatically learn tumor-imaging characteristics that are associated with prognosis.[47] Using the consolidated information from imaging and clinical variables, DeepProfiler provided an estimation of local failure of stereotactic body radiation therapy and enabled individualized dosing to increase tumor control. Studies have also shown the capability of AI to predict gene mutations from histopathology images.[48] Building on these achievements, researchers are actively investigating methods that combine radiomics and genomics information for individualized outcome prediction.[49]

Digital twins of patients are also being developed, inspired by their industrial counterpart. Fueled by the increased digitalization and broad range of biologic measurements of functions of the human body, digital twins combine AI with computational models of human physiology to generate patient-specific models from medical data (Fig. 3). By integrating multimodal information, digital twins have the potential to quantify a patient's pathophysiology (e.g., tumor growth rate) more precisely.[50,51] The hope is that digital twins could enable in silico simulation of various interventions and assess their potential effects on the patient before any treatment begins. For example, an individualized model of the liver, estimated from images, was used to predict ablation extent and tumor coverage.[52] Digital twins is also being explored to model multiscale multi-omics interactions for drug discovery and treatment efficacy prediction.[53]

Artificial Intelligence–Assisted Automation and Services to Improve Access of Care

One of the biggest challenges in health care, within a country and globally, is to provide equal access to the same high-quality care. Staff shortages, differences in levels of provider training and skill, and dissimilarities in infrastructure and availability of equipment have created variable levels of care, including areas known as "medical deserts." Digitalization and AI could address some of these challenges. Artificial intelligence–assisted image reading aims at improving interrater variability for a more consistent and precise diagnosis throughout clinical sites. Medical systems are being reinvented with more intuitive and simplified user experiences thanks to AI-assisted automation. Minimally invasive procedures are benefiting from automation to simplify their execution, making them safer and more cost effective (e.g., through fully automatic multimodality image fusion).[54] Robotics solutions are assisting surgeons with performing more precise procedures; they may even enable highly specialized surgeons to operate on patients remotely in geographically isolated areas with modest assistance from a local health care provider.[55] Strides are being made in the capability of mobile and wearable devices to provide consumers and their care providers with actionable quantitative health information, from wellness to home monitoring of physical activity and vital signs after procedures or discharge from the hospital.

Challenges Ahead

Despite the tremendous progress of the past few years, many challenges still remain to fully harness the potentials of AI in health care.[50] First, scaling up the development of multimodal AI solutions requires more consolidated access to data that are still stored in a variety of systems that do not necessarily share a common data-exchange interface. To address this challenge, electronic medical records and standards like Fast Healthcare Interoperability Resources are facilitating interconnectivity, whereas clinical-decision support solutions are being deployed to integrate data from multiple sources into a single common system.[56]

Second, data privacy needs to be thoroughly ensured. While regulations are being updated to protect patients and consumers (e.g., Health Insurance Portability and Accountability Act [United States], California Consumer Privacy Act, General Data Protection Regulation [Europe]), privacy-by-design AI technologies are actively being investigated. For instance, federated learning proposes to train AI algorithms locally and only pool the resulting models centrally, alleviating the need to share patient data with researchers. Homomorphic encryption techniques are being investigated to encrypt data such that AI processing can be done on the encrypted file directly, whereas blockchain architectures are being explored to ensure full decentralization.[57]

Third, AI in oncology is challenged by the inherent variability of the disease and therapies. Each cancer is unique, with many therapy options possible, making large-scale data acquisition for AI training challenging. Artificial intelligence is already contributing to more precise screening and diagnosis of the most common cancers (e.g., breast and lung cancers). Yet, progress in AI theory and engineering is needed to enable precision medicine at scale, where

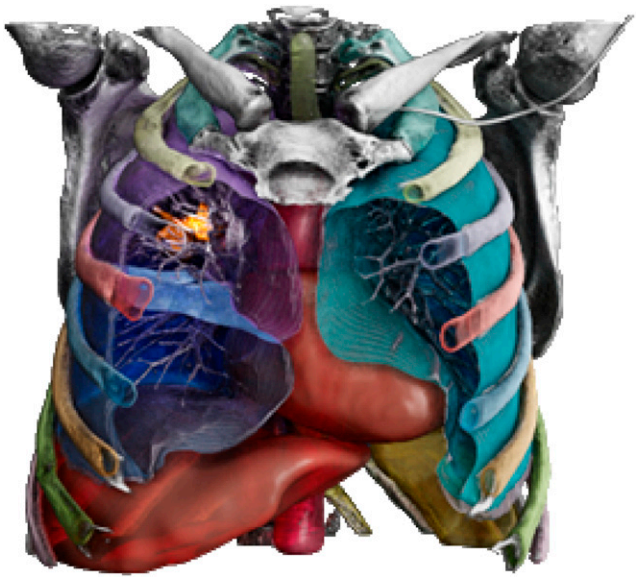

FIGURE 3. Rendering of CT Scans With Artificial Intelligence–Based Automatic Organ Segmentation (in colors) and Lesion Detection (in yellow)
Data courtesy of University Hospital Erlangen, Erlangen, Germany.

therapy can be tailored to the individual. To that end, researchers are investigating methods based on causality, reasoning, and self-supervision (e.g., to be able to train robust and performant AI systems on small data sets).[58]

Lastly, AI systems are required to provide insights and confidence estimates about their decision. On one hand, uncertainty-quantification techniques are being researched by the community. On the other hand, collaborative systems of AI modules are being implemented instead of end-to-end neural networks, to increase transparency and controllability. Similarly, strategies to minimize biases in AI, a very important issue, are currently being defined, such as guidelines for the definition of diverse training cohorts.[59] Finally, educational programs in AI for medicine will be crucial to increase physicians' literacy in AI, teaching them about AI's ever-evolving capabilities and potential limitations.[60]

In conclusion, AI and digitalization are poised to transform health care as we know it. Although challenges still lie ahead, the community is working tirelessly to find solutions for safe, privacy-centric, and trustable AI solutions that have the potential to reduce variability in care throughout regions, enable more precise diagnosis and therapy, and increase the reach of high-quality care worldwide.

ADAPTING INDIVIDUALIZED TREATMENT PLANS TO CARE FOR EACH PATIENT

Individualized treatment plans have come a long way since the Ebers Papyrus. Personalized recommendations are incorporated into the entire spectrum of cancer management (Fig. 4). For example, multivariate risk-prediction models (e.g., The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, BRCAPRO breast cancer risk assessment tool, International Breast Cancer Risk Assessment Study) that incorporate various combinations of personal information, including age, ethnicity, age at menarche, parity, age at first birth, menopausal status, body mass index, history of benign proliferative breast lesions, mammographic density, and detailed family history, can provide individualized percentage risk estimates of developing breast cancer in the next 5 to 10 years.[61] This information can be used to guide genetic testing and breast cancer–screening decisions. Breast cancer mammographic screening also evolved toward increasingly individualized strategies: women with dense breasts now routinely undergo supplementary screening with annual ultrasonograms or MRI, and individuals with very high risk have more frequent screening than do women with average risk. The reporting of breast imaging results has been standardized (Breast Imaging Reporting and Data System, BI-RADS; www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Bi-Rads), and the terminology guides subsequent recommendations for follow-up procedures. If the diagnosis of invasive breast carcinoma is established by a breast biopsy, patients are triaged into one of the three major clinical subtypes of breast cancer: hormone receptor$^+$, HER2$^+$, or TNBC with distinct therapeutic implications. The percentage probabilities of recurrence and overall survival can be estimated for an individual by combining information from age at diagnosis, menopausal status, hormone receptor and HER2 status, tumor proliferative activity (i.e., Ki-67 status), tumor size, number of positive nodes, histologic grade, and detection method (i.e., mammographic screening vs. self-palpated) using a validated multivariate prognostic model (breast.predict.nhs.uk/tool).

After understanding the baseline risk of recurrence, an individualized estimate of percentage benefit from various treatment modalities can be calculated and discussed with the patient. In hormone receptor$^+$ disease, additional gene expression–based molecular tests can further refine the prognostic risk and identify patients who would have excellent long-term disease-free survival with endocrine therapy alone.[62] These molecular diagnostic tests (e.g., Oncotype DX Recurrence Score, MammaPrint, Prosigna, EndoPredict, Breast Cancer Index) have enabled hundreds of thousands of women to avoid adjuvant chemotherapy without jeopardizing their survival. Randomized clinical trials continue to refine our understanding of how to use these molecular assays. Most recently, the first interim results of the RxPONDER trial demonstrated that, even among patients with one to three positive lymph nodes,

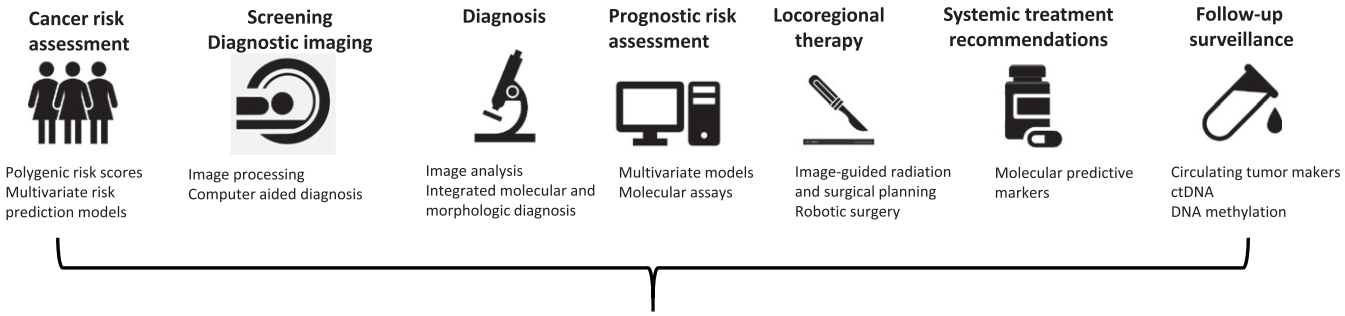

FIGURE 4. Personalization of Treatment Plans Through Technology Across the Spectrum of Disease Management
Abbreviation: ctDNA, circulating tumor DNA.

a subset of postmenopausal women who have a recurrence score less than 26 do not derive benefit from adjuvant chemotherapy and can be safely treated with adjuvant endocrine therapy alone.[63] By using molecular diagnostic tests, we can also make individualized predictions about the probability of benefit from extending adjuvant endocrine therapy beyond 5 years.[64] The increasing use of preoperative chemotherapy in HER2$^+$ and TNBCs allows further customization of postoperative adjuvant chemotherapy based on the extent of residual cancer found at the time of surgery.[65] Patients with substantial residual cancer burden after neoadjuvant chemotherapy can receive further treatment that improves their recurrence-free survival.

Individualized treatment plans do not end at selecting systemic adjuvant therapies for early-stage breast cancer; the previously rather uniform radiation therapy and surgery treatment strategies are also increasingly flexible and tailored for patient age and risk of locoregional recurrence. Clinical nomograms can be used to estimate the probability of finding positive axillary lymph nodes at diagnosis or after an initial positive sentinel node biopsy, and this information can guide decisions about subsequent axillary lymph node dissection or even skipping lymph node sampling altogether.[66] Accelerated postlumpectomy radiation treatment plans also exist that can shorten the traditional 5 weeks of radiation therapy for selected patients.[67]

A truly individualized treatment plan cannot be formulated without input from the patient. We all have different risk-benefit tolerance; perhaps one of the most important contributions of the existing prognostic and predictive tools is that they empower patients to make an informed decision about the various alternative treatment strategies that are available to diagnose and treat early-stage breast cancer.

What Is Next?

The past 20 years have seen remarkable progress in diagnostic technologies, coupled with the introduction of several dozen new drugs to treat cancer that have translated into improved survival for many cancer types. Survival of early-stage breast cancer has improved by 25% to 40% during this time period; unfortunately, it continues to show large variations between regions of the world, as well as by race and socioeconomic status within the United States.[68] Progress in individualizing treatment plans will accelerate further in the coming years. Adding polygenic risk scores derived from germline sequencing to clinical risk-prediction models will likely improve predictions of cancer risk, which will improve individualization of cancer-screening strategies. An example is the ongoing WISDOM study (NCT02620852), which is an adaptive randomized clinical trial comparing a comprehensive risk-based personalized screening with traditional annual breast cancer screening. Artificial intelligence–driven improvements in image analysis are expected to improve the precision of breast imaging to distinguish benign lesions from malignant lesions.[69] Novel molecular diagnostic tests are emerging in TNBC and HER2$^+$ breast cancers to refine prognosis beyond the clinical stage, the same way that gene expression profiling assays did in hormone receptor$^+$ disease. The extent of lymphocytic infiltration is showing clinically meaningful prognostic risk stratification in TNBC,[70] and a combination of HER2 expression, PIK3CA mutation, and molecular subtype may identify HER2$^+$ breast cancers with excellent prognosis.[71] Clinical trials are underway in HER2$^+$ breast cancer (CompassHER2-pCR, NCT04266249) and are planned in TNBC, to explore the potential of using pathologic response to neoadjuvant chemotherapy to optimize chemotherapy intensity. Patients with pCR even after a short minimally toxic therapy may not need more aggressive systemic therapy, whereas those with residual disease could receive more treatment after surgery to improve their survival. Molecular target profiling, which is already used in metastatic breast cancer to identify potentially targetable molecular abnormalities, will likely be explored in the adjuvant/neoadjuvant treatment setting to accelerate the introduction of effective targeted therapies in the early-stage curative setting.

Monitoring of circulating tumor DNA is perhaps one of the most exciting new technologies that could bring about

a paradigm shift in monitoring of patients with early-stage disease who have completed local and systemic therapies. Multiple small studies demonstrated that the presence of tumor-derived DNA in the blood during follow-up of asymptomatic clinically cancer-free patients heralds metastatic recurrence in 70% to 80% of patients within 6 to 10 months. Detection of molecular relapse before clinically apparent metastatic recurrence raises the tantalizing possibility that early intervention with a "second-line" adjuvant therapy might avert the impending clinical recurrence. Molecular monitoring for residual disease in hematologic malignancies, or for prostate-specific antigen failure in prostate cancer, followed by early systemic therapy improved recurrence-free survival in leukemias and in prostate cancer. A clinical trial is now underway to explore this strategy in estrogen receptor$^+$ early-stage breast cancer (DARE, NCT04567420).

Most of the examples in this article are taken from the breast cancer literature because there are extensive data to support screening of asymptomatic individuals, several clinically validated prognostic risk-prediction models exist, and molecular diagnostics tests are used to select patients for adjuvant chemotherapy. These advances clearly illustrate the evolution of individualizing treatment recommendations over the past 20 years, enabling personalized screening and de-escalation of care for many patients, while selecting patients at risk for recurrence who would benefit from more aggressive therapy. These same advances are also happening in most other cancer types and no doubt will accelerate in the coming years.

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The concepts and information presented in the "Opportunities and Challenges to Implementing Artificial Intelligence in Health Care" section are based on research results that are not commercially available.

AFFILIATIONS

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REFERENCES

1. Carmichael AG, Ratzan RM, (eds). Medicine: A Treasury of Art and Literature. New York: Beaux Arts Editions; 2001.
2. O'Connor JP, Aboagye EO, Adams JE, et al. Imaging biomarker roadmap for cancer studies. Nat Rev Clin Oncol. 2017;14:169-186.
3. Fournier L, Costaridou L, Bidaut L, et al. Incorporating radiomics into clinical trials: expert consensus on considerations for data-driven compared to biologically driven quantitative biomarkers. Eur Radiol. Epub 2021 Jan 25.
4. Shukla-Dave A, Obuchowski NA, Chenevert TL, et al. Quantitative imaging biomarkers alliance (QIBA) recommendations for improved precision of DWI and DCE-MRI derived biomarkers in multicenter oncology trials. J Magn Reson Imaging. 2019;49:e101-e121.
5. Huang EP, Lin FI, Shankar LK. Beyond correlations, sensitivities, and specificities: a roadmap for demonstrating utility of advanced imaging in oncology treatment and clinical trial design. Acad Radiol. 2017;24:1036-1049.
6. Barker AD, Sigman CC, Kelloff GJ, et al. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther. 2009;86:97-100.
7. Onishi N, Li W, Gibbs J, et al. Impact of MRI protocol adherence on prediction of pathological complete response in the I-SPY 2 neoadjuvant breast cancer trial. Tomography. 2020;6:77-85.
8. Lobbes MB, Prevos R, Smidt M, et al. The role of magnetic resonance imaging in assessing residual disease and pathologic complete response in breast cancer patients receiving neoadjuvant chemotherapy: a systematic review. Insights Imaging. 2013;4:163-175.
9. Marinovich ML, Macaskill P, Irwig L, et al. Agreement between MRI and pathologic breast tumor size after neoadjuvant chemotherapy, and comparison with alternative tests: individual patient data meta-analysis. BMC Cancer. 2015;15:662.
10. Fukuda T, Horii R, Gomi N, et al. Accuracy of magnetic resonance imaging for predicting pathological complete response of breast cancer after neoadjuvant chemotherapy: association with breast cancer subtype. Springerplus. 2016;5:152.

11. Yu N, Leung VWY, Meterissian S. MRI performance in detecting pCR after neoadjuvant chemotherapy by molecular subtype of breast cancer. World J Surg. 2019; 43:2254-2261.
12. van Loevezijn AA, van der Noordaa MEM, van Werkhoven ED, et al. Minimally Invasive Complete Response Assessment of the Breast After Neoadjuvant Systemic Therapy for Early Breast Cancer (MICRA trial): interim analysis of a multicenter observational cohort study. Ann Surg Oncol. Epub 2020 Dec 2.
13. Sutton EJ, Braunstein LZ, El-Tamer MB, et al. Accuracy of magnetic resonance imaging-guided biopsy to verify breast cancer pathologic complete response after neoadjuvant chemotherapy: a nonrandomized controlled trial. JAMA Netw Open. 2021;4:e2034045.
14. Tasoulis MK, Lee HB, Yang W, et al. Accuracy of post-neoadjuvant chemotherapy image-guided breast biopsy to predict residual cancer. JAMA Surg. 2020; 155:e204103.
15. Graeser M, Schrading S, Gluz O, et al. Early response by MR imaging and ultrasound as predictor of pathologic complete response to 12-week neoadjuvant therapy for different early breast cancer subtypes: Combined analysis from the WSG ADAPT subtrials. Int J Cancer. Epub 2021 Feb 3.
16. Marinovich ML, Sardanelli F, Ciatto S, et al. Early prediction of pathologic response to neoadjuvant therapy in breast cancer: systematic review of the accuracy of MRI. Breast. 2012;21:669-677.
17. Granzier RWY, van Nijnatten TJA, Woodruff HC, et al. Exploring breast cancer response prediction to neoadjuvant systemic therapy using MRI-based radiomics: a systematic review. Eur J Radiol. 2019;121:108736.
18. Zwanenburg A, Vallières M, Abdalah MA, et al. The Image Biomarker Standardization Initiative: standardized quantitative radiomics for high-throughput image-based phenotyping. Radiology. 2020;295:328-338.
19. Li W, Newitt DC, Gibbs J, et al. Predicting breast cancer response to neoadjuvant treatment using multi-feature MRI: results from the I-SPY 2 TRIAL. NPJ Breast Cancer. 2020;6:63.
20 Venters S. Serial MRI and pathology combined to select candidates for therapy de-escalation in the I-SPY 2 TRIAL. Presented at: San Antonio Breast Cancer Symposium. San Antonio, TX; 2020. Abstract PS4-10.
21. Hayes DF. Defining clinical utility of tumor biomarker tests: a clinician's viewpoint. J Clin Oncol. 2021;39:238-248.
22. Payne SJ, Bowen RL, Jones JL, et al. Predictive markers in breast cancer--the present. Histopathology. 2008;52:82-90.
23. Dieci MV, Prat A, Tagliafico E, et al. Integrated evaluation of PAM50 subtypes and immune modulation of pCR in HER2-positive breast cancer patients treated with chemotherapy and HER2-targeted agents in the CherLOB trial. Ann Oncol. 2016;27:1867-1873.
24. Fumagalli D, Venet D, Ignatiadis M, et al. RNA sequencing to predict response to neoadjuvant anti-HER2 Therapy: a secondary analysis of the NeoALTTO randomized clinical trial. JAMA Oncol. 2017;3:227-234.
25. Tanioka M, Fan C, Parker JS, et al. Integrated analysis of RNA and DNA from the phase III Trial CALGB 40601 identifies predictors of response to trastuzumab-based neoadjuvant chemotherapy in HER2-positive breast cancer. Clin Cancer Res. 2018;24:5292-5304.
26. Bianchini G, Kiermaier A, Bianchi GV, et al. Biomarker analysis of the NeoSphere study: pertuzumab, trastuzumab, and docetaxel versus trastuzumab plus docetaxel, pertuzumab plus trastuzumab, or pertuzumab plus docetaxel for the neoadjuvant treatment of HER2-positive breast cancer. Breast Cancer Res. 2017;19:16.
27. Wulfkuhle JD, Yau C, Wolf DM, et al. Evaluation of the HER/PI3K/AKT family signaling network as a predictive biomarker of pathologic complete response for patients with breast cancer treated with neratinib in the I-SPY 2 trial. JCO Precis Oncol. 2018;2:PO.18.00024.
28. Radosa JC, Stotz L, Müller C, et al. Clinical data on immunotherapy in breast cancer. Breast Care (Basel). 2020;15:450-469.
29. Szekely B, Bossuyt V, Li X, et al. Immunological differences between primary and metastatic breast cancer. Ann Oncol. 2018;29:2232-2239.
30. Reisenbichler ES, Han G, Bellizzi A, et al. Prospective multi-institutional evaluation of pathologist assessment of PD-L1 assays for patient selection in triple negative breast cancer. Mod Pathol. 2020;33:1746-1752.
31. Lu S, Stein JE, Rimm DL, et al. Comparison of biomarker modalities for predicting response to PD-1/PD-L1 checkpoint blockade: a systematic review and meta-analysis. JAMA Oncol. 2019;5:1195-1204.
32. Lord CJ, Ashworth A. BRCAness revisited. Nat Rev Cancer. 2016;16:110-120.
33. Telli ML, Timms KM, Reid J, et al. Homologous Recombination Deficiency (HRD) score predicts response to platinum-containing neoadjuvant chemotherapy in patients with triple-negative breast cancer. Clin Cancer Res. 2016;22:3764-3773.
34. Loibl S, Weber KE, Timms KM, et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response-final results from GeparSixto. Ann Oncol. 2018;29:2341-2347.
35. Hoppe MM, Sundar R, Tan DSP, et al. Biomarkers for homologous recombination deficiency in cancer. J Natl Cancer Inst. 2018;110:704-713.
36. Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol. 2020;31:1526-1535.
37. André F, Ciruelos E, Rubovszky G, et al; SOLAR-1 Study Group. Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. N Engl J Med. 2019;380:1929-1940.
38. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol. 2018;29:1541-1547.
39. O'Leary B, Hrebien S, Morden JP, et al. Early circulating tumor DNA dynamics and clonal selection with palbociclib and fulvestrant for breast cancer. Nat Commun. 2018;9:896.

40. Bardia A, Kaklamani V, Wilks S, et al. Phase I study of elacestrant (RAD1901), a novel selective estrogen receptor degrader, in ER-positive, HER2-negative advanced breast cancer. J Clin Oncol. Epub 2021 Jan 29.

41. Jacot W, Cottu P, Berger F, et al. Actionability of HER2-amplified circulating tumor cells in HER2-negative metastatic breast cancer: the CirCe T-DM1 trial. Breast Cancer Res. 2019;21:121.

42. Bi WL, Hosny A, Schabath MB, et al. Artificial intelligence in cancer imaging: clinical challenges and applications. CA Cancer J Clin. 2019;69:127-157.

43. McKinney SM, Sieniek M, Godbole V, et al. International evaluation of an AI system for breast cancer screening. Nature. 2020;577:89-94.

44. Winkel DJ, Wetterauer C, Matthias MO, et al. Autonomous detection and classification of PI-RADS lesions in an MRI screening population incorporating multicenter-labeled deep learning and biparametric imaging: proof of concept. Diagnostics (Basel). 2020;10:951.

45. Huynh E, Hosny A, Guthier C, et al. Artificial intelligence in radiation oncology. Nat Rev Clin Oncol. 2020;17:771-781.

46. Aerts HJWL, Velazquez ER, Leijenaar RTH, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun. 2014;5:4006.

47. Lou B, Doken S, Zhuang T, et al. An image-based deep learning framework for individualising radiotherapy dose: a retrospective analysis of outcome prediction. Lancet Digit Health. 2019;1:e136-e147.

48. Coudray N, Ocampo PS, Sakellaropoulos T, et al. Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning. Nat Med. 2018;24:1559-1567.

49. Murdoch WJ, Singh C, Kumbier K, et al. Definitions, methods, and applications in interpretable machine learning. Proc Natl Acad Sci USA. 2019; 116:22071-22080.

50. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25:44-56.

51. Anderson ARA, Weaver AM, Cummings PT, et al. Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment. Cell. 2006;127:905-915.

52. Audigier C, Mansi T, Delingette H, et al. Efficient lattice boltzmann solver for patient-specific radiofrequency ablation of hepatic tumors. IEEE Trans Med Imaging. 2015;34:1576-1589.

53. Rostami-Hodjegan A, Tucker GT. Simulation and prediction of in vivo drug metabolism in human populations from in vitro data. Nat Rev Drug Discov. 2007; 6:140-148.

54 Liao R, Miao S, de Tournemire P, et al. An artificial agent for robust image registration. In Proceedings of the Thirty-First AAAI Conference on Artificial Intelligence, 2017;4168-4175.

55. Patel TM, Shah SC, Pancholy SB. Long distance tele-robotic-assisted percutaneous coronary intervention: a report of first-in-human experience. EClinicalMedicine. 2019;14:53-58.

56. Zindel C, Herrmann K. A conversation between Christoph Zindel and Ken Herrmann. J Nucl Med. 2020;61:1088-1090.

57. Kaissis GA, Makowski MR, Rückert D, et al. Secure, privacy-preserving and federated machine learning in medical imaging. Nat Mach Intell. 2020;2:305-311.

58. Pearl J. The seven tools of causal inference, with reflections on machine learning. Commun ACM. 2019;62:54-60.

59. Jercich K. "FDA Highlights the Need To Address Bias in AI." Healthcare IT News, October 22, 2020. www.healthcareitnews.com/news/fda-highlights-need-address-bias-ai.

60. Rampton V, Mittelman M, Goldhahn J. Implications of artificial intelligence for medical education. Lancet Digit Health. 2020;2:e111-e112.

61. Terry MB, Liao Y, Whittemore AS, et al. 10-year performance of four models of breast cancer risk: a validation study. Lancet Oncol. 2019;20:504-517.

62. Telli ML, Gradishar WJ, Ward JH. NCCN guidelines updates: breast cancer. J Natl Compr Canc Netw. 2019;17:552-555.

63 Kalinsky K, Barlow WE, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET)+/– chemotherapy (CT) in patients (pts) with 1- 3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS)< 25: SWOG S1007 (RxPonder). Paper presented at: San Antonio Breast Cancer Symposium. San Antonio, TX; 2020. Abstract GS3-00.

64. Anandan A, Sharifi M, O'Regan R. Molecular assays to determine optimal duration of adjuvant endocrine therapy in breast cancer. Curr Treat Options Oncol. 2020;21:84.

65. Pusztai L, Foldi J, Dhawan A, et al. Changing frameworks in treatment sequencing of triple-negative and HER2-positive, early-stage breast cancers. Lancet Oncol. 2019;20:e390-e396.

66. Chang JM, Leung JWT, Moy L, et al. Axillary nodal evaluation in breast cancer: state of the art. Radiology. 2020;295:500-515.

67. Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: long-term results of the randomized phase III APBI-IMRT-Florence trial. J Clin Oncol. 2020;38:4175-4183.

68. Sung H, Ferlay J, Siegel RL, Laversanne M, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. Epub 2021 Feb 4.

69. Yala A, Mikhael PG, Strand F, et al. Toward robust mammography-based models for breast cancer risk. Sci Transl Med. 2021;13:eaba4373.

70. Park JH, Jonas SF, Bataillon G, et al. Prognostic value of tumor-infiltrating lymphocytes in patients with early-stage triple-negative breast cancers (TNBC) who did not receive adjuvant chemotherapy. Ann Oncol. 2019;30:1941-1949.

71. Llombart-Cussac A, Cortés J, Paré L, et al. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. Lancet Oncol. 2017;18:545-554.

BREAST CANCER

When the World Throws You a Curve Ball: Lessons Learned in Breast Cancer Management

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Overview

In the care of patients with operable breast cancer, there has been a shift toward increasing use of neoadjuvant therapy. There are benefits to neoadjuvant therapy, such as monitoring for response, as well as an increased rate of breast conservation and reduction of potential morbidity associated with breast surgery, including axillary management. Among patients with highly proliferative tumors, such as HER2-positive or triple-negative breast cancer, those with residual disease are at higher risk of recurrence, which informs the recommended systemic therapy in the adjuvant setting. For instance, in patients with residual disease after neoadjuvant chemotherapy and HER2-targeted therapy, there is a role for adjuvant trastuzumab emtansine for those with residual disease at the time of surgery. The same holds true regarding the role of adjuvant capecitabine in patients with residual disease after neoadjuvant chemotherapy. With the added complexities of treating patients in the era of the COVID-19 outbreak, additional considerations are critical, including initiation of surgery within an appropriate time from completion of neoadjuvant therapy. National consensus guidelines on time to surgery must be developed to improve measurement and comparison across systems. In addition, there is emerging radiation treatment management research addressing a number of factors, including hypofractionation, role of proton beam therapy, safe omission of radiotherapy, and preoperative radiotherapy with or without drug combination. In this article, the multidisciplinary approach of treating patients with operable breast cancer is highlighted, with updates and future considerations described.

WHY SURGERY IS NOT ALWAYS FIRST: IDEAL INDICATIONS FOR PREOPERATIVE SYSTEMIC THERAPY

Neoadjuvant therapy refers to therapy administered before surgery. When evaluating a one-size-fits-all approach to neoadjuvant compared with adjuvant chemotherapy in randomized trials treating all breast cancer subtypes, there was no benefit in clinical outcomes based on the timing of chemotherapy.[1,2] However, with advances in systemic therapy, such as use of HER2-targeted therapies for HER2-positive breast cancer and evaluation of the prognostic significance of pathologic response by tumor subtype, it has been observed in various pooled analyses that patients with proliferative tumors, such as those with HER2-positive or triple-negative breast cancer, who achieve a pathologic complete response have a lower likelihood of recurrence compared with those with residual disease.[3,4] In addition, patients with HER2-positive or triple-negative breast cancer with residual disease after neoadjuvant therapy are candidates for adjuvant trastuzumab emtansine or capecitabine, respectively. Therefore, when reviewing the indications for neoadjuvant therapy, it is important to consider breast cancer subtype.

HER2-Positive Breast Cancer: The Importance of Neoadjuvant Therapy

HER2-targeted therapy has changed the landscape of treating patients with HER2-positive breast tumors. In patients with high-risk node-negative or node-positive breast cancer, dual HER2-targeted therapy with pertuzumab and trastuzumab in combination with chemotherapy leads to a higher pathologic complete response rate compared with single-agent HER2-targeted therapy with chemotherapy. Data from the neoadjuvant NeoSphere trial led to the accelerated, and eventually full, approval of pertuzumab in the neoadjuvant setting.[5,6] Importantly, in the KATHERINE trial, patients with residual disease after neoadjuvant chemotherapy and HER2-targeted therapy had an improvement in invasive disease-free survival if randomly assigned to receive trastuzumab emtansine as opposed to trastuzumab.[7] The KATHERINE trial led to the approval of trastuzumab emtansine in this setting. It is worth highlighting that patients with T1cN0 disease were eligible for the KATHERINE trial and that, in the forest plot, all subgroups of patients benefited from trastuzumab emtansine.

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PRACTICAL APPLICATIONS

- When considering neoadjuvant therapy, take into account the intent of the therapy, including therapy response monitoring and/or a less invasive surgical approach, such as breast conservation or axillary surgery management.
- Patients with HER2-positive breast cancer with residual disease after HER2 therapies and chemotherapy in the neoadjuvant setting benefit from adjuvant trastuzumab emtansine.
- Patients with triple-negative breast cancer with residual disease after chemotherapy in the neoadjuvant setting benefit from adjuvant capecitabine.
- National consensus guidelines on time to surgery must be developed to improve time to surgery measurement and comparison across systems.
- There are a number of emerging questions regarding radiation treatment, including hypofractionation, safe omission of radiotherapy in those at low risk of relapse, role of proton beam therapy in patients at higher risk of relapse, and preoperative radiotherapy with or without drug combination.

There are a number of ongoing studies in this space, including the CompassHER2 trial, which is enrolling patients with stage III or IIIA HER2-positive breast cancer and administering 12 weeks of a taxane plus trastuzumab and pertuzumab (NCT04266249). If patients achieve pathologic complete response, they complete trastuzumab and pertuzumab treatment. If patients have residual disease, they are eligible for the Alliance 11801 trial, in which patients are randomly assigned to receive trastuzumab emtansine alone or in combination with tucatinib (NCT04457596). In addition, the NSABP B-60 will randomly assign patients with HER2-positive residual disease after neoadjuvant therapy to receive trastuzumab deruxtecan or trastuzumab emtansine (NCT04622319). Given other notable drugs recently approved for the treatment of HER2-positive metastatic breast cancer, it is anticipated that the treatment of HER2-positive breast cancer will continue to evolve in the coming years.

Perioperative Management of Triple-Negative Breast Cancer

Triple-negative breast cancer accounts for 15% of all breast cancers and refers to breast cancers that lack expression of the estrogen receptor, progesterone receptor, and HER2. Compared with hormone receptor–positive and HER2-positive breast cancers, triple-negative breast tumors tend to act more aggressively, with a higher incidence of relapse within the first 3 years of diagnosis and a higher rate of 0.1ptdistant recurrence at first relapse.[8,9] Moreover, unlike hormone receptor–positive and HER2-positive breast cancers, where use of targeted therapy is standard of care to decrease risk of recurrence, there are no targeted therapies available for treatment of triple-negative breast cancer. Multiple studies have demonstrated improvement in outcomes in patients with triple-negative breast cancer who received perioperative chemotherapy compared with patients who did not.[1,10,11] Guidelines recommend patients with tumors larger than 1 cm (at least T1c) or with lymph node–positive disease irrespective of tumor size be offered chemotherapy.[12]

Neoadjuvant chemotherapy achieves the same long-term tumor control and survival as adjuvant therapy. However, neoadjuvant therapy is preferred, given the ability to downstage tumors, allowing for surgical minimization. Receipt of neoadjuvant chemotherapy is also prognostic, with patients who achieve pathologic complete response having a decreased risk of recurrence.[13,14] Moreover, in patients who receive neoadjuvant chemotherapy and have residual disease at time of surgery, additional adjuvant therapy can be used to decrease the risk of recurrence and improve overall survival. In the CREATE-X trial, patients with triple-negative breast cancer with residual disease in the breast and/or lymph node at time of surgery were randomly assigned to receive capecitabine or undergo observation. Patients with triple-negative breast cancer treated with adjuvant capecitabine had improved disease-free survival and overall survival compared with those who did not receive capecitabine.[15]

In terms of choice of neoadjuvant chemotherapy, a regimen containing an anthracycline and taxane is recommended based on clinical trials showing improved outcomes in women with triple-negative breast cancer treated with anthracycline and taxane–containing regimens compared with taxotere and cyclophosphamide without an anthracycline.[16] The use of carboplatin has been shown to improve rates of pathologic complete response.[17,18] However, there have been inconsistent data regarding the addition of carboplatin and improvement in clinical outcomes, given that these studies were not powered to look at outcome differences.[17,19] With associated increased rates of hematologic toxicity, the role of carboplatin remains controversial. The EA1131 trial (NCT02445391) was designed to address the role of platinums in the adjuvant setting. In March 2021, the independent data safety monitoring committee recommended that EA1131 be closed to accrual early because the trial was unlikely to show that a platinum drug was superior or noninferior to capecitabine, given the invasive disease-free survival events observed in both arms. Additionally, more grade 3 and 4 toxicities were observed in the platinum arm.

Despite the current management of triple-negative breast cancer, early recurrence rates remain high. New therapy modalities, including use of immunotherapy, have been explored. The I-SPY 2 study is an ongoing, open-label, adaptively randomized phase II multicenter trial of neoadjuvant chemotherapy for early-stage breast cancer in patients at high risk of recurrence (NCT01042379).[20,21] I-SPY 2 is a platform trial evaluating multiple investigational arms in parallel, each consisting of standard neoadjuvant chemotherapy plus an investigational agent. When added to standard neoadjuvant taxane and anthracycline–based chemotherapy, pembrolizumab more than doubled the estimated pathologic complete response rates for patients with triple-negative and hormone receptor–positive, HER2-negative breast cancer, indicating that checkpoint blockade was highly likely to succeed in a phase III trial.[22] Randomized trials where immunotherapy (pembrolizumab or atezolizumab) was combined with chemotherapy demonstrated improved pathologic complete response rates in patients who received immunotherapy. However, patients who received immunotherapy were also noted to have higher rates of serious adverse events, and long-term outcome data remain immature.[23-25] In February 2021, the Oncologic Drugs Advisory Committee of the U.S. Food and Drug Administration did not recommend approval of pembrolizumab in the surgical setting at this time, because data for event-free survival required additional maturity.[23,24] The S1418 trial is randomly assigning patients with triple-negative or low estrogen receptor–positive, HER2-negative breast cancer and residual disease after neoadjuvant chemotherapy to receive or not receive 1 year of pembrolizumab (NCT02954874).

Implications in Hormone Receptor–Positive/ HER2-Negative Disease and Data From the COVID-19 Era

The indications for preoperative therapy in hormone receptor–positive, HER2-negative breast cancer include large primary tumors and locally advanced disease, with the goal of improving surgical outcomes and controlling disease progression. Pathologic complete response (< 20%), a surrogate endpoint for improved disease-free survival and overall survival, with neoadjuvant chemotherapy is less likely to be achieved in hormone receptor–positive, HER2-negative disease compared with other breast cancer subtypes.[3,13,26,27] In a meta-analysis of 12 trials, the frequency of pathologic complete response in patients with hormone receptor–positive, HER2-negative tumors was greater in those with high- versus low- to intermediate-grade tumors (16% vs. 8%); however, improved survival outcomes were demonstrated in those who achieved pathologic complete response.[3]

In addition to disease burden and likelihood of treatment response, other factors such as menopausal status and medical fitness affect the recommendation for neoadjuvant chemotherapy. Among premenopausal women, superior clinical responses were seen with neoadjuvant chemotherapy compared with neoadjuvant endocrine therapy.[28] There are data in postmenopausal women demonstrating similar clinical responses and less toxicity with neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy, but the subpopulation to which they primarily apply is composed of those with strong hormone receptor expression and low proliferative index.[29-35] For medically fit, postmenopausal patients, the standard practice remains administration of neoadjuvant chemotherapy because of the wealth of data supporting long-term outcomes.[3] In those classified as poor chemotherapy candidates, neoadjuvant endocrine therapy can be considered as an upfront approach. However, if disease progression occurs, surgery should be pursued.

The future direction of the field, however, is in the development and incorporation of predictive tools to determine appropriate preoperative therapy. Factors such as survival, surgical optimization, and treatment toxicity will direct whether patients will benefit from neoadjuvant chemotherapy compared with neoadjuvant endocrine therapy. Several studies have investigated the role of gene expression profiling to guide preoperative therapy, but it has not been established as a standard of care.[36-39] However, in the setting of the COVID-19 pandemic, ASCO has recommended the use of gene expression profiling to assist in the evaluation of biologic risk and guide the preoperative approach.[40] The recent ASCO neoadjuvant guideline highlighted that no prospective trials have determined the clinical utility of genomic markers in deciding whether patients should receive neoadjuvant chemotherapy or selecting specific chemotherapy regimens.[12] Per this guideline, the clinical utility of genomic predictors such as the Oncotype Dx Recurrence Score has not been definitively determined in the context of neoadjuvant therapy.

During the COVID-19 pandemic, there has been a shift in practice patterns in the oncology community, with higher rates of upfront surgery, greater uptake of gene expression profiling, and increased use of neoadjuvant endocrine therapy to postpone surgery.[38-42] Because of the impact on care delivery and resources, the role of neoadjuvant therapy needs to be carefully considered and implemented in situations where the clinical benefits outweigh the risks of exposure to and development of COVID-19.[43-45] Therefore, ASCO created a new therapeutic guideline based on biologic risk classifications to address the management of hormone receptor–positive breast cancer.[40] Patients with low-risk biologic features (e.g., favorable pathology, low score on genomic profile, strong hormone receptor expression, low grade, lobular disease, and luminal A subtype [HER2 negative, low Ki-67]) are considered likely to

experience limited benefit from neoadjuvant chemotherapy compared with those with high-risk features (e.g., unfavorable pathology, high score on genomic profile, weak HR expression [estrogen receptor < 20%], high grade, and premenopausal).[46-48]

For patients with N1 or greater lymph node involvement, preoperative systemic therapy is recommended. Specifically, those with high-risk biologic features should pursue neoadjuvant chemotherapy, whereas those with low-risk biologic features should engage in an individualized discussion about the advantages and disadvantages of neoadjuvant chemotherapy compared with neoadjuvant endocrine therapy. The intent of neoadjuvant therapy should be considered, including increasing the likelihood of breast conservation and/or potentially reducing the axillary burden to improve the rate of postsurgical complications. Even beyond the circumstances of the COVID-19 pandemic, the management of operable, hormone receptor–positive breast cancer continues to shift toward a biologic risk–based approach as research in this area continues to grow.

SURGERY DELAY: WHO IS AT RISK, AND DOES IT AFFECT SURVIVAL?

The recognition of breast cancer as both a systemic and local disease has resulted in considerable deescalation in the management of the breast and axilla.[49] Nevertheless, breast surgery continues to be an integral treatment modality in the management of early-stage breast cancer with curative intent.[50] According to recent estimates from the American Cancer Society, approximately 95% of patients with stage I to II and 88% of patients with stage III breast cancer undergo surgical management.[51] Access to high-quality, high-value breast surgical care and timeliness of surgical management have been implicated in breast cancer outcomes, including surgical morbidity and disease-related mortality, respectively.[52,53] With the purposeful surgical delay imposed by the COVID-19 pandemic, the implications of delay in time to surgery with regard to disease-specific mortality are at the forefront of national discourse. Additionally, there is a robust national debate about the use of time to surgery as a metric for quality of care.[54-56] The objective of this section is to provide a summary of the literature on time to surgery and describe factors contributing to surgical delay.

Time to Surgery and Breast Cancer Survival

Surgery as the first treatment modality The time from biopsy-proven diagnosis to surgical management is a period of increased stress and anxiety for patients with breast cancer.[57,58] Unfortunately, an examination of trends in time to oncologic surgery suggests increasing wait times across multiple cancers, including breast cancer.[59] Studies of the impact of prolonged time to surgery on clinical outcomes, such as survival among patients receiving surgery as their first treatment modality, have been inconsistent. In the study by Bleicher et al[53] of the National Cancer Database and Surveillance, Epidemiology, and End Results-Medicare, a reduction in overall survival and disease-specific survival with each 60-day increase in time to surgery was reported. Notably, these findings were more pronounced in patients with stage I and II cancers. The review by Eaglehouse et al[60] of the U.S. Military Health Systems reported an even lower delay threshold of 36 days or more resulting in increasing mortality compared with shorter timeframes. These findings were confirmed by a recent meta-analysis showing a 6% to 8% increased risk of mortality for each 4-week delay in time to surgery.[61] Moreover, study estimates from the meta-analysis indicated that delays in breast surgical care for up to 12 weeks could result in 6,100 excess deaths in the United States.[61]

Although the results on surgical delay and survival are compelling, other studies have shown no association between delay in time to surgery (≥ 30 days) and overall or disease-specific survival.[62,63] The inconsistency in the data on time to surgery is further compounded by the lack of uniformly measured time intervals (e.g., time from symptoms to surgery, time from biopsy to surgery, or time from first surgical consultation to surgery) across studies and the absence of established national guidelines/benchmarks defining time to surgery. Nevertheless, timeliness of care is an important tenant of cancer care delivery, and consistent efforts should be made to ensure patients with breast cancer have the shortest possible wait time from diagnosis to surgery.[64]

Neoadjuvant systemic therapy and time to surgery For patients undergoing neoadjuvant therapy before surgery, the emerging literature on the relationship between time to surgery and survival is unclear. In their review of the National Cancer Database, Prakash et al[65] reported no association between time to surgery and overall survival among patients receiving neoadjuvant therapy. Conversely, Omarini et al[66] showed patients undergoing surgical management within 21 days of completion of neoadjuvant therapy had better overall survival and relapse-free survival. Additionally, recent data indicate targeting a surgery date within 6 weeks of chemotherapy completion may improve recurrence-free survival and disease-specific survival.[67] Taken together, these results suggest patients receiving neoadjuvant therapy may benefit from treatment within 3 to 6 weeks of completion of systemic therapy.

Factors Contributing to Surgical Delay

Social determinants of health In the Office of Disease Prevention and Health Promotion Healthy People 2020 initiative, social determinants of health are described as where people live, work, play, and worship.[68] Examples of social determinants of health include insurance, finances,

social networks, literacy, employment, transportation, and neighborhood.[69] Studies have implicated social determinants of health in stage of diagnosis, access to treatment, and survival.[70-72] For instance, uninsured or Medicaid-insured patients with breast cancer are more likely to present with advanced stages of breast cancer and have higher mortality than their privately insured counterparts.[73] In addition to presentation and treatment, social determinants of health have also been implicated in delay in time to surgery.[74] Low educational achievement, no insurance or government insurance (Medicaid or Medicare), and low socioeconomic status have been associated with delay in time to surgery.[65,75,76] Notably, the populations of patients described as experiencing surgical delay have traditionally faced barriers in accessing health care across the cancer continuum, from prevention through survivorship.

Race/ethnicity Black patients with breast cancer are more likely to have increased time to surgery compared with their White counterparts.[77] A recent evaluation of time to surgery among patients with stage I to III breast cancer in a national hospital-based registry showed 30% of non-Hispanic Black patients underwent surgery more than 60 days after diagnosis, compared with 18% of non-Hispanic White women.[78] Delay in time to surgery among Black women warrants additional investigation, because Black patients with breast cancer have a higher mortality rate compared with their White counterparts.[79] For surgeons in particular, racial disparities in time to surgery warrant additional knowledge and understanding. An evaluation of awareness among surgeons of racial and ethnic disparities showed only 36.6% of study participants thought racial and ethnic disparities existed.[80] Moreover, just 11.6% acknowledged racial and ethnic disparities existed in their clinics.[80]

The racial differences in time to surgery are most likely a complex interplay between social determinants of health, patient surgical preferences, and surgeon recommendations. To improve time to surgery for Black patients with breast cancer, more granular studies must be conducted to assess patient needs, institutional barriers, and physician attitudes.

Institutional factors contributing to surgical delay Institutional reasons for prolonged time to surgery are multifactorial and complex. For example, possible contributors to institutional delay include referral patterns, clinic time, operating room time, and surgeon availability.[81] Moreover, institutional processes such as patient triage, rereview of outside hospital pathology and images, and presentation of patients at multidisciplinary tumor boards can further contribute to surgical delay.[81,82] These issues are more pronounced at comprehensive cancer centers, academic cancer centers, and National Cancer Institute–designated cancer centers, which are more likely to receive referrals from outside facilities and as a result have increased time to surgery.[59,77,83] Notably, facility transfers can increase time to surgery by approximately 7 days.[84]

Surgery type and delay The decision to pursue mastectomy, breast-conservation surgery, or breast reconstruction depends on patients' personal value systems and cultural beliefs, surgeon recommendations, and availability of reconstructive surgeons. Patients undergoing mastectomy and reconstruction are more likely to experience longer time to surgery compared with patients undergoing breast conservation only.[81] Reasons for surgical delay based on surgery type are most likely secondary to institutional factors, such as surgeon availability (oncology and reconstructive), operating room time, and scheduling.

Purposeful Surgical Delay

As a result of the COVID-19 pandemic, the American Association for Breast Surgeons, Society of Surgical Oncology, and American College of Surgeons issued guidelines for delaying breast surgery for subsets of patients with breast cancer during the pandemic. Recommendations for delay were based on tumor subtype (e.g., hormone receptor positive, triple negative) and stage.[85] Patients with early-stage (stage I or II), hormone receptor–positive tumors received neoadjuvant endocrine therapy while awaiting surgical management.[44] Unfortunately, the long-term implications of purposeful surgical delay imposed by the pandemic are unclear. Although delay may not affect surgical options for the breast (mastectomy vs. breast conservation), the impact of receipt of neoadjuvant endocrine therapy on axillary management warrants additional investigation. Additionally, the effects of surgical delay on the patient population historically facing delay in time to surgery are currently unknown.

Future Directions

Timeliness of surgical care is an important component of breast cancer care delivery. Although the data on the implications of delay for survival seem inconclusive, the stress and anxiety imposed on patients by prolonged wait time are undeniable. Moreover, there are populations of patients, such as Black and low-income women, who warrant special attention secondary to consistent delay in surgical management. Health care systems and national organizations must work on the creation and implementation of uniform time to surgery guidelines to improve delivery of oncologic surgical care and allow uniform measurement and comparison of time to surgery across systems.

EMERGING EVIDENCE IN RADIATION TREATMENT MANAGEMENT IN BREAST CANCER

What Is the Problem Being Addressed?

Breast cancer is the most common cancer in women worldwide, with more than 2 million new cases per year, and

represents approximately 30% of the radiotherapy workload. In recent years, research has shown that breast cancer comprises several distinct molecular subtypes, with different patterns of clinical behavior. As such, systemic therapy is now tailored to these subtypes, whereas radiotherapy for breast cancer has continued with more of a one-size-fits-all approach, resulting in overtreatment of some patients. Many patients now have an excellent prognosis, but this does not mean that breast cancer management has been solved. It is imperative to maintain the excellent local control and survival outcomes already achieved, while avoiding overtreatment and minimizing physical, psychological, and economic adverse effects of breast irradiation.

Some patients develop metastatic disease despite current optimal management. Radiotherapy is a local therapy but can increase overall survival,[86,87] and research aimed at optimizing radiation treatment for very high-risk breast cancer may further improve survival outcomes. Proton beam therapy and the combination of radiotherapy with novel drugs are both promising avenues for potentially practice-changing research. This brief overview will highlight emerging radiation treatment management in key areas.

Five-Fraction Hypofractionation in Whole-Breast Irradiation

Radiation has been delivered to the breast traditionally as 25 daily 2-Gy fractions over 5 weeks. In the last 3 decades, research investigating moderate hypofractionation with daily fractions of 2.5 Gy to 3 Gy has demonstrated comparable 5-year rates of local recurrence and similar or better normal tissue effects with 3-week radiotherapy (in the Ontario Clinical Oncology Group[88,89] and U.K. START[90,91] trials). However, international adoption of this high-quality research has been slow, and 5-week radiotherapy is still practiced in some countries.

The U.K. FAST-Forward randomized trial[92] investigated five-fraction hypofractionation in whole-breast irradiation delivered over 1 week and was conducted in 97 U.K. hospitals among patients with early invasive breast carcinoma (pT1-3, pN0-1, M0) after surgery. Participants were randomly allocated on an equal basis to receive either 40 Gy in 15 fractions over 3 weeks (U.K. standard of care), 27 Gy in five fractions over 1 week, or 26 Gy in five fractions over 1 week. A total of 4,096 patients were recruited. At a median follow-up of 71.5 months, 5-year cumulative incidence of the primary endpoint of local relapse was 2.1% (95% CI, 1.4–3.1), 1.7% (95% CI, 1.2–2.6), and 1.4% (95% CI, 0.9–2.2) for the 40-, 27-, and 26-Gy groups, respectively. Prespecified noninferiority criteria for both investigational groups excluded an increase in ipsilateral breast tumor relapse of 1.6% or more; the upper confidence limits for the estimated differences at 5 years vs. 40 Gy were −0.3% (95% CI, −1.0%–0.9%) for 27 Gy and −0.7% (95% CI, −1.2%–0.3%) for 26 Gy.

Any moderate or marked clinician-assessed normal tissue effects at 5 years were 9.9%, 15.4%, and 11.9% in the 40-Gy, 27-Gy, and 26-Gy groups, respectively. The odds ratios versus 40 Gy across all clinician assessments over follow-up were 1.55 (95% CI, 1.32–1.83; $p < .0001$) for 27 Gy and 1.12 (95% CI, 0.94–1.34; $p = .20$) for 26 Gy. Both patient and photographic assessments showed higher risk of normal tissue effects for 27 Gy, but not for 26 Gy, compared with the control group.

In light of these data, a U.K. consensus meeting took place in October 2020 defining 26 Gy in five fractions over 1 week as a standard of care in whole-breast irradiation, chest wall irradiation, and partial breast irradiation. Although the pressure on resources caused by the COVID-19 pandemic may expedite this process internationally, one challenge remains: the tension between evidence-based medicine and inflexible reimbursement systems.[93]

Safe Omission of Radiotherapy for Patients at Very Low Risk of Relapse

Although radiotherapy is a highly effective treatment, the adverse effects, if incurred, can be permanent and distressing, impairing quality of life for some women. Five-year analysis of National Cancer Research Institute START trials showed that in approximately one-third of women, moderate or severe chronic adverse effects were reported (e.g., breast shrinkage, pain, tenderness, or hardness).[91] Even using intensity-modulated radiotherapy, 12% of patients have poor cosmesis at 5 years.[10] There are also much rarer but life-threatening risks such as cardiac toxicity and radiation-induced second malignancies. Avoidance of radiotherapy means that some patients avoid all potential adverse effects as well as the inconvenience of traveling for treatment.

Biomarkers of relapse risk have been validated in the setting of systemic therapy[94] and are an attractive prospect for similarly directing radiation treatment management strategy. Several ongoing biomarker-directed trials aim to identify a group of women in whom radiotherapy can be safely omitted after breast-conserving surgery. The IDEA (NCT02400190), LUMINA (NCT02400190), PRECISION (NCT01791829), and PRIMETIME[15] studies are all using a biomarker-directed prospective cohort design; in patients who fulfill genomic or immunohistochemical criteria to avoid radiotherapy, incidence of relapse is compared with a predetermined standard of acceptably low risk. The Danish Breast Cancer Cooperative Group Natural (NCT03646955) and EXPERT (NCT03646955) trials are also investigating this question but are using a noninferiority randomized controlled trial design, randomly assigning women thought

to be at low risk of local recurrence to receive or not receive radiotherapy (using traditional clinical and combined clinical and molecular criteria, respectively).

For patients for whom radiotherapy cannot be omitted completely, other aspects can be deescalated. Examples include use of partial-breast irradiation or omission of further axillary treatment (axillary dissection or radiotherapy) in patients presenting with positive lymph nodes that convert to negative after neoadjuvant chemotherapy (e.g., NSABP B51 [NCT01872975] and U.K. ATNEC [NCT04109079] trials).

Role of Proton Beam Therapy for Patients at Higher Risk of Relapse

Standard (photon) radiation delivered to internal mammary nodes in patients at high risk of breast cancer relapse improves disease-free survival.[95-97] However, even with the highest-quality photon radiotherapy, there is increased dose to heart and/or lungs when internal mammary nodes are added to breast/axillary nodal radiotherapy. This can result in rare but serious and potentially life-threatening major cardiac events many years later. In silico research on proton beam therapy suggests much better coverage of the breast and internal mammary nodes, with sparing of heart and lungs,[98] offering the exciting possibility of both better disease-free survival and less long-term toxicity.

Despite the promising dosimetric proton beam therapy studies, there is currently a paucity of high-quality clinical evidence to drive practice. In addition, there are concerns that the planned physical dose may differ from the actual biologic dose received, especially to the lungs. A number of ongoing studies seek to understand if proton beam therapy offers a real clinical advantage for patients, including the U.S. RADCOMP trial (NCT02603341) and the Danish Breast Cancer Cooperative Group randomized trial (NCT04291378). Both trials have a primary endpoint of major cardiac event at 10 years and are testing 5-week proton beam therapy. The Dutch proton beam therapy group has adopted a models-based approach rather than a randomized trial to triage patients with 2% or greater risk of radiation-induced late heart toxicity for breast proton beam therapy and is also using moderately hypofractionated 3-week proton beam therapy. U.K. investigators are developing a randomized trial (PARABLE) in which patients with breast cancer requiring radiotherapy with 2% or greater risk of radiation-induced late heart toxicity will be randomly assigned to receive 3-week proton beam therapy or standard 3-week radiotherapy. Coprimary outcome measures are mean heart dose as an early predictor of late major cardiac events[99] and patient-reported normal tissue toxicity in the breast at 2 years.

Preoperative Radiotherapy With or Without Drug Combination

Increasing breast-conservation rates improves cosmetic appearance and avoids reconstructive surgery. There has been considerable success in using chemotherapy to downstage biologically aggressive breast tumors to enable breast conservation. However, chemotherapy has less effect on lower-grade, strongly estrogen receptor–positive tumors. Therefore, patients with larger but biologically less aggressive tumors are more likely to undergo primary surgery, often with mastectomy (and reconstruction) or complex oncoplastic procedures. Intensity-modulated radiotherapy can target tumor while minimizing dose to nontarget tissue; when administered preoperatively followed by neoadjuvant endocrine therapy, this may increase chances of breast conservation with minimal adverse effects. Patients requiring mastectomy may also benefit from neoadjuvant radiotherapy; the U.K. PRADA trial (NCT02771938) is evaluating the feasibility, safety, and cosmetic outcomes of radiotherapy before mastectomy and immediate deep inferior epigastric perforator reconstruction. This sequencing avoids irradiation of healthy flap tissues, which may worsen cosmetic outcomes, as well as any delay to radiotherapy resulting from wound-healing issues.

The neoadjuvant setting also provides an ideal and unique opportunity for translational research investigating the direct effect of radiation on breast tumor.[27] This could improve the understanding of intrinsic tumor radiosensitivity and resistance and how the complex interactions between tumor and the immune system are influenced by radiation. Translational endpoints have been incorporated into ongoing and recently completed trials of neoadjuvant radiotherapy, such as the PAPBI trial, in which radiation-induced changes in gene expression were analyzed via paired pretreatment and surgical specimens.[100] The ongoing PRECISE study (NCT03359954) has the primary endpoint of change in tumor-infiltrating lymphocytes before and after neoadjuvant boost radiotherapy to estrogen receptor–positive, HER2-negative breast tumors and exploratory objectives investigating other components of immune response, cell death, and interactions between the two. Similar translational work in trials evaluating combinations of radiation and novel drugs, such as the European NeoCheckRay (NCT03875573) and U.S. CBCV (NCT03804944) and PANDoRA (NCT03872505) studies, could contribute additional insights. The greater understanding engendered by such work may enable optimization of radiation treatment strategy.

Summary

Radiotherapy is an important contributor to the treatment of breast cancer, and evolution of radiation treatment management over recent decades has improved outcomes for patients. Emerging approaches hold promise for tailoring strategy to the individual patient to widen the therapeutic

ratio, both by improving oncologic outcomes and by reducing long-term adverse effects.

CONCLUSION

The role of neoadjuvant therapy in the management of breast cancer is increasingly important. Caring for patients with operable breast cancer requires a multidisciplinary approach, with close collaboration among various disciplines, including pathology, radiology, surgical oncology, radiation oncology, and medical oncology. As our systemic therapies continue to improve, it is anticipated that various deescalation and escalation approaches will be evaluated, with adjuvant therapy approaches being based on response to neoadjuvant therapy.

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REFERENCES

1. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 1998;16:2672-2685.
2. Bear HD, Anderson S, Brown A, et al; National Surgical Adjuvant Breast and Bowel Project Protocol B-27. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2003;21:4165-4174.
3. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384:164-172.
4. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012;30:1796-1804.
5. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13:25-32.
6. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17:791-800.
7. von Minckwitz G, Huang C-S, Mano MS, et al; KATHERINE investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med. 2019;380:617-628.
8. Lin NU, Vanderplas A, Hughes ME, et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer. 2012;118:5463-5472.
9. Smid M, Wang Y, Zhang Y, et al. Subtypes of breast cancer show preferential site of relapse. Cancer Res. 2008;68:3108-3114.
10. Berry DA, Cirrincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA. 2006;295:1658-1667.

11. Steenbruggen TG, van Werkhoven E, van Ramshorst MS, et al. Adjuvant chemotherapy in small node-negative triple-negative breast cancer. Eur J Cancer. 2020;135:66-74.
12. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. J Clin Oncol. Epub 2021 Jan 28.
13. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. J Clin Oncol. 2008;26:778-785.
14. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018;19:27-39.
15. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376:2147-2159.
16. Blum JL, Flynn PJ, Yothers G, et al. Anthracyclines in early breast cancer: the ABC trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). J Clin Oncol. 2017;35:2647-2655.
17. Poggio F, Bruzzone M, Ceppi M, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. Ann Oncol. 2018;29:1497-1508.
18. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol. 2018;19:497-509.
19. Petrelli F, Coinu A, Borgonovo K, et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014;144:223-232.
20. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004;351:2817-2826.
21. Rugo HS, Olopade OI, DeMichele A, et al; I-SPY 2 investigators. Adaptive randomization of veliparib-carboplatin treatment in breast cancer. N Engl J Med. 2016;375:23-34.
22. Nanda R, Liu MC, Yau C, et al. Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. JAMA Oncol. 2020;6:676-684.
23. Schmid P, Dent R, O'Shaughnessy J. Pembrolizumab for early triple-negative breast cancer. Reply. N Engl J Med. 2020;382:e108.
24. Schmid P, Salgado R, Park YH, et al. Pembrolizumab plus chemotherapy as neoadjuvant treatment of high-risk, early-stage triple-negative breast cancer: results from the phase 1b open-label, multicohort KEYNOTE-173 study. Ann Oncol. 2020;31:569-581.
25. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020;396:1090-1100.
26. Chollet P, Amat S, Cure H, et al. Prognostic significance of a complete pathological response after induction chemotherapy in operable breast cancer. Br J Cancer. 2002;86:1041-1046.
27. Spring LM, Gupta A, Reynolds KL, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. JAMA Oncol. 2016;2:1477-1486.
28. Kim HJ, Noh WC, Lee ES, et al. Efficacy of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy in pre-menopausal patients with oestrogen receptor-positive and HER2-negative, lymph node-positive breast cancer. Breast Cancer Res. 2020;22:54.
29. Smith IE, Dowsett M, Ebbs SR, et al; IMPACT Trialists Group. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol. 2005;23:5108-5116.
30. Ellis MJ, Ma C. Letrozole in the neoadjuvant setting: the P024 trial. Breast Cancer Res Treat. 2007;105(suppl 1):33-43.
31. Fontein DB, Charehbili A, Nortier JW, et al. Efficacy of six month neoadjuvant endocrine therapy in postmenopausal, hormone receptor-positive breast cancer patients—a phase II trial. Eur J Cancer. 2014;50:2190-2200.
32. Alba E, Calvo L, Albanell J, et al; GEICAM. Chemotherapy (CT) and hormonotherapy (HT) as neoadjuvant treatment in luminal breast cancer patients: results from the GEICAM/2006-03, a multicenter, randomized, phase-II study. Ann Oncol. 2012;23:3069-3074.
33. Semiglazov VF, Semiglazov VV, Dashyan GA, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer. 2007;110:244-254.
34. Palmieri C, Cleator S, Kilburn LS, et al. NEOCENT: a randomised feasibility and translational study comparing neoadjuvant endocrine therapy with chemotherapy in ER-rich postmenopausal primary breast cancer. Breast Cancer Res Treat. 2014;148:581-590.
35. Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol. 2001;19:3808-3816.
36. Bear HD, Wan W, Robidoux A, et al. Using the 21-gene assay from core needle biopsies to choose neoadjuvant therapy for breast cancer: A multicenter trial. J Surg Oncol. 2017;115:917-923.
37. Pease AM, Riba LA, Gruner RA, et al. Oncotype DX® recurrence score as a predictor of response to neoadjuvant chemotherapy. Ann Surg Oncol. 2019;26:366-371.
38. Ueno T, Saji S, Masuda N, et al. Changes in recurrence score by neoadjuvant endocrine therapy of breast cancer and their prognostic implication. ESMO Open. 2019;4:e000476.
39. Akashi-Tanaka S, Shimizu C, Ando M, et al. 21-gene expression profile assay on core needle biopsies predicts responses to neoadjuvant endocrine therapy in breast cancer patients. Breast. 2009;18:171-174.

40. Sheng JY, Santa-Maria CA, Mangini N, et al. Management of breast cancer during the COVID-19 pandemic: a stage- and subtype-specific approach. JCO Oncol Pract. 2020;16:665-674.
41. Gasparri ML, Gentilini OD, Lueftner D, et al. Changes in breast cancer management during the corona virus disease 19 pandemic: An international survey of the European Breast Cancer Research Association of Surgical Trialists (EUBREAST). Breast. 2020;52:110-115.
42. Cavalcante FP, Novita GG, Millen EC, et al. Management of early breast cancer during the COVID-19 pandemic in Brazil. Breast Cancer Res Treat. 2020; 184:637-647.
43. Al-Shamsi HO, Alhazzani W, Alhuraiji A, et al. A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: an international collaborative group. Oncologist. 2020;25:e936-e945.
44. Dietz JR, Moran MS, Isakoff SJ, et al. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. the COVID-19 pandemic breast cancer consortium. Breast Cancer Res Treat. 2020;181:487-497.
45. Registry study describes COVID-19 mortality and hospitalization in patients with breast cancer. Oncologist. 2021;26(suppl 2):S17-s18.
46. Iwata H, Masuda N, Yamamoto Y, et al. Validation of the 21-gene test as a predictor of clinical response to neoadjuvant hormonal therapy for ER+, HER2-negative breast cancer: the TransNEOS study. Breast Cancer Res Treat. 2019;173:123-133.
47. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med. 2018;379:111-121.
48. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat. 2017;165:573-583.
49. Mamounas EP. NSABP breast cancer clinical trials: recent results and future directions. Clin Med Res. 2003;1:309-326.
50. National Comprehensive Cancer Network. NCCN Guidelines: Breast Cancer. Version 3.2021. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419. Accessed April 23, 2021.
51. America Cancer Society. Breast Cancer Facts & Figures 2019-2020. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf. Accessed April 23, 2021.
52. Wang T, Baskin AS, Dossett LA. Deimplementation of the Choosing Wisely recommendations for low-value breast cancer surgery: a systematic review. JAMA Surg. 2020;155:759.
53. Bleicher RJ, Ruth K, Sigurdson ER, et al. Time to surgery and breast cancer survival in the United States. JAMA Oncol. 2016;2:330-339.
54. Kaufman CS, Shockney L, Rabinowitz B, et al; Quality Initiative Committee. National Quality Measures for Breast Centers (NQMBC): a robust quality tool: breast center quality measures. Ann Surg Oncol. 2010;17:377-385.
55. Landercasper J, Bailey L, Buras R, et al. The American Society of Breast Surgeons and quality payment programs: ranking, defining, and benchmarking more than 1 million patient quality measure encounters. Ann Surg Oncol. 2017;24:3093-3106.
56. Del Turco MR, Ponti A, Bick U, et al. Quality indicators in breast cancer care. Eur J Cancer. 2010;46:2344-2356.
57. Drageset S, Lindstrøm TC, Underlid K. Coping with breast cancer: between diagnosis and surgery. J Adv Nurs. 2010;66:149-158.
58. Drageset S, Lindstrøm TC, Giske T, et al. Being in suspense: women's experiences awaiting breast cancer surgery. J Adv Nurs. 2011;67:1941-1951.
59. Bilimoria KY, Ko CY, Tomlinson JS, et al. Wait times for cancer surgery in the United States: trends and predictors of delays. Ann Surg. 2011;253:779-785.
60. Eaglehouse YL, Georg MW, Shriver CD, et al. Time-to-surgery and overall survival after breast cancer diagnosis in a universal health system. Breast Cancer Res Treat. 2019;178:441-450.
61. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ. 2020;371:m4087.
62. Mariella M, Kimbrough CW, McMasters KM, et al. Longer time intervals from diagnosis to surgical treatment in breast cancer: associated factors and survival impact. Am Surg. 2018;84:63-70.
63. Brazda A, Estroff J, Euhus D, et al. Delays in time to treatment and survival impact in breast cancer. Ann Surg Oncol. 2010;17(suppl 3):291-296.
64. Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: National Academies Press; 2001.
65. Prakash I, Thomas SM, Greenup RA, et al. Time to surgery among women treated with neoadjuvant systemic therapy and upfront surgery for breast cancer. Breast Cancer Res Treat. 2021;186:535-550.
66. Omarini C, Guaitoli G, Noventa S, et al. Impact of time to surgery after neoadjuvant chemotherapy in operable breast cancer patients. Eur J Surg Oncol. 2017; 43:613-618.
67. Sutton TL, Schlitt A, Gardiner SK, et al. Time to surgery following neoadjuvant chemotherapy for breast cancer impacts residual cancer burden, recurrence, and survival. J Surg Oncol. 2020;122:1761-1769.
68. Office of Disease Prevention and Health Promotion. Healthy People 2020: social determinants of health. https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health. Accessed April 23, 2021.
69. Artiga S, Hinton E. Beyond Health Care: The Role of Social Determinants in Promoting Health and Health Equity. San Francisco, CA: Kaiser Family Foundation; 2018.
70. Obeng-Gyasi S, O'Neill A, Zhao F, et al. Impact of insurance and neighborhood socioeconomic status on clinical outcomes in therapeutic clinical trials for breast cancer. Cancer Med. 2021;10:45-52.
71. Ayanian JZ, Kohler BA, Abe T, et al. The relation between health insurance coverage and clinical outcomes among women with breast cancer. N Engl J Med. 1993;329:326-331.

72. Byers TE, Wolf HJ, Bauer KR, et al; Patterns of Care Study Group. The impact of socioeconomic status on survival after cancer in the United States: findings from the National Program of Cancer Registries Patterns of Care Study. Cancer. 2008;113:582-591.

73. Shi R, Taylor H, McLarty J, et al. Effects of payer status on breast cancer survival: a retrospective study. BMC Cancer. 2015;15:211.

74. George P, Chandwani S, Gabel M, et al. Diagnosis and surgical delays in African American and White women with early-stage breast cancer. J Womens Health (Larchmt). 2015;24:209-217.

75. Polverini AC, Nelson RA, Marcinkowski E, et al. Time to treatment: measuring quality breast cancer care. Ann Surg Oncol. 2016;23:3392-3402.

76. Smith EC, Ziogas A, Anton-Culver H. Delay in surgical treatment and survival after breast cancer diagnosis in young women by race/ethnicity. JAMA Surg. 2013; 148:516-523.

77. Fedewa SA, Edge SB, Stewart AK, et al. Race and ethnicity are associated with delays in breast cancer treatment (2003-2006). J Health Care Poor Underserved. 2011;22:128-141.

78. Jackson DK, Li Y, Eskander MF, et al. Racial disparities in low-value surgical care and time to surgery in high-volume hospitals. J Surg Oncol. 2021; 123:676-686.

79. DeSantis CE, Miller KD, Goding Sauer A, et al. Cancer statistics for African Americans, 2019. CA Cancer J Clin. 2019;69:211-233.

80. Britton BV, Nagarajan N, Zogg CK, et al. US surgeons' perceptions of racial/ethnic disparities in health care: a cross-sectional study. JAMA Surg. 2016; 151:582-584.

81. Golshan M, Losk K, Kadish S, et al. Understanding process-of-care delays in surgical treatment of breast cancer at a comprehensive cancer center. Breast Cancer Res Treat. 2014;148:125-133.

82. Loftus L, Laronga C, Coyne K, et al. Race of the clock: reducing delay to curative breast cancer surgery. J Natl Compr Canc Netw. 2014;12(suppl 1):S13-S15.

83. Liederbach E, Sisco M, Wang C, et al. Wait times for breast surgical operations, 2003-2011: a report from the National Cancer Data Base. Ann Surg Oncol. 2015; 22:899-907.

84. Bleicher RJ, Chang C, Wang CE, et al. Treatment delays from transfers of care and their impact on breast cancer quality measures. Breast Cancer Res Treat. 2019;173:603-617.

85. Society of Surgical Oncology. Resource for management options of breast cancer during COVID-19. https://www.surgonc.org/wp-content/uploads/2020/03/Breast-Resource-during-COVID-19-3.23.20.pdf. Accessed April 23, 2021.

86. Darby S, McGale P, Correa C, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011; 378:1707-1716.

87. McGale P, Taylor C, Correa C, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014; 383:2127-2135.

88. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst. 2002;94:1143-1150.

89. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362:513-520.

90. Bentzen SM, Agrawal RK, Aird EG, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 2008;9:331-341.

91. Haviland JS, Owen JR, Dewar JA, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013;14:1086-1094.

92. Murray Brunt A, Haviland JS, Wheatley DA, et al; FAST-Forward Trial Management Group. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet. 2020; 395:1613-1626.

93. Marta GN, Ramiah D, Kaidar-Person O, et al. The financial impact on reimbursement of moderately hypofractionated postoperative radiation therapy for breast cancer: an international consortium report. Clin Oncol (R Coll Radiol). 2021;33:322-330.

94. Bhattacharya IS, Kirby AM, Bliss JM, et al. Can interrogation of tumour characteristics lead us to safely omit adjuvant radiotherapy in patients with early breast cancer? Clin Oncol (R Coll Radiol). 2018;30:158-165.

95. Poortmans PM, Collette S, Kirkove C, et al; EORTC Radiation Oncology and Breast Cancer Groups. Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med. 2015;373:317-327.

96. Whelan TJ, Olivotto IA, Levine MN. Regional nodal irradiation in early-stage breast cancer. N Engl J Med. 2015;373:1878-1879.

97. Thorsen LB, Offersen BV, Danø H, et al. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. J Clin Oncol. 2016;34:314-320.

98. Ranger A, Dunlop A, Hutchinson K, et al. A dosimetric comparison of breast radiotherapy techniques to treat locoregional lymph nodes including the internal mammary chain. Clin Oncol (R Coll Radiol). 2018;30:346-353.

99. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368:987-998.

100. Bosma SCJ, Hoogstraat M, van der Leij F, et al. Response to preoperative radiation therapy in relation to gene expression patterns in breast cancer patients. Int J Radiat Oncol Biol Phys. 2020;106:174-181.

CARE DELIVERY AND REGULATORY POLICY

Barriers and Facilitators to Telemedicine: Can You Hear Me Now?

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overview

In its most direct interpretation, telemedicine is medical care provided at a distance. Although telemedicine's use had been steadily increasing, the COVID-19 pandemic prompted an unprecedented interest and urgency among patients, health care professionals, and policymakers to facilitate health care devoid of the need for in-person contact. The growth in personal access to telecommunications technology meant an unprecedented number of people in the United States and around the world had access to the equipment and technology that would make virtual care possible from the home. As the mass implementation of telemedicine unfolded, it became quickly apparent that scaling up the use of telemedicine presented considerable new challenges, some of which worsened disparities. This article describes those challenges by examining the history of telemedicine, its role in both supporting access and creating new barriers to access in trying to get everyone connected, frameworks for thinking about those barriers, and facilitators that may help overcome them, with a particular focus on older adults and patients with cancer in rural communities.

A NOTE ON TERMINOLOGY

The Agency for Healthcare Research and Quality, the American Telemedicine Association, and the Institute of Medicine all recognize that telemedicine is difficult to define.[1,2] Telemedicine is used interchangeably with telehealth and a variety of other terms (e.g., mHealth or telemonitoring), though some draw distinctions between them. "Telehealth" is the umbrella term that broadly houses all health services provided via telecommunication technologies, ranging from websites containing health information, to email reminders for physical therapy, to audio-video visits between a physician and patient, whereas "telemedicine" is more commonly used to describe technologies associated with direct patient clinical services (e.g., just audio-video visits), although this is not a formalized distinction. The changing nature of terminology reflects the fact that providing medical care at a distance entails the use of a wide range of technologies serving a wide range of functions and in constant evolution alongside rapid developments in information technology, telecommunications, and medical practice.[3] Moreover, telemedicine being a service means it also encompasses the clinical practices, workflows, and organizational arrangements that must also exist to make caring for patients from afar possible and effective.[2]

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HEALTH DISPARITIES IN TELECARE

Introduction

Telemedicine describes the delivery of health care at a distance. The technology upon which telemedicine, as currently conceptualized, is based was developed to allow astronauts to receive care when in space.[4] The literature is filled with examples demonstrating telemedicine's success as a mechanism to improve health equity for persons in rural,[5] isolated,[6] or otherwise underserved communities.[7] Efforts to use telemedicine to increase access to specialty and subspecialty care also abound in the literature.[8-10] Using technology to bring care from areas with access to areas without access has consistently been part and parcel of the telemedicine mission. This article explores telemedicine through the health equity lens (Health Disparities in Telecare) and considers facilitators and barriers to telemedicine focused on elders (Telemedicine Readiness in Older Adults) and rural communities (Telemedicine to Improve Oncology Care for Rural Communities).

Early Telemedicine Practice

The practice of telemedicine has evolved over time. From the early transmission of electronic health information to patients accessing health care through apps, virtual appointments are now often being accessed via a smartphone. This is a stark contrast from the early days of telemedicine adoption when telemedicine was generally limited to a clinic-based appointment. For example, the patient in a rural community would travel to the local telemedicine site to connect with the specialist or subspecialist. The local telemedicine site would be equipped with the necessary technology to provide the needed care at a distance. The telehealth-related technology may have

PRACTICAL APPLICATIONS

- Health equity considerations for telemedicine should include demographic factors and their intersections.
- Assessing readiness for telemedicine should include screening for access to devices, adequate broadband internet connectivity, interest in telemedicine, and confidence in navigating access to a specific telemedicine modality.
- In caring for an older patient with cancer, assessing readiness for telemedicine should additionally include sensitivity to and screening for cognitive status and function.
- Telemedicine provides easy and fast access to high-value multidisciplinary subspecialty oncology care to rural residents with cancer at the comfort of the patient's home with better quality and lower cost.
- Telemedicine can be leveraged to improve access to clinical trials and cutting-edge treatments for patients with cancer in rural communities.

included an electronic stethoscope, a handheld camera, and/or a tele-otoscope to assist with the physical assessment. Even when the televisit was based in the home, the needed technology was brought to the patient's home to facilitate care.[11] Home health units might include a camera, an electronic stethoscope, a glucometer, and blood pressure cuff to be read at a distance.

Telemedicine demonstrated success with outcomes generally comparable to in-person care. Data also demonstrated improvements in access to care in specialties that translated seamlessly to tele-interactions, such as telepsychiatry and telenutrition, teleradiology, and telepathology.[12,13] Similar data emerged for teleoncology,[14] including when bundled with teleradiology and telepathology[15]; so, too, were findings for teleorthopedics,[16] telediabetes,[17] telecardiology,[18] telestroke,[19] and more. Examples of these successes in access to care were also noted globally.

Telemedicine in the 21st Century

By the start of this century, a slow and steady uptake in telemedicine services was noted. With that came studies examining the factors that influenced clinician and patient uptake including the role of race, ethnicity, sex, literacy, digital literacy, culture, and language. Age and patient location and rurality are factors that will be explored in greater depth in this article. Hsu et al[20] noted that use of e-health services was lowest in communities that were predominantly non-White or characterized as low socioeconomic status. In their 4-year observational study, disparities seemed to increase over time.

As studies began to explore a more textured understanding of telemedicine and health disparities, benefits to equity were documented. As an example, in 2016, Lyerly et al[21] explored racial and ethnic disparities in acute stroke care in Texas. This team found that telestroke expertise access was extended to 1.5 million residents and that this increased access did not demonstrate disparities in care.

A 2014 assessment of the publicly available National Cancer Institute's 2012 Health Information National Trends Survey revealed an association between sociodemographic predictors of telehealth use among adult internet users across three health communication domains, including health care, health information-seeking, and user-generated content and sharing.[22] The authors did not identify evidence of a digital use divide by race/ethnicity. They found sex, being female, and socioeconomic status (high) were consistent predictors of telehealth use. This was particularly true for health care and health information-seeking items. Patients with less education were significantly less likely to go online to look for a health professional, to use email or a portal to communicate with their doctor, or to download health information to their mobile device. Other studies identified the impact of culture on telehealth use.[23]

Mobile technologies As telehealth technologies shifted to mobile device platforms, such as cell phones, many of us were heartened by the democratization of access that might emerge. With broad uptake of cell phones by all populations,[24] it seemed health care access could virtually be in your pocket, but as in all types of access, it soon became clear that not all access is equal. As the cell phone was touted as the newest medical device, its utility as a tool for health care communication, monitoring, and/or care of acute or chronic illness varied. Cell phone uptake was not the same as smartphone uptake. Cell phone uptake did not mean stable and affordable broadband access, which are essential to access telemedicine care.

Additional identified factors associated with telemedicine adoption included access to culturally appropriate telehealth services, access to linguistically appropriate telehealth services, and confidence in electronic health-related communication or care, with the latter being a noteworthy factor for technology adoption for both patients and health professionals. A primary barrier to both patient and clinician adoption is lack of health insurance coverage and equitable reimbursement for telehealth services.[25,26]

Telemedicine in the Time of the COVID-19 Pandemic

Telemedicine uptake grew at somewhat glacial rates until the COVID-19 global pandemic emerged. In our institution, like in many cancer centers across the country, cancer care

TABLE 1. Factors That Influence Telemedicine Adoption

Patient Demographic Factors	Technological Factors	Patient and Clinician Factors	Health System Factors
Race	Stable broadband access	Digital literacy	Seamless in-person to telemedicine workflows
Ethnicity	Smartphone or digital device access	Appropriate digital access training	Ongoing and appropriate data collection for continuous quality improvement
Age	User-friendliness: consideration of human factors	Trust in electronic communication and care	
Sex		Ease of use	
Education		Health insurance coverage	
Socioeconomic status			
Geography: rural, frontier, dense urban			
Literacy/digital literacy			
Culture			
Language			
Sequestered: facilities including incarcerated people			

quickly adjusted to telecare, with video consultations to support patient safety and to respect social spacing requirements. Because video consultations necessitate a smartphone or another device with stable broadband, persons with limited access to the technology or with limited knowledge regarding the use of the technology were soon identified as having access barriers. As examples, older, non-White, non–English-speaking, and less affluent patients were less likely to access telemedicine services.[27] For a period of time during the COVID-19 pandemic, teleconsultations were the predominant modality for health care delivery. As we consider the sustainability of telemedicine services, resolution of access issues will be necessary to assure equitable care.[28] Access issues to be addressed include access to the technology, access to stable broadband internet, and access to the appropriate knowledge to conduct a televisit successfully. For example, in our work, the first assessment point is to inquire regarding access to a tele-enabled device. If this is not available, efforts to facilitate access to a smartphone or a tablet is initiated. If an appropriate device is available, the next assessment is access to the software that will take you to the telemedicine visit. If not, software access is initiated. If so, the third assessment point is to connect to the telemedicine visit via the software. If not, education to show the patient how to do so is initiated. If so, the next step is to schedule a test appointment, so the patient can practice using the software. Efforts at each assessment point facilitate and encourage telemedicine engagement.

The quick pivot to telecare required the broad and rapid implementation of workflows that would mimic the in-person protocols as seamlessly as possible to preserve quality health care delivery. Rapid training in telehealth technologies by the health care workforce was necessary. Processes that needed to be addressed included obtaining and recording vital signs, reconciling medications, and updating the patient's history. Vital signs require specific patient education and often training in the use of the blood pressure cuff, pulse oximeter, and thermometer.

The literature also revealed that although Black and Latinx persons were less likely to have successful access to telemedicine services, they were also more likely to experience an infection with COVID-19. It appeared that the conglomerate of potential factors that impacted telehealth adoption also placed the patient at greater risk for COVID-19 infection and disruption in cancer care, potentially impacting cancer care outcomes.[29]

From a clinician and health system perspective, a critical facilitator to telemedicine uptake has been insurance coverage and reimbursement. These policy changes in insurance coverage directly supported the wide dissemination of telemedicine during the COVID-19 pandemic. The sustainability of these regulatory changes is essential to long-term telemedicine integration.[30] How to optimize telehealth approaches to assure access to a similar quality of telemedicine care and discerning the right balance between in-person and televisits are essential research questions that remain. In addition, ongoing data collection of the identified predictive at-risk factors will be necessary (e.g., race, ethnicity, age, sex, geography, income [socioeconomic status], education, language, culture, literacy, and digital literacy) to assess improvements and impact on outcome.[31] These factors that influence telemedicine adoption are summarized in Table 1.

Future Considerations

Despite telemedicine's strong history as a tool to enhance access, the impact of the COVID-19 pandemic on the wide-scale implementation of telemedicine led to the uncovering underlying inequities in telemedicine care. The current wider dissemination of telehealth is dependent on telemedicine access via a patient's individual device, which raises concern for the impact of the digital divide.[32] Still, telemedicine remains a tool that can facilitate access to clinical care, including complex cancer care and cancer clinical trials, through careful identification of needs and of means to address the factors necessary for a successful telemedicine visit.[33] As we move beyond the smart phone or digital device, additional opportunities for equity are identified. A thorough collection of sociodemographic data is essential to document and identify opportunities for improvement. The evaluation and integration of other telehealth modalities, such as text messaging, social networking, and online patient education, must also be studied to assess outcomes.[34] Developing strategies to address identified barriers to access such as race, ethnicity, culture, and other notable patient factors and the intersections of these factors will be impactful.[35] For telemedicine to remain a successful bridge to care, gaps that limit access must be identified and addressed.

In the subsequent sections, we will focus on the specific gaps, needs, and bridges necessary for successful telemedicine care for elders (Telemedicine Readiness in Older Adults) and rural communities (Telemedicine to Improve Oncology Care for Rural Communities).

TELEMEDICINE READINESS IN OLDER ADULTS

Introduction

A digital divide based on age was recognized well before the onset of the COVID-19 pandemic. Two-thirds of adults over the age of 65 reported internet use in 2016, which was a considerable increase from 12% in 2000, but still lagged behind the 90% adoption rate of internet for the overall population. The adoption of faster broadband internet at home and smartphones among older adults—two technologies capable of conducting home-based telemedicine visits—lagged behind even more, with 51% and 42% of older adults reporting use in 2016, respectively.[36] When the pandemic started, many providers shifted to telemedicine visits only, assuming patients were ready to make this transition. However, digital divides are not easily crossed, and the pandemic has revealed how barriers to telemedicine persist even when both patients and providers have good reason to try to use it.

Barriers to Telemedicine Adoption in Older Adults Prior to COVID-19

The major barriers that were reported in prepandemic studies of telemedicine in older adults were technological factors such as slow connection speeds or poor video quality, clinician factors such as provider dissatisfaction leading to poor sustainability, and poorly designed interfaces (e.g., small text and widgets, poor color contrast, or menu bars with hidden interfaces) interacting with physical and cognitive impairments commonly present in older persons that make use of telemedicine difficult.[37-39] For some, telemedicine also required learning new skills, and a lack of support could lead to frustration and a reduced desire to continue to engage.[40] Overall, aside from the high prevalence of impairments, older people experienced very similar barriers to other populations facing digital divides.[41,42]

Notably, disinterest was rarely a barrier in the prepandemic literature. Though overall rates of internet and technology use are lower in older adults, older persons consistently reported a willingness to participate in and satisfaction with telemedicine programs prior to the pandemic. Most randomized controlled trials of ambulatory telemedicine and home health telemedicine initiatives for older adults demonstrated considerable acceptability,[37] positive experiences, and an increased sense of security and reassurance because of the access telemedicine provided.[38] Patient experience was often more favorable than that of providers.

Barriers to Telemedicine for Older Adults Revealed During COVID-19

The onset of the COVID-19 pandemic was a tremendous external motivator to get online. Many older adults started using the internet more often and in new ways, including for errands and for medical appointments.[43] Businesses also had to get online; consequently, the number of online services proliferated. Medical care was no exception. For the older population, the provision of medical services was heavily driven by changes to reimbursement; waivers to the Medicare reimbursement program (which covers 96% of adults over age 65 in the United States)[44] adjusted the fees for audio-video visits and to a lesser extent telephone (also known as audio-only) visits to match those of in-office visits.[45] The use of telemedicine by some estimates grew 30-fold in the United States and almost 100-fold in the Medicare population in the second quarter of 2020 compared with before the pandemic.[46,47]

The pandemic experience is useful for understanding which barriers to telemedicine persist when motivation is less of a barrier. Closer examination of trends early in the pandemic indicated that most telemedicine visits were in fact completed by phone rather than via video to accommodate patients lacking the necessary equipment to participate in video visits.[48,49] Furthermore, despite the rise in telemedicine visits, the early pandemic saw a drastic decline in overall visit volume that exceeded what telemedicine tried to replace.[46,48] Taken together, these observations reinforce

the notion that older adults were not ready to suddenly use video visits, and many were left behind in the rapid and poorly coordinated migration to virtual care. Early estimates examining barriers to telemedicine at a population level found 32% of older adults would not readily be able to use video visits because of unfamiliarity with technology, disability, and a lack of social supports to assist. Switching to telephone visits could bridge the gap for an additional 16% of older adults, but issues like dementia and hearing impairment continued to be barriers (as they are during in-person visits).[50]

The published literature during later phases of the pandemic reinforced the above estimates. Epidemiologic studies verified that older age was a considerable risk factor for less video visit use even after adjusting for race, income, and language.[30] Furthermore, population-based studies also challenged earlier optimism about the acceptability of telemedicine in the older population. A nationally representative survey found that 64% of older adults reported they would not want to use telemedicine for a first visit or to discuss a new problem, and 38% reported they would not want to use telemedicine to see a provider they already know.[51] Commonly cited concerns were the inability to conduct a physical examination and that the quality of care via telemedicine was perceived to be not as good as in-person. Other studies have also highlighted that disinterest in telehealth may be a barrier despite the conveniences it affords, even among those who feel confident they can complete a telemedicine visit.[52]

Conceptual Models to Understand Barriers to Telemedicine

Two concepts from implementation science are useful in interpreting the above findings. The first is the framework of an implementation cascade.[53] Readiness for telemedicine operates along a continuum in which several steps must be completed in sequence to successfully complete a video visit (Fig. 1). First, providers must set up the infrastructure—the hardware, software, and workflows for hosting video visits. Next, each patient must have access to internet and devices to be video-visit ready. After this, actual appointments must be made, and the patient must be willing and able to understand when the appointment is, what interface to use to access the virtual visit, and how to navigate the interface itself to connect. Finally, completion of the visit necessitates an ability to operate the interface, including camera, microphone, and stable connection. Defining these steps helps illustrate that attrition occurs in stages.

The pandemic created unprecedented policies and incentives for providers to create infrastructure. However, the rapid effort to migrate to telemedicine ran into an entrenched digital divide, and older adults were simply not ready in time. Furthermore, the barriers of impairments were overlooked. For these reasons, many defaulted to audio-only visits. Still, we suspect many simply missed follow-up, and not for reasons under their control.

The second framework is the diffusion of innovation theory, which argues that innovations spread in stages: first through a minority of early adopters, then through an early majority, and then more slowly through a late majority, and finally laggards.[54] Early studies of telemedicine pilots may have optimistically found great enthusiasm for interventions because they sampled early adopters. With more people using telemedicine during the pandemic, the late majority and laggards ended up being surveyed, and they express greater resistance to telemedicine.

Assessing Readiness and Addressing Unreadiness for Telemedicine in Older Adults

Assessing readiness for telemedicine among older adults, then, involves asking patients about their readiness to handle each step in the implementation cascade and respecting the possibility of genuine and informed disinterest (Fig. 2). Addressing unreadiness involves preparing services and strategies to tackle barriers and reduce attrition at each stage. Internet connectivity, digital literacy, and the digital divide remain the first and foremost challenge for older adults, and programs such as the Lifeline Program through the Federal Communications Commission can be recommended to provide discounted broadband internet. Many local organizations, public libraries, and seniors organizations offer devices and training to facilitate getting older adults online. Disinterest in telemedicine can be addressed by pre-empting common concerns. For example, older patients can be reassured that video visits are used only for visits when a physical examination is unnecessary and that there are mechanisms to arrange a prompt in-person visit if something comes up during a video visit. Appointments and scheduling require an awareness of cognitive impairment and social supports, as these have implications for schedulers when contacting patients or caregivers about appointment details. Finally, human factors and universal design principles recognize that systems, services, and technologies should cater to the needs of people and users rather than the other way around.[55] Consequently, simpler interfaces (e.g., a simple email link, avoiding the need for additional logins and passwords) should be used to reduce barriers that can be substantial for digital immigrants, and alternative tools, such as live closed captioning for those with difficulty hearing and audio-only visits for those with visual impairments, should be used.[56]

Long-term Implications

Looking forward, the concept of readiness for telemedicine in older adults is bound to evolve alongside telemedicine itself. Comfort with technology and the prevalence of high-

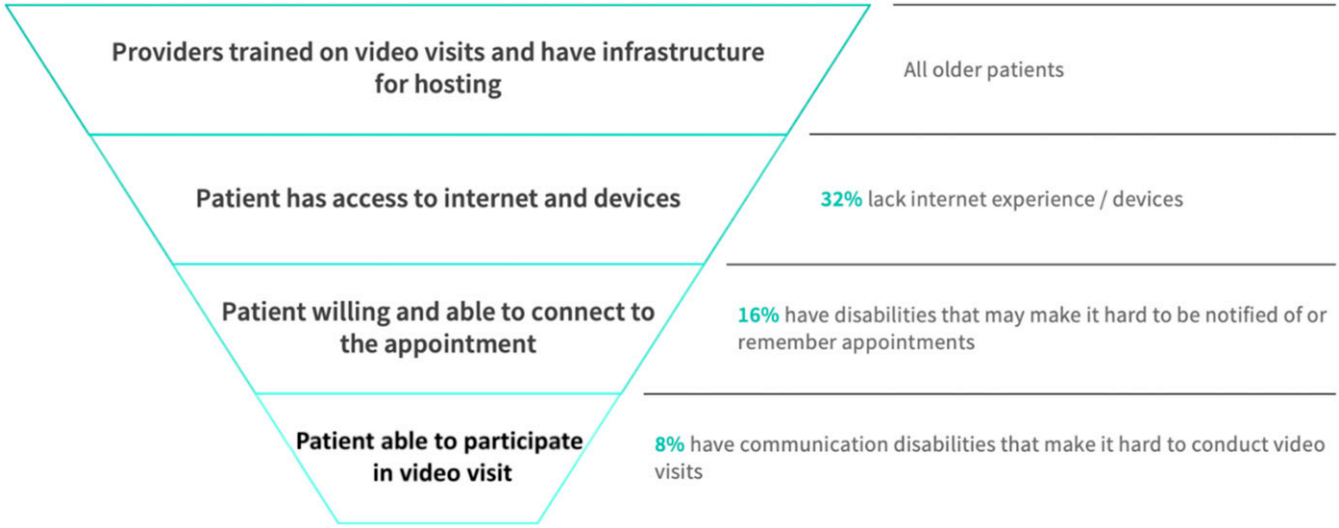

FIGURE 1. An Implementation Cascade for Video Visits in Older Adults[50]

speed internet and internet-ready devices will likely grow as those who learned to use the internet at a younger age get older. However, disparities in digital access that develop earlier in life can become entrenched in older age, underscoring the importance of closing the digital divide in younger persons today. What is less likely to change is the accompaniment of impairments with age, and it will be important for future research and innovation to investigate how human factors and universal design principles might inform the processes of appointment-making and video visits if we want telemedicine to be accessible even for older people. Until then, assessing readiness for telemedicine should focus on assessing interest, familiarity and confidence with technology, and screening for impairments that may make video visits difficult. This can guide targeted strategies for addressing barriers, and, if irremediable problems are anticipated, in-person visits with appropriate protective equipment are a reasonable and necessary alternative.

TELEMEDICINE TO IMPROVE ONCOLOGY CARE FOR RURAL COMMUNITIES

Cancer Care in Rural America

Approximately 20% of all Americans live rurally, and they have limited access to health care and low average incomes, education, and insurance coverage.[22,57-59] Patients with cancer in rural communities are often diagnosed at later stages, are less likely to receive standard-of-care treatment or supportive services, and have significantly higher cancer-related mortality rates compared with nonrural

- Are you interested in a telemedicine visit?
- Do you own a device (e.g. smartphone or tablet) with internet and a camera? Can you borrow one?
- Do you have an internet connection at home?
- Do you (or someone that can help) feel confident you can 1) download the application, 2) open the application, 3) receive and click on a link to connect?
- Do you have difficulty remembering appointments?
- Do you have difficulty reading a computer screen because of your eyesight?
- Does a hearing problem cause you difficulty when listening to TV or radio?

FIGURE 2. Sample Questionnaire to Assess Readiness for Telemedicine Among Older Adults
Abbreviation: TV, television.

residents.[22,58,60] The disparities in outcomes observed in real-world practice diminish when rural patients participate in clinical trials though, suggesting that improving access to uniform health care is important for improving outcomes for rural patients with cancer.[61] In the era of digital transformation, telemedicine provides an opportunity to improve this access, in addition to improving convenience and delivering high-quality cancer care in rural communities.

Recently, ASCO hosted the Closing the Rural Cancer Care Gap event as part of its State of Cancer Care in America series to address rural–nonrural disparities.[62] Based on the experience from three institutions, they highlighted the following strategies to help reduce the rural cancer care gap: improved access to cancer care, increased clinical trial participation by rural residents, and partnership between health care providers and local community leaders.

Leveraging Telemedicine to Improve Cancer Care Delivery in Rural Areas

In rural communities, telemedicine allows delivery of care closer to home with minimal disruption to patients' lives along with an increase in access to standardized treatments and health care services. The key for the successful setup of telemedicine oncology services in rural sites is to identify the local hospitals and health care providers who can manage cancer care with support from the off-site consulting oncologist. To deliver high-quality oncology care remotely, there is a strong need for the collaboration of multidisciplinary teams, including nurse navigators, social workers, palliative care, and other ancillary services. The nonrural tertiary sites can provide administrative support to rural sites, and, with supervision from certified oncology nurses, it is feasible to safely administer chemotherapy and immune therapy at these rural sites.[63] Also, it is crucial to have adequate emergency medical support in case of emergency.

However, despite the general availability and widespread use of telemedicine services, many individuals in rural communities lack access or are not proficient in the use of technology. This gap has led to inequities in the effective use of telemedicine mainly in rural communities.[64]

Benefits of Telemedicine to Rural Communities

Rural communities benefit from telemedicine oncology services in myriad ways, including uninterrupted access to oncologists at nonrural sites and a broad range of resources to support them, from screening to diagnosis, ongoing treatment, follow-up care, and survivorship care.

Improved access Patients with cancer in rural areas may sometimes feel burdened by the physical distance it takes to meet with the closest oncologist, who may be located several hours away. Geographic distance and transportation are commonly reported barriers for cancer care in rural patients.[65,66] Telemedicine allows patients in rural areas without local oncology care or subspecialist care to have access to oncologists and other ancillary services, such as genetic counseling, nutrition counseling, oncofertility counseling, palliative care, psychosocial counseling, oral chemotherapy adherence tracking, support groups, and, above all, cutting-edge clinical trial opportunities that are otherwise not available in most rural settings. For those patients with rare cancers seeking a second opinion or those interested in clinical trials, telemedicine allows for access to cancer care in contiguous states while limiting interstate travel. Thus, medicine provides easy and fast access to high-value multidisciplinary subspecialty oncology care in the comfort of their home with better quality and lower cost.

Reduced travel and cost Telemedicine reduces the travel burden on patients and their families by minimizing the number of in-person visits and cost savings related to avoiding long trips with associated mileage, meal, and hotel costs, time away from work for both patients and family members in the form of lost wages, and additional child or elder care as needed. Reducing financial and physical burdens associated with extended travel allows patients, families, and other loved ones to focus their time and energy on their personal well-being while living with cancer. Telemedicine also allows increased engagement from multiple family members who are otherwise unable to participate in the visit because of travel restrictions.

Treatment adherence Rural residents with cancer often face financial hardship related to co-pays for cancer treatments or lack of insurance leading to nonadherence to routine surveillance or continued cancer treatments.[67] Telemedicine provides the opportunity to improve treatment and surveillance adherence through regular check-ins with patients who cannot travel for toxicity checks or early detection of treatment-related adverse events.

Clinical trial participation Rural patients are often under-recruited and under-represented in clinical trials.[68] Beyond geographic inaccessibility, research also suggests that rural residents are not even informed of the clinical trial opportunities by health care providers.[69] Telemedicine provides patients with cutting-edge treatment through clinical trials.[70] Recent changes made to the conduct of clinical trials during the COVID-19 pandemic, such as the use of telemedicine and e-consent, may address some of these barriers to trial participation if these changes are made permanent moving forward.[71,72]

Collaboration and continuity with local health care providers A close relationship between oncologists and a patient's primary care provider is key to providing telemedicine oncology services and remote monitoring of patients with cancer receiving systemic therapy. This relationship facilitates continuity of care with the rural primary care providers

while providing high-quality subspecialty care from oncologists at the nonrural site. Open communication with local primary care providers has led to a high patient and provider satisfaction, especially if rural residents relocated temporarily or permanently for cancer treatments.[63] Local cancer care also increases awareness of cancer and has an added educational benefit to the local clinical community. This raises the quality of care for the entire rural community beyond just the individual patient.

Financial benefit to rural hospitals With many small rural hospitals closing because of financial pressures, telemedicine provides an opportunity to retain health care within a local community by promoting the use of local laboratory, radiology, infusion services, and local primary care providers. Thus, health care revenue from these essential services is retained within these smaller hospitals.[63] It also provides professional employment opportunities to members of the local community, boosting the local economy.

Challenges With Telehealth in Rural Communities

The rural population has relatively low education, low socioeconomic class, and less use of internet and telecommunications in general. Initial limitations associated with the launch of telemedicine in rural communities included technical complexity, increased burden on patients and the staff, and lack of high-speed broadband access.

Lack of high-speed internet A reliable broadband connection is needed for successful telemedicine. However, high-speed internet remains problematic in rural areas. Addressing this challenge takes time and investment, but working with stakeholders, including federal and state governments, drafting policy frameworks, and continuously improving efforts through expanding digital infrastructure can promote universal access of high-speed broadband. A recent ASCO statement regarding the regulatory burdens on telemedicine suggests expanding broadband access across the United States current through the work led by the Federal Communications Commission.[73] Hopefully, these efforts will make broadband a key utility for rural residents, smoothing opportunities to further expand telemedicine to rural communities.

Federal and state legislation Federal and state governments are promoting health equity by encouraging the use of telemedicine, especially in the rural setting. During the COVID-19 pandemic, several practices have started implementing telemedicine, and the majority report high patient satisfaction. The Centers for Medicare & Medicaid Services have extended Medicare payment for telehealth at least until the end of the calendar year 2021.[74] The expanded insurance coverage was critical for supporting widespread use of telemedicine during the COVID-19 pandemic. These regulations are temporary; they must become permanent. Such policies will enable health care providers to provide a broad range of oncology services to rural patients to bridge the current health care gap and improve the outcomes of the rural patients with cancer.

Cross-state licensures Although state licensing requirements are largely similar across the country, most states require that physicians be separately licensed in each state in which they practice. Differing licensing requirements across states is one of the top issues that prevents more widespread use of telemedicine. During the COVID-19 pandemic, many states waived requirements that physicians with out-of-state licenses be licensed in the state in which they are providing services, allowing for greater provision for telemedicine services.[75] This expanded access to interstate medical practice benefited several patients, especially those interested in clinical trial participation and/or with rare cancers to receive subspecialty expert opinion across states. The federal government needs to collaborate with state medical boards to update medical licensing laws, allowing health care providers to practice telemedicine across state lines.[76] Besides, longer-term cooperation between out-of-state large health systems with local and community providers will help expand telemedicine access to rural areas in need.

Lack of personal connection One of the biggest challenges with telemedicine in cancer care is the lack of a personal connection (human touch) and inability to provide emotional support, especially when delivering bad news such as tumor progression or the need to transition to hospice.[77,78] During the difficult conversations in cancer care, oftentimes we tend to express empathy or show warmth and respect nonverbally by hand-holding or hugging, which can be challenging via telemedicine. There is no replacement for human touch, but by paying special attention to communication and depending on where care is provided, a nurse nearby can help navigate nonverbal communication while physicians remain connected with patients remotely.

Data protection Privacy and data security issues related to health care information technology have been key barriers to the adoption of telemedicine. As large quantities of personal health information and data are generated with the growing use of telemedicine, there is a strong need to invest in technologies that best protect patient privacy and allow for secure patient data transfer and storage.[79,80]

Future Directions

As telemedicine services are expanding to rural residents with cancer, more research is needed to determine the optimal use of technology for oncology visits as well as best practices and standards to ensure consistent approaches to cancer care delivery in rural communities. It is important to assess the potential impact on the cost of cancer care for rural residents, and opportunities to mitigate the financial

burden for those with limited insurance coverage are warranted. Expanding digital infrastructure in rural areas is key to ensuring universal access of high-speed broadband in rural communities. Also, changes to physician credentialing and licensing to practice across state lines will allow for seamless telehealth opportunities.

In conclusion, telehealth provides a means to improve efficiencies and minimize patient burden and disparities in cancer care. Telehealth should be leveraged to improve the quality of cancer care and access to clinical trials and cutting-edge treatments for patients with cancer in rural America.

CONCLUSION

The impact of the COVID-19 pandemic on the wide-scale implementation of telemedicine via patient-dependent tools, generally phones, smartphones, or devices, brought the digital divide to health care. There have been many lessons learned and many to be learned. Research is needed to determine the optimal use of telemedicine in oncology care, to define best practices and standards, and to ensure equitable approaches to cancer care delivery. Essential to ongoing telemedicine sustainability is parity in reimbursement, expanded universal access to high-speed broadband, and limiting credentialing and licensing barriers. Effective tele-cancer care requires the careful identification of the needs and the means to address the factors necessary for successful telemedicine implementation—the integration of telehealth modalities, such as text messaging, social networking, and online patient education—and the deliberative development of strategies to bridge patient factors (e.g., race, ethnicity, age, and geography). Telehealth can improve cancer care quality, minimize patient burden, and ameliorate disparities in cancer care by facilitating access to clinical care, including complex cancer care and cancer clinical trials.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Totten AM, Womack DM, Eden KB, et al. Telehealth: Mapping the Evidence for Patient Outcomes From Systematic Reviews. Technical Briefs, No. 26. Rockville, MD: Agency for Healthcare Research and Quality; 2016.
2. Institute of Medicine. The Role of Telehealth in an Evolving Health Care Environment: Workshop Summary. Washington: National Academies Press; 2012.
3. Weinstein RS. History of telemedicine. evolution, context, and transformation. J Telemed Telecare. 2010;16:167-168.
4. Freiburger G, Holcomb M, Piper D. The STARPAHC collection: part of an archive of the history of telemedicine. J Telemed Telecare. 2007;13:221-223.
5. Brewer R, Goble G, Guy P. A peach of a telehealth program: Georgia connects rural communities to better healthcare. Perspect Health Inf Manag. 2011;8:1c.
6. Egede LE, Frueh CB, Richardson LK, et al. Rationale and design: telepsychology service delivery for depressed elderly veterans. Trials. 2009;10:22.
7. Carroll M, Cullen T, Ferguson S, et al. Innovation in Indian healthcare: using health information technology to achieve health equity for American Indian and Alaska Native populations. Perspect Health Inf Manag. 2011;8:1d.
8. Demaerschalk BM, Bobrow BJ, Raman R, et al; STRokE DOC AZ TIME Investigators. Stroke team remote evaluation using a digital observation camera in Arizona: the initial mayo clinic experience trial. Stroke. 2010;41:1251-1258.
9. Hazin R, Qaddoumi I. Teleoncology: current and future applications for improving cancer care globally. Lancet Oncol. 2010;11:204-210.
10. Cason J. A pilot telerehabilitation program: delivering early intervention services to rural families. Int J Telerehabil. 2009;1:29-38.
11. Shea S, Kothari D, Teresi JA, et al. Social impact analysis of the effects of a telemedicine intervention to improve diabetes outcomes in an ethnically diverse, medically underserved population: findings from the IDEATel Study. Am J Public Health. 2013;103:1888-1894.
12. Hilty DM, Cobb HC, Neufeld JD, et al. Telepsychiatry reduces geographic physician disparity in rural settings, but is it financially feasible because of reimbursement? Psychiatr Clin North Am. 2008;31:85-94.
13. Ventura Marra M, Lilly CL, Nelson KR, et al. A pilot randomized controlled trial of a telenutrition weight loss intervention in middle-aged and older men with multiple risk factors for cardiovascular disease. Nutrients. 2019;11:229.
14. Singh R, Goebel LJ. Rural disparities in cancer care: a review of its implications and possible interventions. W V Med J. 2016;112:76-82.

15. Graham AR, Bhattacharyya AK, Scott KM, et al. Virtual slide telepathology for an academic teaching hospital surgical pathology quality assurance program. Hum Pathol. 2009;40:1129-1136.

16. Ono CM, Lindsey JL. Shriners Hospitals for Children, Honolulu's experience with telemedicine: program implementation, maintenance, growth, and lessons learned. Hawaii Med J. 2004;63:296-299.

17. McLendon SF. Interactive video telehealth models to improve access to diabetes specialty care and education in the rural setting: a systematic review. Diabetes Spectr. 2017;30:124-136.

18. Mehta S, Botelho R, Rodriguez D, et al. A tale of two cities: STEMI interventions in developed and developing countries and the potential of telemedicine to reduce disparities in care. J Interv Cardiol. 2014;27:155-166.

19. Wu T-C, Lyerly MJ, Albright KC, et al. Impact of telemedicine on access to acute stroke care in the state of Texas. Ann Clin Transl Neurol. 2014;1:27-33.

20. Hsu J, Huang J, Kinsman J, et al. Use of e-Health services between 1999 and 2002: a growing digital divide. J Am Med Inform Assoc. 2005;12:164-171.

21. Lyerly MJ, Wu T-C, Mullen MT, et al. The effects of telemedicine on racial and ethnic disparities in access to acute stroke care. J Telemed Telecare. 2016; 22:114-120.

22. Kontos E, Blake KD, Chou W-YS, et al. Predictors of eHealth usage: insights on the digital divide from the Health Information National Trends Survey 2012. J Med Internet Res. 2014;16:e172.

23. Burns MN, Montague E, Mohr DC. Initial design of culturally informed behavioral intervention technologies: developing an mHealth intervention for young sexual minority men with generalized anxiety disorder and major depression. J Med Internet Res. 2013;15:e271.

24. O'Dea S. Smartphone ownership in the US 2011-2019, by ethnicity. https://www.statista.com/statistics/195001/percentage-of-us-smartphone-owners-by-ethnicity/. Accessed February 2, 2021.

25. Tirado M. Role of mobile health in the care of culturally and linguistically diverse US populations. Perspect Health Inf Manag. 2011;8:1e.

26. Heidbuchel H, Hindricks G, Broadhurst P, et al. EuroEco (European Health Economic Trial on Home Monitoring in ICD Patients): a provider perspective in five European countries on costs and net financial impact of follow-up with or without remote monitoring. Eur Heart J. 2015;36:158-169.

27. Eberly LA, Kallan MJ, Julien HM, et al. Patient characteristics associated with telemedicine access for primary and specialty ambulatory care during the COVID-19 pandemic. JAMA Netw Open. 2020;3:e2031640.

28. Kronenfeld JP, Penedo FJ. Novel coronavirus (COVID-19): telemedicine and remote care delivery in a time of medical crisis, implementation, and challenges. Transl Behav Med. 2021;11:659-663.

29. Fortney JC, Burgess JF, Jr., Bosworth HB, et al. A re-conceptualization of access for 21st century healthcare. J Gen Intern Med. 2011;26(Suppl 2):639-647.

30. Schmidt AL, Bakouny Z, Bhalla S, et al. Cancer care disparities during the COVID-19 pandemic: COVID-19 and cancer outcomes study. Cancer Cell. 2020; 38:769-770.

31. Badawy SM, Radovic A. Digital approaches to remote pediatric health care delivery during the COVID-19 pandemic: existing evidence and a call for further research. JMIR Pediatr Parent. 2020;3:e20049.

32. Graboyes E, Cramer J, Balakrishnan K, et al. COVID-19 pandemic and health care disparities in head and neck cancer: scanning the horizon. Head Neck. 2020; 42:1555-1559.

33. Helsper CW, Campbell C, Emery J, et al. Cancer has not gone away: a primary care perspective to support a balanced approach for timely cancer diagnosis during COVID-19. Eur J Cancer Care (Engl). 2020;29:e13290.

34. Sirintrapun SJ, Lopez AM. Telemedicine in cancer care. Am Soc Clin Oncol Educ Book. 2018;38:540-545.

35. Lopez AM, Hudson L, Vanderford NL, et al. Epidemiology and implementation of cancer prevention in disparate populations and settings. Am Soc Clin Oncol Educ Book. 2019;39:50-60.

36. Pew Research Center. Tech Adoption Climbs Among Older Adults. https://www.pewresearch.org/internet/2017/05/17/tech-adoption-climbs-among-older-adults/. Accessed February 2, 2021.

37. Batsis JA, DiMilia PR, Seo LM, et al. Effectiveness of ambulatory telemedicine care in older adults: a systematic review. J Am Geriatr Soc. 2019;67:1737-1749.

38. Radhakrishnan K, Xie B, Berkley A, et al. Barriers and facilitators for sustainability of tele-homecare programs: a systematic review. Health Serv Res. 2016; 51:48-75.

39. Levine DM, Lipsitz SR, Linder JA. Changes in everyday and digital health technology use among seniors in declining health. J Gerontol A Biol Sci Med Sci. 2018; 73:552-559.

40. Foster MV, Sethares KA. Facilitators and barriers to the adoption of telehealth in older adults: an integrative review. Comput Inform Nurs. 2014;32:523-533quiz 534-535.

41. Slightam C, Gregory AJ, Hu J, et al. Patient perceptions of video visits using Veterans Affairs telehealth tablets: survey study. J Med Internet Res. 2020;22:e15682.

42. Donaghy E, Atherton H, Hammersley V, et al. Acceptability, benefits, and challenges of video consulting: a qualitative study in primary care. Br J Gen Pract. 2019; 69:e586-e594.

43. Nimrod G. Changes in internet use when coping with stress: older adults during the COVID-19 pandemic. Am J Geriatr Psychiatry. 2020;28:1020-1024.

44. Montaquila J, Freedman VA, Edwards B, et al. National Health and Aging Trends Study Round 1 Sample Design and Selection. NHATS Technical Paper #1. Johns Hopkins University School of Public Health. https://www.nhats.org/sites/default/files/inline-files/NHATS_Round1_Sample_Design_05_10_12_0.pdf. Accessed November 4, 2020.

45. Centers for Medicaid and Medicare Services. Trump Administration Issues Second Round of Sweeping Changes to Support U.S. Healthcare System During COVID-19 Pandemic. https://www.cms.gov/newsroom/press-releases/trump-administration-issues-second-round-sweeping-changes-support-us-healthcare-system-during-covid. Accessed May 11, 2020.
46. Alexander GC, Tajanlangit M, Heyward J, et al. Use and content of primary care office-based vs telemedicine care visits during the COVID-19 pandemic in the US. JAMA Netw Open. 2020;3:e2021476.
47. Verma S. Early Impact of CMS Expansion of Medicare Telehealth During COVID-19. Health Affairs Blog, July 15, 2020. https://www.healthaffairs.org/do/10.1377/hblog20200715.454789/full/.
48. Baum A, Kaboli PJ, Schwartz MD. Reduced in-person and increased telehealth outpatient visits during the COVID-19 pandemic. Ann Intern Med. 2021;174:129-131.
49. Dewar S, Lee PG, Suh TT, et al. Uptake of virtual visits in a geriatric primary care clinic during the COVID-19 pandemic. J Am Geriatr Soc. 2020;68:1392-1394.
50. Lam K, Lu AD, Shi Y, et al. Assessing telemedicine unreadiness among older adults in the United States during the COVID-19 pandemic. JAMA Intern Med. 2020;180:1389-1391.
51. Malani P, Kullgren J, Solway E, et al. National Poll on Healthy Aging: Telehealth Use among Older Adults before and during COVID-19. University of Michigan. http://hdl.handle.net/2027.42/156253. Accessed October 1, 2020.
52. Hawley CE, Genovese N, Owsiany MT, et al. Rapid integration of home telehealth visits amidst COVID-19: what do older adults need to succeed? J Am Geriatr Soc. 2020;68:2431-2439.
53. Zhang C, McMahon J, Fiscella K, et al. HIV pre-exposure prophylaxis implementation cascade among health care professionals in the United States: implications from a systematic review and meta-analysis. AIDS Patient Care STDS. 2019;33:507-527.
54. Dearing JW, Cox JG. Diffusion of innovations theory, principles, and practice. Health Aff (Millwood). 2018;37:183-190.
55. Charness N, Boissy P, Demiris G, et al. How human factors can influence the elderly in the use of telemedicine. Telemed J E Health. 2010;16:860-866.
56. Nieman CL, Oh ES. Connecting with older adults via telemedicine. Ann Intern Med. 2020;173:831-832.
57. U.S. Census Bureau. Measuring America: Our Changing Landscape. https://www.census.gov/content/dam/Census/library/visualizations/2016/comm/acs-rural-urban.pdf. Accessed February 1, 2021.
58. Henley SJ, Anderson RN, Thomas CC, et al. Invasive cancer incidence, 2004-2013, and deaths, 2006-2015, in nonmetropolitan and metropolitan counties - United States. MMWR Surveill Summ. 2017;66:1-13.
59. Gong G, Phillips SG, Hudson C, et al. Higher US rural mortality rates linked to socioeconomic status, physician shortages, and lack of health insurance. Health Aff (Millwood). 2019;38:2003-2010.
60. Chow CJ, Al-Refaie WB, Abraham A, et al. Does patient rurality predict quality colon cancer care?: a population-based study. Dis Colon Rectum. 2015;58:415-422.
61. Unger JM, Moseley A, Symington B, et al. Geographic distribution and survival outcomes for rural patients with cancer treated in clinical trials. JAMA Netw Open. 2018;1:e181235.
62. Levit LA, Byatt L, Lyss AP, et al. Closing the rural cancer care gap: three institutional approaches. JCO Oncol Pract. 2020;16:422-430.
63. Thota R, Gill DM, Brant JL, et al. Telehealth is a sustainable population health strategy to lower costs and increase quality of health care in rural Utah. JCO Oncol Pract. 2020;16:e557-e562.
64. Makri A. Bridging the digital divide in health care. Lancet Digit Health. 2019;1:e204-e205.
65. Ambroggi M, Biasini C, Del Giovane C, et al. Distance as a barrier to cancer diagnosis and treatment: review of the literature. Oncologist. 2015;20:1378-1385.
66. Guidry JJ, Aday LA, Zhang D, et al. Transportation as a barrier to cancer treatment. Cancer Pract. 1997;5:361-366.
67. McDougall JA, Banegas MP, Wiggins CL, et al. Rural disparities in treatment-related financial hardship and adherence to surveillance colonoscopy in diverse colorectal cancer survivors. Cancer Epidemiol Biomarkers Prev. 2018;27:1275-1282.
68. Zahnd WE, Davis MM, Rotter JS, et al. Rural-urban differences in financial burden among cancer survivors: an analysis of a nationally representative survey. Support Care Cancer. 2019;27:4779-4786.
69. Vanderpool RC, Kornfeld J, Mills L, et al. Rural-urban differences in discussions of cancer treatment clinical trials. Patient Educ Couns. 2011;85:e69-e74.
70. Lopez AM. Telemedicine and clinical trials. In Kelly WK, Halabi S (eds). Oncology Clinical Trials: Successful Design, Conduct, and Analysis. 2nd ed. New York: Demos Medical; 2018.
71. Virani S, Burke L, Remick SC, et al. Barriers to recruitment of rural patients in cancer clinical trials. J Oncol Pract. 2011;7:172-177.
72. Pennell NA, Dillmon M, Levit LA, et al. American Society of Clinical Oncology Road to Recovery report: learning from the COVID-19 experience to improve clinical research and cancer care. J Clin Oncol. 2021;39:155-169.
73. American Society of Clinical Oncology. ASCO Interim Position Statement: Telemedicine in Cancer Care. https://www.asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/2020-ASCO-Interim-Position-Statement-Telemedicine-FINAL.pdf. Accessed February 3, 2021.
74. Center for Connected Health Policy. State Telehealth Laws & Reimbursement Policies. https://www.cchpca.org/sites/default/files/2019-05/cchp_report_MASTER_spring_2019_FINAL.pdf. Accessed February 3, 2021.
75. Center for Connected Health Policy. National Policy: Cross State Licensing. https://www.cchpca.org/telehealth-policy/cross-state-licensing. Accessed February 11, 2021.

76. Mullangi S, Agrawal M, Schulman K. The COVID-19 pandemic-an opportune time to update medical licensing. JAMA Intern Med. 2021;181:307-308.

77. Sanoff HK. Managing grief, loss, and connection in oncology-what COVID-19 has taken. JAMA Oncol. 2020;6:1700.

78. Weaver MS, Neumann ML, Navaneethan H, et al. Human touch via touchscreen: rural nurses' experiential perspectives on telehealth use in pediatric hospice care. J Pain Symptom Manage. 2020;60:1027-1033.

79. Bassan S Data privacy considerations for telehealth consumers amid COVID-19. J Law Biosci. 2020;7:lsaa075.

80. Kruse CS, Frederick B, Jacobson T, et al. Cybersecurity in healthcare: a systematic review of modern threats and trends. Technol Health Care. 2017;25:1-10.

CENTRAL NERVOUS SYSTEM TUMORS

Assessment and Management of Cognitive Symptoms in Patients With Brain Tumors

Michael W. Parsons, PhD[1], and Jörg Dietrich, MD, PhD[1]

overview

Cognitive symptoms occur in almost all patients with brain tumors at varying points in the disease course. Deficits in neurocognitive function may be caused by the tumor itself, treatment (surgery, radiation, or chemotherapy), or other complicating factors (e.g., seizures, fatigue, mood disturbance) and can have a profound effect on functional independence and quality of life. Assessment of neurocognitive function is an important part of comprehensive care of patients with brain tumors. In the neuro-oncology clinic, assessment may include cognitive screening tools and inquiry into subjective cognitive function. Neuropsychological assessment is an important adjunct to identify cognitive symptoms and can be used as an opportunity to intervene through transformative feedback and treatment planning. Preventative measures can be taken to reduce cognitive side effects of treatment, such as awake craniotomies with intraoperative mapping during neurosurgery or prophylactic measures during radiation therapy (e.g., hippocampal avoidance, neuroprotectant treatment with memantine). Rehabilitative therapies, including cognitive rehabilitation and computerized cognitive exercise, are options for managing cognitive problems in an individualized manner. Pharmacotherapy, including use of stimulant medications and acetylcholinesterase inhibitors, has shown benefits for patients with brain tumors when tailored to an individual's cognitive profile. Identification and management of co-occurring issues, such as sleep disturbance, fatigue, and depression, can also improve neurocognitive function. There are promising therapies under development that may provide new options for treatment in the future. Integrating careful assessment and treatment of cognition throughout the disease course for patients with brain tumors can improve functional outcomes and quality of life.

INTRODUCTION

Cognitive symptoms are common for patients with brain tumors. Timely identification of problems with neurocognitive function (NCF) is an important aspect of care for these patients, as cognition is critical for complex activities of daily living,[1] work,[2] and functional independence, thus playing a critical role in quality of life.[3] This review details the factors that contribute to NCF impairment in adults with brain tumors, describes strategies for recognition of these issues in clinical care, and provides options available for treatment of these deficits.

IMPAIRMENT OF NEUROCOGNITIVE FUNCTION IN PATIENTS WITH BRAIN TUMOR

Deficits in NCF occur in 90% of patients with supratentorial brain tumors at varying points in the disease course.[4,5] At the time of diagnosis, these deficits may be related to the tumor, causing disruption of both local and distant brain networks.[4] Mechanisms of these effects include direct tissue damage via necrosis, compression of neural structures due to mass effect from tumor and surrounding edema, and infiltrative growth into critical fiber pathways and networks. Neurosurgical intervention can alleviate some of these symptoms, particularly when resection reduces mass effect,[6,7] but can also cause additional NCF symptoms if critical brain regions or pathways are damaged during surgery.[8,9] Strategies to reduce the risk of neurosurgical deficits, such as functional MRI and awake craniotomies with intraoperative mapping, have improved these outcomes.[10,11] Chemotherapy is also known to contribute to cognitive decline in patients with both primary brain tumors (e.g., about 30% of patients have been shown to have NCF changes after chemotherapy treatment in the absence of disease progression)[12-16] and brain metastases.[17] Furthermore, medications necessary to manage neurologic problems related to brain tumors, such as anti-epileptics, anti-inflammatory therapies (e.g., steroids), and pain medications, may exacerbate cognitive symptoms.[18] Radiation therapy has well-known NCF consequences that may occur during treatment or evolve months or even years later.[17,19] The complex interplay of these multiple etiologies of NCF dysfunction in patients with brain tumors implies that consistent monitoring throughout the course of disease is an important part of comprehensive clinical care. Diverse approaches to management may be called for at different points in the disease course and typically require a multidisciplinary approach.

Author affiliations and support information (if applicable) appear at the end of this article.

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PRACTICAL APPLICATIONS

- Difficulties with neurocognitive function occur in up to 90% of patients with brain tumors at some point during the disease course and are a major detractor from overall quality of life.
- Screening procedures in the neuro-oncology clinic may include brief objective measures, such as the Montreal Cognitive Assessment, but these have limited sensitivity and should be augmented by subjective cognitive assessment using surveys.
- Neuropsychological evaluation is a sensitive and useful method of identifying neurocognitive function difficulties and provides an opportunity to improve the understanding of cognitive problems and develop individualized treatment plans.
- Cognitive rehabilitation conducted by a therapist is an effective method for neurocognitive function improvement using compensatory strategies and assistive devices. Computerized/automated cognitive "exercise" approaches have limited evidence of benefit at this time.
- Medications for cognitive enhancement include stimulant therapy and medications targeted at memory. There is modest evidence of benefit for both approaches in patients with brain tumors, particularly when medication choice is guided by an individual cognitive profile.

ASSESSMENT OF NEUROCOGNITIVE SYMPTOMS

Monitoring for NCF deficits or changes is a challenge for busy neuro-oncology clinicians, given the numerous neurologic and medical issues that must be managed in brief visits. This difficulty is complicated by the fact that brief NCF screening measures, such as the Mini-Mental State Examination[20] and the Montreal Cognitive Assessment,[21] have limited sensitivity to subtle but meaningful changes in NCF that people with brain tumors experience.[22-24] Despite these limitations, neuro-oncologists often must resort to these screeners as the only feasible options for in-clinic performance-based assessment of NCF. To enhance sensitivity to subtle changes in cognition, clinicians often use brief self-report surveys to assess subjective NCF symptoms, along with other quality of life issues. Commonly used scales include the Functional Assessment for Cancer Therapy-Brain[25] and the European Organisation for Research and Treatment of Cancer Quality of Life Scale.[26] These measures can generate specific indices of NCF.[27] If administered on a consistent basis over time, changes in function may be apparent to the clinician, which can prompt referral for more in-depth evaluations.

The gold standard for NCF assessment is a comprehensive neuropsychological evaluation.[28,29] Multidisciplinary brain tumor clinics are increasingly integrating neuropsychologists as members of the patient care team, providing ready access to detailed assessments.[29] In the context of brain tumor management, neuropsychological evaluations may be abbreviated from traditional batteries and tailored to the individual patient needs and level of functioning,[29,30] yet are able to identify NCF changes prior to visible changes on brain imaging[31] and are prognostic of overall and progression-free survival time.[32-34] Integration of neuropsychological evaluations at critical points in the care of patients with brain tumors provides guidance to physicians and allied health personnel regarding the multifaceted treatment options that are important at specific points in the disease course, as detailed below.

Preoperative assessments of NCF may be integrated with neurosurgical procedures used to predict and minimize cognitive morbidity from surgery (e.g., functional MRI and intraoperative mapping).[35] The early identification of issues that might interfere with intraoperative mapping, such as inadequate attention, aphasia, or anxiety, as well as specific neurocognitive patterns that are critical for the interpretation of functional MRI and intraoperative mapping (e.g., nondominant hemisphere language representation[36]) can optimize functional outcome.[10] Perhaps most importantly, NCF performance preoperatively can be used to predict risk of cognitive decline as a function of surgery.[37,38] For instance, in patients with gliomas involving the left temporal lobe, an absence of deficits in the domains of language and verbal memory at presurgical baseline evaluation suggests that the individual may be at increased risk of suffering a surgically induced deficit in those functions.[8] In contrast, patients who have deficits preoperatively tend to show less change as a function of surgery. Many patients who present with brain tumors move quickly to surgical intervention and are experiencing numerous fluctuating factors that affect NCF (e.g., seizures or postictal cognitive changes, new treatment with steroids or anti-epileptic drugs, and the stress of hospitalization and newly discovered brain mass). Thus, preoperative cognitive assessments are ideally brief and focused on very specific questions.

Postoperative NCF evaluation can be used to characterize subacute deficits that may benefit from treatment (see next section). The timing of postoperative assessments depends on patient needs; they may occur immediately after surgery if planning of inpatient rehabilitation is necessary. More commonly, a period of time for postsurgical recovery is appropriate, and a comprehensive neuropsychological evaluation can be conducted on an outpatient basis as the patient receives diagnostic information and makes decisions about adjuvant treatment. Postoperative evaluations at this point may be helpful to identify specific cognitive

issues that can become targets of outpatient treatment and may play an important role in identifying needs regarding return to work or support in high-level activities of daily living, such as medication management, financial decision-making, and driving.[39]

Long-term monitoring of NCF with serial evaluations at regular intervals is helpful as part of comprehensive brain tumor management. Cognitive impairments can have a more significant impact on quality of life than other neurologic symptoms,[40] and one of the goals of ongoing monitoring is to mitigate the negative impacts of NCF on quality of life. Survivors of brain tumors are at risk for NCF decline caused by tumor recurrence/progression, effects of treatment (chemotherapy and radiation therapy[41-43]), and neurologic or medical complications of their illness (seizures and cerebrovascular insults[44]). Patients with a history of radiation therapy to the brain are at particular risk for NCF decline due to progressive leukoencephalopathy, often arising months or years after treatment,[41-43,45] which requires an increased level of management to provide support for patients and caregivers. Not only do longitudinal evaluations provide practical input for management, but the inclusion of periodic NCF assessments is also a method of monitoring for disease progression or the emergence of post-treatment complications.

MANAGEMENT OF NEUROCOGNITIVE SYMPTOMS

Unfortunately, there are no specific guidelines for management of NCF symptoms in patients with brain tumors. Although the National Comprehensive Cancer Network has provided guidelines for the management of cognitive symptoms as part of cancer survivorship, these apply explicitly to non–central nervous system cancers and treatments.[46] Efforts are underway to update National Comprehensive Cancer Network central nervous system guidelines to support appropriate follow-up of the neurocognitive aspects of glioma and other central nervous system tumor/treatment-related complications. We believe that thorough assessment provides a blueprint for treatment. Specific options to improve NCF outcomes in patients with brain tumors may include preventative measures, rehabilitative efforts, and pharmacologic interventions, as detailed below.

The Role of Neuropsychological Feedback and Recommendations

The transition point between assessment and management of neurocognitive symptoms occurs during the neuropsychological evaluation feedback session. Properly conducted, the feedback session is a therapeutic intervention that gives the patient and family a greater understanding and sense of control over their symptoms, reducing the accompanying anxiety.[47,48] Feedback sessions include individualized recommendations based on the patient's pattern of cognitive strength and weakness. Specific cognitive strategies and environmental modifications are recommended, which may allow a patient to independently address the NCF issues arising in their daily activities.[49,50] These recommendations can also be used to develop accommodations at work or school that may allow a person to continue to be successful in those pursuits despite NCF deficits. In cases in which NCF deficits are the cause of disability, an unfortunate but not uncommon occurrence for patients with brain tumors,[51] the objective quantification provided by neuropsychological evaluations may be critical to demonstrate deficits and allow access to benefits. Non-neurologic factors contributing to NCF impairment may also be targeted in the recommendations of a neuropsychological evaluation. When symptoms of depression or anxiety are identified as part of the standardized assessment of mood and emotional functioning, the neuropsychologist may be a link to mental health services. When issues of sleep disturbance arise, education in the use of sleep hygiene strategies or referral for a formal sleep evaluation may be triggered.

Prevention

Proactive efforts to prevent neurologic injury from treatment and increased focus on mitigating the neurotoxicity of cancer therapy have led to considerable improvements in NCF outcomes in recent years. These efforts built upon early work by Meyers and Hess[31] and Meyers and Brown,[52] who demonstrated the feasibility and importance of integrating NCF outcomes in clinical trials. As noted earlier, preoperative NCF assessment is often integrated with functional MRI, diffusion tensor imaging to identify critical fiber tracts, and intraoperative mapping to assist with planning and to reduce the risk of cognitive morbidity from surgery.

In recent years, multiple strategies have been integrated in brain radiation therapy to reduce the risk of NCF sequelae.[53] It has convincingly been demonstrated that use of focal radiation therapy through stereotactic radiosurgery leads to better NCF outcomes than whole-brain radiation therapy, without compromising overall or progression-free survival.[54] As a result, use of focal radiation therapy for solitary or multiple brain metastases is considered standard of care at this time for patients with limited metastatic disease in the brain.[54] When whole-brain radiation therapy is necessary, the use of hippocampal-sparing treatment, in which the field is tailored to avoid the hippocampal region—critical for memory and neuroplasticity—has been shown to reduce NCF morbidity[55] Similarly, the use of neuroprotectant strategies when delivering radiation therapy is frequently recommended. Administration of *N*-methyl-D-aspartate receptor antagonist memantine improved cognitive outcome in patients undergoing whole-brain radiation therapy,[56] and subsequent studies have found that this treatment can be

combined with hippocampal-sparing whole-brain radiation therapy[57] to further reduce the risk of NCF decline.

Rehabilitation

Cognitive rehabilitation is a therapy modality that includes explicit instruction in cognitive compensatory strategies, the use of assistive devices to support daily functioning, and, in some instances, cognitive "exercise" to promote brain recovery and maintain brain health. Studies of cognitive rehabilitation in patients with brain tumors have generally demonstrated a positive impact on NCF performance as well as good satisfaction on the part of patients and their families.[58-61] Most of these trials have been small and have lacked control groups, leading to some limitations in the strength of the literature.[61,62] Nonetheless, methods that use individualized therapy based on use of compensatory strategies and supportive devices have resulted in small to moderate improvements in the targeted cognitive functions based on objective testing and/or subjective report. Other studies have used computerized methods to deliver cognitive strategy training[62] or to provide cognitive stimulation and have shown some benefits in terms of attention and processing speed on cognitive tests,[63] though the degree to which these benefits transfer to real-life activities is unknown.

Physical exercise–based interventions have shown fairly consistent benefits in survivors of pediatric brain tumors,[64-66] and more recent studies have begun to demonstrate the potential for benefit in adults as well. For example, a study of physical exercise, as compared with an active control condition, demonstrated slight improvements in some aspects of performance-based and self-reported cognitive function, as well as quality of life benefits.[67] Although this literature is limited, there are other reasons to believe that exercise is an important aspect of overall care for patients with brain tumors.[68] Thus, integrating a safe and tolerable exercise routine is a recommended strategy to optimize brain health in all patients with cancer, including those with brain tumors. In those with physical limitations such as hemiparesis, gait disturbance, or visuospatial dysfunction, engaging a physical or occupational therapist to develop a safe and effective exercise strategy may be necessary.

Pharmacotherapy

Numerous trials of varying quality have attempted to evaluate the benefits of cognitive-enhancing medications on NCF in patients with brain tumors over the past 2 decades or more.[69] Although an initial uncontrolled single-arm study of methylphenidate for cognitive performance showed benefits in patients with brain tumors,[70] later trials that included control groups and placebos failed to replicate this result.[71-73] Interpretation of these outcome studies is complicated by the fact that some have used objective measurement of cognitive performance, whereas others included only subjective cognitive perceptions or primarily assessed fatigue as outcome measures.

The acetylcholinesterase inhibitor donepezil has shown generally beneficial but mixed effects in patients with brain tumors.[74-76] The only randomized controlled trial of donepezil suggested some benefits, though the effects were limited to improvements in those patients with the most severe cognitive impairment.[76] An uncontrolled pilot study showed improvements in patients with primary brain tumors who were otherwise stable,[75] and an additional open-label study showed improvements in various cognitive functions.[74] As detailed above, memantine has been used in a neuroprotective role during whole-brain radiation therapy with positive effects[56,57] but has not been trialed in other clinical settings. A single-arm study of gingko biloba suggested improvement on tests of executive function, though the possibility of practice effects accounting for this result cannot be excluded.[77] Taken together, these mixed findings suggest that donepezil and methylphenidate may have positive effects, though these may be due in part to expectancy effects on the part of the patient. In individual patients, practitioners must carefully consider the nature of the patient's NCF deficit to determine whether a medication is an appropriate fit. These treatment decisions can be informed by both the neuropsychological profile and patient preferences. For example, patients with demonstrated memory impairment (particularly those with a cognitive profile that suggests deficits in the aspects of memory that depend most heavily on cholinergic activity) may be more likely to benefit from an acetylcholinesterase inhibitor, whereas those with deficits in attention, processing speed, or executive function may respond better to neurostimulant medications.

Management of Additional Factors Contributing to Neurocognitive Function Symptoms

In addition to direct treatment of NCF using rehabilitation or medication, it is important to recognize that numerous neurologic and non-neurologic factors can contribute to cognitive problems in patients with brain tumors. The most prominent factors include fatigue and mood, both of which have strong inter-relationships with individual experience of NCF. In patients with considerable fatigue, insomnia, excessive daytime sleepiness, or other sleep disorders, integration of sleep studies and treatment of relevant issues is important to optimize NCF. Similarly, disorders of mood, anxiety, and other psychiatric symptoms are common in patients with brain tumors[78,79] and correlate highly with subjective NCF symptoms.[3] Thus, careful assessment and treatment of psychological symptoms is an important part of NCF management, with many effective evidence-based strategies available. An additional issue that can arise at any point in the disease course for patients with brain tumors is hydrocephalus (either obstructive or nonobstructive). In

such situations, placement of a ventriculo-peritoneal shunt may be beneficial, though NCF deficits are less likely to improve than incontinence and gait disturbance.[45,80-82] Thus, continued integration of a multidisciplinary treatment model throughout the disease course is critical to the assessment and treatment of NCF problems.

CASE EXAMPLE

The following case illustrates the integrated assessment and treatment of NCF symptoms in comprehensive brain tumor care. This right-handed patient was age 42 when he began to experience spells of lightheadedness accompanied by an unpleasant taste in his mouth that led to brain imaging. An MRI revealed a large nonenhancing mass involving the left inferior and anterior frontal lobe with involvement of the corpus callosum and extending inferiorly to the left anterior temporal lobe (Fig. 1A). A functional MRI was conducted that demonstrated left hemisphere language dominance, with productive speech areas immediately posterior to the mass (Fig. 1B). Preoperative screening suggested essentially

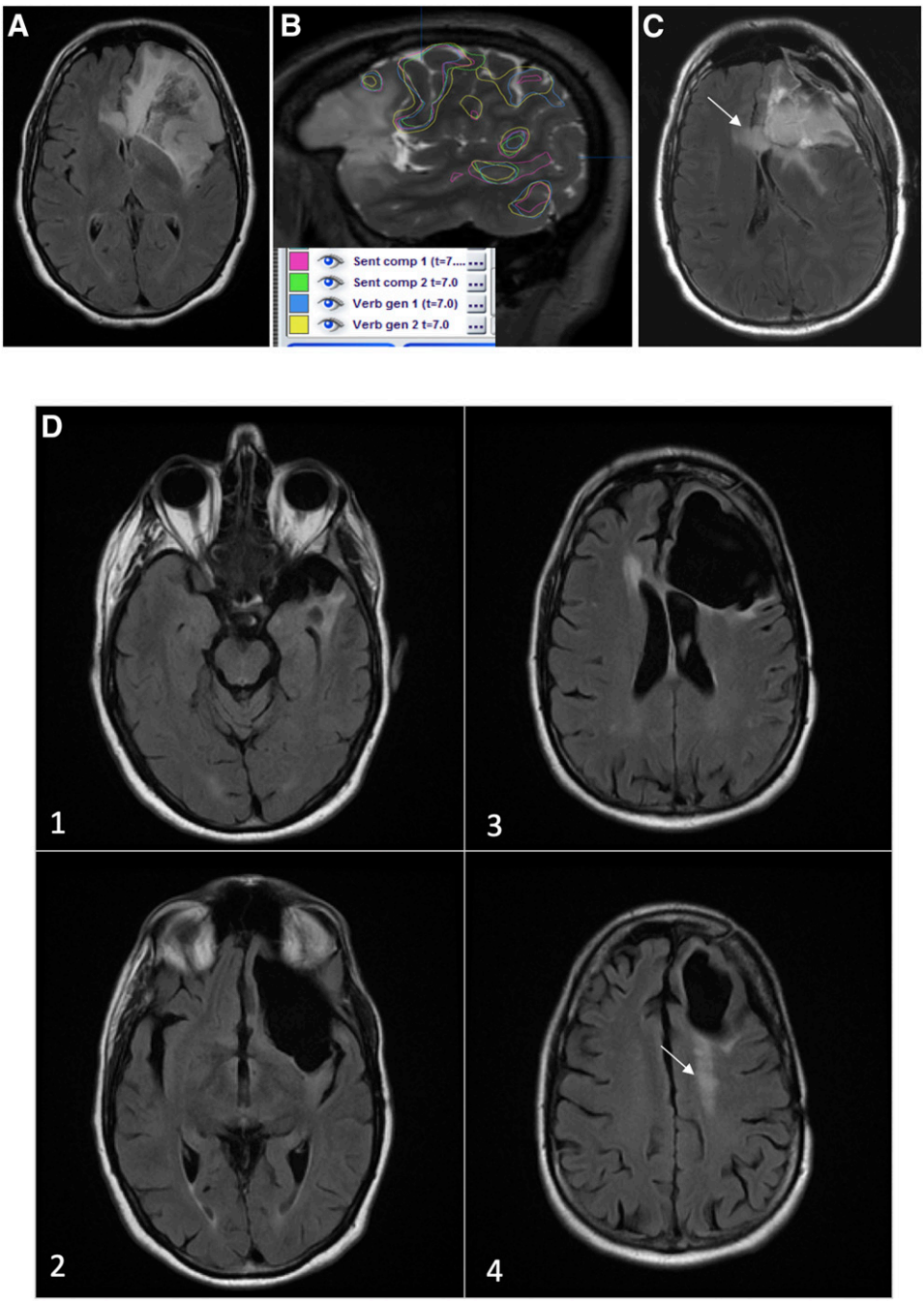

FIGURE 1. Brain MRI of the Patient Described in Case Study
T2/FLAIR study at initial presentation (A); functional MRI mapping of language superimposed on sagittal T2 (B); postoperative T2/FLAIR showing resection cavity and residual mass crossing corpus callosum (Arrow) (C); and (D) four axial T2/FLAIR images from superior to inferior showing resection cavity and post-treatment changes in surrounding brain 2 years after treatment.

intact language function, and surgical procedures included intraoperative mapping of language, which confirmed the location of putative Broca area immediately posterior to the mass. A subtotal resection was accomplished (Fig. 1C), and pathology identified an oligodendroglioma (World Health Organization grade II). The preoperative consideration of NCF risks and collaboration among neurosurgery, speech therapy, and neuroradiology contributed to maximal safe resection.

Approximately 3 weeks after surgery, the patient participated in a comprehensive neuropsychological evaluation to assess surgical outcome and assist with planning regarding return to work. The patient complained of word-finding difficulty postoperatively, which represented a slight decline in functioning compared with his subjective baseline. In addition, it became clear that the patient had been experiencing progressive issues with inattentiveness, disorganization, and disinhibited behavior over 1 to 2 years prior to identification of the brain tumor. The postoperative neuropsychological evaluation showed mild language disturbance as well as notable executive dysfunction, including reduced cognitive flexibility, impaired inhibitory controls, and inattention (Fig. 2).

A family feedback session was conducted, which was transformative. The patient's executive dysfunction had put considerable strain on relationships with his wife and children due to disinhibited behavior. He had lost his job shortly prior to diagnosis due to impulsive behavior. In the feedback session, the patient and his family experienced a reframing of the nature of his cognitive and behavioral issues, and a treatment plan was developed. Treatment included cognitive rehabilitation therapy to improve attention, develop organizational strategies, and address job performance issues. The patient also engaged in psychotherapy (including some couple and family sessions) to identify behavioral changes and had a gradual but impressive improvement in his insight and interpersonal interactions. During this time, he underwent radiation therapy and started treatment with multiagent chemotherapy (procarbazine, lomustine, and vincristine) for the primary disease.

The patient was followed with repeat neuropsychological evaluation 2 years after diagnosis (Fig. 2). Although the evaluation showed a substantial decline in language function (felt to reflect treatment-related tissue damage in left frontal lobe; Fig. 1D), he showed slight improvement in executive function and a marked improvement in overall quality of life. Due to continuing attention difficulties, he started treatment with an attention-enhancing medication (methylphenidate) but discontinued it after a few weeks due to increased feelings of anxiety and irritability. At this time, the patient is currently pursuing new employment and has restarted cognitive rehabilitation therapy to improve organizational techniques. He has been using an online cognitive exercise program (www.brainhq.com) to provide attention and working memory stimulation. The plan is for continued monitoring of the brain tumor with serial imaging and monitoring of NCF with annual neuropsychological evaluations. The patient frequently communicates with his cognitive rehabilitation therapist and neuropsychologist as part of the treatment team.

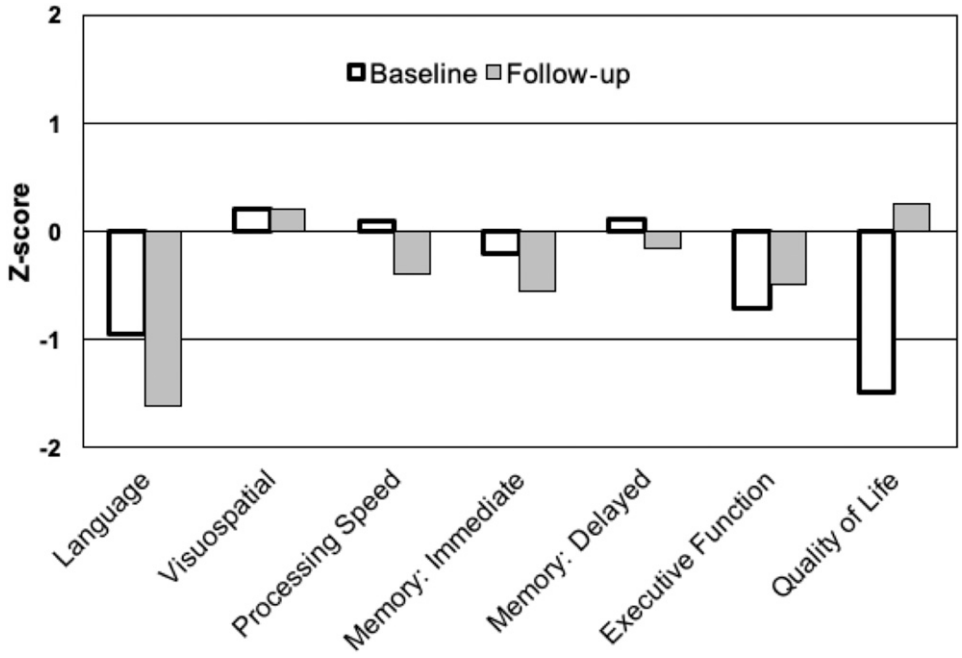

FIGURE 2. Graphical Illustration of Neuropsychological Test Results at Two Points: 1 Month Postsurgery (Baseline) and 2 Years Later (Follow-Up)
Note that patient performance declined on tests of language, reflecting increased difficulty with confrontation naming and verbal fluency tasks, but was not significantly changed in other cognitive domains. There were subtle improvements in some aspects of executive function and a considerable improvement in quality of life.

FUTURE DIRECTIONS

As the field of neuro-oncology strives to develop more effective treatments for brain tumors, simultaneous efforts are ongoing to develop new approaches to reducing NCF morbidity related to the diseases and treatments. There are numerous ongoing clinical trials examining pharmacologic, rehabilitative, and alternative strategies for mitigating NCF deficits related to brain tumors and cancer therapies, including up to 184 studies in a recent search of ClinicalTrials.gov.[83] Promising new therapies are being explored, such as the use of granulocyte colony-stimulating factor to drive bone marrow cells to increase brain plasticity and improve NCF related to radiation injury.[84] New methods of neurocognitive assessment and therapy are being explored, including computerized approaches[62] and remote video neuropsychological assessment, spurred along by the COVID-19 pandemic.[85] Further integration of NCF in clinical care and outcomes research will be critical to continue to improve quality of life for survivors of brain tumors.

CONCLUSIONS

Monitoring of NCF in the care of patients with brain tumors is best accomplished via a combination of cognitive screening tools administered in clinic and routine inquiry regarding cognitive concerns of the patient and, when possible, collateral informant. Integration of formal neuropsychological assessment at critical points in patient care and over the long term improves sensitivity to NCF issues and changes. Feedback on the neuropsychological assessment provides an opportunity to develop a treatment plan for NCF. In addition to preventative measures that have been adopted in neurosurgery and radiation oncology, treatment options include cognitive rehabilitation and pharmacotherapy. Interventions to address additional issues, such as problems with sleep, fatigue, and mood, can also lead to improved NCF. Consistent application of these assessment and treatment modalities can improve quality of life and overall outcome throughout the course of disease for patients with brain tumors.

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REFERENCES

1. Chaytor N, Schmitter-Edgecombe M. The ecological validity of neuropsychological tests: a review of the literature on everyday cognitive skills. Neuropsychol Rev. 2003;13:181-197.
2. Collins C, Gehrke A, Feuerstein M. Cognitive tasks challenging brain tumor survivors at work. J Occup Environ Med. 2013;55:1426-1430.
3. Noll KR, Bradshaw ME, Weinberg JS, et al. Relationships between neurocognitive functioning, mood, and quality of life in patients with temporal lobe glioma. Psychooncology. 2017;26:617-624.
4. Tucha O, Smely C, Preier M, et al. Cognitive deficits before treatment among patients with brain tumors. Neurosurgery. 2000;47:324-333.
5. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. Lancet Neurol. 2004;3:159-168.
6. Tucha O, Smely C, Preier M, et al. Preoperative and postoperative cognitive functioning in patients with frontal meningiomas. J Neurosurg. 2003;98:21-31.
7. Hendrix P, Hans E, Griessenauer CJ, et al. Neurocognitive function surrounding the resection of frontal WHO grade I meningiomas: a prospective matched-control study. World Neurosurg. 2017;98:203-210.
8. Noll KR, Weinberg JS, Ziu M, et al. Neurocognitive changes associated with surgical resection of left and right temporal lobe glioma. Neurosurgery. 2015;77:777-785.
9. Satoer D, Vork J, Visch-Brink E, et al. Cognitive functioning early after surgery of gliomas in eloquent areas. J Neurosurg. 2012;117:831-838.
10. Mandonnet E, De Witt Hamer P, Poisson I, et al. Initial experience using awake surgery for glioma: oncological, functional, and employment outcomes in a consecutive series of 25 cases. Neurosurgery. 2015;76:382-389.
11. Blonski M, Taillandier L, Herbet G, et al. Combination of neoadjuvant chemotherapy followed by surgical resection as a new strategy for WHO grade II gliomas: a study of cognitive status and quality of life. J Neurooncol. 2012;106:353-366.
12. Armstrong TS, Wefel JS, Wang M, et al. Net clinical benefit analysis of radiation therapy oncology group 0525: a phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma. J Clin Oncol. 2013;31:4076-4084.
13. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med. 2014;370:699-708.

14. Wefel JS, Schagen SB. Chemotherapy-related cognitive dysfunction. Curr Neurol Neurosci Rep. 2012;12:267-275.
15. Prust MJ, Jafari-Khouzani K, Kalpathy-Cramer J, et al. Standard chemoradiation for glioblastoma results in progressive brain volume loss. Neurology. 2015; 85:683-691.
16. Prust ML, Jafari-Khouzani K, Kalpathy-Cramer J, et al. Standard chemoradiation in combination with VEGF targeted therapy for glioblastoma results in progressive gray and white matter volume loss. Neuro-oncol. 2018;20:289-291.
17. Wefel JS, Parsons MW, Gondi V, et al. Neurocognitive aspects of brain metastasis. Handb Clin Neurol. 2018;149:155-165.
18. Klein M, Engelberts NH, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life. Ann Neurol. 2003; 54:514-520.
19. Makale MT, McDonald CR, Hattangadi-Gluth JA, et al. Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. Nat Rev Neurol. 2017;13:52-64.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189-198.
21. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695-699.
22. Meyers CA, Wefel JS. The use of the mini-mental state examination to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. J Clin Oncol. 2003;21:3557-3558.
23. Racine CA, Li J, Molinaro AM, et al. Neurocognitive function in newly diagnosed low-grade glioma patients undergoing surgical resection with awake mapping techniques. Neurosurgery. 2015;77:371-379.
24. Block CK, Johnson-Greene D, Pliskin N, et al. Discriminating cognitive screening and cognitive testing from neuropsychological assessment: implications for professional practice. Clin Neuropsychol. 2017;31:487-500.
25. Weitzner MA, Meyers CA, Gelke CK, et al. The Functional Assessment of Cancer Therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. Cancer. 1995;75:1151-1161.
26. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85:365-376.
27. Perez A, Zarrella G, Parsons MW, Dietrich J. Reliability and validity of a new self-report index of cognitive concerns in cancer patients. Presented at: 48th Annual Meeting of the International Neuropsychological Society. Denver, CO; 2020. Poster 65.
28. Noll KR, Bradshaw ME, Rexer J, et al. Neuropsychological practice in the oncology setting. Arch Clin Neuropsychol. 2018;33:344-353.
29. Noll KR, Bradshaw ME, Parsons MW, et al. Monitoring of neurocognitive function in the care of patients with brain tumors. Curr Treat Options Neurol. 2019;21:33.
30. Baum KT, Powell SK, Jacobson LA, et al. Implementing guidelines: proposed definitions of neuropsychology services in pediatric oncology. Pediatr Blood Cancer. 2017;64:e26446.
31. Meyers CA, Hess KR. Multifaceted end points in brain tumor clinical trials: cognitive deterioration precedes MRI progression. Neuro-oncol. 2003;5:89-95.
32. Johnson DR, Sawyer AM, Meyers CA, et al. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. Neuro-oncol. 2012;14:808-816.
33. Meyers CA, Hess KR, Yung WK, et al. Cognitive function as a predictor of survival in patients with recurrent malignant glioma. J Clin Oncol. 2000;18:646-650.
34. Noll KR, Sullaway CM, Wefel JS. Depressive symptoms and executive function in relation to survival in patients with glioblastoma. J Neurooncol. 2019; 142:183-191.
35. Kelm A, Sollmann N, Ille S, et al. Resection of gliomas with and without neuropsychological support during awake craniotomy-effects on surgery and clinical outcome. Front Oncol. 2017;7:176.
36. Bookheimer S. Pre-surgical language mapping with functional magnetic resonance imaging. Neuropsychol Rev. 2007;17:145-155.
37. Gehring K, Sawyer A, Etzel C, et al. Prediction of memory outcomes after resection of high-grade glioma. Neuro-oncol. 2011;13:iii73.
38. Gehring K, Sawyer A, Etzel C, et al. Prediction of language outcomes after resection of high-grade glioma. Neuro-oncol. 2011;13(Suppl 3):iii75.
39. Lundqvist A. Neuropsychological aspects of driving characteristics. Brain Inj. 2001;15:981-994.
40. Henriksson R, Asklund T, Poulsen HS. Impact of therapy on quality of life, neurocognitive function and their correlates in glioblastoma multiforme: a review. J Neurooncol. 2011;104:639-646.
41. Lai R, Abrey LE, Rosenblum MK, et al. Treatment-induced leukoencephalopathy in primary CNS lymphoma: a clinical and autopsy study. Neurology. 2004; 62:451-456.
42. Tallet AV, Azria D, Barlesi F, et al. Neurocognitive function impairment after whole brain radiotherapy for brain metastases: actual assessment. Radiat Oncol. 2012;7:77.
43. Crossen JR, Garwood D, Glatstein E, et al. Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. J Clin Oncol. 1994;12:627-642.
44. Klein M, Heimans JJ, Aaronson NK, et al. [Impaired cognitive functioning in low-grade glioma patients: relationship to tumor localisation, radiotherapy and the use of anticonvulsants]. Ned Tijdschr Geneeskd. 2004;148:2175-2180.
45. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. Neurology. 1989;39:789-796.

46. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Survivorship. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf. Accessed March 21, 2021.
47. Gorske TT. Therapeutic neuropsychological assessment: a humanistic model and case example. J Humanist Psychol. 2008;48:320-339.
48. Postal K, Armstrong K. Feedback That Sticks: The Art of Effectively Communicating Neuropsychological Assessment Results. New York: Oxford University Press; 2013.
49. Gehring K, Aaronson NK, Taphoorn MJ, et al. Interventions for cognitive deficits in patients with a brain tumor: an update. Expert Rev Anticancer Ther. 2010; 10:1779-1795.
50. Ferguson RJ, Ahles TA, Saykin AJ, et al. Cognitive-behavioral management of chemotherapy-related cognitive change. Psychooncology. 2007;16:772-777.
51. Noll KR, Bradshaw ME, Weinberg JS, et al. Neurocognitive functioning is associated with functional independence in newly diagnosed patients with temporal lobe glioma. Neurooncol Pract. 2018;5:184-193.
52. Meyers CA, Brown PD. Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. J Clin Oncol. 2006;24:1305-1309.
53. Attia A, Page BR, Lesser GJ, et al. Treatment of radiation-induced cognitive decline. Curr Treat Options Oncol. 2014;15:539-550.
54. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA. 2016;316:401-409.
55. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. J Clin Oncol. 2014;32:3810-3816.
56. Brown PD, Pugh S, Laack NN, et al; Radiation Therapy Oncology Group (RTOG). Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro-oncol. 2013;15:1429-1437.
57. Brown PD, Gondi V, Pugh S, et al; for NRG Oncology. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG Oncology CC001. J Clin Oncol. 2020;38:1019-1029.
58. Bergo E, Lombardi G, Pambuku A, et al. Cognitive rehabilitation in patients with gliomas and other brain tumors: state of the art. BioMed Res Int. 2016; 2016:3041824.
59. Gehring K, Sitskoorn MM, Gundy CM, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. J Clin Oncol. 2009;27:3712-3722.
60. van Lonkhuizen PJC, Klaver KM, Wefel JS, et al. Interventions for cognitive problems in adults with brain cancer: a narrative review. Eur J Cancer Care (Engl). 2019;28:e13088.
61. Coomans MB, van der Linden SD, Gehring K, et al. Treatment of cognitive deficits in brain tumour patients: current status and future directions. Curr Opin Oncol. 2019;31:540-547.
62. van der Linden SD, Sitskoorn MM, Rutten GM, et al. Feasibility of the evidence-based cognitive telerehabilitation program Remind for patients with primary brain tumors. J Neurooncol. 2018;137:523-532.
63. Yang S, Chun MH, Son YR. Effect of virtual reality on cognitive dysfunction in patients with brain tumor. Ann Rehabil Med. 2014;38:726-733.
64. Sahnoune I, Inoue T, Kesler SR, et al. Exercise ameliorates neurocognitive impairments in a translational model of pediatric radiotherapy. Neuro-oncol. 2018; 20:695-704.
65. Benzing V, Eggenberger N, Spitzhüttl J, et al. The Brainfit study: efficacy of cognitive training and exergaming in pediatric cancer survivors - a randomized controlled trial. BMC Cancer. 2018;18:18.
66. Riggs L, Piscione J, Laughlin S, et al. Exercise training for neural recovery in a restricted sample of pediatric brain tumor survivors: a controlled clinical trial with crossover of training versus no training. Neuro-oncol. 2017;19:440-450.
67. Gehring K, Stuiver MM, Visser E, et al. A pilot randomized controlled trial of exercise to improve cognitive performance in patients with stable glioma: a proof of concept. Neuro-oncol. 2020;22:103-115.
68. Ruden E, Reardon DA, Coan AD, et al. Exercise behavior, functional capacity, and survival in adults with malignant recurrent glioma. J Clin Oncol. 2011; 29:2918-2923.
69. Karschnia P, Parsons MW, Dietrich J. Pharmacologic management of cognitive impairment induced by cancer therapy. Lancet Oncol. 2019;20:e92-e102.
70. Meyers CA, Weitzner MA, Valentine AD, et al. Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. J Clin Oncol. 1998; 16:2522-2527.
71. Boele FW, Douw L, de Groot M, et al. The effect of modafinil on fatigue, cognitive functioning, and mood in primary brain tumor patients: a multicenter randomized controlled trial. Neuro-oncol. 2013;15:1420-1428.
72. Butler JM Jr., Case LD, Atkins J, et al. A phase III, double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCl in brain tumor patients receiving radiation therapy. Int J Radiat Oncol Biol Phys. 2007;69:1496-1501.
73. Gehring K, Patwardhan SY, Collins R, et al. A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. J Neurooncol. 2012;107:165-174.
74. Shaw EG, Rosdhal R, D'Agostino RB Jr., et al. Phase II study of donepezil in irradiated brain tumor patients: effect on cognitive function, mood, and quality of life. J Clin Oncol. 2006;24:1415-1420.
75. Correa DD, Kryza-Lacombe M, Baser RE, et al. Cognitive effects of donepezil therapy in patients with brain tumors: a pilot study. J Neurooncol. 2016; 127:313-319.

76. Rapp SR, Case LD, Peiffer A, et al. Donepezil for irradiated brain tumor survivors: a phase III randomized placebo-controlled clinical trial. J Clin Oncol. 2015; 33:1653-1659.

77. Attia A, Rapp SR, Case LD, et al. Phase II study of Ginkgo biloba in irradiated brain tumor patients: effect on cognitive function, quality of life, and mood. J Neurooncol. 2012;109:357-363.

78. Litofsky NS, Resnick AG. The relationships between depression and brain tumors. J Neurooncol. 2009;94:153-161.

79. Arnold SD, Forman LM, Brigidi BD, et al. Evaluation and characterization of generalized anxiety and depression in patients with primary brain tumors. Neuro-oncol. 2008;10:171-181.

80. Fischer CM, Neidert MC, Péus D, et al. Hydrocephalus after resection and adjuvant radiochemotherapy in patients with glioblastoma. Clin Neurol Neurosurg. 2014;120:27-31.

81. Perrini P, Scollato A, Cioffi F, et al. Radiation leukoencephalopathy associated with moderate hydrocephalus: intracranial pressure monitoring and results of ventriculoperitoneal shunting. Neurol Sci. 2002;23:237-241.

82. Thiessen B, DeAngelis LM. Hydrocephalus in radiation leukoencephalopathy: results of ventriculoperitoneal shunting. Arch Neurol. 1998;55:705-710.

83. ClinicalTrials.gov. Search of brain tumors and cognitive. https://clinicaltrials.gov/. Accessed April 8, 2021.

84. Dietrich J, Baryawno N, Nayyar N, et al. Bone marrow drives central nervous system regeneration after radiation injury. J Clin Invest. 2018;128:281-293.

85. Gardner M, Aslanzadeh F, Zarrella G, et al. COVD-19. cognition, cancer, and COVID: delivering direct-to-home tele-neuropsychology services to neuro-oncology patients. Neuro-oncol. 2020;22(Supplement_2):ii25.

Delivering Equitable Care to Underserved Neuro-oncology Populations

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overview

It is widely recognized that subspecialized multidisciplinary care improves neuro-oncology outcomes. Optimizing patient outcomes relies on the expertise of the treating physicians, neuroradiology and neuropathology, and supportive services familiar with common neurologic syndromes that occur after brain tumor diagnosis and treatment. Despite an increasing number of providers, patient access to specialized multidisciplinary care and clinical trials remains limited. Barriers to equitable health care exist across the United States, with marginalized communities being impacted disproportionately. Such disparity causes increased morbidity and mortality for patients from backgrounds with various elements of diversity. Limited attention to this inequity has resulted in an incomplete understanding of the spectrum of experiences that patients with neuro-oncologic diseases encounter. Clinical trials represent the highest standard and quality of care in medicine, but inclusion of under-represented and underserved groups consistently lags behind counterpart participants from majority racial and ethnic groups. Through provider education as it pertains to issues from bias and health literacy to increasing clinical trial enrollment and offering opportunities through telemedicine, opportunities for improving access to high-quality neuro-oncologic care are explored.

> "The good physician treats the disease; the great physician treats the patient who has the disease."
> — Sir William Osler

Although there have been tremendous gains in neuro-oncology related to our understanding of disease pathogenesis, diagnosis, and, in some instances, treatment, these advances have not benefited all populations equally.[1] Unfortunately, barriers related to access, interventions, and outcomes continue to exist and frequently fall along racial and ethnic lines, with people of diverse backgrounds frequently experiencing disparity. According to the National Institutes of Health, health-disparate populations include "Blacks/African Americans, Hispanic/Latinos, American Indian/Alaska natives, Asian Americans, Native Hawaiians and other Pacific Islanders, socioeconomically disadvantaged populations, underserved and rural populations, and sexual and gender minorities."[2] In striving for the equitable delivery of neuro-oncologic care to all, nuances of the underserved populations must be understood and overcome.

PROVIDER-FOCUSED EDUCATION

The gold standard often inherent in the stated mission of health care organizations is based on a statement from the National Standards for Culturally and Linguistically Appropriate Services to "provide effective, equitable and respectful quality care and services that are responsive to diverse cultural health beliefs and practices, preferred languages, health literacy, and other communication needs."[3] Despite this clear mission, the Institute of Medicine found that racial and ethnic minority patients tend to receive a lower quality of health care than nonminority patients. Based on this finding, the following groups were identified as those receiving disparate care: women; African American and Black people; people living in poverty in Appalachia; Asian American people; elderly people; immigrants and refugees; individuals living with disabilities; Hispanic and Latinx people; members of the lesbian, gay, bisexual, transgender, questioning, intersex, and asexual community; Indigenous American people; people who are overweight; incarcerated people; and some religious minorities.[4] The result of such disparity is complex and known to involve multiple levels of health care, including the team of providers in addition to access. One aspect of intervention toward mitigating disparity is education.

Factors that influence the clinical encounter involve elements of racism, bias and stereotyping, and communication that contribute to the perpetuation of unequal treatment.[5] Although there may be aspects of these subjects incorporated into the medical school curriculum, the majority of education among physicians frequently happens in real time, based on patient experiences. It is well recognized that, when physicians are stressed or multitasking, these factors often impact medical decision-making.[4] To recognize the role

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PRACTICAL APPLICATIONS

- Marginalized populations remain underrepresented in clinical trials.
- Opportunities exist to improve access when it is limited through community oncology and telemedicine.
- Provider education in elements of racism, bias and stereotyping, and communication can improve the clinical encounter, resulting in increased trust, better adherence, and improved outcomes.

racism plays in health outcomes, it must be considered on three levels: institutionalized, personally mediated, and internalized.

Institutionalized racism is defined as differential access to the goods, services, and opportunities of society by race. It is characterized by an initial historical insult followed by the perpetuation of structural barriers, societal norms, and unearned privilege. Examples include differential access to quality education; sound housing; gainful employment; appropriate medical facilities; and a clean environment and differential access to information (including one's own history), resources (including wealth and organizational infrastructure practices), and voice practices (including voting rights, representation of government, and control of the media). This aspect of institutionalized racism frequently emerges in health care through the various aspects of the social determinants of health and access to information. Personally mediated racism is defined as prejudice and discrimination. Prejudice manifests as assumptions about the abilities, motives, and intentions of others according to their race, whereas discrimination means differential actions toward others according to their race. Prejudice can be both intentional and unintentional, ranging from behaviors that indicate a lack of respect to the dehumanization of our patients. Personally mediated racism emerges when stereotypes and biases emerge in medical decision-making, resulting in premature closure and unintended outcomes. Finally, internalized racism is defined as acceptance by members of the stigmatized populations of negative messages about their own abilities and intrinsic worth. Internalized racism reflects systems of privilege as well as societal values and erodes individual sense of value and can undermine collective action.[6] Internalized racism is experienced on an individual basis and requires thoughtful intervention in the clinical encounter to establish a sense of priority and worth along with trust. The recognition of the power of privilege within health care institutions is one that requires introspection and education at all levels. Once empowered through education, providers benefit from an increased level of awareness, with a goal of leveling power differentials throughout the health care encounter. Institutions must hold themselves accountable for fixing power imbalances when they exist.[7]

HEALTH LITERACY AND PATIENT-CENTERED EDUCATION

Personal health literacy is the degree to which individuals can read, find, understand, and use information and services to inform health-related decisions and actions for themselves and others, and it is not always congruent with general literacy. Health literacy becomes more challenging in the neuro-oncologic population, given the accompanying neurologic morbidity resulting from the disease process itself and or the intervention and treatment. As a result, patients frequently experience cognitive limitations, which impact health literacy even more. According to the literature, most adults may lack the skills required to prevent disease and manage their health.[8] Recognizing this limitation in health literacy and seeking to empower patients through their own education is an initiative that must be undertaken by the health care provider to ensure adequate communication and patient-centered decision-making. Improving health literacy can lead to improved disease outcomes, improved patient functional and psychological well-being, increased patient and clinician satisfaction, increased trust in the patient-clinician relationship, and lower health care costs.[9] The failure to address health literacy results in poor health outcomes, higher hospitalization rates, increased utilization of the emergency department, poor medication adherence, poor mental health, decreased physical function, and lower use of preventive services.[10]

Clinicians must create a safe environment where patients feel comfortable talking openly, with the provider seated to achieve eye level with the patient. Communication breakdowns are best avoided when the provider uses plain language instead of technical language or medical jargon. Using visual models to illustrate a procedure or condition is often helpful in addition to asking patients to "teach back" the care instructions given. Another tool is helping the patient learn about their disease through printed or online materials and through support groups. Patients may not be aware of their rights and responsibilities.[11] Inviting a caregiver, whether a friend, partner, or family member, who may serve as an advocate is an option. Using a qualified medical interpreter and encouraging questions and a second opinion can be additional ways to help empower patients.

PROMOTION OF RESEARCH AND EDUCATION

Ensuring access to quality neuro-oncologic care requires understanding the extent of disparity that currently exists. A strategic and sustained approach to research in this area, in addition to education of those interested, must be supported and prioritized. Seeking partnerships and increasing the visibility of neuro-oncologic disease will turn attention

toward access and improvement in outcomes for all populations. Understanding of the spectrum of neuro-oncologic disease relies on the success of clinical trial enrollment and measurement of outcomes. As we seek to improve the representation of our broader communities within trials, we must first understand the limitations that are multifaceted, frequently leading to reduced participation of diverse and underserved populations.

CLINICAL TRIALS

Clinical trials represent the highest standard and quality of care in medicine; however, inclusion of under-represented and underserved groups consistently lags behind counterpart participants from majority racial and ethnic groups. In 2015, the U.S. Food and Drug Administration published Drug Trial Snapshots, which captures the demographics of patients who participated in trials of therapies that led to product approval that year. In 2015, 45 drugs were approved, involving 10,500 participants, of which 5% identified as African American.[12] For comparison, in trials of psychiatric disorders conducted between 2015 and 2016, Black patients and African Americans represented more than 24% of participants, demonstrating that equity in clinical trial participation is possible.

In oncology, during this same time frame, Black and African American patients accounted for only 2.74% of participants in oncology clinical trials.[13] The National Comprehensive Cancer Network specifically states that the best management of disease for any patient with cancer is within a clinical trial. This approach represents the highest standard and the most aggressive form of care by offering new therapies, enhanced follow-up, and the ability to monitor clinical and scientific outcomes. It is also widely believed that patients enrolled in clinical trials, even if randomly assigned to control arms, still receive benefit from enrollment and report improved outcomes and quality of life. As noted, racial, ethnic, sexual, and gender minority patients as well as older adults are under-represented in oncology clinical trials.[14-16] In neuro-oncology, although this trend has been acknowledged, its study has been limited thus far. Work by Taha et al[17] showed that, in 471 brain tumor trials registered through ClinicalTrials.gov, only 28.4% published the demographics of participants, and racial and ethnic minority patients were substantially under-represented across all trials.

It stands to reason that clinical trial diversity benefits all. If study populations are homogeneous, collective understanding and an ability to detect whether an intervention is beneficial are reduced. As trends in oncology and neuro-oncology signal an increasing reliance upon molecular alterations as drivers of disease, therapy, and response, the lack of representation from a broader population will limit our interpretation and application of these data. By harnessing the input and expertise from stakeholders in local communities and government and by exploring the reach of technology with telemedicine, we should be poised to renew the collective effort to advance the field while also ensuring that all who may benefit from new therapies have an opportunity to do so.

Issues Related to Disparities in Clinical Trial Participation

Health care disparities refer to differences in health outcomes and health care between groups. More specifically, a health disparity refers to a higher burden of illness, injury, disability, or mortality experienced by one group relative to another. In the United States, the major social determinants of health are patient sex, race, ethnicity, geography (urban vs. rural), and socioeconomic status. Therefore, racial or ethnic differences in the quality of health care that are not due to access-related factors or clinical needs, preferences, and appropriateness of intervention are the modern definition of a health care disparity.[18]

A HISTORICAL PERSPECTIVE

During the past 20 years, major consensus initiatives have benchmarked health care disparities and their importance. In 1993, the National Institutes of Health Revitalization Act stated that, in conducting or supporting National Institutes of Health–funded clinical research, women and minority populations must be included.[19] This directive led to the establishment of guidelines and outreach efforts geared toward recruiting underserved patient populations. Updated guidance on the inclusion of women and patients from minority groups as participants in clinical research was released in 2001, with a revised amendment released in 2017. In these documents, it was determined that the targeted study population should reflect the age, gender, race, and ethnic distribution of the population affected by the disease or condition under study. If disease-specific mortality is not known, then the study population should reflect the composition of the overall U.S. population.

THE IMPACT OF HEALTH DISPARITIES ON CLINICAL OUTCOMES

Decades of health outcomes research have brought to light disparities in health outcomes between groups of patients. Some of the most obtrusive examples of unequal outcomes include the following: (1) a Black infant mortality rate that is 2.5 times higher than for White babies, (2) a 30% higher rate of diabetes among Indigenous American and Latinx patients compared with White patients, (3) higher death rates from breast and prostate cancer among patients from minority groups, and (4) a life expectancy for Black men and women that is nearly 10 years shorter compared with White men and women.[20] Specific to neuro-oncology, sources of disparities include patient, provider, and systemic factors. Using malignant gliomas as an illustrative case, we know that minority patients present with greater premorbid illness, have longer

symptoms of disease with delayed presentation, experience less information transfer during patient-provider encounters, have greater perioperative surgical morbidity, have less molecular tumor subclassification, and experience greater delays in starting chemoradiation when compared with nonminority patients.[21-23] Each of these factors necessitates specific intervention to improve health outcomes.

SOURCES OF DISPARITIES IN CLINICAL TRIAL ENROLLMENT

Clinical trial enrollment is considered the highest possible level of care for patients; nevertheless, only 3% to 5% of U.S. patients with cancer participate in clinical trials. Enrolled patients are, however, overwhelmingly men with European ancestry.[24] Beyond moral concerns regarding equal access to high-quality health care, disparities in clinical trial enrollment represent a major therapeutic challenge for the general population. First, the lack of diverse patient enrollment has generated a knowledge gap in our understanding of the biologic and therapeutic implications of genomic differences among individuals.[25] Landmark cancer epidemiology studies have poor representation from non-White patients, thereby limiting generalizability. Next, underaccrual often results in premature study termination, and it is estimated that 22% to 50% of clinical trials are terminated as a result of poor accrual. Therefore, poor clinical trial enrollment of diverse patient populations contributes to poor clinical trial enrollment in clinical and translational cancer research. Within neuro-oncology, in addition to minority status, additional modifiable patient factors, such as patient proximity to a tertiary care cancer center, are important correlates of clinical trial enrollment. Morshed et al[26] recently demonstrated that minority patients with glioma who enrolled in clinical trials lived on average 30 miles closer to the cancer center when compared with minority patients who elected to not enroll in a clinical trial. Therefore, patient screening and targeted outreach toward vulnerable populations should be carefully considered.[26,27]

The ultimate goal of all therapeutic drug or device clinical trials in patients with cancer is U.S. Food and Drug Administration treatment approval for the general public. Recent evidence has illustrated disparities in race reporting and representation among clinical cancer trials that lead to U.S. Food and Drug Administration approval.[28] In a study by Loree et al[28] including more than 200 clinical trials and 12,293 study participants during a 10-year period that followed implementation of the National Institutes of Health Revitalization Act, 76.3% of enrolled patients were White, and 23.7% represented Black, Hispanic, and Asian minority groups. However, throughout the 10-year study period, the proportion of race enrollment changed minimally, as Black patient enrollment increased by only 0.7% and Hispanic patient enrollment increased by 1.4%. Most strikingly, compared with their proportional U.S. cancer incidence, Black and Hispanic patients were underrepresented compared with White and Asian patients.

Overcoming Barriers to Neuro-oncology Clinical Trial Enrollment in the Rural Setting

Clinical trial enrollment in a rural setting is particularly challenging, but it is crucial that a diverse population of patients—in terms of age, race, ethnic ethnicity, geographic location, and socioeconomic status—is enrolled in trials to ensure that results are generalizable across these distinct populations. Overall, patient participation in trials for primary brain tumors has been estimated at 21%, whereas only 8% to 11% of newly diagnosed patients with glioblastoma participate in a trial.[29,30] Ensuring that all patients with primary brain tumors, even those in a rural setting, have access to clinical trials will maximize enrollment to speed trial completion. It is clear that rural patients with cancer are less likely to participate in clinical trials.[31,32] The rationale for reduced trial participation among rural patients with brain tumors is likely multifactorial. To examine the barriers to trial enrollment and facilitators to improve enrollment, a conceptual framework for evaluating patient participation in clinical trials has been previously described.[33] In this model, crossing multiple decision points is necessary for a successful patient enrollment. Applying this model to rural patients identifies three key areas that specifically impact enrollment of rural patients to brain tumor trials (Fig. 1): clinical trial site availability, provider engagement, and patient-specific factors.

NEURO-ONCOLOGY CLINICAL TRIAL SITE AVAILABILITY

In a retrospective, single-provider review of patients with glioma, the most common reason cited by patients for declining trial participation was travel distance to the trial site.[34] Thus, ensuring patients have access to available trials close to home is a key factor to improve enrollment. Treatment of primary brain tumors often requires multidisciplinary care that is only available at large academic institutions, and it is therefore unrealistic that some trials can be offered at rural, community cancer treatment sites. For example, trial WF-1801 from the Wake Forest National

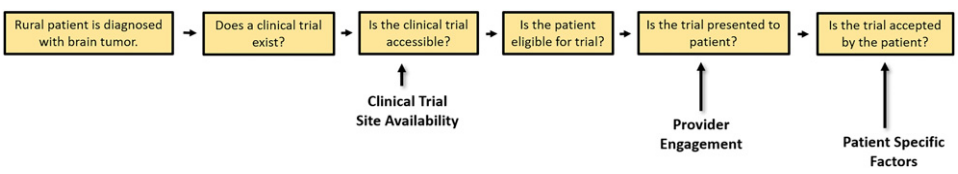

FIGURE 1. Conceptual Model of Rural Trial Enrollment

Clinical Trials Network cooperative group is evaluating ramipril for the prevention of radiation-induced cognitive decline in glioblastoma. This low-complexity trial should be able to be offered at any community site capable of clinical trial participation. In contrast, the Alliance National Clinical Trials Network A071702 trial evaluating immunotherapy in patients with recurrent hypermethylated glioblastoma is a more complex trial that may not be an appropriate study for a rural site. Maximizing enrollment for rural neuro-oncology studies requires that all practical studies are offered as close to home as possible. Therefore, ensuring rural cancer clinics have the infrastructure to participate in brain tumor trials is critical.

The National Cancer Institute recognized the need to include community sites to improve cancer care and trial participation in rural areas, which initially led to the development of the Community Clinical Oncology Program and has now continued with the National Cancer Institute Community Oncology Research Program (NCORP).[35] The NCORP comprises seven research bases and 46 community sites and designs, conducts clinical trials in multiple areas, and provides funding for research activities to community sites. Among the 46 community sites are 14 minority/underserved community sites that are focused on communities with at least 30% racial/ethnic minorities or rural residents. The 46 NCORP sites oversee clinical trial participation at 1,014 locations throughout the contiguous United States as well as in Alaska, Hawaii, and Puerto Rico. The NCORP has demonstrated the ability to enroll rural patients in clinical trials. Data from the Alliance NCORP research base from 2019 show that 527 (20%) of 2,701 patient enrollments at NCORP sites were classified as rural on the basis of rural-urban commuting area analysis of patient ZIP code. Specific for brain tumor trial enrollment, eight (23%) of 35 patients were classified as rural. Continuing efforts by the NCORP and ensuring trials are available through this pathway support rural trial enrollment.

In addition to the NCORP, states have taken the initiative to foster clinical trial participation in rural communities. The Minnesota Legislature supported the development of the Minnesota Cancer Clinical Trials Network under the direction of the University of Minnesota Masonic Cancer Center to improve cancer outcomes through greater access to clinical trials.[36] At present, the Minnesota Cancer Clinical Trials Network supports clinical trial participation at 22 locations in Minnesota, all of which are outside of the greater Minneapolis and Rochester metro areas and primarily serve rural populations. Many of these locations had never participated in clinical research before the inception of the Minnesota Cancer Clinical Trials Network. Funding for research infrastructure provided by Minnesota Cancer Clinical Trials Network and leadership provided by Minnesota Cancer Clinical Trials Network–helmed organizations have led to improved trial access for rural Minnesotans.

Historically, participating in a clinical trial meant that a patient received all trial activities in person at a trial site. Efforts to develop decentralized or hybrid trials may increase trial access in rural communities. Fairly simple changes, such as the use of central institutional review boards and remote consenting, have altered study procedures to facilitate rural enrollment. The COVID-19 pandemic has also provided lessons that highlight potential ways to decentralize study procedures even more, including telemedicine visits, central imaging review, remote trial site monitoring, and local administration of approved therapies for trial participants.[37] It is anticipated that many of the changes to facilitate trial enrollment during the pandemic will continue, particularly benefitting rural trial participants.

PROVIDER ENGAGEMENT

The National Brain Tumor Society conducted a survey to evaluate clinical trial enrollment by patients with brain tumors and their caregivers.[38] Data from a total of 1,463 respondents revealed that the top reason for not participating in a clinical trial was that the patient's provider did not recommend participating in the trial. Thus, ensuring providers who care for rural patients are engaged with clinical trials is necessary to improve rural accrual. A study assessing organizational and physician factors associated with patient enrollment highlighted several key areas to maximize engagement: ensure adequate research staff to support enrollment, educate physicians about studies, and foster direct involvement in the research program.[39] Sites can maximize research staff through participation in programs that financially support research infrastructure, such as NCORP and the Minnesota Cancer Clinical Trials Network. Educating physicians about trials includes maintaining local trial information in an easy-to-access format as well as providing patient-specific information about trials that may be available regionally by using trial databases such as ClinicalTrials.gov. More personalized trial navigation can also occur through navigation programs either locally or as a component of national organizations, such as the National Brain Tumor Society.[40] Providers can become directly involved in research activities, such as NCORP, by attending research base meetings and through committee participation. Improving local physician engagement with research can overcome barriers to enrollment of rural patients with brain tumors in clinical trials.

PATIENT-SPECIFIC FACTORS

Even when an appropriate clinical trial is presented to a patient by an engaged physician, the patient may ultimately decline trial participation. A number of patient-specific factors associated with low accrual rates colocalize with rural patients, including poverty, education level,

employment status, and age.[31,32,41] Although it is beyond the scope of a cancer research program to fix these societal issues, efforts to provide community outreach to rural patients may help alleviate the impact of these issues. Primary care providers are integral to cancer screening and diagnosis, and they are often asked by patients for an opinion on trial involvement. By engaging with primary care teams, local knowledge about cancer clinical trials may be enhanced. Community outreach programs may also relieve the knowledge gap associated with rural communities.[42,43] Minimizing patient-specific factors can also be accomplished by linking patients to resources that facilitate trial enrollment, such as providing gas cards to help defray travel costs or linking patients to national support programs, such as those offered through the American Cancer Society and the National Brain Tumor Association.

Using Telehealth to Optimize Neuro-oncologic Care in Diverse Communities

It is widely recognized that subspecialized multidisciplinary care improves neuro-oncology outcomes. Optimizing patient outcomes relies on the expertise of the treating physicians, neuroradiology and neuropathology, and supportive services like palliative care, social work, and rehabilitation specialists familiar with common neurologic syndromes that occur after brain tumor diagnosis and treatment. Despite an increasing number of providers, patient access to specialized multidisciplinary care remains limited.

Multidisciplinary brain tumor programs often cluster in areas of high population density. They are frequently at academic medical centers or are found at high-volume sites within large regional provider networks. Patients with brain tumors living in rural areas may find themselves faced with traveling several hundred miles to find providers who specialize in their diagnoses. In less population-dense areas of the country, such as the northern plains or northern mountain regions, single brain tumor programs may serve as the sole source of expertise for a region encompassing several states, resulting in tremendous geographic coverage for a limited number of providers.

In addition to geography, economic disparities limit access to multidisciplinary brain tumor care. Socioeconomic challenges can result in limited transportation, social support, child care resources, or other needed resources, making it difficult for low- or middle-income families to seek care outside of their community.[44] Added to the stress of a brain tumor diagnosis, patients, families, and caregivers are left to weigh the benefits of best possible treatment against the financial, logistical, and social burdens associated with traveling for their care.

Telehealth can help bridge the care gap and decrease the burden of treatment. Telehealth utilization has been steadily increasing. Vascular neurologists have been using telehealth to improve stroke outcomes in remote settings.[45] Telehealth is increasingly used in oncology practice to simplify longitudinal care.[46] During the COVID-19 pandemic, as the world turned to virtual workplaces to mitigate health risks, the practice of telemedicine and the use of other telehealth resources were catapulted to the forefront of medical relevancy.

The nature of neuro-oncologic disease and treatment precludes a virtual-only format. Surgery and radiation treatment will always require predominantly in-person care. Patients are often faced with deciding between traveling to a high-volume center for treatment or receiving care closer to home with a provider who may have less experience with their diagnosis. Telehealth can allow for a virtual consultation with a neurosurgical oncologist, potentially in conjunction with a local surgical team. If surgery is deemed straightforward, it could be performed locally, with more complicated cases or surgical clinical trial candidates getting care at the high-volume center. In a similar fashion, a telehealth radiation oncology consultation could be obtained in conjunction with local providers, with more complicated cases managed at the high-volume centers. Additionally, emerging technology might allow for radiation planning to be performed off site and imported to the local equipment for local providers to carry out.

Telemedicine lends itself better to the neuro-oncologic aspects of care. Much of the neurologic examination can be performed through video evaluation without special equipment, though nuanced sensory and visual assessment is challenging. Telemedicine encounters in the setting of considerable cognitive impairment or physical limitations would rely on caregiver support both to assist with the technical aspects and to augment the limitations of the examination. Telemedicine is ideal for symptom management, chemotherapy follow-up, and adverse event triage. Imaging can be obtained locally and transferred digitally or sent on CD and reviewed through screenshare functions. A clear drawback arises with the emotionally challenging aspects of telemedicine encounters, as they do not offer the benefit of physical contact, or comforting gestures, that person-to-person interactions provide, so they risk suffering from an awkward, impersonal quality at inopportune times.

Alternatively, telehealth approaches can be used to connect local providers with a multidisciplinary team from a high-volume center to review case information, imaging, and pathology in a virtual tumor board format. Treatment plans can be formulated and carried out locally. Patients who qualify for clinical trial enrollment could be identified and screened. As technology advances and standardized workflows are established, services such as telepathology[47] could be arranged in advance, and surveillance imaging

could be specified to using standardized protocols for brain tumor surveillance.[48]

Augmenting treatment with brain tumor–specific palliative care,[49] psychosocial support, and cognitive and physical rehabilitation can also be accomplished virtually. As the pandemic developed, many brain tumor–specific support groups responded with increased virtual access.[50]

Telehealth can be used to expand access to clinical research in rural and underserved communities. Screening can be done virtually, eliminating the need for ineligible patients to travel. Coordinator encounters to educate patients on trials, gauge interest, and possibly obtain consent can be implemented.[51] Screening can routinely occur as part of telehealth case review, and local providers can approach eligible patients to gauge interest. Some sponsors have responded to the pandemic by allowing standard-of-care aspects of trials to be performed locally, with scheduled follow-up visits conducted virtually when practical. Exploring other allowances, such as local administration of U.S. Food and Drug Administration–approved medications or loosening requirements on the location of radiation treatment with appropriate oversight, may also help extend clinical trial access while engaging community providers.

Using telehealth to optimize neuro-oncologic care in diverse communities holds great promise; however, there are numerous challenges to address. The COVID-19 pandemic exposed the limitations of virtual learning in communities with limited access to broadband internet as a result of both geographic and socioeconomic factors—a limitation that would likewise impact access to telemedicine. It is unclear how the Centers for Medicare and Medicaid Services will address the relaxed restrictions on telemedicine that were implemented emergently to address the pandemic. Although several small studies have explored telemedicine in the neuro-oncology setting,[52,53] larger studies are needed to validate this practice and ensure there is no detrimental impact on overall care. Additionally, large centers and community practice providers will have to find common ground and work together for collaborative telehealth models to succeed.

CONCLUSION

Despite the challenges presented regarding neuro-oncologic care in underserved populations, the future is promising for increased access through telemedicine and the learning leveraged as a result of the COVID-19 pandemic. Marginalized populations remain under-represented in trials, and continued efforts are needed to increase access and inclusion within neuro-oncology research. As the understanding of the spectrum of neuro-oncologic disease in these populations evolves, so must provider education in areas of institutionalized racism, bias and stereotyping, and communication. Limitations in health literacy, both related and unrelated to general literacy, place an additional burden on the clinical encounter and require providers to lessen the power differential whenever it exists. Through continued attention to education, access, and research, the challenges currently faced by underserved populations will be lessened.

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REFERENCES

1. Marulanda-Londoño ET, Bell MW, Hope OA, et al. Reducing neurodisparity: recommendations of the 2017 AAN Diversity Leadership Program. Neurology. 2019;92:274-280.
2. National Institute on Minority Health and Health Disparities. Overview. www.nimhd.nih.gov/about/overview/. Accessed June 14, 2020.
3. U.S. Department of Health and Human Services Office of Minority Health. The National CLAS Standards. https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53. Accessed June 14, 2020.
4. Nelson A. Unequal treatment: confronting racial and ethnic disparities in health care. J Natl Med Assoc. 2002;94:666-668.
5. White AA III, Stubblefield-Tave B. Some advice for physicians and other clinicians treating minorities, women, and other patients at risk of receiving health care disparities. J Racial Ethn Health Disparities. 2017;4:472-479.
6. Jones CP. Levels of racism: a theoretic framework and a gardener's tale. Am J Public Health. 2000;90:1212-1215.

7. Tervalon M, Murray-García J. Cultural humility versus cultural competence: a critical distinction in defining physician training outcomes in multicultural education. J Health Care Poor Underserved. 1998;9:117-125.
8. Wasserman M, Renfrew MR, Green AR, et al. Identifying and preventing medical errors in patients with limited English proficiency: key findings and tools for the field. J Healthc Qual. 2014;36:5-16.
9. Agency for Healthcare Quality and Research. 2019 National Healthcare Quality and Disparities Report. www.ahrq.gov/research/findings/nhqrdr/nhqdr19/index.html. Accessed June 14, 2020.
10. Berkman ND, Sheridan SL, Donahue KE, et al. Low health literacy and health outcomes: an updated systematic review. Ann Intern Med. 2011;155:97-107.
11. American Board of Internal Medicine Foundation; ACP-ASIM Foundation. American College of Physicians-American Society of Internal Medicine; European Federation of Internal Medicine. Medical professionalism in the new millennium: a physician charter. Ann Intern Med. 2002;136:243-246.
12. U.S. Food and Drug Administration. 2015-2016 Drug Trials Snapshots Summary Report. www.fda.gov/media/103160/download. Accessed June 14, 2020.
13. U.S. Food and Drug Administration. 2015-2016 Global Participation in Clinical Trials Report. www.fda.gov/media/106725/download. Accessed June 14, 2020.
14. Duma N, Vera Aguilera J, Paludo J, et al. Representation of minorities and women in oncology clinical trials: review of the past 14 years. J Oncol Pract. 2018;14:e1-e10.
15. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. JAMA. 2004;291:2720-2726.
16. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 1999;341:2061-2067.
17. Taha B, Winston G, Tosi U, et al. Missing diversity in brain tumor trials. Neurooncology Adv. 2020;2:vdaa059.
18. Institute of Medicine Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care. In Smedley BD, Stith AY, Nelson AR, (eds). Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC: National Academies Press; 2003.
19. Mastroianni AC, Faden R, Federman D (eds). Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies—Volume I. www.ncbi.nlm.nih.gov/books/NBK236531. Accessed June 14, 2020.
20. Riley Wayne J. Health disparities: gaps in access, quality and affordability of medical care. Trans Am Clin Climatol Assoc. 2012;123:167-172.
21. Chandra A, Young JS, Dalle Ore C, et al. Insurance type impacts the economic burden and survival of patients with newly diagnosed glioblastoma. J Neurosurg. 2019;133:1-11.
22. Chandra A, Rick JW, Dalle Ore C, et al. Disparities in health care determine prognosis in newly diagnosed glioblastoma. Neurosurg Focus. 2018;44:E16.
23. Lamba N, Chukwueke UN, Smith TR, et al. Socioeconomic disparities associated with MGMT promoter methylation testing for patients with glioblastoma. JAMA Oncol. 2020;6:1972-1974.
24. Spratt DE, Chan T, Waldron L, et al. Racial/ethnic disparities in genomic sequencing. JAMA Oncol. 2016;2:1070-1074.
25. Rotimi CN. Health disparities in the genomic era: the case for diversifying ethnic representation. Genome Med. 2012;4:65.
26. Morshed RA, Reihl SJ, Molinaro AM, et al. The influence of race and socioeconomic status on therapeutic clinical trial screening and enrollment. J Neurooncol. 2020;148:131-139.
27. Lee EQ, Chukwueke UN, Hervey-Jumper SL, et al. Barriers to accrual and enrollment in brain tumor trials. Neuro-oncol. 2019;21(Supplement_6):1100-1117.
28. Loree JM, Anand S, Dasari A, et al. Disparity of race reporting and representation in clinical trials leading to cancer drug approvals from 2008 to 2018. JAMA Oncol. 2019;5:e191870.
29. Chang SM, Barker FG II, Schmidt MH, et al. Clinical trial participation among patients enrolled in the Glioma Outcomes Project. Cancer. 2002;94:2681-2687.
30. Vanderbeek AM, Rahman R, Fell G, et al. The clinical trials landscape for glioblastoma: is it adequate to develop new treatments? Neuro-oncol. 2018;20:1034-1043.
31. Sateren WB, Trimble EL, Abrams J, et al. How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. J Clin Oncol. 2002;20:2109-2117.
32. Guadagnolo BA, Petereit DG, Helbig P, et al. Involving American Indians and medically underserved rural populations in cancer clinical trials. Clin Trials. 2009;6:610-617.
33. Freyer DR, Seibel NL. The clinical trials gap for adolescents and young adults with cancer: recent progress and conceptual framework for continued research. Curr Pediatr Rep. 2015;3:137-145.
34. Jirka GW, Bisselou KSM, Smith LM, et al. Evaluating the decisions of glioma patients regarding clinical trial participation: a retrospective single provider review. Med Oncol. 2019;36:34.
35. Greenwald P, Cullen JW, McKenna JW. Cancer prevention and control: from research through applications. J Natl Cancer Inst. 1987;79:389-400.
36. University of Minnesota. Masonic Cancer Center: Minnesota Cancer Clinical Trials Network. https://cancer.umn.edu/mncctn. Accessed June 14, 2020.
37. Dorsey ER, Kluger B, Lipset CH. The new normal in clinical trials: decentralized studies. Ann Neurol. 2020;88:863-866.
38. Bates AJ, Couillard SA, Arons DF, et al. HOUT-15. Brain tumor patient and caregiver survey on clinical trials: identifying attitudes and barriers to patient participation. Neuro-oncol. 2017;19(Suppl 6):vi109.
39. Jacobs SR, Weiner BJ, Reeve BB, et al. Organizational and physician factors associated with patient enrollment in cancer clinical trials. Clin Trials. 2014;11:565-575.

40. National Brain Tumor Society. Personalized Support and Navigation Program. https://braintumor.org/brain-tumor-information/personalized-support-and-navigation-program/. Accessed June 14, 2020.
41. Paskett ED, Cooper MR, Stark N, et al. Clinical trial enrollment of rural patients with cancer. Cancer Pract. 2002;10:28-35.
42. Schapira L, Schutt R. Training community health workers about cancer clinical trials. J Immigr Minor Health. 2011;13:891-898.
43. Trant AA, Walz L, Allen W, et al. Increasing accrual of minority patients in breast cancer clinical trials. Breast Cancer Res Treat. 2020;184:499-505.
44. Dickman SL, Himmelstein DU, Woolhandler S. Inequality and the health-care system in the USA. Lancet. 2017;389:1431-1441.
45. Chirra M, Marsili L, Wattley L, et al. Telemedicine in neurological disorders: opportunities and challenges. Telemedicine J E Health. 2019;25:541-550.
46. Patt D, Wilfong L, Kanipe K, et al. Telemedicine for cancer care: implementation across a multicenter community oncology practice. Am J Manag Care. 2020; 26:SP330-SP332.
47. Mpunga T, Hedt-Gauthier BL, Tapela N, et al. Implementation and validation of telepathology triage at cancer referral center in rural Rwanda. J Glob Oncol. 2016; 2:76-82.
48. Ellingson BM, Bendszus M, Boxerman J, et al; Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee. Consensus recommendations for a standardized brain tumor imaging protocol in clinical trials. Neuro-oncol. 2015;17:1188-1198.
49. Worster B, Swartz K. Telemedicine and palliative care: an increasing role in supportive oncology. Curr Oncol Rep. 2017;19:37.
50. Patt DA, Wilfong L, Toth S, et al. Telemedicine in community cancer care: how technology helps patients with cancer navigate a pandemic. JCO Oncol Pract. 2021;17:e11-e15.
51. Bunnell BE, Sprague G, Qanungo S, et al. An exploration of useful telemedicine-based resources for clinical research. Telemedicine J E Health. 2020;26:51-65.
52. Qaddoumi I, Bouffet E. Supplementation of a successful pediatric neuro-oncology telemedicine-based twinning program by e-mails. Telemedicine J E Health. 2009;15:975-982.
53. Qaddoumi I, Mansour A, Musharbash A, et al. Impact of telemedicine on pediatric neuro-oncology in a developing country: the Jordanian-Canadian experience. Pediatr Blood Cancer. 2007;48:39-43.

Diagnosis and Management of Neuroendocrine Disorders of Survivors of Brain Tumors

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overview

Advances in the treatment of brain tumors have led to an increase in the number of survivors of this disease. Consequently, the long-term complications associated with past and current treatments are becoming more apparent. Of relevance to patients who receive treatment of brain tumors are the potential neuroendocrine complications that develop either acutely or several years following treatment. Presentation may differ between adults and children (e.g., short stature or adult growth hormone deficiency) but in both settings can complicate treatment and impact quality of life. The risk for the development of these complications depends on the location of the tumor (proximity to the pituitary/hypothalamus) and/or the treatment delivered (chemotherapy/surgery/radiation). Given the potential overlap in symptoms attributable to the underlying brain tumor and neuroendocrine dysfunction, a high level of suspicion, appropriate investigation, and administration of treatment may reduce morbidity and mortality for patients with brain tumors experiencing neuroendocrine dysfunction.

BACKGROUND AND OVERVIEW

With advances in diagnosis and oncologic treatment of various brain tumors, survivorship issues and quality of life became important in the treatment of survivors of childhood tumors as well as adult tumors. Fortunately, the number of survivors who fall into this category continues to increase. Therefore, it is important that a multidisciplinary team be involved in the care of these individuals to address various medical and psychological issues that arise. In fact, the importance of neuroendocrine sequelae among survivors of childhood cancer, including growth disorders and other hypothalamic-pituitary complications, has been recognized by the Endocrine Society, resulting in the publication of Clinical Practice Guidelines for this area in 2018.[1] Neuroendocrine disorders in patients with brain tumors can occur as a consequence of the disease at presentation, acutely following surgical intervention (for tumors located in the sellar or suprasellar areas, or in hypothalamic proximity) or subacutely with hypothalamic-pituitary dysfunction observed months to years following radiation therapy. The age of the patient might influence phenotypic presentation of endocrine dysfunction. Symptoms due to endocrine dysfunction may be obvious following treatment of brain tumors when acute and severe; however, many can be gradual and subtle, leading to delays in diagnosis and treatment that could have detrimental effects.[2]

Studies assessing presentation, prevalence, and risk factors for the development of endocrine dysfunction have been heterogeneous, with some studies including populations with typical endocrine tumors such as pituitary tumors or craniopharyngiomas, whereas other studies, primarily in neuro-oncology, include only patients with pure brain malignancies. This is important, as the location of the tumor plays a critical role in the degree of neuroendocrine involvement. Tumors located in the sellar or suprasellar region, such as craniopharyngioma, meningioma, germinoma, glioma, and pituitary tumors, can be associated with high rates of pituitary hormone deficiencies. If the hypothalamus is involved, hypothalamic syndrome, characterized by increase in appetite, thirst disorders, sleep disturbance, and impaired temperature regulation, can be seen. It can be observed either at diagnosis or shortly following surgical intervention.[3] Typically, patients with craniopharyngioma have a 55% to 88% prevalence of adrenocorticotropic hormone deficiency before and after surgical treatment, 88% to 100% growth hormone deficiency (GHD), 80% to 95% gonadotropin hormone deficiency, and 39% to 95% of thyroid-stimulating hormone deficiency as well as very high prevalence of diabetes insipidus.[4] In fact, surgical intervention rarely restores pituitary anterior function. Over the last several years, less aggressive resections of primary tumors are being performed with attempts to avoid hypothalamic syndrome and new endocrine deficits.[5] With respect to other tumors, an endocrine abnormality was present at diagnosis in 50% of patients with germ cell tumors and in 27% of those with low-grade glioma.[6]

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PRACTICAL APPLICATIONS

- Advances in treatment of and improved outcomes in patients with brain tumors have resulted in increasing numbers of survivors of brain tumors.
- Neuroendocrine complications due to treatments delivered or the tumor itself are prevalent in survivors of brain tumors.
- Early recognition and appropriate management of neuroendocrine sequelae using a multidisciplinary approach are key to reducing the potential morbidity and mortality associated with neuroendocrine complications.
- Development of less invasive or more tumor-directed therapies may reduce future development of neuroendocrine complications.

In a nationwide study in which craniopharyngiomas and pituitary gland tumors were excluded, 718 survivors of childhood brain tumors from the Netherlands diagnosed between 2002 and 2012 who survived more than 2 years after diagnosis were reviewed. The authors found that after median follow-up of 6.6 years, 178 (24.8%) patients were diagnosed with an endocrine disorder. Nineteen percent (138 patients) presented with at least one neuroendocrine disorder at a median follow-up time of 2.5 years after diagnosis. The most common endocrine disorders were GHD (12.5%), precocious puberty (12.2%), and secondary hypothyroidism (9.2%). About half of the patients had dysfunction in one hypothalamic-pituitary axis, whereas the remaining patients had multiple hormone dysfunctions. Multivariable logistic regression analysis identified the risk of pituitary dysfunction was associated with radiotherapy (odds ratio, 15.74), younger age at diagnosis (odds ratio, 0.9), advanced follow-up time (odds ratio, 1.1), hydrocephalus at diagnosis (odds ratio, 1.77), and suprasellar (odds ratio, 34.18) and infrasellar (odds ratio, 2.65) tumor sites. Of note, diabetes insipidus was observed in 19 (2.6%) patients, primarily in low-grade gliomas or germ cell tumors, with a majority present at tumor diagnosis or immediately after neurosurgery and not related to radiation. In the 145 patients from this cohort who did not undergo radiation therapy and/or suprasellar tumor location who had endocrine evaluation, only six were diagnosed with pituitary damage.[6] The reported prevalence of endocrine dysfunction in this study might be underestimated, as only symptomatic patients were assessed for an endocrine dysfunction, and a considerable proportion were asymptomatic (36%). A somewhat higher prevalence of neuroendocrine dysfunction after radiation was observed in patients who were diagnosed with medulloblastoma at 42%, low-grade glioma at 24.6%, and germ cell tumors at 10%. In a study of 88 children with embryonal brain tumors by Laughton et al,[7] 94% were diagnosed with GHD after 4-year cumulative follow-up. In this cohort, however, high-dose radiation therapy was given to the hypothalamic region (44 Gy) and to the pituitary gland (42.1 Gy). These studies demonstrate that the disease itself is not the only causative factor and is probably confounded by the applied treatment, tumor location, and length of follow-up.

The hypothalamus and pituitary are radiosensitive, and therefore, anterior pituitary dysfunction can occur following various forms of radiotherapy. This can occur irrespective of the mode of delivery—proton beam, intensity-modulated radiation therapy, or Gamma Knife—and is dose dependent. Certainly, proximity of the tumor to the endocrine structures as well as length of follow-up play a considerable role. Chemaitilly et al[2] evaluated 748 survivors of childhood cancers who received cranial radiotherapy (primary diagnosis in 73% was leukemia and central nervous system tumor in 12%) for anterior hypopituitarism. The estimated prevalence of GHD was 46%, luteinizing hormone/follicle-stimulating hormone was 10%, thyroid-stimulating hormone deficiency was 7.5%, and adrenocorticotropic hormone deficiency was 4% after an average of 27 years follow-up. A subsequent publication from the same center, but with an expanded cohort (3,141 patients), including survivors of childhood cancer who did not receive cranial radiation (2,055 patients), revealed that GHD was present in 40% who received hypothalamic-pituitary radiation therapy compared with 6.2% in those who did not. Similarly, a systematic review of 18 studies, including 813 adults who received cranial radiation (75% of patients with nasopharyngeal cancer and 25% with intracerebral tumors), revealed hypopituitarism in 66%, GHD in 45%, and adrenocorticotropic hormone deficiency in 22%, which was the least prevalent. GHD occurred after a mean of 2.6 years, whereas central hypothyroidism occurred after a mean of 11 years.[8]

There is also a strong dose-dependent relationship between radiation therapy and development of hypothalamic-pituitary dysfunction as well as fraction size and radiotherapy schedule.[9-11]

Although primarily GHD occurs after relatively low radiation therapy doses (18–20 Gy), doses of more than 30 Gy almost always cause hypothalamic-pituitary dysfunction.[12] Also, time to development of various deficiencies can vary, as demonstrated by Clement et al,[6] who noted that GHD onset was observed after a median of 2.5 years (range, 0.05–8.4) and adrenocorticotropic hormone deficiency was observed after a median of 2.8 years following primary brain tumor diagnosis, whereas precocious puberty was observed at 3.1 years (range, 0.1–8.8) and luteinizing hormone/follicle-stimulating hormone deficiency at 4.5 years (0.2–9.5).

However, gonadotropin hormone deficiency might be underestimated, as deficiency in this axis might develop with longer follow-up. Changes in radiation therapy practice (e.g., scattered reduction to normal tissue) and the use of protons instead of photons may reduce the negative impact on neuroendocrine axis involvement.[13] In 77 children treated with chemotherapy and protons (40 patients; median follow-up, 5.8 years) or photon therapy (37 patients; median follow-up, 7 years) were screened for endocrine dysfunction. Proton radiation was associated with a reduced risk of hypothyroidism (23% vs. 69%), sex hormone deficiency (3% vs. 19%), and requirement for any endocrine replacement therapy (55% vs. 78%). There was no noteworthy difference in the incidence of GHD (53% vs. 57%), adrenal insufficiency (5% vs. 8%), or precocious puberty (18% vs. 16%). Contrary to this, smaller studies comparing proton and photon beam therapy did not show remarkable differences in endocrine outcomes but had relatively shorter follow-up.[14,15]

It is worth noting that comparison of study outcome is limited by their retrospective nature, heterogeneity of diagnosis, timing or lack of standardization of endocrine testing, and duration of follow-up as well as modality, distribution, and schedule of radiation treatment. There is no convincing evidence that chemotherapy alone for malignant brain tumors causes hypothalamic pituitary dysfunction; however, this cannot be easily studied, as many patients receive additional radiation therapy in the setting of brain tumors.[16] Van Iersel et al[17] showed association between alkylating agents and GHD and luteinizing hormone/follicle-stimulating hormone deficiency; however, the significance was lost after stratification by exposure to hypothalamic-pituitary radiotherapy.

More recently, advances in immunotherapy have revolutionized the treatment of cancer. Although not used as frequently in primary brain tumors, immunotherapy is used in a variety of other tumors with rapidly expanding indications for use.[18] Endocrinopathies including hypophysitis are recognized side effects of checkpoint inhibitors, particularly when used in combination. In a 2018 meta-analysis, the observed incidence of hypophysitis in the 34 studies assessed was highest with CTLA-4 inhibitors (3.4%) or with combination therapy (6.4%).[19] However retrospective studies have reported a higher incidence.[20] Typically, hypophysitis occurs within in 8 to 12 weeks of initiation but can occur outside of this time frame, even up to 19 months.[21] Hypophysitis may present with symptoms due to hypopituitarism and or symptoms of mass effect such as headache. Often treatment is stopped until the patient is stabilized, particularly for severe adverse events (grade 3–4), and the patient may require high-dose glucocorticoids for treatment.[22] However, there is evidence to suggest that patients who develop hypophysitis have a more favorable antitumor response with increased overall survival and that use of high-dose glucocorticoids compared with replacement doses of glucocorticoid to treat hypophysitis may have a negative impact on overall survival.[23] Recovery of anterior pituitary function has been reported but is not common even in the setting of high-dose glucorticoids, especially adrenocorticotropic hormone deficiency requiring long-term replacement.[24] Therefore, multidisciplinary collaboration remains crucial for the treatment of patients with cancer.

CLINICAL MANIFESTATIONS AND TESTING FOR NEUROENDOCRINE HORMONAL DEFICIENCIES

Growth Hormone Deficiency

Growth hormone deficiency manifests in childhood as impaired growth defined by a loss of height standard deviation over time. This can lead to short stature defined by standing adult height more than two standard deviations below the mean for age and sex. However, one cannot assume that a patient presenting with short stature has GHD as a sole reason for this, as other hormonal abnormalities, nutrition factors, and medications can equally contribute to this clinical picture.

Consequently, the growth of a patient has to be assessed in a clinical context, as patients with GHD and concomitant early or precocious puberty might still show good linear growth, which might eventually translate to short stature.[1] In fact, short stature has been reported in as many as 40% of survivors of childhood brain tumors.[17,25] In a study by Gurney et al,[25] 53% of patients diagnosed before age 5 achieved an adult height less than the 10th percentile, the prevalence of which declined with increasing age at diagnosis (46% in age group 5–9 and 26% in age group 10–20).

Growth hormone deficiency in adulthood might be difficult to recognize on clinical grounds but typically can be associated with reduced lean body mass, increased fat mass, possibly impaired bone mineral density, frailty, impaired quality of life, and psychosocial problems as well as adverse lipid profile.[2,17,26-28] Interestingly, during the transition period of adolescence (age 18–22), lack of growth hormone replacement therapy might lead to suboptimal ascertainment of maximum bone mass.

In children, height measurement and documentation in growth charts every 6–12 months have been recommended with consideration to parental heights. Biochemically, IGF-1 levels adjusted for sex, age, and Tanner stage in children is the initial screening test, and values less than two standard deviations are considered abnormal. However, IGF-1 sensitivity is limited[29] and reported to be as low as 74%. Moreover, in adults with documented GHD, up to 20% can have normal IGF-1, and therefore, sole reliance on this test

is not recommended. In adults, a cutoff of less than 84 μg/L for IGF-1 has been proposed in patients with multiple other pituitary insufficiencies as being suggestive of GHD, which is still a value within normal limits.[30]

Growth hormone is secreted in a pulsatile manner, so random growth hormone levels can be misleading and are not recommended. Therefore, provocative growth hormone testing has been developed, including tests for glucagon stimulation, insulin tolerance, and arginine/levodopa stimulation. Recently, macimorelin stimulation testing (a ghrelin hormone oral analog) has been approved by the U.S. Food and Drug Administration.[31] Some of these stimulation tests have very high sensitivity (insulin tolerance test and macimorelin) for diagnosis of GHD. However, one has to recognize the possible risks (insulin tolerance test is contraindicated in those with seizure history and cardiovascular disease and who are older than age 65) and limitations (false-normal results can be obtained when macimorelin testing is used if hypothalamic disease is present without pituitary involvement) of these tests.[32] In children, typical values of peak growth hormone range between 5 and 10 μg/L[1]; in adults, however, the cutoff was substantially lower, between 1 and 5 μg/L depending on the test used.[33] The extent of dynamic testing needs to be discussed with the patient, endocrinologist, and oncologist depending on the clinical scenario.

Central Precocious Puberty

Central precocious puberty has been paradoxically described[34,35] (defined as pubertal development before age 8 in girls and age 9 in boys) as a result of premature activation of neuroendocrine gonadal axis. It has been reported with increased frequency in children with history of hydrocephalus, tumors near the hypothalamic region, and exposure to radiation of more than 18 Gy. Female sex, increased body mass index, and neurofibromatosis type 1 have also been considered as host factors.[1] It was described in 0.9% of patients in a more recent cohort[17] but as high as 11.9% to 15.2% previously.[35,36] Clinical evaluation includes assessment of testicular volume in boys and breast development in girls, and when suspicion is present, laboratory tests include morning fasting serum testosterone (preferably via liquid chromatography–tandem mass spectroscopy method[37]) and luteinizing hormone levels, which are inappropriately elevated in boys. In girls, elevated gonadotropin and estradiol measurement as well as uterine length assessment via ultrasound might be helpful.[38] Determination of bone age x-ray is recommended in this clinical scenario. Recognition is important, as short stature and psychosocial dysfunction can occur if left untreated.[35]

Adrenocorticotropic Hormone Deficiency

Adrenocorticotropic hormone deficiency leads to insufficient production of cortisol and, although occurring less frequently than other insufficiencies (3.2% to 43%),[17,39,40] if not recognized might have catastrophic life-threatening consequences. If this occurs immediately following a neurosurgical procedure, the manifestations can be more obvious; however, subclinical presentations are possible given the nonspecific nature of adrenal insufficiency symptoms, especially partial deficiencies that could be missed without proper testing. Annual lifelong screening for deficiency is recommended in patients with cranial radiation with tumors in the hypothalamic region and those exposed to more than 30 Gy hypothalamic-pituitary radiation, as there can be a delay in presentation in necessitating prolonged assessment. Symptoms include fatigue, decreased appetite, weight loss, prostration with illness, hypotension, decreased stamina, anemia, and loss of hair in axillary or pubic area.

An initial screening test includes an 8 AM serum cortisol level, and a value of less than 3 μg/dL (in the absence of exogenous glucocorticoid use or oral estrogens) is highly suggestive of adrenal insufficiency. In hypothalamic-pituitary dysfunction, a low-normal or below-normal adrenocorticotropic hormone value is observed. Baseline serum cortisol level of more than 15 μg/dL makes adrenal insufficiency unlikely. In-between values might require dynamic endocrine testing. Frequently, the adrenocorticotropic hormone stimulation test is used, either standard (250 μg adrenocorticotropic hormone) or low dose (1 μg). A peak serum cortisol level higher than 18 μg/dL is considered normal. However, both stimulation tests might be falsely normal in 30% to 40% of patients with central adrenal insufficiency, especially when it is of recent onset, which highlights the importance of establishing pretest probability at clinical assessment.[41] Hence, an overnight oral metyrapone test or insulin tolerance test could be considered for assessment but is limited to specialized centers. An abnormally low dehydroepiandrosterone sulfate measurement adjusted for age in adults might be helpful in diagnosis.[42]

Central Hypothyroidism

Central hypothyroidism can be manifested by fatigue, depression, weight gain, cold intolerance, dry skin, heavy periods, and hair loss (lateral eyebrow) and present in 6% to 11.1% of patients.[2,17,43]

Biochemical screening is recommended lifelong and annually for survivors of childhood cancer who were treated for tumors in the region of hypothalamic-pituitary axis and those exposed to more than 30 Gy hypothalamic-pituitary radiation, although this can occur with less frequency in those treated with lower doses of radiation. Diagnosis can be made based on below-normal free thyroxine and inappropriately normal, below normal, or very mildly elevated thyroid-stimulating hormone. Additionally, declining free thyroxine levels over time of more than 20% and signs of hypothyroidism can be consistent with the diagnosis as well. As with adrenal insufficiency, symptoms can be subtle and,

without appropriate biochemical testing diagnosis, could be missed.[2,44]

Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism can be recognized depending on clinical signs such as delayed puberty (absence of signs of puberty after age 13 in girls and age 14 in boys). In adults, hot flashes, reduced bone mass and libido, infertility, and, more specifically, oligo/amenorrhea and vaginal dryness in females, and erectile dysfunction, gynecomastia, and decreased facial hair growth in men are symptoms and signs suggestive of hypogonadism.[45] This clinical entity has been observed after radiation to the hypothalamic-pituitary region, especially in dosages higher than 30 Gy.[2] With very high dosages of radiation more than 50 Gy, risk of hyperprolactinemia has been described that can further suppress production of luteinizing hormone and follicle-stimulating hormone.[10] For diagnosis, testosterone measured by liquid chromatography–mass spectrometry along with luteinizing hormone is used in men, whereas follicle-stimulating hormone and estradiol are measured in women. Prolactin measurement should be obtained in tumors located in the hypothalamic-pituitary axis or previously radiated or in those on psychiatric medications, which can interfere with prolactin secretion to assure that elevation of this hormone is not the key factor in the clinical scenario. For assessment of fertility, sperm analysis or ovarian follicular count by ultrasound can be used to guide further options for assisted reproductive therapy, which is beyond this topic review.

Antidiuretic Hormone Deficiency (Central Diabetes Insipidus)

Antidiuretic hormone deficiency (central diabetes insipidus) is present especially in patients with craniopharyngiomas (20% prior to surgery), unlike patients with nonfunctioning pituitary tumors in which this entity almost never occurs. Following surgery for craniopharyngiomas, permanent diabetes insipidus is observed in up to 80% of patients.[3,46] Diabetes insipidus can serve as a marker for hypothalamic damage, and obesity in these patients is frequently observed. Diagnosis is made by increased urine output (higher than 3 L/day) with inappropriately high serum sodium and plasma osmolality levels and low concomitant urinary osmolality following a certain period of fluid restriction. Copeptin measurements, a surrogate for antidiuretic hormone production, have been recently used in diagnosis of this entity. In patients with considerable hypothalamic involvement, the degree of thirst mechanism needs to be assessed, as patients with adipsia are particularly at risk for severe episodes of hypernatremia.

It is important to recognize that many studies published in this area use a baseline test without dynamic testing, as in GHD or adrenal insufficiency, so the prevalence might be underestimated, especially in the spectrum of milder disease.

Lastly, but very importantly, many patients with brain tumors are exposed to high dosages of glucocorticoid therapy, especially dexamethasone. The oncologist needs to be aware of long-term hypothalamic-pituitary-adrenal suppression and potentially resulting hypoadrenalism, which could last up to 12 months after exposure. Especially if the patient becomes ill and stress dosages are not applied, the patient could experience adrenal crisis.

ENDOCRINE THERAPY OVERVIEW (ADULTS ONLY)

Adrenocorticotropic Hormone Deficiency

Cortisol secretion follows a 24-hour circadian rhythm, resulting in diurnal variation with peak levels noted at approximately 8 AM.[47] Daily physiologic production of cortisol is estimated to be about 5 to 6 mg/m^2 body surface.[48] Although several glucocorticoid agents are available (e.g., hydrocortisone, prednisone, prednisolone, methylprednisolone, and dexamethasone) with differing duration of action, hydrocortisone remains the most common prescribed for adrenal insufficiency. On average, 15–25 mg/day of hydrocortisone is recommended in divided doses twice or three times daily. Similar to normal physiology, two-thirds of the daily dose is administered on waking and one-third is given in the early afternoon.[49] Unlike primary adrenal insufficiency, fludrocortisone replacement is not required given that renin and not adrenocorticotropic hormone regulates aldosterone secretion. Dehydroepiandrosterone, in contrast, is regulated in part by adrenocorticotropic hormone. The use of dehydroepiandrosterone supplementation in women, however, remains controversial (some studies suggest improved well-being and sexual interest).[50]

Biochemical monitoring for glucocorticoid replacement is not recommended, and serum cortisol measurements should not be used to assess the adequacy of treatment. Appropriate dose replacement is determined clinically by the absence of symptoms suggestive of adrenal insufficiency and lack of stigmata of glucocorticoid excess on clinical examination.

In the event of illness or severe stress, glucocorticoids should be doubled or tripled for 3 days to prevent adrenal crisis. However, in the setting of adrenal crisis, persistent vomiting, or surgery, intramuscular or intravenous glucocorticoids are required in addition to appropriate supportive care. Patients should be provided with an adrenal insufficiency action plan to be implemented on sick days. In addition, it is recommended that a medic alert bracelet, necklace, or card highlighting the diagnosis of adrenal insufficiency be used.[49] It is worth noting that several

medications may influence the metabolism of glucocorticoids (i.e., those that alter CYP450 activity). Particularly relevant to survivors of brain tumors are antiepileptic medications (e.g., phenytoin carbamazepine, oxcarbazepine, and topiramate), which may enhance CYP3A4 rapidly metabolizing dexamethasone with less of an effect on hydrocortisone and may necessitate a dose increase.

Central Hypothyroidism

Once the diagnosis of central hypothyroidism is confirmed, replacement with levothyroxine should be implemented only after the hypothalamic-pituitary-adrenal axis is assessed and treated. Failure to do so may precipitate adrenal crisis by enhancing cortisol metabolism with the replacement of thyroid hormone. Replacement doses (typically around 1.6 μg/kg) may vary according to severity of deficiency, pregnancy, use of estrogen supplementation, and age, with lower doses used in older patients.[51] Free thyroxine, not thyroid-stimulating hormone, should be used to monitor adequacy of replacement in central hypothyroidism aiming for the upper half of the normal reference range, as thyroid-stimulating hormone often becomes suppressed when replacement is initiated. A suppressed thyroid-stimulating hormone in this context (central hypothyroidism) should not be interpreted as overreplacement. Thyroid hormone doses may require adjustment following the initiation of growth hormone, as this can increase peripheral deiodination of thyroxine to triiodothyronine.[52] The Endocrine Society does not recommend the use of alternative thyroid hormone preparations or nutraceuticals in patients with central hypothyroidism given the paucity of data regarding their safety and efficacy.[37]

Central Hypogonadism

In premenopausal women who develop hypogonadism, estrogen deficiency is a pathologic compared with postmenopausal women. In the absence of contraindications, hormone replacement therapy is recommended, and evidence regarding its use is primarily extrapolated from the studies of premature ovarian insufficiency. A variety of different forms of estrogen replacement (transdermal, transvaginal, and oral) may be used depending on cost, convenience, and adverse effects. Although the combined birth control pill, either continuous or cyclical, is convenient, it delivers supraphysiologic synthetic estrogens. There is some evidence to suggest, at least among women with premature ovarian insufficiency or following menopause, that transdermal or transvaginal estradiol is the preferred method and form of estrogen replacement therapy. Typically, 0.1 mg/day of transdermal estradiol is given continuously and therefore avoids hypogonadal symptoms that may be seen during the placebo week of the combined pill.[53,54] Moreover, such direct systemic delivery avoids first-pass metabolism, which has been associated with increased risk of venous thromboembolism and a more adverse metabolic profile.[55,56] In women with an intact uterus, progesterone therapy is required to protect the uterus. To date, the longest study available in women with premature ovarian insufficiency and hormone replacement therapy is the National Institutes of Health study.[57] In this study, 10 mg/day of medroxyprogesterone was used for 12 days of the month in addition to transdermal estradiol, which was shown to restore bone mineral density at the hip. Other forms of progesterone, such as micronized progesterone, can be used. Treatment should be continued until the average age of menopause (age 51 in the United States).

In men, testosterone can also be administered in a variety of different routes (transdermal, intramuscular, subcutaneous, oral, and buccal) dependent on cost, convenience, and adverse effects. Doses and frequency of administration are also dependent on the form of testosterone replacement. Therapy is aimed at achieving testosterone levels in the midnormal range.[45] Patients should be monitored for potential adverse effects of testosterone replacement therapy, including erythrocytosis, obstructive lower urinary tract symptoms, and the potential for prostate cancer, all of which are more common with increasing age. If fertility is desired, hormone replacement therapy differs and includes the use of gonadotropins, and patients should be referred to reproductive specialists. Prior to the initiation of treatment, methods of possible fertility preservation should be discussed with a reproductive endocrinologist if desired.

Growth Hormone Replacement

In children, growth hormone replacement is primarily aimed at improving linear growth. In adults, however, GHD has been associated with increased mortality (cardiovascular as well as cerebrovascular), insulin resistance, and fat mass as well as decreased lean mass, bone mineral density, and quality of life. Treatment is therefore aimed at minimizing these effects, particularly quality-of-life measures. Studies have reported improvement in lean body mass, decrease in visceral fat, increase in quality of life, and conflicting effects on bone parameters depending on duration of treatment.[58]

In adults, recombinant growth hormone is typically administered subcutaneously daily, with higher doses used in younger patients, females, and those using estrogen supplementation. Starting doses for patients younger than age 60 is 0.2 to 0.4 mg/day and 0.1 to 0.2 mg/day for patients older than age 60. Doses of growth hormone are titrated in increments of 0.1 to 0.2 mg/day to maintain IGF-1 levels within the age- and sex-appropriate IGF-1 reference range. Compliance remains an issue, and therefore, several long-acting preparations have been developed with recent approval

for use of a once-weekly reversible albumin-bound growth hormone derivative.[59] Both adrenal and thyroid replacement should be monitored during growth hormone initiation and following any dose change, as growth hormone can lower free thyroxine levels and reduce conversion of cortisone to cortisol.

There is concern that the use of growth hormone may be associated with and potentiate malignant tumor growth or recurrence (not primary pituitary adenoma or craniopharyngioma). For this reason, the Endocrine Society and American Association of Clinical Endocrinology do not recommend the use of growth hormone in the setting for active malignancy.[32,60] However, a recent meta-analysis of survivors of childhood cancer did not appear to increase the risk of secondary tumor development.[61] In another meta-analysis of patients with hypopituitarism including 15 studies involving 46,148 patients, growth hormone replacement was not associated with an increased risk of secondary tumor development, tumor growth or recurrence, malignancy, or stroke.[62] Therefore, the initiation of adult growth hormone therapy in a patient needs to be individualized, following remission of the primary disease and after discussion between the endocrinologist and the patient's oncologist.

Diabetes Insipidus

Deficiency of antidiuretic hormone may be transient or chronic and partial or complete. If thirst is intact and the patient has access to water, sodium levels can be maintained; however, chronic polyuria and polydipsia due to diabetes insipidus can be disruptive to sleep and daytime activities, necessitating the use of desmopressin. Desmopressin, a synthetic analog of antidiuretic hormone, has a longer half-life and is used to treat central diabetes insipidus.[63] It can be given via intravenous, subcutaneous, oral, intranasal, or sublingual methods. Bioavailability depends on the mode of administration. Parenteral desmopressin is approximately 100 times that of oral, and, although not exact, 1 μg parenterally is equivalent to 100 μg orally and 10 μg nasally. Initially, replacement is given at night to minimize nocturia and disturbed sleep. A common complication of desmopressin use is hyponatremia, which appears to be somewhat lower with oral formulations.[64] To prevent hyponatremia, it is recommended that at least one dose of desmopressin a week be skipped or delayed, allowing for aquaresis. Close monitoring of sodium levels is crucial in a patient with diabetes insipidus and intercurrent illness or in those who require large fluid volumes during chemotherapy to avoid potentially harmful dysnatremias.

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REFERENCES

1. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-pituitary and growth disorders in survivors of childhood cancer: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103:2761-2784.
2. Chemaitilly W, Li Z, Huang S, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort study. J Clin Oncol. 2015;33:492-500.
3. Crowley RK, Hamnvik OP, O'Sullivan EP, et al. Morbidity and mortality in patients with craniopharyngioma after surgery. Clin Endocrinol (Oxf). 2010;73:516-521.
4. Karavitaki N, Cudlip S, Adams CB, et al. Craniopharyngiomas. Endocr Rev. 2006;27:371-397.
5. Cohen M, Bartels U, Branson H, et al. Trends in treatment and outcomes of pediatric craniopharyngioma, 1975-2011. Neuro-oncol. 2013;15:767-774.
6. Clement SC, Schouten-van Meeteren AY, Boot AM, et al. Prevalence and risk factors of early endocrine disorders in childhood brain tumor survivors: a nationwide, multicenter study. J Clin Oncol. 2016;34:4362-4370.
7. Laughton SJ, Merchant TE, Sklar CA, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. J Clin Oncol. 2008;26:1112-1118.
8. Appelman-Dijkstra NM, Kokshoorn NE, Dekkers OM, et al. Pituitary dysfunction in adult patients after cranial radiotherapy: systematic review and meta-analysis. J Clin Endocrinol Metab. 2011;96:2330-2340.
9. Schmiegelow M, Lassen S, Poulsen HS, et al. Cranial radiotherapy of childhood brain tumours: growth hormone deficiency and its relation to the biological effective dose of irradiation in a large population based study. Clin Endocrinol (Oxf). 2000;53:191-197.

10. Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med. 1993;328:87-94.
11. Crowne E, Gleeson H, Benghiat H, et al. Effect of cancer treatment on hypothalamic-pituitary function. Lancet Diabetes Endocrinol. 2015;3:568-576.
12. Gleeson HK, Shalet SM. The impact of cancer therapy on the endocrine system in survivors of childhood brain tumours. Endocr Relat Cancer. 2004;11:589-602.
13. Eaton BR, Esiashvili N, Kim S, et al. Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. Neuro Oncol. 2016; 18:881-887.
14. Viswanathan V, Pradhan KR, Eugster EA. Pituitary hormone dysfunction after proton beam radiation therapy in children with brain tumors. Endocr Pract. 2011; 17:891-896.
15. Bishop AJ, Greenfield B, Mahajan A, et al. Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. Int J Radiat Oncol Biol Phys. 2014;90:354-361.
16. Bakker B, Oostdijk W, Bresters D, et al. Disturbances of growth and endocrine function after busulphan-based conditioning for haematopoietic stem cell transplantation during infancy and childhood. Bone Marrow Transplant. 2004;33:1049-1056.
17. van Iersel L, Li Z, Srivastava DK, et al. Hypothalamic-pituitary disorders in childhood cncer survivors: prevalence, risk factors and long-term health outcomes. J Clin Endocrinol Metab. 2019;104:6101-6115.
18. Vaddepally RK, Kharel P, Pandey R, et al. Review of indications of FDA-approved immune checkpoint inhibitors per NCCN guidelines with the level of evidence. Cancers (Basel). 2020;12.
19. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol. 2018;4:173-182.
20. Faje A. Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights. Pituitary. 2016;19:82-92.
21. Ryder M, Callahan M, Postow MA, et al. Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: a comprehensive retrospective review from a single institution. Endocr Relat Cancer. 2014;21:371-81.
22. Brahmer JR, Lacchetti C, Schneider BJ, et al; National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2018;36:1714-1768.
23. Faje AT, Lawrence D, Flaherty K, et al. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. Cancer. 2018;124:3706-3714.
24. Min L, Hodi FS, Giobbie-Hurder A, et al. Systemic high-dose corticosteroid treatment does not improve the outcome of ipilimumab-related hypophysitis: a retrospective cohort study. Clin Cancer Res. 2015;21:749-55.
25. Gurney JG, Ness KK, Stovall M, et al. Final height and body mass index among adult survivors of childhood brain cancer: childhood cancer survivor study. J Clin Endocrinol Metab. 2003;88:4731-4739.
26. Hartman ML. The Growth Hormone Research Society consensus guidelines for the diagnosis and treatment of adult GH deficiency. Growth Horm IGF Res. 1998; 8(Suppl A):25-29.
27. Mukherjee A, Tolhurst-Cleaver S, Ryder WD, et al. The characteristics of quality of life impairment in adult growth hormone (GH)-deficient survivors of cancer and their response to GH replacement therapy. J Clin Endocrinol Metab. 2005;90:1542-1549.
28. van den Heijkant S, Hoorweg-Nijman G, Huisman J, et al. Effects of growth hormone therapy on bone mass, metabolic balance, and well-being in young adult survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2011;33:e231-e238.
29. Weinzimer SA, Homan SA, Ferry RJ, et al. Serum IGF-I and IGFBP-3 concentrations do not accurately predict growth hormone deficiency in children with brain tumours. Clin Endocrinol (Oxf). 1999;51:339-345.
30. Hartman ML, Crowe BJ, Biller BMK, et al; U.S. HypoCCS Study Group. Which patients do not require a GH stimulation test for the diagnosis of adult GH deficiency? J Clin Endocrinol Metab. 2002;87:477-485.
31. Garcia JM, Biller BMK, Korbonits M, et al. Macimorelin as a diagnostic test for adult GH deficiency. J Clin Endocrinol Metab. 2018;103:3083-3093.
32. Yuen KCJ, Biller BMK, Radovick S, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care. Endocr Pract. 2019;25:1191-1232.
33. Melmed S. Pathogenesis and diagnosis of growth hormone deficiency in adults. N Engl J Med. 2019;380:2551-2562.
34. Lannering B, Jansson C, Rosberg S, et al. Increased LH and FSH secretion after cranial irradiation in boys. Med Pediatr Oncol. 1997;29:280-287.
35. Chemaitilly W, Merchant TE, Li Z, et al. Central precocious puberty following the diagnosis and treatment of paediatric cancer and central nervous system tumours: presentation and long-term outcomes. Clin Endocrinol (Oxf). 2016;84:361-371.
36. Armstrong GT, Whitton JA, Gajjar A, et al. Abnormal timing of menarche in survivors of central nervous system tumors: a report from the Childhood Cancer Survivor Study. Cancer. 2009;115:2562-2570.
37. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:3888-3921.
38. de Vries L, Phillip M. Role of pelvic ultrasound in girls with precocious puberty. Horm Res Paediatr. 2011;75:148-152.
39. Brignardello E, Felicetti F, Castiglione A, et al. Endocrine health conditions in adult survivors of childhood cancer: the need for specialized adult-focused follow-up clinics. Eur J Endocrinol. 2013;168:465-472.
40. Patterson BC, Truxillo L, Wasilewski-Masker K, et al. Adrenal function testing in pediatric cancer survivors. Pediatr Blood Cancer. 2009;53:1302-1307.

41. Ospina NS, Al Nofal A, Bancos I, et al. ACTH stimulation tests for the diagnosis of adrenal insufficiency: systematic review and meta-analysis. J Clin Endocrinol Metab. 2016;101:427-434.
42. Sayyed Kassem L, El Sibai K, Chaiban J, et al. Measurements of serum DHEA and DHEA sulphate levels improve the accuracy of the low-dose cosyntropin test in the diagnosis of central adrenal insufficiency. J Clin Endocrinol Metab. 2012;97:3655-3662.
43. Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, et al. A population-based study of thyroid function after radiotherapy and chemotherapy for a childhood brain tumor. J Clin Endocrinol Metab. 2003;88:136-140.
44. Rose SR, Lustig RH, Pitukcheewanont P, et al. Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. J Clin Endocrinol Metab. 1999; 84:4472-4479.
45. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103:1715-1744.
46. Thompson CJ, Costello RW, Crowley RK. Management of hypothalamic disease in patients with craniopharyngioma. Clin Endocrinol (Oxf). 2019;90:506-516.
47. Debono M, Ghobadi C, Rostami-Hodjegan A, et al. Modified-release hydrocortisone to provide circadian cortisol profiles. J Clin Endocrinol Metab. 2009; 94:1548-1554.
48. Kerrigan JR, Veldhuis JD, Leyo SA, et al. Estimation of daily cortisol production and clearance rates in normal pubertal males by deconvolution analysis. J Clin Endocrinol Metab. 1993;76:1505-1510.
49. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:364-389.
50. Arlt W, Callies F, van Vlijmen JC, et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med. 1999;341:1013-1020.
51. Persani L, Cangiano B, Bonomi M. The diagnosis and management of central hypothyroidism in 2018. Endocr Connect. 2019;8:R44-R54.
52. Jørgensen JO, Møller J, Laursen T, et al. Growth hormone administration stimulates energy expenditure and extrathyroidal conversion of thyroxine to tri-iodothyronine in a dose-dependent manner and suppresses circadian thyrotrophin levels: studies in GH-deficient adults. Clin Endocrinol (Oxf). 1994; 41:609-614.
53. Chetkowski RJ, Meldrum DR, Steingold KA, et al. Biologic effects of transdermal estradiol. N Engl J Med. 1986;314:1615-1620.
54. Webber L, Anderson RA, Davies M, et al. HRT for women with premature ovarian insufficiency: a comprehensive review. Hum Reprod Open. 2017;2017:hox007.
55. Scarabin PY, Oger E, Plu-Bureau G; EStrogen and THromboEmbolism Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. Lancet. 2003;362:428-432.
56. Hemelaar M, van der Mooren MJ, Rad M, et al. Effects of non-oral postmenopausal hormone therapy on markers of cardiovascular risk: a systematic review. Fertil Steril. 2008;90:642-672.
57. Popat VB, Calis KA, Kalantaridou SN, et al. Bone mineral density in young women with primary ovarian insufficiency: results of a three-year randomized controlled trial of physiological transdermal estradiol and testosterone replacement. J Clin Endocrinol Metab. 2014;99:3418-3426.
58. Jørgensen JOL, Juul A. Therapy of endocrine disease: Growth hormone replacement therapy in adults: 30 years of personal clinical experience. Eur J Endocrinol. 2018;179:R47-R56.
59. Johannsson G, Gordon MB, Højby Rasmussen M, et al. Once-weekly somapacitan is effective and well tolerated in adults with GH deficiency: a randomized phase 3 trial. J Clin Endocrinol Metab. 2020;105:e1358-e1376.
60. Molitch ME, Clemmons DR, Malozowski S, et al; Endocrine Society's Clinical Guidelines Subcommittee. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2006;91:1621-1634.
61. Tamhane S, Sfeir JG, Kittah NEN, et al. GH therapy in childhood cancer survivors: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2018; 103:2794-2801.
62. Jasim S, Alahdab F, Ahmed AT, et al. The effect of growth hormone replacement in patients with hypopituitarism on pituitary tumor recurrence, secondary cancer, and stroke. Endocrine. 2017;56:267-278.
63. Sawyer WH, Acosta M, Manning M. Structural changes in the arginine vasopressin molecule that prolong its antidiuretic action. Endocrinology. 1974; 95:140-149.
64. Vande Walle J, Stockner M, Raes A, et al. Desmopressin 30 years in clinical use: a safety review. Curr Drug Saf. 2007;2:232-238.

Developmental Therapeutics—Immunotherapy

Adoptive Cellular Therapy for Solid Tumors

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Overview

Cancer immunotherapy tools include antibodies, vaccines, cytokines, oncolytic viruses, bispecific molecules, and cellular therapies. This review will focus on adoptive cellular therapy, which involves the isolation of a patient's own immune cells followed by their ex vivo expansion and reinfusion. The majority of adoptive cellular therapy strategies utilize T cells isolated from tumor or peripheral blood, but may utilize other immune cell subsets. T-cell therapies in the form of tumor-infiltrating lymphocytes, T-cell receptor T cells, and CAR T cells may act as "living drugs" as these infused cells expand, engraft, and persist in vivo, allowing adaptability over time and enabling durable remissions in subsets of patients. Adoptive cellular therapy has been less successful in the management of solid tumors because of poor homing, proliferation, and survival of transferred cells. Strategies are discussed, including expression of transgenes to address these hurdles. Additionally, advances in gene editing using CRISPR/Cas9 and similar technologies are described, which allow for clinically translatable gene-editing strategies to enhance the antitumor activity and to surmount the hostilities advanced by the host and the tumor. Finally, the common toxicities and approaches to mitigate these are reviewed.

INTRODUCTION

The past decade has brought unprecedented advances in the field of cancer immunotherapy with the successes of immune checkpoint inhibitor and CAR T-cell therapy, leading to U.S. Food and Drug Administration approvals for the treatment of multiple cancer types. Immuno-oncologic drugs offer a new class of cancer therapy that may prove curative for patients with metastatic disease and may be associated with decreased toxicity compared with conventional treatments, including surgery, radiation, chemotherapy, and targeted small molecules. Cancer immunotherapy is a broad term that encompasses antibodies, vaccines, cytokines, oncolytic viruses, bispecific molecules, and cellular therapies. This article focuses on adoptive cellular therapy, a personalized treatment strategy that involves the isolation of a patient's own immune cells followed by their ex vivo expansion and reinfusion. The majority of adoptive cellular therapy strategies use T cells isolated from tumor or peripheral blood, but other strategies use other immune cell subsets, including natural killer cells. T-cell therapies in the form of tumor-infiltrating lymphocytes (TILs), T-cell receptor T (TCR-T), and CAR T may act as "living drugs," given the potential of these infused cells to expand, engraft, and persist in vivo, allowing adaptability over time and enabling durable remissions in subsets of patients.

Rapid advances in the areas of antigen identification, T-cell biology, gene therapy, and gene editing have nurtured strategies to redirect antigen specificity and enhance T-cell function.[1] These advances have led to curative clinical outcomes for patients with hematologic malignancies treated with CAR T or TCR-T therapy.[2] However, adoptive cellular therapy has been less successful for the treatment of solid tumors because of poor homing, proliferation, and survival of transferred cells. Various strategies have been proposed to improve adoptive cellular therapy activity for the management of solid tumors, including combinatorial management strategies with other immune-modulating agents[3] or the expression of transgenes to enhance the homing, penetration, and persistence of adoptively transferred cells. Finally, advances in gene editing using CRISPR/Cas9 or similar technologies have opened a new frontier in the adoptive cellular therapy field, allowing for clinically translatable gene-editing strategies to enhance the antitumor activity.

TUMOR-INFILTRATING LYMPHOCYTES

Select tumor histologies with a high degree of nonsynonymous gene mutations resulting in an abundance of cancer neoantigens, such as ultraviolet light–associated melanoma, smoking-related lung cancer, and mismatch repair–deficient tumors, are often infiltrated by T lymphocytes. Tumor-infiltrating lymphocytes represent an abundant source of tumor-specific T cells, but they are rendered dysfunctional as a result of tumor-mediated immune suppression. However, these cells may be removed from the immunosuppressive tumor microenvironment and

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PRACTICAL APPLICATIONS

- Adoptive cellular therapy is a personalized treatment strategy that involves the isolation of a patient's own immune cells followed by their ex vivo expansion and reinfusion. Tumor histologies with a high degree of nonsynonymous gene mutations can be harnessed to generate tumor-infiltrating lymphocytes, which in large quantities can surmount the tumor-mediated immune suppression.
- T-cell receptor T cells are limited by the diversity of human leukocyte antigens present in the human population, but have the advantage of being able to target intracellularly expressed proteins.
- CAR T cells can be generated as individualized therapies in most patients but targeting is generally restricted to tumor-associated antigens expressed on the surface of tumor cells.
- Gene therapy and gene editing can be used to redirect antigen specificity and enhance T-cell function in most of these cellular therapies.

expanded in vitro to generate large numbers of tumor-specific T cells with restored functionality.[4] Tumor-infiltrating lymphocytes may then be infused in an autologous manner in the context of nonmyeloablative lymphodepletion and systemic interleukin-2 (IL-2) to enhance engraftment and persistence. Lymphodepletion using chemotherapy or total body irradiation is critical for TIL anti-activity as it depletes regulatory T cells,[5] increases the availability of homeostatic cytokines IL-7 and IL-15,[6] and creates physical space for TIL engraftment and expansion. Studies in melanoma utilizing TILs demonstrated the feasibility of adoptive cellular therapy approaches for the management of solid tumors.[7] Subsequent studies further analyzing immune responses of patients with tumor regression following TIL therapy have identified shared tumor-associated antigens and unique tumor antigens as potential targets of TIL therapy.[8] Early studies in melanoma identified shared, nonmutated melanoma differentiation antigens (e.g., gp100, MART-1) and cancer-testis antigens (e.g., MAGE-family members, NY-ESO-1) as relevant TIL targets.[9] With the advent of next-generation sequencing technologies and bioinformatics pipelines, it is now possible to identify tumor somatic mutations and define putative neoantigens. Neoantigen-specific CD8+ T cells have been identified within TIL populations,[10] and neoantigen-specific T cells have been highlighted as the mediators of antitumor activity in patients with epithelial cancers, including breast and colon cancer, who respond to TIL therapy.[11-13]

Broad applicability of TIL therapy to greater numbers of patients with cancer has been limited by several factors. Tumor-infiltrating lymphocytes must be isolated from tumor tissue that is not always easily accessible. Furthermore, the isolation of TILs relies on de novo T-cell immunity, and tumors that lack a high degree of nonsynonymous gene mutations, such as prostate, breast, and glioblastoma malignancies, often lack infiltrating lymphocytes. Efforts to overcome these hurdles involve the isolation of neoantigen-specific T cells from peripheral blood,[14] as well as cancer vaccination to pre-existing or prime new neoantigen-specific T-cell responses.[15] However, immune checkpoint blockade therapy targeting CTLA-4 or PD-1/PD-L1 has demonstrated clinical efficacy in similar patient populations with pre-existing T-cell immunity,[16] and it represents a readily generalizable and less toxic strategy to reinvigorate neoantigen-specific T cells in vivo compared with TIL therapy. Nevertheless, TIL therapy continues to be actively investigated in multiple clinical trials and a variety of cancer types.[17]

T-CELL RECEPTORS VERSUS CAR T CELLS

As an alternative to TIL therapy, T cells may be isolated from peripheral blood and redirected against tumor cells via the transfer of synthetic TCRs or CARs using gene-therapy techniques. The TCR is a heterodimeric structure composed of α and β chains conferring antigen specificity; it is noncovalently linked to the CD3 complex, which activates downstream signal transduction. T-cell receptors exhibit specificity for peptides derived from processed intracellular or extracellular proteins presented in the context of human leukocyte antigens (HLAs) in association with CD4 or CD8 coreceptors. Extensive HLA allelic diversity in the population poses challenges to the identification of widely generalizable TCR therapies because patients must be selected based on antigen expression and HLA criteria. However, a major advantage of TCR therapy compared with CAR therapy is the ability to target intracellularly expressed proteins, greatly broadening the number of targetable tumor antigens.

CARs are synthetic hybrid receptors that combine an extracellular antigen-recognition domain covalently linked to an intracellular signaling domain, with or without costimulatory signaling domains.[18] The extracellular antigen recognition domain most often consists of an antibody single-chain variable fragment, allowing CARs to recognize surface-expressed tumor-associated antigens. Unlike TCRs, the extracellular antigen recognition domain of a CAR is covalently linked to intracellular CD3ξ via a transmembrane domain, allowing for the activation of T-cell signaling upon antigen engagement. These "first-generation" CAR constructs exhibited limited in vivo activity because of poor T-cell persistence, leading to the addition of single (second-generation) or multiple (third-

generation) costimulatory endodomains (e.g., CD28, 4-1BB, and OX40). CAR-based strategies may be broadly applicable, as they confer T-cell activation in an HLA-independent manner that is not reliant upon antigen processing and presentation. However, because the antigen recognition domain is derived from an antibody-based binder (e.g., single-chain variable fragment, nanobody) or protein ligand, CAR targeting is generally restricted to tumor-associated antigens expressed on the surface of tumor cells.

The particular molecular design of a CAR is a factor that strongly influences the potency of the engineered cell product. For example, the intracellular signaling portion of these chimeric receptors is typically comprised of the CD3ζ chain of the TCR and one or more endodomains derived from CD28, 4-1BB, OX40, CD27, and/or ICOS co-stimulatory molecules (reviewed in Geudan et al[19]). CARs containing either CD28 or 4-1BB domains have been the most widely used, and such constructs have resulted in robust clinical responses.[20-30] A number of reports suggest that although CD28 co-stimulatory endodomains potentiate potent antitumor effector functions, activation of 4-1BB intracellular signaling modules promotes a longer duration of CAR T-cell persistence. The mechanisms by which different intracellular domains influence the expansion, engraftment, function, and persistence of CAR T cells have not been fully elucidated and remain an area of active investigation.

To date, many clinical trials with CAR T cells have been conducted using cell products manufactured from enriched, bulk T-cell populations. Interestingly, the results of some studies suggest that particular T-cell subtypes have distinct antitumor properties following adoptive transfer.[31,32] Although an outgrowth of CAR-expressing CD8+ T cells is commonly observed early following infusion, CD4+ T cells provide cytokines and essential costimulatory signals to CD8+ T-cell populations, which may enhance the priming, trafficking, antitumor function, and persistence of effector CD8+ CAR T cells. CAR-transduced CD4+ T cells may also be directly cytotoxic and/or form long-term, persisting memory populations with effector differentiation potential. Notably, CD4+ T cells are plastic, and the differentiation state and function of these cells can drastically evolve in vivo.[31,33] Thus, it stands to reason that production of more compositionally consistent CAR T-cell products comprised of balanced ratios of CD4+ to CD8+ T cells positively influences product potency with regard to in vivo expansion, persistence, and outcome.[34]

TUMOR ANTIGENS

The majority of immunotherapeutic approaches, including adoptive cellular therapy strategies, have targeted tumor-associated antigens. They are nonmutated self-antigens that include germline (e.g., NY-ESO-1, MAGE-A3), differentiation (e.g., MART-1, CD19), or overexpressed proteins (e.g., CEA, HER2/neu) that are preferentially expressed by tumor cells compared with normal tissue. Tumor-associated antigens may be shared within or across different tumor types. Both intracellular and extracellular tumor-associated antigens may be recognized by TCRs due to the intracellular antigen processing and presentation of immunogenic epitopes in the context of HLA class I alleles. On the contrary, tumor-associated antigen recognition by CARs is limited to cell surface (extracellular) expressed antigens. The targeting of tumor-associated antigens has two predominant limitations. First, the identification of high-avidity receptors to self-antigens is limited by central tolerance as a result of thymic negative selection during T-cell maturation. T-cell receptors may be engineered to enhance their affinity, but affinity enhancement has been associated with increased toxicity in patients with melanoma receiving MART-1 TCR-T cells.[35] Additionally, tumor-associated antigens may have variable or heterogeneous cell surface expression and may pose a greater risk for on-target, off-tumor toxicity, given the potential low-level expression by normal cells. Antigenic targets explored for adoptive cellular therapy in solid tumors include NY-ESO, WT1, MAGE, CEA, HER2/neu, mesothelin, and prostate-specific membrane antigen, among others. Early-phase clinical trials utilizing CAR or TCR-T–cell strategies targeting CEA resulted in marked pneumonitis and colitis resulting in early trial termination,[36,37] and CAR-T therapy targeting HER2/neu resulted in the death of a patient from severe pulmonary toxicity.[38] Additionally, the use of affinity-enhanced TCRs targeting tumor-associated antigens may result in serious and unpredictable off-target toxicity, as in the case of severe cardiotoxicity in patients with cancer treated with an affinity-enhanced MAGE-A3 TCR product, because of cross-reactivity with titin expressed on cardiac myocytes.[39,40] Despite these limitations, the targeting of the cancer testis antigen NY-ESO-1 using T cells modified with an affinity-enhanced TCR restricted to HLA-A2 has demonstrated clinical efficacy for the treatment of patients with myeloma, melanoma, or synovial cell sarcoma without appreciable toxicity.[41,42]

Alternatively, non–self-antigens, such as viral antigens or cancer neoantigens, are uniquely expressed by tumor cells, allowing for the generation of high-avidity T-cell responses with an increased safety profile. Unlike CARs, TCRs may recognize viral or mutated proteins that are internally processed and presented on the cell surface of tumor cells or antigen-presenting cells in the context of HLA class I or class II molecules. Virus-specific TCRs may be broadly applicable to viral-associated cancers, such as HPV-related squamous cell cancers and Epstein-Barr virus–associated nasopharyngeal carcinoma. However, neoantigen-targeted strategies are generally limited by the fact that neoantigens

are rarely shared among patients[43,44] and require personalized treatment approaches that may be laborious and costly. Ideal antigenic targets are those that are exclusively expressed by tumor cells, as well as those that are critical to tumor pathogenesis and maintenance. Hot-spot driver mutations within proto-oncogenes, such as *KRAS* and *TP53*, fulfill these criteria. For example, epitopes derived from somatic DNA missense mutations within the *KRAS* gene may be presented to CD8+ T cells on the surface of tumor cells in the context of HLA class I. Adoptive cellular therapy directed against mutant *KRAS* has demonstrated clinical activity in a patient with metastatic colon cancer.[45] Driver mutations are highly prevalent across human cancers, and critical to tumor pathogenesis, thus strategies targeting these antigens may be broadly generalizable and potentially highly efficacious to patients with cancer.

ENHANCING ADOPTIVE CELLULAR THERAPY VIA TRANSGENE EXPRESSION AND GENE EDITING

Adoptive cellular therapy has demonstrated unprecedented clinical outcomes in patients with leukemia or lymphoma treated with CAR T-cell therapy targeting CD19[46,47] or TCR therapy targeting WT1.[48] Unfortunately, the success of adoptive cellular therapy in hematologic malignancies has not exhibited similar benefits for the management of solid tumors as a result of antigen heterogeneity, poor in vivo persistence, insufficient homing and/or penetration of transferred cells, and an immunosuppressive tumor microenvironment.[49] Various strategies have been proposed to improve adoptive cellular therapy activity in solid tumors, such as the expression of transgenes to enhance homing,[50-53] penetration,[54] persistence,[55,56] and effector functions, as well as combinatorial strategies with immune-modulating agents.[3]

Recent biotechnological advancements now make it feasible to gene edit immune cells to enhance the efficacy and improve the safety of adoptive cellular therapy.[57] Initial strategies used to gene edit primary T cells, including zinc-finger nucleases and mega-nucleases, were highly inefficient; however, newer technologies, including transcription activator-like effector nuclease (TALEN) or CRISPR/Cas9 systems, have greatly improved gene-editing efficiency. To date, gene-editing strategies have largely focused on the disruption of (1) endogenous TCR α- and/or β-chain genes or (2) inhibitory pathways to enhance the efficacy and safety of adoptively transferred cells.

For TCR-based therapeutic applications, the presence of endogenous TCR leads to mispairing of the endogenous and transgenic α and β heterodimers. Heterodimer mispairing results in reduced cell surface expression of the synthetic TCR and can lead to novel peptide recognition that may cause unpredictable autoimmune side effects.[58] Indeed, simultaneous elimination of endogenous TCRα and TCRβ genes enhances transgenic TCR expression and the antitumor activity of modified T cells.[59]

In a recent first-in-human study, Lu et al administered autologous *PD-1*–edited T cells using CRISPR/Cas9 to 12 patients with advanced lung cancer.[60] The generation of *PD-1*–edited T-cell product was determined to be feasible and safe. Edited T cells could be detected in the peripheral circulation for more than 1 year in some cases, but no objective clinical responses were noted in a small cohort of heavily pretreated patients.

With modern techniques, the editing of multiple genes simultaneously, a process known as multiplexing, is feasible. In this manner, "universal" T-cell products may be edited to remove endogenous receptors, inhibitory molecules, and surface molecules that may be the target of host immune rejection or complementary therapies used to treat the patient's cancer. For example, Qasim and colleagues used a universal T-cell product consisting of allogeneic T cells modified to express a CD19 CAR and gene edited to eliminate TCRα and CD52. Gene editing to eliminate TCRα abrogates the risk of graft-versus-host disease, and removal of CD52 allowed for concurrent administration of alemtuzumab to treat the patient's cancer. In this manner, two infants with B-cell acute lymphoblastic leukemia were successfully treated with anti-CD52 and universal CAR T-cell therapy as a bridge to allogeneic stem cell transplantation.[61,62] In a more recent study, Stadtmauer et al demonstrated the feasibility of multiplex editing of TCRα, TCRβ, and PD-1 in a TCR trial targeting NY-ESO-1.[63] Product generation was determined to be feasible, and clinical responses were observed in patients with advanced myeloma or sarcoma without substantial toxicity. Targeted integration of transgenic receptors into endogenous TCRα or TCRβ loci via CRISPR/Cas9–mediated homologous recombination may streamline the production of gene-edited adoptive cellular therapy products because disruption of endogenous TCR and transgene expression may be accomplished simultaneously.[64,65]

A major concern related to gene-editing techniques is off-target double-strand breaks that can result in chromosomal rearrangements that (1) lead to genotoxicity that limits the effectiveness of adoptive cellular therapy or (2) pose a risk for malignant transformation. Attempts to limit off-target chromosomal breaks include optimization of single-guide RNAs and the use of high-fidelity Cas9 systems. Studies using gene-edited T-cell products in humans have demonstrated the safety of this approach, and off-target gene-editing and translocation events tend to be relatively low and may decrease over time, suggesting that they may not confer a survival advantage to edited cells,[60,63] although longer follow-up is needed. Gene silencing via the targeting of splice sites using DNA base-editing systems that do not

induce double-strand DNA breaks may improve the safety profile of gene-edited adoptive cellular therapy products.[66]

THE PENN EXPERIENCE WITH AN "ARMORED" CAR T-CELL THERAPY

We will walk through the clinical development of PSMA (prostate-specific membrane antigen) dominant-negative transforming growth factor β (TGF-β) receptor type II CAR T-cell therapy for the management of prostate cancer, as an example of the iterative enhancement of CAR T-cell activity against solid tumors. PSMA is a tumor-associated antigen that is highly expressed in malignant prostate cancer relative to normal prostate tissue.[67] PSMA expression increases with the development of castration-resistant disease.[68] Early CAR T-cell therapy directed to PSMA was safe but largely ineffective; it was hindered, in part, by the immunosuppressive tumor microenvironment.[69,70] Prostate cancers secrete TGF-β, which inhibits T-cell–mediated immunity and promotes cancer progression.[71-73] Engineering CAR T cells to express dominant-negative TGF-β receptor type II resulted in enhanced proliferation, cytokine secretion, persistence, and resistance to exhaustion, leading to tumor eradication in an aggressive mouse model of human prostate cancer.[56] PSMA dominant-negative TGF-β receptor type II CAR T-cell therapy was tested in a phase I clinical trial of patients with metastatic castration-resistant prostate cancer following lymphodepleting chemotherapy. PSMA dominant-negative TGF-β receptor type II CAR T cells trafficked to metastatic tumor sites and resulted in a decline in prostate-specific antigen and lymph node regression (unpublished data). However, preliminary antitumor effects were accompanied by an upregulation of multiple potential immunosuppressive factors within the tumor microenvironment, indicating mechanisms of adaptive resistance. Multiple approaches to further enhance PSMA dominant-negative TGF-β receptor type II CAR T-cell activity are in development, including the incorporation of switch receptors and the use of gene-editing technology. For example, fusing the PD-1 binding domain with costimulatory endodomains from CD28 and CD27 produces costimulatory switch receptors (PD1-CD28 and PD1-CD27). Stimulation of CAR T cells expressing PD-1/CD28 switch receptors and stimulated with PD-L1+ tumor cell lines increased production of IL-2 and interferon γ (IFN-γ) compared with T cells expressing CARs alone.[74] A recent clinical trial demonstrated the tolerability, safety, and potential efficacy of this approach in patients with PD-L1+ large B-cell lymphoma.[75] Using this technology could potentially augment CAR T-cell antitumor activity against immunologically cold tumors, such as in prostate cancer.[76,77] Alternative approaches include concurrent oncolytic adenovirus therapy, because our group recently demonstrated that oncolytic adenovirus expressing TNF-α and IL-2 cytokines enhances mesothelin CAR T-cell infiltration into tumors and alters the tumor microenvironment to promote antitumor activity in xenogeneic and syngeneic mouse models.[78]

SIDE EFFECTS ASSOCIATED WITH ADOPTIVE CELLULAR THERAPY

Potential side effects of adoptive cellular therapy include tumor lysis syndrome, cytokine release syndrome, and macrophage activation syndrome. Tumor lysis syndrome is related to cancer type and disease burden and is seen more often in hematologic malignancies than in solid tumors. The majority of patients with leukemia who have responded to CD19-directed CAR T-cell therapy experience some degree of cytokine release syndrome, although new strategies have emerged to mitigate the severity of cytokine release syndrome while preserving CAR T-cell efficacy.[79]

The cytokine release syndrome signature is characterized by the systemic elevation of inflammatory cytokines, including IL-6 (high), IFN-γ, TNF-α (moderate), and IL-2 (mild), as well as elevations in ferritin and C-reactive protein levels. The diagnosis of cytokine release syndrome is based on clinical symptoms, including fever, fatigue, myalgias, hypotension, hypoxia, delirium or confusion, disseminated intravascular coagulation, and macrophage activation syndrome. A modified common terminology criteria grading system has been developed to capture adverse events related to cytokine release syndrome.[80] As for cytokine release syndrome, a modified common terminology criteria grading system has been developed to capture neurotoxicity associated with adoptive cellular therapy. Macrophage activation syndrome is a reaction to immune activation that occurs as a result of cytokine release syndrome and is considered a manifestation of this disease. A diagnosis of macrophage activation syndrome is made by having five of the following criteria: fever, splenomegaly, cytopenias (affecting two of three lineages in the peripheral blood), elevated triglycerides, hypofibrinogenemia, hemophagocytosis, low or absent natural killer cell activity, high ferritin, or elevated soluble CD25R. Neurotoxicity is treated with dexamethasone. Anti–IL-6 or IL-6 ligand antibody has been used to address cytokine release syndrome, including hemophagocytic lymphohistiocytosis.[81]

CONCLUSION

Adoptive cellular therapy has played a transformative role in the treatment of select patients with hematologic malignancies; however, thus far it has proven ineffective for the vast majority of solid tumor indications. Solid tumor resistance to adoptive cellular therapy is attributed to poor antigenic quantity/quality and T-cell dysfunction resulting from complex tumor immune-evasion mechanisms and an immunosuppressive tumor microenvironment. Advancements in T-cell engineering have fostered cell-intrinsic combinatorial strategies to enhance adoptive cellular

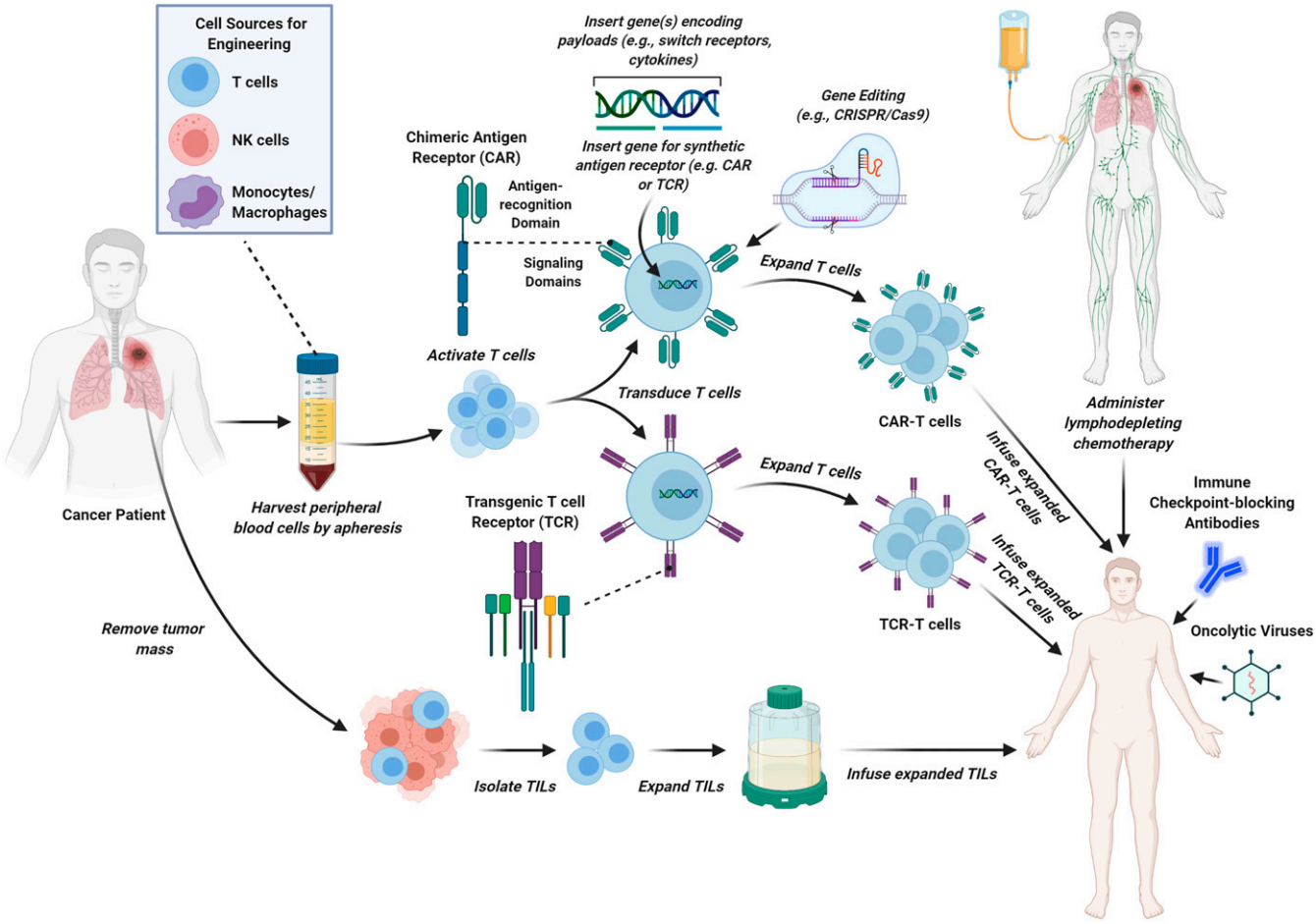

FIGURE 1. General Approaches to Adoptive Cellular Therapy for Advanced Cancer

Tumor-infiltrating lymphocytes are produced following surgical excision of a tumor, and lymphocytes are enriched and expanded from a disaggregated mass. CAR– and T-cell receptor–engineered cells (e.g., T cells, natural killer cells) are generated from the peripheral blood in a manufacturing process that includes delivery of the antigen receptor transgene, genes encoding additional potency-enhancing payloads, and/or gene editing through viral or nonviral methods. Patients may receive lymphodepleting chemotherapy regimens for conditioning prior to adoptive cell transfer. The therapeutic efficacy of adoptive cellular therapy may be augmented via combinatorial strategies, such as administration of immune checkpoint–blocking antibodies or oncolytic viruses.

Abbreviation: NK, natural killer; TCR, transgenic T-cell receptor; TIL, tumor-infiltrating lymphocyte.

therapy activity against solid tumors, and cell-extrinsic combinations using exogenous immune-modulating agents are under active investigation. Finally, multiplex gene editing has exposed a new frontier in the field of adoptive cellular therapy. It is now feasible to generate universal T-cell products with improved safety profiles that are resistant to host immune rejection; this greatly broadens the generalizability of adoptive cellular therapy strategies to the large numbers of patients with solid tumors who are in need of new and innovative therapies (Fig 1).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Guedan S, Ruella M, June CH. Emerging cellular therapies for cancer. Annu Rev Immunol. 2019;37:145-171.
2. June CH, O'Connor RS, Kawalekar OU, et al. CAR T cell immunotherapy for human cancer. Science. 2018;359:1361-1365.
3. Grosser R, Cherkassky L, Chintala N, et al. Combination immunotherapy with CAR T cells and checkpoint blockade for the treatment of solid tumors. Cancer Cell. 2019;36:471-482.
4. Dudley ME, Wunderlich JR, Shelton TE, et al. Generation of tumor-infiltrating lymphocyte cultures for use in adoptive transfer therapy for melanoma patients. J Immunother. 2003;26:332-342.
5. Antony PA, Piccirillo CA, Akpinarli A, et al. CD8+ T cell immunity against a tumor/self-antigen is augmented by CD4+ T helper cells and hindered by naturally occurring T regulatory cells. J Immunol. 2005;174:2591-601.
6. Gattinoni L, Finkelstein SE, Klebanoff CA, et al. Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumor-specific CD8+ T cells. J Exp Med. 2005;202:907-912.
7. Rosenberg SA, Yang JC, Sherry RM, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res. 2011;17:4550-4557.
8. Tran E, Robbins PF, Rosenberg SA. 'Final common pathway' of human cancer immunotherapy: targeting random somatic mutations. Nat Immunol. 2017;18:255-262.
9. Andersen RS, Thrue CA, Junker N, et al. Dissection of T-cell antigen specificity in human melanoma. Cancer Res. 2012;72:1642-1650.
10. Robbins PF, Lu YC, El-Gamil M, et al. Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells. Nat Med. 2013;19:747-752.
11. Tran E, Turcotte S, Gros A, et al. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. Science. 2014;344:641-645.
12. Tran E, Robbins PF, Lu YC, et al. T-cell transfer therapy targeting mutant KRAS in cancer. N Engl J Med. 2016;375:2255-2262.
13. Zacharakis N, Chinnasamy Hi, Black M, et al. Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer. Nat Med. 2018;24:724-730.
14. Gros A, Parkhurst MR, Tran E, et al. Prospective identification of neoantigen-specific lymphocytes in the peripheral blood of melanoma patients. Nat Med. 2016;22:433-438.
15. Carreno BM, Magrini V, Becker-Hapak M, et al. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science. 2015;348:803-808.
16. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359:1350-1355.
17. Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science. 2015;348:62-68.
18. June CH, Sadelain M. Chimeric antigen receptor therapy. N Engl J Med. 2018;379:64-73.
19. Guedan S, Calderon H, Posey AD Jr., et al. Engineering and design of chimeric antigen receptors. Mol Ther Methods Clin Dev. 2019;12:145-156.
20. Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med. 2011;365:725-733.
21. Kalos M, Levine BL, Porter DL, et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. Sci Transl Med. 2011;3:95ra73.
22. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371:1507-1517.
23. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378:439-448.
24. Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med. 2018;378:449-459.
25. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med. 2017;377:2545-2554.
26. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377:2531-2544.
27. Garfall AL, Maus MV, Hwang WT, et al. Chimeric antigen receptor T cells against CD19 for multiple myeloma. N Engl J Med. 2015;373:1040-1047.
28. Ramos CA, Savoldo B, Torrano V, et al. Clinical responses with T lymphocytes targeting malignancy-associated κ light chains. J Clin Invest. 2016;126:2588-2596.
29. Ormhøj M, Bedoya F, Frigault MJ, et al. CARs in the lead against multiple myeloma. Curr Hematol Malig Rep. 2017;12:119-125.
30. Munshi NC, Anderson LD Jr., Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384:705-716.
31. Muranski P, Borman ZA, Kerkar SP, et al. Th17 cells are long lived and retain a stem cell-like molecular signature. Immunity. 2011;35:972-985.

32. Gattinoni L, Lugli E, Ji Y, et al. A human memory T cell subset with stem cell-like properties. Nat Med. 2011;17:1290-1297.
33. Guedan S, Chen X, Madar A, et al. ICOS-based chimeric antigen receptors program bipolar TH17/TH1 cells. Blood. 2014;124:1070-1080.
34. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016;126:2123-2138.
35. Duinkerken CW, Rohaan MW, de Weger VA, et al. Sensorineural hearing loss after adoptive cell immunotherapy for melanoma using MART-1 specific T cells: a case report and its pathophysiology. Otol Neurotol. 2019;40:e674-e678.
36. Thistlethwaite FC, Gilham DE, Guest RD, et al. The clinical efficacy of first-generation carcinoembryonic antigen (CEACAM5)-specific CAR T cells is limited by poor persistence and transient pre-conditioning-dependent respiratory toxicity. Cancer Immunol Immunother. 2017;66:1425-1436.
37. Parkhurst MR, Yang JC, Langan RC, et al. T cells targeting carcinoembryonic antigen can mediate regression of metastatic colorectal cancer but induce severe transient colitis. Mol Ther. 2011;19:620-626.
38. Morgan RA, Yang JC, Kitano M, et al. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. Mol Ther. 2010;18:843-851.
39. Linette GP, Stadtmauer EA, Maus MV, et al. Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma. Blood. 2013; 122:863-871.
40. Cameron BJ, Gerry AB, Dukes J, et al. Identification of a titin-derived HLA-A1-presented peptide as a cross-reactive target for engineered MAGE A3-directed T cells. Sci. Transl. Med. 2013;5:197ra103.
41. Rapoport AP, Stadtmauer EA, Binder-Scholl GK, et al. NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. Nat Med. 2015;21:914-921.
42. Robbins PF, Kassim SH, Tran TL, et al. A pilot trial using lymphocytes genetically engineered with an NY-ESO-1-reactive T-cell receptor: long-term follow-up and correlates with response. Clin Cancer Res. 2015;21:1019-1027.
43. Priestley P, Baber J, Lolkema MP, et al. Pan-cancer whole-genome analyses of metastatic solid tumours. Nature. 2019;575:210-216.
44. ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium. Pan-cancer analysis of whole genomes. Nature. 2020;578:82-93.
45. Tran E, Robbins PF, Lu YC, et al. T-cell transfer therapy targeting mutant KRAS in cancer. N Engl J Med. 2016;375:2255-2262.
46. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371:1507-1517.
47. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med. 2017;377:2545-2554.
48. Chapuis AG, Afanasiev OK, Iyer JG, et al. Regression of metastatic Merkel cell carcinoma following transfer of polyomavirus-specific T cells and therapies capable of re-inducing HLA class-I. Cancer Immunol Res. 2014;2:27-36.
49. Rafiq S, Hackett CS, Brentjens RJ. Engineering strategies to overcome the current roadblocks in CAR T cell therapy. Nat Rev Clin Oncol. 2020;17:147-167.
50. Craddock JA, Lu A, Bear A, et al. Enhanced tumor trafficking of GD2 chimeric antigen receptor T cells by expression of the chemokine receptor CCR2b. J Immunother. 2010;33:780-788.
51. Moon EK, Carpenito C, Sun J, et al. Expression of a functional CCR2 receptor enhances tumor localization and tumor eradication by retargeted human T cells expressing a mesothelin-specific chimeric antibody receptor. Clin Cancer Res. 2011;17:4719-4730.
52. Jin L, Tao H, Karachi A, et al. CXCR1- or CXCR2-modified CAR T cells co-opt IL-8 for maximal antitumor efficacy in solid tumors. Nat Commun. 2019;10:4016.
53. Di Stasi A, De Angelis B, Rooney CM, et al. T lymphocytes coexpressing CCR4 and a chimeric antigen receptor targeting CD30 have improved homing and antitumor activity in a Hodgkin tumor model. Blood. 2009;113:6392-6402.
54. Caruana I, Savoldo B, Hoyos V, et al. Heparanase promotes tumor infiltration and antitumor activity of CAR-redirected T lymphocytes. Nat Med. 2015; 21:524-529.
55. Leen AM, Sukumaran S, Watanabe N, et al. Reversal of tumor immune inhibition using a chimeric cytokine receptor. Mol Ther. 2014;22:1211-1220.
56. Kloss CC, Lee J, Zhang A, et al. Dominant-negative TGF-β receptor enhances PSMA-targeted human CAR T cell proliferation and augments prostate cancer eradication. Mol Ther. 2018;26:1855-1866.
57. Lo Presti V, Buitenwerf F, van Til NP, et al. Gene augmentation and editing to improve TCR engineered T cell therapy against solid tumors. Vaccines (Basel). 2020;8:733.
58. Bendle GM, Linnemann C, Hooijkaas AI, et al. Lethal graft-versus-host disease in mouse models of T cell receptor gene therapy. Nat Med. 2010;16:565-570, 1p following 570.
59. Schober K, Müller TR, Gökmen F, et al. Orthotopic replacement of T-cell receptor α- and β-chains with preservation of near-physiological T-cell function. Nat Biomed Eng. 2019;3:974-984.
60. Lu Y, Xue J, Deng T, et al. Safety and feasibility of CRISPR-edited T cells in patients with refractory non-small-cell lung cancer [published correction appears in Nat Med. 2020;26:1149]. Nat Med. 2020;26:732-740.
61. Qasim W, Zhan H, Samarasinghe S, et al. Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells. Sci Transl Med. 2017; 9:eaaj2013.
62. Benjamin R, Graham C, Yallop D, et al; UCART19 Group. Genome-edited, donor-derived allogeneic anti-CD19 chimeric antigen receptor T cells in paediatric and adult B-cell acute lymphoblastic leukaemia: results of two phase 1 studies. Lancet. 2020;396:1885-1894.
63. Stadtmauer EA, Fraietta JA, Davis MM, et al. CRISPR-engineered T cells in patients with refractory cancer. Science. 2020;367:eaba7365.

64. Roth TL, Li PJ, Blaeschke F, et al. Pooled knockin targeting for genome engineering of cellular immunotherapies. Cell. 2020;181:728-744.e21.

65. Roth TL, Puig-Saus C, Yu R, et al. Reprogramming human T cell function and specificity with non-viral genome targeting. Nature. 2018;559:405-409.

66. Webber BR, Lonetree CL, Kluesner MG, et al. Highly efficient multiplex human T cell engineering without double-strand breaks using Cas9 base editors [published correction appears in Nat Commun. 2019;10:5659]. Nat Commun. 2019;10:5222.

67. Silver DA, Pellicer I, Fair WR, et al. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res. 1997;3:81-85.

68. Wright GL Jr., Haley C, Beckett ML, et al. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. Urol Oncol. 1995; 1:18-28.

69. Slovin SF, Wang X, Hullings M, et al. Chimeric antigen receptor (CAR^+) modified T cells targeting prostate-specific membrane antigen (PSMA) in patients (pts) with castrate metastatic prostate cancer (CMPC). J Clin Oncol. 2013;31 (6 suppl; abstr TPS3115).

70. Westdorp H, Sköld AE, Snijer BA, et al. Immunotherapy for prostate cancer: lessons from responses to tumor-associated antigens. Front Immunol. 2014;5:191.

71. Steiner MS, Barrack ER. Transforming growth factor-beta 1 overproduction in prostate cancer: effects on growth in vivo and in vitro. Mol Endocrinol. 1992; 6:15-25.

72. Matthews E, Yang T, Janulis L, et al. Down-regulation of TGF-β1 production restores immunogenicity in prostate cancer cells. Br J Cancer. 2000;83:519-525.

73. Bendle GM, Linnemann C, Bies L, et al. Blockade of TGF-β signaling greatly enhances the efficacy of TCR gene therapy of cancer. J Immunol. 2013; 191:3232-3239.

74. Liu X, Ranganathan R, Jiang S, et al. A chimeric switch-receptor targeting PD1 augments the efficacy of second-generation CAR T cells in advanced solid tumors. Cancer Res. 2016;76:1578-1590.

75. Liu H, Lei W, Zhang C, et al. CD19-specific CAR T cells that express a PD-1/CD28 chimeric switch-receptor are effective in patients with PD-L1-positive B-cell lymphoma. Clin Cancer Res. 2021;27:473-484.

76. Sad S, Mosmann TR. Single IL-2-secreting precursor CD4 T cell can develop into either Th1 or Th2 cytokine secretion phenotype. J Immunol. 1994; 153:3514-3522.

77. Swain SL, Huston G, Tonkonogy S, et al. Transforming growth factor-beta and IL-4 cause helper T cell precursors to develop into distinct effector helper cells that differ in lymphokine secretion pattern and cell surface phenotype. J Immunol. 1991;147:2991-3000.

78. Watanabe K, Luo Y, Da T, et al. Pancreatic cancer therapy with combined mesothelin-redirected chimeric antigen receptor T cells and cytokine-armed oncolytic adenoviruses. JCI Insight. 2018;3:e99573.

79. Ghorashian S, Kramer AM, Onuoha S, et al. Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. Nat Med. 2019;25:1408-1414.

80. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25:625-638.

81. Maude SL, Barrett D, Teachey DT, et al. Managing cytokine release syndrome associated with novel T cell-engaging therapies. Cancer J. 2014;20:119-122.

Avoiding Stops and Overcoming Roadblocks: Considerations for Improving Patient Access to CAR-Based Cell Therapies

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Overview

Adoptive cell therapy has significantly impacted the immuno-oncology landscape. The number of strategies currently in preclinical and clinical development is increasing at a rapid rate. Indeed, we are experiencing a transformative movement in cancer care as we shift toward highly personalized treatments designed to confront the specific challenges of each cancer. Advancements in genetic engineering methods and single-cell profiling technologies provide a level of understanding of the interactions between the immune system and cancer never before achieved. This knowledge, in turn, can be applied to the design and engineering of effective cancer-fighting treatments. As these promising new therapies progress toward clinical application, it becomes evident that we must develop robust methods for production and validation of cellular products to ensure consistency, safety, and efficacy, irrespective of cell type or indication. Herein, we provide an overview of the innovative approaches guiding the new generation of cell therapies and describe the benefits and challenges associated with emerging autologous and allogeneic platforms. Moreover, we discuss important considerations pertaining to process development, cost of goods, and manufacturing, and highlight their impact on the transfer of therapies from bench to bedside.

INTRODUCTION

The field of cell therapy is prolific, introducing innovative ideas that may become solutions to problems that have long deterred progress in cancer treatment. The number of cell therapies currently in preclinical and clinical development is rapidly growing. A recent survey of new immuno-oncology drug pipelines in development ranks cell therapy first for largest growth of any immuno-oncology therapeutic modality between September 2017 and August 2019, and this trend has remained through 2020.[1,2] We are indeed experiencing a transformative moment in cancer care, driven by innovative science that has culminated in the development of a unique class of personalized therapies. Efficacy data supported by unprecedented clinical responses have led to the U.S. Food and Drug Administration approval of multiple CAR T-cell products for hematologic malignancy indications, marking the official entry of immuno-oncology cell therapies into the clinic.[3-9] Developments continue to expand and diversify, and novel approaches seek to combine the power of multiple modalities to achieve superior outcomes.[10]

This exciting progress, however, has revealed complexities not previously faced with other immuno-oncology drug pipelines that may significantly impact the commercialization and reach of cell therapies. Challenges associated with research and development, cost of goods, manufacturing, and reimbursement present significant hurdles that must be overcome to broaden patient access to cell therapies. It is important to identify strategies for alleviating the encumbrances associated with research and development and cost of goods and to broaden the scope of personalized treatment through the development of customized off-the-shelf cell therapies.

THE IMPACT OF RESEARCH AND DEVELOPMENT AND COST OF GOODS IN BENCH-TO-BEDSIDE TRANSITION

In the early stages of development, cell therapies are frequently born of ideas driven by clinical findings and scientific study of relevant biology. Cost of goods, scalability, and laboratory-to-Good Manufacturing Practice transition are considerations less commonly incorporated in early process development decisions, thus potentially contributing to increased complexities in bench-to-bedside translation and driving the cost of therapy to prohibitively high levels.

To mitigate these issues, it is important to implement, early on, a strategic plan that addresses the feasibility and economic aspects required for the development of viable and commercially successful therapies that will enable broad patient access. Important elements that must be considered in process development include selecting an appropriate cell source, determining

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PRACTICAL APPLICATIONS

- To understand the benefits and limitations of autologous and allogeneic cell therapies.
- To discuss strategies for facilitating successful translation of cell therapies to the clinic by incorporating considerations related to cost of goods, manufacturing, and scalability to early process development decisions.
- To discuss the need for, and to build, a comprehensive multidisciplinary team structure to support the viability and longevity of cell therapy programs.

isolation and purification methods, establishing cell manipulation and characterization pipelines, implementing quality control protocols, optimizing culture conditions, devising scale-up strategies, and outlining a clear transition into robust and reproducible Good Manufacturing Practice–compliant manufacturing protocols. Some of these decisions may evolve as knowledge emerges and will thus take longer to become clear. Others, however, can be solidified early on.[11-13]

The first wave of successful immuno-oncology cell therapies emerged from autologous platforms, which rely on the patient's own cells as a source.[13-16] Although it offers clear benefits as a highly personalized approach without the risk of rejection, the extensive manufacturing requirements are often burdensome to patients presenting with rapidly progressing disease. Furthermore, the need for high-quality cells that are able to withstand rigorous genetic manipulation and expansion protocols may limit patient eligibility, because many are lymphodepleted after several cycles of first-line chemotherapy and radiation treatments and thus may not be able to provide cells in sufficient numbers for therapy. New approaches hoping to address these impediments have focused on allogeneic platforms, which in many instances use a third-party cell source to generate cell therapy products that are available to patients in an "off-the-shelf" manner, thus allowing for true point-of-care treatment administration. Additional advantages that facilitate process development include elimination of postdiagnosis manufacturing time, large-scale production of a well-characterized cell product, low product variability, increased dose-to-dose consistency, reduced cost, and greater patient eligibility.[17]

Both autologous and allogeneic models require implementation of methods for cell harvest and characterization, cellular engineering, and assays for defining the functional and phenotypic properties of the final product to reduce the risk of incorporating unwanted modifications. Selecting appropriate assays and generating reproducible analysis pipelines to address these requirements are essential to successful therapy development and constitute significant steps toward establishing robust manufacturing processes that can be incorporated into Good Manufacturing Practice production.[12,13]

In addition to scientific strategy and quality control considerations, monitoring cost of goods in all areas of development is an important aspect in both models because labor-intensive protocols, expensive raw materials, and specialized testing processes can significantly increase product cost, impact reimbursement strategies, and ultimately impede patient access to potentially curative treatments.

CUSTOM-DESIGNED OFF-THE-SHELF THERAPIES: A NEW PERSPECTIVE ON PERSONALIZED TREATMENT

The remarkable responses seen in CAR T-cell therapy trials highlight the benefits of personalizing cancer care. Because cancer is a heterogeneous disease, and patients with cancer are often subjected to many rounds of treatments before being considered for cell-based therapies, the ability to provide a product uniquely designed for a given patient is very valuable. However, as this idea is reduced to practice, it becomes evident that limitations in patient eligibility, complex manufacturing processes, and the increased costs of these highly personalized autologous approaches are obstacles that hinder the breadth of cell therapy implementation.[13,15,17,18] In response to these challenges, the field has turned to allogeneic models of personalized cell therapies with the goal of developing sustainable platforms that rely on renewable cell sources. Supported by key advancements in gene editing and single-cell profiling technologies, these new products use a third-party cell source that is engineered to address the unique challenges of each cancer. In this model, multiple new drugs are built on the backbone of a single cellular platform, thus creating an arsenal of therapies that are each specifically tailored to a particular disease.

With respect to allogeneic T-cell platforms, strategies concentrate on overcoming T-cell alloreactivity to engineer universal CAR T cells. Efforts have focused on applying genome editing techniques to eliminate expression of the αβ T-cell receptor and/or major histocompatibility class I complexes thus preventing T-cell receptor–mediated nonself recognition of patient HLA antigens and the onset of graft-versus-host disease.[18-20] Additionally, the absence of T-cell receptor may also enhance CAR T-cell function by reducing tonic signaling.[21] These universal CAR T cells can be manufactured in large scale from a healthy donor source and banked for administration to patients in a timely manner, therefore addressing major hurdles associated with current autologous CAR T-cell manufacturing and treatment delays. The first off-the-shelf CAR T-cell therapy to enter clinical trials mirrors its autologous counterpart by targeting

CD19-positive hematologic malignancies. Referred to as UCART19, this healthy donor–derived cell product is gene edited to simultaneously disrupt expression of the T-cell receptor and CD52, as an additional feature, to render UCART19 resistant to higher intensity conditioning lymphodepletion by the anti-CD52 monoclonal antibody alemtuzumab.[22-24] Moreover, UCART19 cells are equipped with a safety switch in the form of a CD20 mimotope to allow for cell elimination by rituximab in the event of excessive toxicity.[24] In the two studies conducted between June 2016 and October 2018, pediatric and adult patients with rapidly progressing refractory or relapsed B-cell acute lymphoblastic leukemia were treated with UCART19.[22,23] Study results showed that UCART19 proliferated well in vivo and exhibited antileukemic activity with a manageable safety profile. Although these first results are very encouraging, concerns still remain, because engineering techniques do not enable 100% efficiency of T-cell receptor deletion; therefore, further screening and purification of T-cell products are necessary to ensure removal of cells retaining their native T-cell receptor. Additionally, it remains to be elucidated whether recipient natural killer (NK) cell–mediated killing of T cells lacking major histocompatibility complex class I molecules may impact their therapeutic efficacy and whether UCART19 rejection could be mediated by class II HLA molecules, often expressed by activated T cells.

Other immune effector cells have also been considered as potential candidates for cell therapy.[25,26] Promising strategies involving NK cells and invariant NK T cells have led to remarkable results in preclinical studies and have thus advanced into clinical trials.[25-28] NK cell–focused approaches have gained significant interest, because of the high cytotoxic potential of NK cells while presenting very low risk of inducing graft-versus-host disease.[25-27] Viable allogeneic NK cell sources include peripheral blood, cord blood, induced pluripotent stem cells, and NK cell line NK-92.[25-36] Important aspects to note are that although peripheral blood–NK and cord blood–NK are primary cell sources readily obtained from healthy donors, induced pluripotent stem cells–NK cells are derived in vitro, and NK-92 cells are an immortalized cell line from a patient with NK lymphoma and thus requires irradiation before administration.[32,35] Recent clinical data show cord blood–NK, induced pluripotent stem cells–NK, and NK-92 engineered products as promising therapeutic modalities for immuno-oncology. Possessing high proliferative capacity and clonality potential, induced pluripotent stem cells can be easily genetically modified, screened, and selected for clones of interest. These, in turn, can be grown into master cell banks and used as a renewable source for mass production of genetically enhanced NK cells, thus constituting a homogenous product.[29,32,33] Work by Li et al[33] demonstrated high antitumor response of induced pluripotent stem cell–derived CAR-expressing NK cells in an ovarian tumor model. An enhanced format of this product is now in a phase I clinical trial under the label FT596. Although the clinical data from the trial are still pending, early results from a single patient with diffuse large B-cell lymphoma show encouraging clinical benefits.[34]

NK-92 cells have shown promising clinical efficacy, and, with at least nine ongoing clinical trials to date, this approach merits discussion.[25] Easy to culture and genetically manipulate and possessing high proliferative capacity and reduced sensitivity to freeze-thaw cycles, NK-92 cells are a suitable source for cell therapy. A clinical study targeting CD33 in acute myeloid leukemia showed a favorable safety profile with no substantial adverse effects.[35] The patient cohort in this trial, however, was very small, and additional clinical data are needed to solidify these observations. It is important to note that the need for irradiation limits in vivo proliferation of NK-92 cells and may potentially decrease their antitumor activity.

Cord blood represents another attractive source of NK cells for cell therapy, because it is broadly available from global cord blood banks and has a greater proportion of NK cells than that found in peripheral blood. NK cells can be readily obtained from umbilical cord blood, genetically enhanced, and subsequently expanded in vitro under controlled culture conditions, yielding a large number of cells that can be stored and made available to patients as needed.[27,36,37] Our group demonstrated that CAR19-engineered cord blood–NK cells coexpressing interleukin-15 exhibit significant antitumor cytotoxicity and persistence in vivo and exert potent activity against Raji lymphoma in a preclinical model.[27] In a first-of-its-kind clinical study, we demonstrated that CAR19/IL-15 CB-NK cells were able to recognize and eliminate lymphoma cells with high efficiency, leading to response rates of 73% in patients with relapsed or refractory disease.[37] Furthermore, CAR NK cells showed a remarkable safety profile and demonstrated great feasibility with minimal toxicity to patients.

With a large number of new therapeutic modalities under preclinical investigation and several transitioning into clinical trials, building a solid infrastructure to support the successful advancement of these new therapies becomes critical. The complexities associated with product characterization, manufacturing, delivery of care, management of toxicities, and immune monitoring of patients require the assembly of multidisciplinary teams encompassing, among others, physicians dedicated to CAR-based therapies, immuno-oncology scientists, study coordinators, nurses, and pharmacists. Ongoing education and close communication between all segments of the team are critical for maintaining high-level performance and vigilance.

We have undoubtedly made great strides in the quest to find cures for cancer. However, many challenges still remain. Current developments in cell therapy are largely focused on hematologic malignancies, with CD19 and B-cell maturation antigen (BCMA) being the most popular targets. Although nearly 90% of cancer incidences worldwide are caused by solid tumors, only about half of the total number of cell therapy trials initiated since 1993 have targeted solid tumors.[2] In large part, this is driven by the many barriers that prevent successful survival and function of immune cells in the suppressive solid tumor microenvironment.[38,39] Selection of appropriate tumor-associated antigens for CAR targeting, limited immune cell trafficking to the tumor site, and overcoming the influence of suppressive cells are a few of the main obstacles that cell therapy must address to achieve success in the setting of solid malignancies.

As the field continues to move forward with the goal of advancing transformative therapies that can bring new hope to patients with cancer, it is imperative that all these requirements discussed herein converge to support successful therapy development and implementation. Decisions made early in the research and development phase will benefit from considerations related to cost of goods, manufacturing and scalability, and product release requirements. Ensuring that a cell therapy program will have a long and prolific life cycle will depend largely on building a solid multidisciplinary team structure.

In sum, implementing the appropriate platform will considerably affect regulatory approval, product commercialization and longevity, and reimbursement eligibility and will ultimately influence the potential of new discoveries to impact every patient, every day, everywhere.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Xin Yu J, Hubbard-Lucey VM, Tang J. Immuno-oncology drug development goes global. Nat Rev Drug Discov. 2019;18:899-900.
2. Xin Yu J, Hubbard-Lucey VM, Tang J. The global pipeline of cell therapies for cancer. Nat Rev Drug Discov. 2019;18:821-822.
3. Mullard A. FDA approves fourth CAR-T cell therapy. Nat Rev Drug Discov. 2021;20:166.
4. Wall DA, Krueger J. Chimeric antigen receptor T cell therapy comes to clinical practice. Curr Oncol. 2020;27(Suppl 2):S115-S123.
5. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377:2531-2544.
6. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med. 2017;377:2545-2554.
7. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378:439-448.
8. Schuster SJ, Bishop MR, Tam CS, et al; JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380:45-56.
9. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2020;382:1331-1342.
10. Laskowski T, Rezvani K. Adoptive cell therapy: Living drugs against cancer. J Exp Med. 2020;217:e20200377.
11. Campbell A, Brieva T, Raviv L, et al. Concise review: process development considerations for cell therapy. Stem Cells Transl Med. 2015;4:1155-1163.
12. Hanley PJ, Lowdell M. Advancing cellular therapies towards standard of care: a focus on testing of cellular therapy products. Cytotherapy. 2019;21:275-277.
13. Harrison RP, Zylberberg E, Ellison S, et al. Chimeric antigen receptor-T cell therapy manufacturing: modelling the effect of offshore production on aggregate cost of goods. Cytotherapy. 2019;21:224-233.
14. Boyiadzis MM, Dhodapkar MV, Brentjens RJ, et al. Chimeric antigen receptor (CAR) T therapies for the treatment of hematologic malignancies: clinical perspective and significance. J Immunother Cancer. 2018;6:137.
15. Frigault MJ, Maus MV. State of the art in CAR T cell therapy for CD19+ B cell malignancies. J Clin Invest. 2020;130:1586-1594.
16. Leick MB, Maus MV, Frigault MJ. Clinical Perspective: treatment of aggressive B cell lymphomas with FDA-approved CAR-T cell therapies. Mol Ther. 2021;29:433-441.
17. Daniyan AF, Brentjens RJ. CARs of the future. Am J Hematol. 2019;94(S1):S55-S58.
18. Rafiq S, Hackett CS, Brentjens RJ. Engineering strategies to overcome the current roadblocks in CAR T cell therapy. Nat Rev Clin Oncol. 2020;17:147-167.

19. Osborn MJ, Webber BR, Knipping F, et al. Evaluation of TCR gene editing achieved by TALENs, CRISPR/Cas9, and megaTAL nucleases. Mol Ther. 2016; 24:570-581.

20. Torikai H, Reik A, Liu PQ, et al. A foundation for universal T-cell based immunotherapy: T cells engineered to express a CD19-specific chimeric-antigen-receptor and eliminate expression of endogenous TCR. Blood. 2012;119:5697-5705.

21. Ajina A, Maher J. Strategies to address chimeric antigen receptor tonic signaling. Mol Cancer Ther. 2018;17:1795-1815.

22. Qasim W, Zhan H, Samarasinghe S, et al. Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells. Sci Transl Med. 2017; 9:eaaj2013.

23. Benjamin R, Graham C, Yallop D, et al; UCART19 Group. Genome-edited, donor-derived allogeneic anti-CD19 chimeric antigen receptor T cells in paediatric and adult B-cell acute lymphoblastic leukaemia: results of two phase 1 studies. Lancet. 2020;396:1885-1894.

24. Poirot L, Philip B, Schiffer-Mannioui C, et al. Multiplex Genome-Edited T-cell Manufacturing Platform for "Off-the-Shelf" Adoptive T-cell Immunotherapies. Cancer Res. 2015;75:3853-3864.

25. Xie G, Dong H, Liang Y, et al. CAR-NK cells: a promising cellular immunotherapy for cancer. EBioMedicine. 2020;59:102975.

26. Chiorean EG, Miller JS. The biology of natural killer cells and implications for therapy of human disease. J Hematother Stem Cell Res. 2001;10:451-463.

27. Liu E, Tong Y, Dotti G, et al. Cord blood NK cells engineered to express IL-15 and a CD19-targeted CAR show long-term persistence and potent antitumor activity. Leukemia. 2018;32:520-531.

28. Heczey A, Liu D, Tian G, et al. Invariant NKT cells with chimeric antigen receptor provide a novel platform for safe and effective cancer immunotherapy. Blood. 2014;124:2824-2833.

29. Zhu H, Lai YS, Li Y, et al. Concise review: human pluripotent stem cells to produce cell-based cancer immunotherapy. Stem Cells. 2018;36:134-145.

30. Swift BE, Williams BA, Kosaka Y, et al. Natural killer cell lines preferentially kill clonogenic multiple myeloma cells and decrease myeloma engraftment in a bioluminescent xenograft mouse model. Haematologica. 2012;97:1020-1028.

31. Williams BA, Wang XH, Leyton JV, et al. CD16$^+$NK-92 and anti-CD123 monoclonal antibody prolongs survival in primary human acute myeloid leukemia xenografted mice. Haematologica. 2018;103:1720-1729.

32. Knorr DA, Ni Z, Hermanson D, et al. Clinical-scale derivation of natural killer cells from human pluripotent stem cells for cancer therapy. Stem Cells Transl Med. 2013;2:274-283.

33. Li Y, Hermanson DL, Moriarity BS, et al. Human iPSC-derived natural killer cells engineered with chimeric antigen receptors enhance anti-tumor activity. Cell Stem Cell. 2018;23:181-192.e5.

34. Goodridge JP, et al. FT596: translation of first-of-kind multi-antigen targeted off-the-shelf CAR-NK cell with engineered persistence for the treatment of B cell malignancies. Blood. 2019;134(suppl 1):134.

35. Tang X, Yang L, Li Z, et al. First-in-man clinical trial of CAR NK-92 cells: safety test of CD33-CAR NK-92 cells in patients with relapsed and refractory acute myeloid leukemia. Am J Cancer Res. 2018;8:1083-1089.

36. Shah N, Li L, McCarty J, et al. Phase I study of cord blood-derived natural killer cells combined with autologous stem cell transplantation in multiple myeloma. Br J Haematol. 2017;177:457-466.

37. Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. N Engl J Med. 2020;382:545-553.

38. Ramakrishna S, Barsan V, Mackall C. Prospects and challenges for use of CAR T cell therapies in solid tumors. Expert Opin Biol Ther. 2020;20:503-516.

39. Labani-Motlagh A, Ashja-Mahdavi M, Loskog A. The tumor microenvironment: a milieu hindering and obstructing antitumor immune responses. Front Immunol. 2020;11:940.

Immune-Based Cancer Treatment: Addressing Disparities in Access and Outcomes

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overview

Avoidable differences in the care and outcomes of patients with cancer (i.e., cancer care disparities) emerge or worsen with discoveries of new, more effective approaches to cancer diagnosis and treatment. The rapidly expanding use of immunotherapy for many different cancers across the spectrum from late to early stages has, predictably, been followed by emerging evidence of disparities in access to these highly effective but expensive treatments. The danger that these new treatments will further widen preexisting cancer care and outcome disparities requires urgent corrective intervention. Using a multilevel etiologic framework that categorizes the targets of intervention at the individual, provider, health care system, and social policy levels, we discuss options for a comprehensive approach to prevent and, where necessary, eliminate disparities in access to the clinical trials that are defining the optimal use of immunotherapy for cancer, as well as its safe use in routine care among appropriately diverse populations. We make the case that, contrary to the traditional focus on the individual level in descriptive reports of health care disparities, there is sequentially greater leverage at the provider, health care system, and social policy levels to overcome the challenge of cancer care and outcomes disparities, including access to immunotherapy. We also cite examples of effective government-sponsored and policy-level interventions, such as the National Cancer Institute Minority-Underserved Community Oncology Research Program and the Affordable Care Act, that have expanded clinical trial access and access to high-quality cancer care in general.

Avoidable differences in the quality and outcomes of health care, or health care disparities, prevail across the cancer care continuum, from prevention and incidence through diagnosis, staging, and treatment and continuing to survivorship care and outcomes.[1-7] Health care disparities emerge or widen with the advent of new therapeutic approaches to cancer, such as immunotherapy, and thereby blunt the population-level impact of innovation.[8] Indeed, even if proximal causes of disparate access and outcomes are temporarily resolved, the persistent lack of access to economic and medical resources experienced by certain demographic or socioeconomic subpopulations will often reestablish existing disparities over the long term.[8]

Over the years, the evaluation of health care disparities has primarily focused on individual demographic and socioeconomic characteristics.[1-3,5,7,9-11] However, such attributes are not readily modifiable, which limits the opportunity for meaningful intervention. For instance, the condition of poverty for individuals of any race or ethnicity may persist for generations, in contradiction to the vision of upward mobility in the United States.[12] Alternatively, a non-Hispanic Black man can do little to change the disadvantage associated with his race. Multiple studies have documented a lower enrollment of non-Hispanic Black patients in clinical trials, leading to the perception that they are less inclined to participate in clinical trials.[13-15] However, careful investigation comparing different barriers and their effects on decision-making with regard to clinical trial participation has demonstrated that personal preference may be the least relevant factor affecting enrollment in cancer trials.[16] The idea that those experiencing cancer care disparities are somehow unwilling to seek high-quality care is a myth.[14,17-20]

Recently, modifiable factors such as provider-, organizational-, and societal-level barriers have been recognized as greater constraints, and thus potential targets, in policy implementation with a community-level scope.[11,16,21-26] To overcome these challenges, a deeper understanding of these drivers of health care disparities is required. Conceptually, the potential for corrective intervention increases directly from the individual to provider, organizational, and social policy levels as the number of intervention targets decreases and the scope of their impact increases in that sequential order.

Overall, individual-level barriers intersect adversely with provider-, institutional-, and societal-level drivers.

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PRACTICAL APPLICATIONS

- Cancer care disparities emerge or worsen with discoveries of new, improved approaches to care.
- Immune checkpoint inhibitor therapy, a new, highly effective, potentially toxic, and expensive therapy still under active clinical trial investigation, bears all the hallmarks of a treatment highly susceptible to access and outcome disparities.
- Understanding disparities is important to preventing and eliminating them; such understanding must be categorized with intervention targets in mind at the individual, provider, health care system, and societal/policy levels.
- Potential race- and income-based differences in access to efficacy and toxicity of immune checkpoint inhibitor therapy require careful investigation.
- This requires active involvement of the full spectrum of patients with cancer in the clinical trials testing immune checkpoint inhibitor therapy.

For example, the providers, clinics, and hospitals that predominantly care for disadvantaged groups tend to lack the infrastructure and human and organizational resources to provide access to clinical research or high-quality care.[27-30] In a glaring example, as of January 2021, the 12 U.S. states that have not adopted the Medicaid expansion opportunity provided under the Affordable Care Act were also some of the most socioeconomically challenged states in the country, with some of the highest per-capita cancer incidence and mortality rates, the most fragile health care infrastructure, and the highest proportions of socioeconomically and demographically disadvantaged residents.[31]

EFFECT OF EMERGENT THERAPEUTICS ON HEALTH CARE DISPARITIES

The dynamic evolution in knowledge of cancer biology has resulted in better prevention, diagnostic, and treatment approaches. Although these discoveries could benefit everyone, differences in access may widen preexisting cancer care and outcome gaps, leading to negative social consequences.[32-34] Therefore, there is an urgent need to transition from describing patterns and associations to implementing and evaluating interventions to mitigate avoidable differences between individuals of different socioeconomic or demographic groups.[23-25,32-35] In the absence of active interventions, health care disparities will continue to worsen, reflecting broader social and economic dynamics.

New treatments, such as immunotherapy, emerge from clinical trials. Disparity in access to cancer clinical trials is an enduring, widely described phenomenon. For example, although the per-capita incidence of lung cancer is higher in non-Hispanic Black populations, only 4.5% of participants in the National Lung Screening Trial were from this racial/ethnic group.[36] Similarly, a recent study demonstrated that non-Hispanic Black patients comprised only 3% of enrollments in pivotal drug trials that led to U.S. Food and Drug Administration approvals, whereas they represent 12% of the same cancers in the U.S. population of patients with cancer.[14] As a practical illustration, only 2% of enrollees in PACIFIC, the trial that established consolidation durvalumab as the standard of care for unresectable stage III non–small cell lung cancer, were non-Hispanic Black patients.[37] This glaring disproportionality is likely influenced by the tendency for industry-initiated trials to recruit patients from large academic centers, in and outside the United States. In contrast, investigator-initiated trials emphasize outreach to both academic and community centers, allowing the participation of sites serving underrepresented populations. Consequently, these trials are more representative of diverse patient groups, although still not fully representative of the real-word racial/ethnic distribution. A comparison of enrollments in similar types of trials over the same time period showed that 9% of enrollees in trials sponsored by the National Cancer Institute were non-Hispanic Black people, compared with 3% in industry-sponsored trials.[14]

In view of these, it will take a systematic and concerted effort to detect, understand, reduce, and ultimately eliminate the multilevel barriers to equal and safe access to highly effective and promising new therapies. Implementing interventions to achieve this aim is greatly required, not only to eliminate emerging disparities in cancer care, but also to allow a better understanding of evaluation, efficacy, adverse effects, and follow-up with regard to new therapeutic approaches in the full spectrum of candidates.

HEALTH CARE DISPARITIES IN THE ERA OF IMMUNOTHERAPY

Treatment with immune checkpoint inhibitors has ushered in a sea change in the management of many different cancers.[37-50] This class of drugs is still new, and the indications for their use are rapidly expanding and remain under intense investigation in clinical trials across all of oncology, as do their toxicity profiles and management of their adverse effects and complications.[51-53] As with all new cancer therapeutics, immunotherapy is exorbitantly priced. In 2015, it was estimated that it cost the United States $174 billion.[54] As clinical trials expand the indications for

immunotherapy drugs in multiple cancer types, further broadening their use, the cost impact at individual and societal levels may continue to rise. It is therefore not surprising that strong evidence already exists for avoidable differences in access to immunotherapy, within the context of routine clinical care and clinical trials.[55-57]

Before the approval and widespread use of immune checkpoint inhibitors, disparities by socioeconomic and demographic variables in cancer outcomes were already well established.[58,59] A seminal article in 2017 highlighted how individuals living in rural areas had much worse outcomes from cancer than their urban counterparts.[9] Worse outcomes for patients with cancer with limited insurance or from areas with high levels of socioeconomic deprivation have long been observed,[60-62] and they have even persisted when patients have had uniform access to protocol-guided care in clinical trials.[63,64] With respect to racial/ethnic disparities, worse survival rates were identified for non-Hispanic Black patients with melanoma (HR, 3.0; 95% CI, 2.7–3.3) and renal cell carcinoma (HR, 1.10; 95% CI, 1.04–1.15), whereas better survival rates were observed in Asian patients compared with non-Hispanic White patients with non–small cell lung cancer (HR, 0.85; 95% CI, 0.76–0.95).[59,65,66] During the last decade, the exponential increase in the use of immune checkpoint inhibitors has led to a decrease in cancer-related mortality; however, population-based cancer registry data suggest that there has been a disproportionate benefit mostly favoring non-Hispanic White patients, broadening the survival gap with minority populations.[59,67] This alarming trend was confirmed in ethnic minority groups with localized melanoma; the discrepancy between non-Hispanic White and ethnic minority patients increased significantly after the approval of immune checkpoint inhibitors.[58,65] Interestingly, an opposite trend was described in patients with lung cancer; Asian patients had increased relative survival compared with non-Hispanic White patients and other racial/ethnic groups.[68]

For many years, inequities were considered to result from a complex interaction of biologic (clinical, pathologic, and molecular features) and social (beliefs/attitudes, access to care, personal motivation, and family support) factors that differed among racial/ethnic groups. For example, a greater burden of aggressive tumor molecular subtypes such as triple-negative breast cancer or *KRAS*-mutant colorectal cancer is seen in non-Hispanic Black patients compared with non-Hispanic White patients, whereas higher frequencies of EGFR (epidermal growth factor receptor) mutations are reported in Asian patients compared with non-Hispanic White patients with non–small cell lung cancer.[69-71] Furthermore, lower rates of therapeutic interventions and longer delays in treatment initiation have been reported in non-Hispanic Black patients compared with non-Hispanic White patients.[1,2,17,19,28,72,73] Nevertheless, survival disparities have persisted after adjusting for these variables, which suggests that additional factors, such as racial differences in immune profiles, might play a role in this inequity.[65]

Because current U.S. Food and Drug Administration–approved immune checkpoint inhibitors exert their activity by blocking interactions between tumor cells and host immune cells in the tumor microenvironment, it seems plausible that distinct immune profiles among racial/ethnic groups could translate to unequal treatment response rates. Although studies have reported no differences in tumor genomic profiles and PD-L1 expression in breast, colorectal, or lung tumors, substantial differences in the composition of immune cells in the tumor microenvironment have been reported.[74] For instance, breast cancer tumors from non-Hispanic Black individuals displayed a stronger overall immune presence, with a stronger $CD4^+$/B-cell response and a more exhausted $CD8^+$ T-cell profile, and had higher expression of inhibitory receptors such as PD-1, LAG-3, and CTLA-4 than those from non-Hispanic White patients, whereas similar $CD8^+$ T-cell infiltration was reported among the groups.[75] In head and neck squamous cell cancer, lower levels of $CD8^+$ cells were seen in non-Hispanic Black patients compared with non-Hispanic White patients.[76] Conversely, proinflammatory genes were overexpressed in non-Hispanic Black patients compared with non-Hispanic White patients with prostate cancer, which should theoretically translate to better responses to immunotherapy.[77] Furthermore, considerable racial differences in tumor mutational burden, a recognized predictive factor, have been reported in five cancer types (urothelial, non–small cell lung, cervical, clear cell, and papillary kidney cancers).[78]

In addition, socioeconomic inequalities affecting biomarker evaluation and access to immunotherapy have been identified as potential factors that could cause or magnify cancer outcome differences among demographic groups. In this regard, a National Cancer Database analysis revealed a lower likelihood of receiving immunotherapy in patients age 65 and older (odds ratio [OR], 0.93), non-Hispanic Black patients (OR, 0.87), individuals with worse performance status (OR, 0.74), and uninsured patients (OR, 0.85), whereas those with private insurance (OR, 1.29) or Medicare (OR, 1.18) were more likely to receive treatment compared with patients with Medicaid (OR, 1.0).[79] Interestingly, an analysis stratified by insurance type revealed that the odds of being treated with immunotherapy remained lower for non-Hispanic Black patients compared with non-Hispanic White patients, even for those with Medicare or private insurance, which suggests that beliefs/attitudes toward treatment among racial minority groups might also play a relevant role.[79]

Currently, data on predictive biomarkers, dosing, efficacy, and adverse events to evaluate whether differences exist

between racial/ethnic groups are insufficient, mainly because of the under-representation of ethnic/racial minority groups in randomized clinical trials.[80] As a result, systematic reviews and meta-analyses have been performed to assess racial disparities in the pharmacokinetics, response, and adverse effects of immunotherapy.[81-83] Nevertheless, data are extremely limited, and clinical decisions for ethnic/racial minority groups are largely based on data extrapolated from non-Hispanic White populations. Regarding pharmacokinetics, two reports indicated no differences in clearance and predicted exposure between Asian and non-Asian patients in secondary analyses among those treated with nivolumab for non–small cell lung cancer/nasopharyngeal carcinoma and gastric/gastroesophageal junction carcinoma, respectively.[84,85]

In relation to variance in treatment response, a meta-analysis that evaluated the association of age, performance status, and race in 21 randomized clinical trials comparing immune checkpoint inhibitors with standard of care did not find a major difference in response among races, with the important limitation that only four randomized controlled trials had data available on race and that available data were gathered from subgroup analysis, susceptible to selection bias.[82] In contrast, a secondary analysis of two trials evaluating atezolizumab in patients with non–small cell lung cancer identified race as an independent prognostic factor using propensity score matching for clinicopathologic features.[68] Finally, differences in immune-related adverse events among racial/ethnic groups have been reported in single-center studies, although with discrepant results. A study conducted in a predominantly non-Hispanic White population (90% of approximately 500 patients with cancer) did not reveal any differences in immune-related adverse events,[86] whereas a report of 2,447 patients with melanoma, 90% of whom were non-Hispanic White, described 50% lower odds of immune-related adverse events in non-Hispanic White patients compared with non-Hispanic Black patients.[87] Another study involving 300 patients with solid tumors reported a higher frequency of immune-related adverse events in non-Hispanic White patients than non-Hispanic Black patients (60.4% vs. 30.8%).[88]

BARRIERS TO EQUAL ACCESS TO IMMUNOTHERAPY

Timely access to new and effective cancer treatments is essential to reducing suffering and death resulting from cancer. However, several barriers to accessing cancer care exist at various levels of care delivery, as documented by the National Academy of Medicine (formerly the Institute of Medicine) in its landmark report "Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care."[89] In the case of immunotherapy, there is accumulating evidence documenting barriers in access to immunotherapy from large population- or hospital-based data, cancer registries, and meta-analyses.[55-57,90-93] This constellation of factors can be summarized as patient-, provider-, health care system–, and societal/policy-level factors.

Patient-Level Factors

Clinical factors such as comorbid conditions and poor performance status may be appropriate individual-level barriers to accessing immunotherapy, in or out of clinical trials. Patient-level factors that may inappropriately affect access to immunotherapy include nonmodifiable (e.g., age, race, and ethnicity) and potentially modifiable (e.g., socioeconomic status and behavior) features. For instance, the likelihood of not receiving recommended immunotherapy is disproportionately higher in older patients and racial/ethnic minoritypopulations.[91] One potential explanation for such treatment differences may be under-representation of older patients in clinical trials, which subsequently may affect the decision to treat these patients in real-world practice.[92,93] This happens despite studies showing that older patients experience toxicity profiles and benefits similar to those experienced by younger patients, after adjusting for differences in comorbid conditions.[94-96]

Similarly, the under-representation of racial/ethnic minority populations has been attributed to an unwillingness of this population to participate in trials. The fact that historically disadvantaged patients are less trusting of clinical research is well founded, given the tragic history of medical experimentation in the United States, exemplified by the infamous Tuskegee syphilis study.[97,98] However, most patients will readily participate in a trial, as evidenced in a recent systematic review and meta-analysis, which showed that more than half of patients offered a trial by their physician agreed to participate. Critically, the study also showed that non-Hispanic Black, Hispanic, and Asian patients were willing to participate at rates on par with or even higher than non-Hispanic White patients.[99]

Regarding socioeconomic factors, major modifiable barriers to accessing cancer treatment and participation in clinical trials include lack of or inadequate health insurance, low income, low education level, and unemployment or underemployment.[100-102] All of these have been associated with lower likelihood of receiving novel therapies such as immunotherapy in several studies. A systematic review and meta-analysis concluded that patients with low socioeconomic status had 16% lower odds of receiving immunotherapy compared with their counterparts with high socioeconomic status. Additional factors such as language or communication gaps and beliefs/attitudes about clinical trials and the health care system may also hinder timely access to cancer care. This may be accentuated by the novelty of these treatments, which has the effect of exacerbating the lack of updated knowledge and understanding among providers and patients.

Provider-Level Factors

Provider-related factors can affect the use of guideline-recommended immunotherapy drugs as well as participation in clinical trials. These include features such as age, sex, race, knowledge, training, skillsets, year of graduation, specialty, certification status, beliefs, and attitudes.[102-105] For instance, a survey of U.S. oncologists treating patients with lung cancer showed differences in knowledge regarding immunotherapy by provider age or year of graduation, whereas another study concluded that oncologists were less likely to offer guideline-recommended biomarker tests, cancer treatment, or clinical trials to their non-Hispanic Black or elderly patients with cancer.[106-108] All these negatively affect interactions with patients and their perception of recommended treatments.[105]

Health Care System–Level Factors

As the complexity of care delivery increases, the probability of missing or delaying effective treatments becomes more dependent on organizational factors such as geographic location, referral and appointment systems, availability of culturally competent services, health care worker diversity, affiliation with research or academic health care systems, and quality of physical infrastructure. Institutional structural characteristics (e.g., community cancer or academic cancer center designation, case volume, and teaching status) and processes (e.g., reimbursement contracts, scheduling methods, hours of operation, and availability of language options) have been shown to influence patients' access to high-quality care, including immunotherapy.[91,109-112] With regard to accessing clinical trials, careful evaluation of multilevel barriers has revealed that three of four patients with cancer are unable to enroll in clinical trials because the institutions where they seek care do not have appropriate clinical trials available for them or, when available, the eligibility criteria prevent enrollment (Fig. 1).[16,26,99]

Societal-Level Factors

Socioeconomic and health care policies influence access to health care, especially to new and expensive treatments such as personalized cancer treatments and immunotherapy. In a predominantly employment-based health insurance system, a high level of unemployment adversely affects access to employer-provided insurance. A high proportion of uninsured or underinsured individuals in a population adversely affects access to care and overall quality of care in the whole population.[113-120]

POTENTIAL INTERVENTIONS TO REDUCE ACCESS BARRIERS TO IMMUNOTHERAPY

Reducing barriers to equal access to immunotherapy to equitably provide patients with the opportunity for longer and better-quality survival will require the design and implementation of effective and integrated multilevel interventions (Table 1).

Patient-Level Interventions

Access to health insurance coverage increases the likelihood of using services across the cancer care continuum, including participation in clinical trials.[121-123] However, health insurance coverage alone does not guarantee full access to cancer treatments or clinical trials. Improving patient literacy using educational methods and through patient-provider communication about cancer, the health care system, treatment options, the cost of treatment, the importance of adherence to treatment, and potential adverse effects, by improving shared decision-making, can increase the use of recommended cancer treatments such as immunotherapy and participation in clinical trials.[124] Patients who had cost discussions with their oncologist believed it helped them reduce their expenses.[117]

Provider-Level Interventions

Improved provider education on fast-changing cancer care standards and the development of appropriate, effective, and culturally competent communication skills for a diverse patient population are much needed.[125] Systematic methods to educate providers about recent advances in cancer care and changes in evidence-based guidelines for treatment could improve quality of care and use of immunotherapy. Implicit bias training may improve patient-provider communication, use of care, and participation in clinical trials.[126,127] Specifically, provider education about the very existence of health care disparities attributable to provider bias and misconception is urgently needed.

Health Care System–Level Interventions

Workforce development programs such as recruitment of a diverse staff representative of the general population, patient-provider communication training, clinical trial enrollment training, and certification will facilitate access to immunotherapy and clinical trials.[128] Establishing multidisciplinary team–based cancer care delivery and care coordination methods that can streamline patient referrals, cancer research, and clinical trials may also improve access to these therapies and outcomes.[129] System-based interventions targeting racial disparities may prevent the emergence of disparities and reduce or eliminate existing disparities in immunotherapy use.[130] High clinical trial participation can also be achieved by diversifying trial sites across geographic areas and types of practices or communities and by targeting financial barriers (e.g., introducing payment waiver policies), insurance coverage adjustment policies, logistic concerns, and resource constraints that patients and clinicians encounter during clinical trial enrollment and retention.[124,131] Various initiatives to increase clinical trial participation of racial/ethnic minority

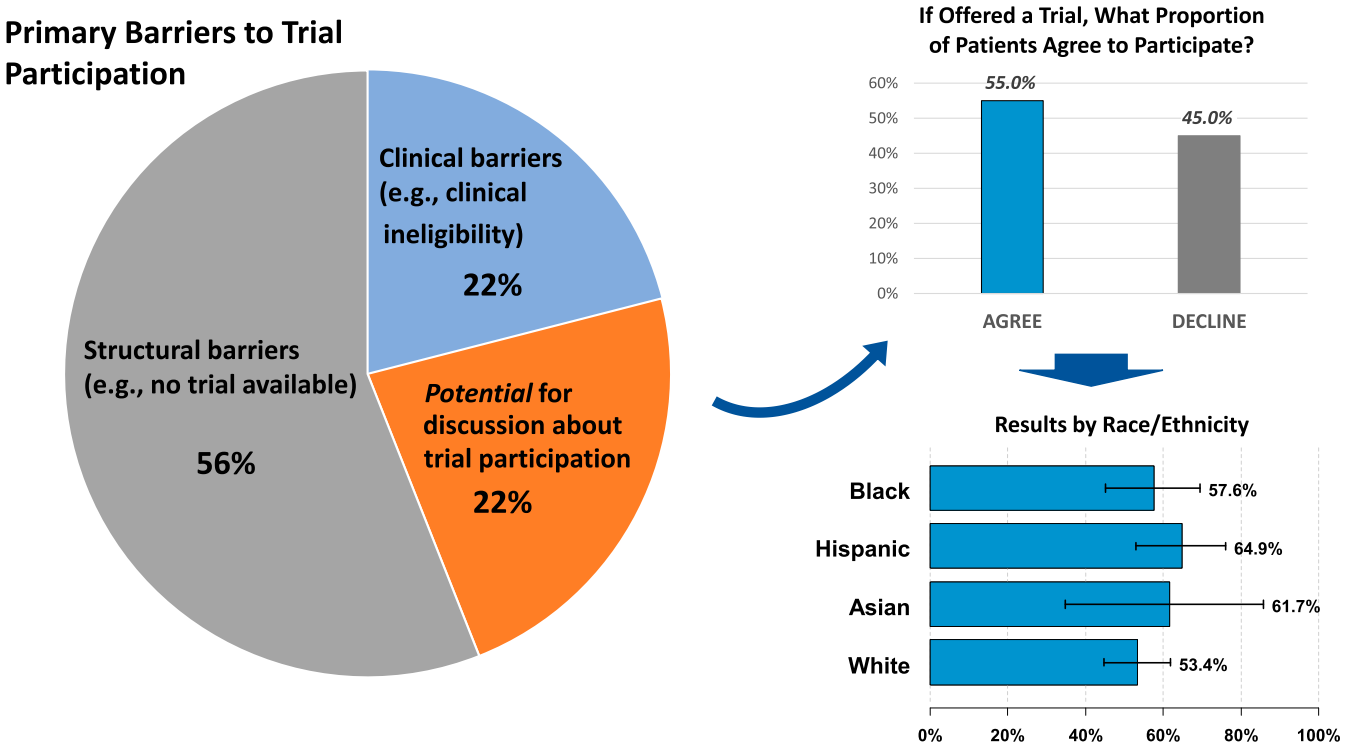

FIGURE 1. Primary Barriers to Trial Participation[16,99]

populations, adolescents and young adults, and older patients will also translate to better access to new and effective immunotherapies.[126]

The National Cancer Institute Community Oncology Research Program (NCORP) Minority-Underserved program is one such national effort to open up access to clinical research to populations that have traditionally been locked out. For example, 42% of all enrollees in the biomarker-driven trial NCI-MATCH were from Community Oncology Research Program sites, and, consequently, 20% of patients enrolled and 18% of those treated in the trial belonged to racial minority groups; 38.6% of enrollees in ALCHEMIST were from Community Oncology Research Program institutions; and 36% of enrollees in the Lung-MAP trial were from Community Oncology Research Program institutions (Worta McCaskill-Stevens, personal communication, January 23, 2021). The success of the National Cancer Institute Community Oncology Research Program Minority-Underserved program in recruiting high proportions of such populations to complicated biomarker-driven trials and clinical trials of immunotherapy illustrates how appropriate societal-level attention to the provider- and organizational-level drivers of cancer care disparities can be extremely effective.

Societal-Level Interventions

Reduction or elimination of health disparities in general has been identified as a major global public health objective.[132] Multipronged approaches involving diverse and critical sectors of society at global, national, and local levels will improve access to new and effective immunotherapies.[128] Collaborative partnerships among stakeholders across nongovernmental organizations, governments, providers, the pharmaceutical industry, and patients will reduce or eliminate barriers such as geographic and cost-related barriers and will improve access to effective cancer therapeutics. Global and national strategies for the production and distribution of immunotherapy drugs in collaboration with the pharmaceutical industry can facilitate equitable access to these essential drugs. For example, including new and effective immunotherapy drugs on the World Health Organization Model List of Essential Medicines can influence stakeholders to make these drugs available globally, stimulate the entry of new manufacturers, and shape market forces to improve affordability.[133,134]

National policies targeting health insurance coverage, cost reduction, financial assistance, and patient navigation systems are important steps in the right direction. Policy makers and the U.S. Congress can greatly influence the availability of cheaper alternatives by encouraging the rapid approval of generic and/or biosimilar drugs. Moreover, laws to prevent or discourage the so-called evergreening of lifesaving pharmaceuticals can be enacted. Policies to address the high prices of new cancer drugs, such as price negotiations between countries and drug makers, can

TABLE 1. Multilevel Examples of Barriers and Potential Solutions to the Problem of Poor Access to Immunotherapy

Barrier	Solution
Patient Level	
Lack of data on minority groups in clinical trials	Educate patients, caregivers, and their influencing network on the value of clinical trial participation (the best treatment is a clinical trial); simplify and demystify the clinical trial enrollment process for patients and caregivers
Minority groups have lower economic profile	End systemic racism; provide economic opportunities
Language barriers and lack of interpretation services	Provide interpreter services and education materials in multiple languages
Lack of adequate health coverage	Provide safety nets for low-income groups and access to health care
Rurality and geographic disadvantage	Improve public transportation services; promote telehealth services; leverage information technology to expand patient-level access to care
Provider Level	
Inability to keep up with latest in diagnostics and therapeutics/CME	Provide effective educational opportunities and medical literacy, especially for those focused on care of minority and other underserved patients
Implicit bias among providers	Educational programs and bias avoidance
Disinclination to provide clinical trials	Incentivize providers to regard clinical trials as a key component of routine care delivery (the best treatment is a clinical trial)
Health Care System–Level	
Excessively stringent criteria for trial enrolment	Recalibrate clinical trial eligibility to promote access while maintaining patient safety and scientific integrity; promote enrollment of clinical trial populations that resemble real-world care delivery populations
Unfavorable geographic location, such as in rural areas	Facilitate transportation and expand trial sites
Absence of clinical trials infrastructure	Incentivize health care systems to provide access to clinical trials as a fundamental part of cancer care delivery (the best treatment is a clinical trial)
Societal/Policy Level	
High cost of immunotherapy	Facilitate patient support programs
	Lower cost of drugs; use economies of scale to lower drug costs in contracts
	Policy changes at levels of legislatures and executive branches
Employer-sponsored health insurance limits coverage for unemployed and underemployed	Increase access to government-sponsored health coverage, such as the Medicaid expansion provision of the Affordable Care Act

Abbreviation: CME, continuing medical education.

enable countries to improve access to these new drugs.[131] Changes in oncology payment models to reward delivery of desired outcomes, and the processes that lead to them, such as the establishment of electronic health record systems, multidisciplinary decision-making, and participation in research activities, may improve access to immunotherapy. Designing and implementing systems for patient navigation, transportation assistance, accommodation (e.g., the American Cancer Society Hope Lodge), and assistance with physical and financial navigation through complex and expensive cancer care delivery systems may improve access to immunotherapy.[135]

Additional interventions should focus on reducing out-of-pocket costs and improving coverage for cancer therapies and clinical trials, as intended by some provisions of the Affordable Care Act. Provisions to close the Medicare Part D coverage gap and increase coverage through Medicaid expansion are intended to reduce out-of-pocket costs and improve access, although improvement is still required. Cost-containment initiatives such as the Health Care Innovation Award, the Oncology Care Model, and pharmaceutical assistance programs will also reduce the financial burden on patients and improve access to immunotherapy.

Access to clinical trials can be improved by eliminating unnecessarily restrictive clinical trial eligibility criteria, such as the ongoing collaboration between ASCO, Friends of Cancer Research, and the U.S. Food and Drug Administration to modernize clinical trial eligibility criteria.[136-142]

Wide adoption of these criteria will make it more feasible to promote attainment of specific targets for opening clinical access to underserved populations that can be set forth by the pharmaceutical industry, contract research organizations, the U.S. Food and Drug Administration, and the National Cancer Institute.

CONCLUSION

New and effective immunotherapies are drastically improving cancer treatment outcomes, but multilevel barriers hinder their use across all population groups. To eliminate access barriers to immunotherapy, creating heightened awareness among stakeholders must be a high priority. This requires high-quality and preferably real-time and real-world cancer care data. Studies of disparities in the safe and effective use of immunotherapy must move past traditional descriptive research to emphasize understanding that leads to implementable solutions to overcome (i.e., prevent, reduce, and eliminate) such disparities. This understanding must embrace the multilevel etiology of the problem, with emphasis on the relative impact at the various levels. The dual challenge to society is to pull the levers with which to eliminate disparities in access to clinical trials, thereby promoting discovery in externally valid populations and promoting safe, equitable access to proven treatments such as immunotherapy for the full spectrum of patients with cancer who stand to benefit from them.

Social policies, such as the Affordable Care Act, which has expanded access to Medicaid for low-income groups, and the Clinical Treatment Act, which mandates Medicaid coverage for the routine care costs of cancer clinical trial participation, are significantly more likely to improve population-level outcomes and eliminate care and outcome disparities than interventions at the individual patient level.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Shavers VL, Brown ML. Racial and ethnic disparities in the receipt of cancer treatment. J Natl Cancer Inst. 2002;94:334-357.
2. Lathan CS, Neville BA, Earle CC. The effect of race on invasive staging and surgery in non-small-cell lung cancer. J Clin Oncol. 2006;24:413-418.
3. Albano JD, Ward E, Jemal A, et al. Cancer mortality in the United States by education level and race. J Natl Cancer Inst. 2007;99:1384-1394.
4. Radley DC, Schoen C. Geographic variation in access to care--the relationship with quality. N Engl J Med. 2012;367:3-6.
5. Atkins GT, Kim T, Munson J. Residence in rural areas of the United States and lung cancer mortality. Disease incidence, treatment disparities, and stage-specific survival. Ann Am Thorac Soc. 2017;14:403-411.
6. Mokdad AH, Dwyer-Lindgren L, Fitzmaurice C, et al. Trends and patterns of disparities in cancer mortality among US counties, 1980-2014. JAMA. 2017;317:388-406.
7. Zahnd WE, James AS, Jenkins WD, et al. Rural-urban differences in cancer incidence and trends in the United States. Cancer Epidemiol Biomarkers Prev. 2018;27:1265-1274.
8. Link BG, Phelan J. Social conditions as fundamental causes of disease. J Health Soc Behav. 1995;(Spec No):80-94.
9. Henley SJ, Anderson RN, Thomas CC, et al. Invasive cancer incidence, 2004-2013, and deaths, 2006-2015, in nonmetropolitan and metropolitan counties - United States. MMWR Surveill Summ. 2017;66:1-13.
10. Thomas AA, Pearce A, O'Neill C, et al. Urban-rural differences in cancer-directed surgery and survival of patients with non-small cell lung cancer. J Epidemiol Community Health. 2017;71:468-474.
11. Unger JM, Moseley A, Symington B, et al. Geographic distribution and survival outcomes for rural patients with cancer treated in clinical trials. JAMA Netw Open. 2018;1:e181235.
12. Iceland J. Poverty in America: A Handbook (ed 3). Oakland: University of California Press; 2013.
13. Loree JM, Anand S, Dasari A, et al. Disparity of race reporting and representation in clinical trials leading to cancer drug approvals from 2008 to 2018. JAMA Oncol. 2019;5:e191870.

14. Unger JM, Hershman DL, Osarogiagbon RU, et al. Representativeness of black patients in cancer clinical trials sponsored by the National Cancer Institute compared with pharmaceutical companies. JNCI Cancer Spectr. 2020;4:pkaa034.
15. Moinpour CM, Atkinson JO, Thomas SM, et al. Minority recruitment in the prostate cancer prevention trial. Ann Epidemiol. 2000;10(suppl):S85-S91.
16. Unger JM, Vaidya R, Hershman DL, et al. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. J Natl Cancer Inst. 2019;111:245-255.
17. Lucas FL, Stukel TA, Morris AM, et al. Race and surgical mortality in the United States. Ann Surg. 2006;243:281-286.
18. Mulligan CR, Meram AD, Proctor CD, et al. Unlimited access to care: effect on racial disparity and prognostic factors in lung cancer. Cancer Epidemiol Biomarkers Prev. 2006;15:25-31.
19. Cykert S, Dilworth-Anderson P, Monroe MH, et al. Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. JAMA. 2010;303:2368-2376.
20. Coffman JM, Rhodes KV, Fix M, et al. Testing the validity of primary care physicians' self-reported acceptance of new patients by insurance status. Health Serv Res. 2016;51:1515-1532.
21. Weinick RM, Hasnain-Wynia R. Quality improvement efforts under health reform: how to ensure that they help reduce disparities--not increase them. Health Aff (Millwood). 2011;30:1837-1843.
22. Koh HK, Graham G, Glied SA. Reducing racial and ethnic disparities: the action plan from the department of health and human services. Health Aff (Millwood). 2011;30:1822-1829.
23. Vaccarella S, Lortet-Tieulent J, Saracci R, et al. Reducing social inequalities in cancer: setting priorities for research. CA Cancer J Clin. 2018;68:324-326.
24. Ray MA, Faris NR, Derrick A, et al. Rurality, stage-stratified use of treatment modalities, and survival of non-small cell lung cancer. Chest. 2020;158:787-796.
25. Osarogiagbon RU, Sineshaw HM, Lin CC, et al. Institutional-level differences in quality and outcomes of lung cancer resections in the United States. Chest. Epub 2020 Nov 20.
26. Minasian LM, Unger JM. What keeps patients out of clinical trials? JCO Oncol Pract. 2020;16:125-127.
27. Bach PB, Pham HH, Schrag D, et al. Primary care physicians who treat blacks and whites. N Engl J Med. 2004;351:575-584.
28. Liu JH, Zingmond DS, McGory ML, et al. Disparities in the utilization of high-volume hospitals for complex surgery. JAMA. 2006;296:1973-1980.
29. Bilimoria KY, Bentrem DJ, Stewart AK, et al. Comparison of commission on cancer-approved and -nonapproved hospitals in the United States: implications for studies that use the National Cancer Data Base. J Clin Oncol. 2009;27:4177-4181.
30. Lutfiyya MN, Sikka A, Mehta S, et al. Comparison of US accredited and non-accredited rural critical access hospitals. Int J Qual Health Care. 2009;21:112-118.
31. Kaiser Family Foundation. Status of state action on the Medicaid expansion decision. https://www.kff.org/health-reform/state-indicator/state-activity-around-expanding-medicaid-under-the-affordable-care-act/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D. Accessed January 24, 2021.
32. Kehl KL, Lathan CS, Johnson BE, et al. Race, poverty, and initial implementation of precision medicine for lung cancer. J Natl Cancer Inst. 2019;111:431-434.
33. Fedewa S, Silvestri GA. Reducing disparities in lung cancer screening: it's not so black and white. J Natl Cancer Inst. Epub 2021 Jan 5.
34. Rohatgi KW, Marx CM, Lewis-Thames MW, et al. Urban-rural disparities in access to low-dose computed tomography lung cancer screening in Missouri and Illinois. Prev Chronic Dis. 2020;17:E140.
35. Ford JG, Howerton MW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer. 2008;112:228-242.
36. Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395-409.
37. Antonia SJ, Villegas A, Daniel D, et al; PACIFIC Investigators. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017;377:1919-1929.
38. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16:375-384.
39. Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017;390:1853-1862.
40. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017;377:1345-1356.
41. Socinski MA, Jotte RM, Cappuzzo F, et al; IMpower150 Study Group. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378:2288-2301.
42. Kowanetz M, Zou W, Gettinger SN, et al. Differential regulation of PD-L1 expression by immune and tumor cells in NSCLC and the response to treatment with atezolizumab (anti-PD-L1). Proc Natl Acad Sci USA. 2018;115:E10119-E10126.
43. Schmid P, Adams S, Rugo HS, et al; IMpassion130 Trial Investigators. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379:2108-2121.
44. Reardon DA, Brandes AA, Omuro A, et al. Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: the CheckMate 143 phase 3 randomized clinical trial. JAMA Oncol. 2020;6:1003-1010.

45. Planchard D, Reinmuth N, Orlov S, et al. ARCTIC: durvalumab with or without tremelimumab as third-line or later treatment of metastatic non-small-cell lung cancer. Ann Oncol. 2020;31:609-618.

46. Paz-Ares L, Dvorkin M, Chen Y, et al; CASPIAN investigators. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394:1929-1939.

47. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2019; 381:1535-1546.

48. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med. 2019;381:432-443.

49. Cloughesy TF, Mochizuki AY, Orpilla JR, et al. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. Nat Med. 2019;25:477-486.

50. Yu Y, Lee NY. JAVELIN Head and Neck 100: a phase III trial of avelumab and chemoradiation for locally advanced head and neck cancer. Future Oncol. 2019; 15:687-694.

51. Dahiya DS, Wani F, Guidi JC, et al. Gastrointestinal adverse effects of immunotherapeutic agents: a systematic review. Gastroenterol Res. 2020;13:227-232.

52. Cao C, Guo A, Chen C, et al. Systematic review of neoadjuvant immunotherapy for patients with non-small cell lung cancer. Semin Thorac Cardiovasc Surg. Epub 2021 Jan 12.

53. Tian Y, Gao A, Wen Q, et al. Immune-related neurological toxicities of PD-1/PD-L1 inhibitors in cancer patients: a systematic review and meta-analysis. Front Immunol. 2020;11:595655.

54. Andrews A. Treating with checkpoint inhibitors-figure $1 million per patient. Am Health Drug Benefits. 2015;8:9.

55. Haque W, Verma V, Butler EB, et al. Racial and socioeconomic disparities in the delivery of immunotherapy for metastatic melanoma in the United States. J Immunother. 2019;42:228-235.

56. Krimphove MJ, Tully KH, Friedlander DF, et al. Adoption of immunotherapy in the community for patients diagnosed with metastatic melanoma. J Immunother Cancer. 2019;7:289.

57. O'Connor JM, Seidl-Rathkopf K, Torres AZ, et al. Disparities in the use of programmed death 1 immune checkpoint inhibitors. Oncologist. 2018;23:1388-1390.

58. Qian Y, Johannet P, Sawyers A, et al. The ongoing racial disparities in melanoma: an analysis of the Surveillance, Epidemiology, and End Results database (SEER) database (1975-2016). J Am Acad Dermatol. Epub 2020 Aug 27.

59. Rose TL, Deal AM, Krishnan B, et al. Racial disparities in survival among patients with advanced renal cell carcinoma in the targeted therapy era. Cancer. 2016; 122:2988-2995.

60. Ayanian JZ, Kohler BA, Abe T, et al. The relation between health insurance coverage and clinical outcomes among women with breast cancer. N Engl J Med. 1993;329:326-331.

61. Ward E, Halpern M, Schrag N, et al. Association of insurance with cancer care utilization and outcomes. CA Cancer J Clin. 2008;58:9-31.

62. Walker GV, Grant SR, Guadagnolo BA, et al. Disparities in stage at diagnosis, treatment, and survival in nonelderly adult patients with cancer according to insurance status. J Clin Oncol. 2014;32:3118-3125.

63. Unger JM, Blanke CD, LeBlanc M, et al. Association of patient demographic characteristics and insurance status with survival in cancer randomized clinical trials with positive findings. JAMA Netw Open. 2020;3:e203842.

64. Unger JM, Moseley AB, Cheung CA, et al. Persistent disparity: socioeconomic deprivation and cancer outcomes in patients treated in clinical trials. J Clin Oncol. Epub 2021 March 17.

65. Ward-Peterson M, Acuña JM, Alkhalifah MK, et al. Association between race/ethnicity and survival of melanoma patients in the United States over 3 decades: a secondary analysis of SEER data. Medicine (Baltimore). 2016;95:e3315.

66. Ou SH, Ziogas A, Zell JA. Asian ethnicity is a favorable prognostic factor for overall survival in non-small cell lung cancer (NSCLC) and is independent of smoking status. J Thorac Oncol. 2009;4:1083-1093.

67. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7-34.

68. Qian J, Nie W, Lu J, et al. Racial differences in characteristics and prognoses between Asian and white patients with nonsmall cell lung cancer receiving atezolizumab: an ancillary analysis of the POPLAR and OAK studies. Int J Cancer. 2020;146:3124-3133.

69. Prakash O, Hossain F, Danos D, et al. Racial disparities in triple negative breast cancer: a review of the role of biologic and non-biologic factors. Front Public Health. 2020;8:576964.

70. Staudacher JJ, Yazici C, Bul V, et al. Increased frequency of KRAS mutations in African Americans compared with Caucasians in sporadic colorectal cancer. Clin Transl Gastroenterol. 2017;8:e124.

71. Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol. 2014;9:154-162.

72. Acuña-Villaorduña AR, Lin J, Kim M, et al. Racial/ethnic disparities in early-onset colorectal cancer: implications for a racial/ethnic-specific screening strategy. Cancer Med. 2021;10:2080-2087.

73. Jones LA, Ferrans CE, Polite BN, et al. Examining racial disparities in colon cancer clinical delay in the Colon Cancer Patterns of Care in Chicago study. Ann Epidemiol. 2017;27:731-738.e1.

74. Mitchell KA, Zingone A, Toulabi L, et al. Comparative transcriptome profiling reveals coding and noncoding RNA differences in NSCLC from African Americans and European Americans. Clin Cancer Res. 2017;23:7412-7425.

75. Yao S, Cheng TD, Elkhanany A, et al. Breast tumor microenvironment in black women: a distinct signature of CD8+ T cell exhaustion. J Natl Cancer Inst. Epub 2021 Jan 5.

76. Chaudhary Sanjib, Dam Vi, Ganguly Koelina, et al. Differential mutation spectrum and immune landscape in African Americans versus Whites: A possible determinant to health disparity in head and neck cancer. Cancer Lett. 2020;492:44-53.

77. Awasthi S, Berglund A, Abraham-Miranda J, et al. Comparative genomics reveals distinct immune-oncologic pathways in African American men with prostate cancer. Clin Cancer Res. 2021;27:320-329.

78. Zhang W, Edwards A, Flemington EK, et al. Racial disparities in patient survival and tumor mutation burden, and the association between tumor mutation burden and cancer incidence rate. Sci Rep. 2017;7:13639.

79. Verma V, Haque W, Cushman TR, et al. Racial and insurance-related disparities in delivery of immunotherapy-type compounds in the United States. J Immunother. 2019;42:55-64.

80. Nazha B, Mishra M, Pentz R, et al. Enrollment of racial minorities in clinical trials: old problem assumes new urgency in the age of immunotherapy. Am Soc Clin Oncol Educ Book. 2019;39:3-10.

81. Peng L, Qin BD, Xiao K, et al. A meta-analysis comparing responses of Asian versus non-Asian cancer patients to PD-1 and PD-L1 inhibitor-based therapy. OncoImmunology. 2020;9:1781333.

82. Butaney M, Satkunasivam R, Goldberg H, et al. Analysis of heterogeneity in survival benefit of immunotherapy in oncology according to patient demographics and performance status: a systematic review and meta-analysis of overall survival data. Am J Clin Oncol. 2020;43:193-202.

83. Li L, Li G, Rao B, et al. Landscape of immune checkpoint inhibitor-related adverse events in Chinese population. Sci Rep. 2020;10:15567.

84. Zhang J, Cai J, Bello A, et al. Model-based population pharmacokinetic analysis of nivolumab in Chinese patients with previously treated advanced solid tumors, including non-small cell lung cancer. J Clin Pharmacol. 2019;59:1415-1424.

85. Osawa M, Hasegawa M, Bello A, et al. Population pharmacokinetics analysis of nivolumab in Asian and non-Asian patients with gastric and gastro-esophageal junction cancers. Cancer Chemother Pharmacol. 2019;83:705-715.

86. Bhandari S, Kumar R, Nice L, et al. Racial differences in development of immune-related adverse events. J Clin Oncol. 2020;38(suppl; abstr 15148).

87. Thompson Leah L, Pan Catherina X, Chang Michael S, et al. Impact of ethnicity on the diagnosis and management of cutaneous toxicities from immune checkpoint inhibitors. J Am Acad Dermatol. 2021;84:851-854.

88. Peravali Monica, Gomes-Lima Cristiane, Tefera Eshetu, et al. Racial disparities in immune-related adverse events of immune checkpoint inhibitors and association with survival based on clinical and biochemical responses. World J Clin Oncol. 2021;12:103-114.

89. Institute of Medicine. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC: National Academies Press; 2003.

90. Moyers JT, Patel A, Shih W, et al. Association of sociodemographic factors with immunotherapy receipt for metastatic melanoma in the US. JAMA Netw Open. 2020;3:e2015656.

91. Molina G, Kasumova GG, Qadan M, et al. Use of immunotherapy and surgery for stage IV melanoma. Cancer. 2020;126:2614-2624.

92. Norris RP, Dew R, Sharp L, et al. Are there socio-economic inequalities in utilization of predictive biomarker tests and biological and precision therapies for cancer? A systematic review and meta-analysis. BMC Med. 2020;18:282.

93. O'Connor JM, Fessele KL, Steiner J, et al. Speed of adoption of immune checkpoint inhibitors of programmed cell death 1 protein and comparison of patient ages in clinical practice vs pivotal clinical trials. JAMA Oncol. 2018;4:e180798.

94. Muss HB, Woolf S, Berry D, et al; Cancer and Leukemia Group B. Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. JAMA. 2005;293:1073-1081.

95. Folprecht G, Seymour MT, Saltz L, et al. Irinotecan/fluorouracil combination in first-line therapy of older and younger patients with metastatic colorectal cancer: combined analysis of 2,691 patients in randomized controlled trials. J Clin Oncol. 2008;26:1443-1451.

96. Betof AS, Nipp RD, Giobbie-Hurder A, et al. Impact of age on outcomes with immunotherapy for patients with melanoma. Oncologist. 2017;22:963-971.

97. Jones JH. Bad Blood: The Tuskegee Syphilis Experiment. New York: New York Free Press; 1993.

98. Senft N, Hamel LM, Manning MA, et al. Willingness to discuss clinical trials among black vs white men with prostate cancer. JAMA Oncol. 2020;6:1-5.

99. Unger JM, Hershman DL, Till C, et al. "When offered to participate:" a systematic review and meta-analysis of patient agreement to participate in cancer clinical trials. J Natl Cancer Inst. 2020;113:244-257.

100. Vaz-Luis I, Lin NU, Keating NL, et al. Treatment of early-stage human epidermal growth factor 2-positive cancers among medicare enrollees: age and race strongly associated with non-use of trastuzumab. Breast Cancer Res Treat. 2016;159:151-162.

101. Freedman RA, Hughes ME, Ottesen RA, et al. Use of adjuvant trastuzumab in women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer by race/ethnicity and education within the National Comprehensive Cancer Network. Cancer. 2013;119:839-846.

102. Gordon HS, Street RL Jr., Sharf BF, et al. Racial differences in doctors' information-giving and patients' participation. Cancer. 2006;107:1313-1320.

103. Serper M, Taddei TH, Mehta R, et al; VOCAL Study Group. Association of provider specialty and multidisciplinary care with hepatocellular carcinoma treatment and mortality. Gastroenterology. 2017;152:1954-1964.

104. Earle CC, Neumann PJ, Gelber RD, et al. Impact of referral patterns on the use of chemotherapy for lung cancer. J Clin Oncol. 2002;20:1786-1792.

105. Penner LA, Dovidio JF, Gonzalez R, et al. The effects of oncologist implicit racial bias in racially discordant oncology interactions. J Clin Oncol. 2016; 34:2874-2880.

106. Benson AB III, Pregler JP, Bean JA, et al. Oncologists' reluctance to accrue patients onto clinical trials: an Illinois Cancer Center study. J Clin Oncol. 1991; 9:2067-2075.

107. Eggly S, Barton E, Winckles A, et al. A disparity of words: racial differences in oncologist-patient communication about clinical trials. Health Expect. 2015; 18:1316-1326.

108. McCarthy AM, Bristol M, Domchek SM, et al. Health care segregation, physician recommendation, and racial disparities in BRCA1/2 testing among women with breast cancer. J Clin Oncol. 2016;34:2610-2618.

109. Yu JA, Ray KN, Park SY, et al. System-level factors associated with use of outpatient specialty palliative care among patients with advanced cancer. J Oncol Pract. 2019;15:e10-e19.

110. Jessup JM, McGinnis LS, Steele GD Jr., et al. The National Cancer Data Base. Report on colon cancer. Cancer. 1996;78:918-926.

111. Guidry JJ, Aday LA, Zhang D, et al. Transportation as a barrier to cancer treatment. Cancer Pract. 1997;5:361-366.

112. Ready NEPA, Lazure P, Peniuta M, et al. Practice gaps and challenges integrating new immuno-oncology agents in the treatment of cancer patients in the United States: a mixed-method study. J Clin Oncol. 2020;38 (suppl; abstr 11028).

113. Neugut AI, Subar M, Wilde ET, et al. Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. J Clin Oncol. 2011;29:2534-2542.

114. Sabatino SA, Coates RJ, Uhler RJ, et al. Health insurance coverage and cost barriers to needed medical care among U.S. adult cancer survivors age<65 years. Cancer. 2006;106:2466-2475.

115. Wagner TH, Heisler M, Piette JD. Prescription drug co-payments and cost-related medication underuse. Health Econ Policy Law. 2008;3:51-67.

116. Narang AK, Nicholas LH. Out-of-pocket spending and financial burden among Medicare beneficiaries with cancer. JAMA Oncol. 2017;3:757-765.

117. Kaisaeng N, Harpe SE, Carroll NV. Out-of-pocket costs and oral cancer medication discontinuation in the elderly. J Manag Care Spec Pharm. 2014;20:669-675.

118. Wilson LE, Greiner MA, Altomare I, et al. Rapid rise in the cost of targeted cancer therapies for Medicare solid tumor patients from 2006 to 2015. J Geriatr Oncol. Epub 2020 Nov 27.

119. Gordon N, Stemmer SM, Greenberg D, et al. Trajectories of injectable cancer drug costs after launch in the United States. J Clin Oncol. 2018;36:319-325.

120. Goulart BHL, Unger JM, Chennupati S, et al. Out-of-pocket costs for tyrosine kinase inhibitors and patient outcomes in *EGFR*- and *ALK*-positive advanced non-small-cell lung cancer. JCO Oncol Pract. 2021;17:e130-e139.

121. Hendryx M, Luo J. Increased cancer screening for low-income adults under the Affordable Care Act Medicaid expansion. Med Care. 2018;56:944-949.

122. Robbins AS, Han X, Ward EM, et al. Association between the Affordable Care Act dependent coverage expansion and cervical cancer stage and treatment in young women. JAMA. 2015;314:2189-2191.

123. Parsons HM, Harlan LC, Seibel NL, et al. Clinical trial participation and time to treatment among adolescents and young adults with cancer: does age at diagnosis or insurance make a difference? J Clin Oncol. 2011;29:4045-4053.

124. Banda DR, Libin AV, Wang H, et al. A pilot study of a culturally targeted video intervention to increase participation of African American patients in cancer clinical trials. Oncologist. 2012;17:708-714.

125. Brach C, Fraser I. Can cultural competency reduce racial and ethnic health disparities? A review and conceptual model. Med Care Res Rev. 2000;57(suppl 1): 181-217.

126. Sukhera J, Watling C. A framework for integrating implicit bias recognition into health professions education. Acad Med. 2018;93:35-40.

127. Saha S, Beach MC, Cooper LA. Patient centeredness, cultural competence and healthcare quality. J Natl Med Assoc. 2008;100:1275-1285.

128. Prager GW, Braga S, Bystricky B, et al. Global cancer control: responding to the growing burden, rising costs and inequalities in access. ESMO Open. 2018; 3:e000285.

129. Newcomer LN, Gould B, Page RD, et al. Changing physician incentives for affordable, quality cancer care: results of an episode payment model. J Oncol Pract. 2014;10:322-326.

130. Mitchell AP, Rotter JS, Patel E, et al. Association between reimbursement incentives and physician practice in oncology: a systematic review. JAMA Oncol. 2019;5:893-899.

131. Shah S, Reh G. Value-based payment models in oncology: will they help or hinder patient access to new treatments? Am J Manag Care. 2017;23:SP188-SP190.

132. Marmot M, Friel S, Bell R, et al; Commission on Social Determinants of Health. Closing the gap in a generation: health equity through action on the social determinants of health. Lancet. 2008;372:1661-1669.

133. World Health Organization. Pricing of cancer medicines and its impacts. https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf?sequence=1&isAllowed=y. Accessed January 24, 2021.

134. Robertson J, Barr R, Shulman LN, et al. Essential medicines for cancer: WHO recommendations and national priorities. Bull World Health Organ. 2016; 94:735-742.

135. Katz ML, Young GS, Reiter PL, et al. Barriers reported among patients with breast and cervical abnormalities in the patient navigation research program: impact on timely care. Womens Health Issues. 2014;24:e155-e162.

136. Kim ES, Bruinooge SS, Roberts S, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research joint research statement. J Clin Oncol. 2017;35:3737-3744.

137. Lichtman SM, Harvey RD, Damiette Smit MA, et al. Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group. J Clin Oncol. 2017;35:3753-3759.

138. Uldrick TS, Ison G, Rudek MA, et al. Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology-Friends of Cancer Research HIV Working Group. J Clin Oncol. 2017;35:3774-3780.

139. Kim ES, Uldrick TS, Schenkel C, et al. Continuing to broaden eligibility criteria to make clinical trials more representative and inclusive: ASCO-Friends of Cancer Research joint research statement. Clin Cancer Res. Epub 2021 Feb 9.

140. Harvey RD, Bruinooge SS, Chen L, et al. Impact of broadening trial eligibility criteria for patients with advanced non-small cell lung cancer: real-world analysis of select ASCO-Friends recommendations. Clin Cancer Res. Epub 2021 Feb 9.

141. Spira AI, Stewart MD, Jones S, et al. Modernizing clinical trial eligibility criteria: recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group. Clin Cancer Res. Epub 2021 Feb 9.

142. Osarogiagbon RU, Vega DM, Fashoyin-Aje L, et al. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Prior Therapies Work Group. Clin Cancer Res. Epub 2021 Feb 9.

Nonsurgical Management of Melanoma Brain Metastasis: Current Therapeutics, Challenges, and Strategies for Progress

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Overview

This review aims to provide an overview of nonsurgical treatment strategies for central nervous system metastases in melanoma as well as discuss treatment challenges and future directions. Recent strategies for melanoma brain metastases have involved proving the intracranial activity of approved therapies as well as identifying novel drug targets. BRAF/MEK combination therapy has intracranial activity in those with *BRAF* V600 mutations, though disease control is shorter for intracranial than extracranial metastases. Immunotherapy and combination immunotherapies have emerged as providing durable responses in melanoma, and newer studies combining immunotherapy with targeted therapies are emerging. Continued challenges include penetration through the blood-brain barrier and development of resistance mechanisms. Novel therapeutic targets and methods to improve central nervous system penetrance are being identified through the application of deep DNA- and RNA-sequencing analyses. Radiation therapy approaches, especially stereotactic radiosurgery in combination or in sequence with systemic therapies, are also being investigated. Both targeted therapies and immunotherapies have revolutionized the field of melanoma treatment. Multimodality approaches with multidisciplinary teams will pave the way for the future of central nervous system disease treatment in melanoma.

INTRODUCTION TO MELANOMA BRAIN METASTASIS

Epidemiology and Risk Factors

Historical case series have shown that up to 44% of patients with advanced melanoma develop brain metastases, with a median overall survival (OS) after diagnosis of approximately 4 to 5 months.[1,2] At the time of autopsy, central nervous system (CNS) disease is identified in up to 75% of patients with melanoma. Multiple clinicopathologic and molecular risk factors for the development of CNS disease have been observed. These include the Breslow thickness (more than 4 mm), primary site of disease, nodular histology, stage, and, recently, mitotic rate, mutations in the *BRAF/NRAS* pathway, *PI3K/AKT* activation, and loss of *PTEN*.[3-7] In advanced melanoma, M1b or M1c disease at diagnosis is associated with a significant increase in the development of CNS metastasis ($p < .0001$; HR, 2.643 and 2.127, respectively) compared with M1a or stage III disease.[8] Incidence of CNS disease is also increased, with primaries arising in the head and neck (6.7%) more than in the trunk/limb (4.7%; $p = .003$).[9] Those who have scalp primaries have the highest incidence (12.7%) of CNS metastasis at 5 years.

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Mechanisms of Central Nervous System Metastasis

Any discussion regarding the therapeutic efficacy of systemic therapy immediately evokes concerns regarding the ability of systemic agents to penetrate the blood-brain barrier. However, it should be noted that multiple blood-brain barrier and tumor microenvironment factors have been identified as playing a role in the development and pathophysiology of melanoma brain metastases (MBM).[10,11] A retrospective review showed emergence of CNS metastasis in approximately 12% of patients with melanoma despite control of other extracranial disease with systemic therapy.[12] The blood-brain barrier serves as both an anatomic and a functional barrier to metastatic colonization of the CNS. Studies have suggested impaired blood-brain barrier in areas of CNS metastasis in multiple cancer sites. For instance, Terrell-Hall et al[13] noted an increased distribution of the anti-HER2 agent trastuzumab in brain metastatic tissues compared with adjacent normal tissue in patients with breast cancer, despite the fact that, because of its molecular weight and negative charge, trastuzumab would typically not be able to cross the blood-brain barrier. Similarly, gadolinium contrast used in MRI enhances in areas of brain metastasis and not in normal brain parenchyma, indicating an impaired blood-brain barrier and the

PRACTICAL APPLICATIONS

- Melanoma brain metastases are a substantial contributor to mortality in patients with metastatic melanoma, and treatment strategies are urgently needed to improve patient outcomes.
- Combination immunotherapy with ipilimumab and nivolumab has shown durable responses in 46% to 55% of patients with asymptomatic melanoma brain metastases.
- BRAF/MEK inhibitor therapy in patients with *BRAF* V600 mutation–positive disease has shown better control of extracranial than intracranial disease; the combination of immunotherapy with targeted therapy is under investigation and is rapidly evolving the landscape of metastatic melanoma treatment.
- Therapeutic strategies that will inform the treatment paradigm of melanoma brain metastases are likely to involve multimodality therapies combining targeted therapy, immunotherapy, and/or radiation therapy to improve response rates and long-term outcomes.

concept of a blood-tumor barrier. Much of the blood-tumor barrier is not well understood; however, certain characteristics that are altered to form the blood-tumor barrier have been described.[11] One of these characteristics is large fenestrations caused by the tumor necrosis factor receptor 1 pathway, which contribute to the increased permeability of the barrier.[14] Additionally, angiopoietin-2–mediated disruption of the endothelial tight junctions and increased desmin expression in pericytes have been described.[15,16]

Despite this increased permeability surrounding metastatic lesions, heterogeneity of these regions has been attributed to varying penetration of cytotoxic agents. There appears to be a difference in permeability between micrometastases (less than 50 μm) compared with macrometastases (more than 50 μm); however, within macrometastases, any additional correlation between tumor size and increased permeability has not been demonstrated.[17,18] Furthermore, many chemotherapy agents have been found to be substrates for efflux pumps such as P-glycoprotein, and this property has been attributed to inhibition of CNS distribution of targeted therapies, including cobimetinib and trametinib (MEK inhibitors), vemurafenib and dabrafenib (BRAF inhibitors), erlotinib (EGFR inhibitor), and axitinib (vascular endothelial growth factor inhibitor) as well as the cytotoxic agents paclitaxel and vincristine.[11] Efflux proteins belong to the family of ATP-binding cassette and solute carrier proteins; development of small-molecule inhibitors, which modulate function of these efflux proteins, is a growing field.[19,20] Other microenvironment factors, such as cytokines and chemokines, and various other signaling pathways have also been described and evaluated in preclinical stages as potential therapeutic targets for melanoma and other CNS metastases.[5,21-24]

REVIEW OF CURRENT TREATMENT STRATEGIES

Molecular Determinants of Melanoma

In melanoma, *BRAF* V600E and V600K mutations are the most common forms, encompassing more than 90% of V600 mutations, and cause constitutive activation of the RAS-RAF-MAPK pathway.[25] *NRAS* Q61L or Q61R mutations are found in approximately 20% to 25% of cutaneous melanomas and tend to be mutually exclusive with *BRAF* mutations.[6] *BRAF/NRAS* mutations occur at increased frequency in brain (70%) and lymph node (62%) sites and at nonacral cutaneous (51.4%) more than acral (16.2%) melanomas. Loss-of-function mutations of *NF1*, a negative regulator of *RAS*, are found in up to 46% of cutaneous melanomas with wild-type *BRAF* and *RAS*.[26] *HRAS* and *KRAS* mutations are observed in 1% to 2%. *KIT* mutations are seen in less than 1% of melanomas overall, with *KIT* V559A in up to 10% to 20% of mucosal and acral melanomas.[27]

Comparison of extracranial and concordant brain metastases has shown increased levels of PI3K/AKT and decreased expression of PTEN in MBM when compared with extracranial sites.[4,5] PTEN appears to be modulated via different mechanisms in *BRAF*-mutated tumors compared with *NRAS*-mutated tumors. In the presence of *BRAF* mutations, increased phosphorylation and thereby activation of AKT are shown to result in low levels of PTEN; however, in *NRAS*-mutated tumors, normal levels of PTEN with low levels of phosphorylated/activated AKT are noted.[4] Despite these differences, patients with stage IV melanoma containing *BRAF* or *NRAS* mutations have a higher incidence of brain metastasis at the time of diagnosis (24% and 23%, respectively) versus patients with wild-type tumors (12%; p = .008).[6,26]

BRAF pathway

Vemurafenib and dabrafenib were the first BRAF V600 inhibitors to achieve U.S. Food and Drug Administration approval, in 2011 and 2013, respectively. Initial results from a phase I trial of dabrafenib had a subset of 10 patients with metastatic melanoma with *BRAF* V600 mutations and noted that nine out of 10 patients had regression of the intracranial tumor.[28] Subsequently, the phase II trial BREAK-MB investigated the efficacy of dabrafenib in patients with metastatic melanoma with at least one measurable brain metastasis that was previously untreated or progressing (Table 1).[29-35] A median OS of 33.1 weeks and a median progression-free survival of 16.1 weeks were seen in the entire cohort. The V600K mutation bearers had a slightly

TABLE 1. Summary of Relevant Systemic Therapy Trials for Melanoma Brain Metastasis

Study; Drug	Study Description	Outcomes	Adverse Events	First Author, Reference (Year)
BREAK-MB (NCT01266967); dabrafenib	Phase II, open-label, multicenter trial. Positive *BRAF* V600E/K mutation and at least one asymptomatic MBM without prior local CNS therapy (cohort A; 89 pts) or with prior CNS therapy and progression (cohort B; 83 pts).	Cohort A: iORR, 39% (95% CI, 28.0%–51.2%); cohort B: iORR, 38% (95% CI, 19.9%–43.4%)	Grade 3 or higher in 22% patients	Long et al[29] (2012)
Vemurafenib	Phase II trial of positive *BRAF* V600 mutation without (cohort 1; 90 pts) or with (cohort 2; 56 pts) prior CNS therapy	Cohort 1: iORR, 18% (2 CR, 14 PR); cohort 2: ORR, 18% (10 PR)	Grade 3 or higher in 66% (cohort 1) and 64% (cohort 2)	McArthur et al[30] (2017)
COMBI-MB; dabrafenib plus trametinib	Phase II, open-label trial in *BRAF* V600E mutation–positive asymptomatic patients without (A; 76 pts) and with (B; 16 pts) prior CNS therapy, V600D/K/R-positive asymptomatic patients (C; 16 pts) with or without prior CNS therapy, all mutations (D; 17 pts), and symptomatic with or without prior therapy	iORR: cohort A, 58%; cohort B, 56%; cohort C, 44%; cohort D, 59%	Grade 3/4 toxicity in 48%; most common were pyrexia (7%) and decreased EF (4%)	Davies et al[31] (2017)
NCT00623766; ipilimumab	Phase II, open-label trial. Cohort A (asymptomatic CNS mets and not on steroids; 51 pts); cohort B (symptomatic and on stable steroid dose; 21 pts). 10 mg/kg dose every 3 weeks for 4 doses. If stable at 24 weeks, continued dose every 12 weeks.	iORR at 12 weeks: cohort A 16% (95% CI, 7%–29%); Cohort B: 5% (95% CI, 0.1%–24%)	Most common grade 3: diarrhea, fatigue, dehydration, hyperglycemia, and high AST. One grade 4 in each cohort: confusion	Margolin et al[32] (2012)
NCT02085070 (long-term follow-up); pembrolizumab	Phase II trial; 23 pts with $\geq$ 1 asymptomatic, untreated MBM. Pembrolizumab up to 24 months	26% had MBM response; 35% unevaluable. Median PFS (2 months), OS (17 months); 48% alive at 24 months	Neurologic AE: 65% (all grade 1/2)	Kluger et al[33] (2019)
CheckMate 204 (NCT02320058); ipilimumab plus nivolumab	Phase II, open-label trial. Asymptomatic MBM without prior irradiation received NIVO 1 mg/kg plus IPI 3 mg/kg every 3 weeks for 4 doses and maintenance NIVO 3 mg/kg every 2 weeks until progression or unacceptable AE (94 pts).	iORR: 55% (95% CI, 45%–66%); CR 26%; PR 30%. Extracranial ORR: 50% (95% CI, 40%–60%)	Grade 3/4 toxicity: 55%	Tawbi et a[34] (2018)
ABC trial (NCT02374242); ipilimumab plus nivolumab vs. nivolumab	Phase II, open-label trial. Asymptomatic MBM without prior CNS therapy: cohort A (IPI plus NIVO; 36 pts) or cohort B (NIVO; 27 pts). Cohort C (MBM with failed CNS therapy, symptoms, LMD received NIVO, 16 pts). IPI dose 3 mg/kg plus NIVO 1 mg/kg every 3 weeks for 4 doses or monotherapy NIVO dose 3 mg/kg every 2 weeks for 6 doses.	iORR (overall population): cohort A, 46%; cohort B, 20%; cohort C, 6%. Intracranial CR: cohort A, 17%; cohort B, 12%; cohort C, 0%	Grade 3/4 toxicity: cohort A, 54%; cohort B, 16%; cohort C, 13%	Long et al[35] (2018)

Abbreviations: MBM, melanoma brain metastasis; ORR, overall response rate; pts, patients; iORR, intracranial overall response rate; CR, complete response; PR, partial response; SD, stable disease; EF, ejection fraction; AST, aspartate aminotransferase; PFS, progression-free survival; OS, overall survival; AE, adverse event; NIVO, nivolumab; IPI, ipilimumab; LMD, leptomeningeal disease.

less favorable outcome, with a median OS of 16.3 weeks in those without prior CNS treatment and 21.9 weeks for those who had received prior CNS treatment. Previously treated patients who were V600E mutation bearers had a median OS of 31.4 weeks. Worse outcomes were associated with elevated serum lactate dehydrogenase (specifically, more than two times upper limit of normal) and with a high number of metastatic lesions.

Investigation into the resistance mechanism of these agents led to combination of BRAF with MEK inhibitors for the U.S. Food and Drug Administration approval of dabrafenib and trametinib, vemurafenib and cobimetinib, and encorafenib and binimetinib in 2014, 2015, and 2018, respectively. Combination BRAF/MEK inhibition led to an improvement in progression-free survival from approximately 6 months to 11 months or longer in patients with metastatic melanoma.[29-31,36] The initial clinical trials excluded patients with active CNS disease; however, the COMBI-MB study evaluated efficacy of dabrafenib plus trametinib in patients with *BRAF* V600E–mutated metastatic melanoma with active CNS metastasis and those with and without prior CNS-directed therapy (Table 1).[31] The median progression-free survival and OS in those without prior CNS therapy were 5.6 and 10.8 months, respectively, and the duration of response was shorter for intracranial versus extracranial disease (6.5 months vs. 10.2 months, respectively; Table 1).[31,36] A multicenter, retrospective case series of 24 patients with *BRAF*-positive disease with CNS metastasis had shown intracranial activity of encorafenib/binimetinib, including in those previously treated (21 patients) with BRAF/MEK inhibitors (intracranial overall response rate, 24%; clinical benefit rate, 57%), warranting additional prospective studies.[37] Encorafenib/binimetinib is being evaluated in the randomized, phase II POLARIS study comparing a standard and a high-dose arm for MBM (NCT03911869). Overall, BRAF/MEK inhibitors in extracranial disease have noted longer survival outcomes compared with intracranial disease; improved understanding of mechanisms of decreased CNS penetrance and resistance are urgently needed.

PI3K/AKT Pathway

Understanding other mechanisms of resistance can aid in the design of combination therapies to improve patient outcomes. Multiple preclinical studies have noted hyperactivation of the AKT and loss of PTEN expression in CNS metastasis compared with extracranial sites.[5,38-43] Inhibition of the PI3K-AKT pathway in a vemurafenib-resistant cell line showed improved growth inhibition compared with vemurafenib alone.[5] Taken together, such data indicate a role for AKT in the pathogenesis of MBM and resistance to *BRAF* mutation–directed therapy in the CNS. PTEN loss has also been shown through in vitro and in vivo preclinical models of melanoma to decrease both T-cell trafficking to tumors and T-cell-mediated tumor cell destruction, conferring a resistance to T-cell-mediated antitumor effects.[44,45] Strategies to target this pathway with PI3K and mTOR inhibitors are currently underway.

Oxidative Phosphorylation Pathway

There is increasing evidence to suggest notable differences in the pathophysiology and molecular determinants of CNS metastasis in melanoma compared with extracranial metastasis. In a recent analysis by Fischer et al,[38] RNA sequencing was performed on 88 samples of resected MBM and 42 matched extracranial metastatic tumor samples from a subset of the same patients. Four hundred ninety-four differentially expressed genes were identified in the matched analysis. The oxidative phosphorylation pathway was greatly enriched in their analysis. The authors validated this finding via inhibition of oxidative phosphorylation in xenograft mouse models that had acquired (A375-R1) and de novo (SKMEL5) resistance to BRAF/MEK inhibition. Treatment with the oxidative phosphorylation inhibitor IACS-010759 significantly improved survival in both murine models (HR, 0.197; 95% CI, 0.075–0.519; $p = .001$) and A375-R1 and SKMEL5 mice (HR, 0.072; 95% CI, 0.024–0.214; $p < .0001$). Incidence of MBM was also significantly reduced ($p = .035$) in an immunocompetent mouse model of spontaneous lung and brain metastasis compared with control, whereas no change in the rate of primary tumor growth or lung metastasis formation was noted.[38]

Immunotherapy

Anti–CTLA-4 and anti–PD-1 checkpoint inhibitors have revolutionized the field of cancer therapeutics. Two case reports in 2008 and 2010 initially showed a response of MBM to immunotherapy, which led to additional investigations.[46,47] A phase II trial of ipilimumab, targeting CTLA-4, in 2012 showed improvement in OS and durable responses.[32] Another study combining ipilimumab with fotemustine (a nitrosourea alkylating agent) had similar outcomes.[48] Anti–PD-1 antibodies soon followed suit, and a phase II trial of pembrolizumab in a small number of patients with non–small cell lung cancer or melanoma (23 patients) with brain metastasis was reported in 2016.[33,49] A majority of patients in this study had multiple prior therapies, and response rates intracranially were approximately 26%. Interestingly, unlike some of the targeted therapy trials described above, the immunotherapy trials tended to show concordance between intracranial and extracranial disease response, indicating likely similar immunomodulation between intra- and extracranial melanoma. Additionally, Engelhardt and Ransohoff[50] have noted that it is likely activated cytotoxic T cells from outside the CNS traffic through the blood-brain barrier for therapeutic efficacy. Decreased efficacy was noted in the initial phase II study of ipilimumab described above in patients who were taking

glucocorticoids. Though it is unclear whether this patient population has more advanced or aggressive disease characteristics and therefore a worse outcome or whether steroids reduce the antitumor effects of immunotherapy, or a combination of both occurs; typically successive large trials have excluded patients who require the use of steroids. Bevacizumab has been put forth as a steroid-sparing agent that may be applicable during immunotherapy, with the ability to reduce required dexamethasone doses by more than 50% in some patients as a result of its effects in reducing edema. Adverse events such as hypertension and hemorrhage, both intracranial and gastrointestinal, would require monitoring with antiangiogenic therapy.[51] In an institutional study at our center, bevacizumab used for treatment of radionecrosis after stereotactic radiosurgery (SRS) with or without whole-brain radiation therapy (WBRT) resulted in symptom improvement and quality-of-life improvement with two to six doses of bevacizumab and radiographic improvement in the majority of patients. In this small cohort, no intra- or extracranial bleeding episodes had occurred, warranting additional investigation into the use of bevacizumab with immunotherapy.[52]

Combination immunotherapy trials have shown improved response rates versus single-agent anti–PD-1 agents. The CheckMate 204 trial conducted in the United States evaluated the rate of intracranial clinical benefit in patients with metastatic melanoma, asymptomatic from CNS disease, and with at least one measurable and nonirradiated intracranial lesion (0.5 cm–3 cm).[34] Ninety-four patients had a median follow-up of 14 months, and the rate of intracranial benefit was 57% (95% CI, 47%–68%). Intracranial benefit was defined as stable disease for at least 6 months, complete response, or partial response. Complete responses were noted in 26%. Updated results from CheckMate 204 with longer follow-up and with inclusion of symptomatic patients and/or those who required corticosteroids had shown that the asymptomatic cohort (101 patients; cohort A) who received a median of three doses of combination immunotherapy had an intracranial clinical benefit rate of 58.4%. The median progression-free survival and OS were not reached at the median 21-month follow-up period. In contrast, cohort B, which included 18 patients with symptomatic CNS disease and/or requiring steroids, had an intracranial clinical benefit rate of 22.2%. These patients had received a median of one dose of combination immunotherapy; the OS and median intracranial progression-free survival were 8.7 months and 1.2 months, respectively (Table 1). Taken together, these updated results show durable responses in 55% of patients with asymptomatic CNS disease treated with combination ipilimumab/nivolumab and showed that patients with symptomatic CNS disease and/or steroid dependence are less likely to benefit.[53]

In 2018, Long and collegues[35] reported the results of the ABC trial conducted in Australia, in which patients treated with combination nivolumab plus ipilimumab had improved intracranial responses compared with nivolumab alone. In this study, asymptomatic patients with MBM without prior CNS-directed treatment had been randomly assigned to receive nivolumab plus ipilimumab (cohort A; 36 patients) at a standard dose for four cycles, followed by maintenance nivolumab, or to receive nivolumab alone (cohort B; 27 patients). A third cohort (cohort C; 16 patients) included nonrandomly assigned patients with symptomatic disease, leptomeningeal disease, or disease for which local therapies had failed. At a median follow-up of 17 months, 46% (95% CI, 29%–63%) had an intracranial response in the combination arm compared with 20% (95% CI, 7%–41%) with nivolumab alone. Complete intracranial response was noted in 17% in cohort A, 12% in cohort B, and none in cohort C.

Combination therapy heralds a higher rate of immune-related toxicity, with grade 3 or 4 toxicity in 55% of patients in CheckMate 204 and a 20% discontinuation rate in this group. Similarly, 54% of patients in the combination arm (cohort A) of the ABC trial experienced grade 3 or 4 toxicity. In the prior single-agent immunotherapy trials, the most common grade 3 toxicities noted were diarrhea and fatigue (12% each). Single-agent anti–PD-1 trials have shown approximately 10% to 15% grade 3 or 4 adverse events.[34,35,49,53]

RADIATION THERAPY

Historically, WBRT and glucocorticoids have been the mainstay of the treatment of multiple brain metastasis across cancer types, including melanoma. However, WBRT can be associated with considerable toxicities, and the long-term neurocognitive effects are an important consideration in the treatment of CNS metastasis.[54-59] SRS has come into the forefront because of its better local control and cognitive outcomes. In 2014, Yamamoto and collegues[60] reported the findings of a prospective observational study to assess noninferiority in OS of SRS to five to 10 lesions up to 3 cm in diameter (less than 10 mL in largest volume) compared with treatment of two to four lesions without WBRT. The findings affirmed noninferiority.[61] An update on safety with up to 48 months of follow-up also showed no marked difference in SRS-related complications or Mini-Mental State Examination score maintenance (less than three-point decrease from baseline) among those who received SRS to one lesion versus two to four lesions versus five to 10 lesions.[60]

A phase III randomized trial studied the role of adjuvant WBRT in the decreased development of new CNS metastasis in melanoma.[62] Two hundred fifteen patients were randomly assigned to WBRT or observation after local treatment with surgery or SRS for one to three MBM. Within 12 months, 42% of patients in the WBRT group and 50.5% in the observation group developed distant intracranial disease (odds ratio, 0.71; 95% CI, 0.41–1.23; p = .22). No

significant difference was noted at the 48.1-month follow-up period (p = .39). Local failure rate was improved after WBRT (20% vs. 33.6%; p = .03), and WBRT resulted in increased grade 1 to 2 toxicity in the first 2 to 4 months; however, no significant differences in toxicity were noted up to 24 months after random assignment. The results of this study suggest a lack of benefit in distant CNS disease control after adjuvant WBRT in those who have had local treatment of one to three CNS lesions in melanoma. A limitation to this trial is that the effect of systemic therapy is unknown on outcomes because, during recruitment between 2009 and 2017, advances in targeted therapies with CNS activity were likely to have an effect on responses.[62]

A prospective, randomized controlled study of 58 patients, of whom 30 received SRS alone and 28 received SRS plus WBRT, aimed at studying neurocognitive risk in CNS metastasis and showed high probability (96%) that patients who received both modalities were at a much higher risk of learning and memory function decline. This finding led to the early discontinuation of the trial; however, 73% of those who had received both modalities were CNS recurrence free at 1 year compared with 27% in the SRS-alone group (p = .0003).[63] Other strategies to lessen the degree of neurocognitive decline include hippocampal-sparing WBRT[58,64] and addition of the *N*-methyl-D-aspartate receptor antagonist memantine to WBRT.[65] In an NRG Oncology CC001 phase III study to evaluate lowered doses of hippocampal radiation in the preservation of neurocognitive function, patients randomly assigned to WBRT plus memantine with or without hippocampal avoidance had a lower neurocognitive failure risk at 7.9 months (HR, 0.74; p = .02). Patients younger than age 61 also had lower neurocognitive failure (HR, 0.60; p = .0002). Symptoms, including fatigue, speech difficulty, and reported memory issues, favored the hippocampal avoidance arm at 6 months, and no differences in OS, CNS progression, or toxicity were reported (NCT02360215).[66]

COMBINATION AND MULTIMODALITY THERAPIES

Multidisciplinary approaches and combinatorial regimens are paving the way for the optimized treatment of CNS metastasis (Fig. 1). Dedicated brain metastasis clinics to streamline patient care is being implemented across several dedicated cancer centers.[67] In these dedicated clinics, patients meet with neurosurgery, medical oncology, radiation oncology, and neuro-oncology consultants during the same visit, which allows for a multidisciplinary evaluation and coordination of optimal patient care in an efficient manner. This patient-centered approach has been met with high patient and physician satisfaction, and approximately one in five patients had a major change in their treatment plan after the multidisciplinary evaluation.[67] Such models can allow for improved patient care as well as advance research by facilitating the development of clinical trials and biomarker discovery in this complex patient population, including for those with symptomatic brain metastases. Below, we review multimodality strategies for the treatment of metastatic melanoma with CNS metastases. Combining radiation therapy and immunotherapy can result in an abscopal phenomenon, defined as regression of the tumor at sites distant from the target lesion receiving the radiation, which has been described in the brain and body.[68] Initially, case studies suggested a potentially improved antitumor effect of combining immunotherapy with SRS.[68-70] A retrospective review of 77 patients treated with definitive radiosurgery for MBM showed an increased median OS in those who had also received ipilimumab (27 patients) from 4.9 months to 21.3 months.[71] Approximately 37% of these patients received ipilimumab before SRS, and 63% received it after. No noteworthy differences in sequencing SRS and immunotherapy had been noted in this study. Another retrospective study of 70 patients who received either WBRT or SRS analyzed those who did (33 patients) or did not (37 patients) also receive ipilimumab.[72] The average time between the first dose of ipilimumab and radiation therapy was 23 weeks. This study found that SRS and ipilimumab were important predictors of improved OS with the magnitude of benefit (of approximately 16 months, though small sample sizes were used) suggesting a possible synergism between SRS and ipilimumab.

Though the former study had adjusted for performance status, both of these retrospective studies are relatively small sample sizes subjected to selection bias toward patients with a better performance status and perhaps a more indolent course. Certain other retrospective analyses have shown no remarkable difference in adverse events such as hemorrhage or necrosis and no statistically noteworthy differences in OS or disease control, though trends toward improved OS had been noted, depending on the timing of ipilimumab with SRS.[73,74] A more recent retrospective analysis of 1,104 patients from the National Cancer Database, in which 192 patients had received radiation therapy and immunotherapy compared with 912 who had received radiation therapy alone for MBM, had shown a significant improvement in median OS (11.1 months [95% CI, 8.9–13.4] vs. 6.2 months [95% CI, 5.6–6.8]; p < .001) favoring combination therapy.[75] Taken together, these data warrant prospective trials of combination immunotherapy and radiation therapy to minimize selection bias in the evaluation of outcomes and to evaluate effects of sequencing and timing of the combination.[69,73-75] Several trials combining radiation therapy with immune checkpoint inhibitors (ABC-X; NCT03340129) or targeted therapy (concurrent dabrafenib/trametinib with SRS; NCT02974803) are currently ongoing (Table 2).[76-79]

Combining targeted and immune checkpoint inhibition is another emerging therapeutic strategy in metastatic melanoma with future application to MBM. Increased T-cell

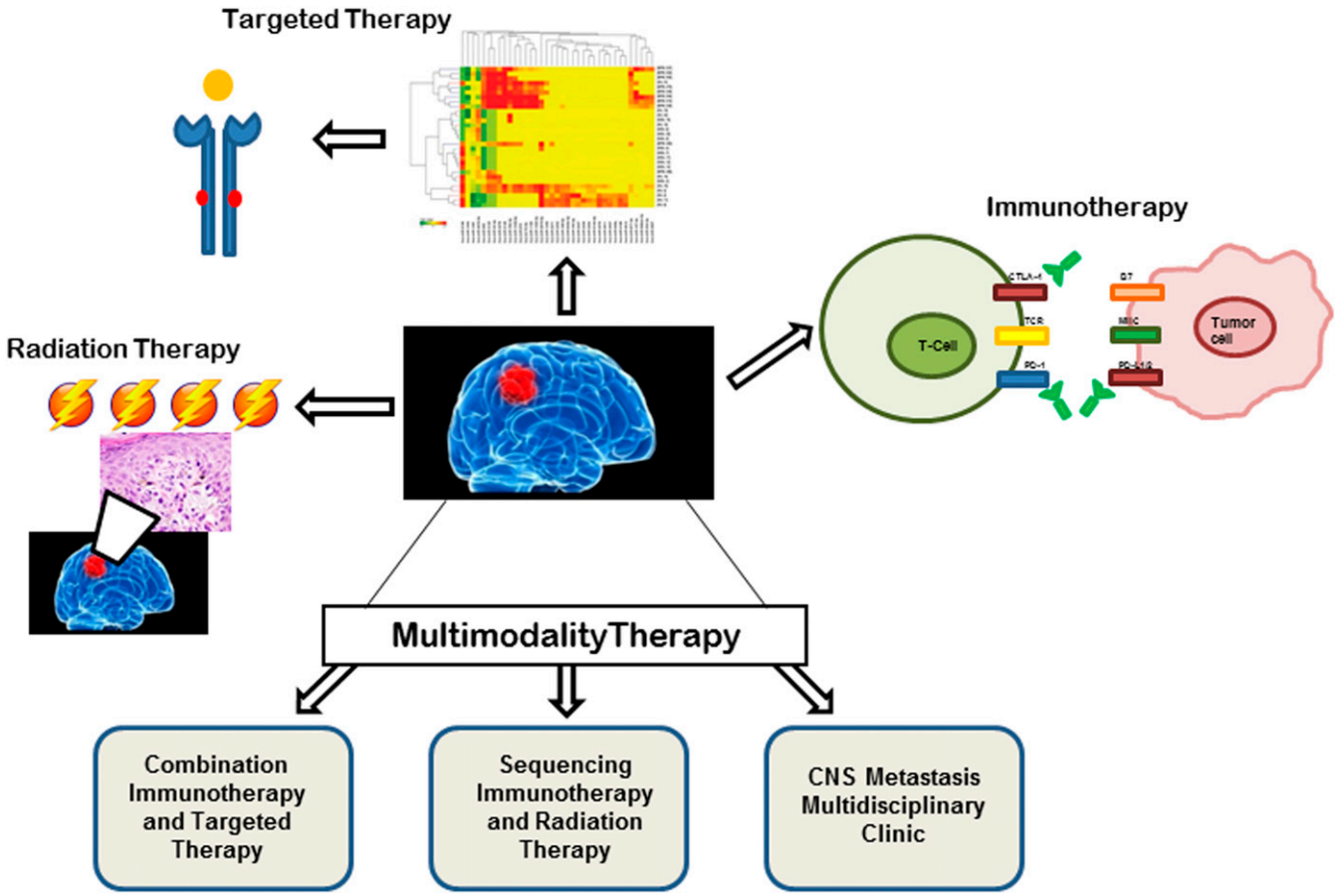

FIGURE 1. Therapeutic Approach to Melanoma Central Nervous System Metastasis
Abbreviation: CNS, central nervous system

infiltration as well as PD-L1 and tumor antigen expression have been seen post-BRAF/MEK inhibition, and preclinical models have shown an increased antitumor effect with the combination of anti–PD-1 checkpoint inhibition and BRAF/MEK inhibition.[80] In a phase I trial of 15 patients with *BRAF* V600 mutations treated with dabrafenib, trametinib, and pembrolizumab, an overall response was seen in 11 of 15 (73%) of patients, and 40% continued to have a response at 27 months of median follow-up.[81] In the phase II setting, the triplet combination showed a trend toward improved progression-free survival versus the placebo arm with dabrafenib/trametinib (16.0 months vs. 10.3 months), though statistical significance had not been reached (Table 2).[76,82] Fifty-eight percent of patients in the triplet arm experienced grade 3 or 4 toxicities compared with 27% in the doublet arm.

Several other studies of combination immunotherapy and targeted therapy are outlined in Table 2. Patients with clinicaly active CNS metastasis were excluded from these studies, though those with asymptomatic or previously treated disease were allowed. These studies include the phase III IMspire150 study of vemurafenib/cobimetinib with atezolizumab or placebo, in which a significant improvement in progression-free survival was seen in the triplet arm (15.1 months vs. 10.6 months; HR, 0.78; 95% CI, 0.63–0.97; p = .025) in patients with untreated *BRAF* V600E mutation–positive metastatic melanoma.[77] Patients with actively progressing or untreated CNS metastatic disease were excluded from the study, though 2% to 3% with previously treated MBM were included in each arm. Part 3 of the COMBI-i trial was a randomized, placebo-controlled phase III study that evaluated spartalizumab (anti–PD-1) versus placebo in combination with dabrafenib and trametinib in *BRAF* V600 mutation–positive metastatic melanoma (NCT02967692).[78] Again, clinically active patients with MBM were not included. This study failed to meet its primary endpoint, and the triplet arm did now show improved investigator-assessed progression-free survival compared with the doublet at the 24-month follow-up. Additionally, a higher number of discontinuations/dose modifications were noted in the triplet arm. The initial safety and efficacy results of the phase II study TRIDeNT (26 patients), which allowed enrollment of patients with asymptomatic CNS

TABLE 2. Summary of Relevant Reported and Ongoing Triplet Therapy and Multimodality Trials in Metastatic Melanoma

Study; Drug	Study Description	Outcomes	First Author, Reference (Year)
NCT02130466; dabrafenib, trametinib, and pembrolizumab	Randomized phase II trial. Treatment naive, *BRAF* V600E/K mutated, advanced melanoma.	PFS, 16.0 vs. 10.3 months (triplet vs. doublet); HR, 0.66; p = .043	Ascierto et al[76] (2019)
	Active MBM not included	Median duration of response: 18.7 months vs. 12.5 months (95% CI, 10.1–22.1 and 6.0–14.1; triplet vs. doublet)	
	Dabrafenib plus trametinib plus (pembrolizumab [60 pts] or placebo [60 pts])		
	Primary endpoint of PFS		
IMspire150 (NCT02908672); atezolizumab, vemurafenib, and cobimetinib	Phase III randomized, placebo-controlled study in treatment	PFS, 15.1 vs. 10.6 months (triplet vs. double); HR, 0.78; p = .025	Gutzmer et al[77] (2020)
	Naive *BRAF* V600 mutated, metastatic melanoma	Triplet combo significantly improved PFS	
	Untreated/active MBM not included	FDA approved on July 30, 2020	
	Vemurafenib plus cobimetinib plus (atezolizumab [256 pts] vs. placebo [258 pts)		
	Primary endpoint of investigator-assessed PFS		
COMBI-i Part 3 (NCT02967692); spartalizumab, dabrafenib, and trametinib	Phase III, randomized, placebo-controlled study in treatment	PFS, 16.2 vs. 12.0 months (triplet vs. doublet); HR, 0.82; p = .042	Nathan et al[78] (2020)
	Naive, *BRAF* V600 mutated, metastatic melanoma	Study did not show significant difference, as p < .025 was threshold	
	Clinically active MBM not included		
	Dabrafenib plus trametinib plus (spartalizumab [267 pts] vs. placebo [265 pts])		
	Primary endpoint of investigator-assessed PFS		
Ongoing Triplet Therapy or Multimodality Clinical Trials			
TRIDeNT (NCT02910700)	Design: phase II, nonrandomized, open label		Burton et al[79] (2019)
	Objective: safety, tolerability, and efficacy of nivolumab plus (dabrafenib with or without trametinib) in two dosing schedules		
	Population: *BRAF* V600–mutated metastatic melanoma		
	CNS metastasis allowed (per predefined criteria)		
ABC-X (NCT03340129)	Design: phase II, randomized, open label		
	Primary outcome: neurologic specific cause of death at 1 year from random assignment.		
	Comparator arms: ipilimumab plus nivolumab with or without stereotactic radiotherapy		
	Population: MBM untreated with radiation or systemic therapy		
NCT02974803	Design: phase II, nonrandomized, open label		
	Primary outcome: intracranial objective response rate with concurrent dabrafenib plus trametinib plus stereotactic radiation		
	Population: *BRAF* mutation–positive melanoma with brain metastasis. Up to 10 brain metastases allowed; 1 cm ≥ 4 cm		

Abbreviations: PFS, progression-free survival; HR, hazard ratio; MBM, melanoma brain metastasis; pts, patients; FDA, U.S Food and Drug Administration; CNS, central nervous system.

disease, had an overall response rate of 91%.[79] At the time of enrollment, eight patients had CNS disease. Of six evaluable patients, 67% had intracranial response, with two complete responses noted. No considerable difference in outcomes had been noted in patients with and without CNS metastasis, advocating for more studies incorporating patients with CNS disease in the inclusion criteria (NCT02910700).[79]

The LEAP-004 phase II study of lenvatinib plus pembrolizumab in previously treated metastatic melanoma showed activity in patients previously treated with a PD-1/PD-L1 inhibitor or a combination with anti–CTLA-4 therapy.[83] Active MBM was excluded, though 67% had M1c/M1d disease (NCT03776136). An ongoing phase II study is also evaluating pembrolizumab plus bevacizumab in the treatment of asymptomatic CNS metastases in melanoma and non–small cell lung cancer, not requiring local therapy at time of enrollment (NCT02681549).

CONCLUSION

Great strides have been made in the nonsurgical management of MBM during the past decades. Additional improvements in patient outcomes are expected with our improved understanding of the complexities of the blood-brain and blood-tumor barriers, thereby enabling application of extracranial systemic therapeutic strategies, such as BRAF/MEK targeting with improved intracranial penetrance. Additional improvements into our understanding of the genetic differences of intracranial versus extracranial melanoma metastasis may lead to novel targeted therapy strategies for systemic control of intracranial disease. More and more focus is shifting to multimodality therapy with a combination of targeted therapy, immunotherapy, and/or radiation therapy to improve disease control and long-term outcomes, though incorporation of more patients with CNS disease into clinical trial design is still lacking. Furthermore, strides to improve local therapies to minimize neurocognitive decline should be an important consideration in the treatment of CNS metastasis. To that end, dedicated brain metastasis clinics to streamline and optimize patient care are being implemented across several dedicated cancer centers and being met with increased patient and physician satisfaction. The success of such models demonstrates the effectiveness and feasibility of a centralized approach in the treatment of this complex patient population.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Glitza Oliva I, Tawbi H, Davies MA. Melanoma brain metastases: current areas of investigation and future directions. Cancer J. 2017;23:68-74.
2. Davies MA, Liu P, McIntyre S, et al. Prognostic factors for survival in melanoma patients with brain metastases. Cancer. 2011;117:1687-1696.
3. Gardner LJ, Ward M, Andtbacka RHI, et al. Risk factors for development of melanoma brain metastasis and disease progression: a single-center retrospective analysis. Melanoma Res. 2017;27:477-484.
4. Davies MA, Stemke-Hale K, Lin E, et al. Integrated molecular and clinical analysis of AKT activation in metastatic melanoma. Clin Cancer Res. 2009;15:7538-7546.
5. Niessner H, Forschner A, Klumpp B, et al. Targeting hyperactivation of the AKT survival pathway to overcome therapy resistance of melanoma brain metastases. Cancer Med. 2013;2:76-85.
6. Jakob JA, Bassett RL Jr., Ng CS, et al. NRAS mutation status is an independent prognostic factor in metastatic melanoma. Cancer. 2012;118:4014-4023.
7. Westphal D, Glitza Oliva IC, Niessner H. Molecular insights into melanoma brain metastases. Cancer. 2017;123(S11):2163-2175.
8. Bedikian AY, Wei C, Detry M, et al. Predictive factors for the development of brain metastasis in advanced unresectable metastatic melanoma. Am J Clin Oncol. 2011;34:603-610.
9. Huismans AM, Haydu LE, Shannon KF, et al. Primary melanoma location on the scalp is an important risk factor for brain metastasis: a study of 1,687 patients with cutaneous head and neck melanomas. Ann Surg Oncol. 2014;21:3985-3991.
10. Ballabh P, Braun A, Nedergaard M. The blood-brain barrier: an overview: structure, regulation, and clinical implications. Neurobiol Dis. 2004;16:1-13.
11. Berghoff AS, Preusser M. Role of the blood-brain barrier in metastatic disease of the central nervous system. Handb Clin Neurol. 2018;149:57-66.

12. O'Connell K, Romo CG, Grossman SA. Brain metastases as a first site of recurrence in patients receiving chemotherapy with controlled systemic cancer: a critical but under-recognized clinical scenario. Curr Treat Options Neurol. 2019;21:55.
13. Terrell-Hall TB, Nounou MI, El-Amrawy F, et al. Trastuzumab distribution in an *in-vivo* and *in-vitro* model of brain metastases of breast cancer. Oncotarget. 2017; 8:83734-83744.
14. Sarin H, Kanevsky AS, Wu H, et al. Physiologic upper limit of pore size in the blood-tumor barrier of malignant solid tumors. J Transl Med. 2009;7:51.
15. Avraham HK, Jiang S, Fu Y, et al. Angiopoietin-2 mediates blood-brain barrier impairment and colonization of triple-negative breast cancer cells in brain. J Pathol. 2014;232:369-381.
16. Adkins CE, Mohammad AS, Terrell-Hall TB, et al. Characterization of passive permeability at the blood-tumor barrier in five preclinical models of brain metastases of breast cancer. Clin Exp Metastasis. 2016;33:373-383.
17. Thorsen F, Fite B, Mahakian LM, et al. Multimodal imaging enables early detection and characterization of changes in tumor permeability of brain metastases. J Control Release. 2013;172:812-822.
18. Adkins CE, Mittapalli RK, Manda VK, et al. P-glycoprotein mediated efflux limits substrate and drug uptake in a preclinical brain metastases of breast cancer model. Front Pharmacol. 2013;4:136.
19. Osswald M, Blaes J, Liao Y, et al. Impact of blood-brain barrier integrity on tumor growth and therapy response in brain metastases. Clin Cancer Res. 2016; 22:6078-6087.
20. Gampa G, Vaidhyanathan S, Sarkaria JN, et al. Drug delivery to melanoma brain metastases: can current challenges lead to new opportunities? Pharmacol Res. 2017;123:10-25.
21. Vogetseder A, Thies S, Ingold B, et al. αv-Integrin isoform expression in primary human tumors and brain metastases. Int J Cancer. 2013;133:2362-2371.
22. Stupp R, Hegi ME, Gorlia T, et al; CENTRIC study team. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomized, open-label, phase 3 trial. Lancet Oncol. 2014;15:1100-1108.
23. Jilaveanu LB, Parisi F, Barr ML, et al. PLEKHA5 as a biomarker and potential mediator of melanoma brain metastasis. Clin Cancer Res. 2015;21:2138-2147.
24. Xie TX, Huang FJ, Aldape KD, et al. Activation of stat3 in human melanoma promotes brain metastasis. Cancer Res. 2006;66:3188-3196.
25. McQuade J, Davies MA. Converting biology into clinical benefit: lessons learned from BRAF inhibitors. Melanoma Manag. 2015;2:241-254.
26. Krauthammer M, Kong Y, Bacchiocchi A, et al. Exome sequencing identifies recurrent mutations in NF1 and RASopathy genes in sun-exposed melanomas. Nat Genet. 2015;47:996-1002.
27. Griewank KG, Scolyer RA, Thompson JF, et al. Genetic alterations and personalized medicine in melanoma: progress and future prospects. J Natl Cancer Inst. 2014;106:djt435.
28. Falchook GS, Lewis KD, Infante JR, et al. Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial. Lancet Oncol. 2012;13:782-789.
29. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13:1087-1095.
30. McArthur GA, Maio M, Arance A, et al. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study. Ann Oncol. 2017;28:634-641.
31. Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with $BRAF^{V600}$-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol. 2017;18:863-873.
32. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol. 2012; 13:459-465.
33. Kluger HM, Chiang V, Mahajan A, et al. Long-term survival of patients with melanoma with active brain metastases treated with pembrolizumab on a phase II trial. J Clin Oncol. 2019;37:52-60.
34. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med. 2018;379:722-730.
35. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomized phase 2 study. Lancet Oncol. 2018;19:672-681.
36. Long GV, Grob JJ, Nathan PD, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomized trials. Lancet Oncol. 2016;17:1743-1754.
37. Holbrook Kourtney, Lutzky Jose, Davies Michael, et al. Intracranial antitumor activity with encorafenib plus binimetinib in patients with melanoma brain metastases: A case series. Cancer. 2020;126:523-530.
38. Fischer GM, Jalali A, Kircher DA, et al. Molecular profiling reveals unique immune and metabolic features of melanoma brain metastases. Cancer Discov. 2019; 9:628-645.
39. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015;15:7-24.
40. Vanhaesebroeck B, Stephens L, Hawkins P. PI3K signalling: the path to discovery and understanding. Nat Rev Mol Cell Biol. 2012;13:195-203.
41. Niessner H, Schmitz J, Tabatabai G, et al. PI3K pathway inhibition achieves potent antitumor activity in melanoma brain metastases in vitro and in vivo [published correction appears in *Clin Cancer Res*. 2017;23:1361]. Clin Cancer Res. 2016;22:5818-5828.
42. Kircher DA, Arave RA, Cho JH, et al. Melanoma metastases caught in the AKT. Mol Cell Oncol. 2016;3:e1128516.

43. Cho JH, Robinson JP, Arave RA, et al. AKT1 activation promotes development of melanoma metastases. Cell Rep. 2015;13:898-905.
44. Peng W, Chen JQ, Liu C, et al. Loss of PTEN promotes resistance to T-cell mediated immunotherapy. Cancer Discov. 2016;6:202-216.
45. Dong Y, Richards JA, Gupta R, et al. PTEN functions as a melanoma tumor suppressor by promoting host immune response. Oncogene. 2014;33:4632-4642.
46. Hodi FS, Oble DA, Drappatz J, et al. CTLA-4 blockade with ipilimumab induces significant clinical benefit in a female with melanoma metastases to the CNS. Nat Clin Pract Oncol. 2008;5:557-561.
47. Schartz NE, Farges C, Madelaine I, et al. Complete regression of a previously untreated melanoma brain metastasis with ipilimumab. Melanoma Res. 2010; 20:247-250.
48. Di Giacomo AM, Ascierto PA, Pilla L, et al. Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial. Lancet Oncol. 2012;13:879-886.
49. Goldberg SB, Gettinger SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. Lancet Oncol. 2016;17:976-983.
50. Engelhardt B, Ransohoff RM. Capture, crawl, cross: the T cell code to breach the blood-brain barriers. Trends Immunol. 2012;33:579-589.
51. Banks PD, Lasocki A, Lau PKH, et al. Bevacizumab as a steroid-sparing agent during immunotherapy for melanoma brain metastases: a case series. Health Sci Rep. 2019;2:e115.
52. Glitza IC, Guha-Thakurta N, D'Souza NM, et al. Bevacizumab as an effective treatment for radiation necrosis after radiotherapy for melanoma brain metastases. Melanoma Res. 2017;27:580-584.
53. Tawbi HA, Forsyth PA, Hodi S, et al. Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204). J Clin Oncol. 2019;37(15_suppl):9501.
54. Borgelt B, Gelber R, Kramer S, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 1980;6:1-9.
55. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998; 280:1485-1489.
56. Baschnagel A, Wolters PL, Camphausen K. Neuropsychological testing and biomarkers in the management of brain metastases. Radiat Oncol. 2008;3:26.
57. Tsao MN, Lloyd N, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev. 2012; 4:CD003869.
58. Goyal S, Silk AW, Tian S, et al. Clinical management of multiple melanoma brain metastases: a systematic review. JAMA Oncol. 2015;1:668-676.
59. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet. 2004;363:1665-1672.
60. Yamamoto M, Serizawa T, Higuchi Y, et al. A multi-institutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901 study update): irradiation-related complications and long-term maintenance of Mini-Mental State Examination scores. Int J Radiat Oncol Biol Phys. 2017;99:31-40.
61. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol. 2014;15:387-395.
62. Hong AM, Fogarty GB, Dolven-Jacobsen K, et al. Adjuvant whole-brain radiation therapy compared with observation after local treatment of melanoma brain metastases: a multicenter, randomized phase III trial. J Clin Oncol. 2019;37:3132-3141.
63. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomized controlled trial. Lancet Oncol. 2009;10:1037-1044.
64. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. J Clin Oncol. 2014;32:3810-3816.
65. Brown PD, Pugh S, Laack NN, et al; Radiation Therapy Oncology Group (RTOG). Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro-oncol. 2013;15:1429-1437.
66. Gondi V, Deshmukh S, Brown PD, et al. NRG Oncology CC001: a phase III trial of hippocampal avoidance (HA) in addition to whole-brain radiotherapy (WBRT) plus memantine to preserve neurocognitive function (NCF) in patients with brain metastases (BM). J Clin Oncol. 2019;37(15_suppl):2009.
67. Li J, Lang FF, Guha-Thakurta N, et al. MLTI-10. Establishment of a multidisciplinary brain metastasis clinic to facilitate patient-centered care and coordinated research. Neuro-Oncology Advances. 2019;1(Suppl_1):i16.
68. Pfannenstiel LW, McNeilly C, Xiang C, et al. Combination PD-1 blockade and irradiation of brain metastasis induces an effective abscopal effect in melanoma. OncoImmunology. 2018;8:e1507669.
69. Patel KR, Lawson DH, Kudchadkar RR, et al. Two heads better than one? Ipilimumab immunotherapy and radiation therapy for melanoma brain metastases. Neuro-oncol. 2015;17:1312-1321.
70. Stamell EF, Wolchok JD, Gnjatic S, et al. The abscopal effect associated with a systemic anti-melanoma immune response. Int J Radiat Oncol Biol Phys. 2013; 85:293-295.
71. Knisely JP, Yu JB, Flanigan J, et al. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival. J Neurosurg. 2012; 117:227-233.

72. Silk AW, Bassetti MF, West BT, et al. Ipilimumab and radiation therapy for melanoma brain metastases. Cancer Med. 2013;2:899-906.

73. Patel KR, Shoukat S, Oliver DE, et al. Ipilimumab and stereotactic radiosurgery versus stereotactic radiosurgery alone for newly diagnosed melanoma brain metastases. Am J Clin Oncol. 2017;40:444-450.

74. Mathew M, Tam M, Ott PA, et al. Ipilimumab in melanoma with limited brain metastases treated with stereotactic radiosurgery. Melanoma Res. 2013; 23:191-195.

75. Gabani P, Fischer-Valuck BW, Johanns TM, et al. Stereotactic radiosurgery and immunotherapy in melanoma brain metastases: patterns of care and treatment outcomes. Radiother Oncol. 2018;128:266-273.

76. Ascierto PA, Ferrucci PF, Fisher R, et al. Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma. Nat Med. 2019;25:941-946.

77. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced $BRAF^{V600}$ mutation-positive melanoma (iMspire150): primary analysis of the randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020;395:1835-1844.

78. Nathan P, Dummer R, Long GV, et al. Spartalizumab plus dabrafenib and trametinib in patients with previously untreated BRAF V600-mutant unresectable or metastatic melanoma: results from the randomized part 3 of the phase III COMBI-i trial. Presented at: ESMO Virtual Congress 2020. Abstract LBA43.

79. Burton EM, Amaria RN, Glitza IC, et al. Safety and efficacy of TRIplet combination of nivolumab (N) with dabrafenib (D) and trametinib (T) [TRIDeNT] in patients (pts) with BRAF-mutated metastatic melanoma (MM): a single center phase II study. Ann Oncol. 2019;30(Suppl_5):v534-v535.

80. Amaral T, Tampouri I, Eigentler T, et al. Immunotherapy plus surgery/radiosurgery is associated with favorable survival in patients with melanoma brain metastasis. Immunotherapy. 2019;11:297-309.

81. Wilmott JS, Long GV, Howle JR, et al. Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clin Cancer Res. 2012; 18:1386-1394.

82. Ribas A, Lawrence D, Atkinson V, et al. Combined BRAF and MEK inhibition with PD-1 blockade immunotherapy in BRAF-mutant melanoma [published correction appears in *Nat Med*. 2019;25:1319]. Nat Med. 2019;25:936-940.

83. Arance Fernandez AM, O'Day SJ, de la Cruz L, et al. Lenvatinib (len) plus pembrolizumab (pembro) for advanced melanoma (MEL) that progressed on a PD-1 or PD-L1 inhibitor: initial results of LEAP-004. Presented at: ESMO Virtual Congress 2020. Abstract LBA44.

Immunotherapy for Advanced Non–Small Cell Lung Cancer: A Decade of Progress

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overview

The treatment paradigm for patients with advanced non–small cell lung cancer has substantially changed with the discovery of immunotherapy. The incorporation of immunotherapy into treatment algorithms has resulted in better outcomes for patients, with fewer side effects compared with classic chemotherapeutic agents. Multiple treatment options are now available for patients with advanced non–small cell lung cancer, ranging from single-agent immunotherapy to quadruple therapy, which involves dual immune checkpoint inhibitor plus chemotherapy or immune checkpoint inhibitor plus chemotherapy plus anti–vascular endothelial growth factor drugs. This article will review landmark studies that have led to U.S. Food and Drug Administration approval of immunotherapy agents alone or in combination with chemotherapy or other immunotherapy drugs to treat advanced non–small cell lung cancer.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death among both men and women in the United States.[1] For many years, treatment options for patients diagnosed with advanced non–small cell lung cancer (NSCLC) were limited to cytotoxic chemotherapies, which conferred a median overall survival (OS) of approximately 6 months.[2] In the past decades, different classes of drugs, including targeted therapies and immune checkpoint inhibitors, have become available, resulting in a shift in the treatment paradigm for patients with NSCLC (Fig. 1).[3] Immune checkpoint inhibitors leverage the ability of lung cancer cells to escape detection through the PD-1 axis. These drugs restore the immune system surveillance by stimulating the cytotoxic T cells to induce cancer cell death.[4] Immune checkpoint inhibitors with varying mechanisms of action are available, including agents directed against PD-1 (nivolumab, pembrolizumab, cemiplimab), PD-L1 (atezolizumab, durvalumab, avelumab), and CTLA-4 (ipilimumab and tremelimumab). This article will review the landmark studies that have led to U.S. Food and Drug Administration (FDA) approval of single-agent immunotherapy, combination immunotherapy (i.e., dual immunotherapy), and immunotherapy in conjunction with chemotherapy for the treatment of patients with advanced NSCLC.

CLINICAL TRIALS WITH SINGLE-AGENT IMMUNOTHERAPY

Nivolumab, a human IgG4 monoclonal antibody to PD-1, was the first immune checkpoint inhibitor approved by the FDA to treat patients with advanced NSCLC.[5] This drug prevents the interaction of PD-1, a proinhibitory signal found on CD4 and CD8 T cells and antigen-presenting cells,[6] with its ligand (PD-L1 or PD-L2). The FDA approval of nivolumab was based on the results of two phase III clinical trials involving heavily pretreated patients with stage IIIB/IV NSCLC (CheckMate 017 and CheckMate 057).[7,8] In these studies, patients were randomly assigned to receive nivolumab monotherapy (3 mg/kg intravenously once every 2 weeks) or docetaxel (75 mg/m^2 intravenously once every 3 weeks).

CheckMate 017 enrolled 272 patients with advanced squamous cell NSCLC.[7] In this study, nivolumab conferred superior OS compared with docetaxel (median OS, 9.2 months vs. 6.0 months, respectively; $p = .002$). In CheckMate 057, 582 patients with nonsquamous NSCLC were enrolled,[8] and OS was longer with nivolumab than with docetaxel (median OS, 12.2 months vs. 9.4 months, respectively; $p < .001$). Nivolumab's survival benefit persisted beyond 1 year, as illustrated by an updated outcomes analysis of both studies that reported a 2-year OS benefit with nivolumab independent of disease histology. When comparing nivolumab and docetaxel, OS was 23% versus 8%, respectively, for squamous NSCLC and 29% versus 16%, respectively, for nonsquamous NSCLC.[9] Although PD-L1 expression was neither prognostic for nor predictive of benefit for patients with squamous cell carcinoma, the results of CheckMate 057 suggested that PD-L1 expression is a predictive biomarker for response to nivolumab among patients with nonsquamous NSCLC.[7,8]

Pembrolizumab is a humanized IgG4 monoclonal antibody directed against PD-1. This therapy was

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PRACTICAL APPLICATIONS

- Immunotherapy consists of a class of drugs that interact with the immune system to induce cancer cell apoptosis. Monoclonal antibodies against PD-1, PD-L1, and CTLA-4 are the most commonly used immune checkpoint inhibitors for patients with non–small cell lung cancer.
- Immune checkpoint inhibitors alone or in combination with chemotherapy or in combination with other immune checkpoint inhibitors should be the first-line treatment of choice for patients with advanced non–small cell lung cancer who do not have contraindications to immunotherapy and whose tumors do not harbor actionable driver mutations.
- The combination of immunotherapy with platinum-based chemotherapy in the first-line setting is beneficial regardless of tumoral PD-L1 status.
- The combination of ipilimumab and nivolumab is approved for the treatment of patients with advanced/metastatic non–small cell lung cancer whose tumoral PD-L1 is $\geq$ 1% in the first-line setting.
- Immunotherapy is generally better tolerated than classic cytotoxic chemotherapeutic agents.

initially approved for NSCLC by the FDA in October 2015[10] according to the results of KEYNOTE-010, a phase II/III study that enrolled previously treated patients with advanced/metastatic NSCLC whose tumors expressed PD-L1 on at least 1% of the cells (i.e., a tumor proportion score [TPS] $\geq$ 1%).[11] The results demonstrated a survival benefit of pembrolizumab compared with docetaxel (median OS, 12.7 months vs. 8.5 months, respectively; $p < .001$). Also, a more pronounced survival benefit was noted among patients whose tumors had a PD-L1 TPS $\geq$ 50% (median OS, 17.3 months vs. 8.2 months for pembrolizumab vs. docetaxel).

Five months before KEYNOTE-010 completed its accrual, a study started that assessed the use of pembrolizumab in the front-line setting for patients with untreated advanced NSCLC with a PD-L1 TPS $\geq$ 50% (KEYNOTE-024).[12] This study, an open-label phase III trial, investigated the role of first-line pembrolizumab monotherapy (200 mg intravenously given every 3 weeks) versus investigator's choice of platinum-based chemotherapy. Three hundred five patients with tumor PD-L1 TPS $\geq$ 50% without actionable mutations in *ALK* or *EGFR* were treated until disease progression occurred.[12] Pembrolizumab therapy conferred improved progression-free survival (PFS) and OS. The median PFS was 10.3 months versus 6.0 months for pembrolizumab versus platinum-based chemotherapy ($p < .001$).[12] On the basis of these findings, pembrolizumab was approved by the FDA in October 2016 for the front-line treatment of patients with advanced NSCLC with tumor PD-L1 expression $\geq$ 50%.[10] Recently, trial updates were published demonstrating a continued survival benefit for patients treated with pembrolizumab monotherapy (median OS, 30 months vs. 14.2 months for pembrolizumab vs. platinum-based chemotherapy).[13]

In parallel with KEYNOTE-024, another multi-institutional, randomized, phase III trial assessing the role of first-line pembrolizumab monotherapy for NSCLC with PD-L1 TPS $\geq$ 1% started enrolling patients (KEYNOTE-042).[14] In this study, 1,274 patients were assigned to receive pembrolizumab (200 mg intravenously once every 3 weeks) or chemotherapy (paclitaxel/carboplatin or pemetrexed/carboplatin). The primary endpoint was OS for patients across three PD-L1 TPS populations: $\geq$ 50%, $\geq$ 20%, and $\geq$ 1%. Of note, 599 patients (47%) had PD-L1 TPS $\geq$ 50%, and 818 patients (64%) had PD-L1 TPS $\geq$ 20%. Patients with PD-L1 TPS $\geq$ 50% were accounted for in the PD-L1 TPS $\geq$ 20% group. PD-L1 expression was determined by an immunohistochemistry assay using the PD-L1 immunohistochemistry pharmDx assay. The median OS was significantly longer in the pembrolizumab arm than the chemotherapy arm for all three TPS populations (respective OS times for the subgroup with TPS PD-L1 $\geq$ 50% was 20.0 months vs. 12.2 months [$p = .0003$], $\geq$ 20% was 17.7 months vs. 13.0 months [$p = .002$], and $\geq$ 1% was 16.7 months vs. 12.1 months [$p = .0018$]).[14] This study led to FDA approval of single-agent pembrolizumab for first-line treatment of unresectable stage III or IV NSCLC with PD-L1 TPS $\geq$ 1% and no actionable mutations.[10]

Atezolizumab is a fully humanized IgG1 monoclonal antibody that targets PD-L1.[15] PD-L1 expression is found on antigen-presenting cells, T cells, B cells, and nonhematopoietic cells, including tumor cells.[6] Two studies demonstrated a survival benefit with the use of atezolizumab monotherapy for patients with advanced/metastatic NSCLC who had received at least one prior therapy.[16,17] The POPLAR and OAK studies, phase II and III clinical trials, respectively, both investigated the efficacy and safety of atezolizumab 1,200 mg versus docetaxel 75 mg/m^2, both of which were given every 3 weeks, among patients with advanced/metastatic NSCLC who received at least one prior therapy. All patients in this study had previously been treated with a platinum doublet before enrollment.

The POPLAR study enrolled 142 patients and demonstrated superior OS with the use of atezolizumab (median OS, 12.6 months vs. 9.7 months for atezolizumab vs. docetaxel;

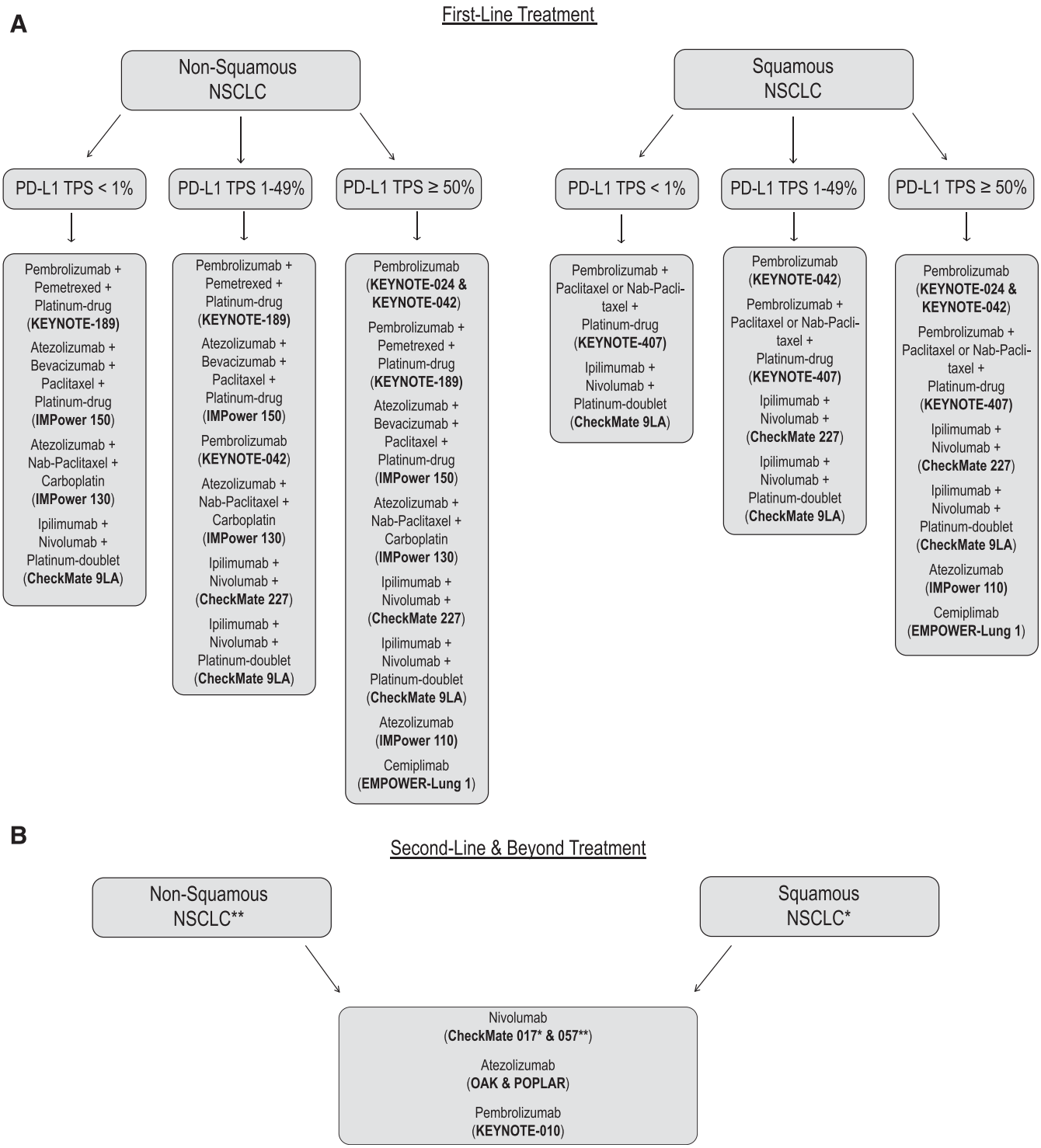

FIGURE 1. Schema of FDA-Approved Immunotherapy-Containing Regimens for Patients With Advanced NSCLC

(A) Treatments approved for use in the first-line setting. Regimens are listed according to histologic subtype and PD-L1 status. Treatments are organized in chronologic order according to FDA approval dates. (B) Treatments approved for use in second-line therapy and beyond. Regimens are listed accordingly to histologic subtype. Treatments are organized in chronologic order according to FDA approval dates.

Abbreviations FDA, U.S. Food and Drug Administration; NSCLC, non–small cell lung cancer; TPS, tumor proportion score.

p = .04). Although investigators noted an OS benefit for all patients independent of tumor PD-L1 expression level, there was an increasing improvement in OS with increasing tumor PD-L1 expression.[17] Twenty days after the accrual was completed for the POPLAR study, the OAK trial, the first phase III study to investigate an anti–PD-L1 agent for advanced NSCLC, started accrual. This trial enrolled 1,225 patients, and the trial showed that atezolizumab significantly improved OS compared with docetaxel (median OS, 13.8 months vs. 9.6 months; p = .0003).[16] Interestingly, in the OAK study, the OS benefit was independent of PD-L1 expression, and even patients with low or undetectable tumor PD-L1 levels (PD-L1 $\leq$ 1% in tumor-infiltrating immune cells and tumor cells) had superior OS when treated with atezolizumab rather than docetaxel (median OS, 12.6 months vs. 8.9 months, respectively; p = .0215).[16]

Given the encouraging results seen in the POPLAR and OAK studies, a randomized, open-label, phase III trial assessing first-line atezolizumab treatment among patients with metastatic NSCLC whose tumor PD-L1 expression was $\geq$ 1% (assessed by Ventana PD-L1 [SP142] immunohistochemistry) opened in July 2015 (IMpower110).[18] The 572 patients enrolled in IMpower110 were assigned to receive either atezolizumab 1,200 mg or platinum-based chemotherapy, both of which were given every 3 weeks. The primary endpoint of this study was OS, and patients were stratified by PD-L1 status (low, PD-L1 TPS $\geq$ 1% or $\geq$ 1% on tumor-infiltrating immune cells; intermediate, PD-L1 TPS $\geq$ 5% or $\geq$ 5% on tumor-infiltrating immune cells; high, PD-L1 TPS $\geq$ 50% or $\geq$ 10% on tumor-infiltrating immune cells). Compared with platinum-based chemotherapy, atezolizumab resulted in significantly longer OS among patients whose tumors had a high PD-L1 TPS (PD-L1 $\geq$ 50%; median OS, 20.2 months vs. 13.1 months for atezolizumab vs. chemotherapy; p = .01).[18] This trial led to FDA approval in May 2020 of atezolizumab as a first-line treatment of stage IV NSCLC (independent of histology) with PD-L1 TPS $\geq$ 50% without genomic alterations in *EGFR* or *ALK*, and Ventana PD-L1 (SP142) immunohistochemistry was also approved as a companion diagnostic for the selection of patients for atezolizumab treatment according to PD-L1 expression.[19]

Cemiplimab is a high-affinity humanized PD-1 antibody that was first approved by the FDA for the treatment of advanced cutaneous squamous cell carcinoma in September 2018.[20] Given its efficacy for cutaneous squamous cell carcinoma, cemiplimab was investigated as a therapy for patients with advanced NSCLC through the EMPOWER-Lung 1 study between June 2017 and February 2020.[20] This open-label, phase III trial enrolled 710 treatment-naïve patients with advanced/metastatic NSCLC whose tumors had a PD-L1 level of $\geq$ 50% (as indicated by the PD-L1 immunohistochemistry 22C3 pharmDx) and did not harbor an *EGFR*, *ALK,* or *ROS1* mutations. Patients were randomly assigned to treatment with cemiplimab 350 mg intravenously every 3 weeks or platinum-doublet chemotherapy (four to six cycles, including cisplatin or carboplatin, plus paclitaxel, pemetrexed, or gemcitabine).[20] The primary endpoint of this study was PFS, and cemiplimab conferred superior PFS compared with platinum-doublet chemotherapy (8.2 months vs. 5.7 months, respectively; p < .0001). Cemiplimab use also resulted in improved OS compared with chemotherapy (median OS, not reached vs. 14.2 months; p = .002). Cemiplimab has a favorable safety profile compared with platinum-doublet chemotherapy, with lower rates of grade 3/4 treatment-related adverse events (28% vs. 39%, respectively).[20] A summary of these trials can be found in Table 1.

CLINICAL TRIALS WITH COMBINED IMMUNOTHERAPY

Ipilimumab is a fully humanized monoclonal antibody directed against CTLA-4. This drug was the first immune checkpoint inhibitor to receive FDA approval in March 2011 for late-stage melanoma.[21] Four years later, a combination of ipilimumab and nivolumab was approved for the treatment of *BRAF* V600 wild-type melanoma.[5] Given the OS benefit of this combination compared with ipilimumab alone for the treatment of melanoma and the known efficacy of nivolumab for the treatment of advanced NSCLC (CheckMate 017 and 057), first-line combined nivolumab and ipilimumab was investigated to treat advanced NSCLC (CheckMate 012).[22,23]

In this open-label, phase I trial, patients were assigned to one of six cohorts, each with different schedules and doses of the two drugs. In three cohorts, the toxicity was considered unacceptable, and in a fourth cohort with a lower dose of nivolumab (1 mg/kg), clinical activity was considered suboptimal. Therefore, only the dosing schedules of two cohorts were considered acceptable for continued development. The first was nivolumab 1 mg/kg intravenously every 2 weeks plus ipilimumab 1 mg/kg intravenously every 12 weeks, and the second was nivolumab 3 mg/kg intravenously every 2 weeks plus ipilimumab 1 mg/kg intravenously every 6 weeks. Seventy-eight patients were assigned to receive therapy under one of these two acceptable cohorts. The median PFS was 8.1 months versus 3.9 months for the cohorts receiving ipilimumab every 12 weeks versus every 6 weeks, respectively. The 1-year OS was not reached in the cohort receiving ipilimumab every 12 weeks and was 69% in the group receiving ipilimumab every 6 weeks.[22] Grade 3/4 treatment-related adverse events were similar between the two groups (37% vs. 33% for ipilimumab every 12 weeks vs. ipilimumab every 6 weeks).

CheckMate 227 (NCT02477826), an open-label, phase III trial for treatment-naïve patients with stage IV or recurrent

TABLE 1. Landmark Clinical Trials: Single-Agent Immunotherapy, Combination Immunotherapy, and Chemoimmunotherapy

Trial (NCT No.)	Phase	Study Population	Treatment Regimen	Outcomes	Safety
Single-Agent Immune Checkpoint Inhibitors					
CheckMate 017[7,9] (NCT01642004)	III	272 patients	Cohort A: nivolumab 3 mg/kg every 2 weeks	mPFS: 3.5 months (A) vs. 2.8 months (B)	Any AE: 58% (A) vs. 86% (B)
		Squamous cell NSCLC	Cohort B: docetaxel 75 mg/m^2 every 3 weeks	mOS: 9.2 months (A) vs. 6.0 months (B)	
		Previous platinum-based chemotherapy			
		Stage IIIB or IV			
		PD-L1 levels measured retrospectively			
CheckMate 057[8,9] (NCT01673867)	IV	582 patients	Cohort A: nivolumab 3 mg/kg every 2 weeks	mPFS: 2.3 months (A) vs. 4.2 months (B)	Any AE: 69% (A) vs. 88% (B)
		Nonsquamous NSCLC	Cohort B: docetaxel 75 mg/m^2 every 3 weeks	mOS: 12.2 months (A) vs. 9.4 months (B)	
		Previous platinum-based chemotherapy			
		Stage IIIB or IV			
		PD-L1 levels measured retrospectively			
EMPOWER-Lung 1[20] (NCT03088540)	III	710 patients	Cohort A: cemiplimab 350 mg every 3 weeks	mPFS: 8.2 months (A) vs. 5.7 months (B)	Grade 3-4 AEs: 28% (A) vs. 39% (B)
		Stage IIIB, IIIC, or IV NSCLC	Cohort B: platinum-based chemotherapy	mOS: NR (A) vs. 14.2 months (B)	
		Treatment-naïve			
		PD-L1 $\geq$ 50%			
		Tobacco exposure			
		No *EGFR, ALK,* or *ROS1* mutations			
KEYNOTE-010[11] (NCT01905657)	II/III	1,034 patients	Cohort A: pembrolizumab 2 mg/kg every 3 weeks	mPFS: 3.9 months (A), 4.0 months (B), and 4.0 months (C). For patients with PD-L1 $\geq$ 50%, 5.0 months (A), 5.2 months (B), and 4.1 months (C)	Any AE: 63% (A), vs. 66% (B), vs. 81% (C)
		Previously treated advanced/ metastatic NSCLC	Cohort B: pembrolizumab 10 mg/kg every 3 weeks	mOS: 10.4 months (A), 12.7 months (B), and 8.5 months (C); 14.9 months. For patients with PD-L1 $\geq$ 50%, (A) 17.3 months (B), and 8.2 months (C)	
		PD-L1 $\geq$ 1%	Cohort C: docetaxel 75 mg/m^2 every 3 weeks		

(Continued on following page)

TABLE 1. Landmark Clinical Trials: Single-Agent Immunotherapy, Combination Immunotherapy, and Chemoimmunotherapy (Continued)

Trial (NCT No.)	Phase	Study Population	Treatment Regimen	Outcomes	Safety
KEYNOTE-024[12,13] (NCT02142738)	III	305 patients	Cohort A: pembrolizumab 200 mg every 3 weeks	mPFS: 10.3 months (A) vs. 6.0 months (B)	Any AE: 73% (A) vs. 90% (B)
		Untreated advanced NSCLC	Cohort B: platinum-based chemotherapy	mOS: 30 months (A) vs. 14.2 months (B)	
		No *EGFR* or *ALK* mutations			
		PD-L1 $\geq$ 50%			
KEYNOTE-042[14] (NCT02220894)	III	1,274 patients	Cohort A: pembrolizumab 200 mg every 3 weeks	mPFS: A: 7.1 months (PD-L1 $\geq$ 50%), 6.2 months (PD-L1 $\geq$ 20%), and 5.4 months (PD-L1 $\geq$ 1%)	Any AE: 63% (A) vs. 90% (B)
		Untreated locally advanced/metastatic NSCLC	Cohort B: platinum-based chemotherapy	B: 6.4 months (PD-L1 $\geq$ 50%), 6.6 months (PD-L1 $\geq$ 20%), 6.5 months (PD-L1 $\geq$ 1%)	
		No *EGFR* or *ALK* mutations		mOS: A: 20.0 months (PD-L1 $\geq$ 50%),17.7 months (PD-L1 $\geq$ 20%), 16.7 months (PD-L1 $\geq$ 1%)	
		ECOG 0-1		B: 12.2 months (PD-L1 $\geq$ 50%) 13.0 months (PD-L1 $\geq$ 20%), and 12.1 months (PD-L1 $\geq$ 1%)	
		Life expectancy > 3 months			
		PD-L1 $\geq$ 1%, $\geq$ 20%, and $\geq$ 50%			
IMpower 110[18] (NCT02409342)	III	572 patients	Cohort A: atezolizumab 1,200 mg every 3 weeks	mPFS: A: 8.1 months (PD-L1 $\geq$ 50%), 7.2 months (PD-L1 $\geq$ 5%), and 5.7% (PD-L1 $\geq$ 1%)	Any AE: 90% (A) vs. 95% (B)
		Metastatic NSCLC	Cohort B: platinum-based chemotherapy	B: 5.7 months (PD-L1 $\geq$ 50%), 5.5 months (PD-L1 $\geq$ 5%), and 5.5 months (PD-L1 $\geq$ 1%)	
		No *EGFR* or *ALK* mutations		mOS: A: 20.2 months (PD-L1 $\geq$ 50%), 18.2 months (PD-L1 $\geq$ 5%), 17.5 months (PD-L1 $\geq$ 1%)	
		No prior therapy		B: 13.1 months (PD-L1 $\geq$ 50%), 14.9 months (PD-L1 $\geq$ 5%), 14.1 months (PD-L1 $\geq$ 1%)	
		PD-L1 $\geq$ 1%			

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TABLE 1. Landmark Clinical Trials: Single-Agent Immunotherapy, Combination Immunotherapy, and Chemoimmunotherapy (Continued)

Trial (NCT No.)	Phase	Study Population	Treatment Regimen	Outcomes	Safety
OAK[17] (NCT02008227)	III	1,225 patients	Cohort A: atezolizumab 1,200 mg every 3 wk	mPFS: 2.8 months (A) vs. 4.0 months (B)	Any AE: 64% (A) vs. 86% (B)
		Stage IIIB or IV NSCLC	Cohort B: docetaxel 75 mg/m^2 every 3 weeks	mOS: A: 13.8 months (IIT analysis), 15.7 months (PD-L1 $\geq$ 1%), 12.6 months (PD-L1 $<$ 1%)	
		Prior 1-2 cytotoxic chemotherapy regimens ($\geq$ 1 platinum-based therapies)		mOS B: 9.6 months (IIT analysis), 10.3 months (PD-L1 $\geq$ 1%), 8.9 months (PD-L1 $<$ 1%)	
		Any PD-L1 levels			
POPLAR[16] (NCT01903993)	II	287 patients	Cohort A: atezolizumab 1,200 mg every 3 weeks	mPFS (ITT analysis): 2.7 months (A) vs. 3.0 months (B)	Any AE: 96% (A) vs. 96% (B)
		Advanced NSCLC	Cohort B: docetaxel 75 mg/m^2 every 3 weeks	mOS (ITT analysis): 12.6 months (A) vs. 9.7 months (B)	
		Previous $\geq$ 1 line of therapy			
		Any PD-L1 levels			
Combined Immunotherapy					
ARCTIC[29] (NCT02352948)	III	595 patients	PD-L1 $\geq$ 25%:	PFS: 3.8 months (A) vs. 2.2 months (B); 3.5 months (C) vs. 3.5 months (D) vs. 3.1 months (E) vs. 2.1 months (F)	Any AE: 96.8% (A), vs. 100% (B); 92.5% (C), vs. 95.5% (D), vs. 93.2% (E), vs. 85% (F)
		Stage IIIB/IV NSCLC with disease progression or recurrence after both a platinum-doublet regimen and one or more additional systemic regimens	Cohort A: durvalumab 10 mg/kg every 2 weeks up to 12 months	OS: 11.7 months (A) vs. 6.8 months (B); 11.5 months (C) vs. 8.7 months (D) vs. 10.0 months (E) vs. 6.9 months (F)	
		No prior anti-CTLA-4, anti-PD-1, or anti-PD-L1 antibody therapy	Cohort B: SoC		
		Any PD-L1 levels	PD-L1 $<$ 25%:		
			Cohort C: durvalumab 20 mg/kg every 4 weeks + tremelimumab 1 mg/kg every 4 weeks up to 12 weeks, followed by durvalumab alone 10 mg/kg every 2 weeks for 34 weeks		
			Cohort D: SoC		
			Cohort E: durvalumab 10 mg/kg every 2 weeks up to 12 months		
			Cohort F: tremelimumab 10 mg/kg every 4 weeks for 24 weeks then every 12 weeks for 24 weeks		

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TABLE 1. Landmark Clinical Trials: Single-Agent Immunotherapy, Combination Immunotherapy, and Chemoimmunotherapy (Continued)

Trial (NCT No.)	Phase	Study Population	Treatment Regimen	Outcomes	Safety
CheckMate 012[22] (NCT01454102)	I	78 patients	Cohort A: nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 12 weeks	mPFS: 8.1 months (A) vs. 3.9 months (B)	Any AE: 82% (A) vs. 72% (B)
		Recurrent stage IIIB or IV NSCLC	Cohort B: nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks	mOS: Not reported	
		Chemotherapy-naïve for advanced disease			
		PD-L1 levels measured retrospectively			
CheckMate 227[24] (NCT02477826)	III	1,739 patients (1,189 patients with PD-L1 1% and 550 pts with PD-L1, 1%)	PD-L1 $\geq$ 1%:	mPFS: 5.1 months (A), 4.2 months (B), 5.6 months (C), 5.1 months (D), 5.6 months (E), 4.7 months (F)	Any AE: 77% (A), 65.5% (B), 84% (C), 76% (D), 92% (E), 78% (F)
		Stage IV or recurrent NSCLC	Cohort A: nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks	mOS: 17.1 months (A), 15.7 months (B), 14.9 months (C), 17.2 months (D), 15.2 (E), 12.2 months (F)	
		Chemotherapy-naïve	Cohort B: Nivolumab 240mg every 2 weeks		
			Cohort C: platinum-based chemotherapy		
			PD-L1 $<$ 1%:		
			Cohort D: nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks		
			Cohort E: nivolumab 360mg every 3 weeks + platinum-based chemotherapy		
			Cohort F: platinum-based chemotherapy		
CheckMate 568[25] (NCT02659059)	II	288 patients	Nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks	mPFS: 4.2 months (all patients), 6.8 months (PD-L1 $\geq$ 50%), 2.8 months (PD-L1 $<$ 1%), 7.1 months (TMB $\geq$ 10), and 2.6 months (TMB $<$ 10)	Any AE: 80%
		Recurrent stage IIIB/IV NSCLC		mOS: Not reported	
		Treatment-naïve			
		Any PD-L1 levels			

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TABLE 1. Landmark Clinical Trials: Single-Agent Immunotherapy, Combination Immunotherapy, and Chemoimmunotherapy (Continued)

Trial (NCT No.)	Phase	Study Population	Treatment Regimen	Outcomes	Safety
MYSTIC[27] (NCT02453282)	III	1,118 patients	Cohort A: durvalumab 20 mg/kg every 4 weeks	Median PFS: 4.7 months (A), 3.9 months (B) and 5.4 months (C)	Any AE: 54% (A) vs. 60% (B) vs. 83% (C)
		Treatment-naïve, metastatic NSCLC	Cohort B: durvalumab 20 mg/kg every 4 weeks + tremelimumab 1 mg/kg every 4 weeks, up to 4 doses	OS: 16.3 months (A), 11.9 months (B), and 12.9 months (C).	
		No *EGFR* or *ALK* mutation	Cohort C: platinum-based chemotherapy	For patients with $\geq$ 20 mut/Mb, 21.9 months (B) and 10 months (C)	
		Any PD-L1 levels			
NCT02000947[26]	Ib	102 patients	Cohort A: durvalumab 10-20 mg/kg every 2 or 4 weeks + tremelimumab 1 mg/kg every 4 weeks	ORR: 23% (A) vs. 20% (B) vs. 0% (C)	Any AE: 23% (A) vs. 47% (B) vs. 44% (C)
		Immunotherapy-naïve	Cohort B: durvalumab 10-20 mg/kg every 2 or 4 weeks + tremelimumab 3 mg/kg every 4 weeks		
		Locally advanced or metastatic NSCLC	Cohort C: durvalumab 15 mg/kg + tremelimumab 10 mg/kg every 4 weeks		
		Any PD-L1 levels			
Chemoimmunotherapy					
CheckMate 9LA[39]	III	719 patients	Cohort A: nivolumab 360 mg intravenously every 3 weeks + ipilimumab 1 mg/kg intravenously every 6 weeks + platinum-based chemotherapy (every 3 weeks for two cycles)	mPFS: 6.8 months (A) vs. 5.0 months (B)	Any AE: 91% (A) vs. 87% (B)
		Stage IV or recurrent NSCLC	Cohort B: platinum-based chemotherapy (4 cycles)	mOS: 15.6 months (A) vs. 10.9 months (B)	
		Therapy-naïve			
		No *EGFR* or *ALK* mutations			
		Any PD-L1 levels			

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TABLE 1. Landmark Clinical Trials: Single-Agent Immunotherapy, Combination Immunotherapy, and Chemoimmunotherapy (Continued)

Trial (NCT No.)	Phase	Study Population	Treatment Regimen	Outcomes	Safety
KEYNOTE-189[30] (NCT02578680)	III	616 patients	Cohort A: pemetrexed and a platinum-based drug + 200 mg of pembrolizumab every 3 weeks for 4 cycles followed by pembrolizumab for up to a total of 35 cycles + pemetrexed maintenance therapy	mPFS: 8.8 months (A) vs. 4.9 months (B)	Any AE: 99.8% (A) vs. 99% (B)
		Metastatic nonsquamous NSCLC No *EGFR* or *ALK* mutations No previous treatment of metastatic disease Any PD-L1 levels	Cohort B: pemetrexed and a platinum-based drug + placebo every 3 weeks for 4 cycles followed by placebo for up to a total of 35 cycles + pemetrexed maintenance therapy	mOS: 22 months (A) vs. 10.7 months (B)	
KEYNOTE-407[32] (NCT02775435)	III	559 patients	Cohort A: 200 mg of pembrolizumab for up to 35 cycles + carboplatin and either paclitaxel or nab-paclitaxel for the first 4 cycles	mPFS: 6.4 months (A) vs. 4.8 months (B)	Any AE: 98.2% (A) vs. 97.9% (B)
		Stage IV squamous NSCLC No prior therapy Any PD-L1 levels	Cohort B: Saline placebo for up to 35 cycles + carboplatin and either paclitaxel or nab-paclitaxel for the first 4 cycles	mOS: 15.9 months (A) vs. 11.3 (B)	
IMpower130[36] (NCT02367781)	III	723 patients	Cohort A: atezolizumab 1,200 mg every 3 weeks + carboplatin AUC 6 every 3 weeks + weekly nab-paclitaxel 100 mg/m^2 followed by atezolizumab maintenance	mPFS: 7.0 months (A) vs. 5.5 months (B)	Any AE: 99.6% (A) vs. 99.1% (B)
		Stage IV nonsquamous NSCLC *EGFR* and *ALK* WT Treatment-naïve Any PD-L1 levels	Cohort B: carboplatin AUC 6 every 3 weeks + weekly nab-paclitaxel 100 mg/m^2 followed by best supportive care or pemetrexed maintenance	mOS: 18.6 months (A) vs. 13.9 months (B)	

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TABLE 1. Landmark Clinical Trials: Single-Agent Immunotherapy, Combination Immunotherapy, and Chemoimmunotherapy (Continued)

Trial (NCT No.)	Phase	Study Population	Treatment Regimen	Outcomes	Safety
IMpower131[37] (NCT02367794)	III	1,021 patients	Cohort A: atezolizumab 1,200 mg + carboplatin AUC 6 + paclitaxel 200 mg/m^2 (175 mg/m^2 for Asian race/ethnicity) every 3 weeks followed by atezolizumab until disease progression	mPFS:	Any AE: 97.9% (A), vs. 99.4% (B), vs. 97% (C)
		Stage IV squamous NSCLC	Cohort B: atezolizumab 1,200 mg + carboplatin AUC 6 + nab-paclitaxel 100 mg/m^2 IV (days 1, 8, and 15) every 3 weeks followed by atezolizumab until disease progression	A: not reported	
		Not received chemotherapy	Cohort C: carboplatin AUC 6 + nab-paclitaxel 100 mg/m^2 IV (days 1, 8, and 15) every 3 weeks	B: 6.3 months (all patients), 10.1 months (PD-L1 $\geq$ 50%), 8.4 months (PD-L1 $\geq$ 5%), 7.1 months (PD-L1 $\geq$ 1%), and 5.7 months (PD-L1 $<$ 1%)	
		EGFR or *ALK* mutations were included if PD with or nontolerability of TKI		C: 5.6 months (all patients), 5.1 months (PD-L1 $\geq$ 50%), 5.6 months (PD-L1 $\geq$ 5%), 5.6 months (PD-L1 $\geq$ 1%), and 5.6 months (PD-L1 $<$ 1%)	
		Any PD-L1 levels		mOS:	
				A: Not reported	
				B: 14.2 months (all patients), 23.4 months (PD-L1 $\geq$ 50%), 20.4 months (PD-L1 $\geq$ 5%), 14.8 months (PD-L1 $\geq$ 1%), and 14.0 months (PD-L1 $<$ 1%)	
				C: 13.5 months (all patients), 10.2 months (PD-L1 $\geq$ 50%), 10.2 months (PD-L1 $\geq$ 50%), 14.5 months (PD-L1 $\geq$ 5%), 15.0 months (PD-L1 $\geq$ 1%), and 12.5 months (PD-L1 $<$ 1%)	

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TABLE 1. Landmark Clinical Trials: Single-Agent Immunotherapy, Combination Immunotherapy, and Chemoimmunotherapy (Continued)

Trial (NCT No.)	Phase	Study Population	Treatment Regimen	Outcomes	Safety
IMpower150[35] (NCT02366143)	III	1,202 patients	Cohort A: atezolizumab 1,200 mg + bevacizumab 15 mg/kg + carboplatin AUC 6 + paclitaxel 200mg/m^2 every 3 weeks (ABCP)	mPFS:	Any AE: 98% (A) vs. 99% (B)
		Stage IV or recurrent metastatic nonsquamous NSCLC	Cohort B: bevacizumab 15 mg/kg + carboplatin AUC 6 + paclitaxel 200mg/m^2 every 3 weeks (BCP)	A: 8.3 months (WT population), 11.3 months (T-eff high), 9. 7 months (*EGFR* and *ALK*-mutant tumors only), 12.6 months (PD-L1 $\geq$ 50%), and 8.0 months (PD-L1 $<$ 50%)	
		Treatment-naïve	Cohort C: atezolizumab 1,200 mg + carboplatin AUC 6 + paclitaxel 200mg/m^2 every 3 weeks (ACP)	B: 6.8 months (WT population), 6.8 month (T-eff high), 6.1 months (*EGFR* and *ALK*-mutant tumors only), 6.8 months (PD-L1 $\geq$ 50%), and 6.8 months (PD-L1 $<$ 50)	
		EGFR or *ALK* mutations were included if PD with or untolerability of TKI		mOS: 19.2 months (A, WT population) vs. 14.7 months (B, WT population)	
		Any PD-L1 levels			

Table 1 lists the landmark clinical trials exploring the use of immune-oncology for patients with metastatic NSCLC.

Abbreviations: ABCP, atezolizumab, bevacizumab, carboplatin, and paclitaxel; ACP, atezolizumab, carboplatin, and paclitaxel; AE, adverse event; AUC, area under the curve; BCP, bevacizumab, carboplatin, and paclitaxel; CI, confidence interval; HR, hazard ratio; ITT, intention to treat; IV, intravenous; mPFS, median progression-free survival; mOS, median overall survival; mut/Mb, mutations/megabase; NR, not reached; NSCLC, non–small cell lung cancer; ORR, overall response rate; PD, progression of disease; RRR, relative risk reduction; SoC, standard of care; T-eff, T-cell effector; TKI, tyrosine kinase inhibitor; TMB, tumor mutational burden; WT, wild type.

NSCLC with PD-L1 TPS $\geq$ 1%, investigated the role of combination nivolumab and ipilimumab. Patients received nivolumab 3 mg/kg intravenously every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (deemed the N3I1 regimen), nivolumab 240 mg intravenously every 2 weeks, or platinum-doublet chemotherapy. Therapy was continued until disease progression occurred or for up to 2 years in the immunotherapy arms or for four cycles in the chemotherapy arm.[24] Among patients with PD-L1 TPS $\geq$ 1%, N3I1 conferred a significant OS benefit compared with platinum-doublet chemotherapy (median OS, 17.1 months vs. 14.9 months, respectively; p = .007). Furthermore, the 1- and 2-year PFS rates also favored combination immunotherapy over chemotherapy (33% vs. 19% and 22% vs. 7% for 1 year and 2 years, respectively).

Among patients with tumor PD-L1 TPS $<$ 1%, nivolumab plus ipilimumab also conferred superior OS compared with platinum-based chemotherapy (median OS, 17.2 months vs. 12.2 months; HR, 0.62). There was no statistically significant difference in PFS or OS between combination immunotherapy and nivolumab monotherapy among patients with tumor PD-L1 TPS $\geq$ 1% (median PFS, 5.1 months vs. 4.2 months, respectively; median OS, 17.1 months vs. 15.7 months, respectively). In an exploratory analysis, tumor mutational burden (TMB) was examined as a predictive biomarker (high TMB denoted as $\geq$ 10 mutations/Mb and low TMB as $<$ 10 mutations/Mb), but it failed to predict OS benefit among patients who received combination immunotherapy versus chemotherapy.[24] Grade 3/4 toxicities were similar between nivolumab plus ipilimumab and chemotherapy treatment arms (32.8% vs. 36%, respectively). On the basis of these findings, in May 2020, the FDA approved combination immunotherapy with nivolumab and ipilimumab in the front-line setting for patients with metastatic NSCLC whose tumor PD-L1 expression is $\geq$ 1%.

Six months after CheckMate 227 started enrollment, a phase II study assessing the efficacy and safety of nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks as first-line treatment of advanced/metastatic NSCLC started accrual (CheckMate 568).[25] In this single-arm, open-label, phase II trial, investigators also examined the association of efficacy with PD-L1 expression and TMB. In this study, 288 treatment-naïve patients received nivolumab plus ipilimumab for 2 or more years, until disease progression or unacceptable toxicity occurred. Patients whose tumor had a positive PD-L1 expression (PD-L1 TPS $\geq$ 1%) had higher PFS compared with individuals with negative tumor PD-L1 expression (median PFS, 6.8 months vs. 2.8 months, respectively). Nonetheless, TMB seemed to be a superior predictive biomarker for response compared with PD-L1 expression, as higher objective response rates were observed among patients with TMB $\geq$ 10 mutations/Mb regardless of PD-L1 levels. In patients whose tumor TMB was high, the objective response rate was 48% and 47% for patients with PD-L1 TPS $\geq$ 1% and PD-L1 TPS $<$ 1%, respectively. Patients with low TMB had an objective response rate of 18% and 5% with PD-L1 TPS $\geq$ 1% and PD-L1 TPS $<$ 1%, respectively. Furthermore, the median PFS was longer among patients with TMB $\geq$ 10 mutations/Mb than among those with $<$ 10 mutations/Mb (7.1 months vs. 2.6 months, respectively). These data suggest that TMB may serve as a biomarker of response to first-line nivolumab plus ipilimumab.[25]

In 2013, a phase Ib trial (NCT02000947) assessing a novel immunotherapy combination with durvalumab, an IgG1 antibody to PD-L1, and tremelimumab, a fully humanized IgG2 antibody to CTLA-4, opened for accrual.[26] The aim of this study was to assess the tolerability and antitumor activity of this combination among patients diagnosed with advanced NSCLC, and 102 patients were enrolled. The combination of durvalumab 20 mg/kg with tremelimumab 1 mg/kg every 4 weeks conferred an overall response rate of 23% regardless of PD-L1 expression, with an acceptable safety profile.[26] Therefore, multiple phase III studies were started to assess the potential of this novel combination for the treatment of patients with NSCLC. To date, three phase III trials (MYSTIC,[27] NEPTUNE,[28] and ARCTIC[29]) have failed to demonstrate an OS or PFS benefit with the use of this combination as a first-line treatment of patients with metastatic NSCLC.

In the phase III MYSTIC trial, 675 treatment-naïve patients with advanced NSCLC were randomly assigned to one of three cohorts: (1) durvalumab 20 mg/kg every 4 weeks until disease progression occurred, (2) durvalumab 20 mg/kg every 4 weeks (up to 12 months) plus tremelimumab 1 mg/kg intravenously every 4 weeks (up to four cycles), or (3) platinum-based chemotherapy up to six cycles. The primary endpoint was PFS, and there was no statistically significant difference in this outcome among the three treatments (median PFS, 4.7 vs. 3.9 vs. 5.4 months for durvalumab, durvalumab plus tremelimumab, and chemotherapy, respectively). Also, OS was similar for patients treated with immunotherapy, immunotherapy combination, or chemotherapy (median OS, 16.3 vs. 11.9 vs. 12.9 months, respectively). In an exploratory analysis, TMB was measured in the blood (i.e., blood TMB), and a blood TMB $\geq$ 20 mutations/Mb was associated with superior OS for patients treated with combination immunotherapy compared with chemotherapy (median OS, 21.9 months vs. 10 months, respectively; HR, 0.49).[27]

In NEPTUNE (NCT02542293), a phase III trial investigating durvalumab 20 mg/kg every 4 weeks (up to 12 months) plus tremelimumab 1 mg/kg intravenously every 4 weeks (up to four cycles) versus platinum-based chemotherapy for the

first-line treatment of patients with advanced NSCLC, the blood TMB was investigated as a predictive biomarker.[28] The primary endpoint was OS among patients with high blood TMB ($\geq$ 20 mutations/Mb). Unfortunately, NEPTUNE did not meet its primary endpoint, and final results are still pending publication.

ARCTIC (NCT02352948), a phase III trial that studied heavily pretreated patients (at least three lines of therapy) with metastatic NSCLC compared durvalumab with or without tremelimumab to standard-of-care (SOC) treatment.[29] This trial had two substudies. In substudy A, patients with tumor PD-L1 TPS $\geq$ 25% were randomly assigned to receive durvalumab 10 mg/kg every 2 weeks (up to 12 months) or SOC. In substudy B, patients with tumor PD-L1 TPS $<$ 25% received one of four regimens: durvalumab plus tremelimumab (durvalumab 20 mg/kg plus tremelimumab 1 mg/kg every 4 weeks [tremelimumab up to 12 weeks] followed by durvalumab 10 mg/kg every 2 weeks for 34 weeks), SOC, durvalumab (20 mg/kg every 4 weeks), or tremelimumab (10 mg/kg every 4 weeks for 24 weeks followed by every 12 weeks for 24 weeks). In substudy A, durvalumab monotherapy provided a survival benefit compared with SOC among patients whose tumors had PD-L1 TPS $\geq$ 25% (median OS, 11.7 months vs. 6.8 months; HR, 0.63). However, in substudy B, durvalumab plus tremelimumab failed to show an OS or PFS benefit among patients whose tumors had PD-L1 TPS $<$ 25%.[29] All combined immunotherapy trial results are summarized in Table 1.

CLINICAL TRIALS WITH CHEMOIMMUNOTHERAPY

KEYNOTE-189, a double-blind, phase III trial, randomly assigned 616 treatment-naïve patients with nonsquamous NSCLC to receive one of two regimens: pembrolizumab (200 mg) plus pemetrexed and a platinum-based drug every 3 weeks for four cycles, followed by pembrolizumab plus pemetrexed maintenance for up to 35 total cycles, or placebo plus pemetrexed and a platinum-based drug for four cycles, followed by placebo plus pemetrexed maintenance for up to 35 total cycles status.[30] Primary endpoints were OS and PFS, and randomization was stratified according to PD-L1 expression (TPS $\geq$ 1% vs. $<$ 1%). Triplet therapy (platinum drug, pemetrexed, and pembrolizumab) conferred superior PFS and OS compared with platinum drug plus pemetrexed (median PFS, 8.8 months vs. 4.9 months, p $<$ .001, respectively; median OS, 22 months vs. 10.7 months, p $<$ .001, respectively). This benefit was independent of PD-L1 status.[30] On the basis of these findings, the FDA granted regular approval for pembrolizumab in combination with chemotherapy for the first-line treatment of metastatic nonsquamous NSCLC in August 2018.[31]

To explore the combination of chemotherapy with immunotherapy for squamous NSCLC, KEYNOTE-407, a phase III trial for treatment-naïve patients with metastatic squamous NSCLC, randomly assigned individuals to receive a platinum drug plus paclitaxel or nanoparticle albumin-bound– (nab-) paclitaxel with either pembrolizumab 200 mg or placebo every 3 weeks for the first four cycles, followed by either pembrolizumab or placebo for up to 35 cycles. The primary endpoints were OS and PFS. This study showed that chemoimmunotherapy conferred a superior PFS and OS compared with platinum-based chemotherapy (median PFS, 6.4 months vs. 4.8 months, p $<$ .001, respectively; median OS, 15.9 months vs. 11.3 months, p $<$ .001, respectively). Furthermore, as previously noted in KEYNOTE-189,[30] the addition of pembrolizumab to platinum-doublet chemotherapy prolonged OS regardless of PD-L1 expression.[32]

Preclinical data with vascular endothelial growth factor inhibitors, such as bevacizumab, suggest that vascular endothelial growth factor inhibitors have biologic off-target immunomodulatory effects, and the efficacy of immunotherapeutics may be enhanced by the combination of angiogenesis inhibitors with immunotherapy.[33,34] IMpower150, an open-label, phase III study, evaluated ABCP (atezolizumab, bevacizumab, carboplatin, and paclitaxel), BCP (bevacizumab, carboplatin, and paclitaxel), and ACP (atezolizumab, carboplatin, and paclitaxel) among treatment-naïve patients with nonsquamous metastatic NSCLC.[35] A small number of patients whose tumors harbored an *EGFR* or *ALK* genomic alteration were allowed to participate if they developed disease progression with or had unacceptable side effects from treatment with at least one approved tyrosine kinase inhibitor. Nonetheless, a protocol amendment was made with the decision to exclude patients with *EGFR* or *ALK* genomic alterations from the primary analysis according to data showing that, with respect to PFS and OS, the benefits of monotherapy with PD-L1 inhibitors or PD-1 inhibitors as second-line or later therapy were similar to the benefits with chemotherapy in these patients. Therefore, primary endpoints were PFS and OS for patients whose tumors had a wild-type genotype (i.e., no *EGFR* or *ALK* alterations) and high expression of effector T-cell gene signature, also known as the effector T-cell–high wild-type (T-cell–high WT) population. In the wild-type population (with or without an effector T-cell gene signature), the median PFS was 8.3 months versus 6.8 months in the ABCP versus BCP cohorts, respectively (p $<$ .001). In the effector T-cell–high WT population, the median PFS was 11.3 months versus 6.8 months, respectively (p $<$ .001). Furthermore, ABCP resulted in longer OS in the wild-type population (with or without an effector T-cell gene signature); median OS, 19.2 months versus 14.7 months for ABCP and BCP, respectively; p = .02). In an exploratory analysis, including 80 patients whose tumors harbored an *EGFR* mutation or an *ALK* rearrangement, ABCP conferred superior PFS compared with BCP (median PFS, 9.7 months vs. 6.1 months, respectively; HR, 0.59). Also, in a subgroup of patients with low or negative PD-L1 (PD-L1 TPS $<$ 1%), ABCP resulted in longer PFS than BCP (median PFS, 8.0 vs. 6.8 months, respectively; HR, 0.68). The results for the ACP group

have not yet been published. These data demonstrated that quadruple therapy (carboplatin, paclitaxel, atezolizumab, and bevacizumab combination) resulted in improved PFS and OS for treatment-naïve patients with nonsquamous NSCLC, irrespective of PD-L1 level or *EGFR* and *ALK* genetic alterations.[35]

IMpower130, an open-label, phase III trial for treatment-naïve patients with nonsquamous metastatic NSCLC, examined the role of atezolizumab (1,200 mg every 3 weeks) in combination with nab-paclitaxel and carboplatin every 3 weeks (for four to six cycles) followed by atezolizumab maintenance versus nab-paclitaxel and carboplatin alone every 3 weeks (for four to six cycles) followed by supportive care or pemetrexed maintenance every 3 weeks.[36] Patients whose tumors harbored an *EGFR* or *ALK* genomic alteration were allowed to participate if they developed disease progression or did not tolerate treatment with at least one approved tyrosine kinase inhibitor. Primary endpoints were PFS and OS, with stratification by sex, baseline liver metastases, and PD-L1 expression. The addition of atezolizumab provided clinically meaningful benefit for both primary endpoints (OS, 18.6 months vs. 13.9 months, respectively [$p < .0001$]; PFS, 7.0 months vs. 5.5 months, respectively [$p = .033$]).[36] However, a subgroup analysis demonstrated that the addition of atezolizumab for the treatment of patients with baseline liver metastasis or in patients whose tumors harbored an *EGFR* or *ALK* genomic alterations was not associated with an improved OS compared with carboplatin and nab-paclitaxel alone.[36] In contrast with the results of IMpower130, a phase III trial assessing the addition of atezolizumab to carboplatin and nab-paclitaxel (IMpower131) in treatment-naïve patients with metastatic squamous NSCLC failed to demonstrate OS improvement with triplet therapy (atezolizumab, carboplatin, nab-paclitaxel).[37] Yet, in this study, the addition of atezolizumab to platinum-based chemotherapy was associated with superior PFS (median PFS, 6.3 months vs. 5.6 months; $p = .0001$).[37]

POSEIDON (NCT03164616) is an open-label, phase III trial that is actively recruiting treatment-naïve patients with NSCLC to determine the efficacy and safety of three regimens—durvalumab plus tremelimumab combination therapy plus SOC chemotherapy versus durvalumab plus SOC versus SOC alone.[38] In an interim analysis released to the press, investigators reported that this study met its primary endpoint, with a statistically significant improvement in PFS with durvalumab plus SOC compared SOC alone, and it also met its secondary endpoint of PFS benefit with the triplet (durvalumab, tremelimumab, and SOC) compared with SOC alone.[38] The final results remain to be published.

To enhance benefit and provide rapid disease control, CheckMate 9LA, an open-label, phase III trial, investigated the role of limited platinum-based doublet chemotherapy (two cycles) with combination immunotherapy (nivolumab and ipilimumab) for advanced NSCLC.[39] In this study, 719 patients were assigned to receive nivolumab and ipilimumab and platinum-based chemotherapy (nivolumab 360 mg every 3 weeks plus ipilimumab 1 mg/kg every 6 weeks with two cycles of histology-based platinum-based chemotherapy) or chemotherapy alone (four cycles of platinum-based chemotherapy). The primary endpoint of this study was OS. At a preplanned interim analysis, the quadruple chemoimmunotherapy resulted in longer OS compared with chemotherapy (median OS, 14.1 months vs. 10.7 months, respectively; $p = .00065$). The most common grade 3/4 treatment-related adverse events were neutropenia (7% vs. 9% for the chemoimmunotherapy cohort vs. chemotherapy cohort, respectively), anemia (6% vs. 14%), diarrhea (4% vs. 1%), increased lipase (6% vs. 1%), and asthenia (1% vs. 2%). Serious treatment-related adverse events occurred among 30% of the patients treated with chemoimmunotherapy versus 18% of patients treated with chemotherapy.[39] This landmark chemoimmunotherapy trial led to FDA approval in May 2020 for the combination of nivolumab plus ipilimumab and two cycles of platinum-doublet chemotherapy as a first-line treatment of patients with metastatic or recurrent NSCLC with no actionable genomic alterations.[40]

A summary of these trials can be found in Table 1.

ONGOING CLINICAL TRIALS AND FUTURE DIRECTIONS

Many exciting therapeutics are under active development and clinical investigation (Table 2). Broad categories include the use of immunotherapy with oral small molecule inhibitors (e.g., tyrosine kinase inhibitors); immunotherapy with concurrent or sequential radiotherapy; immunotherapy with tumor-infiltrating lymphocytes; and novel immunotherapy combinations, such as ipilimumab/nivolumab/paclitaxel, pembrolizumab/ipilimumab, and cemiplimab/ipilimumab. NKTR-214, a CD122-biased cytokine agonist that promotes $CD8^+$ T cell and natural killer cell activation, is being investigated in combination with anti–PD-1 therapies (e.g., nivolumab and pembrolizumab) for advanced solid tumors, including NSCLC, in the PIVOT-02 trial.[41] Administration of CAR T cells against lung cancer–specific antigens, such as mucin 1 (MUC1), MSLN, EGFR, and PD-L1, are under clinical investigation and offer promise given recent successes in hematologic malignancies.[42]

CONCLUSION

Given the recent surge of treatment successes and advances in thoracic oncology drug discovery, reviewing available options and deciding on the best treatment for a particular patient can be overwhelming (Fig. 1). Treatment decisions between the provider and patient/family are a risk/benefit discussion that involves strong considerations of histology (nonsquamous vs. squamous), PD-L1 status (TPS

TABLE 2. Ongoing Clinical Trials and Future Directions

NCT Number	Study Population	Treatment Regimen	Phase	Primary Outcome(s)	Status
Immunotherapy With Targeted Therapy					
NCT03225664	Patients with recurrent unresectable stage III and IV NSCLC who are resistant to anti-PD 1/PD-L1	Pembrolizumab plus trametinib	I/II	ORR	Active, not recruiting
NCT03178552 (B-FAST)	Patients with unresectable, advanced, or metastatic NSCLC treatment-naïve who were determined to harbor targetable somatic mutations (*EGFR* exon 20+, *ALK*, *ROS1*, *BRAF* V600, *RET*) or positive TMB by blood-based NGS	Cohort A: *ALK*+ alectinib Cohort B: *RET*+ alectinib Cohort C: TMB atezolizumab vs. pemetrexed gemcitabine, cisplatin or carboplatin Cohort D: *ROS1*+ entrectinib Cohort E: *BRAF* V600 atezolizumab, vemurafenib, and cobimetinib Cohort F: *EGFR* 20 atezolizumab, bevacizumab, carboplatin, and pemetrexed	II/III	ORR, PFS	Recruiting
NCT03976375	Metastatic NSCLC and PD after platinum-doublet chemotherapy and treatment with 1 prior anti-PD-1/PD-L1 mAb	Cohort A: pembrolizumab with lenvatinib Cohort B: docetaxel Cohort C: lenvatinib alone	III	OS, PFS	Recruiting
NCT03689855	Patients with advanced-stage NSCLC previously treated with an immune checkpoint inhibitor	Ramucirumab with atezolizumab	II	ORR	Recruiting
NCT03337698 (Morpheus Lung)	Patients with metastatic treatment-naïve NSCLC	Monotherapy or combination therapy of the following: atezolizumab +/− cobimetinib, or +/−RO6958688, or +/− cobimetinib, or +/−CPI-444, or +/−ipatasertib, or +/−bevacizumab, or +/−carboplatin with pemetrexed, or +/−carboplatin, with gemcitabine, or +/−bevacizumab, or +/−linagliptin, or +/−sacituzumab govitecan, or +/−bevacizumab with radiation; docetaxel +/− atezolizumab	I/II	ORR	Recruiting
NCT03971474 (Lung-MAP Non-Match Treatment Trial)	Patients with recurrent or metastatic NSCLC with exactly 1 line of anti–PD-1 or anti–PD-L1 therapy, either alone or in combination with platinum-based chemotherapy	Cohort A: docetaxel + gemcitabine + pemetrexed + ramucirumab Cohort B: ramucirumab + pembrolizumab	II	OS	Recruiting
NCT03257722 (PIL)	Patients with metastatic NSCLC whose disease has failed a platinum-based chemotherapy regimen as well as immune checkpoint inhibitor therapy	Pembrolizumab + idelalisib	I/II	DLTs	Recruiting

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TABLE 2. Ongoing Clinical Trials and Future Directions (Continued)

NCT Number	Study Population	Treatment Regimen	Phase	Primary Outcome(s)	Status
NCT04514484	Advanced/metastatic NSCLC and HIV with any number of prior cancer therapies, including treatment-naïve patients	Cabozantinib *S*-malate + nivolumab	I	Safety	Recruiting
Immunotherapy With Radiation Therapy					
NCT03035890	Previously treated stage IV NSCLC	Adapted hypofractionated radiation therapy with nivolumab, atezolizumab, or pembrolizumab	N/A (invitational only)	Best response	Active, not recruiting
NCT03808337	Patients with treatment-naïve metastatic NSCLC without targetable molecular alterations in *EGFR*, *ALK*, or *ROS1*, or those with *EGFR*, *ALK*, or *ROS1* targetable molecular alterations with disease progression on first-line tyrosine kinase inhibitor	SBRT with systemic therapy including immunotherapy	II	PFS, OS	Recruiting
NCT03275597	Patients with stage IV NSCLC without targetable mutations Any number of prior cancer but prior exposure to immunotherapy	SBRT with durvalumab and tremelimumab	I	Safety and tolerability	Recruiting
NCT03313804	Patients with frontline or relapsed NSCLC who are intended to receive standard-of-care immune checkpoint inhibitors	SBRT or fractionated radiotherapy with nivolumab or pembrolizumab or atezolizumab	II	PFS	Recruiting
NCT03168464	Patients with NSCLC and metastatic disease who have failed at least 1 prior treatment and have a minimum of 2 metastatic lesions	Fractionated radiation + nivolumab + ipilimumab	I/II	ORR	Recruiting
NCT03223155 (COSINR)	Patients with stage IV NSCLC therapy-naïve	SBRT with ipilimumab and nivolumab	I	Number or serious AEs	Recruiting
NCT03867175	Patients with metastatic NSCLC who received 4 cycles of chemoimmunotherapy	Cohort A: SBRT + pembrolizumab Cohort B: pembrolizumab alone	III	PFS	Recruiting
NCT04081688	Patients with stage IV NSCLC with documented disease progression after at least 1 line of platinum-based chemotherapy in the metastatic setting	Atezolizumab + varlilumab + SBRT	I	Safety and tolerability	Recruiting
NCT03391869 (LONESTAR)	Patients with stage IV NSCLC who are treatment-naïve or have had only 1 prior line of chemotherapy and/or targeted agents for metastatic disease	Fractionated radiation + nivolumab + ipilimumab	III	OS	Recruiting

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TABLE 2. Ongoing Clinical Trials and Future Directions (Continued)

NCT Number	Study Population	Treatment Regimen	Phase	Primary Outcome(s)	Status
NCT03158883	Patients with metastatic NSCLC with any number of prior treatments with at least 1 line of therapy for metastatic disease, including a platinum-based regimen (or those who are ineligible for platinum-based therapy)	Avelumab + radiation	I		Recruiting
Immunotherapy Combinations					
NCT02542293 (NEPTUNE)	Patients with metastatic NSCLC treatment-naïve with no *EGFR* or *ALK* mutations and any TMB	Cohort A: durvalumab 20 mg/kg every 4 weeks (up to 12 months) + tremelimumab 1 mg/kg every 4 weeks (up to 4 doses) Cohort B: platinum-based chemotherapy	III	mOS	Active, not recruiting
NCT03164616 (POSEIDON)	Patients with nonsquamous or squamous NSCLC with any PD-L1 expression level and no *EGFR* or *ALK* mutations	Cohort A: durvalumab 1,500 mg every 4 weeks + 4 cycles of platinum-based chemotherapy Cohort B: durvalumab + tremelimumab 75 mg every 4 weeks + platinum-based chemotherapy, followed by maintenance durvalumab or durvalumab + one dose of tremelimumab Cohort C: platinum-based chemotherapy (6 cycles)	III	PFS, OS	Recruiting
NCT03377023	Patients with metastatic NSCLC who are treatment-naïve or have received prior chemotherapy, immunotherapy, or targeted therapy	Ipilimumab + nivolumab + nintedanib	I/II	MDT	Recruiting
NCT03573947 (TOP1705)	Patients with therapy-naïve stage IV NSCLC	Ipilimumab + nivolumab + paclitaxel	II	PFS	Recruiting
NCT03262779	Patients with advanced-naïve anti-PD-1/PD-L1 therapy-resistant stage IV NSCLC	Ipilimumab + nivolumab	II	ORR	Recruiting
NCT04043195	Patients with advanced NSCLC who are anti-PD-1/PD-L1 therapy resistant and have no more than 3 lines of prior therapies and at least 1 prior line of platinum-based chemotherapy	Cohort A: nivolumab Cohort B: ipilimumab + nivolumab	I/II	ORR	Recruiting
NCT03515629	Patients with treatment-naïve metastatic NSCLC whose tumors express PD-L1 $\geq$ 50%	Cohort A: pembrolizumab Cohort B: cemiplimab + ipilimumab Cohort C: cemiplimab + ipilimumab + chemotherapy	III	PFS	Active, not recruiting

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TABLE 2. Ongoing Clinical Trials and Future Directions (Continued)

NCT Number	Study Population	Treatment Regimen	Phase	Primary Outcome(s)	Status
NCT03302234 (MK-3475-598/ KEYNOTE-598)	Patients with treatment-naïve metastatic NSCLC whose tumors express PD-L1 ≥ 50%	Cohort A: pembrolizumab + ipilimumab Cohort B: pembrolizumab + placebo	III	OS and PFS	Active, not recruiting
NCT03409614	Patients with treatment-naïve advanced/ metastatic NSCLC whose tumors express PD-L1 < 50%	Cohort A: platinum-based doublet chemotherapy + placebo Cohort B: platinum-based doublet chemotherapy + cemiplimab Cohort C: platinum-based doublet chemotherapy + cemiplimab + ipilimumab	III	OS	Active, not recruiting
Novel Immunotherapy Combinations					
NCT03228667 (QUILT 3.055)	Patients with metastatic NSCLC who were previously treated with nivolumab, pembrolizumab, or atezolizumab,	N-803 + pembrolizumab or nivolumab	II	ORR	Recruiting
NCT02658890	Patients with advanced, metastatic NSCLC who have progressed following at least 1 standard regimen	Cohort A: BMS-986205 + nivolumab Cohort B: BMS-986205 + ipilimumab + nivolumab	I/II	Safety and tolerability, ORR, best response, PFS, and DOR	Recruiting
NCT02922764	Patients with advanced NSCLC who are refractory to standard systemic therapies	Cohort A: RGX-104 Cohort B: RGX-104 + nivolumab or ipilimumab or docetaxel Cohort C: RGX-104 + pembrolizumab + carboplatin + pemetrexed	I	MTD, ORR, PFS, and AEs	Recruiting
NCT03138889 (PROPEL)	Patients with advanced solid malignancies, including NSCLC, who are anti–PD-L1 therapy-naïve and have no actionable mutations	NKTR-214 + pembrolizumab	I/II	Tolerability and safety, MDT, ORR	Recruiting
NCT02983045 (PIVOT-02)	Patients with advanced/metastatic NSCLC with any number of prior therapies, including treatment-naïve patients, who have not received prior IL-2 therapy	NKTR-214 + nivolumab ± ipilimumab	I/II	ORR	Active, not recruiting
Immunotherapy With TILs					
NCT03215810	Patients with stage IV or recurrent NSCLC who are immunotherapy-naïve with no more than 5 prior lines of therapy	TIL + nivolumab	I	DLT	Active, not recruiting
NCT03645928	Patients with stage III or IV NSCLC with ≤ 3 prior lines of systemic therapy and no prior immunotherapy	Autologous TIL (LN-145) + pembrolizumab	II	ORR and safety profile	Recruiting

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TABLE 2. Ongoing Clinical Trials and Future Directions (Continued)

NCT Number	Study Population	Treatment Regimen	Phase	Primary Outcome(s)	Status
Immunotherapy With Tumor Vaccines					
NCT02439450 (DURGA Trial)	Patients with metastatic NSCLC with ≤ 3 prior lines of systemic therapy, including up to 1 prior line of immunotherapy	Cohort A: viagenpumatucel-L + nivolumab Cohort B: viagenpumatucel-L + pembrolizumab +/− pemetrexed	I/II	Frequency of AEs, ORR, ands PFS	Active, not recruiting
CAR-T Cell Trials					
NCT02706392	Patients with ROR1+ (≥ 20% on IHC) advanced malignancies, including stage IV NSCLC, who have been treated with at least 1 line of prior therapy or declined conventional therapy	CAR-T cell targeting ROR1	I	Evaluate safety and tolerability	Recruiting
NCT04025216	Patients with advanced solid malignancies, including NSCLC, who have received both checkpoint inhibition and platinum-based chemotherapy	CAR-T cell targeting MUC1 + cyclophosphamide + fludarabine	I	DLT and ORR	Recruiting
NCT04153799	Patients with treatment-naïve *EGFR*+ advanced NSCLC	CXCR5-modified *EGFR* CAR autologous T cells	I	Safety and ORR	Recruiting
NCT03525782	Patients with MUC-1–expressing advanced NSCLC who have not received any gene therapy products	Anti-MUC1 CAR-T cells and /or PD-1 knockout engineered T cells	I/II	Safety	Recruiting

Table 2 lists ongoing clinical trials exploring novel combinations of immunotherapy with other forms of therapy or other immunotherapy agents.

Abbreviations: AEs; adverse events; DLTs, drug-limiting toxicities; DOR, duration of response; IHC, immunohistochemistry; mAb, monoclonal antibody; MTD, maximum tolerated dose; NGS, next-generation sequencing; NSCLC, non–small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; SBRT, stereotactic body radiotherapy; TILs, tumor-infiltrating lymphocytes; TMB, tumor mutational burden.

≥ 50%, ≥ 1%, vs. < 1%), and lung cancer mutational profiling (including actionable mutations or lack thereof). Unique circumstances to review include a patient's past medical history, including a diagnosis of autoimmune disease; history of treatment-related adverse events; intolerance to a particular therapy; organ transplantation; chronic viral infections; presence of brain metastases; and advanced age.[43] Treatment-related adverse events, including inflammation in vital organs, such as the skin (dermatitis/rash), gastrointestinal system (colitis), liver (hepatitis), pancreas (pancreatitis), lungs (pneumonitis), heart (myocarditis/pericarditis), and brain (encephalitis/meningoencephalitis), are possible with the use of immune checkpoint inhibitors. Adverse events should be closely monitored with common terminology criteria for adverse events (i.e., Common Terminology Criteria for Adverse Events) grading. Early appropriate interventions are crucial to prevent fatal immune checkpoint inhibitor–associated toxic effects.[44,45]

With the above-mentioned considerations in mind, in the front-line setting, for patients with nonsquamous and squamous NSCLC with high tumoral PD-L1 (PD-L1 TPS ≥ 50%) who are asymptomatic, have good performance status and low disease burden, or have oligometastatic disease, we favor single-agent immunotherapy (KEYNOTE-024, IMpower110, EMPOWER-Lung 1). This treatment strategy is associated with fewer side effects and lower costs compared with combined immunotherapy or chemoimmunotherapy. Conversely, for patients with NSCLC who are experiencing clinically notable cancer-related symptoms (i.e., hemoptysis, shortness of breath, cancer-related pain) or have bulky disease requiring faster response, we favor combined chemoimmunotherapy (KEYNOTE-189, KEYNOTE-407, IMpower150, IMpower 130, CheckMate 9LA), regardless of PD-L1 status. For patients with high tumoral TMB (TMB > 10 mut/MB), combined immunotherapy (CheckMate 227) might be considered instead of single-agent immunotherapy or chemoimmunotherapy, provided that patients are not substantially symptomatic from their malignancy. If they have substantial cancer-related symptoms and a high tumoral TMB, combination immunotherapy with chemotherapy (CheckMate 9LA) may be preferred. Also, in patients with a nonsquamous histology, we favor pemetrexed-containing regimens instead of taxane-containing ones, given the higher tolerability of the former. However, for patients with nonsquamous NSCLC whose tumors harbor *EGFR* or *ALK* alterations or PD-L1 TPS < 1% and who have a high burden of liver metastases, quadruple therapy with carboplatin, paclitaxel, atezolizumab, and bevacizumab (IMpower150) may be considered instead of other regimens, provided the patients have excellent clinical performance status. Finally, for patients with fair performance status (Eastern Cooperative Oncology Group performance status of ≥ 2) and whose tumor PD-L1 TPS is ≥ 1%, single-agent immunotherapy (KEYNOTE-042) may be considered. It is also important to consider treatment under available clinical trials, which helps expand and better develop new treatment options for patients with advanced NSCLC.

The innovation of immunotherapy has ushered in an array of effective treatment options in the field of oncology and, in doing so, has raised the bar for the management of metastatic NSCLC. Advances with immunotherapy have offered patients with lung cancer substantial improvements in survival and quality of life. It is our hope that this is only the beginning of a new era in reframing the landscape of the fight against lung cancer.

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7-33.
2. Spiro SG, Silvestri GA. One hundred years of lung cancer. Am J Respir Crit Care Med. 2005;172:523-529.
3. Arbour KC, Riely GJ. systemic therapy for locally advanced and metastatic non-small cell lung cancer: a review. JAMA. 2019;322:764-774.
4. Mittal D, Gubin MM, Schreiber RD, et al. New insights into cancer immunoediting and its three component phases: elimination, equilibrium and escape. Curr Opin Immunol. 2014;27:16-25.
5. Drugs.com. Opdivo FDA Approval History. https://www.drugs.com/history/opdivo.html. Accessed March 2, 2021.
6. Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol. 2008;26:677-704.
7. Brahmer J, Reckamp KL, Baas P, et al. nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373:123-135.
8. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373:1627-1639.
9. Horn L, Spigel DR, Vokes EE, et al. Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057). J Clin Oncol. 2017;35:3924-3933.
10. Stewart J. Keytruda FDA Approval History. https://www.drugs.com/history/keytruda.html. Accessed March 2, 2021.
11. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387:1540-1550.
12. Reck M, Rodríguez-Abreu D, Robinson AG, et al; KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375:1823-1833.
13. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol. 2019;37:537-546.
14. Mok TSK, Wu YL, Kudaba I, et al; aEYNOTE-042 Investigators. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393:1819-1830.
15. Vaddepally RK, Kharel P, Pandey R, et al. Review of indications of FDA-approved immune checkpoint inhibitors per NCCN guidelines with the level of evidence. Cancers (Basel). 2020;12:E738.
16. Rittmeyer A, Barlesi F, Waterkamp D, et al; OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389:255-265.
17. Fehrenbacher L, Spira A, Ballinger M, et al; POPLAR Study Group. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016;387:1837-1846.
18. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. N Engl J Med. 2020;383:1328-1339.
19. Drugs.com. Tecentriq FDA Approval History. https://www.drugs.com/history/tecentriq.html. Accessed March 2, 2021.
20. Sezer A, Kilickap S, Gümüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet. 2021;397:592-604.
21. Drugs.com. Yervoy FDA Approval History. https://www.drugs.com/history/yervoy.html. Accessed March 2, 2021.
22. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017;18:31-41.
23. Hodi FS, Chesney J, Pavlick AC, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2016;17:1558-1568.
24. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med. 2019;381:2020-2031.
25. Ready N, Hellmann MD, Awad MM, et al. First-line nivolumab plus ipilimumab in advanced non-small-cell lung cancer (CheckMate 568): outcomes by programmed death ligand 1 and tumor mutational burden as biomarkers. J Clin Oncol. 2019;37:992-1000.
26. Antonia S, Goldberg SB, Balmanoukian A, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Oncol. 2016;17:299-308.
27. Rizvi NA, Cho BC, Reinmuth N, et al; MYSTIC Investigators. Durvalumab with or without tremelimumab vs standard chemotherapy in first-line treatment of metastatic non-small cell lung cancer: the MYSTIC phase 3 randomized clinical trial. JAMA Oncol. 2020;6:661-674.
28. Inacio P. Imfinzi-Tremelimumab Combo Fails to Prolong Overall Survival in Metastatic NSCLC Phase 3 Trial. https://immuno-oncologynews.com/2019/09/03/imfinzi-tremelimumab-combo-fails-prolong-overall-survival-metastatic-nsclc-patients-phase-3-trial-shows/. Accessed March 2, 2021.
29. Planchard D, Reinmuth N, Orlov S, et al. ARCTIC: durvalumab with or without tremelimumab as third-line or later treatment of metastatic non-small-cell lung cancer. Ann Oncol. 2020;31:609-618.
30. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al; KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;378:2078-2092.
31. Drugs.com. FDA Approves Expanded Label for Merck's Keytruda (pembrolizumab) in Patients With Metastatic Nonsquamous NSCLC With No EGFR or ALK Genomic Tumor Aberrations. https://www.drugs.com/newdrugs/fda-approves-expanded-label-merck-s-keytruda-pembrolizumab-patients-metastatic-nonsquamous-nsclc-no-4805.html. Accessed March 2, 2021.

32. Paz-Ares L, Luft A, Vicente D, et al; KEYNOTE-407 Investigators. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med. 2018;379:2040-2051.
33. Hegde PS, Wallin JJ, Mancao C. Predictive markers of anti-VEGF and emerging role of angiogenesis inhibitors as immunotherapeutics. Semin Cancer Biol. 2018; 52:117-124.
34. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013;39:1-10.
35. Socinski MA, Jotte RM, Cappuzzo F, et al; IMpower150 Study Group. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378:2288-2301.
36. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:924-937.
37. Jotte R, Cappuzzo F, Vynnychenko I, et al. Atezolizumab in combination with carboplatin and nab-paclitaxel in advanced squamous NSCLC (IMpower131): results from a randomized phase III trial. J Thorac Oncol. 2020;15:1351-1360.
38. Baselga J. First-Line Durvalumab Regimens Extend PFS in Metastatic NSCLC. https://www.healio.com/news/hematology-oncology/20191029/firstline-durvalumab-regimens-extend-pfs-in-metastatic-nsclc. Accessed March 2, 2021.
39. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22:198-211.
40. U.S. Food and Drug Administration. FDA Approves Nivolumab Plus Ipilimumab and Chemotherapy for First-line Treatment of Metastatic NSCLC. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-nivolumab-plus-ipilimumab-and-chemotherapy-first-line-treatment-metastatic-nsclc. Accessed March 2, 2021.
41. Diab A, Tannir NM, Bentebibel SE, et al. Bempegaldesleukin (NKTR-214) plus nivolumab in patients with advanced solid tumors: phase I dose-escalation study of safety, efficacy, and immune activation (PIVOT-02). Cancer Discov. 2020;10:1158-1173.
42. Qu J, Mei Q, Chen L, et al. Chimeric antigen receptor (CAR)-T-cell therapy in non-small-cell lung cancer (NSCLC): current status and future perspectives. Cancer Immunol Immunother. 2021;70:619-631.
43. Johnson DB, Sullivan RJ, Menzies AM. Immune checkpoint inhibitors in challenging populations. Cancer. 2017;123:1904-1911.
44. Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol. 2018; 4:1721-1728.
45. Johnson DB, Reynolds KL, Sullivan RJ, et al. Immune checkpoint inhibitor toxicities: systems-based approaches to improve patient care and research. Lancet Oncol. 2020;21:e398-e404.

Differences in Toxicity and Outcomes in Clinical Trial Participants From Minority Populations

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overview

Black men have a higher prevalence of and mortality rate from prostate cancer compared with White men and have been shown to present with more aggressive and later-stage disease. How prostate cancer treatment affects these racial disparities is still unclear. Several studies have shown that Black men who receive treatment have a more pronounced decrease in prostate cancer–specific death; however, there remains a large disparity in all-cause mortality. This disparity may be in part related to a higher risk of death resulting from comorbidities, given the higher rates of cardiovascular disease and diabetes in Black men, both of which are complicated by the use of androgen-deprivation therapy. To further understand these disparities, it is important that we analyze the racial differences in adverse event rates and severity. Increasing the percentage of Black men in clinical trials will improve the understanding of the biologic drivers of racial disparities in prostate cancer. To evaluate the potential differences in adverse event reporting and demonstrate the feasibility of enrolling equal numbers of Black and White men in trials, we performed a prospective, multicenter study of abiraterone plus prednisone with androgen-deprivation therapy in men with metastatic castration-resistant prostate cancer, stratified by race. Racial differences in prostate-specific antigen kinetics and toxicity profile were demonstrated. Higher rates and severity of adverse events related to adrenal hormone suppression, including hypertension, hypokalemia, and hypomagnesemia, were seen in the Black cohort, not previously reported. Increased enrollment of Black men in prostate cancer clinical trials is imperative to further understand the impact of race on clinical outcomes and treatment tolerability.

BACKGROUND

Black men in the United States are 50% more prone to develop prostate cancer in their lifetimes compared with White men, and they die as a result of prostate cancer at a rate greater than twice that among White men.[1] Access to care is a key driver in this disparity and is complicated by many differentiating factors, including those related to socioeconomics, education, culture, and trust.[2] Studies suggest that Black men present with more aggressive and later-stage disease and are more likely to develop disease recurrence after local therapy and experience disease progression to metastasis.[1] What is not as clear, however, is how treatment may affect these outcomes.

Numerous recent retrospective analyses have evaluated the outcomes of Black and White men included in clinical trials with either locally advanced or metastatic castration-resistant prostate cancer to determine if there are differences in efficacy outcomes. The first analysis came in 2007, when a retrospective meta-analysis of baseline characteristics of patients with metastatic castration-resistant prostate cancer participating in cooperative group studies revealed a modest survival advantage associated with men who self-identified as Black.[3,4] This association of race with outcome was independently confirmed through a much larger meta-analysis of nine phase III trials of docetaxel-based regimens in men with metastatic castration-resistant prostate cancer, demonstrating in multivariable analysis a 19% reduction in the risk of death associated with docetaxel treatment in self-described Black men.[4] Subsequently, a prospective observational cohort study of sipuleucel-T, an autologous cellular immunotherapy approved by the U.S. Food and Drug Administration for treatment of men with metastatic castration-resistant prostate cancer, demonstrated a clinically significant 40% improvement in survival for Black men compared with White men, after adjustment for known prognostic factors ($p = .001$).[5,6] In addition, a meta-analysis of randomized controlled trials by the National Radiation Oncology Group revealed that Black men had a lower hazard ratio for prostate cancer–specific death compared with White men during the studies.[7] Nonetheless, a large disparity remained in all-cause mortality for Black men with nonmetastatic prostate cancer.

The higher all-cause mortality for Black men with advanced prostate cancer has been attributed in part to a higher risk of death resulting from comorbidities. Black men have the highest rates of cardiovascular

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PRACTICAL APPLICATIONS

- Black men have a higher incidence of and mortality from prostate cancer and present with more aggressive and later-stage disease; however, how treatment affects these racial disparities is still unclear.
- Black men have been shown to have lower prostate cancer–specific mortality but higher all-cause mortality, which could be attributed to comorbid conditions that are exacerbated by therapy.
- To further understand racial disparities in prostate cancer, more Black men need to be enrolled in clinical trials at all levels, especially phase III trials.
- Our prospective, multicenter study of abiraterone plus prednisone with androgen-deprivation therapy in men with metastatic castration-resistant prostate cancer, stratified by race, showed racial differences in prostate-specific antigen kinetics and toxicity profile.
- Black men had higher rates and severity of adverse events related to adrenal hormone suppression compared with White men.

mortality compared with other ethnicities in the United States.[8] In regard to patients with prostate cancer, Black men have been shown to present with a greater comorbidity index (9%) compared with White men (4.6%) before initiating treatment.[8] However, the extent to which prostate cancer treatment, particularly androgen-deprivation therapy (ADT) and novel androgen receptor inhibitors, contributes to this disparity is unknown.

ADT has been linked to higher incidence of diabetes, hypertension, and metabolic syndrome leading to an increase in cardiovascular mortality.[8] In a large cohort study, the 5-year cumulative incidence of death resulting from cardiovascular disease was 5.5% in patients who received ADT compared with 2.0% in patients who did not receive ADT.[8] To understand if there were racial differences in cardiovascular morbidity and mortality in patients receiving ADT, Gandaglia et al[9] analyzed more than 140,000 patients with nonmetastatic prostate cancer in the Surveillance, Epidemiology, and End Results database, comparing cardiovascular outcomes in those who received ADT versus those who were ADT naïve. The 10-year rates of coronary artery disease, acute myocardial infarction, and sudden cardiac death were evaluated. When broken down by race, the study demonstrated a hazard ratio of 1.41 (95% CI, 1.32–1.51; $p < .001$) for incidence of sudden cardiac death in Black men who received ADT compared with White patients who received ADT, with no difference in coronary artery disease (HR, 0.95) or acute myocardial infarction (HR, 1.02).[8] However, in a similar analysis of those with metastatic prostate cancer who received ADT, Black men did not show an increase in overall cardiovascular mortality compared with White men (HR, 1.15; 95% CI, 0.96–1.38).[8]

With regard to glycemic control, ADT has been associated with decreased insulin sensitivity and increased development of diabetes.[8] In a retrospective analysis of 7,500 patients with previously diagnosed diabetes treated with ADT, nearly 20% of men treated with ADT had an increase in hemoglobin A1c by greater than 1.0 percentage points, compared with only 12% of men who did not receive ADT, leading to an increased need for additional diabetes medications.[8] Although Black and White men were affected equally in this cohort, Black men have a higher prevalence of both diabetes and obesity than White men. On the basis of a database analysis of nearly 5 million patients in the United States, the age-standardized diabetes prevalence was 21.4% in Black patients compared with 12.2% in White patients.[8] Therefore, given the higher prevalence of diabetes in Black patients, the adverse effects of ADT will have a disproportionate impact on the Black population. It is hoped that further long-term prospective analysis of cardiovascular morbidity and mortality in response to ADT, including results from the RADICAL-PC trial,[8] will identify racial differences in the toxicity profile and elucidate strategies to mitigate cardiovascular risk resulting from ADT.

DISCUSSION

How can we better understand the differences in adverse event rates and severity associated with prostate cancer treatment and race? First, the number and percentage of Black men participating in phase III trials should be improved. In the Halabi et al[4] meta-analysis, only 6% of participants were Black, compared with the Dess et al[7] multiple cohort analysis, in which Black men made up 38.1% of Veterans Affairs participants and 17.8% of randomized controlled trial participants. Improving enrollment in phase III trials for regulatory approval would significantly enhance our understanding of how Black men not only respond to and benefit from treatment interventions but also tolerate them. Liberalizing inclusion criteria to allow patients with less-than-optimal functional status and comorbid conditions would better approximate the real-world patients for whom these treatments are ultimately intended. Second, the collection and reporting of comorbidity outcomes in these studies should be prioritized.

Considerable work has been done to retrospectively evaluate the efficacy outcomes associated with prostate cancer treatments by race, but few of these efforts have evaluated or acknowledged the potential for differences in adverse event reporting by race. To begin to address these

challenges, demonstrate the feasibility of enrolling equal numbers of Black and White men, and generate pilot data to prospectively evaluate possible differences in efficacy as well as adverse event rates, we performed a prospective, multicenter study of abiraterone plus prednisone with ADT in men with metastatic castration-resistant prostate cancer, stratified by race.[10]

Differences in prostate-specific antigen kinetics were seen across various time points and thresholds by race. Black men had a median time to prostate-specific antigen progression of 16.6 months (95% CI, 11.6 to not reached), whereas White men had a median of 11.5 months (95% CI, 8.5–19.3), similar to prior retrospective reports.[11] The estimated rates of prostate-specific antigen decline from baseline by 30% or greater, 50% or greater, and 90% or greater were 82%, 74%, and 48%, respectively, in Black men and 78%, 66%, and 38%, respectively, in White men. Black men also had a lower rate of no prostate-specific antigen decline as the best response (4%; 95% CI, 0.004–0.14) compared with White men (10%; 95% CI, 0.03–0.21). The best prostate-specific antigen decline to less than 0.1 ng/mL was observed in 18% of Black men, and the best prostate-specific antigen decline to less than 0.2 ng/mL was observed in 26% of Black men. In White men, the rates of best prostate-specific antigen decline to less than 0.1 and less than 0.2 ng/mL were 8% and 10%, respectively. None of these results were significant, given the small sample size, but they warrant further validation.

Importantly, we also observed differences in toxicity profile by race, not previously reported. The most common adverse events (≥ 10.0%) reported during study are shown in Fig. 1. Overall, the toxicity profile was similar to prior reports; however, the incidence of some toxicities seemed to vary by racial cohort. Black and White men, respectively, reported different rates of fatigue (26.0% and 42.0%), cough (18.0% and 30.0%), headache (6.0% and 18.0%), falls (8.0% and 14.0%), vomiting (6.0% and 16.0%), peripheral edema (26.0% and 16.0%), constipation (28.0% and 10.0%), anorexia (20.0% and 4.0%), hot flashes (20.0% and 2.0%), and dyspepsia (14.0% and 6.0%).

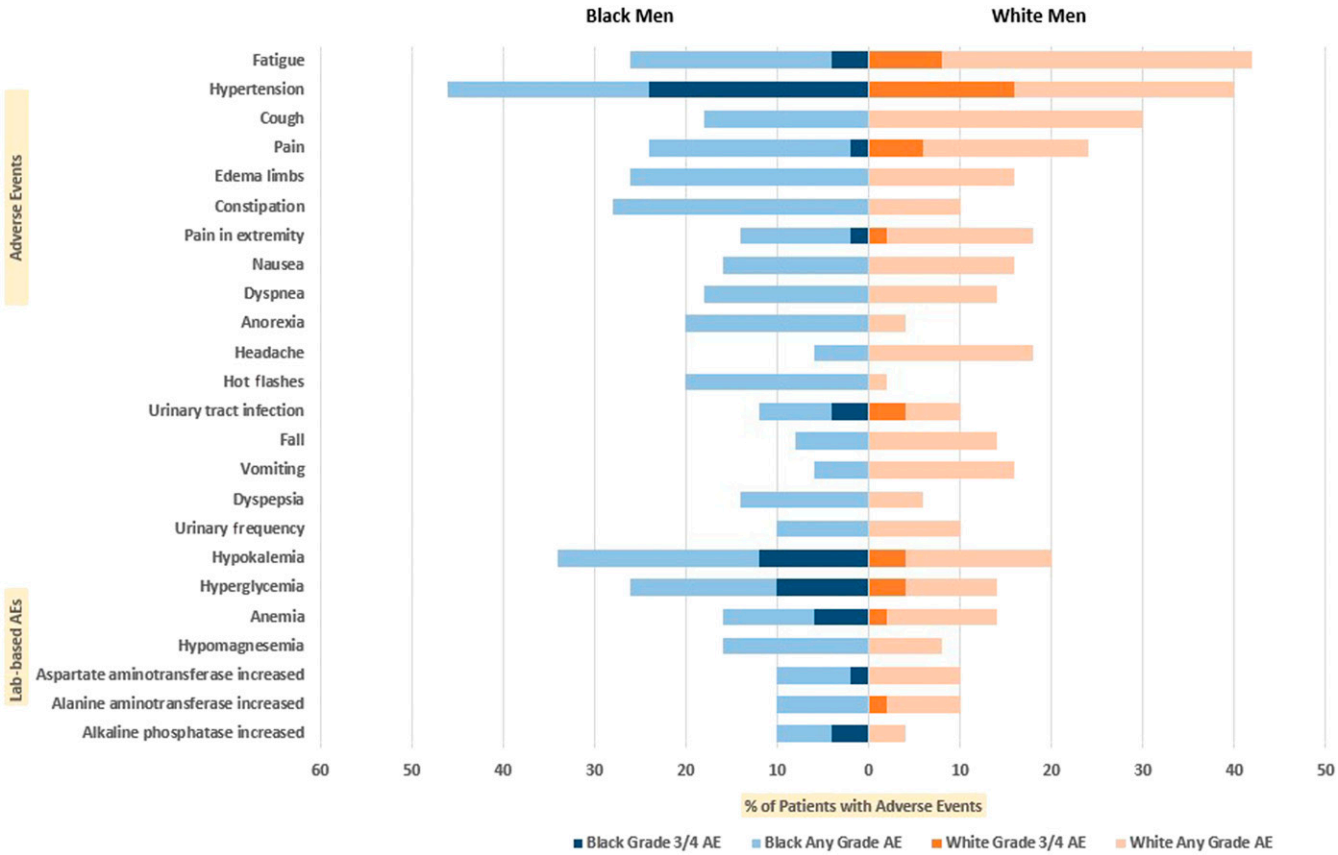

FIGURE 1. Tornado Plot of Adverse Event Reporting From the Abi Race Study, Stratified by Race

Black cohort is represented by blue bars on the left, and White cohort is represented by orange bars on the right. Specific toxicities are represented by name in the column on the left, with corresponding colored bars in light shading (for all-grade toxicity) and darker shades (for Common Terminology Criteria for Adverse Events grade 3 or 4 events).

Abbreviation: AE, adverse event.

Laboratory adverse events were similar to prior reports[11]; however, these varied in incidence by racial cohort. Estimated rates differed in Black and White men, respectively, for hyperglycemia, both all grade (26.0% and 14.0%) and grades 3 to 4 (10% and 4%). Estimated rates of hypokalemia (34% and 20%) and hypomagnesemia (16% and 8%) also differed in Black and White men, respectively. In particular, grade 3 to 4 rates of hypokalemia were more frequent in Black than White men (12% and 4%). There was no evidence of higher baseline screening rates of electrolyte abnormalities, and diuretic antihypertensive medications were not commonly used in either population. Glucocorticoid use (prednisone) was mandated during study (5 mg twice per day), although dose adjustments were allowed at the discretion of the treating physician.

These outcome results for both efficacy and toxicity are exploratory and limited by their number, with wide, overlapping confidence intervals. However, these differences in adverse events by race, which may be clinically important, including higher rates and severity of adverse events related to adrenal hormone suppression (i.e., hypertension, hypokalemia, and hypomagnesemia) in Black men compared with White men, have not been previously recognized. If confirmed, these results could support different thresholds in monitoring and managing these important adverse events by race. For instance, abiraterone plus prednisone has also been studied using a lower starting dose of prednisone (5 mg daily instead of 5 mg twice per day).[12] Although adverse event rates were similar with lower prednisone, Black men were underrepresented in this study, largely conducted in Europe and Canada. We also saw differences in symptom reporting in patients by race (i.e., fatigue). To what extent this was driven by differences in culture, education, or trust is unknown in our study, but further prospective investigation is warranted. Finally, to what extent African ancestry and specific allelic ancestry, more so than self-identified race, factor into possible differences in efficacy and toxicity outcomes is not known, but we are beginning to explore this in parallel by collecting germline DNA.

Finally, increased enrollment of Black men in prostate cancer clinical trials at all levels, but especially in phase III trials, is critical to better understanding what impact race may have on clinical outcomes, both efficacy and safety/tolerability. Potential strategies for improving enrollment of people from minority populations into clinical trials include hiring race-concordant patient navigators,[13] establishing programs to limit the financial burden of clinical trial participation,[14] and engaging community programs to change perceptions of clinical trials and establish trust.[15] Another unique strategy would be to leverage technology, including the use of social media, to recruit more participants from minority populations into clinical trials. Efforts to increase accrual of patients from minority populations should focus on both assessments and patient-reported outcomes.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/index.html. Accessed April 1, 2021.
2. Halabi S, Vogelzang NJ, Kornblith AB, et al. Pain predicts overall survival in men with metastatic castration-refractory prostate cancer. J Clin Oncol. 2008;26:2544-2549.
3. Halabi S, Small EJ, Vogelzang NJ, et al. Impact of race on survival in men with metastatic hormone-refractory prostate cancer. Urology. 2004;64:212-217.
4. Halabi S, Dutta S, Tangen CM, et al. Overall survival of black and white men with metastatic castration-resistant prostate cancer treated with docetaxel. J Clin Oncol. 2019;37:403-410.
5. Higano CS, Armstrong AJ, Sartor AO, et al. Real-world outcomes of sipuleucel-T treatment in PROCEED, a prospective registry of men with metastatic castration-resistant prostate cancer. Cancer. 2019;125:4172-4180.
6. Sartor O, Armstrong AJ, Ahaghotu C, et al. Survival of African-American and Caucasian men after sipuleucel-T immunotherapy: outcomes from the PROCEED registry. Prostate Cancer Prostatic Dis. 2020;23:517-526.
7. Dess RT, Hartman HE, Mahal BA, et al. Association of Black race with prostate cancer-specific and other-cause mortality. JAMA Oncol. 2019;5:975-983.

8. Lloyd-Jones D, Adams RJ, Brown TM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation. 2010;121:948-954.

9. Gandaglia G, Sun M, Popa I, et al. The impact of androgen-deprivation therapy (ADT) on the risk of cardiovascular (CV) events in patients with non-metastatic prostate cancer: a population-based study. BJU Int. 2014;114:E82-E89.

10. George DJ, Halabi S, Heath E, et al. A prospective trial of abiraterone acetate plus prednisone in black and white men with metastatic castrate-resistant prostate cancer. Cancer. 2021, In press.

11. Ryan CJ, Smith MR, de Bono JS, et al; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013; 368:138-148.

12. Fizazi K, Tran N, Fein L, et al; LATITUDE Investigators. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med. 2017; 377:352-360.

13. Strom C, Combs MA, Weaver KE, et al. Hispanic Patient Navigation: Improving Cancer Care & Clinical Trial Participation. Poster presented at: Advancing the Science of Cancer in Latinos; February 22, 2018; San Antonio, TX.

14. Nipp RD, Lee H, Powell E, et al. Financial burden of cancer clinical trial participation and the impact of a cancer care equity program. Oncologist. 2016; 21:467-474.

15. Sprague Martinez L, Freeman ER, Winkfield KM. Perceptions of cancer care and clinical trials in the black community: implications for care coordination between oncology and primary care teams. Oncologist. 2017;22:1094-1101.

DEVELOPMENTAL THERAPEUTICS—MOLECULARLY TARGETED AGENTS AND TUMOR BIOLOGY

Moving Beyond 3+3: The Future of Clinical Trial Design

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overview

Misgivings have been raised about the operating characteristics of the canonical 3+3 dose-escalation phase I clinical trial design. Yet, the traditional 3+3 design is still the most commonly used. Although it has been implied that adhering to this design is due to a stubborn reluctance to adopt change despite other designs performing better in hypothetical computer-generated simulation models, the continued adherence to 3+3 dose-escalation phase I strategies is more likely because these designs perform the best in the real world, pinpointing the correct dose and important side effects with an acceptable degree of precision. Beyond statistical simulations, there are little data to refute the supposed shortcomings ascribed to the 3+3 method. Even so, to address the unique nuances of gene- and immune-targeted compounds, a variety of inventive phase 1 trial designs have been suggested. Strategies for developing these therapies have launched first-in-human studies devised to acquire a breadth of patient data that far exceed the size of a typical phase I design and blur the distinction between dose selection and efficacy evaluation. Recent phase I trials of promising cancer therapies assessed objective tumor response and durability at various doses and schedules as well as incorporated multiple expansion cohorts spanning a variety of histology or biomarker-defined tumor subtypes, sometimes resulting in U.S. Food and Drug Administration approval after phase I. This article reviews recent innovations in phase I design from the perspective of multiple stakeholders and provides recommendations for future trials.

PHASE I CLINICAL TRIAL DESIGN: THE CASE FOR 3+3

Background

Phase I clinical trials include first-in-human trials as well as first-time use of experimental or approved drugs in novel combinations. Historically, the primary objective of a phase I oncology trial was to define maximum tolerated dose (MTD), which is then the dose used for phase II efficacy studies. More recently, emphasis has been placed on defining the recommended phase II dose of a new drug or multiagent combination. The recommended phase II dose is often lower than the MTD because the MTD is defined in a 4-week window, whereas toxicities, especially of gene- and immune-targeted drugs, may emerge with chronic use; furthermore, grade 2 side effects such as diarrhea or mucositis, which may be tolerable for a short period of time, can become intolerable with ongoing dosing. Complicating the matter is the fact that, just a few decades ago, phase I trials were considered toxicity trials only, and whether they had a therapeutic objective was a matter of debate. However, in the last 15 years, as more potent anticancer drugs have been developed, it is has become apparent that phase I trials have definitive therapeutic objectives,[1] and several phase I trials have now even led to U.S. Food and Drug Administration (FDA) approval.[2,3]

Design of 3+3 Phase I Clinical Trials

The traditional 3+3 design was originally introduced in the 1940s[4] and further described by Storer in 1989[5] as well as others.[6] In a "3+3 design," three patients are initially enrolled into a given dose cohort. If there is no dose-limiting toxicity (DLT) seen in any of these participants, the trial proceeds to enroll additional participants into the next higher dose cohort.[7,8] Dose-limiting toxicities are generally defined as clinically relevant toxicities grade 3 or higher by the Common Terminology Criteria for Adverse Events. If one patient manifests a DLT at a specific dose, an additional three individuals are accrued into that same dose cohort. Development of DLTs in two or more out of six patients at a specific dose level indicates that the MTD has been exceeded; further dose escalation is not pursued, and the prior dose level is expanded to six patients; if there is no more than one patient who experiences a DLT among those six patients, that dose level is considered the MTD. The MTD is determined in the first cycle of therapy (often about 4 weeks). The MTD is therefore defined as the highest dose level in which six patients were treated and, at most, one patient experienced a DLT during the first cycle of therapy. If more than six patients are treated at any dose level, the MTD is exceeded if more than one-third of the patients experience a DLT.

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PRACTICAL APPLICATIONS

- In contemporary phase I trials, which often include drugs developed with a deep understanding of biology and with the use of biomarkers to select patients, one of the most important objectives involves finding therapeutic signals. Response signals can be better identified if more patients are treated on early-phase trials.
- Early-phase trials with greater numbers of patients also better identify the spectrum of clinically relevant toxicities.
- Alternative phase I designs that use accelerated escalation often decrease the number of patients on phase I trials, purportedly to minimize the number of patients receiving subtherapeutic dosing. However, the issue of subtherapeutic dosing can be overcome by permitting intrapatient dose escalation. Furthermore, in the era of targeted and immune therapies, evidence suggests that patients on lower doses in early-phase studies do not fare worse.
- There are several rule-based designs, such as traditional 3+3, accelerated titration, pharmacologically guided dose escalation, and interval 3+3, in oncology phase I trials.
- There are two main Bayesian designs, the model-based design and the model-assisted design, in oncology phase I trials. Continual reassessment method (plus escalation with overdose control) and efficacy-toxicity tradeoff are two main model-based designs. Modified toxicity probability interval and Bayesian optimal interval are two main model-assisted designs. Efficacy-toxicity tradeoff and Bayesian optimal interval phase I/II best apply to seamless phase I/II trials of single agents and phase Ib trials of drug-drug combinations.
- Expansion cohorts and telescoped trials, moving directly from phase I to phase II (and theoretically to phase III), expedite drug development.

Dose Escalation in Phase I 3+3 Trials

Dose-escalation methodologies may be predetermined or preferably adjusted to toxicity. The most frequently used predetermined escalation rules use a modified Fibonacci mathematical series to determine the amount of dose increase for cohorts of sequentially enrolled patients. (Fibonacci sequence is the sequence in which each number is the sum of the two numbers that precede it.) The Fibonacci series guarantees that dose increases are initially large, but increments are smaller at higher dose levels.

Other (and in the authors' opinion, better) ways to escalate do not predetermine dose-escalation sequence, but rather plan for toxicity-adjusted escalation. If, within a 3+3 design, there were no toxicities (that are at least possibly drug-related) in the prior dose level, then the next escalation is by 100%; if the highest grade of toxicity was grade 1 in the prior dose level, then the next escalation is by 50%; if the highest grade of toxicity was grade 2, then the next dose escalation is by 25%; if the highest grade of toxicity was grade 3 (or higher), dose escalation is held, and the dose level is expanded; and if less than one-third of the patients have a toxicity of grade 3 or higher at the expanded dose level, a further dose escalation of 25% occurs.

Simulated Reality (Models) Versus Reality

Phase I trials must prioritize safety while not compromising efficiency. Statistical simulations have implied that a 3+3 design pinpoints MTD in as few as 30% of studies.[9] Moreover, it has been claimed that this dose-escalation method can result in a high proportion of participants receiving treatment at subtherapeutic doses.[10] Indeed, many alternative designs limit the number of patients per dose level. The purpose of this limitation is to avoid exposing patients to subtherapeutic doses. However, the reality is that these designs result in much fewer patients enrolled over the first few months of the trial. Indeed, it has been claimed that a cohort size of one patient will provide better operating characteristics than dosing several patients simultaneously at a dose level[11]; optimal dosing is then calculated by complex mathematical formulas. However, in the real world, such strategies are suboptimal, and the concerns regarding 3+3 designs are often not valid for the following reasons:

(1) Gaining experience with a drug requires treating patients with that drug; in accelerated titration or continuous reassessment designs, only one patient may be treated per dose level. Because the next dose level is started when patients at the previous dose level have completed the first cycle of safety monitoring (usually about 4 weeks), for drugs with minimal toxicity at low doses, six or fewer patients will be treated 6 months into the study. Very little can be learned from such a small number of patients. In contrast, in the 3+3 design, up to 18 patients will have been treated in the same 6-month period.
(2) In the modern era, one of the most important objectives of phase I trials involve finding therapeutic signals; finding response signals is more likely if more patients are treated.
(3) With newer targeted drugs, patients exposed to higher doses do not fare better.[12]

(4) Adult patients with cancer entering a clinical trial may be in their twenties or eighties; the doses tolerated will often be much different, and current modeling does not take these differences into account.
(5) When only one patient is treated at a dose level, proper pharmacokinetic studies cannot be performed.

Notably, in an analysis of phase I trials over a 22-year period, the majority of which used a 3+3 design, 70% of clinically relevant toxicities found in later trials were described in the phase I studies. Further, among 28,505 patients in later trials, the death rate that was related to drug was only 1.41%, indicating that traditional phase I trials provide strong safety data for later studies. The final dose approved by the FDA was within 20% of the recommended phase II dose in the majority of assessed drugs/trials. Importantly, a significant relationship ($p = .0032$) was observed between increasing the number of patients in phase I (up to 60) and the ability to describe future clinically relevant toxicities was observed.[13] In contrast, newer phase I trial designs using accelerated titration and/or continuous reassessment often emphasize decreasing the number of patients, even including only one patient per dose level.[8] Taken together, the ability to fulfill the objectives of phase I trials are the reason why the 3+3 design remains popular.

Strategies for Optimizing Phase I 3+3 Designs

Although phase I 3+3 designs function remarkably well in the real world, as noted above, there is still room for improvement/optimization. We suggest the following methodologies for optimization:

(1) Use of toxicity-adjusted dose escalation, as described above, rather than predetermined Fibonacci-related schema. In this way, dose escalation depends on the toxicities seen rather than a predetermined formula divorced from the reality on the ground.
(2) Allow increases in the number of patients at each dose level, because many phase I trials now show activity and because prior studies demonstrate that increasing the number of patients in phase I (rather than decreasing them) enhances the ability to accurately describe clinically meaningful toxicities.[13] Furthermore, expanded phase I cohorts give a better sense of efficacy. This can be done by allowing the entry of a set additional number of patients to any dose level cohort already proven safe; those additional patients can then also be evaluated vis-a-vis toxicity, and if 33% or more of patients in any expanded cohort have greater than or equal to grade 3 toxicity, the MTD is now set at the dose level below that cohort (even if there has been prior higher dose escalation).

Other more complex considerations may include permitting intrapatient dose escalation after a predefined period on the entered dose level, in cases in which there is good reason to believe that higher dose levels are showing efficacy, and using pharmacokinetic drug levels to adjust doses in individual patients. Furthermore, for gene- and immune-targeted agents, extending the DLT window beyond the first cycle (approximately 4 weeks) is essential because of the importance of late toxicities; however, it is critical that this be done by observing and counting toxicities beyond the DLT window without holding up dose escalation, because the latter would tremendously slow down finishing the phase I trial and would not enhance safety, as these trials already have an extremely small death rate at least possibly related to drug (0.49% in a study of 11,935 phase I participants).[14,15] Finally, an important effort involving telescoped trials that segue directly from phase I to phase II expansion cohorts has emerged, saving time creating and approving new studies and allowing activity to be determined in the setting of an expanded phase I trial, with drugs such as selpercatinib targeting RET alterations being an ideal example of such a strategy.[16,17]

PHASE I TRIAL DESIGN: BAYESIAN PERSPECTIVE ON PHASE I TRIAL DESIGN

The traditional 3+3 design had been the most widely adapted design for phase I oncology drug development.[18,19] However, multiple new designs have been proposed.

Bayesian Designs

Bayesian designs are based on the principle of Bayes theorem.[20] According to previous knowledge, experience, or a simple guess, an estimation of the prior probability distribution could be made.[21] When the clinical trial is in progress, the information accumulates as each patient is enrolled, and certain outcomes (e.g., DLT and efficacy endpoint) are present or absent at the received dose level. Integrating the prior probability distribution and accumulating information, a new estimation of probability distribution, the posterior probability distribution, could be made by Bayesian inference. Iterating with the information-updating process, posterior probability distribution with better precision will be achieved. According to the ways of incorporating statistical models in clinical trials, there are two categories of phase I Bayesian design: model-based and model-assisted designs (Table 1).[22]

Model-Based Designs

Model-based designs are earlier Bayesian designs to be applied in phase I trials. There was a prespecified statistical model, but no predetermined algorithm to follow. For example, the dose level of which next-enrolled patient will be treated is unknown unless the information about previous patients could be integrated to model and the designs and parameters are updated.[28] Therefore, in model-based design, the intensive help from statisticians is mandatory, and many clinicians have difficulties understanding the process.

TABLE 1. Characteristics of 3+3 Design, Model-Based Designs, and Model-Assisted Designs[22-27]

Characteristics	3+3 Design	Model-Based Design	Model-Assisted Design
Underlying Bayesian inference	Absent	Present	Present
Variable targeted toxicity level	Absent	Present	Present
Flexible cohort size	Absent	Present	Present
Extension with efficacy consideration	Absent	Present (e.g., EffTox)	Present (e.g., BOIN12)
Intensive calculations and ever-changing designs	Absent	Present	Absent
Predetermined rules to follow	Sometimes present	Absent	Present
More accurate MTD than 3+3	MTD determined with reasonable precision	Present (e.g., CRM)	Present (e.g., mTPI-2 and BOIN)
General picture of dose-toxicity relationship	Notable toxicities determined with reasonable precision	Present	Absent

Abbreviations: EffTox, efficacy-toxicity tradeoff; BOIN, Bayesian optimal interval; MTD, maximum tolerated dose; CRM, continual reassessment method.

With more statistical labors, however, the gains are also fruitful. Based on the underlying statistical model, the estimation of the whole probability distribution (e.g., dose-toxicity curve), not only the single MTD, could be reached with certain precision (Table 1).[23]

Continual Reassessment Method

The continual reassessment method is the most classic Bayesian design in phase I trial. The most common choices of the statistical model are power model or logistic model with one or two parameters. Target toxicity level, which means the probability of DLT at a certain dose level that could be accepted, is prespecified according to clinical scenario and customs (how much risk seemed to be justifiable by most clinicians). The range of target toxicity level is often between 20% and 35%. Before the start of trial, "the prior" dose-toxicity skeleton (specified dose levels d1, d2, d3…, with corresponding DLT probabilities p1, p2, p3….) should be assigned as according to preclinical model, profile of similar class of drug, or simple guess. A trivial constraint is that the assigned DLT probabilities in the dose-toxicity skeleton should be nondecreasing along with increasing dose levels.[11]

After a patient was enrolled, through Bayesian inference, parameters of the statistical model could be updated. The next patient would be treated at the dose with estimated DLT probability closest to target toxicity level. This process not only incorporates the outcome of current dose level (like in traditional 3+3), but also information of all enrolled patients. Finally, the study will be completed when specified stopping criteria are achieved. For instance, a particular number of patients is treated consecutively at the same dose level; the width of Bayesian credible interval for the MTD reaches a certain level; or when the estimated probability of coming consecutive patients will be dosed at the same dose level is higher than a certain degree. As a classic design existed for more than 30 years, the development of many anticancer agents was based on continual reassessment method. Pemetrexed (LY232514, an antimetabolite)[29] and DX-8951f (exatecan mesylate, a topoisomerase I inhibitor; a derivative is used in trastuzumab deruxtecan)[30] are examples.

Escalation With Overdose Control

There are several limitations of original continual reassessment method. An important one is that patients may be exposed to a highly toxic dose. To solve this problem, escalation with overdose control was proposed by Babb et al[31] (Fig. 1). In escalation with overdose control design, an upper bound is set for the next recommended dose level that predicted the probability that the dose exceeding MTD does not surpass the upper bound. Consequently, the overdose risk was protected within a certain degree. PNU-214936 (a murine Fab fragment of 5T4 fused to a mutated superantigen of staphylococcal enterotoxin A)[32] and ribociclib (LEE011, a CDK4/6 inhibitor)[33] are drugs developed by escalation with overdose control design.

Efficacy-Toxicity Tradeoff

In the above-described designs, dose finding is only based on a single binary variable: toxicity. Considering bivariate binary outcomes, toxicity and efficacy, Thall and Cook[34] advocated the efficacy-toxicity tradeoff design. The design not only addresses the concern to treat patients with an excessively toxic dose, but also addresses the concern of excessively low efficacy. The dose titration will be according to this efficacy-toxicity tradeoff until a dose reaches both targeted efficacy and toxicity. If the targets could not both be reached, the dose with maximal desirability (defined by prespecified efficacy-toxicity tradeoff contour) will be selected. Efficacy-toxicity tradeoff was adopted in the phase I/II MATCHPOINT study (combination of ponatinib, a multikinase

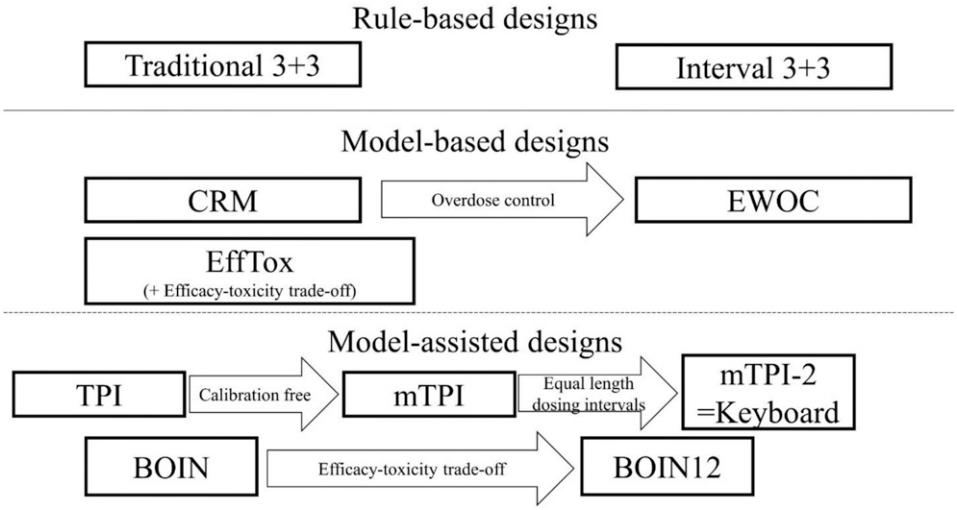

FIGURE 1. Relationship Between Mentioned Trial Designs

Arrows represent the direct evolution between designs. Abbreviations: CRM, continual reassessment method; EWOC, escalation with overdose control; EffTox, efficacy-toxicity tradeoff; TPI, toxicity probability interval; mTPI, modified toxicity probability interval; BOIN, Bayesian optimal interval.

inhibitor, with targets including ABL-1 and chemotherapy for blast-phase chronic myelogenous leukemia)[35] and phase I STM-01 study (combination of alisertib [MLN8237], an Aurora-kinase A inhibitor, with pazopanib, a multikinase vascular endothelial growth factor receptor inhibitor).[36]

Model-Assisted Design

Despite several advantages of model-based designs over traditional 3+3 designs, the high requirement of expertise and infrastructure and the lack of predetermined algorithms to be followed hindered wide adoptions of model-based designs.[5] In model-assisted designs, attempts are made to combine both the clear predetermined algorithm to guide the dose escalation/de-escalation in rule-based designs and the underlying statistical models in model-based designs (Table 1). In numerical simulation such as the Monte-Carlo method, some model-assisted designs, such as Bayesian optimal interval (BOIN) design, performed comparably to continual reassessment method.[24]

Modified Toxicity Probability Interval

The original toxicity probability interval (TPI) design proposed by Ji et al[37] in 2007 may be the first model-assisted design. It was based on a binomial model, but the dose-assignment actions could be tabulated predeterminedly. However, there were difficulties in applying the method, including parameter calibrations. In 2010, Ji et al[38] proposed a modified toxicity probability interval (mTPI) with improvements, including overdose protection, calibration free, and correspondence to Bayes rule.

In mTPI design, an equivalence interval $(pT - \varepsilon 1, pT + \varepsilon 2)$, $\varepsilon 1, \varepsilon 2 \geq 0$ was set. The pT denotes targeted toxicity level and $pT - \varepsilon 1$, $pT + \varepsilon 2$ represent the lower bound and upper bound of the acceptable toxicity probability for MTD, respectively. With an equivalence interval, the toxicity probability could be divided into three intervals: underdosing, proper dosing, and overdosing. For each interval and information from enrolled patients, the unit probability mass could be calculated for each interval, and the largest unit probability mass will guide the dose selection. For example, if unit probability mass is largest in underdosing interval, the next step is to escalate the dose. Given the equivalence interval and sample size, the dose escalation/stay at current dose/dose de-escalation guidance could be tabulated at the beginning of the study. The phase Ib study of selinexor (selective nuclear export inhibitor) and doxorubicin for soft tissue sarcoma (NCT03042819)[39] and phase Ib part of KEYNOTE 651 (combination of pembrolizumab, chemotherapy, and binimetinib, a MAPK inhibitor; NCT03374254) are examples of mTPI.

Modified Toxicity Probability Interval-2

Although mTPI is a concise design using a simple model to guide the dose finding, there were some counterintuitive results. For example, if there are three DLTs among six enrolled patients, the guidance of mTPI is to stay at the current dose, and this may be considered too risky by many clinicians.[21] In contrast, if there are two DLTs among nine enrolled patients, the guidance of mTPI is to stay at the current dose, and this may be considered too conservative. mTPI-2 is an extension of mTPI proposed by Guo et al[40] (Fig. 1). In general, mTPI-2 makes more decisions of escalation/de-escalation rather than stay at current dose compared with mTPI. mTPI-2 avoids the above-mentioned counterintuitive examples, and it demonstrated superior safety (less patients are exposed to doses higher than MTD) and better reliability (probability of true MTD to be chosen) than mTPI in most scenarios in simulation studies.

Keyboard Design

Another attempt to improve mTPI is keyboard design proposed by Yan et al.[41] The mTPI design compares unit

probability mass of underdosing, proper dosing, and overdosing intervals. In contrast, keyboard design defines evenly divided dosing intervals—"keys"—and the strongest key (key with highest posterior probability) guides the dose-decision rule. Notably, even though mTPI-2 and keyboard designs are developed independently,[40,41] they are actually equivalent.[24,42] The ongoing phase I study of JAK2 inhibitor ruxolitinib and BCL2 inhibitor venetoclax combination (NCT03874052) used keyboard design.

Bayesian Optimal Interval

BOIN design compares the DLT rate at current dose to dose escalation and de-escalation boundaries.[43] The boundaries are dependent on target toxicity rate. If DLT rate lies in interval between the boundaries, stay at current dose. If DLT rate is not more than escalation boundary or not less than de-escalation boundaries, then escalate/de-escalate the dose, respectively. BOIN design was shown to be superior to 3+3 in selecting correct MTD and to be associated with less overdose compared with mTPI. Some recent studies applied this design; for instance, a phase I study of zotiraciclib (TG02, multikinase inhibitor of CDK1,2,7,9, FLT3, and JAK2) and temozolomide combination.[44]

Bayesian Optimal Interval Phase I/II

BOIN phase I/II (BOIN12) design is an extension of BOIN design to cover efficacy-toxicity tradeoff (Fig. 1). Considering efficacy and toxicity as binary variables (yes or no), there are four possible combinations: (toxicity −, efficacy +), (toxicity −, efficacy −), (toxicity +, efficacy +), and (toxicity +, efficacy −). From the clinical viewpoint, weight (utility) could be assigned to each outcome in that higher weight represents a more desirable outcome. Let p1, p2, p3, and p4 denote the probabilities of different outcomes, and u1, u2, u3, and u4, denote the respective utilities. The desirability = p1u1 + p2u2 + p3u3 + p4u4 defines optimal biologic dose, the dose with highest desirability.[31]

To conduct a study with BOIN12 design, upper toxicity limit, lower efficacy limit, and utilities must be specified initially. Afterward, a rank-based desirability table could be established. The dose-finding process is based on de-escalation/escalation boundaries (values of boundaries are like those in the BOIN design) and rank-based desirability table. In simulations, BOIN12 was shown to more accurately identify optimal biologic dose than the 3+3 design and was shown to be more robust than efficacy-toxicity tradeoff design (highly variable result regarding assumed models).[25]

Interval 3+3

Interval 3+3 is a model-free, rule-based design.[32] Similar to mTPI design, the target toxicity level and equivalence interval (pT − ε1, pT + ε2) are specified. Let n denote the number of patients at current dose, and x denote the number of patients with DLT at current dose. The dose-finding algorithm is based on comparison between x/n, (x − 1)/n, and equivalence level. The dose-finding decisions could be tabulated like mTPI and mTPI-2 designs.[45] Although the model-free nature may lead to less flexibility and generalizability, in common scenarios, interval 3+3 design may operate with safety and reliability comparable to model-based designs but superior to traditional 3+3 design. The ongoing phase I study of XL102 (a CDK7 inhibitor; NCT04726332) applied interval 3+3 design.

Challenges and Prospects

Despite plenty of literature demonstrating superiority of model-based or model-assisted designs compared with traditional 3+3 design in reliability, safety, and flexibility,[23] the application of novel Bayesian designs in oncology drug development is still limited. Although an increasing proportion of Bayesian designs has been shown in some institutions,[46] overall, the impact of statistical models on development of approved drug has not been expanded yet.[47]

A powerful novel design could not benefit any patient or drug if it is not applied in real trial and drug development. As we embrace the novel mechanism of drug to derive maximal benefit for the patients, it is time to value novel design to serve the patients in early phase oncology trials with better safety and precision. The alliance between clinicians and statisticians and among academic institutions, industrial sponsors, and regulatory agencies must be established to form the consensus about implementation of novel Bayesian phase I designs based on solid evidence from theoretical calculation and extensive scenario simulations.[26]

In the trial-designing phase, not only should "standard of care" be updated, but also there is no reason that the "standard of trial design" has to be fixed in the traditional 3+3 design, ignoring the demonstrated advantages of novel designs.[48] This is particularly important when certain issues that could not be addressed by the less flexible 3+3 design are concerned, such as efficacy-toxicity tradeoff, different targeted toxicity level, or late toxicities.[27,35,49] With the assistance of web tools and software,[40,50,51] implementing novel designs are not so daunting now. In addition, the understanding from regulatory agencies is pivotal for successful drug development, given the record that proposals with model-based designs were rejected by regulatory agencies, and it was recommended to obey the traditional design with poorer operating characteristics.[52]

PHASE I CLINICAL TRIAL DESIGN: THE EXPANDING ROLE OF DOSE-EXPANSION COHORTS

The predominate pathway for regulatory submissions to the FDA has required two or more adequate and well-controlled human clinical trials that provide evidence of treatment benefit that can be replicated.[53] Subsequent amendments

to FDA guidelines provide exceptions. Sponsors, for example, may implement one large controlled trial in place of running two trials.[54,55] The FDA instituted a program for Accelerated Approval in 1992, which allowed for approvals on the basis of surrogate endpoints for drugs treating serious conditions that filled an unmet medical need. The FDA Safety and Innovation Act, passed in 2012, allows accelerated approvals for appropriate drugs and indications by evaluating the effects of drugs on surrogate markers.[56] More recently, the FDA has established three additional pathways to speed the review process for emerging therapies with Fast Track, Breakthrough Therapy, and Priority Review pathways.[57] Drugs designated as breakthrough therapies, for example, may be approved without a control group using interim results of ongoing studies or with enrichment strategies devised to select patients who are most likely to benefit.[57] These changes prompted innovations in trial design with master protocol[58] and seamless designs.[59,60]

Advances in cancer biology and immunology continue to refine our understanding of cancer mechanisms and actionable therapeutic targets, extending treatment options for patients beyond conventional cytotoxic drug regimens. These advances have led to the development of biomarker-targeted treatments that transcend traditional classification criteria based on tissue histology. The discovery of microsatellite-instability high as a biomarker for increased neoantigen burden and sensitivity to immune checkpoint blockage, for example, led to the design of a series of trials investigating pembrolizumab (an anti–PD-1 antibody) in patients with tumors harboring microsatellite-instability high regardless of organ of cancer origin.[61,62] Positive results spanning several tumor types prompted a landmark decision by the FDA in May 2017 by which pembrolizumab was designated as the first tissue-agnostic cancer treatment.[63,64] The development of pembrolizumab as well as immune checkpoint inhibitors nivolumab and atezolizumab involved extensive use of dose-expansion cohorts. This article reviews their designs and use of dose expansion cohorts and compares to more traditional development strategies in the era before immune checkpoint inhibitor therapies.

Dose-Expansion Cohorts Prior to Immune Checkpoint Inhibition

The conventional paradigm for drug development, established for cytotoxic therapies, evaluates dose, safety, activity, and comparative benefit in a sequence of phases using trials and endpoints specifically devised for each phase. Expanding phase I trials to include dose-expansion (denoted phase Ib) cohorts following dose escalation and evaluation of MTD (denoted phase Ia) was less common. Reviewing 611 phase I trials published from 2006 to 2011, Manji et al[65] provide perhaps the most comprehensive overview of the use of dose-expansion cohorts during this period. The authors identified 149 (25%) phase I trials that included at least one dose-expansion cohort. Phase I trials with expansion cohorts enrolled a median of 22 patients in phase Ia (range, 3 to 17). The phase Ib component of these trials enrolled a median of 17 (range, 2 to 271) patients. A more recent analysis by Bugano et al[66] of 533 of these trials (phase I trials evaluating new indications for previously approved drugs were excluded) found that trials with expansion cohorts were statistically significantly less likely to be cytotoxic (12% vs. 25%; p = .006). Moreover, phase I trials incorporating dose-expansion cohorts were also more likely to enroll more than 47 patients.

Dose-Expansion Cohorts for Three Immune Checkpoint Inhibitors

The current era has yielded innovations in drug development strategies emphasizing large phase I trials facilitating simultaneous investigations of multiple dose levels, schedules, as well as tumor and biomarker subtypes with dose-expansion cohorts. This strategy has been successfully used to develop three immune checkpoint inhibitors. Table 2 describes the use of expansion cohorts in pivotal phase I trials of the immune checkpoint inhibitors.

Pembrolizumab

Enrolling 1,260 participants, the KEYNOTE-001 trial (NCT01295827)[67] evaluated pembrolizumab as a monotherapy for patients with progressive locally advanced or metastatic carcinoma, melanoma, and non–small cell lung carcinoma (NSCLC). In total, 1,205 patients were enrolled in phase Ib. Four melanoma expansion cohorts (655 patients) were added based on encouraging findings from phase Ia. Initially, a cohort enrolled 135 patients with ipilimumab-naive (87 patients) or ipilimumab-treated (48 patients) melanoma (cohort B1) to receive pembrolizumab at three dose levels, with no randomization: 10 mg/kg every 2 or 3 weeks and 2 mg/kg every 3 weeks. A cohort with ipilimumab-refractory melanoma was later initiated (cohort B2) to assess pembrolizumab in patients who had confirmed disease progression after ipilimumab, defined per immune-related response criteria (iRECIST). These patients were randomly assigned 1:1 to receive 2 or 10 mg/kg every 3 weeks. Additional expansion cohorts included: (1) ipilimumab-treated and ipilimumab-naive patients randomly assigned to receive 10 mg/kg every 2 weeks or every 3 weeks (cohort B3, 244 patients), and (2) ipilimumab-naive patients randomly assigned to 2 or 10 mg/kg every 3 weeks (cohort D, 103 patients).

The KEYNOTE-001 trial also included four NSCLC dose-expansion cohorts. First, 38 patients with previously treated NSCLC (cohort C) were enrolled to receive pembrolizumab 10 mg/kg every 3 weeks based on preliminary activity in

TABLE 2. Summary of the Use of Dose-Expansion Cohorts for Three Immune Checkpoint Inhibitors

Drug, Trial	Number of Expansion Cohorts	Expansion Cohort Characterization
Pembrolizumab, KN-001 NCT01295827	8	Melanoma in four cohorts (655 patients)
		B1: nonrandomly assigned, ipilimumab-naive and ipilimumab-treated (135 subjects)
		B2: ipilimumab-refractory, randomly assigned to two dose levels. 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks (173 subjects)
		B3: ipilimumab-naive or -treated, randomly assigned to two dose levels, 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks (244 patients)
		D: ipilimumab-naive, randomly assigned to two dose levels, 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks (103 patients)
		NSCLC in four cohorts (550 patients)
		C: Any PD-L1, two or more prior therapies, 10 mg/kg every 3 weeks (38 patients)
		F1: PD-L1+, treatment-naive, randomly assigned to three dose levels (2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, 10 mg/kg every 2 weeks) (101 patients)
		F2: previously treated, nonrandomly assigned 10 mg/kg every 3 weeks, other part randomly assigned to 10 mg/kg every 2 or 3 weeks (356 patients)
		F3: PD-L1+, one or more prior therapy, 2 mg/kg every 3 weeks (55 patients)
Nivolumab, NCT00730639	10	Melanoma in four cohorts (104 patients)
		I: dose level 1 mg/kg every 2 weeks (35 patients in total for this dose level, together with same dose level in cohort IV)
		II: dose level 3 mg/kg every 2 weeks (17 subjects)
		III: dose level 10 mg/kg every 2 weeks (20 subjects)
		IV: randomly assigned to three dose levels (0.1 mg/kg, 0.3 mg/kg, and 1 mg/kg) every 2weeks (17 patients, 18 patients, and not reported, respectively)
		RCC in two cohorts (34 patients)
		I: dose level 10 mg/kg every 2 weeks (16 patients)
		II: dose level 1 mg/kg every 2 weeks (18 patients)
		NSCLC in two cohorts (129 patients)
		I: dose level 10 mg/kg every 2 weeks (59 subjects in total for this dose level, together with same dose level in cohort II)
		II: randomly assigned to three dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg) every 2 weeks (33 patients, 37 patients, and not reported, respectively)
		Colorectal cancer in one cohort (19 patients)
		I: dose level 10 mg/kg every 2 weeks
		Prostate cancer = 1 cohort (17 patients)
		I: dose level 10 mg/kg every 2 weeks

(Continued on following page)

TABLE 2. Summary of the Use of Dose-Expansion Cohorts for Three Immune Checkpoint Inhibitors (Continued)

Drug, Trial	Number of Expansion Cohorts	Expansion Cohort Characterization
Atezolizumab, NCT01375842	9	I: melanoma (45 patients), dose level 10, 15, or 20 mg/kg
		II: NSCLC (88 patients), dose level 10, 15, or 20 mg/kg
		III: RCC (70 patients), dose level 10, 15, or 20 mg/kg
		IV: bladder cancer (97 patients), dose level 10, 15, or 20 mg/kg
		V: TNBC (116 patients), dose level 10, 15, or 20 mg/kg
		VI: glioblastoma (16 patients), dose level 10, 15, or 20 mg/kg
		VII: HNSCC (32 patients), dose level 10, 15, or 20 mg/kg
		VIII: uterine (12 patients), dose level 10, 15, or 20 mg/kg
		IX: basket cohort, other tumor types
		SCLC (17 patients), dose level 10, 15, or 20 mg/kg
		Ovarian (15 patients), dose level 10, 15, or 20 mg/kg

Abbreviations: NSCLC, non–small cell lung carcinoma; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer; HNSCC, head and neck squamous cell carcinoma; SCLC, small cell lung cancer.

phase Ia, in which 4 out of 7 patients with NSCLC had stable disease as best overall response. Three cohorts in NSCLC (512 patients), enrolling both patients in the first- and later-lines of therapy (cohorts F1, F2, and F3), were later added to further investigate dose response using randomized dose assignment.

Nivolumab

A phase I study (NCT00730639) evaluated nivolumab in 395 patients with selected advanced or recurrent malignancies using 10 dose-expansion cohorts. Initially, five dose-expansion cohorts were designed for five indications: melanoma, NSCLC, renal cell carcinoma, colorectal cancer, and prostate cancer. Additional cohorts were added through protocol amendments facilitating randomized dose assignment in NSCLC (randomly assigned to three dose levels) and melanoma (randomly assigned to three dose levels) as well as adding a low-dose cohort for renal cell carcinoma. A total of 340 patients were enrolled into phase Ib.

Atezolizumab

The phase I trial (NCT01375842)[68] evaluated atezolizumab as a monotherapy in 661 patients with locally advanced or metastatic solid tumors or hematologic malignancies. Dose expansion cohorts were designed to enroll specific histologies, including: melanoma, renal cell carcinoma, NSCLC, bladder cancer, triple-negative breast cancer, glioblastoma, head and neck squamous cell carcinoma, and uterine. A basket cohort also enrolled other tumor types including small cell lung cancer and ovarian cancer. A total of 495 patients were enrolled into phase Ib. All dose-expansion cohorts evaluated three dose levels.

DISCUSSION

Designs with inclusive eligibility may conserve patient and financial resources when compared with the expense of conducting a series of stand-alone trials for each indication. The statistical implications of expansive phase I trials require further consideration, however. Trialists and regulators must decide how to evaluate a trial's operating characteristics in the presence of heterogeneity among tumor types. The conventional paradigm for trial design emphasizes a few or single possible scenarios or outcomes; however, this reduces the potential scope of possibilities when explicitly considering dose-expansion cohorts that span multiple tumor types. Conventional approaches to statistical design may fail to provide a comprehensive evaluation of the trial's properties across various scenarios of heterogeneity.

Moreover, expanding sample sizes to hundreds of patients facilitates an extent of information that would traditionally require an appropriate level of type I error control and strategies for interim monitoring to halt enrollment to cohorts that underperform the trial's prespecified expectations. Several Bayesian solutions, developed for basket trials, offer opportunities to formalize the designs of large expansion cohorts and integrate the information across dose-expansion cohorts to facilitate evidence synthesis for planning the next phase of development.[69-74]

CONCLUSIONS

Classic 3+3 phase I trial designs have withstood the test of time. They offer rapid, but reasonable, dose escalation, with negligible rates of toxic death. Dose escalation based on toxicities (toxicity-adjusted dose escalation) seen rather than predetermined formulas may prove optimal. The data show that increased (rather than decreased) numbers of

patients in phase I allow more precise determination of important side effects.[13] Furthermore, expansion of cohorts in a phase I trial can even lead to regulatory approval after phase I in cases in which substantial activity is observed.[2,3] Other considerations may include allowing intrapatient dose escalation, measuring concentration of drugs, and adjusting dosing for age, patient comorbidities, and drug levels. Bayesian designs in early phase oncology trials may also expedite knowledge acquisition.[53] Trials evaluating immune checkpoint inhibitors also made extensive use of expanded phase I trials, enrolling hundreds of patients into dose-expansion cohorts following dose escalation, hence accelerating drug development.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Kurzrock R, Benjamin RS. Risks and benefits of phase 1 oncology trials, revisited. N Engl J Med. 2005;352:930-932.
2. Chabner BA. Approval after phase I: ceritinib runs the three-minute mile. Oncologist. 2014;19:577-578.
3. Chuk MK, Chang JT, Theoret MR, et al. FDA approval summary: accelerated approval of pembrolizumab for second-line treatment of metastatic melanoma. Clin Cancer Res. 2017;23:5666-5670.
4. Dixon WJ, Mood AM. The statistical sign test. J Am Stat Assoc. 1946;41:557-566.
5. Storer BE. Design and analysis of phase I clinical trials. Biometrics. 1989;45:925-937.
6. Hansen AR, Graham DM, Pond GR, et al. Phase 1 trial design: is 3 + 3 the best? Cancer Contr. 2014;21:200-208.
7. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. J Natl Cancer Inst. 2009;101:708-720.
8. Ivy SP, Siu LL, Garrett-Mayer E, et al. Approaches to phase 1 clinical trial design focused on safety, efficiency, and selected patient populations: a report from the clinical trial design task force of the national cancer institute investigational drug steering committee. Clin Cancer Res. 2010;16:1726-1736.
9. Reiner J, Paoletti X, O'Quigley J. Operating characteristics of the standard phase I clinical trial design. Comput Stat Data Anal. 1999;30:303-315.
10. Simon R, Freidlin B, Rubinstein L, et al. Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst. 1997;89:1138-1147.
11. Wheeler GM, Mander AP, Bedding A, et al. How to design a dose-finding study using the continual reassessment method. BMC Med Res Methodol. 2019;19:18.
12. Jain RK, Lee JJ, Hong D, et al. Phase I oncology studies: evidence that in the era of targeted therapies patients on lower doses do not fare worse. Clin Cancer Res. 2010;16:1289-1297.
13. Jardim DL, Hess KR, Lorusso P, et al. Predictive value of phase I trials for safety in later trials and final approved dose: analysis of 61 approved cancer drugs. Clin Cancer Res. 2014;20:281-288.
14. Wages NA, Chiuzan C, Panageas KS. Design considerations for early-phase clinical trials of immune-oncology agents. J Immunother Cancer. 2018;6:81.
15. Horstmann E, McCabe MS, Grochow L, et al. Risks and benefits of phase 1 oncology trials, 1991 through 2002. N Engl J Med. 2005;352:895-904.
16. Kurzrock R. Selpercatinib aimed at RET-altered cancers. N Engl J Med. 2020;383:868-869.
17. Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of selpercatinib in RET fusion-positive non-small cell lung cancer. N Engl J Med. 2020;383:813-824.
18. Rogatko A, Schoeneck D, Jonas W, et al. Translation of innovative designs into phase I trials. J Clin Oncol. 2007;25:4982-4986.
19. van Brummelen EM, Huitema AD, van Werkhoven E, et al. The performance of model-based versus rule-based phase I clinical trials in oncology: a quantitative comparison of the performance of model-based versus rule-based phase I trials with molecularly targeted anticancer drugs over the last 2 years. J Pharmacokinet Pharmacodyn. 2016;43:235-242.

20. Lin C-C. Novel Trial Designs for Early Phase Clinical Trials. In Yap TA, Rodon J, Hong D, (eds). Phase I Oncology Drug Development. New York: Springer International Publishing; 2020;85-93.
21. Berry DA. Bayesian clinical trials. Nat Rev Drug Discov. 2006;5:27-36.
22. Yuan Y, Lee JJ, Hilsenbeck SG. Model-assisted designs for early-phase clinical trials: simplicity meets superiority. JCO Precis Oncol. 2019;3:PO.19.00032.
23. Love SB, Brown S, Weir CJ, et al. Embracing model-based designs for dose-finding trials. Br J Cancer. 2017;117:332-339.
24. Zhou H, Yuan Y, Nie L. Accuracy, safety, and reliability of novel phase I trial designs. Clin Cancer Res. 2018;24:4357-4364.
25. Lin R, Zhou Y, Yan F, et al. BOIN12: Bayesian optimal interval phase I/II trial design for utility-based dose finding in immunotherapy and targeted therapies. JCO Precis Oncol. 2020;4:PO.20.00257.
26. James GD, Symeonides S, Marshall J, et al. Assessment of various continual reassessment method models for dose-escalation phase 1 oncology clinical trials: using real clinical data and simulation studies. BMC Cancer. 2021;21:7.
27. Yan F, Thall PF, Lu KH, et al. Phase I-II clinical trial design: a state-of-the-art paradigm for dose finding. Ann Oncol. 2018;29:694-699.
28. Iasonos A, Gönen M, Bosl GJ. Scientific review of phase I protocols with novel dose-escalation designs: how much information is needed? J Clin Oncol. 2015; 33:2221-2225.
29. Rinaldi DA, Burris HA, Dorr FA, et al. Initial phase I evaluation of the novel thymidylate synthase inhibitor, LY231514, using the modified continual reassessment method for dose escalation. J Clin Oncol. 1995;13:2842-2850.
30. Rowinsky EK, Johnson TR, Geyer CE Jr., et al. DX-8951f, a hexacyclic camptothecin analog, on a daily-times-five schedule: a phase I and pharmacokinetic study in patients with advanced solid malignancies. J Clin Oncol. 2000;18:3151-3163.
31. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med. 1998;17:1103-1120.
32. Cheng JD, Babb JS, Langer C, et al. Individualized patient dosing in phase I clinical trials: the role of escalation with overdose control in PNU-214936. J Clin Oncol. 2004;22:602-609.
33. Infante JR, Cassier PA, Gerecitano JF, et al. A phase I study of the cyclin-dependent kinase 4/6 inhibitor ribociclib (LEE011) in patients with advanced solid tumors and lymphomas. Clin Cancer Res. 2016;22:5696-5705.
34. Thall PF, Cook JD. Dose-finding based on efficacy-toxicity trade-offs. Biometrics. 2004;60:684-693.
35. Brock K, Billingham L, Copland M, et al. Implementing the EffTox dose-finding design in the Matchpoint trial. BMC Med Res Methodol. 2017;17:112.
36. Shah HA, Christian S, Ahmed B, et al. STM-01: phase I EffTox study of aurora A kinase inhibitor alisertib (MLN8237) given in combination with selective VEGFR inhibitor pazopanib for therapy of solid tumors. J Clin Oncol. 2016;34 (15_suppl; abst 2587) .
37. Ji Y, Li Y, Nebiyou Bekele B. Dose-finding in phase I clinical trials based on toxicity probability intervals. Clin Trials. 2007;4:235-244.
38. Ji Y, Liu P, Li Y, et al. A modified toxicity probability interval method for dose-finding trials. Clin Trials. 2010;7:653-663.
39. Malone ER, Lewin JH, Al-Ezzi EM, et al. Phase 1b study of selinexor, a first-in-class selective inhibitor of nuclear export (SINE) compound, in combination with doxorubicin in patients (pts) with locally advanced or metastatic soft tissue sarcoma (STS). J Clin Oncol. 2019;37(15_suppl):3123.
40. Guo W, Wang SJ, Yang S, et al. A Bayesian interval dose-finding design addressingOckham's razor: mTPI-2. Contemp Clin Trials. 2017;58:23-33.
41. Yan F, Mandrekar SJ, Yuan Y. Keyboard: a novel Bayesian toxicity probability interval design for phase I clinical trials. Clin Cancer Res. 2017;23:3994-4003.
42. Zhou H, Murray TA, Pan H, et al. Comparative review of novel model-assisted designs for phase I clinical trials. Stat Med. 2018;37:2208-2222.
43. Yuan Y, Hess KR, Hilsenbeck SG, et al. Bayesian optimal interval design: a simple and well-performing design for phase I oncology trials. Clin Cancer Res. 2016; 22:4291-4301.
44. Wu J, Yuan Y, Cordova C, et al. Phase I trial of TG02 plus dose-dense or metronomic temozolomide for recurrent anaplastic astrocytoma and glioblastoma in adults. J Clin Oncol. 2019;37 (15_suppl; abstr 2031).
45. Liu M, Wang SJ, Ji Y. The i3+3 design for phase I clinical trials. J Biopharm Stat. 2020;30:294-304.
46. Tidwell RSS, Peng SA, Chen M, et al. Bayesian clinical trials at The University of Texas MD Anderson Cancer Center: an update. Clin Trials. 2019;16:645-656.
47. Lyauk YK, Jonker DM, Lund TM. Dose finding in the clinical development of 60 US Food and Drug Administration-approved drugs compared with learning vs. confirming recommendations. Clin Transl Sci. 2019;12:481-489.
48. Paoletti X, Ezzalfani M, Le Tourneau C. Statistical controversies in clinical research: requiem for the 3 + 3 design for phase I trials. Ann Oncol. 2015; 26:1808-1812.
49. Yuan Y, Lin R, Li D, et al. Time-to-event Bayesian optimal interval design to accelerate phase I trials. Clin Cancer Res. 2018;24:4921-4930.
50. Wages NA, Petroni GR. A web tool for designing and conducting phase I trials using the continual reassessment method. BMC Cancer. 2018;18:133.
51. Pallmann P, Wan F, Mander AP, et al. Designing and evaluating dose-escalation studies made easy: the MoDEsT web app. Clin Trials. 2020;17:147-156.
52. Rogatko A, Cook-Wiens G, Tighiouart M, et al. Escalation with overdose control is more efficient and safer than accelerated titration for dose finding. Entropy (Basel). 2015;17:5288-5303.
53. U.S. Department of Health and Human Services, U.S. Food and Drug Administration. Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. https://www.fda.gov/files/drugs/published/Providing-Clinical-Evidence-of-Effectiveness-for-Human-Drug-and-Biological-Products..pdf. Accessed February 12, 2021.

54. U.S. Department of Health and Human Services, U.S. Food and Drug Administration. Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. https://www.fda.gov/media/133660. Accessed February 12, 2021.
55. U.S. Department of Health and Human Services, U.S. Food and Drug Administration. Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Draft Guidance for Industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products. Accessed February 12, 2021.
56. U.S. Department of Health and Human Services, U.S. Food and Drug Administration. CFR: Code of Federal Regulations Title 21.https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314h. Accessed February 12, 2021.
57. U.S. Department of Health and Human Services, U.S. Food and Drug Administration. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review. Accessed February 12, 2021.
58. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. N Engl J Med. 2017;377:62-70.
59. Prowell TM, Theoret MR, Pazdur R. Seamless oncology-drug development. N Engl J Med. 2016;374:2001-2003.
60. Hobbs BP, Barata PC, Kanjanapan Y, et al. Seamless designs: current practice and considerations for early-phase drug development in oncology. J Natl Cancer Inst. 2019;111:118-128.
61. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509-2520.
62. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357:409-413.
63. Poh A. First tissue-agnostic drug approval issued. Cancer Discov. 2017;7:656.
64. Pestana RC, Sen S, Hobbs BP, et al. Histology-agnostic drug development - considering issues beyond the tissue. Nat Rev Clin Oncol. 2020;17:555-568.
65. Manji A, Brana I, Amir E, et al. Evolution of clinical trial design in early drug development: systematic review of expansion cohort use in single-agent phase I cancer trials. J Clin Oncol. 2013;31:4260-4267.
66. Bugano DDG, Hess K, Jardim DLF, et al. Use of expansion cohorts in phase I trials and probability of success in phase II for 381 anticancer drugs. Clin Cancer Res. 2017;23:4020-4026.
67. Garon EB, Rizvi NA, Hui R, et al; KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372:2018-28.
68. Petrylak DP, Powles T, Bellmunt J, et al. Atezolizumab (MPDL3280A) monotherapy for patients with metastatic urothelial cancer: long-term outcomes from a phase 1 study. JAMA Oncol. 2018;4:537-544.
69. Kaizer AM, Koopmeiners JS, Kane MJ, et al. Basket designs: statistical considerations for oncology trials. Precision Oncol. 2019;3:1-9.
70. Hobbs BP, Landin R. Bayesian basket trial design with exchangeability monitoring. Stat Med. 2018;37:3557-3572.
71. Kaizer AM, Koopmeiners JS, Hobbs BP. Bayesian hierarchical modeling based on multisource exchangeability. Biostatistics. 2018;19:169-184.
72. Kaizer AM, Hobbs BP, Koopmeiners JS. A multi-source adaptive platform design for testing sequential combinatorial therapeutic strategies. Biometrics. 2018;74:1082-1094.
73. Kaizer AM, Koopmeiners JS, Chen N, et al. Statistical design considerations for trials that study multiple indications. Stat Methods Med Res. 2021;30:785-798.
74. Kane MJ, Chen N, Kaizer AM, et al. Analyzing basket trials under multisource exchangeability assumptions. R J. 2020;12:359-371.

The Right Dose: From Phase I to Clinical Practice

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Overview

To realize the full potential of promising new anticancer drugs, it is of paramount importance to administer them at the right dose. The aim of this educational article is to provide several opportunities to optimize anticancer drug dosing, focusing on oral targeted therapies. First, therapeutic drug monitoring can optimize exposure in individual patients, if the optimal concentration is known. This approach is of particular interest in regard to oral kinase inhibitors with high interindividual pharmacokinetic variability. If exposure is related to response, then therapeutic drug monitoring is potentially feasible, although the clinical utility of this approach has not yet been established. Other approaches to reduce variability include administration of more frequent, smaller doses and administration under optimal prandial conditions. However, for many drugs, the labeled dose has not been demonstrated to be the optimal dose; for such agents, the vast majority of patients may be receiving excessive doses, which results in excessive toxicity. Furthermore, administration of lower off-label doses may reduce both medical and financial toxicity. These strategies should be applied from registration studies to clinical practice, with the goal of better optimizing anticancer treatment.

During the past decades, the focus of oncology drug development has largely switched from classic nonselective cytotoxic agents to drugs developed to inhibit specific targets, such as tyrosine kinases. To realize the full potential of these new anticancer drugs, it is of paramount importance to administer them at the right dose. Although finding the right dose encompasses a broader theme (i.e., phase I clinical trial design), the scope of this article focuses on alternative mechanisms to potentiate biologic effect, minimize toxicity, and reduce costs through dose modification. Herein, we describe how therapeutic drug monitoring can potentially optimize exposure for individual patients, how off-label use of lower doses or alternative dosing schedules can reduce toxicities and treatment costs, and how receptor occupancy can guide dosing of irreversible inhibitors. Then, several example drugs are discussed to illustrate how these different strategies and tactics can be applied in clinical practice.

THE RIGHT DOSE IN CLINICAL PRACTICE

Overview

A major breakthrough in the treatment of cancer was the development of imatinib, widely praised as the magic anticancer bullet.[1] This success has been followed by the development and approval of an increasing number of targeted drugs, in some cases for small subsets of patients. With the advent of these small molecule kinase inhibitors, the focus has increasingly shifted toward precision medicine, by selecting the right drug for individual patients according to molecular characteristics of their tumors. However, much less attention has been paid to optimizing the dosing of these drugs, both for the population as a whole and for individual patients with very high or low apparent oral clearance.[2]

First, there may not be good evidence that the approved dose is optimal, because the recommended dose is often determined from a small sample size in phase I studies, primarily on the basis of toxicity rather than efficacy.[3] These studies are not designed to define the optimal dose, only the maximum tolerated dose. Second, compared with intravenously administered drugs, orally administered drugs will generally exhibit higher interindividual and intraindividual pharmacokinetic variability because of differences in drug absorption and first pass effects (i.e., due to CYP3A4 and P-gp).[4,5] Third, and most important, for some drugs, there is an apparent concentration-response relationship.[5,6]

To select drugs that are candidates for therapeutic drug monitoring, specific criteria should be met[2]:

1. absence of an easily measurable biomarker for drug effect;
2. long-term therapy;
3. availability of a validated and sensitive bioanalytic method;
4. substantial interindividual pharmacokinetic variability, with relatively modest intraindividual pharmacokinetic variability;
5. narrow therapeutic range;
6. defined and consistent exposure-response and exposure-toxicity relationships; and
7. feasible dose-adaptation strategies.

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PRACTICAL APPLICATIONS

- Many oral drugs show a high variability in pharmacokinetic exposure, and, for drugs with exposure related to efficacy, therapeutic drug monitoring can help optimize exposure in individual patients.
- Other approaches to reduce variability include administration of more frequent, smaller doses and administration under optimal prandial conditions.
- For many drugs, the labeled dose is not the optimal dose, and, for these drugs, the vast majority of patients may be receiving excessive doses; administration of lower off-label doses may reduce both medical and financial toxicity.

Understanding and Minimizing Variability

The interindividual variability in apparent oral clearance of many oral targeted therapies is high; coefficients of variation typically range between 40% and 70%.[5,7-9] As illustrated in Fig. 1, many factors contribute to this high variability.

Many oral targeted therapies—especially kinase inhibitors—have low solubility, resulting in substantial challenges in formulation. By optimizing the formulation, bioavailability can be improved, resulting in decreased interindividual and intraindividual pharmacokinetic variability.[10,11]

Other causes of variability are drug-food and drug-drug interactions.[12,13] Pharmacokinetic exposure of many targeted therapies is dramatically affected by gastric-acid suppressive agents and CYP3A4 inhibitors or inducers.[14] Gastric-acid suppressive agents increase the stomach pH, and, because most kinase inhibitors are weakly basic, this increase results in a shift to the nonionized form, decreasing solubility and absorption. The extent to which CYP3A4 inhibitors or inducers affect exposure depends on the proportion of drug that is metabolized by this enzyme. It is important to quantify the effect sizes of these drug-drug interactions to determine appropriate dose adjustments in routine clinical management, which is required by the U.S. Food and Drug Administration (FDA) and other global regulatory agencies. In addition, food effects may not be understood during early development and may result in a pivotal trial being conducted under the wrong prandial conditions. Thus, food can sometimes be used as a simple and inexpensive approach to increase bioavailability.

Moreover, both genetic differences and disease can affect absorption, distribution, metabolism, and excretion. Another key determinant of variability in pharmacokinetic exposure is treatment adherence.[15] Many oral targeted therapies are extensively metabolized by CYP enzymes, so polymorphisms in these enzymes could theoretically result

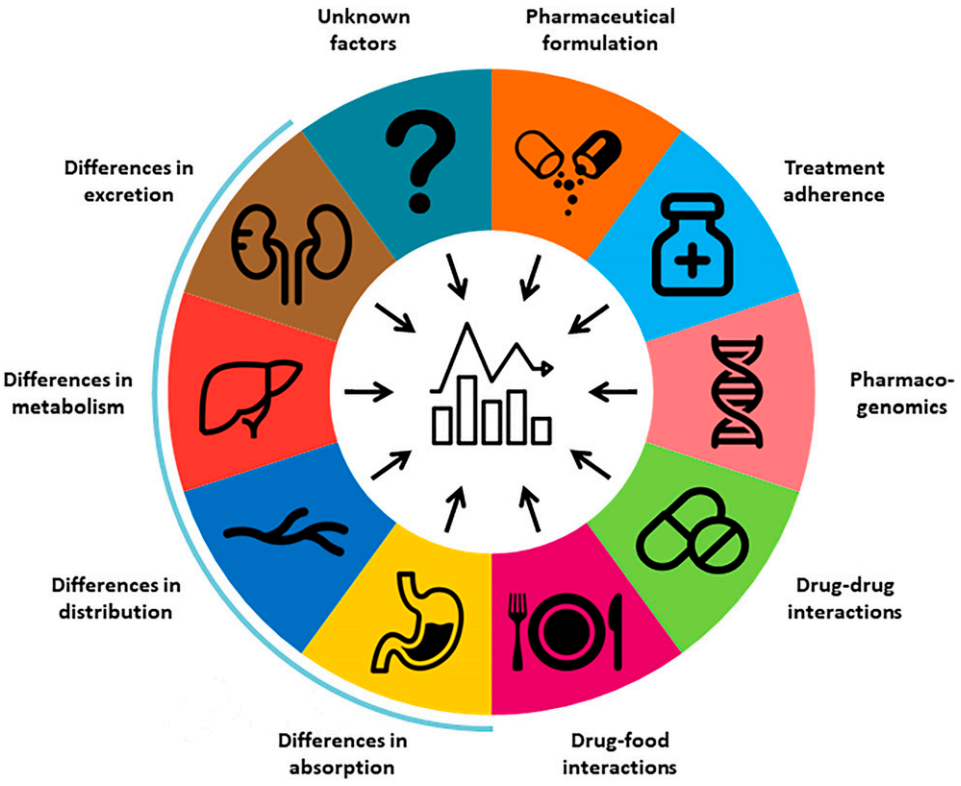

FIGURE 1. Hallmarks of Variability in Pharmacokinetic Exposure of Oral Targeted Therapies in Oncology

in altered clearance, although this possibility must be studied in more detail.[16,17]

It is essential to enhance our knowledge about how each of these factors contributes to the variability in pharmacokinetic exposure within and between patients. Many of these aspects are already addressed in the requisite clinical pharmacology package, which must be submitted to regulatory authorities to support new drug approval. In this way, variability in exposure can be reduced, and the fraction of patients who are treated at toxic and/or nontherapeutic concentrations can thereby be reduced.

Therapeutic Drug Monitoring

Although therapeutic drug monitoring is widely used in other therapeutic areas (e.g., anti-infectives, antiepileptics, psychotropic drugs, immunosuppressants, and digoxin), it has infrequently been applied in oncology.

Several recent reviews have summarized the available literature on exposure-response relationships and proposed target concentrations that can be used for therapeutic drug monitoring in oncology.[5,6,18-22] In addition, prospective clinical studies have been performed for several oral targeted therapies and have demonstrated that this practice is feasible and results in more patients achieving a target exposure.[23-29]

To implement therapeutic drug monitoring in clinical practice, a solid infrastructure should be in place (i.e., sample collection, shipment and measurement, short turnaround time). Target concentrations and dose adaptation strategies can be based upon previously performed feasibility studies as well as the requisite exposure-response and exposure-toxicity models. Prior to implementation, attention should be paid to treatment adherence and drug-drug interactions. It is important to address treatment adherence first, because dose increments could lead to toxicity if low concentrations are due to nonadherence rather than high clearance. Alternative dosing strategies alone, such as divided doses for pazopanib or administration (of lower doses) concomitantly with food, may reduce interindividual variability and optimize exposure.[25,30-33] Figure 2 visualizes how

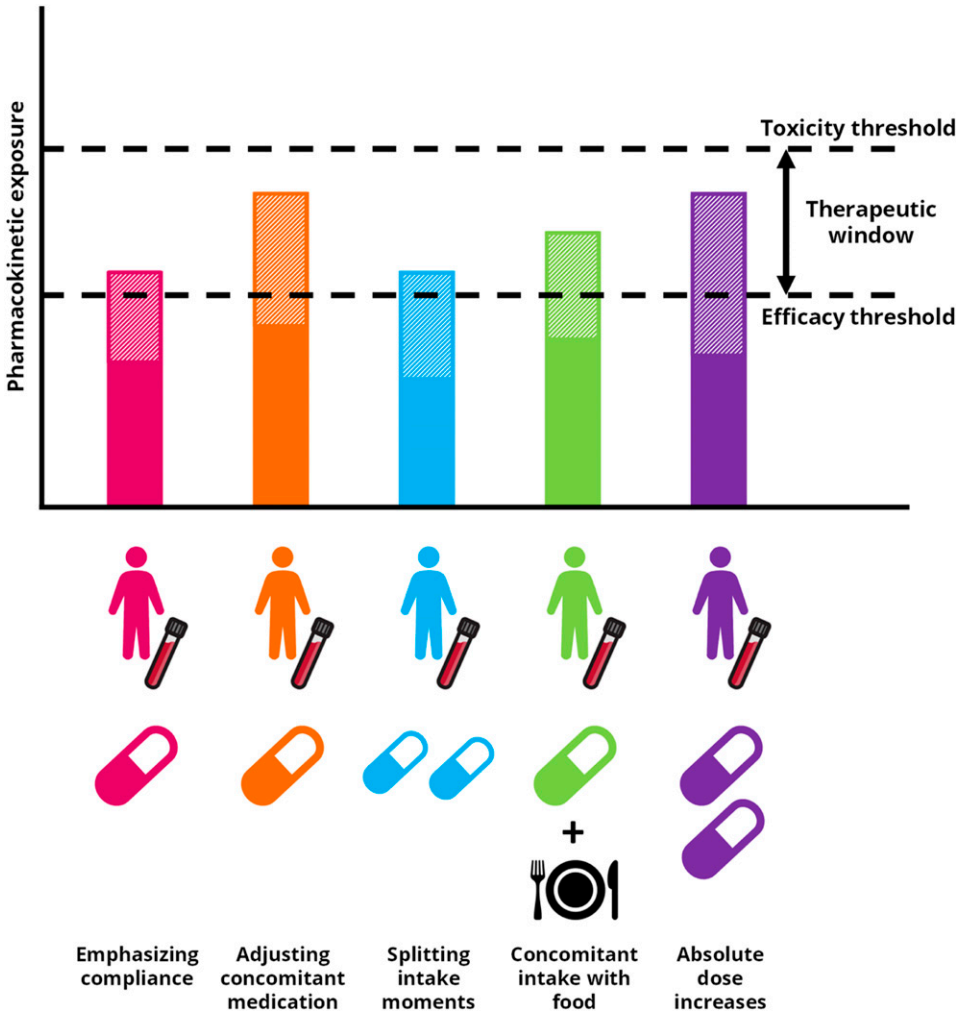

FIGURE 2. Precision Dosing to Titrate Individual Patients Toward the Therapeutic Window
The heights of the bars were chosen at random and do not represent a certain pharmacokinetic exposure or effect size of the pharmacokinetically guided intervention.

different interventions can reduce the proportion of patients treated outside the target range.

In the Netherlands, the Dutch Pharmacology Oncology Group–Therapeutic Drug Monitoring (DPOG-TDM) study provides a framework to perform feasibility studies and subsequently enables extended nationwide implementation using the existing infrastructure of the DPOG-TDM study.[34,35] This systematic approach can also be used internationally for this purpose, within the same protocol or by setting up similar frameworks in other countries.

Opportunities for Improvement in Oncology Drug Development

The discipline of clinical pharmacology should have a more prominent role in (early) drug development. As proposed by Sheiner,[36] cycles of learning and confirming should be alternated throughout a drug's life cycle. In fact, incentives by regulatory authorities have now resulted in a drug's pharmacokinetics and pharmacodynamics being more extensively studied. Yet, more action can be taken upon this knowledge to optimize treatment.

More attention should be paid to optimize pharmaceutical formulations, which will help increase bioavailability and reduce variability. In addition, intraindividual variability must be characterized in more detail, as this increases our understanding of the pharmacokinetic behavior of a new drug as well as the feasibility of therapeutic drug monitoring.[37] Furthermore, efforts should be made to optimize the approved dose and to identify a potential therapeutic range. As one example, imatinib was approved for the treatment of chronic myeloid leukemia in 2001, but the first publication on its exposure-response relationship appeared only in 2007.[38] Similarly, pazopanib was marketed in 2010, but it took until 2014 before its efficacy threshold was proposed.[39] Regulatory authorities now conduct exposure-response analyses for the vast majority of new drugs, which the FDA makes publicly available.[40]

Some of the issues discussed in this section could be circumvented by new phase I clinical trial designs that focus on finding the optimal biologic dose and/or minimum effective dose. However, most of these new clinical trials designs are still aimed at identifying a single optimum dose for all patients, whereas individualized dosing is more rational for certain oral targeted therapies.

FINANCIALLY GUIDED DOSING

Overview

The inexorable rise in global oncology drug sales has created incentives for payers, physicians, and patients to develop strategies to reduce prescribing costs.[41] There is a long history of pill splitting to reduce costs, which has been widely implemented despite uncertainties about its clinical effectiveness.[42] Repurposing is another strategy to reduce costs, as exemplified by the widespread off-label use by ophthalmologists of very small intravitreal doses of bevacizumab as a cost-effective alternative to ranibizumab (and related drugs) for the treatment of age-related macular degeneration.[43-46]

However, in oncology, there is another important opportunity to reduce costs; simply using less drug than is labeled, ideally supported by randomized trials conducted after regulatory approval. This opportunity is prevalent, given that most oncology drugs continue to be developed on the false premise that more is better. Although this premise was reasonable in the era of cytotoxic chemotherapy, it is not valid for all drugs that have a specific target. In fact, more can be worse if higher doses lead to adverse events that lead to interruption of treatment.

This general concept of developing off-label, lower-cost treatment regimens has been called "interventional pharmacoeconomics,"[47,48] and it is exemplified by a small randomized study of low-dose abiraterone (250 mg), administered with food, compared with the labeled dose of 1,000 mg administered under modified fasting conditions.[33] A 2018 analysis of oral patent-protected oncology drugs revealed that financially guided dosing could reduce costs by more than 33% for 62% of the drugs analyzed, with at least 50% cost reductions potentially feasible for almost half the drugs. Although a similar analysis has not been performed (to our knowledge) for patent-protected parenteral drugs, there are some important opportunities, best exemplified by the immune checkpoint inhibitors.[49-54] Furthermore, because many patients treated with immune checkpoint inhibitors have prolonged progression-free survival (PFS) despite treatment discontinuation (e.g., due to adverse events),[55-60] the optimal duration of treatment is unknown.[61-63]

Strategy to Identify Candidate Drugs for Financially Guided Dosing

Although a requirement for dose-response information to support drug registration is clearly articulated in FDA and European Medicines Agency guidance,[64,65] this requirement has not been enforced for oncology drugs in the absence of a substantial toxicity concern. Notably, oncology regulators, oncologists, and patients with cancer all expect oncology drugs to cause at least mild to moderate toxicity, so many toxicity signals are considered acceptable in the context of cancer care—even if the toxicities are potentially avoidable.

In the absence of a randomized, dose-ranging, phase II trial (which is the norm outside of oncology), candidate drugs for interventional pharmacoeconomic studies can be identified on the basis of phase I data and exposure-response data generated in the context of phase II to III trials. For example, it may be quite clear from a phase I trial that responses were observed at doses well below the labeled dose (e.g.,

ibrutinib[66]). It may also be clear from review of the prescribing information and food-effect studies that a drug is labeled under prandial conditions that minimize drug absorption, leading to the obvious suggestion to simply give a lower dose with food.[32,48,67,68] This strategy also eliminates the risk of a food-induced overdose, which could, theoretically, even be fatal.[69,70] However, this strategy must consider that many pharmaceutical companies have attempted to obviate this strategy by pricing all strengths of a drug at the same monthly cost.

The issues in regard to parenteral monoclonal antibodies are a bit more challenging. Improved understanding of immunology-related host-disease interactions, microbiota, and the development of biomarkers and predictive factors will be paramount to understand the optimal dose for immuno-oncology therapy. An observed exposure-response relationship in a population of patients who all received the same dose does not imply that more is better and, in fact, does not even imply that a drug has anticancer activity, given the confounding effects of high clearance and poor performance status.[71] If a drug is labeled at the optimal dose, one would expect to see a clear dose-response relationship and an exposure-response relationship. If these relationships are lacking, then potential strategies include either reduction of the dose or extension of the dosing interval, with the latter being preferable because of its greater patient convenience, reduction of drug preparation and infusion costs, and marketing of many drugs in single-dose vials.

DOSING BY RECEPTOR OCCUPANCY

With the discovery that many cancers are driven by oncogenes and the resulting oncoprotein products, it is of paramount importance to create agents that inhibit these oncotargets. Among these oncoproteins, kinases that are involved in the pathogenesis of cancers have been successfully targeted both in preclinical investigations and in clinical trials. The majority of these agents reversibly bind the kinase, inhibiting its activity via an on-and-off rate with the target. Because these inhibitors must maintain a sustained inhibition of the enzyme, an irreversible antagonist is preferred. Numerous examples of irreversible inhibitors exist, and one of the most studied examples is ibrutinib.

Ibrutinib and Chronic Lymphocytic Leukemia

Ibrutinib (PCI-32765) is the first-in-class irreversible inhibitor of Bruton tyrosine kinase (BTK) that has revolutionized the treatment of chronic lymphocytic leukemia (CLL). Chronic lymphocytic leukemia, the most common leukemia in the Western world, is an incurable cancer of B cells characterized by the accumulation of mature-appearing lymphocytes in the blood, bone marrow, and lymphoid tissues.[72] Survival, proliferation, maintenance, and migration of CLL cells are dependent on the signaling of the B-cell receptor pathway.[73] The importance of the B-cell receptor in CLL pathophysiology[74,75] and the role of BTK as a pivotal enzyme in the pathway resulted in a concerted effort to target BTK.[76]

Ibrutinib binds covalently and, hence, irreversibly to the BTK protein at the cysteine 481 residue in the kinase domain, inactivating BTK; thus, synthesis of new protein is required to reinitiate B-cell receptor signal transduction. However, ibrutinib is not highly selective and inhibits several other kinases.[77] Clinical trials established the utility of BTK inhibition, and this drug achieved all four positive attributes from the FDA: fast-track designation, breakthrough therapy status, priority review, and accelerated approval.[78] Multiple clinical trials demonstrated overall survival and PFS benefits with ibrutinib in several B-cell malignancies, such as mantle cell and marginal zone lymphomas, Waldenström macroglobulinemia, chronic graft-versus-host disease, and CLL. Within CLL, ibrutinib was approved for patients with relapsed or refractory disease,[79,80] elderly individuals,[81] patients with 17p deletion,[82] and treatment-naïve patients.[83]

Ibrutinib and Clinical Dose Selection

Because ibrutinib binds irreversibly and covalently to inhibit the BTK protein, BTK occupancy is an indicative measure for receptor BTK occupancy inhibition. Hence, during a phase I dose-escalation study, target (BTK) occupancy assay in peripheral blood cells was performed for every patient to select the dose. Bruton tyrosine kinase occupancy, which correlates with efficacy, was greater than 95% and was considered complete in patients who were dosed at 2.5 mg/kg per day (approximately 175 mg/day). Despite these data, the recommended phase II dose in CLL was determined to be 420 mg/day[66]; however, the FDA recommended evaluation of lower doses in future trials.[84]

Scientific Rationale for Lower Dose of Ibrutinib After One Cycle of Full Dose

Results from the phase I investigation indicated that, at the selected dose (420 mg/day), greater than 95% of BTK is occupied and inactivated by ibrutinib. In this circumstance, for B-cell receptor signaling to be restored, new BTK protein must be synthesized.

In a murine model system, B-cell receptor cross-linking resulted in increased BTK expression in splenic normal B lymphocytes,[85] and, in a murine model of CLL, treatment with ibrutinib lowered BTK protein levels.[86] Results were similar in primary CLL cells obtained during standard-dose ibrutinib therapy,[87] and an approximately 50% decline in both transcript and protein levels was observed after one cycle (4 weeks) of ibrutinib.

Mechanistically, a reason for a decline in the BTK transcript level by ibrutinib may be inhibition of the transcription factor NFκB (nuclear factor-kappa B; Fig. 3). This transcription

factor is responsible for promoting transcription of NFκB and BTK,[88] and inhibition of NFκB has been demonstrated in CLL cells during ibrutinib therapy.[89,90]

In summary, BTK protein levels decline in CLL cells after one or more cycles of ibrutinib, suggesting that the full dose of ibrutinib may not be needed in subsequent cycles. Furthermore, this decrease in dose may also mitigate ibrutinib adverse events related to off-target effects of excess free drug.

Clinical Rationale for a Lower Dose of Ibrutinib After One Full-Dose Cycle

Although ibrutinib is considered well tolerated, toxicities are common and include arthralgia, skin rash, diarrhea, bleeding, and atrial fibrillation. Some of the cardiac effects of ibrutinib, as well as its inhibitory effects on platelet function, may stem from inhibition of kinases other than BTK.[91,92] In a murine model, C-terminal Src kinase inhibition by ibrutinib[77] was identified as the likely cause of ibrutinib-mediated atrial fibrillation.[93,94] Notably, the half-maximal inhibitory concentration for C-terminal Src kinase is 4.6-fold higher than that concentration for BTK, suggesting a 4.6-fold therapeutic window.[77] The frequency of incident atrial fibrillation reported in the randomized, controlled registration trials of ibrutinib (up to 12% in longer-term follow-up)[95,96] markedly underestimates the occurrence of atrial fibrillation observed in patients treated in real-world settings, in which up to 25% of patients develop new-onset atrial fibrillation.[97,98] In addition, long-term follow-up suggests that 21% patients experience hypertension.[96] Severe and fatal cardiac toxicities (including in the first month of treatment) were also reported recently in real-world studies,[99] underscoring a need for a randomized clinical trial of lower doses.[100] Additionally, serious infections have been reported in patients taking ibrutinib.[101-105] C-terminal Src kinase inhibition may also be responsible for the hemorrhagic complications of ibrutinib.[106] Management of some of the most common toxicities includes treatment interruption, dose reduction, and/or treatment discontinuation.[107,108] However, treatment interruption has been demonstrated to lead to decreased PFS.[109]

In addition to the issues of safety and tolerability, the cost of ibrutinib in the United States exceeds $130,000/year for patients with CLL—more than double the average annual U.S. household income.[110,111] In addition, because complete remissions with ibrutinib are rare, indefinite use of the drug or combination with other agents is recommended, which compounds the financial toxicity and causes a profound individual impact.[112] Thus, lowering the dose of ibrutinib has substantial potential to reduce toxicities.

Pilot Clinical Trial to Test Scientific Rationale for Lower Dose of Ibrutinib After One Full-Dose Cycle

On the basis of the investigations described above, it was hypothesized that BTK transcript and protein levels would be reduced after one cycle of ibrutinib at 420 mg/day.

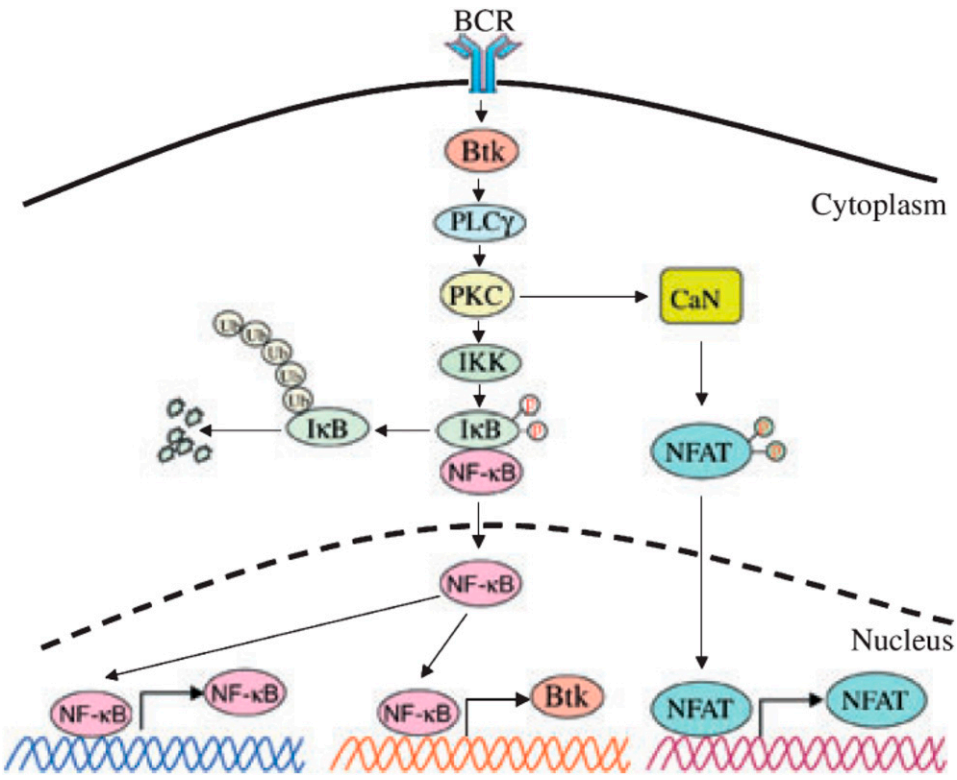

FIGURE 3. Schematic Model Showing Reciprocal Regulation of Bruton Tyrosine Kinase and NF-κB Signaling
B-cell receptor (BCR)–dependent activation of Bruton tyrosine kinase (Btk) induces signaling pathways that converge on the transcription factors NF-κB and nuclear factor of activated T cells (NFAT). In both cases, it is mediated by protein kinase C (PKC). NF-κB subsequently induces transcription of the *Btk* gene (depicted) and other NF-κB–dependent genes, including IκB (not shown). Reproduced with permission from Mohamed et al.[88]

Consequently, lower doses of ibrutinib would be sufficient over time to achieve and maintain full BTK occupancy. Because of the 1:1 binding of ibrutinib to the BTK protein target, lower subsequent dosing of ibrutinib could also result in decreased levels of free drug in plasma and reduced binding to off-target kinases, potentially resulting in decreased incidence of adverse events. To test this hypothesis, Chen et al[89] completed a study of a pre-emptive dose-reduction strategy of ibrutinib during three 28-day cycles. After an initial cycle of standard-dose ibrutinib (420 mg/day; three capsules/day), the dose was reduced to 280 mg/day (two capsules/day) in cycle 2 and then to 140 mg/day (one capsule/day) in cycle 3. Eleven patients began the study treatment, and nine completed the three cycles of ibrutinib therapy; several pharmacokinetic and pharmacodynamic endpoints were compared. Plasma and intracellular levels of ibrutinib were dose dependent, and even the lowest (140 mg) dose was sufficient to occupy, on average, greater than 95% of the BTK protein according to a method to measure covalent binding of ibrutinib to BTK protein. This result was consistent with a decline in the phospho-BTK protein, as determined via immunoblot analysis. Achievement of greater than 95% BTK occupancy at all three doses in all patients clearly established the scientific rationale. Plasma chemokine CCL3 and CCL4 levels, considered biomarkers of ibrutinib response, similarly declined during the three cycles. These pharmacokinetic and pharmacodynamic data demonstrate that, after one cycle of the standard dose of ibrutinib, the dose can be reduced without loss of biologic activity. Although clinical response was not formally assessed in this pilot study, seven of the nine evaluable patients were treated with 140 mg/day of ibrutinib, or lower daily doses, by their physicians after the study ended. Collectively, these data provide scientific rationale that supports a prospective randomized study to discern the clinical utility of this approach.

Real-World Studies

The most compelling clinical evidence for ibrutinib dose reduction comes from myriad real-world experiences. Because of ibrutinib's success, approval, and availability, the drug has been tested in many centers in the United States,[80,113-118] Canada,[119] the United Kingdom,[120] France,[121] Sweden,[122] Denmark,[123] and Poland.[124] Data from these investigations are detailed in Table 1. These results clearly demonstrate four key points. First, approximately 20%–50% of patients discontinued or reduced doses; thus, although the drug has been successful, it is only successful in 50% to 80% of patients with CLL. The dose-reduction/discontinuation percentage is higher in elderly patients and patients with relapsed/refractory disease (Table 1), and this number increases even more with continued long-term dosing. Second, compared with patients on the standard dose (420 mg/day), patients who received lower doses (either 280 mg/day or 140 mg/day) had similar overall survival and PFS, again demonstrating that a lower dose does not decrease effectiveness. Third, in clinical studies, adverse events rather than disease progression represented the primary reason for interruption, dose reduction, and even discontinuation of ibrutinib.[114,125] Fourth, treatment interruptions of ibrutinib for more than 14 days in a U.K. multicenter study[120] culminated in inferior outcomes, suggesting that dose reduction should be preferred instead of dose interruptions, consistent with the finding from a pivotal trial.[109]

Prospective Randomized Trial

Although the data are clear from the real-world studies, a prospective randomized trial is required to evaluate the efficacy of a lower dose of ibrutinib.[100] This study should incorporate laboratory and clinical endpoints to demonstrate superiority, near equivalence, or noninferiority of a reduced dose.[129] This message was also given by the FDA when ibrutinib was assessed for approval in the United States.[84] Although it is likely that 140 mg/day is equally efficacious to higher doses, the optimal strategy—starting at 140 mg/day or starting at 420 mg/day followed by reduction to 140 mg/day—has not yet been determined.

Future Directions

Although this section is focused on ibrutinib, such approaches to dose reduction and identification of optimal doses are implicated for any irreversible covalent inhibitors. Other examples of irreversible covalent inhibitors are acalabrutinib, abiraterone (to CYP17A1), and the KRAS G12C inhibitors sotorasib and adagrasib. Notably, it has been suggested that the sotorasib dose used in its pivotal trial is excessive.[130]

CLINICAL EXAMPLES

The strategies that have been discussed in the sections above have been addressed comprehensively in several recent reviews.[5,6,48,53,131] In the previous section, ibrutinib was elaborately discussed as an example drug for receptor occupancy–guided dosing, but a few additional examples are worth highlighting in this article to illustrate how the discussed dosing strategies can be applied in clinical practice. It has to be noted, though, that most of the cited studies are early-phase trials and observational studies with relatively small sample sizes that do show equivalent pharmacokinetics but do not demonstrate survival noninferiority. However, if pharmacokinetics have been related to efficacy, it may be logically assumed that equivalent pharmacokinetics will result in equivalent efficacy.

Pazopanib

The initial FDA clinical pharmacology review of pazopanib in 2009 concluded that there was no exposure-response relationship, although the number of patients evaluated was fairly small (48 patients).[132] A few years later, Suttle et al[39] reported that patients with renal cell carcinoma who had

TABLE 1. Clinical Trials and Real-World Experiences With Ibrutinib Discontinuation and Dose Reductions

Country (Year) and Reference	CLL Subgroup	Total No. of Patients	Median Follow-Up	Discontinued IBR	IBR Dose-Reduced
United States (2014)[80]	R/R	195	9.4 months	4%	4%
United States (2015)[113]	TN (31 patients)	132	3 years	30% (39 patients)	10% (13 patients)
	R/R (101 patients)				
United States (2017)[114]	TN	308 (237 with IBR monotherapy)	3.4 years	51%	NR
	R/R				
United States (2018)[126]	TN (37 patients)	197	NR	19% (37 patients)	NR
	R/R (160 patients)				
United States (2018)[115]	TN (80 patients)	616	17 months	41%	TN: 15%
	R/R (536 patients)				R/R: 20%
United States (2018)[116]	TN (31 patients)	132	5 years	TN (45%)	13%
	R/R (101 patients)			R/R (72%)	
United States (2019)[117]	TN (7 patients)	70	21.9 months	40% (28 patients)	31% (23 patients)
	R/R (63 patients)				
United States (2019)[118]	TN (52 patients)	84	5.1 years	NR	14% (12 patients)
	R/R (32 patients)				
United States (2020)[127]	TN (162 patients)	209 full dose (122 patients, 58%)	24 months	29% (61/209 patients)	39% (48/122 patients)
	R/R (47 patients)				
Canada (2019)[119]	R/R	64	24 months	17% (11 patients)	52% (33 patients)
Denmark (2020)[123]	TN (166 patients)	205	21.4 months	42% (86 patients)	NR
	R/R (39 patients)			TN (13 patients, 33%)	
				R/R (73 patients, 44%)	
United Kingdom (2016)[120]	R/R	315	16 months	26% (83 patients)	26% (82 patients)
United Kingdom (2019)[128]	R/R	38	NR	24% (9 patients)	NR
France (2017)[121]	R/R	71	NA	32% (23 patients)	40%
Sweden (2019)[122]	Poor prognosis	95	30 months	49% (47 patients)	24% (23 patients), (13) 280 mg, (10) 140 mg
Poland (2017)[124]	R/R	165	9.5 months	19% (32 patients)	21% (35 patients)

Abbreviations: CLL, chronic lymphocytic leukemia; IBR, ibrutinib; R/R, relapsed/refractory; TN, treatment naïve; NR, not reported; NA, not available.

a minimum plasma concentration of at least 20.5 mg/L had a significantly longer PFS compared with patients who had exposure below this threshold (52.0 weeks vs. 19.6 weeks; p = .004; 177 patients).[39] The median PFS in patients with an exposure below this efficacy threshold was comparable to exposure in the placebo arm of the pivotal trial (i.e., 4.2 months).[133] This efficacy threshold was later replicated in the adjuvant setting (most patients in this study were treated at an off-label dose of 600 mg)[134] and in a real-life patient cohort,[9] with a similar trend observed for soft-tissue sarcoma.[9]

In a prospective study in 30 patients, therapeutic drug monitoring of pazopanib was demonstrated to be feasible; patients with minimum plasma concentrations less than 20 mg/L received dose increases up to 1,800 mg.[24] Notably, the low bioavailability of pazopanib (i.e., 14%–39%) is a result of its poor solubility and is dose dependent.[135,136] Therefore, dividing the dose (i.e., 400 mg twice daily instead of 800 mg once daily) is a simple approach to increase the relative bioavailability and thereby boost pazopanib exposure without increasing costs.[30,31] In addition, administering pazopanib with food can also increase drug exposure without increasing costs.[30-32]

As a proof of concept, an improved pharmaceutical formulation of pazopanib with a much better dissolution profile was developed (containing the excipient Soluplus in a 8:1 ratio with pazopanib). In a clinical study in 12 patients, a dose of 300 mg yielded similar exposure and reduced variability compared with 800 mg of the commercial formulation (minimium plasma concentration, 11.3 mg/L [coefficient of variation, 41] vs. 9.4 mg/L [coefficient of variation, 240]).[137]

There appears to be a subset of patients with poor absorption of pazopanib, which is not surprising, given that the drug is labeled to be taken while fasting, which minimizes bioavailability. The proportion of patients with an exposure lower than the efficacy threshold of 20 mg/L may be reduced if the labeled dose and schedule would be selected more carefully.

Although it appears that therapeutic drug monitoring is useful to identify patients with low concentrations when pazopanib is prescribed with fasting according to the label, it is not clear that this practice is required with an off-label prescribing approach, such as 400 to 600 mg daily with food.[32] This question should be addressed in future trials, particularly because pazopanib's full exposure-efficacy and exposure-toxicity relationships have not been established.

Abiraterone

The first clinical study of this irreversible CYP17A inhibitor demonstrated that a single 500-mg dose administered after an overnight fast could suppress androgen levels for a week or more.[138] Despite this knowledge, the drug was eventually developed by Cougar Pharmaceuticals and approved by the FDA at a dose of 1,000 mg (as four 250-mg tablets) administered daily on an empty stomach.[68] The development of this dosing regimen is particularly surprising given the lack of dose-response and marked food effects evident in Cougar's phase I study.[139] More recently, a randomized study demonstrated the apparent equivalence of 250 mg with food (low-fat breakfast) and the labeled dosing regimen,[33] leading to incorporation of this off-label dosing regimen in National Comprehensive Cancer Network guidelines,[140] soon followed by adoption in India,[141] Brazil,[142] and Thailand.[143] Furthermore, given the prolonged effect of a single dose of this irreversible inhibitor, it is likely that a 500-mg dose administered with food every 2 to 7 days may be as effective as the labeled dosing regimen of 1,000 mg once daily on an empty stomach.

Abiraterone exposure has been related to efficacy, with patients who have a minimal plasma concentration of abiraterone of at least 8.4 ng/mL having significantly longer PFS in two independent patient cohorts.[8,144] However, these results have not been replicated by others.[33] Data for the first 32 patients treated with abiraterone in the DPOG-TDM study show that therapeutic drug monitoring of abiraterone using a food intervention is feasible in clinical practice and significantly increases the minimum plasma concentration.[25]

Lenvatinib

Although originally approved at a dose of 24 mg once daily for differentiated thyroid cancer, lenvatinib has a labeled dose for hepatocellular cancer of 8 to 12 mg once daily, depending on weight. Because the drug is only marketed in 4-mg and 10-mg capsules, Eisai Pharmaceuticals has created a variety of monthly dosing packs to accommodate different combinations of capsules to achieve a daily dose of 8 to 24 mg. These dosing packs all have the same price despite the threefold range of doses, which creates an opportunity to "pack split," or spread one of the higher-dose 1-month packs across as long as 3 months.[145] This strategy does not require a clinical trial to demonstrate equivalence, so it can be rapidly implemented as a cost-savings opportunity for patients whose prescribed daily dose is 12 mg or less.

Nivolumab

The first clinical study of nivolumab—the first FDA-approved PD-1 pathway inhibitor—demonstrated that doses of 0.1 to 10 mg/kg every 2 weeks were active in metastatic melanoma, without evidence of a dose-response relationship.[146] A subsequent three-arm, randomized, dose-ranging trial was conducted in renal cell carcinoma and showed no evidence of a dose-response relationship at 0.3 to 10 mg/kg every 3 weeks.[147] Despite these findings, the drug was first approved at a dose of 3 mg/kg every 2 weeks. Modeling and simulation have been used to support label changes, and the current prescribing information includes

the choice of 240 mg every 2 weeks or 480 mg every 4 weeks, likely at least twice that required for maximal efficacy.[50,148] As noted above, similar opportunities to reduce dose and/or frequency of administration for several other immune checkpoint inhibitors likely exist,[53] and an ongoing randomized trial to evaluate this hypothesis is ongoing.[149] In addition, multiple case reports and small case series, as well as a single-arm phase II trial in Hodgkin lymphoma, provide more justification for a formal evaluation of lower doses of these agents.[150-160]

CONCLUSION

In this educational article, we provided opportunities to optimize dose selection of anticancer drugs by therapeutic drug monitoring, off-label use of lower doses or alternative dosing schedules to reduce toxicities and treatment costs, and receptor occupancy–guided dosings. These strategies should be applied from registration studies to clinical practice, with the goal of better optimizing anticancer treatment.

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REFERENCES

1. Longo DL. Imatinib changed everything. N Engl J Med. 2017;376:982-983.
2. Groenland SL, Mathijssen RHJ, Beijnen JH, et al. Individualized dosing of oral targeted therapies in oncology is crucial in the era of precision medicine. Eur J Clin Pharmacol. 2019;75:1309-1318.
3. van Brummelen EM, Huitema ADR, van Werkhoven E, et al. The performance of model-based versus rule-based phase I clinical trials in oncology: a quantitative comparison of the performance of model-based versus rule-based phase I trials with molecularly targeted anticancer drugs over the last 2 years. J Pharmacokinet Pharmacodyn. 2016;43:235-242.
4. Yu H, Steeghs N, Nijenhuis CM, et al. Practical guidelines for therapeutic drug monitoring of anticancer tyrosine kinase inhibitors: focus on the pharmacokinetic targets. Clin Pharmacokinet. 2014;53:305-325.
5. Mueller-Schoell A, Groenland SL, Scherf-Clavel O, et al. Therapeutic drug monitoring of oral targeted antineoplastic drugs. Eur J Clin Pharmacol. 2021;77:441-464.
6. Verheijen RB, Yu H, Schellens JHM, et al. Practical recommendations for therapeutic drug monitoring of kinase inhibitors in oncology. Clin Pharmacol Ther. 2017;102:765-776.
7. Groenland SL, Geel DR, Janssen JM, et al. Exposure-response analyses of anaplastic lymphoma kinase inhibitors crizotinib and alectinib in non–small cell lung cancer patients. Clin Pharmacol Ther. 2021;109:394-402.
8. van Nuland M, Groenland SL, Bergman AM, et al. Exposure-response analyses of abiraterone and its metabolites in real-world patients with metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis. 2020;23:244-251.
9. Verheijen RB, Swart LE, Beijnen JH, et al. Exposure-survival analyses of pazopanib in renal cell carcinoma and soft tissue sarcoma patients: opportunities for dose optimization. Cancer Chemother Pharmacol. 2017;80:1171-1178.
10. Hellriegel ET, Bjornsson TD, Hauck WW. Interpatient variability in bioavailability is related to the extent of absorption: implications for bioavailability and bioequivalence studies. Clin Pharmacol Ther. 1996;60:601-607.
11. Herbrink M, Nuijen B, Schellens JHM, et al. High-tech drugs in creaky formulations. Pharm Res. 2017;34:1751-1753.
12. Veerman GDM, Hussaarts KGAM, Jansman FGA, et al. Clinical implications of food-drug interactions with small-molecule kinase inhibitors. Lancet Oncol. 2020;21:e265-e279.
13. Hussaarts KGAM, Veerman GDM, Jansman FGA, et al. Clinically relevant drug interactions with multikinase inhibitors: a review. Ther Adv Med Oncol. 2019;11:1758835918818347.

14. Groenland SL, Martínez-Chávez A, van Dongen MGJ, et al. Clinical pharmacokinetics and pharmacodynamics of the cyclin-dependent kinase 4 and 6 inhibitors palbociclib, ribociclib, and abemaciclib. Clin Pharmacokinet. 2020;59:1501-1520.
15. Cardoso E, Csajka C, Schneider MP, et al. Effect of adherence on pharmacokinetic/pharmacodynamic relationships of oral targeted anticancer drugs. Clin Pharmacokinet. 2018;57:1-6.
16. Bins S, Huitema ADR, Laven P, et al. Impact of CYP3A4*22 on pazopanib pharmacokinetics in cancer patients. Clin Pharmacokinet. 2019;58:651-658.
17. Diekstra MHM, Klümpen HJ, Lolkema MPJK, et al. Association analysis of genetic polymorphisms in genes related to sunitinib pharmacokinetics, specifically clearance of sunitinib and SU12662. Clin Pharmacol Ther. 2014;96:81-89.
18. Janssen JM, Dorlo TPC, Steeghs N, et al. Pharmacokinetic targets for therapeutic drug monitoring of small molecule kinase inhibitors in pediatric oncology. Clin Pharmacol Ther. 2020;108:494-505.
19. Groenland SL, van Nuland M, Verheijen RB, et al. Therapeutic drug monitoring of oral anti-hormonal drugs in oncology. Clin Pharmacokinet. 2019;58:299-308.
20. Paci A, Veal G, Bardin C, et al. Review of therapeutic drug monitoring of anticancer drugs: part 1—cytotoxics. Eur J Cancer. 2014;50:2010-2019.
21. Widmer N, Bardin C, Chatelut E, et al. Review of therapeutic drug monitoring of anticancer drugs part two--targeted therapies. Eur J Cancer. 2014; 50:2020-2036.
22. de Wit D, Guchelaar HJ, den Hartigh J, et al. Individualized dosing of tyrosine kinase inhibitors: are we there yet? Drug Discov Today. 2015;20:18-36.
23. Lankheet NAG, Desar IME, Mulder SF, et al. Optimizing the dose in cancer patients treated with imatinib, sunitinib and pazopanib. Br J Clin Pharmacol. 2017; 83:2195-2204.
24. Verheijen RB, Bins S, Mathijssen RHJ, et al; Dutch Pharmacology Oncology Group. Individualized pazopanib dosing: a prospective feasibility study in cancer patients. Clin Cancer Res. 2016;22:5738-5746.
25. Groenland SL, van Nuland M, Bergman AM, et al; Dutch Pharmacology Oncology Group (DPOG). Concomitant intake of abiraterone acetate and food to increase pharmacokinetic exposure: real life data from a therapeutic drug monitoring programme. Eur J Cancer. 2020;130:32-38.
26. Fox P, Balleine RL, Lee C, et al. Dose escalation of tamoxifen in patients with low endoxifen level: evidence for therapeutic drug monitoring—the TADE study. Clin Cancer Res. 2016;22:3164-3171.
27. Gotta V, Widmer N, Decosterd LA, et al. Clinical usefulness of therapeutic concentration monitoring for imatinib dosage individualization: results from a randomized controlled trial. Cancer Chemother Pharmacol. 2014;74:1307-1319.
28. IJzerman NS, Groenland SL, Koenen AM, et al. Therapeutic drug monitoring of imatinib in patients with gastrointestinal stromal tumours: results from daily clinical practice. Eur J Cancer. 2020;136:140-148.
29. Lankheet NA, Kloth JS, Gadellaa-van Hooijdonk CG, et al. Pharmacokinetically guided sunitinib dosing: a feasibility study in patients with advanced solid tumours. Br J Cancer. 2014;110:2441-2449.
30. Groenland SL, van Eerden RAG, Verheijen RB, et al; Dutch Pharmacology Oncology Group (DPOG). Cost-neutral optimization of pazopanib exposure by splitting intake moments: a prospective pharmacokinetic study in cancer patients. Clin Pharmacokinet. 2020;59:941-948.
31. Groenland SL, van Eerden RAG, Koolen SLW, et al. Therapeutic drug monitoring (TDM) of pazopanib: using cost-neutral PK-guided interventions to optimize exposure. J Clin Oncol. 2020;38(15 suppl; abstr 3598).
32. Lubberman FJE, Gelderblom H, Hamberg P, et al. The effect of using pazopanib with food vs fasted on pharmacokinetics, patient safety and preference (DIET study). Clin Pharmacol Ther. 2019;106:1076-1082.
33. Szmulewitz RZ, Peer CJ, Ibraheem A, et al. Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. J Clin Oncol. 2018;36:1389-1395.
34. Groenland SL, van Eerden RAG, Verheijen RB, et al. Therapeutic drug monitoring of oral anticancer drugs: the Dutch Pharmacology Oncology Group–therapeutic drug monitoring protocol for a prospective study. Ther Drug Monit. 2019;41:561-567.
35. Groenland S, van Eerden R, Koolen S, et al. Therapeutic drug monitoring of oral anticancer drugs - preliminary results of a prospective study. Ann Oncol. 2019; 30:v161.
36. Sheiner LB. Learning versus confirming in clinical drug development. Clin Pharmacol Ther. 1997;61:275-291.
37. Chatelut E, Bruno R, Ratain MJ. Intraindividual pharmacokinetic variability: focus on small-molecule kinase inhibitors. Clin Pharmacol Ther. 2018; 103:956-958.
38. Picard S, Titier K, Etienne G, et al. Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia. Blood. 2007;109:3496-3499.
39. Suttle AB, Ball HA, Molimard M, et al. Relationships between pazopanib exposure and clinical safety and efficacy in patients with advanced renal cell carcinoma. Br J Cancer. 2014;111:1909-1916.
40. U.S. Food and Drug Administration; Center for Drug Evaluation and Research. Guidance for Industry: Exposure-Response Relationships—Study Design, Data Analysis and Regulatory Applications. Silver Spring, MD: U.S. Food and Drug Administration; 2003.
41. Polite BN, Ratain MJ, Lichter AS. Oncology's "hockey stick" moment for the cost of cancer drugs: the climate is about to change. JAMA Oncol. 2021;7:25-26.
42. Canadian Agency for Drugs and Technologies in Health. Pill Splitting: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines; 2015. www.ncbi.nlm.nih.gov/books/NBK304655/. Accessed February 12, 2021.

43. Solomon SD, Lindsley KB, Krzystolik MG, et al. Intravitreal bevacizumab versus ranibizumab for treatment of neovascular age-related macular degeneration: findings from a Cochrane Systematic Review. Ophthalmology. 2016;123:70-77.e1.

44. Rosenfeld PJ, Windsor MA, Feuer WJ, et al. Estimating Medicare and patient savings from the use of bevacizumab for the treatment of exudative age-related macular degeneration. Am J Ophthalmol. 2018;191:135-139.

45. van Asten F, Michels CTJ, Hoyng CB, et al. The cost-effectiveness of bevacizumab, ranibizumab and aflibercept for the treatment of age-related macular degeneration: a cost-effectiveness analysis from a societal perspective. PLoS One. 2018;13:e0197670.

46. Brown GC, Brown MM, Rapuano S, et al. Cost-utility analysis of VEGF inhibitors for treating neovascular age-related macular degeneration. Am J Ophthalmol. 2020;218:225-241.

47. Ratain MJ, Goldstein DA, Lichter AS. Interventional pharmacoeconomics: a new discipline for a cost-constrained environment. JAMA Oncol. 2019; 5:1097-1098.

48. Serritella AV, Strohbehn GW, Goldstein DA, et al. Interventional pharmacoeconomics: a novel mechanism for unlocking value. Clin Pharmacol Ther. 2020; 108:487-493.

49. Goldstein DA, Gordon N, Davidescu M, et al. A pharmacoeconomic analysis of personalized dosing vs fixed dosing of pembrolizumab in firstline PD-L1–positive non–small cell lung cancer. J Natl Cancer Inst. 2017;109:1-6.

50. Ratain MJ, Goldstein DA. Time is money: optimizing the scheduling of nivolumab. J Clin Oncol. 2018;36:3074-3076.

51. Goldstein DA, Ratain MJ. Alternative dosing regimens for atezolizumab: right dose, wrong frequency. Cancer Chemother Pharmacol. 2019;84:1153-1155.

52. Goldstein DA, Ratain MJ. Safety, clinical activity, and biological correlates of response in patients with metastatic melanoma: results from a phase I trial of atezolizumab-letter. Clin Cancer Res. 2020;26:2435.

53. Peer CJ, Goldstein DA, Goodell JC, et al. Opportunities for using in silico-based extended dosing regimens for monoclonal antibody immune checkpoint inhibitors. Br J Clin Pharmacol. 2020;86:1769-1777.

54. Goldstein DA, Ratain MJ, Saltz LB. Weight-based dosing of pembrolizumab every 6 weeks in the time of COVID-19. JAMA Oncol. 2020;6:1694-1695.

55. Schadendorf D, Wolchok JD, Hodi FS, et al. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: a pooled analysis of randomized phase II and III trials. J Clin Oncol. 2017;35:3807-3814.

56. Takeuchi E, Okamoto Y, Takahashi N, et al. Complete response of squamous cell carcinoma of the lung following treatment with pembrolizumab in an elderly patient: a case report. Thorac Cancer. 2020;12:259-263.

57. Bover M, Yarza R, Iglesias Docampo L. Four-year lasting sustained complete response after nivolumab in a patient with non–small-cell lung cancer and confirmed leptomeningeal carcinomatosis: changing the paradigm. Clin Lung Cancer. 2020;21:E1-E5.

58. de Jong WK, Mulders ACM, Westendorp W, et al. Exceptional response of brain metastases to short course nivolumab while on high-dose steroids. Netherlands J Med. 2019;77:338-340.

59. Mimura C, Tachihara M, Kusuhara S, et al. Complete response in a patient with lung cancer suffering from three pembrolizumab-induced immune-related adverse events including retinal vasculitis. Respirol Case Rep. 2021;9:e00730.

60. Yilmaz M, Mese SG. Durable response after discontinuation of nivolumab therapy in the absence of disease progression or toxicity with two advanced NSCLC patients. J Oncol Pharm Pract. 2019;26:761-767.

61. Nomura S, Goto Y, Mizutani T. A randomized phase III study comparing continuation and discontinuation of PD-1 pathway inhibitors for patients with advanced non–small cell lung cancer (JCOG1701, SAVE study). J Clin Oncol. 2020;50:821-825.

62. Iivanainen S, Koivunen JP. Early PD-1 therapy discontinuation in responding metastatic cancer patients. Oncology. 2019;96:125-131.

63. Friedlaender A, Kim C, Addeo A. Rethinking the optimal duration of immune checkpoint inhibitors in non–small cell lung cancer throughout the COVID-19 pandemic. Front Oncol. 2020;10:862.

64. U.S. Food and Drug Administration; Center for Drug Evaluation and Research. Guideline for Industry: Dose-Response Information to Support Drug Registration; 1994. www.fda.gov/media/71279/download. Accessed February 12, 2021.

65. European Medicines Agency; Committee for Medicinal Products for Human Use. Note for Guidance on Dose Response Information to Support Drug Registration; 1994. www.ema.europa.eu/en/documents/scientific-guideline/ich-e-4-dose-response-information-support-drug-registration-step-5_en.pdf. Accessed February 12, 2021.

66. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol. 2013;31:88-94.

67. Ratain MJ, Cohen EE. The value meal: how to save $1,700 per month or more on lapatinib. J Clin Oncol. 2007;25:3397-3398.

68. Ratain MJ. Flushing oral oncology drugs down the toilet. J Clin Oncol. 2011;29:3958-3959.

69. Szmulewitz RZ, Ratain MJ. Playing Russian roulette with tyrosine kinase inhibitors. Clin Pharmacol Ther. 2013;93:242-244.

70. Sinha G. Experts Push for New Cancer Drug Dosing Recommendations. https://undark.org/2020/12/09/cancer-drugs-less-might-be-more/. Accessed February 12, 2021.

71. Papachristos A, Ratain MJ. Accelerated approval of anticancer drugs: lessons learned from the example of olaratumab. Clin Pharmacol Ther. Epub 2020 Nov 4.

72. Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leukaemia. Nat Rev Dis Primers. 2017;3:17008.

73. Stevenson FK, Forconi F, Packham G. The meaning and relevance of B-cell receptor structure and function in chronic lymphocytic leukemia. Semin Hematol. 2014;51:158-167.

74. Stevenson FK, Krysov S, Davies AJ, et al. B-cell receptor signaling in chronic lymphocytic leukemia. Blood. 2011;118:4313-4320.

75. Packham G, Stevenson F. The role of the B-cell receptor in the pathogenesis of chronic lymphocytic leukaemia. Semin Cancer Biol. 2010;20:391-399.

76. Ponader S, Burger JA. Bruton's tyrosine kinase: from X-linked agammaglobulinemia toward targeted therapy for B-cell malignancies. J Clin Oncol. 2014; 32:1830-1839.

77. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci USA. 2010;107:13075-13080.

78. de Claro RA, McGinn KM, Verdun N, et al. FDA approval: Ibrutinib for patients with previously treated mantle cell lymphoma and previously treated chronic lymphocytic leukemia. Clin Cancer Res. 2015;21:3586-3590.

79. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369:32-42.

80. Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371:213-223.

81. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. Lancet Oncol. 2014;15:48-58.

82. O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol. 2016;17:1409-1418.

83. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med. 2015;373:2425-2437.

84. U.S. Food and Drug Administration; Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review: Ibrutinib, 2013. www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf. Accessed February 12, 2021.

85. Nisitani S, Satterthwaite AB, Akashi K, et al. Posttranscriptional regulation of Bruton's tyrosine kinase expression in antigen receptor-stimulated splenic B cells. Proc Natl Acad Sci USA. 2000;97:2737-2742.

86. Chen SS, Chang BY, Chang S, et al. BTK inhibition results in impaired CXCR4 chemokine receptor surface expression, signaling and function in chronic lymphocytic leukemia. Leukemia. 2016;30:833-843.

87. Cervantes-Gomez F, Kumar Patel V, Bose P, et al. Decrease in total protein level of Bruton's tyrosine kinase during ibrutinib therapy in chronic lymphocytic leukemia lymphocytes. Leukemia. 2016;30:1803-1804.

88. Mohamed AJ, Yu L, Bäckesjö CM, et al. Bruton's tyrosine kinase (Btk): function, regulation, and transformation with special emphasis on the PH domain. Immunol Rev. 2009;228:58-73.

89. Chen LS, Bose P, Cruz ND, et al. A pilot study of lower doses of ibrutinib in patients with chronic lymphocytic leukemia. Blood. 2018;132:2249-2259.

90. Herman SEM, Mustafa RZ, Gyamfi JA, et al. Ibrutinib inhibits BCR and NF-κB signaling and reduces tumor proliferation in tissue-resident cells of patients with CLL. Blood. 2014;123:3286-3295.

91. McMullen JR, Boey EJH, Ooi JYY, et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood. 2014; 124:3829-3830.

92. Levade M, David E, Garcia C, et al. Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. Blood. 2014;124:3991-3995.

93. Xiao L, Salem J-E, Clauss S, et al. Ibrutinib-mediated atrial fibrillation attributable to inhibition of C-terminal Src kinase. Circulation. 2020;142:2443-2455.

94. Awan FT, Tong D, Zaha VG. Cardio-oncology: a win-win situation: how solving the mystery of an ibrutinib off-target effect reveals new insights into atrial fibrillation mechanisms. Circulation. 2020;142:2456-2458.

95. Byrd JC, Hillmen P, O'Brien S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. Blood. 2019;133:2031-2042.

96. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol. 2019;94:1353-1363.

97. Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017;102:1796-1805.

98. Wiczer TE, Levine LB, Brumbaugh J, et al. Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib. Blood Adv. 2017;1:1739-1748.

99. Salem JE, Manouchehri A, Bretagne M, et al. Cardiovascular toxicities associated with ibrutinib. J Am Coll Cardiol. 2019;74:1667-1678.

100. Ratain MJ, Moslehi JJ, Lichter AS. Ibrutinib's cardiotoxicity: an opportunity for postmarketing regulation. JAMA Oncol. 2021;7:177-178.

101. Varughese T, Taur Y, Cohen N, et al. Serious infections in patients receiving ibrutinib for treatment of lymphoid cancer. Clin Infect Dis. 2018;67:687-692.

102. Ghez D, Calleja A, Protin C, et al; French Innovative Leukemia Organization (FILO) CLL group. Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib. Blood. 2018;131:1955-1959.

103. Ruchlemer R, Ben-Ami R, Bar-Meir M, et al. Ibrutinib-associated invasive fungal diseases in patients with chronic lymphocytic leukaemia and non-Hodgkin lymphoma: an observational study. Mycoses. 2019;62:1140-1147.

104. Maffei R, Maccaferri M, Arletti L, et al. Immunomodulatory effect of ibrutinib: reducing the barrier against fungal infections. Blood Rev. 2020;40:100635.

105. Ahn IE, Jerussi T, Farooqui M, et al. Atypical *Pneumocystis jirovecii* pneumonia in previously untreated patients with CLL on single-agent ibrutinib. Blood. 2016; 128:1940-1943.

106. Mori J, Nagy Z, Di Nunzio G, et al. Maintenance of murine platelet homeostasis by the kinase Csk and phosphatase CD148. Blood. 2018;131:1122-1144.

107. Rhodes J, Mato A, Sharman JP. Monitoring and management of toxicities of novel B cell signaling agents. Curr Oncol Rep. 2018;20:49.

108. Gribben JG, Bosch F, Cymbalista F, et al. Optimising outcomes for patients with chronic lymphocytic leukaemia on ibrutinib therapy: European recommendations for clinical practice. Br J Haematol. 2018;180:666-679.

109. Barr PM, Brown JR, Hillmen P, et al. Impact of ibrutinib dose adherence on therapeutic efficacy in patients with previously treated CLL/SLL. Blood. 2017; 129:2612-2615.

110. Chen Q, Jain N, Ayer T, et al. Economic burden of chronic lymphocytic leukemia in the era of oral targeted therapies in the United States. J Clin Oncol. 2017; 35:166-174.

111. Shanafelt TD, Borah BJ, Finnes HD, et al. Impact of ibrutinib and idelalisib on the pharmaceutical cost of treating chronic lymphocytic leukemia at the individual and societal levels. J Oncol Pract. 2015;11:252-258.

112. Bose P, Gandhi VV, Keating MJ. Pharmacokinetic and pharmacodynamic evaluation of ibrutinib for the treatment of chronic lymphocytic leukemia: rationale for lower doses. Expert Opin Drug Metab Toxicol. 2016;12:1381-1392.

113. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood. 2015;125:2497-2506.

114. Woyach JA, Ruppert AS, Guinn D, et al. BTKC481S-Mediated resistance to ibrutinib in chronic lymphocytic leukemia. J Clin Oncol. 2017;35:1437-1443.

115. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. Haematologica. 2018;103:874-879.

116. O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. Blood. 2018;131:1910-1919.

117. Akhtar OS, Attwood K, Lund I, et al. Dose reductions in ibrutinib therapy are not associated with inferior outcomes in patients with chronic lymphocytic leukemia (CLL). Leuk Lymphoma. 2019;60:1650-1655.

118. Ahn IE, Basumallik N, Tian X, et al. Clinically indicated ibrutinib dose interruptions and reductions do not compromise long-term outcomes in CLL. Blood. 2019; 133:2452-2455.

119. Uminski K, Brown K, Bucher O, et al. Descriptive analysis of dosing and outcomes for patients with ibrutinib-treated relapsed or refractory chronic lymphocytic leukemia in a Canadian centre. Curr Oncol. 2019;26:e610-e617.

120. UK CLL Forum. Ibrutinib for relapsed/refractory chronic lymphocytic leukemia: a UK and Ireland analysis of outcomes in 315 patients. Haematologica. 2016; 101:1563-1572.

121. Michallet AS, Campidelli A, Lequeu H, et al. Ibrutinib in very elderly patients with relapsed/refractory chronic lymphocytic leukemia: a real-world experience of 71 patients treated in France: a study from the French Innovative Leukemia Organization (FILO) group. Am J Hematol. 2017;92:E105-E107.

122. Winqvist M, Andersson P-O, Asklid A, et al; Swedish CLL Group. Long-term real-world results of ibrutinib therapy in patients with relapsed or refractory chronic lymphocytic leukemia: 30-month follow up of the Swedish compassionate use cohort. Haematologica. 2019;104:e208-e210.

123. Aarup K, Rotbain EC, Enggaard L, et al. Real-world outcomes for 205 patients with chronic lymphocytic leukemia treated with ibrutinib. Eur J Haematol. 2020; 105:646-654.

124. Iskierka-Jażdżewska E, Hus M, Giannopoulos K, et al. Efficacy and toxicity of compassionate ibrutinib use in relapsed/refractory chronic lymphocytic leukemia in Poland: analysis of the Polish Adult Leukemia Group (PALG). Leuk Lymphoma. 2017;58:2485-2488.

125. Jain P, Thompson PA, Keating M, et al. Long-term outcomes for patients with chronic lymphocytic leukemia who discontinue ibrutinib. Cancer. 2017; 123:2268-2273.

126. Mato AR, Timlin C, Ujjani C, et al. Comparable outcomes in chronic lymphocytic leukaemia (CLL) patients treated with reduced-dose ibrutinib: results from a multi-centre study. Br J Haematol. 2018;181:259-261.

127. Parikh SA, Achenbach SJ, Call TG, et al. The impact of dose modification and temporary interruption of ibrutinib on outcomes of chronic lymphocytic leukemia patients in routine clinical practice. Cancer Med. 2020;9:3390-3399.

128. Nuttall E, Tung J, Trounce E, et al. Real-world experience of ibrutinib therapy in relapsed chronic lymphocytic leukemia: results of a single-center retrospective analysis. J Blood Med. 2019;10:199-208.

129. Tannock IF, Ratain MJ, Goldstein DA, et al. Near-equivalence: generating evidence to support alternative cost-effective treatments. J Clin Oncol. 2021; 39:950-955.

130. Ratain MJ, Lichter AS. Empowering the FDA to Require Dose Optimization of All New Oncology Drugs, 2021. https://ascopost.com/issues/january-25-2021/empowering-the-fda-to-require-dose-optimization-of-all-new-oncology-drugs/. Accessed February 12, 2021.

131. Goldstein DA, Strohbehn GW, Serritella AV, et al. Interventional pharmacoeconomics. Cancer J. 2020;26:330-334.

132. U.S. Food and Drug Administration; Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review: Pazopanib, 2009. www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022465s000_clinpharmr.pdf. Accessed February 12, 2021.

133. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010;28:1061-1068.

134. Sternberg CN, Donskov F, Haas NB, et al. Pazopanib exposure relationship with clinical efficacy and safety in the adjuvant treatment of advanced renal cell carcinoma. Clin Cancer Res. 2018;24:3005-3013.

135. Deng Y, Sychterz C, Suttle AB, et al. Bioavailability, metabolism and disposition of oral pazopanib in patients with advanced cancer. Xenobiotica. 2013; 43:443-453.

136. Yu H, van Erp N, Bins S, et al. Development of a pharmacokinetic model to describe the complex pharmacokinetics of pazopanib in cancer patients. Clin Pharmacokinet. 2017;56:293-303.

137. Herbrink M, Groenland SL, Huitema ADR, et al. Solubility and bioavailability improvement of pazopanib hydrochloride. Int J Pharm. 2018;544:181-190.

138. O'Donnell A, Judson I, Dowsett M, et al. Hormonal impact of the 17α-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. Br J Cancer. 2004;90:2317-2325.

139. Ryan CJ, Smith MR, Fong L, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. J Clin Oncol. 2010;28:1481-1488.

140. NCCN Validates Path Toward De-escalated Doses and Reduced Costs of Cancer Drugs. https://cancerletter.com/articles/20190329_1/. Accessed February 12, 2021.

141. Patel A, Tannock IF, Srivastava P, et al. Low-dose abiraterone in metastatic prostate cancer: is it practice changing? Facts and facets. JCO Glob Oncol. 2020; 6:382-386.

142. Zucca LER, Neif JAJ, Preto DDA, et al.; OncoGU. Real-world outcome with abiraterone low-dose plus prednisone in patients with mCRPC in a Brazilian Public Cancer Center. J Clin Oncol. 2020;38 (15 suppl; abstr e17563).

143. Makphanchareonkit K, Dejthevaporn TS, Dittapol M, et al. The study of the treatment efficacy in metastatic castration-resistant prostate cancer of low dose abiraterone with food. J Clin Oncol. 2020;38(15 suppl; abstr e17571).

144. Carton E, Noe G, Huillard O, et al. Relation between plasma trough concentration of abiraterone and prostate-specific antigen response in metastatic castration-resistant prostate cancer patients. Eur J Cancer. 2017;72:54-61.

145. Harvey RD, Ratain MJ. A cost-focused alternative cancer medication dispensing strategy: pack splitting. JAMA Oncol. 2019;5:1691-1692.

146. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366:2443-2454.

147. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. J Clin Oncol. 2015;33:1430-1437.

148. Peer CJ, Goldstein DA, Ratain MJ, et al. A modeling and simulation study of less frequent dosing of nivolumab 480 mg. J Clin Oncol. 2019;37(15 suppl; abstr 3115).

149. NCT04295863. Comparing Dosing Intervals of Nivolumab or Pembrolizumab in Locally Advanced or Metastatic Cancers. https://clinicaltrials.gov/ct2/show/NCT04295863. Accessed February 12, 2021.

150. Yoo SH, Keam B, Kim M, et al. Low-dose nivolumab can be effective in non-small cell lung cancer: alternative option for financial toxicity. ESMO Open. 2018; 3:e000332.

151. Chan TSY, Khong PL, Au-Yeung R, et al. Low-dose nivolumab induced durable complete response in relapsed primary central nervous system diffuse large B cell lymphoma. Ann Hematol. 2019;98:2227-2230.

152. Chan TSY, Sim JPY, Kwong YL. Low-dose nivolumab-induced responses in acute lymphoblastic leukaemia relapse after allogeneic haematopoietic stem cell transplantation. Ann Hematol. 2017;96:1569-1572.

153. Chan TSY, Li J, Loong F, et al. PD1 blockade with low-dose nivolumab in NK/T cell lymphoma failing L-asparaginase: efficacy and safety. Ann Hematol. 2018; 97:193-196.

154. Chan TSY, Hwang YY, Khong PL, et al. Low-dose pembrolizumab and nivolumab were efficacious and safe in relapsed and refractory classical Hodgkin lymphoma: experience in a resource-constrained setting. Hematol Oncol. 2020;38:726-736.

155. Lepik KV, Fedorova LV, Kondakova EV, et al. A phase 2 study of nivolumab using a fixed dose of 40 mg (Nivo40) in patients with relapsed/refractory Hodgkin lymphoma. HemaSphere. 2020;4:e480.

156. Low JL, Sooi K, Huang Y, et al. Cost and efficacy of low-dose pembrolizumab in the treatment of non–small cell lung cancer patients in Asia. J Clin Oncol. 2020; 38(15 suppl; abstr e19385).

157. Sim JPY, Au-Yeung R, Kwong YL. Low-dose pembrolizumab induced complete radiologic and molecular response of posttransplant lymphoproliferative disorder presenting as classical Hodgkin lymphoma. Ann Hematol. 2020;99:385-388.

158. Kwong YL, Loong F, Khong PL. Low-dose pembrolizumab re-treatment induced complete radiologic and molecular remission in Hodgkin lymphoma recurring from a previous relapse successfully treated by pembrolizumab. Ann Hematol. 2019;98:2451-2455.

159. Kwong YL, Lopes D, Khong PL. Low-dose pembrolizumab induced remission in patients with refractory classical Hodgkin lymphoma. Br J Haematol. 2017; 176:131-132.

160. Onizuka M, Kojima M, Matsui K, et al. Successful treatment with low-dose nivolumab in refractory Hodgkin lymphoma after allogeneic stem cell transplantation. Int J Hematol. 2017;106:141-145.

Taking Aim at the Undruggable

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overview

The term "undruggable" is used to describe a protein that is not pharmacologically capable of being targeted; recently, however, substantial efforts have been made to turn these proteins into "druggable" targets. Thus, "difficult to drug" or "yet to be drugged" are perhaps more appropriate terms. In cancer, a number of elusive targets fall into this category, including transcription factors such as STAT3, TP53, and MYC. Pharmacologically targeting these intractable proteins is now a key challenge of modern drug development, requiring innovation and the development of new technologies. In this article, we discuss some of the recent technologic and pharmacologic advances that have underpinned the erosion of the concept of undruggability. We describe recent successes in drugging the undruggable *RAS* (*KRAS* G12C and *HRAS*), and discuss the advances that have led to the validation of further targets previously believed to be undruggable, such as HIF-2α, BCL-2, MDM2, and MLL. Finally, we look to the future and describe important advances that are likely to have a major impact on targeting undruggable targets, such as the advent of proteolysis-targeting chimeras and protein-protein modulators, which are leading to considerable excitement surrounding the development of cancer targets.

CONCEPTS

If we look at the relationship among the human proteome, diseases, and drugs (approved or in development), it is striking to realize that only between 1% and 2% of disease-modifying proteins are known, or predicted, to be druggable. In therapeutics, the most frequent drug target is catalytic sites of proteins, but there are other entities that could be modulated for therapeutic intent, such as nucleic acids (and nucleic acid complexes [e.g., ribosomes]), intracellular small molecules, and protein-protein or protein–nucleic acid interactions. Druggability,[1] then, can be defined as the property of a target for being known, or predicted, to bind with high affinity to a drug and modulate its function with a therapeutic benefit. There are several methods to predict target druggability, based on empirical analyses of libraries of compounds or based on structural analysis. "Drug likeness" refers to the compounds that bind the target. The concept includes the properties that enable pharmaceutical attributes of a viable therapeutic entity, such as structural, physicochemical (e.g., chemical stability, solubility), pharmacokinetic (e.g., bioavailability, distribution), and toxicity characteristics. Related to druggability (of the target) and drug likeness (drug candidate) is the concept of "developability," which considers the whole process, from target discovery and lead compound development to its clinical entry. In addition to the preclinical pharmacokinetic/pharmacodynamic properties, it encompasses factors, such as physiochemical properties, formulation, performance, manufacturability, development risks, and patient convenience, that enable the development of a drug candidate.

In cancer, some of these disease-modifying targets seem difficult to address; they seem "undruggable" because they lack accessible deep hydrophobic pockets where ligands and drugs can bind, or they lack enzymatic activity (have no active site), referring to the loss of function of the target. In cancer, the classic undruggables include β-catenin, RAS, and transcription factors (e.g., *STAT3, TP53, MYC*).[2] Some recent technologic advances have eroded the concept of undruggability, including structural biology advances (protein nuclear magnetic resonance and crystal structures), three-dimensional annotated chemical libraries, and novel computational methods to visualize or predict aspects of molecular targets and interactions. Other advances in pharmacology have contributed as well, including expanded reengineered therapeutic antibodies and biologics, strategies to enable the selective degradation of specific proteins, and improved delivery systems for nucleic acid–based compounds.[2] In this article, we review the later developments, addressing how some new molecular entities show encouraging signs that they will change the landscape of undruggability.

HISTORICAL PERSPECTIVE

In the early 20th century, drug discovery was initially based on random screening for active substances from biologic extracts (e.g., plants, microorganisms). For cancer drug development, the attention initially was focused on cytotoxic agents aiming at DNA replication,

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PRACTICAL APPLICATIONS

- Recent successes in targeting *KRAS* G12C and *HRAS* represent significant advances in drugging "the undruggable" and provide proof of concept.
- Pharmacologic targeting of intractable proteins is now a key challenge of modern drug development, requiring innovation and the development of new technologies.
- Important advances that are likely to have a major impact on targeting undruggable targets include the advent of proteolysistargeting chimeras and protein-protein modulators, which are leading to considerable excitement in the field of drug development.

mitotic machinery, or DNA integrity, targeting, for example, dihydrofolate reductase and topoisomerase. The advent of molecular biology fueled efforts to seek drugs directed against relevant molecular targets, such as growth factor receptors, enzymes, or other biologic targets driving the disease. Alongside the development of targeted therapies, in the 1970s the pharmacologic industry moved toward a rational drug discovery methodology of small molecules. Marked advancements in the experimental and computational techniques used in the drug discovery process have changed the development of small molecules and antibodies, moving from an empirical screening toward a structured rational design. With the parallel development of recombinant protein-based therapeutic agents in the 1980s, rational development became the standard practice. Thus, the modern drug development paradigm was born.[3]

When considering the class of drugs approved by the U.S. Food and Drug Administration for management of cancer under this paradigm, the vast majority fall into two categories: small-molecule drugs (those with composite molecular mass $<$ 1,000 daltons) and protein therapeutics or biologics (primarily monoclonal antibodies, some peptides, and a few vaccines). Until now, biologics have been designed to bind to specific target epitopes in extracellular or cell surface targets, whereas small chemical entities are intended to access and modulate intracellular proteins. Typically, small molecules bind to accessible hydrophobic invaginations in the target, more frequently in the catalytic site (also known as catalytic inhibitors; e.g., erlotinib, sunitinib, or copanlisib), as well as in other sites, "an allosteric site," but altering the shape of the active site so that the target can no longer bind to its substrate ("allosteric inhibitors" such as everolimus or trametinib). Although it depends on their size and chemical properties, most small molecules developed as anticancer agents are orally available. Biologics, in contrast, can interact with larger surfaces; however, because of their larger molecular size, they have limited delivery, requiring intravenous treatment and targeting only extracellular targets (e.g., EGFR, HER2, VEGFR2, PD-1). In cancer, many validated drug targets are druggable with small molecules or antibodies: serine/threonine/tyrosine kinases, growth factor receptors, and receptor ligands. Other classes of cancer molecular targets seem difficult to address by either of these two classes of agents: the so-called undruggable targets.

New Technologies and Pharmacologic Entities Enable Drugging the Undruggable

Along with tumor heterogeneity and drug-resistance mechanisms, developing therapeutics for apparently intractable targets is one of the key challenges of targeted therapeutics. Novel chemical entities are now being developed that may change the tide. Some examples of chemical entities, beyond the classic inhibitors of kinases, include protein-protein interaction (PPI) modulators, multifunctional small molecules (e.g., proteolysis-targeting chimeras [PROTACs]), peptides/peptidomimetics, nucleic acid–based therapeutics (e.g., oligonucleotides), and even cell therapies and T-cell receptor (TCR) mimetics. This major expansion of the "chemical matter" (chemical space used in drug discovery) used for therapeutics brings along new chemical, biologic, and pharmaceutical properties that could enable the modulation of difficult targets. Because of some of the characteristics of these compounds, most of these entities may require intravenous delivery; however, nanomedicine approaches could reduce dosing frequency, while improving therapeutic windows.

Of these novel compound types, one notable recent success is venetoclax, a first-in-class BCL-2 inhibitor. It took 20 years of extensive chemistry efforts,[4,5] several lead candidates, and many clinical trials, but its approval by the U.S. Food and Drug Administration in 2016 demonstrated the possibility of developing agents that impede PPIs with small molecules. Since that time, BCL-2 is no longer on the list of undruggables.

The recent successes with targeting *KRAS* G12C and *HRAS* are also important breakthroughs in targeting the undruggable. The three RAS oncogene products, KRAS, NRAS, and HRAS, have been among the most interesting, sought after, and challenging targets, in part because of the frequency of these lesions (approximately 30% of human cancers). In the case of *KRAS* G12C, the breakthrough came from structural insights provided by x-ray crystallography and nuclear magnetic resonance that showed that this specific mutation creates a pocket that can be exploited therapeutically. Using state-of-the-art chemistry, pharmacologists have been able to synthesize covalent inhibitors that attach to Cys12, thereby inhibiting MAPK signaling.

Sotorasib is one such small-molecule inhibitor, and its use has resulted in confirmed objective response rates (complete or partial response) of 32.2% in patients with *KRAS* G12C non–small cell lung cancer, as well as disease control rates (objective response or stable disease) of 88.1% in non–small cell lung cancer and 73.8% in colorectal cancer.[6] Consequently, several additional compounds are in clinical development.

In the case of *HRAS*, the breakthrough came from the observation of the exquisite dependency of HRAS on farnesyl transferase for prenylation, a critical step that is necessary for RAS to bind to the inner layer of the cell membrane and function (other members of the RAS family have redundant pathways). Tipifarnib, a farnesyl transferase inhibitor, has been granted fast track designation by the U.S. Food and Drug Administration for the treatment of patients with *HRAS*-mutant head and neck squamous cell carcinomas. Early clinical trials are showing an overall response rate of 50.0% (95% CI, 26.0–74.0) and a median duration of response of 14.7 months (95% CI, 2.1–not reported) in patients with these diseases.[7]

Another recent success story related to the use of modern crystallography and structure-based design is the targeting of HIF-2α. von Hippel-Lindau disease and many clear cell renal cell carcinomas have inactivating mutations in VHL, resulting in constitutive activation of the HIF-2α transcription factor. The finding of a large cavity within the HIF-2α PAS-B domain permitted the development of molecules (e.g., PT2399, PT2385, and PT2977, later known as MK-6482) that bind to the allosteric site and block its dimerization with the HIF-1α/2α transcriptional dimerization partner ARNT/HIF-1β. Treatment of 61 patients with VHL-associated clear cell renal cell carcinoma using MK-6482 (NCT03401788) showed a confirmed response rate of 27.9%, as well as 13.1% unconfirmed responses at the time of reporting (86.9% of patients experienced some decrease in the size of their target lesions).[8] This was the first story of successful drug development against a transcription factor.

Some other programs are aiming to develop multispecific drugs. These compounds work through two or more chemical entities (one effector and one target), with several drug-target binding interfaces that work sequentially or concurrently. This multispecificity allows limiting drug activity to a specific location or anchors the target close to an endogenous effector, allowing the effector to modulate the target. Some of them are antibody/peptide-based, such as heteroduplex immunoglobulin G, bispecific CD3 engagers, or antibody-toxin, antibody-drug, or antibody-cytokine fusion proteins. Others are small molecules called "matchmakers," which pull two entities together (the effector and target), such that one (the effector) acts upon the other (the target). These act as chemical inducers of degradation utilizing endogenous biologic mechanisms, such as the ubiquitin-proteasome degradation system: the therapeutic effect is produced by modulating protein levels of the target.

PROTEOLYSIS-TARGETING CHIMERAS

PROTACs are one class of bifunctional small molecules. They simultaneously bind to a target protein and an E3 ubiquitin ligase, thereby causing ubiquitylation and degradation of the target protein (Fig. 1).[9] The ability of PROTACs to degrade proteins, regardless of their function, makes this approach highly attractive, especially for those targets for which compounds can be developed that bind to a given target without inhibiting its activity. Degradation of the target protein by PROTACs is also suitable for targets that overcome the effect of an inhibitor by overexpression, which is often seen in cancer. As such, targeted protein degradation offers tremendous promise. In fact, PROTACs have a number of advantages; because of their unique mechanism of action, a PROTAC molecule is capable of catalyzing the degradation of multiple molecules of the protein of interest. Consequently, compared with small-molecule inhibitors, PROTACs may require significantly lower concentrations to elicit a desired pharmacologic effect. PROTACs also have the potential to target so-called undruggable proteins, such as transcription factors. For example, STAT3 is a key factor for cell survival, proliferation, angiogenesis, metastasis, and chemotherapy resistance; thus, blocking STAT3 activity is an attractive strategy that has been pursued for many years, with little success.[10] However, PROTACs targeting STAT have been recently reported,[11,12] opening new possibilities.

PROTACs can be used to overcome drug resistance resulting from mutations of a protein of interest, such as PROTACs targeting mutated forms of BCR-ABL,[13] receptor tyrosine kinases,[14] estrogen receptor-α,[15] and Bruton tyrosine kinase.[16] PROTACs can overcome resistance to small-molecule inhibitors resulting from target upregulation by degrading the target; one such example is androgen receptor degraders, which have recently overcome resistance developed to the androgen receptor antagonist enzalutamide during prostate cancer treatment.[17]

Although the field of PROTAC research is still relatively new, these rapid exciting clinical developments, such as PROTAC-mediated targeting of androgen receptors, demonstrate proof of principle, proving that this approach is broadly applicable. Numerous proteins are now reported to have been degraded in this manner, including Bruton tyrosine kinase, BCR-Abl, FKBP12, BRD9, and CDK6.[18]

One of the most exciting and compelling aspects of unlocking the vast potential of protein degraders is the opportunity to bring the wide variety of the historically undruggable proteome into play for therapeutic benefit. In spite of these promising prospects, there are challenges in

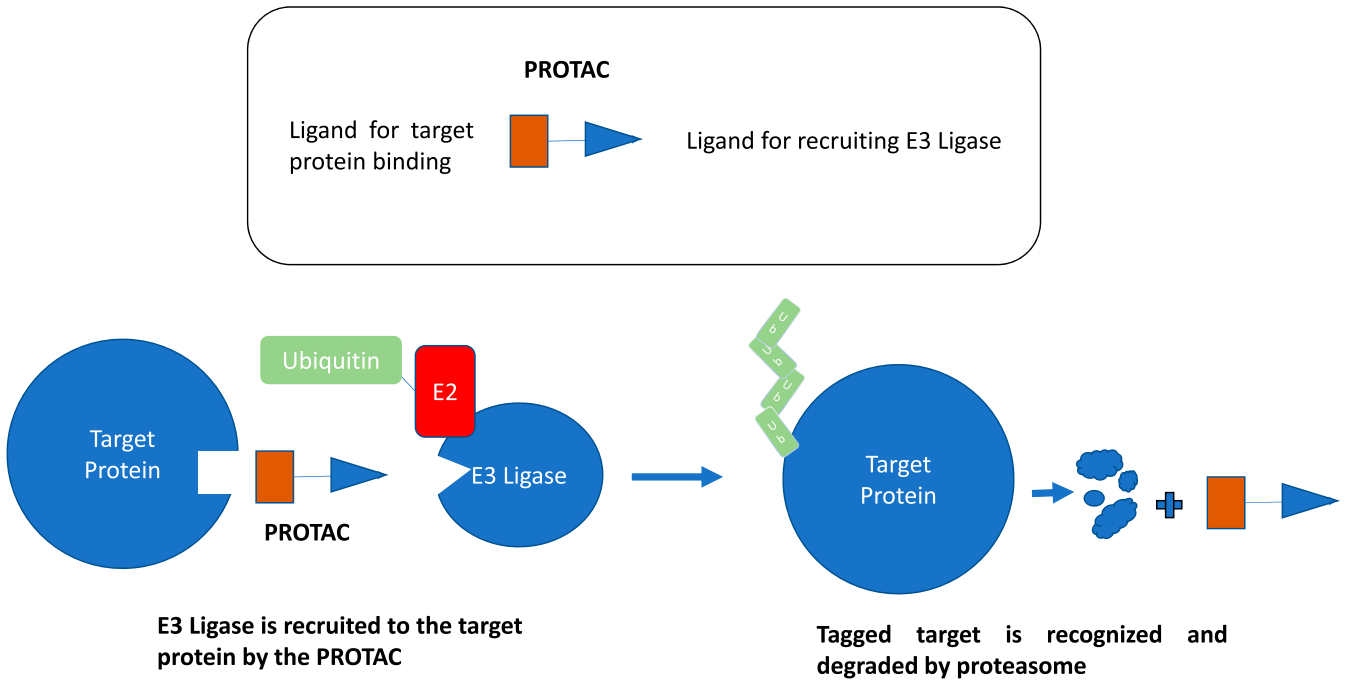

FIGURE 1. General Mechanism of Proteolysis-Targeting Chimera–Induced Degradation of the Protein of Interest
A proteolysis-targeting chimera molecule recruits an E3 ligase to a protein of interest, followed by polyubiquitin of the latter by an E2-conjugating enzyme. The polyubiquitinated protein of interest is recognized by the proteasome for its degradation. The proteolysis-targeting chimera molecule is recycled to induce the next round of degradation.

utilizing PROTAC molecules, such as attaining suitable physicochemical properties; adequate absorption, distribution, metabolism, and excretion properties for oral dosing; and/or even achieving adequate central nervous system exposure.[18] Therefore, overcoming some of these pharmacologic obstacles will undoubtedly be essential in paving the way for the broader therapeutic potential of PROTAC molecules.

Small Molecules Modulating Protein-Protein Interactions

Critical biologic processes, such as DNA replication, transcription, translation, and transmembrane signal transduction, rely on functional specific proteins that are regulated through protein complexes and controlled via PPIs[19,20]; aberrant PPIs are associated with many human cancers.[21] In contrast with small molecules targeting protein-ligand interactions (found in enzymes, ion channels, or receptors), targeting PPIs, previously regarded as undruggable targets, is a more challenging and novel therapeutic approach.[22]

Designing a small molecule to bind to a PPI interface has proven to be difficult for a number of reasons. First, the unique interface structure is a challenge for drug design: compared with the binding pockets of conventional protein targets, the interface of PPIs tends to be flat and contains few pockets, making it difficult for small-molecule compounds to bind.[23-25] The interface area of the interaction is also typically large, larger than that of the receptor-ligand contact area,[26,27] and is highly hydrophobic.[24,26] In addition, the amino acid residues involved in PPIs result in high-affinity binding between the proteins, making it more challenging for small molecular compounds to inhibit.[28] Compared with traditional drug target enzymes or receptors, PPIs also lack endogenous ligands,[28] and compared with traditional small-molecule drugs, drugs acting on PPIs have a higher molecular weight (> 400 daltons).

In spite of these obstacles, progress is being made. In recent years, some PPI modulators have entered clinical studies; some have been approved for marketing, indicating that the modulators targeting PPIs may have broad prospects. In comparison with peptides targeting PPIs, small-molecular inhibitors of PPIs are increasingly appealing, because these drugs tend to have lower research costs, oral preparations, and better tumor microenvironment penetration.

Inhibitors of MDM2/p53 interaction (small molecules, peptides) p53 regulates the cell cycle and functions as a tumor suppressor. Almost 50% of human cancers have alterations in the *TP53* gene, which results in the inactivation of p53 function or loss of p53 expression.[29] The MDM2 protein is the p53 E3 ubiquitin ligase that, under cellular stress conditions, ubiquitinates p53 and facilitates p53 nuclear export and inhibition of transcription activity or ubiquitin-dependent proteasomal degradation of p53.

Utilizing small molecules or peptides to block the p53/MDM2 interaction is one way to restore the p53 pathway in wild-type p53 tumors, thereby preventing the inactivation of p53. Nutlins are the most well-characterized small molecules that disrupt this p53-MDM2 interaction, binding to the N-terminal pocket of MDM2 and stabilizing p53, which helps to retain tumor-suppressive functionality. There is extensive in vitro and in vivo evidence to demonstrate that nutlins increase p53 levels and apoptosis, as well as decrease tumorigenicity.[30]

Building on this momentum, the nutlin derivative RG7112 has advanced to clinical trials for leukemia and sarcomas along with a number of other small molecules with similar mechanisms of action that are currently in phase I clinical trials, including SAR405838, CGM097, HDM201, DS-3032, MK-8242, and AMG232.[31-33] Thus, there is considerable clinical interest and activity focused on inhibiting p53-protein interactions using small molecules. Another target being modulated by the use of PPI is the interaction of MLL1 and menin. Once the crystal structure of menin was available, the binding site with MLL became clear; currently, drugs such as KO-539 show promising clinical activity in refractory acute myeloid leukemia.[34]

Other Approaches Using Small Molecules

An indirect approach to targeting challenging and difficult targets is the search for "synthetic"[35,36] and "collateral"[37] lethality scenarios. In synthetic lethality, cancer-specific mutations that impair the function of one gene (e.g., *BRCA1*) can be exploited with pharmacologic inhibition of another key component of the pathway (e.g., inhibiting PARP with olaparib), which would lead to the death of cancer cells with the genetic mutation but spare normal cells that lack the genetic vulnerability. In addition to the approval of many PARP inhibitors for the management of *BRCA1/2* ovarian and breast cancers, current clinical trials are exploring this paradigm by using these agents in tumors with alterations in other DNA-repair enzymes, such as *PALB2*, *ATM*, and *RAD51*. Synthetic lethality is also observed in tumors bearing mutations in the SWI/SNF chromatin remodeling complexes (e.g., SMARCA2, SMARCA4, ARID1A, and ARID1B); tazemetostat, an EZH2 inhibitor, has recently been approved by the U.S. Food and Drug Administration for the management of malignant rhabdoid tumors, a disease driven by SMARCA4 mutations.

The term "collateral lethality" is preferred to synthetic lethality when a "passenger" gene mutation (alteration not playing an active role in tumor progression) is lost along with an adjacent oncogenic or "driver" alteration (in our case, an undruggable tumor-suppressor gene). Using the lack of function of passenger-deleted genes for a therapeutic advantage could exploit cancer-selective vulnerabilities. Such is the case with *MTAP*, a gene that is frequently codeleted with CDKN2A (cyclin-dependent kinase inhibitor). MTAP-null cancer cells seem to have a dependency on PRMT5 (a methyltransferase); therefore, inhibition of PRMT5 could be exploited for cancer treatment. In fact, PRMT5 inhibitors are in clinical development.[38] Based on this hypothesis, MTAP/CDKN2A-null tumors could be sensitive to PRMT5 inhibitors while normal cells are spared, offering a wide therapeutic window. Other examples of this paradigm include the 1p36 deletion (which includes tumor-suppressor genes, such as CAMTA1, mir34A, or KIF1B), the passengers enolase 1 or 6-phosphogluconate dehydrogenase, and the therapeutic inhibition of enolase 2 or components of the nonoxidative pentose phosphate shunt.[39]

Another way to modulate an undruggable protein with small molecules is to modulate its transcription levels: either indirectly, by targeting chromatin regulation, or directly, by the targeting of transcription factors or RNA that regulates its expression. There are ongoing drug-discovery efforts focusing on small-molecule drugs targeting transcription factors, such as P53, MYC, and STAT3. These transcription factors, which are frequently altered in cancer, form protein complexes that are directed to specific sites on DNA and regulate oncogenic events. Small molecules interacting with MYC, STAT3, or P53 are in development. These agents mostly aim to prevent the formation of these multiprotein complexes, rather than to disrupt the transcription factor–DNA interaction.[2]

Targeting chromatin regulation, the main goal of epigenetics, has also seen tremendous development with the expansion of technologies that allow analysis of the epigenome and drug discovery now aiming for new targets, such as EZH2, LSD1, PRMT inhibitors, and others. However, the field of epigenetics drug development is beyond the scope of this review and can be found elsewhere.[40]

There is a conventional view that it is not possible to bind RNAs with small molecules because they present unrelated structures and complex pockets for druggability (RNA interference–based therapeutics are discussed in the next section). However, it has since been discovered that RNA molecules actually adopt secondary and tertiary structures that could be attractive targets for small molecules. In fact, many drugs, including several antibiotics (e.g., aminoglycosides) bind bacterial RNA in the ribosomes. This field changed in 2020, when the U.S. Food and Drug Administration approved risdiplam, an SMN2-splicing modifier, to treat spinal muscular atrophy. This is the first drug designed specifically against a particular messenger RNA (it modifies the splicing of SMN2 messenger RNA, resulting in an increase in the concentration of the functional SMN protein in vivo).[41] The development of anticancer small molecules that specifically bind RNA, although still in its early stages, aims to design similar small-molecule RNA modulators that

bind RNA molecules and change protein synthesis by modifying RNA processing (RNA splicing) or impeding protein production.[42]

NEW BIOLOGICS CAN ALSO ENABLE THE IMPOSSIBLE

Despite efforts to modulate RNA and protein expression with small molecules, described above, biologic molecules, such as antisense technologies, have remained the most commonly deployed method to target disease-associated RNAs. First-generation oligonucleotide structures had poor cell permeability and distribution and triggered immunoreactivity; as a result of their poor pharmacology, their development languished for years. Now, these initial problems of RNA therapeutics have been addressed with improvements in trigger design, sequence selection (to avoid unintended off-target RNA interference effects), chemical formulation (to avoid degradation by endonucleases and exonucleases), and delivery mechanisms (lipid nanoparticles and others), enabling a second generation of drugs. Consequently, in 2018, the U.S. Food and Drug Administration approved patisiran, a small interfering RNA for the treatment of hereditary transthyretin amyloidosis with polyneuropathy. Since then, two more drugs of this kind, lumasiran and givosiran, have been approved. Patisiran, which primarily acts on the liver, is not a metabolically stabilized small interfering RNA, but it uses a lipid nanoparticle delivery formulation. More recently, small interfering RNA therapeutics have been metabolically stabilized to improve their stability.

However, not all RNA transcripts transmit a message for protein coding and translation, but there is a diverse range of noncoding RNA molecules (e.g., long noncoding RNAs, microRNAs, small nuclear and small nucleolar RNAs) with broad roles in modulating gene expression, including cancer deregulation. Because of recent developments in the field, RNA therapeutics are not limited to antisense oligonucleotides; investigators are exploring small interfering RNA, microRNA, messenger RNA, RNA aptamers, short activating RNA, and single guide RNA for CRISPR/Cas9 systems as potential therapeutic platforms. Some of these novel RNA therapeutics are also aiming for some undruggable targets that are relevant in cancer, such as EWS/FLI1 (Ewing sarcoma), *KRAS* G12D (pancreatic cancer), miR-155 (lymphoma and leukemias), and miR-16 (malignant pleural mesothelioma and non–small cell lung cancer).

One final approach using biologics to target complicated intracellular targets involves the TCR-HLA (human leukocyte antigen) system. The target, processed in the immunoproteasome, is broken into different peptides that are presented by the tumor cell's HLA system to the immune system via the TCR; this interaction activates the immune system against the tumor cell. Antigens that can be leveraged for this approach include those arising from cancer mutations (e.g., in otherwise undruggable proteins), known as neoantigens, and tumor-associated antigens, which result from overexpressed genes. This principle, which is the basis for modern cell therapy (e.g., CAR T cells, engineered TCR therapy) is now also being replicated by different types of peptides (TCR "mimetics")[43]: TCR-like antibodies and TCR fusion proteins. These TCR mimetics are advantageous in that they can have more drug-like properties and avoid some of the limitations of traditional cell therapies (e.g., prolonged and expensive production times, cost). In addition to CD19, which was the first target for leukemias (tisagenlecleucel, the first CAR T-cell therapy was approved for acute lymphoblastic leukemia in 2017[44]), in solid tumors, initial research with cell therapy and TCR mimetics initially focused on tumor-associated antigens, such as GP100, MAGEA4, NYESO1, and PRAME; the first generation of studies is ongoing. Theoretically, neoantigen-specific CAR T cells or TCR mimetics (antibodies or soluble TCRs) that are specific for the peptide–major histocompatibility complex could be a promising strategy to tackle repetitive mutated variants in undruggables, such as fusion peptides in sarcoma (breakpoint-specific neoantigens have been predicted and validated, in part, for EWSR1-FLI1, PAX3-FOXO1, and SS18-SSX1)[45,46] or *KRAS* in pancreatic cancer.[47]

The clinical proof of concept for cell therapy came from targeting CD19.[48] For TCR mimetics, this has likely been achieved with the recently presented data on tebentafusp (IMCgp100) that showed clinical benefit, including target lesion reduction.[49] Tebentafusp is a solution of soluble TCRs stabilized by a disulfide bond and fused to an anti-CD3 scFv (a so-called "ImmTAC molecule"). Early data from a phase II trial in patients with HLA-A*0201$^+$ gp100$^+$ metastatic uveal melanoma showed that, although the overall response rate by response evaluation criteria in solid tumors was low (5%), it was accompanied by a reduction in target lesion in 44% of patients. The median overall survival was 16.8 months (95% CI, 12.9–21.3), which seems promising compared with historical controls.[50]

CONCLUSION

There is considerable excitement surrounding the development of cancer targets considered undruggable, with classic classes of agents, including transcription factors, such as STAT3, TP53, MYC. Others, like *RAS* (*KRAS* G12C and *HRAS*), HIF-2α, BCL-2, MDM2, and MLL, are now validated druggable targets.

Because of the possibility that many other pharmacologic barriers might be overcome by the new entities described here, the concept of undruggable is being challenged, and some now consider it an inappropriate or démodé term. In the presence of novel molecular entities that promise to

become game changers, some advocate for using terms such as "undrugged," "difficult-to-drug targets," or "targets with developability challenges" rather than undruggable. Time, and the efforts of a new generation of drug developers, will tell.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_325885.

REFERENCES

1. Abi Hussein H, Geneix C, Petitjean M, et al. Global vision of druggability issues: applications and perspectives. Drug Discov Today. 2017;22:404-415.
2. Lazo JS, Sharlow ER. Drugging undruggable molecular cancer targets. Annu Rev Pharmacol Toxicol. 2016;56:23-40.
3. Martin-Liberal J, Hierro C, Ochoa de Olza M, et al. Immuno-oncology: the third paradigm in early drug development. Target Oncol. 2017;12:125-138.
4. DeGoey DA, Chen HJ, Cox PB, et al. Beyond the rule of 5: lessons learned from AbbVie's Drugs and Compound Collection. J Med Chem. 2018;61:2636-2651.
5. Mullard A. Pioneering apoptosis-targeted cancer drug poised for FDA approval [published correction appears in *Nat Rev Drug Discov*. 2016;15:292]. Nat Rev Drug Discov. 2016;15:147-149.
6. Hong DS, Fakih MG, Strickler JH, et al. KRAS^{G12C} inhibition with sotorasib in advanced solid tumors. N Engl J Med. 2020;383:1207-1217.
7. Ho AL, Hanna GJ, Scholz CR, et al. Preliminary activity of tipifarnib in tumors of the head and neck, salivary gland and urothelial tract with HRAS mutations. J Clin Oncol. 2020;38(15_suppl):6504.
8. Jonasch E, Donskov F, Iliopoulos O, et al. Phase II study of the oral HIF-2α inhibitor MK-6482 for von Hippel-Lindau disease–associated renal cell carcinoma. J Clin Oncol. 2020;38(15_suppl):5003.
9. Lai AC, Crews CM. Induced protein degradation: an emerging drug discovery paradigm. Nat Rev Drug Discov. 2017;16:101-114.
10. Redell MS. A STAT3 decoy lures AML out of hiding. Blood. 2016;127:1628-1629.
11. Bai L, Zhou H, Xu R, et al. A potent and selective small-molecule degrader of STAT3 achieves complete tumor regression in vivo. Cancer Cell. 2019;36:498-511.e17.
12. Zhou H, Bai L, Xu R, et al. Structure-based discovery of SD-36 as a potent, selective, and efficacious PROTAC degrader of STAT3 protein. J Med Chem. 2019;62:11280-11300.
13. Zhao Q, Ren C, Liu L, et al. Discovery of SIAIS178 as an effective BCR-ABL degrader by recruiting von Hippel-Lindau (VHL) E3 ubiquitin ligase. J Med Chem. 2019;62:9281-9298.
14. Deng J. How to unleash mitochondrial apoptotic blockades to kill cancers? Acta Pharm Sin B. 2017;7:18-26.
15. Gonzalez TL, Hancock M, Sun S, et al. Targeted degradation of activating estrogen receptor α ligand-binding domain mutations in human breast cancer [published correction appears in *Breast Cancer Res Treat*. 2020;180:623]. Breast Cancer Res Treat. 2020;180:611-622.
16. Buhimschi AD, Armstrong HA, Toure M, et al. Targeting the C481S ibrutinib-resistance mutation in Bruton's tyrosine kinase using PROTAC-mediated degradation. Biochemistry. 2018;57:3564-3575.
17. Kregel S, Wang C, Han X, et al. Androgen receptor degraders overcome common resistance mechanisms developed during prostate cancer treatment. Neoplasia. 2020;22:111-119.
18. Chamberlain PP, Hamann LG. Development of targeted protein degradation therapeutics. Nat Chem Biol. 2019;15:937-944.
19. Rual JF, Venkatesan K, Hao T, et al. Towards a proteome-scale map of the human protein-protein interaction network. Nature. 2005;437:1173-1178.
20. Stelzl U, Worm U, Lalowski M, et al. A human protein-protein interaction network: a resource for annotating the proteome. Cell. 2005;122:957-968.
21. Nero TL, Morton CJ, Holien JK, et al. Oncogenic protein interfaces: small molecules, big challenges. Nat Rev Cancer. 2014;14:248-262.
22. Santos R, Ursu O, Gaulton A, et al. A comprehensive map of molecular drug targets. Nat Rev Drug Discov. 2017;16:19-34.

23. Buchwald P. Small-molecule protein-protein interaction inhibitors: therapeutic potential in light of molecular size, chemical space, and ligand binding efficiency considerations. IUBMB Life. 2010;62:724-731.
24. Arkin MR, Wells JA. Small-molecule inhibitors of protein-protein interactions: progressing towards the dream. Nat Rev Drug Discov. 2004;3:301-317.
25. Díaz-Eufracio BI, Naveja JJ, Medina-Franco JL. Protein–protein Interaction Modulators for Epigenetic Therapies. In Donev R, (ed). Advances in Protein Chemistry and Structural Biology. Cambridge, MA: Academic Press; 2018;65-84.
26. Smith MC, Gestwicki JE. Features of protein-protein interactions that translate into potent inhibitors: topology, surface area and affinity. Expert Rev Mol Med. 2012;14:e16.
27. Cheng AC, Coleman RG, Smyth KT, et al. Structure-based maximal affinity model predicts small-molecule druggability. Nat Biotechnol. 2007;25:71-75.
28. Ivanov AA, Khuri FR, Fu H. Targeting protein-protein interactions as an anticancer strategy. Trends Pharmacol Sci. 2013;34:393-400.
29. Feki A, Irminger-Finger I. Mutational spectrum of p53 mutations in primary breast and ovarian tumors. Crit Rev Oncol Hematol. 2004;52:103-116.
30. Vassilev LT, Vu BT, Graves B, et al. In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. Science. 2004;303:844-848.
31. Sun D, Li Z, Rew Y, et al. Discovery of AMG 232, a potent, selective, and orally bioavailable MDM2-p53 inhibitor in clinical development. J Med Chem. 2014; 57:1454-1472.
32. Zhao Y, Bernard D, Wang S. Small molecule inhibitors of MDM2-p53 and MDMX-p53 interactions as new cancer therapeutics. BioDiscovery. 2013;8:4.
33. Wang S, Sun W, Zhao Y, et al. SAR405838: an optimized inhibitor of MDM2-p53 interaction that induces complete and durable tumor regression. Cancer Res. 2014;74:5855-5865.
34. Wang ES, Altmann JK, Pettit K, et al. Preliminary data on a phase 1/2A first in human study of the menin-KMT2A (MLL) inhibitor KO-539 in patients with relapsed or refractory acute myeloid leukemia. Blood. 2020;136(suppl 1):7-8.
35. Hartwell LH, Szankasi P, Roberts CJ, et al. Integrating genetic approaches into the discovery of anticancer drugs. Science. 1997;278:1064-1068.
36. Kaelin WG Jr. Choosing anticancer drug targets in the postgenomic era. J Clin Invest. 1999;104:1503-1506.
37. Muller FL, Aquilanti EA, DePinho RA. Collateral lethality: a new therapeutic strategy in oncology. Trends Cancer. 2015;1:161-173.
38. Rugo HS, Jacobs I, Sharma S, et al. The promise for histone methyltransferase inhibitors for epigenetic therapy in clinical oncology: a narrative review. Adv Ther. 2020;37:3059-3082.
39. Garbers C, Hermanns HM, Schaper F, et al. Plasticity and cross-talk of interleukin 6-type cytokines. Cytokine Growth Factor Rev. 2012;23:85-97.
40. Cheng Y, He C, Wang M, et al. Targeting epigenetic regulators for cancer therapy: mechanisms and advances in clinical trials. Signal Transduct Target Ther. 2019;4:62.
41. Ratni H, Ebeling M, Baird J, et al. Discovery of risdiplam, a selective survival of motor neuron-2 (SMN2) gene splicing modifier for the treatment of spinal muscular atrophy (SMA). J Med Chem. 2018;61:6501-6517.
42. Costales MG, Hoch DG, Abegg D, et al. A designed small molecule inhibitor of a non-coding RNA sensitizes HER2 negative cancers to herceptin. J Am Chem Soc. 2019;141:2960-2974.
43. Chang AY, Dao T, Gejman RS, et al. A therapeutic T cell receptor mimic antibody targets tumor-associated PRAME peptide/HLA-I antigens. J Clin Invest. 2017; 127:2705-2718.
44. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378:439-448.
45. Worley BS, van den Broeke LT, Goletz TJ, et al. Antigenicity of fusion proteins from sarcoma-associated chromosomal translocations. Cancer Res. 2001; 61:6868-6875.
46. Chang TC, Carter RA, Li Y, et al. The neoepitope landscape in pediatric cancers. Genome Med. 2017;9:78.
47. Sim MJW, Lu J, Spencer M, et al. High-affinity oligoclonal TCRs define effective adoptive T cell therapy targeting mutant KRAS-G12D [published correction appears in *Proc Natl Acad Sci USA*. 2020;117:27743-27744]. Proc Natl Acad Sci USA. 2020;117:12826-12835.
48. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371:1507-1517.
49. Sacco JJ, Carvajal R, Butler MO, et al. 64MO A phase (ph) II, multi-center study of the safety and efficacy of tebentafusp (tebe) (IMCgp100) in patients (pts) with metastatic uveal melanoma (mUM). Ann Oncol. 2020;31:S1442-S1443.
50. Sato T, Nathan PD, Hernandez-Aya L, et al. Redirected T cell lysis in patients with metastatic uveal melanoma with gp100-directed TCR IMCgp100: overall survival findings. J Clin Oncol. 2018;36(15_suppl):9521.

GASTROINTESTINAL CANCER—COLORECTAL AND ANAL

Colorectal Cancer: In the Pursuit of Health Equity

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Overview

Colorectal cancer mortality has decreased considerably following the adoption of national screening programs, yet, within at-risk subgroups, there continue to be measurable differences in clinical outcomes from variations in screening, receipt of chemotherapy, radiation or surgery, access to clinical trials, research participation, and survivorship. These disparities are well-described and some have worsened over time. Disparities identified have included race and ethnicity, age (specifically young adults), socioeconomic status, insurance access, geography, and environmental exposures. In the context of the COVID-19 pandemic, colorectal cancer care has necessarily shifted dramatically, with broad, immediate uptake of telemedicine, transition to oral medications when feasible, and considerations for sequence of treatment. However, it has additionally marginalized patients with colorectal cancer with historically disparate cancer-specific outcomes; among them, uninsured, low-income, immigrant, and ethnic-minority patients—all of whom are more likely to become infected, be hospitalized, and die of either COVID-19 or colorectal cancer. Herein, we outline measurable disparities, review implemented solutions, and define strategies toward ensuring that all have a fair and just opportunity to be as healthy as possible.

DEFINING HEALTH EQUITY IN COLORECTAL CANCER

Colorectal cancer (CRC) mortality has dropped by 50% over the last 30 years, but with measurable differences in at-risk subgroups. Over time, the World Health Organization International Agency for Research on Cancer and the U.S. National Cancer Institute Surveillance, Epidemiology, and End Results programs have highlighted that variations in screening, access to treatment, participation in clinical trials, stage at diagnosis, morbidity, and mortality exist. Disparate cancer outcomes have been identified in subgroups classified by race and ethnicity, age (specifically young adults), socioeconomic status, insurance access, geography, environmental exposures, and others. The World Health Organization defines health equity as "the absence of unfair and unavoidable or remediable differences in health among population groups defined socially, economically, demographically, or geographically" whereas ASCO describes it as everyone having a fair and just opportunity to be as healthy as possible.[1,2] Its deterrent, cancer disparities, have persisted and, in some areas, worsened over time. Although disenfranchised subgroups in the CRC care continuum have been well described, contextualizing cancer care disparities in the context of a global pandemic highlights additional areas of concern toward our goal of improving equitable access to high-quality CRC care and the necessary research conducted to better inform and define the future of CRC care.

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CANCER AND THE COVID-19 PANDEMIC

As the world surpasses a year since the COVID-19 pandemic began at the time of this publication, the pandemic has led to over 2 million lives lost; new, more infectious genetic variants of SARS-CoV-2 have emerged; and mounting evidence suggests it will be an endemic virus that will continue to shape health care delivery for the foreseeable future. In the United States, over 450,000 deaths have been documented, 11% of households reported they did not have enough food in the past week, and 9.4 million jobs lost in the beginning of the pandemic have not been recovered as of January 2021.[3]

In this context, health care delivery along the cancer care continuum has suffered globally. Screening for early-stage curable cancers has declined or been halted in some countries, as "elective procedures" that assist with diagnosis have been suspended in many areas. Clinical trials have been arrested.[4] Expected new patient volumes have dwindled with concerns that they will reemerge later at more advanced disease stages.

Early and more recent reports have shown that patients with cancer are more likely to become infected and are at high risk for severe clinical events, defined as a need for ventilation, admission to an intensive care unit, or death.[5-7] Additionally, patients receiving active treatment, including chemotherapy or immunotherapy, are at higher risk for adverse outcomes.[8] An initial report of hospitalized patients from Wuhan, China, suggested that up to 40% of infections were acquired in the health care setting.[9] Together, cancer care during the pandemic has focused on patient susceptibility for infection and exposure in the health care settings. These efforts have included the immediate, vast uptake of

PRACTICAL APPLICATIONS

- Health disparities in colorectal cancer are measurable, rising over time, and exacerbated by the COVID-19 pandemic.
- Redesigning colorectal cancer care delivery paradigms should focus on just access to high-quality care and access to research, both of which are necessary to achieve health equity.
- Implementing evidence-based adaptable interventions should be predicated on community engagement, representation, measurable outcomes, and success metrics.

virtual health; integrating surveillance SARS-CoV-2 testing for patients receiving active treatment; prioritizing oral treatment regimens; and limiting patient visitors in both the outpatient and inpatient settings, often to zero.[10]

COVID-19 PANDEMIC EFFECTS ON COLORECTAL CANCER CARE DELIVERY

There is mounting evidence that the COVID-19 pandemic has had negative effects on CRC care. Morris et al[11] extracted data from four population-based data sets spanning the National Health Service in England between January 2019 and October 2020. Compared with 2019, in 2020, there was a 63% reduction in monthly referrals for suspected cancer, a 92% reduction in colonoscopies, and a 31% relative reduction in patients receiving surgery.[11] Among patients receiving surgery, fewer underwent laparoscopic procedures and more presented from emergency admissions, elevating concerns about delayed care resulting in a stage shift at diagnosis. These findings highlight a sustained decrease in the number of people referred, diagnosed, and treated for CRC and a dramatic shift in treatment paradigms among patients who were treated.

Survival in CRC is highly associated with stage at diagnosis. It is anticipated that this rate-limiting step in the CRC diagnostic equation will have far-reaching effects on CRC outcomes. Modeling the effects of COVID-19 on cancer screening and management of breast cancer and CRC suggests an excess of 10,000 deaths over the next decade, which does not take into account additional morbidity from advanced-stage diagnosis and assumes the disruption in cancer care was limited to only 6 months during the pandemic.[12]

COVID-19 HEALTH DISPARITIES MIRROR AND EXACERBATE COLORECTAL CANCER DISPARITIES

Although the COVID-19 pandemic has unquestionably disrupted the CRC care delivery paradigm, it has also disproportionately affected subgroups of patients with CRC who are already known to have disparate outcomes. Black patients, Hispanic patients, patients residing in rural areas, and those without health insurance are more likely to be infected with SARS-CoV-2[13,14] and are at higher risk for severe illness from COVID-19. These subgroups are more likely to have comorbidities such as diabetes, obesity, hypertension, and kidney disease—all of which place patients at higher risk for COVID-19–related complications and have been strongly linked to adverse cancer treatment outcomes, including more aggressive disease biology, poor cancer surgery outcomes, radiation toxicity, an inability to receive systemic therapies, and worse overall survival.

Evidence linking CRC disparities to those observed in COVID-19 are most robust in Black patients. It is well known that Black patients fare worse in multiple phases of the CRC care continuum—they are less likely to be screened with colonoscopy,[15] are more likely to present with late disease stages, and have lower 5-year rates of survival following a diagnosis despite adjustments for disease stage at presentation.[16] Simultaneously, in financial surveys gauging the impact of the COVID-19 pandemic, Black populations are more likely to have someone in their households who have lost a job or taken a pay cut because of the coronavirus outbreak. These systemic disadvantages rooted in historical infrastructure are exacerbated by the pandemic.[3] Indeed, they highlight a need to not only address the sequelae of COVID-19 on our communities, but also its anticipated effects on accessing services for CRC prevention and care.

SCREENING LEADS TO PREVENTION AND EARLY DETECTION OF COLORECTAL CANCER

Colorectal cancer screening reduces both CRC incidence and CRC-related mortality by identifying precancerous and cancerous lesions in the colon and rectum, but is not widely used or available globally.[17,18] High incidence of CRC, as well as data from the National Polyp Study[19,20] and randomized trials investigating screening effectiveness,[21-36] have promoted a population approach to CRC prevention and early detection. Implementation of screening programs is not universal, however, with poor access to screening tests in low- and middle-income countries and inequities in screening utilization within many countries that endorse its use.[18]

ACCESS TO COLORECTAL CANCER SCREENING VARIES GLOBALLY

Colorectal cancer screening was pioneered in the United States but has become well established in many parts of the world, including Canada, Europe, and Asia, over the past 4 decades. National strategies include both organized screening programs and opportunistic screening efforts.[18] Few low- and middle-income countries have nationwide population-based programs or activities toward CRC prevention, mostly as a consequence of limited resources and

a lack of diagnostic services and cancer care that screening generates. Many low- and middle-income countries that have launched pilot programs to introduce screening have done so with support from the World Health Organization, International Agency for Research on Cancer, or other research-focused agencies, or in partnership with researchers or advocates from high-income countries.[18]

COLORECTAL CANCER SCREENING GUIDELINES AND MODALITIES IN THE UNITED STATES

In the United States, CRC screening began in the late 1980s and has contributed to an over 50% reduction in CRC-related mortality.[16,17,37] CRC screening has also been shown to be cost-effective.[38] Current national guidelines recommend that average-risk individuals begin routine screening at age 45 (American Cancer Society)[39] or age 50 (U.S. Preventive Services Task Force)[36] and continue screening until at least age 75. Screening may be extended to age 85 on an individual basis, based on health status and prior screening history.[36] The U.S. Preventive Services Task Force recommends screening with one of seven screening strategies that aim to either detect colon and rectal polyps before they progress into malignancies or to detect cancers at an early stage when there are favorable treatment options and higher survival rates. These strategies include the following: (1) colonoscopy every 10 years; (2) annual fecal immunochemical testing (FIT); (3) annual high-sensitivity fecal occult blood testing; (4) stool DNA-FIT testing every 3 years; (5) flexible sigmoidoscopy every 5 years; (6) flexible sigmoidoscopy every 10 years with FIT every year; and (7) CT colonography (virtual colonoscopy) every 5 years.[36] Of these, colonoscopy is the most common screening method in the United States, followed by FIT.[40] When a non-colonoscopic screening modality is used and the result is abnormal, colonoscopy is recommended to complete the screening process.[36] Individuals at increased risk for CRC (e.g., family history of CRC or colorectal polyps, or personal history of inflammatory bowel disease) should initiate screening before age 50 with colonoscopy.[36] Several novel screening modalities are currently under active development and evaluation, including blood-based biomarker tests, colon capsule endoscopy, and other noninvasive and imaging modalities.[41,42]

SCREENING UTILIZATION AND SCREENING DISPARITIES IN THE UNITED STATES

Despite strong effectiveness data supporting screening and national guidelines, screening utilization is suboptimal in the United States. Estimates from Behavioral Risk Factor Surveillance System data (Centers for Disease Control and Prevention) show that 68.8% of Americans age 50 to 75 were up-to-date with CRC screening in 2018.[43] Furthermore, screening rates vary considerably by race, ethnicity, and socioeconomic status in the United States. Rates are highest among White Americans (71.1%) and lowest among Hispanic Americans (56.1%). Black Americans (70.1%), American Indian/Native Americans (62.1%), and Asian Americans/Pacific Islanders (64.8%) also have rates lower than rates for White Americans.[43]

Differences in screening utilization by race and ethnicity are at least partially explained by differences in socioeconomic status.[44] However, it is the overall impact of adverse social determinants of health—recognized as barriers to care at the patient, provider, health system, and policy levels—that have led to disparities in uptake of CRC screening.[45] Social determinants of health include upstream governmental policies, environmental factors, and social-structural influences on health and health systems that disproportionately negatively impact marginalized communities and determine downstream health outcomes. The effect of these political, environmental, and social factors on screening utilization is underscored in data demonstrating that lack of participation in CRC screening is associated with low household income, rural residence, lack of health insurance, lack of a regular health care provider, and low educational attainment (Fig. 1).[43,46,47]

Patient-level barriers to screening in medically underserved populations also include lack of knowledge of CRC risk and the importance of screening, medical distrust, language barriers, and competing health demands.[15,45,48-50] Barriers to screening are not limited to patients, however, as lack of a provider recommendation for screening is highly associated with lack of screening uptake and occurs more frequently among patients from racial and ethnic minority populations.[45,51,52] Health policy and health system factors such as insurance coverage for preventive services and reimbursement policy also impact uptake of screening in medically underserved communities.[45,48,49] Lack of a true organized screening program in the United States and near reliance on opportunistic screening are felt to contribute to low screening rates and screening disparities (Table 1).[45]

INTERVENTIONS TO INCREASE OVERALL SCREENING RATES AND ADDRESS SCREENING DISPARITIES

Increasing uptake of CRC screening overall and in medically underserved communities has been a major focus in the United States. The implementation of the Affordable Care Act, Medicaid expansion, and increased use of noninvasive screening technologies like FIT have reduced barriers to screening and improved access in health care settings that provide care for ethnic and racial minorities.[46,53-56] There have also been targeted efforts to increase screening uptake, the most effective of which are multilevel interventions that address patient, provider, health system, and policy barriers to screening and increase access to and acceptance of screening tests.[57-59]

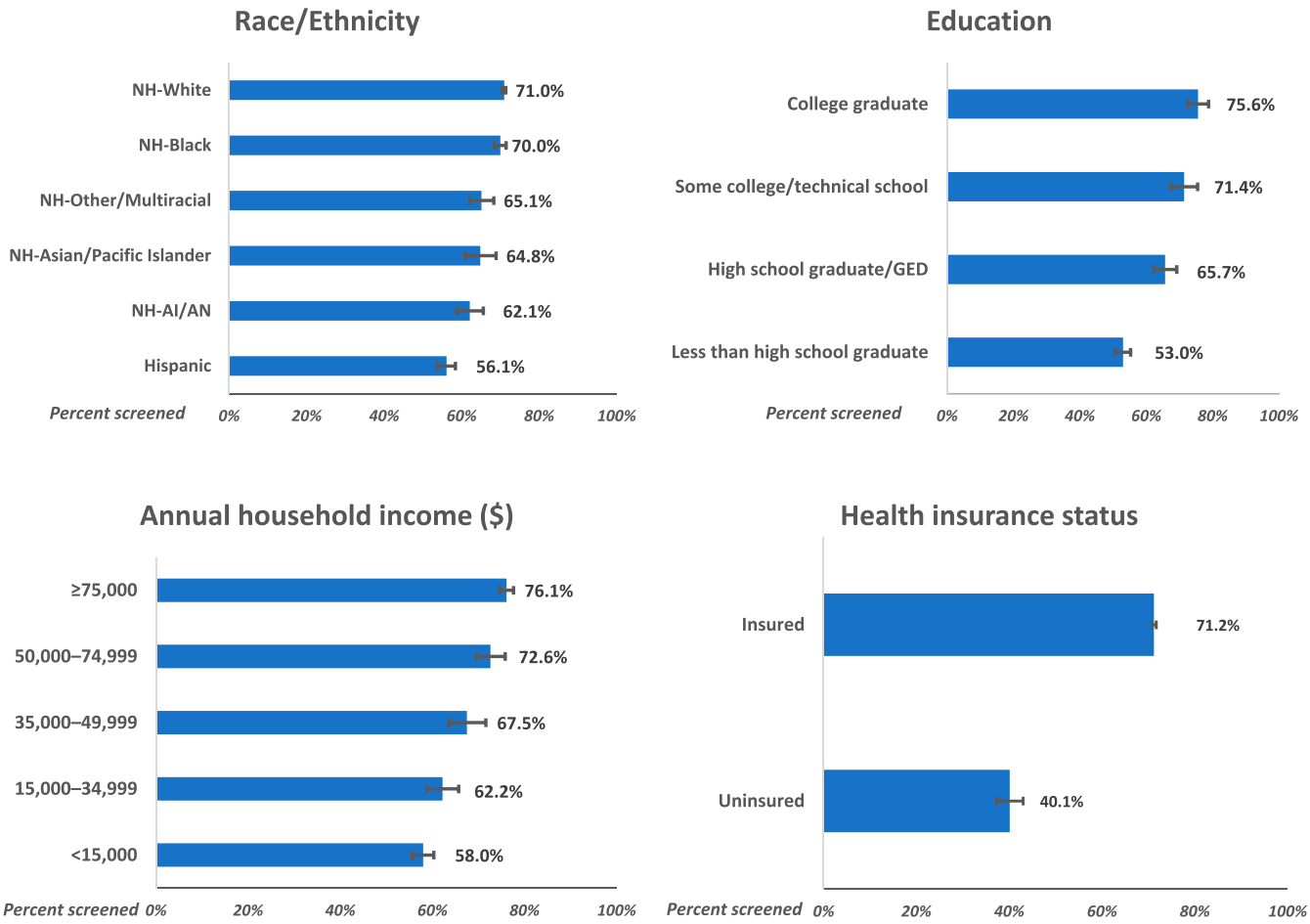

FIGURE 1. U.S. Colorectal Cancer Screening Rates by Race/Ethnicity, Socioeconomic Status, and Health Insurance Status; Behavioral Risk Factor Surveillance System, 2018[43]

Abbreviations: AI, American Indian; AN, Alaskan Native; GED, general educational diploma; NH, non-Hispanic.

Offering patients both invasive (i.e., colonoscopy) and noninvasive (i.e., FIT) screening modalities and engaging patients in shared decision-making can help address patient hesitancy and increase screening uptake. Noninvasive, stool-based screening tools like FIT and other stool-based screening tests are low-cost, highly accessible in health care settings in which there is no access to colonoscopy, and often more acceptable among racial and ethnic minorities.[60,61] Other effective strategies in diverse patient populations include patient navigation, decision aids, provider and patient reminders, and mailed FIT programs.[45,62] Above all, health systems that provide care for medically underserved populations must have the institutional support to prioritize CRC screening, including infrastructures to facilitate the identification and tracking of patients overdue for screening and to measure screening rates.

Government agencies, national organizations, and medical societies have played an essential role in raising awareness about CRC risk and screening and encouraging screening participation in the United States. Healthy People 2020 (U.S. Department of Health and Human Services) and the National Colorectal Cancer Roundtable (cofounded by the American Cancer Society and the Centers for Disease Control and Prevention) set goals in 2010 and 2014, respectively, to screen at least 70.5% (Healthy People 2020) and 80% (National Colorectal Cancer Roundtable) of adults age 50 to 75.[63,64] From 2010 to 2018, the national screening rate increased from 65.4% to 68.8%, with some reduction in racial/ethnic and socioeconomic status disparities.[43,46,65] Recognizing that not all patient populations benefit equally from screening technologies, the National Colorectal Cancer Roundtable announced a transition to the "80% in Every Community" campaign in 2018.[66] This campaign recognizes that to realize the full potential of CRC screening to reduce morbidity and mortality in the United States, we must address low screening participation in populations with suboptimal rates and the most unfavorable CRC outcomes.

TABLE 1. Barriers to Colorectal Cancer Screening in Medically Underserved Communities[15,45,48-51]

Patient Factors	Provider Factors	Health System Factors	Policy Factors
Knowledge of CRC risk	Knowledge of guidelines	Practice setting	Screening guidelines
Attitudes toward screening	Beliefs about screening effectiveness	Access to specialty care	Insurance policy
Beliefs about screening	Counseling practices	Colonoscopy capacity	Reimbursement policy
Perceived risk of CRC	Lack of recommendation	Reminder systems	Financial barriers to care
Perceived benefits of screening	Bias and discrimination	Care coordination	
Health literacy	Time constraints		
Language	Perceived need		
Fear of colonoscopy	Referral practices		
Fear of a cancer diagnosis	Lack of support		
Cost/copay			
Distrust in medicine/science			
Family history			
Competing demands (medical, other)			
Lack of transportation or escort for colonoscopy			

Abbreviation: CRC, colorectal cancer.

DISPARITIES IN COLORECTAL CANCER

Although an estimated 149,500 people will be diagnosed with CRC in 2021, it is well recognized that the overall death rate has declined. Yet, CRC is the third most common cause of cancer death identified in men and women in the United States, and is second in overall mortality when men and women are combined.[40] As of 2018, the mortality rate for CRC had decreased by 53% among men since 1990 and by 30% in women since 1969. However, CRC incidence and mortality rates as well as outcomes vary between racial and ethnic minority groups. Among the five patient groups from whom data are routinely collected—non-Hispanic White, non-Hispanic Black, Hispanic, Asian/Pacific Islander, and American Indian/Alaskan Native—mortality rates are highest in non-Hispanic Black patients, followed by American Indian/Alaskan Native patients, and lowest in Asian/Pacific Islander patients.[40] During the period of 2012 through 2016, incidence rates in non-Hispanic Black patients accounted for 45.7 per 100,000 population and were approximately 20% higher than non-Hispanic White patients at 38.6 per 100,000 population and 50% higher than the rates of Asian/Pacific Islander patients at 30.0 per 100,000 population. For mortality, however, the magnitude of the disparity was even greater and is double that of incidence rate. During the period of 2013 through 2017, CRC death rates in non-Hispanic Black patients (19.0 per 100,000 population) were nearly 40% higher than those in non-Hispanic White patients (13.8 per 100,000) and twice that of Asian/Pacific Islander patients (9.5 per 100,000 population).[67]

Reasons for the disparities identified, such as the higher incidence and mortality rates in non-Hispanic Black patients, have been attributed to multiple complex socioeconomic and social determinants of health, such as low median family income, with the non-Hispanic Black population median family income being $41,361 compared with the non-Hispanic White population income of $70,642 during 2018. During the same period, 21% of non-Hispanic Black and 8% of non-Hispanic White populations were living in poverty.[45] Other factors include a higher prevalence of risk factors, including smoking and obesity, and lower rates of screening and likelihood of timely follow-up on a positive stool-based screening test and a quality colonoscopy.[67]

Additionally, non-Hispanic Black patients experience higher inequities in comorbidities that may limit therapeutic interventions. Moreover, tumor characteristics such as location of tumors within the colon or rectum, grade, and histology may be contributing factors to treatment response and thus overall mortality.[67]

The high incidence and mortality rate in the Alaskan Native population of 89 per 100,000 population and 40 per 100,000 population, respectively, are double the rates of the non-Hispanic Black population. Contributing factors may include diets with higher levels of fats and lower consumption of fruits, vegetables, and vitamin D, coupled with smoking, obesity, diabetes,[68,6970] and a high prevalence of *Helicobacter pylori*.[71] Other factors include distance from diagnostic endoscopic facilities.[72]

Of all racial and ethnic groups, the non-Hispanic Black population has the highest rates of advanced distant-stage CRC[73] and has the lowest 5-year survival.[74,75] These differences are mainly the result of inferior access to early detection and quality diagnostic and treatment interventions. Thus, equity across the continuum, including prevention, early

detection, adequate treatment, and clinical trial participation, are important factors contributing to overall outcomes.[74-76]

COLORECTAL CANCER IN YOUNG PATIENTS

Incidence rates in individuals younger than age 50 have demonstrated an increase since the 1990s, with the greatest numbers observed in rectal tumors.[73] Among those younger than age 50, rectal tumors account for 37%, whereas 25% of tumors occur in the distal colon.[77]

Since the period 2012 through 2016, incidence rates increased approximately 1.8% per year in the proximal and distal colon and 2.2% annually overall. This increase in those younger than age 50 is associated with more advanced-stage tumors and is steepest in the non-Hispanic White population with 2.2% per year and the American Indian/Alaskan Native population with 2.2% per year.[78] Causes for this increase of CRC in young individuals is unknown but thought to be related to diet.

In an analysis of data from 13 Surveillance, Epidemiology, and End Results cancer registries from 1992 to 2005, an evaluation of young patients with CRC was made utilizing data on trends by sex, race/ethnicity, age, stage at diagnosis, and anatomic subsite.[79] From 1992 to 2005, these authors noted increases in CRC incidence rates of 1.5% per year in men and 1.6% per year in women per 100,000 in young adults between age 20 and 49. There were higher rates in the non-Hispanic White population in all stages of the disease, and the increase was associated with a higher prevalence of rectal cancer in women and men over this time period. Additional research was suggested as important and necessary to determine the etiology of the change in CRC patterns and to develop potential preventive, diagnostic, and interventional strategies. Increasing trends in CRC rates in young individuals have also been noted by other authors.[80-82]

PROGNOSTIC FACTORS IN YOUNG PATIENTS WITH COLORECTAL CANCER

Reports indicate that hereditary CRCs occur in 38.4% of patients younger than age 40 and in 3.5% of individuals older than age 55.[82] Others have likewise confirmed that hereditary tumors are detected more frequently in young individuals, suggesting hereditary factors as etiology rather than diet and lifestyle.[83,84]

Earlier reports indicated a worse survival rate in young patients with CRCs.[80,82] Young patients are more likely to present with advanced- and late-stage disease and higher-grade tumors.[80] Approximately 60% to 67% of young patients with CRC present with stage III or IV disease, with the majority being poorly differentiated or mucinous tumors, having signet-ring cell, infiltrating tumor edge, and aggressive histologic grade in the primary tumor.[85,86] Distal location and advanced stage of tumor at diagnosis were reported as independent prognostic factors.[87] Liang et al[86] reported age, type of operation, blood transfusion, histologic type, diameter of tumor, invasion, lymphatic invasion, and distant metastasis (TNM) stage as predictors of survival in young patients with colon cancer after surgery.[86] Levi et al[88] reported an increase in second primary CRCs in young patients with a history of CRC. Adloff et al[89] reported virulence but delay in diagnosis and 5-year survival rates being no different in young and older patients. Young patients survived as well as or better than their older patient counterparts. The most frequent symptoms were bleeding and abdominal pain.[89]

Siegel et al[79] reported that, at initial presentation of early-onset CRC in patients younger than age 50 with sporadic disease and no obvious history of evidence of known risk factors, it was found that at least 86% demonstrated a history of abdominal symptoms evident by the time of diagnosis. The most common findings were rectal bleeding in 51%, abdominal pain in 32%, and change in bowel habits in 18%. The most frequent clinical and laboratory parameters were anemia in 14% and positive fecal occult blood tests in 7%.[79] These authors emphasize that, with the findings of a recent increase in CRC among those younger than age 50, an adequate evaluation of young patients with abdominal symptoms is necessary to impact this trend. They further imply that early recognition of CRC in patients without known established risks factors requires enhanced clinical awareness and education of providers of these changing trends to allow for aggressive diagnostic evaluation of symptoms and thus treatment at a potentially earlier stage of disease.

MUTATION STATUS

Berg et al[90] examined the mutation status of five known CRC genes and compared the genomic complexity of tumors from young patients without known inherited CRC syndrome with older patients. Among 181 CRC tumors stratified by microsatellite instability status, DNA sequence changes were observed in *KRAS* in 32%, *BRAF* in 16%, *PIK3CA* in 4%, *PTEN* in 14%, and *TP53* in 51%.[90] Interestingly, among younger patients, *PIK3CA* mutations were not observed, and *TP53* mutations occurred more frequently. Additionally, the total gene mutation index was lowest—although genomic complexity as determined by copy-number aberrations was highest—in tumors from the younger participants. A similar number of tumors from young and older patients were quadruple negative for the four predictive gene mutations (*KRAS*, *BRAF*, *PIK3CA*, *PTEN*). However, tumors from 16% of young patients compared with only 1% of elderly patients showed mutations in *PTEN/PIK3CA* exclusively.

These results indicate that different genetic profiles exist in tumors from young and elderly patients with comparable pathologic features, potentially indicating a different genetic risk profile of CRC tumorigenesis in young patients.90 Other studies have demonstrated microsatellite instability and

other molecular biomarkers as being different in young patients with CRC.

The incidence rates of CRCs are increasing in young adults. Tumors in the young population appear to be more aggressive, to present with later stage and more advanced disease at diagnosis, and to have poorer histopathologic features compared with tumors in older patients. Despite more advanced disease at the time of diagnosis, response to therapy and overall survival appear similar to older patients. Early reports indicate genetic mutation profiles that differ from older patients. These findings indicate a need for health care providers to have a heightened awareness of this continuously increasing trend and institute diagnostic evaluation of gastrointestinal symptoms when caring for this young patient population. It is necessary that future research focuses attention on studies to elucidate and delineate factors contributing to the disparate trend and to design and develop potential diagnostic and early detection, interventional, and preventive strategies to address the causes of and reverse the current trend.[91]

A CALL TO ACTION

The COVID-19 pandemic's aftershocks on CRC care and outcomes will be long-lasting and worldwide. Although its challenges have forced a reckoning in how we provide care, the pandemic also provides an unparalleled opportunity to reorganize and address CRC disparities. To do so, we must focus on just access to high-quality care and access to research, both of which are necessary to achieve health equity. As a means toward this end, implementation of evidence-based adaptable interventions should be predicated on community engagement, representation, measurable outcomes, and clearly defined success metrics.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Braveman P, Arkin E, Orleans T, et al. What Is Health Equity? And What Difference Does a Definition Make? Princeton, NJ: Robert Wood Johnson Foundation; 2017.
2. Patel MI, Lopez AM, Blackstock W, et al. Cancer disparities and health equity: a policy statement from the American Society of Clinical Oncology. J Clin Oncol. 2020;38:3439-3448.
3. Newman LA, Winn RA, Carethers JM. Similarities in risk for COVID-19 and cancer disparities. Clin Cancer Res. 2021;27:24-27.
4. Waterhouse DM, Harvey RD, Hurley P, et al. Early impact of COVID-19 on the conduct of oncology clinical trials and long-term opportunities for transformation: findings from an American Society of Clinical Oncology survey. JCO Oncol Pract. 2020;16:417-421.
5. Yu J, Ouyang W, Chua MLK, et al. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. JAMA Oncol. 2020;6:1108-1110.
6. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21:335-337.
7. Kuderer NM, Choueiri TK, Shah DP, et al; COVID-19 and Cancer Consortium. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet. 2020;395:1907-1918.
8. Robilotti EV, Babady NE, Mead PA, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med. 2020;26:1218-1223.
9. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061-1069.
10. Raghavan D, Kim ES, Chai SJ, et al. Levine Cancer Institute approach to pandemic care of patients with cancer. JCO Oncol Pract. 2020;16:299-304.
11. Morris EJA, Goldacre R, Spata E, et al. Impact of the COVID-19 pandemic on the detection and management of colorectal cancer in England: a population-based study. Lancet Gastroenterol Hepatol. 2021;6:199-208.
12. Sharpless NE. COVID-19 and cancer. Science. 2020;368:1290.

13. Escobar GJ, Adams AS, Liu VX, et al. Racial disparities in COVID-19 testing and outcomes: retrospective cohort study in an integrated health system. Ann Intern Med. 2021;M20-6979.
14. Rogawski McQuade ET, Guertin KA, Becker L, et al. Assessment of seroprevalence of SARS-CoV-2 and risk factors associated with COVID-19 infection among outpatients in Virginia. JAMA Netw Open. 2021;4:e2035234.
15. Bromley EG, May FP, Federer L, et al. Explaining persistent under-use of colonoscopic cancer screening in African Americans: a systematic review. Prev Med. 2015;71:40-48.
16. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7-33.
17. Zauber AG. The impact of screening on colorectal cancer mortality and incidence: has it really made a difference? Dig Dis Sci. 2015;60:681-691.
18. IARC Working Group on the Evaluation of Cancer-Preventive Interventions. Colorectal cancer screening. Lyon, France: International Agency for Research on Cancer; 2019. https://www.ncbi.nlm.nih.gov/books/NBK553200/. Accessed February 19, 2021.
19. Winawer SJ, Zauber AG, Ho MN, et al; The National Polyp Study Workgroup. Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med. 1993; 329:1977-1981.
20. Winawer SJ, Zauber AG, O'Brien MJ, et al; The National Polyp Study Workgroup. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. N Engl J Med. 1993;328:901-906.
21. Mandel JS, Church TR, Ederer F, et al. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst. 1999; 91:434-437.
22. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996; 348:1472-1477.
23. Shaukat A, Mongin SJ, Geisser MS, et al. Long-term mortality after screening for colorectal cancer. N Engl J Med. 2013;369:1106-1114.
24. Faivre J, Dancourt V, Lejeune C, et al. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. Gastroenterology. 2004;126:1674-1680.
25. Kronborg O, Fenger C, Olsen J, et al. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996;348:1467-1471.
26. Atkin WS, Edwards R, Kralj-Hans I, et al; UK Flexible Sigmoidoscopy Trial Investigators. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375:1624-1633.
27. Segnan N, Armaroli P, Bonelli L, et al; SCORE Working Group. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. J Natl Cancer Inst. 2011;103:1310-1322.
28. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med. 2013;369:1095-1105.
29. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143:844-857.
30. Schoen RE, Pinsky PF, Weissfeld JL, et al; PLCO Project Team. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med. 2012;366:2345-2357.
31. Yang DX, Gross CP, Soulos PR, et al. Estimating the magnitude of colorectal cancers prevented during the era of screening: 1976 to 2009. Cancer. 2014; 120:2893-2901.
32. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67:177-193.
33. American Cancer Society. Colorectal Cancer Facts & Figures 2017-2019. Atlanta, GA: American Cancer Society; 2017.
34. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. BMJ. 2014;348(apr09 1):g2467.
35. Chiu HM, Chen SL, Yen AM, et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. Cancer. 2015;121:3221-3229.
36. Bibbins-Domingo K, Grossman DC, Curry SJ, et al; US Preventive Services Task Force. Screening for colorectal cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315:2564-2575.
37. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology. 1997;112:594-642.
38. Khalili F, Najafi B, Mansour-Ghanaei F, et al. Cost-effectiveness analysis of colorectal cancer screening: a systematic review. Risk Manag Healthc Policy. 2020; 13:1499-1512.
39. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68:250-281.
40. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70:145-164.
41. Dey N, Kochman ML, Komanduri S, et al. Report from the AGA Center for GI innovation and technology's consensus conference: envisioning next-generation paradigms in colorectal cancer screening and surveillance. Gastroenterology. 2020;158:455-460.
42. Melson JE, Imperiale TF, Itzkowitz SH, et al. AGA white paper: Roadmap for the future of colorectal cancer screening in the United States. Clin Gastroenterol Hepatol. 2020;18:2667-2678.e2.
43. Joseph DA, King JB, Dowling NF, et al. Vital signs: colorectal cancer screening test use - United States, 2018. MMWR Morb Mortal Wkly Rep. 2020;69:253-259.

44. Liss DT, Baker DW. Understanding current racial/ethnic disparities in colorectal cancer screening in the United States: the contribution of socioeconomic status and access to care. Am J Prev Med. 2014;46:228-236.
45. Carethers JM, Doubeni CA. Causes of socioeconomic disparities in colorectal cancer and intervention framework and strategies. Gastroenterology. 2020; 158:354-367.
46. May FP, Yang L, Corona E, et al. Disparities in colorectal cancer screening in the United States before and after implementation of the Affordable Care Act. Clin Gastroenterol Hepatol. 2020;18:1796-1804.e2.
47. Beydoun HA, Beydoun MA. Predictors of colorectal cancer screening behaviors among average-risk older adults in the United States. Cancer Causes Control. 2008;19:339-359.
48. White PM, Itzkowitz SH. Barriers driving racial disparities in colorectal cancer screening in African Americans. Curr Gastroenterol Rep. 2020;22:41.
49. Viramontes O, Bastani R, Yang L, et al. Colorectal cancer screening among Hispanics in the United States: disparities, modalities, predictors, and regional variation. Prev Med. 2020;138:106146.
50. Ashktorab H, Nouraie M, Hosseinkhah F, et al. A 50-year review of colorectal cancer in African Americans: implications for prevention and treatment. Dig Dis Sci. 2009;54:1985-1990.
51. May FP, Almario CV, Ponce N, et al. Racial minorities are more likely than whites to report lack of provider recommendation for colon cancer screening. Am J Gastroenterol. 2015;110:1388-1394.
52. Peterson EB, Ostroff JS, DuHamel KN, et al. Impact of provider-patient communication on cancer screening adherence: a systematic review. Prev Med. 2016; 93:96-105.
53. Brown ML, Klabunde CN, Cronin KA, et al. Challenges in meeting Healthy People 2020 objectives for cancer-related preventive services, National Health Interview Survey, 2008 and 2010. Prev Chronic Dis. 2014;11:E29.
54. Goodwin SM, Anderson GF. Effect of cost-sharing reductions on preventive service use among Medicare fee-for-service beneficiaries. 2012;2:002.01.a03.
55. Golberstein E, Gonzales G, Sommers BD. California's early ACA expansion increased coverage and reduced out-of-pocket spending for the state's low-income population. Health Aff (Millwood). 2015;34:1688-1694.
56. Wilensky SE, Gray EA. Existing Medicaid beneficiaries left off the Affordable Care Act's prevention bandwagon. Health Aff (Millwood). 2013;32:1188-1195.
57. Taplin SH, Anhang Price R, Edwards HM, et al. Introduction: understanding and influencing multilevel factors across the cancer care continuum. J Natl Cancer Inst Monogr. 2012;2012:2-10.
58. Yano EM, Green LW, Glanz K, et al. Implementation and spread of interventions into the multilevel context of routine practice and policy: implications for the cancer care continuum. J Natl Cancer Inst Monogr. 2012;2012:86-99.
59. Wheeler SB, Leeman J, Hassmiller Lich K, et al. Data-powered participatory decision making: Leveraging systems thinking and simulation to guide selection and implementation of evidence-based colorectal cancer screening interventions. Cancer J. 2018;24:136-143.
60. Inadomi JM, Vijan S, Janz NK, et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. Arch Intern Med. 2012; 172:575-582.
61. Honein-AbouHaidar GN, Kastner M, Vuong V, et al. Systematic review and meta-study synthesis of qualitative studies evaluating facilitators and barriers to participation in colorectal cancer screening. Cancer Epidemiol Biomarkers Prev. 2016;25:907-917.
62. Doubeni CA, Selby K, Gupta S. Framework and strategies to eliminate disparities in colorectal cancer screening outcomes. Annu Rev Med. 2021;72:383-398.
63. Wender RC, Doroshenk M, Brooks D, et al. Creating and implementing a national public health campaign: the American Cancer Society's and National Colorectal Cancer Roundtable's 80% by 2018 Initiative. Am J Gastroenterol. 2018;113:1739-1741.
64. U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Healthy People 2020. https://www.healthypeople.gov/2020/topics-objectives/topic/cancer/objectives. Accessed February 1, 2021.
65. Centers for Disease Control and Prevention (CDC). Vital signs: colorectal cancer screening, incidence, and mortality--United States, 2002-2010. MMWR Morb Mortal Wkly Rep. 2011;60:884-889.
66. Wender R, Brooks D, Sharpe K, et al. The National Colorectal Cancer Roundtable: past performance, current and future goals. Gastrointest Endosc Clin N Am. 2020;30:499-509.
67. Doubeni CA, Major JM, Laiyemo AO, et al. Contribution of behavioral risk factors and obesity to socioeconomic differences in colorectal cancer incidence. J Natl Cancer Inst. 2012;104:1353-1362.
68. Conway AA, Gerry JM, Sacco F, et al. High prevalence of adenomatous polyps in Alaska native people aged 40-49 years. J Surg Res. 2019;243:524-530.
69. Kelly JJ, Alberts SR, Sacco F, et al. Colorectal cancer in Alaska Native people, 2005-2009. Gastrointest Cancer Res. 2012;5:149-154.
70. Perdue DG, Haverkamp D, Perkins C, et al. Geographic variation in colorectal cancer incidence and mortality, age of onset, and stage at diagnosis among American Indian and Alaska Native people, 1990-2009. Am J Public Health. 2014;104(suppl 3):S404-S414.
71. McMahon BJ, Bruce MG, Koch A, et al. The diagnosis and treatment of Helicobacter pylori infection in Arctic regions with a high prevalence of infection: expert commentary. Epidemiol Infect. 2016;144:225-233.
72. Day LW, Espey DK, Madden E, et al. Screening prevalence and incidence of colorectal cancer among American Indian/Alaskan natives in the Indian Health Service. Dig Dis Sci. 2011;56:2104-2113.

73. Austin H, Henley SJ, King J, et al. Changes in colorectal cancer incidence rates in young and older adults in the United States: what does it tell us about screening. Cancer Causes Control. 2014;25:191-201.
74. Coughlin SS, Blumenthal DS, Seay SJ, et al. Toward the elimination of colorectal cancer disparities among African Americans. J Racial Ethn Health Disparities. 2016;3:555-564.
75. Sineshaw HM, Ng K, Flanders WD, et al. Factors that contribute to differences in survival of black vs white patients with colorectal cancer. Gastroenterology. 2018; 154:906-915.e7.
76. Wallace K, Grau MV, Ahnen D, et al. The association of lifestyle and dietary factors with the risk for serrated polyps of the colorectum. Cancer Epidemiol Biomarkers Prev. 2009;18:2310-2317.
77. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: North American Association of Central Cancer Registries (NAACCR) Incidence–CiNA Analytic File, 1995-2016, for NHIAv2 Origin, Custom File With County, ACS Facts and Figures projection Project. North American Association of Central Cancer Registries; 2019.
78. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974-2013. J Natl Cancer Inst. 2017;109.
79. Siegel RL, Jemal A, Ward EM. Increase in incidence of colorectal cancer among young men and women in the United States. Cancer Epidemiol Biomarkers Prev. 2009;18:1695-1698.
80. O'Connell JB, Maggard MA, Liu JH, et al. Rates of colon and rectal cancers are increasing in young adults. Am Surg. 2003;69:866-872.
81. Cress RD, Morris C, Ellison GL, et al. Secular changes in colorectal cancer incidence by subsite, stage at diagnosis, and race/ethnicity, 1992-2001. Cancer. 2006; 107(suppl 5):1142-1152.
82. Fante R, Benatti P, di Gregorio C, et al. Colorectal carcinoma in different age groups: a population-based investigation. Am J Gastroenterol. 1997;92:1505-1509.
83. Minardi AJ Jr., Sittig KM, Zibari GB, et al. Colorectal cancer in the young patient. Am Surg. 1998;64:849-853.
84. Ikenaga M, Tomita N, Sekimoto M, et al. Use of microsatellite analysis in young patients with colorectal cancer to identify those with hereditary nonpolyposis colorectal cancer. J Surg Oncol. 2002;79:157-165.
85. Taylor MC, Pounder D, Ali-Ridha NH, et al. Prognostic factors in colorectal carcinoma of young adults. Can J Surg. 1988;31:150-153.
86. Liang JT, Huang KC, Cheng AL, et al. Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. Br J Surg. 2003;90:205-214.
87. Alici S, Aykan NF, Sakar B, et al. Colorectal cancer in young patients: characteristics and outcome. Tohoku J Exp Med. 2003;199:85-93.
88. Levi F, Randimbison L, Te VC, et al. Re: Effect of age on risk of second primary colorectal cancer. J Natl Cancer Inst. 2002;94:529-530.
89. Adloff M, Arnaud JP, Schloegel M, et al. Colorectal cancer in patients under 40 years of age. Dis Colon Rectum. 1986;29:322-325.
90. Berg M, Danielsen SA, Ahlquist T, et al. DNA sequence profiles of the colorectal cancer critical gene set KRAS-BRAF-PIK3CA-PTEN-TP53 related to age at disease onset. PLoS One. 2010;5:e13978.
91. Mitchell EP. Colorectal cancer in the young. Colorectal Cancer. 2012;1:355-358.

Current Management of Appendiceal Neoplasms

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Overview

Appendiceal neoplasms include a heterogeneous group of epithelial and nonepithelial tumors that exhibit varying malignant potential. This review article summarizes current diagnostic criteria, classification systems, and optimal therapeutic strategies for the five main histopathologic subtypes of appendiceal neoplasms. In particular, the management of epithelial appendiceal neoplasms has evolved. Although their treatment has historically been extrapolated from colon cancer, improved understanding of their unique histopathologic and molecular characteristics and a growing body of published clinical data support a more nuanced approach to their management.

Appendiceal neoplasms include a heterogeneous group of epithelial and nonepithelial tumors that exhibit varying malignant potential. They are rare tumors, with an age-adjusted annual incidence of six cases per 1,000,000 people in recent years.[1] The prognosis of appendiceal neoplasms is predominantly dependent on tumor type and grade, with long-term survival ranging between 10% and 90%.[2]

There are five main histopathologic subtypes of appendiceal neoplasms: neuroendocrine neoplasms (NENs), which are nonepithelial tumors; and mucinous neoplasms, goblet cell adenocarcinomas (GCAs), colonic-type (nonmucinous) adenocarcinomas, and signet ring cell adenocarcinomas, which are epithelial tumors. The diagnostic and staging criteria for epithelial appendiceal neoplasms have been significantly revised recently in the updated 8th edition of the *American Joint Committee on Cancer Staging Manual* (AJCC 8th edition; Table 1)[3] and the 5th edition of the *WHO Classification of Digestive System Tumours*.[4] The diagnosis and treatment of appendiceal neoplasms have become increasingly nuanced as our understanding of their histopathologic and molecular characteristics has evolved. For example, neoplasms formerly called "goblet cell carcinoids" have been renamed "goblet cell adenocarcinoma," because the neuroendocrine component of these tumors is understood to be less significant. Also, unique and more specific staging and grading systems have been developed for primary and metastatic mucinous neoplasms of the appendix to better reflect their biologies.

Primary appendiceal tumors are difficult to diagnose preoperatively when confined to the appendix. Patient presentation often resembles acute appendicitis, with tumors found in approximately 1% of appendectomy specimens.[5] Intraoperatively, the diagnosis often remains ambiguous. Even when the surgeon suspects malignancy, associated inflammation may preclude a definitive intraoperative diagnosis. Consequently, most cases of appendiceal cancer are diagnosed postoperatively.

Cytoreductive Surgery With Hyperthermic Intraperitoneal Chemoperfusion

Epithelial appendiceal neoplasms demonstrate a propensity for peritoneal metastasis and metastasize outside the peritoneal cavity less frequently. They are therefore especially amenable to regional therapies. Several regional therapy variations have been described over the past 4 decades, but the most commonly used technique is cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemoperfusion (HIPEC). Cytoreductive surgery refers to surgical removal of all visible (macroscopic) intra-abdominal tumors, whereas HIPEC refers to the circulation of heated high-dose chemotherapy within the peritoneal cavity immediately after CRS to kill any residual microscopic cells left behind. Intraoperatively, surgeons most commonly use the Peritoneal Carcinomatosis Index (PCI; range, 0–39) to quantify the intra-abdominal tumor burden.[6] After CRS, surgeons most commonly use the Completeness of Cytoreduction Score (CC-score) to document the extent of residual macroscopic disease after surgery.[7] Ideally, complete macroscopic resection (CC-0) should be achieved; however, residual tumors less than 2.5 mm are considered acceptable, especially for less aggressive tumor subtypes, because preclinical data suggest successful penetration of intraperitoneally delivered chemotherapeutic drugs up to a depth of 2 mm to 5 mm.[8]

MUCINOUS NEOPLASMS

Diagnosis and Staging

Mucinous appendiceal neoplasms (MANs) are unique tumors in which more than 50% of the tumor volume is

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PRACTICAL APPLICATIONS

- The recently updated 8th edition of the *American Joint Committee on Cancer Staging Manual* and the 5th edition of the *WHO Classification of Digestive System Tumours* provide a three-tiered grading system for mucinous appendiceal neoplasms, a unique tumor in situ category for low-grade appendiceal mucinous neoplasms, new descriptions of peritoneal tumors and mucin metastases, more nuanced grading for neuroendocrine neoplasms, and a renaming of "goblet cell carcinoids" to "goblet cell adenocarcinoma."
- The diagnosis and treatment of epithelial appendiceal neoplasms have become increasingly nuanced as our understanding of their variable histopathologic and molecular characteristics has evolved.
- Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy have become standard of care for many patients with metastatic epithelial appendiceal cancer.

composed of extracellular mucin. They may present as an unruptured mucin-filled appendix or, more commonly, with peritoneal metastases after rupture or transmural invasion of the primary tumor. Peritoneal spread is characterized by marked intra-abdominal accumulation of mucinous ascites and mucinous tumor nodules, referred to as pseudomyxoma peritonei (PMP) or mucinous carcinoma peritonei. A recent expert consensus statement by the Peritoneal Surface Oncology Group International (PSOGI) provides detailed recommendations for classification and pathologic reporting of primary MANs and metastatic PMP.[9] The updated AJCC 8th edition adopted the PSOGI diagnostic terminology for MANs and provided guidelines for staging MANs/PMP (Table 2).

According to the updated diagnostic terminology for primary MANs, low-grade MANs are characterized by low-grade cytology without evidence of infiltrative (destructive) invasion, and lymph node involvement is quite rare. Although uncommon, tumors with high-grade cytologic features but without evidence of infiltrative (destructive) invasion are considered high-grade MANs. Tumors that demonstrate infiltrative invasion of the appendiceal wall are considered mucinous appendiceal adenocarcinomas (AAs) and carry an increased risk for lymph node metastasis. Mucinous AAs may be moderately differentiated (grade 2) or poorly differentiated, often with signet ring cells (grade 3), according to the AJCC 8th edition.

Both the PSOGI and the AJCC 8th edition use a three-tier diagnostic grading system for PMP. These tiers include PMP with low-grade cytohistologic features (PSOGI)/grade G1, well differentiated (AJCC 8th edition); PMP with high-grade cytohistologic features (PSOGI)/grade 2, moderately differentiated (AJCC 8th edition); and PMP with signet ring cells (PSOGI)/grade 3, poorly differentiated (AJCC 8th edition). Using this grading system, Davison et al[10] found that patients with grade 1, grade 2, and grade 3 tumors had lymph node involvement in 1%, 17%, and 72% of cases, respectively, and demonstrated corresponding 5-year survival rates of 91%, 61%, and 23%.

The mutation spectrum in MAN varies depending on the type of neoplasm. *KRAS* hotspot mutations are very frequent in low-grade MANs and high-grade MANs, with a reported prevalence of 81% to 100%.[11,12] *GNAS* hotspot mutations are also more commonly enriched in low-grade MANs[11-13] and are frequently seen in mucinous neoplasms across various organs.[14,15] *TP53* mutations are infrequent in low-grade MANs[11,12] but are more frequent in high-grade MANs and mucinous adenocarcinomas.[11,12] Although the data on microsatellite instability and tumor mutation burden are relatively scarce, it has been reported that approximately 1% of mucinous adenocarcinomas have high microsatellite instability and/or have a high tumor mutation burden, whereas virtually no low-grade MANs have high microsatellite instability/high tumor mutation burden.[11]

Contrast-enhanced CT or MRI is used to assess the burden of intra-abdominal tumors and determine resectability. Chest imaging is usually performed to rule out systemic spread in high-grade disease and pleural disease in low-grade disease. PET/CT is not recommended for these patients.[16] Tumor markers, including CEA, CA 19-9, and CA-125 levels, should be assessed at diagnosis and are often useful to assess treatment effect and detect tumor recurrence after resection.[16,17]

Management

There is some controversy regarding the surgical management of localized MAN, which is often diagnosed intra- or postoperatively. Clearly, when a dilated and enlarged appendix is encountered, it must be removed carefully to avoid spillage of any potentially malignant cells. This can usually be done laparoscopically, with care to make a sufficient extraction site.

It has been suggested that right hemicolectomy after a diagnosis of MAN confers no survival benefit over appendectomy alone.[18] A limitation of that study is its inclusion of multiple tumor types and presentations, all of which had peritoneal metastases. Other studies have found lymph node status to be an important prognostic factor.[19] Although low-grade (grade 1) tumors rarely have lymph node involvement, grade 2 and grade 3 MANs have positive lymph nodes in 17% and 72% of cases, respectively.[10] Therefore, nonperforated low-grade tumors (grade 1) completely

TABLE 1. American Joint Committee on Cancer 8th Edition Staging System for Appendiceal Tumors[3]

Category	Criteria
T	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intramucosal carcinoma; invasion of the lamina propria or extension into but not through the muscularis mucosae)
Tis(LAMN)	Low-grade appendiceal mucinous neoplasm confined by the muscularis propria. Acellular mucin or mucinous epithelium may invade into the muscularis propria. T1 and T2 are not applicable to LAMN. Acellular mucin or mucinous epithelium that extends into the subserosa or serosa should be classified as T3 or T4a, respectively.
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa or the mesoappendix
T4	Tumor invades the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix, and/or directly invades adjacent organs or structures
T4a	Tumor invades through the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or serosa of the mesoappendix
T4b	Tumor directly invades or adheres to adjacent organs or structures
N	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph node measuring $\geq$ 0.2 mm) or any number of tumor deposits is present, and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa or mesentery
N2	Four or more regional lymph nodes are positive
M	
M0	No distant metastasis
M1	Distant metastasis
M1a	Intraperitoneal acellular mucin, without identifiable tumor cells in the disseminated peritoneal mucinous deposits
M1b	Intraperitoneal metastasis only, including peritoneal mucinous deposits containing tumor cells
M1c	Metastasis to sites other than peritoneum
G	G definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

When T Is...	and N Is...	and M Is...	and the Grade Is...	Then the Stage Group Is...
Tis	N0	M0		0
Tis(LAMN)	N0	M0		0
T1	N0	M0		I
T2	N0	M0		I
T3	N0	M0		IIA
T4a	N0	M0		IIB

(Continued on following page)

TABLE 1. American Joint Committee on Cancer 8th Edition Staging System for Appendiceal Tumors[3] (Continued)

When T Is...	and N Is...	and M Is...	and the Grade Is...	Then the Stage Group Is...
T4b	N0	M0		IIC
T1	N1	M0		IIIA
T2	N1	M0		IIIA
T3	N1	M0		IIIB
T4	N1	M0		IIIB
Any T	N2	M0		IIIC
Any T	Any N	M1a		IVA
Any T	Any N	M1b	G1	IVA
Any T	Any N	M1b	G2, G3, or GX	IVB
Any T	Any N	M1c	Any G	IVC

Abbreviation: LAMN, low-grade appendiceal mucinous neoplasm.

excised with appendectomy alone may undergo surveillance,[16] but right hemicolectomy should be performed for grade 2 and grade 3 MANs for staging and oncologic purposes.

In addition to formal colectomy, a thorough examination of the abdomen is required to assess for evidence of peritoneal metastases. This involves searching for tumor or mucin deposits in the omentum, paracolic gutters, diaphragmatic surface, and pelvis. Any findings should be thoroughly examined by an experienced pathologist. Low-grade MANs with localized acellular mucinous deposits carry a low risk for developing PMP (4%), whereas those with cellular mucin are at a much higher risk for PMP (40%).[20] These findings clearly influence prognostic discussions and surveillance decisions for patients.

Many patients eventually present with metastatic disease that is limited to the peritoneum and amenable to CRS with intraperitoneal chemotherapy. Although historically done with palliative intent, it is now understood that an aggressive surgical approach can result in long-term disease control and even cure in many patients. Recent studies have found an overall median survival of 51 to 156 months and a 10-year overall survival up to 70%, with surgical morbidity of 20% to 50% and postoperative mortality between 1% and 10% (Table 3).[21]

There is little evidence to guide the use of systemic therapy for MAN, but it is generally accepted that there is no role for systemic chemotherapy in low-grade MAN and low-grade PMP.[16] The natural history of most grade 1 tumors suggests that systemic chemotherapy may be of little use, and retrospective studies have not found a benefit.[31]

For grade 2/grade 3 MAN/PMP, pre- and/or postoperative systemic chemotherapy is generally recommended using fluorouracil-based regimens, similar to those used for colorectal cancer.[16] Perioperative systemic chemotherapy may lead to lower abdominal tumor burdens, fewer visceral resections, and improved progression-free survival.[32,33] In one series, preoperative chemotherapy resulted in partial or complete histologic response in 29% of patients, which correlated with improved survival.[32] For patients with unresectable disease, systemic chemotherapy can provide disease control in more than 50% of cases.[34]

APPENDICEAL NEUROENDOCRINE NEOPLASMS

Diagnosis and Staging

Neuroendocrine neoplasms have historically been referred to as carcinoid because of their intermediate behavior that was observed to be less aggressive than traditional carcinomas. This is an outdated term and has evolved as we learn more about these tumors. Although they can occur throughout the entire gastrointestinal tract, as well as the lung, the appendix is the third most common site of primary NENs behind the small bowel and rectum.[35] Appendiceal NENs appear to arise from subepithelial neuroendocrine cells rather than epithelial neuroendocrine cells, as in other gastrointestinal NENs.[36] These subepithelial neuroendocrine cells are concentrated in the tip of the appendix, which explains the propensity for NENs to develop in this location.

The most recent World Health Organization classification system defines three categories for gastrointestinal NENs (Table 4): well-differentiated neuroendocrine tumors (NETs), poorly differentiated neuroendocrine carcinomas, and mixed neuroendocrine-nonneuroendocrine neoplasms. The majority of cases are diagnosed as grade 1/grade 2 NETs. Given the rarity of neuroendocrine carcinomas and mixed neuroendocrine-nonneuroendocrine neoplasms and the common confusion with goblet cell carcinoids, these cases should be always be reviewed by experienced centers and pathologists.

Patients diagnosed with NENs often have their chromogranin A and serotonin levels monitored to assess response to treatment and early signs of tumor recurrence, although

TABLE 2. Peritoneal Surface Oncology Group International Classification of Primary Mucinous Appendiceal Neoplasms and Metastatic Pseudomyxoma Peritonei[9]

PSOGI Terminology	Characteristics	Other Terminology
Primary Mucinous Appendiceal Neoplasm		
LAMN	Dysplastic lesion with low-grade cytohistologic features* and any of the following architectural features:	Mucinous tumor of uncertain malignant potential
	Loss of the lamina propria and muscularis mucosae	Mucinous tumor of low malignant potential
	Fibrosis of the submucosa	
	No infiltrative invasion** by neoplastic cells	
	With or without pushing invasion†	
	With or without mucin dissecting in wall	
	With or without mucin or cells outside appendix	
	With or without rupture of the appendix	
High-grade appendiceal mucinous neoplasms	Similar characteristics as LAMN except for the presence of high-grade cytohistologic features	Noninvasive mucinous adenocarcinoma
Mucinous adenocarcinoma	Infiltrative invasion** by neoplastic epithelial cells	Mucinous adenocarcinoma
		AJCC grade 2 (moderately differentiated)
		AJCC grade 3 (poorly differentiated with or without signet ring cells)
Pseudomyxoma Peritonei		
Mucin without epithelial cells	Acellular mucin	NA
PMP with low-grade histologic features*	Low-grade cytohistologic features	Well-differentiated mucinous adenocarcinoma (AJCC grade 1)
		PMP1
		DPAM
		Low-grade mucinous carcinoma peritonei
PMP with high-grade histologic features	One or more high-grade cytohistologic features	Moderately differentiated mucinous adenocarcinoma (AJCC grade 2)
		PMP2
		PMCA, PMCA-I/D
		High-grade mucinous carcinoma peritonei
PMP with signet ring cells	Presence of signet ring cells (regardless of other high-grade cytohistologic features)	Poorly differentiated mucinous adenocarcinoma (AJCC grade 3)
		PMP3
		Peritoneal mucinous carcinomatosis
		High-grade mucinous carcinoma peritonei

Abbreviations: PSOGI, Peritoneal Surface Oncology Group International; MAN, mucinous appendiceal neoplasm; LAMN, low-grade appendiceal mucinous neoplasm; AJCC, American Joint Committee on Cancer; PMP, pseudomyxoma peritonei; NA, not applicable; DPAM, disseminated peritoneal adenomucinosis; PMCA, peritoneal mucinous carcinomatosis; I/D, intermediate/discordant.

*Low-grade cytohistologic features: mildly enlarged hyperchromatic nuclei, mild nuclear stratification, maintenance of cell polarity, minimal mitotic activity, minimally prominent nucleoli, low cellularity (< 20%), no infiltrative invasion, no signet cells, no angiolymphatic invasion, no perinuclear invasion.

**Features of infiltrative invasion: tumor budding (discohesive single cells or clusters of up to five cells) and/or small irregular glands, typically within a desmoplastic stroma characterized by a proteoglycan-rich extracellular matrix with activated fibroblasts/myofibroblasts with vesicular nuclei.

†Pushing invasion: broad front of cells expanding into surrounding tissue without "infiltrative" features (i.e., expansile or diverticulum-like growth).

these levels are not universally reliable. Imaging should include contrast-enhanced CT of the chest/abdomen/pelvis with triphasic protocol through the liver, the most frequent site of metastasis. A newer option is somatostatin receptor imaging with ^{68}Ga-DOTATATE PET/CT. This method should not be used routinely for diagnostic workup because of its high costs and the high sensitivity of current contrast-enhanced CT imaging. ^{68}Ga-DOTATATE PET/CT is useful

TABLE 3. Cytoreductive Surgery With Intraperitoneal Chemotherapy for Pseudomyxoma Peritonei

Year	No. of Patients	Complete Cytoreduction (CC-0/1; %)	Chemotherapy Used	5-Year OS (%)	Median OS (months)	Grade III/IV Morbidity (%)	Mortality (%)
2005[22]	27	41	MMC, cisplatin	52	NR	22	0
2006[18]	356	89	MMC, 5-FU	72	156	40	2
2006[10]	110	64	MMC	53	64	38	4
2006[23]	50	88	MMC, 5-FU	69	NR	48	4
2007[24]	104	87	MMC, cisplatin	72	NA	27	1
2012[25]	282	82	MMC	53	79	25	1
2012[26]	2,298	83	MMC, oxaliplatin	74	196	22	2
2015[27]	481	72	MMC, oxaliplatin	—	17–175	28	3
2016[28]	1,000	74	MMC	39–87	53–103	15	1
2017[29]	444	95	MMC, oxaliplatin	65	103	—	—
2018[30]	210	98	MMC, cisplatin	75	149	34	4

Abbreviations: CC-0, no residual visible tumor; CC-1, residual tumor deposits smaller than 2.5 mm; OS, overall survival; MMC, mitomycin C; NR, not reached; 5-FU, fluorouracil; NA, not applicable; —, data not available.

for three scenarios: assessing somatostatin receptor positivity when considering treatment (discussed later), assessing biologic activity of treated tumors, and investigating inconclusive soft tissue findings on CT.

Management

Despite an overall favorable prognosis, appendiceal NENs have a relatively high incidence of lymph node metastasis. A study of Surveillance, Epidemiology, and End Results data, which does not provide granular histologic characterization as described above, found lymph node involvement in 15% of appendiceal NENs 1 cm or smaller, 47% of NENs between 1 and 2 cm, and 86% of NENs larger than 2 cm.[37] The corresponding 10-year survival rates for patients with nonmetastatic node-positive disease in these groups were 100%, 92%, and 91%, respectively. An older single-institution study found that no patient with carcinoid tumors smaller than 2 cm treated with appendectomy alone developed metastases.[38] Based on these findings, it is generally recommended that appendectomy alone is sufficient for well-differentiated NETs smaller than 2 cm or tumors that are 1 to 2 cm with low-risk features.[39] If completely resected and node negative, no long-term follow up is necessary.[40]

For well-differentiated NETs larger than 2 cm or those involving the base of the appendix, right hemicolectomy is generally recommended,[39] although it may not improve overall survival and is questioned by some investigators.[39] A recent series found that tumor size and type of resection did not predict survival; presentation with metastatic disease did predict inferior survival and was associated with older age, serosal invasion, lymphovascular invasion, and tumor grade.[39] Although current guidelines suggest right hemicolectomy for all appendiceal NETs larger than 2 cm,[39] patient selection may be better tailored using histologic grading and other characteristics that are more predictive of metastatic disease and inferior survival.

There is less debate regarding patients with high-grade NETs, neuroendocrine carcinomas, and mixed neuroendocrine–non-neuroendocrine neoplasms, although the rarity of these tumors limits their study. Although the risk of lymph node or distant metastases for these patients is higher and survival is worse than for low-grade NETs, it is unclear whether right hemicolectomy improves survival.[41] Without clear guidelines, these tumors should be considered high-risk histology and treated with right hemicolectomy according to the published guidelines.[39]

As mentioned, the most common site of metastasis for appendiceal NENs is the liver. All patients with anatomically resectable disease should be considered for surgical resection and/or ablation, because this approach offers an opportunity for cure. However, many patients cannot undergo resection for anatomic or medical reasons. These patients should be evaluated for liver-directed therapies, such as transarterial bland embolization, transarterial chemoembolization, or transarterial radioembolization. Transarterial bland embolization is performed with a variety of embolizing agents (e.g., gelfoam, polymers, or endospheres) that occlude the predominantly arterial blood supply to these metastatic tumors. Transarterial chemoembolization can be performed using agents such as cisplatin, doxorubicin, streptozocin, or drug-eluting beads. Transarterial radioembolization is most commonly done with ^{90}Y microspheres. Although outside the scope of this review, the choice of agent is institution dependent, and no study has demonstrated a clear superiority at this time.

NENs also metastasize to the peritoneal cavity. As with other causes of carcinomatosis, CRS with or without HIPEC can improve disease control and survival in well-selected patients.[42,43] The ideal patients are those with well-differentiated tumors and modest intra-abdominal tumor burdens. The addition of chemoperfusion and the choice of agent are variable, but platinum agents are the most common.

Currently, there are no studies indicating a clear role for systemic therapy in the adjuvant setting for well-differentiated NETs. However, there are several options for patients with recurrent or metastatic disease. The PROMID study compared treatment with octreotide long-acting release (Sandostatin LAR) versus placebo for patients with metastatic midgut NETs. The median time to tumor progression was improved in the octreotide group (14.3 vs. 6 months).[44] There was no difference in long-term overall survival (83.7 vs. 84.7 months), but most patients in the placebo group eventually crossed over to receive octreotide, which likely confounds these results.[45] Similarly, the CLARINET study compared treatment with lanreotide versus placebo for locally advanced or metastatic gastrointestinal NETs and found improved progression-free survival (not reached vs. 18 months).[46] Treatment with somatostatin analogs is tumoristatic, rather than tumoricidal, and should be used to control unresectable disease rather than to downstage tumors to surgical resectability.

Everolimus has been studied in this setting as well. The RADIANT-2 trial found that the addition of everolimus improved progression-free survival for patients with advanced NETs and carcinoid syndrome compared with octreotide alone (16.4 vs. 11.3 months).[47] The subsequent RADIANT-4 trial compared everolimus with placebo for progressive, nonfunctional, lung or gastrointestinal NETs and found improved progression-free survival (11.0 vs. 3.9 months). As a result, everolimus can be considered for patients with progressive, metastatic gastrointestinal NETs.

Another option for patients with advanced disease is peptide receptor radionuclide therapy. In a group of advanced midgut NETs, the phase III randomized NETTER-1 study

TABLE 4. World Health Organization 2019 Classification and Grading Criteria for Neuroendocrine Neoplasms of the Gastrointestinal Tract and Hepatobiliary Organs[4]

Terminology	Differentiation	Grade	Mitotic Rate* (mitoses/2 mm^2)	Ki-67 Index* (%)
NET, G1	Well differentiated	Low	< 2	< 3
NET, G2	Well differentiated	Intermediate	2–20	3–20
NET, G3	Well differentiated	High	> 20	> 20
NEC, small-cell type	Poorly differentiated	High**	> 20	> 20
NEC, large-cell type	Poorly differentiated	High**	> 20	> 20
MiNEN	Well or poorly differentiated†	Variable†	Variable†	Variable†

Abbreviations: NET, neuroendocrine tumor; G1, grade 1; G2, grade 2; G3, grade 3; NEC, neuroendocrine carcinoma; MiNEN, mixed neuroendocrine-nonneuroendocrine neoplasm.

*Mitotic rates are expressed as the number of mitoses per 2 mm^2 (equaling 10 high-power fields at 40× magnification and an ocular field diameter of 0.5 mm), as determined by counting in 50 fields of 0.2 mm^2 (i.e., total area of 10 mm^2); the Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labeling (hot spots), which are identified at scanning magnification; the final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher-grade category.

**Poorly differentiated NECs are not formally graded but are considered high grade by definition.

†In most MiNENs, the neuroendocrine and nonneuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indexes in the same range as other NECs. This conceptual category allows for the possibility that one or both components may be well differentiated; therefore, when feasible, each component should be graded separately.

found that ^{177}Lu-DOTATATE led to improved progression-free survival (not reached vs. 8.4 months) and objective tumor response (18% vs. 3%) compared with octreotide.[48] As such, the National Comprehensive Cancer Network panel currently recommends peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE for patients with advanced/metastatic gastrointestinal NETs that are somatostatin receptor–positive on imaging.[49]

Adjuvant therapy should be considered for patients with surgically resected neuroendocrine carcinomas.[49] For patients with resectable disease that is locally advanced or metastatic, neoadjuvant therapy may be considered. Potential regimens include cisplatin/etoposide, carboplatin/etoposide, folinic acid/fluorouracil/oxaliplatin, folinic acid/fluorouracil/irinotecan, or capecitabine with or without temozolomide. Patients with locally advanced or metastatic disease should be treated with similar regimens.

GOBLET CELL ADENOCARCINOMA

Diagnosis and staging

Goblet cell adenocarcinomas demonstrate a mixed histology, including neuroendocrine features as well as mucin-secreting gland formation seen in typical adenocarcinomas. They have historically been referred to as goblet cell carcinoids, goblet cell tumors, adenocarcinoids, mixed crypt cell carcinoma, and mucinous adenocarcinoids. These tumors are more aggressive than typical NETs, with more frequent transmural invasion, lymph node involvement, and peritoneal metastasis, and are generally treated like adenocarcinomas.

Previously, the standard classification system was based on a study from 2008 by Tang et al[50]: type A was typical goblet cell carcinoids with minimal atypia or desmoplasia; type B was signet ring type; and type C was poorly differentiated. This grading system predicted rates of lymph node involvement (19% vs. 73% vs. 100%), extra-appendiceal spread (33% vs. 88% vs. 100%), 3-year disease-specific survival (100% vs. 85% vs. 17%), and 5-year disease-specific survival (100% vs. 36% vs. 0%) for types A, B, and C, respectively. Survival was more closely linked to goblet cell carcinoid type than to disease stage.

Our understanding of these tumors has evolved, and the most recent World Health Organization classification has renamed these tumors GCAs, acknowledging the relatively minor neuroendocrine component.[4] GCAs are characterized by the degree of high-grade histologic features observed (i.e., infiltrating tumor cells, complex tubules, cribriform masses, loss of tubular or clustered growth, high-grade cytology, and necrosis): grade 1 has less than 25% high-grade patterns, grade 2 has 25% to 50% high-grade patterns, and grade 3 has more than 50% high-grade patterns.[4]

GCAs differ significantly from AAs in terms of molecular profile. Approximately 10% and 6% of GCAs have *KRAS* and *GNAS* hotspot mutations, respectively, which is less frequent than mutation rates for either gene in appendiceal MANs or nonmucinous adenocarcinoma.[11,51] The frequency of high tumor mutation burden or high microsatellite instability in GCA has been reported to range from 0% to 3%.[11,51]

As with most appendiceal tumors, GCAs are typically diagnosed on pathology after surgery for presumed appendicitis. Workup at that time should include contrast-enhanced CT of the chest/abdomen/pelvis, although hematogenous spread is rare. Serotonin, chromogranin A, and imaging used

for NETs (e.g., DOTATATE PET/CT) are typically not helpful for GCAs, but tumor markers, namely CEA, CA 19-9, and CA-125, may be informative.[52]

Management

For GCA diagnosed after appendectomy without visible carcinomatosis, a formal right hemicolectomy is recommended for all patients.[39] Some studies have challenged the survival benefit of formal resection. Based on a small institutional series, it has been suggested that GCAs smaller than 1 cm confined to the appendix and completely resected with appendectomy may be spared right hemicolectomy.[53] An analysis of the Surveillance, Epidemiology, and End Results database similarly found no improvement in survival associated with formal resection, although 94% of patients underwent right hemicolectomy.[54] Given the paucity of studies, we must rely on consensus guidelines that recommend formal resection for these patients.

As with other appendiceal tumors, patients with GCA often develop carcinomatosis. In well-selected patients, CRS/HIPEC can significantly improve survival, with median overall survival reported from 18 to 37 months and up to 24% 4-year survival rates.[55–57] As with other conditions, survival is best for low-grade tumors and those that can undergo complete cytoreduction.

Shyu et al[58] recently reported their experience with CRS/HIPEC stratified according the more recent World Health Organization classification of GCA. The majority of patients had grade 3 GCA (73%), which predicted a similar tumor burden but a lower likelihood of achieving complete cytoreduction. Median survival was 33 months for grade 3 compared with 98 months for grades 1/2, and 5-year survival was 23% versus 54%, respectively. On multivariate analysis, grade 3 tumors and more than 50% extracellular mucin correlated with inferior survival. Survival did not correlate with PCI or complete cytoreduction (CC-0; HR, 1.96; p = .07).

Adjuvant chemotherapy is recommended for patients with resected stage III/IV disease. Although no randomized data exist, most investigators recommend fluorouracil-based regimens similar to those used to treat other types of gastrointestinal adenocarcinoma.[40,57] Retrospective studies have failed to show differences in survival, likely as a result of small numbers and selection bias.[59] However, a recent report of the National Cancer Database suggested improved survival for patients with node-positive disease who received adjuvant chemotherapy.[60]

COLONIC-TYPE (NONMUCINOUS) AND SIGNET RING ADENOCARCINOMAS

Diagnosis and Staging

Nonmucinous AA is similar to other lower gastrointestinal tumors and is often referred to as colonic-type adenocarcinoma. Although the prognosis for most of these patients is similar to that for stage-matched colon cancer, survival is significantly worse for patients with signet ring cell tumors.[3] Genetically, AA is not identical to typical colon cancer.

Like other appendiceal tumors, AA often presents as acute appendicitis and is diagnosed at an advanced stage. Standard AA presents with T3/T4 in 68% of cases, lymph node involvement in 29% of cases, and metastatic disease in 22% of cases. Signet ring cell tumors are more biologically aggressive and present with T3/T4, N1, and M1 disease in 91%, 61%, and 56% of cases, respectively. The median survival for standard AA is 48 months, whereas it is 24 months for signet ring cell tumors.[1] Lymph node involvement is predictive of tumor recurrence, the majority of which occur in the peritoneum.[61] Most patients with signet ring cell tumors develop metastatic disease, all with peritoneal disease and only 10% occurring at distant sites.[62]

Although AAs have a lower rate of *KRAS* and *GNAS* mutations (56% and 25%, respectively) compared with appendiceal MAN,[11,63,64] the rates are still higher than those seen in colorectal cancer. Mutation rates in *TP53* (23%), *APC* (2%), and *PIK3CA* (2%) are also lower than those seen in colorectal cancer.[63] Approximately 2% to 3% of AAs have high tumor mutation burden status, almost all attributable to high microsatellite instability status.[11,51]

Patients diagnosed with AA should undergo a metastatic workup similar to colon cancer.[65] This includes contrast-enhanced CT of the chest/abdomen/pelvis as well as biochemical testing, including CEA.

Management

Given the prognostic and therapeutic implications as well as the frequency of lymph node involvement, all patients with AA should undergo formal right hemicolectomy. A recent National Cancer Database study found that 19% of AAs larger than 1 cm had lymph node involvement; the rate was 28% for AAs that were 1 to 2 cm.[66] Rates of lymph node involvement were 0%, 11%, and 12% for tumors that were in situ, T1, and T2, respectively. These numbers were quite similar to those for primary colon adenocarcinomas. Subsequently, the investigators concluded that all patients with invasive AA should undergo right hemicolectomy, regardless of tumor size.

Retrospective data suggest that the addition of CRS/HIPEC to standard systemic chemotherapy improves survival for patients with AA and peritoneal metastases compared with systemic therapy alone, with median disease-free survival and overall survival of 23 and 48 months, respectively, and 5-year overall survival and disease-free survival of 56% and 36%, respectively.[67,68] Improved survival is predicted by PCI less than 7, CEA less than 6 ng/mL, and complete cytoreduction.[67] Inferior survival is predicted by nonmucinous

histology, signet ring cells, and increasing PCI.[68] All patients with perforated tumors or known peritoneal metastases should be evaluated by a multidisciplinary team to assess for resectability and coordinate treatment planning.

Systemic chemotherapy is recommended for AA, but there are no appendix-specific guidelines. Because of the lack of high-level data, recommendations for patients with AA follow treatment algorithms for colon cancer. Patients with nonmetastatic disease confined to the appendix and without lymph node involvement do not need systemic therapy. Patients with completely resected localized tumors who have lymph node involvement may benefit from adjuvant chemotherapy with a fluoropyrimidine/oxaliplatin doublet. Patients with metastatic disease should receive systemic regimens similar to those used for metastatic colorectal cancer. This guidance includes perioperative regimens for patients who are candidates for surgical resection.

There are small series that describe nuances in chemotherapy options for appendiceal tumors. Most use regimens with a combination of fluorouracil, platinum, and irinotecan.[62] It has been suggested that EGFR inhibitors have less of an impact on appendiceal *KRAS* wild-type tumors than on their colorectal counterparts.[61] EGFR inhibitors have shown greater benefit for patients with left-sided tumors versus right-sided tumors,[69] and appendiceal tumors have generally been excluded from such trials. More work is needed to understand targetable aspects of AA that may respond more favorably to specific systemic regimens.

CONTROVERSIES

Role of HIPEC

A large and growing body of literature supports the application of CRS/HIPEC in well-selected patients with peritoneal metastases arising from certain histologies. However, CRS/HIPEC remains controversial in the general medical community, especially outside of specialized centers. Some investigators have questioned the additional benefit of HIPEC compared with CRS alone.

A recently published phase III randomized French trial (PRODIGE 7) failed to demonstrate an overall survival benefit from combined CRS/HIPEC compared with CRS alone in patients with colorectal peritoneal metastases.[70] The specific HIPEC regimen used in the trial (bidirectional therapy using intraperitoneal oxaliplatin for 30 minutes at 42°C and concurrent intravenous fluorouracil infusion) has several important limitations: (1) most patients had previously been exposed to intravenous oxaliplatin-containing chemotherapy regimens, so cancer cells that survived this treatment were likely resistant to oxaliplatin[71]; (2) preclinical studies have consistently demonstrated that exposure to a longer duration of chemohyperthermia (> 90 minutes) is required to induce a sufficient fraction of irreversible cell death[72]; and (3) the trial was designed to demonstrate an 18-month improvement in overall survival, which is an overly optimistic endpoint to assess the additional benefit of a locoregionally delivered chemotherapeutic agent. Notably, although this trial failed to demonstrate a survival benefit attributable to short-duration oxaliplatin-based HIPEC, it certainly provided encouraging data to support CRS for patients with peritoneal metastases (median survival was 41 months, and 5-year survival was > 36%).[73]

Certain patients demonstrate clinicopathologic features associated with an elevated risk for metachronous peritoneal metastases, including T4 mucinous and signet ring cancers, perforated and/or obstructed tumors, positive resection margins, and synchronous ovarian or low-volume peritoneal metastases that are resected with the primary tumor. In a recently published phase III French trial (PROPHYLOCHIP-PRODIGE 15), patients with colorectal cancer with synchronous and localized peritoneal metastases removed during tumor resection (55%), perforated primary tumor (44%), or resected ovarian metastases (17%) were randomly selected to receive surveillance or second-look CRS/HIPEC (predominantly with oxaliplatin) after 6 months of adjuvant systemic chemotherapy and the absence of recurrence by imaging. There was no difference in 3-year disease-free survival or peritoneal relapse-free survival between the groups.[74] There are important limitations that make this study challenging to interpret. The trial included a heterogeneous group of patients with stage II/III cancers (perforated) and stage IV cancers (ovarian and peritoneal metastases). Because all patients in the experimental arm underwent CRS/HIPEC regardless of the presence/absence of peritoneal disease, some patients underwent prophylactic CRS/HIPEC, whereas the others received therapeutic CRS/HIPEC. Although this study may conclude that routine CRS/HIPEC for similar patients does not improve survival, it did not specifically study the benefit of CRS/HIPEC for patients with visible and resectable peritoneal metastases. Indeed, the median PCI in the CRS/HIPEC group was 4, and peritoneal metastases were only confirmed on surgical pathology for 37% of the patients. Therefore, extrapolating these results to patients with known peritoneal metastases may not be prudent.

Similarly, in a Dutch phase III randomized trial (COLOPEC), patients with T4 or perforated colon cancer were randomly selected to receive standard surgical resection, with or without adjuvant HIPEC (oxaliplatin, 30 minutes), at the time of primary resection, followed by routine adjuvant systemic chemotherapy for both groups. There was no difference in peritoneal metastasis-free survival at 18 months.[75] Again, this was not a study of patients with known peritoneal metastases; thus, conclusions cannot be made regarding the effect of CRS/HIPEC in that setting.

There is heterogeneity with regard to the HIPEC agent used, with most institutions preferring oxaliplatin or mitomycin. A multicenter randomized trial in the United States compared HIPEC with mitomycin or oxaliplatin for patients with appendiceal neoplasms (77% were low grade).[76] The HIPEC protocol for both agents was 120 minutes of chemohyperthermia, compared with 30 minutes in the European trials. That study found slightly more hematologic toxicity and lower quality-of-life scores with mitomycin relative to oxaliplatin, with no difference in overall survival, leading the investigators to conclude that oxaliplatin may be superior to mitomycin for HIPEC in MAN.[76,77] Less than 20% of the patients received preoperative chemotherapy; we cannot extrapolate these recommendations to patients with colorectal adenocarcinoma who receive neoadjuvant oxaliplatin-containing regimens, as discussed previously.[71]

In summary, expert consensus supports CRS/HIPEC for well-selected patients with appendiceal cancer based on numerous retrospective studies and institutional experiences showing improved survival and quality of life relative to chemotherapy alone.[16] However, there are no high-level data comparing CRS/HIPEC with CRS alone or modern systemic chemotherapy for appendiceal cancer specifically. The aforementioned studies have all included colorectal cancer, not specifically appendiceal cancer.

High Grade, High Peritoneal Carcinomatosis Index

Patient selection is crucial, but criteria for CRS/HIPEC are often vague and multifactorial. It has been suggested that tumors with high-grade cytology or signet ring cells may not benefit from CRS/HIPEC. However, there are many factors at play. Omohwo et al[78] found that, although low-grade tumors had better 3-year survival than high-grade tumors overall, there was no difference if complete cytoreduction was achieved. The interaction between grade and completeness of cytoreduction was quite strong. Patients with low-grade tumors with complete cytoreduction had a 3-year survival of 100% compared with 80% for incomplete cytoreduction. For patients with high-grade tumors, survival rates were 68% and 9%, respectively.[78] Other studies also found that complete cytoreduction predicted improved survival for patients with high-grade or signet ring cell tumors.[79–81]

Some studies have assessed PCI cutoffs that may predict futility of CRS/HIPEC. A French group studied CRS/HIPEC for colorectal cancer and found a linear relationship between PCI and survival.[82] Although this linearity makes a definitive threshold difficult to define, they concluded that CRS/HIPEC was indicated for PCI less than 12 and contraindicated for PCI greater than 17; for PCI between 12 and 17, other parameters must be taken into account. This group also suggested that PCI greater than 15 is a relative contraindication and strongly predicts small bowel involvement.[83] All patients in this cohort underwent complete cytoreduction (CC-0), and the vast majority had PCI less than 17.

In a retrospective study from three high-volume American institutions, PCI alone did not predict survival for patients with high-grade appendiceal tumors.[84] That group found that the ability to achieve complete cytoreduction (CC-0) was the most important predictor and that arbitrary PCI cutoffs were not meaningful. High PCI was predictive of incomplete cytoreduction, but PCI did not predict survival for patients with CC-0 resection.

Other groups have similarly tried to identify PCI inflection points, with suggested thresholds ranging from 13 to 20.[85,86] It is important to recognize that these studies include patients with colorectal cancer, many nonmucinous. Appendiceal tumors are unique with regard to their biology, propensity to develop peritoneal-only metastases, and susceptibility to CRS/HIPEC. Indeed, even patients with extensive carcinomatosis and high-grade tumors may benefit from CRS/HIPEC.[78,87] Strict application of PCI cutoffs are difficult to define; these patients should always be evaluated by experienced surgeons and teams familiar with the disease when assessing the utility of CRS/HIPEC.

CONCLUSION

Appendiceal neoplasms are a rare group of malignancies with a wide variety of biologic characteristics and malignant behaviors. Our understanding of these tumors and their treatment options has expanded dramatically in recent years, and many patients experience improved survival and quality of life as a result of more aggressive surgical therapies and evolving systemic treatment options. Because of the low incidence and lack of randomized data for most scenarios, patients are best evaluated at high-volume institutions by medical and surgical oncologists who are familiar with these diseases.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Turaga KK, Pappas SG, Gamblin T. Importance of histologic subtype in the staging of appendiceal tumors. Ann Surg Oncol. 2012;19:1379-1385.
2. McCusker ME, Coté TR, Clegg LX, et al. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. Cancer. 2002;94:3307-3312.
3. Overman MJ, Asare EA, Compton CC, et al. Appendix: Carcinoma. In Amin MB (ed). AJCC Cancer Staging Manual, 8th Ed. New York, NY: Springer; 2017.
4. Nagtegaal ID, Klimstra DS, Washington MK. Tumours of the appendix, WHO Classification of Tumours: Digestive System Tumours, 5th Ed. Lyon, France: International Agency for Research on Cancer; 2019.
5. Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. Dis Colon Rectum. 1998;41:75-80.
6. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996; 82:359-374.
7. Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. Ann Surg Oncol. 1999;6:727-731.
8. de Bree E, Michelakis D, Stamatiou D, et al. Pharmacological principles of intraperitoneal and bidirectional chemotherapy. Pleura Peritoneum. 2017;2:47-62.
9. Carr NJ, Bibeau F, Bradley RF, et al. The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei. Histopathology. 2017;71:847-858.
10. Davison JM, Choudry HA, Pingpank JF, et al. Clinicopathologic and molecular analysis of disseminated appendiceal mucinous neoplasms: identification of factors predicting survival and proposed criteria for a three-tiered assessment of tumor grade. Mod Pathol. 2014;27:1521-1539.
11. Ang CS, Shen JP, Hardy-Abeloos CJ, et al. Genomic landscape of appendiceal neoplasms. JCO Precis Oncol. 2018;2:1-18.
12. Liao X, Vavinskaya V, Sun K, et al. Mutation profile of high-grade appendiceal mucinous neoplasm. Histopathology. 2020;76:461-469.
13. Nishikawa G, Sekine S, Ogawa R, et al. Frequent GNAS mutations in low-grade appendiceal mucinous neoplasms. Br J Cancer. 2013;108:951-958.
14. Ritterhouse LL, Vivero M, Mino-Kenudson M, et al. GNAS mutations in primary mucinous and non-mucinous lung adenocarcinomas. Mod Pathol. 2017; 30:1720-1727.
15. Tan MC, Basturk O, Brannon AR, et al. GNAS and KRAS mutations define separate progression pathways in intraductal papillary mucinous neoplasm-associated carcinoma. J Am Coll Surg. 2015;220:845-854.e1.
16. Chicago Consensus Working Group. The Chicago consensus on peritoneal surface malignancies: management of appendiceal neoplasms. Cancer. 2020; 126:2525-2533.
17. Canbay E, Ishibashi H, Sako S, et al. Preoperative carcinoembryonic antigen level predicts prognosis in patients with pseudomyxoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Surg. 2013;37:1271-1276.
18. González-Moreno S, Sugarbaker PH. Right hemicolectomy does not confer a survival advantage in patients with mucinous carcinoma of the appendix and peritoneal seeding. Br J Surg. 2004;91:304-311.
19. Halabi HE, Gushchin V, Francis J, et al. Prognostic significance of lymph node metastases in patients with high-grade appendiceal cancer. Ann Surg Oncol. 2012;19:122-125.
20. Yantiss RK, Shia J, Klimstra DS, et al. Prognostic significance of localized extra-appendiceal mucin deposition in appendiceal mucinous neoplasms. Am J Surg Pathol. 2009;33:248-255.
21. Choudry MH, Pai RK, Bartlett DL. Mucinous Appendiceal Tumors. In Morita SY, Balch CM, Klimberg V, et al, (eds). Textbook of Complex General Surgical Oncology. New York, NY: McGraw-Hill; 2018;1281-1292.
22. Bevan KE, Mohamed F, Moran BJ. Pseudomyxoma peritonei. World J Gastrointest Oncol. 2010;2:44-50.
23. Gough DB, Donohue JH, Schutt AJ, et al. Pseudomyxoma peritonei. Long-term patient survival with an aggressive regional approach. Ann Surg. 1994; 219:112-119.
24. Ronnett BM, Zahn CM, Kurman RJ, et al. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". Am J Surg Pathol. 1995; 19:1390-1408.
25. Austin F, Mavanur A, Sathaiah M, et al. Aggressive management of peritoneal carcinomatosis from mucinous appendiceal neoplasms. Ann Surg Oncol. 2012; 19:1386-1393.
26. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol. 2012;30:2449-2456.

27. Votanopoulos KI, Russell G, Randle RW, et al. Peritoneal surface disease (PSD) from appendiceal cancer treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC): overview of 481 cases. Ann Surg Oncol. 2015;22:1274-1279.
28. Ansari N, Chandrakumaran K, Dayal S, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in 1000 patients with perforated appendiceal epithelial tumours. Eur J Surg Oncol. 2016;42:1035-1041.
29. Huang Y, Alzahrani NA, Chua TC, et al. Histological subtype remains a significant prognostic factor for survival outcomes in patients with appendiceal mucinous neoplasm with peritoneal dissemination. Dis Colon Rectum. 2017;60:360-367.
30. Baratti D, Kusamura S, Milione M, et al. Validation of the recent PSOGI pathological classification of pseudomyxoma peritonei in a single-center series of 265 patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2018;25:404-413.
31. Lu P, Fields AC, Meyerhardt JA, et al. Systemic chemotherapy and survival in patients with metastatic low-grade appendiceal mucinous adenocarcinoma. J Surg Oncol. 2019;120:446-451.
32. Bijelic L, Kumar AS, Stuart OA, et al. Systemic chemotherapy prior to cytoreductive surgery and HIPEC for carcinomatosis from appendix cancer: impact on perioperative outcomes and short-term survival. Gastroenterol Res Pract. 2012;2012:163284.
33. Blackham AU, Swett K, Eng C, et al. Perioperative systemic chemotherapy for appendiceal mucinous carcinoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Surg Oncol. 2014;109:740-745.
34. Shapiro JF, Chase JL, Wolff RA, et al. Modern systemic chemotherapy in surgically unresectable neoplasms of appendiceal origin: a single-institution experience. Cancer. 2010;116:316-322.
35. Moris D, Tsilimigras DI, Vagios S, et al. Neuroendocrine neoplasms of the appendix: a review of the literature. Anticancer Res. 2018;38:601-611.
36. Shaw PA. The topographical and age distributions of neuroendocrine cells in the normal human appendix. J Pathol. 1991;164:235-239.
37. Mullen JT, Savarese DM. Carcinoid tumors of the appendix: a population-based study. J Surg Oncol. 2011;104:41-44.
38. Moertel CG, Weiland LH, Nagorney DM, et al. Carcinoid tumor of the appendix: treatment and prognosis. N Engl J Med. 1987;317:1699-1701.
39. Boudreaux JP, Klimstra DS, Hassan MM, et al; North American Neuroendocrine Tumor Society (NANETS). The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. Pancreas. 2010;39:753-766.
40. Pape UF, Perren A, Niederle B, et al; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology. 2012;95:135-156.
41. Zheng M, Li T, Li Y, et al. Survival profile and prognostic factors for appendiceal mixed neuroendocrine non-neuroendocrine neoplasms: a SEER population-based study. Front Oncol. 2020;10:1660.
42. Elias D, David A, Sourrouille I, et al. Neuroendocrine carcinomas: optimal surgery of peritoneal metastases (and associated intra-abdominal metastases). Surgery. 2014;155:5-12.
43. Goéré D, Passot G, Gelli M, et al. Complete cytoreductive surgery plus HIPEC for peritoneal metastases from unusual cancer sites of origin: results from a worldwide analysis issue of the Peritoneal Surface Oncology Group International (PSOGI). Int J Hyperthermia. 2017;33:520-527.
44. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27:4656-4663.
45. Rinke A, Wittenberg M, Schade-Brittinger C, et al; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): results of long-term survival. Neuroendocrinology. 2017;104:26-32.
46. Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371:224-233.
47. Pavel ME, Hainsworth JD, Baudin E, et al; RADIANT-2 Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011;378:2005-2012.
48. Strosberg J, El-Haddad G, Wolin E, et al; NETTER-1 Trial Investigators. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376:125-135.
49. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Neuroendocrine and Adrenal Tumors. Version 2.2020.
50. Tang LH, Shia J, Soslow RA, et al. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. Am J Surg Pathol. 2008;32:1429-1443.
51. Arai H, Baca Y, Battaglin F, et al. Molecular characterization of appendiceal goblet cell carcinoid. Mol Cancer Ther. 2020;19:2634-2640.
52. Holt N, Grønbæk H. Goblet cell carcinoids of the appendix. ScientificWorldJournal. 2013;2013:543696.
53. Bucher P, Gervaz P, Ris F, et al. Surgical treatment of appendiceal adenocarcinoid (goblet cell carcinoid). World J Surg. 2005;29:1436-1439.
54. Shaib W, Krishna K, Kim S, et al. Appendiceal neuroendocrine, goblet and signet-ring cell tumors: a spectrum of diseases with different patterns of presentation and outcome. Cancer Res Treat. 2016;48:596-604.
55. Mahteme H, Sugarbaker PH. Treatment of peritoneal carcinomatosis from adenocarcinoid of appendiceal origin. Br J Surg. 2004;91:1168-1173.

56. Cashin P, Nygren P, Hellman P, et al. Appendiceal adenocarcinoids with peritoneal carcinomatosis treated with cytoreductive surgery and intraperitoneal chemotherapy: a retrospective study of in vitro drug sensitivity and survival. Clin Colorectal Cancer. 2011;10:108-112.

57. Yu HH, Yonemura Y, Hsieh MC, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for appendiceal goblet cell carcinomas with peritoneal carcinomatosis: results from a single specialized center. Cancer Manag Res. 2017;9:513-523.

58. Shyu S, Choudry H, Hall L, et al. Clinicopathological analysis of appendiceal goblet cell adenocarcinoma with peritoneal metastasis: World Health Organization grade predicts survival following cytoreductive surgery with intraperitoneal chemotherapy. Histopathology. 2020;77:798-809.

59. Gilmore G, Jensen K, Saligram S, et al. Goblet cell carcinoid of the appendix - diagnostic challenges and treatment updates: a case report and review of the literature. J Med Case Reports. 2018;12:275.

60. AlMasri S, Nassour I, Kowalsky SJ, et al. The role of adjuvant chemotherapy in non-metastatic goblet cell carcinoid of the appendix: an 11-year experience from the National Cancer Database. Ann Surg Oncol. Epub 2020 Nov 24.

61. Nash GM, Smith JD, Tang L, et al. Lymph node metastasis predicts disease recurrence in a single-center experience of 70 stages 1-3 appendix cancers: a retrospective review [published correction appears in *Ann Sur Oncol.* 2015;22(suppl 3):S1613]. Ann Surg Oncol. 2015;22:3613-3617.

62. Lieu CH, Lambert LA, Wolff RA, et al. Systemic chemotherapy and surgical cytoreduction for poorly differentiated and signet ring cell adenocarcinomas of the appendix. Ann Oncol. 2012;23:652-658.

63. Tokunaga R, Xiu J, Johnston C, et al. Molecular profiling of appendiceal adenocarcinoma and comparison with right-sided and left-sided colorectal cancer. Clin Cancer Res. 2019;25:3096-3103.

64. Raghav K, Shen JP, Jácome AA, et al. Integrated clinico-molecular profiling of appendiceal adenocarcinoma reveals a unique grade-driven entity distinct from colorectal cancer. Br J Cancer. 2020;123:1262-1270.

65. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. Version 1.2021.

66. Gahagan JV, Whealon MD, Phelan MJ, et al. Lymph node positivity in appendiceal adenocarcinoma: should size matter? J Am Coll Surg. 2017;225:69-75.

67. Aziz O, Jaradat I, Chakrabarty B, et al. Predicting survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for appendix adenocarcinoma. Dis Colon Rectum. 2018;61:795-802.

68. Grotz TE, Overman MJ, Eng C, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for moderately and poorly differentiated appendiceal adenocarcinoma: survival outcomes and patient selection. Ann Surg Oncol. 2017;24:2646-2654.

69. Boeckx N, Koukakis R, Op de Beeck K, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. Ann Oncol. 2017;28:1862-1868.

70. Quénet F, Elias D, Roca L, et al; UNICANCER-GI Group and BIG Renape Group. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2021; 22:256-266.

71. Nagourney RA, Evans S, Tran PH, et al. Colorectal cancer cells from patients treated with FOLFOX or CAPOX are resistant to oxaliplatin. Eur J Surg Oncol. 2020; S0748-7983-7.

72. Kirstein MN, Root SA, Moore MM, et al. Exposure-response relationships for oxaliplatin-treated colon cancer cells. Anticancer Drugs. 2008;19:37-44.

73. Quenet F, Elias D, Roca L, et al. A UNICANCER phase III trial of hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. J Clin Oncol. 2018;36 (suppl; abstr LBA3503).

74. Goéré D, Glehen O, Quenet F, et al; BIG-RENAPE group. Second-look surgery plus hyperthermic intraperitoneal chemotherapy versus surveillance in patients at high risk of developing colorectal peritoneal metastases (PROPHYLOCHIP-PRODIGE 15): a randomised, phase 3 study. Lancet Oncol. 2020;21:1147-1154.

75. Klaver CEL, Wisselink DD, Punt CJA, et al; COLOPEC collaborators group. Adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer (COLOPEC): a multicentre, open-label, randomised trial. Lancet Gastroenterol Hepatol. 2019;4:761-770.

76. Levine EA, Votanopoulos KI, Shen P, et al. A Multicenter Randomized Trial to Evaluate Hematologic Toxicities after Hyperthermic Intraperitoneal Chemotherapy with Oxaliplatin or Mitomycin in Patients with Appendiceal Tumors [published correction appears in J Am Coll Surg. 2018;227:633]. J Am Coll Surg. 2018; 226:434-443.

77. Moaven O, Votanopoulos KI, Shen P, et al. Health-related quality of life after cytoreductive surgery/HIPEC for mucinous appendiceal cancer: results of a multicenter randomized trial comparing oxaliplatin and mitomycin. Ann Surg Oncol. 2020;27:772-780.

78. Omohwo C, Nieroda CA, Studeman KD, et al. Complete cytoreduction offers longterm survival in patients with peritoneal carcinomatosis from appendiceal tumors of unfavorable histology. J Am Coll Surg. 2009;209:308-312.

79. Cummins KA, Russell GB, Votanopoulos KI, et al. Peritoneal dissemination from high-grade appendiceal cancer treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). J Gastrointest Oncol. 2016;7:3-9.

80. Polanco PM, Ding Y, Knox JM, et al. Outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion in patients with high-grade, high-volume disseminated mucinous appendiceal neoplasms. Ann Surg Oncol. 2016;23:382-390.

81. Levinsky NC, Morris MC, Wima K, et al. Should we be doing cytoreductive surgery with HIPEC for signet ring cell appendiceal adenocarcinoma? A study from the US HIPEC Collaborative. J Gastrointest Surg. 2020;24:155-164.

82. Faron M, Macovei R, Goéré D, et al. Linear relationship of peritoneal cancer index and survival in patients with peritoneal metastases from colorectal cancer. Ann Surg Oncol. 2016;23:114-119.

83. Elias D, Mariani A, Cloutier AS, et al. Modified selection criteria for complete cytoreductive surgery plus HIPEC based on peritoneal cancer index and small bowel involvement for peritoneal carcinomatosis of colorectal origin. Eur J Surg Oncol. 2014;40:1467-1473.

84. Votanopoulos KI, Bartlett D, Moran B, et al. PCI is not predictive of survival after complete CRS/HIPEC in peritoneal dissemination from high-grade appendiceal primaries. Ann Surg Oncol. 2018;25:674-678.

85. Yan TD, Chu F, Links M, et al. Cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma: non-mucinous tumour associated with an improved survival. Eur J Surg Oncol. 2006;32:1119-1124.

86. da Silva RG, Sugarbaker PH. Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. J Am Coll Surg. 2006;203:878-886.

87. Sarkar A, Lansom J, Dey A, et al. Outcomes in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for maximal volume (PCI 39) appendiceal tumours. Eur J Surg Oncol. Epub 2020 Nov 27.

Locoregional Therapies for Colorectal Cancer Liver Metastases: Options Beyond Resection

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Overview

Colorectal cancer was the third most common malignancy worldwide in 2018, and most patients present with or develop distant metastases. Colorectal liver metastases are most commonly observed because of the vascular drainage of the colon and superior rectum. Current guidelines recommend surgical resection as first-line treatment; however, 80% to 90% of patients with colorectal liver metastases are ineligible for primary resection. For patients with unresectable disease, a multidisciplinary treatment approach is favored, incorporating systemic therapy and a toolbox of local ablative therapies. These treatments either aim at cytoreduction to enable a conversion to surgical resectability or control of disease progression and spread. Each of these treatments carries unique outcomes and risk profiles, thereby contributing to an individualized treatment strategy for patients with colorectal liver metastases. This review summarizes evidence on hepatic artery infusion, stereotactic body radiation therapy, thermal ablation, transarterial chemoembolization with drug-eluding beads, and transarterial radioembolization for treatment of colorectal liver metastases. Results of large-scale prospective and retrospective studies and international guidelines are discussed to provide detailed background on the current and prospective use of local ablative techniques in management of colorectal liver metastases.

In 2018, colorectal cancer (CRC) was the third most common malignancy, accounting for 10.2% of incident cancer cases worldwide.[1] A total of 9.2% of cancer-related deaths worldwide were attributed to CRC in 2018, ranking CRC second after lung cancer.[1] Among patients with CRC, 20% to 25% present with distant metastases at the time of diagnosis, and another 50% to 60% of initially localized CRC will spread over the disease course.[2,3] Because of the portal venous drainage of the colon and superior rectum, CRC most commonly metastasizes to the liver. Up to 80% of patients with stage IV CRC with at least one metastatic site will have involvement of the liver (colorectal liver metastases).[4]

TREATMENT ALGORITHM FOR PATIENTS WITH COLORECTAL LIVER METASTASES

According to international guidelines by ASCO and the European Society of Medical Oncology (ESMO), surgical resection should be considered as first-line treatment for patients with colorectal liver metastases.[5,6] However, approximately 80% to 90% of patients with colorectal liver metastases are ineligible for primary resection based on the extent of their disease, presence of other metastases, and/or patients' clinical performance.[7] For patients with unresectable disease, a multidisciplinary approach is favored, incorporating systemic therapy and a toolbox of local ablative therapies.[5] These treatments either aim to achieve cytoreduction to enable a conversion to surgical resectability or to control progression of colorectal liver metastases and extrahepatic disease.[5]

One specific scenario for patients with metastatic CRC is the so-called oligometastatic disease, which is defined by the presence of limited metastases; most guidelines arbitrarily define oligometastatic disease as up to three sites and five lesions.[5] In oligometastatic disease, treatment strategies should be directed at complete tumor destruction or control at all sites, using surgical resection alone or in combination with local ablative therapy after an initial course of systemic therapy.[5] For patients with oligometastatic disease with colorectal liver metastases alone, systemic therapy may even be omitted.

The toolbox of local ablative therapies for colorectal liver metastases includes several treatments implemented by a multidisciplinary team, including therapies such as hepatic artery infusion, stereotactic body radiation therapy (SBRT), thermal ablation, transarterial radioembolization (TARE), and transarterial chemoembolization. Each of these techniques carries unique outcomes and risk profiles, thereby contributing to an individualized treatment strategy for patients with colorectal liver metastases.

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PRACTICAL APPLICATIONS

- Colorectal liver metastases are the most common metastases observed in patients with colorectal cancer.
- Guidelines recommend surgical resection as first-line treatment of colorectal liver metastases; however, most patients are surgically ineligible.
- For patients who have surgically ineligible colorectal liver metastases, a multidisciplinary treatment approach is favored, incorporating systemic therapy and a toolbox of local ablative therapies.
- Local ablative therapies aim at cytoreduction to enable a conversion to surgical resectability or disease control.
- Local ablative therapies include hepatic artery infusion, stereotactic body radiation therapy, thermal ablation, transarterial chemoembolization with drug-eluding beads, and transarterial radioembolization.

HEPATIC ARTERY INFUSION FOR COLORECTAL LIVER METASTASES

Hepatic artery infusion chemotherapy has been available to oncologists for more than 25 years as a therapeutic option for patients with colorectal liver metastases. Hepatic artery infusion has not gained widespread acceptance outside of select high-volume tertiary centers, such as Memorial Sloan Kettering Cancer Center (MSKCC), due to multiple factors, including the need for complex yet precise dosing and monitoring to avoid toxicity, specialized surgical techniques, and multidisciplinary expertise. In addition, there is a paucity of large, prospective, multi-institutional clinical trials evaluating hepatic artery infusion, and this treatment method has not been directly compared with standard-of-care combination systemic chemotherapy, which has demonstrated efficacy. Nonetheless, long-term survival is achievable for patients with colorectal liver metastases who undergo complete liver resection, and therefore, modalities such as hepatic artery infusion that facilitate reaching this goal should be considered. Hepatic artery infusion has shown to improve response rates in liver disease with long-term control, without reaching resection. In 2020, ASCO guidelines encouraged consideration of surgical resection at institutions with a high level of experience, provided that patients respond to chemotherapy.[6]

The hepatic artery is the main supply of nutrients for liver metastases (> 3 mm diameter), whereas the portal vein supplies the normal unaffected liver parenchyma.[8] Importantly, the liver also metabolizes certain drugs at first pass through hepatic arterial circulation. This results in high intrahepatic concentrations with limited systemic exposure, making drugs with short half-lives ideal for use in hepatic artery infusion.[9] Floxuridine (FUDR), a prodrug of 5-fluoruracil (5-FU), exhibits these features and in preclinical studies demonstrated a 94% to 99% extraction by the liver during first-pass metabolism.[10] The major toxicity of hepatic artery infusion FUDR is biliary toxicity, requiring close monitoring; the risk of toxicity may be reduced with concurrent use of dexamethasone during hepatic artery infusion and close adherence to established dose reductions.[11] Other drugs including oxaliplatin and mitomycin have also been administered through hepatic artery infusion, especially in countries without access to FUDR.

Hepatic Artery Infusion as Adjuvant Therapy After Liver Resection

Recurrence after liver resection in colorectal liver metastases has been observed in more than 50% of patients, with liver-only recurrence in nearly half of those patients[12]; thus, there is a strong rationale for incorporation of adjuvant hepatic artery infusion therapy to decrease risk of hepatic recurrence and improve survival. In 1999, 156 patients who underwent complete resection of their colorectal liver metastases at MSKCC were randomly assigned to receive adjuvant hepatic artery infusion FUDR with systemic 5-FU/leucovorin compared with adjuvant systematic therapy alone. Hepatic artery infusion improved hepatic progression-free survival (PFS) at 2 years, with a median of 37.4 months versus 17.2 months, respectively. At 2 years, overall survival (OS) was 86% versus 72% ($p = .03$), with a risk ratio for death in monotherapy of 2.13 ($p = .05$).[11] An update in 2005 showed that longer hepatic PFS persisted in the hepatic artery infusion FUDR arm (median, not reached vs. 32.5 months; $p < .01$), with a 10-year survival of 41.1% versus 27.2% (median, 68.4 months vs. 58.8 months); however, the p value was no longer significant ($p = .13$).[13] Hepatic artery infusion therapy was criticized for failure to retain OS benefit; however, OS may have been affected by crossover to the group that received hepatic artery infusion. Critics of adjuvant hepatic artery infusion also noted that this study was not performed in the era of modern systemic therapy. Subsequent smaller prospective studies lacked power or failed to accrue leading to incomplete studies; however, retrospective studies continued to show improvement in liver-related outcomes[14,15] and an association of adjuvant hepatic artery infusion with longer OS and disease-free survival.[15] Overall, although hepatic artery infusion remains a promising modality to control liver recurrence after complete resection of colorectal liver metastases, controversy has persisted as to its true benefit.

In current treatment regimens, oxaliplatin and irinotecan are often administered in the adjuvant setting paired with systemic 5-FU/leucovorin and hepatic artery infusion FUDR. A retrospective study of 125 patients treated between 2000 and 2005 with adjuvant hepatic artery infusion FUDR and concurrent systemic chemotherapy including 5-FU plus oxaliplatin or irinotecan found that patients who received hepatic artery infusion FUDR with systemic chemotherapy demonstrated improved OS and hepatic PFS compared with those who received systemic therapy alone.[16] Another study showed similar results for patients who underwent ablation of resection of recurrent colorectal liver metastases along with adjuvant hepatic artery infusion.[17] In perhaps the strongest evidence for adjuvant hepatic artery infusion in the modern era, the MSKCC group reported results from 2,368 patients with consecutive colorectal liver metastases resections who received modern systemic chemotherapy, 785 of which also had adjuvant hepatic artery infusion FUDR. Despite a higher disease burden, patients who received combined therapy had a longer median OS of 67 months compared with 44 months for those who were treated with adjuvant systemic chemotherapy alone ($p < .01$). Using propensity score matching, this survival benefit persisted with an OS hazard ratio (HR) for hepatic artery infusion of 0.67 ($p < .001$).[18] Ten-year OS was 38.0% in the hepatic artery infusion/modern systemic therapy group compared with 23.8% in the systemic theapy–alone group, an outcome that has been corroborated in a separate study of actuarial 10-year survivors.[19] Although future confirmation is needed in prospective multi-institutional trials, it is evident that for appropriately selected patients, long-term benefit can be achieved with liver resection followed by adjuvant hepatic artery infusion FUDR combined with modern systemic therapy.

Hepatic Artery Infusion in Unresectable Liver Metastases

In 2006, one of the few multi-institutional studies of hepatic artery infusion was reported by the Cancer and Leukemia Group B for patients with unresectable colorectal liver metastases. A total of 135 patients with hepatic metastases were randomly assigned to receive hepatic artery infusion FUDR/leucovorin/dexamethasone compared with 5-FU/leucovorin. Crossover was prohibited. Overall survival favored hepatic artery infusion FUDR at 24.4 months versus 20.0 months for systemic therapy, with 2-year survival rates of 51% versus 35% ($p = .0034$), respectively. Time to hepatic progression was 9.8 months versus 7.3 months ($p = .034$), respectively. However, time to extrahepatic progression favored the systemic chemotherapy arm (14.8 months vs. 7.7 months; $p = .29$).[20] Subsequent to this study, future studies of hepatic artery infusion included systemic chemotherapy for control of distant micrometastatic disease.

For patients who have progressed on multiple lines of chemotherapy, new therapies for metastatic CRC (excluding targeted molecular and immunotherapies) have been limited to two drugs: regorafenib and trifluridine/tipiricil. Placebo-controlled studies published in 2013 and 2015 revealed a median OS of 6.4 months and 7.1 months, respectively, both showing a less than 2-month survival advantage compared with placebo.[21,22] In contrast, another study reported the results of 110 patients with colorectal liver metastases who had progressed on at least three lines of therapy (including anti-EGFR therapy in *KRAS* wild type) and who had received hepatic artery infusion FUDR with systemic therapy. Fifty-seven patients had hepatic involvement only, whereas 53 patients also had extrahepatic disease. In the hepatic-only group, 19 patients experienced partial response, and 31 patients experienced stable disease, whereas in the hepatic/extrahepatic group, 19 patients experienced partial response and 24 patients had stable disease; response rates were 33% and 36%, respectively. Overall survival was 20.0 months and 11.4 months, respectively, comparing favorably to the outcomes observed in regorafinib and trifluridine/tipiricil studies, although patient selection for hepatic artery infusion may have biased the results.[23]

Hepatic Artery Infusion as Therapy to Increase Conversion to Resectability

Although liver resection for colorectal liver metastases is associated with long-term survival, this is only possible in 10% to 20% of patients at initial diagnosis. Hepatic artery infusion has been used as a strategy to convert more patients to resection. In one retrospective report, 49 patients with disease deemed unresectable received hepatic artery infusion FUDR with systemic therapy (fluorouracil/leucovorin/oxaliplatin [FOLFOX] or fluorouracil/leucovorin/irinotecan) until resectable or progression.[24] Forty-five patients experienced complete (8%) or partial (84%) responses, allowing 47% to then undergo resection (57% in chemotherapy-naïve disease), many of which had more than five lesions and bilobar liver disease. Overall survival was 50.8 months in patients with chemotherapy-naïve disease compared with 35 months in those with previously treated disease.

In a prospective phase II study, 33 of 64 (52%) patients were reported to have conversion to resection after receiving hepatic artery infusion FUDR with modern systemic chemotherapy.[25] The overall response rate was 73% in the entire group and 86% for patients who had not yet received chemotherapy. Twenty-five of the patients who received resection had more than 75% necrosis. Of the 31 patients (48%) who did not reach resection, one had a complete response, 18 had partial responses, and 12 had stable disease. Conversion to resection was associated with long-

term survival, with a 5-year OS for resected disease at 63.3% compared with 12.5% for patients who did not undergo resection. Univariate analysis revealed that absence of previous therapy and conversion to resection were associated with improved OS. Of note, bevacizumab (anti-VEGF monoclonal antibody) was given initially; however, because of correlation with higher biliary toxicity, it was removed from the trial. Overall, these studies support use of hepatic artery infusion to increase the number of patients who are eligible for resection, which is associated with longer survival.

Multidisciplinary Approach to Hepatic Artery Infusion and Future Outlook

One of the main barriers to successful implementation of hepatic artery infusion programs outside of MSKCC has been amassing adequate multidisciplinary expertise to navigate the complexities of care for colorectal liver metastases, including a highly trained team of surgical oncologists, medical oncologists, nurses, pharmacists, radiologists, and interventional radiologists. Perhaps more importantly, another key barrier has been the lack of broad consensus as to the utility, indications, and management of hepatic artery infusion given the lack of modern level 1 evidence either for or against the treatment. However, an increasing number of centers have recently reported establishment of active programs across North America and Europe,[26-28] an achievement that we have also accomplished at our institution (16 hepatic artery infusion pumps implanted in 9 months; Patel RA et al, unpublished data, 2021). In addition, a group of hepatic artery infusion programs at 36 centers across the United States and abroad (Netherlands, Canada, and Mexico) led by Duke University and MSKCC has been established, with the goal of designing and implementing prospective, randomized clinical trials of hepatic artery infusion chemotherapy to fill the gaps that currently exist in the literature and improve long-term survival for patients with colorectal liver metastases.

STEREOTACTIC BODY RADIATION THERAPY FOR COLORECTAL LIVER METASTASES

SBRT has historically played a minor role in the potentially curative treatment of patients with liver metastases because of the limited radiotolerance of the liver and high doses required to achieve local control. SBRT is a highly conformal radiation technique that delivers large doses of radiation in one or few fractions to well-defined targets, using image-guidance and motion management.[29] With SBRT, steep dose gradients are created near the tumor edge, limiting the dose delivered to the surrounding liver and adjacent organs-at-risk.[30] Because of its noninvasive nature and high rates of local control, it has become an attractive option for patients with oligometastases, including colorectal liver metastases. SBRT has been shown to achieve high rates of local control with minimal toxicity, delay the need for systemic therapy, and improve PFS.[31,32] Additionally, long-term results of the SABR-COMET randomized phase II clinical trial have demonstrated an improvement in OS at 5 years (17.7% vs. 42.3%; p = .006) with the use of SBRT in the management of oligometastatic disease (although the minority of patients had colorectal liver metastases).[33] A U.K. prospective registry reported that the use of SBRT for patients with metachronous CRC oligometastases (any site) achieved a 1-year and 2-year OS of 92% (95% CI, 86.6%–95.3%) and 80.3% (95% CI, 71.8%–86.5%), respectively.[32]

Although there are no phase III randomized trials evaluating the use of SBRT in the treatment of colorectal liver metastases, several phase I and II prospective studies along with retrospective case series have demonstrated promising results in terms of OS, local control, and toxicity profile.[34-41]

Median OS after SBRT for colorectal liver metastases ranges from 16 months to 32 months (Table 1); the wide range of reported outcomes is likely secondary to the heterogeneity of patients included in these studies, various lines of systemic treatment used over time, and variable tumor biology and mutation status. A 2018 systematic review evaluated the efficacy of SBRT for patients with colorectal liver metastases; 18 studies were included, totaling 656 patients.[42] The pooled 1- and 2-year OS, respectively, were 67.2% (95% CI, 42.1%–92.2%) and 56.5% (95% CI, 36.7%–76.2%).[37] Median OS in the pooled estimates was 31.5 months (range, 15–24.4 months).[37] An important consideration when evaluating these results in the context of surgical series is that most patients enrolled in SBRT studies were not eligible for surgery or presented with metastases that were too large for radiofrequency ablation and thus represent a group with a poorer prognosis at baseline.

Local control for colorectal liver metastases treated with SBRT ranges from 50% to 95% at 1 year, with better results in more recent years (Table 1). A pooled 1- and 2-year local control estimate was 67% (95% CI, 43.8%–90.2%) and 59.3% (95% CI, 37.2%–81.5%), respectively.[42] Several authors have reported improved local control for smaller volume tumors (diameter generally less than 3 cm) and higher prescribed radiation dose.[33,34,38] In particular, the biologically equivalent dose (BED) has been reported to be an independent prognostic factor for local control.[36,42,43] In a retrospective review of 65 patients with colorectal liver metastases, a BED_{10} of more than 75 Gy was an independent prognostic factor for local control and a BED_{10} of more than 117 Gy was required to achieve a 1-year local control of 90%.[39] Similar results were reported in a retrospective analysis of 70 patients: the 2-year local control rates were 52% with a BED_{10} of 80 Gy or less; 83% with a BED_{10} between 100 Gy–112 Gy; and 89% with a BED_{10} of 132 Gy or more.[43] Although delivery

TABLE 1. Summary of Phase I to II Prospective Studies Evaluating the Use of SBRT in the Treatment of Colorectal Liver Metastases

Reference	No. of Patients	Dose Fractionation (Gy; BED_{10} Gy)	Median Follow-up (mo)	Overall Survival		Local Control (1 year %)	Toxicity
				Median (mo)	1-year/ 2-year (%)		
Scorsetti et al, 2015,[34] 2018[41]	42	75 Gy/3 fr (262.5 Gy)	24	29	65/65	95	Fatigue (55); transient hepatic transaminase increase (25); nausea (12)
Herfath et al, 2004[35]	18	14–26 Gy/1 fr (33.6–93.6 Gy)	5.7	25	72/NR	71	No significant toxicity
Lee et al, 2009[36]	40	27.7–60 Gy/ 5–6 fr (40.44–120 Gy)	10.8	17.6	63/NR	71	Rib fracture (3); gastritis (2); nausea (2); grade 4 thrombocytopenia (1)
Rusthoven et al, 2009[37]	15	36–60 Gy/3 fr (79.2–180 Gy)	16	32	NR/30	95	No significant toxicity
Hoyer et al, 2006[38]	44	45 Gy/3 fr (112.5 Gy)	52	19.2	67/38	—	Grade 1-2 nausea (34), grade 1-2 diarrhea (23)
							Grade 3 intestinal toxicity (5), liver failure (2), death (1)
Chang et al, 2011[39]	65	22–60 Gy/1–6 fr (40.5–180 Gy)	14	—	72/38	62	Grade 1-2 GI toxicity (17)
							Grade 3+ GI toxicity (3)
McPartlin et al, 2017[40]	60	22.7–62.1/5–6 fr (31.28–126.37 Gy)	28.1	16	63/26	50	Grade 3 nausea (2)

Abbreviations: BED, biologically equivalent dose; GI, gastrointestinal; NR, not recorded.

of a high BED appears to be associated with favorable outcomes in terms of local control, it may not always be achievable because of tumor factors (number of lesions, size of lesions, tumor location), patient factors (volume of normal liver, proximity of target lesion to organs at risk, motion of liver and organs at risk), and treatment factors (radiation technique, motion management, image matching).

Local control after SBRT is also related to genomic subtypes of CRC. It has been reported that tumors with *KRAS* mutations have inferior local control compared with *KRAS* wild-type tumors (1-year local control, 43% vs. 72%; p = .02).[44] Local control is further decreased in tumors with both *KRAS* and *TP53* mutations (1-year local control, 20% vs. 69%; p = .001).[44] Similar results were reported by Jethwa et al,[45] who demonstrated that tumors with a *TP53* mutations had an increased risk of local failure (HR, 3.1; 95% CI, 0.9–10.6; p = .06) and those with both *TP53* and *KRAS* mutations had an even higher risk (HR, 4.5; 95% CI, 1.1–18.7; p = .04). Conversely, a prospective multicenter cohort study of CRC oligometastases at various sites (liver, node, lung, bone) found no difference in local control between *KRAS* wild-type and mutant cases (log rank, p = .63), although there was an improvement in PFS (HR, 0.42; 95% CI, 0.2–0.87; p = .02).[46] Although not yet validated in prospective studies, when planning SBRT, the molecular genomic subtype of the tumor should be incorporated into decision making; for patients with either *TP53* mutations, *KRAS* mutations, or both, consideration should be given to dose escalation wherever possible.

SBRT is generally well tolerated; the reported toxicity is summarized in Table 1. The most common treatment-related toxicities are fatigue, mild nausea, and transient elevation of liver enzymes. The risk of significant (grade 3+) toxicity, particularly radiation-induced liver disease, is less than 10%, with most studies reporting no incidence of grade 3+ liver toxicity.[35-39] Gastrointestinal toxicity has also been reported secondary to the proximity of luminal structures (stomach, duodenum, bowel) to the liver. One study reported that five of 44 (11%) patients treated developed grade 3 intestinal toxicity within 6 months after SBRT.[36] Hoyer et al[38] reported two duodenal ulcerations (conservative management), one colonic perforation (surgically managed), and one treatment-related death caused by hepatic failure. Adherence to liver and luminal gastrointestinal radiation dose tolerances is important to ensure the risk of toxicity is low. This makes SBRT of colorectal liver metastases adjacent to the stomach or bowels less effective, because of the need to reduce the prescribed dose to avoid toxicity.

There are several important considerations when proceeding with SBRT for colorectal liver metastases including: patient positioning and CT/MRI simulation, treatment planning, and motion management strategies. SBRT may

be used to treat multiple liver metastases simultaneously if possible and if clinically appropriate. Additionally, SBRT can be used to treat larger tumors than those treated with radiofrequency ablation (most studies included tumors up to 6 cm). MRI may aid in target definition because of its superior soft tissue contrast resolution compared with CT. When defining organs at risk for treatment planning, wherever possible, standardized protocols and naming conventions should be adopted. There are various strategies that can be used to increase the therapeutic ratio and dose escalate the primary tumor while reducing the dose deposited in organs at risk. The planning target volume accounts for internal organ motion and daily set-up variation; larger planning target volumes are more likely to overlap with greater areas of organs at risk. Therefore, implementing techniques that allow for the reduction of planning target volume size may concurrently allow for the reduction of the dose deposited in organs at risk. For example, improved image guidance and motion management (e.g., treatment using active breathing control for liver tumors rather than free breathing) generally allow for the use of smaller planning target volume margins. The use of new technologies, such as MRI-guided radiation therapy, may also allow for planning target volume reduction by improving target visualization and facilitating adaptive radiation therapy. Last, biomarkers may be useful in patient selection for treatment and dose selection during radiation treatment planning.

A clinical example of oligometastasis treatment is demonstrated in Fig. 1. A 76-year-old patient who was otherwise healthy completed treatment in February 2019 for a T2N1M0 moderately differentiated adenocarcinoma of the colon. In July 2020, a new segment 7 lesion was noted on surveillance CT; biopsy was consistent with metastatic CRC. Given the patient's comorbidities and preference for a noninvasive treatment option, multidisciplinary consensus was to proceed with SBRT. Figure 1A and 1B demonstrate the gross tumor volume on the radiation planning CT and MRI. Figure 1C shows the dose distribution; the lesion was treated to a dose of 45 Gy in five fractions ($BED_{10} = 85.5$ Gy) in August 2020. The treatment was delivered using an active breathing control device for motion management. Figure 1D demonstrates a 3-month follow-up CT scan (December 2020). Response is seen within the treated lesion (yellow arrow), and radiation-related change is seen in the surrounding tissue (red arrow) corresponding to the low dose isodose lines.

In summary, SBRT is an effective noninvasive option for patients with liver metastases secondary to CRC, providing high rates of local tumor control without significant toxicity, in colorectal liver metastases that are not adjacent to luminal

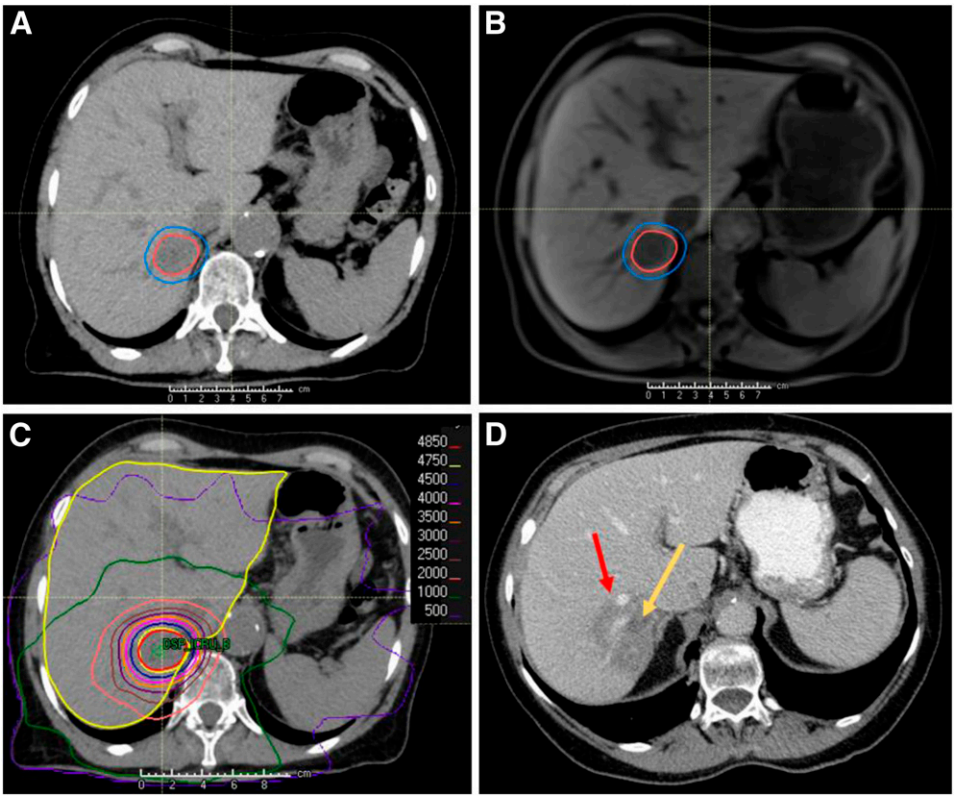

FIGURE 1. Stereotactic Body Radiation Therapy Case Study

(A) CT simulation demonstrating the gross tumor volume (GTV; red) and planning target volume (PTV; blue). (B) MRI simulation (T1-weighted MRI) demonstrating the GTV (red) and PTV (blue). MRI was obtained to aid in target volume definition in this case. (C) Axial CT slice demonstrating the isodose distribution for an SBRT plan delivering 45 Gy in five fractions (BED_{10}, 85.5 Gy). (D) Diagnostic CT obtained at 3 months after treatment. Response is seen within the treated lesion (yellow arrow) and radiation-related change is seen in the surrounding tissue (red arrow) corresponding to the low isodose lines.

gastrointestinal organs. Going forward, we advocate for definitive prospective evaluation and validation of SBRT in this setting.

THERMAL ABLATION FOR COLORECTAL LIVER METASTASES

Thermal ablation techniques induce tumoral cell death through frictional heating resulting in tissue charring (radiofrequency ablation) or through electromagnet agitation of water molecules resulting in coagulation necrosis (microwave ablation; Fig. 2). According to expert consensus, thermal ablation can be considered for patients with colorectal liver metastases that are deemed unresectable because of tumor distribution, insufficient liver reserve, and comorbidities, as well as for patients with specific treatment preference.[47] Thermal ablation is preferred for patients with less than three lesions, each with a diameter less than 3 cm, and those distant from vulnerable structures. The use of thermal ablation in more advanced cases with up to nine lesions, each with a diameter less than 5 cm, has also been described.[47] Generally, an ablation margin of at least 5 mm surrounding the colorectal liver metastases is recommended to attain adequate local control.[48,49]

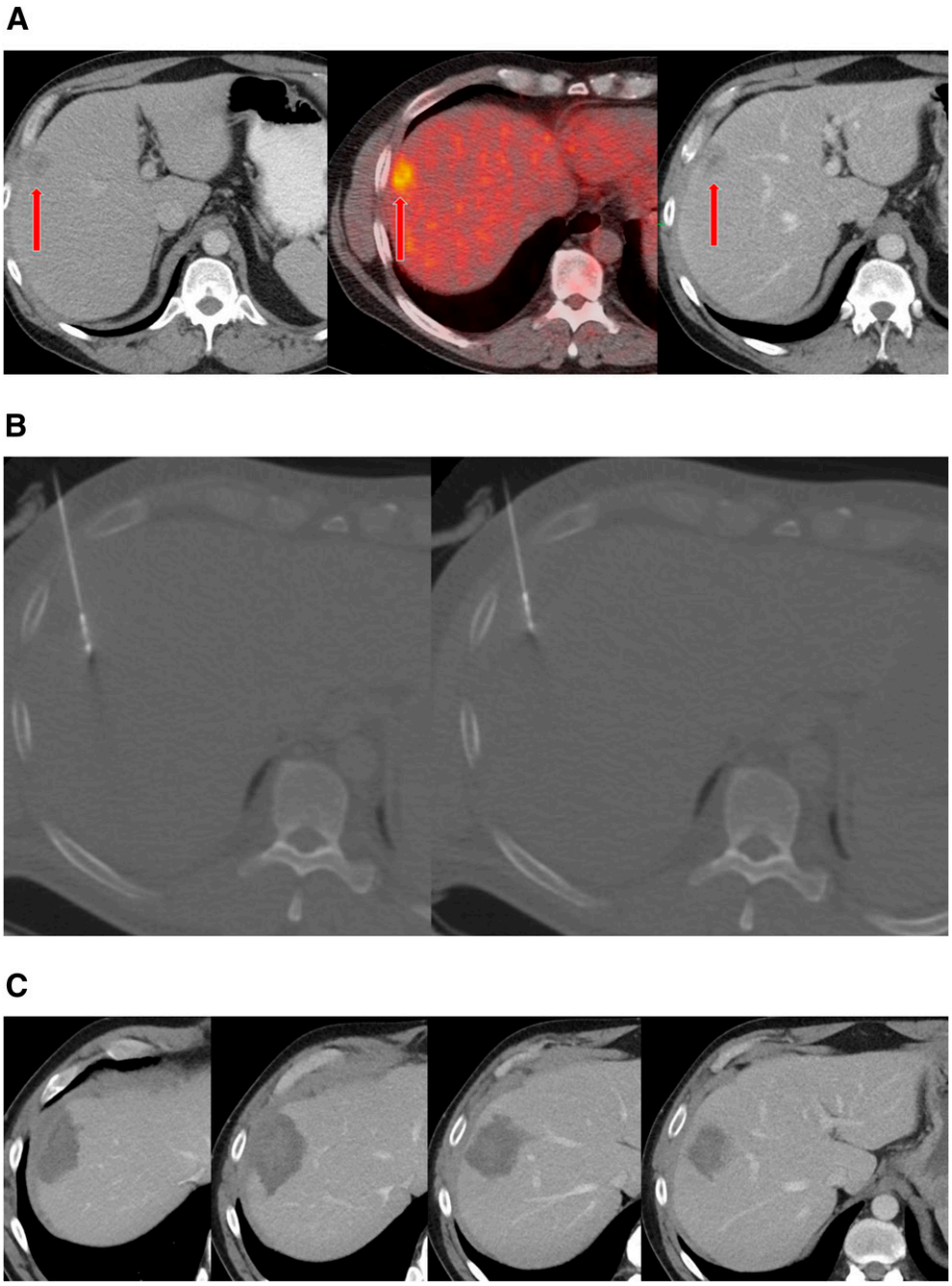

FIGURE 2. Thermal Ablation Case Study

(A) CT and PET CT demonstrating oligoprogression in the liver 2 years after the initial diagnosis of stage IV colorectal cancer. (B) Image guidance for targeted thermal ablation (microwave ablation) of colorectal liver metastases. (C) Contrast-enhanced CT after thermal ablation showing no enhancement in the treated colorectal liver metastases, demonstrating complete response after microwave ablation.

Several studies have been published over the last 2 decades demonstrating the effectiveness and safety of thermal ablation for colorectal liver metastases (Table 2).

One phase II trial randomnly assigned 119 patients with colorectal liver metastases to systemic therapy versus radiofrequency ablation plus systemic therapy with or without surgical resection. Longer OS was reported for the combination treatment (HR, 0.58; 95% CI, 0.38–0.88; p = .01).[53] Associated 5-year OS rates were 43.1% versus 30.3%, with a median OS of 45.6 months versus 40.5 months.

Sobiati et al[51] reported results from 99 patients who were treated with percutaneous radiofrequency ablation for colorectal liver metastases at a technical success rate of 93%, demonstrating a median OS of 53.2 months; major complications were encountered in only 1.3% of the cases. Similarly, Wang et al[52] described excellent outcomes in 115 patients with colorectal liver metastases who underwent percutaneous ultrasound-guided microwave ablation; 3-year OS was 78.7% and the 3-year recurrence rate was 59.3%. Thoracocentesis was necessary in five cases for pleural effusion drainage (4.3%).

Both radiofrequency ablation and microwave ablation show comparable technical success rates, outcomes, and safety in patients with colorectal liver metastases.[55] However, microwave ablation demonstrates a technical advantage over radiofrequency ablation because of a reduced heat-sink effect and it might thus be favorable in colorectal liver metastaess that are in proximity to major vessels.[49]

TRANSARTERIAL CHEMOEMBOLIZATION FOR COLORECTAL LIVER METASTASES

Transarterial therapies aim at delivering a high focal dose of chemotherapy to colorectal liver metastases driven by their rich vascularity while minimizing systemic drug exposure and side effects. Promising a slower and constant release of chemotherapeutic agents compared with conventional chemoembolization, drug-eluting beads loaded with irinotecan (DEBIRI) have been increasingly studied over the last years.[56] According to the ESMO guideline, DEBIRI should be considered for patients with colorectal liver metastases that are not responding to chemotherapy,[5] based on one prospective phase III trial.[57] Randomnly assigning 74 patients to receive either DEBIRI or fluorouracil/leucovorin/irinotecan, Fiorentini et al[57] demonstrated a longer OS (median, 22 months vs. 15 months; p = .031) and PFS (median, 7 months vs. 4 months; p = .006) for DEBIRI.[57] Common terminology criteria for adverse events (CTCAE) grade 3/4 toxicities were reported in 2% in the DEBIRI arm and in 4% in the fluorouracil/leucovorin/irinotecan arm.

The effectiveness of DEBIRI for patients with treatment-naïve, nonresectable colorectal liver metastases has been evaluated in one recent phase III trial.[58] Martin et al[58] randomly assigned 70 patients to receive DEBIRI/FOLFOX versus FOLFOX, each with or without addition of bevacizumab. Although PFS was numerically higher for DEBIRI/FOLFOX, no statistical significance was reached compared with FOLFOX alone (median PFS, 15 months vs. 12 months; p = .18). However, liver PFS was longer for DEBIRI/FOLFOX (median, 17 months vs. 12 months; p = .05), whereas CTCAE grade 3/4 toxicities were less common in the FOLFOX arm (60% vs. 80%; p = .03).

Summarizing the evidence on DEBIRI for 850 patients with colorectal liver metastases, one meta-analysis reported average DEBIRI response rates of 51% to 56%; high-grade toxicities were observed in 10% of patients.[56]

TRANSARTERIAL RADIOEMBOLIZATION FOR COLORECTAL LIVER METASTASES

TARE is a catheter-based intra-arterial technique that focally delivers a high radiation dose to hepatic lesions, resulting in tumoral necrosis and fibrosis.[59] Most commonly, microspheres loaded with the β-radiator Yittrium-90 (^{90}Y) are used.[60]

According to ESMO and National Comprehensive Cancer Network guidelines, TARE should be considered for patients with colorectal liver metastases and liver-limited disease that has failed to respond to chemotherapeutic options.[5,61] This recommendation is based on a phase III randomized controlled clinical trial of 44 patients with chemorefractory disease who were treated with FU or TARE/FU.[62] Combined TARE/FU demonstrated longer time to tumor progression (median, 4.5 months vs. 2.1 months; p = .03) and longer time to liver progression (median, 5.5 months vs. 2.1 months; p = .003). Although median OS was numerically longer for TARE/FU, no statistical significance was reached (10 months vs. 7.3 months; p = .8). CTCAE grade 3/4 toxicities were reported in only one patient who received TARE/FU (5%) compared with six patients in the FU arm (26%).

More recently, the utility of TARE for patients with treatment-naïve colorectal liver metastases has been evaluated in three large randomized controlled trials. In the SIRFLOX trial, van Hazel et al[63] randomly assigned 530 patients with treatment-naïve disease to FOLFOX versus TARE/FOLFOX with or without bevacizumab. Although TARE/FOLFOX did not improve PFS (median, 10.7 months vs. 10.2 months; p = .43), median liver PFS was longer in the TARE trial arm (20.5 months vs. 12.6 months; p = .002). CTCAE grade 3/4 toxicities were reported in 85.4% and 73.4% of patients in the TARE/FOLFOX and FOLFOX treatment arms, respectively.

The combined results of the three phase III trials, SIRFLOX, FOXFIRE, and FOXFIRE Global, which evaluated the effectiveness of TARE/FOLFOX as first-line treatment for 1,103 patients with treatment-naïve colorectal liver metastases, no prolonged OS was noted compared with FOLFOX alone (median OS, 22.6 months vs. 23.3 months; p = .61).[64] Subgroup analyses suggested that selected

TABLE 2. Selected Studies Evaluating Thermal Ablation for Treatment of Colorectal Liver Metastases

Reference	Year	Design	Patient Cohort	CRLM Characteristics	Intervention	Technical Success Rate	Outcomes	Complications
Sofocleous et al[50]	2011	Prospective, single-center	56 patients with CRLM developing after partial hepatectomy	Median diameter, 1.9 cm Mean, 1.4 lesions/patient	Percutaneous RFA	94%	Median OS, 31 months Median PFS, 12 months	1 liver abscess (2%) 1 pleural effusion (2%)
Solbiati et al[51]	2012	Retrospective, single-center	99 patients with metachronous CRLM	Median diameter, 2.1 cm Mean, 2 lesions/patient	Percutaneous RFA	93%	Median OS, 53.2 months	Major complication rate, 1.3%
Wang et al[52]	2014	Retrospective, single-center	115 patients with CRLM	Mean diameter, 3.1 cm	Percutaneous MWA	NA	3-year OS rate, 78.7% 3-year recurrence rate, 59.3%	Pleural effusion necessitating thoracocentesis (5 patients; 4.3%)
Ruers et al[53]	2017	RCT	119 patients randomly assigned to FOLFOX vs. RFA/FOLFOX +/- surgical resection*	Median, 5/4 lesions/patient	RFA: Laparotomy (90%), 45.6 vs. 40.5 mo; Percutaneously (7%)	NA	Median OS (RFA/FOLFOX vs. FOLFOX): 45.6 vs. 40.5 mo 5-year OS: 43.1% vs. 30.3%	3 postoperative complications (5.9%)
Bonne et al[54]	2018	Retrospective, single-center	193 patients with CRLM	Median diameter, 1.7 cm	Percutaneous RFA Percutaneous MWA	NA	RFA: 2-year OS, 88%; 5-year OS, 35%; local recurrence rate, 45% MWA: 2-year OS, 89%; 5-year OS, 66%; local recurrence rate, 28%	Major complication rate, 8%

Abbreviations: CRLM, colorectal liver metastases; FOLFOX, fluorouracil/leucovorin/oxaliplatin; MWA, microwave ablation; NA, not available; OS, overall survival; RFA, radiofrequency ablation; RCT, randomized controlled trial.

*Bevacizumab was added to both arms after clinical approval.

TABLE 3. Selected Studies Evaluating TARE for Treatment of Colorectal Liver Metastases

Study Author/ Trial Name	Year	Design	Patient cohort	Intervention	Comparison	Outcomes	Complications
Hendlisz et al[62]	2010	RCT	44 patients with chemorefractory CRLM	TARE + FU	FU	Median time to tumor progression: 4.5 vs. 2.1 months ($p < .05$) Median time to liver progression: 5.5 vs. 2.1 months ($p < .05$) Median OS: 10 vs. 7.3 months ($p = .8$)	CTCAE grade 3/4 toxicities: FU, 6 patients (26%); TARE + FU, 1 patient (5%)
SIRFLOX[63]	2016	RCT	530 patients with treatment-naïve CRLM	TARE + FOLFOX	FOLFOX	Median PFS: 10.7 vs. 10.2 months, $p = .43$ Median PFS in the liver: 20.5 vs. 12.6 months, $p = .002$	CTCAE grade 3/4 toxicities: TARE + FOLFOX, 85.4%; FOLFOX, 73.4%
FOXFIRE Global Trial Investigators[64]	2017	Combined RCT	1,103 patients with treatment-naïve CRLM	TARE + FOLFOX	FOLFOX	Median OS: 22.6 vs. 23.3 months, $p = .61$	CTCAE grade 3/4 toxicities: TARE + FOLFOX, 74%; FOLFOX, 67%

Abbreviations: CRLM, colorectal liver metastases; CTCAE, Common Terminology Criteria for Adverse Events; FOLFOX, fluorouracil/leucovorin/oxaliplatin; FU, fluorouracil; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; TARE, transarterial radioembolization.

patients might benefit from TARE.[65] These analyses highlight the necessity for optimized patient selection to maximize the clinical effectiveness of TARE and to provide individualized treatment schemes.

Biomarkers for TARE Effectiveness

To further optimize treatment planning for patients with colorectal liver metastases, several studies have evaluated predictive TARE biomarkers (Table 3). Analyzing the combined SIRFLOX, FOXFIRE, and FOXFIRE Global clinical trials, Wasan et al[65] reported that patients with right-sided CRC showed longer OS if treated with TARE/FOLFOX versus FOLFOX (median OS, 22 months vs. 17.1 months; $p = .007$). In the same analysis, *KRAS* status did not affect TARE effectiveness, with no significant OS difference reported for TARE/FOLFOX versus FOLFOX, both in *KRAS* wild-type and *KRAS* mutant disease ($p > .05$, each). Conversely, Case et al showed that for patients with chemorefractory colorectal liver mestastases receiving TARE, OS was shorter for those with *KRAS* mutations compared with those with wild-type mutations (median OS, 5.7 months vs. 8 months; $p < .01$).[66] Favorable TARE outcomes for patients with *KRAS* wild-type colorectal liver metastases have also been described by Lahti et al[67] and Magnetta et al.[68]

Another biomarker in patients with colorectal liver metastases undergoing TARE is the neutrophil-lymphocyte ratio: an elevated neutrophil-lymphocyte ratio has been shown to be associated with poorer TARE outcomes, suggested to be mediated by a decreased lymphocytic response to tumor cells.[69-71] Further TARE biomarkers that have been assessed in smaller single-center studies include CEA, CA 19-9, LDH, HMGB1, and VEGF.[72-74]

There are currently no prospectively validated biomarkers to guide use of TARE for patients with colorectal liver metastases, and TARE treatment is mainly driven by the clinical expertise of the interventional radiologist.

ONGOING TRIALS AND FUTURE DIRECTIONS OF LOCAL ABLATIVE THERAPIES IN COLORECTAL LIVER METASTASES

In the progressing field of colorectal liver metastases treatment, there are several clinical trials aiming to improve local ablative therapy outcomes and to optimize patient selection. In particular, there is interest in the combination of local ablative therapy and immunotherapy in colorectal liver metastases: for example, one multicenter European trial evaluated the effectiveness of combined thermal ablation and immunotherapy (NCT03101475), whereas two other trials from Europe and the United States assessed the added benefit of TARE with immunotherapy (NCT04659382 and NCT04108481). One large phase III randomized controlled trial from the Netherlands is currently comparing primary thermal ablation versus surgical resection of colorectal liver metastases; the study aims to accrue 618 patients (COLLISION trial, NCT03088150). Furthermore, in the United Kingdom, there are efforts to establish a national

registry to monitor the use and outcomes of DEBIRI in colorectal liver metastases (NCT03697044).

CONCLUSION

With the advancement of CRC therapies and surgical, radiation, and interventional technologies, patients with colorectal liver metastases have several local ablative therapy options. In particular, with improvements of systemic therapeutic strategies and outcomes, metastatic CRC with oligometastatic disease may benefit from local ablative therapy approaches, of which strategies are in active investigations. In most situations, there is lack of high-level evidence for selection of one modality over the other, and decisions are best made in a multidisciplinary team based on patient and disease factors, prior treatment schemes, institutional expertise, and patient preferences.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_320519.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [correction published in *CA Cancer J Clin*. 2020;70(4):313]. CA Cancer J Clin. 2018;68:394-424.
2. Donadon M, Ribero D, Morris-Stiff G, et al. New paradigm in the management of liver-only metastases from colorectal cancer. Gastrointest Cancer Res. 2007; 1:20-27.
3. Rees M, Tekkis PP, Welsh FK, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg. 2008;247:125-135.
4. Riihimäki M, Hemminki A, Sundquist J, et al. Patterns of metastasis in colon and rectal cancer. Sci Rep. 2016;6:29765.
5. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016; 27:1386-1422.
6. Chiorean EG, Nandakumar G, Fadelu T, et al. Treatment of patients with late-stage colorectal cancer: ASCO resource-stratified guideline. JCO Glob Oncol. 2020; 6:414-438.
7. Adam R, Vinet E. Regional treatment of metastasis: surgery of colorectal liver metastases. Ann Oncol. 2004;15(Suppl 4):iv103-iv106.
8. Bierman HR, Byron RL Jr., Kelley KH, et al. Studies on the blood supply of tumors in man. III. Vascular patterns of the liver by hepatic arteriography in vivo. J Natl Cancer Inst. 1951;12:107-131.
9. Ensminger WD, Gyves JW. Clinical pharmacology of hepatic arterial chemotherapy. Semin Oncol. 1983;10:176-182.
10. Ensminger WD, Rosowsky A, Raso V, et al. A clinical-pharmacological evaluation of hepatic arterial infusions of 5-fluoro-2′-deoxyuridine and 5-fluorouracil. Cancer Res. 1978;38:3784-3792.
11. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med. 1999;341:2039-2048.
12. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg. 2009;250:440-448.
13. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. N Engl J Med. 2005;352:734-735.
14. Srouji R, Narayan R, Boerner T, et al. Addition of adjuvant hepatic artery infusion to systemic chemotherapy following resection of colorectal liver metastases is associated with reduced liver-related mortality. J Surg Oncol. 2020;121:1314-1319.
15. Buisman FE, Galjart B, van der Stok EP, et al. The impact of hepatic arterial infusion pump chemotherapy on hepatic recurrences and survival in patients with resected colorectal liver metastases. HPB (Oxford). 2020;22:1271-1279.

16. House MG, Kemeny NE, Gönen M, et al. Comparison of adjuvant systemic chemotherapy with or without hepatic arterial infusional chemotherapy after hepatic resection for metastatic colorectal cancer. Ann Surg. 2011;254:851-856.

17. Buisman FE, Filipe WF, Kemeny NE, et al. recurrence after liver resection of colorectal liver metastases: repeat resection or ablation followed by hepatic arterial infusion pump chemotherapy. Ann Surg Oncol. 2020;28:808-816.

18. Koerkamp BG, Sadot E, Kemeny NE, et al. Perioperative hepatic arterial infusion pump chemotherapy is associated with longer survival after resection of colorectal liver metastases: a propensity score analysis. J Clin Oncol. 2017;35:1938-1944.

19. Creasy JM, Sadot E, Koerkamp BG, et al. Actual 10-year survival after hepatic resection of colorectal liver metastases: what factors preclude cure? Surgery. 2018; 163:1238-1244.

20. Kemeny NE, Niedzwiecki D, Hollis DR, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). J Clin Oncol. 2006;24:1395-1403.

21. Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381:303-312.

22. Mayer RJ, Van Cutsem E, Falcone A, et al; RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015; 372:1909-1919.

23. Cercek A, Boucher TM, Gluskin JS, et al. Response rates of hepatic arterial infusion pump therapy in patients with metastatic colorectal cancer liver metastases refractory to all standard chemotherapies. J Surg Oncol. 2016;114:655-663.

24. Kemeny NE, Melendez FD, Capanu M, et al. Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. J Clin Oncol. 2009;27:3465-3471.

25. Pak LM, Kemeny NE, Capanu M, et al. Prospective phase II trial of combination hepatic artery infusion and systemic chemotherapy for unresectable colorectal liver metastases: long term results and curative potential. J Surg Oncol. 2018;117:634-643.

26. Muaddi H, D'Angelica M, Wiseman JT, et al. Safety and feasibility of initiating a hepatic artery infusion pump chemotherapy program for unresectable colorectal liver metastases: a multicenter, retrospective cohort study. J Surg Oncol. 2021;123:252-260.

27. Creasy JM, Napier KJ, Reed SA, et al. Implementation of a hepatic artery infusion program: initial patient selection and perioperative outcomes of concurrent hepatic artery infusion and systemic chemotherapy for colorectal liver metastases. Ann Surg Oncol. 2020;27:5086-5095.

28. Buisman FE, Grünhagen DJ, Homs MYV, et al. Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases: results of a safety and feasibility study in The Netherlands. Ann Surg Oncol. 2019;26:4599-4607.

29. Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. J Clin Oncol. 2014; 32:2847-2854.

30. Kavanagh BD, Miften M, Rabinovitch RA. Advances in treatment techniques: stereotactic body radiation therapy and the spread of hypofractionation. Cancer J. 2011;17:177-181.

31. Tree AC, Khoo VS, Eeles RA, et al. Stereotactic body radiotherapy for oligometastases. Lancet Oncol. 2013;14:e28-e37.

32. Chalkidou A, Macmillan T, Grzeda MT, et al. Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study. Lancet Oncol. 2021;22:98-106.

33. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the sabr-comet phase II randomized trial. J Clin Oncol. 2020;38:2830-2838.

34. Scorsetti M, Comito T, Clerici E, et al. Phase II trial on SBRT for unresectable liver metastases: long-term outcome and prognostic factors of survival after 5 years of follow-up. Radiat Oncol. 2018;13:234.

35. Herfarth KK, Debus J, Wannenmacher M. Stereotactic radiation therapy of liver metastases: update of the initial phase-I/II trial. Front Radiat Ther Oncol. 2004; 38:100-105.

36. Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol. 2009;27:1585-1591.

37. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol. 2009; 27:1572-1578.

38. Hoyer M, Roed H, Traberg Hansen A, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. Acta Oncol. 2006;45:823-830.

39. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. Cancer. 2011;117:4060-4069.

40. McPartlin A, Swaminath A, Wang R, et al. Long-term outcomes of phase 1 and 2 studies of SBRT for hepatic colorectal metastases. Int J Radiat Oncol Biol Phys. 2017;99:388-395.

41. Scorsetti M, Comito T, Tozzi A, et al. Final results of a phase II trial for stereotactic body radiation therapy for patients with inoperable liver metastases from colorectal cancer. J Cancer Res Clin Oncol. 2015;141:543-553.

42. Petrelli F, Comito T, Barni S, et al; SBRT for CRC liver metastases. Stereotactic body radiotherapy for colorectal cancer liver metastases: A systematic review. Radiother Oncol. 2018;129:427-434.

43. Joo JH, Park JH, Kim JC, et al. Local control outcomes using stereotactic body radiation therapy for liver metastases from colorectal cancer. Int J Radiat Oncol Biol Phys. 2017;99:876-883.

44. Hong TS, Wo JY, Borger DR, et al. Phase II study of proton-based stereotactic body radiation therapy for liver metastases: importance of tumor genotype. J Natl Cancer Inst. 2017;109:109.

45. Jethwa KR, Jang S, Mullikin TC, et al. Association of tumor genomic factors and efficacy for metastasis-directed stereotactic body radiotherapy for oligometastatic colorectal cancer. Radiother Oncol. 2020;146:29-36.

46. O'Cathail SM, Smith T, Owens R, et al. Superior outcomes of nodal metastases compared to visceral sites in oligometastatic colorectal cancer treated with stereotactic ablative radiotherapy. Radiother Oncol. 2020;151:280-286.

47. Gillams A, Goldberg N, Ahmed M, et al. Thermal ablation of colorectal liver metastases: a position paper by an international panel of ablation experts, The Interventional Oncology Sans Frontières meeting 2013. Eur Radiol. 2015;25:3438-3454.

48. Wang X, Sofocleous CT, Erinjeri JP, et al. Margin size is an independent predictor of local tumor progression after ablation of colon cancer liver metastases. Cardiovasc Intervent Radiol. 2013;36:166-175.

49. Shady W, Petre EN, Do KG, et al. Percutaneous microwave versus radiofrequency ablation of colorectal liver metastases: ablation with clear margins (a0) provides the best local tumor control. J Vasc Interv Radiol. 2018;29:268-275.e1.

50. Sofocleous CT, Petre EN, Gonen M, et al. CT-guided radiofrequency ablation as a salvage treatment of colorectal cancer hepatic metastases developing after hepatectomy. J Vasc Interv Radiol. 2011;22:755-761.

51. Solbiati L, Ahmed M, Cova L, et al. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. Radiology. 2012;265:958-968.

52. Wang J, Liang P, Yu J, et al. Clinical outcome of ultrasound-guided percutaneous microwave ablation on colorectal liver metastases. Oncol Lett. 2014;8:323-326.

53. Ruers T, Van Coevorden F, Punt CJ, et al; National Cancer Research Institute Colorectal Clinical Study Group (NCRI CCSG). Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. J Natl Cancer Inst. 2017;109:109.

54. Bonne L, Paepe KD, Fotiadis N, et al. Percutaneous radiofrequency versus microwave ablation for the treatment of colorectal liver metastases. J Clin Oncol. 2018; 36(4 suppl):401-401.

55. Pathak S, Jones R, Tang JM, et al. Ablative therapies for colorectal liver metastases: a systematic review. Colorectal Dis. 2011;13:e252-e265.

56. Akinwande O, Dendy M, Ludwig JM, et al. Hepatic intra-arterial injection of irinotecan drug eluting beads (DEBIRI) for patients with unresectable colorectal liver metastases: a systematic review. Surg Oncol. 2017;26:268-275.

57. Fiorentini G, Aliberti C, Tilli M, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res. 2012;32:1387-1395.

58. Martin RC II, Scoggins CR, Schreeder M, et al. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. Cancer. 2015;121:3649-3658.

59. Justinger C, Gruden J, Kouladouros K, et al. Histopathological changes resulting from selective internal radiotherapy (SIRT). J Surg Oncol. 2018;117:1084-1091.

60. Wang DS, Louie JD, Sze DY. Intra-arterial therapies for metastatic colorectal cancer. Semin Intervent Radiol. 2013;30:12-20.

61. National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Colon cancer. Version 4. 2018, 2021.

62. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010;28:3687-3694.

63. van Hazel GA, Heinemann V, Sharma NK, et al. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer [correction published in *J Clin Oncol.* 2016;34(33):4059]. J Clin Oncol. 2016;34:1723-1731.

64. Wasan HS, Gibbs P, Sharma NK, et al; FOXFIRE-Global trial investigators. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. 2017;18:1159-1171.

65. Wasan H, Sharma R, Heinemann V, et al. FOXFIRE-SIRFLOX-FOXFIRE global prospective randomised studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer: KRAS mutation and tumour site analysis. Ann Oncol. 2017;28:v615.

66. Case MD, Ghodadra A, Novelli PM, et al. KRAS status and survival in multicenter study of RAS mutations (MURAS) in patients with colorectal liver metastases receiving Y90 radioembolization treatment. J Clin Oncol. 2020;38:(suppl; abstr 239).

67. Lahti SJ, Xing M, Zhang D, et al. kras status as an independent prognostic factor for survival after yttrium-90 radioembolization therapy for unresectable colorectal cancer liver metastases. J Vasc Interv Radiol. 2015;26:1102-1111.

68. Magnetta MJ, Ghodadra A, Lahti SJ, et al. Connecting cancer biology and clinical outcomes to imaging in KRAS mutant and wild-type colorectal cancer liver tumors following selective internal radiation therapy with yttrium-90. Abdom Radiol (NY). 2017;42:451-459.

69. Tohme S, Sukato D, Chalhoub D, et al. Neutrophil-lymphocyte ratio is a simple and novel biomarker for prediction of survival after radioembolization for metastatic colorectal cancer. Ann Surg Oncol. 2015;22:1701-1707.

70. Bester L, Meteling B, Pocock N, et al. Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. J Vasc Interv Radiol. 2012;23:96-105.

71. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc Intervent Radiol. 2012;35:1066-1073.

72. Fahmueller YN, Nagel D, Hoffmann RT, et al. Predictive and prognostic value of circulating nucleosomes and serum biomarkers in patients with metastasized colorectal cancer undergoing Selective Internal Radiation Therapy. BMC Cancer. 2012;12:5.

73. Fahmueller YN, Nagel D, Hoffmann RT, et al. Immunogenic cell death biomarkers HMGB1, RAGE, and DNAse indicate response to radioembolization therapy and prognosis in colorectal cancer patients. Int J Cancer. 2013;132:2349-2358.

74. Carpizo DR, Gensure RH, Yu X, et al. Pilot study of angiogenic response to yttrium-90 radioembolization with resin microspheres. J Vasc Interv Radiol. 2014; 25:297-306.e1.

Management of Long-Term Toxicity From Pelvic Radiation Therapy

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overview

Pelvic radiation therapy is an integral component in the treatment of various gastrointestinal, gynecologic, and genitourinary cancers. As survival rates from these malignancies improve, the prevalence of toxicity secondary to pelvic radiation has increased. Gastrointestinal toxicities are the most common complications and greatly impact quality of life. Toxicities can present in acute or late stages; although symptoms may be similar during both, the management may differ. Acute toxicities represent an inflammatory reaction in response to the radiation exposure, whereas late toxicities may arise as a result of small vessel disease, ischemia, and fibrosis. Currently, there are no large clinical trials and only limited guidelines on the management of late gastrointestinal radiation toxicities. Therapy is generally approached in a stepwise manner from medical to endoscopic to surgical methods. Several endoscopic therapies, such as the treatment of radiation proctitis with argon plasma coagulation and dilation of radiation bowel strictures, may prevent the need for surgical intervention, which may be associated with high morbidity and mortality. Given that late toxicities can occur years after radiation therapy, they are often difficult to recognize and diagnose. Successful management of late toxicities requires recognition, an understanding of the underlying pathophysiology, and a multidisciplinary approach. More dedicated research could clarify the prevalence of gastrointestinal pelvic radiation toxicities, permit a better understanding of the efficacy and safety profile of current therapies, and allow for the development of novel therapeutic approaches.

INTRODUCTION

During the past few decades, pelvic radiation has become an integral treatment modality for various genitourinary, gynecologic, and gastrointestinal cancers. With increasing rates of early diagnosis and successful treatment, survivorship has improved. As a result, delayed toxicities from pelvic radiation have become more evident, greatly affecting patients' quality of life. Pelvic radiation disease is defined as transient or longer-term issues arising in noncancerous tissues from pelvic radiotherapy; gastrointestinal manifestations are the most common.[1] Large cohort studies with long-term follow-up periods have suggested that 10% to 20% of patients may develop gastrointestinal toxicities during a 10-year period.[2] The incidence is likely higher, because symptoms can present several decades after therapy. Overall, 50% of patients report that their gastrointestinal symptoms affect their quality of life, and 20% to 40% say that this effect is moderate or severe.[3] The most common gastrointestinal toxicities include diarrhea, bleeding, and incontinence, and different presentations occur in acute versus late stages. The severity of toxicity is affected by cancer type, size, location, and radiation regimen. There are several available therapies for the management of pelvic radiation disease; however, they are often underutilized, with late symptoms in particular going underrecognized and or underreported. In this review, we discuss the management of long-term gastrointestinal toxicity secondary to pelvic radiation therapy.

ACUTE VERSUS LATE RADIATION TOXICITY

Radiation toxicity is classified as acute if it occurs within the first 3 months after treatment and is classified as late if it occurs after 3 months.[4] These time frames were developed in studies by the Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer to evaluate radiation-induced toxicities. Successful treatment of pelvic radiation disease requires understanding of the disease process. Traditionally, the terms radiation enteritis, ileitis, and proctitis are used; however, the late course of toxicity does not always reflect inflammation. On the contrary, late toxicity is related more to ischemic changes from small vessel disease. As a result, common anti-inflammatory medications, such as aminosalicylates, which are frequently used in inflammatory bowel disease, may not provide relief for late presentations. Acute gastrointestinal toxicity is a response from therapy leading to epithelial inflammation that can manifest as diarrhea, bleeding, urgency, and

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PRACTICAL APPLICATIONS

- Late gastrointestinal radiation toxicities are becoming more prevalent, because patients undergoing pelvic radiation have improved overall survival.
- The current terms of radiation proctitis and enteritis are misleading for late toxicity and can lead to improper treatment, because the injury is actually mediated by small vessel ischemia and not necessarily by mucosal inflammation.
- Current management of late gastrointestinal radiation toxicities occurs in a stepwise escalation of therapy from medical to endoscopic to surgical methods.
- Because symptoms of late radiation toxicity can occur several years after therapy, accurate diagnosis and treatment require a strong understanding of disease pathology and a multidisciplinary treatment plan.
- Dedicated clinical trials and longitudnal studies are required to understand disease prevalence, evaluate the efficacy and safety of current therapies, and develop new treatments.

tenesmus. These symptoms are often self-limited, improved with cessation of additional radiation, and mitigated with medications or endoscopic therapies. In some cases, these adverse effects can interrupt or limit additional radiation treatment.[5] Late injury as a result of small vessel endothelial damage, fibrosis, ischemia, and necrosis may become symptomatic after a latent period between the end of acute effects and the development of late effects.[6] Although symptoms can be similar in acute and late stages, the treatment approach differs because the underlying insult differs.

RISK FACTORS FOR PELVIC RADIATION TOXICITY

The risk of late gastrointestinal toxicity from pelvic radiation is based on several factors. Tumor characteristics, such as size and location, impact the potential for injury because certain tumors may require a larger field or dose of radiation. Advanced-stage tumors with local invasion to the bowel also increase the risk of toxicity.[7] During the past decade, radiotherapy equipment and techniques have evolved in terms of conformality, dose escalation, and normal tissue sparing. Specifically, intensity-modulated radiotherapy has become generalized in practice now, because it delivers a more homogenous dose distribution with sharper fall-off doses at target boundaries, aiming to spare adjacent normal tissue.[8] Intensity-modulated radiotherapy has been demonstrated to reduce acute pelvic radiation toxicity; however, late-phase toxicity studies remain limited.[9] In a study comparing conventional pelvic radiation therapy with intensity-modulated radiotherapy in women with cervical and endometrial cancers, fewer patient-reported gastrointestinal adverse events occurred in the intensity-modulated radiotherapy group compared with the conventional pelvic radiation therapy group for up to 1 year. However, these differences were not seen between the two groups at the 3-year follow-up.[10] The overall reduction in late gastrointestinal toxicities with intensity-modulated radiotherapy remains unclear at this time, because symptoms can present several decades after therapy. Patient factors can also contribute to late-stage gastrointestinal toxicities. Patients with diabetes mellitus, inflammatory bowel disease, concurrent chemotherapy, prior abdominal surgery, collagen vascular disease, HIV, lower body mass index (< 18.5 kg/m^2), and chronic tobacco use have an increased risk for developing late gastrointestinal toxicities.[2]

MANAGEMENT OF LATE GASTROINTESTINAL TOXICITY: CHRONIC RADIATION PROCTITIS

Definition of Chronic Radiation Proctitis

The term radiation proctitis describes the manifestations of long-term toxicity in patients who have received pelvic radiation therapy. The term itself can be deceptive, because it describes injury to the rectum secondary to radiation that may or may not involve inflammation. In this review, we focus on chronic radiation proctitis as opposed to acute radiation proctitis, which is often self-limited and occurs within several weeks to 3 months after pelvic radiation therapy. Chronic radiation proctitis can develop starting at 3 months or longer after exposure to radiation or as a result of progression of acute radiation proctitis beyond 3 months.[11-14] Delayed onset of chronic radiation proctitis typically occurs within 1 year of radiation exposure but has been documented to occur up to decades later.[13-15] Because of the wide variation in severity and the variability in onset, it is difficult to estimate the true prevalence and incidence of chronic radiation proctitis. The incidence has been estimated to be between 2% and 20% according to the type of malignancy and the radiation dosing received.[16] Although data are limited, they suggest that the risk of chronic radiation proctitis varies according to the type of radiation therapy delivered (i.e., external beam therapy vs. brachytherapy), the dose of radiation delivered, and the volume of tissue being radiated.[17] Dose-volume relationships for radiation-induced rectal injury were examined and revealed that the volume of rectal tissue exposed to 60 Gy or more correlated with increased rectal bleeding and overall toxicity.[18]

Symptoms of Chronic Radiation Proctitis

Symptom profiles for acute and chronic radiation proctitis overlap greatly, but the symptoms of chronic radiation

proctitis are generally more severe and less reversible as a result of the degree of transmural damage secondary to fibrosis and ischemia.[14,19] Acute and chronic radiation proctitis can present with diarrhea, tenesmus, abdominal discomfort (including rectal/perineal areas), fecal urgency, fecal incontinence, cramping, and mucus in the stool. Rectal bleeding, although occasionally seen with acute radiation proctitis, is much more pronounced in chronic radiation proctitis secondary to radiation-induced formation of telangiectasias and neovascularization. It is one of the most common presenting symptoms that prompts referral to a gastroenterologist. Additionally, patients with chronic radiation proctitis are more likely to experience severe or multiorgan manifestations of radiation toxicity, such as fistulas, strictures, small bowel obstruction, and perforation.[17,20,21]

Diagnosis of Chronic Radiation Proctitis

In patients presenting with a history of pelvic radiation therapy and lower gastrointestinal tract symptoms, radiation is often identified as the suspected etiology. However, it is important to consider chronic radiation proctitis as a diagnosis of exclusion that may require endoscopic evaluation. Clinicians must rule out other common causes of proctitis, including ischemic colitis, infectious colitis, diversion colitis, inflammatory bowel disease (Crohn's disease or ulcerative colitis), sexually transmitted infections, physical trauma, and secondary or recurrent malignancy.[22-25] Patients with suspected chronic radiation proctitis generally undergo sigmoidoscopy or colonoscopy based on clinical suspicion for disease etiology. Direct visualization of mucosa often shows pale friable tissue. In patients with severe rectal bleeding, endoscopy typically reveals multiple telangiectasias (Fig. 1).[19,26] Biopsies of the rectum in patients with suspected chronic radiation proctitis are generally avoided because of the high risks of complications, such as bleeding and the formation of fistulas. However, when biopsies are necessary to establish diagnosis and guide therapy (e.g., suspected malignancy), tissue is obtained from the posterior and lateral rectal walls.[22,27] Adjunctive imaging studies, such as barium enema, MRI, or CT, may also assist in the detection of cancer recurrence or fistula formation.[28]

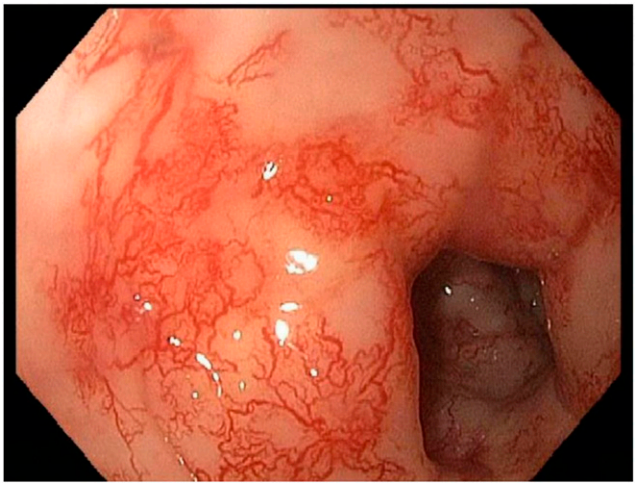

FIGURE 1. Chronic Radiation Proctitis With Nonbleeding Ectasias

Management of Chronic Radiation Proctitis

There is not a consensus on a gold-standard therapeutic approach for chronic radiation proctitis, and currently there are only small and limited randomized controlled trials (Table 1). Therapeutic options for treatment are often classified as noninvasive or invasive (including endoscopic and surgical) approaches.[28] Approaches to therapy vary according to the predominance of the symptoms, but they generally start with less invasive approaches and escalate in a stepwise manner. Patients with mild symptoms that do not notably impact qualify of life can be treated conservatively without therapy.[19]

Noninvasive approaches Although anti-inflammatory medications are often regarded as a first-line therapy, data suggesting efficacy are limited. Agents commonly used include 5-aminosalicylic acid preparations and steroids (oral/enemas). Data suggest that these agents may be more likely to benefit patients with acute rather than chronic radiation proctitis.[21] A prospective study suggested clinical and endoscopic improvement among patients receiving oral sulfasalazine and rectal prednisolone enemas. However, this regimen was compared with sucralfate enema rather than a placebo control.[34] Sucralfate enemas are commonly used if a trial of anti-inflammatory medications is unsuccessful. Sucralfate stimulates prostaglandin production, which is theorized to promote barrier protection and tissue repair.[39] Similar endoscopic response has been found between groups (sucralfate enema vs. oral sulfasalazine and rectal prednisolone enemas); however, there was a better clinical response and fewer adverse events in the sucralfate arm.[34] Currently, there are no large placebo-controlled trials for sucralfate enemas. Oral metronidazole has been shown to be effective in the treatment of chronic radiation proctitis–associated bleeding and diarrhea in two randomized controlled trials when combined with other therapies, such as anti-inflammatory medications or irrigation and ciprofloxacin.[29,36] Some studies suggest that, by reducing oxidative stress, antioxidants (e.g., vitamins A, C, and E) may be beneficial in reducing symptoms of chronic radiation proctitis.[32,40,41] Vitamin A may improve symptoms in combination with formalin therapy.[41] Finally, although short-chain fatty acid enemas may be beneficial in acute radiation proctitis, randomized trials suggest that their roles in prevention and treatment are limited.[37,42]

TABLE 1. Randomized Controlled Trials in Chronic Radiation Proctitis

Study	Article Title	Year	No. of Patients	Therapy Approach	Arms
Cavcić et al[29]	Metronidazole in the treatment of chronic radiation proctitis: clinical trial	2000	60	Noninvasive	Mesalamine plus betamethasone enemas with and without metronidazole
Chruscielewska-Kiliszek et al[30]	Sucralfate or placebo following argon plasma coagulation for chronic radiation proctitis: a randomized double-blind trial	2013	122	Invasive	Oral sucralfate (with APC) vs. placebo (with APC)
Clarke et al[31]	Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled blind-blind crossover trial with long-term follow-up	2008	150	Noninvasive	Hyperbaric oxygen vs. atmospheric air
Ehrenpreis et al[32]	A prospective, randomized, double-blind, placebo-controlled trial of retinol palmitate (vitamin A) for symptomatic chronic radiation proctopathy	2005	10	Noninvasive	Retinol palmitate vs. placebo
Glover et al[33]	Hyperbaric oxygen for patients with chronic bowel dysfunction after pelvic radiotherapy (HOT2): a randomised, double-blind, sham-controlled phase 3 trial	2016	84	Noninvasive	Hyperbaric oxygen vs. sham control
Kocchar et al[34]	Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids vs. rectal sucralfate	1991	37	Noninvasive	Oral sulfasalazine plus rectal prednisolone enemas vs. rectal sucralfate enemas plus oral placebo
Lenz et al[35]	Comparative study of bipolar electrocoagulation versus argon plasma coagulation for rectal bleeding due to chronic radiation coloproctopathy	2011	30	Invasive	Bipolar electrocoagulation vs. APC
Sahakitrungruang et al[36]	A randomized controlled trial comparing colonic irrigation and oral antibiotics administration versus 4% formalin application for treatment of hemorrhagic radiation proctitis	2012	50	Combined	Colonic irrigation plus ciprofloxacin plus metronidazole vs. 4% formalin
Talley et al[37]	Short-chain fatty acids in the treatment of radiation proctitis: a randomized, double-blind, placebo-controlled, cross-over pilot trial	1997	50	Noninvasive	Butyric acid enemas vs. placebo
Yeoh et al[38]	Argon plasma coagulation therapy versus topical formalin for intractable rectal bleeding and anorectal dysfunction after radiation therapy for prostate carcinoma	2013	30	Invasive	APC vs. topical formalin

Abbreviation: APC, argon plasma coagulation.

Invasive approaches Formalin has been used for decades in the treatment of chronic radiation proctitis, particularly for hemorrhagic proctitis.[43–45] It serves as an agent for chemical cauterization that can be applied in minimally invasive techniques under light sedation (topically with endoscopy or through rectal instillation of a solution).[43] A systematic review analyzing prospective and retrospective studies found high response rates of 80% to 100%. However, existing studies have variable primary outcomes, limited qualify-of-life data, and no control groups.[11,46] Moreover, safety concerns with formalin therapy include fistulas, anal ulceration, pain, and fecal incontinence.[11,19,47]

Hyperbaric oxygen therapy has been hypothesized to be beneficial for patients in promoting wound healing.[22,46] A randomized controlled trial showed a marked treatment response and improved quality of life in patients with refractory chronic radiation proctitis; however, outcomes are mixed, with another randomized trial showing no benefit or improvement in symptoms for chronic radiation proctitis.[31,33] Although hyperbaric oxygen has its own complications, it may be considered in refractory cases that are unlikely to benefit from interventional approaches.[31,48] Larger-scale trials may clarify the role and outcomes.

Endoscopic coagulation has become the preferred approach in the management of rectal bleeding from chronic radiation proctitis. The most common method utilizes argon plasma coagulation, which delivers high-frequency, noncontact thermal therapy to control bleeding in the gastrointestinal tract.[49,50] In a systematic review of 33 studies and more than 900 patients, a success rate of 87%, with an adverse event rate of 4%, was found in a pooled analysis.[50] Argon plasma coagulation has been shown to be effective and safe in multiple randomized trials. However, these trials had multiple treatment arms without placebo control. When argon plasma coagulation was compared with topical formalin and bipolar electrocoagulation, there was no marked differences in the control of rectal bleeding. The addition of sucralfate enemas to argon plasma coagulation did not change clinical or endoscopic outcomes.[30,35,38]

Consensus guidelines The American Society of Colon and Rectal Surgeons published clinical practice guidelines in 2018 for the treatment of chronic radiation proctitis. These recommendations included medical and interventional approaches to treatment, as well as grading of recommendations according to the quality of available evidence. In the medical management of chronic radiation proctitis, sucralfate enemas were moderately effective in chronic radiation proctitis–associated bleeding (grade 1c). Short-chain fatty acid enemas were not effective in the treatment or prevention of hemorrhagic chronic radiation proctitis (grade 1b). Endoscopic argon plasma coagulation, hyperbaric oxygen, and formalin therapy were found to be effective for chronic radiation proctitis–associated bleeding (grade 1b). Other medical therapeutics and interventions were deemed to have low evidence to support their widespread use for chronic radiation proctitis.[47] The American Society for Gastrointestinal Endoscopy released updated practice guidelines in 2019 that provided evidence of the effectiveness of argon plasma coagulation, bipolar electrocoagulation, heater probe, and radiofrequency ablation in the control of chronic radiation proctitis–associated bleeding.[50]

Future therapy Although important advancements have been made, it is clear that there is much more work to be done, especially as it relates to improving the quality of life in patients treated with pelvic radiation therapy. Early recognition and prevention of fibrosis are key to future therapies targeting chronic radiation proctitis.[51] The ability of new radiation therapy techniques to minimize exposure to rectal tissue and consequences, such as chronic radiation proctitis, may improve patient outcomes and quality of life after pelvic radiation.[22]

MANAGEMENT OF LATE GASTROINTESTINAL TOXICITY: CHRONIC RADIATION ENTERITIS

Definition of Chronic Radiation Enteritis

Although definitions vary, the term radiation enteritis describes damage that occurs to the small or large intestine secondary to radiation therapy and that may or may not involve inflammation. Damage to the rectum is excluded from this definition and is classified separately as radiation proctitis. In this review, we focus on chronic, as opposed to acute, radiation enteritis. Acute radiation enteritis, which may be self-limited, often occurs within 3 months of radiation therapy and can frequently be managed with supportive care. Chronic radiation enteritis can develop from 3 months to decades after radiation therapy.[52-54]

Symptoms of Chronic Radiation Enteritis

Patients with acute radiation enteritis typically present with nonspecific gastrointestinal symptoms (nausea, vomiting, diarrhea, cramping, tenesmus, abdominal pain, anorexia) within weeks of receiving radiation therapy. Symptom profiles of patients with chronic radiation enteritis can be similar to those of patients with acute radiation enteritis but often are also accompanied by malabsorptive or obstructive features. Patients can experience bleeding, but it is often less profuse than that seen in chronic radiation proctitis. Colicky abdominal pain is a common symptom experienced by patients who have a partial small bowel obstruction, often secondary to a stricture. Chronic radiation enteritis can become severe, sometimes involving multiple segments of bowel. Fistulas, abscesses, and intestinal perforation are less common but more severe manifestations of chronic radiation enteritis.[55-57] Similar to chronic radiation proctitis, chronic radiation enteritis results from ischemic and fibrotic changes within gastrointestinal tissue as a result of damage to blood vessels.[54] Although the true incidence of chronic radiation enteritis is unknown, estimates are concerning. Up to 89% of patients may develop long-term changes in bowel habits after pelvic radiation therapy, and nearly half of these patients report a negative impact on quality of life.[58] Similar to other radiation-associated gastrointestinal toxicities, the manifestations of chronic radiation enteritis are considered related to the type, length, and dose of radiation therapy as well as the volume of tissue irradiated.[54,59]

Diagnosis of Chronic Radiation Enteritis

The diagnosis of chronic radiation enteritis requires a high clinical suspicion with supporting history/physical findings, laboratory studies, and imaging.[60,61] In a prospective cohort of patients with new-onset gastrointestinal symptoms after pelvic radiation therapy, fewer than half of the patients had a singular gastrointestinal diagnosis, and one-third of diagnoses were unrelated to prior radiation therapy.[51] Coexisting conditions and a wide array of presenting symptoms increase the difficulty in establishing a diagnosis and selecting the proper management.

A stepwise approach for suspected chronic radiation enteritis based on predominant symptoms has been proposed.[60] Colonic symptoms, such as diarrhea and rectal bleeding, can be evaluated with colonoscopy, whereas upper gastrointestinal symptoms (e.g., nausea/vomiting, abdominal pain, dyspepsia, bloating) can be evaluated with upper endoscopy or small bowel fluoroscopic studies. Nonspecific symptoms (bloating, weight loss, abdominal pain) can be evaluated with CT or magnetic resonance enterography. If the above work-up is unrevealing, malabsorption may be considered. Etiologies may include bile salt malabsorption, carbohydrate malabsorption, or small intestinal bacterial overgrowth.[60-62] In patients with presentations suggestive of bleeding and with negative upper and lower endoscopic studies, enteroscopy or capsule endoscopy can be considered. However, caution must be used with capsule endoscopy in patients who have undergone pelvic radiation because of the risk of capsule impaction secondary to stricturing.[63-65] In chronic radiation enteritis, direct visualization through standard endoscopy, enteroscopy, or capsule endoscopy may show telangiectasias, strictures, adhesions, mucosal ulceration, or, rarely, necrotic changes.[60,66] Laboratory values, such as C-reactive protein, have limited utility in chronic radiation enteritis.[60,67] Diagnoses that can mimic chronic radiation enteritis must be excluded. These include, but are not limited to, recurrence of malignancy, small intestinal bacterial overgrowth, pancreatic insufficiency, inflammatory bowel disease, inflammatory bowel syndrome, infection, drug-induced colitis, and ischemic colitis.[68]

Management of Chronic Radiation Enteritis

The management of chronic radiation enteritis is largely symptom based and can be stratified by noninvasive and invasive approaches. Noninvasive approaches may be used as first-line therapies; however, patients with severe features, such as fistulas, strictures, and perforations, may require invasive endoscopic or surgical management. Consensus expert guidelines are not readily available for the management of chronic radiation enteritis.

Noninvasive approaches Dietary modifications are often a first-line treatment of symptoms in chronic radiation enteritis, especially for patients experiencing diarrhea; they may be trialed on a case-by-case basis. A systematic review of nutritional interventions for acute gastrointestinal toxicity during pelvic radiotherapy concluded that there was not enough evidence to make general recommendations during or after radiotherapy.[69] A large review that included acute and chronic nutritional interventions in patients receiving pelvic radiotherapy did not find any clear benefit in the prevention or management of symptoms. Although evidence is limited, patients are generally asked to try some combination of a lactose-free, low-residue, and/or low-fat diet.[52,70] In severe cases or for patients with short gut syndrome, parenteral nutrition may be required.[52,61]

Antidiarrheal agents can be effective in symptomatic management. A randomized crossover trial in patients with and without chronic radiation enteritis concluded that loperamide can effectively slow intestinal transit and even increase the absorption of bile acids.[71] Some patients with diarrhea may benefit from bile acid sequestrants (e.g., cholestyramine). This class of medications can be beneficial for patients experiencing diarrhea secondary to bile salt malabsorption.[72,73] Patients presenting with symptoms of small intestinal bacterial overgrowth (bloating, diarrhea, abdominal pain) secondary to radiation therapy can be treated with antibiotic therapy; local resistance patterns are used to determine an appropriate regimen.[52,60,74] Although randomized trials suggest a role for probiotics for diarrhea after radiation acutely, data regarding the role of probiotics in chronic radiation enteritis are limited.[57,75-77] Other medications, such as angiotensin-converting enzyme inhibitors and statins, have been suggested to be protective of gastrointestinal symptoms in patients for up to 1 year after pelvic radiotherapy; however, the data are limited, and no randomized controlled trial has been performed.[78]

Invasive approaches In patients who present with bleeding or iron-deficiency anemia, endoscopic therapy with cauterization can be used as in non–radiation-associated bleeds.[79] Argon plasma coagulation has been successful in radiation-induced enteritis caused by telangiectasias in the large and small bowel.[80,81] Although not routinely performed in chronic radiation enteritis, double-balloon enteroscopy could be used to reach bleeds deep in the small bowel or for dilation of downstream small bowel strictures. This procedure could decrease the need for surgical intervention in some patients; however, more data would be beneficial.[82,83]

Compared with chronic radiation proctitis, approximately one-third of patients with chronic radiation enteritis may ultimately require surgical intervention for indications such as obstruction, strictures, fistulas, or severe refractory bleeding.[60,79,84] Operating on these patients may pose multiple challenges. At baseline, the bowel often has severe adhesions and fibrosis. Postoperative complications are

fairly common; it is estimated that half of patients undergoing surgery require repeat intervention, often resulting in short gut syndrome. Healthy tissue can be difficult to distinguish from irradiated tissue, thereby resulting in high rates of anastomotic leaks.[60,84,85] Endoscopy may play a role intraoperatively to assess the viability of tissue.[86] Hyperbaric oxygen remains an option for the treatment of chronic radiation enteritis, especially as a result of its ability to target multiple portions of noncontiguous small bowel. Marked clinical improvement was found in a majority of patients in a case series of 65 patients with chronic radiation enteritis.[48,87] Notably, this modality of treatment can be expensive, making widespread adoption difficult without larger trials.

MANAGEMENT OF LATE GASTROINTESTINAL TOXICITY: RADIATION STRICTURES

Small bowel and rectosigmoid colon strictures are an uncommon complication of late toxicity from pelvic radiation; however, they can be associated with high morbidity and mortality. Over time, the submucosa of the affected bowel becomes injured as endarteritis obliterans progresses from inflammation to ischemia leading to fibrosis, predisposing patients to strictures and obstruction.[88] Patients with small bowel strictures can present with postprandial nausea, vomiting, abdominal pain, and distension. A diagnosis can be made with a clinical history of prior radiation therapy and cross-sectional or contrast-enhanced imaging.

Small Bowel Radiation Strictures

Complete small bowel obstructions from radiation strictures may require surgical intervention. Approximately 30% of patients with chronic radiation enteropathy may require surgery.[84] Surgical intervention is associated with a high rate of postoperative morbidity (30%) and mortality (5%).[89] The affected segment can be resected with a primary anastomosis or bypassed. Intestinal bypass has a lower operative mortality and a decreased incidence of anastomotic dehiscence.[90] Patients who are not surgical candidates can obtain a decompressive gastrostomy and parental nutrition. Partial small bowel obstructions caused by radiation strictures are managed on the basis of presenting symptoms. Generally, diet modification is recommended, with a soft low-fiber/low-residue diet and small, frequent meals to reduce symptoms. Surgery is often avoided unless absolutely necessary given the associated morbidity and mortality. Endoscopic therapy for small bowel strictures is often limited, because the location can be difficult to access with standard endoscopes. Endoscopic dilation of benign small bowel strictures using double-balloon enteroscopy has been demonstrated to have good technical and clinical success in small retrospective studies. Most of these dilations were performed on fibrostenotic strictures in patients with Crohn's disease; as a result, the efficacy and safety profile for small bowel radiation strictures are inferred.[91]

Large Bowel Radiation Strictures

Pelvic radiation strictures can also occur in the sigmoid colon and rectum. These patients can present with constipation, abdominal pain, distension, nausea, and vomiting. The diagnosis of a rectosigmoid colon radiation stricture can be made with abdominal-pelvic imaging; however, the etiology and characteristics are generally determined endoscopically. Initial work-up may include a colonoscopy or flexible sigmoidoscopy with biopsies to determine whether the stricture is benign or malignant. Additionally, if the stricture can be traversed with the scope, stricture length and mucosal detail should be assessed. It is important to maintain a broad differential for colonic strictures, because malignant, nonsteroidal anti-inflammatory drug–induced, and inflammatory bowel disease strictures can have similar presentations. In the setting of a complete colonic obstruction, surgical management is indicated with a diverting colostomy or a resection with anastomosis.

In cases of partial colonic obstruction (Fig. 2), endoscopic therapy can be performed to decrease the need for surgical intervention. During the past 4 decades, small prospective and cohort studies have suggested that endoscopic colonic dilation may have good technical and clinical success for radiation strictures.[92] Dilations can be performed with a push-type bougie dilator, which has a fixed diameter, or radial expanding balloon dilators. Balloon dilators exert a radial force across a stricture, whereas bougie dilators exert radial and longitudinal shearing force across a stricture.[93] Typically, a flexible guide wire is advanced through the scope to approximately 30 cm proximal to the stricture under fluoroscopy, whereas the bougie dilator or balloon apparatus can safely be advanced. Dilations may require multiple sessions to achieve long-term patency.[94] Stricture length, diameter, and location determine the type of dilator that is used. Through-the-scope balloon dilators are typically used for shorter, more focal strictures. Major adverse events (perforation, bleeding, abscess, fistula, sepsis) for dilation are reported to occur in fewer than 4% of patients.[95]

Several other endoscopic techniques have been studied for the management of radiation strictures of the colon. Intrastricture steroid injections can be performed after a dilation to help prolong the time needed for repeat dilation. Current data are equivocal and are limited to small case series in anastomotic colonic strictures in Crohn's disease; as a result, the technique is performed on a case-by-case basis.[96] Self-expanding metal stents have been used for malignant colonic strictures for palliative intent or as a bridge to surgery. The current use for self-expanding metal stents in benign colonic strictures is generally reserved for refractory strictures that did not respond to endoscopic dilation in selected patients.[97] Stent use in benign strictures may be limited by stent migration.[98]

CONCLUSION

With the increase in the use of pelvic radiation for gastrointestinal, gynecologic, and genitourinary cancers and the improving survival rates, more patients are presenting with pelvic radiation disease. Gastrointestinal toxicities are the most common complications, and they can greatly impact quality of life. Acute gastrointestinal toxicities can generally be identified during or soon after treatment. Late toxicities can occur in 3 months to decades after treatment. Medical, endoscopic, and surgical therapies are available for the treatment of late gastrointestinal toxicities. Successful delivery requires a multidisciplinary approach with a strong understanding of disease pathophysiology. Ongoing work to better focus the field of radiation delivery may reduce complications in surrounding regions. Trials for medical and endoscopic therapies may allow for a better understanding of treatment efficacy and safety profiles and may reduce the need for surgical intervention. Alternatives to radiation therapy may offer locoregional control with reduced adverse effect profiles for suitable patients.

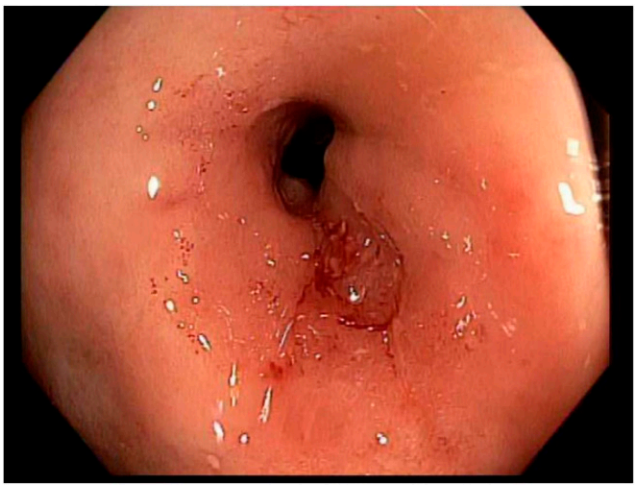

FIGURE 2. Radiation Stricture in the Rectum Causing Partial Obstruction

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Andreyev HJ, Wotherspoon A, Denham JW, et al. Defining pelvic-radiation disease for the survivorship era. Lancet Oncol. 2010;11:310-312.
2. Fuccio L, Guido A, Andreyev HJ. Management of intestinal complications in patients with pelvic radiation disease. Clin Gastroenterol Hepatol. 2012;10:1326-1334.e4.
3. Mahmood S, Billipo S, Steele S, et al. It's all the RAVE: time to give up on the chronic radiation proctitis misnomer. Gastroenterology. 2021;160:P635-P638.
4. Lei C, Ma S, Huang M, et al. Long-term survival and late toxicity associated with pelvic intensity modulated radiation therapy (IMRT) for cervical cancer involving CT-based positive lymph nodes. Front Oncol. 2019;9:520.
5. Andreyev HJ. GI consequences of cancer treatment: a clinical perspective. Radiat Res. 2016;185:341-348.
6. Kuku S, Fragkos C, McCormack M, et al. Radiation-induced bowel injury: the impact of radiotherapy on survivorship after treatment for gynaecological cancers. Br J Cancer. 2013;109:1504-1512.
7. Fuccio L, Frazzoni L, Guido A. Prevention of pelvic radiation disease. World J Gastrointest Pharmacol Ther. 2015;6:1-9.

8. Kwak YK, Lee SW, Kay CS, et al. Intensity-modulated radiotherapy reduces gastrointestinal toxicity in pelvic radiation therapy with moderate dose. PLoS One. 2017;12:e0183339.
9. Klopp AH, Yeung AR, Deshmukh S, et al. Patient-reported toxicity during pelvic intensity-modulated radiation therapy: NRG Oncology-RTOG 1203 [published corrections appear in J Clin Oncol. 2019;37:761 and 2020;38:1118]. J Clin Oncol. 2018;36:2538-2544.
10. Yeung AR, Pugh S, Klopp AH, et al. IMRT improves late toxicity compared to conventional RT: an update on NRG Oncology-RTOG 1203. Int J Radiat Oncol Biol Phys. 2019;105:S50.
11. Denton AS, Andreyev HJ, Forbes A, et al. Systematic review for non-surgical interventions for the management of late radiation proctitis. Br J Cancer. 2002; 87:134-143.
12. Denham JW, O'Brien PC, Dunstan RH, et al. Is there more than one late radiation proctitis syndrome? Radiother Oncol. 1999;51:43-53.
13. Eifel PJ, Levenback C, Wharton JT, et al. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys. 1995;32:1289-1300.
14. van de Wetering FT, Verleye L, Andreyev HJN, et al. Non-surgical interventions for late rectal problems (proctopathy) of radiotherapy in people who have received radiotherapy to the pelvis. Cochrane Database Syst Rev. 2016;4:CD003455.
15. Lucarotti ME, Mountford RA, Bartolo DC. Surgical management of intestinal radiation injury. Dis Colon Rectum. 1991;34:865-869.
16. Tagkalidis PP, Tjandra JJ. Chronic radiation proctitis. ANZ J Surg. 2001;71:230-237.
17. Grodsky MB, Sidani SM. Radiation proctopathy. Clin Colon Rectal Surg. 2015;28:103-111.
18. Michalski JM, Gay H, Jackson A, et al. Radiation dose-volume effects in radiation-induced rectal injury [published correction appears in Int J Radiat Oncol Biol Phys. 2019;104:1185]. Int J Radiat Oncol Biol Phys. 2010;76 (3 suppl):S123-S129.
19. Do NL, Nagle D, Poylin VY. Radiation proctitis: current strategies in management. Gastroenterol Res Pract. 2011;2011:917941.
20. Williams HRT, Vlavianos P, Blake P, et al. The significance of rectal bleeding after pelvic radiotherapy. Aliment Pharmacol Ther. 2005;21:1085-1090.
21. Kennedy GD, Heise CP. Radiation colitis and proctitis. Clin Colon Rectal Surg. 2007;20:64-72.
22. Vanneste BGL, Van De Voorde L, de Ridder RJ, et al. Chronic radiation proctitis: tricks to prevent and treat. Int J Colorectal Dis. 2015;30:1293-1303.
23. Wu XR, Liu XL, Katz S, et al. Pathogenesis, diagnosis, and management of ulcerative proctitis, chronic radiation proctopathy, and diversion proctitis. Inflamm Bowel Dis. 2015;21:703-715.
24. Voth ML, Akbari RP. Sexually transmitted proctitides. Clin Colon Rectal Surg. 2007;20:58-63.
25. Friedman LS, Hong TS. Clinical manifestations, diagnosis, and treatment of radiation proctitis. www.uptodate.com/contents/clinical-manifestations-diagnosis-and-treatment-of-radiation-proctitis. Accessed January 20, 2021.
26. O'Brien PC, Hamilton CS, Denham JW, et al. Spontaneous improvement in late rectal mucosal changes after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2004;58:75-80.
27. Theodorescu D, Gillenwater JY, Koutrouvelis PG. Prostatourethral-rectal fistula after prostate brachytherapy. Cancer. 2000;89:2085-2091.
28. Porouhan P, Farshchian N, Dayani M. Management of radiation-induced proctitis. J Family Med Prim Care. 2019;8:2173-2178.
29. Cavcić J, Turcić J, Martinac P, et al. Metronidazole in the treatment of chronic radiation proctitis: clinical trial. Croat Med J. 2000;41:314-318.
30. Chruscielewska-Kiliszek MR, Regula J, Polkowski M, et al. Sucralfate or placebo following argon plasma coagulation for chronic radiation proctitis: a randomized double blind trial. Colorectal Dis. 2013;15:e48-e55.
31. Clarke RE, Tenorio LMC, Hussey JR, et al. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled blind-blind crossover trial with long-term follow-up. Int J Radiat Oncol Biol Phys. 2008;72:134-143.
32. Ehrenpreis ED, Jani A, Levitsky J, et al. A prospective, randomized, double-blind, placebo-controlled trial of retinol palmitate (vitamin A) for symptomatic chronic radiation proctopathy. Dis Colon Rectum. 2005;48:1-8.
33. Glover M, Smerdon GR, Andreyev HJ, et al. Hyperbaric oxygen for patients with chronic bowel dysfunction after pelvic radiotherapy (HOT2): a randomised, double-blind, sham-controlled phase 3 trial. Lancet Oncol. 2016;17:224-233.
34. Kochhar R, Patel F, Dhar A, et al. Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate. Dig Dis Sci. 1991;36:103-107.
35. Lenz L, Tafarel J, Correia L, et al. Comparative study of bipolar eletrocoagulation versus argon plasma coagulation for rectal bleeding due to chronic radiation coloproctopathy. Endoscopy. 2011;43:697-701.
36. Sahakitrungruang C, Patiwongpaisarn A, Kanjanasilp P, et al. A randomized controlled trial comparing colonic irrigation and oral antibiotics administration versus 4% formalin application for treatment of hemorrhagic radiation proctitis. Dis Colon Rectum. 2012;55:1053-1058.
37. Talley NA, Chen F, King D, et al. Short-chain fatty acids in the treatment of radiation proctitis: a randomized, double-blind, placebo-controlled, cross-over pilot trial. Dis Colon Rectum. 1997;40:1046-1050.
38. Yeoh E, Tam W, Schoeman M, et al. Argon plasma coagulation therapy versus topical formalin for intractable rectal bleeding and anorectal dysfunction after radiation therapy for prostate carcinoma. Int J Radiat Oncol Biol Phys. 2013;87:954-959.
39. Rees WD. Mechanisms of gastroduodenal protection by sucralfate. Am J Med. 1991;91:58S-63S.

40. Kennedy M, Bruninga K, Mutlu EA, et al. Successful and sustained treatment of chronic radiation proctitis with antioxidant vitamins E and C. Am J Gastroenterol. 2001;96:1080-1084.
41. Patel P, Subhas G, Gupta A, et al. Oral vitamin A enhances the effectiveness of formalin 8% in treating chronic hemorrhagic radiation proctopathy. Dis Colon Rectum. 2009;52:1605-1609.
42. Vernia P, Fracasso PL, Casale V, et al. Topical butyrate for acute radiation proctitis: randomised, crossover trial. Lancet. 2000;356:1232-1235.
43. Tabaja L, Sidani SM. Management of Radiation Proctitis. Dig Dis Sci. 2018;63:2180-2188.
44. Luna-Pérez P, Rodríguez-Ramírez SE. Formalin instillation for refractory radiation-induced hemorrhagic proctitis. J Surg Oncol. 2002;80:41-44.
45. Dziki Ł, Kujawski R, Mik M, et al. Formalin therapy for hemorrhagic radiation proctitis. Pharmacol Rep. 2015;67:896-900.
46. Henson C. Chronic radiation proctitis: issues surrounding delayed bowel dysfunction post-pelvic radiotherapy and an update on medical treatment. Therap Adv Gastroenterol. 2010;3:359-365.
47. Paquette IM, Vogel JD, Abbas MA, et al; Clinical Practice Guidelines Committee of The American Society. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the treatment of chronic radiation proctitis. Dis Colon Rectum. 2018;61:1135-1140.
48. Feldmeier JJ, Hampson NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. Undersea Hyperb Med. 2002;29:4-30.
49. Tjandra JJ, Sengupta S. Argon plasma coagulation is an effective treatment for refractory hemorrhagic radiation proctitis. Dis Colon Rectum. 2001; 44:1759-1765, discussion 1771.
50. Lee JK, Agrawal D, Thosani N, et al. ASGE guideline on the role of endoscopy for bleeding from chronic radiation proctopathy. Gastrointest Endosc. 2019; 90:171-182.e1.
51. Andreyev J. Gastrointestinal complications of pelvic radiotherapy: are they of any importance? Gut. 2005;54:1051-1054.
52. Stacey R, Green JT. Radiation-induced small bowel disease: latest developments and clinical guidance. Ther Adv Chronic Dis. 2014;5:15-29.
53. Bhutta BS, Fatima R. Radiation enteritis. www.statpearls.com/nurse/ce/activity/32578. Accessed January 20, 2021.
54. Andreyev J. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. Lancet Oncol. 2007; 8:1007-1017.
55. Bismar MM, Sinicrope FA. Radiation enteritis. Curr Gastroenterol Rep. 2002;4:361-365.
56. Chater C, Saudemont A, Zerbib P. Chronic radiation enteritis. J Visc Surg. 2019;156:175-176.
57. Harb AH, Abou Fadel C, Sharara AI. Radiation enteritis. Curr Gastroenterol Rep. 2014;16:383.
58. Olopade FA, Norman A, Blake P, et al. A modified inflammatory bowel disease questionnaire and the Vaizey incontinence questionnaire are simple ways to identify patients with significant gastrointestinal symptoms after pelvic radiotherapy. Br J Cancer. 2005;92:1663-1670.
59. Wang Y, Kong W, Lv N, et al. Incidence of radiation enteritis in cervical cancer patients treated with definitive radiotherapy versus adjuvant radiotherapy. J Cancer Res Ther. 2018;14 (8 suppl):S120-S124.
60. Theis VS, Sripadam R, Ramani V, et al. Chronic radiation enteritis. Clin Oncol (R Coll Radiol). 2010;22:70-83.
61. Webb GJ, Brooke R, De Silva AN. Chronic radiation enteritis and malnutrition. J Dig Dis. 2013;14:350-357.
62. Algin O, Turkbey B, Ozmen E, et al. Magnetic resonance enterography findings of chronic radiation enteritis. Cancer Imaging. 2011;11:189-194.
63. Lee DW, Poon AO, Chan AC. Diagnosis of small bowel radiation enteritis by capsule endoscopy. Hong Kong Med J. 2004;10:419-421.
64. Rai M, Hookey L, Bechara R. A case of radiation-induced enteritis diagnosed by video capsule endoscopy. Gastrointest Endosc. 2019;90:315-316.
65. Jazwinski A, Palazzo J, Kastenberg D. Capsule endoscopy diagnosis of radiation enteritis in a patient previously considered to have celiac sprue. Endoscopy. 2007;39(suppl 1):E66.
66. Oya M, Yao T, Tsuneyoshi M. Chronic irradiation enteritis: its correlation with the elapsed time interval and morphological changes. Hum Pathol. 1996; 27:774-781.
67. Khalid U, Norman AR, Andreyev HJ. Elevated C-reactive protein levels are not a feature of uncomplicated radiation-induced bowel injury. Eur J Cancer Care (Engl). 2007;16:346-350.
68. Roberts I. Diagnosis and management of chronic radiation enteritis. www.uptodate.com/contents/diagnosis-and-management-of-chronic-radiation-enteritis. Accessed January 20, 2021.
69. Wedlake LJ, Shaw C, Whelan K, et al. Systematic review: the efficacy of nutritional interventions to counteract acute gastrointestinal toxicity during therapeutic pelvic radiotherapy. Aliment Pharmacol Ther. 2013;37:1046-1056.
70. McGough C, Baldwin C, Frost G, et al. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. Br J Cancer. 2004; 90:2278-2287.
71. Yeoh EK, Horowitz M, Russo A, et al. Gastrointestinal function in chronic radiation enteritis: effects of loperamide-N-oxide. Gut. 1993;34:476-482.
72. Arlow FL, Dekovich AA, Priest RJ, et al. Bile acids in radiation-induced diarrhea. South Med J. 1987;80:1259-1261.
73. Heusinkveld RS, Manning MR, Aristizabal SA. Control of radiation-induced diarrhea with cholestyramine. Int J Radiat Oncol Biol Phys. 1978;4:687-690.
74. Quigley EM, Abu-Shanab A. Small intestinal bacterial overgrowth. Infect Dis Clin North Am. 2010;24:943-959, viii-ix.

75. Delia P, Sansotta G, Donato V, et al. Use of probiotics for prevention of radiation-induced diarrhea. World J Gastroenterol. 2007;13:912-915.
76. Floch MH, Walker WA, Guandalini S, et al. Recommendations for probiotic use, 2008. J Clin Gastroenterol. 2008;42(suppl 2):S104-S108.
77. Urbancsek H, Kazar T, Mezes I, et al. Results of a double-blind, randomized study to evaluate the efficacy and safety of *Antibiophilus* in patients with radiation-induced diarrhoea. Eur J Gastroenterol Hepatol. 2001;13:391-396.
78. Wedlake LJ, Silia F, Benton B, et al. Evaluating the efficacy of statins and ACE-inhibitors in reducing gastrointestinal toxicity in patients receiving radiotherapy for pelvic malignancies. Eur J Cancer. 2012;48:2117-2124.
79. Kountouras J, Zavos C. Recent advances in the management of radiation colitis. World J Gastroenterol. 2008;14:7289-7301.
80. Pasha SF, Harrison ME, Leighton JA. Obscure GI bleeding secondary to radiation enteritis diagnosed and successfully treated with retrograde double-balloon enteroscopy. Gastrointest Endosc. 2007;65:552-554.
81. Toyoda H, Jaramillo E, Mukai K, et al. Treatment of radiation-induced hemorrhagic duodenitis with argon plasma coagulation. Endoscopy. 2004;36:192.
82. Haruta H, Yamamoto H, Mizuta K, et al. A case of successful enteroscopic balloon dilation for late anastomotic stricture of choledochojejunostomy after living donor liver transplantation. Liver Transpl. 2005;11:1608-1610.
83. Kita H, Yamamoto H, Yano T, et al. Double balloon endoscopy in two hundred fifty cases for the diagnosis and treatment of small intestinal disorders. Inflammopharmacology. 2007;15:74-77.
84. Regimbeau JM, Panis Y, Gouzi JL, et al; French University Association for Surgical Research. Operative and long term results after surgery for chronic radiation enteritis. Am J Surg. 2001;182:237-242.
85. Galland RB, Spencer J. Surgical management of radiation enteritis. Surgery. 1986;99:133-139.
86. Kuroki F, Iida M, Matsui T, et al. Intraoperative endoscopy for small intestinal damage in radiation enteritis. Gastrointest Endosc. 1992;38:196-197.
87. Marshall GT, Thirlby RC, Bredfeldt JE, et al. Treatment of gastrointestinal radiation injury with hyperbaric oxygen. Undersea Hyperb Med. 2007;34:35-42.
88. Galland RB, Spencer J. Natural history and surgical management of radiation enteritis. Br J Surg. 1987;74:742-747.
89. Ashburn JH, Kalady MF. Radiation-induced problems in colorectal surgery. Clin Colon Rectal Surg. 2016;29:85-91.
90. Lillemoe KD, Brigham RA, Harmon JW, et al. Surgical management of small-bowel radiation enteritis. Arch Surg. 1983;118:905-907.
91. Irani S, Seven BBG, Ross A, et al. Balloon dilation of benign small bowel strictures using double balloon enteroscopy: 5-year review from a single tertiary referral center. Gastrointestinal Intervention. 2012;1:74-78.
92. Siddiqui UD, Banerjee S, Barth B, et al; ASGE Technology Committee. Tools for endoscopic stricture dilation. Gastrointest Endosc. 2013;78:391-404.
93. Abele JE. The physics of esophageal dilatation. Hepatogastroenterology. 1992;39:486-489.
94. Triadafilopoulos G, Sarkisian M. Dilatation of radiation-induced sigmoid stricture using sequential Savary-Guilliard dilators: a combined radiologic-endoscopic approach. Dis Colon Rectum. 1990;33:1065-1067.
95. Klag T, Wehkamp J, Goetz M. Endoscopic balloon dilation for Crohn's disease-associated strictures. Clin Endosc. 2017;50:429-436.
96. East JE, Brooker JC, Rutter MD, et al. A pilot study of intrastricture steroid versus placebo injection after balloon dilatation of Crohn's strictures. Clin Gastroenterol Hepatol. 2007;5:1065-1069.
97. Caruso A, Conigliaro R, Manta R, et al. Fully covered self-expanding metal stents for refractory anastomotic colorectal strictures. Surg Endosc. 2015;29:1175-1178.
98. Yates MR III, Baron TH. Treatment of a radiation-induced sigmoid stricture with an expandable metal stent. Gastrointest Endosc. 1999;50:422-426.

Strategies to Minimize Late Effects From Pelvic Radiotherapy

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overview

During the past 30 years, radiation treatment techniques have significantly improved, from conventional external-beam radiation therapy, to three-dimensional conformal radiation therapy, to current intensity-modulated radiation therapy, benefiting patients who undergo treatment of pelvic malignancies. Modern treatment options also include proton beam irradiation as well as low and high dose rate brachytherapy. Although the acute adverse effects of these modalities are well documented in clinical trials, less well known are the true incidence and optimal management of those late adverse effects that can occur months to years later. In a population of survivors of cancer that is steadily increasing, with many such patients receiving radiotherapy at some time during their disease course, these late effects can become a considerable management and quality-of-life issue. This review will examine the range of late toxicities that can occur from pelvic radiotherapy and explore strategies to prevent and mitigate them.

Improved overall survival rates for all cancers during the past 40 years translate to higher numbers of survivors of cancer, with more than 16.9 million U.S. survivors alive on January 1, 2019.[1] With survivors of prostate, gynecologic, and colorectal/anal cancers living longer, increased attention centers on how to best evaluate the potential for long-term pelvic radiation–induced toxicity. Tissue within the irradiated volume of the pelvis can be subject to both acute (occurring within 90 days) and late adverse effects of treatment. Structurally, there can be effects on the pelvic bones resulting in pelvic insufficiency fractures or femoral head necrosis/fractures.[2,3] Accelerated atherogenesis can occur to the blood vessels of the pelvis secondary to vascular endothelial injury and result in peripheral vascular disease.[4] Late urinary effects, such as radiation cystitis, urethral stricture, ureteral stricture, defunctionalized bladder, hemorrhagic cystitis, and fistulas, can occur decades after treatment.[5] Considerable long-term disruption in bowel function due to radiation enteritis or proctitis can occur with additional problems such as chronic diarrhea, bowel dysfunction, or fecal incontinence.[6] In addition, fertility is disrupted, with serious preservation implications for both men and women caused by lack of viable sperm and oocyte production after treatment.[7] Sexual health is also affected, with vaginal stenosis and early menopause affecting women and erectile dysfunction and low testosterone affecting men.[8]

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RADIATION THERAPY ADVANCES

Radiation techniques have advanced significantly during the past 30 years, designed to increase the ability to escalate dose to the tumor while significantly sparing the surrounding healthy tissue. External-beam radiotherapy and internal radiation with brachytherapy can be delivered to pelvic tumors as definitive therapy, either alone or in combination, as well as both pre- and postoperatively. Moreover, some patients also receive concurrent radiosensitizing chemotherapy or induction therapy before pelvic radiotherapy. The sequence of treatment matters with respect to pelvic toxicity; for example, results reported in the setting of colorectal cancer showed a notable decrease in grade 3 or 4 toxic effects from 24% when delivered in the adjuvant setting to 14% when the treatment was delivered preoperatively.[9] Studies have shown that intensity-modulated radiation therapy significantly decreases the acute toxicities in many tumor types[10-12] and may also reduce late gastrointestinal side effects compared with three-dimensional conformal radiation therapy, but additional long-term data are needed for confirmation.[13]

Advanced radiation technologies allow more precise dose delivery through the capability to fuse diagnostic studies, such as MRI and PET imaging, directly to the radiation-planning CT scan to optimize slice-by-slice determination of gross disease. Not only does that increase confidence of delineation of the exact tumor-bearing primary and nodal targets, but it also allows for increased determination of the more viable normal tissues to exclude, such as the PET-defined active pelvic bone marrow.[14] The dosimetric advances of conforming the high-dose region to the shape of the target with intensity-modulated techniques allow

PRACTICAL APPLICATIONS

- Late toxicities after pelvic radiation can occur from 3 months to many decades after treatment.
- Long-term side effects can significantly impact the quality of life of the increasing population of survivors cured of their gynecologic, gastrointestinal, and genitourinary primary cancers, but robust data on true incidence are lacking because of late onset.
- Toxicities can affect any tissue in the irradiated pelvis from the bone (insufficiency fractures), blood vessels (accelerated peripheral vascular disease), gastrointestinal system (proctitis, enteritis, strictures, incontinence, and fistula), and genitourinary system (urethral or ureteral stricture, erectile dysfunction, bladder dysfunction, ejaculatory dysfunction, fistula, low testosterone, and infertility), to the gynecologic system (vaginal stenosis, dyspareunia, and ovarian failure with premature menopause, infertility, and uterine dysfunction).
- Despite improved advances in radiation therapy treatment planning and delivery, which have evolved to decrease the dose to the normal tissues, late effects remain a persistent clinical management challenge.
- Future radiation innovative strategies, including vessel-sparing radiotherapy, rectal spacers, placement of intravaginal dilators during treatment, improvements in intensity-modulated photon and proton therapy, and real-time adaptive replanning with magnetic resonance–guided therapies and stereotactic body radiation therapy, are undergoing active investigation to prevent late treatment morbidity.

decreased mean and maximum doses to the surrounding normal tissues, which leads to an improved therapeutic ratio.[15] These techniques can be combined with proton delivery, with steep fall off, called the Bragg peak, secondary to the physical properties of the beam.[16] Intensity-modulated proton therapy is currently being investigated as a strategy to mitigate acute and potentially late toxicity, with recent data in the prostate setting suggesting less acute gastrointestinal toxicity secondary to enhanced sparing of the small intestine.[17] Another strategy designed to improve the therapeutic ratio is stereotactic body radiation therapy, which is defined as the delivery of one to five high dose-per-fraction treatments. This treatment option is also being explored for patients with favorable early-stage prostate cancer and it has favorable short-term adverse effect profiles, but more evidence is needed to fully characterize the incidence of late adverse effects.[18]

Improved image-guided radiation therapy techniques have also been developed to verify the position of the tumor before each daily radiation treatment.[19] On standard radiation delivery linear accelerator units, either cone beam CT scans or kilovoltage AP and lateral imaging scans can reliably reproduce the intended treatment plan with narrow margins. With the integration of MRI linear accelerator units, there are now additional options for real-time imaging throughout the course of a patient's treatment to account for the differences in target position caused by dynamic changes in position as a result of bladder and rectal filling, expanding the potential for improving the therapeutic ratio even more.[20,21] As part of this MRI-guided process, the plan from the day of simulation can be applied to the day's anatomy, and, if the normal tissue constraints are not met on that particular day, an adaptive replan can be triggered in real time.[22] This adaptation provides additional benefit to determine optimal dose delivery based on the anatomy of the day. Long-term data are awaited to see if adaptive replanning will result in improved outcomes.

As radiation treatment planning and delivery systems have improved, so too have innovative strategies to integrate these tools to minimize the potential for late adverse effects. In the setting of prostate cancer, erectile dysfunction remains the most common late effect from treatment, with 40% of men noting treatment-induced erectile dysfunction.[23] Prior work by Zelefsky and Eid[24] attributed erectile dysfunction to arteriogenic, cavernosal, mixed, or neurologic factors, finding that patients receiving definitive radiotherapy had a predominantly arteriogenic pathology. Investigators from the University of Michigan recently reported a novel strategy of vessel-sparing radiotherapy to preserve erectile function in their single-arm, phase II trial, finding that nearly 90% of patients at 5 years remained sexually active.[25] To accomplish this, they integrated the diagnostic MRI as well as an MRI angiogram. By contouring the internal pudendal artery and the corpus cavernosum, they were able to significantly limit the arterial dose.[26,27] Additional data are awaited to confirm the efficacy of this approach to preserve long-term erectile function.

Additional innovations have been developed to improve the therapeutic ratio, such as the integration of rectal displacement devices.[28] Recent data comparing an implanted hydrogel spacer between the prostate and the rectum versus an endorectal balloon has shown significantly improved dosimetry with the spacer, resulting in less 2-year, grade 2 or higher, late rectal bleeding (19% vs. 3%;

p = .003).[29] Additional data from a recent phase III trial of patients with prostate cancer also reported significantly decreased rectal toxicity with a spacer and improved quality of life.[30] Figures 1 and 2 depict a rectal spacer being used for the treatment of a patient with magnetic resonance–guided stereotactic body radiation therapy as well as a patient receiving high dose rate brachytherapy as monotherapy. This work has been pioneered in prostate cancers, suggesting a benefit with less late rectal toxicity, so additional data in other cancer pelvic sites are eagerly awaited.

RADIATION FIBROSIS SYNDROME

Damage to blood vessels within the irradiated field can result in a chronic condition termed radiation fibrosis syndrome.[31] In radiation fibrosis syndrome, the first phase consists of chronic inflammation in which endothelial cells play a role. This is followed by a phase of patchy areas of increased fibrosis with a high density of myofibroblasts. The third phase is the fibroatrophic phase, which is characterized by the loss of parenchymal cells. The exact mechanism of radiation fibrosis syndrome is unknown, but injury to the vascular endothelium is thought to play a role, such that excessive fibrin accumulates in the intravascular, perivascular, and extravascular compartments. Radiation increases chronic free radical production and oxidative stress in treated tissues, upregulating numerous pathways pertinent to vascular disease.[32] These events cause progressive fibrosis, which is precipitated by molecular signals, such as cytokines, chemokines, and growth factors. Indeed, such high serum levels of proinflammatory cytokines have been found in long-term survivors of atomic bombs consistent with the postradiation development of a state of chronic systemic inflammation.[4] Additional clinical risk factors for development include a patient's age, medical comorbidities, and exposure to chemotherapy[33] as well as additional treatment modalities (surgery), large-volume radiotherapy plans, high total dose, concurrent infections, operative complications, and inhomogeneity of dose delivery. Radiation fibrosis syndrome can affect nerves in an irradiated field, causing neuropathic pain,[34] with damage to autonomic nerves causing orthostatic hypotension, bowel and bladder dysfunction, and sexual dysfunction.[35]

When these changes affect irradiated pelvic arteries in higher-risk patients, they are identical to those found in atherosclerosis, with the acute endothelial cell damage leading to the coagulation cascade and fibrin deposition as well as transformation of fibroblasts into fibrocytes mediated by transforming growth factor-β.[36] The oxidative stress induced by the radiation activates nuclear factor-kappa B in the affected arteries, which induces proinflammatory genes.[37] This can result in radiation-induced peripheral vascular disease of the common femoral and superficial femoral arteries, which can present with intermittent claudication and limb ischemia. Radiation-induced peripheral vascular disease is managed the same way as non–radiation-induced atherosclerosis, with consideration of medical therapy and percutaneous therapy for revascularization.[38] If patients have hypertension or diabetes, those conditions should be treated aggressively to mitigate these risks. Given the risk of peripheral vascular disease, patients should be counseled on smoking cessation and lipid modification as well as lifestyle optimization. Future preventive strategies may also include inhibitors of nuclear factor-kappa B or other pharmacologic agents directed against components of the upregulated oxidative stress pathway to treat radiation-induced vascular disease.[39,40]

Because many patients receive multimodality treatments, multidisciplinary evaluations, with consideration of the sequence of treatments as well as their individual and synergistic side effects and the range of potential onset, are important to consider. This evaluation is especially important when patients receive systemic therapies, such as immunotherapy or targeted therapy, which can have synergistic toxicity even when delivered sequentially. Overlapping gastrointestinal toxicity in the form of ulceration or perforation can occur and should promote increased vigilance at surveillance following treatment.[41] Current models optimizing long-term survivorship of patients

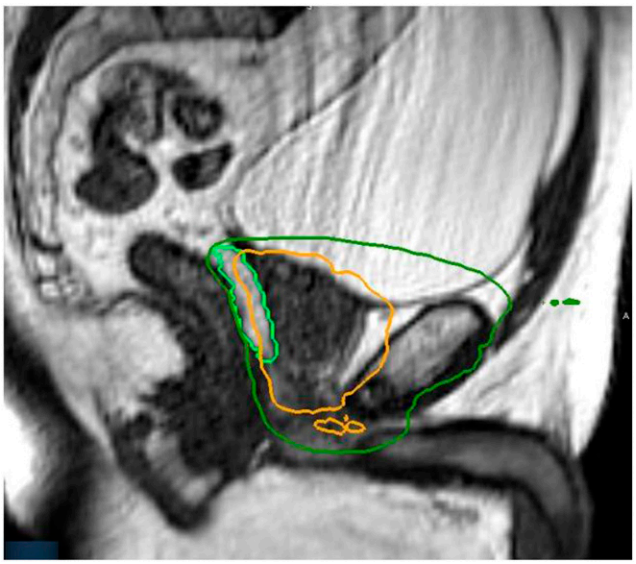

FIGURE 1. Sagittal View of Magnetic Resonance–Guided Stereotactic Body Radiation Therapy With a Rectal Spacer

The orange outline is the prescription dose of 36.25 Gy, which is delivered over 5 days, with a rectal spacer outlined in the lighter green between the prostate and the rectum. Note that the 55% dose line is in darker green, encompassing just a few millimeters of the rectum because of the increased separation from the rectal spacer.

Courtesy of Daniel Grass, MD, PhD, and Kujtim Latifi, PhD.

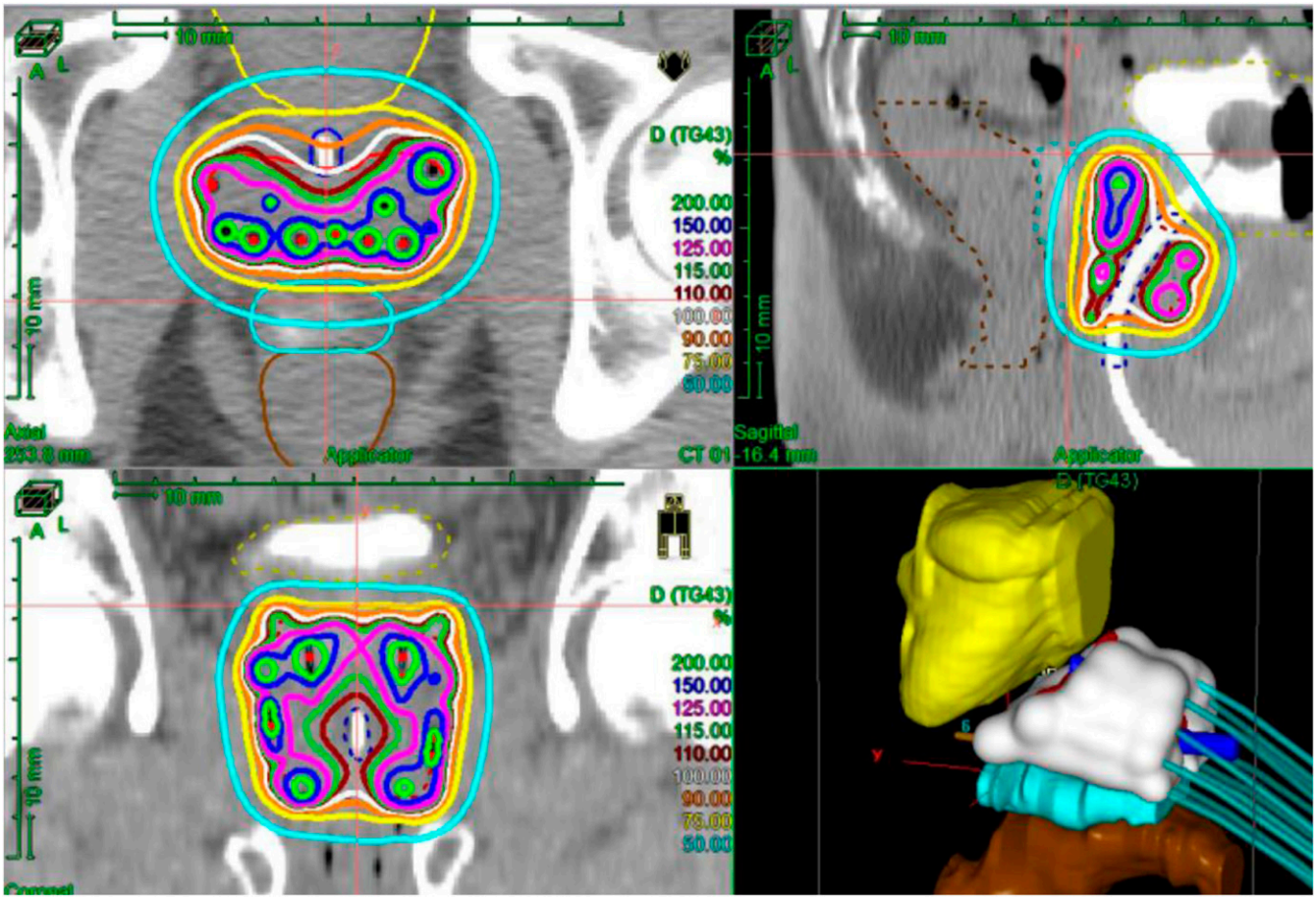

FIGURE 2. High Dose Rate Brachytherapy for Favorable-Risk Prostate Cancer With a Rectal Spacer

The axial (A), sagittal (B), and coronal (C) images represent the treatment doses received by a patient with favorable-risk prostate cancer receiving brachytherapy alone delivered with a high dose rate technique. (D) Note the light blue rectal spacer between the prostate (white) and rectum (brown), with the bladder (yellow) above. Note on A and B that very little dose is received by the anterior rectal wall because of the rectal spacer.

Courtesy of Daniel Fernandez, MD, PhD, and Kujtim Latifi, PhD.

who received multimodality systemic therapies and pelvic radiation therapy are currently lacking, but recent reports suggest that new, personalized, gastrointestinal-centric models for such patients are needed.[42] In the sections that follow (Table 1), we will detail how radiotherapy can affect individual tissues in the irradiated pelvis, with implications for survivorship.

URINARY SYSTEM

Within the first 6 months after prostate radiotherapy, patients commonly report dysuria, urinary frequency, and hesitancy as well as nocturia, but there is considerable recovery back to baseline after a year,[43] and most symptoms are grade 1 to 2. Urinary retention is rare, with 3% of men requiring catheter drainage after brachytherapy and higher rates seen in patients with larger preimplant prostate volumes or higher grades on the International Prostate Symptom Score.[44] Decades after pelvic radiotherapy, urinary adverse events can be seen,[45] including radiation cystitis, defunctionalized bladder due to scarring, hemorrhagic cystitis, ureteral stricture, urethral stricture, and fistulas,[46,47] and estimates of high-grade adverse effects are in the 5% to 13% range long term.[5] Although the type of radiation delivery has the potential to influence the adverse effect profile, recent phase III data report the equivalence of both acute and late urinary adverse effects if treatment was given either conventionally over 8 weeks to 78 Gy or hypofractionated over 7 days,[48] suggesting that future strategies of offering fewer daily treatment fractions may become more accepted. Severe late urinary adverse effects are most common after radiotherapy to the prostate, bladder, and cervix, where combination treatment with brachytherapy and radiotherapy increases the risk. The type of late urinary adverse effect varies by treatment site, with more urethral strictures in patients treated for prostate cancer, bladder hemorrhage and necrosis after bladder cancer, and ureteral strictures after cervical

TABLE 1. Possible Long-Term Sequelae of Pelvic Radiotherapy With Associated Management Options

	Toxicity	Management Options
Sexual: Female		
	Vaginal stenosis	Vaginal dilator insertion three times per week starting 1-month postradiotherapy; some data to suggest insertion daily during radiotherapy
	Ovarian failure/infertility	Fertility consult for ovarian preservation, possible ovarian transposition, or oophorexy
	Uterine dysfunction	Not possible to carry fetus to term
	Vaginal dryness	Water-based lubricant early when healing, then can use oil- or silicone-based lubricant; hormone replacement/intravaginal estrogen, if appropriate
	Premature menopause	Hormone replacement/intravaginal estrogen, if appropriate
	Dyspareunia	Vaginal dilator, lubricant, or hormone replacement therapy/intravaginal estrogen, if appropriate
	Sexual dissatisfaction	Referral to psychologist with expertise in postradiotherapy sexual dysfunction
Sexual: Male		
	Erectile dysfunction	Prevent, if possible, with vessel-sparing radiotherapy; treat with phosphodiesterase-5 inhibitor. If unresponsive, consider penile implant, vacuum erection device, or intracavernosal injections.
	Low testosterone	Consider hormone replacement, if appropriate.
	Infertility	Fertility consult for sperm banking
	Ejaculatory issues	Prevent as much as possible during radiotherapy planning with avoidance of dose to vessels, penile bulb/bodies, and neurovascular bundles.
	Sexual dissatisfaction	Referral to psychologist with expertise in postradiotherapy sexual dysfunction
Genitourinary		
	Fistula	Surgical evaluation
	Cystitis	Cystoscopy for diagnosis; to start, hydration, transfusion, and bladder irrigation. If severe, consider embolization, endoscopic bladder procedures, or hyperbaric oxygen.
	Urethral stricture	Dilation/stent
	Ureteral stricture	Dilation/stent
	Bladder dysfunction	Antispasmodics
Pelvic Arteries		
	Peripheral vascular disease	Advise smoking cessation, maintain lipids in normal range, and educate about signs of peripheral vascular disease. Treat aggressively if hypertension or diabetes.
Pelvic Bone		
	Insufficiency fracture	First: osteoporosis prevention, calcium, vitamin D, weight-bearing exercise, and bisphosphonates. If fracture, consider sacroplasty.
	Necrosis	Surgical evaluation for fixation

(Continued on following page)

TABLE 1. Possible Long-Term Sequelae of Pelvic Radiotherapy With Associated Management Options (Continued)

	Toxicity	Management Options
Gastrointestinal		
	Chronic diarrhea	Loperamide or diphenoxylate/atropine, modify diet to avoid raw vegetables, and add stool-bulking agents
	Fecal incontinence	Pelvic rehabilitation consult for Kegel exercises; consider sacral stimulator if pelvic rehabilitation fails
	Malabsorption	Support nutrition, may need low-fat diet or cholestyramine for bile salt deficiency

NOTE. The related topics of radiation proctitis, enteritis, stricture, and obstruction are covered in the article entitled "Management of Long-Term Toxicity From Pelvic Radiation Therapy" by Dalsania et al in the 2021 *ASCO Educational Book*.

treatment.[5] Urinary adverse effects are less commonly reported in patients treated for anal cancer.[49] In patients with rectal cancer receiving total mesorectal excision, urinary dysfunction can occur in up to one-third of patients, but it has historically been attributed to surgical nerve damage,[35] which may improve as nerve-sparing surgical techniques evolve. It is not known whether late urinary adverse effects are detected more often after bladder and prostate cancer because the patients are seen by urologists. Although most trials are underpowered or lack sufficient follow-up to measure late urinary adverse effects, the ones that do follow up suggest that urinary adverse effects continue to accrue at a consistent rate even 2 decades after treatment.[5]

FERTILITY

ASCO guidelines suggest a fertility preservation consult as early as possible before treatment initiation to allow consideration of multiple options.[7] Oocytes are extremely radiosensitive, with 50% destruction at doses less than 2 Gy.[50] Given this, doses used in conventionally fractionated pelvic radiotherapy will cause ovarian failure. Premature menopause and the ensuing hormonal changes can lead to hot flashes, mood changes, and vaginal dryness.[8] ASCO guidelines for patients receiving pelvic radiotherapy include embryo or unfertilized oocyte cryopreservation, ovarian transposition, and ovarian tissue cryopreservation and transplantation. Ovarian transposition and oophoropexy are surgical methods of moving the ovaries out of the radiation field before initiation of treatment, and they are currently done laparoscopically, with reported success rates ranging from 16% to 90%; when the radiation field covers the entire pelvis, the ovarian transposition procedure would be done to move the ovaries out of the pelvis and into the upper abdomen.[51] A suggested distance of at least 4 cm is recommended between the new position of the ovary and the edge of the radiation field as long as the blood supply to the ovaries is not compromised.[52] In addition, the uterus in an irradiated pelvis will not function to carry a fetus to term, resulting in miscarriage, preterm labor, low birth weight, and placental abnormalities.[53] These pelvic radiotherapy effects on the function of both the ovaries and the uterus must be discussed with the patient before initiation so that appropriate counseling and planning can be done.

Male fertility is also negatively affected by pelvic radiotherapy. Although the testicular tissues are not in the radiation target volumes, the scatter dose of the nearby field border can lead to permanently decreased populations of radiosensitive germ cells that produce spermatocytes and Leydig cells that produce testosterone. With respect to germ cells, doses of 0.75 Gy to 3 Gy can cause permanent azoospermia.[54] Decreased testosterone production can occur after Leydig cells receive radiotherapy doses higher than 20 Gy.[55] For male fertility preservation, ASCO guidelines suggest sperm cryopreservation before initiation of therapy, because sperm DNA integrity may be compromised after a single treatment; testicular tissue cryopreservation and reimplantation or grafting of such tissues is only recommended in the setting of a clinical trial.[7]

SEXUAL HEALTH

In the long term, women treated for cervical, endometrial, rectal, and anal cancers who receive pelvic radiotherapy can develop vaginal stenosis as well as vaginal dryness and dyspareunia. Vaginal stenosis occurs secondary to increased collagen production within the fibroconnective tissue, leading to shortening and narrowing of the vagina; changes in the vaginal mucosa also lead to atrophy of these cells.[56] Despite the advances in radiation technology with intensity-modulated radiation therapy, high doses are given to the upper and lower vagina because of the location of the vagina immediately anterior to the anus and lower rectum and for coverage of the gross and elective target volumes. Vaginal stenosis can be scored according to a modified version of the National Cancer Institute Common Terminology Criteria for Adverse Events, which is based on physician-assessed symptoms of grade 1, dyspareunia; grade 2, pain with dilator use; or grade 3, vaginal dryness. In the setting of patients treated definitively with chemoradiation for anal cancer, such scoring showed a 79% incidence, with 14.3% as grade 1, 27.1% as grade 2, and 37.1% as grade 3 during

a median follow-up of 2.5 years,[57] with only 21.5% having no identifiable vaginal stenosis at all. Similar reports of late vaginal morbidity occur in the majority of patients treated for gynecologic cancers.[58] Regular use of vaginal dilators has been shown to decrease clinically noteworthy vaginal shortening and/or tightening.[59,60] In addition to radiation volume and dose, patient age older than 50 and lack of vaginal dilator compliance increase the risk of vaginal stenosis.[61,62]

To mitigate these risks, sexual rehabilitation after pelvic radiotherapy has included the regular insertion of vaginal dilators starting when the vaginal mucosa is healed, typically 1 month after treatment, with a frequency of two to three times per week for 1 to 3 minutes and a duration of 1 year,[60] with some investigators recommending treatment continuation for the duration of the patient's lifetime.[63] A prospective study from Memorial Sloan Kettering Cancer Center noted issues with vaginal dilator compliance, with only 25% of patients compliant in the fourth quarter of the year; those who used vaginal dilators had efficacy, with 82% of patients maintaining preradiotherapy vaginal dilator size at 1 year, and, of the 49% who had a decrease in vaginal dilator size at 1 month post-treatment, the majority (71%) had returned to preradiotherapy vaginal dilator size at 1 year.[63] To reduce the potential for vaginal stenosis even more, investigators from MD Anderson Cancer Center studied vaginal dilator use during simulation and treatment and reported decreases in the mean dose to the vagina by 5.5 Gy, which may, decrease future late vaginal morbidity long term.[64] A similar concept with a tampon to be inserted during daily treatment is currently being assessed in a prospective, ongoing European trial designed to measure the incidence and grade of vaginal stenosis in patients definitively treated for anal cancer.[65]

Dyspareunia is experienced by up to one in five women after pelvic radiotherapy.[66] Strategies to improve symptoms of superficial dyspareunia at the level of the vaginal introitus and mucosa in patients who are now functionally menopausal include intravaginal estrogens and hormone replacement therapy, if appropriate.[67-69] If hormone therapy is contraindicated, application of vaginal moisturizers can be applied two to three times each week to restore the vaginal pH and improve the moisture content of the mucosa, with consideration for oil-based or silicone-based lubricants 3 months postradiotherapy to relieve possible friction and pain with intercourse.[70] There is a strong correlation between sexual dysfunction and psychosocial distress.[71] In a study of survivors of anal cancer treated at MD Anderson Cancer Center with a median of 5 years of follow-up, the majority of recipients (65%) reported that lack of sexual interest was "somewhat" or "very much" of a problem, with (71%) noting that the inability to relax and enjoy sex was also "somewhat" or "very much" of a problem.[49] Indeed, sexual difficulties after radiotherapy can include difficulty with desire, arousal, orgasm, and sexual pain.[72] Nonbiomedical strategies, ranging from cognitive behavioral therapy to mindfulness, may be effective to improve patients' distress.[73,74]

For male patients, erectile dysfunction and ejaculatory issues remain major issues in the setting of pelvic radiotherapy,[72] with a range of possible ejaculatory issues, such as reduced ejaculate, ejaculatory pain, hematospermia, altered orgasmic sensation, and reduced orgasmic intensity.[75] These changes are thought to be secondary to arterial damage as well as damage to the neurovascular bundles, penile bulb, and penile bodies.[76,77] To treat erectile dysfunction after radiotherapy, sildenafil was effective in 57% of patients treated in a randomized trial.[78] Similar efficacy has been reported for tadalafil for erectile dysfunction post-treatment, with successful intercourse in almost 50% of patients,[51] but not if given during treatment and for 24 weeks thereafter to prevent erectile dysfunction.[23] For men with erectile dysfunction not responsive to phosphodiesterase-5 inhibitors, other options include penile implants, vacuum erection devices, topical alprostadil, or constriction loops/rings, whereas psychosexual therapy is advised for men with orgasmic or ejaculatory issues.[72]

BONE EFFECTS

After pelvic radiotherapy, bones of the pelvic region can undergo changes secondary to decreased osteoblast proliferation and decreased bone blood flow as a result of blood vessel fibrosis combined with bone resorption from osteoclast activity that can result in fracture or necrosis; risk is increased in the settings of osteoporosis, kidney disease, vascular disease, and long-term use of steroids or bisphosphonates.[8] The most commonly affected bones are the sacrum, pubic symphysis, and rami.[79] The extent of radiation-induced reactions is secondary to treatment-related factors, such as the volume and dose irradiated as well as the technique, and whether additional therapies are delivered, as well as patient-specific factors, such as age, body weight, sex, osteoporosis, and medications like corticosteroids.[80] Insufficiency fractures resulting from progressive radiation-induced reactions can lead to biomechanical bone instability, which could be symptomatic with pain such that CT-guided sacroplasty may be recommended.[81] Post-treatment, the bone marrow can recover, but this recovery is delayed, with a median time from occurrence of radiation-induced reactions until first signs of recovery, as demonstrated on MRI, of 16.5 months and a time of 39.5 months to return completely to normal.[80]

GASTROINTESTINAL SIDE EFFECTS

Late effects of pelvic radiotherapy can negatively affect gastrointestinal quality of life and have been reported in 6% to 78% of patients.[6] These late gastrointestinal effects can include diarrhea, dysmotility, food intolerance, nutrient

malabsorption, or fecal incontinence, with rare development of fistula, obstruction, or hemorrhage.[8] Please see the article entitled "Management of Long-Term Toxicity From Pelvic Radiation Therapy" by Dalsania et al in the 2021 *ASCO Educational Book* for additional discussion of radiation proctitis, enteritis, and bowel strictures.

In addition to toxicities from pelvic radiotherapy, patients may experience anal discharge as well as clustering and frequency of bowel movements.[82] Surgically treated survivors of long-term rectal cancer may also be at risk for low anterior resection syndrome, which occurs in 60% to 90% of patients[83] and consists of fecal and gas incontinence, urgency, frequent bowel movements, clustering of stools, and difficulty with bowel emptying.[84] Multidisciplinary discussion of the cumulative toxicities from all modalities a patient is likely to experience is important before treatment.

Multiple strategies have been investigated to improve side effects in patients who develop fecal incontinence. Studies have shown that a dose effect less than 40 Gy to the anal sphincter is associated with less fecal leakage,[85] which may be helpful in the treatment of men with prostate cancer but does not offer improvement for the other pelvic cancers, in which radiotherapy to the sphincter complex exceeds 40 Gy for curative-intent therapy. Thus, additional options are needed and have ranged from adding bulking agents as well as appropriate antidiarrheal treatments (loperamide and diphenoxylate/atropine) to eliminating raw vegetables from the diet.[86] In addition, pelvic floor rehabilitation has been explored to improve muscular function, because these muscles are involved in continence, elimination, and sexual arousal, with results showing improved pelvic floor strength and sexual function.[87] There are also some data to support the integration of probiotics, with the suggestion that this therapy can decrease loperamide use and decrease the incidence of loose watery stools,[88] but more data are needed to understand the true impact of such therapy. If conservative measures fail, the patient can also be considered for a trial of a sacral nerve stimulator, which has been shown to improve function in those with severe incontinence.[89]

CONCLUSION

Techniques of pelvic radiotherapy have evolved during the past few decades, with an improved therapeutic ratio such that higher dose delivery to the tumor-bearing target region is accompanied simultaneously by lower doses to the surrounding healthy tissue. The modern range of treatment techniques takes advantage of improved dosimetry (intensity-modulated radiation therapy and intensity-modulated proton therapy); better image guidance, including real-time tissue visualization with an MRI linear accelerator; and mechanical devices to be used during therapy, including vaginal dilators and rectal spacers. Yet, despite these advances, late toxicity from pelvic radiotherapy continues to be a clinical problem as the number of survivors of cancer continues to increase. Future studies are needed to prospectively evaluate patient-reported long-term outcomes so that we can develop more effective strategies to mitigate these long-term sequelae of treatment.

AFFILIATIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Viale PH. The American Cancer Society's facts & figures: 2020 edition. J Adv Pract Oncol. 2020;11:135-136.
2. Oh D, Huh SJ. Insufficiency fracture after radiation therapy. Radiat Oncol J. 2014;32:213-220.
3. Baxter NN, Habermann EB, Tepper JE, et al. Risk of pelvic fractures in older women following pelvic irradiation. JAMA. 2005;294:2587-2593.
4. Venkatesulu BP, Mahadevan LS, Aliru ML, et al. Radiation-induced endothelial vascular injury: a review of possible mechanisms. JACC Basic Transl Sci. 2018;3:563-572.
5. Elliott SP, Malaeb BS. Long-term urinary adverse effects of pelvic radiotherapy. World J Urol. 2011;29:35-41.
6. Andreyev HJN, Vlavianos P, Blake P, et al. Gastrointestinal symptoms after pelvic radiotherapy: role for the gastroenterologist? Int J Radiat Oncol Biol Phys. 2005;62:1464-1471.

7. Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2018;36:1994-2001.
8. Nicholas S, Chen L, Choflet A, et al. Pelvic radiation and normal tissue toxicity. Semin Radiat Oncol. 2017;27:358-369.
9. Sauer R, Becker H, Hohenberger W, et al; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731-1740.
10. Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys. 2013;86:27-33.
11. Michalski JM, Yan Y, Watkins-Bruner D, et al. Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial. Int J Radiat Oncol Biol Phys. 2013;87:932-938.
12. Poorvu PD, Sadow CA, Townamchai K, et al. Duodenal and other gastrointestinal toxicity in cervical and endometrial cancer treated with extended-field intensity modulated radiation therapy to paraaortic lymph nodes. Int J Radiat Oncol Biol Phys. 2013;85:1262-1268.
13. Lawrie TA, Green JT, Beresford M, et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database Syst Rev. 2018;1:CD012529.
14. Franco P, Fiandra C, Arcadipane F, et al. Incorporating ^{18}FDG-PET-defined pelvic active bone marrow in the automatic treatment planning process of anal cancer patients undergoing chemo-radiation. BMC Cancer. 2017;17:710.
15. Mok H, Crane CH, Palmer MB, et al. Intensity modulated radiation therapy (IMRT): differences in target volumes and improvement in clinically relevant doses to small bowel in rectal carcinoma. Radiat Oncol. 2011;6:63.
16. Lühr A, von Neubeck C, Pawelke J, et al; Radiobiology of Proton Therapy. Radiobiology of Proton Therapy: results of an international expert workshop. Radiother Oncol. 2018;128:56-67.
17. Chuong MD, Hartsell W, Larson G, et al. Minimal toxicity after proton beam therapy for prostate and pelvic nodal irradiation: results from the proton collaborative group REG001-09 trial. Acta Oncol. 2018;57:368-374.
18. Henderson DR, Tree AC, van As NJ. Stereotactic body radiotherapy for prostate cancer. Clin Oncol (R Coll Radiol). 2015;27:270-279.
19. De Los Santos J, Popple R, Agazaryan N, et al. Image guided radiation therapy (IGRT) technologies for radiation therapy localization and delivery. Int J Radiat Oncol Biol Phys. 2013;87:33-45.
20. Hoffmann A, Oborn B, Moteabbed M, et al. MR-guided proton therapy: a review and a preview. Radiat Oncol. 2020;15:129.
21. Tchelebi LT, Romesser PB, Feuerlein S, et al. Magnetic resonance guided radiotherapy for rectal cancer: expanding opportunities for non-operative management. Cancer Control. 2020;27:1073274820969449.
22. Hunt A, Hansen VN, Oelfke U, et al. Adaptive radiotherapy enabled by MRI guidance. Clin Oncol (R Coll Radiol). 2018;30:711-719.
23. Pisansky TM, Pugh SL, Greenberg RE, et al. Tadalafil for prevention of erectile dysfunction after radiotherapy for prostate cancer: the Radiation Therapy Oncology Group [0831] randomized clinical trial. JAMA. 2014;311:1300-1307.
24. Zelefsky MJ, Eid JF. Elucidating the etiology of erectile dysfunction after definitive therapy for prostatic cancer. Int J Radiat Oncol Biol Phys. 1998;40:129-133.
25. Spratt DE, Lee JY, Dess RT, et al. Vessel-sparing radiotherapy for localized prostate cancer to preserve erectile function: a single-arm phase 2 trial. Eur Urol. 2017;72:617-624.
26. Lee JY, Spratt DE, Liss AL, et al. Vessel-sparing radiation and functional anatomy-based preservation for erectile function after prostate radiotherapy. Lancet Oncol. 2016;17:e198-e208.
27. McLaughlin PW, Narayana V, Meirowitz A, et al. Vessel-sparing prostate radiotherapy: dose limitation to critical erectile vascular structures (internal pudendal artery and corpus cavernosum) defined by MRI. Int J Radiat Oncol Biol Phys. 2005;61:20-31.
28. Afkhami Ardekani M, Ghaffari H, Navaser M, et al. Effectiveness of rectal displacement devices in managing prostate motion: a systematic review. Strahlenther Onkol. 2021;197:97-115.
29. Dinh T-KT, Lee HJ Jr., Macomber MW, et al. Rectal hydrogel spacer improves late gastrointestinal toxicity compared to rectal balloon immobilization after proton beam radiation therapy for localized prostate cancer: a retrospective observational study. Int J Radiat Oncol Biol Phys. 2020;108:635-643.
30. Hamstra DA, Mariados N, Sylvester J, et al. Continued benefit to rectal separation for prostate radiation therapy: final results of a phase III trial. Int J Radiat Oncol Biol Phys. 2017;97:976-985.
31. Hojan K, Milecki P. Opportunities for rehabilitation of patients with radiation fibrosis syndrome. Rep Pract Oncol Radiother. 2013;19:1-6.
32. Weintraub NL, Jones WK, Manka D. Understanding Radiation-Induced Vascular Disease. Washington, DC: American College of Cardiology Foundation; 2010.
33. Delanian S, Lefaix JL. Current management for late normal tissue injury: radiation-induced fibrosis and necrosis. Semin Radiat Oncol. 2007;17:99-107.
34. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 2010;9:807-819.
35. Lange MM, van de Velde CJ. Urinary and sexual dysfunction after rectal cancer treatment. Nat Rev Urol. 2011;8:51-57.
36. Jurado JA, Bashir R, Burket MW. Radiation-induced peripheral artery disease. Catheter Cardiovasc Interv. 2008;72:563-568.
37. Halle M, Gabrielsen A, Paulsson-Berne G, et al. Sustained inflammation due to nuclear factor-kappa B activation in irradiated human arteries. J Am Coll Cardiol. 2010;55:1227-1236.
38. Saliou C, Julia P, Feito B, et al. Radiation-induced arterial disease of the lower limb. Ann Vasc Surg. 1997;11:173-177.
39. Gloire G, Legrand-Poels S, Piette J. NF-kappaB activation by reactive oxygen species: fifteen years later. Biochem Pharmacol. 2006;72:1493-1505.

40. Zhao W, Diz D, Robbins M. Oxidative damage pathways in relation to normal tissue injury. Br J Radiol. 2007;80:S23-S31.
41. Zheng Y, Gao W, Spratt DE, et al. Management of gastrointestinal perforation related to radiation. Int J Clin Oncol. 2020;25:1010-1015.
42. Hutchinson T, et al. Gastrointestinal disease–specific survivorship care: A new personalized model integrating onco-wellness. Cancer Control. In press.
43. Donovan JL, Hamdy FC, Lane JA, et al; ProtecT Study Group. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med. 2016;375:1425-1437.
44. Mabjeesh NJ, Chen J, Stenger A, et al. Preimplant predictive factors of urinary retention after iodine 125 prostate brachytherapy. Urology. 2007;70:548-553.
45. Fujikawa K, Miyamoto T, Ihara Y, et al. High incidence of severe urologic complications following radiotherapy for cervical cancer in Japanese women. Gynecol Oncol. 2001;80:21-23.
46. Crew JP, Jephcott CR, Reynard JM. Radiation-induced haemorrhagic cystitis. Eur Urol. 2001;40:111-123.
47. deVries CR, Freiha FS. Hemorrhagic cystitis: a review. J Urol. 1990;143:1-9.
48. Fransson P, Nilsson P, Gunnlaugsson A, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer (HYPO-RT-PC): patient-reported quality-of-life outcomes of a randomised, controlled, non-inferiority, phase 3 trial. Lancet Oncol. 2021;22:235-245.
49. Das P, Cantor SB, Parker CL, et al. Long-term quality of life after radiotherapy for the treatment of anal cancer. Cancer. 2010;116:822-829.
50. Wallace WH, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. Hum Reprod. 2003;18:117-121.
51. Turkgeldi L, Cutner A, Turkgeldi E, et al. Laparoscopic ovarian transposition and ovariopexy for fertility preservation in patients treated with pelvic radiotherapy with or without chemotherapy. Facts Views Vis ObGyn. 2019;11:235-242.
52. Van Beurden M, Schuster-Uitterhoeve A, Lammes F. Feasibility of transposition of the ovaries in the surgical and radiotherapeutical treatment of cervical cancer. Eur J Surg Oncol. 1990;16:141-146.
53. Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. Int J Radiat Oncol Biol Phys. 2009;73:1304-1312.
54. Howell SJ, Shalet SM. Spermatogenesis after cancer treatment: damage and recovery. J Natl Cancer Inst Monogr. 2005;2005:12-17.
55. Giwercman A, von der Maase H, Berthelsen JG, et al. Localized irradiation of testes with carcinoma in situ: effects on Leydig cell function and eradication of malignant germ cells in 20 patients. J Clin Endocrinol Metab. 1991;73:596-603.
56. Kirchheiner K, Nout RA, Lindegaard JC, et al; EMBRACE Collaborative Group. Dose-effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. Radiother Oncol. 2016;118:160-166.
57. Mirabeau-Beale K, Hong TS, Niemierko A, et al. Clinical and treatment factors associated with vaginal stenosis after definitive chemoradiation for anal canal cancer. Pract Radiat Oncol. 2015;5:e113-e118.
58. Kirchheiner K, Nout RA, Tanderup K, et al. Manifestation pattern of early-late vaginal morbidity after definitive radiation (chemo) therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: an analysis from the EMBRACE study. Int J Radiat Oncol Biol Phys. 2014;89:88-95.
59. Velaskar SM, Martha R, Mahantashetty U, et al. Use of indigenous vaginal dilator in radiation induced vaginal stenosis. Indian J Occup Ther. 2007;39:3-6.
60. Bakker RM, ter Kuile MM, Vermeer WM, et al. Sexual rehabilitation after pelvic radiotherapy and vaginal dilator use: consensus using the Delphi method. Int J Gynecol Cancer. 2014;24:1499-1506.
61. Bahng AY, Dagan A, Bruner DW, et al. Determination of prognostic factors for vaginal mucosal toxicity associated with intravaginal high-dose rate brachytherapy in patients with endometrial cancer. Int J Radiat Oncol Biol Phys. 2012;82:667-673.
62. Brand AH, Bull CA, Cakir B. Vaginal stenosis in patients treated with radiotherapy for carcinoma of the cervix. Int J Gynecol Cancer. 2006;16:288-293.
63. Law E, Kelvin JF, Thom B, et al. Prospective study of vaginal dilator use adherence and efficacy following radiotherapy. Radiother Oncol. 2015;116:149-155.
64. Briere TM, Crane CH, Beddar S, et al. Reproducibility and genital sparing with a vaginal dilator used for female anal cancer patients. Radiother Oncol. 2012;104:161-166.
65. Arians N, Häfner M, Krisam J, et al. Intrafractional vaginal dilation in anal cancer patients undergoing pelvic radiotherapy (DILANA): a prospective, randomized, 2-armed phase-II-trial. BMC Cancer. 2020;20:52.
66. Stinesen Kollberg K, Waldenström A-C, Bergmark K, et al. Reduced vaginal elasticity, reduced lubrication, and deep and superficial dyspareunia in irradiated gynecological cancer survivors. Acta Oncol. 2015;54:772-779.
67. Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized controlled trial. J Sex Med. 2014;11:1262-1270.
68. Gilbert E, Ussher JM, Perz J. Sexuality after gynaecological cancer: a review of the material, intrapsychic, and discursive aspects of treatment on women's sexual-wellbeing. Maturitas. 2011;70:42-57.
69. Viswanathan AN, Lee LJ, Eswara JR, et al. Complications of pelvic radiation in patients treated for gynecologic malignancies. Cancer. 2014;120:3870-3883.
70. Carter J, Goldfrank D, Schover LR. Simple strategies for vaginal health promotion in cancer survivors. J Sex Med. 2011;8:549-559.
71. Philip EJ, Nelson C, Temple L, et al. Psychological correlates of sexual dysfunction in female rectal and anal cancer survivors: analysis of baseline intervention data. J Sex Med. 2013;10:2539-2548.
72. White ID. Sexual difficulties after pelvic radiotherapy: improving clinical management. Clin Oncol (R Coll Radiol). 2015;27:647-655.

73. Brotto LA, Erskine Y, Carey M, et al. A brief mindfulness-based cognitive behavioral intervention improves sexual functioning versus wait-list control in women treated for gynecologic cancer. Gynecol Oncol. 2012;125:320-325.

74. Robinson JW, Faris PD, Scott CB. Psychoeducational group increases vaginal dilation for younger women and reduces sexual fears for women of all ages with gynecological carcinoma treated with radiotherapy. Int J Radiat Oncol Biol Phys. 1999;44:497-506.

75. Incrocci L. Radiotherapy for prostate cancer and sexual health. Transl Androl Urol. 2015;4:124-130.

76. van der Wielen GJ, Mulhall JP, Incrocci L. Erectile dysfunction after radiotherapy for prostate cancer and radiation dose to the penile structures: a critical review. Radiother Oncol. 2007;84:107-113.

77. Huyghe E, Delannes M, Wagner F, et al. Ejaculatory function after permanent 125I prostate brachytherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2009;74:126-132.

78. Incrocci L, Koper PC, Hop WC, et al. Sildenafil citrate (Viagra) and erectile dysfunction following external beam radiotherapy for prostate cancer: a randomized, double-blind, placebo-controlled, cross-over study. Int J Radiat Oncol Biol Phys. 2001;51:1190-1195.

79. Papadopoulou I, Stewart V, Barwick TD, et al. Post–radiation therapy imaging appearances in cervical carcinoma. Radiographics. 2016;36:538-553.

80. Meixel AJ, Hauswald H, Delorme S, et al. From radiation osteitis to osteoradionecrosis: incidence and MR morphology of radiation-induced sacral pathologies following pelvic radiotherapy. Eur Radiol. 2018;28:3550-3559.

81. Heron J, Connell DA, James SL. CT-guided sacroplasty for the treatment of sacral insufficiency fractures. Clin Radiol. 2007;62:1094-1100; discussion 1101-1103.

82. Capp A, Inostroza-Ponta M, Bill D, et al. Is there more than one proctitis syndrome? A revisitation using data from the TROG 96.01 trial. Radiother Oncol. 2009; 90:400-407.

83. Bazzell A, Madsen LT, Dains J. Clinical management of bowel dysfunction after low anterior resection for rectal cancer. J Adv Pract Oncol. 2016;7:618-629.

84. Chen TY-T, Emmertsen KJ, Laurberg S. Bowel dysfunction after rectal cancer treatment: a study comparing the specialist's versus patient's perspective. BMJ Open. 2014;4:e003374.

85. Alsadius D, Hedelin M, Lundstedt D, et al. Mean absorbed dose to the anal-sphincter region and fecal leakage among irradiated prostate cancer survivors. Int J Radiat Oncol Biol Phys. 2012;84:e181-e195.

86. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients—a Dutch colorectal cancer group study. J Clin Oncol. 2005;23:6199-6206.

87. El-Shami K, Oeffinger KC, Erb NL, et al. American Cancer Society colorectal cancer survivorship care guidelines. CA Cancer J Clin. 2015;65:428-455.

88. Hamad A, Fragkos KC, Forbes A. A systematic review and meta-analysis of probiotics for the management of radiation induced bowel disease. Clin Nutr. 2013; 32:353-360.

89. Altomare DF, Giuratrabocchetta S, Knowles CH, et al; European SNS Outcome Study Group. Long-term outcomes of sacral nerve stimulation for faecal incontinence. Br J Surg. 2015;102:407-415.

GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Personalizing Medicine With Germline and Somatic Sequencing in Advanced Pancreatic Cancer: Current Treatments and Novel Opportunities

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overview

Performing germline and somatic sequencing in locally advanced and metastatic pancreatic cancer can identify potentially targetable genomic aberrations that impact current standard treatment options or eligibility for biomarker-targeted clinical trials. Testing for deleterious germline mutations in *BRCA1/2* impacts patient selection for platinum-based chemotherapy regimens and selection of patients who are candidates to receive maintenance therapy with olaparib. Additional germline mutations also similarly introduce potential vulnerabilities to the cancers that arise and may be targeted by clinical trials. Somatic mutation testing also provides opportunities for optimal selection of patients for biomarker-driven clinical trials. Although *KRAS* mutations are found in 90% to 93% of pancreatic cancers, there are increasing opportunities for therapies against particular mutant KRAS isoforms, especially with the advent of KRAS G12C–specific small molecule inhibitors, and KRAS targeting trials will increasingly require identification of the specific *KRAS* mutation present. There are also a range of tumor site–agnostic molecular features, such as microsatellite instability and NTRK fusions that, although rarely found in pancreatic cancers, impact selection of patients who have the potential for dramatic benefit with immune checkpoint inhibitors such as pembrolizumab or TRK inhibitors such as larotrectinib or entrectinib, respectively, and thus motivate broader somatic mutation and fusion testing for patients with locally advanced and metastatic pancreatic cancers. Multiple other rare actionable aberrations, particularly gene fusions in the 8% to 10% of KRAS wild-type pancreatic cancers, are also known, and enrollment in basket trials for these rare patient cohorts is highly encouraged.

Pancreatic cancer is the third most common cause of cancer mortality in the United States[1] and the seventh most common worldwide.[2] The current standard of care for patients with metastatic pancreatic cancer with adequate performance status is multiagent combination chemotherapy regimens such as 5-fluorouracil/irinotecan/oxaliplatin[3] or gemcitabine/nab-paclitaxel,[4] but median overall survival with these regimens is less than 12 months. Until recently, there were no predictive biomarkers to personalize selection of targeted or biologic therapies as a part of standard of care treatment. However, there is now a clear role for testing pancreatic cancer for germline mutations, somatic mutations and fusions, and microsatellite instability (MSI)/mismatch repair deficiency to optimize selection of therapies and identify clinical trials of targeted agents.

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GERMLINE SEQUENCING

Several studies have shown that 3.8% to 9.7% of patients with pancreatic cancer carry a deleterious germline mutation,[5-9] with some large single-center analyses having rates as high as 19.8%.[10] As many as 41.8% to 57% of patients ultimately found to have a germline mutation did not have a suspicious family history and would not have met prior screening criteria for germline testing.[8,10] The most commonly found germline mutation is *BRCA2*, although additional commonly mutated genes include *BRCA1*, *PALB2*, *ATM*, *CDKN2A*, and *TP53*, and mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). *BRCA1/2* mutations and deficient mismatch repair have effective therapies that are currently standard of care, and several other germline mutations have a strong rationale for novel targeted therapies that are under investigation.

BRCA1/2 Germline Mutations

Mutations in *BRCA1* and *BRCA2* cause homologous recombination defects (HRD), impairing normal DNA damage repair and enabling the accumulation of mutations, contributing to carcinogenesis. However, cancers arising in this context are particularly prone to chemotherapies that induce double-stranded DNA

PRACTICAL APPLICATIONS

- Germline mutation testing is recommended for all patients diagnosed with pancreatic cancer, regardless of stage, and patients with *BRCA1/2* germline mutations should be treated with platinum-based chemotherapy and considered for maintenance olaparib therapy as a standard treatment or for clinical trials of agents targeting DNA damage repair pathways.
- Testing for actionable somatic genetic aberrations, including fusions and mutations, and for microsatellite instability/mismatch repair deficiency is recommended for patients with locally advanced or metastatic pancreatic cancer who are candidates for anticancer therapy.
- One percent to 3% of patients with pancreatic cancer have KRAS G12C–mutated tumors, and these patients should be identified and highly considered for clinical trials of KRAS G12C inhibitor–based combination therapies.
- SHP2 inhibitors and SOS1 inhibitors are highly promising new classes of drugs that impair GTP loading and thus activation of certain mutant KRAS isoforms, such as most codon 12 mutations.
- Eight percent to 10% of patients with pancreatic cancer have KRAS wild-type tumors, and this cohort is enriched for patients with other actionable driver mutations or fusions.

breaks requiring homologous recombination for repair, like platinum agents. Indeed, a recent phase II trial demonstrated a response rate of 70% with a gemcitabine plus cisplatin backbone regimen among patients with germline HRD mutations (94% with *BRCA1/2* germline mutations),[11] and retrospective studies demonstrate that patients with HRD pancreatic cancers have significantly better progression-free survival when treated with first-line platinum-based therapies.[12] Moreover, cancers with HRD and mutations in *BRCA1/2* are unable to correct DNA damage and prevent mitotic catastrophe and cell death when DNA damage is induced. PARP inhibitors impair repair of single-strand DNA breaks and also on binding to their PARP substrate trap PARP on the DNA strand, generating additional double-strand breaks and cell death.[13] PARP inhibitors are effective in a range of tumors with germline *BRCA1/2* mutations that are platinum-sensitive. In the phase III POLO trial, among patients with metastatic pancreatic cancer with germline *BRCA1/2* mutations with disease control after 4 to 6 months of induction platinum chemotherapy, maintenance therapy with olaparib was superior to placebo, improving median progression-free survival from 3.8 to 7.4 months (HR, 0.53; 95% CI, 0.35–0.82).[14] Additionally, health-related quality-of-life questionnaires showed no significant difference in time to sustained clinically meaningful deterioration in health-related quality-of-life or physical functioning scores between patients who received maintenance olaparib compared with placebo.[15] However, there was no difference in overall survival, with median overall survival of 19.0 versus 19.2 months (HR, 0.83; 95% CI, 0.56–1.22), although there was a trend toward improved 36-month survival with olaparib (33.9% vs. 17.8%).[16] Olaparib maintenance therapy is now U.S. Food and Drug Administration approved and a standard-of-care option for patients with metastatic pancreatic adenocarcinoma with germline *BRCA1/2* mutations after at least 16 weeks of first-line platinum-based chemotherapy.

Several studies are ongoing to study new combinations of PARP inhibitors with additional therapies, notably with immune checkpoint inhibitors. In *BRCA1/2*-deficient cancer models, PARP inhibition stimulated innate and adaptive immune responses by upregulating interferon-stimulated genes and thestimulator of interferon genes pathway, with immune responses potentiated by addition of anti–PD-1 antibody therapy.[17,18] The SWOG S2001 trial is enrolling patients who would be eligible for maintenance olaparib to be randomly assigned to either olaparib alone or olaparib plus pembrolizumab (NCT04548752). Multiple additional DNA damage repair inhibitors are in development, but clinical trials of combinations of these inhibitors, although rational in patients with germline *BRCA1/2* mutations, are in early phases at this time.

Other HRD Germline Mutations

A range of additional germline mutations that confer HRD are found in pancreatic cancer. Among these, mutations in *PALB2* and *ATM* are most common. *PALB2* germline mutation confers similar HRD phenotype as *BRCA1/2* mutations, and case reports and small prospective trials have suggested efficacy of PARP inhibitors for patients with *PALB2* germline mutated breast or prostate cancers.[19-21] In pancreatic cancer, many of the trials enrolling *BRCA1/2* germline-mutated cancers also enrolled a small number of patients whose tumors had *PALB2* germline mutations, with similar results suggesting *PALB2* mutations also are predictive of response to platinum-based chemotherapy and PARP inhibitors. For example, in a phase II study of maintenance rucaparib after induction platinum-based chemotherapy with 24 evaluable patients with germline HRD mutations, two out of two tumors with *PALB2* germline mutation had response to rucaparib.[22]

Deleterious *ATM* germline mutations are found in 1.7% to 3.3% of pancreatic cancers.[23,24] Preclinical studies suggested that PARP inhibitors and topoisomerase-1 inhibitors,

such as irinotecan, would be effective in *ATM*-mutated cancers.[24,25] However, case reports of *ATM*-mutated pancreatic cancers have not shown disease control with PARP inhibitor maintenance therapy.[26,27] Indeed, PARP inhibitor monotherapy was only cytostatic but did not induce cell killing in *ATM*-deficient preclinical pancreatic cancer cell models.[28] There are preclinical data suggesting efficacy of ATM inhibitors, ATR inhibitors, and CHK1 inhibitors[29] or of combination therapies of multiple DNA damage repair–targeting therapies,[24] and there are ongoing early-phase clinical trials at this time.[30]

Deficient Mismatch Repair and Lynch Syndrome

Germline mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, or *PMS2* cause Lynch syndrome, with an increased risk of developing multiple cancer types, particularly colorectal and endometrial cancers, but also pancreatic cancer. A registry study from 147 families with Lynch syndrome revealed a 3.7% (95% CI, 1.45–5.88) cumulative risk of pancreatic cancer up to age 70, which is an 8.6-fold (95% CI, 4.7–15.7) increase compared with the broader population.[31] Given that these cancers are MSI-High, pembrolizumab is an important standard therapy option, as described in more detail later.

SOMATIC SEQUENCING

KRAS Mutations

Oncogenic *KRAS* mutations are found in 90% to 93% of pancreatic cancers.[32-34] KRAS is a small GTPase that normally cycles between an inactive GDP-bound state and an active GTP-bound state in response to activation of upstream receptor tyrosine kinases, like the EGFR (epidermal growth factor receptor) and the related family members ERBB2 (HER2), ERBB3 (HER3), and ERRB4 (HER4). KRAS signaling is further modulated by guanine exchange factors like SOS1 that catalyze exchange of GDP for GTP to activate KRAS, and GTPase-activating proteins that catalyze the intrinsic hydrolysis of GTP back to GDP to inactivate KRAS. Activated KRAS binds to and activates multiple downstream effector pathways, notably including the RAF-MEK-ERK MAPK signaling pathway. Oncogenic *KRAS* mutations impair GTP hydrolysis or accelerate GDP-GTP exchange, resulting in an excess of active GTP-bound KRAS.[35,36] There are multiple activating mutations in *KRAS,* found in varying proportions in different cancer types. Although in pancreatic cancer the most commonly found mutations are G12D, G12V, and G12R (Fig. 1), in lung cancer, the most common mutation is G12C (46% of codon 12 mutations).[35] Different *KRAS* mutations have different effects on the rate of intrinsic or GTPase-activating protein–mediated GTP hydrolysis and GDP exchange; for example, G12C has a nearly normal rate of intrinsic GTP hydrolysis but has impairment in GTPase-activating protein–mediated hydrolysis.[37]

Direct KRAS inhibitors have been challenging to develop for multiple reasons. Competitive inhibitors binding the GTP binding site have not been feasible because of very high picomolar affinity for GTP that cannot be outcompeted, and allosteric inhibitors have been challenging because of KRAS surface topology being thought to lack pockets for drug binding.[36] However, new approaches to target specific *KRAS* mutations or impair the interaction of guanine exchange factors with KRAS are enabling targeting of this previously undruggable gene.

KRAS G12C inhibitors *KRAS* G12C mutation is uncommon in pancreatic cancer, comprising 1% of cases,[32] but this subgroup is important to identify. Specific G12C inhibitors now can bind to a recently discovered P2 surface pocket on KRAS and covalently bind to the reactive cysteine residue in the mutant G12C protein.[38,39] Sotorasib (AMG510) is a G12C inhibitor that has a promising response rate in *KRAS* G12C–mutant non–small-cell lung cancer of 32.2%, although it yields primarily stable disease when given as a monotherapy in colorectal and pancreatic cancer. Among 11 response-evaluable *KRAS* G12C–mutant pancreatic cancers, there was 1 of 11 partial response, 8 of 11 stable disease, and 2 of 11 progressive disease with sotorasib.[40] Adagrasib (MRTX849), another KRAS G12C inhibitor, also had highest response rate in *KRAS* G12C–mutant non–small-cell lung cancer of 45%[41]; one patient with pancreatic cancer had a confirmed response.[42] More effective combinations of various targeted therapies with KRAS G12C inhibitors in colorectal cancer and non–small-cell lung cancer have been studied preclinically,[43,44] and multiple combinations are now in clinical trials. Ongoing studies include new combination arms in the CodeBreak 101 trial combining sotorasib with a MEK inhibitor, PD-1 inhibitor, SHP2 inhibitor, pan-ERBB inhibitor, PD-L1 inhibitor, CDK inhibitor, or mTOR inhibitor (NCT04185883); and the KRYSTAL-2 trial of adagrasib combined with the SHP2 inhibitor TNO155 (NCT04330664). Multiple additional G12C inhibitors are currently in clinical development as well, including JNJ-74699157 (NCT04006301), GDC-6036 (NCT04449874), and JDQ443 (NCT04699188).

Other mutation-specific direct inhibitors Additional *KRAS* mutation–specific small molecule inhibitors are in preclinical development, including novel KRAS G12D inhibitors,[45] such as MRTX1133, which is currently undergoing investigational new drug–enabling studies. RMC-6236 is a RAS-selective inhibitor that binds the chaperone protein cyclophilin A and then forms a tricomplex with the target RAS protein, inhibiting signaling of multiple RAS mutants in their GTP-bound conformations, including KRAS G12V and KRAS G12D, and is also currently in investigational new drug–enabling studies.[46]

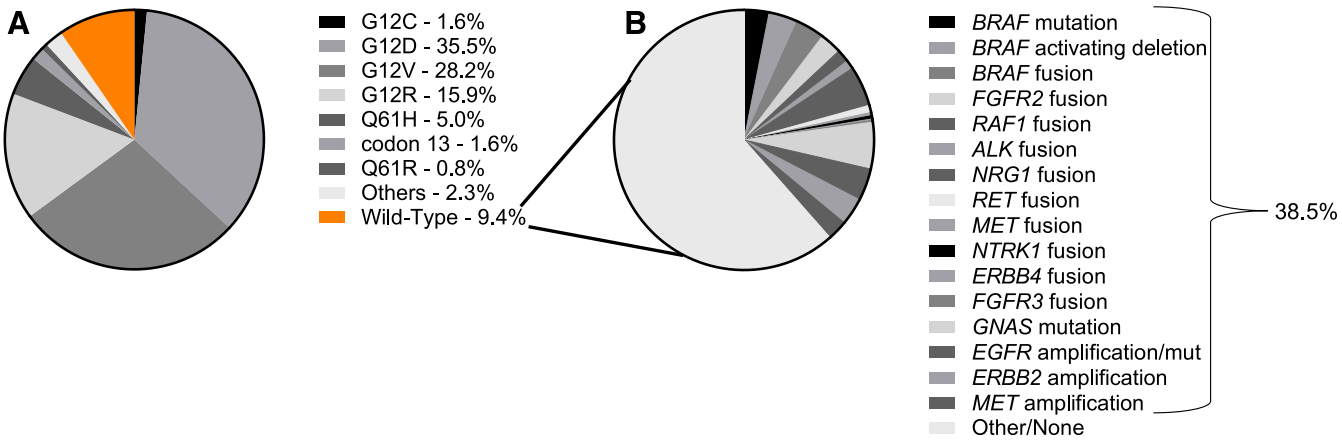

FIGURE 1. Frequency of Selected Somatic Mutations in Pancreatic Cancer
(A) Frequency of specific *KRAS* mutations in pancreatic cancer.[32] (B) Among *KRAS* wild-type pancreatic cancers, there is enrichment for actionable gene fusions and other actionable aberrations.[76]

SOS1 inhibitors SOS1 is a guanine exchange factor that catalyzes GDP exchange for GTP to activate KRAS and impair the SOS1-KRAS interaction, thus impairing GTP-loading of KRAS.[47] MEK inhibitor treatment decreases the ERK-mediated phosphorylation of SOS1 and relieves negative feedback to SOS1,[48] enabling SOS1-mediated feedback loops to reactivate RAS-mediated signaling. Novel small molecule SOS1 inhibitors impair SOS1-KRAS binding in multiple *KRAS* mutations. BI-3406 is a SOS1 inhibitor that significantly decreased GTP-bound RAS and impaired proliferation in nearly all *KRAS* codon 12 and 13 mutants tested and synergized with MEK inhibitors by alleviating feedback reactivation.[49] However, resistance to BI-3406 was noted in *KRAS* G12R–mutant cancer, because KRAS G12R does not interact with SOS1,[50] and in *KRAS* codon 61–mutant cancers, which have lower intrinsic GTPase activity[37] and thus would be better able to maintain higher GTP-bound KRAS levels despite impairment of guanine exchange factor activity. The SOS1 inhibitor BI1701963 is a clinical drug candidate that also synergized with trametinib and induced regressions in vivo.[51] Clinical trials are underway of BI1701963 alone and in combination with trametinib in *KRAS*-mutant cancers (NCT04111458). SOS1 inhibitors also have been shown preclinically to synergize with KRAS G12C inhibitors in preclinical models,[47,49] and clinical trials of BI1701963 with MRTX849 in *KRAS* G12C–mutant cancers are planned.

SHP2 inhibitors in codon 12–mutant KRAS SHP2 (*PTPN11*) is a nonreceptor protein tyrosine phosphatase that forms signaling complexes in association with activation of multiple receptor tyrosine kinases and facilitates SOS1-dependent guanine exchange factor function and GTP-loading and activation of KRAS.[52] SHP2 is indispensable for oncogenic *KRAS* mutations to drive carcinogenesis in mouse models, and SHP2 inhibitors synergize with MEK inhibitors in *KRAS*-mutant cancer models in vivo.[53] Allosteric SHP2 inhibitors such as RMC-4550 impaired activation of multiple codon 12–mutated *KRAS* proteins, although there was heterogeneous single-agent activity across different cell lines that shared the same *KRAS* mutation; notably, RMC-4550 monotherapy was ineffective against codon 13 and codon 61 *KRAS* mutations.[52] SHP2 inhibitor and MEK inhibitor combinations were more effective in mitigating feedback reactivation of the MAPK pathway than either single agent in *KRAS* codon 12–mutant models,[54,55] with the possible exception of G12R mutation,[55] because G12R does not require SOS1 for its activity.[50] SHP2 inhibitors also synergized with KRAS G12C inhibitors in preclinical models.[56] Multiple SHP2 inhibitors trials, either as monotherapy (JAB-3312; NCT04045496) or in combination with MEK inhibitors (RMC-4630/cobimetinib; NCT03989115) or G12C inhibitors, are ongoing in *KRAS*-mutant pancreatic cancers. Given the early stage of development, trials do not currently select for specific *KRAS* mutations, but we expect that future studies will likely need to select for specific *KRAS* codon 12 mutations, which do comprise most *KRAS*-mutated pancreatic cancers.

KRAS mutation–specific oligonucleotide approaches Oligonucleotide therapies modulate gene expression to promote degradation of target mRNA molecules, enabling targeting of specific oncogenic mutant alleles. The most notable barriers in development of oligonucleotide therapies include the need to optimize delivery to target tissues and to avoid off-target interactions, and therapeutic candidates require drug delivery strategies, including chemical modification, conjugation to cell-targeting molecules, and drug formulation within nanoparticles.[57] One recent example of an attempt to target KRAS was AZD4785, an antisense oligonucleotide against *KRAS* mRNA, targeting both mutant and wild-type KRAS for degradation via ribonuclease H.

AZD4785 showed in vivo activity when administered via subcutaneous injections, inhibiting tumor growth, although maximum *KRAS* mRNA knockdown was only observed after 2 weeks of dosing.[58] Although AZD4785 proceeded to a phase I trial (NCT03101839), further development was halted, likely related to nonselective targeting of both wild-type and mutant *KRAS*. Indeed, more targeted oligonucleotide therapies specifically targeting mutant *KRAS* are now being studied. For example, in locally advanced pancreatic cancer, an anti-KRAS G12D small interfering RNA embedded in a biodegradable polymer matrix, dubbed siG12D-LODER, can be directly injected into locally advanced *KRAS* G12D–mutated pancreatic tumors, with in vivo studies demonstrating increased tumor necrosis after injection of siG12D-LODER.[59] A phase I/IIa clinical trial of siG12D-LODER was performed with good tolerance,[60] and a phase II study continues in *KRAS* G12D–mutant pancreatic cancer (NCT01676259). Additional *KRAS* mutation–specific oligonucleotide therapies are in development.[61,62] Therapeutic oligonucleotides can be packaged within exosomes, extracellular vesicles that contain membrane-anchored proteins like CD47, which helps protect cells from phagocytosis by macrophages and monocytes and enhances half-life within the circulation as compared with liposomes. Anti–*KRAS* G12D small interfering RNA was electroporated into exosomes, dubbed iExosomes, and injected into *KRAS* G12D–mutated pancreatic cancer mouse models, improving overall survival compared with gemcitabine-treated mice.[61] Clinical-grade iExosomes are now being manufactured,[63] and clinical trials specifically for *KRAS* G12D–mutated pancreatic cancer are starting (NCT03608631).

KRAS mutation–specific vaccine and cellular therapy approaches Because *KRAS* mutations generate a neoepitope that could provoke a mutant protein-specific adaptive immune response, immunologic therapeutic approaches are being studied. As proof of concept, a patient with metastatic *KRAS* G12D–mutant colorectal cancer had tumor-infiltrating lymphocytes cultured and expanded ex vivo, with identification of HLA-C*08:02–restricted $CD8^+$ T-cell clones that recognized the *KRAS* G12D epitope, and reinfusion of the expanded T cells resulted in significant response.[64] Additionally, HLA-peptide prediction algorithms noted that HLA-A*11:01 could potentially present mutated *KRAS* epitopes, and in mouse models, T cells reactive to *KRAS* G12V and G12D were generated.[65] Indeed, HLA-A*11:01–restricted T cells present in the peripheral blood of patients with cancer were found to recognize KRAS G12V.[66] Clinical trials of adoptive T-cell therapies targeting these mutations were planned (NCT03190941), although they have been suspended. Nevertheless, these studies demonstrate the potential for a clinically effective adaptive immune response against mutant *KRAS* epitopes.

mRNA-5671/V941 is an mRNA vaccine of the four most common *KRAS* mutations (G12D, G12V, G13D, and G12C). Murine in vivo studies showed that $CD8^+$ T-cell responses to mutant KRAS antigen exposure were significantly greater after prior injection with mRNA-5671. mRNA-5671/V941 is being studied as a monotherapy or in combination with pembrolizumab in clinical trials, although at least initially restricted to HLA-A*11:01 or HLA-C*08:02 markers (NCT03948763).[67] Additionally, a pooled mutant KRAS–targeted long peptide vaccine is being combined with nivolumab and ipilimumab in patients with colorectal or pancreatic cancer harboring *KRAS* G12C, G12V, G12D, G12A, G13D, or G12R mutation (NCT04117087).

Considerations in inhibiting effector pathway signaling Multiple trials of MEK inhibitors have unfortunately failed to demonstrate meaningful clinical activity in patients with pancreatic cancer,[68-70] likely because of feedback reactivation of upstream pathways as previously described. Notably, different *KRAS* mutations may confer differential susceptibility to MEK inhibitors. Studies in organoid and patient-derived xenograft mouse models have shown that *KRAS* G12R–mutated pancreatic tumors have their growth more significantly suppressed with MEK or ERK inhibitors compared with other *KRAS*-mutant tumors, mechanistically explained by the inability of the *KRAS* G12R–mutant protein to bind to PI3K and activate the PI3K-AKT effector pathway and thus having lower activity in this compensatory signaling pathway that could otherwise help facilitate adaptation and rescue from the effects of MEK or ERK inhibition.[50] However, even in the *KRAS* G12R–mutant pancreatic tumor patient-derived xenograft models, selumetinib only resulted in tumor stability rather than regression, suggesting stable disease is more likely to be attained rather than response. Indeed, a prospective trial of selumetinib monotherapy in *KRAS* G12R–mutated pancreatic cancer found zero of eight patients had an objective response, and the study was stopped for futility, although three of eight patients did have stable disease for more than 6 months.[71] These results suggest that treatment with a more potent MEK or ERK inhibitor and with rational combination therapies would likely be necessary to yield responses, even in *KRAS* G12R–mutant disease. A study of six patients with chemorefractory *KRAS* G12R–mutated pancreatic cancer who received cobimetinib and gemcitabine showed that one of six patients had a partial response and six of six patients had disease control, with median progression-free survival of 6.0 months (95% CI, 3.0–9.3).[72] Indeed, trials of MEK or ERK inhibitor–based combinations selecting for patients with *KRAS*-mutant pancreatic cancer are ongoing, particularly in combination with autophagy inhibitors, because preclinical studies showed that MEK or ERK inhibition caused a protective increase in autophagic flux, and autophagy inhibitors such as hydroxychloroquine synergized with MEK or ERK

inhibitors.[73,74] Case reports have shown individual patients who had response with MEK inhibitors combined with chloroquine or hydroxychloroquine.[74,75] Selected trials are described in Table 1.

Patients with KRAS Wild-Type Tumors: Enriched for Other Actionable Aberrations

The pancreatic cancer of approximately 7% to 10% of patients is wild-type in *KRAS*.[32,33] *KRAS* wild-type status is more common in younger patients under age 50[76,77]; in a large study of 3,594 patients, 20% of patients under age 50 had *KRAS* wild-type tumors compared with 11% of patients over age 50 ($p < .001$).[76] This *KRAS* wild-type population is enriched for alternative driver aberrations that are potentially actionable. The Cancer Genome Atlas found that significantly more pancreatic cancers that were *KRAS* wild-type harbored germline mutations ($p = .027$), particularly in *ATM* or *PRSS1* (which causes familial pancreatitis) but not in *BRCA2*.[33] Both The Cancer Genome Atlas study (10 patients with *KRAS* wild-type tumors) and a larger international study (445 patients with *KRAS* wild-type tumors) identified multiple actionable gene mutations and fusions enriched in or exclusively found in *KRAS* wild-type pancreatic cancers. The most common aberrations included *BRAF*-activating missense mutations (3.1% of *KRAS wild-type* tumors), *BRAF*-activating in-frame intragenic deletions (3.6%), *BRAF* kinase fusions (3.6%), *FGFR2* fusions (2.7%), *RAF1* fusions (1.6%), and *ALK* fusions (1.1%), with additional genes found to have fusions at less than 1% frequency, including *RET*, *MET*, *NTRK1*, *ERBB4*, and *FGFR3*. Additionally, *HER2* amplification (3.4%) and *MET* amplification (2.9%) were enriched in the *KRAS* wild-type subgroup. Overall, 38% of the *KRAS* wild-type tumors had other driver mutations or fusions activating the RAS-MAPK pathway,[76] many of which are potentially actionable (Fig. 1).

***BRAF* mutations** Activating *BRAF* mutations are significantly enriched in patients with *KRAS* wild-type tumors (11% of *KRAS* wild-type vs. 0.4% of *KRAS*-mutant), and activating in-frame deletions in *BRAF* are uniquely found in patients with *KRAS* wild-type pancreatic cancer.[76] *BRAF* mutations are most commonly V600E mutations; a study of 445 KRAS wild-type pancreatic cancers found 14 *BRAF* point mutations, of which more than half were V600E, but additional mutations found at lower frequencies included D594G, G469V, and G469S.[76] Case reports or trials with small pancreatic cancer cohorts describe partial responses with vemurafenib[78,79] and improvement in CA19-9 with dabrafenib plus trametinib[80] in *BRAF* V600E–mutant pancreatic cancer. Clinical trials are underway to test this combination in BRAF V600E–mutant pancreatic cancer, such as encorafenib plus binimetinib (NCT04390243).

BRAF non-V600 mutations are more heterogeneous in their activity, but mechanistically have different effects on BRAF dimerization and effector signaling activation, and *BRAF* mutations can be classified in three classes.[81] Class 1 is composed of the canonical *BRAF* V600E mutation, causing strong constitutive kinase activation in a dimerization- and RAS-independent fashion. Class 2 *BRAF* mutations, such as G469V/S, cause aberrant kinase activation via dimerization in a RAS-independent fashion, and preclinical studies suggest use of downstream effector signaling inhibitors like MEK inhibitors. Class 3 *BRAF* mutations, like D594G, cause decreased or deficient kinase activity, but instead promote aberrant overactive signaling on activation by upstream receptor tyrosine kinases and RAS, suggesting that a combination of MEK inhibitors and receptor tyrosine kinases inhibitors or SHP2 inhibitors would be optimal.[82,83] Thus, drugs with different active sites and mechanisms on the BRAF protein have different effectiveness, and clinical trials must account for this heterogeneity. For example, in the MATCH trial, patients with multiple different cancer types (although none with pancreatic cancer) with primarily class 2 and 3 BRAF mutations who were treated with the

TABLE 1. Selected MEK or ERK Inhibitor–Based Combination Clinical Trials in Pancreatic Cancer

Therapies	Biomarker Criterion	ClinicalTrials.gov
MEK inhibitor + autophagy inhibitor (binimetinib + hydroxychloroquine)	Any *KRAS* mutation on tumor or liquid biopsy	NCT04132505
MEK inhibitor + anti–PD-L1 (selumetinib + durvalumab) – randomized against FOLFIRI	Any *KRAS* mutation	NCT04348045
MEK inhibitor + autophagy inhibitor + anti–PD-L1 (cobimetinib + hydroxychloroquine + atezolizumab)	Any *KRAS* mutation	NCT04214418
ERK inhibitor + CDK4/6 inhibitor (ulixertinib + palbociclib)	Unselected	NCT03454035
ERK inhibitor +/– autophagy inhibitor (LY3214996 +/– hydroxychloroquine)	Unselected	NCT04386057
MEK inhibitor + autophagy inhibitor (trametinib + hydroxychloroquine)	Unselected	NCT03825289
MEK inhibitor + JAK1/2 inhibitor (trametinib + ruxolitinib)	Any *KRAS* mutation	NCT04303403

Abbreviation: FOLFIRI, folinic acid/5-fluorouracil/irinotecan.

MEK inhibitor trametinib had only a 3% response rate and a 34% disease control rate.[84]

Additionally, activating in-frame *BRAF* deletions were found in 3.6% of *KRAS* wild-type pancreatic cancers. The most commonly found *BRAF* deletion was ΔN486_P490 (ΔNVTAP; 13/445 *KRAS* wild-type), with additional low-frequency deletions including ΔV487_P492 and ΔV600_K601.[76] The most common ΔNVTAP deletion in *BRAF* caused constitutive activation of *BRAF*, independent of homodimerization or heterodimerization with *CRAF*.[85] Crystal structures of the mutant protein showed that the deletion constrains the protein into an active conformation by locking the αC helix in an "in" conformation,[85,86] and this conformational change prevents some BRAF inhibitors, such as vemurafenib, from binding the mutant BRAF protein; indeed, cells with the ΔNVTAP *BRAF* mutation were resistant to vemurafenib, partially sensitive to GDC-0879 and dabrafenib, and sensitive to AZ-628.[85] This indicates that knowledge of the biochemistry and requisite conformation for effective drug binding to mutant *BRAF* is required. A case report of a patient with *BRAF* ΔNVTAP–mutated pancreatic cancer described a partial response and clinical improvement with dabrafenib therapy.[87] Clinical trials are enrolling patients with both atypical non-V600E mutations and other aberrations (including activating deletions) in *BRAF*, including trials of the ERK inhibitor ulixertinib (NCT04488003 and NCT02465060).

***BRAF* fusions** *BRAF* fusions are found in 3.1% of *KRAS* wild-type pancreatic cancers. Of note, pancreatic acinar cell carcinomas have a significantly higher incidence of *BRAF* fusions, with 23% of pancreatic acinar cell carcinomas having *BRAF* or *RAF1* fusions, most commonly a *SND1-BRAF* fusion causing activation of the MAPK pathway.[88] In pancreatic cancer, the *BRAF* fusion partner is again most commonly *SND1*, but multiple additional fusion partner genes are described. The effects of *BRAF* fusions are heterogeneous and dependent on the breakpoint and the fusion partner. For example, in melanoma cell lines with a range of *BRAF* fusions, there was a wide range of sensitivity to BRAF inhibitors across different *BRAF* fusion models in vitro. However, all cell lines were resistant to vemurafenib and dabrafenib, and some fusion partner genes had dimerization domains that actually promoted paradoxical activation of MAPK signaling pathways during treatment with classic RAF inhibitors.[89] The impact of these preclinical observations on clinical efficacy of BRAF inhibitors is not well established, but different inhibitors are likely to have varying effectiveness in different *BRAF* fusions. A patient with *CUX1-BRAF* fusion pancreatic cancer who received vemurafenib did experience a partial response in the MyPathway basket trial.[90] The MATCH trial is currently enrolling patients with *BRAF* fusions to receive ulixertinib (NCT02465060).

***NRG1* fusion** Several groups have also identified activating in-frame *NRG1* fusions in *KRAS* wild-type pancreatic cancers. *NRG1* encodes neuregulin, a ligand of the kinase-dead ERBB3 receptor, which then heterodimerizes with ERBB2 and activates downstream RAS-RAF-MAPK pathways. In these fusion proteins, the EGF-like domain of NRG1 that binds to ERBB2 is preserved, and the fusion partner encodes a transmembrane domain, with high transcriptional activity of the fusion partner.[91,92] Treatment with the pan-ERBB inhibitor afatinib resulted in responses in two out of three patients with *NRG1*-fusion pancreatic cancer in a prospective case series.[91] Another study specifically in 17 young adults with pancreatic cancer found four patients who had *KRAS* wild-type tumors, three of whom had an *NRG1* fusion, and two responded to ERBB family-directed treatments (one of afatinib, one of erlotinib/pertuzumab).[77] Another report showed two patients responded to zenocutuzumab (MCLA-128), a bispecific antibody targeting ERBB2 and ERBB3.[93] Given the rarity of the *NRG1* fusion and presence in multiple different cancer types, most prospective studies are basket trials, although there may be differences in response rates between different tumor types.[94] Multiple ongoing prospective trials of targeted ERBB family inhibitors in patients with *NRG1* fusion cancers are ongoing, including afatinib in TAPUR (NCT02693535), zenocutuzumab (NCT02912949), and tarloxitinib (a hypoxia-activated prodrug of ERBB family inhibitor) (NCT03805841).

***ALK* fusions** A case series showed three-fourths of patients with *ALK* rearrangements treated with ALK inhibitors such as crizotinib or ceritinib had disease control or response.[95] Another recent case report described a patient with *ALK*-rearranged pancreatic cancer who had stable disease with alectinib treatment and during progression had biopsy showing novel *ALK*-resistance mutations G1202R and V1180L, with disease stabilization with treatment with the newer-generation ALK inhibitor lorlatinib.[96] Several basket trials are enrolling patients with *ALK*-rearranged solid tumors including pancreatic cancer, such as crizotinib in MATCH (NCT02465060), alectinib in the French Mega-MOST trial (NCT04116541) and TAPISTRY (NCT04589845), or entrectinib (NCT02568267).

***NTRK1/2/3* fusions** *NTRK1/2/3* fusions are occasionally found in pancreatic cancer, and entrectinib and larotrectinib are approved by the U.S. Food and Drug Administration for management of TRK-fusion cancers in a tumor-agnostic fashion, with entrectinib having an overall response rate of 57% (95% CI, 43.2–70.8) and median duration of response of 10.4 months (95% CI, 7.1–not evaluable)[97] and larotrectinib having an overall response rate of 79% (95% CI, 72.0–85.0) with 16% complete responses and median duration of response of 35.2 months (95% CI, 21.2–not evaluable).[98,99] From the seminal clinical

trials for TRK inhibitors, two out of three patients with pancreatic cancer treated with entrectinib had a partial response,[97] and one of one patient with pancreatic cancer treated with larotrectinib had a partial response.[99] Case series have also shown the benefit of TRK inhibitors in *TRK*-fusion pancreatic cancers, including a case of larotrectinib yielding partial response in a patient with *CTRC-NTRK1* fusion[100] and two cases of entrectinib yielding either partial response or clinical benefit in two patients with *TPR-NTRK1* fusions.[101]

Additional rare fusions *MET* fusions are occasionally found in *KRAS* wild-type pancreatic cancer. A case report found a patient with *RDX-MET* fusion had a complete response to crizotinib lasting for more than 12 months.[102]

ROS1 fusions are rarely found in pancreatic cancer, and a case report of a patient with *KRAS* wild-type pancreatic cancer with an *SLC4A4-ROS1* fusion treated with entrectinib showed stable disease per RECIST 1.1 with clinical benefit.[101]

RET fusions are also found in *KRAS* wild-type pancreatic cancer. Selpercatinib (LOXO-292) resulted in stable disease in two of two pancreatic cancers.[103] Pralsetinib (BLU-667) resulted in three of three partial responses in *RET*-fusion pancreatic cancer.[104] Ongoing basket trials for RET fusions include a study of the dual RET/SRC inhibitor TPX-0046 (NCT04161391) and a study of BOS172738 (NCT03780517).

FGFR1-3 fusions or rearrangements are also occasionally found in pancreatic cancers. A case report of a patient with an *FGFR2* rearrangement in intron 17 who was treated with the FGFR inhibitor erdafitinib showed partial response.[105] Studies are ongoing to evaluate patients with *FGFR* fusions to receive FGFR inhibitors, such as erdafitinib (NCT04083976) and pemigatinib (NCT03822117).

MSI/Deficient Mismatch Repair

MSI-High is found in 1% to 2% of pancreatic ductal adenocarcinoma and is associated with medullary and mucinous/colloid histology and with a *KRAS* wild-type and *TP53* wild-type mutation profile.[106] Patients with deficient mismatch repair/MSI-High tumors benefit from immune checkpoint inhibitor therapy, and pembrolizumab is approved by the U.S. Food and Drug Administration for use in previously treated MSI-High cancers in a tumor/site-agnostic fashion. In an early study of pembrolizumab in MSI-High cancers, of eight patients with pancreatic cancer, two (25%) had complete response and three (37%) had partial response.[107] In an update from the KEYNOTE-158 trial, of 22 patients with MSI-High pancreatic cancer, there was one complete response and three partial responses, for an overall response rate of 18.2% (95% CI, 5.2–40.3), with median progression-free survival of 2.1 months (95% CI, 1.9–3.4), median overall survival of 4.0 months (95% CI, 2.1–9.8), and median duration of response of 13.4 months (ranging from 8.1 to over 16.0 months). Although these findings are meaningful, the response rate differed substantially between different tumor types, and the outcomes among the pancreatic cancer subgroup were less favorable than among the entire group of 233 noncolorectal MSI-High cancers, where the overall response rate was 34.3% (95% CI, 28.3–40.8), median progression-free survival was 4.1 months (95% CI, 2.4–4.9), and median overall survival was 23.5 months (95% CI, 13.5–not reached).[108]

Tumor mutation burden: limited data in pancreatic cancer In 2020, the U.S. Food and Drug Administration approved pembrolizumab for cancers with a tumor mutation burden of at least 10 mutations per megabase, based on data from KEYNOTE-158 of nine cancer types (of which pancreatic cancer was not one of the studied cancer types), showing a high response rate of 29% (95% CI, 21.0–39.0) in tumor mutation burden–high cancers, compared with a response rate of 6% (95% CI, 5.0–8.0) in non–tumor mutation burden–high cancers.[109] In a recent retrospective cohort study of 2,834 patients at Memorial Sloan Kettering Cancer Center with a range of microsatellite stable solid tumors, only two out of 36 (6%) pancreatic cancers had tumor mutation burden of at least 10 mutations/Mb, and zero out of two of these patients had a response to anti–PD-1 or PD-L1 therapy.[110] Thus, unfortunately, there are limited to no data to date of the efficacy of pembrolizumab in the small subgroup of tumor mutation burden–high pancreatic cancer.

Additional Selected Actionable Genomic Events

Somatic BRCA1/2 mutations and HRD Although the POLO trial establishing the efficacy of maintenance olaparib was only conducted in patients with germline *BRCA1/2* mutations, somatic *BRCA1/2* mutations occur in up to 2% of pancreatic cancers, and up to 4% of patients with pancreatic cancer harbor a somatic HRD mutation of any kind.[12] In a study of rucaparib in patients with either germline or somatic *BRCA1/2* mutations, among three patients who had somatic *BRCA2* mutations, one had a complete response and one had a partial response.[111] Indeed, a meta-analysis of eight studies describing response rates for both somatic and germline *BRCA1/2* mutations across a range of cancer types showed comparable response rates with PARP inhibitor therapy with somatic mutations (55.8%) and germline mutations (43.9%).[112] Clinical trials for pancreatic cancer patients including those with somatic *BRCA1/2* or *PALB2* mutations are ongoing, including niraparib combined with the PD-1 antibody dostarlimab (NCT04493060) or olaparib plus pembrolizumab (NCT04666740).

***MTAP* deletion and PRMT1 inhibitors** *MTAP* (methylthioadenosine phosphorylase) is an enzyme needed in adenine and methionine salvage. *MTAP* is located on chromosome 9p, adjacent to the tumor suppressor *CDKN2A* (p16), which is very frequently deleted in cancers and thus results in codeletion of *MTAP* in 25% of pancreatic cancers. In the context of *MTAP* loss, there is intracellular accumulation of its substrate, methylthioadenosine, which partially inhibits the activity of protein arginine methyltransferase 5. *MTAP*-deficient cells display synthetic lethality when treated with protein arginine methyltransferase 5 inhibitors, as they cannot survive further decrease in protein arginine methyltransferase 5 activity,[113,114] or with methionine adenosyltransferase 2a inhibitors, which further reduce protein arginine methyltransferase 5 activity.[115,116] A clinical trial in *MTAP* and/or *CDKN2A* homozygously deleted pancreatic cancers of the methionine adenosyltransferase 2a inhibitor AG-270 combined with gemcitabine/nab-paclitaxel is ongoing (NCT03435250).

CONCLUSION AND GUIDELINES

Germline and somatic sequencing to identify predictive biomarkers and targeted therapies are now a standard of care in management of metastatic pancreatic cancer. Identification of germline mutations in *BRCA1/2* is necessary to identify patients who should receive platinum-based chemotherapy regimens and who are candidates for maintenance therapy with olaparib after induction chemotherapy with a platinum-based regimen. Tumor tissue testing for MSI/deficient mismatch repair is recommended to identify patients who are candidates to receive pembrolizumab. Although *NTRK* fusions are rare, patients with *NTRK* fusions are candidates to receive larotrectinib or entrectinib. Besides *NTRK* fusions, multiple additional gene fusions are enriched in the 7% to 10% of patients with *KRAS* wild-type pancreatic cancer, and these patients should be highly considered for clinical trials. Among the 90% to 93% of pancreatic cancers that have *KRAS* mutations, the roughly 1% with a *KRAS* G12C mutation should be identified for highly promising G12C inhibitor trials. There are a wide range of clinical trials enrolling patients depending on their underlying mutation profiles, and widespread adoption of sequencing is necessary to identify these patients. Consensus guidelines recommend germline testing for any patient with confirmed pancreatic cancer using comprehensive gene panels for hereditary cancer syndromes and recommend testing patients with locally advanced or metastatic disease who are candidates for anticancer therapy for actionable somatic aberrations, including fusions, mutations, and mismatch repair deficiency as described above. Although testing of tumor tissue is preferred, there is often insufficient tissue for extensive testing, and cell-free DNA testing is a reasonable alternative if tumor tissue testing is not possible.[117]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7-33.
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;caac.21660.
3. Conroy T, Desseigne F, Ychou M, et al; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817-1825.
4. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691-1703.
5. Shindo K, Yu J, Suenaga M, et al. Deleterious germline mutations in patients with apparently sporadic pancreatic adenocarcinoma. J Clin Oncol. 2017;35:3382-3390.
6. Hu C, Hart SN, Polley EC, et al. association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. JAMA. 2018;319:2401-2409.
7. Yurgelun MB, Chittenden AB, Morales-Oyarvide V, et al. Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med. 2019;21:213-223.

8. Holter S, Borgida A, Dodd A, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol. 2015; 33:3124-3129.
9. Grant RC, Selander I, Connor AA, et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015;148:556-564.
10. Lowery MA, Wong W, Jordan EJ, et al. Prospective evaluation of germline alterations in patients with exocrine pancreatic neoplasms. J Natl Cancer Inst. 2018; 110:1067-1074.
11. O'Reilly EM, Lee JW, Zalupski M, et al. Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline *BRCA/PALB2* mutation. J Clin Oncol. 2020;38:1378-1388.
12. Park W, Chen J, Chou JF, et al. Genomic methods identify homologous recombination deficiency in pancreas adenocarcinoma and optimize treatment selection. Clin Cancer Res. 2020;26:3239-3247.
13. Pommier Y, O'Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. Sci Transl Med. 2016;8:362ps17.
14. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381:317-327.
15. Hammel P, Kindler HL, Reni M, et al; POLO Investigators. Health-related quality of life in patients with a germline BRCA mutation and metastatic pancreatic cancer receiving maintenance olaparib. Ann Oncol. 2019;30:1959-1968.
16. Golan T, Hammel P, Reni M, et al. Overall survival from the phase 3 POLO trial: maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. J Clin Oncol. 2021;39 (3 suppl; abstr 378).
17. Reisländer T, Lombardi EP, Groelly FJ, et al. BRCA2 abrogation triggers innate immune responses potentiated by treatment with PARP inhibitors. Nat Commun. 2019;10:3143.
18. Ding L, Kim HJ, Wang Q, et al. PARP inhibition elicits STING-dependent antitumor immunity in BRCA1-deficient ovarian cancer. Cell Rep. 2018;25:2972-2980.
19. Grellety T, Peyraud F, Sevenet N, et al. Dramatic response to PARP inhibition in a PALB2-mutated breast cancer: moving beyond BRCA. Ann Oncol. 2020; 31:822-823.
20. Horak P, Weischenfeldt J, von Amsberg G, et al. Response to olaparib in a *PALB2* germline mutated prostate cancer and genetic events associated with resistance. Cold Spring Harb Mol Case Stud. 2019;5:a003657.
21. Tung NM, Robson ME, Ventz S, et al. TBCRC 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. J Clin Oncol. 2020;38:4274-4282.
22. Binder KAR, Mick R, O'Hara M, et al. A phase II, single arm study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic mutation in BRCA1, BRCA2 or PALB2. Cancer Res. 2019;79.
23. Brand R, Borazanci E, Speare V, et al. Prospective study of germline genetic testing in incident cases of pancreatic adenocarcinoma. Cancer. 2018; 124:3520-3527.
24. Gout J, Perkhofer L, Morawe M, et al. Synergistic targeting and resistance to PARP inhibition in DNA damage repair-deficient pancreatic cancer. Gut. 2021; 70:743-760.
25. Perkhofer L, Schmitt A, Romero Carrasco MC, et al. ATM deficiency generating genomic instability sensitizes pancreatic ductal adenocarcinoma cells to therapy-induced DNA damage. Cancer Res. 2017;77:5576-5590.
26. Borazanci E, Korn R, Liang WS, et al. An analysis of patients with DNA repair pathway mutations treated with a PARP inhibitor. Oncologist. 2020;25:e60-e67.
27. Martino C, Pandya D, Lee R, et al. ATM-mutated pancreatic cancer: clinical and molecular response to gemcitabine/nab-paclitaxel after genome-based therapy resistance. Pancreas. 2020;49:143-147.
28. Jette NR, Kumar M, Radhamani S, et al. ATM-deficient cancers provide new opportunities for precision oncology. Cancers (Basel). 2020;12:E687.
29. Armstrong SA, Schultz CW, Azimi-Sadjadi A, et al. ATM dysfunction in pancreatic adenocarcinoma and associated therapeutic implications. Mol Cancer Ther. 2019;18:1899-1908.
30. Yap TA, Plummer R, Azad NS, et al. The DNA damaging revolution: PARP inhibitors and beyond. Am Soc Clin Oncol Educ Book. 2019;39:185-195.
31. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA. 2009;302:1790-1795.
32. Bailey P, Chang DK, Nones K, et al; Australian Pancreatic Cancer Genome Initiative. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016;531:47-52.
33. Cancer Genome Atlas Research Network. Integrated genomic characterization of pancreatic ductal adenocarcinoma. Cancer Cell. 2017;32:185-203.
34. Waddell N, Pajic M, Patch AM, et al; Australian Pancreatic Cancer Genome Initiative. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518:495-501.
35. Moore AR, Rosenberg SC, McCormick F, et al. RAS-targeted therapies: is the undruggable drugged [correction published in *Nat Rev Drug Discov*. 2020;19: 902]? Nat Rev Drug Discov. 2020;19:533-552.
36. Waters AM, Der CJ. KRAS: the critical driver and therapeutic target for pancreatic cancer. Cold Spring Harb Perspect Med. 2018;8:a031435.
37. Hunter JC, Manandhar A, Carrasco MA, et al. Biochemical and structural analysis of common cancer-associated KRAS mutations. Mol Cancer Res. 2015; 13:1325-1335.
38. Canon J, Rex K, Saiki AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature. 2019;575:217-223.

39. Hallin J, Engstrom LD, Hargis L, et al. The KRAS^{G12C} inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers in mouse models and patients. Cancer Discov. 2020;10:54-71.

40. Hong DS, Fakih MG, Strickler JH, et al. KRAS^{G12C} inhibition with sotorasib in advanced solid tumors. N Engl J Med. 2020;383:1207-1217.

41. Jänne PA, Rybkin II, Spira AI, et al. KRYSTAL-1: activity and safety of adagrasib (MRTX849) in advanced/metastatic non–small-cell lung cancer (NSCLC) harboring KRAS G12C mutation. Eur J Cancer. 2020;138(Suppl 2):S1-S2.

42. Johnson ML, Ou SHI, Barve M, et al. KRYSTAL-1: activity and safety of adagrasib (MRTX849) in patients with colorectal cancer (CRC) and other solid tumors harboring a KRAS G12C mutation. Eur J Cancer. 2020;138(Suppl 2):S2.

43. Amodio V, Yaeger R, Arcella P, et al. EGFR blockade reverts resistance to KRAS^{G12C} inhibition in colorectal cancer. Cancer Discov. 2020;10:1129-1139.

44. Molina-Arcas M, Moore C, Rana S, et al. Development of combination therapies to maximize the impact of KRAS-G12C inhibitors in lung cancer. Sci Transl Med. 2019;11:eaaw7999.

45. Sakamoto K, Masutani T, Hirokawa T. Generation of KS-58 as the first K-Ras(G12D)-inhibitory peptide presenting anti-cancer activity in vivo. Sci Rep. 2020; 10:21671.

46. Kelsey S, ed. Approaches to inhibiting RAS driven tumors beyond KRAS-G12C. Paper presented at: 2nd Annual RAS-Targeted Drug Development Conference; September 14-16, 2020; Virtual Meeting.

47. Hillig RC, Sautier B, Schroeder J, et al. Discovery of potent SOS1 inhibitors that block RAS activation via disruption of the RAS-SOS1 interaction. Proc Natl Acad Sci USA. 2019;116:2551-2560.

48. Rozakis-Adcock M, van der Geer P, Mbamalu G, et al. MAP kinase phosphorylation of mSos1 promotes dissociation of mSos1-Shc and mSos1-EGF receptor complexes. Oncogene. 1995;11:1417-1426.

49. Hofmann MH, Gmachl M, Ramharter J, et al. BI-3406, a potent and selective SOS1-KRAS interaction inhibitor, is effective in KRAS-driven cancers through combined MEK inhibition. Cancer Discov. 2021;11:142-157.

50. Hobbs GA, Baker NM, Miermont AM, et al. Atypical KRAS^{G12R} mutant is impaired in PI3K signaling and macropinocytosis in pancreatic cancer. Cancer Discov. 2020;10:104-123.

51. Gerlach D, Gmachl M, Ramharter J, et al. BI-3406 and BI 1701963: potent and selective SOS1::KRAS inhibitors induce regressions in combination with MEK inhibitors or irinotecan. Cancer Res. 2020;80:1091.

52. Nichols RJ, Haderk F, Stahlhut C, et al. RAS nucleotide cycling underlies the SHP2 phosphatase dependence of mutant BRAF-, NF1- and RAS-driven cancers. Nat Cell Biol. 2018;20:1064-1073.

53. Ruess DA, Heynen GJ, Ciecielski KJ, et al. Mutant KRAS-driven cancers depend on PTPN11/SHP2 phosphatase. Nat Med. 2018;24:954-960.

54. Ahmed TA, Adamopoulos C, Karoulia Z, et al. SHP2 drives adaptive resistance to ERK signaling inhibition in molecularly defined subsets of ERK-dependent tumors. Cell Rep. 2019;26:65-78.

55. Lu H, Liu C, Velazquez R, et al. SHP2 inhibition overcomes RTK-mediated pathway reactivation in KRAS-mutant tumors treated with MEK inhibitors. Mol Cancer Ther. 2019;18:1323-1334.

56. Fedele C, Li S, Teng KW, et al. SHP2 inhibition diminishes KRASG12C cycling and promotes tumor microenvironment remodeling. J Exp Med. 2021; 218:e20201414.

57. Roberts TC, Langer R, Wood MJA. Advances in oligonucleotide drug delivery. Nat Rev Drug Discov. 2020;19:673-694.

58. Ross SJ, Revenko AS, Hanson LL, et al. Targeting KRAS-dependent tumors with AZD4785, a high-affinity therapeutic antisense oligonucleotide inhibitor of KRAS. Sci Transl Med. 2017;9:eaal5253.

59. Zorde Khvalevsky E, Gabai R, Rachmut IH, et al. Mutant KRAS is a druggable target for pancreatic cancer. Proc Natl Acad Sci USA. 2013;110:20723-20728.

60. Golan T, Khvalevsky EZ, Hubert A, et al. RNAi therapy targeting KRAS in combination with chemotherapy for locally advanced pancreatic cancer patients. Oncotarget. 2015;6:24560-24570.

61. Kamerkar S, LeBleu VS, Sugimoto H, et al. Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. Nature. 2017;546:498-503.

62. Pecot CV, Wu SY, Bellister S, et al. Therapeutic silencing of KRAS using systemically delivered siRNAs. Mol Cancer Ther. 2014;13:2876-2885.

63. Mendt M, Kamerkar S, Sugimoto H, et al. Generation and testing of clinical-grade exosomes for pancreatic cancer. JCI Insight. 2018;3:99263.

64. Tran E, Robbins PF, Lu YC, et al. T-cell transfer therapy targeting mutant KRAS in cancer. N Engl J Med. 2016;375:2255-2262.

65. Wang QJ, Yu Z, Griffith K, et al. Identification of T-cell receptors targeting KRAS-mutated human tumors. Cancer Immunol Res. 2016;4:204-214.

66. Cafri G, Yossef R, Pasetto A, et al. Memory T cells targeting oncogenic mutations detected in peripheral blood of epithelial cancer patients. Nat Commun. 2019; 10:449.

67. Mullard A. Cracking KRAS. Nat Rev Drug Discov. 2019;18:887-891.

68. Infante JR, Somer BG, Park JO, et al. A randomised, double-blind, placebo-controlled trial of trametinib, an oral MEK inhibitor, in combination with gemcitabine for patients with untreated metastatic adenocarcinoma of the pancreas. Eur J Cancer. 2014;50:2072-2081.

69. Ko AH, Bekaii-Saab T, Van Ziffle J, et al. A multicenter, open-label phase II clinical trial of combined MEK plus EGFR inhibition for chemotherapy-refractory advanced pancreatic adenocarcinoma. Clin Cancer Res. 2016;22:61-68.

70. Bodoky G, Timcheva C, Spigel DR, et al. A phase II open-label randomized study to assess the efficacy and safety of selumetinib (AZD6244 [ARRY-142886]) versus capecitabine in patients with advanced or metastatic pancreatic cancer who have failed first-line gemcitabine therapy [correction published in *Invest New Drugs*. 2012;30:1272-1273]. Invest New Drugs. 2012;30:1216-1223.

71. Kenney C, Kunst T, Webb S, et al. Phase II study of selumetinib, an orally active inhibitor of MEK1 and MEK2 kinases, in $KRAS^{G12R}$-mutant pancreatic ductal adenocarcinoma. Invest New Drugs. 2021.

72. Ardalan B, Cotta JA, Gombosh M, et al. Cobimetinib plus gemcitabine is an active combination in KRAS G12R-mutated in previously chemotherapy-treated and failed pancreatic patients. J Clin Oncol. 2020;38 (15_suppl; abstr 4642).

73. Bryant KL, Stalnecker CA, Zeitouni D, et al. Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer [correction published in *Nat Med*. 2020;26:982]. Nat Med. 2019;25:628-640.

74. Kinsey CG, Camolotto SA, Boespflug AM, et al. Protective autophagy elicited by RAF→MEK→ERK inhibition suggests a treatment strategy for RAS-driven cancers [correction published in *Nat Med*. 2019;25:861]. Nat Med. 2019;25:620-627.

75. Rahib L, Chen K, Ocean AJ, et al. Use of a real-world data approach to rapidly generate outcomes data following a case study of a novel treatment combination in pancreatic adenocarcinoma. J Clin Oncol. 2020;38 (15 suppl; abstr e16735).

76. Singhi AD, George B, Greenbowe JR, et al. Real-time targeted genome profile analysis of pancreatic ductal adenocarcinomas identifies genetic alterations that might be targeted with existing drugs or used as biomarkers. Gastroenterology. 2019;156:2242-2253.

77. Heining C, Horak P, Uhrig S, et al. *NRG1* fusions in *KRAS* wild-type pancreatic cancer. Cancer Discov. 2018;8:1087-1095.

78. Seghers AK, Cuyle PJ, Van Cutsem E. Molecular targeting of a BRAF mutation in pancreatic ductal adenocarcinoma: case report and literature review. Target Oncol. 2020;15:407-410.

79. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med. 2015;373:726-736.

80. Grinshpun A, Zarbiv Y, Roszik J, et al. Beyond KRAS: practical molecular targets in pancreatic adenocarcinoma. Case Rep Oncol. 2019;12:7-13.

81. Yao Z, Torres NM, Tao A, et al. BRAF mutants evade ERK-dependent feedback by different mechanisms that determine their sensitivity to pharmacologic inhibition. Cancer Cell. 2015;28:370-383.

82. Dankner M, Rose AAN, Rajkumar S, et al. Classifying BRAF alterations in cancer: new rational therapeutic strategies for actionable mutations. Oncogene. 2018;37:3183-3199.

83. Yao Z, Yaeger R, Rodrik-Outmezguine VS, et al. Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. Nature. 2017;548:234-238.

84. Johnson DB, Zhao F, Noel M, et al. Trametinib activity in patients with solid tumors and lymphomas harboring BRAF non-V600 mutations or fusions: results from NCI-MATCH (EAY131). Clin Cancer Res. 2020;26:1812-1819.

85. Foster SA, Whalen DM, Özen A, et al. Activation mechanism of oncogenic deletion mutations in BRAF, EGFR, and HER2. Cancer Cell. 2016;29:477-493.

86. Chen SH, Zhang Y, Van Horn RD, et al. Oncogenic BRAF deletions that function as homodimers and are sensitive to inhibition by RAF dimer inhibitor LY3009120. Cancer Discov. 2016;6:300-315.

87. Wrzeszczynski KO, Rahman S, Frank MO, et al. Identification of targetable BRAF ΔN486_P490 variant by whole-genome sequencing leading to dabrafenib-induced remission of a *BRAF*-mutant pancreatic adenocarcinoma. Cold Spring Harb Mol Case Stud. 2019;5:a004424.

88. Chmielecki J, Hutchinson KE, Frampton GM, et al. Comprehensive genomic profiling of pancreatic acinar cell carcinomas identifies recurrent RAF fusions and frequent inactivation of DNA repair genes. Cancer Discov. 2014;4:1398-1405.

89. Botton T, Talevich E, Mishra VK, et al. Genetic heterogeneity of BRAF fusion kinases in melanoma affects drug responses. Cell Rep. 2019;29:573-588.

90. Hainsworth JD, Meric-Bernstam F, Swanton C, et al. Targeted therapy for advanced solid tumors on the basis of molecular profiles: results from MyPathway, an open-label, phase IIa multiple basket study [correction published in *J Clin Oncol*. 2019;37;360]. J Clin Oncol. 2018;36:536-542.

91. Jones MR, Williamson LM, Topham JT, et al. *NRG1* gene fusions are recurrent, clinically actionable gene rearrangements in *KRAS* wild-type pancreatic ductal adenocarcinoma. Clin Cancer Res. 2019;25:4674-4681.

92. Drilon A, Somwar R, Mangatt BP, et al. Response to ERBB3-directed targeted therapy in *NRG1*-rearranged cancers. Cancer Discov. 2018;8:686-695.

93. Schram AM, O'Reilly EM, Somwar R, et al. Clinical proof of concept for MCLA-128, a bispecific HER2/3 antibody therapy, in NRG1 fusion-positive cancers. Mol Cancer Ther. 2019;18:PR02.

94. Laskin J, Liu SV, Tolba K, et al. NRG1 fusion-driven tumors: biology, detection, and the therapeutic role of afatinib and other ErbB-targeting agents. Ann Oncol. 2020;31:1693-1703.

95. Singhi AD, Ali SM, Lacy J, et al. Identification of targetable *ALK* rearrangements in pancreatic ductal adenocarcinoma. J Natl Compr Canc Netw. 2017;15:555-562.

96. Gower A, Golestany B, Gong J, et al. Novel *ALK* fusion, *PPFIBP1-ALK*, in pancreatic ductal adenocarcinoma responsive to alectinib and lorlatinib. JCO Precis Oncol. 2020;4:4.

97. Doebele RC, Drilon A, Paz-Ares L, et al; Trial Investigators. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020;21:271-282.

98. Hyman D, Tan DSW. Durability of response with larotrectinib in adult and pediatric patients with TRK fusion cancer. Ann Oncol. 2019;30:ix123.

99. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378:731-739.

100. O'Reilly EM, Hechtman JF. Tumour response to TRK inhibition in a patient with pancreatic adenocarcinoma harbouring an NTRK gene fusion. Ann Oncol. 2019;30(suppl 8):viii36-viii40.

101. Pishvaian MJ, Garrido-Laguna I, Liu SV, et al. Entrectinib in TRK and ROS1 fusion-positive metastatic pancreatic cancer. JCO Precis Oncol. Epub 2018 Jul 25.

102. Fusco MJ, Saeed-Vafa D, Carballido EM, et al. Identification of targetable gene fusions and structural rearrangements to foster precision medicine in KRAS wild-type pancreatic cancer. Precision Oncol. 2021;5:65-74.

103. Drilon AE, Subbiah V, Oxnard GR, et al. A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers. J Clin Oncol. 2018;36 (15 suppl; abstr 102).

104. Subbiah V, Hu MI-N, Gainor JF, et al. Clinical activity of the RET inhibitor pralsetinib (BLU-667) in patients with RET fusion+ solid tumors. J Clin Oncol. 2020;38 (15 suppl; abstr 109).

105. Fusco MJ, Saeed-Vafa D, Carballido EM, et al. Identification of targetable gene fusions and structural rearrangements to foster precision medicine in KRAS wild-type pancreatic cancer. JCO Precis Oncol. 2021;5:65-74.

106. Luchini C, Brosens LAA, Wood LD, et al. Comprehensive characterisation of pancreatic ductal adenocarcinoma with microsatellite instability: histology, molecular pathology and clinical implications. Gut. 2021;70:148-156.

107. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357:409-413.

108. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol. 2020;38:1-10.

109. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020;21:1353-1365.

110. Valero C, Lee M, Hoen D, et al. Response rates to anti-PD-1 immunotherapy in microsatellite-stable solid tumors with 10 or more mutations per megabase. JAMA Oncol. Epub 2021 Feb 18.

111. Shroff RT, Hendifar A, McWilliams RR, et al. Rucaparib monotherapy in patients with pancreatic cancer and a known deleterious BRCA mutation. JCO Precis Oncol. Epub 2018 May 16.

112. Mohyuddin GR, Aziz M, Britt A, et al. Similar response rates and survival with PARP inhibitors for patients with solid tumors harboring somatic versus germline BRCA mutations: a meta-analysis and systematic review. BMC Cancer. 2020;20:507.

113. Kryukov GV, Wilson FH, Ruth JR, et al. MTAP deletion confers enhanced dependency on the PRMT5 arginine methyltransferase in cancer cells. Science. 2016; 351:1214-1218.

114. Mavrakis KJ, McDonald ER III, Schlabach MR, et al. Disordered methionine metabolism in MTAP/CDKN2A-deleted cancers leads to dependence on PRMT5. Science. 2016;351:1208-1213.

115. Kalev P, Hyer ML, Gross S, et al. MAT2A inhibition blocks the growth of MTAP-deleted cancer cells by reducing PRMT5-dependent mRNA splicing and inducing DNA damage. Cancer Cell. 2021;39:209-224.

116. Marjon K, Cameron MJ, Quang P, et al. MTAP deletions in cancer create vulnerability to targeting of the MAT2A/PRMT5/RIOK1 axis. Cell Rep. 2016; 15:574-587.

117. National Comprehensive Cancer Network. Pancreatic adenocarcinoma (version 2.2021). https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed March 10, 2021.

The Right Treatment of the Right Patient: Integrating Genetic Profiling Into Clinical Decision Making in Advanced Gastric Cancer in Asia

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overview

Gastric cancer is a major global health burden, especially when patients are diagnosed with recurrent or metastatic gastric cancer. Despite recent advances in treatment options with palliative chemotherapy, the median overall survival of patients with gastric cancer remains within 1 or 2 years after the diagnosis of metastatic disease. Gastric cancer is significantly more prevalent in eastern Asia (e.g., Japan and Korea). Next-generation sequencing is rapidly being adopted as part of clinical practice in Korea and Japan, especially in patients with gastric cancer. Approximately 10% to 15% of the patients with gastric cancer who undergo next-generation sequencing of their tumor specimen are allocated to target-matched clinical trials in Japan and Korea. In Japan and Korea, a cell-free DNA next-generation sequencing panel is also actively being investigated as an alternative next-generation sequencing test for patients with gastric cancer, which may reflect the tumor heterogeneity of gastric cancer. In Japan and Korea, multiple biomarkers, such as HER2, mismatch repair, Epstein-Barr virus, PD-L1 (combined positive score), EGFR, FGFR2, and CLDN18.2, are routinely assessed through immunohistochemistry or in situ hybridization before initiation of the first-line treatment in all patients with gastric cancer. Most tertiary cancer centers in Korea routinely perform HER2, mismatch repair, Epstein-Barr virus, and PD-L1 next-generation sequencing before palliative chemotherapy in patients with gastric cancer. Biomarker evaluation for all patients with metastatic gastric cancer enables clinicians to identify available biomarker-based clinical trials early during the course of treatment, which expands treatment opportunities while patients are medically fit for clinical trials, if available. Comprehensive genomic profiling using a tissue or circulating tumor DNA next-generation sequencing panel is considered necessary during second-line or subsequent treatment. It is hoped that a comprehensive molecular profiling strategy will facilitate greater use of precision medicine through molecularly targeted therapies for patients with gastric cancer in the near future.

Gastric cancer is significantly more prevalent in eastern Asia (e.g., Japan and Korea, which have the highest rates worldwide among both sexes), whereas the rates in North America and northern Europe are generally low and are equivalent to those seen across Africa.[1]

Since 1965, gastric cancer has been divided into diffuse and intestinal subtypes by histologic morphology according to Lauren classification.[2] The two subtypes have distinct clinical features, with diffuse gastric cancer showing poor survival.[3] It is well established that intestinal and diffuse subtypes appear different under hematoxylin and eosin staining (tubular vs. stromal, respectively) and have different demographic populations (old vs. young, respectively) and different survival (good vs. poor, respectively). Gastric cancer is a largely heterogeneous disease based on genomic sequencing. The Cancer Genome Atlas genomically separated 300 gastric cancer specimens into four subtypes: Epstein-Barr virus–associated tumors, microsatellite instability–high tumors, genomically stable tumors, and tumors with chromosomal instability.[4] Hence, several lines of evidence support that gastric cancer is a heterogeneous disease with different molecular segments present in one tumor specimen, different levels of molecular targets present within the tumor, or tumor molecular targets changing during or after chemotherapy.[5-8] One of the reasons for the relatively low success rate in recent phase III trials for gastric cancer may be due to intratumoral or interpatient tumor heterogeneity. A list of recent phase III trials with targeted agents and/or immunotherapy is provided in Table 1. As seen in Table 1, the pattern of clinical trial design in gastric cancer is different before and after next-generation sequencing (NGS) became available in the clinic.

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PRACTICAL APPLICATIONS

- Gastric cancer is the most prevalent cancer type in Korea and Japan.
- Next-generation sequencing is widely used as a practice in patients with gastric cancer in Korea and Japan.
- For metastatic gastric cancer, patients undergo HER2, mismatch repair, Epstein-Barr virus, PD-1, and tumor or cell-free DNA next-generation sequencing as a routine practice.
- Approximately 10% to 15% of the patients with gastric cancer who undergo next-generation sequencing will be allocated to an available biomarker-driven trial or practice.
- Biomarker evaluation for all patients with metastatic gastric cancer enables clinicians to identify available biomarker-based clinical trials early during the course of treatment, which expands treatment opportunities while patients are medically fit for clinical trials, if available.

Moreover, the trials in which the patient population was selected based on immunohistochemistry of a limited number of tumor slides or without consideration of biomarkers generally showed minimal clinical benefit, especially for targeted agents.

GENOMIC LANDSCAPE OF GASTRIC CANCER, FOCUSING ON POTENTIAL THERAPEUTIC TARGETS

In 2014, The Cancer Genome Atlas reported the most comprehensive analysis of gastric cancer.[4] On the basis of this analysis, gastric cancer was categorized into four subtypes: genomically stable tumors, tumors with chromosomal instability, Epstein-Barr virus–associated tumors, and microsatellite instability–high tumors.[4] Since then, several key trials have highlighted the importance of this molecular characterization. One of the key advances in metastatic gastric cancer treatment in the past few years has been the realization of the effectiveness of anti–PD-L1 inhibitors in a subset of patients based on The Cancer Genome Atlas subtypes.[31,32] In 2020, the recent approval of anti–PD-1 treatments in all patients with microsatellite instability–high tumors, regardless of cancer type, indicates that a majority of patients with metastatic gastric cancer are receiving either mismatch repair tests by immunohistochemistry or microsatellite instability tests by pentaplex polymerase chain reaction during the course of their treatment globally. Most of the molecularly targeted agents tested in clinical trials for gastric cancer, such as inhibitors against RTK amplification, are more enriched in the chromosomally unstable subtype. For instance, the chromosomally unstable subtype is characterized by a high frequency of copy-number amplifications, especially in RTKs (*ERBB2*, *EGFR*, *MET*, and *FGFR2*), cell-cycle genes (*CCND1*, *CCNE1*, and *CDK6*), and transcription factor oncogenes (*GATA4*, *GATA6*, and *MYC*). The chromosomally unstable subtype is more frequent in the Western population, with chromosomally unstable tumors being more prevalent in the proximal stomach.

Genomically stable tumors, in contrast, are characterized by a lack of the hypermethylation, mutation, and aneuploidy found in tumors with chromosomal instability. Most genomically stable tumors are diffuse type, with a high prevalence of *CDH1* and *RHO* mutations. The genomically stable subtype has a high recurrence rate, is less enriched in conventional molecular targets, and has the worst survival rate among the four subtypes. Because of their aggressive biology, genomically stable tumors require more focused clinical trials with an improved treatment approach. Recently, recurrent fusion genes in CLDN18 were identified and investigated using an anti-CLDN18 antibody in a phase III clinical trial.

NEXT-GENERATION SEQUENCING CANCER PANEL IN ASIA

With the rapid application of NGS cancer panels using tumor specimens in the past few years, we are learning that each patient with gastric cancer has distinct genomic aberrations and therefore unique therapeutic targets. Globally, more countries are approving NGS as part of their programs for patients with cancer, including Asian countries such as Korea, Singapore, and Japan. In Japan, NGS using tumor tissue has been approved and reimbursed; additionally, circulating tumor DNA NGS is under review by the national health insurance system (as of March 2020). In Korea, NGS cancer panels have been approved for all patients with metastatic cancer (as of April 2017). In 2020, the European Society for Medical Oncology published a general guideline for using NGS in patients with cancer (Table 2); NGS is recommended in gastric cancer if the patient is likely to benefit from a clinical trial based on NGS.[33] Of note, many commercially available NGS tests now include microsatellite instability and tumor mutational burden status as part of the panel; there is a growing body of evidence that microsatellite instability and tumor mutational burden are two important biomarkers for immune checkpoint inhibitors, and the role of NGS tests in practice will expand in the next few years.

The average turnaround time for an NGS panel using a tumor tissue specimen ranges from 4 to 8 weeks, and the identification and screening of appropriate clinical trials may take another 6 to 8 weeks. To make this biomarker-drug match process more efficient and feasible for patients with cancer, novel clinical trial designs, such as umbrella (or basket) and expansion-platform studies with simultaneous multiple arms, have been introduced. An umbrella (or basket) trial was designed to match patients according to the molecular traits of their individual tumors. Several

TABLE 1. Recently Reported Metastatic Gastric Cancer Phase III Trials and Treatment Outcomes

Target	Trial	Type of Study/Line	Patient Selection Method	Regimen	Results (Primary Endpoint)	Reference
HER2-Targeted Clinical Trials						
HER2	ToGA	Phase III/first	HER2 IHC/ amplification	FU/capecitabine + cisplatin ± trastuzumab	Positive (OS)	[9]
HER2	LOGIC	Phase III/first	HER2 amplification	Lapatinib + XELOX vs. XELOX	Negative (OS)	[10]
HER2	TYTAN	Phase III/ second	HER2 amplification	Paclitaxel + lapatinib vs. paclitaxel	Negative (OS)	[11]
HER2	GATSBY	Phase II/III/ second	HER2 IHC/ amplification	T-DM1 vs. paclitaxel or docetaxel	Negative (OS)	[12]
HER2	JACOB	Phase III/first	HER2 IHC/ amplification	Pertuzumab	Negative (OS)	[13,14]
EGFR-Targeted Clinical Trials						
EGFR	EXPAND	Phase III/first	All comers	Cetuximab/XP vs. placebo/ XP	Negative (PFS)	[15]
EGFR	REAL-III	Phase III/first	All comers	Panitumumab/EOC vs. EOC	Negative (OS)	[16]
EGFR	ENRICH	Phase III/ second	EGFR IHC	Nimotuzumab/irinotecan vs. irinotecan	Terminated	NCT01813253
MET-Targeted Clinical Trials						
HGF	RILOMET-1	Phase III/first	MET IHC	Rilotumumab/ECX vs. ECX	Negative (OS)	[17]
MET	METGastric	Phase III/first	MET IHC	Onartuzumab/FOLFOX vs. FOLFOX	Negative (OS)	[18]
Antiangiogenesis Therapy Clinical Trials						
VEGF	AVAGAST	Phase III/first	All comers	XP/bevacizumab vs. XP	Negative (OS)	[19]
VEGFR-2	RAINBOW	Phase III/ second	All comers	Paclitaxel/ramucirumab vs. paclitaxel/placebo	Positive (OS)	[20]
VEGFR-2	REGARD	Phase III/ second	All comers	Ramucirumab vs. placebo	Positive (OS)	[21]
VEGFR-2	ANGEL	Phase III/> third	All comers	Apatinib vs. placebo	Negative (OS)	[22]
Others						
mTOR	GRANITE-1	Phase III/ second or third	All comers	Everolimus vs. placebo	Negative (OS)	[23]
ATM	GOLD	Phase III/ second	All comers ATM IHC	Paclitaxel/olaparib vs. paclitaxel/placebo	Negative (OS)	[24]
PD-1	KN062	Phase III/first	PD-L1	Pembrolizumab or pembrolizumab/chemo vs. chemotherapy	Negative for superiority (OS)	[25]
PD-1	KN061	Phase III/ second	PD-L1	Pembrolizumab vs. paclitaxel	Negative (OS)	[26]
PD-1	KN059	Phase III/first	PD-L1	Pembrolizumab	Positive (ORR)	[27]
PD-1	CheckMate649	Phase III/first	PD-L1	Nivolumab/chemotherapy vs. chemotherapy	Positive (OS, PFS)	[28]

(Continued on following page)

TABLE 1. Recently Reported Metastatic Gastric Cancer Phase III Trials and Treatment Outcomes (Continued)

Target	Trial	Type of Study/Line	Patient Selection Method	Regimen	Results (Primary Endpoint)	Reference
PD-1	ATTRACTION-4	Phase III/first	All comers	Nivolumab/chemotherapy vs. chemotherapy/placebo	Positive (PFS) Negative (OS)	[29]
PD-1	ATTRACTION-2	Phase III/≥ third	All comers	Nivolumab vs. placebo	Positive (OS)	[30]

Abbreviations: ECX, epirubicin, cisplatin, and capecitabine; EOC, epirubicin, oxaliplatin, and capecitabine; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; FU, fluorouracil; IHC, immunohistochemistry; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor 2; XELOX, oxaliplatin and capecitabine; XP, capecitabine and cisplatin.

platform trials have been investigated for gastric cancer. In the United States, the PANGEA trial assigned patients with gastric cancer to matched treatment according to biomarker, such as *MET* amplification, *EGFR2* amplification, EGFR expression, or *FGFR2* amplification. Briefly, the PANGEA trial demonstrated that the first-line response rate was significantly superior to that in historical controls when patients underwent biomarker-based treatment.[41] The targeted-agent VIKTORY trial, a Korean study, was designed to classify patients with metastatic gastric cancer based on clinical sequencing and focused on eight different biomarker groups (*RAS* aberration, *TP53* mutation, *PIK3CA* mutation/amplification, *MET* amplification, *MET* overexpression, and all negative) to assign patients to one of 10 associated clinical trials for second-line treatment.[42] Capivasertib (AKT inhibitor), savolitinib (MET inhibitor), selumetinib (MEK inhibitor), adavosertib (WEE1 inhibitor), and vistusertib (TORC inhibitor) were tested in the presence or absence of chemotherapy. Between 2014 and 2018, 772 patients with gastric cancer were enrolled, and NGS was successfully performed for 715 patients (92.6%).[42] This trial showed that when NGS was accompanied by seamless access to parallel biomarker-matched trials, 14.7% (105 patients) of patients received biomarker-assigned drug treatment. In addition, the VIKTORY trial showed that the biomarker-assigned treatment cohort (105 patients) demonstrated significantly prolonged progression-free survival when compared with the conventional second-line treatment cohort (266 patients; median progression-free survival, 5.7 vs. 3.8 months, respectively; $p < .0001$). The highest response rate was observed in the study arm of patients with *MET* amplification matched to savolitinib monotherapy (20 patients). Of note, responders were enriched for higher *MET* copy number (7 of 10 with > 10 *MET* copies), a biologic phenomenon seen in *HER2*- and *EGFR*-amplified gastric cancer.[9,36] On the basis of the trial, patients with gastric cancer with high levels of circulating tumor DNA *MET* amplification (by Guardant360 assay; Guardant Health, Redwood City, CA) also demonstrated more profound tumor shrinkage from MET-targeted therapy; however, this must be validated in an expansion cohort. Overall, when NGS tests are performed at the right time and are aligned with parallel biomarker-assigned clinical trials in patients with metastatic gastric cancer, there is a patient population who will benefit from the matched treatment.

NEXT-GENERATION SEQUENCING AND BEYOND: FOCUS ON JAPAN

In Japan, SCRUM-Japan GI-SCREEN, a nationwide cancer biomarker screening project using tissue-based NGS testing, was launched in 2015 to accelerate the identification of targetable alterations in advanced gastrointestinal cancers, including gastric cancer. An analysis of 513 gastric cancers revealed frequent recurrent mutations in *TP53* and a large number of alterations in only a small fraction of patients, showing a long-tail distribution.[43] This screening study identified extremely rare rearrangements: *FGFR3-TACC3* fusion and *EGFR* vIII in two patients each (0.4%) and *WIPF2-ERBB2* and *GOPC-ROS1* fusions in one patient each (0.2%). Patients in whom *MET* amplification, *FGFR2* amplification, *AKT1* mutation, *ERBB2* amplification, and *ROS1* fusion were identified were enrolled in matched targeted therapy trials.

Circulating tumor DNA has been shown to detect genomic alterations for therapeutic selection in patients with advanced solid tumors. The SCRUM-Japan GI-SCREEN/GOZILA study, a screening study using comprehensive circulating tumor DNA sequencing to rapidly screen patients for trial eligibility, was initiated in Japan. The GOZILA study detected genomic alterations with a prevalence comparable to that previously reported in tissue genotyping and successfully identified rare alterations, including *NTRK1* fusion.[44] Comparison of utility between GI-SCREEN (5,621 patients) and GOZILA (1,687 patients) revealed that circulating tumor DNA genotyping demonstrated a more rapid turnaround time than tissue genotyping (11 vs. 33 days). Furthermore, circulating tumor DNA genotyping led to a considerable increase in genotype-matched enrollment in clinical trials relative to such enrollment via tumor-based screening (9.5% vs. 4.1% of patients; $p < .0001$), without compromising treatment efficacy (response rate,

20.0% vs. 16.7%; median progression-free survival, 2.4 vs. 2.8 months).

Additionally, circulating tumor DNA genotyping has been used to identify heterogeneous alterations with minimal invasiveness, which may be particularly advantageous for gastric cancer, a heterogeneous cancer type. Longitudinal circulating tumor DNA genotyping in a patient with *EGFR*-amplified gastric cancer revealed the emergence of *MET* amplification as well as a far higher number of *EGFR* mutations than that seen in metastatic colorectal cancer after anti-EGFR therapy, suggesting a high level of heterogeneity in gastric cancer.[45] Using circulating tumor DNA genotyping, umbrella/basket-type targeted clinical trials have been conducted for rare fractions of patients with advanced solid malignancies, including gastric cancer with *FGFR* alteration, *BRCA1/2* mutation, *ROS1* fusion, and high tumor mutational burden, in the GOZILA study.[46]

Since June 2019, reimbursement has been provided for two comprehensive genomic profiling tests, the FoundationOne CDx Cancer Genomic Profile and the OncoGuide NCC Oncopanel System, in Japan. Genomic profiling has been recommended for patients with any type of advanced cancer receiving systemic chemotherapy,[47] although the indication is restricted to those with advanced solid tumors with disease progression during standard therapies or for whom there are no appropriate standard treatments. The Japanese Gastric Cancer Treatment Guidelines 2021 (version 6), which will be published this year, will weakly recommend NGS testing for unresectable gastric cancer; according to preliminary data, 747 patients, including those with gastric cancer, underwent reimbursed comprehensive genomic profiling tests as of January 2020, and 28 (3.7%) received genomically matched treatments.[48] The regulatory application of the NGS-based circulating tumor DNA assay, FoundationOne Liquid CDx, which has been approved by the U.S. Food and Drug Administration, was submitted to the Japanese Pharmaceuticals and Medical Devices Agency in March 2020.

One of the greatest achievements in precision medicine for patients with gastric cancer from Asia is the development of trastuzumab deruxtecan in HER2-positive gastric cancer. Trastuzumab deruxtecan is a novel HER2-targeting antibody-drug conjugate composed of a humanized anti-HER2 antibody, an enzymatically cleavable peptide linker, and a topoisomerase I inhibitor. On the basis of the promising activity in a phase I trial, a randomized phase II trial (DESTINY-Gastric01) was conducted to evaluate the efficacy of trastuzumab deruxtecan compared with chemotherapy in patients with HER2-positive advanced gastric cancer who received at least two previous therapies, including trastuzumab.[49] A total of 188 patients were randomly assigned in the primary cohort of high-level HER2-positive disease; 80% of these patients were enrolled from Japan, and 20% were from Korea. In the primary cohort, trastuzumab deruxtecan demonstrated a significantly higher response rate (51% vs. 14%; $p < .001$) and longer overall survival than chemotherapy (median, 12.5 vs. 8.4 months; HR, 0.59; 95% CI, 0.39–0.88). On the basis of these results, trastuzumab deruxtecan was approved for patients with previously treated HER2-positive gastric cancer in Japan, followed by approval by the U.S. Food and Drug Administration. This study also demonstrated preliminary efficacy in patients with lower HER2 expression. In total, 20 and 24 patients were enrolled in the immunohistochemistry 2+/in situ hybridization–negative and immunohistochemistry 1+ cohorts, respectively. The confirmed response rate was 26.3% in the immunohistochemistry 2+/in situ hybridization–negative cohort and 9.5% in the immunohistochemistry 1+ cohort; the median progression-free survival was 4.4 and 2.8 months, respectively, and the median survival was 7.8 and 8.5 months, respectively. Importantly, not all patients with high HER2 expression responded to trastuzumab deruxtecan, and several patients responded even with HER2-low status. Additional studies analyzing HER2 expression in fresh biopsy tissues and circulating tumor DNA are needed to clarify the relationship between status of HER2 or other genes and trastuzumab deruxtecan efficacy, possibly leading to improved patient selection or clarification of the resistance mechanism.

TABLE 2. List of Level I/II/III Genomic Alterations by ESCAT in Metastatic Gastric Cancer According to ESMO

Gene	Genomic Alteration	Prevalence (%)	ESCAT*	Reference
ERBB2	Amplification	16	IA	11
	Mutation	3	IIIA	34
MSI-high		8	IC	4
NTRK	Fusion	2	IC	35
EGFR	Amplification	6	IIB	36
MET	Amplification	3	IIB	37
FGFR2	Amplification	4	IIIA	38
ATM	Mutation	3	IIIA	24
BRCA1/2	Mutation	1–5	IIIA	39
ROS1	Fusion	< 1	IIIA	40

Data adapted.[33]

Abbreviations: ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESMO, European Society for Medical Oncology; MSI, microsatellite instability.

*ESCAT level I, the match of an alteration and a drug has been validated in clinical trials and should drive treatment decision in daily practice; level II, a drug that matches the alteration has been associated with responses in phase I/II or in retrospective analyses of randomized trials; level III, alterations that are validated in another cancer but not in the disease to treat; and level IV, includes hypothetically targetable alterations based on preclinical data.

CONCLUSION

The success of studies evaluating molecular stratification strategies, especially in Japan and Korea, such as VIKTORY and GI-SCREEN/GOZILA, has highlighted the importance of comprehensive molecular profiling for precision medicine in gastric cancer therapy. From global perspectives, there is a huge effort in establishing guidelines for NGS testing for patients with cancer. It is complicated to establish a uniform guideline for NGS because of the various medical insurance and medical care systems. Nevertheless, in general, NGS tests are being adopted more in clinical practice in a growing number of countries. In addition, the provision of NGS tests in pathology service is becoming more advanced because of the availability of NGS analysis programs. In the National Cancer Center Hospital East (Japan), multiple biomarkers, such as HER2, mismatch repair, Epstein-Barr virus, PD-L1 (combined positive score), EGFR, FGFR2, and CLDN18.2, are routinely assessed through immunohistochemistry or in situ hybridization before initiation of first-line treatment in all patients with gastric cancer. Most tertiary cancer centers in Korea routinely perform HER2, mismatch repair, Epstein-Barr virus, and PD-L1 NGS before palliative chemotherapy in patients with gastric cancer. Biomarker evaluation for all patients with metastatic gastric cancer enables clinicians to identify available biomarker-based clinical trials early during the course of treatment, which expands treatment opportunities while patients are medically fit for clinical trials, if available. Comprehensive genomic profiling using a tissue or circulating tumor DNA NGS panel is considered necessary during second-line or subsequent treatment. It is hoped that a comprehensive molecular profiling strategy will facilitate greater use of precision medicine through molecularly targeted therapies for patients with gastric cancer and improve treatment outcomes.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
2. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31-49.
3. Cristescu R, Lee J, Nebozhyn M, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med. 2015; 21:449-456.
4. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202-209.
5. Kim ST, Banks KC, Pectasides E, et al. Impact of genomic alterations on lapatinib treatment outcome and cell-free genomic landscape during HER2 therapy in HER2+ gastric cancer patients. Ann Oncol. 2018;29:1037-1048.
6. Zhou KI, Peterson B, Serritella A, et al. Spatial and temporal heterogeneity of PD-L1 expression and tumor mutational burden in gastroesophageal adenocarcinoma at baseline diagnosis and after chemotherapy. Clin Cancer Res. 2020;26:6453-6463.
7. Maron S, Bass A. Tumor heterogeneity: ignorance is not bliss. JAMA Netw Open. 2020;3:e203677.
8. Nagaraja AK, Kikuchi O, Bass AJ. Genomics and targeted therapies in gastroesophageal adenocarcinoma. Cancer Discov. 2019;9:1656-1672.
9. Bang YJ, Van Cutsem E, Feyereislova A, et al; ToGA trial investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010; 376:687-697.
10. Hecht JR, Bang Y-J, Qin S, et al. Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma (AC): the TRIO-013/LOGiC trial. J Clin Oncol. 2013;31:18s (suppl; abstr LBA4001).
11. Bang Y-J. A randomized, open-label, phase III study of lapatinib in combination with weekly paclitaxel versus weekly paclitaxel alone in the second-line treatment of HER2 amplified advanced gastric cancer in Asian population: TyTAN study. J Clin Oncol. 2013;31:4s (suppl; abstr 11).

12. Kang Y-K, Shah MA, Ohtsu A, et al. A randomized, open-label, multicenter, adaptive phase 2/3 study of trastuzumab emtansine (T-DM1) versus a taxane (TAX) in patients (pts) with previously treated HER2-positive locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma (LA/MGC/GEJC). J Clin Oncol. 2016;34:4s (suppl; abstr 5).

13. Tabernero J, Hoff PM, Shen L, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2018;19:1372-1384.

14. Yao JC, Ajani JA. Gastric cancer. Curr Opin Gastroenterol. 2000;16:516-521.

15. Lordick F, Kang YK, Chung HC, et al; Arbeitsgemeinschaft Internistische Onkologie and EXPAND investigators. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol. 2013;14:490-499.

16. Waddell T, Chau I, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol. 2013;14:481-489.

17. Cunningham D, Tebbutt NC, Davidenko I, et al. Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study. J Clin Oncol. 2015;33:15s (suppl; abstr 2000).

18. Shah MA, Bang Y-J, Lordick F, et al. METGastric: a phase III study of onartuzumab plus mFOLFOX6 in patients with metastatic HER2-negative (HER2-) and MET-positive (MET+) adenocarcinoma of the stomach or gastroesophageal junction (GEC). J Clin Oncol. 2015;33:15s (suppl; abstr 4012).

19. Van Cutsem E, de Haas S, Kang YK, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. J Clin Oncol. 2012;30:2119-2127.

20. Wilke H, Van Cutsem E, Oh SC, et al. RAINBOW: a global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy rainbow IMCL CP12-0922 (I4T-IE-JVBE). J Clin Oncol. 2014;32:3s (suppl; abstr LBA7).

21. Fuchs CS, Tomasek J, Yong CJ, et al; REGARD trial investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383:31-39.

22. Kang YK, Kang WK, Di Bartolomeo M, et al. Randomized phase III ANGEL study of rivoceranib (apatinib) + best supportive care (BSC) vs placebo + BSC in patients with advanced/metastatic gastric cancer who failed ≥2 prior chemotherapy regimens. Ann Oncol. 2019;30:v877-v878.

23. Ohtsu A, Ajani JA, Bai YX, et al. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J Clin Oncol. 2013;31:3935-3943.

24. Bang YJ, Xu RH, Chin K, et al. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18:1637-1651.

25. Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. JAMA Oncol. 2020;6:1571-1580.

26. Shitara K, Özgüroğlu M, Bang YJ, et al; KEYNOTE-061 investigators. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet. 2018;392:123-133.

27. Muro K, Fuchs CS, Jang RW-J, et al. KEYNOTE-059 cohort 1: pembrolizumab (Pembro) monotherapy in previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer in patients (Pts) with PD-L1+ tumors—Asian subgroup analysis. J Clin Oncol. 2018;36:4s (suppl; abstr 723).

28. Moehler M, Shitara K, Garrido M, et al. LBA6_PR nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): first results of the CheckMate 649 study. Ann Oncol. 2020;31:S1191.

29. Boku N, Ryu MH, Oh D-Y, et al. Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/gastroesophageal junction (G/GEJ) cancer: ATTRACTION-4 (ONO-4538-37) study. Ann Oncol. 2020;31:S1192.

30. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390:2461-2471.

31. Kim ST, Cristescu R, Bass AJ, et al. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. Nat Med. 2018;24:1449-1458.

32. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509-2520.

33. Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2020;31:1491-1505.

34. Hyman DM, Piha-Paul SA, Won H, et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. Nature. 2018;554:189-194.

35. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378:731-739.

36. Maron SB, Alpert L, Kwak HA, et al. Targeted therapies for targeted populations: anti-EGFR treatment for *EGFR*-amplified gastroesophageal adenocarcinoma. Cancer Discov. 2018;8:696-713.

37. Lennerz JK, Kwak EL, Ackerman A, et al. MET amplification identifies a small and aggressive subgroup of esophagogastric adenocarcinoma with evidence of responsiveness to crizotinib. J Clin Oncol. 2011;29:4803-4810.

38. Loriot Y, Necchi A, Park SH, et al; BLC2001 study group. Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med. 2019;381:338-348.

39. Balasubramaniam S, Beaver JA, Horton S, et al. FDA approval summary: rucaparib for the treatment of patients with deleterious *BRCA* mutation-associated advanced ovarian cancer. Clin Cancer Res. 2017;23:7165-7170.
40. Lee J, Lee SE, Kang SY, et al. Identification of ROS1 rearrangement in gastric adenocarcinoma. Cancer. 2013;119:1627-1635.
41. Pectasides E, Stachler MD, Derks S, et al. Genomic heterogeneity as a barrier to precision medicine in gastroesophageal adenocarcinoma. Cancer Discov. 2018; 8:37-48.
42. Lee J, Kim ST, Kim K, et al. Tumor genomic profiling guides patients with metastatic gastric cancer to targeted treatment: the VIKTORY umbrella trial. Cancer Discov. 2019;9:1388-1405.
43. Yuki S, Shitara K, Kadowaki S, et al. The nationwide cancer genome screening project in Japan SCRUM-Japan GI-SCREEN: efficient identification of cancer genome alterations in advanced gastric cancer (GC). J Clin Oncol. 2018;36:15s (suppl; abstr 4050).
44. Nakamura Y, Taniguchi H, Ikeda M, et al. Clinical utility of circulating tumor DNA sequencing in advanced gastrointestinal cancer: SCRUM-Japan GI-SCREEN and GOZILA studies. Nat Med. 2020;26:1859-1864.
45. Nakamura Y, Sasaki A, Yukami H, et al. Emergence of concurrent multiple EGFR mutations and MET amplification in a patient with EGFR-amplified advanced gastric cancer treated with cetuximab. JCO Precis Oncol. 2020;4:PO.20.00263.
46. Nakamura Y, Shitara K. Development of circulating tumour DNA analysis for gastrointestinal cancers. ESMO Open. 2020;5(suppl 1):e000600.
47. Naito Y, Aburatani H, Amano T, et al. Clinical practice guidance for next-generation sequencing in cancer diagnosis and treatment (edition 2.1). Int J Clin Oncol. 2021;26:233-283.
48. Sunami K, Naito Y, Aimono E, et al. The initial assessment of expert panel performance in core hospitals for cancer genomic medicine in Japan. Int J Clin Oncol. 2021;26:443-449.
49. Shitara K, Bang YJ, Iwasa S, et al; DESTINY-Gastric01 investigators. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382:2419-2430.

Where to Start and What to Do Next: The Sequencing of Treatments in Metastatic Esophagogastric Cancer

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Overview

Esophagogastric cancer is associated with rising incidence and high mortality. Nearly 40% of patients have metastatic disease at the time of diagnosis with poor 5-year overall survival. The treatment of squamous cell carcinoma of the esophagus and gastroesophageal adenocarcinoma has started to bifurcate in recent years, owing to the evolving understanding of the biologic and genomic characteristics of these tumors. Incorporation of HER2-directed therapy in the form of monoclonal antibody and antibody-drug conjugate is now standard of care for patients with HER2-positive disease. The addition of immune checkpoint inhibitors to the therapeutic landscape of metastatic esophagogastric cancer is associated with modest improvement in overall survival, and definition of predictive biomarkers of response to checkpoint inhibition remains imprecise. A number of therapeutic targets including FGFR2b, Claudin 18.2, DKK-1, and DNA repair defects are being explored in clinical trials. Similarly, combination immunotherapy and novel HER2-targeting agents, such as bispecific antibody and small-molecule inhibitors, are at various stages of clinical development. Despite the progress made in the field of targeted therapies and checkpoint inhibition, chemotherapy remains an integral part of treatment of metastatic esophagogastric cancer but is associated with considerable toxicity. Clinical trials focusing on minimizing toxicity of currently available therapeutic agents, development of novel biomarker-driven treatment strategies, and overcoming resistance to immune checkpoint inhibition will define the future of this traditionally indelible disease.

BURDEN OF DISEASE

Cancers of the upper gastrointestinal tract are associated with high morbidity and mortality. Esophagogastric cancer is among the top 10 leading causes of cancer-related mortality in the world and in the United States.[1,2] The turn of the 21st century has witnessed a revolutionary change in the therapeutic and prognostic landscape of several malignancies, including non–small cell lung cancer, leading to substantial improvement in overall survival of patients with advanced disease.[3] In contrast, development of novel treatment strategies for patients with metastatic esophagogastric cancer has lagged behind. This is in striking contrast with the dramatic rise in the incidence of adenocarcinoma of the esophagus (EAC) and gastroesophageal junction (AGEJ), especially among the adult White male population in the Western countries.[4,5] Although the incidence of squamous cell carcinoma of the esophagus (ESCC) has steadily declined, the incidence rate of distal EAC increased by more than 350% in White males between the 1970s and 1990s.[6] Most of this increased incidence involved tumors at the gastroesophageal junction and gastric cardia and was largely accounted for by increasing prevalence of gastroesophageal reflux disease and obesity.[7,8] In 2020, esophageal and gastric cancer accounted for over 46,000 new cases and 27,180 deaths in the United States.[9] Nearly 40% of patients have metastatic disease at the time of diagnosis, with 5-year overall survival of less than 5%.[9]

MOLECULAR HETEROGENEITY

Despite the obvious differences between ESCC and EAC with regards to histology, anatomic location of the primary tumor, and risk factors, the majority of the landmark clinical trials have enrolled patients with both histologies grouped together. Similarly, the distinction among EAC, AGEJ, and gastric adenocarcinoma has remained imprecise at best. The development and wider availability of cutting-edge technology allowing comprehensive molecular profiling of solid tumors have offered an invaluable insight into biologic differences among various types of esophagogastric cancers. For example, next-generation sequencing-based genomic profiling of 302 tumors, including 71 ESCC and 231 EAC, demonstrated several key molecular differences between ESCC and EAC. Genomic alterations involving *KRAS*, *ERBB2*, and *SMAD4* were more common in EAC, whereas those involving *PIK3CA*,

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PRACTICAL APPLICATIONS

- Squamous cell carcinoma and adenocarcinoma of the esophagus are two distinct disease entities with significant genomic differences. Clinical trials should not group them together, especially with the growing evidence of differential response to checkpoint inhibitors and the unique genomic targets.
- Gastric and gastroesophageal junction adenocarcinomas should be tested for microsatellite instability status, as microsatellite instability–high status correlates with higher response rates and longer duration of responses to checkpoint inhibitors.
- The first-line treatment of metastatic esophageal adenocarcinomas is evolving. The standard of care for patients with HER2-positive disease is trastuzumab in combination with chemotherapy. Chemotherapy has been the standard of care in HER2-negative patients, but recent data suggest benefit with the addition of checkpoint inhibitors to chemotherapy. The combination is not U.S. Food and Drug Administration approved yet, and it remains to be seen whether this will be approved in both squamous and adenocarcinomas and what the PD-L1 cutoff will be for that approval.
- Second-line treatment options remain limited, with trastuzumab deruxtecan as an active agent for patients with HER2-positive disease progressing on trastuzumab-based therapies. For patients with HER2-negative disease, paclitaxel with or without ramucirumab remains standard of care.
- Reducing toxicities of chemotherapy and development of biomarker-driven treatment strategies should continue to be the main goals of clinical trials.

PTEN, *NOTCH1*, *RB1*, *SOX2*, and *NFE2L2* were common in ESCC.[10] Similarly, another study evaluating the molecular profile of 164 tumors demonstrated that ESCC resembled squamous cell carcinoma of other organs, such as head and neck, more than it did EAC, whereas EAC strongly resembled the chromosomally unstable variant of gastric adenocarcinoma.[11] Accumulating evidence suggests that AGEJ also consists of a molecularly heterogeneous group of tumors. A study evaluating genomic, transcriptomic, and proteomic characteristics of AGEJ samples from The Cancer Genome Atlas cohort and Seoul National University cohort identified two molecularly distinct subgroups: the EAC-like group, with a significantly higher copy number amplification and increased protein expression of ERBB2 and EGFR; and the gastric adenocarcinoma located at the fundus or body of the stomach–like group, with significantly activated phosphoinositide 3-kinase–AKT signaling with decreased expression of ERBB2.[12] Finally, comprehensive molecular analysis of primary gastric adenocarcinoma tumors from The Cancer Genome Atlas has suggested four distinct molecular subtypes, including tumors positive for Epstein-Barr virus, with recurrent PIK3CA mutations, extreme DNA hypermethylation, and amplification of JAK2, PD-L1, and PD-L2; microsatellite unstable tumors, with elevated mutation rates; gnomically stable tumors, with mutations or fusions involving RHO family GTPase-activating proteins; and tumors with chromosomal instability, with marked aneuploidy and focal amplification of receptor tyrosine kinases.[13] Interestingly, the proportion of microsatellite instability–high (MSI-H) tumors increases with more distal location of the primary tumor within the upper gastrointestinal tract.[14]

WHERE TO START?

Clinical trials conducted between the late 1980s and early 2000s established that treatment with chemotherapy improved overall survival of patients with metastatic esophagogastric cancer compared with best supportive care and that combination chemotherapy regimens, mostly including 5-fluorouracil and a platinum, were superior to single-agent chemotherapy.[15-21] Subsequently, addition of a third drug in the form of an anthracycline was shown to improve response rates but did not improve overall survival in advanced AGEJ and gastric adenocarcinoma, and randomized trials confirmed noninferiority of capecitabine and oxaliplatin–containing regimen (epirubicin, oxaliplatin, and capecitabine) compared with 5-fluorouracil and cisplatin–based regimens (epirubicin, cisplatin, and 5-fluorouracil).[22-24] Finally, in a randomized phase II trial, 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) had comparable efficacy and better tolerability compared with epirubicin, cisplatin, and 5-fluorouracil, and addition of cetuximab to either regimen failed to show improvement in efficacy.[25] The majority of these early trials either combined ESCC and EAC under the umbrella term of "esophageal cancer" or grouped EAC, AGEJ, and gastric adenocarcinoma as "esophagogastric cancer." Based on these data, combination chemotherapy containing fluoropyrimidine and platinum became a standard of care first-line treatment of patients with metastatic esophagogastric cancer, regardless of the histology. Despite the overall response rate (ORR) ranging from 35% to 45%, median overall survival on these trials ranged from approximately 9 to 11 months, clearly indicating the need for development of novel treatment strategies.

The expanding understanding of the molecular differences between ESCC and EAC and those between different

subtypes of AGEJ and gastric adenocarcinoma has marked the beginning of the era of precision medicine for patients with metastatic esophagogastric cancer. In the recent years, the treatment of metastatic esophagogastric cancer has started to diverge based on the histology, immune phenotype, and applicability of targeted therapies.

The first and best-known targetable genomic alteration identified in patients with esophagogastric adenocarcinoma is HER2 amplification. HER2 is amplified and/or overexpressed in 7% to 34% of esophagogastric adenocarcinomas, being more common in AGEJ compared with gastric adenocarcinoma.[26-28] A randomized phase III trial (ToGA) evaluated efficacy and safety of combining trastuzumab, a monoclonal antibody targeting HER2, with chemotherapy (cisplatin plus capecitabine or 5-fluorouracil) compared with chemotherapy alone for first-line treatment of patients with HER2-positive advanced gastric adenocarcinoma or AGEJ.[26] HER2 positivity was defined as either 3+ staining on immunohistochemistry or fluorescence in situ hybridization positivity (HER2/CEP17 ratio 2 or higher).[29] Overall, 22% of screened patients were found to have HER2-positive disease. Compared with chemotherapy alone, addition of trastuzumab to chemotherapy resulted in higher ORR (47% vs. 35%; p = .0017), longer progression-free survival (median, 6.7 vs. 5.5 months; hazard ratio [HR], 0.71; 95% CI, 0.59–0.85; p = .0002), and longer overall survival (median, 13.8 vs. 11.1 months; HR, 0.74; 95% CI, 0.60–0.91; p = .0046). The rate of all-grade and grade 3 to 4 adverse events was similar between the two groups. Cardiac adverse events were rare, with no difference between the two arms.[26] Based on these results, the combination of trastuzumab with chemotherapy became the standard of care first-line treatment of patients with HER2-positive metastatic AGEJ or gastric adenocarcinoma and was approved by the U.S. Food and Drug Administration in 2010. In a similar randomized phase III trial (TRIO-013/LOGiC), lapatinib, a small-molecule inhibitor of HER2, in combination with chemotherapy failed to show statistically noteworthy overall survival benefit compared with chemotherapy alone in patients with HER2-amplified gastroesophageal adenocarcinoma.[30] Furthermore, addition of pertuzumab to trastuzumab and chemotherapy did not show an improvement in overall survival compared with trastuzumab and chemotherapy in this patient population.[31] Therefore, trastuzumab remains the only HER2-targeted agent with proven efficacy in the first-line setting at this time. Assessment of left ventricular ejection fraction at baseline and periodically during treatment with trastuzumab is recommended. Patients who develop clinically significant decline in left ventricular ejection fraction should discontinue trastuzumab. Considering variability in practice patterns across the globe with regards to preferred first-line chemotherapy regimens, these data are sometimes extrapolated to different chemotherapy backbones, such as FOLFOX or capecitabine plus oxaliplatin. Although patient selection for HER2-directed therapy is largely informed by the criteria used in the ToGA trial, currently available data suggest that HER2/CEP17 ratio of greater than 3.69 and HER2 gene copy number of higher than 7.75 predict better outcomes in patients with HER2 immunohistochemistry 2+ or less.[32] These cutoffs are higher than the traditional fluorescence in situ hybridization positivity threshold.

In recent years, there has been a growing interest in exploring synergy between HER2-targeted therapy and immune checkpoint inhibition because of data suggesting augmented HER2-specific immunity during treatment with trastuzumab.[33,34] Combination of trastuzumab with PD-1 inhibitor pembrolizumab has shown remarkable activity in previously untreated HER2-positive advanced esophagogastric cancer with an ORR of 91% and median overall survival of 27.3 months.[35] The ongoing phase III KEYNOTE-811 trial (NCT03615326) is evaluating the combination of pembrolizumab with trastuzumab and chemotherapy for first-line treatment of HER2-positive metastatic esophagogastric cancer.

For patients with HER2-negative tumors, the standard of care first-line therapy paradigm is shifting. Two recently presented phase III trials have introduced the role of immune checkpoint inhibitors in combination with chemotherapy as a frontline treatment option for these patients. Pembrolizumab was approved by the U.S. Food and Drug Administration in 2017 for third-line and beyond treatment of PD-L1–positive esophagogastric cancer, based on results of the phase II KEYNOTE-059 trial showing an ORR of 16.4% with pembrolizumab among patients receiving third-line therapy, including 22.7% in PD-L1–positive tumors and 8.6% in PD-L1–negative tumors. Median duration of response was 8.1 months in the PD-L1–positive group. PD-L1 positivity was defined as combined positive score (CPS) of 1 or higher as determined by 22C3 pharmDx immunohistochemistry.[36] In 2019, pembrolizumab was approved for second-line and beyond treatment of advanced ESCC with PD-L1 CPS of 10 or higher based on a randomized phase III trial (KEYNOTE-181) comparing pembrolizumab with investigator-choice chemotherapy (paclitaxel, docetaxel, or irinotecan) as second-line treatment of patients with advanced ESCC and EAC, which showed longer overall survival with pembrolizumab in patients with CPS 10 or higher (median, 9.3 vs. 6.7 months; HR, 0.69; 95% CI, 0.52–0.93; p = .0074) and ESCC (median, 8.2 vs. 7.1 months; HR, 0.78; 95% CI, 0.63–0.96; p = .0095). Of note, the overall survival was not different between the two groups in the overall patient population, including EAC. Additionally, the comparator arm did not include paclitaxel plus ramucirumab, which is the standard second-line

treatment option for advanced EAC.[37] Therefore, pembrolizumab remained a third-line option for EAC.

Building up on these data showing modest efficacy of immune checkpoint inhibition in later line settings and the success of combining immune checkpoint inhibition with chemotherapy in other tumor types, such as non–small cell lung cancer, a randomized phase III trial (KEYNOTE-590) evaluated the efficacy and safety of combining pembrolizumab with cisplatin and 5-fluorouracil as first-line treatment of patients with advanced gastroesophageal cancer. In this trial, 749 treatment-naive patients with advanced EAC, ESCC, or Siewert type I AGEJ were randomly assigned to receive either pembrolizumab plus chemotherapy or placebo plus chemotherapy for up to six cycles, followed by maintenance pembrolizumab plus 5-fluorouracil or placebo plus 5-fluorouracil for up to 35 cycles. Although the majority of patients had ESCC (73.5%), this was the first randomized phase III trial in esophagogastric cancer that stratified patients based on histology. Nearly 50% of patients had PD-L1 CPS of 10 or higher. At preplanned interim analysis and median follow-up of 10.8 months, pembrolizumab plus chemotherapy, compared with chemotherapy alone, was associated with higher ORR (45% vs. 29.3%; $p < .001$) and longer overall survival (median, 12.4 vs. 9.8 months; HR, 0.73; 95% CI, 0.62–0.86; $p < .001$).[38] Although the benefit was seen across most of the subgroups including patients with ESCC, ESCC with PD-L1 CPS of 10 or higher, and all patients with PD-L1 CPS of 10 or higher, the HR for overall survival in patients with adenocarcinoma and those with PD-L1 CPS of less than 10 was associated with a wider confidence interval and did not reach statistical significance. Although this could be partly because of the relatively small number of patients in these subgroups, the data are consistent with KEYNOTE-181 in which most of the benefit of immune checkpoint inhibition was observed among patients with ESCC and those with PD-L1 CPS of 10 or greater. Treatment-related adverse events and immune-mediated adverse events were consistent with what is previously reported in similar trials.[39,40] The final analysis and longer-term follow-up of KEYNOTE-590 results are eagerly awaited. In the meantime, the U.S. Food and Drug Administration has granted a priority review to pembrolizumab plus chemotherapy as first-line treatment of advanced esophageal and gastroesophageal junction cancer. As noted above, chemotherapy backbones other than cisplatin and 5-fluorouracil are commonly used as first-line treatment of metastatic esophagogastric cancers, and it remains to be determined whether the data from KEYNOTE-590 can be extrapolated to a combination of pembrolizumab with other chemotherapy regimens.

Another randomized phase III trial (CheckMate 649) presented at the European Society for Medical Oncology Virtual Congress in 2020 addressed the same question. This trial was based on two prior studies showing activity of nivolumab in advanced esophagogastric cancer.[41,42] CheckMate 649 trial randomly assigned patients with previously untreated, HER2-negative, advanced EAC, AGEJ, or gastric adenocarcinoma to receive either nivolumab plus ipilimumab, nivolumab plus chemotherapy (capecitabine plus oxaliplatin or FOLFOX), or chemotherapy alone until disease progression or unacceptable toxicity. Nivolumab was given for a maximum of 2 years. The primary endpoints of the study were overall survival and progression-free survival in patients with PD-L1 CPS 5 or higher determined by PD-L1 immunohistochemistry 28-8 pharmDx assay. Nearly 70% of patients had gastric adenocarcinoma. Of note, 4% of patients who received nivolumab plus chemotherapy had MSI-H disease. At data cutoff with minimum follow-up of 12.1 months, nivolumab plus chemotherapy was found to be superior to chemotherapy in patients with PD-L1 CPS 5 or greater, with higher ORR (60% vs. 45%) and longer overall survival (median, 14.4 vs. 11.1 months; HR, 0.71; 95% CI, 0.59–0.86; $p < .0001$). The toxicity profile of the combination was similar to previous studies combining immunotherapy with chemotherapy.[43] The U.S. Food and Drug Administration has granted a priority review to nivolumab plus chemotherapy as first-line treatment of patients with advanced gastroesophageal adenocarcinoma.

Although both KEYNOTE-590 and CheckMate 649 compared chemoimmunotherapy with chemotherapy as a first-line treatment, there are a few key differences and similarities. First, the majority of patients on KEYNOTE-590 had ESCC, and patients with gastric adenocarcinoma were not included in this trial. In contrast, CheckMate 649 included patients with adenocarcinoma histology only, and the majority had gastric adenocarcinoma. Second, both studies used different immunohistochemistry assays and cutoffs to determine PD-L1 positivity. This is important because the impact of addition of immunotherapy to chemotherapy seemed to be different based on the cutoff of PD-L1 expression. Third, only 25% to 30% of patients on both studies had EAC or AGEJ. In a subset analysis, these patients seemed to derive less benefit from the addition of immunotherapy to chemotherapy compared with ESCC in KEYNOTE-590 and with gastric adenocarcinoma in CheckMate 649. Third, the chemotherapy arm in KEYNOTE-590 seemed to have underperformed compared with historical data from first-line trials. In contrast, the outcomes of the chemotherapy arm in CheckMate 649 were consistent with prior studies. Finally, the improvement in median overall survival in both trials was modest compared with what is seen with chemoimmunotherapy in other disease types, such as non–small cell lung cancer. Regardless, these trials do establish the role of chemoimmunotherapy as first-line treatment of patients with PD-L1–positive, HER2-negative,

advanced gastroesophageal cancer, and these regimens are now added to the NCCN guidelines.

In addition to PD-L1 expression, mismatch repair deficiency or MSI-H is an important consideration in determining the patient population that is likely to benefit from an immunotherapy-based regimen. The subset analysis of CheckMate 649 showed that among the 34 patients with mismatch repair deficiency/MSI-H tumors, median overall survival was not reached for those treated with chemoimmunotherapy versus 8.8 months with chemotherapy alone (HR for death, 0.33).[43] Similar results were observed in the randomized phase III KEYNOTE-062 trial. In this trial, patients with previously untreated advanced gastric adenocarcinoma or AGEJ were randomly assigned to receive pembrolizumab, pembrolizumab plus chemotherapy, or chemotherapy plus placebo. Although the overall analysis showed that pembrolizumab-based therapy was not superior to chemotherapy, the subset analysis demonstrated higher ORR and longer median overall survival with the immunotherapy-based regimen in patients with MSI-H tumors in the PD-L1 CPS 1 or higher cohort.[44] Recently reported data from the KEYNOTE-177 trial showing longer progression-free survival with pembrolizumab compared with chemotherapy as first-line treatment of MSI-H/mismatch repair deficiency advanced colon cancer provide further evidence to support the use of pembrolizumab in this biomarker-selected patient population.[45] Finally, KEYNOTE-158, a phase II trial of pembrolizumab in previously treated mismatch repair deficiency/MSI-H advanced noncolorectal cancer, which included 24 patients with gastric adenocarcinoma, showed an ORR of 34.3% and median overall survival of 23.5 months with pembrolizumab.[46] Altogether, these data show checkpoint inhibitors have considerable activity in mismatch repair deficiency/MSI-H esophagogastric cancer.

As new biomarker-driven treatment strategies continue to emerge, it is now recommended that molecular profiling be performed for every patient with newly diagnosed metastatic esophagogastric cancer. This should include analysis of HER2, PD-L1, and MSI status at the very least. However, with the accelerating pace of development of targeted therapies and availability of clinical trials, comprehensive molecular profiling at the time of diagnosis may be a reasonable approach to guide treatment.

WHAT TO DO NEXT?

HER2-Positive Disease

The optimum second-line and beyond treatment option for patients with HER2-positive disease who progress on first-line trastuzumab and chemotherapy combination is not well established. The most promising results have been reported with trastuzumab deruxtecan, an antibody-drug conjugate consisting of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor payload. In an open-label randomized phase II trial (DESTINY-Gastric01), 187 patients with advanced HER2-positive gastric adenocarcinoma or AGEJ with disease progression after at least two prior lines of therapy, including trastuzumab, were randomly assigned to receive trastuzumab deruxtecan or physician's choice of chemotherapy.[47] Documentation of HER2 positivity was required at the time of enrollment. Trastuzumab deruxtecan was associated with a higher ORR (51% vs. 14%; $p < .001$), longer progression-free survival (median, 5.6 vs. 3.5 months; HR, 0.47; 95% CI, 0.31–0.71), and longer overall survival (median, 12.5 vs. 8.4 months; HR, 0.59; 95% CI, 0.39–0.88, $p = .01$). Notable toxicities were cytopenia, including 38% grade 3 to 4 neutropenia, and 10% drug-related interstitial lung disease or pneumonitis. Trastuzumab deruxtecan is now approved by the U.S. Food and Drug Administration for treatment of patients with locally advanced or metastatic HER2-positive gastric adenocarcinoma or AGEJ who have received a prior trastuzumab-based therapy. The recommended dose for this indication is 6.4 mg/kg every 3 weeks, which is higher than the dose for HER2-positive breast cancer. Monitoring of complete blood count and close clinical monitoring for development of new respiratory symptoms is recommended during treatment with trastuzumab deruxtecan. Patients with clinically significant lung disease, including pneumonitis and pulmonary fibrosis, were excluded from the trial and may not be ideal candidates to receive trastuzumab deruxtecan.

Another antibody-drug conjugate, ado-trastuzumab emtansine, consisting of trastuzumab, a thioether linker, and a microtubule inhibitor payload, failed to show overall survival benefit compared with taxane-based chemotherapy in patients with previously treated HER2-positive advanced gastric adenocarcinoma or AGEJ.[48] Nearly 80% of patients in this study had received prior trastuzumab. Similarly, lapatinib, either as a single agent or in combination with chemotherapy, has failed to show convincing evidence of superiority over chemotherapy in second-line and beyond settings.[49,50] The question of continuation of trastuzumab after disease progression after a prior trastuzumab-containing regimen, largely derived by the literature in HER2-positive breast cancer, was addressed by a randomized phase II trial (T-ACT study) in which 91 patients with disease refractory to trastuzumab plus fluoropyrimidine and platinum-based chemotherapy were randomly assigned to receive either trastuzumab plus paclitaxel or paclitaxel alone.[51] The ORR, median progression-free survival, and median overall survival were not different between the two arms. A possible explanation for these results is loss of HER2 positivity following first-line therapy. On exploratory analysis of the T-ACT study, HER2 positivity was lost after first-line therapy in 11 (69%) out of 16 patients whose tumor tissues were available, and circulating HER2

DNA amplification was detected in 41 (60%) out of 68 patients.

Putting these data in clinical context, trastuzumab deruxtecan is a reasonable option for second-line treatment of patients with HER2-positive disease who progress on trastuzumab-based therapy. Third-line and beyond treatment options for this patient population are not well established. Trastuzumab combined with single-agent chemotherapy is sometimes used in this setting, but this approach is not data driven, and confirmation of HER2 positivity is strongly recommended prior to considering it. Treatment regimens used for patients with HER2-negative disease (as discussed in the next section) are reasonable treatment options in this setting.

HER2-Negative Disease, Previously Treated With Immunotherapy

At least five randomized trials and a pooled analysis have established the survival benefit of systemic therapy, including ramucirumab, a monoclonal antibody targeting VEGFR-2 plus paclitaxel, single-agent ramucirumab, docetaxel, and irinotecan, for patients with previously treated advanced esophagogastric cancer when compared with best supportive care.[52-57] The choice of regimen largely depends on patient-related factors, including performance status, coexisting comorbidities, and patient preferences; disease-related factors, such as molecular characteristics and histology; and the type of prior therapy, duration of benefit from prior therapy, and presence of persistent side effects from prior regimen. For example, patients with persistent severe peripheral neuropathy from first-line oxaliplatin-based regimens may not be able to receive subsequent therapy with a taxane. Similarly, ramucirumab-based regimens are indicated in adenocarcinoma alone and may not be safe for patients with recent history of substantial gastrointestinal bleeding. In general, enrollment in a clinical trial is always preferred whenever possible.

In the absence of an option of enrollment in a clinical trial, ramucirumab plus paclitaxel is the preferred second-line treatment option for patients with HER2-negative advanced esophagogastric adenocarcinoma who have either previously received chemoimmunotherapy or are ineligible to receive immunotherapy, based on results of the randomized phase III RAINBOW trial. In this trial, 665 patients with advanced gastric adenocarcinoma or AGEJ who had disease progression at or within 4 months after first-line chemotherapy were randomly assigned to receive either ramucirumab plus paclitaxel or placebo plus paclitaxel. Ramucirumab plus paclitaxel resulted in longer median overall survival (9.6 vs. 7.4 months; HR, 0.807; 95% CI, 0.678–0.962; p = .017) and higher ORR (28% vs. 16%; p = .0001) compared with paclitaxel plus placebo. Grade 3 or higher adverse events were more frequent in the ramucirumab arm, including neutropenia, hypertension, and fatigue.[52] Within the caveat of cross-trial comparison, ramucirumab and paclitaxel combination has shown superior ORR and median overall survival compared with placebo-controlled trials evaluating single-agent ramucirumab, docetaxel, and irinotecan.[53-56] Therefore, it is a preferable regimen if there are no contraindications. With regards to single-agent chemotherapy, there are no data to suggest superiority of one over the other. For example, two clinical trials comparing second-line irinotecan with paclitaxel showed no statistically noteworthy difference between the two.[58,59] Another study showed no difference between irinotecan and docetaxel.[56] These agents can be sequenced based on prior treatment history and toxicity profile. Trifluridine/tipiracil, an oral cytotoxic chemotherapy consisting of a thymidine-based nucleoside analog, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil, is another U.S. Food and Drug Administration–approved option for third-line and beyond treatment of advanced esophagogastric adenocarcinoma based on a randomized phase III trial (TAGS)[60] showing improvement in overall survival with trifluridine/tipiracil compared with placebo (median, 5.7 vs. 3.6 months; HR, 0.69; 95% CI, 0.56–0.85; p = .00058). Grade 3 or worse adverse events of any cause occurred in 80% of patients in the trifluridine/tipiracil group, with neutropenia (34%) and anemia (19%) being most frequent.

With ramucirumab-based therapy being an option for adenocarcinoma only, treatment options for second-line therapy of patients with advanced ESCC who are either ineligible to receive immunotherapy or received immunotherapy as a part of first-line treatment include chemotherapy agents not used in the first-line regimen.

HER2-Negative Disease, Immunotherapy Naive

For patients with advanced esophagogastric cancer with mismatch repair deficiency/MSI-H tumors who did not receive immunotherapy as a part of their frontline treatment, single-agent pembrolizumab is a reasonable second- and later line treatment option based on data from KEYNOTE-158 and KEYNOTE-062 as discussed previously.[44,46] Second-line U.S. Food and Drug Administration–approved treatment options for immunotherapy-naive patients with advanced ESCC include pembrolizumab (for PD-L1 CPS 10 or higher) and nivolumab (irrespective of PD-L1 expression).[37,61] The U.S. Food and Drug Administration approval of nivolumab in this setting was based on the randomized phase III ATTRACTION-3 trial showing superior overall survival with nivolumab compared with investigator's choice of taxane in patients who had received at least one prior line of chemotherapy. Approximately 50% of patients had PD-L1 expression of less than 1%.[61]

Second-line treatment options for immunotherapy-naive patients with gastroesophageal adenocarcinoma are still ramucirumab plus paclitaxel or single-agent taxane or irinotecan if there is a contraindication to ramucirumab. The only immune checkpoint inhibitor approved in the United States for treatment of gastroesophageal adenocarcinoma is pembrolizumab for patients with PD-L1 CPS 1 or higher after failure of two separate chemotherapy regimens based on data from the KEYNOTE-059 trial.[36]

Tumor mutational burden is one of the predictive biomarkers of activity of immunotherapy. Approximately 2.4% of esophageal cancers and 5% to 19% of gastric cancers harbor high tumor mutational burden, using 20 or more mutations per megabase as the cutoff.[62,63] Based on results of a randomized phase II trial (KEYNOTE-158), pembrolizumab is approved for treatment of patients with unresectable or metastatic tumor mutational burden–high solid tumors that have progressed following prior treatment.[64] Tumor types included in this study were anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small cell lung, thyroid, and vulvar cancer. Although these data open a new treatment option for a variety of solid tumors, the study did not include patients with gastroesophageal cancer. Additionally, the tumor mutational burden cutoff used in this study was largely validated in non–small cell lung cancer and urothelial cancer cohorts, and it is unclear if the same threshold is applicable to other tumor types. Finally, the tumor mutational burden was assessed using FoundationOne CDx, and correlation of results with tumor mutational burden analyzed through other platforms remains speculative. Therefore, we do not recommend single-agent pembrolizumab in patients with high tumor mutational burden if the PD-L1 expression is negative.

Table 1 summarizes the results of landmark clinical trials in metastatic esophagogastric cancer. The preferred treatment algorithm for these patients is outlined in Fig. 1.

CHALLENGES AND FUTURE DIRECTIONS

Although the introduction of immunotherapy in the frontline setting and a building of momentum in the field of HER2-positive disease are exciting, the incremental benefit offered by addition of a PD-1 inhibitor to first-line chemotherapy is relatively small. This can be partly explained by lack of a well-defined cutoff for PD-L1 expression and other biomarkers of response to immunotherapy in esophagogastric cancer to guide optimum patient selection. However, accumulating evidence suggests that esophagogastric cancer, especially adenocarcinoma, is associated with a immunosuppressive tumor microenvironment, and the tumors are either inherently resistant or quickly acquire resistance to PD-1 inhibition. The putative mechanisms include decreased level of interferon gamma and granzyme B and high expression of immune-suppressive factors, such as cyclooxygenase-2, vascular endothelial growth factor, and interleukin-8 in the tumor microenvironment; interleukin-6–driven epithelial-to-mesenchymal transition; IDO1 expression; and abundance of cancer-associated fibroblasts and tumor-associated macrophages in the tumor microenvironment.[65-69] Therefore, treatment strategies beyond PD-1/PD-L1 inhibitors are needed.

Armed with this information and accumulating genomic, transcriptomic, and proteomic data from deep sequencing of tumors, further efforts to improve treatment strategies for esophagogastric cancer should pivot around several broad aspects. First, attempts to improve the efficacy of immunotherapy through combination approaches should be undertaken. Several ongoing clinical trials are evaluating the combination of PD-1 or PD-L1 inhibition in combination with TIGIT (T cell immunoreceptor with immunoglobulin and ITIM domains). The results of the nivolumab and ipilimumab arm of the CheckMate 649 trial are still pending and would shed light on whether combination immune checkpoint inhibition can replace traditional chemotherapy-based regimens in a biomarker-selected patient population. Combination of immune checkpoint inhibition with vascular endothelial growth factor–directed therapy is another interesting avenue that has shown promising results in renal cell cancer and hepatocellular carcinoma, yet remains to be explored in esophagogastric cancer.[70,71]

Second, development of treatment strategies beyond immunotherapy, including molecularly targeted therapies, is of paramount importance. Several ongoing trials are incorporating novel HER2-targeted treatments, such as tucatinib, and combination of immune checkpoint inhibition as well as chemotherapy with HER2-directed therapy. An ongoing trial is evaluating the efficacy of PARP inhibitor niraparib for the treatment of homologous recombination-deficient or loss of heterozygosity–high gastroesophageal cancer.[72] FGFR2b has emerged as another exciting therapeutic target in esophagogastric cancer.[73] The expanding spectrum of biomarker-driven treatment options further emphasizes the importance of obtaining comprehensive molecular profiling for every patient with esophagogastric cancer. Additionally, the role of circulating tumor DNA or blood-based biomarkers in patient selection for treatment and follow-up is gradually unfolding.[74] Table 2 summarizes notable ongoing clinical trials.

Third, advancement of treatment strategies for curable, nonmetastatic, esophagogastric cancer by leveraging the advances in the metastatic setting is of prime necessity. Recently reported results of phase II and III trials have shown the role of immune checkpoint inhibition following trimodality therapy in a select subset of patients with locally

TABLE 1. Landmark Clinical Trials in Metastatic Esophagogastric Cancer

Trial	Phase	Regimen	Distribution According to Histology and Anatomic Location	Results
HER2 Positive, First Line				
ToGA[26]	III	Trastuzumab plus chemotherapy vs. chemotherapy	80% GA and 20% AGEJ	Trastuzumab and chemotherapy improved ORR, PFS, and OS compared with chemotherapy alone.
TRIO-013/LOGiC[30]	III	Lapatinib plus CapeOX vs. placebo plus CapeOx	86% GA, 9% AGEJ, and 5% EAC	Lapatinib combination was associated with superior ORR and PFS, but OS improvement was not statistically remarkable.
JACOB[31]	III	Trastuzumab plus chemotherapy plus pertuzumab vs. trastuzumab plus chemotherapy plus placebo	72% GA and 28% AGEJ	Addition of pertuzumab did not improve OS and was associated with more frequent grade 3 to 5 adverse events.
HER2 Positive, Second Line and Beyond				
DESTINY-Gastric01[47]	Randomized phase II	Trastuzumab deruxtecan vs. investigator's choice of chemotherapy	86% GA and 14% AGEJ	ORR and OS were superior in trastuzumab deruxtecan arm. All patients had received prior trastuzumab; 47% of patients received $\geq$ three prior lines of therapy.
GATSBY[48]	II/III	T-DM1 vs. investigator's choice of taxane (docetaxel or paclitaxel)	72% GA and 28% AGEJ	No difference in OS between the two arms. T-DM1 was associated with lower incidence of grade 3 or worse adverse events. Seventy-nine percent of patients had received prior trastuzumab.
TyTAN[49]	III	Lapatinib plus paclitaxel vs. paclitaxel	Approximately 100% GA	ORR was better with lapatinib plus paclitaxel, but OS and PFS were not different between the two arms. Only 6% of patients received prior trastuzumab.
HER2 Negative, First Line				
KEYNOTE-590[38]	III	Pembrolizumab plus chemotherapy vs. chemotherapy	73.5% ESCC, 15.5% EAC, and 11% AGEJ	Pembrolizumab plus chemotherapy improved OS in patients with ESCC, ESCC with PD-L1 CPS of $\geq$ 10, and all patients with PD-L1 CPS of $\geq$ 10 assessed by 22c3 pharmDx IHC.
CheckMate 649[43]	III	Nivolumab plus ipilimumab vs. nivolumab plus chemotherapy vs. chemotherapy	70% GA, 18% AGEJ, and 12% EAC	Compared with chemotherapy alone, nivolumab + chemotherapy improved OS in patients with PD-L1 CPS $\geq$ 5 determined by 28-8 pharmDx IHC. Results of nivolumab plus ipilimumab arm are pending.

(Continued on following page)

TABLE 1. Landmark Clinical Trials in Metastatic Esophagogastric Cancer (Continued)

Trial	Phase	Regimen	Distribution According to Histology and Anatomic Location	Results
HER2 Negative, Second Line and Beyond				
KEYNOTE-181[37]	III	Pembrolizumab vs. investigator's choice of paclitaxel, docetaxel, or irinotecan	63% ESCC and 37% EAC	OS was longer with pembrolizumab vs. chemotherapy for patients with CPS $\geq$ 10 and ESCC. Slightly over one-third of patients had PD-L1 CPS $\geq$ 10. Pembrolizumab was associated with much lower incidence of grade 3 or higher adverse events.
KEYNOTE-059[36]	II	Pembrolizumab following at least two prior lines of therapy	48% GA and 52% AGEJ	ORR 16.4% among patients receiving third-line therapy; 22.7% in patients with PD-L1–positive (CPS $\geq$ 1) tumors; and 8.6% in patients with PD-L1–negative tumors. Median duration of response was 8. 1 months in PD-L1–positive group and 6. 9 months in PD-L1–negative group.
ATTRACTION-3[61]	III	Nivolumab vs. chemotherapy	100% ESCC	OS and toxicity profile favored nivolumab. Half of the patients had PD-L1 expression of $<$ 1%.
RAINBOW[52]	III	Ramucirumab plus paclitaxel vs. placebo plus paclitaxel	80% GA and 20% AGEJ	ORR, disease control rate, and OS favored ramucirumab plus paclitaxel. However, the combination was associated was higher incidence of grade 3 or higher adverse events.
TAGS[60]	III	Trifluridine/tipiracil vs. placebo	71% GA and 29% AGEJ	Total of 40% of patients had received $\geq$ three prior therapies. Trifluridine/tipiracil showed 2-month improvement in mOS. Grade 3 or worse adverse events of any cause occurred in 80% of patients in the trifluridine/tipiracil group.
REGARD[53]	III	Ramucirumab vs. placebo	75% GA and 25% AGEJ	Ramucirumab led to approximately 6 weeks improvement in mOS and higher ORR compared with placebo. Treatment-related adverse events were more frequent with ramucirumab.
COUGAR-02[54]	III	Docetaxel plus active symptom control vs. active symptom control	46% GA, 32% AGEJ, and 22% EAC	Docetaxel was associated with approximately 6 weeks improvement in mOS, higher ORR, and more frequent adverse events.

Abbreviations: GA, gastric adenocarcinoma; AGEJ, adenocarcinoma of gastroesophageal junction; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; CapeOX, capecitabine plus oxaliplatin; EAC, esophageal adenocarcinoma; T-DM1, ado-trastuzumab emtansine; ESCC, esophageal squamous cell carcinoma; CPS, combined positive score; IHC, immunohistochemistry; mOS, median overall survival.

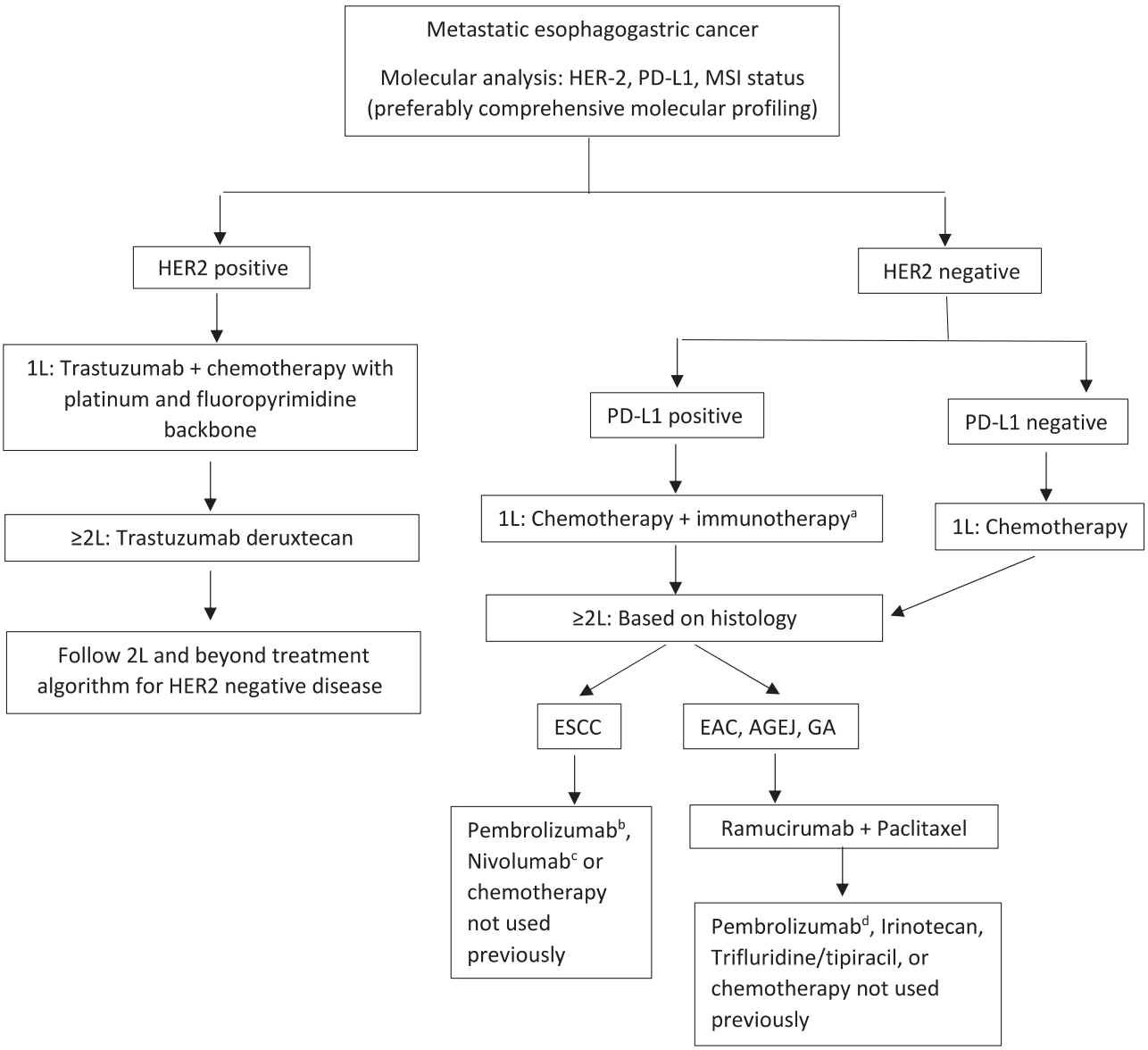

FIGURE 1. Treatment Algorithm for Metastatic Esophagogastric Cancer

Patients with MSI-H tumors should receive pembrolizumab as first-line or second-line treatment, regardless of PD-L1 expression. Enrollment in a clinical trial is always preferable if a suitable trial is available.

Abbreviations: MSI-H, microsatellite instability high; 1L, first line; 2L, second line; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; AGEJ, adenocarcinoma; GA, gastric adenocarcinoma; CPS, combined positive score; 3L, third line.

[a]The combination of immunotherapy with chemotherapy in 1L setting and the PD-L1 cutoff for the indication are awaiting U.S. Food and Drug Administration approval.

[b]Pembrolizumab is approved for 2L and beyond treatment of advanced ESCC with PD-L1 CPS $\geq$ 10, in the absence of prior treatment with an immune checkpoint inhibitor.

[c]Nivolumab is approved for 2L and beyond treatment of advanced ESCC regardless of PD-L1 expression, in the absence of prior treatment with an immune checkpoint inhibitor.

[d]Pembrolizumab is approved for 3L treatment of advanced gastroesophageal adenocarcinoma with PD-L1 CPS $\geq$ 1, in the absence of prior treatment with an immune checkpoint inhibitor.

TABLE 2. Notable Ongoing Clinical Trials in Metastatic Gastroesophageal Cancer

Clinical Trial Identifier	Phase	Trial	Intervention	Comments
NCT03777657	III	Tislelizumab in Combination With Chemotherapy as First-Line Treatment in Adults With Inoperable, Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Carcinoma	Addition of PD-1 inhibitor tislelizumab to first-line chemotherapy backbone	Patients with HER2-positive disease are excluded.
NCT03748134	III	Sintilimab or Placebo With Chemotherapy in Esophageal Squamous Cell Carcinoma (ORIENT-15)	Addition of PD-1 inhibitor sintilimab to first-line chemotherapy backbone	Chemotherapy regimens allowed: cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil
NCT03653507	III	A Study of Zolbetuximab (IMAB362) Plus CapeOX Compared With Placebo Plus CapeOX as First-line Treatment of Subjects With Claudin (CLDN) 18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (GLOW)	Addition of zolbetuximab, a monoclonal antibody against isoform 2 of Claudin-18, to chemotherapy for biomarker selected patients	Expression of CLDN18.2 in 75% or more of tumor cells demonstrating moderate to strong membranous staining as determined by central IHC testing is required.
NCT03615326	III	Pembrolizumab/Placebo Plus Trastuzumab Plus Chemotherapy in Human Epidermal Growth Factor Receptor 2 Positive (HER2+) Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (MK-3475-811/KEYNOTE-811)	Addition of pembrolizumab to first-line HER2-directed therapy plus chemotherapy	Chemotherapy regimens: cisplatin plus 5-fluorouracil, CapeOX, and SOX. HER2 positivity defined as IHC 3+ or IHC 2+ in combination with FISH positive.
NCT04082364	II/III	Combination Margetuximab, INCMGA00012, MGD013, and Chemotherapy Phase 2/3 Trial in HER2+ Gastric/GEJ Cancer (MAHOGANY)	Multiarm study evaluating addition of monoclonal antibody targeting HER2 and PD-1 and bispecific antibody engaging PD-1 and LAG-3 with or without chemotherapy	Patients with known MSI-H status are excluded.
NCT04499924	II/III	Tucatinib, Trastuzumab, Ramucirumab, and Paclitaxel Versus Paclitaxel and Ramucirumab Previously Treated HER2+ Gastroesophageal Cancer (MOUNTAINEER-02)	Multi-arm study evaluating addition of trastuzumab and/or small molecule HER2 inhibitor tucatinib to standard second-line therapy backbone	HER2 amplification detected on a blood-based NGS assay is a part of inclusion criteria.
NCT03929666	II	A Safety and Efficacy Study of ZW25 (Zanidatamab) Plus Combination Chemotherapy in HER2-Expressing Gastroesophageal Adenocarcinoma	Addition of novel bispecific antibody, simultaneously binding two nonoverlapping epitopes of HER2, resulting in dual HER2 signal blockade to first-line chemotherapy backbone	Chemotherapy regimens allowed: cisplatin plus 5-fluorouracil, FOLFOX, and CapeOX
NCT03918499	I/II	IRX-2, Cyclophosphamide, and Pembrolizumab in Treating Participants With Recurrent or Metastatic Gastric or Gastroesophageal Junction Cancer	Addition of allogeneic, human cell–derived IL-2 with multiple active cytokine components (IRX-2) to immunotherapy	Two or more prior lines of therapy required
NCT03281369	Ib/II	A Study of Multiple Immunotherapy-Based Treatment Combinations in Patients With Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Cancer (G/GEJ) or Esophageal Cancer (Morpheus-Gastric and Esophageal Cancer)	Multi-arm study evaluating addition of atezolizumab with or without novel therapeutic agents to standard first- and second-line treatments	Agents used in combination with atezolizumab: cobimetinib, PEGylated recombinant human hyaluronidase (PEGPH20), CXCR4 antagonist BL-8040, dipeptidylpeptidase-4 inhibitor linagliptin, and anti-TIGIT antibody tiragolumab

(Continued on following page)

TABLE 2. Notable Ongoing Clinical Trials in Metastatic Gastroesophageal Cancer (Continued)

Clinical Trial Identifier	Phase	Trial	Intervention	Comments
NCT03995017	I/II	Rucaparib Plus Ramucirumab With or Without Nivolumab in Advanced Gastric and Esophageal Adenocarcinoma (RiME)	Addition of PARP inhibitor to VEGF inhibitor and nivolumab in biomarker selected patients	Up to two prior lines of therapy allowed. Half of the study population in phase II must have a deleterious tumor alteration in at least one protocol specified DNA repair gene
NCT03840967	II	A Study Evaluating Safety and Efficacy of Niraparib in Patients With Previously Treated Metastatic Esophageal/Gastroesophageal Junction/Proximal Gastric Adenocarcinoma	Single-agent PARP inhibitor in DNA repair deficient esophagogastric cancer	One prior line of chemotherapy allowed. Patients must not have progressed during first 2 months of prior platinum-containing regimen.
NCT04363801	II	A Study of DKN-01 in Combination With Tislelizumab ± Chemotherapy as Patients With Gastric or Gastroesophageal Cancer (DisTinGuish)	Addition of monoclonal antibody targeting the Dickkopf-1 (DKK1) protein in combination with PD-1 inhibitor with or without chemotherapy in biomarker selected patients	Patients with HER2-positive disease are excluded. Treatment-naive and patients with one prior treatment are eligible.

Abbreviations: CapeOX, capecitabine plus oxaliplatin; IHC, immunohistochemistry; SOX, S1 plus oxaliplatin; FISH, fluorescent in situ hybridization; MSI-H, microsatellite instability high; NGS, next-generation sequencing; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; IL-2, interleukin-2; PEG, polyethylene glycol; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domains; VEGF, vascular endothelial growth factor.

advanced esophageal adenocarinoma and AGEJ.[75,76] Several clinical trials are evaluating the role of immune checkpoint inhibitor and HER2-directed therapy as a part of neoadjuvant or adjuvant treatment in patients with resectable disease. These strategies are likely to improve the cure rate of patients who are diagnosed in the nonmetastatic stage; however, this will make it challenging to interpret and apply the recently emerged frontline chemoimmunotherapy data in the metastatic setting and may limit treatment options if these patients in fact go on to develop metastatic disease.

Fourth, the design of clinical trials should move away from combining ESCC and EAC without predefined stratification because they are biologically distinct diseases. Similarly, whether AGEJ tumors are combined with distal EAC or gastric tumors should be determined based on molecular characteristics.

Finally, efforts should be made to reduce morbidity associated with treatment. Most of the agents used in the treatment of esophagogastric cancer, including oxaliplatin, taxane, and ramucirumab, are associated with considerable burden of toxicity. More research is needed in the area of developing biomarkers to predict toxicity and approaches to tailor treatment regimens for high-risk patients.

CONCLUSION

The treatment of metastatic esophagogastric cancer has evolved and diverged in the recent years owing to the advancing grasp of the biology and molecular characteristics of the disease. Immunotherapy is now moving to the frontline treatment of patients with metastatic ESCC, EAC, AGEJ, and gastric adenocarcinoma with modest improvement in overall survival. Chemotherapy in combination with trastuzumab is a standard of care first-line regimen for patients with HER2-positive disease. The preferred second-line treatment option for patients with adenocarcinoma who have received immunotherapy in the first-line setting is ramucirumab plus paclitaxel, whereas chemotherapy not used in prior lines is an option for patients with squamous cell carcinoma. Trastuzumab deruxtecan is approved for patients with HER2-positive disease following progression on trastuzumab-based therapy. Pembrolizumab is a good option for patients with mismatch repair deficiency/MSI-H disease, regardless of PD-L1 expression. Although the incorporation of immunotherapy and molecularly targeted therapies may not have shown dramatic improvement in overall survival, the strides made in this field have certainly created a foundation for the development of precision medicine–driven treatment approaches for the disease in which chemotherapy has remained a standard treatment for over 4 decades. Development of new, well-designed, biomarker-selected clinical trials and robust patient enrollment will be the key to build on the early success we have witnessed in the past 2 years.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Global Cancer Observatory; International Agency for Research on Cancer; World Health Organization. Estimated age-standardized mortality rates (World) in 2020, worldwide, both sexes, all ages. https://gco.iarc.fr/today/online-analysis-multi-bars?v=2020&mode=cancer&mode_population=countries&population=900&populations=900&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=10&group_cancer=1&include_nmsc=1&include_nmsc_other=1&type_multiple=%257B%2522inc%2522%253Afalse%252C%2522mort%2522%253Atrue%252C%2522prev%2522%253Afalse%257D&orientation=horizontal&type_sort=0&type_nb_items=%257B%2522top%2522%253Atrue%252C%2522bottom%2522%253Afalse%257D. Accessed January 29, 2021.
2. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7-33.
3. Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. N Engl J Med. 2020;383:640-649.
4. Hur C, Miller M, Kong CY, et al. Trends in esophageal adenocarcinoma incidence and mortality. Cancer. 2013;119:1149-1158.
5. Derakhshan MH, Arnold M, Brewster DH, et al. Worldwide inverse association between gastric cancer and esophageal adenocarcinoma suggesting a common environmental factor exerting opposing effects. Am J Gastroenterol. 2016;111:228-239.
6. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer. 1998;83:2049-2053.

7. Pohl H, Wrobel K, Bojarski C, et al. Risk factors in the development of esophageal adenocarcinoma. Am J Gastroenterol. 2013;108:200-207.
8. Thrift AP. The epidemic of oesophageal carcinoma: where are we now? Cancer Epidemiol. 2016;41:88-95.
9. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Esophageal and Stomach Cancer. https://seer.cancer.gov/statfacts/html/esoph.html and https://seer.cancer.gov/statfacts/html/stomach.html. Accessed January 29, 2021.
10. Wang K, Johnson A, Ali SM, et al. Comprehensive genomic profiling of advanced esophageal squamous cell carcinomas and esophageal adenocarcinomas reveals similarities and differences. Oncologist. 2015;20:1132-1139.
11. Cancer Genome Atlas Research Network; Analysis Working Group: Asan University; BC Cancer Agency. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017;541:169-175.
12. Suh YS, Na D, Lee JS, et al. Comprehensive molecular characterization of adenocarcinoma of the gastroesophageal junction between esophageal and gastric adenocarcinomas. Ann Surg. Epub 2020 Oct 19.
13. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202-209.
14. Liu Y, Sethi NS, Hinoue T, et al; Cancer Genome Atlas Research Network. Comparative molecular analysis of gastrointestinal adenocarcinomas. Cancer Cell. 2018;33:721-735.e8.
15. Janmaat VT, Steyerberg EW, van der Gaast A, et al. Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer. Cochrane Database Syst Rev. 2017;11:CD004063.
16. Wagner AD, Grothe W, Haerting J, et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol. 2006;24:2903-2909.
17. Wagner AD, Syn NL, Moehler M, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev. 2017;8:CD004064.
18. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol. 1997;15:261-267.
19. Ilson DH, Ajani J, Bhalla K, et al. Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol. 1998;16:1826-1834.
20. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol. 2002;20:1996-2004.
21. Bleiberg H, Conroy T, Paillot B, et al. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer. 1997;33:1216-1220.
22. Cunningham D, Starling N, Rao S, et al; Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358:36-46.
23. Findlay M, Cunningham D, Norman A, et al. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). Ann Oncol. 1994;5:609-616.
24. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol. 1997;15:261-267.
25. Enzinger PC, Burtness BA, Niedzwiecki D, et al. CALGB 80403 (Alliance)/E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. J Clin Oncol. 2016;34:2736-2742.
26. Bang YJ, Van Cutsem E, Feyereislova A, et al; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687-697.
27. Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol. 2008;19:1523-1529.
28. Tanner M, Hollmén M, Junttila TT, et al. Amplification of HER-2 in gastric carcinoma: association with topoisomerase IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Oncol. 2005;16:273-278.
29. Hofmann M, Stoss O, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology. 2008;52:797-805.
30. Hecht JR, Bang YJ, Qin SK, et al. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC--a randomized phase III trial. J Clin Oncol. 2016;34:443-451.
31. Tabernero J, Hoff PM, Shen L, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2018;19:1372-1384.
32. Ock CY, Lee KW, Kim JW, et al. Optimal patient selection for trastuzumab treatment in HER2-positive advanced gastric cancer. Clin Cancer Res. 2015;21:2520-2529.
33. Park S, Jiang Z, Mortenson ED, et al. The therapeutic effect of anti-HER2/neu antibody depends on both innate and adaptive immunity. Cancer Cell. 2010;18:160-170.
34. Taylor C, Hershman D, Shah N, et al. Augmented HER-2 specific immunity during treatment with trastuzumab and chemotherapy. Clin Cancer Res. 2007;13:5133-5143.
35. Janjigian YY, Maron SB, Chatila WK, et al. First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial. Lancet Oncol. 2020;21:821-831.

36. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. JAMA Oncol. 2018;4:e180013.

37. Kojima T, Shah MA, Muro K, et al; KEYNOTE-181 Investigators. Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. J Clin Oncol. 2020;38:4138-4148.

38. Kato K, Sun J, Shah MA, et al. Pembrolizumab plus chemotherapy vs chemotherapy as first-line therapy in patients with advanced esophageal cancer: the phase III KEYNOTE-590 study. Ann Oncol. 2020;31(suppl_4): S1142-S1215.

39. Gadgeel S, Rodríguez-Abreu D, Speranza G, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. J Clin Oncol. 2020;38:1505-1517.

40. Paz-Ares L, Luft A, Vicente D, et al; KEYNOTE-407 Investigators. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med. 2018;379:2040-2051.

41. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017; 390:2461-2471.

42. Boku N, Ryu MH, Kato K, et al. Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4). Ann Oncol. 2019;30:250-258.

43. Moehler M, Shitara K, Garrido M, et al. Nivolumab (nivo) plus chemotherapy (chemo) versus chemotherapy as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): first results of the CheckMate 649 study. Ann Oncol. 2020;31(suppl_ 4):S1191.

44. Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. JAMA Oncol. 2020;6:1571-1580.

45. André T, Shiu KK, Kim TW, et al; KEYNOTE-177 Investigators. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med. 2020; 383:2207-2218.

46. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high mcrosatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol. 2020;38:1-10.

47. Shitara K, Bang YJ, Iwasa S, et al; DESTINY-Gastric01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382:2419-2430.

48. Thuss-Patience PC, Shah MA, Ohtsu A, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol. 2017; 18:640-653.

49. Satoh T, Xu RH, Chung HC, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. J Clin Oncol. 2014;32:2039-2049.

50. Lorenzen S, Riera Knorrenschild J, Haag GM, et al. Lapatinib versus lapatinib plus capecitabine as second-line treatment in human epidermal growth factor receptor 2-amplified metastatic gastro-oesophageal cancer: a randomised phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Eur J Cancer. 2015; 51:569-576.

51. Makiyama A, Sukawa Y, Kashiwada T, et al. Randomized, phase II study of trastuzumab beyond progression in patients with HER2-positive advanced gastric or gastroesophageal junction cancer: WJOG7112G (T-ACT Study). J Clin Oncol. 2020;38:1919-1927.

52. Wilke H, Muro K, Van Cutsem E, et al; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15:1224-1235.

53. Fuchs CS, Tomasek J, Yong CJ, et al; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383:31-39.

54. Ford HE, Marshall A, Bridgewater JA, et al; COUGAR-02 Investigators. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 2014;15:78-86.

55. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer. 2011;47:2306-2314.

56. Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol. 2012;30:1513-1518.

57. Tomita Y, Moldovan M, Chang Lee R, et al. Salvage systemic therapy for advanced gastric and oesophago-gastric junction adenocarcinoma. Cochrane Database Syst Rev. 2020;11:CD012078.

58. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol. 2013; 31:4438-4444.

59. Lee KW, Maeng CH, Kim TY, et al. A phase III study to compare the efficacy and safety of paclitaxel versus irinotecan in patients with metastatic or recurrent gastric cancer who failed in first-line therapy (KCSG ST10-01). Oncologist. 2019;24:18-e24.

60. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2018;19:1437-1448.

61. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:1506-1517.

62. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med. 2017; 9:34.

63. Parikh AR, He Y, Hong TS, et al. Analysis of DNA damage response gene alterations and tumor mutational burden across 17,486 tubular gastrointestinal carcinomas: implications for therapy. Oncologist. 2019;24:1340-1347.

64. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020;21:1353-1365.

65. Blum AE, Venkitachalam S, Ravillah D, et al. Systems biology analyses show hyperactivation of transforming growth factor-β and JNK signaling pathways in esophageal cancer. Gastroenterology. 2019;156:1761-1774.

66. Ebbing EA, van der Zalm AP, Steins A, et al. Stromal-derived interleukin 6 drives epithelial-to-mesenchymal transition and therapy resistance in esophageal adenocarcinoma. Proc Natl Acad Sci USA. 2019;116:2237-2242.

67. Higashino N, Koma YI, Hosono M, et al. Fibroblast activation protein-positive fibroblasts promote tumor progression through secretion of CCL2 and interleukin-6 in esophageal squamous cell carcinoma. Lab Invest. 2019;99:777-792.

68. Kiyozumi Y, Baba Y, Okadome K, et al. IDO1 expression is associated with immune tolerance and poor prognosis in patients with surgically resected esophageal cancer. Ann Surg. 2019;269:1101-1108.

69. Milano F, Jorritsma T, Rygiel AM, et al. Expression pattern of immune suppressive cytokines and growth factors in oesophageal adenocarcinoma reveal a tumour immune escape-promoting microenvironment. Scand J Immunol. 2008;68:616-623.

70. Finn RS, Qin S, Ikeda M, et al; IMbrave150 Investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020; 382:1894-1905.

71. Rini BI, Plimack ER, Stus V, et al; KEYNOTE-426 Investigators. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380:1116-1127.

72. Mamdani H, Mehta R, Fountzilas C, et al. A phase II study evaluating safety and efficacy of niraparib in patients with previously treated homologous recombination (HR) defective or loss of heterozygosity (LOH) high-metastatic esophageal/GEJ/proximal gastric adenocarcinoma: A Big Ten Cancer Research Consortium study. J Clin Oncol. 2020;38 (4 suppl; abstr TPS472).

73. Wainberg ZA, Enzinger PC, Kang Y-K, et al. Randomized double-blind placebo-controlled phase 2 study of bemarituzumab combined with modified FOLFOX6 (mFOLFOX6) in first-line (1L) treatment of advanced gastric/gastroesophageal junction adenocarcinoma (FIGHT). J Clin Oncol. 2021;39 (3 suppl; abstr 160).

74. Mody K, Manochakian R, Ahn DH, et al. A landscape of circulating tumor DNA in esophageal adenocarcinoma and squamous cell carcinoma. J Clin Oncol. 2019; 37 (15 suppl; abstr 4070).

75. Mamdani H, Schneider BJ, Abushahin LI, et al. Safety and efficacy of durvalumab following trimodality therapy for locally advanced esophageal and GEJ adenocarcinoma: Early efficacy results from Big Ten Cancer Research Consortium study. J Clin Oncol. 2019;37 (4 suppl; abstr 5).

76. Kelly RJAJ, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study. Ann Oncol. 2020;31(suppl_4): S1142-S1215.

GENITOURINARY CANCER—KIDNEY AND BLADDER

Breaking Barriers: Addressing Issues of Inequality in Trial Enrollment and Clinical Outcomes for Patients With Kidney and Bladder Cancer

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overview

Despite recent treatment advances, kidney and bladder cancer cases have continued to rise in both incidence and mortality over the last few decades. Not every demographic subgroup of patients diagnosed with these cancers has an equivalent outcome. Women diagnosed with bladder cancer have worse overall survival than men diagnosed with bladder cancer. Older adults with muscle-invasive bladder cancer have worse cancer-specific outcomes than do younger patients. Black patients diagnosed with kidney and bladder cancers appear to have worse overall survival than White patients diagnosed with these cancers. Although these differences in outcomes are likely multifactorial, in many cases they may be based on modifiable approaches to screening, diagnosing, and treating patients. We explore various causes of these differences in outcomes between patients and address patient engagement strategies and avenues to effect change. In 2021, equity in cancer and cancer care delivery has a more prominent place in the hierarchy of the continuum of medicine. Continued focus on this topic is critical, with clear accountabilities established and barriers to best care for patients eliminated.

Kidney and bladder cancers remain among the top 10 most common cancers diagnosed in the United States annually and, despite recent treatment advances, were the cause of death of more than 32,000 individuals in 2020.[1] Cases have continued to rise in both incidence and mortality over the last few decades, with an estimated 73,750 new diagnoses of kidney cancer and 81,400 urinary bladder cancer cases in the United States in 2020.[2] Data suggest that not every demographic subgroup of patients diagnosed with these cancers has an equivalent outcome. For example, women diagnosed with bladder cancer appear to have worse overall survival than men diagnosed with bladder cancer.[3] Older adults with localized, muscle-invasive bladder cancer have worse cancer-specific outcomes than younger patients.[4] Black patients diagnosed with kidney and bladder cancers appear to have worse overall survival than White patients diagnosed with these cancers.[5,6] These observed differential outcomes are most likely multifactorial; however, in many cases, they may be based on modifiable approaches to screening, diagnosing, and treating patients.

We explore various aspects and root causes of differences in outcomes between patients and address some ways to address these issues going forward, via avenues such as patient engagement strategies, systemic change, and strategic changes to clinical trial enrollment. We outline what an equity framework would look like, where all patients diagnosed with kidney or bladder cancer have equal access to care, including the equal chance to enroll in appropriate clinical trials and to obtain the best possible outcomes for their cancers. We also discuss the disparities that lead to current differences in access to care and to outcomes, and thoughts about how these could be modified to optimize outcomes for all patients.

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BARRIERS TO BEST CARE: A PATIENT'S PERSPECTIVE

In 2020, COVID-19, COVID-19 vaccinations, and the death of Mr. George Floyd amplified concerns about inequities in health care delivery in the United States and globally. Although disparities in outcomes and barriers to equitable access to care have long been recognized and often discussed by clinicians and researchers, public awareness of these issues has been increasing since the events of 2020. In the last year, there has been a call to action for diversity, equity, and inclusion in medicine and cancer (and bladder and kidney cancers are no exception).

What does equity look like? Patients diagnosed with cancer all seek one thing: the best possible outcome

PRACTICAL APPLICATIONS

- An equity framework would ideally provide the opportunity to learn about potential variability in response and safety because of increased diversity of clinical trial participation.
- Sex-based outcomes in trial design should be considered as the bladder cancer community strives to improve outcomes for women.
- Older patients with kidney or bladder cancers who are fit should receive the same type of treatment as their younger counterparts.
- The U.S. Food and Drug Administration has specifically encouraged enrollment of a diverse group of patients whose ethnic and racial makeup is representative of the U.S. population in clinical trials for kidney and bladder cancer.
- By necessity, the COVID-19 reality may have brought innovative approaches to expanding accessibility of care and may thus have demonstrated the feasibility of this approach.

with the least possible burden. No matter what the cancer diagnosis, most patients will believe results to be insufficient in one or more dimensions: incidence may be higher for their cohort; treatments may not work as well, may not work as quickly, may have side effects, may not exist at all, may cost too much, may require too much time, or may not be locally available; and/or outcomes may vary from patient to patient.

An equity framework would ideally provide the opportunity to learn about potential variability in response and safety because of increased diversity of clinical trial participation. That is not the current state of knowledge for many cancers, because these dimensions are not consistent across cancers. Some cancers have deep knowledge, extensive research and research funding, effective and widely available treatments, modest side effects, and good outcomes. Others do not. Although this type of equity framework is the desired end state, a more pragmatic goal must be established: improved knowledge of variability in results relative to patients with that same diagnosis, no matter who the patient is and where they are located and treated.

Achieving such consistency will require the removal or mitigation of barriers driving disparities. Such barriers must be mitigated along the continuum of medicine: Knowledge → Research → Clinical Trials → Results/Publication → Standard of Care → Pattern of Practice.

In the context of bladder and kidney cancer, the barriers across this continuum are like those in other cancers but with unique characteristics. To start, knowledge is relatively immature compared with other cancers. In addition, research is underfunded compared with other cancers based on incidence and death rate.[7] Research also tends to focus on the rule and not the exceptions. The larger subpopulations within kidney and bladder cancer have historically received the most funding, the most research emphasis, and the highest prioritization overall. Funding, then, is the first barrier to overcome, followed by emphasis. Funding research for subpopulations must not continue to be a lower priority, characterized as something we cannot afford.

Within bladder and kidney cancers, the more common types of disease (such as urothelial bladder cancer) have been emphasized. Within that context, White males are predominant. The second barrier to overcome is to work from the bottom up instead of the top down, recalibrating the emphasis on other histologies, racial and ethnic subpopulations, and women. More research across a more diverse population is needed to elucidate the factors contributing to differences in incidence rates and outcomes in these subpopulations (women, Blacks adults, older adults, etc.) and, until that occurs, there can be no equity. Research priorities must be more equitable. Sponsors and funders must incentivize research equity and force acknowledgment of deficiencies where they exist. A recalibration of priorities and mindset is achievable by convening a multidisciplinary group of stakeholders and assessing what is known and not known about subpopulations in a think tank or similar construct.

Within clinical trials, forecasts should be created during design that account for subpopulations. Accrual cannot be viewed independent of subpopulations: the characteristics of patient subpopulations matter. Representative accrual must be the goal or signal will never be found, let alone definitive evidence of disparate outcomes. Results must be continually monitored against those forecasts at multiple checkpoints after activation and not just at the trial's conclusion.

Equally as important is that diversity, equity, and inclusion goals for patients relative to trials and clinical care are stated by major stakeholders: the U.S. Food and Drug Administration (FDA), industry partners, the National Cancer Institute and the National Clinical Trials Network groups, other clinical trial consortiums, ASCO and professional oncology societies, institutions and care facilities, payers, advocacy groups, and others. Such guidance has been issued by several of these groups already.

In addition, however, every member of the clinical trial study team must have equity as a goal and be clear on the role they play to make that happen at every step. The clinical trial team must also have no impediments to doing so. Such a methodology (i.e., "equity as goal") is not in the public

domain today and represents a significant barrier. At the Southwest Oncology Group, for example, a multidisciplinary team has developed a methodology to overcome this barrier.

Within both the clinical trial and clinical practice settings, barriers to delivery of equitable care must be overcome. Patients face tremendous barriers in their search for equitable care: health literacy, logistical costs and time, and comorbidities that increase with age and reduce treatment options (such as receipt of platinum chemotherapy or surgeries such as radical cystectomy). Removal of the health literacy barrier will require acknowledgment that reading levels alone are insufficient; cultural calibrations and messengers are also important. Logistical costs and time are significant barriers for many patients and may reduce referrals by clinicians for trials and state-of-the-art treatment and self-referral by patients. The increasing use of multimodality therapies that include immunotherapy may make logistical and cost considerations even more significant and potentially untenable for patients. A current Southwest Oncology Group bladder cancer trial requires a minimum of 35 treatment visits in the less burdensome arm. The time considerations alone are substantial, but the costs of that, conservatively estimated at more than $1,500, may be insurmountable even in the absence of medical costs. Failure to address the costs related to clinical trial participation and logistical considerations will not only impact time to market but also representative accrual.

WOMEN AND BLADDER CANCER: ENSURING THE BEST CARE FOR ALL OF OUR PATIENTS

The issue of equity in care and differential outcomes is particularly pronounced when looking at women with urothelial cancers of the bladder and upper urothelial tract (as opposed to kidney cancers, where disparities in outcomes based on sex may be less pronounced). Urothelial cancers comprise the fourth most common cancer in men.[2] Although this cancer is less common in women, with an incidence of approximately 25% that of men, women tend to present with more advanced disease and tend to die of urothelial cancers at a higher rate than men.[3] The reasons for this sex disparity in bladder cancer are partially understood, primarily because the most common presenting symptom of urothelial cancer is hematuria. Although evidence-based evaluation guidelines exist for hematuria workup,[8] during workup, many women experience more deviations from these guidelines, including a longer time from first symptoms to diagnosis, compared with men.[9,10] During this lead time, women have been found to see more nonurology specialists, undergo more urine culture evaluations, and receive more antibiotic courses than their male counterparts.[11,12] In a study of Medicare beneficiaries, compared with men, women are less likely to undergo a complete evaluation for hematuria within 180 days of initial presentation with the symptom.[13] How these variations and interventions affect patients or how they impact bladder cancer prognosis is unknown. It is generally believed that diagnostic delay contributes to stage migration in female patients.

Like all cancers, treatment algorithms are predicated on tumor stage. For bladder cancer, therapeutic plans diverge significantly if a cancer is stage II or muscle-invasive. Early-stage (nonmuscle-invasive) bladder cancers are treated locally with resection and intravesical therapy, and, in the United States, this is mostly managed by urologists. Muscle-invasive bladder cancer is a potentially lethal disease state, with standard recommendations for systemic chemotherapy followed by cystectomy or trimodality therapy of combined transurethral resection, radiation, and radiosensitizing chemotherapy.[14] Thus, it is surprising to find that even when women present to urology specialists, care can continue to deviate from standard compared with male counterparts. Using the Los Angeles Surveillance, Epidemiology, and End Results database from 2004 to 2005, Chamie et al[15] found that poor staging quality (as defined as no muscle in tumor specimen to accurately assess stage) was more likely in women compared with men. This and other studies have shown that poor staging accuracy is predictive of inferior survival outcomes, likely related to delayed treatment and undertreatment.[16] Furthermore, women undergoing definitive radical cystectomy were more likely to have non–organ-confined disease, and, not surprisingly, increased cancer-specific mortality in several cohorts.[17-19] Finally, inside and outside of the United States, women were less likely to undergo definitive curative radical cystectomy compared with men.[10,20] It is unclear if advanced age or other comorbidities factor into these decisions.

In the last decade, a significant amount of research has described the heterogeneity of invasive bladder cancer, elucidating different subtypes with predictive disease characteristics and responses to therapy. Like breast cancer, subtypes of luminal-like and basal-like clusters and additional subclusters have been identified based on gene expression data.[21-24] Tumors that were identified in the basal-like clusters had poorer survival and were more likely to be enriched, with women recapitulated in several cohorts. How these subtypes correlate with response or resistance to anticancer therapies is a topic of ongoing discovery.[22,25]

Less is understood about the interaction of female sex with responses to treatment of bladder cancer; however, several retrospective studies have shown that women are less likely to receive chemotherapy compared with men.[10,26] Although outcomes in retrospective studies appear consistently inferior in women compared with men, women treated in the context of clinical trials appear to have similar tolerance to

and similar overall survival with chemotherapy compared with men.[27] Immunotherapy is a therapeutic option for several different disease states in urothelial cancer, and, for other cancers, it has been demonstrated that outcomes may be impacted by host factors, including sex.[28] Hoffman-Censits et al presented data pooling patient outcomes with atezolizumab in IMvigor studies, finding nonsignificant higher response rates in men compared with women, without survival difference, at the European Society for Medical Oncology 2019 Congress.[29]

To date, no trials have prespecified endpoints defined by sex in urothelial cancer. Based on the population characteristics, trials in urothelial cancer are universally skewed with more men (approximately 75%–80% males in most studies) compared with women, which makes understanding sex-based considerations in outcomes particularly challenging. In the last 5 years, discovery in urothelial cancer has exploded, with multiple new targets and therapies available to treat patients. Moving forward, sex-based outcomes in trial design should be considered as the bladder cancer community strives to improve outcomes for women.

OLDER, WISER, BETTER: CLINICAL TRIAL ENROLLMENT AND OPTIMAL CARE FOR OLDER ADULTS WITH KIDNEY AND BLADDER CANCERS

Kidney and bladder cancers predominantly afflict older adults, with nearly half of all patients newly diagnosed with kidney cancer and bladder cancer diagnosed at age 65 and older.[30] Optimal care of older adults with these cancers would ideally require treatment that has undergone the rigor of clinical trials that have specifically evaluated these therapies as safe and efficacious in older adults. However, fewer than a quarter of the adults enrolled in clinical trials that enroll in the United States are age 70 or older. Moreover, patients enrolled in these trials are generally fitter and have fewer comorbidities than the average older adult in the general population and thus may not fully represent the concerns of treating all older adults.[31]

To decide what is optimal care for older adults with kidney or bladder cancer, a geriatric assessment should be performed.[30,32] Based on the outcome of the geriatric assessment, these patients can be broadly classified as fit, vulnerable, or frail. Older patients with kidney or bladder cancers who are fit should receive the same type of treatment as their younger counterparts.[30,32]

Fit patients with localized kidney cancer should be offered surgical resection of their tumors or nephrectomy when indicated. Frail older adults with localized kidney cancer, however, can be treated with less radical but effective approaches like local ablation or observation, which offer reasonable outcomes while preserving quality of life.[33] In the metastatic renal cell carcinoma setting, fit older adults receiving standard-of-care, first-line treatment were found to derive similar benefits in terms of efficacy as younger adults, although there were limited data regarding toxicities stratified by age in the pivotal studies.[30] Selected frail older adults with metastatic renal cell carcinoma can be offered observation or single-agent immunotherapy in the first line,[34] with the caveat that there is currently no immunotherapy labeled for single-agent (non-combination) use in this setting.

Older adults with localized muscle-invasive bladder cancer have been found to have poorer survival and higher morbidity compared with younger patients, likely because of a smaller proportion receiving radical curative therapy, implying gross undertreatment in this population.[4] Specialized perioperative treatment (the incorporation of preoperative assessment and optimization, intraoperative care, and enhanced postoperative care) for older adults may help increase the number of older adults suitable for optimal radical treatment, such as neoadjuvant chemotherapy followed by surgery.[32] For patients who desire bladder preservation, a randomized control trial using trimodality therapy showed that adults age 75 or older derive similar efficacy benefits as those who were younger.[35] In the metastatic setting, older adults who are fit and who are deemed cisplatin-eligible should get standard-of-care, cisplatin-based regimens.[36] The advent of immunotherapy in metastatic bladder cancer has enabled older adults who are unfit for chemotherapy to still receive effective and tolerable life-prolonging systemic treatment.[37]

Although there has been some improvement seen in the treatment of older adults with bladder and kidney cancers over the last decade, there are still many unanswered questions and gaps in care that must urgently be addressed. The International Society of Geriatric Oncology has organized disease-specific task forces to update the knowledge base and to provide evidence-based clinical guidance on how best to treat these patients.[30,32] One major area of need is for clinical trials to include more older adults with kidney and bladder cancers. A recent systematic review has outlined critical barriers to the enrollment of older adults with cancer, which were divided into system-related, patient-related, provider-related, and caregiver-related barriers.[31] This review article highlighted important recent advances made by the FDA in collaboration with ASCO in creating a geriatric oncology workshop in 2017. The FDA released a Draft Guidance to Industry in 2020, providing specific suggestions for inclusion of older adults in all phases of oncology drug development, including registration trials.[31,38] Public policy initiatives like this will ultimately provide the much needed impetus for an increase in the enrollment of older adults with kidney and bladder cancer. This will help address the numerous unknowns regarding this vulnerable

group of patients and in turn will help oncologists provide optimal care for them.

RACIAL DISPARITIES IN KIDNEY AND BLADDER CANCERS

Much has been written about the overall decrement in outcomes seen in patients diagnosed with cancer who are members of underserved minority groups, such as Black patients in the United States. For example, Black patients have a higher cancer burden and face greater obstacles to cancer prevention, detection, treatment, and survival. Overall, Black patients have the highest death rate and shortest survival of any racial or ethnic group for most cancers in the United States.[39]

Kidney and bladder cancers are no exception to this trend. In kidney cancer, a disparity in survival exists between Black and White patients. This is true even when controlling for specific treatment received and for other prognostic factors including stage, tumor size, and grade.[5,40] Although the exact cause of this disparity in mortality is unknown, it is likely multifactorial and may be because of a disparity in access to health care, differences in health care quality, and disadvantages related to differential socioeconomic status.[40] Research has shown that overall, Black patients present with higher-stage bladder cancer than White, Hispanic, or Asian patients. Five-year disease-specific survival is consistently worse for African American patients than for those who are members of other racial groups, even when stratified by stage and grade.[6]

When looking at clinical trial enrollment, recent registrational trials for kidney and bladder cancer enrolled predominantly White patients. An FDA analysis combining data from seven trials that led to the approval of various immunotherapy agents in advanced bladder cancer reveals that, overall, 82% of enrolled patients were White and 10% were Asian, with only 7% of patients overall enrolled being members of other races or ethnicities.[41] The same is true for kidney cancers, in which the vast majority of patients enrolled in randomized trials that led to approval of several immunotherapy-containing combinations were White (75%–87%).[42-44] This disparity in clinical trial enrollment in these settings between White patients and those patients of other races/ethnicities is likely indicative of other, entrenched systemic barriers to care that are prevalent in the U.S. health care system. Underrepresentation in clinical trials is also problematic from an equity standpoint given that, for many diseases, clinical trials are the preferred treatment option and outcomes for patients enrolled in clinical trials have been shown to be better than outcomes for patients not enrolled in clinical trials.[45] Unfortunately, the race and ethnicity data are infrequently described in the manuscripts reporting the results of notable trials in kidney and bladder cancers, including those trials that support FDA approval; rather, they were obtained from U.S. product labeling. This emphasizes the importance of appropriate considerations when it comes to journal articles describing clinical research. Efforts to improve the reporting of enrollment of patients according to race and ethnicity in clinical trials in journal articles are ongoing and have been described.[46] The gap in reporting these data in an easy-to-find way is an ongoing issue and one that should be corrected, as we cannot change what we do not measure.

REGULATING CHANGE

On the regulatory front, one way to encourage a change in the conduct of clinical trials is through encouraging enrollment of a diverse group of patients who best reflect the population of patients likely to use a drug if approved. The FDA has primarily done this through publication of guidance encouraging broadening eligibility criteria for clinical trial enrollment.[47-51] This effort includes encouragement of enrollment of broader age ranges of patients, especially at the young and older range end of potentially eligible patients, as well as via developing strategies to enroll patients traditionally excluded from clinical trials, such as those who have organ impairment. The general expectation is that broadening eligibility criteria and adopting more inclusive enrollment practices should improve the quality of studies by not only ensuring a more representative population but also by facilitating discovery of important safety information about use of the investigational agent in those who will be prescribed the agent after approval. Despite these efforts, challenges to participation in clinical trials remain, and many groups continue to be underrepresented in clinical trials.

The FDA has specifically encouraged enrollment of study populations whose demographic characteristics, such as sex, age, and race and ethnicity, are reflective of the U.S. population; the FDA has conveyed this expectation to sponsors of clinical trials for bladder and kidney cancer. The FDA has observed that, in trials submitted to the FDA that enroll patients globally, a minority are enrolled from U.S. sites. For example, a review of four of the bladder cancer trials that led to approval of immunotherapy agents in the metastatic setting revealed that 39% of patients enrolled were from the United States.[52] In kidney cancer, the percentage of patients enrolled from the United States was even smaller in three of the trials that supported recent approval of combination immunotherapy regimens and that reported statistics for U.S. enrollment, with none enrolling more than 30% of patients from the United States.[53-55] The representation of U.S. racial and ethnic minorities in these trials may therefore be impacted by this trend. Efforts to increase enrollment of U.S. patients may result in a study population that is more reflective of the racial/ethnic diversity in the United States, particularly as the categories that denote race and ethnicity in the United States may not be applicable to

other regions. Notwithstanding this limitation, the FDA encourages diverse regional representation, including countries in sub-Saharan Africa, Central and South America, and Southeast Asia.

Even in trials that enroll primarily in the United States, many barriers to care affect access to clinical trials and resultant enrollment by patients who are members of minority groups. These barriers are multifactorial and must be addressed in conjunction with efforts by the health care system in general to address issues of access to care. However, recent experience with conducting clinical trials in the era of COVID-19 has in many cases introduced some flexibility in the modalities used to access care by patients, and many have considered what clinical trial conduct might look like in a post–COVID-19 era. These may be particularly relevant to underserved and/or rural populations. For example, the FDA's guidance on conduct of clinical trials during COVID-19 considers trial participation of those who may not be able to come to the investigational site for protocol-specified visits and encourages sponsors to evaluate whether alternative methods for assessments could be implemented when feasible, in a manner that would be sufficient to assure the safety of trial participants.[56] This flexibility in conducting on-study evaluations is a real-life example of an approach that is also championed in the FDA's guidance on enhancing diversity in clinical trial enrollment by aiding in accessibility of participation.[47] This guidance encourages consideration of strategies such as the use of interactions via telephone/mobile telephone, secured electronic mail, social media platforms, or digital health technology as tools that might be used to replace site visits.[56] By necessity, the COVID-19 reality may have in many cases brought these innovative approaches to expand the accessibility of care to many settings and may have demonstrated the feasibility of this approach to successfully broaden access to care. However, further study to determine the potential for disparities resulting from these approaches is also important, as this may impact those patients with no internet or smartphone access and those who may be technologically challenged.

In terms of specific recommendations to remove barriers to clinical trial enrollment when designing a new trial in kidney and bladder cancer, there are many possible approaches, and this area of focus continues to evolve. An important strategy is the involvement of additional stakeholders on the trial design team who represent the interests, values, and beliefs of underrepresented populations. These may include diversity, equity, and inclusion experts, engaged community and research advocates, and advocacy groups. Suggestions made by these stakeholders could then be implemented early to address barriers to enrollment at the earliest planning stages of the clinical trial. Forecasts for enrollment can then be made that reflect known demographic trends for kidney and bladder cancer incidence, with the protocol proactively reviewed for feedback on ways to make changes that would make it easier for patients to enroll and remain under study. Additional resources may be required to help with outreach and engagement efforts, and these can also be identified early. Accrual plans can be developed that specifically take into account diversity of enrollment at identified sites, and study accrual can be monitored in real time, with diversity of subpopulations reviewed as a primary metric. Early and prospective attention to these issues can have a large downstream impact on enrolling a trial population that best reflects the population affected by kidney and bladder cancer in the real-world setting.

CONCLUSION

In 2021, equity in cancer and cancer care delivery has a more prominent place in the hierarchy of the continuum of medicine. Continued focus on this topic is critical, with clear accountabilities established and barriers to best care for patients eliminated.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. SEER Cancer Stat Facts. https://seer.cancer.gov/statfacts/. Accessed March 1, 2021.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.

3. Liu S, Yang T, Na R, et al. The impact of female gender on bladder cancer-specific death risk after radical cystectomy: a meta-analysis of 27,912 patients. Int Urol Nephrol. 2015;47:951-958.
4. Noon AP, Albertsen PC, Thomas F, et al. Competing mortality in patients diagnosed with bladder cancer: evidence of undertreatment in the elderly and female patients. Br J Cancer. 2013;108:1534-1540.
5. Chow WH, Shuch B, Linehan WM, et al. Racial disparity in renal cell carcinoma patient survival according to demographic and clinical characteristics. Cancer. 2013;119:388-394.
6. Yee DS, Ishill NM, Lowrance WT, et al. Ethnic differences in bladder cancer survival. Urology. 2011;78:544-549.
7. Action to Cure Kidney Cancer. Federal funding for the top 18 cancer types. https://www.ackc.org/federal-funding-for-the-top-18-cancer-types/. Accessed March 1, 2021.
8. Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. https://www.auanet.org//guidelines/archived-documents/asymptomatic-microhematuria-(amh)-guideline. Accessed April 29, 2021.
9. Cohn JA, Vekhter B, Lyttle C, et al. Sex disparities in diagnosis of bladder cancer after initial presentation with hematuria: a nationwide claims-based investigation. Cancer. 2014;120:555-561.
10. Weiner AB, Keeter MK, Manjunath A, et al. Discrepancies in staging, treatment, and delays to treatment may explain disparities in bladder cancer outcomes: an update from the National Cancer Data Base (2004-2013). Urol Oncol. 2018;36:237.
11. Aziz A, Madersbacher S, Otto W, et al. Comparative analysis of gender-related differences in symptoms and referral patterns prior to initial diagnosis of urothelial carcinoma of the bladder: a prospective cohort study. Urol Int. 2015;94:37-44.
12. Henning A, Wehrberger M, Madersbacher S, et al. Do differences in clinical symptoms and referral patterns contribute to the gender gap in bladder cancer? BJU Int. 2013;112:68-73.
13. Bassett JC, Alvarez J, Koyama T, et al. Gender, race, and variation in the evaluation of microscopic hematuria among Medicare beneficiaries. J Gen Intern Med. 2015;30:440-447.
14. Flaig TW, Spiess PE, Agarwal N, et al. Bladder cancer, version 3.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020;18:329-354.
15. Chamie K, Ballon-Landa E, Bassett JC, et al. Quality of diagnostic staging in patients with bladder cancer: a process-outcomes link. Cancer. 2015;121:379-385.
16. Lee CT, Madii R, Daignault S, et al. Cystectomy delay more than 3 months from initial bladder cancer diagnosis results in decreased disease specific and overall survival. J Urol. 2006;175:1262-1267, discussion 1267.
17. Rosiello G, Palumbo C, Pecoraro A, et al. The effect of sex on disease stage and survival after radical cystectomy: a population-based analysis. Urol Oncol. 2021;39:236.e1-236.e7.
18. Messer JC, Shariat SF, Dinney CP, et al. Female gender is associated with a worse survival after radical cystectomy for urothelial carcinoma of the bladder: a competing risk analysis. Urology. 2014;83:863-867.
19. Kluth LA, Rieken M, Xylinas E, et al. Gender-specific differences in clinicopathologic outcomes following radical cystectomy: an international multi-institutional study of more than 8000 patients. Eur Urol. 2014;66:913-919.
20. Thorstenson A, Hagberg O, Ljungberg B, et al. Gender-related differences in urothelial carcinoma of the bladder: a population-based study from the Swedish National Registry of Urinary Bladder Cancer. Scand J Urol. 2016;50:292-297.
21. Damrauer JS, Hoadley KA, Chism DD, et al. Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology. Proc Natl Acad Sci USA. 2014;111:3110-3115.
22. Choi W, Porten S, Kim S, et al. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell. 2014;25:152-165.
23. Robertson AG, Kim J, Al-Ahmadie H, et al; TCGA Research Network. Comprehensive molecular characterization of muscle-invasive bladder cancer [correction published in *Cell.* 2018;174(4):P1033]. Cell. 2017;171:540-556.e25.
24. de Jong JJ, Boormans JL, van Rhijn BWG, et al. Distribution of molecular subtypes in muscle-invasive bladder cancer is driven by sex-specific differences. Eur Urol Oncol. 2020;3:420-423.
25. Seiler R, Ashab HAD, Erho N, et al. Impact of molecular subtypes in muscle-invasive bladder cancer on predicting response and survival after neoadjuvant chemotherapy. Eur Urol. 2017;72:544-554.
26. Rose TL, Deal AM, Nielsen ME, et al. Sex disparities in use of chemotherapy and survival in patients with advanced bladder cancer. Cancer. 2016;122:2012-2020.
27. Haines L, Bamias A, Krege S, et al. The impact of gender on outcomes in patients with metastatic urothelial carcinoma. Clin Genitourin Cancer. 2013;11:346-352.
28. Conforti F, Pala L, Bagnardi V, et al. Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol. 2018;19:737-746.
29. Hoffman-Censits J, Rosenberg JE, Van der Heijden MS, et al. 1221 - Clinical outcomes by sex with atezolizumab (atezo) monotherapy in patients (pts) with locally advanced/metastatic urothelial carcinoma (mUC). Ann Oncol. 2019;30(5):v356-v402.
30. Kanesvaran R, Le Saux O, Motzer R, et al. Elderly patients with metastatic renal cell carcinoma: position paper from the International Society of Geriatric Oncology. Lancet Oncol. 2018;19:e317-e326.

31. Sedrak MS, Freedman RA, Cohen HJ, et al; Cancer and Aging Research Group (CARG). Older adult participation in cancer clinical trials: A systematic review of barriers and interventions. CA Cancer J Clin. 2021;71:78-92.
32. Mottet N, Ribal MJ, Boyle H, et al. Management of bladder cancer in older patients: Position paper of a SIOG Task Force. J Geriatr Oncol. 2020;11:1043-1053.
33. Borghesi M, Brunocilla E, Volpe A, et al. Active surveillance for clinically localized renal tumors: an updated review of current indications and clinical outcomes. Int J Urol. 2015;22:432-438.
34. Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol. 2016;17:1317-1324.
35. Christodoulou M, Reeves KJ, Hodgson C, et al. Outcomes of radiosensitisation in elderly patients with advanced bladder cancer. Radiother Oncol. 2018; 129:499-506.
36. Galsky MD, Krege S, Lin CC, et al. Cisplatin-based combination chemotherapy in septuagenarians with metastatic urothelial cancer. Urol Oncol. 2014;32:30.
37. Vuky J, Balar AV, Castellano D, et al. Long-term outcomes in KEYNOTE-052: phase II study investigating first-line pembrolizumab in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer. J Clin Oncol. 2020;38:2658-2666.
38. U.S. Food and Drug Administration. FDA draft guidance for industry on inclusion of older adults in cancer clinical trials. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/inclusion-older-adults-cancer-clinical-trials. Accessed March 1, 2021.
39. American Cancer Society. ACS cancer disparities. https://www.cancer.org/about-us/what-we-do/health-equity/cancer-disparities-in-the-black-community.html. Accessed March 1, 2021.
40. Sims JN, Yedjou CG, Abugri D, et al. Racial disparities and preventive measures to renal cell carcinoma. Int J Environ Res Public Health. 2018;15:1089.
41. Maher VE, Fernandes LL, Weinstock C, et al. Analysis of the association between adverse events and outcome in patients receiving a programmed death protein 1 or programmed death ligand 1 antibody. J Clin Oncol. 2019;37:2730-2737.
42. U.S. Food and Drug Administration. Avelumab U.S. Product Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761049s005lbl.pdf. Accessed March 1, 2021.
43. U.S. Food and Drug Administration. Nivolumab U.S. Product Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125554s090lbl.pdf. Accessed March 1, 2021.
44. U.S. Food and Drug Administration. Pembrolizumab U.S. Product Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s088lbl.pdf. Accessed March 1, 2021.
45. Zaorsky NG, Zhang Y, Walter V, et al. Clinical Trial Accrual at Initial Course of Therapy for Cancer and Its Impact on Survival. J Natl Compr Canc Netw. 2019; 17:1309.
46. Flanagin A, Frey T, Christiansen SL, et al. The Reporting of Race and Ethnicity in Medical and Science Journals: Comments Invited. JAMA. 2021;325:1049-1052.
47. U.S. Department of Health and Human Services. Enhancing the diversity of clinical trial populations: eligibility criteria. Enrollment practices, and trial designs guidance for industry. https://www.fda.gov/media/127712/download. Accessed March 1, 2021.
48. U.S. Department of Health and Human Services. Cancer clinical trial eligibility criteria. Patients with organ dysfunction or prior or concurrent malignancies guidance for industry. https://www.fda.gov/media/123745/download. Accessed March 1, 2021.
49. U.S. Department of Health and Human Services. Cancer clinical trial eligibility criteria. Brain metastases guidance for industry. https://www.fda.gov/media/121317/download. Accessed March 1, 2021.
50. U.S. Department of Health and Human Services. Cancer clinical trial eligibility criteria. Minimum age considerations for inclusion of pediatric patients guidance for industry. https://www.fda.gov/media/121318/download. Accessed March 1, 2021.
51. U.S. Department of Health and Human Services. Cancer clinical trial eligibility criteria. Patients with HIV, hepatitis B virus, or hepatitis C virus infections guidance for industry. https://www.fda.gov/media/121319/download. Accessed March 1, 2021.
52. Ison G, Maher VE, Weinstock C, et al. Causes of patient ineligibility in clinical trials of metastatic urothelial cancer. J Clin Oncol. 2019;37(15 suppl):4556.
53. Motzer RJ, Tannir NM, McDermott DF, et al; CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378:1277-1290.
54. Rini BI, Plimack ER, Stus V, et al; KEYNOTE-426 Investigators. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380:1116-1127.
55. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380:1103-1115.
56. U.S. Department of Health and Human Services. Conduct of clinical trials of medical products during the covid-19 public health emergency guidance for industry, investigators, and institutional review boards. https://www.fda.gov/media/136238/download. Accessed March 1, 2021.

Immune Checkpoint Inhibition in Advanced Bladder and Kidney Cancer: Responses and Further Management

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Overview

Immune checkpoint inhibitors have an established role in the treatment of newly diagnosed metastatic kidney cancer. Treatment regimens combining nivolumab plus ipilimumab, pembrolizumab plus axitinib, nivolumab plus cabozantinib, and pembrolizumab plus lenvatinib have demonstrated superior overall survival compared with sunitinib in randomized studies. Response rates vary from 42% to 71.1% with these combinations. Atezolizumab and pembrolizumab have been approved for the treatment of cisplatin-ineligible patients with metastatic bladder cancer. These and other checkpoint inhibitors have been studied in metastatic bladder cancer and are routinely used after progression on platinum-based chemotherapy. Durable responses are observed in bladder and kidney cancer. Although some patients may experience immune-related adverse events requiring treatment discontinuation, a portion of these patients will continue to experience a response off-therapy. At the time of progression, patients with metastatic kidney cancer may be treated with anti-angiogenesis agents, and there are data suggesting that they may also be treated with a rechallenge of immunotherapy. In patients with metastatic bladder cancer who have progression after immune checkpoint inhibition, there are considerable data supporting the use of enfortumab vedotin. Ongoing studies are evaluating novel combinations of immune checkpoint inhibitors with other agents; thus, the treatment landscape of metastatic bladder and kidney cancer is expected to continue to evolve rapidly.

INTRODUCTION

Monoclonal antibodies targeting immune checkpoints, such as CTLA-4, PD-1, and PD-L1, have become important components of the treatment for advanced solid tumors. Checkpoint inhibition can restore anti-tumor immunity, reverse immune evasion, and promote cell death.[1] Treatment of advanced or metastatic clear cell renal cell carcinoma (mRCC) and advanced or metastatic urothelial carcinoma (mUC) has evolved rapidly in recent years as a result of markedly improved outcomes with the use of these antibodies. Based on the CheckMate 214, CheckMate 9ER, KEYNOTE-426, and CLEAR trials, immune checkpoint inhibitor therapy has been incorporated into first-line treatment of patients with mRCC.[2-5] Previously, patients with mUC who were ineligible to receive cisplatin or had platinum-refractory disease had few options for treatment; however, they can now be treated with immune checkpoint inhibitors based on several clinical trials establishing efficacy in mUC.[6-13] These treatments result in improved responses compared with previous standards of care; as a result of the mechanism of immune modulation, long-term responses are observed. Thus, it is important to review the nature of responses to immune checkpoint inhibitors in mUC and mRCC, as well as options for further treatment of patients who respond.

RESPONSES IN METASTATIC RENAL CELL CARCINOMA

Immune modulation has been known to play a role in the management of mRCC for decades, because the first therapies that showed benefit in patients with mRCC were the cytokines interleukin-2 and interferon alpha, but the use of immune checkpoint inhibitors led to further strides in treatment. Nivolumab, a PD-1 inhibitor, was first studied in refractory mRCC and resulted in an improvement in overall survival (OS) compared with everolimus in the CheckMate 025 trial.[14] In that study, 25% of patients treated with nivolumab experienced an objective response; OS of 25.0 months (95% CI, 21.8–not evaluable) was observed with nivolumab compared with 19.6 months (95% CI, 17.6–23.1) with everolimus. The KEYNOTE-427 study enrolled patients with newly diagnosed mRCC; in that study, pembrolizumab, a PD-1 inhibitor, resulted in a 33.6% objective response rate (ORR; 95% CI, 24.8–43.4).[15] These results demonstrated that immune checkpoint inhibitors have efficacy as single agents in mRCC; however, given the relatively modest response rates, combination therapies were studied in the setting of untreated mRCC.

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PRACTICAL APPLICATIONS

- Immune checkpoint inhibitors have demonstrated efficacy in patients with metastatic renal cell carcinoma and have become a standard of care in the treatment of patients with newly diagnosed metastatic renal cell carcinoma. Durable responses are seen.
- Immune checkpoint inhibitors also have demonstrated efficacy in patients with metastatic urothelial carcinoma, both in those patients who are ineligible to receive first-line cisplatin-based chemotherapy and in those who have developed platinum-refractory disease. Durable responses are observed in both of these settings.
- For those patients who develop adverse events requiring discontinuation of immune checkpoint inhibitor therapy, some will continue to maintain a response to therapy and enjoy a treatment-free interval.
- There are treatment options for those patients who develop progression on immune checkpoint inhibitor therapy. For patients with metastatic renal cell carcinoma, this includes treatment with antiangiogenesis agents. For patients with metastatic urothelial carcinoma, treatment with antibody-drug conjugates has established efficacy.

Currently, four treatment regimens are approved by the U.S. Food and Drug Administration for patients with newly diagnosed mRCC based on superior OS compared with sunitinib. The first approved combination regimen is nivolumab and ipilimumab, which are anti–PD-1 and anti-CTLA4 antibodies, respectively; the combination has shown benefit in the treatment of mRCC that is deemed to be intermediate or poor risk per the International Metastatic RCC Database Consortium criteria.[2,16] The combination of nivolumab plus ipilimumab was compared with sunitinib in the randomized CheckMate 214 trial of patients with newly diagnosed mRCC.[2] Among patients with intermediate- or poor-risk disease, OS was not reached for the nivolumab plus ipilimumab combination compared with 26.0 months with sunitinib (HR for death, 0.63; $p < .001$). The ORR for nivolumab plus ipilimumab among patients with intermediate- or poor-risk mRCC was 42% (95% CI, 37%–47%) compared with 27% (95% CI, 22%–31%) with sunitinib ($p < .0001$). Of note, complete responses (CRs) were seen in 9% of patients treated with nivolumab plus ipilimumab versus 1% of patients treated with sunitinib. Of the intermediate- and poor-risk patients enrolled in the trial, 81% of the patients in the nivolumab plus ipilimumab group had a duration of response of at least 1 year, with the median duration of response not reached.[2] With an extended follow-up of at least 4 years, OS among patients with intermediate- or poor-risk mRCC was 48.1 months (95% CI, 35.6 months–not evaluable) in the nivolumab plus ipilimumab group and 26.6 months (95% CI, 22.1–33.5) in the sunitinib group.[17] Of the 59 patients who experienced a CR, 19 (32.2%) were still on therapy, 27 (45.8%) discontinued therapy without a need for further treatment, and 13 (22%) required a change to subsequent systemic treatment. Among the 156 patients who experienced a partial response (PR), 28 (17.9%) remained on therapy, 67 (42.9%) discontinued treatment without additional therapy needed, and 61 (39.1%) required a change to additional systemic therapy. The median duration of response was not reached in the nivolumab plus ipilimumab group.

The remaining three immune checkpoint inhibitor combinations for treatment-naive mRCC involve the use of an immune checkpoint inhibitor with agents that target the vascular endothelial growth factor (VEGF) pathway. In the phase III KEYNOTE-426 trial, patients with untreated mRCC were randomly selected to receive pembrolizumab combined with axitinib or sunitinib.[3] In that trial, in which patients were stratified by International Metastatic RCC Database Consortium (IMDC) risk groups, pembrolizumab plus axitinib resulted in an ORR of 59.3% (95% CI, 54.5%–63.9%) compared with 35.7% (95% CI, 31.1%–40.4%) in the sunitinib group regardless of IMDC risk. In that study, 5.8% of patients treated with pembrolizumab plus axitinib experienced a CR. Superior OS was also observed in comparison with sunitinib (HR, 0.53; 95% CI, 0.38–0.74; $p < .0001$). At 1 year, 70.6% of patients in the pembrolizumab plus axitinib group had an ongoing response. With a median follow-up of 12.8 months, 59% of patients receiving pembrolizumab plus axitinib were still receiving treatment. With extended follow-up, the CR rate increased to 9%.[18] The median duration of response was 23.5 months for patients treated with pembrolizumab plus axitinib (95% CI, 19.4–29.0) compared with 15.9 months (95% CI, 13.8–20.4) in the sunitinib group. At 24 months, 47% of patients (95% CI, 40%–54%) in the pembrolizumab plus axitinib group had an ongoing response.

Nivolumab combined with cabozantinib is another regimen combining an immune checkpoint inhibitor with a VEGF-targeting agent that was recently approved for patients with untreated mRCC. The phase III CheckMate 9ER trial randomly assigned patients, stratified by International Metastatic RCC Database Consortium risk, to receive nivolumab plus cabozantinib or sunitinib.[4] Across risk groups, the combination of nivolumab plus cabozantinib resulted in superior OS (HR, 0.60; 95% CI, 0.40–0.89; $p < .001$). Median OS was not reached in either group, but the probability of OS at 12 months was 85.7% (95% CI,

81.3%–89.1%) with nivolumab plus cabozantinib and 75.6% (95% CI, 70.5%–80%) with sunitinib. The combination of nivolumab plus cabozantinib also resulted in an ORR of 55.7% (95% CI, 50.1%–61.2%). Complete responses were noted in 8.0% of patients treated with this regimen. Median duration of response for patients treated with nivolumab plus cabozantinib was 20.2 months.

The final combination was evaluated in the phase III CLEAR study, which led to the approval of lenvatinib plus pembrolizumab for the treatment of mRCC.[5] This study stratified patients by Memorial Sloan Kettering Cancer Center risk criteria and randomly assigned patients with untreated mRCC to receive lenvatinib plus pembrolizumab, lenvatinib plus everolimus, or sunitinib. Again, OS was improved across risk groups with the use of lenvatinib plus pembrolizumab compared with sunitinib (HR, 0.66; 95% CI, 0.49–0.88; p = .005). The combination of lenvatinib plus pembrolizumab resulted in an ORR of 71.1%, with 16.1% of patients treated with this combination experiencing a CR. The median duration of response was 25.8 months (95% CI, 22.1–27.9). At a median follow-up of 26.6 months, 79.2% of patients receiving lenvatinib plus pembrolizumab were alive.

All four of these studies established that combination therapies with immune checkpoint inhibitors result in durable efficacy. However, treatment of patients with responses to immune checkpoint inhibitors can be complicated, in part because of the propensity of immune checkpoint inhibitors to result in immune-mediated adverse events. Management of immune-mediated adverse events is well described,[19,20] but it is worthwhile to review the rate of immune-mediated adverse events in patients with mRCC treated with combination immune checkpoint inhibitor therapy. For example, in the CheckMate 214 study, 80% of patients treated with nivolumab plus ipilimumab had an immune-mediated adverse event; 35% required high-dose glucocorticoids.[2] In that trial, 22% of patients treated with nivolumab plus ipilimumab discontinued treatment as a result of a treatment-related adverse event. In the KEYNOTE-426 study, adverse events of interest were noted in 51.3% of patients treated with pembrolizumab plus axitinib.[3] As a result of those adverse events and the 28% rate of serious adverse events also occurring in patients treated with pembrolizumab plus axitinib, 44% of patients in the pembrolizumab plus axitinib group required interruption of pembrolizumab, 62% required interruption of axitinib, and 30% required interruption of both. Moreover, adverse events led to discontinuation of pembrolizumab, axitinib, or the combination in 21%, 20%, and 7% of patients, respectively. In the CheckMate 9ER study, immune-mediated adverse events led to treatment with high-dose glucocorticoids in 19.1% of patients receiving nivolumab plus cabozantinib. Discontinuation of at least one drug prior to progression occurred in 19.7% of patients, with 5.7% of patients requiring discontinuation of nivolumab and cabozantinib.[4] Among patients receiving pembrolizumab plus lenvatinib in the CLEAR study, 37.2% required treatment discontinuation, with 13.4% requiring discontinuation of the combination.[5] These combinations have not been studied with as much follow-up as nivolumab plus ipilimumab or pembrolizumab plus axitinib.

Although adverse events from VEGF-targeting agents tend to manifest early in treatment, immune-mediated adverse events from immune checkpoint inhibitors can occur at any time. Thus, vigilance is required, even in patients who have had a sustained response to immune checkpoint inhibitor therapy. Extended follow-up in the CheckMate 214 and KEYNOTE-426 trials has been reassuring; no worsening of safety events were observed with extended treatment.[17,18] Interestingly, examining the current regimens for first-line treatment of mRCC, there are data that durable responses can persist, despite discontinuation of therapy because of adverse events. In one small retrospective study of 19 patients with mRCC who experienced any clinical benefit from PD-1 or PD-L1 inhibitor therapy and who also discontinued all systemic therapy because of immune-mediated adverse events, 68% of patients experienced a durable benefit of at least 6 months off-therapy, and 36% remained off subsequent treatment for more than 1 year.[21] This small study supports treatment holidays for patients with mRCC who experience immune-mediated adverse events that are severe enough to require treatment discontinuation. Similar trends have been seen in patients with advanced melanoma who are treated with immune checkpoint inhibitors and experience immune-mediated adverse events.[22]

FURTHER MANAGEMENT IN METASTATIC RENAL CELL CARCINOMA

Because patients with immune-mediated adverse events may have a durable response, despite discontinuation of therapy, there has been interest in determining whether a response-adaptive approach could be taken to therapy. The phase II TITAN-RCC trial enrolled patients with mRCC who were treatment naive or had received one prior VEGF tyrosine kinase inhibitor. Patients were treated with nivolumab every 2 weeks for four cycles of therapy. Those patients with a PR or CR were continued on nivolumab alone, whereas those with stable disease or progression received intensified therapy with the addition of ipilimumab.[23] Of the 108 patients who were treatment naive and were treated with nivolumab monotherapy, ORR was 28.7%. The ORR increased to 37% when including patients who went on to receive nivolumab with ipilimumab. In another phase II study, the OMNIVORE trial, immune checkpoint inhibitor–naive patients with mRCC received nivolumab alone. If a PR or CR was confirmed within

6 months of treatment, nivolumab was discontinued; it was reinitiated only if progressive disease developed.[24] Patients with stable disease continued treatment with nivolumab while receiving additional intensified therapy with two doses of ipilimumab. Partial responses were seen in 11% of patients, with 45% of these patients remaining off nivolumab for at least 1 year. Of those who had stable disease after treatment with nivolumab, 4% converted to a PR with intensification of ipilimumab. This study argues against premature discontinuation of nivolumab, as well as deintensification of nivolumab plus ipilimumab.

In contrast to efforts at deintensification, an ongoing trial in patients with intermediate- or poor-risk mRCC is evaluating the possibility of improved response with early incorporation of VEGF-targeting therapy. In the Alliance A031704 (PDIGREE) trial, patients with untreated intermediate- or poor-risk mRCC received nivolumab plus ipilimumab.[25] If patients experience a PR or stable disease after initial treatment with four cycles of nivolumab plus ipilimumab, they will be randomly selected to receive nivolumab alone or nivolumab plus cabozantinib. The primary objective of the trial is OS; thus, it will evaluate whether early introduction of cabozantinib is beneficial to patients with incomplete responses to immune checkpoint inhibitor therapy.

Data are limited with regard to rechallenging with immune checkpoint inhibitor therapy after progression on initial immune checkpoint inhibitor–based treatment. A retrospective analysis of 69 patients who had been treated with at least two lines of immune checkpoint inhibitor–based therapy evaluated responses and immune-mediated adverse events.[26] Although most patients discontinued treatment as a result of disease progression or immune-mediated adverse events, the ORR to second treatment with immune checkpoint inhibitor–based therapy was 23%. Responses appeared to be more likely in those with previous responses to immune checkpoint inhibitors. Among patients receiving a rechallenge with immune checkpoint inhibitor therapy, 16% had grade 3 or higher immune-mediated adverse events.

A phase II study of lenvatinib combined with pembrolizumab enrolled patients who had experienced disease progression after at least two doses of immune checkpoint inhibitor therapy.[27] In this study, the ORR was 55% (95% CI, 45%–65%), with a median duration of response of 12 months (95% CI, 9–18). This response appeared to be independent of prior immune checkpoint inhibitor combination therapy. Data are not available about whether the patients had a previous response to immune checkpoint inhibitors. There may be a role for novel immune checkpoint inhibitor combinations in patients with mRCC progressing on initial immune checkpoint inhibitor treatment; however, further studies are needed.

Many of the therapies available for the treatment of mRCC, such as sunitinib, pazopanib, and axitinib, were developed prior to the adoption of immune checkpoint inhibitors in the first-line setting. Thus, there is a paucity of prospective data on the efficacy of treatments in patients with mRCC who have previously been treated with or responded to immune checkpoint inhibitors. The phase III METEOR study, which established the superior efficacy of nivolumab compared with cabozantinib in patients with refractory mRCC, allowed for patients with prior immune checkpoint inhibitor therapy.[28] When the 32 patients with prior immune checkpoint inhibitor treatment were evaluated, ORR was 22% for cabozantinib compared with 0% for everolimus. Median OS was not reached for patients treated with cabozantinib.[28]

Some retrospective studies have also evaluated VEGF-targeting agents after immune checkpoint inhibitor therapy. A retrospective analysis of 86 patients with mRCC who received cabozantinib after progression on immune checkpoint inhibitors or immune checkpoint inhibitor combinations found that 36% of patients (95% CI, 26%–47%) had an ORR.[29] The median OS in these patients was 13.1 months (95% CI, 8.7–not reached). Another retrospective analysis of 84 patients with mRCC who received cabozantinib after nivolumab treatment revealed an ORR of 52%, with a median OS of 17.3 months.[29] In general, retrospective data suggest that VEGF-targeting agents still have efficacy in patients with mRCC who were previously treated with mRCC.[30,31] Thus, it is quite reasonable for patients who progress after immune checkpoint inhibitor therapy to be treated with VEGF-targeting agents with the expectation of similar responses as those previously seen in immune checkpoint inhibitor–naive patients.

RESPONSES IN METASTATIC UROTHELIAL CARCINOMA

Patients with mUC who are treated with immune checkpoint inhibitors generally fall into three categories: those who have experienced progression on platinum-based chemotherapy regimens, those who are cisplatin ineligible and have adequate expression of PD-L1, and those who are chemotherapy ineligible. A number of anti–PD-1 and anti–PD-L1 antibodies have been approved for treatment of mUC, although it should be noted that pembrolizumab and atezolizumab are the only immune checkpoint inhibitors that have been studied specifically in cisplatin-ineligible patients with mUC.

Patients with untreated cisplatin-ineligible mUC were studied in the IMvigor210 trial, a phase II study in which patients were treated with atezolizumab, an anti–PD-L1 antibody.[8] Among those patients, an ORR of 23% (95% CI, 16%–31%) was observed, with a CR rate of 9%. With a 17.2-month median follow–up, the median duration of response was not reached among these patients, and 70% of responses persisted. The KEYNOTE-052 trial was another

TABLE 1. Responses to Immune Checkpoint Inhibitors in Chemotherapy-Refractory Metastatic Urothelial Carcinoma

Agent	Mechanism	No. Patients	Follow-up, Median (range), Months	ORR (95% CI), %	CR, %	Median DOR, Months	Patients With Ongoing Responses, %
Atezolizumab[32]*	PD-L1 inhibitor	467	17.3	23 (15.6–31.9)	7	15.9	62
Avelumab[9]	PD-L1 inhibitor	44	16.5 (15.8–16.7)	18.2 (8.2–32.7)	11.4	Not reached	75
Durvalumab[11]*	PD-L1 inhibitor	191	5.78 (0.4–25.9)	17.8 (12.7–24)	3.7	Not reached	76.5
Nivolumab[10]	PD-1 inhibitor	270	7.00 (2.96–8.77)	19.6 (15.0–24.9)	2	Not reached	77
Pembrolizumab[13]	PD-1 inhibitor	270	27.7	21.1 (16.4–26.5)	9.3	Not reached	68

Abbreviations: DOR, duration of response; ORR, objective response rate.
*U.S. Food and Drug Administration approval was voluntarily withdrawn based on phase III data.

phase II study of untreated cisplatin-ineligible patients with mUC.[6] A single arm evaluated pembrolizumab in these patients; it resulted in an ORR of 28.6% (95% CI, 24.1%–33.5%), with 9% of patients experiencing a CR. After a median follow-up of 29.3 months, the median duration of response was 30.1 months (95% CI, 18.1 months–not reached). Of responding patients, 67% maintained a response for at least 12 months, and 52% maintained response for at least 24 months.

The IMvigor210 and KEYNOTE-052 studies treated patients regardless of PD-L1 status. Subsequent to the approval of atezolizumab and pembrolizumab, evaluation of data indicated that cisplatin-ineligible patients should only be treated if their tumor tissue exhibited adequate PD-L1 expression. In patients without adequate PD-L1 expression, atezolizumab and pembrolizumab resulted in detrimental outcomes compared with chemotherapy. However, for patients with adequate PD-L1 expression, response rates were only slightly more robust. In the IMvigor210 study, the ORR was 28% for patients with PD-L1 tumor-infiltrating cells at least 5%.[8] In the KEYNOTE-052 trial, for patients who had a PD-L1 combined positive score of at least 10, the ORR was 47.3%, with a 20% CR rate.[6]

Two phase III studies evaluated immune checkpoint inhibitors compared with chemotherapy in patients with mUC who had recurrence or progression after platinum-based chemotherapy. The phase III KEYNOTE-045 study was a randomized study of patients with mUC who were refractory to platinum-based treatment; it demonstrated that treatment with pembrolizumab resulted in superior OS compared with investigator's choice of paclitaxel, docetaxel, or vinflunine (HR, 0.73; 95% CI, 0.59–0.91; p = .002).[12,13] Among patients treated with pembrolizumab, the ORR was 21.1% (95% CI, 16.4%–26.5%), with 9.3% of patients experiencing a CR (95% CI, 6.1%–13.4%). After a median follow-up of 27.7 months, the median duration of response was not reached for pembrolizumab. Of patients who responded, 68% had a response persisting for at least 12 months. In terms of long-term responders, 9.8% of patients completed 2 years of pembrolizumab therapy. In contrast, atezolizumab was compared with chemotherapy in patients with mUC that was refractory to platinum-based treatment in the phase III IMVigor211 study.[32] In this study, atezolizumab was not associated with significantly improved OS compared with chemotherapy. Although ORR for atezolizumab versus chemotherapy was not significantly different (23% and 22%, respectively), the duration of response was longer in the atezolizumab group. With a median follow-up of 17.3 months, the median duration of response was 15.9 months (95% CI, 10.4 months–not reached) for patients treated with atezolizumab. Other single-arm phase II studies demonstrated that nivolumab, durvalumab, and avelumab have benefit in patients with mUC that is refractory to platinum-based treatment.[9-11] These are outlined in Table 1. Although the ORR for these immune checkpoint inhibitors ranges from 17.8% to 19.6%, CRs are observed and durable responses are seen with these treatments.[9-11] Of note, approvals for atezolizumab and durvalumab have recently been voluntarily withdrawn for patients with refractory mUC as the result of follow-up efficacy data from the phase III IMVigor211 and DANUBE studies, respectively.[32]

Similar to the treatment of mRCC, immune checkpoint inhibitors lead to adverse events in patients with mUC that require monitoring and vigilance (Table 2). The rate of grade 3/4 treatment-related adverse events ranges from 6.8% to 20% with immune checkpoint inhibitors in patients with mUC, and the rate of discontinuation ranges from 1.6% to 9.1%.[7,9-12] Interestingly, there are data suggesting that immune-mediated adverse events may be associated with responses to therapy in mUC, as well as in other solid tumors.[33-36] Again, as in mRCC, some of these responses persist despite discontinuation of therapy. Thus, patients with a response to immune checkpoint inhibitors who require discontinuation of therapy should be monitored for evidence of clinical or radiographic progression prior to initiating further treatment.

TABLE 2. Safety of Immune Checkpoint Inhibitors in Refractory Metastatic Urothelial Carcinoma

Agent	Grade 3/4 Treatment-Related AEs, %	Discontinuation Due to AEs, %
Atezolizumab[32]	20	7
Avelumab[9]	6.8	9.1
Durvalumab[11]	6.8	1.6
Nivolumab[10]	18	5
Pembrolizumab[13]	16.5	6.8

Abbreviation: AE, adverse event.

FURTHER MANAGEMENT IN METASTATIC UROTHELIAL CARCINOMA

Perhaps in contrast to the treatment of mRCC, patients with mUC who have been treated with immune checkpoint inhibitor therapy have been enrolled in recent trials evaluating agents that are now approved for the treatment of refractory mUC. For example, the phase II BLC2001 trial enrolled patients with mUC with prespecified FGFR alterations to receive erdafitinib.[37] Patients enrolled in this trial had progressed on at least one course of chemotherapy and were permitted to have received prior immune checkpoint inhibitors. Of the 99 patients enrolled, 22 (22%) had experienced progression or relapse after immune checkpoint inhibitor treatment; however, only one had exhibited a response prior to enrollment in the BLC2001 trial. Erdafitinib resulted in an ORR of 34% (95% CI, 25-44); however, the ORR was 59% among patients who were treated previously with immune checkpoint inhibitors. It appears that patients with FGFR3 mutations or FGFR2/3 fusion alterations do not tend to respond to immune checkpoint inhibitors. However, not enough patients with these FGFR alterations who respond to immune checkpoint inhibitors have been studied to conclude whether erdafitinib would benefit them, likely as a result of their scarcity.

Most notably, enfortumab vedotin, an antibody drug conjugate that targets nectin-4, which is highly expressed in urothelial cancer, was studied in the phase II EV-201 trial.[38] To be eligible for enrollment, the trial required that patients with mUC had been treated with platinum-based chemotherapy and a immune checkpoint inhibitor. The ORR was 44% (95% CI, 35.1%–53.2%) for the 125 patients enrolled in the trial. Of the patients treated with enfortumab vedotin, those who were deemed to be prior responders to immune checkpoint inhibitors had a better ORR (56%; 95% CI, 34.9%–75.6%) compared with patients classified as nonresponders (ORR, 41%; 95% CI, 31.3%–51.3%). Based on the results of that trial, enfortumab vedotin was approved by the U.S. Food and Drug Administration. A follow-up phase III study (EV-301 study), in which patients who were refractory to platinum and had immune checkpoint inhibitor exposure were randomly selected to receive enfortumab vedotin or investigator-chosen chemotherapy, confirmed the efficacy of enfortumab vedotin.[39] That study demonstrated that enfortumab vedotin had superior OS (HR, 0.70; 95% CI, 0.56–0.89; p = .001).

Based on these data, patients with mUC who have experienced progression after immune checkpoint inhibitors should be treated first with enfortumab vedotin. Trials studying the combination of enfortumab vedotin with pembrolizumab are ongoing; the results could further alter the treatment landscape for mUC.

CONCLUSION

The rapidly evolving landscape of treatment of mRCC and mUC has now incorporated immune checkpoint inhibitor treatment in nearly all patients. Combinations of immune checkpoint inhibitors or immune checkpoint inhibitors with VEGF-targeting agents have become first-line therapy for mRCC and they result in substantial and durable responses. Currently, single-agent immune checkpoint inhibitors have established efficacy in the treatment of mUC, with durable responses observed. Although treatment discontinuations are sometimes required because of immune-mediated adverse events, a large portion of patients continue to respond to therapy and enjoy a treatment-free interval. Future studies should include endpoints, such as time to subsequent therapy or treatment-free survival, to better quantify the nature of durable PRs and CRs. Patients with mUC who were treated previously with immune checkpoint inhibitors should be treated with enfortumab vedotin at the time of progression, given the robust data regarding its efficacy. Immune checkpoint inhibitors combined with novel agents may further alter the treatment landscape in mUC. In patients with mRCC who were previously treated with immune checkpoint inhibitors, single-agent VEGF-targeting agents are reasonable options for treatment. Future combinations of immune checkpoint inhibitors, alone or with novel agents in the second- and third-line setting in mRCC, may result in further responses to immunotherapy. More studies are needed to better characterize responders to immune checkpoint inhibitors and whether their responses are associated with true differences in responses to subsequent therapy.

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REFERENCES

1. Blank CU, Haanen JB, Ribas A, et al. CANCER IMMUNOLOGY. The "cancer immunogram". Science. 2016;352:658-660.
2. Motzer RJ, Tannir NM, McDermott DF, et al; CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378:1277-1290.
3. Rini BI, Plimack ER, Stus V, et al; KEYNOTE-426 Investigators. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380:1116-1127.
4. Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2021;384:829-841.
5. Motzer R, Alekseev B, Rha SY, et al; CLEAR Trial Investigators. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med. 2021;384:1289-1300.
6. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017;18:1483-1492.
7. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016;387:1909-1920.
8. Balar AV, Galsky MD, Rosenberg JE, et al; IMvigor210 Study Group. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017;389:67-76.
9. Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study. J Clin Oncol. 2017;35:2117-2124.
10. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017;18:312-322.
11. Powles T, O'Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA Oncol. 2017;3:e172411.
12. Bellmunt J, de Wit R, Vaughn DJ, et al; KEYNOTE-045 Investigators. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med. 2017;376:1015-1026.
13. Fradet Y, Bellmunt J, Vaughn DJ, et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. Ann Oncol. 2019;30:970-976.
14. Motzer RJ, Escudier B, McDermott DF, et al; CheckMate 025 Investigators. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1803-1813.
15. Donskov F, McDermott DF, Lee JL, et al. KEYNOTE-427 cohort A: pembrolizumab monotherapy as first-line therapy in advanced clear cell renal cell carcinoma (ccRCC). Ann Oncol. 2018;29(suppl 8):VIII307.
16. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27:5794-5799.
17. Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open. 2020;5:e001079.
18. Powles T, Plimack ER, Soulières D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. Lancet Oncol. 2020;21:1563-1573.
19. Puzanov I, Diab A, Abdallah K, et al; Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5:95.
20. Haanen JBAG, Carbonnel F, Robert C, et al; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv264-iv266.
21. Martini DJ, Hamieh L, McKay RR, et al. Durable clinical benefit in metastatic renal cell carcinoma patients who discontinue PD-1/PD-L1 therapy for immune-related adverse events. Cancer Immunol Res. 2018;6:402-408.

22. Robert C, Ribas A, Hamid O, et al. Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. J Clin Oncol. 2018; 36:1668-1674.
23. Grimm MO, Schmidinger M, Duran Martinez I, et al. Tailored immunotherapy approach with nivolumab in advanced renal cell carcinoma (TITAN-RCC). Ann Oncol. 2019;30(suppl 5):v892.
24. McKay RR, McGregor BA, Xie W, et al. Optimized management of nivolumab (Nivo) and ipilimumab (Ipi) in advanced renal cell carcinoma (RR): a response-based phase II study (OMNIVORE). J Clin Oncol. 2020;38:4240-4248.
25. Zhang T, Ballman KV, Choudhury AD, et al. PDIGREE: an adaptive phase 3 trial of PD-inhibitor nivolumab and ipilimumab (IPI-NIVO) with VEGF TKI cabozantinib (CABO) in metastatic untreated renal cell cancer (Alliance A031704). J Clin Oncol. 2019;37 (15 suppl; abstr TPS4596).
26. Ravi P, Mantia C, Su C, et al. Evaluation of the safety and efficacy of immunotherapy rechallenge in patients with renal cell carcinoma. JAMA Oncol. 2020; 6:1606-1610.
27. Lee CH, Shah AY, Hsieh JJ, et al. Phase II trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) for disease progression after PD-1/PD-L1 immune checkpoint inhibitor (ICI) in metastatic clear cell renal cell carcinoma (mccRCC). J Clin Oncol. 2020;38 (15 suppl; abstr 5008) .
28. Powles T, Motzer RJ, Escudier B, et al. Outcomes based on prior therapy in the phase 3 METEOR trial of cabozantinib versus everolimus in advanced renal cell carcinoma. Br J Cancer. 2018;119:663-669.
29. McGregor BA, Lalani AA, Xie W, et al. Activity of cabozantinib after immune checkpoint blockade in metastatic clear-cell renal cell carcinoma. Eur J Cancer. 2020; 135:203-210.
30. Iacovelli R, Ciccarese C, Facchini G, et al. Cabozantinib after a previous immune checkpoint inhibitor in metastatic renal cell carcinoma: a retrospective multi-institutional analysis [published correction appears in *Target Oncol*. 2020;15:691]. Target Oncol. 2020;15:495-501.
31. Deuker M, Chun FKH, Karakiewicz PI. Second-line tyrosine kinase inhibitor-therapy after immunotherapy-failure. Curr Opin Support Palliat Care. 2020; 14:276-285.
32. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2018;391:748-757.
33. Kijima T, Fukushima H, Kusuhara S, et al. Association between the occurrence and spectrum of immune-related adverse events and efficacy of pembrolizumab in Asian patients with advanced urothelial cancer: multicenter retrospective analyses and systematic literature review. Clin Genitourin Cancer. 2020; S1558-7673-4.
34. Maillet D, Corbaux P, Stelmes JJ, et al. Association between immune-related adverse events and long-term survival outcomes in patients treated with immune checkpoint inhibitors. Eur J Cancer. 2020;132:61-70.
35. Gauci M-L, Lanoy E, Champiat S, et al. Long-term survival in patients responding to anti-PD-1/PD-L1 therapy and disease outcome upon treatment discontinuation. Clin Cancer Res. 2019;25:946-956.
36. Shimozaki K, Sukawa Y, Beppu N, et al. Multiple immune-related adverse events and anti-tumor efficacy: real-world data on various solid tumors. Cancer Manag Res. 2020;12:4585-4593.
37. Loriot Y, Necchi A, Park SH, et al; BLC2001 Study Group. Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med. 2019;381:338-348.
38. Rosenberg JE, O'Donnell PH, Balar AV, et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. J Clin Oncol. 2019;37:2592-2600.
39. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med. 2021;384:1125-1135.

Next Steps: Sequencing Therapies in Metastatic Kidney Cancer in the Contemporary Era

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overview

Systemic therapy for first-line metastatic renal cell carcinoma has evolved toward immune checkpoint blockade combinations incorporating a PD-1/L1 inhibitor along with CTLA-4 inhibition or VEGF-targeted therapy. The new treatment paradigm that integrates immunotherapy for treatment-naïve advanced metastatic renal cell carcinoma creates a new therapeutic challenge for clinicians including the optimal way to integrate multidisciplinary care involving surgery, radiotherapy, and application of contemporaneous systemic treatment in subsequent lines of therapy following discontinuation of combination therapy. We outline the available data for the multidisciplinary management of metastatic renal cell carcinoma, systemic therapy options in the post–immune checkpoint blockade setting, and novel therapies in development for advanced renal cell carcinoma. We provide practical considerations to assist clinicians in treatment choice and map future directions for progress.

Combination therapy incorporating immune checkpoint blockade (ICB) with a PD-1/L1 inhibitor along with CTLA-4 inhibition or VEGF-targeted therapy has created a new standard of care with improved outcomes for patients with metastatic renal cell carcinoma (mRCC).[1-4] Historical data used to guide treatment decisions and inform guideline recommendations were from the era predating ICB. As patients now develop resistance or toxicity to ICB in the first-line treatment of mRCC, a new challenge has emerged of how to optimally treat patients in the second line who have received first-line immunotherapy. The applicability of evidence formed in the context of a targeted therapy or cytokine backbone requires repeat evaluation for the application of subsequent systemic therapies and integration of complementary modalities of surgery and radiotherapy.

ROLE OF VEGF-TARGETED THERAPY FOLLOWING IMMUNOTHERAPY

Data for the role of VEGF-targeted agents following immunotherapy stem from small prospective cohorts and collection of retrospective series (Table 1). Prospective data come from a phase II trial where dose escalation of axitinib was performed in 40 patients who had received ICB (alone or in combination) as the most recent line of therapy. Seventy-two percent of patients had at least two prior systemic therapies, and 70% received prior VEGF therapy. Although the trial did not meet its primary endpoint (an improvement in progression-free survival [PFS] from 6.5 to 9.5 months defined from historical cohorts), the reported 8.8-month PFS and overall response rate (ORR) of 45% are favorable in a pretreated setting; dose-titrated axitinib was safe and active in the post-ICB space.[5]

The utility of tivozanib post-ICB was detailed in a posthoc analysis from the TIVO-3 study, where tivozanib was compared with sorafenib as third- or fourth-line therapy in mRCC. In 91 patients (26% of 350 total patients) having previously received treatment with ICB, median PFS favored tivozanib at 7.3 months compared with 5.1 months with sorafenib (hazard ratio [HR], 0.55; 95% CI, 0.32–0.94). Overall response rate was not reported within the ICB cohort but was 18% for tivozanib and 8% for sorafenib in the intention-to-treat population.[7]

Data outlining VEGF blockade single-agent activity are also available from a posthoc analysis of the METEOR trial, which compared cabozantinib to everolimus for patients with VEGF-pretreated mRCC. Of 32 patients who had received prior ICB therapy (5% of the total cohort), activity metrics favored cabozantinib over everolimus consistent with the overall population, with ORR of 22% versus 0%, median PFS (HR, 0.22; 95% CI, 0.07–0.65), and overall survival (OS; HR, 0.56; 95% CI, 0.21–1.52).[6] The single-agent activity of cabozantinib is also reported in a large retrospective series by McGregor et al[18] in 86 patients with a median of two total lines of prior therapy. Cabozantinib demonstrated an ORR of 36% with a median time to treatment failure of 6.5 months.[6]

Large retrospective series have detailed the utility of VEGF monotherapy, reporting the pooled activity for multiple tyrosine kinase inhibitors following treatment with ICB. These series differ in the number of lines of

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PRACTICAL APPLICATIONS

- Choice of second-line systemic treatment is dependent on the agent(s) used in the frontline setting; use of VEGF inhibition is supported by prospective clinical data and retrospective series.
- Treatment utilizing a second immune checkpoint blockade combination regimen appears active and safe; the activity relative to VEGF monotherapy is unclear.
- Surgery remains an important modality, preferentially used when patients can have the majority of their disease burden resected (cytoreduction) or rendered free of macroscopic disease (metastasectomy).
- Stereotactic body radiation therapy use has high rates of locoregional control, but the role for synergy with systemic treatment for patients with oligometastatic and oligoprogressive disease is still being defined.
- Clinical trials are important to inform future practice; novel agents such as HIF-2α antagonists demonstrate activity in patients pretreated with immune checkpoint blockade.

prior therapy, prior ICB regimen, timing of exposure to prior ICB, and prior VEGF-directed therapy. Collectively, the ORR ranges from 13%–36%, with a median PFS or time to treatment failure of 4 to 13 months (Table 1).

Data also support the combination of VEGF- and mTOR-targeted therapy with lenvatinib/everolimus. Wiele et al[9] conducted a retrospective study of patients treated with lenvatinib alone (30%) or in combination with everolimus (70%) following ICB. Patients had received at least two (median, 4) prior lines of therapy. The combination strategy yielded an ORR of 30% with a median PFS of 4.2 months and median OS of 10.8 months.[9] A small case series also detailed the activity of lenvatinib and everolimus in patients whose tumors were refractory to first-line therapy with tyrosine kinase inhibitor or ICB. Hamieh et al[10] described the outcomes in seven patients, five of which had been exposed to ICB. In this limited series, two of five patients (40%) with primary progression on ICB-based therapy (both pretreated with ipilimumab/nivolumab) had tumors that responded to lenvatinib/everolimus.

Collectively, this prospective and retrospective data support the role of VEGF inhibition following ICB. Further prospective trials are warranted to investigate the relative efficacy of these agents alone or in combination following modern frontline regimens, which include ICB combination therapies.

ROLE OF IMMUNE CHECKPOINT BLOCKADE FOLLOWING IMMUNOTHERAPY

The combination of ipilimumab and nivolumab improves outcomes compared with sunitinib in intermediate and poor International mRCC Database Consortium risk mRCC.[1] Given that single-agent anti–PD-1 monotherapy is well tolerated and associated with a significant response rate and durable remission, an important clinical question is whether toxicity may be reduced by avoiding the upfront use of ipilimumab in some patients by starting on nivolumab monotherapy, with "salvage" ipilimumab administered for nonresponding or progressive disease.[19] Three trials (TITAN-RCC, OMNIVORE, and HCRN GU16-260), utilizing an adaptive therapy design, have interrogated this question and provide evidence on the activity of ipilimumab/nivolumab in a group of patients who experience primary progression on, or achieve a best response of stable disease to nivolumab monotherapy (Table 2).[20-22] These trials were not performed in a uniform setting, differing in the proportion of pretreated patients and the number of salvage ipilimumab cycles delivered. However, the additional response rate is consistent between studies at 5%–15% with addition of ipilimumab to nivolumab, with limited complete responses reported.

Further evidence comes from the FRACTION-RCC study, an open-label, randomized, phase II trial.[23] In contrast to the adaptive trial designs outlined above, track 2 of this study evaluated the activity of ipilimumab/nivolumab for patients who had been heavily pretreated (50% received three or more lines of prior therapy), and all had eventually progressed on PD-1/L1 immunotherapy (as opposed to receiving ipilimumab for nonresponse). The primary endpoint, ORR, was 15%; seven of 46 patients had tumors that achieved a partial response, duration of response ranged from 2–19 months, and no patients experienced a documented complete response. The median PFS was 3.7 months (95% CI, 2.2–7.3). These data indicate that there is a potential role of ipilimumab blockade, though efficacy parameters appear inferior to use in the frontline setting.

Additional data on the activity of ipilimumab and nivolumab in a real-world setting following progression or exposure to prior PD-1/L1 therapy stem from a retrospective series by Gul et al.[24] This retrospective multi-institutional analysis included 45 patients who received salvage ipilimumab/nivolumab after a median of three lines of prior therapy that included PD-1/L1 with or without VEGF therapy.[24] At a median follow-up of 12 months, the ORR was 20%; nine patients (20%) had tumors achieving a partial response and seven patients (16%) had stable disease. The median PFS was 4 months (range, 0.8–19 months), with median duration of response of 7 months (range, 2–17 months).

TABLE 1. Activity of Targeted Therapy Following Immune Checkpoint Blockade

Author	Study	Agents	No. of Patients	ORR	PFS/TTF
Ornstein et al[5]	Prospective; phase II	Axitinib, dose titrated	38	45%	8.8 months
Choueiri et al[6]	Subgroup; phase III, METEOR	Cabozantinib/everolimus	32	22%	NR/4.1 months
Rini et al[7]	Subgroup; phase III, TIVO-3	Tivozanib	47	NR	7.3 months
Singh et al[8]	Retrospective	Cabozantinib	86	36%	6.5 months
Wiele et al[9]	Retrospective	Lenvatinib +/– everolimus	40	30%	4.2 months
Hamieh et al[10]	Retrospective	Lenvatinib + everolimus	5	40%	NR
Shankar et al[11]	Retrospective	VEGF TKI	70	41%	13.2 months
Powles et al[12]	Retrospective	VEGF TKI	70	28%	6.4 months
Hammers et al[13]	Retrospective	VEGF TKI	56	13%	6.9 months
Ravi et al[14]	Retrospective	VEGF TKI	56	33%	8.0 months
Choueiri et al[15]	Retrospective	VEGF TKI	55	30%	3.7/5.4 months*
Choueiri et al[16]	Retrospective	VEGF TKI	33	36%	8 months
Tykodi et al[17]	Retrospective	VEGF TKI	33	29%	6.4 months

Abbreviations: ORR, overall response rate; PFS, progression-free survival; TTF, time to treatment failure; NR, not reported; TKI, tyrosine kinase inhibitor.
*Following immune checkpoint blockade-VEGF and ipilimumab-nivolumab combination, respectively.

Overall, in patients who have been previously exposed to or progressed on PD-1/L1 therapies, the use of ipilimumab/nivolumab provides a response rate of 5%–15%, with limited complete responses observed. The duration of response in patients with tumors that respond remains poorly defined with low sample sizes, a heterogeneous population, and limited follow-up duration. The additional benefit of continuing nivolumab during ipilimumab salvage therapy remains unresolved; given the long biologic half-life of ICB, there may be limited benefit in continuing PD-1 therapy with concurrent ipilimumab. Yang et al[25] previously reported a response rate of 13% for ipilimumab monotherapy in patients with cytokine-pretreated mRCC, albeit utilizing higher doses of ipilimumab to 3 mg/kg.[25]

Given the activity of combinations in first-line therapy, an enticing strategy is to incorporate VEGF inhibition with PD-1/L1 blockade in patients pretreated with ICB therapy. Following promising activity in a phase Ib/II trial, the combination of lenvatinib 20 mg daily and pembrolizumab was tested in a phase II expansion cohort of 104 patients with mRCC, all of whom had recently progressed on PD-1/L1 inhibition; 65% had prior VEGF exposure, and most (58%) patients had received two or more prior anticancer regimens. Overall response rate was a robust 51% with a median PFS of 11.7 months and a median duration of response of 9.9 months.[26]

The activity of immunotherapy combinations other than nivolumab and ipilimumab have been detailed in a retrospective series from Ravi et al[27] who described the outcomes of utilizing a second ICB-containing regimen in a multicenter study of 69 patients with mRCC. The majority of patients had previously received single-agent ICB (27 patients; 39%) or ICB in combination with a VEGF-targeted therapy (29 patients; 42%) as the prior immunotherapy regimen. Immune checkpoint blockade rechallenge included mixed regimens; salvage PD-1/L1 plus a VEGF pathway–targeted agent (42%), PD-1/L1 monotherapy (39%), or ipilimumab/nivolumab therapy (13%). Use of a second ICB regimen was associated with an ORR of 23%, and 16% of patients experienced a grade 3 or higher immune-related adverse event.[27]

SAFETY OF RECHALLENGE WITH IMMUNE CHECKPOINT BLOCKADE

The presence of comorbid autoimmune disease or prior immune-related adverse events is important when considering subsequent systemic therapy incorporating ICB.

Limited data suggest that rechallenge with ICB following interruption for toxicity appears safe. Abou Alaiwi et al[28] performed a multicenter retrospective study that identified patients with mRCC treated with ICB who had more than 1 week of therapy interruption for immune-related adverse events. Within this cohort, 47% had experienced a grade 3 or 4 event. After retreatment following a median treatment interruption of approximately 1 month, 50% experienced subsequent immune-related adverse events (12 new, 6 recurrent) with 19% being grade 3 or greater events. Rechallenge resulted in 23% additional complete or partial responses in patients whose disease had not previously responded. Clinicians who rechallenged ICB in this cohort likely selected patients in whom serious sequelae from the

TABLE 2. Regimen Activity in Patients Exposed to Prior Immunotherapy

	TITAN-RCC[21]	OMNIVORE[22]	HCRN GU16-260[20]	FRACTION-RCC[23]	Gul et al[24]	Yang et al[25]
Regimen (mg/kg)	Nivo 3/ipi 1	Nivo 3/ipi 1	Nivo 3/ipi 1	Nivo 3/ipi 1	Nivo 3/ipi 1	Ipi 1 or 3
Total Patients	207	83	123	46	45	61
ccRCC, (n [%])	207 (100)	80 (99)	123 (100)	44 (96)	40 (89)	61 (100)
First-Line (n [%])	108 (52)	42 (51)	123 (100)	1 (2)	0 (0)	0 (0)
Prior VEGF	Yes	Yes	No	Yes	Yes	No
Induction Nivo Duration (months)	4	6	3	NA	NA	NA
Salvage Nivo/Ipi Cycles (n)	4	2	4	4	4	NA
IMDC Risk (%)	—	—	—	—	—	—
Favorable	3	33	24	NR	20	NR
Intermediate	71	54	65	NR	64	NR
Poor	27	13	10	NR	7	NR
ORR for Nivo/Ipi (%)	12	4	13	15	20	13 *for ipi
CR (%)	3	0	0	0	0	0

Abbreviations: nivo, nivolumab; ipi, ipilimumab; ccRCC, clear cell renal cell carcinoma; NA, not applicable; IMDC, International mRCC Database Consortium; NR, not reported; ORR, overall response rate; CR, complete response.
*3 mg/kg loading followed by 1 mg/kg (cohort A) or 3 mg/kg (cohort B) very 3 weeks.

primary immune-related adverse events were considered a limited risk in the event of recurrence. Notably, one-third of the immune-related adverse events observed with rechallenge constituted a new, rather than recurrent, toxicity. Serious adverse events such as neurologic sequelae or myocarditis would represent a contraindication to rechallenge. Furthermore, where an immune-related adverse event had been experienced on ipilimumab/nivolumab, the future use of single-agent PD-1/L1 is likely associated with a lower risk of further immune-related adverse events compared with ipilimumab rechallenge.[28]

INTEGRATION OF SURGERY AND RADIATION THERAPY IN THE MANAGEMENT OF METASTATIC RENAL CELL CARCINOMA

The role of surgery and radiotherapy in treating mRCC are both evolving (Tables 3 and 4). The precise role of surgery and its timing with systemic therapy in treating patients with mRCC remains controversial, especially in the context of contemporary frontline treatment combinations for patients with advanced disease. Risk stratification is an important element of determining prognosis and selecting treatments for patients with mRCC. The Memorial Sloan Kettering Cancer Center/Motzer and International mRCC Database Consortium/Heng criteria are two models that use baseline serum laboratory values and clinical factors to assign patients to either favorable, intermediate, or poor risk categories.[29,30] These models have been widely used to better inform prognosis, to interpret study results, and more recently to guide therapy selection for treatment-naïve patients with advanced disease. Moreover, differences in survival based on histologic subtype and location of metastasis may also help guide selecting patients for surgery.[31]

Surgical options for mRCC encompass both cytoreductive nephrectomy and metastasectomy. Cytoreductive nephrectomy is thought to palliate symptoms and prolong survival in patients with mRCC, potentially mediated through enhancement of the antineoplastic immunologic response by removal of an "immunologic sink," where circulating antibodies and lymphocytes may be diverted to the primary tumor and away from distant metastases, or through decreased production of cytokines and growth factors by the primary tumor.[32,33] Cytoreductive nephrectomy can also be performed to relieve tumor-related symptoms, such as hematuria or pain.

Similarly, metastasectomy is generally used to supplement resection of the primary tumor and systemic therapy to improve survival and delay disease progression in carefully selected patients, predominantly those with International mRCC Database Consortium favorable risk disease where complete resection of oligometastatic disease is feasible.[34] Radiation therapy, delivered via stereotactic body radiation therapy (SBRT), can be used as metastasis-directed therapy and is now being investigated to treat the primary tumor in combination with systemic therapy.

Cytoreductive Nephrectomy

Cytoreductive nephrectomy became the gold standard for treating mRCC in the 2000s after the SWOG-8949 and EORTC-3047 trials both demonstrated increased OS for patients with mRCC who underwent cytoreductive nephrectomy

TABLE 3. Select Ongoing Clinical Trials Investigating Cytoreductive Nephrectomy or Metastasectomy With Systemic Therapy

Trial Number (Trial Name)	Phase	No. of Patients	Treatment Sequence	Primary Endpoint	Status	Trial Start
NCT03977571 (NORDIC-SUN)	III	400	(1) Nivolumab/ipilimumab → CN → nivolumab (2) Nivolumab/ipilimumab → nivolumab	OS	Recruiting	September 2019
NCT04510597 (PROBE)	III	364	(1) Nivolumab, pembrolizumab, or avelumab → ongoing (2) Nivolumab or pembrolizumab or avelumab → CN → systemic therapy	OS	Recruiting	November 2020
NCT04322955 (Cyto-KIK)	II	48	Nivolumab/cabozantinib → CN (cabozantinib stopped 21 or 14 days prior) → nivolumab/cabozantinib	Complete response	Recruiting	March 2020
NCT04370509	II	84	(1) Pembrolizumab → CN or metastasectomy → pembrolizumab (2) Pembrolizumab + axitinib → CN or metastasectomy → pembrolizumab + axitinib	Tumor-infiltrating immune cells	Recruiting	November 2020
NCT02210117	I	105	(1) Nivolumab/bevacizumab → CN → nivolumab (2) Nivolumab/ipilimumab → CN → nivolumab	Adverse events	Active	November 2014
NCT03473730	I	30	Daratumumab → CN → daratumumab	Adverse events	Recruiting	May 2018
NCT03324373	I	15	Lenvatinib/everolimus → CN → systemic therapy	Adverse events	Recruiting	March 2019

Abbreviations: CN, cytoreductive nephrectomy; OS, overall survival.

with interferon alfa-2b compared with interferon alfa-2b alone.[35-37] However, as the armamentarium of systemic therapies has significantly expanded and outpaced surgical clinical trials, data incorporating the use of systemic therapy in conjunction with cytoreductive nephrectomy have been largely limited to retrospective studies.[38]

In 2018 and 2019, two landmark trials, CARMENA and SURTIME, respectively, were published that challenged the value of cytoreductive nephrectomy for patients receiving frontline single-agent VEGF inhibition.[39,40] CARMENA (NCT00930033), a noninferiority randomized phase II trial that was open to accrual for 8 years but closed before reaching its planned enrollment target of 576 patients, randomly assigned 450 patients with Memorial Sloan Kettering Cancer Center intermediate and poor risk clear cell mRCC to receive either cytoreductive nephrectomy followed by sunitinib or sunitinib alone. Notably, 18% of patients in the cytoreductive nephrectomy/sunitinib group never received systemic therapy, and 17% in the sunitinib-only group ultimately underwent cytoreductive nephrectomy. The trial population differed from that traditionally thought to benefit from cytoreductive nephrectomy (favorable International mRCC Database Consortium risk patients and/or those with limited extrarenal disease), as 43% of patients harbored Memorial Sloan Kettering Cancer Center poor risk disease reflected in the control arm OS of 18 months compared with 22–26 months in contemporary VEGF trials. After 50.9 months of follow-up, there was nodifference in OS between the sunitinib-only and cytoreductive nephrectomy/sunitinib groups (18.4 vs. 13.9 months, respectively; HR, 0.89; 95% CI, 0.71–1.10) demonstrating that the results of the sunitinib-only group were noninferior to those in the cytoreductive nephrectomy followed by sunitinib group.[40] Subsequent subgroup analyses (that were not prespecified) have explored outcomes based on International mRCC Database Consortium risk score; for intermediate risk patients with two risk factors, the sunitinib alone group demonstrated a median OS of 16.6 months compared with 31.2 months for sunitinib with cytoreductive nephrectomy (HR, 0.61; 95% CI, 0.41–0.91; p = .015). However, of the 48% of patients who had one risk factor (interval between diagnosis and treatment less than 1 year), the use of cytoreductive nephrectomy in combination with sunitinib suggests a modest benefit compared with sunitinib alone (median OS, 30.5 vs. 25.2 months; HR, 1.24; 95% CI, 0.81–1.90).

The phase III SURTIME trial (NCT01099423) evaluated the optimal sequencing of targeted therapy and cytoreductive

TABLE 4. Select Ongoing Clinical Trials Investigating Radiotherapy in the Treatment of mRCC

Trial Number (Name)	Phase	No. of Patients	Intervention	Control	Primary Endpoint(s)	Trial Start
NCT02811250 (RSR-1)	I	13	SBRT (8–12 Gy in 4–5 fractions)	NA	Safety	October 2010
NCT01896271	II	26	High-dose IL-2 + SBRT (8–20 Gy in 1–3 fractions)	NA	ORR	October 2013
NCT02019576	II	68	Sunitinib + SBRT to metastatic sites	NA	Locoregional control at 1 year	May 2014
NCT02306954	II	84	High-dose IL-2	High-dose IL-2 and SBRT (2 doses, 20 Gy)	ORR	December2014
NCT02781506	II	7	Nivolumab + SBRT (1–3 fractions)	NA	ORR	June 2016
NCT02599779 (OZM-065)	II	35	Pembrolizumab with SBRT at progression	Pembrolizumab lead-in SBRT given before second course of pembrolizumab	PFS	December 2016
NCT03065179 (RADVAX)	II	29	Ipilimumab + nivolumab + SBRT	NA	Safety	March 2017
NCT03469713 (NIVES)	II	69	Nivolumab + SBRT (30 Gy in 3 fractions)	NA	ORR	July 2017
NCT04299646 (GETUG-StORM-01)	II	114	Systemic treatment (VEGF, mTOR inhibitor, immunotherapy)	Systemic treatment + SBRT	PFS	July 2020
NCT04090710 (CYTOSHRINK)	II	78	Ipilimumab + nivolumab	Ipilimumab + nivolumab and SBRT (30–40 Gy in 5 fractions)	PFS	January 2020

Abbreviations: mRCC, metastatic renal cell carcinoma; SBRT, stereotactic body radiation therapy NA, not available; IL-2, interleukin-2; ORR, overall response rate; PFS, progression-free survival.

nephrectomy by randomly assigning patients to receive either upfront cytoreductive nephrectomy followed by sunitinib or sunitinib with subsequent cytoreductive nephrectomy. Enrollment was closed early given poor accrual leading to an underpowered analysis and difficult to draw conclusions. However, cytoreductive nephrectomy following sunitinib was demonstrated as safe and feasible. The intention-to-treat analysis displayed that median OS was longer for the delayed cytoreductive nephrectomy compared with the upfront cytoreductive nephrectomy arm (32.4 vs. 15.0 months, respectively; HR, 0.57; 95% CI, 0.34–0.95; p = .03).[39]

The imperfections of these studies underscore the importance of patient selection and highlight the need for high-quality prospective studies utilizing contemporary treatment strategies to optimally assess the role and timing of systemic therapy plus cytoreductive surgery.[38] The NORDIC-SUN trial (NCT03977571) is enrolling patients with International mRCC Database Consortium intermediate and poor risk treatment-naïve mRCC. Patients will be randomly assigned to receive delayed cytoreductive nephrectomy following induction treatment with ipilimumab and nivolumab, followed by maintenance nivolumab. The primary endpoint is OS with secondary endpoints including PFS, time to subsequent systemic therapy, and ORR.[41]

Two new trials investigating the role of cytoreductive nephrectomy with immuno-oncologic agents were opened in 2020. The phase III PROBE trial (NCT04510597) aims to enroll 364 patients with treatment-naïve mRCC who will undergo treatment with modern ICB combination therapies. Patients deemed surgical candidates will then be randomly assigned to receive either cytoreductive nephrectomy followed by the continuation of systemic therapy or systemic therapy alone. The primary endpoint is OS.[42]

Cyto-KIK (NCT04322955) is a phase II multicenter trial where patients with mRCC will receive cabozantinib and nivolumab in combination for 12 weeks prior to undergoing cytoreductive nephrectomy. Patients in both cohorts will resume systemic combination therapy postoperatively. The primary outcome is complete response rate with secondary outcomes being OS, PFS, primary tumor size reduction, toxicity, and surgical complications.[43]

Metastasectomy

Metastasectomy is another surgical option used in select patients with advanced RCC. Mostly performed for oligometastatic disease, much of the evidence surrounding

metastasectomy is derived from retrospective studies in the pretargeted therapy era and is likely influenced by selection bias with fitter patients harboring more favorable disease more likely to receive surgical intervention. A 2020 study using the Canadian Kidney Cancer information system compared 229 patients with mRCC diagnosed between 2011 and 2018 who underwent complete metastasectomy matched with 803 patients not treated with metastasectomy.[34] There was no difference in preoperative rates of treatment with targeted agents. After both 1 and 5 years, survival rates were higher in the metastasectomy group; these patients also exhibited longer time to initiation of systemic therapy after surgery.[34] A 2021 analysis investigating the utility of complete and incomplete metastasectomy in the era prior to frontline ICB regimens evaluated 314 patients with mRCC. After a mean follow-up of 25.3 months, those who underwent complete metastasectomy displayed longer OS than patients with incomplete or no metastasectomy. Metastasectomy status was found to be a predictor of OS on multivariate analysis.[44]

The role of systemic therapies to complement metastasectomy has not been well studied in mRCC. The best prospective evidence comes from the E2810 trial, an adjuvant trial of pazopanib versus placebo in patients rendered with no evaluable disease after metastasectomy. The trial enrolled 129 patients, and the study did not meet the primary endpoint of disease-free survival (HR, 0.85; 95% CI, 0.55–1.31; p = .47) in favor of pazopanib, with a trend toward worse OS with the pazopanib arm (HR, 2.65; 95% CI, 1.02–6.9; p = .05).[45] Trials evaluating the role of adjuvant VEGF tyrosine kinase inhibitor therapy following nephrectomy for localized disease also did not translate into an improvement in survival, although these did not include patients with metastatic disease rendered with no evaluable disease by surgical resection.[46-49] Current trials recruiting in the adjuvant space utilizing ICB with PD-1/L1 inhibitors may add useful insights. The KEYNOTE-564 trial is investigating adjuvant treatment following nephrectomy for high-risk localized disease and will include patients with metastatic disease that has been completely resected, utilizing pembrolizumab compared with placebo.[50] Similarly, the IMmotion010 trial is assessing the role of adjuvant atezolizumab following nephrectomy for high-risk localized disease and will include patients following complete resection of metastatic disease.[51] Also exploring the benefits of metastasectomy with targeted therapy and ICB, a phase II trial (NCT04370509) will randomly assign patients with advanced or mRCC to receive neoadjuvant pembrolizumab or pembrolizumab/axitinib followed by cytoreductive nephrectomy with or without metastasectomy followed by adjuvant therapy. The primary endpoint is an increase in tumor-infiltrating immune cells with secondary endpoints of OS, disease-free survival, and PFS.[4]

STEREOTACTIC BODY RADIATION THERAPY

Data supporting use of radiation therapy in treating RCC are limited but quickly expanding with the adoption of modern techniques.[52,53] Traditionally, RCC has been considered radio-resistant, but the advent of SBRT, which delivers very high localized doses of radiation, has demonstrated success in treating both localized and advanced RCC, with high rates of locoregional control and low rates of toxicity.[53] Moreover, SBRT has been used successfully to treat RCC brain metastases, a more common and problematic site of failure as systemic therapy improves.[54]

Considering the use of SBRT within a multidisciplinary treatment plan involving systemic therapy or surgery is important; limited evidence informs therapy in the setting of oligoprogression, where loss of disease control is experienced at one or a small number of sites. One approach is to use SBRT at the site or sites of progressive disease. Promising safety and efficacy data in combination with systemic therapy have been reported. In a retrospective analysis of 28 patients with oligoprogressive mRCC, Gebbia et al[55] examined patients who received pazopanib with subsequent hypofractionated SBRT to growing metastatic sites. Oligoprogression occurred after a median of 9.5 months on pazopanib. Treatment to progressive sites with SBRT resulted in a PFS following radiotherapy of 4.6 months.[55]

The effect of changing or continuing systemic therapy after SBRT in oligoprogressive mRCC has been described by Barata et al[56] where patients received SBRT for progressive brain or spinal disease in the setting of controlled or responding disease outside the SBRT target fields. The treatment and disease outcomes were defined based on whether patients continued on current therapy or were switched to another regimen. No difference was noted in treatment duration or OS between groups.[56]

Stereotactic body radiation therapy–treated tumors demonstrate an increased expression of immunomodulatory molecules, suggesting a rationale for combining SBRT with immune-activating approaches including checkpoint inhibition and vaccination.[8] Data supporting the use of sequential SBRT and pembrolizumab for oligometastatic disease were reported by Shankar et al[11] from the RAPPORT trial, where SBRT was administered to one to five sites of oligometastatic disease followed by PD-1 therapy. Median PFS was 15.6 months, with freedom from local progression at 2 years of 92%, and no concerning safety signal. Also exploring this concept, a retrospective international multicenter register study evaluated 53 patients who underwent both SBRT and either systemic therapy with targeted therapy or ICB. After 1 year of follow-up, OS, local metastasis control, and PFS rates were 71%, 75%, and 25%, respectively. Both oligometastatic disease and Eastern Cooperative Oncology Group status were predictors of prognosis.[53]

RADVAX (NCT03065179) is an ongoing single-arm phase II trial assessing the use of nivolumab/ipilimumab and subsequent SBRT and maintenance nivolumab in patients with mRCC. Toxicity and ORR are the primary and secondary endpoints, respectively.[12] Preliminary results in 25 patients demonstrated a 56% ORR and a median PFS of 8.2 months. All 25 patients experienced a grade 1 or 2 adverse event, the most common being fatigue, pruritis, and diarrhea. Thirty-six percent of patients reported grade 3 or 4 treatment-related adverse events, only one of which, colitis, was attributed directly to radiation.[13]

The need for prospective randomized trials is important in determining the benefit and optimal context of SBRT in treating mRCC. With a reduction in cytoreductive nephrectomy being performed in the post-CARMENA era, treating the primary with SBRT is being evaluated in CYTOSHRINK (NCT04090710), a phase II study that will enroll 78 patients with advanced treatment-naïve RCC classified as having International mRCC Database Consortium intermediate or poor risk disease who are not candidates for cytoreductive nephrectomy. Patients will be randomly assigned to receive nivolumab/ipilimumab with or without SBRT to the primary renal mass. PFS is the primary endpoint.[1] The NRG SAMURAI trial will randomly assign patients with International mRCC Database Consortium intermediate and poor risk mRCC undergoing ICB combination therapy to receive SBRT to the primary tumor and will complement the data to be derived from the CYTOSHRINK trial. Patients who qualify may also undergo subsequent cytoreductive nephrectomy, with PFS as the primary endpoint.

NOVEL TARGETS IN METASTATIC RENAL CELL CARCINOMA

A progressive understanding of the molecular basis of mRCC has been key in the development of novel therapies. Several are under development or have clinical trials in progress, utilizing pathways that are upregulated in mRCC such as HIF (hypoxia-inducible factor), stimulating the immune response through novel immune checkpoint or cytokine therapies, or exploiting metabolic dysregulation.[14]

The HIF-2α transcription factor is a key oncogenic driver for clear cell RCC. Small molecule inhibitors against HIF-2α have been successfully developed and demonstrate significant activity in ICB-pretreated patients. In a phase I/II trial of 55 patients, belzutifan (MK-6482), the second generation HIF-2α inhibitor, produced an ORR of 24% with 69% of patients experiencing some tumor shrinkage. Forty patients (73%) had received prior PD-1/L1 therapy, and 34 (62%) had received three or more lines of therapy.[15] These promising results have translated into a large phase III trial that will examine the activity of MK-6482 relative to everolimus in the pretreated setting (patients must have received three or fewer prior systemic regimens, which must include a PD-1/L1 inhibitor and a VEGF-targeted therapy).[16]

Combination therapy incorporating MK-6482 is being explored; a phase II study of MK-6482 with cabozantinib in mRCC is in progress; cohort 2 will comprise patients who have received prior ICB and no more than two prior regimens for mRCC and will detail the safety and activity of the combination.[17] Expanding on the use of doublets, a large phase III study of MK-6482 in combination with lenvatinib versus cabozantinib as second-line or third-line treatment is planned in participants with advanced RCC whose disease has progressed after prior anti–PD-1/L1 therapy.[57]

Metabolic dysregulation is another pathway for therapeutic development in mRCC. Glutamine metabolism is upregulated in mRCC and important for tumor cell proliferation and survival. Inhibition of the mitochondrial enzyme glutaminase, a regulator in a critical step of tumor cell metabolism of glutamine, may modulate tumor growth. The glutaminase inhibitor telaglenastat (CB-839) showed promising activity in heavily pretreated mRCC, for which a combination of telaglenastat with everolimus extended PFS compared with everolimus alone.[58] The large phase III CANTANA trial evaluated a combination of telaglenastat in combination with cabozantinib compared with cabozantinib monotherapy in a less pretreated setting (patients had received one or two prior lines of systemic therapy including either a VEGF inhibitor or combination treatment with nivolumab and ipilimumab). A press release has reported the primary outcome PFS as negative; median PFS was 9.2 months among the telaglenastat and cabozantinib arm compared with 9.3 months with cabozantinib and placebo (HR, 0.94; p = .65).[59]

TRIALS IN PROGRESS

With frontline ICB-containing combination therapy established as the standard of care, trials in the post-ICB space are needed to inform optimal treatment sequencing. The additive utility of combining ICB with VEGF compared with VEGF monotherapy is an important undefined question; the CONTACT-03 clinical trial is an international randomized, open-label phase III study of atezolizumab/cabozantinib versus cabozantinib monotherapy following progression on or after ICB treatment in patients with mRCC.[60] Using a 1:1 randomization, the trial will explore the additional activity of PD-L1 blockade to cabozantinib monotherapy, with PFS and OS as primary outcome measures.

Prospective data on the activity of cabozantinib monotherapy are also being explored. The European CaboPoint trial is a phase II, open-label, single-arm study of cabozantinib in adults with mRCC whose disease has progressed after therapy with ipilimumab and nivolumab alone (cohort A) or a combination of ICB with VEGF-targeted therapy (cohort B). The primary endpoint is ORR.[61]

CONCLUSION

Significant advances in systemic treatment have required the re-evaluation of previous multidisciplinary care standards and treatment pathways for patients with therapy-naïve mRCC and required new insights in the immunotherapy pretreated setting. The optimal timing and sequence for interventions is informed by less high-level evidence, and ongoing clinical trials will provide firmer insights on which to base future practice and guideline recommendations.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Motzer RJ, Escudier B, McDermott DF, et al. Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. J Immunother Cancer. 2020;8:e000891.
2. Choueiri TK, Powles T, Burotto M, et al. 696O_PR Nivolumab + cabozantinib vs sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase III CheckMate 9ER trial. Ann Oncol. 2020;31:S1159.
3. Rini BI, Plimack ER, Stus V, et al; KEYNOTE-426 Investigators. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380:1116-1127.
4. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med. Epub 2021 Feb 13.
5. Ornstein MC, Pal SK, Wood LS, et al. Individualised axitinib regimen for patients with metastatic renal cell carcinoma after treatment with checkpoint inhibitors: a multicentre, single-arm, phase 2 study. Lancet Oncol. 2019;20:1386-1394.
6. Choueiri TK, Escudier B, Powles T, et al; METEOR Investigators. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016;17:917-927.
7. Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. Lancet Oncol. 2020;21:95-104.
8. Singh AK, Winslow TB, Kermany MH, et al. A pilot study of stereotactic body radiation therapy combined with cytoreductive nephrectomy for metastatic renal cell carcinoma. Clin Cancer Res. 2017;23:5055-5065.
9. Wiele AJ Jr., Chahoud J, Lim Z, et al. Lenvatinib (Len) alone or in combination with everolimus (Eve) in heavily pretreated patients (pts) with metastatic renal cell carcinoma (mRCC) after immune checkpoint inhibitors (ICI) and VEGFR-targeted therapies: a single-institution experience. Ann Oncol. 2019;30:v356-v402.
10. Hamieh L, Beck RL, Le VH, et al. The efficacy of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma exhibiting primary resistance to front-line targeted therapy or immunotherapy. Clin Genitourin Cancer. 2020;18:252-257.e2.
11. Shankar S, Mathias B, Wood S, et al. Stereotactic radiotherapy and pembrolizumab for oligometastatic renal tumors: the RAPPORT trial. J Clin Oncol. 2021;39:6s (suppl; abstr 277).
12. Powles T, Plimack ER, Soulières D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. Lancet Oncol. 2020;21:1563-1573.
13. Hammers HJ, Vonmerveldt D, Ahn C, et al. Combination of dual immune checkpoint inhibition (ICI) with stereotactic radiation (SBRT) in metastatic renal cell carcinoma (mRCC) (RADVAX RCC). J Clin Oncol. 2020;38:6s (suppl; abstr 614).
14. Ravi P, Bakouny Z, Schmidt A, et al. Novel therapeutic approaches and the evolution of drug development in advanced kidney cancer. Cancer J. 2020;26:464-470.
15. Choueiri TK, Plimack ER, Bauer TM, et al. Phase I/II study of the oral HIF-2 α inhibitor MK-6482 in patients with advanced clear cell renal cell carcinoma (RCC). J Clin Oncol. 2020; 38:6s (suppl; abstr 611).
16. Choueiri TK, Albiges L, Fan L, et al. Phase III study of the hypoxia-inducible factor 2α (HIF-2α) inhibitor MK-6482 versus everolimus in previously treated patients with advanced clear cell renal cell carcinoma (ccRCC). J Clin Oncol. 2020;38:15s (suppl; abstr TPS5094).

17. Tykodi SS, Bauer TM, McDermott DF, et al. Phase II study of the oral hypoxia-inducible factor 2α (HIF-2 α) inhibitor MK-6482 in combination with cabozantinib in patients with advanced clear cell renal cell carcinoma (ccRCC). J Clin Oncol. 2020;38:6s (suppl; abstr TPS766).

18. McGregor BA, Lalani AA, Xie W, et al. Activity of cabozantinib after immune checkpoint blockade in metastatic clear-cell renal cell carcinoma. Eur J Cancer. 2020; 135:203-201.

19. McDermott DF, Lee J-L, Bjarnason GA, et al. First-line pembrolizumab (pembro) monotherapy in advanced clear cell renal cell carcinoma (ccRCC): updated follow-up for KEYNOTE-427 cohort A. J Clin Oncol. 2020;38:15s (suppl; abstr 5069).

20. Atkins MB, Jegede O, Haas NB, et al. Phase II study of nivolumab and salvage nivolumab + ipilimumab in treatment-naïve patients (pts) with advanced renal cell carcinoma (RCC) (HCRN GU16-260). J Clin Oncol. 2020;38:15s (suppl; abstr 5006).

21. Grimm MO, Schmidinger M, Duran Martinez I, et al. Tailored immunotherapy approach with nivolumab in advanced renal cell carcinoma (TITAN-RCC). Ann Oncol. 2019;30:v892.

22. McKay RR, McGregor BA, Xie W, et al. Optimized management of nivolumab and ipilimumab in advanced renal cell carcinoma: a response-based phase II study (OMNIVORE). J Clin Oncol. 2020;38:4240-4248.

23. Choueiri TK, Kluger HM, George S, et al. FRACTION-RCC: innovative, high-throughput assessment of nivolumab + ipilimumab for treatment-refractory advanced renal cell carcinoma (aRCC). J Clin Oncol. 2020;38:15s (suppl; abstr 5007).

24. Gul A, Stewart TF, Mantia CM, et al. Salvage ipilimumab and nivolumab in patients with metastatic renal cell carcinoma after prior immune checkpoint inhibitors. J Clin Oncol. 2020;38:3088-3094.

25. Yang JC, Hughes M, Kammula U, et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. J Immunother. 2007;30:825-830.

26. Lee C-H, Shah AY, Hsieh JJ, et al. Phase II trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) for disease progression after PD-1/PD-L1 immune checkpoint inhibitor (ICI) in metastatic clear cell renal cell carcinoma (mccRCC). J Clin Oncol. 2020;38:15s (suppl; abstr 5008).

27. Ravi P, Mantia C, Su C, et al. Evaluation of the safety and efficacy of immunotherapy rechallenge in patients with renal cell carcinoma. JAMA Oncol. 2020; 6:1606-1610.

28. Abou Alaiwi S, Xie W, Nassar AH, et al. Safety and efficacy of restarting immune checkpoint inhibitors after clinically significant immune-related adverse events in metastatic renal cell carcinoma. J Immunother Cancer. 2020;8:e000144.

29. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27:5794-5799.

30. Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol. 1999; 17:2530-2540.

31. Dudani S, de Velasco G, Wells JC, et al. Evaluation of clear cell, papillary, and chromophobe renal cell carcinoma metastasis sites and association with survival. JAMA Netw Open. 2021;4:e2021869.

32. Bhindi B, Abel EJ, Albiges L, et al. Systematic review of the role of cytoreductive nephrectomy in the targeted therapy era and beyond: an individualized approach to metastatic renal cell carcinoma. Eur Urol. 2019;75:111-128.

33. Lahn M, Fisch P, Köhler G, et al. Pro-inflammatory and T cell inhibitory cytokines are secreted at high levels in tumor cell cultures of human renal cell carcinoma. Eur Urol. 1999;35:70-80.

34. Dragomir A, Nazha S, Wood LA, et al. Outcomes of complete metastasectomy in metastatic renal cell carcinoma patients: The Canadian Kidney Cancer information system experience. Urol Oncol. 2020;38(10):799.e1-799.e10.

35. Flanigan RC, Mickisch G, Sylvester R, et al. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol. 2004; 171:1071-1076.

36. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med. 2001;345:1655-1659.

37. Mickisch GH, Garin A, van Poppel H, et al; European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet. 2001; 358:966-970.

38. Tabakin AL, Stein MN, Anderson CB, et al. Cytoreductive nephrectomy for metastatic renal cell carcinoma, the ultimate urologic 'Choosing Wisely' campaign: a narrative review. Transl Cancer Res. 2020;9:7337-7349.

39. Bex A, Mulders P, Jewett M, et al. Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: the SURTIME randomized clinical trial. JAMA Oncol. 2019;5:164-170.

40. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med. 2018;379:417-427.

41. Karie Runcie EAS, Ornstein MC, Anderson CB, et al. Phase II trial of cytoreductive surgery in kidney cancer plus immunotherapy (nivolumab) and targeted kinase inhibition (cabozantinib) (Cyto-KIK). J Clin Oncol. 2021;39:6s (suppl; abstr TPS371).

42. Ishihara H, Takagi T, Kondo T, et al. Prognostic impact of metastasectomy in renal cell carcinoma in the postcytokine therapy era. Urol Oncol. 2021;39:77. e17-77.e25.

43. Appleman LJ, Puligandla M, Pal SK, et al. Randomized, double-blind phase III study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease following metastasectomy: a trial of the ECOG-ACRIN cancer research group (E2810). J Clin Oncol. 2019;37:15s (suppl; abstr 4502).

44. Ravaud A, Motzer RJ, Pandha HS, et al; S-TRAC Investigators. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. N Engl J Med. 2016; 375:2246-2254.

45. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet. 2016;387:2008-2016.

46. Motzer RJ, Haas NB, Donskov F, et al; PROTECT Investigators. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. J Clin Oncol. 2017;35:3916-3923.

47. Gross-Goupil M, Kwon TG, Eto M, et al. Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. Ann Oncol. 2018;29:2371-2378.

48. Quinn DI, Zhang T, Gurney H, et al. Phase 3, randomized, double-blind trial of pembrolizumab in the adjuvant treatment of renal cell carcinoma (RCC): KEYNOTE-564. J Clin Oncol. 2018;36:6s (suppl; abstr TPS712).

49. Uzzo R, Bex A, Rini BI, et al. A phase III study of atezolizumab (atezo) vs placebo as adjuvant therapy in renal cell carcinoma (RCC) patients (pts) at high risk of recurrence following resection (IMmotion010). J Clin Oncol. 2017;35:15s (suppl; abstr TPS4598).

50. Chalkidou A, Macmillan T, Grzeda MT, et al. Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study. Lancet Oncol. 2021;22:98-106.

51. Kroeze SGC, Fritz C, Schaule J, et al. Stereotactic radiotherapy combined with immunotherapy or targeted therapy for metastatic renal cell carcinoma. BJU Int. Epub 2020 Oct 28.

52. Kothari G, Foroudi F, Gill S, et al. Outcomes of stereotactic radiotherapy for cranial and extracranial metastatic renal cell carcinoma: a systematic review. Acta Oncol. 2015;54:148-157.

53. Gebbia V, Girlando A, DI Grazia A, et al. Stereotactic radiotherapy for the treatment of patients with oligo-progressive metastatic renal cell carcinoma receiving vascular endothelial growth factor receptor tyrosine kinase inhibitor: data from the real world. Anticancer Res. 2020;40:7037-7043.

54. Barata PC, Mendiratta P, Kotecha R, et al. Effect of switching systemic treatment after stereotactic radiosurgery for oligoprogressive, metastatic renal cell carcinoma. Clin Genitourin Cancer. 2018;16:413-419.e1.

55. NCT04586231. A Study of Belzutifan (MK-6482) in Combination With Lenvatinib Versus Cabozantinib for Treatment of Renal Cell Carcinoma (MK-6482-011). https://clinicaltrials.gov/ct2/show/NCT04586231?term=mk6482&draw=2&rank=3. Accessed March 17, 2021.

56. Motzer RJ, Lee CH, Emamekhoo H, et al. ENTRATA: randomized, double-blind, phase II study of telaglenastat (tela; CB-839) + everolimus (E) vs placebo (pbo) + E in patients (pts) with advanced/metastatic renal cell carcinoma (mRCC). Ann Oncol. 2019;30:v889-v890.

57. Calithera Biosciences, Inc. CANTATA Study of Telaglenastat in Renal Cell Carcinoma Did Not Achieve Primary Endpoint. https://bit.ly/3oiDZfN. Accessed March 17, 2021.

58. Pal S, Albiges L, Suárez C, et al. CONTACT-03: randomized, open-label phase III study of atezolizumab plus cabozantinib vs cabozantinib monotherapy following progression on/after immune checkpoint inhibitor (ICI) treatment in patients with advanced/metastatic renal cell carcinoma (RCC). Presented at: 19th Annual Meeting of the International Kidney Cancer Symposium (IKCS 2020); Kidney Cancer Association; 2020.

59. Albiges L, Schmidinger M, Taguieva Pioger N, et al. CaboPoint, a phase II, open-label study of cabozantinib as second-line therapy for patients with clear cell metastatic renal cell carcinoma (RCC), whose disease progressed after therapy with checkpoint inhibitors (CPIs). J Clin Oncol. 2020;38:6s (suppl; abstr TPS772).

60. NCT04510597. Comparing the Outcome of Immunotherapy-Based Drug Combination Therapy With or Without Surgery to Remove the Kidney in Metastatic Kidney Cancer, the PROBE Trial (PROBE). https://clinicaltrials.gov/ct2/show/NCT04510597. Accessed March 17, 2021.

32. NCT03977571. Deferred Cytoreductive Nephrectomy in Synchronous Metastatic Renal Cell Carcinoma: The NORDIC-SUN-Trial (NORDIC-SUN). https://clinicaltrials.gov/ct2/show/NCT03977571. Accessed March 22, 2021.

Beyond the Androgen Receptor: The Sequence, the Mutants, and New Avengers in the Treatment of Castrate-Resistant Metastatic Prostate Cancer

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Overview

Targeting the androgen receptor by depriving testosterone with gonadotropin-releasing hormone agonists or antagonists, or surgical castration, has been the backbone of metastatic prostate cancer treatment. Although most prostate cancers initially respond to androgen deprivation, metastatic castration-resistant prostate cancer evolves into a heterogeneous disease with diverse drivers of progression and mechanisms of therapeutic resistance. Development of castrate resistance phenotype is associated with lethality despite the recent noteworthy strides gained via increase in therapeutic options. Identification of novel therapeutics to further improve survival and achieve durable responses in metastatic castration-resistant prostate cancer is a clinical necessity. In this review, we outline the existing avengers for treatment of metastatic castration-resistant prostate cancer by clinical presentation, placing into context the clinical state of the patient, such as burden of disease and symptoms. Doing so might aid in the ability to optimize the sequence of agents and allow for maximal exposure to life-prolonging therapeutics. Realizing the limitations of the androgen signaling inhibition, we explore the androgen-indifferent prostate cancer: the mutants. Classically, these subtypes have been associated with variant histology, but androgen-indifferent prostate cancer features are now frequently observed in association with heterogeneous morphologies, including double-negative prostate cancers, lacking both androgen receptor and neuroendocrine features, or clinicopathologic criteria, such as the aggressive variant prostate cancer criteria. The framework of new avengers against metastatic castration-resistant prostate cancer based on mechanism, including DNA repair, immune checkpoint inhibition, PTEN/PI3K/AKT pathway, prostate-specific membrane antigen targets, bispecific T-cell engagers, and radionuclide therapies, is summarized in this review.

Targeting the androgen receptor (AR) by depriving testosterone with gonadotropin-releasing hormone agonists or antagonists, or surgical castration, has been the backbone of metastatic prostate cancer treatment for the past 80 years. Castration-resistant prostate cancer (CRPC) is defined as cancer that progresses radiographically, clinically, or biochemically when castrate levels of testosterone (less than 50 ng/dL) were achieved either chemically or surgically. Metastatic CRPC (mCRPC) is a heterogeneous disease with diverse drivers of progression and mechanisms of therapeutic resistance. Development of a castrate resistance phenotype is associated with lethality driven by the lack of therapies capable of generating durable responses, as evident by the 5-year survival rate dropping to less than 10%.[1] In recent years, the molecular characterization of mCRPC has proved critical to improving disease outcome and understanding responses to antiandrogen therapy, chemotherapy, targeted therapies, and immunotherapy.[2-12] Identification of novel therapeutics to improve survival and achieve durable responses in CRPC is a clinical necessity. In this review, we discuss the sequencing of the available avengers, the mutant avengers (i.e., targeting androgen-indifferent prostate cancers [AIPC]), and the evolving new avengers for the treatment of mCRPC.

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THE AVENGERS

Advances in understanding the biology of prostate cancer, availability of next-generation sequencing tools to identify predictive and prognostic genetic alterations, and newer therapeutics have given us hope that much needed gains in improving survival in prostate cancer are possible. Targeting the AR signaling axis by depriving testosterone with gonadotropin-releasing hormone agonists or antagonists, or surgical castration, has been the backbone of metastatic prostate cancer treatment for the past 80 years. The majority of prostate cancers initially respond to androgen deprivation and are considered hormone sensitive at the time of diagnosis. Castration-resistant prostate cancer is defined as cancer that progresses radiographically, clinically,

PRACTICAL APPLICATIONS

- A summary of the existing avengers in the treatment of metastatic castration-resistant prostate cancer is provided.
- The goal is to provide a framework to optimize sequencing of existing avengers to allow optimal exposure to life-prolonging therapies.
- Androgen-indifferent prostate cancer is outlined, including variant histology, double-negative prostate cancer, and aggressive variant prostate cancer criteria.
- The framework of new avengers against metastatic castration-resistant prostate cancer based on mechanism, including DNA repair, immune checkpoint inhibition, PTEN/PI3K/AKT pathway, prostate-specific membrane antigen targets, bispecific T-cell engagers, and radionuclide therapies, is summarized.

or biochemically when castrate levels of testosterone (less than 50 ng/dL) were achieved either chemically or surgically.[8] Earliest known mechanisms of castrate resistance were identified to be enhancement of autocrine and paracrine androgen synthesis in the tumor microenvironment, increased expression of AR, and stimulation by extra gonadal sources of androgen.[8] The discovery of these mechanisms translated to advent of second-generation novel hormonal therapies like abiraterone acetate and enzalutamide.[9,10] Additional avengers approved against mCRPC include cabazitaxel, docetaxel, radium-223, and sipuleucel-T.[13-16] Similarly, olaparib and rucaparib were recently approved for those harboring defects in homologous DNA repair mechanisms.[4,5] Pembrolizumab is approved in cancers with high tumor mutation burden (more than 10 per megabase) or those with microsatellite instability and is not just specific to prostate cancer.[17]

CHOOSING THERAPEUTIC AGENTS BASED ON CLINICAL PRESENTATION

Despite this arsenal, real-world use of available agents in treating mCRPC has been poor, and there are no definitive guidelines on the optimal sequence. A retrospective review of a large health care analytics database identified about 77% of patients with mCRPC receive at least one line of treatment, but the rate of subsequent therapy use declined by more than 50%.[11] Patient-related factors, like the presence of symptoms, performance status, comorbidities, and disease burden, affect the number of lines of therapy received. Improved survival is associated with receiving subsequent lines of treatment. In this review, we discuss the sequencing of available therapies based on clinical presentation, cancer-specific factors, and available evidence using the clinical state model.[12]

Nonmetastatic Castration-Resistant Prostate Cancer

Nonmetastatic CRPC is an early spectrum of CRPC in which the prostate-specific antigen (PSA) continues to rise despite achieving castrate levels of testosterone with no radiologic evidence of metastasis. Second-generation AR antagonists darolutamide, enzalutamide, and apalutamide were approved to treat nonmetastatic CRPC based on improved metastasis-free survival compared with placebo in patients with rapid PSA doubling time (less than 10 months).[18-20] Across the studies, these drugs also showed overall survival benefit (Table 1). Currently, there is no evidence to support use of advanced androgen blockade in nonmetastatic CRPC with PSA doubling time of more than 10 months.

Asymptomatic Metastatic Castration-Resistant Prostate Cancer

Next in the spectrum of CRPC is mCRPC with limited disease burden, no visceral metastasis, and minimal or no cancer-related symptoms. Abiraterone acetate, an androgen synthesis inhibitor targeting CYP17A1 in the adrenal steroidogenesis pathway, enzalutamide, and sipuleucel-T, a cellular immunotherapy, are current agents approved for use in this presentation. Sipuleucel-T, a personalized dendritic cell–based cellular immunotherapy, has been indicated for management of mCRPC with minimal or no symptoms and no visceral metastasis since 2010. Two randomized clinical trials have proven an overall survival benefit with sipuleucel-T compared with placebo.[16,24] Abiraterone and enzalutamide also showed similar survival benefit in mCRPC that were chemotherapy naive[22,25] (Table 2).

Symptomatic Metastatic Castration-Resistant Prostate Cancer

Patients with mCRPC may develop symptoms from cancer based on extent of disease and location of metastasis. These can be local effects of metastasis causing pain, systemic effects like fatigue, decreased appetite, or end-organ damage, like pathologic fracture or liver failure. Docetaxel, a cytotoxic microtubule inhibitor, was one of the first agents that showed improved survival in mCRPC over other chemotherapeutic agents and has been standard of care for many years before the advent of novel hormonal therapies radium 223 and cabazitaxel.[14]

Radium 223, an alpha-emitting bone-seeking calcium mimetic, has been approved in mCRPC with symptomatic bone metastasis but without visceral metastasis or bulky lymphadenopathy.[15] Real-world data show that radium 223 is mostly used in second-line and third-line treatment of mCRPC, and observational evidence suggests early use of radium 223 to be associated with improved overall survival.[27]

TABLE 1. Studies Showing Efficacy of Novel Hormonal Therapies in Nonmetastatic Castration-Resistant Prostate Cancer

	Clinical Trial	mMFS (Months)	Survival Benefit	Reference
Darolutamide	ARAMIS	40.4 vs. 18.4 (HR for metastasis or death, 0.41; 95% CI, 0.34–0.50; p < .001)	83% vs. 77% OS at 3 years (HR for death, 0.69; 95% CI, 0.53–0.88, p = .003)	Fizazi et al[18,21]
Enzalutamide	PROSPER	36.6 vs. 14.7 (HR for metastasis or death, 0.29; 95% CI, 0.24–0.35; p < .001)	67 months vs. 56.3 months mOS (HR, 0.73; 95% CI, 0.61–0.89; p = .001)	Sternberg et al[19] and Beer et al[22]
Apalutamide	SPARTAN	40.5 vs. 16.2 (HR for metastasis or death, 0.28; 95% CI, 0.23–0.35; p < .001)	73.9 vs. 59.9 months mOS (HR, 0.78; 95% CI, 0.64–0.96, p = .016)	Small et al[20] and Smith et al[23]

NOTE. All drugs were compared with placebo.
Abbreviations: mMFS, median metastasis-free survival; OS, overall survival; mOS, median overall survival.

Both abiraterone acetate and enzalutamide showed similar survival benefit in patients with mCRPC that progressed after docetaxel when compared with placebo.[9,10] Cabazitaxel, another cytotoxic microtubule inhibitor, has showed activity in mCRPC that progressed after docetaxel (Table 3).[13]

Few studies have evaluated the sequencing of available agents and its impact on outcomes of mCRPC. A small, randomized phase II crossover trial showed advantage of time to second PSA progression and PSA response on second-line therapy using abiraterone first followed by enzalutamide, based on good activity of enzalutamide in those who failed abiraterone but not vice versa. A trend toward improvement in overall survival is noted but not statistically remarkable.[28] Another systematic review of various clinical trials evaluating abiraterone and enzalutamide sequencing arrived at a similar conclusion.[27]

Another evidence-based sequencing strategy in patients who progressed on docetaxel and novel hormonal therapies (either abiraterone or enzalutamide) is to prefer cabazitaxel as third-line treatment rather than using alternate novel hormonal therapy, as shown in the CARD study. The cabazitaxel arm had improved outcomes compared with novel hormonal therapies, including imaging-based progression-free survival (8 months vs. 3.7 months; HR, 0.54; 95% CI, 0.40–0.73) and overall survival (13.6 months vs. 11 months; HR, 0.64; 95% CI, 0.46–0.89).[29]

There is limited evidence to recommend a sequencing strategy for patients who were treated with novel hormonal therapies or docetaxel up front in the mCRPC setting. Some studies have looked at rechallenging with docetaxel in mCRPC and found it is a reasonable strategy in those who have achieved more than a 50% drop in PSA and in those who had progression-free interval more than 6 months.[30]

CHOOSING THERAPEUTIC AGENTS BASED ON MOLECULAR AND PATHOLOGIC FEATURES

A subset of patients with mCRPC develop neuroendocrine differentiation and the AR splice variant 7 (AR-V7) and are resistant to novel hormonal therapies due to AR-independent proliferation of cells.[31,32] They have an aggressive clinical course and present with visceral metastasis. These patients benefit more from chemotherapy regimens. These are further discussed in the "Androgen-Indifferent Prostate Cancers: The Mutants" and "The New Avengers in the Treatment of Prostate Cancer" sections below. Metastatic castration-resistant prostate cancer has a wide spectrum of clinical presentation with varied prognosis. It is important to use the appropriate choice of treatment based on clinical scenario and underlying pathologic features, so patients can use all available agents for clinical benefit. Further discussion on mechanisms of androgen independence, how to target these, and new therapeutics on the horizon are discussed below.

TABLE 2. Studies Showing Efficacy of Approved Agents in Metastatic Castration-Resistant Prostate Cancer With Less Disease Burden and Chemotherapy Naive

	Clinical Trial	PFS (Months)	OS (Months)	Reference
Sipuleucel-T	IMPACT	3.7 vs. 3.6 (HR, 0.95; 95% CI, 0.77–1.17; p = .63)	25.8 vs. 21.7 (HR, 0.78; 95% CI, 0.61–0.98; p = .03)	Kantoff et al[16]
Abiraterone Acetate	COU-AA-302	16.5 vs. 8.3 (HR, 0.53; 95% CI, 0.45–0.62; p < .001	34.7 vs. 30.3 (HR, 0.81; 95% CI, 0.70–0.93; p = .0033)	Ryan et al[25,26]
Enzalutamide	PREVAIL	20 vs. 5.4 (HR, 0.32, 95% CI, 0.28–0.37; p < .0001)	32.4 vs. 30.2 (HR, 0.77, 95% CI, 0.67–0.88; p = .0002)	Beer et al[22]

NOTE. Study drugs were compared with placebo.
Abbreviations: PFS, progression-free survival; OS, overall survival.

Androgen-Indifferent Prostate Cancers: The Mutants

Androgen signaling inhibition is the backbone of prostate cancer systemic therapy and results in profound and prolonged responses in a majority of men with this disease.[33] However, most ultimately progress, and a subset appears to have primary resistance to androgen signaling inhibitors. Although the AR is likely to remain a driver in many of the tumors that progress, others are considered AIPC. Androgen indifference has been classically associated with variant histology, such as the poorly differentiated small cell or neuroendocrine prostate cancer (SCPC/NEPC) or sarcomatoid carcinomas. With the increase in biopsies of CRPC metastases, an increased prevalence of SCPC/NEPC has been described and termed secondary or treatment-emergent NEPC.[34,35] However, it has also become clear that AIPC features are frequently observed in association with heterogeneous morphologies, including adenocarcinomas and poorly differentiated carcinomas with or without the expression of neuroendocrine markers such as chromogranin A, synaptophysin, or CD56.[36] For example, a subset of CRPC tumors demonstrating androgen indifference following initial response to AR signaling inhibition and lacking expression of both AR and neuroendocrine markers has been described and termed double-negative prostate cancer.[37]

Another approach to provide a framework for the development of objective biomarkers and enable the prospective evaluation of candidate therapies for the AIPC has been to compile clinicopathologic criteria characteristic of the SCPC/NEPC for patient selection, regardless of their prostate tumors' morphologies. One such set of criteria, termed aggressive variant prostate cancer criteria, include: (1) the presence of exclusive visceral metastases; (2) predominantly lytic bone metastases; (3) bulky (5 cm or more) tumor masses, including lymphadenopathy or high-grade tumor masses in the prostate or pelvis; (4) low PSA relative to tumor burden, specified as a PSA 10 ng/mL or less at initial presentation (before androgen-deprivation therapy) or at the time of symptomatic progression of castrate-resistant disease plus high-volume (20 or more) bone metastases; (5) serum carcinoembryonic antigen and/or lactate dehydrogenase twice the upper limit of normal; (6) short interval (6 months or less) to castration-resistant progression following initiation of hormonal therapy; and (7) SCPC/NEPC morphology.[38] Additional criteria that have been used in prospective studies to evaluate therapies for the AIPC have included clinically progressive disease and low PSA and development of liver metastases in the absence of PSA progression.[39,40] Molecular studies in samples from patients meeting aggressive variant prostate cancer criteria showed that these tumors are characterized by combined (two or more) alterations in the tumor suppressors TP53, RB1 and PTEN.[41] Similarly, studies of SCPC/NEPC identified recurrent loss of *RB1* and *TP53* at the DNA and mRNA level.[34,42] This profile has been linked to lineage plasticity and androgen indifference in murine prostate cancer models.[43-46] Others have linked the AIPC to the loss of RB1 alone and to low transcriptional output of AR signaling pathways.[47-49]

Are the androgen-indifferent prostate cancers induced by potent androgen signaling inhibition? The AIPC have been postulated to arise as a result of exposure to potent androgen signaling inhibitors.[34,37,47] An autopsy study of patients dying with mCRPC observed an increase in the proportion of patients with SCPC/NEPC and double-negative prostate cancer tumors obtained during the modern era (2012–2016) compared with the pre-AR signaling inhibitor era.[37] Two contemporary studies of men with mCRPC found that SCPC/NEPC was present at higher rates after treatment with an AR signaling inhibitor and was associated with a shorter overall survival.[34,47]

However, markers linked to androgen indifference have been observed in samples from hormone-naive prostate tumors. In a large transcriptomic study of AR activity in

TABLE 3. Drugs Approved in Metastatic Castration-Resistant Prostate Cancer With Symptoms

Study Drug	Clinical Trial	TTP PSA (Months)	mOS (Months)	Reference
Docetaxel	TAX 327	7.7 vs. 7.8	18.9 vs. 16.5* (HR 0.76, 95% CI, 0.62–0.94; p = .009)	Tannock et al[14]
Radium 223	ALSYMPCA	3.6 vs. 3.4	14.9 vs. 11.3 (HR, 0.70; 95% CI, 0.58–0.83; p < .001)	Parker et al[15]
Abiraterone acetate	COU-AA-301	10.2 vs. 6.6 (HR 0.58; 95% CI, 0.46–0.73; p < .001)	14.8 vs. 10.9 (HR, 0.65; 95% CI, 0.54–0.77; p < .001)	de Bono et al[9]
Enzalutamide	AFFIRM	8.3 vs. 3.0 (HR 0.25; 95% CI, 0.20–0.30; p < .001)	18.4 vs. 13.6 (HR 0.63; 95% CI, 0.53–0.75; p < .001)	Scher et al[10]
Cabazitaxel	TROPIC	6.4 vs. 3.1 (HR 0.75; 95% CI, 0.63–0.90, p = .001)	15.1 vs. 12.7* (HR 0.70 (95% CI, 0.59–0.83, p < .0001)	de Bono et al[13]

NOTE. Compared with placebo.

Abbreviations: TTP, time to progression; PSA, prostate-specific antigen; mOS, median overall survival.

*Compared with mitoxantrone.

treatment-naive primary prostate tumors, a distinct subset of low AR activity tumors was identified in approximately 10% of samples. This low AR activity subset was enriched in higher-grade tumors with less sensitivity to androgen-deprivation therapy and increased sensitivity to platinum chemotherapy.[48] In another report, clinical-grade, targeted, massively parallel sequencing assay of samples from 43 patients with de novo metastatic and 205 localized hormone-naive prostate cancers revealed combined (two or more) alterations in the tumor suppressors *TP53*, *RB1*, and *PTEN* in 28% and 11% of cases, respectively, and was associated with a poor prognosis.[50]

Thus, pre-existing AIPC subclones may already exist in some untreated tumors and emerge under the selective pressure imposed by androgen signaling inhibition in some cases, whereas in others, mutations and/or other molecular alterations may be acquired during castrate-resistant progression that results in androgen indifference. This indicates that, for a subset of prostate cancers, inclusion of therapies directed at AIPC early in the course of the disease may be beneficial and that, for the remainder, biomarkers that can be monitored serially will be critical to be able to identify its emergence and initiate effective therapy in a timely manner.

Existing therapies for the androgen-indifferent prostate cancers The lack of biomarkers that can identify the AIPC prospectively has, until recently, hampered the development of therapies specific to this subset. Extrapolating data from small cell lung cancer, the National Comprehensive Cancer Network guidelines for prostate cancer recommend combination platinum-based (carboplatin or cisplatin) chemotherapy as first-line therapy for primary SCPC/NEPC. One prospective phase II clinical trial evaluated the addition of doxorubicin to cisplatin and etoposide in patients with both primary and treatment-emergent NEPC. Although 22 of 36 (61%; 95% CI, 43%–77%) of the patients achieved a partial response in measurable disease, the median time to progression was only 5.8 months (95% CI, 4.1–6.9), and the median overall survival was only 10.5 months (95% CI, 7.5–14.3) at the cost of severe toxicity. Thus, the addition of doxorubicin to the platinum combination is not recommended.[39,51]

In contrast to the histologically defined SCPC/NEPC, neuroendocrine marker expression alone has not been shown to predict for response to platinum-based chemotherapy.[52,53] In fact, approximately 20% to 30% of metastatic prostate adenocarcinomas without SCPC/NEPC features also have favorable responses to platinum-based chemotherapy.[54] However, the presence of aggressive variant prostate cancer clinicopathologic and/or molecular features described above do seem to enrich for platinum sensitivity.[41,55] In a single-arm phase II study of 113 men with mCRPC demonstrating at least one aggressive variant prostate cancer clinical feature, a median overall survival of 16.0 months (95% CI, 13.6–19.0) was observed following sequential carboplatin plus docetaxel followed by salvage cisplatin plus etoposide upon progression.[38] In a subsequent phase II study, 160 men with mCRPC stratified by the presence of aggressive variant prostate cancer clinicopathologic criteria were randomly assigned to receive to cabazitaxel with or without carboplatin. The hazard ratio for progression in men meeting aggressive variant prostate cancer criteria treated with the combination versus single-agent cabazitaxel was 0.58 (95% CI, 0.37–0.89).[55] Furthermore, the presence of combined (two or more) alterations in TP53, RB1, and PTEN in a post hoc analysis of participants' tumor samples was associated with meaningful improvements in outcomes with the addition of carboplatin to cabazitaxel, which was not observed in patients without these molecular alterations. A follow-up phase III study with stratification by presence or absence of aggressive variant prostate cancer criteria is planned.

It should be noted that, although the need for androgen-deprivation therapy has not been evaluated prospectively in AIPC, common practice has been to maintain castration to address potential AR-driven adenocarcinoma components that may be admixed within AIPC tumors.

Therapies in development for the androgen-indifferent prostate cancer Over the last decade, an increased awareness of the AIPC subset has led to an improved understanding of their underlying biology and the evaluation of several novel therapies in prospective clinical trials. For example, the observation that mitotic genes, including Aurora kinase A, are overexpressed in SCPC/NEPC led to a phase II study of the Aurora kinase A inhibitor alisertib in metastatic NEPC. Although the study failed to meet its primary endpoint, the authors observed some examples of treatment response.[40] The implication of EZH2 in AIPC pathogenesis has provided the rationale for a phase Ib/II trial combining the EZH2 inhibitor CPI-1205 with enzalutamide or abiraterone acetate in men with mCRPC who progressed on a second-generation androgen signaling inhibitor (NCT03480646), with preliminary results indicating the combination is well tolerated and has antitumor activity.[56,57] Additional EZH2 inhibitors are being investigated in early-phase trials for men with mCRPC in general (NCT03460977 and NCT04179864) and aggressive variant prostate cancer in particular (NCT04388852). In the double-negative prostate cancer, mitogen-activated protein kinase pathway activation via aberrant fibroblast growth factor receptor signaling has been implicated as a mechanism of resistance to androgen signaling inhibitors, so multiple studies are evaluating fibroblast growth factor inhibitors in these tumors (NCT00831792 and NCT03999515).[37] Also,

based on the observation that the loss of tumor suppressor genes increases DNA replication stress and that platinum sensitivity is associated with response to PARP inhibition, an ongoing phase II study is evaluating the efficacy of maintenance PARP inhibition with olaparib following induction of carboplatin plus cabazitaxel in men meeting aggressive variant prostate cancer criteria (NCT03263650).[43]

Finally, whereas the experience in clinical trials of unselected mCRPC has suggested that men with visceral metastases, high lactate dehydrogenase levels, and other virulent features associated with AIPC have limited benefit from immune checkpoint inhibitor therapies, the survival improvements observed in SCLC with the addition of anti–PD-1 or anti–PD-L1 immune checkpoint inhibitors to platinum-based chemotherapy or their use in the salvage setting have led to off-label use for the AIPC by many providers.[58-63] In a phase II basket trial of dual anti–CTLA-4 and anti–PD-1 blockade in nonpancreatic neuroendocrine tumors, the DART SWOG 1609, two patients with high-grade SCPC/NEPC were included. One patient progressed rapidly, whereas the other had a prolonged partial response.[64] Ongoing prospective clinical trials dedicated to the AIPC are evaluating the efficacy of immune checkpoint inhibitors with or without chemotherapy (e.g., NCT03179410, NCT04592237, NCT04709276, and NCT03582475) or in combination with various other agents such as the EZH1/2 inhibitor valemetostat (NCT03263650) or the dipeptidyl peptidase inhibitor BXCL701 (NCT03910660) and should be prioritized over off-label use. Alternative immune modulators are also being examined for the treatment of AIPC. For example, an anti-DLL3 × CD3 bispecific T-cell engager (NCT04702737) and a DLL3-targeted trispecific T-cell–activating construct (NCT04471727) have recently entered clinical trials based on the observation that the transmembrane ligand DLL3 is frequently overexpressed in SCPC/NEPC.[65]

Whether induced using increasingly potent androgen signaling inhibitors or present de novo, an increased recognition of AIPC subsets has led to an improved understanding of their underlying biology. It is important for the treating oncologist to recognize this entity, as these tumors are associated with poor responses to conventional therapies and dismal outcomes. Patients with AIPC should be encouraged to participate in ongoing clinical trials whenever possible. Alternatively, the use of platinum-based chemotherapy combinations may be considered in men with AIPC features.

THE NEW AVENGERS IN THE TREATMENT OF PROSTATE CANCER

mCRPC is a heterogeneous disease with diverse drivers of progression and mechanisms of therapeutic resistance. Its lethality is driven by the lack of therapies capable of generating durable responses. In recent years, the molecular characterization of mCRPC has proved critical to improving disease outcome and understanding responses to antiandrogen therapy, chemotherapy, targeted therapies, and immunotherapy.[2-7]

Androgen Receptors and Resistance to Hormonal Therapy and Chemotherapy in Prostate Cancer

Androgens and the AR play a crucial role in prostate carcinogenesis; studies have shown that changes in AR expression in part related to gene amplification as well as *AR* mutation and alternative splicing contribute to AR reactivation despite castrate levels of androgens.[2,66,67] *AR* copy gains are associated with worse outcomes for patients on novel hormonal therapy; somatic *AR* mutations can also promote its promiscuous activation by noncanonical steroid ligands, and expression of the splice variant AR-V7 correlates with worse outcomes (lower PSA response and shorter progression-free survival and overall survival) in patients treated with novel hormonal therapies.[2,66-68] Next-generation sequencing and polymerase chain reaction–based methods are being used to analyze *AR* genomic alterations in plasma using cell-free DNA, unlocking the potential for these to be used as a biomarker for selecting treatment in mCRPC.[69] For example, *AR* mutations causing ligand promiscuity, and making corticosteroids activating ligands, may lead to recommending iatrogenic steroid discontinuation.

DNA Damage Repair, Homologous Recombination Pathway, and Prostate Cancer

DNA damage and defective DNA repair drive the development of cancer by inducing deleterious genetic alterations.[70] DNA damage response proteins including ataxia telangiectasia mutated are activated by DNA damage and activate repair, including homologous recombination repair maintaining genomic integrity.[70] In this setting, the PARP1 and PARP2 enzymes are key to DNA damage response, acting as DNA damage sensors and signal transducers to repair DNA lesions.[70] At least 20% to 30% of mCRPC harbor defects in DNA repair genes, and some of these defects confer increased sensitivity to PARP inhibitors based on the concept of synthetic lethality.[71]

At present, two PARP inhibitors (olaparib and rucaparib) are approved by the U.S. Food and Drug Administration for use in mCRPC with germline or somatic homologous recombination repair mutations.[4,5] The TOPARP A and B trials showed superior activity for olaparib in patients with mCRPC and specific DNA damage response gene alterations compared with those without.[3,72] The randomized phase III PROfound trial subsequently demonstrated that treatment with olaparib, 300 mg twice daily, improved radiographic progression-free survival in patients whose tumors had deleterious alterations in *BRCA2*, *BRCA1*, and *ATM*, when compared with enzalutamide or abiraterone.[4] The final analysis also showed notable overall survival benefit in

patients with BRCA1/2 or *ATM* alterations treated with olaparib, despite allowing crossover from the control arm at progression.[4] Rucaparib was the second PARP inhibitor approved by the U.S. Food and Drug Administration for patients with mCRPC. This drug was granted accelerated approval based on the results of the open-label, single-arm TRITON phase II trial.[5] Treatment with rucaparib, 600 mg twice daily, showed promising results with respect to objective response rate (43.5%; 95% CI, 31–56.7%) and radiographic progression-free survival (9 months; 95% CI, 8.3–13.5) in patients with mCRPC and deleterious germline or somatic alterations in *BRCA1/2* previously treated with novel hormonal therapies and taxane chemotherapy.[5] Full approval of this drug is contingent upon a favorable efficacy and safety profile in the phase III randomized TRITON 3 study, which is currently ongoing. The efficacy of other PARP inhibitors, such as talazoparib and niraparib, is also under investigation in patients with mCRPC and DNA repair deficits.[73,74]

Despite promising results with PARP inhibitors, intrinsic and acquired resistance along with differential intrapatient responses, probably due to genomic heterogeneity, have impacted efficacy.[75] The antitumor activity of PARP inhibitors is particularly impressive in tumors harboring mutations in *BRCA2*; deleterious alterations in other DNA repair genes did not appear to be as sensitizing, and further investigation to identify predictive biomarkers is of high importance.[4]

Loss of the ataxia telangiectasia mutated protein is a common DNA repair defect, being present in up to 10% of advanced prostate cancers.[76] Interestingly, ataxia telangiectasia mutated loss can confer sensitivity to ataxia telangiectasia and Rad3-related protein inhibition in preclinical models; preclinical studies have shown that olaparib-resistant cancer cells with or without ataxia telangiectasia mutated loss may be resensitized to olaparib when combined with ataxia telangiectasia and Rad3-related protein inhibitors.[76-78] This has provided rationale for using ataxia telangiectasia and Rad3-related protein inhibitors, either alone or in combination with PARP inhibitors, in phase I and II clinical trials, which are currently ongoing.[79,80]

Immune Checkpoint Inhibitors and Prostate Cancer

In recent years, immunotherapy has impacted cancer care with several immune checkpoint inhibitors demonstrating durable responses and improved overall survival for multiple tumors considered more immunologically "hot" due to their inflamed microenvironment with considerable T-cell infiltration, increased PD-L1 expression, high neoantigen load, and high level of microsatellite instability or defective mismatch repair.[81] However, prostate cancer is a "cold" tumor with minimal T-cell infiltration, lower mutational load, a very limited response to single-agent immune checkpoint inhibition, and a variable estimated prevalence of defective mismatch repair (3% to 12%) as a result of different assays currently used to identify these aberrations.[81-90] For that reason, identifying the subset of patients most likely to benefit from immune checkpoint inhibitors is key to optimize treatment responses. Prostate cancers with defective mismatch repair, high level of microsatellite instability, and cyclin-dependent kinase 12 (*CDK12*) biallelic alterations can be sensitive to immunotherapy with higher PD-L1 expression, increased neoantigen load due to single nucleotide alterations or tandem duplications causing high genomic rearrangements, and frequently higher T-cell infiltration; these T-cell subsets may, however, be immunosuppressive in nature, with this meriting further study.[83]

PTEN/PI3K/AKT Pathway in Prostate Cancer

Genomic aberrations in the PI3K-AKT axis are common in primary prostate cancer and enriched in mCRPC (approximately 17% and 50%, respectively).[91] This pathway is mainly activated due to mutations in the tumor suppressor gene *PTEN*, although alterations in *PIK3CA*, *PIK3CB*, *PIK3R1*, and *AKT* have also been reported.[92,93] PTEN loss is associated with adverse outcomes such as increased tumor grade and stage, earlier biochemical recurrence after radical prostatectomy, metastases, prostate cancer–specific death, and androgen-independent progression.[85] The PI3K/AKT pathway has also been implicated in resistance to antiandrogen therapy, as AR inhibition is associated with an increase in AKT pathway activation, suggesting that the tumor compensates for the loss of one pathway with another.[93,94]

Pathogenic alterations of the PTEN/PI3K/AKT pathway therefore represent putative predictive biomarkers of response to PI3K and AKT inhibitors. The randomized phase III IPATential trial showed that the combination of the AKT inhibitor ipatasertib and abiraterone, as first-line treatment of mCRPC, resulted in significantly improved radiographic progression-free survival and antitumor activity compared with abiraterone and placebo in patients with mCRPC with PTEN loss (18.5 months vs. 16.5 months; HR, 0.77; 95% CI, 0.61–0.98; p = .0335).[95] The pan-AKT inhibitor capivasertib, in combination with enzalutamide, is also currently under investigation in this setting.[96]

Prostate-Specific Membrane Antigen–Targeted Radiopharmaceuticals

Prostate-specific membrane antigen (PSMA) is overexpressed in most prostate cancers, making it a promising molecular target for imaging and treatment.[97-99] Expression is higher in castration-resistant disease.[100] PSMA-targeting tracers have been labeled with a wide variety of radionuclides for both diagnostic (e.g., positron emitter ^{68}Ga) and therapeutic purposes (e.g., with the alpha-particle emitter ^{225}Ac and the beta-particle emitter ^{177}Lu). Tracers are delivered intravenously and accumulate at PSMA-expressing tumor sites, where radioactive decay of

alpha and beta particle–emitting radionuclides induce DNA damage that can result in cancer cell death. Although these agents clearly have antitumor activity, because PSMA is also expressed in other tissues, including the kidney and salivary glands, off-target radiotoxicity can be problematic.[97] Intra- and interpatient heterogeneity in PSMA expression also provides challenges with respect to biomarker development and patient selection.[101,102] Multiple clinical trials are assessing PSMA-targeting radionuclides, as monotherapy and in combinations, but phase III data are awaited.

Beta-emitting radionuclide therapy ^{177}Lu-PSMA-617, a PSMA ligand labeled with beta-emitter ^{177}Lu, has shown promising antitumor activity in early phase trials and is the most clinically developed PSMA-targeting agent. A single-arm phase II study enrolled 50 patients with progressive mCRPC after standard of care treatments.[103] Patients underwent both PSMA-PET and fluorodeoxyglucose-PET/CT to confirm high PSMA expression and exclude discordant PSMA-negative metastases prior to enrolment. A total of 32 patients (64%) achieved the primary endpoint and had a PSA decline 50% or higher, including 22 patients (44%) with a PSA decline of 80% or higher. Of the 27 patients who had measurable soft tissue disease at baseline, 15 (56%) had an objective response by RECIST 1.1 criteria. The most common treatment-related toxicities included grade 1 to 2 dry mouth (66%), transient grade 1 to 2 nausea (48%), grade 3 anemia (10%), and grade 3 to 4 thrombocytopenia (10%). Results from the TheraP trial, a randomized phase II trial comparing ^{177}Lu-PSMA-617 against cabazitaxel for men with mCRPC whose disease has progressed after docetaxel, has revealed a significantly higher PSA response rate (PSA decline 50% or higher) in those who received ^{177}Lu-PSMA-617 (66% vs. 37%; difference 29%; 95% CI, 16–42; $p < .0001$), and there were fewer grade 3 to 4 adverse events (33% vs. 53%).[104] Overall survival data, however, remain immature. VISION is the first phase III randomized controlled trial evaluating ^{177}Lu-PSMA-617, and the results are eagerly awaited. The trial has successfully recruited 750 men with mCRPC whose disease has progressed after at least one taxane and one novel androgen axis drug. Patients have been randomly assigned 2:1 to either ^{177}Lu-PSMA-617 in addition to best standard/best supportive care or best standard/best supportive care alone.[105] Other beta-emitting radionuclides in clinical development with early phase antitumor activity include a ^{177}Lu-labeled 1,4,7,10-tetraazacyclododecane-1-(glutamic acid)-4,7,10-triacetic acid (DOTAGA)–based PSMA ligand [^{177}Lu-DOTAGA-(I-y)fk(Sub-KuE)], also known as PSMA-I&T for "imaging and therapy," and ^{177}Lu-labeled anti-PSMA monoclonal antibody J591 (*^{177}Lu-J591*).[106,107]

Alpha-emtting radionuclide therapy PSMA-targeted alpha particle–emitting radionuclides are also being developed and may overcome beta-emitter resistance. Alpha particles have higher linear energy transfer, resulting in more double-stranded DNA breaks and increased cytotoxicity.[108,109] Consequently, alpha emitters may produce superior antitumor activity than beta emitters but can also result in higher toxicity to PSMA-expressing healthy tissues, although they do have shorter penetration depths. Multiple retrospective case series have reported favorable outcomes using PSMA-targeted actinium (^{225}Ac-PSMA-617) for patients with chemotherapy-naive or ^{177}Lu-PSMA-617–resistant CRPC, but dose-limiting xerostomia leading to weight loss and treatment discontinuation was problematic.[110,111] Several other alpha particle–emitting PSMA-targeting radionuclides are in clinical development, including ^{225}Ac-J591, an antibody-based radionuclide; PSMA-TTC, a small-molecule PSMA-targeted thorium-227 conjugate; and ^{225}AC-PSMA-I&T, a DOTAGA conjugate.[112-114]

Prostate-Specific Membrane Antigen–Targeted T-Cell Engagers

Immune checkpoint inhibitors are efficacious in only a small subset of patients with mCRPC, most likely due to the immunosuppressive microenvironment in prostate cancer.[81,82,84,85,115-117] T-cell engager therapy uses the cytotoxic nature of a patient's own immune system to kill cancer cells by physically linking endogenous T cells to tumor-expressed antigens. Bispecific T-cell engager molecules are artificial antibody constructs with two binding domains, one targeting a tumor-expressed antigen (e.g., PSMA) and the other binding to CD3 on T cells.[118] Anti-PSMA/CD3 bispecific T-cell engagers have demonstrated antitumor activity in preclinical models with tumor-specific cell lysis, T-cell activation, and cytokine release.[119,120] Several agents (e.g., pasotuxizumab/AMG212/BAY2010112 and AMG160) are in clinical development, either as monotherapy or in combination with an anti–PD-1 antibody. Pasotuxizumab has been shown to induce clinical activity with an acceptable safety profile in a first-in-human phase I trial.[121] Initially, subcutaneous administration was studied, but this resulted in antidrug antibody development, leading to termination of this cohort. Sixteen patients with mCRPC refractory to standard therapy were enrolled into five continuous intravenous dosing groups. The most common adverse events were fever (94%) and chills (69%). Adverse events of grade 3 or higher were reported in 81% (13 out of 16), with the most common being decreased lymphocyte count (44%) and infection (31%). Three patients (16%) developed cytokine release syndrome. A dose-dependent PSA decline was observed with a PSA decrease 50% or more in three patients with two long-term responders, one of which had a near-complete regression of lymph node and bone metastases.

AMG160, a half-life–extended anti-PSMA/CD3 bispecific T-cell engager, is being assessed in a two-part phase I study

as monotherapy and in combination with pembrolizumab (anti–PD-1) in patients with mCRPC refractory to prior novel hormonal therapy and one to two taxane regimens. Interim results in the monotherapy group (32 subjects) demonstrated a manageable toxicity profile, with cytokine release syndrome as the most common adverse event (84%), and preliminary efficacy with a dose-dependent reduction in PSA.[122] HPN424 is a trispecific T-cell–activating construct with three binding domains, targeting PSMA, CD3, and albumin (for half-life extension). Preliminary data from a first-in-human study have revealed an acceptable safety profile and early signs of clinical activity, with reductions in PSA and circulating tumor cells.[123]

CONCLUSION

This concise update of the avengers against mCRPC provides a framework for all clinicians to rationally approach the sequencing of life-prolonging therapies and approach AIPC. Finally, the future avengers are promising to target the heterogeneous disease of mCRPC via translational mechanism–based approaches.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Siegel DA, O'Neil ME, Richards TB, et al. Prostate cancer incidence and survival, by stage and race/ethnicity - United States, 2001-2017. MMWR Morb Mortal Wkly Rep. 2020;69:1473-1480.
2. Wang Z, Shen H, Ma N, et al. The prognostic value of androgen receptor splice variant 7 in castration-resistant prostate cancer treated with novel hormonal therapy or chemotherapy: a systematic review and meta-analysis. Front Oncol. 2020;10:572590.
3. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate Cancer. N Engl J Med. 2015;373:1697-1708.
4. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med. 2020;382:2091-2102.
5. Abida W, Patnaik A, Campbell D, et al; TRITON2 investigators. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a *BRCA1* or *BRCA2* gene alteration. J Clin Oncol. 2020;38:3763-3772.
6. Bilusic M, Madan RA, Gulley JL. Immunotherapy of prostate cancer: facts and hopes. Clin Cancer Res. 2017;23:6764-6770.
7. de Bono JS, De Giorgi U, Rodrigues DN, et al. Randomized phase II study evaluating Akt blockade with ipatasertib, in combination with abiraterone, in patients with metastatic prostate cancer with and without PTEN loss. Clin Cancer Res. 2019;25:928-936.
8. Watson PA, Arora VK, Sawyers CL. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nat Rev Cancer. 2015;15:701-711.
9. de Bono JS, Logothetis CJ, Molina A, et al; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364:1995-2005.
10. Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367:1187-1197.
11. George DJ, Sartor O, Miller K, et al. Treatment patterns and outcomes in patients with metastatic castration-resistant prostate cancer in a real-world clinical practice setting in the United States. Clin Genitourin Cancer. 2020;18:284-294.
12. Scher HI, Heller G. Clinical states in prostate cancer: toward a dynamic model of disease progression. Urology. 2000;55:323-327.
13. de Bono JS, Oudard S, Ozguroglu M, et al; TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376:1147-1154.
14. Tannock IF, de Wit R, Berry WR, et al; TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351:1502-1512.
15. Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213-223.
16. Kantoff PW, Higano CS, Shore ND, et al; IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363:411-422.
17. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357:409-413.

18. Fizazi K, Shore N, Tammela TL, et al; ARAMIS Investigators. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. N Engl J Med. 2020;383:1040-1049.
19. Sternberg CN, Fizazi K, Saad F, et al; PROSPER Investigators. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2020;382:2197-2206.
20. Small EJ, Saad F, Chowdhury S, et al. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. Ann Oncol. 2019;30:1813-1820.
21. Fizazi K, Shore N, Tammela TL, et al; ARAMIS Investigators. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2019; 380:1235-1246.
22. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. Eur Urol. 2017;71:151-154.
23. Smith MR, Saad F, Chowdhury S, et al. Apalutamide and overall survival in prostate cancer. Eur Urol. 2021;79:150-158.
24. Higano CS, Schellhammer PF, Small EJ, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. Cancer. 2009;115:3670-3679.
25. Ryan CJ, Smith MR, Fizazi K, et al; COU-AA-302 Investigators. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16:152-160.
26. Ryan CJ, Smith MR, de Bono JS, et al; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368:138-148.
27. Pereira-Salgado A, Kwan EM, Tran B, et al. Systematic review of efficacy and health economic implications of real-world treatment sequencing in prostate cancer: where do the newer agents enzalutamide and abiraterone fit in? Eur Urol Focus. Epub 2020 Apr 6.
28. Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol. 2019;20:1730-1739.
29. de Wit R, de Bono J, Sternberg CN, et al; CARD Investigators. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med. 2019; 381:2506-2518.
30. Oudard S, Kramer G, Caffo O, et al. Docetaxel rechallenge after an initial good response in patients with metastatic castration-resistant prostate cancer. BJU Int. 2015;115:744-752.
31. Antonarakis ES, Lu C, Luber B, et al. Androgen receptor splice variant 7 and efficacy of taxane chemotherapy in patients with metastatic castration-resistant prostate cancer. JAMA Oncol. 2015;1:582-591.
32. Armstrong AJ, Halabi S, Luo J, et al. Prospective multicenter validation of androgen receptor splice variant 7 and hormone therapy resistance in high-risk castration-resistant prostate cancer: the PROPHECY Study. J Clin Oncol. 2019;37:1120-1129.
33. Teo MY, Rathkopf DE, Kantoff P. Treatment of advanced prostate cancer. Annu Rev Med. 2019;70:479-499.
34. Aggarwal R, Huang J, Alumkal JJ, et al. Clinical and genomic characterization of treatment-emergent small-cell neuroendocrine prostate cancer: a multi-institutional prospective study. J Clin Oncol. 2018;36:2492-2503.
35. Nadal R, Schweizer M, Kryvenko ON, et al. Small cell carcinoma of the prostate. Nat Rev Urol. 2014;11:213-219.
36. Parimi V, Goyal R, Poropatich K, et al. Neuroendocrine differentiation of prostate cancer: a review. Am J Clin Exp Urol. 2014;2:273-285.
37. Bluemn EG, Coleman IM, Lucas JM, et al. Androgen receptor pathway-independent prostate cancer is sustained through FGF signaling. Cancer Cell. 2017; 32:474-489.e6.
38. Aparicio AM, Harzstark AL, Corn PG, et al. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. Clin Cancer Res. 2013;19:3621-3630.
39. Sella A, Konichezky M, Flex D, et al. Low PSA metastatic androgen- independent prostate cancer. Eur Urol. 2000;38:250-254.
40. Beltran H, Oromendia C, Danila DC, et al. A phase II trial of the aurora kinase A inhibitor alisertib for patients with castration-resistant and neuroendocrine prostate cancer: efficacy and biomarkers. Clin Cancer Res. 2019;25:43-51.
41. Aparicio AM, Shen L, Tapia ELN, et al. Combined tumor suppressor defects characterize clinically defined aggressive variant prostate cancers. Clin Cancer Res. 2016;22:1520-1530.
42. Beltran H, Prandi D, Mosquera JM, et al. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. Nat Med. 2016;22:298-305.
43. Ku SY, Rosario S, Wang Y, et al. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. Science. 2017;355:78-83.
44. Mu P, Zhang Z, Benelli M, et al. SOX2 promotes lineage plasticity and antiandrogen resistance in TP53- and RB1-deficient prostate cancer. Science. 2017; 355:84-88.
45. Zhou Z, Flesken-Nikitin A, Corney DC, et al. Synergy of p53 and Rb deficiency in a conditional mouse model for metastatic prostate cancer. Cancer Res. 2006; 66:7889-7898.
46. Zou M, Toivanen R, Mitrofanova A, et al. Transdifferentiation as a mechanism of treatment resistance in a mouse model of castration-resistant prostate cancer. Cancer Discov. 2017;7:736-749.
47. Abida W, Cyrta J, Heller G, et al. Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci USA. 2019;116:11428-11436.

48. Spratt DE, Alshalalfa M, Fishbane N, et al. Transcriptomic heterogeneity of androgen receptor activity defines a *de novo* low AR-active subclass in treatment naïve primary prostate cancer. Clin Cancer Res. 2019;25:6721-6730.

49. Alumkal JJ, Sun D, Lu E, et al. Transcriptional profiling identifies an androgen receptor activity-low, stemness program associated with enzalutamide resistance. Proc Natl Acad Sci USA. 2020;117:12315-12323.

50. Hamid AA, Gray KP, Shaw G, et al. Compound genomic alterations of TP53, PTEN, and RB1 tumor suppressors in localized and metastatic prostate cancer. Eur Urol. 2019;76:89-97.

51. Papandreou CN, Daliani DD, Thall PF, et al. Results of a phase II study with doxorubicin, etoposide, and cisplatin in patients with fully characterized small-cell carcinoma of the prostate. J Clin Oncol. 2002;20:3072-3080.

52. Culine S, El Demery M, Lamy P-J, et al. Docetaxel and cisplatin in patients with metastatic androgen independent prostate cancer and circulating neuroendocrine markers. J Urol. 2007;178:844-848, discussion 848.

53. Loriot Y, Massard C, Gross-Goupil M, et al. Combining carboplatin and etoposide in docetaxel-pretreated patients with castration-resistant prostate cancer: a prospective study evaluating also neuroendocrine features. Ann Oncol. 2009;20:703-708.

54. Humeniuk MS, Gupta RT, Healy P, et al. Platinum sensitivity in metastatic prostate cancer: does histology matter? Prostate Cancer Prostatic Dis. 2018;21:92-99.

55. Corn PG, Heath EI, Zurita A, et al. Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1-2 trial. Lancet Oncol. 2019;20:1432-1443.

56. Dardenne E, Beltran H, Benelli M, et al. N-Myc induces an EZH2-mediated transcriptional program driving neuroendocrine prostate cancer. Cancer Cell. 2016;30:563-577.

57. Taplin M-E, Hussain A, Shah S, et al. ProSTAR: a phase Ib/II study of CPI-1205, a small molecule inhibitor of EZH2, combined with enzalutamide (E) or abiraterone/prednisone (A/P) in patients with metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol. 2019;37 (7_suppl; abstr TPS335).

58. Kwon ED, Drake CG, Scher HI, et al; CA184-043 Investigators. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014;15:700-712.

59. Beer TM, Kwon ED, Drake CG, et al. Randomized, double-blind, phase III trial of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naive castration-resistant prostate cancer. J Clin Oncol. 2017;35:40-47.

60. Subudhi SK, Aparicio A, Gao J, et al. Clonal expansion of CD8 T cells in the systemic circulation precedes development of ipilimumab-induced toxicities. Proc Natl Acad Sci USA. 2016;113:11919-11924.

61. Goswami S, Apostolou I, Zhang J, et al. Modulation of EZH2 expression in T cells improves efficacy of anti-CTLA-4 therapy. J Clin Invest. 2018;128:3813-3818.

62. Chung HC, Piha-Paul SA, Lopez-Martin J, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: results from the KEYNOTE-028 and KEYNOTE-158 studies. J Thorac Oncol. 2020;15:618-627.

63. Horn L, Mansfield AS, Szczęsna A, et al; IMpower133 Study Group. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379:2220-2229.

64. Patel SP, Othus M, Chae YK, et al. A phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART SWOG 1609) in patients with nonpancreatic neuroendocrine tumors. Clin Cancer Res. 2020;26:2290-2296.

65. Puca L, Gavyert K, Sailer V, et al. Delta-like protein 3 expression and therapeutic targeting in neuroendocrine prostate cancer. Sci Transl Med. 2019;11:eaav0891.

66. Conteduca V, Jayaram A, Romero-Laorden N, et al. Plasma androgen receptor and docetaxel for metastatic castration-resistant prostate cancer. Eur Urol. 2019;75:368-373.

67. O'Mahony OA, Steinkamp MP, Albertelli MA, et al. Profiling human androgen receptor mutations reveals treatment effects in a mouse model of prostate cancer. Mol Cancer Res. 2008;6:1691-1701.

68. Sharp A, Coleman I, Yuan W, et al. Androgen receptor splice variant-7 expression emerges with castration resistance in prostate cancer. J Clin Invest. 2019;129:192-208.

69. Romanel A, Gasi Tandefelt D, Conteduca V, et al. Plasma AR and abiraterone-resistant prostate cancer. Sci Transl Med. 2015;7:312re10.

70. Rimar KJ, Tran PT, Matulewicz RS, et al. The emerging role of homologous recombination repair and PARP inhibitors in genitourinary malignancies. Cancer. 2017;123:1912-1924.

71. Athie A, Arce-Gallego S, Gonzalez M, et al. Targeting DNA repair defects for precision medicine in prostate cancer. Curr Oncol Rep. 2019;21:42.

72. Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol. 2020;21:162-174.

73. De Bono JS, Mehra N, Higano CS, et al. TALAPRO-1: a phase II study of talazoparib (TALA) in men with DNA damage repair mutations (DDRmut) and metastatic castration-resistant prostate cancer (mCRPC)—First interim analysis (IA). J Clin Oncol. 2020;38(6_suppl):119.

74. Smith MR, Fizazi K, Sandhu SK, et al. Niraparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD): Correlative measures of tumor response in phase II GALAHAD study. J Clin Oncol. 2020;38 (6_suppl; abstr118).

75. Li H, Liu Z-Y, Wu N, et al. PARP inhibitor resistance: the underlying mechanisms and clinical implications. Mol Cancer. 2020;19:107.

76. Neeb A, Herranz N, Arce-Gallego S, et al. Advanced prostate cancer with ATM loss: PARP and ATR inhibitors. Eur Urol. 2021;79:200-211.

77. Yazinski SA, Comaills V, Buisson R, et al. ATR inhibition disrupts rewired homologous recombination and fork protection pathways in PARP inhibitor-resistant BRCA-deficient cancer cells. Genes Dev. 2017;31:318-332.

78. Kim H, Xu H, George E, et al. Combining PARP with ATR inhibition overcomes PARP inhibitor and platinum resistance in ovarian cancer models. Nat Commun. 2020;11:3726.

79. Reichert ZR, Daignault S, Teply BA, et al. Targeting resistant prostate cancer with ATR and PARP inhibition (TRAP trial): a phase II study. J Clin Oncol. 2020;38 (6_suppl; abstrTPS254).

80. Yap TA, Tan DSP, Terbuch A, et al. First-in-human trial of the oral ataxia telangiectasia and RAD3-related (ATR) inhibitor BAY 1895344 in patients with advanced solid tumors. Cancer Discov. 2020;11:80-91.

81. Mahoney KM, Atkins MB. Prognostic and predictive markers for the new immunotherapies. Oncology (Williston Park). 2014;28(Suppl 3):39-48.

82. Nghiem B, Zhang X, Lam H-M, et al. Mismatch repair enzyme expression in primary and castrate resistant prostate cancer. Asian J Urol. 2016;3:223-228.

83. Rescigno P, Gurel B, Pereira R, et al. Characterizing CDK12-mutated prostate cancers. Clin Cancer Res. 2021;27:566-574.

84. Hansen AR, Massard C, Ott PA, et al. Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. Ann Oncol. 2018; 29:1807-1813.

85. Antonarakis ES, Piulats JM, Gross-Goupil M, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. J Clin Oncol. 2020;38:395-405.

86. Pritchard CC, Morrissey C, Kumar A, et al. Complex MSH2 and MSH6 mutations in hypermutated microsatellite unstable advanced prostate cancer. Nat Commun. 2014;5:4988.

87. Latham A, Srinivasan P, Kemel Y, et al. Microsatellite instability is associated with the presence of Lynch syndrome pan-cancer [published correction appears in *J Clin Oncol.* 2019;37:942]. J Clin Oncol. 2019;37:286-295.

88. Abida W, Cheng ML, Armenia J, et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. JAMA Oncol. 2019;5:471-478.

89. Schweizer MT, Cheng HH, Tretiakova MS, et al. Mismatch repair deficiency may be common in ductal adenocarcinoma of the prostate. Oncotarget. 2016; 7:82504-82510.

90. Hempelmann JA, Lockwood CM, Konnick EQ, et al. Microsatellite instability in prostate cancer by PCR or next-generation sequencing. J Immunother Cancer. 2018;6:29.

91. Abeshouse A, Ahn J, Akbani R, et al; Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer. Cell. 2015;163:1011-1025.

92. Jamaspishvili T, Berman DM, Ross AE, et al. Clinical implications of PTEN loss in prostate cancer. Nat Rev Urol. 2018;15:222-234.

93. Yang J, Nie J, Ma X, et al. Targeting PI3K in cancer: mechanisms and advances in clinical trials. Mol Cancer. 2019;18:26.

94. Crumbaker M, Khoja L, Joshua AM. AR signaling and the PI3K pathway in prostate cancer. Cancers (Basel). 2017;9:34.

95. de Bono JS, Bracarda S, Sternberg CN, et al. LBA4 IPATential150: phase III study of ipatasertib (ipat) plus abiraterone (abi) vs placebo (pbo) plus abi in metastatic castration-resistant prostate cancer (mCRPC). Ann Oncol. 2020;31(Suppl 4):S1153-S1154.

96. Kolinsky MP, Rescigno P, Bianchini D, et al. A phase I dose-escalation study of enzalutamide in combination with the AKT inhibitor AZD5363 (capivasertib) in patients with metastatic castration-resistant prostate cancer. Ann Oncol. 2020;31:619-625.

97. Silver DA, Pellicer I, Fair WR, et al. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res. 1997;3:81-85.

98. Sweat SD, Pacelli A, Murphy GP, et al. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Urology. 1998;52:637-640.

99. Bostwick DG, Pacelli A, Blute M, et al. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer. 1998;82:2256-2261.

100. Evans MJ, Smith-Jones PM, Wongvipat J, et al. Noninvasive measurement of androgen receptor signaling with a positron-emitting radiopharmaceutical that targets prostate-specific membrane antigen. Proc Natl Acad Sci USA. 2011;108:9578-9582.

101. Mannweiler S, Amersdorfer P, Trajanoski S, et al. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. Pathol Oncol Res. 2009;15:167-172.

102. Paschalis A, Sheehan B, Riisnaes R, et al. Prostate-specific membrane antigen heterogeneity and DNA repair defects in prostate cancer. Eur Urol. 2019; 76:469-478.

103. Violet J, Sandhu S, Iravani A, et al. Long-term follow-up and outcomes of retreatment in an expanded 50-patient single-center phase II prospective trial of ^{177}Lu-PSMA-617 theranostics in metastatic castration-resistant prostate cancer. J Nucl Med. 2020;61:857-865.

104. Hofman MS, Emmett L, Sandhu S, et al; TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group. [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet. 2021; 397:797-804.

105. Sartor AO, Morris MJ, Messman R, et al. VISION: an international, prospective, open-label, multicenter, randomized phase III study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol. 2020;38(6_suppl):TPS259.

106. Baum RP, Kulkarni HR, Schuchardt C, et al. ^{177}Lu-labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: safety and efficacy. J Nucl Med. 2016;57:1006-1013.

107. Tagawa ST, Milowsky MI, Morris M, et al. Phase II study of Lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. Clin Cancer Res. 2013;19:5182-5191.

108. Ruigrok EAM, van Weerden WM, Nonnekens J, et al. The future of PSMA-targeted radionuclide therapy: an overview of recent preclinical research. Pharmaceutics. 2019;11:560.

109. Poty S, Francesconi LC, McDevitt MR, et al. α-Emitters for radiotherapy: from basic radiochemistry to clinical studies-part 1. J Nucl Med. 2018;59:878-884.

110. Kratochwil C, Haberkorn U, Giesel FL. ^{225}Ac-PSMA-617 for therapy of prostate cancer. Semin Nucl Med. 2020;50:133-140.

111. Sathekge M, Bruchertseifer F, Knoesen O, et al. ^{225}Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: a pilot study [published correction appears in *Eur J Nucl Med Mol Imaging*. 2019;46:1988]. Eur J Nucl Med Mol Imaging. 2019;46:129-138.

112. Tagawa ST, Osborne J, Niaz MJ, et al. Dose-escalation results of a phase I study of ^{225}Ac-J591 for progressive metastatic castration resistant prostate cancer (mCRPC). J Clin Oncol. 2020;38 (6_suppl; abstr114).

113. Hammer S, Hagemann UB, Zitzmann-Kolbe S, et al. Preclinical efficacy of a PSMA-targeted thorium-227 conjugate (PSMA-TTC), a targeted alpha therapy for prostate cancer. Clin Cancer Res. 2020;26:1985-1996.

114. Zacherl MJ, Gildehaus FJ, Mittlmeier L, et al. First clinical results for PSMA-targeted α-therapy using ^{225}Ac-PSMA-I&T in advanced-mCRPC patients. J Nucl Med. 2021;62:669-674.

115. Ciavarra RP, Holterman DA, Brown RR, et al. Prostate tumor microenvironment alters immune cells and prevents long-term survival in an orthotopic mouse model following flt3-ligand/CD40-ligand immunotherapy. J Immunother. 2004;27:13-26.

116. Sfanos KS, Bruno TC, Maris CH, et al. Phenotypic analysis of prostate-infiltrating lymphocytes reveals TH17 and Treg skewing. Clin Cancer Res. 2008; 14:3254-3261.

117. Pasero C, Gravis G, Guerin M, et al. Inherent and tumor-driven immune tolerance in the prostate microenvironment impairs natural killer cell antitumor activity. Cancer Res. 2016;76:2153-2165.

118. Einsele H, Borghaei H, Orlowski RZ, et al. The BiTE (bispecific T-cell engager) platform: development and future potential of a targeted immuno-oncology therapy across tumor types. Cancer. 2020;126:3192-3201.

119. Leconet W, Liu H, Guo M, et al. Anti-PSMA/CD3 bispecific antibody delivery and antitumor activity using a polymeric depot formulation. Mol Cancer Ther. 2018; 17:1927-1940.

120. Friedrich M, Raum T, Lutterbuese R, et al. Regression of human prostate cancer xenografts in mice by AMG 212/BAY2010112, a novel PSMA/CD3-Bispecific BiTE antibody cross-reactive with non-human primate antigens. Mol Cancer Ther. 2012;11:2664-2673.

121. Hummel H-D, Kufer P, Grüllich C, et al. Pasotuxizumab, a BiTE® immune therapy for castration-resistant prostate cancer: phase I, dose-escalation study findings. Immunotherapy. 2021;13:125-141.

122. Tran B, Horvath L, Dorff T, et al. 609O Results from a phase I study of AMG 160, a half-life extended (HLE), PSMA-targeted, bispecific T-cell engager (BiTE®) immune therapy for metastatic castration-resistant prostate cancer (mCRPC). Ann Oncol. 2020;31(Suppl 4):S507.

123. Bendell JC, Fong L, Stein MN, et al. First-in-human phase I study of HPN424, a tri-specific half-life extended PSMA-targeting T-cell engager in patients with metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol. 2020;38 (15_suppl; abstr5552).

Evolution of Disparities in Prostate Cancer Treatment: Is This a New Normal?

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overview

Despite notable screening, diagnostic, and therapeutic advances, disparities in prostate cancer incidence and outcomes remain prevalent. Although commonly discussed in the context of men of African descent, disparities also exist based on socioeconomic level, education level, and geographic location. The factors in these disparities span systemic access issues affecting availability of care, provider awareness, and personal patient views and mistrust. In this review, we will discuss common themes that patients have noted as impediments to care. We will review how equitable access to care has helped improve outcomes among many different groups of patients, including those with local disease and those with metastatic castration-resistant prostate cancer. Even with more advanced presentation, challenges with recommended screening, and lower rates of genomic testing and trial inclusion, Black populations have benefited greatly from various modalities of therapy, achieving comparable and at times superior outcomes with certain types of immunotherapy, chemotherapy, androgen receptor–based inhibitors, and radiopharmaceuticals in advanced disease. We will also briefly discuss access to genomic testing and differences in patterns of gene expression among Black patients and other groups that are traditionally underrepresented in trials and genomic cohort studies. We propose several strategies on behalf of providers and institutions to help promote more equitable care access environments and continued decreases in prostate cancer disparities across many subgroups.

Prostate cancer continues to be the leading cancer among men in the United States, with 33,000 deaths and 191,000 cases occurring in 2020.[1] One in nine men overall in the United States develops prostate cancer in his lifetime. In Black men, however, this rate is one in seven, and the incidence rate among Black men is 2.2 times that in White men, with the death rate 1.7 times higher.[1] Moreover, although Black men are diagnosed at younger ages, they present routinely with more advanced disease and higher prostate-specific antigen (PSA) levels at presentation than other groups.[2-7]

Disparities have been shown to exist not only between ethnic groups but also based on socioeconomic level,[8,9] education level,[10] and rural versus urban residency.[11] Here, we will examine common areas of disparity in prostate cancer. We will also address some of the systemic and personal patient views that contribute to these disparities. We will show how equitable access to care may alleviate some of these areas of disparity, especially in the context of challenges brought on by the COVID-19 pandemic. Lastly, we will examine molecular signatures and the trends and roles they may play in disparate outcomes in patients with prostate cancer.

CHANGING TRENDS

Over the last few decades, technologic and screening advances have led to a decrease in some of the noted prostate cancer disparities.[12] U.S. Surveillance, Epidemiology, and End Results database analyses show that at a peak in 1992, there were approximately 237 new cases per 100,000 patients. This decreased markedly over time to a nadir of 102 cases per 100,000 patients.[13,14] Five-year overall survival increased during the same period of time, from 96% to greater than 98% for all patients registered.[13,15] Moreover, the disparities between Black and White patients have narrowed over time, with recent analyses of prostate cancer survival rates between 2001 and 2016 showing Black men with metastatic prostate cancer are surviving at a similar rate to White men, with approximately 31% of men alive at 5 years.[12,15] There are likely several reasons for this, including screening increases as well as treatment advances being available. The rates and any differences in incidence and mortality in the future remain to be seen. Changes in screening recommendations by the U.S. Preventive Services Task Force in 2012 against general PSA screening and later in 2018 to favor open-ended discussion on screening for most men at general risk of prostate cancer may have played a role in a disproportionate effect within Black populations, which had a 29% decrease in screening rates after the recommendation changes, despite being at higher risk.[16] Decreases in screening have previously been shown to have an effect on later presentation patterns. Indeed, in the 5 years after the initial

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PRACTICAL APPLICATIONS

- Prostate cancer disparities exist in the context not only of race and ethnicity but also of socioeconomic level, education level, and geographic location.
- Systemic hurdles to access with regard to screening, diagnostics, and therapeutics, as well as personal patient views and medical hesitancy, may play a role in noted disparities.
- Despite presenting with more advanced disease, Black patients demonstrate favorable outcomes in trial formats and equal access environments with regard to multiple types of therapy.
- Genomic trial data and information useful for all patients depend on diverse patient inclusion to ensure applicability to a wide population.

decreased PSA screening recommendation, there was a decrease in incidence of local stage disease but increases in regional and distant metastases.[17-19] Drops in screening rates have also become more problematic during the COVID-19 pandemic. Data demonstrate that prostate cancer screening rates dropped approximately 60% to 75% in different series during the COVID-19 pandemic when compared with prior time periods.[20,21] Prostate cancer pathologic diagnoses have also decreased in several series examined, with declines ranging from 20% to 39% lower than the preceding year.[20,22] The total effects of the COVID-19 pandemic on overall outcomes are not yet clear, but early analyses paint a challenging picture. A recent case control analysis of more than 73 million electronic medical records showed that Black patients with prostate cancer were five times more likely to be infected with COVID-19 (odds ratio, 5.10; 95% CI, 4.34–5.98; $p < .001$). There was a synergistic adverse effect of COVID-19 and cancer with regard to patient rates of hospitalization (Black patients, 55.56% vs. White patients, 43.24%; $p = .003$).[23] The life expectancy for all men in the United States is estimated to have dropped by approximately 1.13 years during the early parts of the COVID-19 pandemic, but the life expectancy for Black men decreased by approximately 2.10 years and the life expectancy for Latino men decreased by approximately 3.05 years during the same period.[24] This rapid decrease in life expectancy has been suggested to be due in large part to COVID-19 effects. The long-term effects of delayed care with regard to the most common medical comorbidities, such as cardiovascular disease, chronic kidney disease, diabetes, and cancer, present in these groups remain to be seen, but indeed, these groups seem to have increased COVID-19–related mortality in the short term in meta-analyses.[25] Moreover, loss of insurance stemming from jobs that were disproportionally affected during the pandemic can amplify the effects of normal medical visits and screening to detect these comorbid conditions and cancers, especially among Black and Hispanic workers.[26]

Whereas some of these changes in prostate cancer epidemiology are related to policy changes on screening and recent pandemic-related factors, there remains a host of other underlying problems affecting clinical care and even beneficial measures such as clinical trial participation. Standard-of-care benchmark treatments and clinical trials are vitally important parts of cancer care progress. Limited access to care, language barriers, transportation, and cost of care, even among insured patients, can also play a role in trial participation.[27] Patients who live farther from cancer centers have been shown to be less likely to enroll in clinical trials as well.[28] Underserved patients have also been shown to be less likely to regularly visit their physicians or enroll in interventional clinical trials.[29-32] Importantly, hurdles remain because of patient perception and medical mistrust among many affected high-risk groups.

Engaging local resources within respective communities may help provide culturally appropriate screening strategies and methods to address prostate cancer treatment. Surveyed men noted insufficient information regarding prostate cancer, medical mistrust, poor relationships with medical providers, and lack of sustained relationships from within the community as barriers to an emphasis on prostate health.[33] Embarrassment and fear of a positive diagnosis, reluctance to talk about sexually related complications, and beliefs that prostate cancer may stem from sexual behavior have also been cited during focus groups, which may affect continuity of cancer education and care.[34] Strong emphasis on a role for information from cancer survivors was noted.[33,35,36] Successful outreach efforts have used community institutions such as churches and barbershops along with trusted community educators and local patients with cancer and contacts.[37-41] Indeed, familiarity with presenters has been shown to lead to more highly rated and effective engagement during educational ventures.[42,43] Partners and spouses are also highly useful participants in educational efforts.

DIFFERENCES IN PATTERN OF AND RESPONSE TO TREATMENT: NOT JUST RACE

In the last several years, patients, the research community, and the press have appropriately paid an increasing amount of attention to disparities in outcomes based on race for prostate cancer and other malignancies. However, prostate cancer disparities also exist based on other factors, including rural versus urban location, socioeconomic status, ethnicity, clinical trial participation, and country of treatment. Here, we briefly discuss the multiple demographic

determinants of disparities in prostate cancer and focus on treatment and response to treatment rather than purely on outcomes. These disparities are complex in etiology and may be addressed in part by providers familiarizing themselves with where disparities exist and options for care,[44] improving communication skills,[42] and standardizing treatment options.[45] Health care entities may also help by providing more broadly based support with navigators and other support mechanisms for clinical choices and presenting trial opportunities for patients.[46-48]

Race and Ethnicity

Patients with prostate cancer may receive different treatments based on stage, but there is a striking racial disparity in the treatment of localized disease. Using U.S. Surveillance, Epidemiology, and End Results data, Moses et al[45] reported that Black men were less likely than White men to receive definitive treatment by either prostatectomy or definitive radiation therapy for localized prostate cancer (odds ratio, 0.73; 95% CI, 0.71–0.75; $p < .001$). Although of a smaller magnitude, a significant disparity also existed between Hispanic and White patients, with fewer Hispanic patients receiving definitive treatment (odds ratio, 0.95; 95% CI, 0.92–0.98; $p < .001$). The racial disparity also seems to extend to the use of molecular imaging. In a single-center study, Black patients were more likely than White patients to receive the older fluciclovine PET/CT as opposed to the newer gallium-68 prostate-specific membrane antigen PET/CT to evaluate biochemically recurrent prostate cancer.[49] Although direct comparison studies do not exist, prostate-specific membrane antigen–based PET scans are generally agreed to be more sensitive than fluciclovine PET scans.[50] Although on average Black patients with prostate cancer receive less intensive treatment of localized disease, they unfortunately are more likely to have decisional regret afterward and may later wish they had opted for more aggressive approaches to their treatment.[51] Lastly, even if assigned the same treatment, Black patients might be less likely to complete it. In a study of 25,727 Black and 126,199 White patients, 12.8% of Black men did not complete definitive radiation therapy for localized prostate cancer as compared with 11.8% of White men (odds ratio, 1.14; 95% CI, 1.09–1.19; $p < .001$).[52]

Geographic Location

Other factors besides race and ethnicity are associated with disparities in prostate cancer treatment. Patients in nonurban areas are more likely than patients in urban areas to receive no treatment of prostate cancer. Conversely, patients in urban areas are more likely to receive radical prostatectomy than patients in nonurban areas.[53] Many researchers might expect that underserved patients treated at academic centers might receive more optimal or perhaps more aggressive care for prostate cancer than those patients treated at nonacademic centers. However, this does not consistently seem to be the case. Black, Hispanic, and uninsured patients were all more likely to experience treatment delays than White patients at both academic and nonacademic centers.[54] Delays were actually slightly longer at academic centers, although academic and nonacademic centers were not directly compared. However, in a different study, patients at an academic center were more likely to be treated with radical prostatectomy (odds ratio, 2.57; 95% CI, 2.45–2.69; $p < .001$) as compared with community sites.[55]

Financial and Socioeconomic Status

Another key area affecting treatment of prostate cancer comprises financial concerns and socioeconomic status. Sayyid et al[56] found in a U.S. population that high socioeconomic status was associated with an increased odds ratio for receipt of definitive treatment of localized disease. Socioeconomic status is interrelated with race, and the two can be difficult to disentangle. In a large series of patients from Detroit, Michigan, Black patients with prostate cancer had lower survival, but adjustment for treatment and socioeconomic status removed the survival difference.[57] However, even in a more homogenous population (Geneva, Switzerland), patients with prostate cancer of lower socioeconomic status had shorter survival. The survival difference was attributed to delayed diagnosis, different diagnostic workup, and less invasive treatment.[58] Prostate cancer treatment also differs on a wider scale, between rich and poor countries, as opposed to between patients of different socioeconomic status within a country. As an example, clinical trial participation varies greatly between countries. A recent study estimated that 96% of participants in clinical trials are White and that only 3% of African and Caribbean countries are even included in any clinical trials.[59] Cooperative group trials in the United States are somewhat better, but Black patients make up only approximately 9% of participants, less than the overall population and less than the overall percentage of patients with prostate cancer.[60,61] The relatively low population of patients in clinical trials across many trial formats makes it challenging to apply trial results to a diverse population.

RESPONSE TO PROSTATE CANCER TREATMENT AND MITIGATION OF DISPARITIES

Despite the disparities in outcome discussed earlier and the differing treatment patterns outlined, one may argue that meaningful differences can be made by the practice patterns of individual physicians.[44,62] Other points of view would support that often-touted biologic differences are minimal as opposed to large-scale societal issues that may address disparities.[63] Despite the complexity and multiple factors at play, mitigation of prostate cancer disparities will likely involve efforts such as enrollment in clinical trials that contribute toward better outcomes. Importantly, Black men in

particular seem to respond at least as well as White men to standardized prostate cancer treatments.

Black Patients Have Equal or Better Treatment Response

In the metastatic setting, Black men seem to respond better than or similar to White men to multiple different treatments. Among those with metastatic castration-resistant prostate cancer, Black patients have better and more durable PSA responses.[64,65] In the area of immunotherapy, which has overall been disappointing in prostate cancer, the survival data in Black men are more encouraging. In a registry analysis, Black men treated with sipuleucel-T had a significant reduction in risk of death, with hazard ratios of 0.81 (95% CI, 0.68–0.97; p = .03) for all patients and 0.70 (95% CI, 0.57–0.86; p < .001) in patients with matched PSA values.[66] This pattern was corroborated on additional analyses.[67] Black men treated with docetaxel for metastatic castration-resistant prostate cancer had a similar survival to that of White men by raw numbers but had a lower risk of death when adjusted in a multivariable fashion within a large meta-analysis (HR, 0.81; 95% CI, 0.72–0.91; p < .001).[68] Differences have also been examined in the use of radium-223, a radiopharmaceutical agent approved in the castration-resistant prostate cancer setting. In a retrospective analysis of 318 patients receiving this agent, Black men had a lower risk of death from the time of radium-223 initiation (HR, 0.75; 95% CI, 0.57–0.99; p = .045).[69] Differences in treatment response have also been well elucidated with regard to oral novel androgen receptor pathway inhibitors. In the prechemotherapy castration-resistant prostate cancer setting, Black patients had a 53% rate of PSA decrease to greater than 90%, whereas only 31% of corresponding White patients had a similar reduction with abiraterone, a CYP-17 lyase inhibitor.[70] Statistical power in this study was limited by the low number of Black patients (28 of 1,088 total patients).[70] Patients treated in an equal access center had similar patterns of PSA decline with abiraterone, with 68.9% of Black patients demonstrating PSA level decline of 50% or greater versus 48.9% of White patients (p = .028).[64] A separate analysis of abiraterone or enzalutamide in castration-resistant prostate cancer showed improved overall survival of 918 days for Black patients versus 781 days over their White counterparts (HR, 0.826; 95% CI, 0.732–0.933).[71] Importantly, this benefit of androgen-based therapies has also been analyzed in a prospective fashion, where PSA progression-free survival was approximately 16.6 months in Black patients (95% CI, 11.5 to not reached) versus 11.5 months in non-Black patients (95% CI, 8.5–19.3) treated for castration-resistant prostate cancer.[65] These various outcomes in prostate cancer for Black patients are summarized in Table 1.[72]

The reason for similar or enhanced responses in Black patients versus White patients with metastatic castration-resistant prostate cancer is not completely understood. Genomic differences that may play a role in effects on various treatment pathways are explored more in depth later in this review. For example, in small cohorts of patients with metastatic castration-resistant prostate cancer, Black men demonstrated more tumor mutations in androgen receptor and DNA repair genes compared with other men.[73] Lastly, Black patients may have an equal or better response to therapy in localized disease as well, if they receive the same treatment as their White counterparts. As mentioned, in selected U.S. Surveillance, Epidemiology, and End Results analyses, Black men were more likely to receive no treatment at all or to receive radiotherapy versus radical prostatectomy when compared with White men (HR, 1.03; p = .041).[62] The patients with similar risk profiles analyzed in this study had no difference in overall survival. In a separate analysis of data from the U.S. Veterans Administration, however, Black men had a lower 10-year all-cause mortality than White men who received definitive radiation therapy for localized prostate cancer.[74] The mortality racial differences by type of primary treatment seen in some series of patients with prostate cancer but not others require more study and analysis. Most analyses have been retrospective and may have been affected by various types of bias. Additional prospective analyses for localized prostate cancer treatment outcomes by race are necessary.

Treatment in Clinical Trials Mitigates Disparities

Black men and patients from other minority groups have a lower rate of participation in prostate cancer clinical trials, both in the United States[75] and globally.[59] Additionally, rural residents are less likely to enroll in clinical trials overall, although there are limited analyses specific to prostate cancer.[76] However, treatment in a clinical trial has been shown to eliminate differences in overall survival, both for Black patients with metastatic castration-resistant prostate cancer[77] and for patients with cancer in rural areas overall.[76] Several problematic issues exist even with large clinical trials that may confound trial availability and outcomes for marginalized patients. These may include site selection that favors more affluent populations, criteria that neglect comorbidities with real-world populations, distance from trial sites, and lack of insurance.

Importantly, additional confounding issues may also affect clinical trial availability. Lack of accrual has been shown to be a major reason for clinical trial closure and affects the presence of clinical treatment options for future patients.[78] Poor performance status is often a major reason for patients not qualifying for or being excluded from clinical trials.[28] Analyses of large phase III clinical trials demonstrated that 96% of patients enrolled across 600 analyzed trials had an Eastern Cooperative Oncology Group performance status of 0 or 1.[79] Analysis of clinical trial enrollment in

TABLE 1. Analyses Demonstrating Therapeutic Efficacy in Black Patients With Metastatic Prostate Cancer

Author	Agent Investigated	Trial and Analysis Type	Number of Patients	Endpoint	Outcomes
Halabi et al[68]	Docetaxel	Meta-analysis	8,820 (White, 7,528 [85%]; Black, 500 [6%])	Median OS and risk of death	Median OS, 21.0 vs. 21.2 months; (multivariable HR, 0.81; 95% CI, 0.72–0.91; $p < .001$)
Ramalingam et al[64]	Abiraterone	Case control analysis	135 (White, 90 [66%]; Black, 45 [33%])	PSA response	68.9%; $\geq$ 50% PSA level decline in Black patients vs. 48.9% in White patients ($p = .028$)
Efstathiou et al[70]	Abiraterone	Retrospective subset analysis	28 Black patients (of 1,088 total patients in COU-AA-302)	PSA response, radiographic PFS	> 90% PSA in 53% of Black patients vs. 31% of White patients; radiographic PFS, 16.6 months in Black patients vs. 11.1 in White patients
McNamara et al[71]	Abiraterone or enzalutamide in CRPC	Retrospective medical record review of VA database	787 Black patients and 2,123 White patients with CRPC	Median OS and risk of death	Median OS, 918 days for Black patients and 781 days for White patients (multivariable HR, 0.826; 95% CI, 0.732–0.93; $p = .0020$)
George et al[65]	Abiraterone in metastatic CRPC	Prospective parallel group study	50 Black patients and 50 White patients	PSA, PFS, PSA response	Median PSA PFS, 16.6 months for Black patients vs. 11.5 for White patients; > 90% PSA decline in 48% of Black patients vs. 38% of White patients
Sartor et al,[66] Higano et al[67]	Sipuleucel-T	Registry cohort analysis	1,976 (White, 1,649 [83.4%]; Black, 221 [11.1%])	Median OS and risk of death	Median OS, 25.8 vs. 35.3 months (HR, 0.81; 95% CI, 0.68–0.97; $p = .03$) in all patients (HR, 0.70; 95% CI, 0.57–0.86; $p < .001$) in PSA-matched set (HR, 0.60; 95% CI, 0.48–0.74; $p < .001$)
Zhao et al[69]	Radium-223	Retrospective medical record review of VA database	87 Black patients (27%) of 318 patients treated with radium-223	Risk of death	Black race was associated with decreased risk of mortality (HR, 0.75; 95% CI, 0.57–0.99; $p = .045$)

Abbreviations: OS, overall survival; PSA, prostate-specific antigen; PFS, progression-free survival; CRPC, castration-resistant prostate cancer; VA, Veterans Affairs.
Data adapted from Carthon et al.[72]

a predominantly Black population also showed that these patients were often unable to take part in clinical trials because of comorbid conditions.[80] Although large clinical trials may help answer pertinent and relevant questions, they often exclude the very groups that may benefit most. These limitations in clinical trial design highlight the importance of including a diverse population of patients who are able to safely enroll.

Outreach, Communication, and Action Items

Individual physicians and other health care providers have the capacity to educate and help mitigate disparities in prostate cancer treatment and outcomes in their practice. Given that Black men have had similar or better responses to treatment than White men for both localized and metastatic prostate cancer, we recommend treatment for Black men should be as intensive as is safe and supported by the literature. This contrasts with a potential pitfall of treating Black patients more conservatively to avoid doing harm. Second, we recommend treatment in a clinical trial for any patient, but especially for underserved populations. Because Black men in particular have higher mistrust of the medical system in general and of clinical trials in particular, special efforts in communication may be required for Black patients. Although working to help rectify entrenched societal differences may seem daunting for an individual practitioner, recognizing that there are existing organizations in place can be the first step in countering systemic obstacles to care. These include the National Cancer Institute Geographic Management of Cancer Health Disparities and National Cancer Institute Center to Reduce Cancer Health Disparities.[81,82] These entities not only support research but also provide assistance to cancer health professionals and patients and work to diversify the cancer care workforce.

Patient beliefs may also play a role in outcomes, both during screening and also once a patient is actually diagnosed with cancer and must undergo therapy. The exact contribution of patient beliefs (versus implicit or explicit bias) to systemic access issues is difficult to determine.[83,84] Race alone has not been shown to be predictive of poor outcomes when examining multiple forms of treatment, including watchful waiting,[85] prostatectomy,[85] or even definitive radiation therapy.[86,87] Various studies suggest that hurdles such as more adverse presenting features, negative patient beliefs, and systemic access issues may be overcome to some degree by receiving care in more equitable access environments or via other mechanisms.

Patient navigation is an opportunity to make use of nursing and other support professionals for better health outcomes. This also has the potential to provide increased access to clinical trial enrollment among diverse populations. This approach has been used in several cancers and has been shown to help with screening and treatment planning in Black patients with prostate cancer. Men benefited by having more timely and increased rates of follow-up.[43,88] Standard use of patient navigators may improve patient outcomes with regard to disparities in screening and overall outcomes in prostate cancer.

As we discussed, treatment in a clinical trial can help eliminate racial disparities,[89] but Black patients are less likely than White patients to participate in prostate cancer clinical trials.[75] Therefore, we encourage prostate cancer physicians to offer clinical trials to patients in all demographic groups. Additionally, the U.S. Food and Drug Administration has studied potential solutions to disparate clinical trial enrollment in patients from multiple demographic groups in part through workshops.[90] Multiple solutions were proposed in a nonbinding U.S. Food and-Drug Administration guidance document,[91] including loosening exclusion criteria throughout clinical trials, not copying overly restrictive phase II exclusion criteria in phase III trials, making trials less burdensome for patients by including more telehealth visits and reimbursing trial participants for travel expenses, conducting community outreach events, and including trial sites with a high percentage of underrepresented populations in patient pools. Although Black people make up approximately 12% of the U.S. population and approximately 22% of patients with cancer in the United States,[60] they constitute a small proportion of patients enrolled in pharmaceutical industry–sponsored trials (approximately 3%) and are enrolled less frequently in general in cooperative group (approximately 9%) and other types of trials.[61] Therefore, in addition to individual physicians, authors of clinical trial protocols in academia and industry have an opportunity to lessen prostate cancer health disparities through thoughtful trial design.

PROSTATE CANCER DISPARITIES: GENOMIC DATA

A historical and persistent difficulty in the management of prostate cancer is being able to identify and distinguish indolent from aggressive disease.[92-94] Prostate cancer incidence and mortality rates vary widely by ancestry, with men of African ancestry experiencing the greatest burden of disease, likely because of the interplay of socioeconomic factors, environmental exposures, and biologic/epigenetic phenomena.[95-100] Decades of evidence have clearly established that Black men have a much greater burden of prostate cancer than men of European ancestry, including a nearly two-fold increased risk of developing prostate cancer and a more than 2.2-fold increased risk of dying as a result of prostate cancer.[1] As noted earlier, Black men present at earlier ages and with more advanced disease but are less likely to have access to screening and guideline-concordant care, when compared with other men.[101]

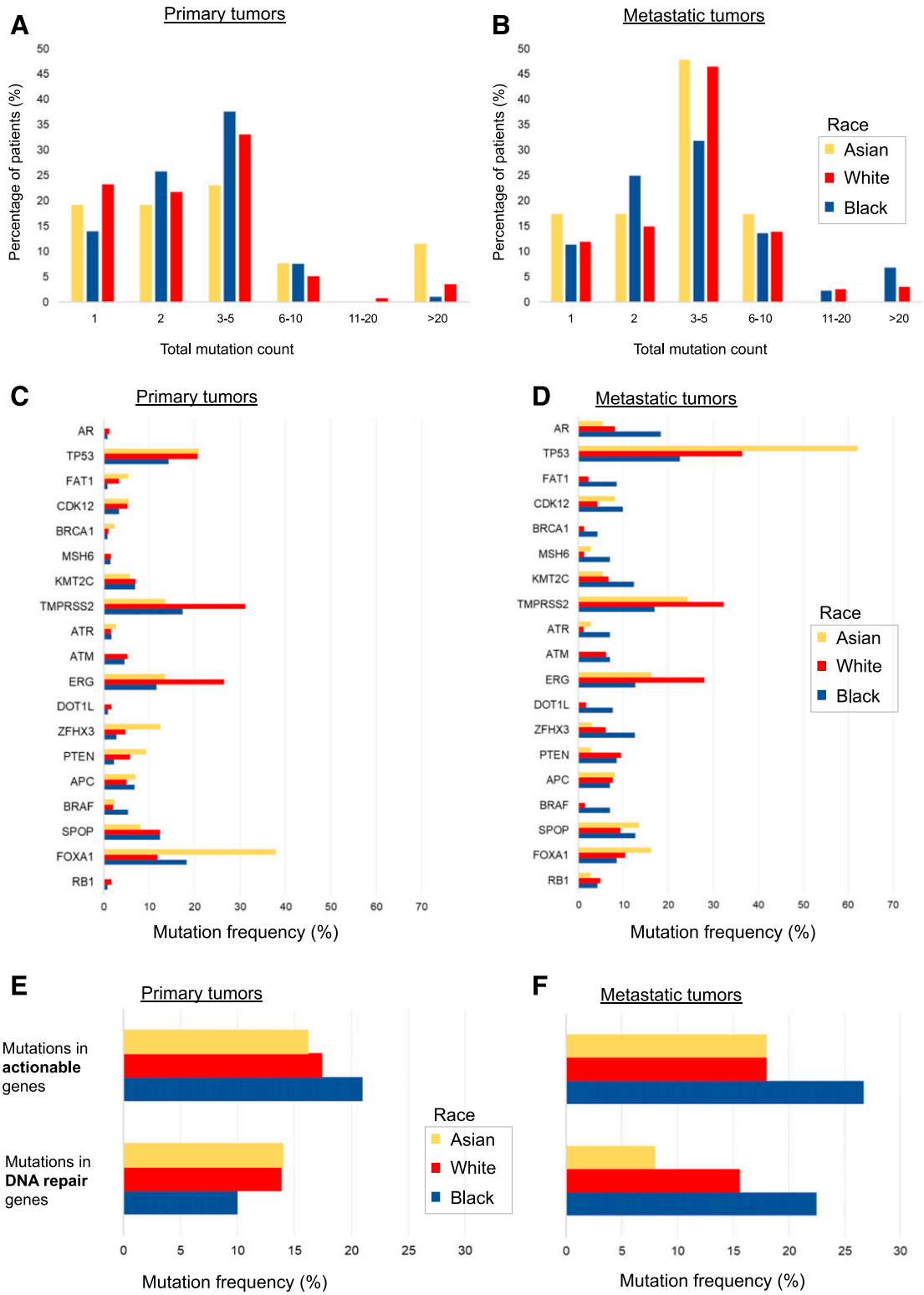

FIGURE 1. Tumor Mutation Profiles by Race in Primary and Metastatic Prostate Cancer

Tumor mutation profiles (MSK-IMPACT and Dana-Farber Sequencing) by race in 2,393 patients (2,109 White; 204 Black; 80 Asian) with primary (1,484 patients [1,308 White; 133 Black; 45 Asian]) or metastatic prostate cancer (909 patients [801 White; 71 Black; 37 Asian]). (A, B) Total mutation count was calculated in the MSK-468 cohort. (C, D) Mutation frequency in primary

FIGURE 1. (Continued). and metastatic tumors. (E, F) DNA repair genes include *ERCC5, MRE11, TP53BP1, POLE, RAD21, MSH2, MSH6, BRCA1/2, ATR, and ATM*. In metastatic cases, DNA repair gene mutations occurred more often in Black men (22.5%) compared with White men (15.6%; p = .05). Mutations in *ATR* and *MSH6* occurred more often in Black compared with White men (7.0% vs. 1.1%; p = .0002 for both). Actionable mutations include *ABL1, EGFR, ERBB2, BRAF, BRCA1/2, FGFR2/3, KIT, NTRK1/2/3, PDGFRA, RET, ROS1, ALK*, and *PIK3CA*. In metastatic cases, actionable gene mutations occurred more often in Black (26.7%) compared with White men (18.0%; p = .05).

The increasing use of precision genomics and medicine has the potential to improve outcomes for all men with prostate cancer; however, genomic efforts and clinical studies have been highly Eurocentric, and there is a risk of widening disparities in the precision medicine era if efforts continue to not include cohorts that are representative of local, national, and global populations.[102-106] Efforts to address racial differences in prostate cancer outcomes have largely been focused on investigating the contribution of social versus biologic factors in high-risk populations.[107-109] Now, there is increasing evidence that many genomic prognostic models and subsequent targeted therapies are most likely to benefit White patients and least likely to benefit Black patients with cancer and other diseases.[102-106] Furthermore, there are no specific tumor-based biomarkers or tailored nomograms to guide workup and management of prostate cancer among the subset of patients of African descent who are known to have a higher risk of death resulting from prostate cancer.[110,111] This is largely due to insufficient minority participation in cancer research, hence the present lack of validated predictive tools for this patient population.

This lack of inclusion of men of African descent is a particular potential hazard in prostate cancer, given the disease has some of the greatest disparities recorded to date. Clinically relevant alterations may occur at different frequencies across race that could have implications for prognosis, therapy response, and enrollment of minority populations in clinical trials and precision oncology studies. An alternative possibility for outcome disparities would suggest that outcome differences could be accounted for by differences in environment, socioeconomic differences, and/or contributors from structural racism. However, there may be a more complex biologic component to these outcomes as well. Preliminary studies in small cohorts of men with metastatic prostate cancer have demonstrated that Black men were more likely to have tumor mutations in androgen receptor, actionable mutations, and DNA repair genes compared with other men (Fig. 1).[73,110,111] Nevertheless, conclusions cannot be drawn until appropriate studies are conducted with large numbers of non-White patients and that include data on environmental exposures.

Of note, only 13% of the samples from a recent study examining genomic variants in prostate cancer were from Black patients.[112] Several issues complicate the availability of genomic clinical trials and next-generation sequencing to all patients. Insurance issues and cost may make these items financially unavailable. Patients may also refuse genomic testing because of a misunderstanding of terminology and hesitancy regarding what is believed to be genomic research.[113] Availability of appropriate and standard genetic counseling may also provide a major impetus to overcoming such hurdles. Adherence to recent consensus meeting recommendations regarding genomic testing and utility of navigation may provide a way to definitely decrease the disparity in genomic analyses,[114] but this will require resources to implement.

FUTURE DIRECTIONS

Despite the progress in prostate cancer survival, treatment, and disparity, much work remains. Because the etiology of these disparities is multifactorial and based not only on ethnicity, geographic location, and socioeconomics, the approach to address these disparities must also be multifaceted. We encourage and recommend:

1. More studies of novel therapies stratified by race
2. Use of patient navigation with clinical therapies and trial enrollment in underserved patient settings
3. Enhanced and guideline-driven use of genomic testing to personalize therapies
4. Standardization of treatment such that care is delivered in more equal access environments and pathways for optimal outcomes

It is hoped that ongoing community-based educational efforts using invested and familiar partners will continue to address the advances made in cancer therapies and approaches that have led to progress in eliminating prostate cancer disparities.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_321195.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
2. Jemal A, Culp MB, Ma J, et al. Prostate cancer incidence 5 years after US Preventive Services Task Force recommendations against screening. J Natl Cancer Inst. 2020;113:64-71.
3. Pietro GD, Chornokur G, Kumar NB, et al. Racial differences in the diagnosis and treatment of prostate cancer. Int Neurourol J. 2016;20(suppl 2):S112-S119.
4. Noone AM, Lund JL, Mariotto A, et al. Comparison of SEER treatment data with Medicare claims. Med Care. 2016;54:e55-e64.
5. Leung AK, Hugar L, Patil D, et al. The clinical course of patients with prostate-specific antigen ≥100 ng/ml: insight into a potential population for targeted prostate-specific antigen screening. Urology. 2018;117:101-107.
6. Tsodikov A, Gulati R, de Carvalho TM, et al. Is prostate cancer different in black men? Answers from 3 natural history models. Cancer. 2017;123:2312-2319.
7. Miller EA, Pinsky PF, Black A, et al. Secondary prostate cancer screening outcomes by race in the Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial. Prostate. 2018;78:830-838.
8. Tewari AK, Gold HT, Demers RY, et al. Effect of socioeconomic factors on long-term mortality in men with clinically localized prostate cancer. Urology. 2009;73:624-630.
9. Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA Cancer J Clin. 2004;54:78-93.
10. Singh GK, Jemal A. Socioeconomic and racial/ethnic disparities in cancer mortality, incidence, and survival in the United States, 1950-2014: over six decades of changing patterns and widening inequalities. J Environ Public Health. 2017;2017:2819372.
11. Dasgupta P, Baade PD, Aitken JF, et al. Geographical variations in prostate cancer outcomes: a systematic review of international evidence. Front Oncol. 2019;9:238.
12. Kim IE Jr., Jang TL, Kim S, et al. Abrogation of survival disparity between Black and White individuals after the USPSTF's 2012 prostate-specific antigen-based prostate cancer screening recommendation. Cancer. 2020;126:5114-5123.
13. National Cancer Institute Surveillance, Epidemiology, and End Results Program. SEER incidence data, 1975-2018: prostate cancer mortality. https://seer.cancer.gov/data/. Accessed March 30, 2021.
14. National Cancer Institute Surveillance, Epidemiology, and End Results Program. SEER incidence data, 1975-2017: prostate cancer incidence. https://seer.cancer.gov/data/. Accessed March 30, 2021.
15. Siegel DA, O'Neil ME, Richards TB, et al. Prostate cancer incidence and survival, by stage and race/ethnicity - United States, 2001-2017. MMWR Morb Mortal Wkly Rep. 2020;69:1473-1480.
16. Patel NH, Bloom J, Hillelsohn J, et al. Prostate cancer screening trends after United States Preventative Services Task Force guidelines in an underserved population. Health Equity. 2018;2:55-61.
17. Hu JC, Nguyen P, Mao J, et al. Increase in prostate cancer distant metastases at diagnosis in the United States. JAMA Oncol. 2017;3:705-707.
18. Bernstein AN, Shoag JE, Golan R, et al. Contemporary incidence and outcomes of prostate cancer lymph node metastases. J Urol. 2018;199:1510-1517.
19. Negoita S, Feuer EJ, Mariotto A, et al. Annual Report to the Nation on the Status of Cancer, part II: recent changes in prostate cancer trends and disease characteristics. Cancer. 2018;124:2801-2814.
20. Bakouny Z, Paciotti M, Schmidt AL, et al. Cancer screening tests and cancer diagnoses during the COVID-19 pandemic. JAMA Oncol. 2021;7:458-460.
21. Patt D, Gordan L, Diaz M, et al. Impact of COVID-19 on cancer care: how the pandemic is delaying cancer diagnosis and treatment for American seniors. JCO Clin Cancer Inform. 2020;4:1059-1071.
22. De Vincentiis L, Carr RA, Mariani MP, et al. Cancer diagnostic rates during the 2020 'lockdown', due to COVID-19 pandemic, compared with the 2018-2019: an audit study from cellular pathology. J Clin Pathol. 2021;74:187-189.
23. Wang Q, Berger NA, Xu R. Analyses of risk, racial disparity, and outcomes among US patients with cancer and COVID-19 infection. JAMA Oncol. 2021;7:220-227.
24. Andrasfay T, Goldman N. Reductions in 2020 US life expectancy due to COVID-19 and the disproportionate impact on the Black and Latino populations. Proc Natl Acad Sci USA. 2021;118:e2014746118.
25. Ssentongo P, Ssentongo AE, Heilbrunn ES, et al. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: a systematic review and meta-analysis. PLoS One. 2020;15:e0238215.
26. Agarwal SD, Sommers BD. Insurance coverage after job loss - the importance of the ACA during the Covid-associated recession. N Engl J Med. 2020;383:1603-1606.

27. Ford JG, Howerton MW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer. 2008; 112:228-242.
28. Horn L, Keedy VL, Campbell N, et al. Identifying barriers associated with enrollment of patients with lung cancer into clinical trials. Clin Lung Cancer. 2013; 14:14-18.
29. Wasserman J, Flannery MA, Clair JM. Raising the ivory tower: the production of knowledge and distrust of medicine among African Americans. J Med Ethics. 2007;33:177-180.
30. Kennedy BR, Mathis CC, Woods AK. African Americans and their distrust of the health care system: healthcare for diverse populations. J Cult Divers. 2007; 14:56-60.
31. Shavers-Hornaday VL, Lynch CF, Burmeister LF, et al. Why are African Americans under-represented in medical research studies? Impediments to participation. Ethn Health. 1997;2:31-45.
32. Shavers VL, Brown ML. Racial and ethnic disparities in the receipt of cancer treatment. J Natl Cancer Inst. 2002;94:334-357.
33. Allen JD, Kennedy M, Wilson-Glover A, et al. African-American men's perceptions about prostate cancer: implications for designing educational interventions. Soc Sci Med. 2007;64:2189-2200.
34. Forrester-Anderson IT. Prostate cancer screening perceptions, knowledge and behaviors among African American men: focus group findings. J Health Care Poor Underserved. 2005;16(suppl A):22-30.
35. Vijaykumar S, Wray RJ, Jupka K, et al. Prostate cancer survivors as community health educators: implications for informed decision making and cancer communication. J Cancer Educ. 2013;28:623-628.
36. Wray RJ, Vijaykumar S, Jupka K, et al. Addressing the challenge of informed decision making in prostate cancer community outreach to African American men. Am J Men Health. 2011;5:508-516.
37. Frencher SK Jr., Sharma AK, Teklehaimanot S, et al. PEP talk: prostate education program, "cutting through the uncertainty of prostate cancer for Black men using decision support instruments in barbershops". J Cancer Educ. 2016;31:506-513.
38. Luque JS, Rivers BM, Kambon M, et al. Barbers against prostate cancer: a feasibility study for training barbers to deliver prostate cancer education in an urban African American community. J Cancer Educ. 2010;25:96-100.
39. Drake BF, Shelton RC, Gilligan T, et al. A church-based intervention to promote informed decision making for prostate cancer screening among African American men. J Natl Med Assoc. 2010;102:164-171.
40. Hill BC, Black DR, Shields CG. Barbershop prostate cancer education: factors associated with client knowledge. Am J Men Health. 2017;11:116-125.
41. Howard A, Morgan P, Fogel J, et al. A community/faith-based education: factors associated with client knowledge and shared decision making behavior for prostate cancer screening among Black men. ABNF J. 2018;29:61-68.
42. Walsh-Childers K, Odedina F, Poitier A, et al. Choosing channels, sources, and content for communicating prostate cancer information to Black men: a systematic review of the literature. Am J Men Health. 2018;12:1728-1745.
43. Troy C, Brunson A, Goldsmith A, et al. Implementing community-based prostate cancer education in rural South Carolina: a collaborative approach through a statewide cancer alliance. J Cancer Educ. Epub 2020 Jun 20.
44. Holmes JA, Bensen JT, Mohler JL, et al. Quality of care received and patient-reported regret in prostate cancer: analysis of a population-based prospective cohort. Cancer. 2017;123:138-143.
45. Moses KA, Orom H, Brasel A, et al. Racial/ethnic disparity in treatment for prostate cancer: does cancer severity matter? Urology. 2017;99:76-83.
46. Raich PC, Whitley EM, Thorland W, et al; Denver Patient Navigation Research Program. Patient navigation improves cancer diagnostic resolution: an individually randomized clinical trial in an underserved population. Cancer Epidemiol Biomarkers Prev. 2012;21:1629-1638.
47. Fouad MN, Acemgil A, Bae S, et al. Patient navigation as a model to increase participation of African Americans in cancer clinical trials. J Oncol Pract. 2016; 12:556-563.
48. Dobbs RW, Stinson J, Vasavada SR, et al. Helping men find their way: improving prostate cancer clinic attendance via patient navigation. J Community Health. 2020;45:561-568.
49. Bucknor MD, Lichtensztajn DY, Lin TK, et al. Disparities in PET imaging for prostate cancer at a tertiary academic medical center. J Nucl Med. Epub 2020 Sep 25.
50. Tan N, Oyoyo U, Bavadian N, et al. PSMA-targeted radiotracers versus ^{18}F rluciclovine for the detection of prostate cancer biochemical recurrence after definitive therapy: a systematic review and meta-analysis. Radiology. 2020;296:44-55.
51. DeWitt-Foy ME, Gam K, Modlin C, et al. Race, decisional regret and prostate cancer beliefs: identifying targets to reduce racial disparities in prostate cancer. J Urol. 2021;205:426-433.
52. Dee EC, Muralidhar V, Arega MA, et al. Factors influencing noncompletion of radiation therapy among men with localized prostate cancer. Int J Radiat Oncol Biol Phys. 2021;109:1279-1285.
53. Maganty A, Sabik LM, Sun Z, et al. Under treatment of prostate cancer in rural locations. J Urol. 2020;203:108-114.
54. Bea M. National sociodemographic disparities in the treatment of high-risk prostate cancer: do academic cancer centers perform better than community cancers? Cancer. In press.
55. Agrawal V, Ma X, Hu JC, et al. Trends in diagnosis and disparities in initial management of high-risk prostate cancer in the US. JAMA Netw Open. 2020; 3:e2014674.

56. Sayyid RK, Klotz L, Benton JZ, et al. Influence of sociodemographic factors on definitive intervention among low-risk active surveillance patients. Urology. Epub 2021 Feb 10.

57. Schwartz K, Powell IJ, Underwood W 3rd, et al. Interplay of race, socioeconomic status, and treatment on survival of patients with prostate cancer. Urology. 2009;74:1296-1302.

58. Rapiti E, Fioretta G, Schaffar R, et al. Impact of socioeconomic status on prostate cancer diagnosis, treatment, and prognosis. Cancer. 2009;115:5556-5565.

59. Rencsok EM, Bazzi LA, McKay RR, et al. Diversity of enrollment in prostate cancer clinical trials: current status and future directions. Cancer Epidemiol Biomarkers Prev. 2020;29:1374-1380.

60. Loree JM, Anand S, Dasari A, et al. Disparity of race reporting and representation in clinical trials leading to cancer drug approvals from 2008 to 2018. JAMA Oncol. 2019;5:e191870.

61. Unger JM, Hershman DL, Osarogiagbon RU, et al. Representativeness of Black patients in cancer clinical trials sponsored by the National Cancer Institute compared with pharmaceutical companies. JNCI Cancer Spectr. 2020;4:pkaa034.

62. Moses KA, Orom H, Brasel A, et al. Racial/ethnic differences in the relative risk of receipt of specific treatment among men with prostate cancer. Urol Oncol. 2016;34:415.e7-415.e12.

63. Bach PB, Schrag D, Brawley OW, et al. Survival of Blacks and Whites after a cancer diagnosis. JAMA. 2002;287:2106-2113.

64. Ramalingam S, Humeniuk MS, Hu R, et al. Prostate-specific antigen response in Black and White patients treated with abiraterone acetate for metastatic castrate-resistant prostate cancer. Urol Oncol. 2017;35:418-424.

65. George DJ, Health EI, Sartor AO, et al. Abi Race: a prospective, multicenter study of black (B) and white (W) patients (pts) with metastatic castrate resistant prostate cancer (mCRPC) treated with abiraterone acetate and prednisone (AAP). J Clin Oncol. 2018;36:18s (suppl; abstr LBA5009).

66. Sartor O, Armstrong AJ, Ahaghotu C, et al. Survival of African-American and Caucasian men after sipuleucel-T immunotherapy: outcomes from the PROCEED registry. Prostate Cancer Prostatic Dis. 2020;23:517-526.

67. Higano CS, Armstrong AJ, Sartor AO, et al. Real-world outcomes of sipuleucel-T treatment in PROCEED, a prospective registry of men with metastatic castration-resistant prostate cancer. Cancer. 2019;125:4172-4180.

68. Halabi S, Dutta S, Tangen CM, et al. Overall survival of Black and White men with metastatic castration-resistant prostate cancer treated with docetaxel. J Clin Oncol. 2019;37:403-410.

69. Zhao H, Howard LE, De Hoedt A, et al. Racial discrepancies in overall survival among men treated with ^{223}radium. J Urol. 2020;203:331-337.

70. Efstathiou EDH, George D, Joshua AM, et al. An exploratory analysis of efficacy and safety of abiraterone acetate (AA) in black patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) without prior chemotherapy (ctx). Cancer Res. 2014;74(19 Suppl):Abstract nr CT313.

71. McNamara MAGD, Ramaswamy K, Lechpammer S, et al. Overall survival by race in chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) patients treated with abiraterone acetate or enzalutamide. J Clin Oncol. 2019;27:7s (suppl; abstr 212) .

72. Carthon B, Sibold HC, Blee S, et al. Prostate cancer: disparities in diagnosis and treatment, and community education. Oncologist. Epub 2021 Mar 8.

73. Mahal BA, Alshalalfa M, Kensler KH, et al. Racial differences in genomic profiling of prostate cancer. N Engl J Med. 2020;383:1083-1085.

74. McKay RR, Sarkar RR, Kumar A, et al. Outcomes of Black men with prostate cancer treated with radiation therapy in the Veterans Health Administration. Cancer. 2021;127:403-411.

75. Balakrishnan AS, Palmer NR, Fergus KB, et al. Minority recruitment trends in phase III prostate cancer clinical trials (2003 to 2014): progress and critical areas for improvement. J Urol. 2019;201:259-267.

76. Kim SH, Tanner A, Friedman DB, et al. Barriers to clinical trial participation: a comparison of rural and urban communities in South Carolina. J Community Health. 2014;39:562-571.

77. Spratt DE, Chen YW, Mahal BA, et al. Individual patient data analysis of randomized clinical trials: impact of Black race on castration-resistant prostate cancer outcomes. Eur Urol Focus. 2016;2:532-539.

78. Khunger M, Rakshit S, Hernandez AV, et al. Premature clinical trial discontinuation in the era of immune checkpoint inhibitors. Oncologist. 2018;23:1494-1499.

79. Abi Jaoude J, Kouzy R, Mainwaring W, et al. Performance status restriction in phase III cancer clinical trials. J Natl Compr Canc Netw. 2020;18:1322-1326.

80. Adams-Campbell LL, Ahaghotu C, Gaskins M, et al. Enrollment of African Americans onto clinical treatment trials: study design barriers. J Clin Oncol. 2004;22:730-734.

81. Springfield SA, Van Duyn MAS, Aguila HN, et al. The NCI Center to Reduce Cancer Health Disparities: moving forward to eliminate cancer health disparities and diversify the cancer biomedical workforce. J Natl Med Assoc. 2020;112:308-314.

82. Wells KJ, Lima DS, Meade CD, et al; Region 3 GMaP/BMaP investigators. Assessing needs and assets for building a regional network infrastructure to reduce cancer related health disparities. Eval Program Plann. 2014;44:14-25.

83. Dovidio JF, Penner LA, Albrecht TL, et al. Disparities and distrust: the implications of psychological processes for understanding racial disparities in health and health care. Soc Sci Med. 2008;67:478-486.

84. Boulware LE, Cooper LA, Ratner LE, et al. Race and trust in the health care system. Public Health Rep. 2003;118:358-365.

85. Koscuiszka M, Hatcher D, Christos PJ, et al. Impact of race on survival in patients with clinically nonmetastatic prostate cancer who deferred primary treatment. Cancer. 2012;118:3145-3152.

86. Johnstone PA, Kane CJ, Sun L, et al. Effect of race on biochemical disease-free outcome in patients with prostate cancer treated with definitive radiation therapy in an equal-access health care system: radiation oncology report of the Department of Defense Center for Prostate Disease Research. Radiology. 2002; 225:420-426.

87. Kupelian PA, Buchsbaum JC, Patel C, et al. Impact of biochemical failure on overall survival after radiation therapy for localized prostate cancer in the PSA era. Int J Radiat Oncol Biol Phys. 2002;52:704-711.

88. Allen JD, Akinyemi IC, Reich A, et al. African American Women's Involvement in Promoting Informed Decision-Making for Prostate Cancer Screening Among Their Partners/Spouses. Am J Mens Health. 2018;12:884-893.

89. Unger JM, Moseley A, Symington B, et al. Geographic distribution and survival outcomes for rural patients with cancer treated in clinical trials. JAMA Netw Open. 2018;1:e181235.

90. U.S. Food and Drug Administration. Public Workshop: Evaluating Inclusion and Exclusion Criteria in Clinical Trials—Workshop Report. https://www.fda.gov/media/134754/download. Accessed April 1, 2021.

91. U.S. Food and Drug Administration. Enhancing the Diversity of Clinical Trial Populations - Eligibility Criteria, Enrollment Practices and Trial Designs Guidance for Industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial. Accessed April 1, 2021.

92. Partin AW, Kattan MW, Subong EN, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. JAMA. 1997;277:1445-1451.

93. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998;280:969-974.

94. Carroll PH, Mohler JL. NCCN Guidelines Updates: Prostate Cancer and Prostate Cancer Early Detection. J Natl Compr Canc Netw. 2018;16:620-623.

95. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7-30.

96. Sundi D, Ross AE, Humphreys EB, et al. African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? J Clin Oncol. 2013;31:2991-2997.

97. Mahal BA, Aizer AA, Ziehr DR, et al. Trends in disparate treatment of African American men with localized prostate cancer across National Comprehensive Cancer Network risk groups. Urology. 2014;84:386-392.

98. Mahal BA, Chen YW, Muralidhar V, et al. Racial disparities in prostate cancer outcome among prostate-specific antigen screening eligible populations in the United States. Ann Oncol. 2017;28:1098-1104.

99. Taksler GB, Keating NL, Cutler DM. Explaining racial differences in prostate cancer mortality. Cancer. 2012;118:4280-4289.

100. Hamilton RJ, Aronson WJ, Presti JC Jr., et al. Race, biochemical disease recurrence, and prostate-specific antigen doubling time after radical prostatectomy: results from the SEARCH database. Cancer. 2007;110:2202-2209.

101. Presti J Jr., Alexeeff S, Horton B, et al. Changes in prostate cancer presentation following the 2012 USPSTF screening statement: observational study in a multispecialty group practice. J Gen Intern Med. 2020;35:1368-1374.

102. Spratt DE, Yousefi K, Deheshi S, et al. Individual patient-level meta-analysis of the performance of the decipher genomic classifier in high-risk men after prostatectomy to predict development of metastatic disease. J Clin Oncol. 2017;35:1991-1998.

103. Zhao SG, Chang SL, Erho N, et al. Associations of luminal and basal subtyping of prostate cancer with prognosis and response to androgen deprivation therapy. JAMA Oncol. 2017;3:1663-1672.

104. Beltran H, Rickman DS, Park K, et al. Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. Cancer Discov. 2011; 1:487-495.

105. Grasso CS, Wu Y-M, Robinson DR, et al. The mutational landscape of lethal castration-resistant prostate cancer. Nature. 2012;487:239-243.

106. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med. 2016;375:443-453.

107. Taksler GB, Keating NL, Cutler DM. Explaining racial differences in prostate cancer mortality. Cancer. 2012;118:4280-4289.

108. Vastola ME, Yang DD, Muralidhar V, et al. Laboratory eligibility criteria as potential barriers to participation by black men in prostate cancer clinical trials. JAMA Oncol. 2018;4:413-414.

109. Mahal AR, Mahal BA, Nguyen PL, et al. Prostate cancer outcomes for men aged younger than 65 years with Medicaid versus private insurance. Cancer. 2018; 124:752-759.

110. Yamoah K, Johnson MH, Choeurng V, et al. Novel biomarker signature that may predict aggressive disease in African American men with prostate cancer. J Clin Oncol. 2015;33:2789-2796.

111. Huang FW, Mosquera JM, Garofalo A, et al. Exome sequencing of African-American prostate cancer reveals loss-of-function *ERF* mutations. Cancer Discov. 2017;7:973-983.

112. Kwon DH-M, Borno HT, Cheng HH, et al. Ethnic disparities among men with prostate cancer undergoing germline testing. Urol Oncol. 2020;38:80.e1-80.e7.

113. Rogers CR, Rovito MJ, Hussein M, et al. Attitudes toward genomic testing and prostate cancer research among black men. Am J Prev Med. 2018; 55:S103-S111.

114. Szymaniak BM, Facchini LA, Giri VN, et al. Practical considerations and challenges for germline genetic testing in patients with prostate cancer: recommendations from the germline Genetics Working Group of the PCCTC. JCO Oncol Pract. 2020;16:811-819.

Care Disparities Across the Health Care Continuum for Older Adults: Lessons From Multidisciplinary Perspectives

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Overview

Older adults comprise a considerable proportion of patients with cancer in the world. Across multiple cancer types, cancer treatment outcomes among older age groups are often inferior to those among younger adults. Cancer care for older individuals is complicated by the need to adapt treatment to baseline health, fitness, and frailty, all of which vary widely within this age group. Rates of social deprivation and socioeconomic disparities are also higher in older adults, with many living on reduced incomes, further compounding health inequality. It is important to recognize and avoid undertreatment and overtreatment of cancer in this age group; however, simply addressing this problem by mandating standard treatment of all would lead to harms resulting from treatment toxicity and futility. However, there is little high-quality evidence on which to base these decisions, because older adults are poorly represented in clinical trials. Clinicians must recognize that simple extrapolation of outcomes from younger age cohorts may not be appropriate because of variance in disease stage and biology, variation in fitness and treatment tolerance, and reduced life expectancy. Older patients may also have different life goals and priorities, with a greater focus on quality of life and less on length of life at any cost. Health care professionals struggle with treatment of older adults with cancer, with high rates of variability in practice between and within countries. This suggests that better national and international recommendations that more fully address the needs of this special patient population are required and that primary research focused on the older age group is urgently required to inform these guidelines.

Medical care for the older adult, who for the purpose of this article is defined as a patient older than age 65, is a high priority because of the rapid increases in life expectancy, which have doubled in the last 200 years. Although early gains from several decades ago were the result of reduced infant mortality, more recently, improvements in life expectancy have occurred predominantly among older adults.[1,2] The proportion of the population older than age 65 will more than double in the next 20 years.[3] Older adults also carry a higher burden of comorbidity[3] and frailty[4] compared with younger adults. Moreover, cancer is a disease of older adults, with incidence rates predicted to increase by almost 50% in the next 15 years, largely because of the increase in the older adult population. The link between cancer and aging is complex and reflects substantial overlap in the molecular etiology of aging[5] and cancer.[6]

For a majority of cancers, modern-day treatment is often delivered in a multimodal manner, with combinations of surgery, radiation therapy (RT), chemotherapy, and targeted biologic therapies all applied. Multimodal cancer treatment may create both benefits and harms, particularly among older adults in whom cancer often occurs in a complex setting of multimorbidity and geriatric conditions, including frailty and functional and cognitive impairment. Interactions between these factors and cancer treatments have a substantial impact on cancer outcomes and quality of life among older adults. These interactions can (and sadly often do) have a negative impact on survival rates and quality of life. Addition of geriatric assessment measures can lead to better care when performed by clinicians at the outset of therapy.

A majority of cancer therapies may be associated with higher toxicity burdens in individuals with comorbid geriatric conditions. The therapeutic window is therefore narrower, and tighter selection criteria must be used. These criteria in terms of age, frailty, and comorbidity are poorly defined and often overly simplistic. With regard to chemotherapy criteria in breast cancer, many of the earlier chemotherapy trials had upper age limits of 60 or 65 (with the exception of CALGB 49907,[7] among others). Consequently, there are few data for chemotherapy outcomes in adults older than age 70.

Eliciting and incorporating patients' values and preferences into treatment decision-making is a critically

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PRACTICAL APPLICATIONS

- Health care inequalities disproportionately affect older adults because of a complex range of social, health-related, and economic factors.
- All older adults with cancer should undergo a full geriatric assessment, including their comorbidities as well as physical and cognitive function, frailty, nutritional status, and medication use, before treatment decisions are made.
- All health care professionals caring for older adults with cancer should have training and facility in the use of assessments for evaluating physical function, frailty, and cognitive impairment.
- Health care professionals should involve older adults (and/or their caregivers as appropriate) in shared decision-making and should respect patient preferences for nonstandard care, without making assumptions regarding patients' prioritization of quality of life versus length of life.
- Rehabilitation and prehabilitation tailored to the needs of the individual should be appropriately initiated before surgery and radiation therapy and before or during systemic treatment among older adults to reduce the adverse impacts of all types of cancer treatments and to increase functional, physical, and psychological resilience.

important endeavor when caring for individuals of any age. This takes on particular significance in geriatric oncology practice, because as people age, many develop a pragmatic acceptance of the inevitability of death and wish to preserve their quality of life and independence.[8] It is therefore crucial that oncology professionals have the training and facility to be able to effectively explore the preferences, thresholds, and potential tradeoffs relevant to each patient when making shared treatment decisions.

OVERCOMING BARRIERS TO EQUITABLE CARE AMONG OLDER ADULTS WITH CANCER

Many factors, including social determinants of health, mobility, social support, cognition, geriatric syndromes, organ function, transportation, technology, ageism, access, and assessment, play a role in creating barriers to equitable care for older adults with cancer. This section will briefly address three key targetable areas in which to overcome existing barriers to cancer care: ageism, access, and assessment (Fig. 1). These three domains work together to increase health care disparities among older adults but are modifiable factors through which the average clinician, whether in an academic setting or community practice, can implement real change within a short period of time.

Ageism

Age is just a number. Cancer screening, diagnosis, and treatment planning should never be based on age alone. However, ageism persists and contributes to global health care disparities.[9,10] Physiologic age does not equal chronologic age. Unfortunately, age is a factor associated with disparities in cancer screening, diagnostic procedures, clinical trials, and treatments.[11] Clinicians early in training are taught to recite as follows in each clinical case: "This is an 80-year-old man with a history of chronic obstructive pulmonary disease admitted for worsening shortness of breath…" Instantly, the listener starts weighing the benefits and challenges of potential screening, diagnosis, and treatment options based on the patient's age. This is problematic, because extensive heterogeneity exists within and between age groups. One octogenarian may still be running, gardening, living independently, and completely independent in all activities of daily living[12] and instrumental activities of daily living.[13] A second octogenarian may be playing cards and socializing but living in a skilled nursing facility and dependent in activities of daily living and instrumental activities of daily living. If a provider solely chose and discussed treatment options based on age, these two patients would receive the same treatment. This could result in undertreatment of the fit octogenarian, withholding potentially life-extending treatment, but overtreatment of the frail octogenarian, leading to treatment toxicity and perhaps life-shortening treatment. Additional information is needed to synthesize potential treatment options and plan next steps that are required before clinicians can engage in shared decision-making with the older adults and their caregivers, if present. Overcoming ageism as a barrier will require a paradigm shift not only for clinicians but also for clinical trialists, payers, industry, and policy makers.

Access

As a result of ageism, older adults can be discouraged from seeking medical attention or simply cannot navigate the health care system to engage in health care. Limited access can be the result of insurance status, mobility limitations, cognitive impairment, lack of transportation, or complexity of the health care system. In the United States, insurance should be accessible through Medicare (age 65 or older benefit); however, many older adults remain underinsured.[14] Their out-of-pocket medication costs and/or high health plan deductibles are prohibitive to seeking care when on a fixed monthly income. Physical mobility limitations and cognitive impairment may delay or prohibit access by resulting in an inability to navigate the complexity of the health care system or simply by limiting their ability to drive.

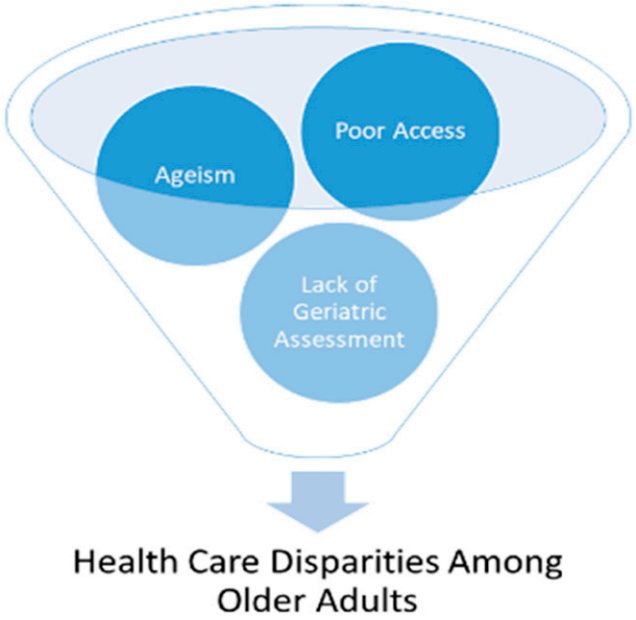

FIGURE 1. Three Modifiable Barriers to Equitable Cancer Care

Lack of transportation increases with age, particularly in the United States and in rural areas because of the lack of public transportation. There are basic steps a practice can take to improve access in these areas. Asking patients about their finances and transportation needs can help link them to available resources in the community. Patient navigators, case managers, community health workers, and social workers are some of the potential resource-rich staff that can break down barriers to health care access.[15] Telehealth or virtual health is also an emerging technology (which has advanced rapidly during 2020 because of the COVID-19 pandemic) that can reach older adults in rural areas,[16] but it is still not available equally to all older adults.[17]

Assessment

The lack of assessment of older adults can result in both overtreatment and undertreatment.[18] As oncology providers, we may deliver treatment that could result in toxicity, poorer quality of life, and even death (overtreatment). Alternatively, we may withhold treatment that could improve symptoms, quality of life, functional status, and life expectancy (undertreatment). Brief tools to ascertain functional status and patient goals that could ameliorate both under- and overtreatment are sporadically implemented across health care systems. In addition, trainees in medical oncology should be exposed to and should learn baseline geriatric oncology competencies.[19] The assessment of older adults is imperative in order for oncology clinicians and trainees to understand underlying geriatric syndromes and barriers to health care not explained by Eastern Cooperative Oncology Group performance status. For older adults with solid tumors, the use of a geriatric assessment and optimization has led to less treatment-related toxicity,[20,21] improved quality of life and survival,[22] and lower health care resource use[23] in randomized controlled trials. Fried's frailty phenotype and Rockwood's clinical frailty scale are among the most commonly used measures to characterize frailty.[24,25] Comprehensive geriatric assessment and geriatric comanagement can take place in multiple health care settings and can be performed by a primary care physician or geriatrician,[22] or in a multidisciplinary onco-geriatric clinic.[26] Comprehensive geriatric assessment can be resource- and time-consuming; however, there are brief assessment tools that can be implemented in a short amount of time.[27] Using these screening tools, such as the G8[28] and the EQ-5D-5L, or simply asking about activities of daily living and instrumental activities of daily living can uncover functional disability,[29] pain,[30] and psychological[31] impairments that would otherwise go unrecognized and are independently associated with poor patient outcomes. More recently, the ELDERS study demonstrated that older adults with advanced lung cancer or melanoma receiving immunotherapy with a positive G8 screening test ($\leq$ 14 points) had a higher risk of hospital admissions ($p = .03$) and death ($p = .01$), but not a higher incidence of treatment-related toxicity.[28] There are also brief tools to assess the risk of high-grade chemotherapy toxicity, such as the Cancer and Aging Research Group chemotherapy toxicity tool,[32] the Chemotherapy Risk Assessment Scale for High-Age Patients tool,[33] and the Cancer and Aging Research Group breast cancer–specific tool.[34] These brief tools can identify disability and other areas of impairment such that we are able to intervene in a meaningful way to improve health care disparities. Multiple tools are currently available for the practicing oncologist, as described by Loh et al.[27] However, these tools must be validated among patients receiving newer systemic treatment, such as immunotherapy and/or oral targeted treatments. There also is a need to adapt the geriatric assessment based on specific cancer types or receipt of combined treatment modalities. This is currently an active area of geriatric oncology research.

DISPARITIES IN THE CARE OF OLDER ADULTS: A RADIATION ONCOLOGIST'S PERSPECTIVE

More than 11.2 million older adults with a history of cancer were alive on January 1, 2019, in the United States, and this number is projected to grow by more than 30% by January 1, 2030. Approximately half of these individuals receive RT as part of cancer treatment to accomplish one or more of the following: cure cancer, alleviate symptoms from cancer, and/or improve quality of life with cancer.[35-39] Geriatric conditions are commonplace among older adults with cancer, but their relationship to RT outcomes is still unclear. Studies have shown that older adults with cancer have a higher prevalence of geriatric conditions than those without cancer.[40] These include conditions such as hearing

impairments, falls, and urinary incontinence.[41] Older patients with cancer are also more likely to have functional impairments, low self-rated health, and frailty.[40,42-44]

Medical oncologists, having recognized the link between geriatric conditions and cancer treatment outcomes more than 2 decades ago, have developed[32-34] and validated[32,34] chemotherapy toxicity risk prediction tools that evaluate key health domains in older adults (e.g., functional status, comorbidity, cognition, and nutritional status) and predict the occurrence of grade 3 or higher adverse events according to the Common Terminology Criteria for Adverse Events[45] from chemotherapy with higher accuracy than traditional oncology performance measures (e.g., Karnofsky performance status).[46,47] As a result, geriatric assessment is now recommended by ASCO before chemotherapy initiation in older adults.[48] However, in radiation oncology, the data are nascent, and little is known about the relevance of geriatric assessment to outcomes from RT. The delivery of RT (daily treatments over several weeks) and its adverse effects are distinct as compared with chemotherapy, and, as such, a separate study of these is indicated. The goals of the particular radiation course matter as well, because expected toxicity profiles as well as an individual's values and preferences for treatment and outcome differ for different tumor types, anatomic treatment sites, and treatment intents (e.g., curative intent vs. palliative [noncurative] intent). Prediction of functional outcomes after RT is equally important for decision-making for older adults considering RT as part of their cancer treatment.

The paucity of evidence for risk stratification of older adults and lack of knowledge among radiation oncologists about optimal treatment both drive treatment variability and consequently care disparities. Surveys of radiation oncologists reveal that up to 80% do not routinely incorporate any geriatric assessment during evaluation of older adults before RT. Almost 50% of radiation oncologists report low levels of confidence in treating complex issues in older adults.[49-51] Therefore, it is no surprise that there is wide variability in how radiation oncologists make treatment decisions in older adults. Older adults less often receive guideline-based RT and are more likely to receive deintensified regimens (e.g., fewer sessions or lower RT doses).[52,53]

Although RT use does decline with age,[54-58] suggesting that radiation oncologists may variably account for age and its associated geriatric conditions in treatment decisions, data as to which subgroups of older adults are most likely to benefit from specific types (e.g., short vs. long treatment durations, high vs. low dose, external beam vs. brachytherapy, and wider vs. narrower field sizes) of RT are not yet available.[59] Potential overtreatment with palliative RT is evident in data showing that one in six RT courses is interrupted and one in five prematurely terminated.[60,61] Up to 30% of patients older than age 65 have major adverse outcomes, including hospitalization or death, soon after RT completion.[62-64] However, potential undertreatment in RT is a problem as well. For instance, two population-based data set studies of older adults with curable-stage soft tissue sarcoma revealed that adults older than age 70 were less likely to receive definitive therapy, suggesting that older adults were less often being offered curative treatment based on their age.[52,65] Another study of palliative (noncurative) RT found that receipt of palliative RT decreased with increasing patient age, implying that older adults with advanced cancer were less likely to be offered this potentially quality of life–enhancing treatment as well.[54]

The variability in radiation oncology decision-making is partially related to the presence of an evidence base for the utility of geriatric assessment for RT that is both limited and conflicting. There have been 13 small nonrandomized studies (mean of 63 participants) and two systematic reviews that have attempted to assess the link between geriatric conditions and RT outcomes. Because of their small numbers and underpowered nature, these studies have produced conflicting results and have left outstanding knowledge gaps.[66-68] For instance, although geriatric assessment tools (e.g., Vulnerable Elders Survey-13[69] and G8 screening tools[70,71]) have predicted RT incompletion in patients older than age 75,[69] mortality in patients older than age 70 with head and neck cancer receiving chemoradiation,[72] and late-occurring[68] (but not acute[73]) adverse effects from lung irradiation, post-RT functional status was not examined in any of these studies.[60] In another analysis of 46 patients undergoing chemoradiation, pre-RT functional disability, defined as a score of 14 or lower on the Instrumental Activities of Daily Living scale, predicted lower quality of life and increased patient-reported toxicities 6 weeks after RT, but did not predict treatment delays, change in prescribed therapy, hospitalization, or death.[74] RT completion was not assessed. Geriatric assessment was performed once pre- and once post-RT; possible changes in functioning occurring between these time points were not able to be captured. The remaining studies did not show any link between geriatric conditions and RT-related outcomes and did not follow trajectories of function or quality of life after RT. Additionally, participation of older adults in clinical trials that include RT has been low, with such trials being plagued by the same recruitment limitations as chemotherapy and other cancer drug trials, namely age cutoffs and minimum performance status restrictions.[11]

For older adults to consistently receive truly equitable treatment from radiation oncologists, a redesign of the system of how we think about fitness for (and recover from) RT is needed at several levels. First, the gap in geriatric education must be addressed during radiation oncology training. Residents should have a basic understanding of

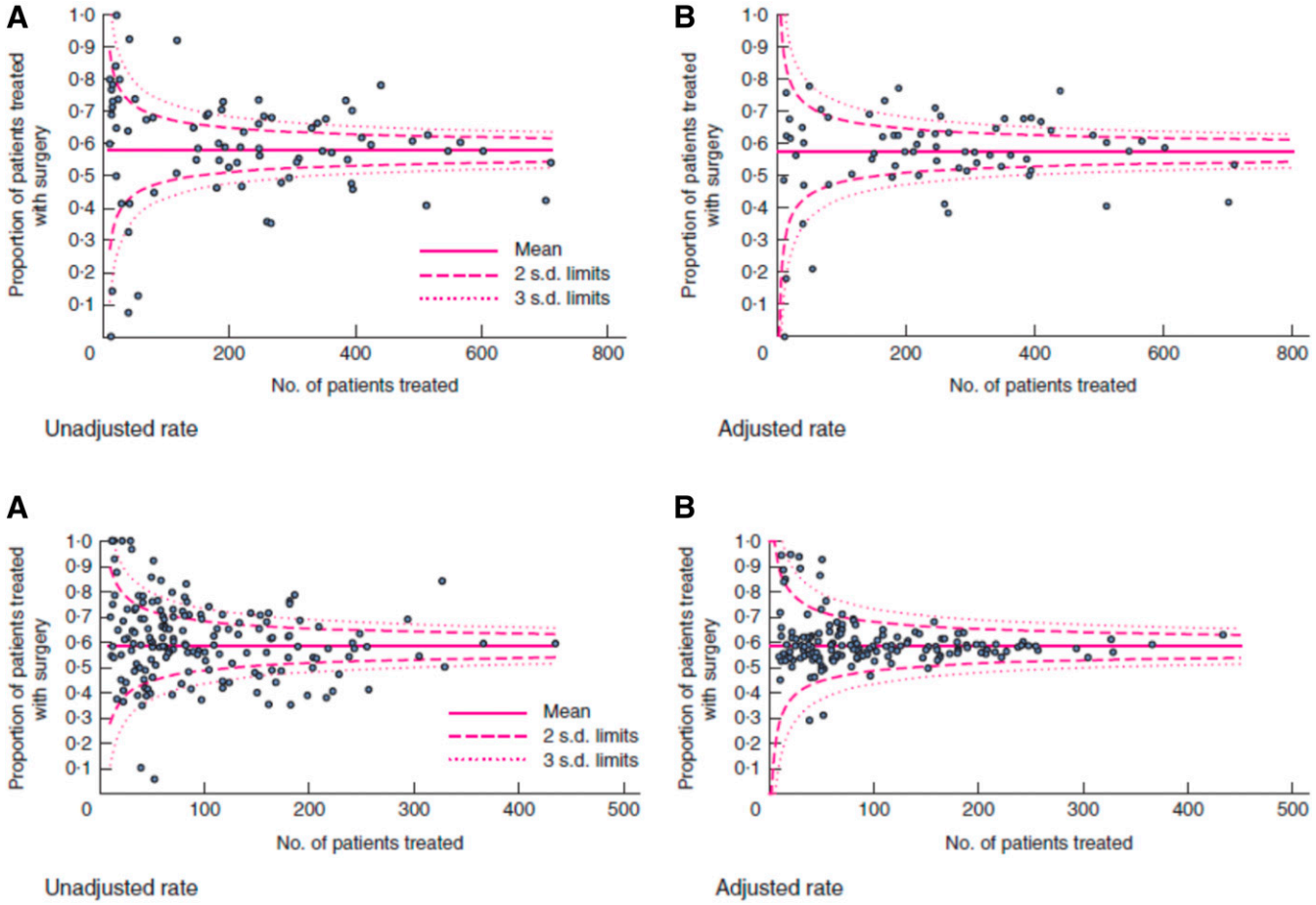

FIGURE 2. Rates of Surgery for Breast Cancer in the United Kingdom

Funnel plots showing (A) case mix–unadjusted and (B) case mix–adjusted (for age, comorbidity, social deprivation status, tumor stage, and grade) rates of surgery (proportion) against the number of breast cancers treated annually either by breast unit (top row) or by breast surgeon (bottom row) in the United Kingdom, based on U.K. registry data for women older than age 70 at the time of diagnosis.

Abbreviation: s.d., standard deviation.

Reproduced with permission from Morgan et al.[81]

the components of a geriatric assessment and the common screening tools used to evaluate each of these components. Next, there is an urgent need for high-quality prospective research to better understand how, and for how long, RT affects older adults' functioning, quality of life, independence, and other potentially modifiable factors important and pertinent to older adults with or without geriatric conditions. Finally, clinical trials that involve RT should use more nuanced eligibility criteria by incorporating components of the geriatric assessment, rather than simply using age cutoffs or performance status (e.g., Eastern Cooperative Oncology Group or Karnofsky performance status) alone.

ACHIEVING HEALTH EQUITY AMONG OLDER ADULTS: A SURGICAL ONCOLOGIST'S PERSPECTIVE

Surgery is the primary treatment modality for a majority of early-stage solid tumors. The morbidity and mortality associated with most forms of surgery have improved dramatically in the past 3 decades as a result of technologic advances in surgical techniques, better perioperative care, and safer anesthesia.[75] However, surgery is still associated with postoperative death and major complications, which are more common among older adults.[76] In addition, older adults are more likely to experience a decline in physical function after surgery because of muscle disuse atrophy, which they may never regain.[77] Some of these harms may be mitigated by the use of prehabilitation[78] and enhanced perioperative care, which should be tailored to the physical health status of the individual. Such personalized care is not routine, and high rates of variability in outcomes exist in clinical practice.[79]

In some types of cancer, in addition to variability in outcomes from surgery itself, there are variations in rates of surgery used as compared with less oncologically effective

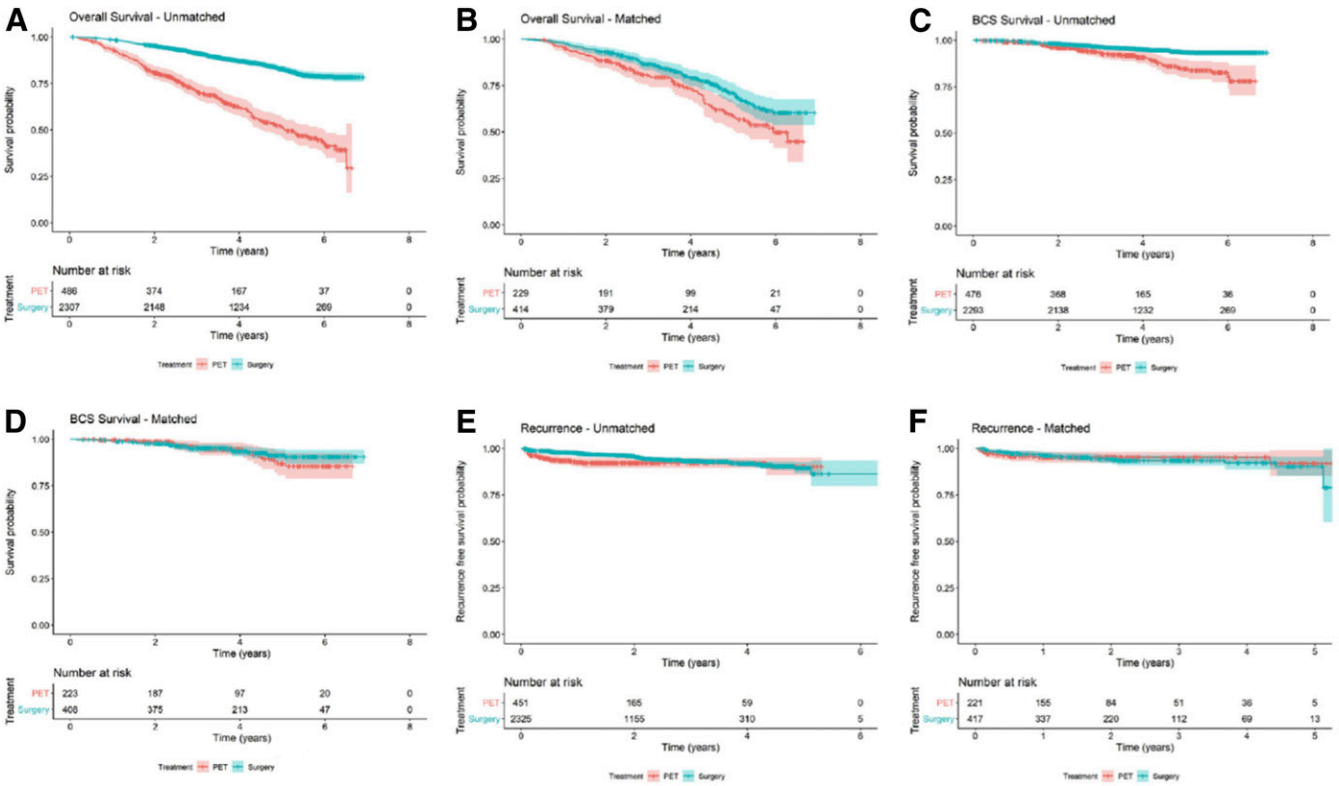

FIGURE 3. Outcomes for Older Women With Early Breast Cancer

Comparison of a range of outcomes (unadjusted and propensity score–matched outcomes [matched for age, health, frailty, tumor stage, and grade]) for older women (age > 70) with estrogen receptor–positive early breast cancer according to whether they were treated with surgery (plus adjuvant therapy; blue) or primary endocrine therapy (orange). (A, B) Overall survival, (C, D) breast cancer–specific survival, and (E, F) recurrence-free survival.
Abbreviations: BCS, breast cancer–specific survival; PET, primary endocrine therapy.
Reproduced with permission from Wyld et al.[87]

alternatives. Nonsurgical treatment options tend to be preferred in the very frail or comorbid patient for whom the risks of surgery are very high. Examples include the use of palliative endocrine therapy in prostate cancer rather than prostatectomy, stenting in luminal gastrointestinal cancers (e.g., colorectal and esophageal) rather than colectomy or esophagectomy, and primary endocrine therapy in estrogen-sensitive breast cancer rather than mastectomy or breast-conservation surgery.

Reflecting in more detail on breast cancer, rates of primary endocrine therapy vary widely around the world. In Europe, rates of surgery for stage I breast cancer vary widely, from almost 94% in Poland to 75% in the United Kingdom.[80] Surgery is the norm in the United States for almost all women, regardless of age. Even within countries, variation is marked. In the United Kingdom, for example, rates of surgery vary between 30% and 100%[81] based on national U.K. registration data. Even when adjusting for case mix (i.e., stage, age, and comorbidities), the variation persists (Fig. 2). Detailed exploration of the reasons for this variation using qualitative interviews and questionnaires with health care professionals found a wide variation in thresholds for age, fitness, frailty, and cognition.[82,83] A key problem is the lack of detailed guidelines setting reproducible thresholds. A majority of guidelines simply state that if a woman is fit for surgery, she should have surgery.[84] However, although a majority of older women will survive breast cancer surgery because it has moderate morbidity and very low mortality rates,[85] this does not mean that surgery is appropriate for all older women. Primary endocrine therapy, when selected appropriately, may be a reasonable option for frail women or women with complex comorbidities and/or low estimated life expectancy. Randomized trials comparing surgery and primary endocrine therapy found no significant survival advantage with surgery after 5-year follow-up,[86] although these trials were flawed by modern standards, because participants were younger than the age at which women would generally be offered primary endocrine therapy and did not all have estrogen receptor–positive cancers. On longer-term follow-up, surgery does have a beneficial effect. The key is to select older women with a predicted life expectancy of fewer than 3 to 5 years for primary endocrine therapy. The Age Gap observational cohort

study attempted to define the health characteristics of women suitable for primary endocrine therapy by recruiting women older than age 70 with early breast cancer and adjusting for baseline health and fitness using detailed propensity score matching. The study found that when matched cohorts with similar health status treated with either surgery or primary endocrine therapy were compared, there was no survival advantage with surgery (Fig. 3).[87] The median age of this matched cohort was 82 to 83, with higher rates of frailty and comorbidity than the general population.

Surgery for all women with breast cancer regardless of their health and fitness may cause needless harm to some. This may be particularly true among women residing in nursing homes who receive breast cancer surgery. Tang et al[88] found high rates of morbidity and mortality among women after surgery for early breast cancer in the postoperative period, and many of the women died within 12 months of surgery, suggesting that the surgery was likely to have had little benefit. Another factor to consider is the views of the women themselves. When surgery and primary endocrine therapy choices were adequately explained with the use of a decision support tool,[89] a higher percentage of women chose less aggressive therapy.[90] Qualitative interviews with older women about this treatment choice revealed that for many, a key priority was the maintenance of independence and quality of life, even if survival outcomes were less certain.[91]

The above highlights the need for focused research to set advisory thresholds of health, fitness, and frailty in cancer settings where less aggressive options may be offered. These may be used to develop decision support tools to aid in shared decision-making with older patients. One example of this is the Age Gap Decision Tool,[92] which has been developed to support the choice between surgery and primary endocrine therapy in older women.[93]

CONCLUSION

Disparities in cancer care among older adults are multifactorial. The causes include ageism, a sweeping generalization of health status based upon chronologic age rather than physiologic age; variable access to medical care resulting from difficulty navigating the health care system and/or being discouraged from receiving care in the first place; and lack of proper use of geriatric assessment measures. In radiation oncology, the causes of age disparity additionally include a lack of geriatric education among radiation oncologists, a paucity of older adults in clinical trials, and a paucity of high-quality research detailing the linkage between geriatric conditions and RT outcomes. In surgical oncology, there is a lack of detailed guidelines that set reproducible advisory thresholds of health, fitness, and frailty in cancer settings in which less aggressive options may be offered; for instance, in breast cancer, there may be reasonable nonsurgical treatment options. Further research and guideline development would lead to more appropriate personalized care for older adults with cancer. Interventions targeting these sources of disparity would lead to improved cancer management outcomes.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_319841.

REFERENCES

1. Oeppen J, Vaupel JW. Demography. Broken limits to life expectancy. Science. 2002;296:1029-1031.
2. Collado M, Gil J, Efeyan A, et al. Tumour biology: senescence in premalignant tumours. Nature. 2005;436:642.
3. Storey A. Living longer: How our population is changing and why it matters. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/livinglongerhowourpopulationischangingandwhyitmatters/2018-08-13. Accessed February 10, 2021.
4. Crimmins EM. Lifespan and healthspan: past, present, and promise. Gerontologist. 2015;55:901-911.

5. Partridge L, Deelen J, Slagboom PE. Facing up to the global challenges of ageing. Nature. 2018;561:45-56.
6. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646-674.
7. Muss HB, Berry DA, Cirrincione CT, et al; CALGB Investigators. Adjuvant chemotherapy in older women with early-stage breast cancer [published correction appears in *N Engl J Med*. 2009;361:1714]. N Engl J Med. 2009;360:2055-2065.
8. Fried TR, Bradley EH, Towle VR, et al. Understanding the treatment preferences of seriously ill patients. N Engl J Med. 2002;346:1061-1066.
9. Butler RN. Age-ism: another form of bigotry. Gerontologist. 1969;9:243-246.
10. Schroyen S, Marquet M, Jerusalem G, et al. The link between self-perceptions of aging, cancer view and physical and mental health of older people with cancer: a cross-sectional study. J Geriatr Oncol. 2017;8:64-68.
11. Ludmir EB, Mainwaring W, Lin TA, et al. Factors associated with age disparities among cancer clinical trial participants. JAMA Oncol. 2019;5:1769-1773.
12. Katz S, Downs TD, Cash HR, et al. Progress in development of the index of ADL. Gerontologist. 1970;10:20-30.
13. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9:179-186.
14. Horton S, Johnson RJ. Improving access to health care for uninsured elderly patients. Public Health Nurs. 2010;27:362-370.
15. Natale-Pereira A, Enard KR, Nevarez L, et al. The role of patient navigators in eliminating health disparities. Cancer. 2011;117(suppl):3543-3552.
16. Hirko KA, Kerver JM, Ford S, et al. Telehealth in response to the COVID-19 pandemic: implications for rural health disparities. J Am Med Inform Assoc. 2020;27:1816-1818.
17. Lam K, Lu AD, Shi Y, et al. Assessing telemedicine unreadiness among older adults in the United States during the COVID-19 pandemic. JAMA Intern Med. 2020;180:1389-1391.
18. DuMontier C, Loh KP, Bain PA, et al. Defining undertreatment and overtreatment in older adults with cancer: a scoping literature review. J Clin Oncol. 2020;38:2558-2569.
19. Hsu T, Kessler ER, Parker IR, et al. Identifying geriatric oncology competencies for medical oncology trainees: a modified Delphi consensus study. Oncologist. 2020;25:591-597.
20. Mohile SG, Mohamed MR, Culakova E, et al. A geriatric assessment (GA) intervention to reduce treatment toxicity in older patients with advanced cancer: a University of Rochester Cancer Center NCI community oncology research program cluster randomized clinical trial (CRCT). J Clin Oncol. 2020;38 (suppl; abstr 12009).
21. Giri S, Chakiba C, Shih YY, et al. Integration of geriatric assessment into routine oncologic care and advances in geriatric oncology: a Young International Society of Geriatric Oncology report of the 2020 American Society of Clinical Oncology (ASCO) annual meeting. J Geriatr Oncol. 2020;11:1324-1328.
22. Shahrokni A, Tin AL, Sarraf S, et al. Association of geriatric comanagement and 90-day postoperative mortality among patients aged 75 years and older with cancer. JAMA Netw Open. 2020;3:e209265.
23. Soo W-K, King M, Pope A, et al. Integrated geriatric assessment and treatment (INTEGERATE) in older people with cancer planned for systemic anticancer therapy. J Clin Oncol. 2020;38 (suppl; abstr 12011).
24. Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-M156.
25. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci. 2007;62:722-727.
26. Presley CJ, Krok-Schoen JL, Wall SA, et al. Implementing a multidisciplinary approach for older adults with cancer: geriatric oncology in practice. BMC Geriatr. 2020;20:231.
27. Loh KP, Soto-Perez-de-Celis E, Hsu T, et al. What every oncologist should know about geriatric assessment for older patients with cancer: Young International Society of Geriatric Oncology position paper. J Oncol Pract. 2018;14:85-94.
28. Gomes F, Lorigan P, Woolley S, et al. A prospective cohort study on the safety of checkpoint inhibitors in older cancer patients - the ELDERS study. ESMO Open. 2021;6:100042.
29. Presley CJ, Han L, Leo-Summers L, et al. Functional trajectories before and after a new cancer diagnosis among community-dwelling older adults. J Geriatr Oncol. 2019;10:60-67.
30. Presley CJ, Canavan M, Wang SY, et al. Severe functional limitation due to pain & emotional distress and subsequent receipt of prescription medications among older adults with cancer. J Geriatr Oncol. 2020;11:960-968.
31. Andersen BL, Valentine TR, Lo SB, et al. Newly diagnosed patients with advanced non-small cell lung cancer: a clinical description of those with moderate to severe depressive symptoms. Lung Cancer. 2020;145:195-204.
32. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011;29:3457-3465.
33. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer. 2012;118:3377-3386.
34. Magnuson A, Sedrak MS, Gross CP, et al. Development and validation of a risk tool for predicting severe toxicity in older adults receiving chemotherapy for early-stage breast cancer. J Clin Oncol. 2021;39:608-618.
35. Lutz S, Korytko T, Nguyen J, et al. Palliative radiotherapy: when is it worth it and when is it not? Cancer J. 2010;16:473-482.

36. Bryant AK, Banegas MP, Martinez ME, et al. Trends in radiation therapy among cancer survivors in the United States, 2000-2030. Cancer Epidemiol Biomarkers Prev. 2017;26:963-970.
37. Parker RG. Palliative radiation therapy. JAMA. 1964;190:1000-1002.
38. Browner I. Geriatric Workforce Enhancement Program: applications in geriatric oncology. https://www.hopkinsmedicine.org/gec/series/cancer_aging.html. Accessed January 3, 2021.
39. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019;69:363-385.
40. Mohile SG, Xian Y, Dale W, et al. Association of a cancer diagnosis with vulnerability and frailty in older Medicare beneficiaries. J Natl Cancer Inst. 2009; 101:1206-1215.
41. Mohile SG, Fan L, Reeve E, et al. Association of cancer with geriatric syndromes in older Medicare beneficiaries. J Clin Oncol. 2011;29:1458-1464.
42. Balducci L, Extermann M. Management of the frail person with advanced cancer. Crit Rev Oncol Hematol. 2000;33:143-148.
43. Balducci L. Aging, frailty, and chemotherapy. Cancer Contr. 2007;14:7-12.
44. Ferrucci L, Guralnik JM, Cavazzini C, et al. The frailty syndrome: a critical issue in geriatric oncology. Crit Rev Oncol Hematol. 2003;46:127-137.
45. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed January 3, 2021.
46. Jolly TA, Deal AM, Nyrop KA, et al. Geriatric assessment-identified deficits in older cancer patients with normal performance status. Oncologist. 2015; 20:379-385.
47. Carbonell AL, de Lourdes Chauffaille M. Limitations of performance status assessment in elderly with acute myeloid leukemia. Rev Bras Hematol Hemoter. 2015; 37:259-262.
48. Mohile SG, Dale W, Somerfield MR, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol. 2018;36:2326-2347.
49. Morris L, Thiruthaneeswaran N, Lehman M, et al. Are future radiation oncologists equipped with the knowledge to manage elderly patients with cancer? Int J Radiat Oncol Biol Phys. 2017;98:743-747.
50. Zereshkian A, Cao X, Puts M, et al. Do Canadian radiation oncologists consider geriatric assessment in the decision-making process for treatment of patients 80 years and older with non-metastatic prostate cancer? - National survey. J Geriatr Oncol. 2019;10:659-665.
51. Leifer R, Bristow B, Puts M, et al. National survey among radiation oncology residents related to their needs in geriatric oncology. J Cancer Educ. 2019;34:9-13.
52. Venigalla S, Carmona R, VanderWalde N, et al. Disparities in perioperative radiation therapy use in elderly patients with soft-tissue sarcoma. Int J Radiat Oncol Biol Phys. 2018;102:155-165.
53. Fang P, He W, Gomez DR, et al. Influence of age on guideline-concordant cancer care for elderly patients in the United States. Int J Radiat Oncol Biol Phys. 2017; 98:748-757.
54. Wong J, Xu B, Yeung HN, et al. Age disparity in palliative radiation therapy among patients with advanced cancer. Int J Radiat Oncol Biol Phys. 2014;90:224-230.
55. Guadagnolo BA, Liao KP, Elting L, et al. Use of radiation therapy in the last 30 days of life among a large population-based cohort of elderly patients in the United States. J Clin Oncol. 2013;31:80-87.
56. Hayman JA, Abrahamse PH, Lakhani I, et al. Use of palliative radiotherapy among patients with metastatic non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2007;69:1001-1007.
57. Huang J, Zhou S, Groome P, et al. Factors affecting the use of palliative radiotherapy in Ontario. J Clin Oncol. 2001;19:137-144.
58. Murphy JD, Nelson LM, Chang DT, et al. Patterns of care in palliative radiotherapy: a population-based study. J Oncol Pract. 2013;9:e220-e227.
59. VanderWalde N, Hurria A, Jagsi R. Improving consistency and quality of care for older adults with cancer: the challenges of developing consensus guidelines for radiation therapy. Int J Radiat Oncol Biol Phys. 2017;98:721-725.
60. Spyropoulou D, Pallis AG, Leotsinidis M, et al. Completion of radiotherapy is associated with the Vulnerable Elders Survey-13 score in elderly patients with cancer. J Geriatr Oncol. 2014;5:20-25.
61. Lee JA, Lee NK, Yoon WS, et al. Treatment interruption during radiation therapy: experience at a single institution in the Republic of Korea. Asia Pac J Clin Oncol. 2017;13:e481-e488.
62. Pignon JP, le Maître A, Maillard E, et al; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92:4-14.
63. Marar M, Gabriel P, Hwang WT, et al. Acute hospital encounters in cancer patients treated with definitive radiation therapy. Int J Radiat Oncol Biol Phys. 2018; 101:935-944.
64. Schad MD, Moore J, Camacho F, et al. Predictors of quality of care and survival in a three-state cohort of locally advanced cervical cancer patients and development of a predictive model to identify women at risk of incomplete treatment. Medicine (Baltimore). 2019;98:e16874.
65. Horton JK, Gleason JF Jr., Klepin HD, et al. Age-related disparities in the use of radiotherapy for treatment of localized soft tissue sarcoma. Cancer. 2011; 117:4033-4040.
66. Szumacher E, Sattar S, Neve M, et al. Use of comprehensive geriatric assessment and geriatric screening for older adults in the radiation oncology setting: a systematic review. Clin Oncol (R Coll Radiol). 2018;30:578-588.
67. Shinde A. The role of comprehensive geriatric assessment in radiation oncology. J Geriatr Oncol. 2020;11:194-196.

68. Cuccia F, Mortellaro G, Mazzola R, et al. Prognostic value of two geriatric screening tools in a cohort of older patients with early stage non-small cell lung cancer treated with hypofractionated stereotactic radiotherapy. J Geriatr Oncol. 2020;11:475-481.
69. Saliba D, Elliott M, Rubenstein LZ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. J Am Geriatr Soc. 2001; 49:1691-1699.
70. Bellera CA, Rainfray M, Mathoulin-Pélissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012; 23:2166-2172.
71. Kenis C, Decoster L, Van Puyvelde K, et al. Performance of two geriatric screening tools in older patients with cancer. J Clin Oncol. 2014;32:19-26.
72. Pottel L, Lycke M, Boterberg T, et al. G-8 indicates overall and quality-adjusted survival in older head and neck cancer patients treated with curative radiochemotherapy. BMC Cancer. 2015;15:875.
73. Middelburg JG, Mast ME, de Kroon M, et al; LPRO (Dutch National Organization for Radiotherapy in the Elderly). Timed Get Up and Go test and Geriatric 8 scores and the association with (chemo-)radiation therapy noncompliance and acute toxicity in elderly cancer patients. Int J Radiat Oncol Biol Phys. 2017;98:843-849.
74. VanderWalde NA, Deal AM, Comitz E, et al. Geriatric assessment as a predictor of tolerance, quality of life, and outcomes in older patients with head and neck cancers and lung cancers receiving radiation therapy. Int J Radiat Oncol Biol Phys. 2017;98:850-857.
75. Wyld L, Audisio RA, Poston GJ. The evolution of cancer surgery and future perspectives. Nat Rev Clin Oncol. 2015;12:115-124.
76. Turrentine FE, Wang H, Simpson VB, et al. Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg. 2006;203:865-877.
77. Stabenau HF, Becher RD, Gahbauer EA, et al. Functional trajectories before and after major surgery in older adults. Ann Surg. 2018;268:911-917.
78. Daniels SL, Lee MJ, George J, et al. Prehabilitation in elective abdominal cancer surgery in older patients: systematic review and meta-analysis. BJS Open. 2020; 4:1022-1041.
79. Oresanya LB, Lyons WL, Finlayson E. Preoperative assessment of the older patient: a narrative review. JAMA. 2014;311:2110-2120.
80. Derks MGM, Bastiaannet E, Kiderlen M, et al; EURECCA Breast Cancer Group. Variation in treatment and survival of older patients with non-metastatic breast cancer in five European countries: a population-based cohort study from the EURECCA Breast Cancer Group. Br J Cancer. 2018;119:121-129.
81. Morgan J, Richards P, Ward S, et al. Case-mix analysis and variation in rates of non-surgical treatment of older women with operable breast cancer. Br J Surg. 2015;102:1056-1063.
82. Morgan JL, Collins K, Robinson TG, et al. Healthcare professionals' preferences for surgery or primary endocrine therapy to treat older women with operable breast cancer. Eur J Surg Oncol. 2015;41:1234-1242.
83. Morgan JL, Walters SJ, Collins K, et al. What influences healthcare professionals' treatment preferences for older women with operable breast cancer? An application of the discrete choice experiment. Eur J Surg Oncol. 2017;43:1282-1287.
84. Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012;13:e148-e160.
85. Morgan JL, George J, Holmes G, et al; Bridging the Age Gap Trial Management Team. Breast cancer surgery in older women: outcomes of the Bridging Age Gap in Breast Cancer study. Br J Surg. 2020;107:1468-1479.
86. Morgan JL, Reed MW, Wyld L. Primary endocrine therapy as a treatment for older women with operable breast cancer - a comparison of randomised controlled trial and cohort study findings. Eur J Surg Oncol. 2014;40:676-684.
87. Wyld L, Reed MWR, Morgan J, et al. Bridging the age gap in breast cancer. Impacts of omission of breast cancer surgery in older women with oestrogen receptor positive early breast cancer. A risk stratified analysis of survival outcomes and quality of life. Eur J Cancer. 2021;142:48-62.
88. Tang V, Zhao S, Boscardin J, et al. Functional status and survival after breast cancer surgery in nursing home residents. JAMA Surg. 2018;153:1090-1096.
89. Lifford KJ, Edwards A, Burton M, et al. Efficient development and usability testing of decision support interventions for older women with breast cancer. Patient Prefer Adherence. 2019;13:131-143.
90. Wyld L, Reed MWR, Collins K, et al. Bridging the age gap in breast cancer: cluster randomized trial of the effects of two decision support interventions for older women with operable breast cancer on quality of life, survival, decision quality, and treatment choices. Br J Surg. 2021. doi:10.1093/bjs/znab005.
91. Husain LS, Collins K, Reed M, et al. Choices in cancer treatment: a qualitative study of the older women's (>70 years) perspective. Psychooncology. 2008; 17:410-416.
92. University of Sheffield. Age Gap Decision Tool. https://agegap.shef.ac.uk/. Accessed February 10, 2021.
93. Collins K, Reed M, Lifford K, et al. Bridging the age gap in breast cancer: evaluation of decision support interventions for older women with operable breast cancer: protocol for a cluster randomised controlled trial. BMJ Open. 2017;7:e015133.

GLOBAL HEALTH

GLOBAL HEALTH

Improving Oncology-Pathology Collaboration in Resource-Limited Settings: An American Society of Clinical Oncology/College of American Pathologists Initiative

Jose Angel Sanchez, MD[1]; Silvia Portillo, MD[2]; Matthew A. Zarka, MD[3]; Devon Snedden, BS[4]; Doug Pyle, MBA[5]; Harris Goodman, MD[6]; and Daniel F. Hayes, MD[7]

overview

Accurate pathologic evaluation is essential for proper diagnosis and treatment of patients with cancer. ASCO and the College of American Pathologists have successfully collaborated over the last 15 years to improve collaboration between clinical oncologists and pathologists and to standardize pathologic assay techniques. Cancer is an increasingly recognized societal burden in low- and middle-income countries. In 2015, ASCO and the College of American Pathologists implemented an initiative to identify countries that could benefit from peer insights by jointly convening an international workshop among members of both organizations and pathologists and clinical oncologists from Haiti, Honduras, Vietnam, and Uganda. Honduras was chosen as a pilot site, and representatives of ASCO, the College of American Pathologists, and the Honduras pathology and clinical oncology communities have identified areas in which collaboration might be productive. Multiple barriers, including high poverty levels, poor cancer awareness educational programs, lack of human resources, and delayed diagnosis and treatment, have resulted in a higher cancer mortality rate in Honduras compared with high/moderate-income countries and are shared by other low-income countries. ASCO and the College of American Pathologists member faculty supported a symposium led by Honduras colleagues for interested Honduran pathologists and oncologists. The Honduran communities are now working to establish national resource-appropriate guidelines for both pathology and clinical oncology. Taken together, these efforts indicate that barriers to meet the needs of the clinical oncologists in a low-income country such as Honduras are challenging but not insurmountable.

COLLABORATION BETWEEN ASCO AND THE COLLEGE OF AMERICAN PATHOLOGISTS

Accurate and reliable pathologic evaluation is essential for proper diagnosis and treatment of patients with cancer. ASCO and the College of American Pathologists (CAP) have successfully collaborated over the last 15 years to improve cooperation between clinical oncologists and pathologists and standardization of pathologic assay techniques. This initiative began in the mid-2000s with the identification of the need for standardized methods of analysis of HER2 in breast cancer coincident with the astounding results of adjuvant trastuzumab. Representatives of the two organizations met and proposed precise methods of analysis and determination of cutoffs for HER2, and most importantly established proficiency testing for this biomarker linked to CAP laboratory accreditation. These recommendations were simultaneously published in the *Journal of Clinical Oncology* and the *Archives of Pathology & Laboratory Medicine*.[1-3] A similar project was completed regarding hormone receptor analysis (estrogen and progesterone receptors) in breast cancer.[4,5] These guidelines have now been updated on several occasions.[6-11] Taken together, these papers represent some of the most commonly cited articles in both journals.

CAP and ASCO established shared goals and expected outcomes at the genesis of their collaboration. Each of these goals and outcomes is designed to optimize care for patients with cancer; to foster excellence in the practices of pathology and oncology; and to promote interprofessional education, policy advocacy, quality improvement, international outreach, and practice guideline development.

The ASCO/CAP collaboration for HER2 guidelines set the stage for ongoing and future initiatives. Subsequently, ASCO and CAP have collaborated on developing other evidence-based guidelines to help oncologists make informed decisions and provide the highest quality of care, including ongoing provision of

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PRACTICAL APPLICATIONS

- Multiple barriers to adequate cancer treatment in low-income countries include a high level of poverty, lack of human resources, lack of specific diagnosis and treatment guidelines, lack of educational programs, diminished scientific research in oncology, lack of national tumor registries, and inadequate and insufficient cancer facilities and infrastructure.
- Practical resolutions to barriers include the following: adequate training (professional [pathologists, medical oncologists]; staff [histology technicians]); communication among clinical oncologists and pathologists (what assays/tests do clinical oncologists need relevant to what therapies are available; what assays/tests can be performed with high levels of accuracy); and resource-appropriate guidelines (diagnosis and treatment; pathology [analytical]).

pathology training, laboratory accreditation, and proficiency testing for selected tumor biomarker tests in breast as well as other cancers, such as gastrointestinal, colorectal, and lung malignancies.[12-23] Moreover, ASCO and CAP partnered to develop a guide adoption of "liquid biopsies" into clinical care.[24,25]

The following other areas are examples in which ASCO and CAP are currently working together:

- Advocacy and Policy: ASCO and CAP have consulted or collaborated in the following areas:
  - Regulatory review of policies
    - CAP and ASCO have consulted and both commented over the years regarding reform of the regulatory oversight of laboratory developed tests as well as the designation of companion diagnostics.
  - Reimbursement
    - CAP, ASCO, and the American Society of Hematology collaborated to make relative value units and practice expense recommendations to the American Medical Association Relative Value Scale Update Committee for new Current Procedural Terminology codes 38220, 38221, and new Current Procedural Terminology code 38222 (diagnostic bone marrow biopsy and aspiration).
    - Additionally, ASCO and CAP worked in conjunction with the American Society for Transplantation and Cellular Therapy and the American Society of Hematology to develop Category III Current Procedural Terminology codes for CAR T-cell therapy.
    - CAP and ASCO worked together to advise the Center for Medicare and Medicaid Services regarding National Coverage Determination for certain genetic tests and for fluorescence in situ hybridization.
- Professional Education:
  - CAP and ASCO collaborated with the Association for Molecular Pathology and ASCO University on a Molecular Oncology Tumor Board series, an online and user-driven resource, and a published consensus statement regarding Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer[26] to help cancer care providers interpret and understand tumor molecular profiling tests and studies.
- Patient Education (principally, postings on ASCO's patient-focused Cancer.Net website):
  - CAP and ASCO provide pathologist-generated content, primarily videos and infographics, from the existing CAP patient-focused landing page, YourPathologist.org, and the YouTube channel for the health-engaged public.
  - CAP and ASCO have posted pathologist-generated content for patient information, including blogs from CAP members, on Cancer.Net with CAP's Professional and Community Engagement Committee. Some examples include:
    - "Reading a Pathology Report": http://www.cancer.net/navigating-cancer-care/diagnosing-cancer/reports-and-results/reading-pathology-report
    - "Understanding Targeted Therapy": http://www.cancer.net/navigating-cancer-care/how-cancer-treated/personalized-and-targeted-therapies/understanding-targeted-therapy
    - "Biopsy: 5 Things Every Patient Should Know": http://www.cancer.net/blog/2016-05/biopsy-5-things-every-patient-should-know
    - "Spotlight On: Pathologists": http://www.cancer.net/blog/2015-03/spotlight-pathologists
- Scientific Initiatives:
  - Health information technology:
    - CAP and ASCO worked together to standardize data capture and transmission of structured data for patients with cancer and on initiatives and working groups resulting from the ASCO 2016 Oncology Standards & Interoperability Summit.
    - CAP is represented on ASCO's CancerLinQ Oncology Leadership Council. CancerLinQ harnesses the power of big data to help improve the quality of care for every person living with cancer. CAP's inclusion is a direct result of the intention of CancerLinQ to convene oncology professional societies and other stakeholders in a multidisciplinary collaboration for learning and quality improvement, and current initiatives include an analysis of CancerLinQ data elements used for oncology quality reporting.
    - CAP has a full member on the ASCO's Targeted Agent and Profiling Utilization Registry (TAPUR) Steering Group and is represented on the Molecular Oncology Tumor Board, which helps with difficult cases that cannot be dealt with through the automated drug assignment

system. TAPUR is a nonrandomized clinical trial conducted by ASCO that aims to describe the performance (both safety and efficacy) of commercially available, targeted anticancer drugs.
    - CAP collaboration also exists within the ASCO TRG (technical review group) for mCODE (minimal Oncology Data Elements).
- International Humanitarian Initiatives:
    - CAP and ASCO have worked to identify actions that would be both relevant and sustainable in low- and middle-income countries.

CANCER IN LOW- AND MIDDLE-INCOME COUNTRIES AND THE ASCO/CAP INITIATIVE

The latter initiative is directly relevant to this article and the accompanying 2021 ASCO Annual Meeting Education Session. Cancer is a progressively recognized societal burden in low- and middle-income countries where the incidence of cancer is rapidly increasing. The International Agency for Research on Cancer projects that, by 2030, there will be 13 million new cases of cancer annually in low- and middle-income countries (or nearly double the number projected for high-income countries; https://www.iarc.who.int/research-groups-csu-rationale/). In 2015, the World Health Organization expanded its Essential Medicines List, which is used by national governments around the world to prioritize health care investments, to include 16 additional drugs for cancer (https://www.who.int/news-room/fact-sheets/detail/cancer). The list was derived from 29 disease-based documents where effective treatment was possible. For each of these 29 diseases, specific needs of pathology expertise were delineated. The World Health Organization determined that without pathologic diagnosis, appropriate treatment with these essential drugs cannot be successful.

In 2015, responding to the clear need for enhanced pathology in low- and middle-income countries, ASCO and CAP held an international workshop among members of both organizations and pathologist and clinical oncologist delegates from Haiti, Honduras, Vietnam, and Uganda to identify opportunities to improve pathology services in resource-limited settings. One outcome of the workshop was the selection of Honduras as a pilot site to determine a pathway for improvement of diagnosis and pathology with the intent to subsequently provide "lessons learned" to other interested countries. To proceed with this pilot initiative, a joint Task Force was formed, consisting of representatives of CAP (Drs. Matthew Zarka and Harris Goodman, and staff member Devon Snedden), ASCO (Dr. Daniel F. Hayes and staff member Doug Pyle), and Honduras pathology (Dr. Sylvia Portillo) and clinical oncology (Dr. Jose Angel Sanchez) communities.

Over the last 5 years, led by the Task Force, representatives of ASCO, CAP, and the Honduras pathology and clinical communities have conducted regular meetings to identify areas in which collaboration might be productive. In 2018, ASCO and CAP worked with Honduran colleagues to send a letter to the Government of Honduras articulating the importance of pathology in overall cancer care, which resulted in the appointment of a governmental representative to liaise with the ASCO/CAP initiative (Fig. 1). The collaboration has included the following components, some of which will be outlined in greater detail below:

- Analysis of oncology and pathology capacity in Honduras and initial assessment of key gaps, published in ASCO's *JCO Global Oncology*;
- Initial implementation of CAP accreditation program checklists in Honduras, which are a global standard in pathology;
- Networking among oncology and pathology colleagues in Honduras for coordinated action nationwide;
- Establishment of routine, monthly conference calls with oncology and pathology experts appointed by ASCO and CAP for international collaboration and development of an action plan for improving pathology in Honduras; and
- Conducting a workshop hosted by ASCO, CAP, and Honduran pathology and oncology faculty via videoconference with pathologists and oncologists from around Honduras (Fig. 2).

Cancer Treatment Resources in Honduras

Honduras was chosen as a pilot country in part due to its high mortality rate of patients with cancer. Honduras encompasses 112,492 km^2 and has 9,900,000 inhabitants. The Honduran public health system consists of 30 state hospitals distributed in 18 departments that serve more than 60% of the population (https://www.ine.gob.hn/). According to GLOBOCAN, there were 10,602 new cases of cancer and 6,378 cancer deaths in 2020 (https://gco.iarc.fr/today/data/factsheets/populations/340-honduras-fact-sheets.pdf). Cancer management is provided in two of the 30 state hospitals, one in San Pedro Sula and a second in Tegucigalpa (Hospital General San Felipe).

Recently, Dr. Sanchez published the results of a study of the incidence and prevalence of the factors that might lead to worse cancer outcomes in Honduras.[27] He studied 202 patients diagnosed with a variety of cancers at the Hospital General San Felipe (female urogenital; digestive and hepatobiliary; head and neck; colorectal; skin, muscle, and bone; male urogenital; respiratory tract; hematologic; and unknown primary tumor), specifically to address the interval from onset of first symptoms to treatment.

Ninety-five percent of these patients presented as a result of symptoms or signs of their diseases. Only 5% sought medical attention because of findings on x-ray imaging studies or cervical cytology. Nearly one-half of the patients presented with pain. Other reasons were self-detected

ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

COLLEGE of AMERICAN PATHOLOGISTS

September 19, 2018

Dr. Octavio Sanchez
Secretary of Health
Government of Honduras
Tegucigalpa, Honduras

Dear Dr. Sanchez:

On behalf of the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP), the world's largest organizations for cancer professionals and pathology professionals respectively, we would like to congratulate the Honduran Government on your response to the many demands on your national health resources to improve patient care. We would also like to take this opportunity to highlight an emerging and cost-effective opportunity for you to dramatically improve cancer care in Honduras through pathology services that support earlier and accurate diagnosis.

As recently highlighted by the World Health Association, low- and middle- income countries (LMCs) are facing a dual threat from communicable and non-communicable diseases like cancer. As you know, the incidence of cancer is rapidly increasing in LMCs. The International Agency for Research on Cancer projects that by 2030, there will be 13 million new cases of cancer annually in LMCs (or nearly double the number projected for high-income countries).

With regard to Honduras, as you know, the International Agency for Research on Cancer estimates that Honduras has more than 7,400 new cancer patients per year (the tumor registry at the Hospital San Felipe reports about 1,500 cases per year), and more than 5,000 deaths. In discussions with our professional colleagues in Honduras, ASCO and CAP have learned that most of these individuals present with advanced disease, a situation in which a chance for cure is substantially reduced. With earlier, and proper, diagnoses, these patients could be more effectively treated. This lack of appropriate early diagnosis in cancer can lead to increased treatment costs, less effective treatment and premature death. In addition to the impact this has on individual patients, these tragic circumstances disrupt the family unit with consequential economic and social issues that adversely affect the entire country. It is therefore critical that health resources are applied in the most effective way possible.

In this regard, pathology services are critical in applying effective use of cancer resources and optimal outcomes for patients with cancer. Appropriate pathology analysis not only provides an accurate diagnosis, but it includes critical tumor characteristics, without which clinicians cannot deliver effective treatment. It is essential to understand how important it is for clinicians to be provided with these complex pathologic analyses by the pathologist, so that they can deliver appropriate, evidence-based cancer treatment in an efficient manner.

In 2015 the World Health Organization revised its essential medicines list for cancer, adding 16 drugs. The list was derived from 29 disease-based documents where effective treatment was possible. For each of these 29 diseases specific needs of pathology expertise were delineated. The WHO determined that without pathologic diagnosis, appropriate treatment with these essential drugs cannot be successful.

Treating patients with anti-cancer drugs in the absence of an accurate diagnosis will result in a very poor chance of benefit and a very high chance of unnecessary treatment-related toxicity, ultimately leading to deaths due to the disease or inappropriate treatment that could have been avoided. Further, such inefficient application of anti-cancer treatments will result in a major waste of scarce healthcare resources.

FIGURE 1. Letter From College of American Pathologists and ASCO to Honduras Secretary of Health

Effective delivery of fundamental pathology resources requires attention to the following factors:

1. Accuracy of pathology testing, including:
    a. High-quality technical processing of tumors.
    b. Skilled interpretation of the specimens.
2. Speed of the test
    a. Prompt processing of the tissue to avoid degradation once it has been collected from the patient.
    b. Rapid turnaround times for to deliver the results to the treating physician, so that cancer therapy can be initiated quickly, reducing immediate suffering and preventing reduction in therapeutic efficacy associated with delays in starting treatment.
3. Availability of key tests that will drive individual patient care. For example, testing for estrogen receptor status is critical to determine if a patient with breast cancer should be treated with relatively inexpensive and low-toxicity anti-estrogen therapy. This type of therapy, which is indicated for approximately one-half of patients with breast cancer, has had a major beneficial impact on patient survival in upper income countries over the last four decades.

ASCO and CAP believe this issue is so critical to global public health that the societies have formed a strategic alliance to support pathology development around the world, and Honduras has been selected to be the initial focus of our efforts together. We are pleased to be working with Dr. Jose Angel Sanchez, Professor of Medical Science, Faculty UNAH, and Dra. Silvia Portillo Chief of Pathology from El Instituto Nacional Cardiopulmonar. Dr. Sanchez and Dra. Portillo have demonstrated exceptional leadership and have already accomplished the following in collaboration with ASCO and CAP:

1. Analysis of oncology and pathology capacity in Honduras and initial assessment of key gaps, with further analysis to come
2. Initial implementation of CAP accreditation program checklists in Honduras, which are a global standard in pathology
3. Networking among oncology and pathology colleagues in Honduras for coordinated action nationwide
4. Establishment of routine, monthly conference calls with oncology and pathology experts appointed by ASCO and CAP for international collaboration and develop an action plan for improving pathology in Honduras

These critical steps taken by Dr. Sanchez and Dra. Portillo create the framework and basis for actions to come. We would like to thank you for your kind attention and look forward to sharing with you our progress. Proposed next steps in this relationship are being identified and will be shared with you in a subsequent letter. We look forward to working together with Drs. Sanchez and Portillo, their colleagues and the Honduran government to improve care of cancer patients in the country.

Sincerely,

Monica Bertagnolli, MD, FASCO
President
American Society of Clinical Oncology

R. Bruce Williams, MD, FCAP
President
College of American Pathologists

FIGURE 1. Letter From College of American Pathologists and ASCO to Honduras Secretary of Health (Continued)

TRADUCCION

19 de Septiembre del 2018

Dr. Octavio Sánchez
Secretario de Salud en el Despacho de Salud Pública
República de Honduras
Tegucigalpa, Honduras, C.A.

Estimado Dr. Sánchez:

En representación de la Asociación Americana de Oncología Clínica (ASCO siglas en inglés) y del Colegio Americano de Patólogos (CAP siglas en inglés), las organizaciones más grandes del mundo de profesionales del cáncer y de la patología, respectivamente, nos gustaría felicitar al gobierno hondureño por su respuesta a las muchas demandas que su sistema de salud tiene para mejorar el cuidado del paciente. Nos gustaría aprovechar esta ocasión para resaltar una oportunidad costo efectiva que está surgiendo para que dramáticamente se pueda mejorar el cuidado del paciente con cáncer en Honduras a través de los servicios de Patología que apoyan el diagnóstico temprano y preciso de esta enfermedad.

Tal como recientemente lo ha resaltado la Organización Mundial de la Salud, los países con ingresos bajos y medios están enfrentando la doble amenaza de las enfermedades trasmisibles y de las no trasmisibles como el cáncer. Como usted sabe, la incidencia se ha incrementado rápidamente en estos países. La Agencia Internacional para la Investigación en Cáncer (IARC siglas en inglés) proyecta que para el año 2030 habrá 13 millones de nuevos casos de cáncer por año en los países de ingresos bajos y medios (cifras que duplican el número de los casos proyectados para los países de ingresos altos).

En lo referente a Honduras, como usted sabe, la Agencia Internacional para la Investigación en Cáncer estima que en Honduras hay más de 7,400 nuevos casos de cáncer por año (el Registro de Tumores del Hospital San Felipe reporta aproximadamente 1,500 casos por año), y más de 5,000 muertes anuales. En conversaciones con nuestros colegas hondureños, ASCO y CAP nos hemos enterado de que la mayoría de estas personas se presentan en estadíos avanzados de la enfermedad, una situación en la cual la oportunidad de cura está sustancialmente reducida. Con un diagnóstico temprano y apropiado estos pacientes podrían ser tratados en una forma más efectiva. La falta de un diagnóstico temprano apropiado en cáncer puede llevar al incremento en los costos de tratamiento, tratamientos menos efectivos y a la muerte prematura. Adicionalmente esto tiene un impacto individual en cada paciente, estas trágicas circunstancias rompen con la unidad familiar con los consecuentes aspectos económicos y sociales que afectan al país entero. Por lo cual es crítico que los recursos en salud sean usados de la forma más efectiva posible.

En este sentido, los servicios de patología son cruciales en el uso efectivo de los recursos contra el cáncer y en el resultado positivo en el cuidado del paciente con esta enfermedad. Un correcto estudio de patología no sólo brinda un diagnóstico preciso, sino que proporciona características del tumor de suma importancia sin las cuales los clínicos no pueden dar tratamientos efectivos. Es esencial comprender lo importante que es para los clínicos que el patólogo les provea de estos complejos estudios de patología, de tal forma que a su vez ellos puedan dar en forma efectiva tratamientos contra el cáncer basados en evidencia.

En el 2015 la Organización Mundial de la Salud revisó el listado de los medicamentos esenciales contra el cáncer agregando 16 medicamentos. La lista se originó de documentos con las 29 enfermedades donde el tratamiento efectivo era posible. Para cada una de estas 29 enfermedades se estableció la necesidad del expertismo de la patología. La OMS determinó que sin un diagnóstico de patología un tratamiento apropiado con estos medicamentos no sería exitoso.

Tratar a los pacientes con medicamentos contra el cáncer en ausencia de un diagnóstico preciso resultará en una muy pobre oportunidad de beneficio y en una alta posibilidad de tratamiento innecesario con toxicidad asociada, que finalmente llevará a la muerte por la enfermedad o por el tratamiento inadecuado, lo cual pudo haberse evitado. Además, tales aplicaciones ineficientes de los tratamientos contra el cáncer conducirán a un gran desperdicio de los escasos recursos para los cuidados de la salud.

FIGURE 1. Letter From College of American Pathologists and ASCO to Honduras Secretary of Health (Continued)

Entregar efectivamente los recursos fundamentales a patología requiere atención por los siguientes aspectos:

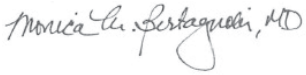
1. Precisión en las pruebas de patología que incluyen:
    a. Alta calidad en el procesamiento técnico de los tumores.
    b. Hábil interpretación de las muestras.
2. Velocidad en las pruebas:
    a. Un pronto procesamiento del tejido para evitar su deterioro una vez que ha sido tomado del paciente.
    b. Rápidos tiempos de entrega al médico tratante, de manera que la terapia contra el cáncer pueda iniciarse lo más pronto posible, reduciendo así el sufrimiento inmediato y previniendo la disminución de la eficacia terapéutica asociada con los retrasos en el inicio del tratamiento.
3. El acceso a las pruebas claves que llevaran al cuidado individual del paciente. Por ejemplo, las pruebas que establecen la situación de los receptores de estrógenos son críticas para determinar si la paciente con cáncer de mama deberá ser tratada con terapia antiestrógénica que es relativamente barata y con baja toxicidad. Este tipo de terapia, la cual está indicada en aproximadamente la mitad de las pacientes con cáncer de mama, ha tenido un alto impacto benéfico en la sobrevida en países de altos ingresos en las últimas cuatro décadas.

ASCO y CAP creen que este asunto es tan crítico para la salud pública global que las sociedades han formado una alianza estratégica para apoyar el desarrollo de la patología alrededor del mundo y Honduras ha sido seleccionada para ser el proyecto piloto en nuestros esfuerzos conjuntos. Estamos muy satisfechos de poder trabajar con el Dr. José Ángel Sánchez, Profesor de Medicina en la Facultad de Ciencias Médicas de la UNAH y con la Dra. Silvia Portillo, jefe del Servicio de Patología del Instituto Nacional Cardiopulmonar. El Dr. Sánchez y la Dra. Portillo han demostrado un excepcional liderazgo y ya han logrado lo siguiente en colaboración con ASCO y CAP:

1. Análisis de las capacidades de la Oncología y la Patología en Honduras con una evaluación inicial de las brechas importantes, con proyecciones hacia el futuro.
2. Implementación inicial de las listas de chequeo para la acreditación del CAP en Honduras, las cuales son un estándar global en patología.
3. Formar una red entre sus colegas oncólogos y patólogos en Honduras con una coordinación en toda la nación.
4. Establecer una rutina de conferencias mensuales con oncólogos y patólogos expertos invitados por ASCO y CAP para colaboración internacional y el desarrollo de un plan de acción que busca mejorar la patología en Honduras.

Estos pasos críticos tomados por el Dr. Sánchez y la Dra. Portillo crean el marco y las bases para las acciones futuras. Nos gustaría agradecerle por su fina atención y esperamos compartirle en el futuro nuestros avances. Se han propuesto los próximos pasos en esta relación y los compartiremos con usted en una carta posterior. Esperamos entusiasmados poder trabajar con los doctores Sánchez y Portillo, sus colegas y el gobierno de Honduras en la mejora del cuidado de los pacientes con cáncer del país.

Sinceramente,



Monica Bertagnolli, MD, FASCO
Presidente
American Society of Clinical Oncology

R. Bruce Williams, MD, FCAP
Presidente
College of American Pathologists

FIGURE 1. Letter From College of American Pathologists and ASCO to Honduras Secretary of Health (Continued)

palpable tumors, bleeding, unexplained weight loss, and gastrointestinal abnormalities. These symptoms were specific to the cancer diagnoses, including digestive, hepatobiliary, female urogenital, and colorectal cancers.

Eighty-three percent of the patients were initially diagnosed by general doctors, gynecologists, internists, general surgeons, or nonmedical personnel, such as nurses and naturalists. Subsequent evaluation and care was principally provided for over 90% of the patients by surgical and medical oncologists.

Some form of cancer treatment was initiated in 123 patients, and 79 patients had not received treatment when the study was closed. The reason why patients had not received treatment was beyond the objective of this study. The survey demonstrated a median of more than 7 months' delay from first clinical manifestations of the cancer to initiation of treatment. This included a mean of 68 days between symptom onset and seeing any health provider, and a mean time from first symptom to evaluation by a cancer specialist of 147 days.

Most relevant to this manuscript, over 10% of patients did not have a biopsy report in their medical record. Of those who did, 44% did not have a biopsy before seeing a cancer specialist, further delaying the start of effective therapy.

For patients whose date of beginning of treatment was possible to determine, the mean time to surgery was 7 days (range, 1 day to 858 days), and to chemotherapy and radiation it was 88 days and 102 days, respectively. The difference in time interval from onset of symptoms to treatment in patients who had an ordered sequence of evaluation (meaning from general practitioner, oncologist's consultation, or biopsy report to treatment) versus those who did not have an ordered sequence was not statistically significant (Table 1).

Taken together, these data demonstrate that in Honduras, as in many low-income countries, cancer mortality is higher than in high-income countries. The causes of this disparity are likely multifactorial, including, as suggested by these data, delayed diagnosis, with an accompanying advanced state of disease before oncologic treatment is initiated.[28,29] These data are similar to those in other low-income countries and stand in contrast to those reported in high-income countries, in which the interval is 1 to 2 months.[30-32]

Moreover, these data indicated that there is not a rigid system of public health attention in Honduras. However, surprisingly, following an ordered sequence did not decrease the time to cancer treatment initiation, probably because of other sources of delay, such as multiple medical evaluations before oncologist consultation, time of referral to a cancer specialist, and delays in obtaining diagnostic test results or in initiation of treatment.

The observation that first presentation was due to symptoms associated with advanced disease, including bleeding, weight loss, and changes in bowel habits, highlights the necessity of better public information services, like those that are available in high-income countries. Indeed, public announcements by well-known celebrities in the United States, for example former First Lady Betty Ford (breast cancer) and former President Ronald Reagan (colon cancer), highlighted the importance of cancer discussions and led to many citizens seeking the attention of a health provider in a timely fashion.[30,33]

FIGURE 2. First Honduras Joint Pathology/Oncology Workshop With CAP and ASCO Faculty Contributing Virtually
Abbreviation: CAP, College of American Pathologists.

In addition to a delay in seeking or receiving cancer services, this study also identified a major inconsistency in timing and reporting of biopsies. Importantly, patients with a biopsy report obtained before being evaluated by a cancer specialist started treatment much more quickly than those whose biopsy report was not available.

In summary, these cumulative delays are thought to be responsible for the high cancer mortality in Honduras, and likely in other low-income countries as well. Such delays are unacceptable because they result in greater cancer morbidity and mortality when compared with diagnoses and treatment initiated earlier in the disease process. In addition to adversely affecting quality and length of life, these delays also result in downstream cultural and economic adversity. These results strongly suggest that appropriate measures must be taken to reduce the time to initiate cancer therapy in Honduras.

Models for Pathology Improvement in Resource-Limited Settings

The work of the Task Force allowed CAP and ASCO to understand opportunities and limitations for reproducible and sustainable collaborations in resource-limited settings.

TABLE 1. Time Intervals Between Clinical Manifestations of Cancer and Treatment at the Hospital General San Felipe in Tegucigalpa, Honduras

	No. of Patients (%)					
Interval	**≤ 30 Days**	**31–90 Days**	**≥ 90 Days**	**UD**	**Total No. of Patients**	**Mean Time (Days)**
IST1	87 (43.07)	32 (15.84)	48 (23.76)	35 (17.33)	202	67.84
IST2	58 (28.71)	42 (20.79)	86 (42.57)	13 (6.44)	199	146.57
IST3	64 (31.68)	8 (3.96)	7 (3.47)	14 (6.93)	93	25.63
IST4	46 (22.77)	30 (14.85)	22 (10.89)	9 (4.46)	107	85.52

NOTE. Table does not include the following information: three patients (1.49%) went directly to the cancer specialist; 24 patients (11.88%) had not had a biopsy when they were referred, whereas 85 patients (42.08%) had a biopsy; 79 patients (39.11%) had not begun treatment with an average time elapsed of 101.63 days; and 16 patients (7.92%) had begun treatment before receiving a histopathologic diagnosis.
Abbreviations: IST1, mean time between symptom onset and seeing any health provider; IST2, mean time from first symptom to evaluation by a cancer specialist; IST3, mean time elapsed from cancer specialist evaluation to obtaining the biopsy report; IST4, mean time elapsed after obtaining a biopsy report to initiation of specific treatment; UD, undefined (patients did not remember dates).
From Sánchez et al[27] with permission.

As referenced in the project overview, the Task Force first identified areas of opportunity for leverage of existing CAP and ASCO resources to help guide associated objectives. Eventually, more focused needs were identified, and more aspirational deliverables were supported in later phases of the collaboration.

Phase I: Evaluation In the early phase of the project, the Task Force worked toward improving laboratory operations and functionalities to support Honduran pathologists with continuing education and mentorship for access to advancements in anatomic pathology practiced in the United States. All pathologic cases were shared using digital images. Although this is not the predominant method of review of slides, it is certainly becoming more prevalent and more accepted within the pathology community. Use of digital images is particularly useful for consultation, as it eliminates the delay and cost of shipping, as well as the risk of loss of materials, and is especially useful in this setting. Consensus on cases is obtained exactly the same way as in-person cases, via a collegial discussion. If no consensus can be reached, experts in the specific area of pathology are then consulted.

On the positive side, the Honduran pathologists and residents were extremely enthusiastic about these collaborative continuing education sessions with CAP pathologist cohorts. Teaching conferences, conducted remotely, were always welcomed and a positive experience, and appeared to motivate residents to improve the overall delivery of anatomic pathology services in Honduras.

However, hurdles to effectively provide these sessions were identified, including connectivity issues, time zone differences, and preferred spoken language. Each of these hampered the overall learning experiences. Nonetheless, some of these issues (e.g., connectivity) conceivably could be easily overcome with only a limited amount of additional resources.

The pathologists in Honduras were also very enthusiastic about implementing the CAP accreditation requirements (also known as the CAP Checklists). Accreditation by CAP requires meeting all of the requirements and represents the highest level of patient care and laboratory safety. CAP does not have more lenient requirements for international or under-resourced laboratories. Therefore, given the limited resources in personnel and equipment in Honduras, CAP accreditation was not believed to be achievable in the short term.

However, again in a positive aspect, the CAP accreditation policy did not prevent Honduran pathologists from utilizing the CAP Checklists to improve upon the analysis, diagnosis, and consistent and reproducible reporting of cancer cases, which we maintain will ultimately lead to improved cancer care. Additionally, evaluation of the shared CAP Checklists compared with Honduran laboratory operations allowed the team to identify foundational areas for improvement and focused action.

Phase II: Foundational Action Insights from phase I stimulated the Honduran pathology and oncology team to establish a formal engagement with the Honduran Department of the Secretary of Health. A 1-day workshop among Honduran pathologists, pathology residents, and medical oncologists, as well as faculty from CAP and ASCO, was held to discuss provision of Honduran patients with breast cancer with better quality of life and longer lifespans while managing limited oncologic resources (Fig. 2). The proceedings were used as a case study to exemplify opportunities for action with leaders of the Honduran Secretary of Health, who were in attendance. In the case study, a view of the Honduran oncology situation was outlined, and the Task Force suggested areas for support in early detection, correct diagnosis, preanalytic factors, and reporting detail, comprehensiveness, and consistency. At the conclusion of the workshop, Honduran health officials pledged to support efforts through future centers of

excellence established by practice and incidence data evaluation.

In the spirit of the pilot initiative, the workshop served not only as a positive event but also provided a "lessons-learned" opportunity. It was initially planned as an in-person activity to be held in Tegucigalpa. However, continued political unrest in Honduras resulted in three subsequent postponements, and, finally, the Task Force elected to hold it in person for participants in Honduras but virtually for faculty in the United States. In spite of these obstacles, the meeting was quite successful in establishing our goals and strategies. Although the workshop preceded the COVID-19 pandemic, it illustrated the opportunity to use virtual interactions to accomplish collaboration between CAP/ASCO and a low-income country, such as Honduras.

The Task Force worked together to identify areas for future resource prioritization by performing two separate surveys (see Fig. 3 for example of the surveys, in English and Spanish): (1) a survey of Honduras pathologists to outline factors, laboratory and pathology capabilities, and important preanalytic and postanalytic factors. Both of these surveys raised considerations for prioritization of allocation of health care resources; and (2) a survey of Honduras medical/clinical oncologists (surgical, radiation, and medical oncologists) to determine what pathology services they would like to meet their needs relative to available therapeutic opportunities and delivery of treatment to patients, including availability of medical specialists.

These evaluations focused on variables unique to Honduras. Pathology and oncology landscapes were assessed by location and practitioner demographics as well as by resources available and in need. Surveys among respective country practitioners supported insights for focus as well as foundational actions for improved outcomes. For oncology practitioners, the survey results included the following downstream activities (Table 1): (1) leveraging the Honduras Secretary of Health data for incidence at clinical sites, (2) filtering by oncologist locations, (3) filtering by therapeutic opportunities for outcome impact (overlaying medical oncology therapeutic sites) to assess unaddressed treatment opportunity, (4) supporting sites with guidelines and complement CAP and ASCO checklists and references for laboratory and radiology and other diagnostic needs, (5) identifying key oncology/diagnostic, laboratory, and pathologist champions at each site, and (6) implementation of checkpoints for adoption with identified ASCO and CAP champions as virtual mentors.

For pathology practitioners, the survey results were also helpful in initiating the following new processes: (1) assessing the Honduras Secretary of Health for incidence at clinical sites, (2) filtering by methodology capabilities for high incidence disease states, (3) filtering by therapeutic opportunities for outcome impact (overlaying medical oncology therapeutic sites), (4) supporting sites with guidelines that complement CAP checklists for laboratories, (5) identifying key laboratory, pathologist, and medical oncologist champions at each site, and (6) outlining implementation checkpoints for adoption with ASCO/CAP champions as virtual mentors.

Data from these surveys were provided by the Honduran representatives of the Task Force to the Honduras Secretary of Health to propose important legislative change. Perhaps the most concrete and impactful of these is consideration of establishment of an Oncology Center of Excellence in Tegucigalpa.

Again, to highlight another "lesson-learned" from this pilot initiative, the Task Force initially sent out the survey to pathologists in both English and a strictly translated version in Spanish. Several of those who were surveyed noted difficulty in filling out the spreadsheet to answer some of the questions. For the subsequent survey sent to clinicians, an adjusted survey with a more precise interpretation was provided, leading to better acceptance and satisfaction among those surveyed.

Phase III: Ongoing Best Practice Collaboration Medium- and long-term areas for continued collaboration among CAP/ASCO and Honduras pathologists and oncologists have also been identified and discussed. Implementation of support for the foundational needs provided a more stable base for the Task Force clinicians' goal of advancing the quality of care delivered to patients. Additional opportunities that were considered include observership opportunities in the United States for Honduran pathology and oncology trainees, support for online patient information and synoptic reporting, support through industry-sponsored programs, and in-person workshops. These efforts will build on past work in Honduras by ASCO and its collaborator Health Volunteers Overseas to provide training in multidisciplinary cancer treatment and palliative care through volunteer visits to Honduran medical facilities, in-person training workshops, and professional development awards for young oncologists.[34]

The established collaboration has endured through political unrest, natural disasters, and global pandemics. Focus on needs identified by endemic Honduran clinicians allowed investment and agility by local clinicians and Honduran authorities, lending sustainability and evergreen collaboration to the project.

Applying a similar evaluation in different resource-limited situations could support unique insights and solutions relevant to a setting's needs and proposed outcomes. Notably, this model allows for application in a whole-country setting or a defined region within a country. More importantly, this model and evaluation algorithm can be applied to different disease incidence situations and country need situations

A

EXPLICACION: En el contexto del Proyecto de Apoyo Educativo que la Iniciativa Global para Honduras de la Sociedad del Colegio Americano de Patologos está desarrollando con la Asociación Hondureña de Anatomía Patologica, se ha estandarización del diagnóstico de los cánceres más frecuentes en el país y en la práctica diagnóstica cotidiana de continuación se desea conocer la frecuencia del uso de estas guias y protocolos por parte de su persona y su opin

INSTRUCCIÓN: Agradeceremos marque con una cruz la opción que considere mas adecuada para usted en las colum deben marcarse.
Todos los campos son de llenado obligatorio. Si quiere conocer mas de las guias y protocolos que se detallan, puede co vinculo de cada item.

COMPROMISO DE CONFIDENCIALIDAD: los datos personales que se solicitan sólo son para análisis de las necesidad no serán revelados ni asociados a sus respuestas.

Años de ejercicio profesional:	

Practica profesional diagnosticando: (sólo marcar con una cruz la opción que más se acerque a su situación actual)	Publica:
	Privada:
	Ambas:
	Ninguna:

GUIAS O PROTOCOLOS EXISTENTES EN EL COLEGIO AMERICANO DE PATOLOGOS		
Existing CAP Guideline		**TRADUCCION AL ESPAÑOL PARA ESTA CONSULTA**
General Pathology		**Patologia General (aspectos de gestión de la calidad)**
Uniform Labeling of Blocks and Slides in Surgical Pathology	**1**	*Rotulación uniforme de los bloques y láminas en Patología Quirúrgica*

FIGURE 3. Surveys of Current Practices and Needs of Honduras Pathologists and Clinical Oncologists
A. Survey of Honduras Pathologists (in English and Spanish)
B. Survey of Honduras Clinical Oncologists (in Spanish only)

Principles of Analytic Validation of Immunohistochemical Assays	2	*Principios para la validadción analítica de las pruebas de inmunohistoquímica*
Validating Whole Slide Imaging for Diagnostic Purposes in Pathology	3	*Validación de la Imagenologia Completa de la Lámina (sistema WSI) para propósitos de diagnóstico en Patología*
Effective Communication of Urgent Diagnoses and Significant Unexpected Diagnoses in Surgical Pathology and Cytopathology - Reaffirmation	4	*Comunicación efectiva de diagnósticos urgentes y diagnósticos inesperados en Patología Quirurgica y Citopatologia (reiteración/reafirmación)*
Interpretive Diagnostic Error Reduction	5	*Reducción de errores interpretativos en el diagnostico*
Hematológico		
Hematológico linfoma		
https://documents.cap.org/protocols/cp-hodgkinlymphoma-17protocol-3101.pdf	6	*protocolo para el diagnostico de linfoma de hodgkin*
https://documents.cap.org/protocols/nonhodgkinlymph-17protocol-3201.pdf	7	*protocolo para el diagnostico de linfoma no hodgkin*
Hematological		**Hematológico**
Bone Marrow Synoptic Reporting for Hematologic Neoplasms	8	Reporte sinoptico de médula osea para neoplasias hematológicas
Initial Diagnostic Workup of Acute Leukemia	9	Elaboración inicial del diagnostico de leucemia aguda
Cervix		
https://documents.cap.org/protocols/cp-femalereproductive-uterinecervix-excision-19-4200.pdf	10	*protocolo para el diagnostico de excision de cuello uterino*
https://documents.cap.org/protocols/cp-femalereproductive-uterinecervix-resection-19-4200.pdf	11	*protocolo para el diagnostico de resección de cuello uterino*
HPV		**VPH**
The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions	12	Proyecto de estandarización de la terminología para las lesiones asociadas a la infección por VPH en las lesiones escamosas del tracto anogenital bajo
Human Papillomavirus Testing in Head and Neck Carcinomas	13	Pruebas para detección del Virus del Papiloma Humano en cabeza y cuello
Guia para el diagnóstico de cancer de mama		

FIGURE 3. Surveys of Current Practices and Needs of Honduras Pathologists and Clinical Oncologists (Continued)

https://documents.cap.org/protocols/cp-breast-dcis-resection-19-4301.pdf	14	*protocolo para el diagnostico de resección de carcinoma ductal in situ de mama*
https://documents.cap.org/protocols/cp-breast-dcis-biopsy-19-1000.pdf	15	*protocolo para el diagnostico de biopsia de carcinoma ductal in situ de mama*
https://documents.cap.org/protocols/cp-breast-invasive-resection-19-4301.pdf	16	*protocolo para el diagnostico de resección de carcinoma ductal de mama invasor*
https://documents.cap.org/protocols/cp-breast-invasive-biopsy-19-1001.pdf	17	*protocolo para el diagnostico de biopsia de carcinoma ductal de mama invasor*
https://documents.cap.org/protocols/cp-breast-biomarker-19-1300.pdf		*protocolo para el reporte de biomarcadores de cancer de mama.*
Non-Her2 IHC (Breast)		**Inmunohistoquimica para mama (diferentes a Her2)**
Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer	18	Pruebas de inmunohistoquimica de Receptores de Estrogeno y Progesterona en cancer de mama
Her2 (Breast)		**Her2 (mama)**
Quantitative Image Analysis of HER2 IHC for Breast Cancer	19	Analisis cuantitativo de la imagen de la inmunohistoquimica del Her2 para cancer de mama
HER2 Testing in Breast Cancer - 2018 Focused Update	20	Prueba para Her2 en cancer de mama - actualización concreta del 2018
Guia para el diagnóstico de cancer de estomago		
https://cap.objects.frb.io/protocols/cp-stomach-17protocol-4000.pdf	21	*protocolo para el diagnostico de carcinoma gastrico por biopsia*
Her2 (Gastroesophageal)		**Her2 (gastroesofágico)**
HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma	22	Prueba de Her2 y toma de decisiones en el adenocarcinoma gastroesofágico
Guia para el diagnóstico de cancer de pulmón		
https://documents.cap.org/protocols/cp-thorax-lung-resection-19-4100.pdf	23	*protocolo para el diagnostico de reseccion de carcinoma de pulmón*
Lung Cancer Biomarkers: TKIs		**Biomarcadores de cancer de pulmón - Inhibidores de Tirosinquinasa (TKI)**

FIGURE 3. Surveys of Current Practices and Needs of Honduras Pathologists and Clinical Oncologists (Continued)

Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors – Update	**24**	Guía de las pruebas moleculares para la selección de pacientes con cancer de pulmon para el tratamiento dirigido a los inhibidores de la tirosinquinasa -actualización
Guia para el diagnóstico de cancer de colon y recto		
https://documents.cap.org/protocols/cp-gilower-colonrectum-17protocol-4010.pdf	**25**	*protocolo para el diagnostico de resección de carcinoma colon y recto*
Colorectal Cancer Biomarkers/ EGFR		**Biomarcadores de cancer colorectal/EGFR**
Molecular Biomarkers for the Evaluation of Colorectal Carcinoma	**26**	*Biomarcadores para la evaluación de carcinoma colorectal*
Guia para el diagnóstico de cancer de tiroides		
https://documents.cap.org/protocols/cp-endocrine-thyroid-19-4200.pdf	**27**	*protocolo para el diagnostico de carcinoma de tiroides*
Guia para el diagnóstico de cancer de prostata		
https://documents.cap.org/protocols/cp-malegenital-prostate-radicalprostatectomy-19-4041.pdf	**28**	*protocolo para el diagnostico de prostatectomia radical por carcinoma prostatico*
https://documents.cap.org/protocols/cp-malegenital-prostate-turp-19-4041.pdf	**29**	*protocolo para el diagnostico de biopsia trasuretral de carcinoma prostatico*
https://documents.cap.org/protocols/cp-malegenital-prostate-18protocol-4030.pdf	**30**	*protocolo para el diagnostico de biopsia de carcinoma de prostata*
Guia para el diagnóstico generico (de cualquier tipo de muestra)		
https://documents.cap.org/protocols/cp-other-genericteplate-biopsy-19-1000.pdf	**31**	*protocolo para el diagnostico de biopsia de cualquier carcinoma no protocolizado*
https://documents.cap.org/protocols/cp-other-genericteplate-resection-19-1000.pdf	**32**	*protocolo para el diagnostico de resección de cualquier carcinoma no protocolizado*

FIGURE 3. Surveys of Current Practices and Needs of Honduras Pathologists and Clinical Oncologists (Continued)

B

Consentimiento Informado

El presente documento es un estudio de carácter científico. Toda la información proporcionada por usted, será utilizada únicamente con fines científicos y educativos, con el objetivo de homogeneizar las guías de diagnóstico y con ello, tratar de mejorar el diagnóstico de enfermedades neoplásicas. Su colaboración es de carácter confidencial y voluntario.

NECESIDADES DE ONCOLOGOS DE HONDURAS PARA LA UTILIZACIÓN DE GUÍAS DE DIAGNÓSTICO DEL COLEGIO AMERICANO DE PATOLOGOS CON FINES DE MEJORA EL MANEJO EN PACIENTES ONCOLOGICOS

OBJETIVO:

Saber si los patólogos de Honduras utilizan guías de diagnóstico

DEMOGRAFÍA:

- Sexo:
- Edad:
- Título:
- Institución:
- Años de práctica:
- Utiliza de Guías de manejo en la institucion donde labora Sí ☐ No ☐
- ¿Qué guía utiliza?: ASCO: ☐ ESMO: ☐ Ninguna: ☐ Otras ☐

- Marque con una X su respuesta para cada pregunta en la casilla que corresponda siguiendo las opciones del encabezado

		SI NO	IGNORA	YA SE UTILIZA
	Patología General			

FIGURE 3. Surveys of Current Practices and Needs of Honduras Pathologists and Clinical Oncologists (Continued)

¿Qué se etiquetan los bloques y placas en patología de manera uniforme?			
¿qué se utilicen principios de validación analítica de los estudios inmunohistoquímicos?			
	SI NO	IGNORA	YA SE UTILIZA
¿Establece usted una comunicación efectiva con el patologo en casos urgentes, inesperados o especiales?			
¿Se confirma el diagnóstico oral de su discusion con el patologo en el informe oficial?			
Cáncer de cérvix			
¿Ques se estandarice la terminología para lesiones anogenitales de tipo escamoso asociadas a VPH?			
¿Qué se realicen pruebas de VPH en carcinoma de cabeza y cuello?			
Cáncer de mama			
¿ Que se realicen pruebas inmunohistoquímicas de receptores de estrógeno y progesterona en cáncer de mama?			
¿Qué se realizara estudios de HER2 en forma rutinaria?			
¿Qué se analizara cuantitativamente las pruebas de HER2 mediante Inmunohistoquimica?			
Cáncer Gastroesofágico			
¿ Que se realizara rutinariamente la prueba de			

FIGURE 3. Surveys of Current Practices and Needs of Honduras Pathologists and Clinical Oncologists (Continued)

HER2 para la toma decisiones terapeuticas en adenocarcinoma gastroesofágico?				
Cáncer de pulmón				
¿Qué se utilizara las guías diagnósticas de pruebas moleculares de inhibidores de tirosina quinasa con orientacion terapéutica?				
Cáncer colorrectal				
¿Qué se utilizara pruebas o biomarcadores de factor de crecimiento epidérmico (EGFR) ?				
¿Le gustria que se realizaran estudio Moleculares y o Geneticos con fines diagnosticos en los siguientes tipos de cancer				
Cáncer gástrico				
Cáncer de colón				
Hematología				
Cáncer de tiroides				

FIGURE 3. Surveys of Current Practices and Needs of Honduras Pathologists and Clinical Oncologists (Continued)

TABLE 2. Overall Status of CAP/ASCO/Honduras Pilot Project

Initiative	Goal	Accomplishments	Lessons Learned/ Obstacles to Success	Strategies to Overcome Obstacles	Next Steps
Monthly program planning conference calls	• Plan and troubleshoot ongoing initiatives • Discuss potential new initiatives	Held monthly	• Calls cancelled for months during the pandemic • Poor internet confounded some discussions • Competing priorities and scheduling conflicts	• Asynchronous communications, such as email • Recent improvement in communication capabilities	• Resume regular calls • Consider broadening the planning calls to include other stakeholders as initiatives evolve postpandemic
Joint CAP/ASCO letter to Honduras Secretary of Health	• Bring issues of cancer care and pathology limitations and opportunities to attention of Secretary of Health • Highlight role and contributions of Honduran pathology and oncology representatives • Communicate ASCO and CAP support for these efforts	• Personal engagement of Honduras Secretary of Health • Appointment of a representative liaison to the pilot program • Consideration for allocating resources to cancer diagnosis and treatment	• Civil unrest, COVID-19 pandemic and economic impacts disrupt governmental plans and priorities	• Need for sustained, ongoing support and effort to ensure sustainable governmental commitment	• Re-engage governmental representatives in concert with Honduran representatives postpandemic
In-person symposium regarding pathology and oncology care in Honduras	• Gain perspectives of clinical and pathology cohorts in Honduras • Present a breast cancer case study for support in early detection, diagnosis, preanalytical issues and reporting detail to facilitate discussion for areas of collaboration opportunity • Engagement of Honduras stakeholders, including governmental authorities, in issues regarding oncology care in Honduras • Identify issues that CAP and ASCO could help support	• In-person symposium held, but CAP and ASCO had to join virtually • Proceedings and recommendations presented to Honduras Secretary of Health • Development of resource-appropriate guidelines identified as a key priority • Opportunities to engage ASCO and CAP in guidelines development were identified	• Political unrest (and later pandemic-related concerns) prevented CAP and ASCO faculty from attending in person	• Establishing virtual attendance	• Holding in-person training workshops and symposia postpandemic • Consider ongoing virtual initiatives to sustain engagement of relevant stakeholders
Pathologist workshop for sample collection improvement	• Improve diagnoses through optimized sample collection • Educate pathology leaders to teach improved methods to other colleagues	• To be determined	• In-person workshop on hold until postpandemic travel resumes	• Discussion refocused to plan for Honduras residents to spend time in sponsored programs in the United States	• Identify resident and fellow support programs for Honduras pathologists to receive hands-on, resource-based training

(Continued on following page)

TABLE 2. Overall Status of CAP/ASCO/Honduras Pilot Project (Continued)

Initiative	Goal	Accomplishments	Lessons Learned/ Obstacles to Success	Strategies to Overcome Obstacles	Next Steps
Conduct surveys of Honduras pathologists and clinicians	• Identify current resources for diagnosis and treatment of cancer • Identify resource limitations and obstacles to providing modern cancer care in Honduras • Identify needs for improving cancer care in Honduras	• Surveys completed • Results summarized • Results provided to Honduras Secretary of Health	• Initial translation from English to Spanish too literal • Incomplete participation among those asked to participate in survey	• Improved translation from literal to colloquial Spanish	• Establish resource-appropriate programs to improve cancer care in Honduras
Introduce CAP laboratory accreditation and accreditation checklists in Honduras	• Improve and standardize pathology diagnostic reports		• CAP checklists as written not feasible in low-income countries • CAP accreditation not attainable if all checklist requirements are not met	• Used CAP checklists to improve care despite lack of CAP accreditation	• Identification of foundational areas for improvement
Monthly seminars between Honduran pathologists and CAP faculty	• Provide continuing education and mentorship for access to advances in anatomic pathology		• Connectivity problems • Time zone differences • Language barriers		• Planned submission of proposal to CAP Foundation to support needed expansion of pathology services

Abbreviation: CAP, College of American Pathologists.

and produce actionable results. This model is not dependent on attenuated guidelines or American intervention.

THE WAY FORWARD: LESSONS FROM HONDURAS FOR RESOURCE-LIMITED SETTINGS

As noted, with only 43 pathologists, the pathology workforce in Honduras is insufficient in size and is concentrated in the biggest cities, Tegucigalpa and San Pedro Sula. Though it is estimated that only about one-half of them currently use CAP Guidelines in their pathology reports, the remainder have indicated a willingness to implement the guidelines into their practices. Currently, in the public health care setting, in which the majority of patients with cancer are treated, there are three units of classic pathology with limited immunohistochemistry techniques. There are no laboratories of molecular pathology in the country. Taken together, these data reflect that cancer diagnosis in Honduras is based generally in classic pathology.

How can this situation be rectified? To start, at least 18 pathology units are needed around the country, and at least a single molecular pathology laboratory is urgently needed. Continued mentorship from colleagues and countries who are familiar with these standards, guidelines, and implementations has proven successful; indeed, this mentorship must be established for ongoing support and implemented in other countries to continue to effect change.

Recognizing this need, the College of American Pathologists Foundation has had a history of grant support for humanitarian teaching and research projects in pathology in resource-limited settings in developing countries over the last decade. In 2020, the Foundation inaugurated the College of American Pathologists Foundation Global Pathology Committee charged with identifying impactful, sustainable, and accretive global health care initiatives/opportunities for CAP members for result of the expansion and advancement of the specialty of pathology under-resourced areas internationally. The CAP/ASCO/Honduras Task Force is currently discussing an application to College of American Pathologists Foundation to support needed expansion of pathology services.

Perhaps more importantly, this experience has identified obstacles that could be overcome with visionary changes in public policies to provide a more comprehensive approach against cancer in Honduras. The support of international partners like ASCO and CAP offers an opportunity to improve local medical capacity. However, as established at the start of this initiative, ultimately change can only come from within the respective country, based on perceived needs and priorities. The most important aspect that arose from the initiative is the concept that advocacy for policy changes will drive building a structure that can be developed through the

years. Coupled with the experience of colleagues within Honduras and from the United States, we have developed a vision of a world full of opportunities to provide improved care for patients with cancer.

We began this initiative prior to the COVID-19 pandemic. As noted, due to travel and safety concerns, we encountered obstacles to providing our planned in-person interactions. However, we successfully overcame these obstacles with virtual telecommunication technology, both for the workshop and subsequent interactions between Honduras pathologists and members of CAP, including monthly meetings of the steering committee (Drs. Hayes, Goodman, Sanchez, and Portillo and members of ASCO and CAP staff). With the advent of the pandemic, as the world became more comfortable with virtual telecommunication technologies, such interactions became easier logistically. Indeed, as noted, virtual productive review sessions were held between pathologists from Honduras and CAP. We continue to believe that face-to-face interactions are important to build collegial collaborations, but use of such technologies for virtual meetings provide great opportunities to more easily continue our long-distance efforts.

This exchange of opinions and vision has taught us that we live in a world that can get closer using the communication technology that we share in this part of the world. It is always a barrier to speak a different language. However, this barrier can be overcome to encourage people to get involved in different educational activities. In the end, the most important task is to find the way to have people coming to share their experience face to face in ways that circumvent issues related to national security and global pandemics, which will continue to be problems on a global scale. With clever use of available technologies, and a will to succeed, we can work on building bridges with local organizations (nurses, pharmacists, patients, families, etc.) to keep cancer in the national health agenda as an important issue. This ongoing pilot experience, arising from commitment of all involved, has already improved, and will continue to improve, the situation of patients and their families in Honduras and other low- and middle-income countries (Table 2).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Wolff A, Hammond EH, Schwartz JN, et al. Human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol. 2007;25:4021-4022 (in reply).
2. Wolff AC, Hammond ME, Schwartz JN, et al; American Society of Clinical Oncology/College of American Pathologists. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med. 2007;131:18-43.
3. Wolff AC, Hammond ME, Schwartz JN, et al; College of American Pathologists. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol. 2007;25:118-145.
4. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010;28:2784-2795.
5. Hammond ME, Hayes DF, Dowsett M, et al; College of American Pathologists. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). Arch Pathol Lab Med. 2010;134:e48-e72.
6. Wolff AC, Hammond ME, Hicks DG, et al; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31:3997-4013.
7. Wolff AC, Hammond ME, Hicks DG, et al; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol Lab Med. 2014;138:241-256.
8. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. J Clin Oncol. 2018;36:2105-2122.

9. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. Arch Pathol Lab Med. 2018;142:1364-1382.
10. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists guideline update. Arch Pathol Lab Med. 2020;144:545-563.
11. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP Guideline Update. J Clin Oncol. 2020; 38:1346-1366.
12. Bartley AN, Washington MK, Ventura CB, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. Am J Clin Pathol. 2016;146:647-669.
13. Bartley AN, Washington MK, Ventura CB, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. Arch Pathol Lab Med. 2016; 140:1345-1363.
14. Bartley AN, Washington MK, Colasacco C, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. J Clin Oncol. 2017;35:446-464.
15. Bartley AN, Washington MK, Ismaila N, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline summary from the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. J Oncol Pract. 2017;13:53-57.
16. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. Arch Pathol Lab Med. 2017; 141:625-657.
17. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. J Clin Oncol. 2017; 35:1453-1486.
18. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular biomarkers for the evaluation of colorectal cancer: guideline summary from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. J Oncol Pract. 2017; 13:333-337.
19. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. J Mol Diagn. 2017; 19:187-225.
20. Kalemkerian GP, Narula N, Kennedy EB. Molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology Endorsement Summary of the College of American Pathologists/International Association for the Study of Lung Cancer/ Association for Molecular Pathology Clinical Practice Guideline Update. J Oncol Pract. 2018;14:323-327.
21. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/ Association for Molecular Pathology Clinical Practice Guideline Update. J Clin Oncol. 2018;36:911-919.
22. Leighl NB, Rekhtman N, Biermann WA, et al. Molecular testing for selection of patients with lung cancer for epidermal growth factor receptor and anaplastic lymphoma kinase tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Association for the study of lung cancer/association for molecular pathology guideline. J Clin Oncol. 2014;32:3673-3679.
23. Rekhtman N, Leighl NB, Somerfield MR. Molecular testing for selection of patients with lung cancer for epidermal growth factor receptor and anaplastic lymphoma kinase tyrosine kinase inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Guideline. J Oncol Pract. 2015;11:135-136.
24. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. J Clin Oncol. 2018;36:1631-1641.
25. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. Arch Pathol Lab Med. 2018;142:1242-1253.
26. Li MM, Datto M, Duncavage EJ, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: a joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 2017; 19:4-23.
27. Sánchez JA, Handal MG, Vílchez Rodriguez JF, et al. Time intervals from onset of clinical manifestations to treatment in patients with cancer at Hospital General San Felipe, Tegucigalpa, Honduras. J Glob Oncol. 2019;5:1-7.
28. Lyratzopoulos G, Wardle J, Rubin G. Rethinking diagnostic delay in cancer: how difficult is the diagnosis? BMJ. 2014;349(dec09 3):g7400.
29. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144:1941-1953.
30. Tiwari V, Yogi V, Ghori HU, et al. Identifying the factors causing delayed presentation of cancer patients to a government medical college of Central India. J Clin Diagn Res. 2015;9:XC09-XC12.

31. Ozmen V, Boylu S, Ok E, et al. Factors affecting breast cancer treatment delay in Turkey: a study from Turkish Federation of Breast Diseases Societies. Eur J Public Health. 2015;25:9-14.

32. Unger-Saldaña K. Challenges to the early diagnosis and treatment of breast cancer in developing countries. World J Clin Oncol. 2014;5:465-477.

33. Car LT, Papachristou N, Urch C, et al. Preventing delayed diagnosis of cancer: clinicians' views on main problems and solutions. J Glob Health. 2016;6:020901.

34. Chuang L, Sarchet V, Pyle D, et al. Volunteering in Honduras: results and reflections. J Clin Oncol. 2015;33:2001-2003.

GLOBAL HEALTH

Is Independent Clinical Research Possible in Low- and Middle-Income Countries? A Roadmap to Address Persistent and New Barriers and Challenges

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overview

Cancer is an increasing and significant problem for both high- and low- and middle-income countries. Basic, translational, and clinical research efforts have been instrumental in generating the outstanding improvements we have witnessed over the last few decades, answering important questions, and improving patient outcomes. Arguably, a substantial portion of currently ongoing research is sponsored by the pharmaceutical industy and specifically addresses questions under industry interests, most of which apply to high-income countries, leaving behind problems related to the much larger and underserved population of patients with cancer in low- and middle-income countries. In this scenario, discussing independent academic research is an important challenge, particularly for these countries. Although different countries and institutions face different problems while establishing independent research agendas, some generalizable barriers can be identified. A solid regulatory and ethical framework, a strong and sustainable technical supporting infrastructure, and motivated and experienced investigators are all paramount to build a viable and productive academic research program. Securing funding for research, although not the only hurdle, is certainly one of the most basic hurdles to overcome. Noticeably, and as an added impediment, public and governmental support for cancer research has been decreasing in high-income countries and is almost nonexistent in the rest of the world. We propose an initial careful diagnostic assessment of the research resource scenario of each institution/country and adjustment of the strategic development plan according to four different research resource restriction levels. Although not necessarily applicable to all situations, this model can be helpful if adjusted to each local or regional situation.

Although cancer remains a formidable challenge for humankind, the recent impressive advances observed in the understanding and management of the disease need wholehearted recognition. Unquestionably, laborious, and well-conducted basic, translational, and clinical research represent the underlying mechanism driving the introduction of much-needed innovations in oncology. Of utmost importance for this discussion is the fact that low- and middle-income countries (LMICs) are home to most of the world's population and, as a consequence, where most of the world's cancer burden is now concentrated. In these nations, although infectious and communicable diseases still represent a major burden, the ongoing epidemiologic transition is making noncommunicable diseases, in particular cancer, a growing challenge.[1] Of note, health care priorities of LMICs, such as tackling the cancer epidemic and its growing role in mortality, the persistent burden of relatively preventable types of cancer, such as head and neck, lung, cervical, and gastric cancers, and the challenge of constantly incorporating costly novel technologies should be considered important drivers of the current clinical research agenda. Yet, we see instead a persistent under-representation of the generally more vulnerable population of LMICs in ongoing cancer clinical trials.[2,3]

Acknowledging the multidimensional nature of the scientific process, the question posed in this article is timely and important. The future of cancer research is a major issue in both high-income countries and LMICs, but the latter do cope with many more hardships in addressing the problem and face greater challenges and barriers to conducting independent research.[4] Within a global perspective, scientific development should reflect and address the variations and different problems we see across the world. Different countries and cultures face dissimilar challenges and can have varying priorities when adopting a clinical research agenda. This is a multifaceted and complex problem with important consequences for the future of health care. Arguably, LMICs have not been properly

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PRACTICAL APPLICATIONS

- Academic research is a challenge in low- and middle-income countries.
- Pertinent questions for local populations remain largely unaddressed.
- Countries and regions are heterogeneous in terms of research infrastructure and output.
- This article proposes a four-level diagnostic restriction assessment.
- A workforce of motivated investigators is required for success.

exploring the immense potential of addressing pertinent regional questions in their mostly underserved populations.

Clinical research is a mandatory step in the evaluation and development of new therapies to treat cancer.[5] A deeper analysis of currently ongoing cancer clinical trials registered at ClinicalTrials.gov indicates that more than 87% are being conducted in the United States, Canada, Europe, Australia, and Japan, whereas less than 30% are available in other countries.[6] Therefore, it should not come as a surprise that most of these trials address questions that are much more relevant to high-income countries than to LMICs.[7] From this perspective, focusing on the needs of these underserved populations, for which the benefit of clinical research would be the greatest, should be a priority.[8]

The objective of this article is to address aspects of clinical research related to the development of academic or independent research in LMICs. We will focus on some of the perceived barriers and propose mechanisms to improve the current situation.

ANALYSIS OF CURRENTLY ONGOING CLINICAL RESEARCH

Cancer clinical research is an essential part of the process of bringing new treatment alternatives to clinical practice. Importantly, the ultimate goal of clinical trials is to improve the outcomes of patients in the real world.

Appropriately, clinical research directed to drug development is an evolving and highly regulated activity.[9] Although erratic information varies according to the area, current estimates indicate that research and development costs for a new medicine have been increasing over the last few decades and are placed between US$200 million and US$2.9 billion.[10] This current explosion in costs and the associated regulatory and bureaucratic demands make academic participation in clinical research much more challenging and help explain the fact that most ongoing cancer clinical research is now being conducted and sponsored by pharmaceutical companies.

This raises an important discussion with far-reaching consequences. As a very telling example, available evidence from the United States indicates a decreasing trend in the number of independent trials and public National Institutes of Health funding.[11] Data obtained from ClinicalTrials.gov indicate a decrease of 24% in National Institutes of Health–funded trials from 2006 to 2014, with a parallel impressive 43% increase in pharmaceutical industry–sponsored trials over the same period of time.[6] According to the National Cancer Institute and adjusted for inflation, the support for cancer research has been stable with a decreasing trend over the last 10 years.[12]

Furthermore, analyzing abstracts presented at ASCO Annual Meeting plenary sessions (most of which were selected for their potential practice-changing impact) over the last 10 years (2010 to 2020), of the 46 reported studies, 56% were pharmaceutical industry sponsored, 23% were supported by the National Cancer Institute or other North American institutions, and only 19% were sponsored by non-American research groups.[13,14] Importantly, only two of 20 nonindustry-sponsored trials that we can consider as independent clinical research were conducted and coordinated outside high-income countries. These were two trials designed in India addressing early diagnosis of cervical cancer and the optimal surgical approach to regional lymph nodes in head and neck cancer—two situations we can consider outside the current scope of pharmaceutical industry interests.[15,16]

These numbers reflect the imbalance between pharmaceutical industry–sponsored and academic research and the imbalance of scientific output from high-income countries and LMICs that deserve careful analysis. Limited available evidence indicates that the imbalance is worse in some regions of the world where the availability of governmental agency support for clinical research is almost nonexistent. This is particularly true in LMICs, where resource allocation and funding priorities are preferentially directed to other areas. Figure 1 shows a distribution of research and development expenditure as a percentage of gross domestic product (including public and private investments) across the world and clearly illustrates current regional scientific outcomes.[17] At the same time, and with a significant impact on our ability to propose strategies to address the problem of independent research in LMICs, we must recognize that among different regions of the world, we find different scenarios that do require locally adapted solutions. Clearly, the research agenda and the research output of different LMICs reflect the extreme heterogeneity and diversity these countries show in all other areas of development.

Pharmaceutical companies mostly support research that is oriented to their specific interests. The commercial impact

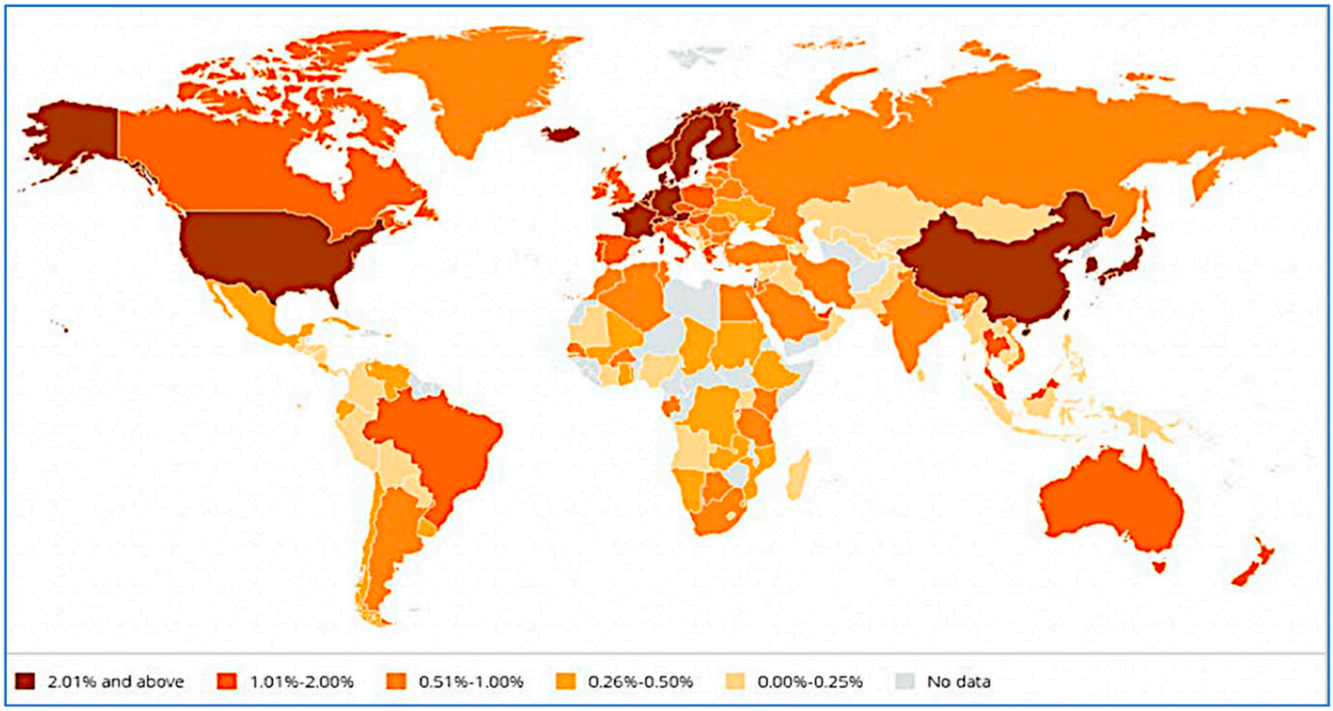

FIGURE 1. Gross Domestic Expenditure on Research and Development as a Percentage of Gross Domestic Product, 2018 or Latest Year Available (http://uis.unesco.org)

of the results is certainly one of the main concerns when discussions of a new trial are started. Disease burden, the size of the specific patient population, or the market share being addressed are certainly major discriminating issues from the start, leaving behind important clinical questions with lower commercial impact that remain unexplored. Therefore, diseases or specific situations more prevalent in countries that are able to pay the ever-increasing prices of new medicines take priority over clinical situations more frequent in less-developed settings.

A few examples include issues such as the ideal duration of therapies, the optimal sequencing of drugs for certain diseases, and many head-to-head comparisons. Furthermore, simple but important analysis such as more detailed exploration of postprogression therapies (with an impact on overall survival interpretation) are routinely not adequately performed. Although these questions impact all cancer clinical research in general, issues addressing special tumor types with particular impact on LMICs have usually been left outside of the pharmaceutical industry's interest and should be the focus of independent research. In summary, pharmaceutical industry–sponsored research interests are, in general, not aligned with LMIC needs, most of which can only be addressed by independent or partially independent research.

To be fair, the potentially different interests in research questions of pharmaceutical industry–sponsored and academic research are clearly observed in high-income countries as well. Based on a logic of survival, hybrid models of trial and research design have been applied by most large academic research groups (Breast International Group, European Organisation for Research and Treatment of Cancer, Southwest Oncology Group, Eastern Cooperative Oncology Group, Alliance for Clinical Trials in Oncology, National Cancer Institute of Canada, Latin American Cooperative Oncology Group, etc.). In this sense, the groups propose investigator-initiated ideas that, if aligned with the development interests of the pharmaceutical industry, are likely to succeed. Financial resources obtained in the process of conducting these clinical trials are then applied within each group to smaller studies and academic projects not otherwise supported. Most academic leaderships recognize this hybrid model as challenging to implement, requiring a great deal of effort and being significantly vulnerable. For a more detailed and instructive discussion on this interaction, refer to the article, "Overcoming Barriers to Clinical Trials Cooperation: The Breast International Group Example," by Piccart-Gebhart et al in the 2021 *ASCO Educational Book*.

Therefore, in the current scenario and with the globalization of clinical research, the participation of high-income countries in cancer research has been mostly limited to recruiting patients to trials designed by the pharmaceutical industry or North American or European academic groups.[8]

Although this is not an ideal situation, it should be noted that this process brings a number of important benefits for participating centers and countries. Arguably, the most important one is providing access to drugs that otherwise would not be available to most patients in those underserved scenarios. At the same time, we should recognize the stimulus to the creation of clinical research centers and the valuable associated experience in conducting research. Certainly, this process leads to better training and development of qualified and experienced human resources, a key requirement for countries and institutions to be able to conduct independent research at a later development stage. However, all these benefits should not overshadow the fact that the most important goal of conducting clinical research in LMICs is to address and answer questions that are pertinent to that particular setting.

THE CHALLENGE OF ACADEMIC OR INDEPENDENT CLINICAL RESEARCH

There is no single definition of independent/academic research, but the term is mainly applied toresearch performed free from commercial interests. In clinical research, this usually means research that is independent from pharmaceutical companies' interests.

Academic freedom is considered a hallmark of independent research. This applies not only to independence in the analysis and interpretation of the data but also all other steps of the research process, including hypothesis formulation and study design. Therefore, the standing of a research study has a wide spectrum of possible independence status, ranging from fully industry driven to fully independent. The subtlety here is the (common) situation in which a reportedly independent study (i.e., officially non–pharmaceutical industry sponsored) is in fact fully or partially funded by grants from pharmaceutical companies, because companies might scrutinize the study design and propose changes/adjustments that are not necessarily inappropriate or unfair but require balanced judgment. Importantly, the very existence of such a study implies a certain level of bias because a pharmaceutical company is unlikely to fund a study that turns against its interests; such studies may end up never being conceived/performed. We could refer to this situation (of a relative conflict of interest) as partially independent research. This is why even minor potential conflicts of interest must always be reported to the scientific community: a policy that has become standard practice among scientific journals and meetings.

However, we acknowledge that partially independent research is still a broad definition, and different levels of breach of a study's independence may apply. A favorable scenario would be a study fully conceived by the investigator, addressing a question that is truly relevant to the community, that underwent no or very limited changes imposed by the sponsor, and that will be conducted and analyzed independently and with a commitment from both parties to disclose the results regardless of the outcome. A much less independent study would be one addressing a topic of ultimate importance to the sponsor (and potentially not as much to the community), which is their own idea, in which the data are not owned by the investigator/research group and the data analyses are fully performed by the sponsor or its affiliates.

It is difficult to measure precisely how much research is independent in a specific country. However, by applying the search terms "type of sponsor-industry" and selecting "interventional studies" at the ClinicalTrials.gov website (a widely used clinical research search tool), it appears that only 884 (30%) of 2,834 studies were non–industry sponsored in Latin America compated with 20,792 (55%) of 37,924 in the United States and Canada, roughly indicating the scale of the gap between high-income countries and LMICs in terms of independent research output as previously addressed.[6]

In the modern world of clinical research, collaboration between individual investigators and/or independent research groups with pharmaceutical companies has been increasingly common and should probably be encouraged. However, data ownership and sharing remain challenging interfaces that have evolved significantly over the years as the relationship between independent investigators/research groups and pharmaceutical companies has reached a higher level of maturity. In clinical research, a healthy collaboration involves trust and credibility. As this relationship is still maturing in LMICs, independent investigators/research groups should seek opportunities to collaborate with more mature researchers/research groups either in specific projects or within the context of official partnerships. This strategy might facilitate the accomplishment of specific projects because of the high level of expertise and credibility owned by renowned international research groups.

Another significant benefit of performing independent research is the education of new investigators/researchers. By conducting independent research, they will be confronted with a wide range of hurdles and challenges that are usually unfamiliar to investigators participating in pharmaceutical industry–sponsored clinical trials. This includes securing funds and insurance, assigning responsibility for ethics and safety reports, setting up independent monitoring committees, finding and affording specialized biostatistical support, and even reporting the study results. In the authors' long experience trying to conduct independent research in an LMIC, these challenges are highest for individual (institutional) researchers trying to conduct research on their own and lower when research is conducted under the

umbrella of a well-structured collaborative research group. As an example, the structure of the Latin American Cooperative Oncology Group provides support for aspiring investigators in every step of the clinical research process.

Although this article mainly addresses clinical research as clinical trials or drug development trials, there are other forms of independent clinical research that are easier to perform in LMICs and may still produce meaningful data. These include, but are not limited to, retrospective and epidemiologic studies (now greatly facilitated by the high level of digitalization of patient charts and clinical data in general) that can have significant regional impact on generating important and pertinent information addressing local unexplored issues. Translational research studies and studies addressing quality of life, cancer survivorship issues, and career development can also be considered. Other significant areas of research that can be the focus of an independent research agenda include surgical procedures, radiotherapy schedules, and epidemiologic and pharmacoeconomic questions.[18-21] Some of these studies can be conducted with significantly lower costs and may represent optimal choices for students entering a formal postgraduate training program that will lead to a thesis. Ideally, developing research groups should have a structure allowing for nonclinical trial projects that help to enrich the group's curriculum and gradually increase its credibility, which is a key requirement for further developments (Table 1).

The barriers to perform independent clinical research are identifiable at system, organizational, and individual levels and can be summarized as follows: (1) insufficient financial and/or human capacity; (2) ethical and regulatory system hurdles; (3) lack of a research environment/culture; and (4) operational barriers and competing demands.[22] Although the relative importance of these barriers may vary depending on the country/region, they are usually familiar to all. These barriers, along with potential solutions, are further addressed in Table 2.

In Latin America, for example, the most successful projects carried out by the Latin American Cooperative Oncology Group did involve partnerships with pharmaceutical companies, proving that the model might also work for LMICs.[23] However, these initial experiences have yet to evolve into a significant source of practice-changing clinical trials, and thus far, they remain no more than an unreliable source of scientific output and income for the group. We believe this is partly because of a persistent culture of "second-class grants only" from the pharmaceutical companies' partners and of "low-profile grants for clinical research" from our public funding agencies. In a way, this is not surprising, because our credibility as a reliable partner for performing cutting-edge clinical research is still evolving, and this is a slow process. However, we find this regretful, because many fully capable research centers with enormous patient recruitment potential are available in the region, as proven by their past performance in competitive global clinical trials.

Other than the pharmaceutical industry, main potential sources for clinical research funding include governmental agencies and philanthropy. However, in LMICs, public investment in research is scarce, if there is any. Philanthropy, on the other hand, remains largely unexplored, and we can surely state that the culture of donating to research remains a major challenge in LMICs. Even when philanthropy initiatives are identified, they have not been directed to cancer research. Although, as mentioned, National Cancer Institute funding of independent clinical research has decreased over the years (it is still huge compared with the funding available to LMICs), this strategy has been key to the establishment of independent research groups in the United States. However, these mature research groups have now been able to make independent research possible through other sources of funding and partnerships. We acknowledge that National Cancer Institute sponsorship of independent research has been a successful model that should definitely be used by LMICs to boost independent research of their own interest.

Of note, the complex relationship between independent research groups and pharmaceutical companies is not restricted to research funding and may involve individual group member's conflicts of interest with pharmaceutical companies (most commonly with compensated educational/advisory activities) and sponsorships of the group's educational activities, among others; many of them are still considered crucial for the group's survival. It is therefore of paramount importance that the research group and its members draw clear lines separating these potential conflicts of interest from the research development process so that its core concepts of independence remain untouched.

Finally, and as per previous experiences of other collaborative research groups, a typical clinical trial portfolio of a research group should contain a healthy mixture of fully sponsored, partially independent, and fully independent studies. Although the former tends to develop naturally and quickly, it is the group's task to exploit the ground provided by sponsored research to set up a growing portfolio of independent research. We understand that this cannot be achieved without effective leadership, which must motivate the driving force of scientific output (i.e., the young generation of investigators) to create the right incentives for a career dedicated to clinical research and to remove the regulatory and cultural barriers that stand in the way of many LMICs' full scientific development.

Although there are certainly many individual and/or institutional success stories of independent research

TABLE 1. Other Forms (Nonclinical Trials) of Independent Research That Are Easy to Perform in LMICs and Still Potentially Relevant

Type of Study	Barriers	Potential Solutions
Retrospective and epidemiologic studies	Lack of appropriate digital medical charts in many institutions	Provide greater access to high-quality digital charts
	Low cultural and financial stimulus to invest in databases	Promote the value of investing in databases for the only purpose of research
	Low availability of qualified biostatisticians	Invest in training and valuation of biostatisticians' careers
	Barriers in terms of tougher patient data protection regulations	Work together with authorities to remove potentially excessive regulatory barriers
Translational research studies	Low availability of tumor banks	Promote the establishment of properly regulated tumor banks
	Heterogeneous capacity to perform complex laboratory analyses	Invest in cell-free DNA translational research, potentially much simpler to collect and store
		Establish collaboration with foreign or regional laboratories or more developed research groups
Studies on quality of life and cancer survivorship	Sometimes attract limited interest from physicians; often too focused on clinical trials and patient care	Can often be carried out by nonmedical staff in collaboration with the medical team
Studies on career development		Can sometimes be linked to a postgraduate thesis, which enhances the motivation of younger investigators
New surgical procedures and radiotherapy schedules	Also require insurance but the regulatory process is less complex than drug clinical trials	Integrate surgeons and radiation oncologists into the research environment of the oncology collaborative groups in the region
	Trial-associated costs are significantly lower than drug development protocols	
Pharmacoeconomic studies, including of shorter, less toxic, and lower-cost schedules	Complex regulations (similar to those used for sponsored research) often apply	Work together with authorities to simplify the regulatory path
	Limited expertise in biostatistical support	Invest in training and valuation of biostatisticians' careers

Abbreviation: LMICs, low- and middle-income countries.

development that would be impossible to report in this article, in our personal experience and that of most other investigators in the region, the establishment of an active, well-structured, multicultural, and multispecialty collaborative research group such as the Latin American Cooperative Oncology Group (although there are other examples) was the most important step ever taken to promote independent research in the region. The group has been able to attract new (independent and pharmaceutical industry–sponsored) clinical trials, provide solid biostatistical support, and assist busy investigators with the hard task of writing protocols and clearing regulatory processes, among many other services. The results of these efforts are now becoming evident; for instance, one of the Latin American Cooperative Oncology Group's investigator-initiated trials was selected for an oral presentation during the 2020 ASCO Virtual Scientific Meeting.[23] Furthermore, at least in our experience in Brazil, organizing investigators and promoting an active discussion of our regulatory barriers has generated a proposal of new legislation that is currently being evaluated by the legislative chamber to improve and speed the approval process facilitating access to research.

PROPOSED STRATEGIES FOR THE DEVELOPMENT OF INDEPENDENT CLINICAL RESEARCH IN LMICs

Considering the different and very heterogeneous research situations we encounter in different regions of the world, it is clearly challenging to offer solutions that could be applicable in all regions. A regionally adaptable and context-conscious approach is likely to result in the best outcomes. The initial approach is to perform a careful and detailed analysis of the existing academic research situation at an individual, institutional, and country level. This diagnosis is paramount to enable all involved stakeholders to tackle all identified barriers and build a solid research agenda. Seeking the help of more experienced researchers or independent research collaborative groups while performing this initial evaluation is important to accurately identify the major needs for each specific country or institution.

TABLE 2. Main Barriers to Perform Independent Clinical Research in LMICs and Potential Solutions

Nature of the Barrier	Likely Causes of the Barrier	Potential Solutions
Insufficient financial and/or human capacity	Training staff and physicians in research skills is not a priority (training is instead driven to clinical practice skills)	Promote value in research jobs
	Salaries are usually higher in clinical practice than in research, both for physicians and research staff	Make training in research skills mandatory in graduation and residency training programs
	Highly skilled staff are easily attracted by the higher wages offered by pharma companies	Secure funding for research fellowship programs
Ethical and regulatory system hurdles	Too much control over the regulatory process, though potentially necessary at the initial stages, may become counterproductive	Gradually delegate decision-making power to (qualified) institutions
	IRBs and central ethics committees and not professional activities	Create professionalized ethics committees
	Contract handling is often not specialized	Promote specialization in research for lawyers and their supporting team
		Establish clear and reasonable deadlines for regulatory approvals
Lack of a research environment/ culture	CV development and research output are not sufficiently valued in LMICs	Promote the value of CV development and research output at the institutional and society level
		Promote the notion that an institutional claim of being a "reference cancer treatment facility" is dependent on the existence of a comprehensive research program
Operational barriers and competing demands	The regulatory burden of research is often absorbed by busy and burned-out physicians	Provide sufficient operational infrastructure to free physicians to focus on research and clinical care of the research subject
	There is a persistent culture of physician-centralized patient care	

Abbreviations: CV, curriculum vitae; IRBs, institutional reviews boards; LMICs, low- and middle-income countries; pharma, pharmaceutical.

Unquestionably, the three main focuses of this initial approach include establishing a regulatory and ethical framework, building an adequate research infrastructure, and developing human resource experience in all aspects involved in academic or independent research. As these requirements are heterogeneously distributed in different regions, a careful assessment of the local needs is essential for successful strategic planning. From a practical perspective, research resource scenarios can be explored according to the availability of an appropriate infrastructure, experienced medical and supporting professionals, and the basic and extremely important regulatory and ethical legislation—one of the most critical starting points. Importantly, a motivated investigator and/or institution remains the main driving force behind the whole process in all possible scenarios.

For instance, in many LMICs, there has been a tendency from health authorities to centralize the regulatory handling of clinical trials. Although this has varied from country to country, in Brazil, for instance, proposals have a sequential local and central ethics approval process. Although this process has theoretical advantages (of enhanced control and a more homogeneous decision-making process), in our experience, it has mainly generated further delays with limited added safety for research subjects. Therefore, LMICs should remain attentive to the research flow process they will implement to ensure it will not become an additional barrier.

Based on previous work addressing different resource scenarios, we propose a prioritized stratification that should be considered according to the specific scenario (also summarized in Table 3).[24]

The first or initial research resource level includes a scenario where there is interest in developing research activities, but there is no established regulatory legislation in place. Interested investigators and or institutions in this situation should concentrate on building the regulatory and ethical framework addressing the issue with the appropriate authorities.

The second research resource level could be identified as one in which the regulatory/ethical framework is already in place, but there is no adequate infrastructure to support the conduct of independent research. Many times, investigators can overcome the lack of this kind of support by personal effort and dedication; however, this strategy is unlikely to

TABLE 3. Research Resource Restriction Levels

Research Resource Restriction Level	Needs Assessment	Required Strategies
1	Interest in research but no regulatory or ethical framework	Build a solid regulatory and ethical research framework; requires involved discussion with government authorities
2	Lack of technical infrastructure or experience to conduct independent research	Investments in building a supporting structure of dedicated administrative staff, data managing and monitoring staff, statistician, dedicated nursing, and pharmacy personnel among other professionals; gain hands-on experience with international independent groups or pharma-sponsored trials
3	Lack of experience in protocol development, implementation, conduct and analysis	Generate regionally pertinent questions that can lead to protocol proposals; seek funding and carry out all steps involved in protocol development and implementation; build credibility
4	Requires sustainability strategies and expansion of initial established experience and infrastructure	Expand and disseminate independent research efforts; develop strategies to guarantee sustainability of the research infrastructure; stimulate and mentor the development of a new generation of academic researchers; foster a culture of international collaboration and data sharing in research

result in continuous and significant scientific output. Investments in building a supporting structure of dedicated administrative staff, data management and monitoring staff, a statistician, and dedicated nursing and pharmacy personnel, among other professionals are probably a very good starting point in this kind of setting. Guidance and training from established research groups and pharmaceutical industry partners has been extremely helpful in this situation. The experience gained in the conduct of pharmaceutical industry–sponsored or international collaborative group research is invaluable to develop expertise that is essential to focus further independent research.

One caveat to be considered when looking at established regulatory frameworks is the fact that they may actually be too restrictive to allow independent research. Many times, while concentrating on regulating pharmaceutical industry–sponsored research, specific legislation may unwillingly establish significant barriers for academic investigators. In this regard, one example reported in some countries is legislation requiring sponsors to pay for standard-of-care procedures involved in the treatment of patients participating in research protocols. Although this is an undesirable but manageable hurdle in most pharmaceutical industry–sponsored trials, it is an unsurmountable barrier for independent research.

A third research resource level would be one where the ethical infrastructure is in place and where experience with large phase III trials has been gathered in different research centers. Here, the objectives are to identify potential research questions of interest and go through the process of protocol development with all the required steps, many of which only become apparent when you actually decide to face the challenge of undertaking independent research (secure funding, insurance, case report form development, statistical plan, etc.). As mentioned in the previous step, guidance from more experienced researchers and groups should certainly ease the way and should be an important part of this process. One of the most critical aspects of this stage of independent research development is building credibility. As you are able to identify an appropriate and important question, develop a protocol, and conduct and publish the research, you start constructing a reputation that will be helpful for future ideas and will serve as an example for other colleagues or institutions in your region or in similar settings tofollow. Collaboration among research centers and investigators and dissemination of the initial effort are essential parts of building a strong and sustainable regional academic network.

The fourth research resource level involves more mature and experienced infrastructures that can be identified in some LMICs or regions. In this situation, the challenge is to expand independent research, build sustainable strategies to guarantee sources of funding (pharmaceutical industry, philanthropy, government, etc.), and, very importantly, develop new generations of investigators. Building on the experience of having reached this stage of development, two fundamental aspects should guide investigators at this stage: first, the clear mission of focusing research on problems that are pertinent to the region and will impact important patient outcomes; and second, and not less critical, develop a collaborative

international culture of sharing efforts, ideas, and data. Only with the collective involvement and a strong sense of collaboration between academic research groups and the engagement of many branches of society will we be able to address the unanswered questions so vital for patients from high-income countries.

CONCLUSION

Independent research has a long way to go in LMICs, and, at least in the near future, it will remain hard to compete with high-income countries in cutting-edge, practice-changing research. However, in the meantime, with the right infrastructure in place and motivated investigators, independent or academic research should be able to produce meaningful data, provided that the right strategy is chosen and the appropriate investments are made.[25] Furthermore, it should be noted that, contrary to most high-tech pharmaceutical industry–sponsored research, LMICs themselves may be the greatest beneficiaries of this type of investment.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. Epub 2021 Feb 4.
2. Loree JM, Anand S, Dasari A, et al. Disparity of race reporting and representation in clinical trials leading to cancer drug approvals from 2008 to 2018. JAMA Oncol. 2019;5:e191870.
3. U.S. Food and Drug Administration. Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents. Accessed on February 8, 2021.
4. Perel P, Miranda JJ, Ortiz Z, et al. Relation between the global burden of disease and randomized clinical trials conducted in Latin America published in the five leading medical journals. PLoS One. 2008;3:e1696.
5. WHO Expert Committee. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, the use of essential drugs. Sixth report of the WHO expert committee, WHO technical report series. Geneva, Switzerland: World Health Organization; 1995.
6. National Institutes of Health. ClinicalTrials.gov. www.clinicaltrials.gov. Accessed December 29, 2020.
7. Røttingen J-A, Regmi S, Eide M, et al. Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? Lancet. 2013;382:1286-1307.
8. Barrios CH, Werutsky G, Martinez-Mesa G. The global conduct of cancer clinical trials: challenges and opportunities. Am Soc Clin Oncol Educ Book. 2015;35:e132-e139.
9. Good Clinical Practice Network. ICH harmonised guideline integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) ICH Consensus Guideline. https://ichgcp.net/. Accessed February 8, 2021.
10. World Health Organization. Access to Medicines and Health Products. http://www.who.int/medicines/areas/access/Improving-affordabilityeffectiveness-of-cancer-medicines/en/. Accessed February 8, 2021.
11. Ehrhardt S, Appel LJ, Meinert CL. Trends in National Institutes of Health funding for clinical trials registered in. JAMA. 2015;314:2566-2567.
12. NCI Office of Budget and Finance. National Cancer Institute. https://www.cancer.gov/about-nci/organization/obf. Accessed February 8, 2021.
13. ASCO. Meeting Library. meetinglibrary.asco.org. Accessed January 30, 2021.
14. Vandross A, Prasad V, Mailankody S. ASCO plenary sessions: impact, legacy, future. Semin Oncol. 2016;43:321-326.
15. D'Cruz AK, Vaish R, Kapre N, et al; Head and Neck Disease Management Group. Elective versus therapeutic neck dissection in node-negative oral cancer. N Engl J Med. 2015;373:521-529.
16. Shastri SS, Mittra I, Mishra GA, et al. Effect of visual inspection with acetic acid (VIA) screening by primary health workers on cervical cancer mortality: a cluster randomized controlled trial in Mumbai, India. J Natl Cancer Inst. 2014;106:dju009.
17. UIS Statistics - UNESCO. Institute for Statistics. http://data.uis.unesco.org. Accessed February 6, 2021.

18. Veronesi U, Saccozzi R, Del Vecchio M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med. 1981;305:6-11.

19. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347:1227-1232.

20. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst. 2002;94:1143-1150.

21. Yarnold J, Ashton A, Bliss J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. Radiother Oncol. 2005;75:9-17.

22. Alemayehu C, Mitchell G, Nikles J. Barriers for conducting clinical trials in developing countries: a systematic review. Int J Equity Health. 2018;17:37.

23. Maluf F, Schutz FA, Cronemberger EH, et al. Phase II randomized study of abiraterone acetate plus prednisone added to ADT versus apalutamide alone vs AAP+APA in patients with advanced prostate cancer: LACOG 0415. J Clin Oncol. 2020;38:15s (suppl; abstr 5505).

24. Koh WJ, Anderson BO, Carlson RW. NCCN resource-stratified and harmonized guidelines: a paradigm for optimizing global cancer care. Cancer. 2020;126(suppl 10):2416-2423.

25. Mano MS. Pathologic response at the epicenter of the treatment decision-making process in human epidermal receptor-type 2 overexpressing (Her2+) early breast cancer (EBC): challenges and opportunities for financially-constrained healthcare systems. Breast. 2020;54:331-334.

GLOBAL HEALTH

Overcoming Barriers to Clinical Trials Cooperation: The Breast International Group Example

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Overview

Clinical trials cooperation is not a luxury; it is a necessity, now more than ever, first in light of the segmentation of tumors according to their molecular targets—which are being matched to an increasing number of competitive drugs—and second because it is the only chance to maintain academic research centered on addressing patients' needs. In its 21 years of existence, the Breast International Group, an umbrella organization supporting the activities of 54 member groups across six continents, has been confronted with challenges that include (1) keeping trust and motivation within the network; (2) improving the interface between academia and industry; (3) improving patient involvement and trust in clinical trials; and (4) fundraising for noncommercial research. We describe how these challenges have been addressed so far, with the hope of empowering the next generation of clinical investigators.

The great progress in the management of cancer is linked, to a large extent, to decades of sustained commitment to randomized clinical trials. The landscape of clinical research, however, has undergone drastic changes since the turn of the century: on one hand, the broad access to next-generation sequencing technologies has revealed the genomic complexity of tumors, which are now segmented according to their molecular targets, against which new drugs are being developed in an exponential fashion; on the other hand, the dramatic increase in clinical trial bureaucracy and complexity has contributed to rising costs, which are strangling noncommercial research.

It is in this climate that the Breast International Group (BIG) was created in 1999 as an umbrella organization harnessing the efforts and supporting the activities of numerous national and international collaborative groups and trial data centers worldwide conducting breast cancer research (Figs. 1 and 2).

Its aims were to reinvigorate academic involvement in practice-changing clinical trials, avoid duplication of efforts, and accelerate the delivery of innovative therapies to patients with common but also with rare breast cancer subtypes.

In its 21 years of existence, BIG has been confronted with a number of challenges. Here we describe how we attempted to solve them, with the hope of providing a useful roadmap for the next generation of clinical investigators who are interested in the setup and the running of umbrella networks of cooperative groups.

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KEEPING TRUST AND MOTIVATION WITHIN THE NETWORK

The longevity of an umbrella network of cooperative groups depends on several pillars, illustrated in Fig. 3.

Agreeing on the vision and mission of the collaboration is the first building block to be constructed. BIG's vision is to cure breast cancer through global research and collaboration, while its mission is to facilitate breast cancer research internationally and to do so by enabling groups to do more than their individual parts while agreeing on specific research principles that will preserve academic freedom. All studies are developed with substantial input from and control by BIG investigators, even when partnering with the pharmaceutical industry, and aim to answer potentially practice-changing clinical questions essential for improving and saving the lives of patients with breast cancer.

Irrespective of sponsorship and funding models, BIG's scientific independence from industry must be preserved, a principle that has been increasingly challenged nowadays, as discussed in the next section.

Although the vision raises immediate enthusiasm from partners, the long-term adherence to the mission requires demonstrating the added value brought by the network to the clinical trial enterprise. In the case of BIG, it is the HERA trial that cemented its member groups together 20 years ago and helped to convince the most skeptical ones: the recruitment of more than 5,000 patients with a relatively uncommon breast

PRACTICAL APPLICATIONS

- The Breast International Group is one example of clinical trials cooperation involving a large network of national and international collaborative groups with the goal to accelerate the delivery of innovative therapies to patients with breast cancer and to reinvigorate academic leadership in breast cancer clinical cancer research.
- Keeping trust and motivation within such a large umbrella network is the first challenge to be overcome, with solutions including agreement on the vision and mission of the collaboration, rotation of leadership roles within the network, recognition of the contribution of all involved, reinforced cross-talk between the regions represented, and willingness to solve conflicts as they arise.
- The Breast International Group implemented an alternative partnership model with the pharmaceutical industry for the conduct of pivotal adjuvant breast cancer trials; it is an attempt to build on the strengths of the two worlds in the best interests of patients. Examples of how conflicts emerging along this journey can be solved are provided.
- Although the Breast International Group is starting to involve patients more closely in its scientific agenda, it is also the guardian of a not-for-profit research enterprise on the academic side, as this is an absolute requirement for keeping patients' trust in clinical trials.
- Fundraising can be part of the solution for the conduct of noncommercial trials, but it is particularly challenging for international research initiatives.

cancer subtype—namely, HER2-positive breast cancer—was accomplished in fewer than 3 years across Europe, North America, Latin America, and Australasia. This was rapidly followed by the European Medicines Agency's endorsement of the life-saving drug trastuzumab, an achievement that was unmatched at the time.

Rotating Leadership Roles Within the Network

The centralization of most clinical trial functions within one data center specialized in breast cancer was the model used for HERA and several other subsequent pivotal trials (such as APHINITY), with a rapid learning curve about how best to organize the clinical trial machinery and respond to the industry's needs. However, a single model of collaboration cannot be the only one used by the umbrella network; it will nourish frustrations and progressively demotivate cooperative group members, which themselves are competent in running clinical trials.

For this reason, BIG developed the collaborative "colead" model, in which tasks and responsibilities linked to the clinical trial are shared between two or three member groups (for example, one group is responsible for the clinical trial database, another for the statistical analyses, and a third for the translational research). The fine-tuning of this model is still ongoing, as clearly defining roles and responsibilities to avoid overlap and duplication of efforts among the study partners may sometimes be challenging. This requires a basis of trust and regular and open communication between the partners.

Recognizing the Contributions of All Those Involved

Although day-to-day problems during the trial's conduct are best tackled by a small joint study management team, all clinical research groups must have a feeling of ownership of the clinical trial they participate in. This is achieved in three ways: establishing a representative clinical trial steering committee, which for BIG trials can be very large (up to 55 people); producing a periodic clinical trial newsletter; and allocating authorship on the clinical trial related to publications.

Because academic promotions still heavily depend on peer-reviewed publications, this last point should never be neglected and requires a great deal of time and diplomacy in allocating authorship positions on papers with transparency and fairness. In BIG's experience, it is quite helpful to discuss authorship positions early on, with a distribution agreed upon for at least the two main publications, namely the ones related to the primary and secondary endpoints. Revisions can always be introduced based on the true merit of the partners. BIG also avoids redundancy in the allocation of the most prominent authorship positions (namely, the first and last authors must be different from one publication to the other).

Facilitating Involvement Across Regions

BIG began as a largely European network but was quickly found to be attractive by cooperative groups in other regions of the world, such as Latin America and Asia. With their patient recruitment, these groups have contributed substantially to the successful and rapid recruitment to many of BIG's largest adjuvant trials. Nevertheless, there has been an inherent European bias in much of BIG's research, which the network has also tried to address. With Latin American groups, for example, the BIG Executive Board and the Latin American cooperative group members organized a retreat in Brazil with the aim of understanding the local challenges of each group, discussing common concerns, and determining areas of highest need to facilitate participation in international clinical trials or the conduct of collaborative

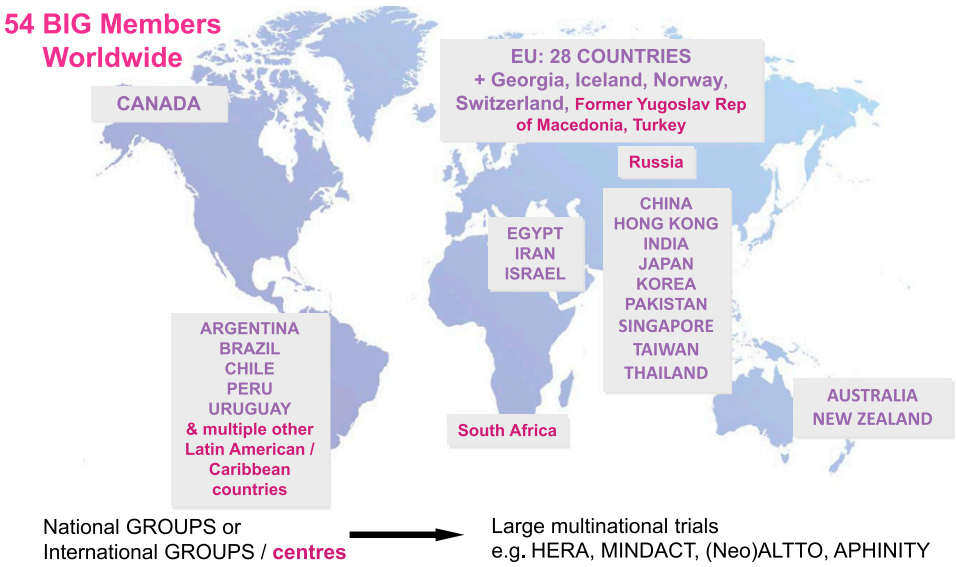

FIGURE 1. Who Is in the Breast International Group?

research important for the region. This led to a training program for young investigators identified as the groups' future leaders. A similar initiative has been ongoing with some of the Asian cooperative groups in BIG, with the aim to mentor a young generation of researchers to lead future breast cancer trials across multiple Asian countries, or even more broadly under the BIG umbrella.

Solving Conflicts As They Arise

Conflicts between group leaders within the network cannot be avoided, but ignoring them can be highly detrimental to the network and compromise its survival. The network headquarters plays an essential role in resolving such conflicts, as do officers of the Executive Board, who oversee the global collaboration and understand that this is also part of their responsibilities.

IMPROVING THE INTERFACE BETWEEN ACADEMIA AND INDUSTRY

Although generating trust among partners of an umbrella organization takes time, it is a slowly growing construction that in principle is there to stay. The same cannot be said about building trust between the academic network and the pharmaceutical industry; indeed, the rapid turnover of leaders in the pharmaceutical industry implies that one must be prepared to constantly renew efforts to create the best possible synergies between the two worlds. There is also very little room for mistakes on the part of academia: bad news disseminates much faster than good news.

Although many studies under the BIG umbrella are purely academic, many of BIG's most well-known trials have involved pharmaceutical partners that have also served as study sponsors. Figure 4 highlights all the critical pieces one must bring together for a successful partnership between these two worlds. This puzzle applies to any type of cooperative group trial run in collaboration with industry, but it comes with some added layers of complexity for an umbrella network. Negotiating this complexity means that trial initiation may be slightly slower, but fortunately this is compensated by the significant acceleration in patient recruitment, which in most cases is successfully completed long before the projected timelines.

Study Design, Statistical Plan, and Finalization of the Protocol

These critical and essential initial steps require a mutual understanding of the sometimes-divergent interests of the two worlds and talent for negotiating compromise. There is no doubt that the pharmaceutical industry's role in clinical research is fundamental. Although companies today are trying to do their best for patients, the fact that they must generate profit for their shareholders results understandably in their preference for clinical trial designs that bring greater and faster returns on investment and may be more likely to result in a positive outcome.

Academia has no such limitations and therefore it plays a key role as the guardian of patients' interests when it comes to assessing the burden of treatment, studying long-term side effects, or identifying early on the specific populations for whom therapies will be ineffective. As long as governments leave the financial risks of pivotal trials entirely in the hands of the pharmaceutical industry, academia will be in a weak position to defend, for example, shorter duration treatment arms. But with the support of a very large network of cooperative groups, the negotiation can sometimes be successful, as was the case for the design of the BIG1-98 trial, in which academia managed to include two arms of sequential adjuvant endocrine therapies

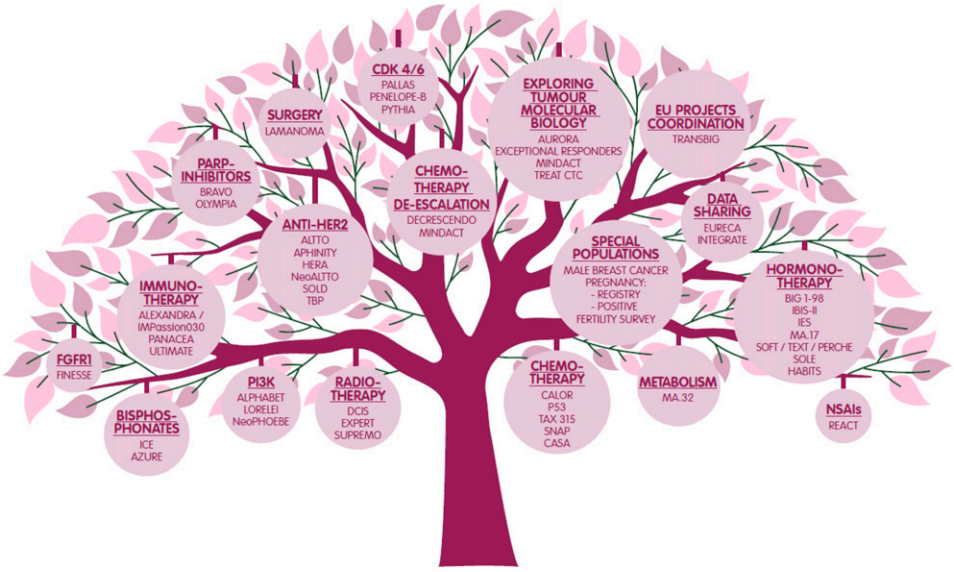

FIGURE 2. Past and Ongoing Breast International Group Clinical Trials and Research Programs

(tamoxifen/letrozole or the reverse) in the study design initially set out to include only two single-drug arms (tamoxifen or letrozole) selected by the industry partner. In BIG's experience, close collaboration with pharmaceutical partners to develop the statistical plan and finalize the protocol jointly is the best way to start building a strong partnership.

Selection of Countries and Sites

In an ideal world, any cooperative group from the network should be able to join the trial, if interested. Unfortunately, this is rarely the case, as the cost of clinical research in oncology is considerable, and the approval process for clinical trials can be very complicated in some countries. Therefore, pharmaceutical industry partners, based on prior experience, logistical issues, or budget constraints, will make the final decisions about which countries can participate.

Contract

It should be noted that in BIG trials, the sponsor may be either the industry partner, or one of the network's cooperative groups. When a pharmaceutical company is involved in a study, either as a sponsor or as the entity providing the funding, a clear contract between academia and the industry partner is an essential building block for successful collaboration, but it can take many months—in some cases, more than 1 year—to agree on the model of collaboration, the distribution of tasks, the timelines, the budget, and, last but not least, the intellectual property rights.

When conducting clinical studies with BIG, the industry partner first needs to accept BIG's principles of research conduct, which are nonnegotiable:

- BIG does not function as a contract research organization, nor does it carry out studies solely conceived by industry. All studies are developed and conducted with substantial input from BIG investigators and leadership and aim to answer potentially practice-changing clinical questions essential for improving and saving the lives of patients with breast cancer.
- The main study (clinical) database is managed by one of the academic partners involved in the study. Industry partners may access the full trial study data only after the release of the study results.
- All statistical analyses and study reports related to a BIG study are executed or supervised by one or more academic statisticians.
- The study steering committee is representative of the groups and centers participating in the study. Industry collaborators may be represented on the steering committee, but neither hold the majority of seats, nor have the power of veto. However, the steering committee may not take decisions that have a major impact on the study budget, timelines, or the sponsor's ability to be compliant with legal requirements.

In consideration of the importance of long-term efficacy and safety evaluations, BIG strongly endorses the long-term follow-up of patients participating in clinical studies. The length of the follow-up is an element that can trigger negotiations with many industry partners, who may not want to commit to this, unless the study has a positive outcome for their drug.

In terms of intellectual property rights, BIG accepts that all intellectual property rights related to the drug under development by the industry partner, as well as biomarkers linked to its use, will be attributed to them. However, a lot of

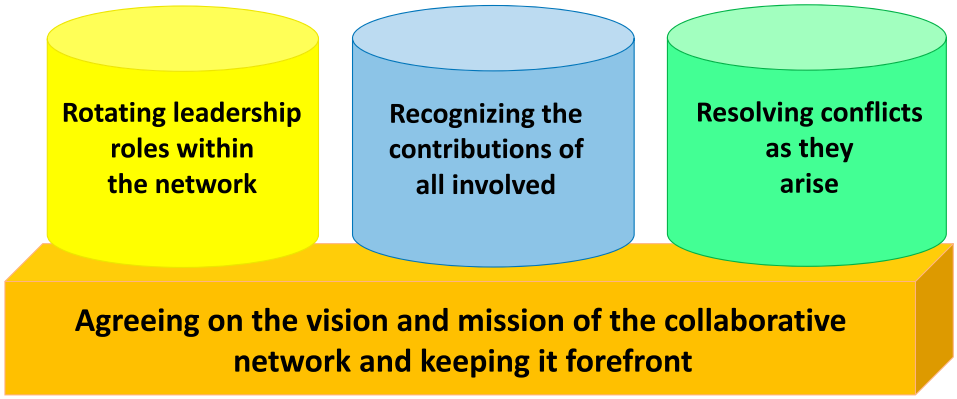

FIGURE 3. Keeping Trust and Motivation Within the Clinical Research Network

time is spent on negotiating intellectual property rights that may be generated by the future research conducted by investigators using the study data and biologic materials to which patients have consented, beyond the objectives of the study, and that is not funded by the industry partner. BIG acknowledges that industry partners should obtain freedom to operate with their study drug, but a return to an inventor for new discoveries not related to the drug is also appropriate. Unfortunately, some industry partners do not agree with this, which can be a blocking factor for further research.

Many barriers along the path toward an agreement between the legal teams can be overcome through regular teleconferences—and, whenever necessary and feasible, face-to-face meetings—involving the parties, rather than emails. When blocking points are identified, early escalation to the individuals with decision-making authority on both sides is often the best solution, with all partners and lawyers attending the meeting.

How to Ensure Smooth Trial Conduct and Adherence to the Protocol

An efficient way to identify and solve problems as they arise during the trial setup and conduct is to establish a joint study management team early on, with representatives from both the pharmaceutical industry and academic partners holding regular virtual meetings. This provides the industry partner with the reassurance that issues that may affect the quality of the data will be tackled from the beginning.

Study monitoring is also implemented with this goal: in BIG's experience, site monitoring can be conducted in part or

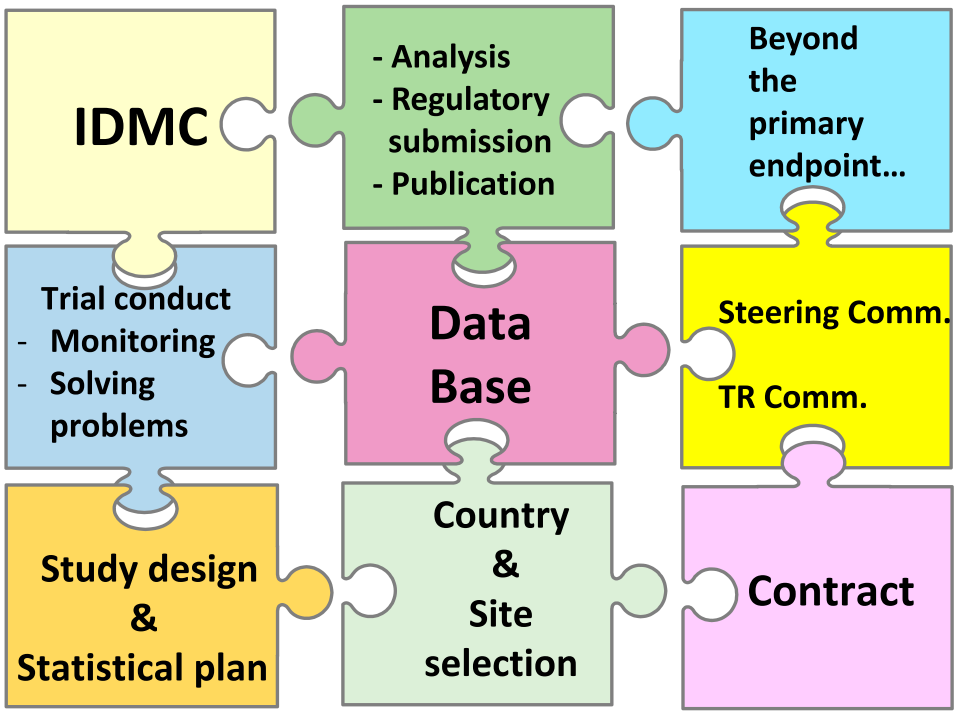

FIGURE 4. Improving the Interface Between Academia and Pharmaceutical Partners

exclusively by industry partners; however, involvement of the cooperative groups in the site monitoring whenever this is feasible seems to be of great value, because it usually results in a better spirit of collaboration with the participating hospitals. As for the central monitoring of the study and associated monitoring plan, supervision by academia is necessary.

Handling the Clinical Trial Database

In recent years, there has been an increasing push by the pharmaceutical industry to exert greater control over clinical trial data, eroding academic leadership. In such scenarios, the latter is confined to the role of "member of the trial steering committee," which is set up by the industry and consulted periodically for advice. The control of the trial database is lost; it is put in the hands of the pharmaceutical industry, often outsourced to a contract research organization. In this scenario, academic investigators' involvement in overseeing the database is only theoretical, as is their involvement in the data analysis. They may provide input on the study results they receive, as well as on related presentations and publications, but are unable to exert their expertise in a scientifically independent way.

BIG continues to defend the old model of partnering with pharmaceutical partners, which requires substantial involvement from the academic cooperative groups and their leaders, but secures a higher degree of scientific independence, and in principle can contribute to a better balance between commercial and public health interests (Fig. 5). Of note, in this model, all the responsibilities of a company related to safety reporting and preparation for the regulatory submissions are respected; safety data are transferred to the sponsor real-time, as needed, and all the necessary actions to ensure timely submission of the data to the regulatory authorities are agreed between the academic partners and the company during the setup of the study.

Steering Committee and Translational Research Committee

Recognition of all the partners involved in the trial is vital, and it materializes through the setting up of a trial steering committee, which will also allocate seats to the pharmaceutical partner.

With the increasing complexity of tools that are being used in translational research, BIG often favors the creation of a parallel translational research committee of experts with hands-on experience using these tools and who are in charge of recommending the best possible use of the precious patients' biologic specimens collected in the trial. The final decision-making, however, resides with the steering committee.

It should be noted that, because translational research committee members are selected based on their specific expertise and personal track record, and because pharmaceutical companies employ individuals with strong translational research expertise, the translational research committee also involves company scientists.

These committees can become poorly functional when their—often overly extended—members cannot commit the time needed to move things forward efficiently. It is therefore recommended to have a policy in place to replace nonperforming members whenever necessary. Finally, interest from investigators can decrease markedly after the publication of the primary endpoint, and the formation of a smaller steering committee comprising the members most committed to the study is recommended at that point.

Independent Data Monitoring Committee

The independent data monitoring of clinical trials has long been recognized as essential for the protection of patients, and it is the task of a small group of individuals who have clinical trial experience but who neither participate in the

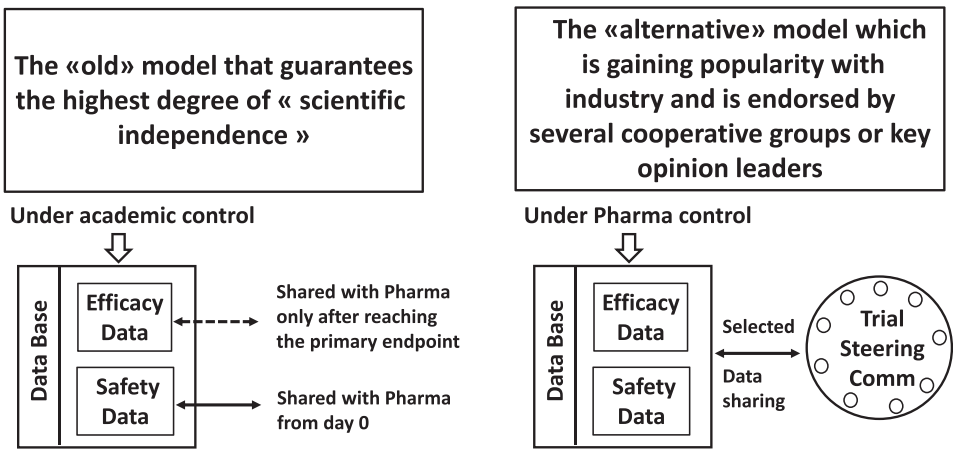

FIGURE 5. Variations of the Partnership Model Between Industry and Academia

trial nor are representatives of the sponsor. Independent data monitoring committees always involve an independent statistician and often a patient representative.

For the conduct of one of BIG's very large registration trials conducted with a pharmaceutical partner, BIG encountered a new challenge. Based on apparently past negative experiences with a poorly functional independent data monitoring committee, the partner requested the creation of an interface committee. The role of this entity is to examine independent data monitoring committee recommendations and decide whether they should be adopted; this decision is then forwarded to the trial steering committee for final decision. The rationale for the creation of this committee, as presented to the academic partners, was that regulatory authorities have expressed concerns that clinical studies may be biased if clinical investigators (i.e., steering committee members or the study partner teams managing the study) are made aware of independent data monitoring committee recommendations that are not eventually adopted and that may, unintentionally, convey unblinded information. For non-BIG studies sponsored by this company, the interface committee only consists of representatives from the company. In the case of the BIG study mentioned, a tough negotiation ensued, with the final agreement being that this new entity would be composed of an equal number of representatives from the company and the academic partners (3+3) but would be chaired by an additional member, a statistician not employed by the sponsor. The same principle was applied for other BIG studies sponsored by the same company.

Analysis, Regulatory Submission, and Publication

There will be no challenges to overcome here if three conditions are fulfilled: (1) the statistical plan was jointly prepared by the academic and the pharmaceutical partner statisticians; (2) the company had the opportunity to test the database to prepare its registration file by accessing the full data of a small segment of the trial population; (3) the list of coauthors of the publication has been discussed and agreed upon long in advance.

Beyond the Primary Endpoint

Considering the importance of long-term efficacy and safety evaluations, BIG strongly endorses the long-term follow-up of patients participating in its randomized clinical trials, particularly trials run in the early disease setting. However, securing this long-term follow-up is very challenging nowadays. Pharmaceutical companies, being under considerable pressure today in a highly competitive environment, often lose interest in a trial after obtaining the new drug registration and prioritize investment in other diseases or other studies.

The two potential solutions here are

(1) to negotiate a reasonable budget to secure long-term follow-up as part of the main contract; or

(2) to turn to patient-reported outcomes with the use of digital tools to capture worrisome side effects as well as late relapses or secondary cancers.

Data sharing in the era of General Data Protection Regulation can also be a challenge. For example, the definition of identifiable data is rather broad and can include restrictive conditions on data sharing within the European Union and even more outside the European Union, where different data protection standards apply. Although we understand that the aim of General Data Protection Regulation is to protect patients' data protection rights, data sharing is very important for progress in science because it maximizes the potential for scientists from around the world to make new discoveries. We believe that legislators and researchers should engage in dialogue to develop a privacy framework that is better suited for clinical and translational research.

Tremendous knowledge can be gathered through clinical data sharing—as already exemplified by the impressive work of the Early Breast Cancer Trial Cooperative Group in the last 30 years—but the time has also come to share biomarker data linked to clinical data, as this will be the driving force in the transition toward truly personalized oncology. Therefore, conditioning such data sharing on the requirements of General Data Protection Regulation may ultimately come at a cost of patient access to better treatments.

IMPROVING PATIENT INVOLVEMENT AND PATIENT TRUST IN CLINICAL TRIALS

As stated by one of our most vocal patient representatives,[1] "Greatness in medical research is measured in lives well lived, not in articles published or honors received." How can we make sure that our clinical research is relevant to patients? The answer is clear: by involving them more closely, but how we involve them is not straightforward. Once again, this involves an interface between different worlds, and the relationship takes time and effort to build.

One essential building block, besides offering training in clinical research, is to define expectations on both sides. This was done through a recent initiative of BIG—joined by the North American Breast Cancer Group—where a brainstorming meeting involving patients took place on the theme of adjuvant treatment de-escalation, and resulted in the writing of a consensus paper to which patients greatly contributed.[2]

Patients should be on the board in trial committees, and they can be of great help in improving informed consent forms as well as communicating trial results to the external world. Moreover, over time, as the relationship builds, they should be present at the same table with the leadership of academic research networks to contribute to strategic decision-making.

A more delicate issue is the one related to conflicts of interest, which may jeopardize the patient's best interests.[3] The conflicts of interest of pharmaceutical companies are clear and known to the public; they must ensure a reasonable return on investment in a challenging environment characterized by more demanding regulatory procedures, diminished market exclusivity, and progressively smaller markets resulting from the rapidly increasing molecular segmentation of the cancer population.

Academia, for many years, has faced conflicts of interest in the form of the "publish or perish" principle, which encourages financial relationships with pharmaceutical companies allowing the conduct of or the participation in clinical trials. More recently, another source of conflicts of interest has emerged that is less transparent to the public: this is the setting-up of for-profit academic research groups. Although the legislative and fiscal context in some countries may lead some cooperative groups to decide to operate under a for-profit structure, two scenarios should be differentiated here: the for-profit academic research group that re-invests all the profit in a foundation to suppor noncommercial trials and to secure the sustainability of the group, and the for-profit academic research group that distributes the profit among its members, research staff, or shareholders.

BIG considers the second scenario noncompatible with the spirit of truly academic research and potentially risky for patients, and calls for greater transparency in declaring this new research model, which is inappropriately named "academic."

FUNDRAISING

As noncommercial research is under threat nowadays, some cooperative groups have created separate foundations to help raise funds for patient-centered trials of no interest to the pharmaceutical industry, or they have established philanthropy units within their existing legal structures, which is the case with BIG. Fundraising for an international organization like BIG is not straightforward. When BIG's Executive Board decided to establish a unit within its headquarters in late 2012, it was aware that this effort would require several years of investment, primarily in fundraising staff, before seeing any returns.

In the meantime, BIG has been greatly helped by the substantial financial support it has received from the Breast Cancer Research Foundation for the conduct of its ambitious academic research program on metastatic breast cancer, called AURORA. Once a BIG fundraising team was on board, decisions had to be made about how to engage well beyond BIG's hitherto purely scientific public and make BIG's work both visible and tangible to a lay audience. A first step was to rebrand BIG with a new logo, incorporating graphic elements and colors symbolic of BIG's vision to cure breast cancer through global research and collaboration. A new name to complement BIG's formal, legal denotation used for all research activities (Breast International Group) was also created for all philanthropic activities: *BIG against breast cancer*. Purely academic studies requiring support were identified, and the challenge of writing compelling cases for support began. Fundraisers for research must appeal to the emotion of potential donors and explain study objectives in simple terms, but doing this in a way that does not distort the research being conducted or inappropriately raise expectations about outcomes is not always easy. In parallel, the strategy implemented first focused on potential major donors and organizing gala events, but gradually expanded to include establishing corporate partnerships, seeking grant opportunities from a range of foundations, and building a broad base of supporters through social media and targeted communications campaigns. Another challenge is that although donors should see the impact of their donations on a local level, BIG's trials are international, and thus funds raised should not in principle be restricted geographically, as long as they support costs such as patient enrollment or other legitimate study costs. Moreover, crossing borders to raise funds means potentially coming into conflict with national research groups, and thus such initiatives are only feasible if working in close collaboration with them and when a common and relevant local story can be told. Finally, many real funding needs are related to the human research infrastructure required to facilitate the international research process (for example, at BIG's headquarters), but this is much less tangible, and attractive, than investing in a new hospital machine. Despite these challenges, and with the help of an enthusiastic group of ambassadors, after 4 years, the funds raised versus costs of supporting a philanthropic unit within BIG reached the break-even point, and, during subsequent years, the level of funds raised annually increased substantially. Notwithstanding the COVID-19 pandemic and its significant impact on the ability to raise funds in 2020, the expectation is that with patience, persistence, and creativity, *BIG against breast cancer* will continue to provide a steady stream of funding for the network's purely academic trials.

AFFILIATIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_321475.

REFERENCES

1. Ryll B. From good to great: what patients can do for your medical research. Nat Med. 2020;26:1508.
2. Piccart MJ, Hilbers FS, Bliss JM, et al; BIG-NABCG Collaboration. Road map to safe and well-designed de-escalation trials of systemic adjuvant therapy for solid tumors. J Clin Oncol. 2020;38:4120-4129.
3. Piccart M, Goldhirsch A, Wood W, et al. Keeping faith with trial volunteers. Nature. 2007;446:137-138.

GLOBAL HEALTH

Supportive Care: Low Cost, High Value

Razvan Andrei Popescu, MD, MRCP(UK)[1]; Fausto Roila, MD[2]; Jann Arends, MD[3]; Giulio Metro, MD[2]; and Maryam Lustberg, MD, MPH[4]

Overview

Supportive care aims to prevent and manage adverse effects of cancer and its treatment across the entire disease continuum. Research and clinical experience in dedicated centers have demonstrated that early appropriate supportive care interventions improve symptoms, quality of life, and overall survival in a cost-effective manner. The challenge is to assess symptoms and needs with validated tools regularly and, ideally, between clinic appointments; electronic patient-reported outcome measures and dedicated easily accessible supportive care units can help. As management of certain problems improves, others come to the fore. Cancer-related fatigue and malnutrition are very frequent and need regular screening, assessment of treatable causes, and early intervention to improve. Pharmacologic agents and phytopharmaceuticals are of little use, but other interventions are valuable: physical exercise, counseling on fatigue, and cognitive behavioral therapy/mind-body interventions (e.g., for fatigue). Nutrition should be oral, rich in proteins, and accompanied by muscle training adapted to the patient's condition. Psychological and societal counseling is often useful; nausea or other problems such as gastrointestinal dysmotility or metabolic derangements must be tackled. Chemotherapy-induced peripheral neuropathy frequently worsens quality of life and has no established prevention strategy (notwithstanding current interest in cryotherapy and compression therapy) and thus requires careful assessment of patient predisposition to develop it with the consideration of feasible dose and treatment alternatives. When painful, duloxetine helps. Nonpharmacologic strategies, including acupuncture, physical exercise, cryotherapy/compression, and scrambler therapy, are promising but require large phase III trials to become the accepted standard. Personalization of chemotherapy, dependent on realistic goals, is key.

EARLY AND APPROPRIATE INTEGRATION OF SUPPORTIVE CARE IN TREATMENT OF PATIENTS WITH CANCER

The Multinational Association of Supportive Care in Cancer definition of supportive care highlights "the prevention and management of the adverse effects of cancer and its treatment. This includes management of physical and psychological symptoms and side effects across the continuum of the cancer experience from diagnosis through treatment to post-treatment care. Enhancing rehabilitation, secondary cancer prevention, survivorship, and end-of-life care are integral to supportive care."[1] In 2012, ASCO was the first oncology society to publish a clinical opinion on integration of palliative care in oncology, to then update and establish it,[2] and to develop a global resource-stratified guideline.[3] The European Society for Medical Oncology (ESMO) has also stated in 2014 that oncologists should be committed to preserving the quality of life of patients with cancer through the entire "cancer journey," including optimal supportive care.[4] In a more recent position paper on supportive and palliative care,[5] ESMO has suggested that the term "patient-centered care" be used to cover both supportive and palliative care approaches during the continuum of cancer illness, with regular multidisciplinary team assessments of patients' needs, which vary and evolve over time. Multiple possible assessments and interventions tailored to cancer-related symptoms and toxicities of anticancer treatments are listed, including appropriate prevention and training goals agreed in the ESMO/ASCO curriculum.

A cancer pandemic has been triggered by the COVID-19 crisis, leading to delayed diagnoses and initiations of treatment that will have a staggering cost in human lives.[6] Thus far not quantified is the impact of the COVID-19 pandemic on quality of treatment and supportive care for patients with cancer. New barriers to access to cancer specialists, clinics, and hospitals, perceived or real, mean that many patients may have unnecessary symptoms caused by disease or toxicity of oncologic treatments. Unfortunately, this comes at a time when it has been established beyond doubt that appropriate timely supportive care interventions improve symptom burden, performance status, overall management costs, and survival.

Basch et al[7] used electronic patient-reported outcome measures systematically to monitor patients' symptoms and to detect problems earlier. Through early intervention, this led to improved symptom management, decreased symptom severity and number of hospitalizations or emergency room visits, and increased survival, probably through more time on effective therapy.[8]

Author affiliations and support information (if applicable) appear at the end of this article.

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PRACTICAL APPLICATIONS

- The "cancer pandemic" caused by the COVID-19 crisis raised obstacles for patients to be treated in a timely fashion but also to reach appropriate and early supportive care.
- Regular symptoms-monitoring using digital patient-reported outcome measures or dedicated supportive care units facilitating information access and management of symptoms will improve symptom burden, performance status, overall management costs, and survival.
- Cancer-related fatigue is among the most distressing issues for patients with cancer and should be approached mainly with non-pharmacologic interventions.
- Nausea and other risks of malnutrition require close attention and multiprofessional care.
- Neuropathy symptoms must be monitored, and dose reductions/modifications should be considered based on functional status.

Concurrently, patients with lung cancer after initial treatment were randomly assigned in five French centers[9] to either receive routine clinical and CT scan follow-up or web-guided follow-up. In this latter group, weekly patient-scored symptoms triggered an alert when predefined criteria were met. In the experimental arm, progression was spotted earlier, and performance status had not yet significantly deteriorated in a higher proportion of patients who were thus able to receive optimal treatment, leading to a 7-month improvement in overall survival that increased with longer follow-up.[10]

VARIOUS MODELS OF EARLY SUPPORTIVE CARE IMPLEMENTATION HAVE BEEN DEVELOPED

One strategy is regular digital monitoring and management of symptoms and needs using regular electronic patient-reported outcome measures, as pioneered by the above-discussed trials, with data being evaluated by the cancer professionals treating the patients, often primarily led by experienced nurses.[11] This approach has the advantage of picking up deteriorations in overall well-being between scheduled clinic visits and potentially predicting toxicity, with high patient and health care provider satisfaction with improved workflow in oncology units and time savings by reduction of phone calls and emergency visits.[12] Modern digital health monitoring apps allow both an overview of all patients in the program within the last week (Fig. 1) and of symptoms development in given patients over time. Given the wide availability of smartphones, even in low-income countries in which primary care structures may be weak and access to specialist care constrained, such follow-up strategies, possibly automated, may greatly improve outcomes.

Another strategy developed in many cancer centers worldwide is the establishment of ambulatory and inpatient supportive care units that grant patients low-barrier access to expertise in supportive care while at the same time minimizing disruption to acute oncology clinics. The Multinational Association of Supportive Care in Cancer has begun to certify centers of excellence in supportive care in cancer that apply this principle to optimize supportive care along the whole disease trajectory.[13]

Finally, successful models of supportive care implementation are promoted by national supportive care societies, such as those of France (Association Francophone des Soins Oncologiques de Support), Italy (Network Italiano Cure di Supporto in Oncologia), Russia (Russian Society of Supportive Care in Oncology), India (Indian Association of Supportive Care in Cancer), and Japan (Japanese Association of Supportive Care in Cancer). In the United Kingdom, the "enhanced supportive care" program initiated by Dr. Richard Berman, consultant in palliative care at the Christie Hospital, was so successful regarding earlier referral of patients with supportive care needs, improved symptom control, improved quality of life, improved overall survival, and reduced health care costs that the National Health Service in the United Kingdom supported its implementation in 21 cancer centers across the United Kingdom.[14] The key steps in achieving this feat in the United Kingdom are summarized in this guidance document.[15]

As availability and quality of supportive and palliative care have improved, there have been vast shifts in symptoms and toxicities most feared by patients and their families.[16] A classic example is the fear of vomiting with highly emetogenic chemotherapy; this was once a nearly universal occurrence. Advances in understanding emesis mechanisms, an early report,[17] and rigorous trials that established 5-HT3 antagonists as standard in nausea and vomiting led to recognition of this supportive care breakthrough as one of ASCO's top five advances in 50 years.[18] Incorporation of neurokinin 1 receptor antagonists and olanzapine in strategies to optimize antiemetic efficacy[19] has further improved nausea and vomiting control, the latter drug also being cheap and widely available. However, adherence to guidelines for prevention of nausea and vomiting is still low in certain settings,[20] and nonadherence is associated with avoidable acute health care use and costs.[21]

High-quality guidelines exist for most supportive care topics. Table 1[2,3,22-44] provides an overview of selected guidelines, as well as the ASCO guidelines (www.asco.org/research-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues%20), ESMO guidelines (www.esmo.org/guidelines/supportive-and-palliative-care), and National

FIGURE 1. Bird's-Eye View of Symptoms for Patients Replying to a Chemotherapy Questionnaire in the Last 2 Weeks
Symptoms are sorted by ascending fatigue severity. Each line represents a patient, and each column represents a symptom.

Comprehensive Cancer Network recommendations (www.nccn.org/professionals/physician_gls/default.aspx#supportive).

This 2021 ASCO Annual Meeting educational session this article is based on will further focus on three major symptoms that are leading current symptoms and toxicities lists and on where appropriate intervention (or refraining from therapies with unproven benefit) may greatly improve the well-being of patients with cancer.

EXHAUSTED: DEALING WITH FATIGUE

Cancer-related fatigue is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment. Cancer-related fatigue is not proportional to recent physical activity and interferes with usual functioning. In comparison with the fatigue experienced by healthy individuals, fatigue related to cancer is seldom alleviated by rest or sleep.[24,26,45]

Cancer-related fatigue is reported by 60% to 65% of patients and can occur at any time for patients with cancer, before, during, and even long after the completion of antineoplastic treatment. Cancer-related fatigue occurs in up to 40% of patients at diagnosis, 80% and 90% of patients during chemotherapy and radiotherapy, respectively, and

TABLE 1. Overview of Selected Supportive Care Guidelines From ASCO, the European Society for Medical Oncology, the Multinational Association of Supportive Care in Cancer, and the European Society for Clinical Nutrition and Metabolism

Symptom/Toxicity	ASCO [First Author, Reference (Year)]	ESMO [First Author, Reference (Year)]	MASCC [First Author, Reference (Year)]	General Recommendations
Nausea and vomiting	Hesketh et al[22] (2020)	Roila et al[23] (2016)	Roila et al[23] (2016)	Determine prevention and rescue options for antiemetics based on emetogenic potential of agent, alleviate fear and pain, and advise on sensible food choices
Nutrition/cancer/cachexia	Bower et al[24] (2014)		Arends et al[25] (2017)	Screen regularly, offer dietary counseling, avoid routine enteral/parenteral feeding; insufficient evidence to strongly endorse pharmacologic interventions
Fatigue	Bower et al[24] (2014)	Fabi et al[26] (2020)		Screen regularly, promising nonpharmacologic interventions
Neuropathy	Loprinzi et al[27] (2020)	Jordan et al[28] (2020)		No prevention strategy; duloxetine only proven pharmacologic strategy
Mucositis		Peterson et al[29] (2011)	Elad et al[30] (2020)	Routine oral care, oral cryotherapy, recombinant human keratinocyte growth factor-1 (KGF-1/palifermin), and low-level laser therapy
Immune adverse events	Brahmer et al[31] (2018)	Haanen et al[32] (2017)	Rapoport et al[33] (2020)	Close monitoring and multidisciplinary management of toxicities are needed
Febrile neutropenia	Taplitz et al[34] (2018)	de Naurois et al[35] (2010)	MASCC[36] (2021)	Early antibiotics, MASCC Cancer Index for outpatient treatment
Growth factors	Smith et al[37] (2015) Bohlius et al[38] (2019)	Aapro et al[39] (2018)		Prophylactic use to reduce the risk is warranted when the risk of febrile neutropenia is approximately 20%
Diarrhea	Benson et al[40] (2004)	Bossi et al[41] (2018)		Early intervention with fluids and loperamide; aggressive interventions, including testing for infection and antibiotics
Bone health/medication-related osteonecrosis of the jaw	Yarom et al[42] (2019)	Coleman et al[43] (2014)	Yarom et al[42] (2019)	Preventive care, treatment with antimicrobial mouth rinses, antibiotics, and conservative surgical interventions
Vulnerable populations: older adults	Mohile et al[44] (2018)			Geriatric assessment for patients older than age 65 to inform recommendations for treatment
Palliative care in the global setting	Osman et al[3] (2018)			Standards for psychosocial support, spiritual support, and pain management
Integration of palliative care into oncology setting	Ferrell et al[2] (2017)			Inpatients and outpatients with advanced cancer should receive early access to palliative care

Abbreviations: ESMO, European Society for Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer.

in approximately 30% to 35% of patients in the post-treatment phase.

Possible causes of cancer-related fatigue are 5-HT neurotransmitter dysregulation, vagal afferent activation, alterations in muscle and ATP metabolism, hypothalamic-pituitary-adrenal axis dysfunction, circadian rhythm disruption, and cytokine dysregulation.[46]

All patients with cancer should be routinely screened for the presence and severity of fatigue at their first visit and then during therapy and approximately every year in the post-treatment phase. Screening should be done using brief and validated tools with established cutoff values for severity, such as the Numerical Rating Scale and the Brief Fatigue Inventory, which integrate the assessment of fatigue severity and its impact on important functional domains. For patients who test positive for cancer-related fatigue (values of Numerical Rating Scale > 3, indicating moderate to severe fatigue), it is necessary to identify treatable contributing factors (e.g., anemia, pain, sleep dysfunction, weight loss, concomitant medications such as opioids, and type of anticancer therapies) and comorbid conditions (e.g., endocrinopathies; cardiopulmonary disorders; hepatic, renal, and neurologic dysfunctions). To do this, oncologists should address the fatigue history, perform a physical examination, evaluate the status of the malignant disease and psychological status of the patient, and ask for a minimum battery of laboratory tests.[26]

If patients refer with mild fatigue (Numerical Rating Scale ≤ 3), not interfering with activities of daily living, patients can be reassured and counseled about strategies for coping with fatigue (physical activity and energy conservation). If patients refer with moderate/severe fatigue (Numerical Rating Scale > 3) interfering with activities of daily living, the factors that contribute to cancer-related fatigue should be identified and, whenever possible, treated. Management of cancer-related fatigue can benefit from both pharmacologic and nonpharmacologic interventions.

Several randomized, double-blind, placebo-controlled studies have been carried out to evaluate the fatigue effects of various pharmacologic, phytopharmaceutic, and nutraceutic interventions. At the present time, no pharmacologic treatment has been approved by the U.S. Food and Drug Administration for the management of cancer-related fatigue.

Psychostimulants have been evaluated in 19 randomized controlled trials (11 with methylphenidate and dexmethylphenidate, four with modafinil, three with armodafinil, and one with dexamphetamine). In 15 of these trials, no superiority with respect to placebo was demonstrated, whereas four studies showed less fatigue with methylphenidate. As a result, more well-conducted studies are still necessary to define the role of psychostimulants.

Antidepressants were studied in three double-blind controlled studies (two using paroxetine and one sertraline) of patients with fatigue submitted to chemotherapy and did not demonstrate superiority with respect to placebo.

The acetylcholinesterase inhibitor donepezil was not superior to placebo in controlling fatigue.

Two double-blind studies with corticosteroids (one with dexamethasone and one with methylprednisolone administered for 7–14 days) have been carried out with patients with end-stage cancer and demonstrated superiority with respect to placebo.

Eszopiclone, a sedative hypnotic drug, and the progestinic agent megestrol acetate have not yet shown enough evidence to be recommended for cancer-related fatigue treatment.

In conclusion, all studied drugs evaluated for cancer-related fatigue, with the exception of dexamethasone and methylprednisolone for patients with terminal cancer, yielded negative results.

There is not enough evidence to support the use of either phytopharmaceutics such as American or Wisconsin ginseng (*Panax quinquefolius*) or Asian ginseng (*Panax ginseng*), guarana, mistletoe (*Viscum album*), or astragalus or nutraceutic agents such as L-carnitine, coenzyme Q_{10}, melatonin, or taurine for the management of cancer-related fatigue. In one study, Wisconsin ginseng was superior to placebo, but this study enrolled a very heterogenous cancer population (different neoplasms and different stages of disease).

Nonpharmacologic interventions have been carefully studied. The role of physical exercise for patients with cancer-related fatigue during and after active cancer treatment has been documented by multiple systematic reviews and meta-analyses. Some guidelines encourage 150 minutes of moderate aerobic exercise per week, such as fast walking, cycling, or swimming, with an additional 2 to 3 days of strength training per week, such as weightlifting, unless contraindicated (e.g., extensive lytic bone metastases, fever, or active infection).

Psychosocial interventions (e.g., information on cancer-related fatigue, its potential causes, and contributing factors) should be offered to patients with cancer. Counseling can help patients cope with fatigue (recommendations about physical activity, energy preservation, and how to delegate less important activities). Psychoeducation may be helpful for patients to identify sources of psychosocial distress and eliminate stress-producing activities whenever possible. Cognitive behavioral therapy has been demonstrated to decrease cancer-related fatigue, addressing the following factors: coping with the experience of cancer, fear

of disease recurrence, dysfunctional thoughts and beliefs regarding fatigue, sleep dysregulation, and so on.

Mindfulness-based clinical interventions combine meditation exercises with psychoeducational elements, cognitive-behavioral interventions, and movement exercises. Mindfulness-based clinical interventions in oncology demonstrated some benefits in the management of cancer-related fatigue for patients after treatment.

A Cochrane review evaluating 24 studies carried out with patients with breast cancer showed that yoga reduced cancer-related fatigue compared with no therapy. This has been confirmed recently by a systematic review including 29 randomized controlled trials. Finally, a randomized clinical trial conducted in 410 survivors of cancer showed a significant effect of yoga on cancer-related fatigue.

Several randomized controlled trials have been carried out to evaluate acupuncture for the control of cancer-related fatigue. Recently, a meta-analysis of 10 randomized clinical trials including 1,327 patients who have completed cancer treatment showed that acupuncture reduced cancer-related fatigue.

The following other mind-body interventions may offer some benefit against cancer-related fatigue, although additional studies, particularly of patients after cancer treatment, are needed: biofield therapies (touch therapy), massage, music therapy, relaxation, moxibustion (applications of heat of burning herbs on the skin), reiki, and qigong (traditional Chinese energy exercises and therapies).

NUTRITION AND NAUSEA

Weight loss occurs frequently during anticancer treatments and impacts quality of life, completion of therapies, and risk of complications. For many patients with advanced cancer, ongoing weight loss and accelerated catabolism lead to malnutrition (weight loss $>$ 5%), sarcopenia (low muscle mass, below the fifth percentile of healthy reference), and cachexia (disease-related malnutrition [i.e., weight loss worsened by activated systemic inflammation]),[47,48] with negative effects on quality of life, activities of daily living, and overall prognosis. Nausea may exhaust patients during anticancer treatment and during advanced disease, restricting quality of life and body resources.

Best supportive care regarding nutrition requires (1) early identification of patients at risk, performed most reliably using validated screening tools; (2) careful diagnosis of relevant impairments, best performed as professional assessment by trained experts; and (3) individualized targeted supportive care aiming to abolish or at least diminish symptomatic and prognostically unfavorable deficits.[25,49]

All patients with cancer should be screened every 3 to 6 months, if with stable disease, or else more frequently for the risk or presence of malnutrition. A number of validated brief questionnaire tools are available (Numerical Rating Scale 2002, Malnutrition Universal Screening Tool, Malnutrition Screening Tool, Short Nutritional Assessment Questionnaire, etc.)[50]; it is less important which tool to choose than to reliably screen all patients. Most screening tools ask for the presence of weight loss, impaired food intake, and a feeling of sickness. Further expert assessment should ask diligently for nutritional impact symptoms impairing food intake; quantify body resources (body weight and, if possible, body composition [e.g., by anthropometry, bioelectrical impedance, or CT if available]); estimate food (including protein) intake; define gastrointestinal deficits and metabolic derangements such as systemic inflammation; determine the physical activity level; and, finally, screen for the presence of chronic pain and for psychological and social distress.[25]

While designing and preparing for nutritional care, if required, expert support should be invited from gastroenterology, surgery, pain specialists, psychologists, and social workers. The first goal of nutritional care should be to enable the patient to eat normally or, if this is not possible, to offer dietary counseling to allow adequate feeding by implementing changes in food selection, food texture, meal frequency, guidance on choosing high-energy, high-protein foods, enriching foods (e.g., by adding fat/oils, protein powder), and use of oral nutritional supplements. If these measures prove inadequate, tube feeding should be offered if the lower gastrointestinal tract is working; otherwise, parenteral nutrition is the method of choice. Separate routes of feeding may be combined for optimal effect. Nutritional requirements depend on age, sex, physical activity, disease-associated metabolic rate, and other factors, but in general may be assumed as a first approximation to be per kilogram body weight and day: energy, 25 to 30 kcal; water, 30 to 40 mL; protein, 1.2 to 1.5 g; carbohydrates, 3 to 4 g; fat, 1 to 1.5 g. In tube feeding and parenteral nutrition, requirements of electrolytes, vitamins, and trace elements must be supplied daily.[25]

To antagonize catabolism of body proteins in general and muscle mass in particular, nutritional interventions for patients who are catabolic and cachectic should ensure an adequate provision of proteins (see earlier) and should always be accompanied by muscle training, best guided by a physiotherapist or exercise physiologist. Physical exercise is known to mediate anabolic and anti-inflammatory effects. In addition, to attenuate systemic inflammation, every effort should be made to prevent and rapidly treat bouts of infection, use surgical techniques minimizing metabolic stress, avoid and effectively treat all wounds, and, given the presently not clearly defined benefit-risk ratios, prudently consider symptomatic anti-inflammatory agents (e.g., corticosteroids, nonsteroidal anti-inflammatory drugs, or long-chain *n*-3 fatty acids/fish oil).[25] Several pharmacologic agents are being studied to enhance appetite, stimulate protein anabolism,

and dampen systemic inflammatory activity; the growth hormone receptor analog and appetite stimulant anamorelin recently has been approved for use in cancer cachexia in Japan,[51] whereas none of the other experimental agents have reached approval yet.

Nausea may be induced by pharmacologic agents (e.g., opioids, chemotherapy agents) and other toxins, gastrointestinal motility disorders (e.g., obstruction, stenosis, paresis), stomatitis, [hypo]pharyngeal disorders or esophagitis (e.g., radiation injury, thrush), metabolic derangements (hypercalcemia, uremia), and raised intracranial pressure (e.g., brain metastases).[52] Nausea may also result indirectly from pain, fear, or other serious psychological stressors. Fear and stress should be alleviated, and all settings that might possibly induce nausea via sight or odor should be avoided. In cases of exulcerated wounds, small bowls may be positioned (filled with coffee powder, lemon, or mint). Prevention and treatment of chemotherapy-induced nausea and vomiting should follow standard guideline recommendations, including the structured use of dexamethasone, serotonin/5-HT3 inhibitors, and the neurokinin 1 antagonist aprepitant.[22] In the palliative setting, the following agents are recommended as single agents: butyrophenones (droperidol and haloperidol) in low doses for metabolic/toxic causes; metoclopramide or domperidone for gastroparesis; diphenhydramine in case of brain metastases or in cases of accompanying hypersalivation or diarrhea; phenothiazines (promethazine, levomepromazine) are effective but should be limited to very low doses because of side effects of dizziness and sedation; and corticosteroids are effective especially in cases of brain metastases. Escalation may be achieved by combining butyrophenones and metoclopramide or metoclopramide and phenothiazines. Finally, serotonin antagonists may be added.[52] If all these efforts fail, agents may be applied intravenously with separate infusion of fluids and nutrients. A percutaneous endoscopic gastrostomy may be inserted to drain gastric fluids, and gastrointestinal secretions may be reduced effectively by parenteral somatostatin or analogs.[53]

Nutritional guidance should include conveying the importance of adequate drinking to replace fluid losses, loose clothing, keeping the head elevated, getting distracted by reading or other media, trying to carefully warm the belly, and using ginger (fresh, tea, or other).[54] Examples of practical knowledge include chewing well and slowly and drinking slowly, chewing some dry bread before rising from bed, preferring several small to few large meals, trying warm broth, preferring simple foods with few ingredients to facilitate detection of incompatibilities or aversions, preferring light foods and steaming to roasting, and trying soft foods, possibly puréed; oatmeal gruel may be helpful, as may be bitter vegetables (e.g., endive, radicchio). Fatty and spicy foods, foods with a strong aroma or smell, and flatulent foods (e.g., cabbage, legumes, onions) are best avoided.

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Chemotherapy-induced peripheral neuropathy (CIPN) is among the most common adverse effects of chemotherapy. Symptoms can include pain, tingling, numbness, and increased temperature sensitivity. The chemotherapeutic agents most commonly associated with CIPN include paclitaxel and oxaliplatin, although this toxicity is reported with a variety of other agents, including other taxanes (docetaxel) and platinum agents (cisplatin and carboplatin), vinca alkaloids (particularly vincristine), thalidomide, carfilzomib, and bortezomib. Chemotherapy-induced peripheral neuropathy poses a global health burden worldwide; it negatively impacts survivors of cancer by reducing dose intensity of cancer treatments, can cause permanent functional impairments, and adversely affects quality of life and well-being.

The biologic mechanisms underlying neurotoxic injury that lead to clinical symptoms of CIPN are multifactorial and include inflammatory, apoptotic, and neurodegenerative pathways.[55,56] Despite the extensive research effort focused on understanding mechanisms involved in the development of CIPN, the translation of this mechanistic understanding into rationally designed, clinical intervention studies remains problematic and limited in scope.[27,28,57]

While we await improved biologic insights into CIPN, clinicians and patients continue to grapple with how to best manage this very common toxicity. The clinical prevention and management of CIPN has a number of knowledge gaps. Two recent clinical guidelines from ASCO and ESMO appraised most of these gaps.[27] According to the most recent 2020 ASCO CIPN guideline,[27] no agents can be recommended for the prevention of CIPN because of lack of high-quality evidence in general, which remains unchanged since the initial 2014 guideline. The ASCO guideline also supports duloxetine as the sole treatment option for established painful CIPN. There are insufficient data for the use of tricyclic antidepressants, gabapentinoids, or topical amitriptyline/ketamine/baclofen for treatment of CIPN, although these agents are used commonly in routine clinical practice. ESMO–European Oncology Nursing Society–European Association of Neuro-Oncology 2020 guidelines,[28] which characterized the level of evidence for the different CIPN strategies, were in agreement with ASCO and included detailed adjudication of the levels of evidence for the different strategies that are used, including various pharmacologic and nonpharmacologic approaches.

Therefore, in light of these limited levels of evidence for management of CIPN, what are patients and clinicians to do to manage this very common toxicity? One of the most important considerations includes the evaluation of fitness

for neurotoxic chemotherapy, including the presence of other comorbidities such as preexisting neuropathy, diabetes, or family hereditary neuropathy.[58] For older patients, a comprehensive geriatric assessment can evaluate the likelihood of chemotherapy's causing harm.[44] Clinicians and patients are encouraged to review together goals of care, and, if appropriate, substitution of non- or less neurotoxic regimens can be considered.

The oncology field has also recognized that there is a need to adapt the maximum tolerated dose of chemotherapy to an optimal patient-centered dose. Per ASCO 2020 guidelines, clinicians should assess and discuss with patients the appropriateness of dose delays and dose reductions for patients who are symptomatic from CIPN.[27] Dose modifications and prescription of drugs at lowest dose that produced the maximum biologic effect have been the subject of active discussion within the field and can lead to significant cost-savings and decreased toxicity.

An additional high-yield strategy for management of CIPN is to actually avoid interventions that have been shown to be of no benefit or even detrimental. For example, although the supplement industry actively markets a variety of supplements to patients undergoing cancer treatment, not one single supplement has been shown to be beneficial for the prevention or treatment of CIPN.[27] Hence, there are insufficient data to recommend any supplement per both ESMO and ASCO guidelines, and these should not be recommended as part of routine oncologic care for prevention of CIPN.[27,28]

There is currently increasing interest in nonpharmacologic strategies for prevention or treatment of CIPN because of promising early-phase studies and better tolerability. However, phase III evidence of benefit for these approaches, including acupuncture, physical exercise, cryotherapy/compression, and scrambler therapy, is not yet available, and larger clinical trials are needed to better delineate their utility.

Several studies have evaluated acupuncture therapy as a nonpharmacologic option for CIPN. One small randomized, sham-controlled trial of weekly electro-acupuncture for the prevention of taxane-induced peripheral neuropathy did not show any differences in neuropathy between groups.[59] A recent randomized controlled trial comparing 8-week acupuncture intervention with usual care led to clinically meaningful and statistically significant improvements in neuropathic sensory symptoms in survivors of breast cancer with mild and moderate CIPN.[58] Additional larger studies are needed to confirm the effect of acupuncture therapy on CIPN.

In recent years, the efficacy of cryotherapy and compression therapy to prevent taxane-induced peripheral neuropathy has been investigated by several groups. Several clinical trials also revealed that compression therapy using surgical gloves is a safe and potentially effective therapy for the amelioration of CIPN.[60,61] However, a recent study compared the efficacy of cryotherapy and compression therapy for CIPN and found no difference in incidence of CIPN using either cryotherapy or compression therapy.[62] Additional trials are ongoing to evaluate the benefits of cryotherapy, compression therapy, and/or cryo-compression therapy for prevention of CIPN.[63]

Another emerging approach is scrambler therapy for treatment of CIPN. Scrambler therapy is a cutaneous neurostimulatory treatment for the management of chronic pain syndromes and for the management of CIPN.[64] A recent randomized phase II pilot trial was conducted to evaluate the effect of scrambler therapy for treating CIPN.[65] Compared with transcutaneous electrical nerve stimulation, scrambler therapy showed at least a 50% documented improvement for patients. To confirm the effect of scrambler therapy on treatment of CIPN, larger, sham-controlled, double-blinded clinical trials are needed.

Several studies have suggested that exercise may be beneficial for other types of peripheral neuropathy. Physical exercise may attenuate CIPN through its influence on blood circulation/oxidative stress, inflammation, neurotransmitters, endogenous opioids, growth factors, neuroplasticity, and coping and symptom interaction mechanisms.[66] Several studies have shown promise in CIPN.[67-69] Additional primary studies are being planned.

Considering the debilitating consequences of CIPN on quality of life, it is imperative that shared decision-making and patient-reported outcomes are evaluated in making treatment decisions and treatment modifications for toxicity. The future development of improved, efficient intervention strategies for CIPN requires collaborative strategies that involve a multidisciplinary team of experienced pharmacologists, statisticians, and oncologists, partnered with patients.

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REFERENCES

1. Multinational Association of Supportive Care in Cancer. What is supportive care? https://www.mascc.org/about-mascc. Accessed February 7, 2021.
2. Ferrell BR, Temel JS, Temin S, et al. Integration of palliative care into standard oncology care: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2017;35:96-112.
3. Osman H, Shrestha S, Temin S, et al. Palliative care in the global setting: ASCO Resource-Stratified Practice Guideline. J Glob Oncol. 2018;4:1-24.
4. Popescu RA, Schäfer R, Califano R, et al. The current and future role of the medical oncologist in the professional care for cancer patients: a position paper by the European Society for Medical Oncology (ESMO). Ann Oncol. 2014;25:9-15.
5. Jordan K, Aapro M, Kaasa S, et al. European Society for Medical Oncology (ESMO) position paper on supportive and palliative care. Ann Oncol. 2018;29:36-43.
6. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ. 2020;371:m4087.
7. Basch E, Deal AM, Kris MG, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: A randomized controlled trial [published correction appears in *J Clin Oncol*. 2016;34:2198]. J Clin Oncol. 2016;34:557-565.
8. Basch E, Deal AM, Dueck AC, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA. 2017;318:197-198.
9. Denis F, Lethrosne C, Pourel N, et al. Randomized trial comparing a web-mediated follow-up with routine surveillance in lung cancer patients [published correction appears in *J Natl Cancer Inst*. 2018;110:436]. J Natl Cancer Inst. 2017;109:1-8.
10. Denis F, Basch E, Septans AL, et al. Two-year survival comparing web-based symptom monitoring vs routine surveillance following treatment for lung cancer. JAMA. 2019;321:306-307.
11. Mooney KH, Beck SL, Wong B, et al. Automated home monitoring and management of patient-reported symptoms during chemotherapy: results of the symptom care at home RCT. Cancer Med. 2017;6:537-546.
12. Schmalz O, Jacob C, Ammann J, et al. Digital monitoring and management of patients with advanced or metastatic non-small cell lung cancer treated with cancer immunotherapy and its impact on quality of clinical care: interview and survey study among health care professionals and patients. J Med Internet Res. 2020;22:e18655.
13. Multinational Association of Supportive Care in Cancer. MASCC Designated Centers of Excellence in Supportive Care in Cancer. https://www.mascc.org/mascc-designated-centers-of-excellence-in-supportive-care-in-cancer. Accessed December 7, 2020.
14. National Health Service. Thousands of cancer patients to benefit from early supportive care. https://www.england.nhs.uk/2016/07/early-supportive-care/. Accessed March 4, 2021.
15. National Health Service. Enhanced supportive care integrating supportive care in oncology. https://www.england.nhs.uk/wp-content/uploads/2016/03/ca1-enhncd-supprtv-care-guid.pdf. Accessed March 4, 2021.
16. Carelle N, Piotto E, Bellanger A, et al. Changing patient perceptions of the side effects of cancer chemotherapy. Cancer. 2002;95:155-163.
17. Leibundgut U, Lancranjan I. First results with ICS 205-930 (5-ht3 receptor antagonist) in prevention of chemotherapy-induced emesis. Lancet. 1987;329:P1198.
18. Goldberg K. ASCO 50th anniversary poll names the top 5 advances from the past 50 years. https://www.asco.org/about-asco/press-center/news-releases/asco-50th-anniversary-poll-names-top-5-advances-past-50-years. Accessed March 4, 2021.
19. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update [published correction appears in J Clin Oncol. 2018;361459]. J Clin Oncol. 2017;35:3240-3261.
20. Roeland EJ, Ruddy KJ, LeBlanc TW, et al. What the HEC? Clinician adherence to evidence-based antiemetic prophylaxis for highly emetogenic chemotherapy. J Natl Compr Canc Netw. 2020;18:676-681.
21. Navari RM, Ruddy KJ, LeBlanc TW, et al. Avoidable acute care use associated with nausea and vomiting among patients receiving highly emetogenic chemotherapy or oxaliplatin. Oncologist. Epub 2020 Dec 1.
22. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO Guideline Update [published corrections appear in *J Clin Oncol*. 2020;38:3825 and 2021;39:96]. J Clin Oncol. 2020;38:2782-2797.
23. Roila F, Molassiotis A, Herrstedt J, et al; Participants of the MASCC/ESMO Consensus Conference Copenhagen 2015. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol. 2016;27(Suppl 5):v119-v133.
24. Bower JE, Bak K, Berger A, et al; American Society of Clinical Oncology. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical Oncology Clinical Practice Guideline Adaptation. J Clin Oncol. 2014;32:1840-1850.
25. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36:11-48.

26. Fabi A, Bhargava R, Fatigoni S, et al; ESMO Guidelines Committee. Cancer-related fatigue: ESMO Clinical Practice Guidelines for diagnosis and treatment. Ann Oncol. 2020;31:713-723.
27. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO Guideline Update. J Clin Oncol. 2020;38:3325-3348.
28. Jordan B, Margulies A, Cardoso F, et al; EANO Guideline Committee. Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO-EONS-EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up. Ann Oncol. 2020;31:1306-1319.
29. Peterson DE, Bensadoun RJ, Roila F; ESMO Guidelines Working Group. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. Ann Oncol. 2011;22(Suppl 6):vi78-vi84.
30. Elad S, Cheng KKF, Lalla RV, et al; Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2020; 126:4423-4431.
31. Brahmer JR, Lacchetti C, Schneider BJ, et al; National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36:1714-1768.
32. Haanen JBAG, Carbonnel F, Robert C, et al; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(Suppl 4):iv119-iv142.
33. Rapoport BL, Anderson R, Cooksley T, et al. MASCC 2020 recommendations for the management of immune-related adverse events of patients undergoing treatment with immune checkpoint inhibitors. Support Care Cancer. 2020;28:6107-6110.
34. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol. 2018;36:1443-1453.
35. de Naurois J, Novitzky-Basso I, Gill MJ, et al; ESMO Guidelines Working Group. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Ann Oncol. 2010;21(Suppl 5):v252-v256.
36. Multinational Association of Supportive Care in Cancer. Identifying Patients at Low Risk for Febrile Neutropenia Complications. https://www.mascc.org/mascc-fn-risk-index-score. Accessed February 10, 2021.
37. Smith TJ, Bohlke K, Lyman GH, et al; American Society of Clinical Oncology. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33:3199-3212.
38. Bohlius J, Bohlke K, Castelli R, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH Clinical Practice Guideline Update. J Clin Oncol. 2019;37:1336-1351.
39. Aapro M, Beguin Y, Bokemeyer C, et al. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29:iv96-iv110.
40. Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol. 2004;22:2918-2926.
41. Bossi P, Antonuzzo A, Cherny NI, et al. Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29:iv126-iv142.
42. Yarom N, Shapiro CL, Peterson DE, et al. Medication-related osteonecrosis of the jaw: MASCC/ISOO/ASCO Clinical Practice Guideline. J Clin Oncol. 2019; 37:2270-2290.
43. Coleman R, Body JJ, Aapro M, et al; ESMO Guidelines Working Group. Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2014; 25(Suppl 3):iii124-iii137.
44. Mohile SG, Dale W, Somerfield MR, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018;36:2326-2347.
45. Berger AM, Mooney K, Aranha O, et al. NCCN Guidelines version 1.2021, cancer-related fatigue. https://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf. Accessed March 4, 2021.
46. Ryan JL, Carroll JK, Ryan EP, et al. Mechanisms of cancer-related fatigue. Oncologist. 2007;12(Suppl 1):22-34.
47. Cederholm T, Jensen GL, Correia MITD, et al; GLIM Working Group. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. Clin Nutr. 2019;38:1-9.
48. Jensen GL, Mirtallo J, Compher C, et al; International Consensus Guideline Committee. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. JPEN J Parenter Enteral Nutr. 2010;34:156-159.
49. Arends J. Struggling with nutrition in patients with advanced cancer: nutrition and nourishment—focusing on metabolism and supportive care. Ann Oncol. 2018; 29:ii27-ii34.
50. van Bokhorst-de van der Schueren MA, Guaitoli PR, Jansma EP, et al. Nutrition screening tools: does one size fit all? A systematic review of screening tools for the hospital setting. Clin Nutr. 2014;33:39-58.
51. Wakabayashi H, Arai H, Inui A. The regulatory approval of anamorelin for treatment of cachexia in patients with non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer in Japan: facts and numbers. J Cachexia Sarcopenia Muscle. 2021;12:14-16.
52. Singh P, Yoon SS, Kuo B. Nausea: a review of pathophysiology and therapeutics. Ther Adv Gastroenterol. 2016;9:98-112.
53. Naeim A, Dy SM, Lorenz KA, et al. Evidence-based recommendations for cancer nausea and vomiting. J Clin Oncol. 2008;26:3903-3910.
54. American Cancer Society. Managing nausea and vomiting at home. https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/nausea-and-vomiting/nausea-and-vomiting.html. Accessed February 8, 2021.

55. Chan A, Hertz DL, Morales M, et al. Biological predictors of chemotherapy-induced peripheral neuropathy (CIPN): MASCC neurological complications working group overview. Supportive Care Cancer. 2019;27:3729-3737.

56. Hu S, Huang KM, Adams EJ, et al. Recent developments of novel pharmacologic therapeutics for prevention of chemotherapy-induced peripheral neuropathy. Clin Cancer Res. 2019;25:6295-6301.

57. St. Germain DC, O'Mara AM, Robinson JL, et al. Chemotherapy-induced peripheral neuropathy: Identifying the research gaps and associated changes to clinical trial design. Cancer. 2020;126:4602-4613.

58. Lu W, Giobbie-Hurder A, Freedman RA, et al. Acupuncture for chemotherapy-induced peripheral neuropathy in breast cancer survivors: a randomized controlled pilot trial. Oncologist. 2020;25:310-318.

59. Greenlee H, Crew KD, Capodice J, et al. Randomized sham-controlled pilot trial of weekly electro-acupuncture for the prevention of taxane-induced peripheral neuropathy in women with early stage breast cancer. Breast Cancer Res Treat. 2016;156:453-464.

60. Tsuyuki S, Senda N, Kanng Y, et al. Evaluation of the effect of compression therapy using surgical gloves on nanoparticle albumin-bound paclitaxel-induced peripheral neuropathy: a phase II multicenter study by the Kamigata Breast Cancer Study Group. Breast Cancer Res Treat. 2016;160:61-67.

61. Tsuyuki S, Yamagami K, Yoshibayashi H, et al. Effectiveness and safety of surgical glove compression therapy as a prophylactic method against nanoparticle albumin-bound-paclitaxel-induced peripheral neuropathy. Breast. 2019;47:22-27.

62. Kanbayashi Y, Sakaguchi K, Ishikawa T, et al. Comparison of the efficacy of cryotherapy and compression therapy for preventing nanoparticle albumin-bound paclitaxel-induced peripheral neuropathy: A prospective self-controlled trial. Breast. 2020;49:219-224.

63. Loprinzi CL, Lustberg MB, Hershman DL, et al. Chemotherapy-induced peripheral neuropathy: ice, compression, both, or neither? Ann Oncol. 2020;31:P5-P6.

64. Pachman DR, Weisbrod BL, Seisler DK, et al. Pilot evaluation of Scrambler therapy for the treatment of chemotherapy-induced peripheral neuropathy. Support Care Cancer. 2015;23:943-951.

65. Loprinzi C, Le-Rademacher JG, Majithia N, et al. Scrambler therapy for chemotherapy neuropathy: a randomized phase II pilot trial. Support Care Cancer. 2020; 28:1183-1197.

66. Kanzawa-Lee GA, Larson JL, Resnicow K, et al. Exercise effects on chemotherapy-induced peripheral neuropathy: a comprehensive integrative review. Cancer Nursing. 2019;43:E172-E185.

67. Kleckner IR, Kamen C, Gewandter JS, et al. Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: a multicenter, randomized controlled trial. Support Care Cancer. 2018;26:1019-1028.

68. Streckmann F, Zopf EM, Lehmann HC, et al. Exercise intervention studies in patients with peripheral neuropathy: a systematic review. Sports Med (Auckland, NZ). 2014;44:1289-1304.

69. van Waart H, Stuiver MM, van Harten WH, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: Results of the PACES randomized clinical trial. J Clin Oncol. 2015; 33:1918-1927.

GYNECOLOGIC CANCER

Expanding Our Impact in Cervical Cancer Treatment: Novel Immunotherapies, Radiation Innovations, and Consideration of Rare Histologies

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overview

Cervical cancer is a socially and scientifically distinguishable disease. Its pathogenesis, sexual transmission of high-risk HPV to a metaplastic portion of the uterine cervix, makes cervical cancer preventable by safe and effective HPV vaccines commercially available since 2006. Despite this, cervical cancer remains the deadliest gynecologic cancer in the world. Regrettably, global incidence and mortality rates disproportionately affect populations where women are marginalized, where HIV infection is endemic, and where access to preventive vaccination and screening for preinvasive disease are limited. In the United States, cervical cancer incidence has gradually declined over the last 25 years, but mortality rates remain both constant and disparately higher among communities of color because of the adverse roles that racism and poverty play in outcome. Until these conditions improve and widespread prevention is possible, treatment innovations are warranted. The last standard-of-care treatment changes occurred in 1999 for locally advanced disease and in 2014 for metastatic and recurrent disease. The viral and immunologic nature of HPV-induced cervical cancer creates opportunities for both radiation and immunotherapy to improve outcomes. With the advent of T cell–directed therapy, immune checkpoint inhibition, and techniques to increase the therapeutic window of radiation treatment, an overdue wave of innovation is currently emerging in cervical cancer treatment. The purpose of this review is to describe the contemporary developmental therapeutic landscape for cervical cancer that applies to most tumors and to discuss notable rare histologic subtypes that will not be adequately addressed with these treatment innovations.

Cervical cancer is nearly 99% attributable to HPV infection, whereby HPV subtypes 16 and 18 are responsible for more than 70% of all cases. Effective preventive vaccines have been commercially available since 2006, but because of low uptake and poor access, cervical cancer remains the leading cause of gynecologic cancer death worldwide.[1] The United States has lower incidence and mortality rates with 13,800 and 4,290 annual cases, respectively,[2] largely because of pap and HPV screening programs and treatment of preinvasive disease. Cervical cancer treatment recommendations are based on stage at diagnosis and, in some cases, plans for future childbearing. Patients with early-stage disease (International Federation of Gynecology and Obstetrics IA-IB2 and IIA1[3]) are candidates for curative-intent surgery inclusive of radical hysterectomy and pelvic lymphadenectomy, with or without adjuvant radiation and with or without chemotherapy.[4,5] Some women with tumors 2 cm or smaller and disease localized to the cervix are candidates for fertility-sparing radical trachelectomy with utero-vaginal reconstruction.[6,7]

Locally advanced disease (International Federation of Gynecology and Obstetrics stages IB3-IIIA and IVA[3]) is treated with a combination of external beam radiotherapy with concurrent low-dose radiosensitizing cisplatin followed by intracavitary brachytherapy; this treatment has a 3-year overall survival rate of approximately 67%. Cervical cancer that is metastatic at presentation or is recurrent or persistent following chemoradiotherapy is generally incurable but controllable with systemic platinum, paclitaxel, and bevacizumab in the first line.[8] Second-line treatment and beyond is an area of high unmet medical need where the sole U.S. Food and Drug Administration–approved agent is pembrolizumab under the accelerated approval mechanism and limited to PD-L1^{+} tumors. The relative success of bevacizumab in 2014 and of pembrolizumab in 2018 are driving further development of antiangiogenic and immune-oncology agents in the spaces of the highest unmet needs: locally advanced and metastatic recurrent or persistent disease.

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PRACTICAL APPLICATIONS

- Cervical cancer is associated with profound socioeconomic, sex, and racial disparities in incidence, mortality, and clinical trial participation.
- Preventive vaccination and screening and treatment of preinvasive disease remain key to cervical cancer control but are inconsistently adopted and not widely accessible.
- Immune checkpoint inhibitors are changing the landscape of cervical cancer clinical trials in all lines of therapy, with one accelerated regulatory approval in the United States to date.
- Innovations in radiation delivery and in choices of radiosensitizing agents are improving the therapeutic window of curative-intent pelvic radiotherapy.
- Rare histologies, such as adenocarcinoma and neuroendocrine tumors, are biologically distinct from squamous cell carcinoma and may benefit from alternative targeted therapies. However, their rarity is a barrier to systematically improving outcomes given the challenges of conducting pivotal trials in rare patient populations.

THE EMERGING ROLE OF IMMUNOTHERAPY IN MANAGEMENT OF CERVICAL CANCER

Although most cervical HPV infections are cleared by a robust immune response, establishment of a latent infection with eventual integration of the genes expressing viral oncogenic proteins (predominantly E6 and E7) leads to cellular transformation and ultimate cancer development. Integrated HPV sequences persist in the cancer cells and thus serve as a source of antigens recognized as foreign by the adaptive immune system. Because of the immunogenicity conferred by HPV protein expression, the process of cervical cancer carcinogenesis is thus highly dependent on multiple mechanisms of immune resistance that allow cervical cancers to evade T cell–mediated killing of cancer cells expressing HPV and other neoantigens. Over the last decade, a variety of immunotherapeutic approaches targeting HPV oncoproteins, mechanisms of immune evasion, and other cancer-associated surface markers have been explored in cervical cancer.

HPV-DIRECTED VACCINES

The principal mechanism of action of cancer vaccines relies on the provision of tumor-associated antigens in a preparation that is optimized to stimulate activation of antigen-presenting cells, ultimately leading to priming of new T-cell responses or boosting of preexisting T cells targeting the antigen of interest.[9] Preventive vaccines against the most common oncogenic HPV strains have been shown to be highly effective in preventing HPV infection and will likely result in reduction of HPV-mediated malignancies.[10,11] However, these vaccines predominantly target the viral surface glycoproteins and thus play no therapeutic role in the setting of therapy against HPV-transformed cells that lack expression of these genes. Most therapeutic vaccines against HPV to date have targeted HPV16 and HPV18 E6 and E7 proteins. Data from the trials exploring this strategy in the setting of preinvasive cervical and vulvar lesions have provided compelling evidence that vaccination against HPV can induce robust T-cell response leading to elimination of precancerous cells. A phase Ib trial of HLA-restricted peptides HPV16 E712-20 and E86-93 was conducted in patients with high-grade vulvar or cervical lesions and demonstrated an overall response rate of close to 50% and an increase in inflammatory response in the lesions.[12] Similar results were observed in a study of ISA-101, a vaccine using overlapping HPV16 E6 and E7 synthetic long peptides with incomplete Freund's adjuvant. A response rate of 79% with complete response of 47% was seen in the patients at 12 months.[13] A phase IIb trial using a DNA-based VGX-3100 vaccine encoding HPV 16/18 E6 and E7 in patients with cervical preinvasive lesions (CIN2/3) similarly demonstrated clinical regression in 50% of patients.[14] A phase III trial for VGX-3100 in this patient population is currently accruing (NCT03185013). Finally, vaccination regimens in precancerous lesions using prime-boost approaches using viral vectors have also been reported with similar clinical response rates and evidence of induction of HPV-specific immunity.[15,16]

Several HPV vaccination strategies have been explored in the setting of advanced and recurrent cervical cancer, albeit with lower efficacy. Axalimogene filolisbac (ADXS11- 001) is a live attenuated *Listeria* monocytogenes vaccine encoding HPV-16 E7 protein fused with the endogenous Listeriolysin O protein. A phase II trial of ADXS11-001 administered with or without cisplatin for treatment of recurrent/refractory cervical cancer (GOG-265) demonstrated a response rate of 14% to 17%, with a median overall survival of approximately 8 months.[17] A follow-up study of ADXS11-001 in 50 patients with advanced cervical cancer demonstrated an overall response rate of only 6% but with 12-month overall survival of 38%, which compared favorably to the historical 12-month survival rate of 21%.[18] A study of an HPV16 synthetic long peptide vaccine in 13 patients with advanced cervical cancer demonstrated an overall response rate of 0%, despite the evidence of vaccine-induced T-cell response in most patients.[19]

Overall, although therapeutic vaccination against HPV E6 and E7 demonstrates compelling evidence for induction of HPV-specific immune responses and regression of

precancerous lesions, data from HPV vaccination in an advanced setting to date have failed to demonstrate evidence of significant clinical activity. It is likely that the immunosuppressive mechanisms present in established cervical cancer tumors dampen the activity of HPV-targeted T cells generated in response to vaccination, arguing that combination therapies targeting the mechanisms of immune resistance will be required to explore the full therapeutic potential of therapeutic HPV vaccines.

IMMUNE CHECKPOINT BLOCKADE

As a strategy to reverse tumor-mediated immune resistance, agents targeting immune checkpoints, most commonly PD-1, PD-L1, and CTLA-4, have been explored across a number of disease settings. KEYNOTE-158 was a basket phase II trial in which 98 patients with cervical cancer were treated with pembrolizumab. Twelve patients achieved an objective response, with responses only observed in the tumors expressing PD-L1, leading to the aforementioned accelerated approval of pembrolizumab by the U.S. Food and Drug Administration for advanced PD-L1$^+$ cervical cancers.[20] The results were comparable to the outcomes of the phase I/II CHECKMATE-358 trial, a multicohort study of nivolumab with or without ipilimumab for virus-associated cancers. In the monotherapy arm of this trial, an overall response rate of 26.3% and 20% was observed in the 19 treated patients with cervical cancer and the five treated patients with vulvar/vaginal cancer, respectively.[21] The combination of ipilimumab and nivolumab appeared to increase the response rate, particularly in patients who had not previously received chemotherapy in the advanced disease setting, with a 36% response rate in previously treated patients and a 46% response rate in untreated patients.[22]

Although these findings were too preliminary to warrant regulatory approval or off-label adoption of the combination, these findings are consistent with immune-oncology trials in other tumor types in which checkpoint inhibitors were shown to be more efficacious in earlier lines of therapy. A separate cohort of the KEYNOTE-158 study focusing on patients with tumors exhibiting high tumor mutational burden, defined as 10 or more mutations per megabase, has led to U.S. Food and Drug Administration approval of pembrolizumab for patients with a tumor mutational burden of 10 or more irrespective of cancer type, including cervical cancer.[23]

addition of bevacizumab to the PD-L1 blockade with atezolizumab in patients pretreated wtih bevacizumab did not appear to increase the response rate in an ETCTN-sponsored phase II study, prompting the study discontinuation after accrual of 10 patients to the first stage,[24] although interest still remains in this combination in an earlier line of therapy and with a survival end point. The number of additional agents targeting PD-1 and PD-L1 are currently being explored across a number of studies in recurrent/metastatic cervical cancer, both alone and in combination with frontline chemotherapy and bevacizumab (NCT03257267, NCT03830866, NCT03635567), or antibodies targeting other checkpoints such as CTLA-4 and TIGIT (NCT03894215, NCT04300647).

Highlighting the potential of therapeutic vaccines in this setting, a recently reported trial of HPV16- and HPV18-directed DNA vaccine GX-188E administered in combination with pembrolizumab in 36 patients with advanced cervical cancer demonstrated an overall response rate of 42%, including responses in patients whose tumors were negative for PD-L1 expression.[25] Despite the small trial size, these preliminary data compare quite favorably to single-agent activity of pembrolizumab in KEYNOTE-158.[20]

In line with the findings of improved efficacy in the earliest possible line of therapy, a number of studies are currently evaluating the combination of chemoradiation with PD-1 or PD-L1 blockade in the upfront locally advanced setting, including durvalumab, pembrolizumab, and atezolizumab (NCT02635360, NCT03830866, NCT03738228). As optimal sequencing of chemoradiation and immunotherapy is not known, the NRG-GY017 study (NCT03738228) is specifically investigating whether administration of atezolizumab prior to chemoradiation versus concurrent administration with chemoradiation results in superior immune outcomes.

ADOPTIVE T-CELL THERAPY

Adoptive cell therapies refer to therapeutic approaches relying on infusion of large numbers of antigen-specific T cells into patients. In cervical cancer, approaches based on infusion of ex vivo–expanded tumor-infiltrating lymphocytes and T cells genetically modified to express HPV-targeted T-cell receptors have been explored in several studies.

In a study of nine patients with metastatic cervical cancer, infusion of tumor-infiltrating lymphocytes resulted in two durable complete responses and one partial response.[26] In a larger phase II trial of adoptive T-cell therapy conducted at the National Institutes of Health, responses were observed in 28% of 18 patients with cervical cancer.[27] An interim analysis of another phase II trial of tumor-infiltrating lymphocyte therapy in 27 patients with advanced cervical cancer demonstrated a response rate of 44%.[28] Using an engineered T-cell receptor targeted to HLA-A*02:01-restricted epitope of HPV-16 E6, Hinrichs et al demonstrated responses in two of nine patients (both with anal cancer).[29] In a separate study using HPV16 E7–targeted T-cell receptors, a response was seen in four of 12 treated patients.[30]

TUMOR-TARGETED ANTIBODIES AND ANTIBODY-DRUG CONJUGATES

Identification of surface proteins predominantly restricted to tumor cells provides for an opportunity for development of antibodies and antibody-drug conjugates targeting these

antigens. Tissue factor is a cell surface protein playing a key role in coagulation cascade and is involved in cancer-related signaling pathways, angiogenesis, and metastasis,[31] with high expression observed in most cervical cancers.[32] Tisotumab vedotin is a monomethyl auristatin E–like anti-tissue factor antibody-drug conjugate that has been evaluated in a phase I/II study in patients with advanced solid tumors. In the cohort of 55 pretreated patients with cervical cancer, tisotumab vedotin resulted in an overall investigator-assessed response rate of 24% and a 6-month progression-free survival of 40%.[33] A phase III trial of tisotumab vedotin versus chemotherapy in patients with pretreated cervical cancer is ongoing (NCT04697628).

PROGRESS AND FUTURE DIRECTIONS IN RADIATION ONCOLOGY FOR THE MANAGEMENT OF LOCALLY ADVANCED CERVICAL CANCER

Radiation is used for both postoperative adjuvant therapy and primary curative-intent therapy for locally advanced disease. Adjuvant therapy is recommended for patients whose tumors have high-risk pathologic factors after radical surgery including lymphovascular invasion, tumors larger than 2 cm, deep stromal invasion, lymph node and/or parametrial metastases, and/or positive margins. External beam therapy alone is curative in 85% of patients and is generally well tolerated.[4] In the locally advanced setting, external beam radiation therapy is escalated by adding concurrent cisplatin and intracavitary or interstitial brachytherapy,[7] but the cure rate is much lower than that for high-risk early-stage disease, specifically 67% survival at 3 years as previously mentioned. In addition, the doses needed to achieve this outcome are associated with morbidity in the form of radiation inflammation, fibrosis, and, less commonly, fistulae of the bladder, vagina, and/or rectum. Therefore, there is room for continued improvement in the therapeutic window of radiation therapy. The field of radiation oncology has seen a remarkable transformation over the last few decades with advances in treatment planning and delivery techniques. One of the most significant innovations over the last 20 years in the management of cervical cancer has been the implementation of image-guided adaptive brachytherapy, which allows for personalized prescription doses and treatment volumes to ensure adequate coverage of disease while minimizing damage to normal tissues. One strategy to improve the efficacy and tolerability of radiation therapy is to use novel systemic therapies during radiation to selectively sensitize the tumor while sparing normal tissue. There are many ongoing clinical trials combining novel systemic therapies with radiation in the management of cervical cancer. This review focuses on the benefits of image-guided adaptive brachytherapy and the promising combination strategies with novel systemic agents, including immunotherapy and radiation.

IMAGE-GUIDED ADAPTIVE BRACHYTHERAPY

Radiation therapy is essential for the definitive treatment of locally advanced (i.e., International Federation of Gynecology and Obstetrics IB2–IVA) cervical cancer. The standard treatment consists of 45 Gy to 50 Gy of external beam radiation therapy delivered over 5 to 6 weeks to the primary tumor and regional nodes with concurrent cisplatin-based chemotherapy.[34] Radiographically involved nodes receive higher doses up to 54 Gy to 66 Gy depending on size and proximity to adjacent normal structures. This is followed by a brachytherapy boost to the primary tumor to increase dose to tumor up to at least 80 Gy to 85 Gy in 2-Gy equivalents.

Brachytherapy uses internal placement of a radioactive source directly adjacent to or within a target. In cervical cancer, the steep dose gradient in brachytherapy allows delivery of high doses to the residual primary tumor while sparing surrounding normal tissue.

Beginning in the 1920s, various brachytherapy treatment planning systems were developed to provide guidelines for implantation geometries and dose prescriptions for cervical cancer. The most widely used was the Manchester system.[35] The classic intracavitary implant consists of an intrauterine tandem that carries radioactive sources through the cervix and into the uterus in a straight line and intravaginal ovoids on either side of the tandem that allow for radioactive source placement on either side of the cervix. Traditional planning with a two-dimensional technique used orthogonal x-ray images to prescribe dose to an arbitrary point in space, known as point A. This point was defined as 2 cm cephalad along the tandem from the apices of the lateral vaginal fornices and 2 cm perpendicularly lateral to the tandem and cervical canal. As such, point A does not represent the same fixed point in all individuals because it is relative to the placement of the device and therefore follows the axis of the tandem. Although a two-dimensional technique was quite effective and remained the standard of care until the 2000s, tumor and soft tissue anatomy were poorly visualized on orthogonal x-ray imaging, making it difficult to tailor treatment plans to a patient's unique anatomy and tumor characteristics. This led to incomplete tumor coverage in some cases and overtreatment of adjacent normal tissues, increasing the risk for disease recurrence and treatment complications.[36]

The ability to delineate target volume and identify normal organs at risk can be achieved with CT or MRI, thus allowing three-dimensional–based treatment planning, which is the current standard of care in the United States.[37] Image guidance allows for both adaptive target volume delineation and risk-adapted dose prescription. Adaptive target volume delineation refers to prescribing the dose to cover gross disease and areas of microscopic disease rather than to an arbitrary point in space. This method accounts for tumor

shrinkage and topography of normal tissues at the end of chemoradiation. Similarly, risk-adapted dose prescription refers to tailoring the prescribed dose to the precise volume of residual disease at the time of brachytherapy, because smaller tumors can be eradicated with lower doses of radiation and larger tumors require a higher dose. In a nonrandomized prospective French study that compared two-dimensional planning on orthogonal x-rays with three-dimensional planning (82% used CT, 18% used MRI) in patients with early-stage and advanced-stage cervical cancer, three-dimensional–based planning demonstrated improved local control with an approximate 50% reduction in toxicity. In patients treated with concurrent chemoradiation followed by brachytherapy, 2-year local control was 73.9% versus 78.5% (p = .003), favoring three-dimensional planning, with a 20% reduction in grade 3 to 4 urinary or gastrointestinal toxicities in the three-dimensional planning arm (22.7% vs. 2.6%, p = .002).[5] Other retrospective cohort data of three-dimensional–based planning for brachytherapy also indicate high rates of local control and decreased toxicity.[38,39]

Although organs at risk can be delineated as well on CT as on MRI, the extent of tumor invasion of the parametria, vagina, uterus, bladder, and rectum are better visualized on MRI.[40,41] Use of MRI at the time of brachytherapy allows for optimization of the dose delivered to the tumor and areas likely to contain microscopic disease.[42] The GEC-ESTRO GYN Working Group, established in 2000, first published recommendations on MRI-based image-guided adaptive brachytherapy to define tumor volume in the context of treatment response and to standardize dose and volume reporting.[43,44] In 2008, GEC-ESTRO initiated the EMBRACE study (external beam radio-chemotherapy and MRI-based adaptive brachytherapy in locally advanced cervical cancer), with the goal of benchmarking image guided brachytherapy and improving clinical outcomes.

The first EMBRACE study (EMBRACE I) was a prospective observational study that accrued a total of 1,416 patients who were treated with external beam radiation therapy and MRI-based image-guided adaptive brachytherapy. The individualized dose prescription in EMBRACE I resulted in improved target dose coverage, whereas the isodose surface volumes decreased by 23% overall compared with standard two-dimensional plans used with point A brachytherapy. Twenty-one percent of patients with high-volume residual gross disease had an escalation in isodose surface volumes compared with the point A prescription technique, suggesting that without image guidance, there would be areas of gross disease that would have received an insufficient dose. EMBRACE I has also provided valuable information regarding dose volume effects and toxicities, and these data were collectively used to define standardized constraints for organs at risk.[45-47] In 2016, EMBRACE II was launched with the primary aim to prospectively validate the findings of EMBRACE I and benchmark excellent clinical outcomes using advanced target volume delineation, detailed contouring protocols, a multiparametric brachytherapy dose prescription protocol, use of advanced external beam radiation therapy techniques including intensity-modulated radiation therapy and image-guided radiation therapy, and use of advanced brachytherapy techniques, including MRI-guided adaptive brachytherapy. The study also incorporates translational research including imaging and tissue biomarkers.[48]

It is important to remember that cervical cancer is largely a disease of lower- and middle-income countries. There are a number of barriers to implementing image-guided adaptive brachytherapy in these countries including lack of brachytherapy equipment, diagnostic imaging devices, and qualified personnel. There is a need to explore different techniques and workflows to ensure that these innovations are available in other countries. These issues are currently the focus of the GEC-ESTRO Brachy-HERO (Health Economics in Radiation Oncology) working group in collaboration with the International Atomic Energy Agency and the World Health Organization.[49]

NOVEL SYSTEMIC THERAPIES UNDER INVESTIGATION FOR USE CONCURRENTLY WITH RADIATION

The value of adding cisplatin or cisplatin-based chemotherapy to radiation for the treatment of locally advanced cervical cancer is strongly supported by randomized studies and meta-analysis.[34] Nevertheless, therapeutic results are far from optimal with many patients treated with definitive intent ultimately dying of metastatic disease. As such, there is significant interest in investigating novel therapies for use with radiation for the definitive management of locally advanced cervical cancer. Mechanistically these agents can be considered in three general categories: (1) immunomodulatory agents; (2) DNA damage response inhibitors; and (3) other novel therapeutics including agents that interfere with cell signal pathways. Herein, we explore the mechanisms underlying some of these novel strategies and highlight some ongoing trials. Although the timing and sequence of therapies is under active investigation and radiation–drug combinations are explored in a number of disease settings, for the purposes of this review, we will focus on agents being studied for use concurrently with radiation in the management of cervical cancer. Table 1 summarizes the ongoing clinical trials in this area.

IMMUNOMODULATORY AGENTS

Although radiation has historically been viewed as an immunosuppressant, more recent data demonstrate that radiation can enhance the antitumor immune response via a number of mechanisms including induction of pro-inflammatory chemokines and cytokines, modification of

TABLE 1. Ongoing Clinical Trials of Radiotherapy and Novel Systemic Therapies in Cervical Cancer

Class	Target	Drug/Biologic	Phase	Randomized?	Primary Endpoint(s)	NCT Identifier	Trial Name	Estimated Completion Date	Cancer Sites
Immunomodulatory									
	PD-L1	Durvalumab	III	Yes	PFS	NCT03830866	CALLA	April 2024	Cervix
	PD-1	Pembrolizumab	III	Yes	PFS, OS	NCT04221945	KEYNOTE-A18	December 2024	Cervix
	PD-L1	Atezolizumab	II	Yes	PFS	NCT03612791	ATEZOLACC	July 2022	Cervix
	PD-1	Toripalimab	I	No	Safety	NCT04368273		December 2022	Cervix
	PD-L1	Atezolizumab	I	No	Translational	NCT03738228	NRG-GY017	November 2021	Cervix
	PD-1	Nivolumab	I	No	Safety	NCT03298893	NiCOL	September 2022	Cervix
	PD-1	Nivolumab	I	No	Safety, PFS	NCT03527264	BrUOG3355	December 2023	Cervix
	PD-L1, CTLA-4	Durvalumab, tremelimumab	I	No	Safety	NCT03277482		November 2022	Recurrent/metastatic gynecologic cancers
	PD-1	Pembrolizumab and immune cocktail	II	No	ORR	NCT03192059	PRIMMO	June 2022	Recurrent/metastatic cervix, uterus
	HPV viral proteins	PDS0101	I	No	Safety	NCT04580771	IMMUNOCERV	March 2024	Cervix
	E6 and E7	HB101	0	No	Translational	NCT04630353		February 2021	HPV+ cervix and oropharynx
DNA Damage Repair									
	RNR	Triapine	III	Yes	OS	NCT02466971		July 2023	Cervix, vagina
	PARP	Talazoparib	I	No	MTD	NCT03968406		October 2021	Refractory/recurrent gynecologic cancers
	PARP	Niraparib	I/II	No	MTD, local PFS	NCT03644342		March 2026	Cervix
	RNR	Triapine	I	No	MTD, PK	NCT02595879		December 2021	Cervix, vagina
	ATM/ATR	AZD6738	I	No	MTD	NCT02223923	PATRIOT	December 2020	Solid tumors
	ATR	M6620	I	No	RP2D	NCT03641547	CHARIOT	May 2023	Solid tumors
	WEE1	Adavosertib	I	No	RP2D	NCT03345784		April 2021	Cervix, vagina, uterus
Other									
	PI3k/Akt?	Nelfinavir	III	Yes	3-year DFS	NCT03256916	NELCER	September 2025	Cervix
	PI3k/Akt?	Nelfinavir	I	No	Safety	NCT02363829		February 2020	Cervix
	High Z → radiosensitization	AguIX-NP	I	No	MTD, RP2D	NCT03308604	NANOCOL	May 2021	Gynecologic cancers
	Hypoxia modifier?	Metformin	II	Yes	Change in hypoxic volume (FAZA-PET)	NCT02394652		December 2023	Cervix

Abbreviations: PFS, progression-free survival; OS, overall survival; ORR, overall response rate; MTD, maximum tolerated dose; PK, pharmacokinetics; RP2D, recommended phase II dose; DFS, disease-free survival.

adhesion molecules on tumor vasculature, enhancing T-cell receptor diversity, and increasing the density of tumor-infiltrating lymphocytes.[16] DNA damage and its associated inflammatory cascade may be capable of reinvigorating an anergic, tumor-tolerant immune system. Thus, immunomodulatory agents are uniquely poised for potential synergy with radiation.[50]

It is well established that radiation modulates the expression of immune checkpoint ligands, including PD-L1 on the surface of cancer cells.[51] In a recent phase I clinical trial in locally advanced cervical cancer, chemoradiation increased PD-L1 expression, thus providing additional rationale for use of PD-1/PD-L1 inhibitors with radiation as a combination strategy in cervical cancer.[52] As previously mentioned, there are two ongoing randomized, placebo-controlled, phase III trials investigating the benefit of PD-1/PD-L1 inhibitors in combination with chemoradiation for the treatment of patients with locally advanced cervical cancer: KEYNOTE-A18/GOG 3047/ENGOT cx-11 (pembrolizumab; NCT04221945) and CALLA (durvalumab; NCT03830866). Both studies randomly assigned patients to receive standard-of-care chemoradiation plus placebo followed by adjuvant placebo compared with chemoradiation plus checkpoint inhibitor followed by maintenance checkpoint inhibitor. Accrual to CALLA is completed and KEYNOTE-A18 remains ongoing.

DNA DAMAGE RESPONSE INHIBITORS

The primary mechanism of action of radiation therapy is DNA damage, which triggers a network of cellular DNA damage responses (DDRs) that allow a cell to sense, signal, and attempt to repair DNA lesions. The fact that ionizing radiation is an effective treatment for cancer indicates that, for the most part, normal (i.e., nonmalignant) cells are better equipped to repair DNA than malignant cells. This is supported by evidence that abnormalities in the DDR network are a fundamental characteristic of tumorigenesis As such, the capacity of malignant cells to repair such damage can contribute to treatment resistance. Inhibition of DNA repair via DDR inhibitors in combination with radiation is actively being investigated given the potential for exploiting these pathways as a means of radiosensitization. The DDR network consists of molecules that both regulate DNA repair such as PARP and cell cycle regulators, including ataxia telangiectasia and RAD3-related kinase, WEE1, and ribonucleotide reductase.

A number of early-phase clinical trials are exploring the use of DDR inhibitors in combination with radiation as shown in Table 1. To our knowledge, triapine, an inhibitor of the M2 subunit of ribonucleotide reductase, is the only agent in this class currently being explored in a phase III trial (NCT02466971), with an estimated study completion date in 2023. Triapine increases a cell's vulnerability to radiation by prolonging DNA repair time and arresting cancer cells at the G1/S checkpoint. This agent has shown promise in cervical cancer, which is associated with overactive ribonucleotide reductase.[53]

SPECIAL CONSIDERATIONS FOR RARE HISTOLOGIES

HPV infection and cervical cancer malignant transformation occur in the squamo-columnar (glandular) junction of the ecto- and endocervical epithelium. This metaplastic zone, widely accepted to contribute to the pathogenesis of the HPV virus, is predominantly comprised of squamous epithelium. Therefore, approximately 70% of cervical cancers are of squamous histology. Furthermore, nearly 90% of patients treated on cervical cancer clinical trials had squamous tumors. Thus, our treatment paradigms are not only most validated for this cell type but also difficult to meaningfully study in rarer types, of which adenocarcinomas of the glandular epithelium are most common, with neuroendocrine tumors and adenoma malignum comprising the remainder.

Adenocarcinoma accounts for approximately 20% of all cervical cancer. Although the incidence of squamous tumors has declined, interestingly, the relative and absolute incidence of adenocarcinoma has increased.[54] A large ancillary analysis of patients with adeno- and adenosquamous carcinoma treated on Gynecologic Oncology Group chemoradiotherapy trials showed 10% inclusion of these types and a worse comparative prognosis that was mitigated with the addition of cisplatin.[55] Biologically these tumors have higher rates of hormone-receptor positivity[56] and are more frequently negative for PD-L1[57] than their squamous counterparts to the degree that squamous histology is a surrogate for PD-L1 expression. KEYNOTE-158 reported pembrolizumab response in only one of six adenocarcinomas that was atypically PD-L1^{+}.[20] The long-known epidemiologic associations between cervical adenocarcinoma and oral contraceptives and obesity are consistent with these biologic characteristics.[58]

Neuroendocrine carcinoma is a rare and aggressive cervical cancer histology accounting for approximately 1.4% to 2% of invasive cervical cancer.[59] Classified as high grade (encompassing small cell and large cell histology) or low grade (carcinoid), the small cell histology accounts for more than 80% of tumors, with the large cell variant being much less common at 12% to 15% of cases and low-grade histology at 2% to 5%.[1] They are more likely to be diagnosed at a later stage with symptoms of local and/or metastatic disease and are unlikely to be detected by routine cervical cancer screening because of this aggressive behavior.[60,61] Median overall survival remains 22 months to 25 months, with a 5-year survival rate of just more than 30%.[62] Much of the traditional information regarding prognosis and therapeutics in this disease has been extrapolated from small cell lung cancer data given their histologic similarities. Most studies

of cervical neuroendocrine carcinoma are small and retrospective, making treatment decisions difficult for providers.

Initially thought to be less commonly associated with HPV infection, more recent data including a meta-analysis of 143 studies have revealed evidence of HPV infection in up to 85% of women with small cell carcinoma, with similar rates in the large cell variant.[63] However, its distinctly aggressive biology suggests additional driver mutations are a factor. Frumovitz et al studied 44 small cell or mixed tumors that underwent mutational analysis with next-generation sequencing and identified the most common mutations as *PIK3CA, KRAS*, and *TP53*, noting that of 24 patients in which a mutation was identified, 88% had at least one targetable mutation with a currently available class of agents.[64] A systematic review highlighted the importance of a similar spectrum of mutations including p52, *KRAS, PIK3CA*, and *c-Myc* and also identified loss of heterozygosity in 30% of cases.[65,66] Additionally, somatic *BRCA* mutations have been reported, as well as recent data indicating a high rate of s*PARP-1* mutations.[6769]

Evaluation for PD-L1 expression and microsatellite instability has been found to be universally negative in these studies. One study examining immunohistochemistry factors associated with prognosis found Her-2/neu expression in 41% samples and saw evidence of longer survival in those patients.[68] These findings were supported by the Cancer Genome Atlas Program as well.[56]

Multimodal treatment remains the mainstay of neuroendocrine carcinoma management. With little evidence to guide practice, squamous histology practices are also extrapolated to neuroendocrine carcinoma tumors. Their known poor prognosis leads most providers to recommend platinum-etoposide–based chemotherapy in addition to stage-based surgery or chemoradiotherapy.[70,71]

Acceptable second-line regimens include carboplatin, paclitaxel and bevacizumab, or topotecan, paclitaxel, and bevacizumab because they have been shown to be both efficacious and tolerable in this population.[72] Despite being characterized as PD-L1^{-}, immunotherapy for neuroendocrine tumors includes a phase II study of nivolumab (PD-1 inhibitor) and ipilimumab (anti–CTLA-4) as combination therapy, with case reports showing responses in patients.[73] Additionally, an open-label, multicenter phase II basket study exploring the efficacy and safety of neratinib as monotherapy or in combination with other therapies in participants with HER (EGFR, her2) mutation–positive solid tumors included patients with her2 mutation–positive heavily pretreated metastatic cervical cancer and showed a durable response and disease control.[74] Although most of these patients had adenocarcinoma histology, given the evidence for HER-2/neu expression in some neuroendocrine tumors, this regimen may show promise for these patients. Given the evidence of BRCA and PARP mutations identified in these tumors, PARP inhibitors are an attractive potential therapeutic agent either as monotherapy or in combination with other targeted agents. Such studies are nearly impossible to execute by traditional clinical trial procedures given the rarity of disease and the frequent exclusion of these poor prognosis patients from clinical

SIDEBAR 1. KEY POINTS

- Immunotherapeutic approaches in cervical cancer have focused on targeting HPV oncoproteins, mechanisms of immune evasion, and cancer-associated surface proteins.
- Therapeutic vaccines against HPV E6 and E7 have shown efficacy for therapy of preinvasive lesions but have had limited single-agent activity against advanced cervical cancers to date.
- Adoptive T-cell therapies have demonstrated an ability to induce deep and durable responses in a subset of patients with cervical cancer.
- Antibody-drug conjugates targeting cancer-associated surface proteins such as tissue factor have demonstrated promising early signals of activity; confirmatory trials are ongoing.
- Pembrolizumab is currently the only approved immunotherapy agent in PD-L1(+) cervical cancers and cervical cancers exhibiting a tumor mutational burden of 10 or greater.
- Image-guided adaptive brachytherapy allows for individualized treatment delivery to ensure adequate coverage of gross disease while reducing dose to normal structures.
- Retrospective data consistently demonstrate improved rates of local control and toxicity with image-guided brachytherapy over two-dimensional techniques.
- MRI-guided brachytherapy allows for improved tumor delineation compared with CT-guided brachytherapy, particularly in determining extent of parametrial disease.
- Checkpoint blockade with concurrent chemoradiation in locally advanced cervical cancer is being explored in a number of clinical trials, including two phase III trials.
- A number of DNA damage response inhibitors are in early-phase clinical development for the use in combination with radiation.

trials. To improve knowledge of this disease, MD Anderson Cancer Center maintains an actively recruiting tumor registry for patients with a diagnosis of neuroendocrine carcinoma of the cervix, with both a retrospective record review and frequent patient contact,[75] aimed to serve as a surrogate for systematic prospective trials.

Finally, adenoma malignum represents less than 1% of all cervical cancers. Characterized by benign clinical appearance with paradoxically aggressive biology, this rare tumor has recently been associated with *STK11* mutation and identified as part of the Peutz-Jeghers syndrome.[76] Patients identified as Peutz-Jeghers probands can be offered risk-reducing hysterectomy after completion of childbearing. Because of the rarity of disease, quantification of the benefit is not likely possible, but the relative risk of cancer is likely more than 100-fold in mutation carriers.

CONCLUSION

The novel therapies discussed in this review give hope for improved outcomes in women with cervical cancer (Sidebar 1). The accelerated approval pathway in the United States is changing the landscape and pace at which treatments become available to patients. Despite this excitement, it is imperative that the very patients who experience high-risk cervical cancer by virtue of their socioeconomic status and race are not at a disadvantage for clinical trial participation and novel therapy access and affordability.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359-E386.
2. National Cancer Institute. Cancer Stat Facts: Cervical Cancer. https://seer.cancer.gov/statistics/. Accessed February 12, 2021.
3. Bhatla N, Berek JS, Cuello Fredes M, et al. Revised FIGO staging for carcinoma of the cervix uteri [published correction appears in *Int J Gynecol Obstet*. 2019;147:279-280]. Int J Gynecol Obstet. 2019;145:129-135.
4. Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group study. Gynecol Oncol. 1999;73:177-183.
5. Peters WA III, Liu PY, Barrett RJ II, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol. 2000;18:1606-1613.
6. Pareja R, Rendón GJ, Sanz-Lomana CM, et al. Surgical, oncological, and obstetrical outcomes after abdominal radical trachelectomy: a systematic literature review. Gynecol Oncol. 2013;131:77-82.
7. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340:1144-1153.
8. Tewari KS, Sill MW, Long HJ III, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014;370:734-743.
9. Blass E, Ott PA. Advances in the development of personalized neoantigen-based therapeutic cancer vaccines. Nat Rev Clin Oncol. 2021.
10. Lei J, Ploner A, Elfström KM, et al. HPV vaccination and the risk of invasive cervical cancer. N Engl J Med. 2020;383:1340-1348.
11. Vesikari T, Brodszki N, van Damme P, et al. A randomized, double-blind, phase III study of the immunogenicity and safety of a 9-valent human papillomavirus l1 virus-like particle vaccine (V503) versus Gardasil in 9-15-year-old firls. Pediatr Infect Dis J. 2015;34:992-998.
12. Muderspach L, Wilczynski S, Roman L, et al. A phase I trial of a human papillomavirus (HPV) peptide vaccine for women with high-grade cervical and vulvar intraepithelial neoplasia who are HPV 16 positive. Clin Cancer Res. 2000;6:3406-3416.
13. Kenter GG, Welters MJ, Valentijn AR, et al. Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. N Engl J Med. 2009;361:1838-1847.
14. Trimble CL, Morrow MP, Kraynyak KA, et al. Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. Lancet. 2015;386:2078-2088.
15. Maldonado L, Teague JE, Morrow MP, et al. Intramuscular therapeutic vaccination targeting HPV16 induces T cell responses that localize in mucosal lesions. Sci Transl Med. 2014;6:221ra13.

16. Brun JL, Dalstein V, Leveque J, et al. Regression of high-grade cervical intraepithelial neoplasia with TG4001 targeted immunotherapy. Am J Obstet Gynecol. 2011;204:169.e1-8.

17. Basu P, Mehta A, Jain M, et al. A randomized phase 2 study of ADXS11-001 *Listeria monocytogenes*-listeriolysin O immunotherapy with or without cisplatin in treatment of advanced cervical cancer. Int J Gynecol Cancer. 2018;28:764-772.

18. Huh WK, Brady WE, Fracasso PM, et al. Phase II study of axalimogene filolisbac (ADXS-HPV) for platinum-refractory cervical carcinoma: an NRG oncology/gynecologic oncology group study. Gynecol Oncol. 2020;158:562-569.

19. van Poelgeest MI, Welters MJ, van Esch EM, et al. HPV16 synthetic long peptide (HPV16-SLP) vaccination therapy of patients with advanced or recurrent HPV16-induced gynecological carcinoma, a phase II trial. J Transl Med. 2013;11:88.

20. Chung HC, Ros W, Delord JP, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol. 2019;37:1470-1478.

21. Naumann RW, Hollebecque A, Meyer T, et al. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: results from the phase I/II CheckMate 358 trial. J Clin Oncol. 2019;37:2825-2834.

22. Naumann RW, et al. Efficacy and safety of nivolumab (Nivo) + Ipilimumab (Ipi) in patients (pts) with recurrent/metastatic (R/M) cervical cancer: results from CheckMate 358. Ann Oncol. 2019;30:v851-v934.

23. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020;21:1353-1365.

24. Friedman CF, Snyder Charen A, Zhou Q, et al. Phase II study of atezolizumab in combination with bevacizumab in patients with advanced cervical cancer. J Immunother Cancer. 2020;8:e001126.

25. Youn JW, Hur SY, Woo JW, et al. Pembrolizumab plus GX-188E therapeutic DNA vaccine in patients with HPV-16-positive or HPV-18-positive advanced cervical cancer: interim results of a single-arm, phase 2 trial. Lancet Oncol. 2020;21:1653-1660.

26. Stevanović S, Draper LM, Langhan MM, et al. Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells [correction published in *J Clin Oncol.* 2016;34(5):519]. J Clin Oncol. 2015;33:1543-1550.

27. Stevanović S, Helman SR, Wunderlich JR, et al. A phase II study of tumor-infiltrating lymphocyte therapy for human papillomavirus-associated epithelial cancers. Clin Cancer Res. 2019;25:1486-1493.

28. Jazaeri AA, et al. Safety and efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma. J Clin Oncol. 2019; 37(15, suppl)2538-2538 .

29. Doran SL, Stevanović S, Adhikary S, et al. T-cell receptor gene therapy for human papillomavirus-associated epithelial cancers: a first-in-human, phase I/II study. J Clin Oncol. 2019;37:2759-2768.

30. Norberg S, et al. Safety and clinical activity of gene-engineered T-cell therapy targeting HPV-16 E7 for epithelial cancers. J Clin Oncol. 2020; 38(15 suppl)101-101 .

31. Han X, Guo B, Li Y, et al. Tissue factor in tumor microenvironment: a systematic review. J Hematol Oncol. 2014;7:54.

32. Zhao X, Cheng C, Gou J, et al. Expression of tissue factor in human cervical carcinoma tissue. Exp Ther Med. 2018;16:4075-4081.

33. Hong DS, Concin N, Vergote I, et al. Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer. Clin Cancer Res. 2020;26:1220-1228.

34. Vale C, Tierney JF, Stewart LA, et al; Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol. 2008;26:5802-5812.

35. Tod M, Meredith WJ. Treatment of cancer of the cervix uteri, a revised Manchester method. Br J Radiol. 1953;26:252-257.

36. Tanderup K, Georg D, Pötter R, et al. Adaptive management of cervical cancer radiotherapy. Semin Radiat Oncol. 2010;20:121-129.

37. Grover S, Harkenrider MM, Cho LP, et al. Image guided cervical brachytherapy: 2014 survey of the American Brachytherapy Society. Int J Radiat Oncol Biol Phys. 2016;94:598-604.

38. Charra-Brunaud C, Harter V, Delannes M, et al. Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: results of the French STIC prospective study. Radiother Oncol. 2012;103:305-313.

39. Sturdza A, Pötter R, Fokdal LU, et al. Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. Radiother Oncol. 2016;120:428-433.

40. Eskander RN, Scanderbeg D, Saenz CC, et al. Comparison of computed tomography and magnetic resonance imaging in cervical cancer brachytherapy target and normal tissue contouring. Int J Gynecol Cancer. 2010;20:47-53.

41. Viswanathan AN, Erickson B, Gaffney DK, et al. Comparison and consensus guidelines for delineation of clinical target volume for CT- and MR-based brachytherapy in locally advanced cervical cancer. Int J Radiat Oncol Biol Phys. 2014;90:320-328.

42. Tanderup K, Nielsen SK, Nyvang GB, et al. From point A to the sculpted pear: MR image guidance significantly improves tumour dose and sparing of organs at risk in brachytherapy of cervical cancer. Radiother Oncol. 2010;94:173-180.

43. Pötter R, Haie-Meder C, Van Limbergen E, et al; GEC ESTRO Working Group. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol. 2006;78:67-77.

44. Serban M, Kirisits C, Pötter R, et al; EMBRACE Collaborative Group. Isodose surface volumes in cervix cancer brachytherapy: change of practice from standard (Point A) to individualized image guided adaptive (EMBRACE I) brachytherapy. Radiother Oncol. 2018;129:567-574.
45. Kirchheiner K, Nout RA, Tanderup K, et al. Manifestation pattern of early-late vaginal morbidity after definitive radiation (chemo)therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: an analysis from the EMBRACE study. Int J Radiat Oncol Biol Phys. 2014;89:88-95.
46. Stanic S, Mayadev JS. Tolerance of the small bowel to therapeutic irradiation: a focus on late toxicity in patients receiving para-aortic nodal irradiation for gynecologic malignancies. Int J Gynecol Cancer. 2013;23:592-597.
47. Mazeron R, Fokdal LU, Kirchheiner K, et al; EMBRACE collaborative group. Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: results from the prospective multicenter EMBRACE study. Radiother Oncol. 2016;120:412-419.
48. Pötter R, Tanderup K, Kirisits C, et al; EMBRACE Collaborative Group. The EMBRACE II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. Clin Transl Radiat Oncol. 2018;9:48-60.
49. The European SocieTy for Radiotherapy and Oncology. GEC-ESTRO Brachy - HERO, Members. https://www.estro.org/About/ESTRO-Organisation-Structure/Committees/GEC-ESTRO-Committee/GEC-ESTRO-Brachy-HERO. Accessed October 2, 2021.
50. Sharabi AB, Lim M, DeWeese TL, et al. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. Lancet Oncol. 2015;16:e498-e509.
51. Parikh F, Duluc D, Imai N, et al. Chemoradiotherapy-induced upregulation of PD-1 antagonizes immunity to HPV-related oropharyngeal cancer. Cancer Res. 2014;74:7205-7216.
52. Mayadev JS, Enserro D, Lin YG, et al. Sequential ipilimumab after chemoradiotherapy in curative-intent treatment of patients with node-positive cervical cancer. JAMA Oncol. 2019;6:92-99.
53. Kunos CA, Sherertz TM. Long-term disease control with triapine-based radiochemotherapy for patients with stage IB2-IIIB cervical cancer. Front Oncol. 2014;4:184.
54. Gien LT, Beauchemin MC, Thomas G. Adenocarcinoma: a unique cervical cancer. Gynecol Oncol. 2010;116:140-146.
55. Rose PG, Java JJ, Whitney CW, et al. Locally advanced adenocarcinoma and adenosquamous carcinomas of the cervix compared to squamous cell carcinomas of the cervix in gynecologic oncology group trials of cisplatin-based chemoradiation. Gynecol Oncol. 2014;135:208-212.
56. Cancer Genome Atlas Research Network. Integrated genomic and molecular characterization of cervical cancer. Nature. 2017;543:378-384.
57. Heeren AM, Punt S, Bleeker MC, et al. Prognostic effect of different PD-L1 expression patterns in squamous cell carcinoma and adenocarcinoma of the cervix. Mod Pathol. 2016;29:753-763.
58. Brinton LA, Tashima KT, Lehman HF, et al. Epidemiology of cervical cancer by cell type. Cancer Res. 1987;47:1706-1711.
59. Kurman RJ, Carcanglu ML, Herrington CS, et al. WHO Classification of Tumours of Female Reproductive Organs. Lyon, France: International Agency for Research on Cancer; 2014.
60. Chen J, Macdonald OK, Gaffney DK. Incidence, mortality, and prognostic factors of small cell carcinoma of the cervix. Obstet Gynecol. 2008;111:1394-1402.
61. McCusker ME, Coté TR, Clegg LX, et al. Endocrine tumors of the uterine cervix: incidence, demographics, and survival with comparison to squamous cell carcinoma. Gynecol Oncol. 2003;88:333-339.
62. Gardner GJ, Reidy-Lagunes D, Gehrig PA. Neuroendocrine tumors of the gynecologic tract: a Society of Gynecologic Oncology (SGO) clinical document. Gynecol Oncol. 2011;122:190-198.
63. Castle PE, Pierz A, Stoler MH. A systematic review and meta-analysis on the attribution of human papillomavirus (HPV) in neuroendocrine cancers of the cervix. Gynecol Oncol. 2018;148:422-429.
64. Frumovitz M, Burzawa JK, Byers LA, et al. Sequencing of mutational hotspots in cancer-related genes in small cell neuroendocrine cervical cancer [correction published in *Gynecol Oncol.* 2016;143(1):P224]. Gynecol Oncol. 2016;141:588-591.
65. Tempfer CB, Tischoff I, Dogan A, et al. Neuroendocrine carcinoma of the cervix: a systematic review of the literature. BMC Cancer. 2018;18:530.
66. Carroll MR, Ramalingam P, Salvo G, et al. Evaluation of PARP and PDL-1 as potential therapeutic targets for women with high-grade neuroendocrine carcinomas of the cervix. Int J Gynecol Cancer. 2020;30:1303-1307.
67. Rose PG, Sierk A. Treatment of neuroendocrine carcinoma of the cervix with a PARP inhibitor based on next generation sequencing. Gynecol Oncol Rep. 2019;30:100499.
68. Tangjitgamol S, Ramirez PT, Sun CC, et al. Expression of HER-2/neu, epidermal growth factor receptor, vascular endothelial growth factor, cyclooxygenase-2, estrogen receptor, and progesterone receptor in small cell and large cell neuroendocrine carcinoma of the uterine cervix: a clinicopathologic and prognostic study. Int J Gynecol Cancer. 2005;15:646-656.
69. Salvo G, Gonzalez Martin A, Gonzales NR, et al. Updates and management algorithm for neuroendocrine tumors of the uterine cervix. Int J Gynecol Cancer. 2019;29:986-995.
70. Hoskins PJ, Wong F, Swenerton KD, et al. Small cell carcinoma of the cervix treated with concurrent radiotherapy, cisplatin, and etoposide. Gynecol Oncol. 1995;56:218-225.
71. Chan JK, Loizzi V, Burger RA, et al. Prognostic factors in neuroendocrine small cell cervical carcinoma: a multivariate analysis. Cancer. 2003;97:568-574.

72. Frumovitz M, Munsell MF, Burzawa JK, et al. Combination therapy with topotecan, paclitaxel, and bevacizumab improves progression-free survival in recurrent small cell neuroendocrine carcinoma of the cervix. Gynecol Oncol. 2017;144:46-50.

73. Klein O, et al. A phase II clinical trial of ipilimumab/nivolumab combination immunotherapy in patients with rare upper gastrointestinal, neuroendocrine, and gynecological malignancies. J Clin Orthod. 2019;37(15_suppl):2570-2570.

74. Oaknin A, Friedman CF, Roman LD, et al. Neratinib in patients with HER2-mutant, metastatic cervical cancer: Findings from the phase 2 SUMMIT basket trial. Gynecol Oncol. 2020;159:150-156.

75. NCT04723095. Tumor registry for patients with neuroendocrine cancer of the cervix. https://clinicaltrials.gov/ct2/show/NCT04723095. Accessed February 11, 2021.

76. Gilks CB, Young RH, Aguirre P, et al. Adenoma malignum (minimal deviation adenocarcinoma) of the uterine cervix. A clinicopathological and immunohistochemical analysis of 26 cases. Am J Surg Pathol. 1989;13:717-729.

HEAD AND NECK CANCER

Artificial Intelligence and Radiomics in Head and Neck Cancer Care: Opportunities, Mechanics, and Challenges

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Overview

The advent of large-scale high-performance computing has allowed the development of machine-learning techniques in oncologic applications. Among these, there has been substantial growth in radiomics (machine-learning texture analysis of images) and artificial intelligence (which uses deep-learning techniques for "learning algorithms"); however, clinical implementation has yet to be realized at scale. To improve implementation, opportunities, mechanics, and challenges, models of imaging-enabled artificial intelligence approaches need to be understood by clinicians who make the treatment decisions. This article aims to convey the basic conceptual premises of radiomics and artificial intelligence using head and neck cancer as a use case. This educational overview focuses on approaches for head and neck oncology imaging, detailing current research efforts and challenges to implementation.

INTRODUCTION: BEATING THE HUMAN EYE OR BRAIN

Radiomics and artificial intelligence (AI) have become buzzwords in the oncology research field and are now often the go-to proposed solution for complex clinical prediction problems when imaging is available. This is fueled by the promise of radiomics (machine-learning approaches for image features analyses) and AI (neural networks that learn from the image directly) to be able to extract information in images that cannot be observed by the human eye.[1] Nevertheless, more than just detecting meaningful features that cannot visually be observed, these machine-learning pipelines can facilitate pattern recognition in images, detection in biomarker data, and integration with nonimaging variables that cannot be comprehended by the human brain, due to the large number of potential variables.[2-4]

This article aims to convey the basics of radiomics and AI in relation to head and neck oncologic imaging by addressing the application space for leveraging medical images, radiomics, and basic deep-learning mechanics and the challenges of cancer imaging–enabled AI specifically for patients with head and neck cancer.

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OPPORTUNITIES: MODEL-BASED PERSONALIZED TREATMENT DECISION-MAKING

In general, medical machine learning can be categorized as focused on regression or classification tasks, which depends on the predicted outcome. Regression methods (e.g., linear regression, polynomial, and support vector regression) aim to predict continuous values, such as tumor volume reduction, weight loss, or biomarker values, whereas classification methods (e.g., logistic regression and random forest) aim to predict a binary/categorical value, such as tumor recurrence or toxicity development. An additional deviation of the classification is Cox hazard regression, which incorporates the time-to-event together with a binary event (e.g., death or censored). Using these classification and regression approaches, a broad swath of problems can be addressed that, on the surface, seem radically distinct in scope. For example, similar deep-learning approaches can be used for tasks as different as risk stratification, biomarker detection, image segmentation, and image reconstruction.

The most evident example is risk prediction of overall survival or tumor control after treatment based on imaging tumor and clinical characteristics in patients with head and neck cancer. By identifying patients who are at specific high or low risk of treatment failure before treatment, therapy can be tailored to their anticipated risk. For instance, HPV-positive tumors have exceptionally good outcome rates (5-year overall survival approximately 80%[5-7]); thus, having provoked clinical trials to reduce radiation fractionation dose,[8] magnetic resonance (MR)–guided adaptive radiation dose de-escalation,[9] and sparked discussions about the relative, as-yet-unquantified, potential benefits associated with chemotherapy for these patients.[10,11] Nevertheless, not all patients with HPV-associated oropharyngeal cancer may do well with a de-escalated treatment regimen; thus, models based on radiomics

PRACTICAL APPLICATIONS

- Radiomics and imaging artificial intelligence are rapidly being deployed in research-level applications in head and neck cancer.
- Personalized medicine using radiomics and artificial intelligence is necessarily dependent on the quality, robustness, and generalizability of generated prediction/classification models.
- Though exceptionally promising, rigor in model development, reporting, and implementation will require oncologists to have a general understanding of these approaches, their advantages over traditional methods, and their limitations.

combined with clinical variables (e.g., smoking status) and biomarkers (e.g., HPV subtypes) can play a role in directing treatment alterations more effectively. Similarly, for patients with head and neck cancer at high risk of treatment failure, clinical trials can target these patients specifically for intensified treatment regimens (e.g., image-guided dose-escalation or induction chemotherapy). Although intensified regimens may not be effective when applied to the full population with head and neck cancer and may do more harm by increasing treatment-induced toxicity rates, it could be effective in a cohort saturated with high-risk patients only. Moreover, in general, for any treatment approach in which variable effectiveness response can be observed, such as immunotherapy for patients with head and neck cancer,[12,13] prediction models can be potentially developed to identify patients who are likely to experience treatment success versus treatment failure and alter treatment accordingly.

Another application for image biomarkers is toxicity development after chemoradiation, as it is highly variable in patients with head and neck cancer (i.e., patients who receive a similar dose to critical organs can have a completely different toxicity profile after treatment). Tumor information is readily available not only in the form of clinical CT, PET, and MRI but also that of the normal tissues. Normal tissue image features can be extracted and may provide patient-specific radiosensitivity characteristics that are associated with toxicity development. For instance, the prediction of late xerostomia was improved with parotid gland CT radiomics features,[14] which indicated that higher heterogeneity of the parotid glands was associated with a higher risk of xerostomia. Subsequently, from T1-weighted MRI image biomarkers, it was observed that higher fat concentrations in the parotid gland were associated with a higher risk of developing xerostomia.[15] A handful of other studies have investigated the relationship between CT information and the development of a radiation-induced toxicity,[16-18] whereas the use of MRI information on normal tissues is a relatively uncharted domain.[19,20]

Other areas within head and neck oncology imaging in which AI has already had a practical impact is autosegmentation of tumor or organ at risk, which is, in essence, a voxel-based classification task.[21] The clinical usability of autosegmentation is to aid radiation oncologists (or clinicians) in organ and tumor definition, decreasing delineation times.[22-25] Furthermore, AI is being deployed for MRI deformation,[26-28] improved image reconstruction,[29-31] and MRI to pseudo-CT.[32-35] These applications show particular promise for MRI-based adaptive radiation and combined imaging-treatment device (such as MRI-linear accelerator) applications, as improved deformation can improve adaptive warping of contours to new scans. Adequate pseudo-CT approximations will allow for dose optimization from MRI only, whereas today, a CT scan is required to calculate radiation absorption for treatment planning.

This capacity to generate usable data is not limited to therapy delivery, however. For example, AI is being applied to develop MR fingerprinting, which is an acquisition strategy allowing multiparametric MRI reconstruction from a single acquisition.[36,37] The practical benefit of MR fingerprinting is that it allows for the acquisition of multiple quantitative MR sequences (such as T1 or T2 maps) from a single scan acquisition, significantly reducing the total scan time. Because this process involves deep learning to reconstruct the images, the same deep-learning approach could simultaneously allow front-end integration of radiomics, segmentation, and motion correction in a "near live" time interval. This idea of solving multiple algorithmic processes simultaneously is an especially exciting developmental opportunity for AI-based approaches (but necessarily requires sufficiently large and representative training data sets).

Although radiomics and AI research studies are emerging exponentially, clinical implementation is often not (yet) reached for most of the prediction models at a level of clinical usability or with interpretable visualization interfaces. To improve implementation, models must be presented in a manner in which the results can be understood and adequately interpreted by clinicians, whom are responsible for making the treatment decisions. Moreover, the models must be reliable (i.e., well trained and validated on representative data), as well as transparently inform on risk uncertainty per individual prediction. This need for decision-support tools that allow for automatic integration of data processing, prediction, and quality assurance with effective interpretability to the end user is an imperative. The next sections will deal with the mechanics of

radiomics and AI in head and neck cancer to improve the understanding of their potential and challenges.

MECHANICS: FROM PICTURE APPRECIATION TO ARTIFICIAL INTERPRETATION

Current oncology practice is necessarily dependent upon medical images, and this dependence has increased in the last decades. CT scans are generally considered the standard imaging modality for diagnostic and therapy planning purposes, with their intensities consistently representing electron tissue density. For patients with head and neck cancer in particular, MRI is a valuable additional image modality[38] due to its exceptional soft tissue contrast as a result of the decomposition of radiofrequency resonance. Additionally, by detecting metabolic activity of tissues, PET can provide physiologic information to aid in distinguishing between normal and tumor tissues. This explains why MRI and PET are generally regarded as indispensable in tumor diagnosis, delineation, and response assessment,[39,40] as well as detection and tumor border definitions.[41-43] Moreover, the introduction of functional MRI sequences, such as diffusion-weighted imaging and dynamic contrast enhanced, provide spatially localized physiologic information in frame with anatomy, introducing an additional dimensionality to differentiate tumor from normal tissue.[44-51]

Semantic Image Evaluation

Because a trained human eye is excellent in pattern recognition, qualitative image evaluation by the radiologist has historically been the conventional clinical standard. Consequently, initial imaging research focused on semantic image features, which are image content descriptions according to human perception (e.g., "radiologically positive lymph node," "hypodense tumor," or "heterogeneous lesion" on a radiologist report), or simple image characteristic values (e.g., maximum longitudinal tumor diameter and mean intensity values). For instance, simple MRI and ^{18}F-fluorodeoxyglucose PET evaluation measures improved the diagnostic accuracy for malignant lymph node detection.[52] The predictive value of semantic imaging features directly translates to the clinical TNM staging based on radiologic image evaluation.[53] Furthermore, Wang et al[54] showed that tumor invasion and heterogeneity evaluation on MRI were predictive for local control in patients with nasopharyngeal cancer.

The improved quality and quantity of medical imaging of the last decades have opened doors to move from semantic or qualitative observer assessments (primary classification tasks) to quantitative machine-readable image measures for model-based treatment decision support. Additionally, the current climate of computational processing power, available large-scale (imaging) data, machine-learning, and AI approaches are now reaching a stage to exploit the ever-growing imaging data.

Machine Learning

In the early 2000s, terms such as computer-aided treatment, computer-aided detection, or computer-aided diagnosis were used to describe computational processes that process clinically useful image information.[55] In the last decades, AI has made is entrance in the head and neck oncology field. The definition of AI is the capability of a machine to imitate intelligent human behavior and is a collective term for all computer processes that fall under this definition.

Machine learning is a subfield within AI (Fig. 1), which in a broader sense refers to a computerized algorithm that learns to solve tasks by recognizing patterns in the data.[56] In other words, the "machine" (i.e., statistical model) learns from the associations in the presented data by minimizing the model's cost function. Predefined variables can be continuous (e.g., height and weight), categorical (smoking status: never, former, or current), ordinal (e.g., T-stage and performance score), or binary (yes or no; 1 or 0). Machine learning for medical images requires feature extraction from specific areas in the images, such as mean intensity or volume of the delineated tumor. More advanced image-processing techniques have allowed for image characteristic extraction that can quantify more comprehensive and complex aspects of an image, referring to the umbrella terminology radiomics.

RADIOMICS: IMAGE FEATURE MINING

The wealth of raw images acquired for oncology treatment is a great source of information for patient-specific anatomy and physiology and can be used beyond the scope of tumor detection and delineation. Radiomics refers to the process of quantifying patient-specific tissue characteristics from images into features (i.e., image biomarkers), translating intensity, texture, and geometric properties of the tissue from a specific volume of interest into single variables that can be fed into a machine-learning modeling process (Fig. 2). Although these features can describe similar characteristics as semantic features (think: heterogeneity of the tumor), the hypothesis is that they can reveal more information in a quantitative manner, because the medical images are processed as data not as pictures.[57,58] Although image texture analyses originated in the 1970s to 1980s,[59-61] the radiomics concept was not introduced until 2012 by Aerts et al,[4] proposing comprehensive extraction of geometric, first-order, and texture feature extraction, thereby converting medical images into high-dimensional minable data.[3,58,62] Aerts et al[4] showed that pretreatment CT-based radiomics features, describing the density, heterogeneity, and shape of the tumor, could predict overall survival of patients with non–small cell lung cancer and validated this

in an independent patient cohort of both head and neck and lung cancer. Several subsequent studies have confirmed that tumor radiomics features can contribute to the prediction of overall, disease-free, and progression-free survival in patients with head and neck,[4,63-66] lung,[4,67] cervical,[68] prostate, and rectal[69] cancer. The explanation of radiomics features is often intuitive and relatable to the semantics, such that high values of texture feature that capture higher heterogeneity of the tumor are associated with a higher risk of recurrence.[57,66] The geometric features can indicate that larger (e.g., volume) and more irregularly shaped (e.g., surface and bounding box) tumors are related to worse survival rates.[66] Radiomics features have been shown to have additional prediction value to clinical variables such as age, TNM stage, and performance score, but they can also replace them. As shown by Zhai et al,[66] the feature major axis length of all lymph nodes (i.e., the maximum length between pathologic lymph nodes) performed better in predicting survival than N stage. This indicates the potential of quantification of clinical variables, as well as the importance of being wary of multicollinearity (i.e., high interassociations between the independent variables).

DEEP LEARNING: MODELING DIRECTLY FROM THE IMAGE

Deep learning is a subtype of machine learning (Fig. 1) yet distinguishes itself from general machine learning by not requiring predefined features or variables, but rather inculcating both feature selection and variable weighting simultaneously directly from the image or data within the deep-learning network.[70,71] In imaging, the first layers of the neural network are convolutional layers, which are different sequential combinations of imaging filters that emphasize or suppress certain textures or patterns (Fig. 3). The convolution and fully connected network layers can extract image characteristics (e.g., eyes, tumor heterogeneity, and organ at-risk edges) without the human engineering of variables, thus being autodidactic in determining the most important aspect of the images. Similar to other machine-learning techniques, but even more prominent for deep learning, is the need to be wary for overfitting and lack of generalizability of the deep-learning model to new data. Important algorithm implementations have been made to charge a network for overfitting (e.g., dropout, internal cross validation, and permutations); nevertheless, it is extremely important to have a completely independent validation test set that has not been used during any part of model training process.

CHALLENGES IN MODELING

As for any statistical model, an overarching challenge is generating a generalizable model, meaning that the model will perform well in new unseen data. Key challenges that jeopardize the model generalizability and fragility are (1) the risk of false-positive associations, (2) over- and underfitting,

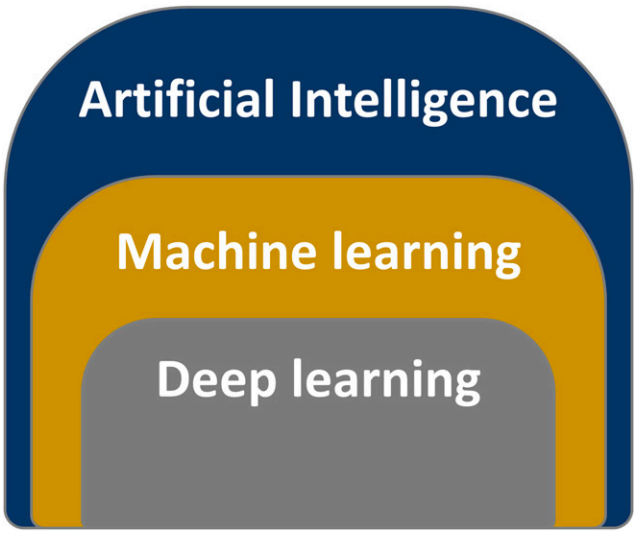

FIGURE 1. Definitions in Artificial Intelligence

(3) data representation bias, (4) unbalanced data, (5) multicollinearity, and (6) model result interpretability.

A false-positive variable refers to a statistically significant variable (p value less than set threshold) without a real underlying association of a variable with the outcome.[72] This is particularly important for radiomics features, as they may be highly coherent in the representation of an imaging characteristic of a given region of interest. Radiomics approaches specifically would be well advised to carefully implement correction strategies as a function of the number of candidate biomarkers/thresholds/features. A proposed approach is multiple testing corrections,[73] but they are often considered too simplistic for machine-learning approaches, and there is limited consensus on p-value adaptation in machine learning, as other methods may be more appropriate. This is a less direct issue for deep learning, but a network can detect "significant" areas in an image that for a biased relation with the endpoint or creating false areas in case of reconstruction.[74]

Overfitting or underfitting are main concerns in machine learning.[75] Although underfitting refers to not giving the model enough degrees of freedom to fit to the data (Fig. 4, left), overfitting refers to fitting a model very specifically on training data (Fig. 4, right). In both scenarios, this results in a model that does not perform well when presented to new data. In other words, the model is not "generalizable" to external data. Addressing under- and overfitting remains a challenge during all steps of any machine-learning analysis that requires serious and continuous considerations.

The patient sample size can cause incorrect model fitting and, hence, make a model ungeneralizable to new data. The main concern of training a model on a small data set is

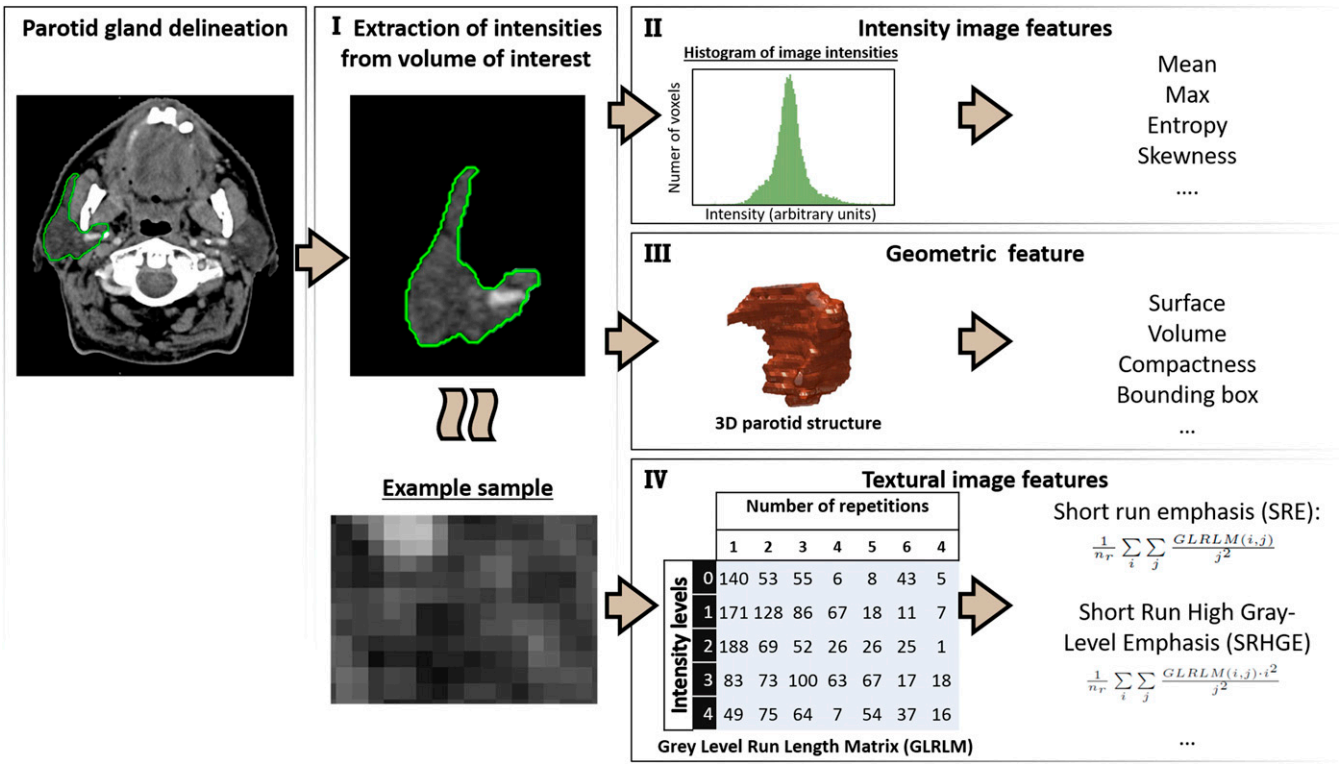

FIGURE 2. Radiomics Extraction Process

The segmented volume of interest is extracted from an image (I). The following radiomics types are extracted from this volume of interest: intensity image intensity features (II), geometric features (III), and texture features (IV). A gray-level run length matrix is given as example for texture calculation, which quantifies the number of repetitions of gray intensities from left to right.

Abbreviations: 3D, three-dimensional; Max, maximum.

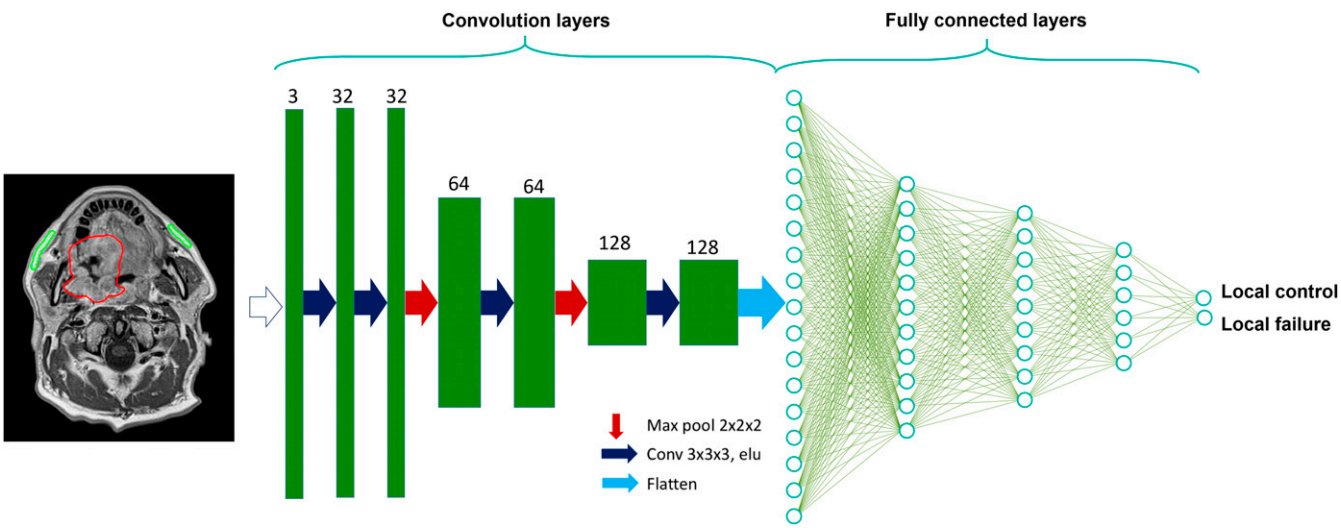

FIGURE 3. Deep Convolutional Neural Network Example for Classification Prediction Problem

Starting with an MRI, for example, as the input layer, followed by convolutional, pooling, and flatten layers, which is followed by fully connected layers to output the endpoint local tumor control vs. local tumor failure.

Abbreviation: Max, maximum.

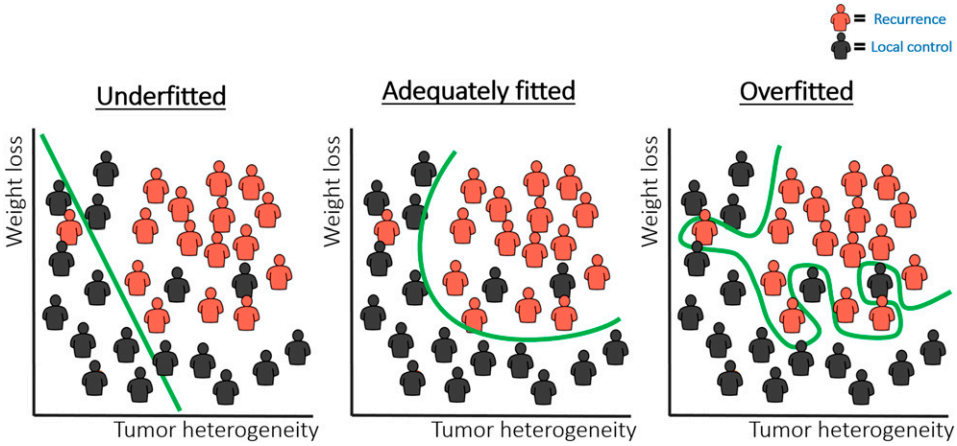

FIGURE 4. Example Case for a Classification Task

To distinguish the patients in red (e.g., recurrences) from those in black (e.g., local tumor control), a model is optimized to define a borderline that increases the distance between the two groups. Examples of model fits that are underfitted (left), adequately fitted (middle), and overfitted (right) are depicted.

that it is not an accurate representation of the full population. Moreover, medical data are often noisy, contain outliers, and nearly always hold some incorrect or erroneous information, due to clinical complexity and human error. Moreover, processes and reactions within the body are rarely fully predicted with a handful of variables in a simple linear manner. In other words, adequate patient numbers are required to represent medical processes and predict clinical outcome measures.

Unbalanced data can be a concern even in a representative cohort, as the dependent variable can be imbalanced, referring to a low number of events in the data set. For example, predicting the local recurrence with tumor image features in a cohort of patients with HPV-positive stage I to II oropharynx carcinomas is problematic due to extremely low local recurrence rates (approximately 2 in 100 patients). Fig. 5 demonstrates that the area under the curve performance measure is likely to be unrealistically high in unbalanced data, as isolated events can be falsely be detected. To mitigate this, the number of patients and events need to be increased. The pragmatic rule of thumb is that per 10 events in a data set, a model can contain a variable. Nevertheless, this is just a guideline and should be carefully evaluated in combination with overfitting monitoring measures.[76] For deep learning, upsampling methods have been proposed to overcome the shortcoming of imbalanced data; however, similar to general machine learning, the training performance measures must be evaluated with caution, and effectiveness needs to be better investigated[77]; regardless, the model will always need to be tested on a large enough imbalanced data set.

Multicollinearity refers to the high correlated relation between variables; if variables are introduced in a model without having added value to each other, that can result in overcompensation and redundancy. This a particular concern for radiomics approaches, as this is better mitigated in deep learning. It is important to be aware of multicollinearity during the modeling process, as it can easily occur due to the competition of similar variables, and variables are wrongfully selected or omitted.

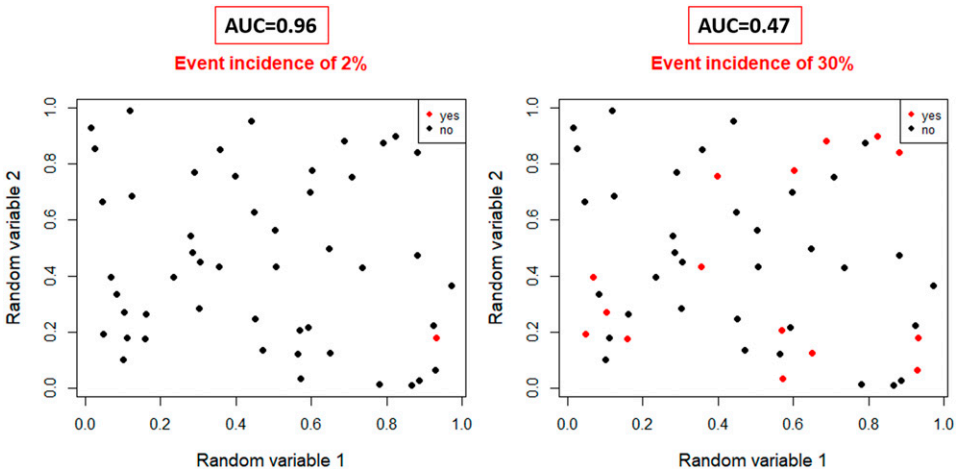

FIGURE 5. Logistic Regression Area Under the Curve Performance in Random Data for Highly Imbalanced Event Data (2% Event Rate, Left) and More Balanced Data (30% Event, Right)

AUC for imbalanced data is unrealistically high.

Abbreviation: AUC, area under the curve.

Model result interpretability can aid in the understanding of the modeling process, generalizability, and acceptance of a model by the medical community. The benefit of deep learning is that it allows for learning directly of the image itself and comes with the trade-off that it is much more a black box compared with radiomics machine-learning approaches, in which selected features, generally, can be compared with semantic understandings (e.g., tumor size and high heterogeneity). Efforts are arising to improve the human interpretability of deep-learning networks by visualizing the determining convolutional filters.[78,79] However, there is an unmet need for a transition from representation to derive the underpinning biologic processes or conditions detected by machine learning. For example, radiomics features derived algorithmically have been demonstrated to serve as representations of physiologic tissue-level characteristics, such as fattiness[15] and physiologic activity[80] of the parotid glands associated with the development of xerostomia.

CHALLENGES IN ONCOLOGIC IMAGING USING RADIOMICS AND ARTIFICIAL INTELLIGENCE

The largest challenge for image-based machine-learning approaches is in consistent and large-scale curated and standardized image data acquisition. Ger et al[81] showed that even if the same scanning protocol was used for CT image acquisition, this still resulted in differences in radiomics feature calculation on 100 scanners in 35 institutes. This illustrates that even CT, which is a much easier calibrated modality than PET or MRI, still suffers from substantial inter- and intrascanner variations. Many other studies have also illustrated the impact of different image reconstruction kernels, tube current, slice thickness, and scanner manufacturers on radiomics features.[82-84] This emphasizes both the importance of image acquisition standardization and calibration as well as testing the robustness of prediction image-based models in a new patient population that are scanned with different scanners or imaging acquisition protocols. This challenges interinstitutional implementation of prediction models.

For MRI, an additional hurdle is the lack of consistently available scans, which consequently results in small cohort sizes and lack of external validation in research studies. Systematic MRI acquisition is hampered due to continuous MRI sequence development, resulting in periodical changes in the image acquisition parameters and large differences in acquisition settings between treatment sites. Furthermore, the vast majority of the MR radiomics studies do not incorporate any intensity standardization of MR scans, which is questionable due to known biases in MR intensities.[85] A major, and often underestimated, challenge of MR-based AI applications is the lack of intrinsic value of MR intensities for the majority of acquisition methods (e.g., T1-/T2-/proton density–weighted images), meaning that they do not represent a specific fixed entity (i.e., they have arbitrary units), but rather have relative contrast value to adjacent MR intensity and structures (Fig. 6). MR normalization is currently still somewhat uncharted terrain outside the brain area.[86-88] Quantitative imaging modalities have been introduced, designed to represent diagnostically meaningful intensity values. Examples are diffusion-weighted imaging, T1-weighted or T2-weighted maps, and dynamic contrast-enhanced MRI,[89-91] yet currently, these MR sequences often have a limited signal-to-noise and courser resolution.

REPORTING AND SHARING RADIOMICS AND ARTIFICIAL INTELLIGENCE APPROACHES

One major limitation is that processes and approaches of AI development and testing do not conform to historical frequentist hypothesis framework in many instances, thus making reporting of radiomics[92] and AI models[93,94] difficult and representing a considerable barrier to advanced application for clinical use and external validation. Nevertheless, the field is evolving to more consistency and more rigorous modeling approaches. Many standardized guidelines are being introduced for modeling reporting (e.g., Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis [TRIPOD] methods),[95] image acquisition (e.g., Quantitative Imaging Biomarkers Alliance),[96] consistent image biomarker/radiomics extraction (e.g., Image Biomarker Standardization Initiative),[97] AI-driven clinical trials[98] and general AI reporting,[99] and imaging-specific applications.[100] Moreover, to propel the field forward, more efforts are surfacing to publish data to make head and neck cancer imaging data FAIR ("Findable, Accessible, Interoperable, Reusable")[101] and thus spur new model building and validation. Similarly, through platforms like GIThub software/script publication, sharing and validation has become highly efficient. Finally, ontologies[102] has made a concerted effort through improving the data annotation and informatics standards across data sources,[103] allowing facilitation of model development[103] and data transfer. These processes contribute to the implementation of robust actionable models in the head and neck cancer clinical practice and thereby consequently make it possible to tailor the treatment of head and neck cancer to improve therapy outcome and quality of life, allowing the transition of radiomics and AI from the laboratory to the clinic.

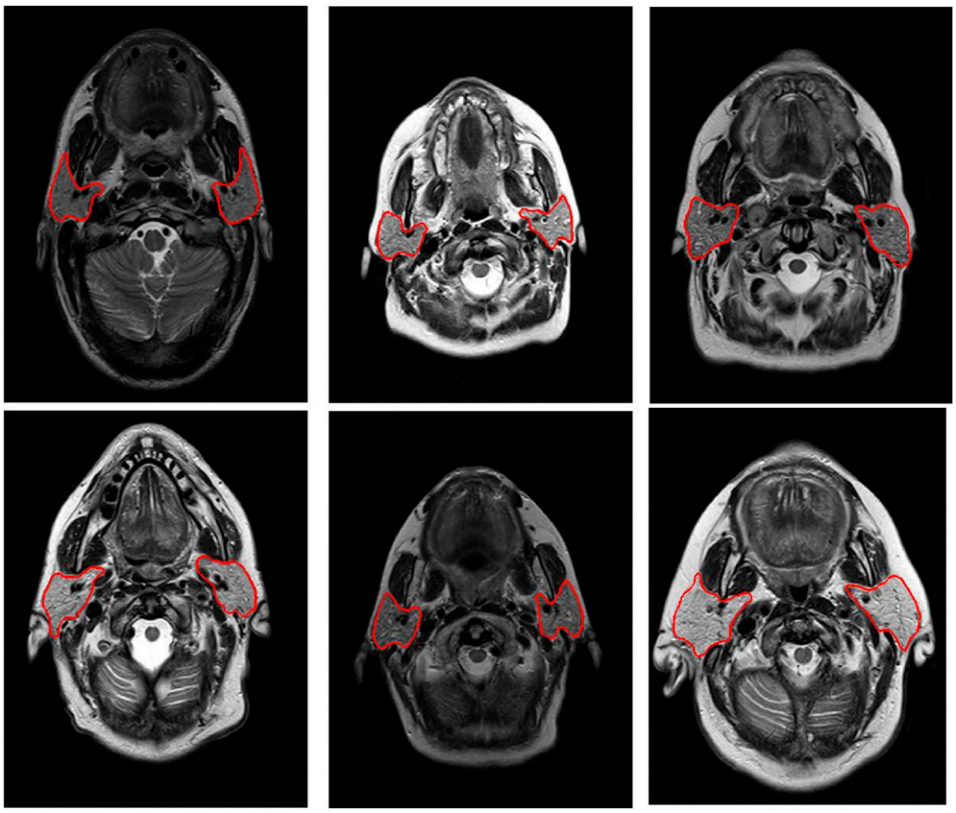

FIGURE 6. Pretreatment T1-Weighted MRIs Displayed With the Same Window Level (50–350 Arbitrary MR Units)
Clear differences can be observed in brightness (i.e., signal intensity) between the patients in tissues that are comparable in nature, such as fat and muscle.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Hatt M, Tixier F, Visvikis D, et al. Radiomics in PET/CT: more than meets the eye? J Nucl Med. 2017;58:365-366.
2. Leite AF, Vasconcelos KDF, Willems H, et al. Radiomics and machine learning in oral healthcare. Proteomics Clin Appl. 2020;14:e1900040.
3. Kumar V, Gu Y, Basu S, et al. Radiomics: the process and the challenges. Magn Reson Imaging. 2012;30:1234-1248.
4. Aerts HJWL, Velazquez ER, Leijenaar RTH, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun. 2014;5:4006.
5. Benson E, Li R, Eisele D, et al. The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas. Oral Oncol. 2014;50:565-574.
6. Marur S, D'Souza G, Westra WH, et al. HPV-associated head and neck cancer: a virus-related cancer epidemic. Lancet Oncol. 2010;11:781-789.
7. Braakhuis BJM, Visser O, Leemans CR. Oral and oropharyngeal cancer in The Netherlands between 1989 and 2006: Increasing incidence, but not in young adults. Oral Oncol. 2009;45:e85-e89.
8. Mirghani H, Blanchard P. Treatment de-escalation for HPV-driven oropharyngeal cancer: where do we stand? Clin Transl Radiat Oncol. 2017;8:4-11.
9. Bahig H, Yuan Y, Mohamed ASR, et al. Magnetic resonance-based response assessment and dose adaptation in human papilloma virus positive tumors of the oropharynx treated with radiotherapy (MR-ADAPTOR): an R-IDEAL stage 2a-2b/Bayesian phase II trial. Clin Transl Radiat Oncol. 2018;13:19-23.

10. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet. 2019;393:40-50.
11. Blanchard P, Baujat B, Holostenco V, et al; MACH-CH Collaborative group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol. 2011;100:33-40.
12. Gavrielatou N, Doumas S, Economopoulou P, et al. Biomarkers for immunotherapy response in head and neck cancer. Cancer Treat Rev. 2020;84:101977.
13. Dogan V, Rieckmann T, Münscher A, et al. Current studies of immunotherapy in head and neck cancer. Clin Otolaryngol. 2018;43:13-21.
14. van Dijk LV, Brouwer CL, van der Schaaf A, et al. CT image biomarkers to improve patient-specific prediction of radiation-induced xerostomia and sticky saliva. Radiother Oncol. 2017;122:185-191.
15. van Dijk LV, Thor M, Steenbakkers RJHM, et al. Parotid gland fat related magnetic resonance image biomarkers improve prediction of late radiation-induced xerostomia. Radiother Oncol. 2018;128:459-466.
16. Colen RR, Fujii T, Bilen MA, et al. Radiomics to predict immunotherapy-induced pneumonitis: proof of concept. Invest New Drugs. 2018;36:601-607.
17. Anthony GJ, Cunliffe A, Castillo R, et al. Incorporation of pre-therapy ^{18}F-FDG uptake data with CT texture features into a radiomics model for radiation pneumonitis diagnosis. Med Phys. 2017;44:3686-3694.
18. Pota M, Scalco E, Sanguineti G, et al. Early prediction of radiotherapy-induced parotid shrinkage and toxicity based on CT radiomics and fuzzy classification. Artif Intell Med. 2017;81:41-53.
19. Thor M, Tyagi N, Hatzoglou V, et al. A magnetic resonance imaging-based approach to quantify radiation-induced normal tissue injuries applied to trismus in head and neck cancer. Phys Imaging Radiat Oncol. 2017;1:34-40.
20. Abdollahi H, Mahdavi SR, Mofid B, et al. Rectal wall MRI radiomics in prostate cancer patients: prediction of and correlation with early rectal toxicity. Int J Radiat Biol. 2018;94:829-837.
21. Cardenas CE, Yang J, Anderson BM, et al. Advances in auto-segmentation. Semin Radiat Oncol. 2019;29:185-197.
22. Teguh DN, Levendag PC, Voet PWJ, et al. Clinical validation of atlas-based auto-segmentation of multiple target volumes and normal tissue (swallowing/mastication) structures in the head and neck. Int J Radiat Oncol Biol Phys. 2011;81:950-957.
23. Han X, Hoogeman MS, Levendag PC, et al. Atlas-based auto-segmentation of head and neck CT images. Med Image Comput Comput Assist Interv. 2008;11(Part 2):434-441.
24. van Dijk LV, Van den Bosch L, Aljabar P, et al. Improving automatic delineation for head and neck organs at risk by Deep Learning Contouring. Radiother Oncol. 2020;142:115-123.
25. Ibragimov B, Xing L. Segmentation of organs-at-risks in head and neck CT images using convolutional neural networks. Med Phys. 2017;44:547-557.
26. Yang X, Kwitt R, Styner M, et al. Quicksilver: fast predictive image registration - a deep learning approach. Neuroimage. 2017;158:378-396.
27. de Vos BD, Berendsen FF, Viergever MA, et al. A deep learning framework for unsupervised affine and deformable image registration. Med Image Anal. 2019;52:128-143.
28. Hu Y, Modat M, Gibson E, et al. Weakly-supervised convolutional neural networks for multimodal image registration. Med Image Anal. 2018;49:1-13.
29. Rodriguez-Ruiz A, Teuwen J, Vreemann S, et al. New reconstruction algorithm for digital breast tomosynthesis: better image quality for humans and computers. Acta Radiol. 2018;59:1051-1059.
30. Putzky P, Karkalousos D, Teuwen J, et al. i-RIM applied to the fastMRI challenge. arXiv. Epub 2019 Oct 20.
31. Pinckaers H, Litjens G. Training convolutional neural networks with megapixel images. Medical Imaging Deep Learning. Epub 2018 Apr 16.
32. Dinkla AM, Wolterink JM, Maspero M, et al. MR-only brain radiation therapy: dosimetric evaluation of synthetic CTs generated by a dilated convolutional neural network. Int J Radiat Oncol Biol Phys. 2018;102:801-812.
33. Maspero M, Savenije MHF, Dinkla AM, et al. Dose evaluation of fast synthetic-CT generation using a generative adversarial network for general pelvis MR-only radiotherapy. Phys Med Biol. 2018;63:185001.
34. Gupta D, Kim M, Vineberg KA, et al. Generation of synthetic CT images from MRI for treatment planning and patient positioning using a 3-channel U-net trained on sagittal images. Front Oncol. 2019;9:964.
35. Florkow MC, Zijlstra F, Willemsen K, et al. Deep learning-based MR-to-CT synthesis: The influence of varying gradient echo-based MR images as input channels. Magn Reson Med. 2020;83:1429-1441.
36. Cohen O, Zhu B, Rosen MS. MR fingerprinting Deep RecOnstruction NEtwork (DRONE). Magn Reson Med. 2018;80:885-894.
37. Virtue P, Yu SX, Lustig M. Better than real: complex-valued neural nets for MRI fingerprinting. Proc IEEE Int Conf Image Process. 2017;2017:3953-3957.
38. Dai YL, King AD. State of the art MRI in head and neck cancer. Clin Radiol. 2018;73:45-59.
39. Stieb S, Kiser K, van Dijk L, et al. Imaging for response assessment in radiation oncology: current and emerging techniques. Hematol Oncol Clin North Am. 2020;34:293-306.
40. Stieb S, McDonald B, Gronberg M, et al. Imaging for target delineation and treatment planning in radiation oncology: current and emerging techniques. Hematol Oncol Clin North Am. 2019;33:963-975.
41. Buchbender C, Heusner TA, Lauenstein TC, et al. Oncologic PET/MRI, part 1: tumors of the brain, head and neck, chest, abdomen, and pelvis. J Nucl Med. 2012;53:928-938.
42. Patel SG, Shah JP. TNM staging of cancers of the head and neck: striving for uniformity among diversity. CA Cancer J Clin. 2005;55:242-258quiz 261-262, 264.

43. Adams S, Baum RP, Stuckensen T, et al. Prospective comparison of ^{18}F-FDG PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. Eur J Nucl Med. 1998;25:1255-1260.
44. Tofts PS, Kermode AG. Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1. Fundamental concepts. Magn Reson Med. 1991;17:357-367.
45. Zheng D, Chen Y, Liu X, et al. Early response to chemoradiotherapy for nasopharyngeal carcinoma treatment: Value of dynamic contrast-enhanced 3.0 T MRI. J Magn Reson Imaging. 2015;41:1528-1540.
46. Shukla-Dave A, Lee NY, Jansen JFA, et al. Dynamic contrast-enhanced magnetic resonance imaging as a predictor of outcome in head-and-neck squamous cell carcinoma patients with nodal metastases. Int J Radiat Oncol Biol Phys. 2012;82:1837-1844.
47. Huang Z, Yuh KA, Lo SS, et al. Validation of optimal DCE-MRI perfusion threshold to classify at-risk tumor imaging voxels in heterogeneous cervical cancer for outcome prediction. Magn Reson Imaging. 2014;32:1198-1205.
48. Lu Y, Jansen JFA, Stambuk HE, et al. Comparing primary tumors and metastatic nodes in head and neck cancer using intravoxel incoherent motion imaging: a preliminary experience. J Comput Assist Tomogr. 2013;37:346-352.
49. Maeda M, Maier SE. Usefulness of diffusion-weighted imaging and the apparent diffusion coefficient in the assessment of head and neck tumors. J Neuroradiol. 2008;35:71-78.
50. Kono K, Inoue Y, Nakayama K, et al. The role of diffusion-weighted imaging in patients with brain tumors. AJNR Am J Neuroradiol. 2001;22:1081-1088.
51. Heijmen L, Verstappen MCHM, Ter Voert EEGW, et al. Tumour response prediction by diffusion-weighted MR imaging: ready for clinical use? Crit Rev Oncol Hematol. 2012;83:194-207.
52. Braams JW, Pruim J, Freling NJM, et al. Detection of lymph node metastases of squamous-cell cancer of the head and neck with FDG-PET and MRI. J Nucl Med. 1995;36:211-216.
53. Veit-haibach P, Luczak C, Wanke I, et al. TNM staging with FDG-PET/CT in patients with primary head and neck cancer. Eur J Nucl Med Mol Imaging. 2007; 34:1953-1962.
54. Wang Y, Zhao H, Zhang ZQ, et al. MR imaging prediction of local control of nasopharyngeal carcinoma treated with radiation therapy and chemotherapy. Br J Radiol. 2014;87:20130657.
55. Mahmood H, Shaban M, Indave BI, et al. Use of artificial intelligence in diagnosis of head and neck precancerous and cancerous lesions: a systematic review. Oral Oncol. 2020;110:104885.
56. Neri E, de Souza N, Brady A, et al; European Society of Radiology (ESR). What the radiologist should know about artificial intelligence - an ESR white paper. Insights Imaging. 2019;10:44.
57. Yip SSF, Liu Y, Parmar C, et al. Associations between radiologist-defined semantic and automatically computed radiomic features in non-small cell lung cancer. Sci Rep. 2017;7:3519.
58. Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. Radiology. 2016;278:563-577.
59. Haralick R, Shanmugan K, Dinstein I. Textural features for image classification [Internet]. Vol. 3. IEEE Trans Syst Man Cybern. 1973;SMC-3:610-621.
60. Galloway MM. Texture analysis using gray level run lengths. Comput Graph Image Process. 1975;4:172-179.
61. Amadasun M, King R. Textural features corresponding to textural properties. IEEE Trans Syst Man Cybern. 1989;19:1264-1273.
62. Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer. 2012;48:441-446.
63. Abgral R, Keromnes N, Robin P, et al. Prognostic value of volumetric parameters measured by 18F-FDG PET/CT in patients with head and neck squamous cell carcinoma. Eur J Nucl Med Mol Imaging. 2014;41:659-667.
64. Koyasu S, Nakamoto Y, Kikuchi M, et al. Prognostic value of pretreatment ^{18}F-FDG PET/CT parameters including visual evaluation in patients with head and neck squamous cell carcinoma. AJR Am J Roentgenol. 2014;202:851-858.
65. Alluri KC, Tahari AK, Wahl RL, et al. Prognostic value of FDG PET metabolic tumor volume in human papillomavirus-positive stage III and IV oropharyngeal squamous cell carcinoma. AJR Am J Roentgenol. 2014;203:897-903.
66. Zhai T-T, van Dijk LV, Huang B-T, et al. Improving the prediction of overall survival for head and neck cancer patients using image biomarkers in combination with clinical parameters. Radiother Oncol. 2017;124:256-262.
67. Thawani R, McLane M, Beig N, et al. Radiomics and radiogenomics in lung cancer: a review for the clinician. Lung Cancer. 2018;115:34-41.
68. Lucia F, Visvikis D, Desseroit MC, et al. Prediction of outcome using pretreatment ^{18}F-FDG PET/CT and MRI radiomics in locally advanced cervical cancer treated with chemoradiotherapy. Eur J Nucl Med Mol Imaging. 2018;45:768-786.
69. Yi X, Pei Q, Zhang Y, et al. MRI-based radiomics predicts tumor response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer. Front Oncol. 2019;9:552.
70. Krizhevsky A, Sutskever I, Hinton GE. ImageNet classification with deep convolutional neural networks. Communications of the ACM. 2017;60:84-90
71. McCulloch WS, Pitts W. A logical calculus of the ideas immanent in nervous activity. Bull Math Biophys. 1943;5:115-133.
72. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B. 1995;57:289-300.
73. Aickin M, Gensler H. Adjusting for multiple testing when reporting research results: the Bonferroni vs Holm methods. Am J Public Health. 1996;86:726-728.
74. Antun V, Renna F, Poon C, et al. On instabilities of deep learning in image reconstruction and the potential costs of AI. Proc Natl Acad Sci USA. 2020; 117:30088-30095.

75. van der Schaaf A, Xu CJ, van Luijk P, et al. Multivariate modeling of complications with data driven variable selection: guarding against overfitting and effects of data set size. Radiother Oncol. 2012;105:115-121.

76. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2007;165:710-718.

77. Viloria A, Pineda Lezama OB, Mercado-Caruzo N. Unbalanced data processing using oversampling: Machine Learning. Procedia Comput Sci. 2020; 175:108-113.

78. Men K, Geng H, Zhong H, et al. A deep learning model for predicting xerostomia due to radiation therapy for head and neck squamous cell carcinoma in the RTOG 0522 clinical trial. Int J Radiat Oncol Biol Phys. 2019;105:440-447.

79. Yosinski J, Clune J, Nguyen A, et al. Understanding neural networks through deep visualization. Paper presented at: Deep Learning Workshop, 32nd International Conference on Machine Learning; July 6–1, 2015; Lille, France.

80. van Dijk LV, Noordzij W, Brouwer CL, et al. ^{18}F-FDG PET image biomarkers improve prediction of late radiation-induced xerostomia. Radiother Oncol. 2018; 126:89-95.

81. Ger RB, Zhou S, Chi PM, et al. Comprehensive investigation on controlling for CT imaging variabilities in radiomics studies. Sci Rep. 2018;8:13047.

82. He L, Huang Y, Ma Z, et al. Effects of contrast-enhancement, reconstruction slice thickness and convolution kernel on the diagnostic performance of radiomics signature in solitary pulmonary nodule. Sci Rep. 2016;6:34921.

83. Larue RTHM, van Timmeren JE, de Jong EEC, et al. Influence of gray level discretization on radiomic feature stability for different CT scanners, tube currents and slice thicknesses: a comprehensive phantom study. Acta Oncol. 2017;56:1544-1553.

84. Mackin D, Fave X, Zhang L, et al. Measuring CT scanner variability of radiomics features. Invest Radiol. 2015;50:757-765.

85. Shiri I, Abdollahi H, Shaysteh S, et al. Test-retest reproducibility and robustness analysis of recurrent glioblastoma MRI radiomics texture features. Iran J Radiol. 2017;31:e48035.

86. Nyúl LG, Udupa JK, Zhang X. New variants of a method of MRI scale standardization. IEEE Trans Med Imaging. 2000;19:143-150.

87. Sun X, Shi L, Luo Y, et al. Histogram-based normalization technique on human brain magnetic resonance images from different acquisitions. Biomed Eng Online. 2015;14:73.

88 Loizou CP, Pantziaris M, Seimenis I, et al. Brain MR image normalization in texture analysis of multiple sclerosis. Paper presented at: 9th International Conference on Information Technology and Applications in Biomedicine; November 1–5, 2009; Larnaca, Cyprus.

89. Koh D-M, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. AJR Am J Roentgenol. 2007;188:1622-1635.

90. Rosenkrantz AB, Mendiratta-Lala M, Bartholmai BJ, et al. Clinical utility of quantitative imaging. Acad Radiol. 2015;22:33-49.

91. Abramson RG, Burton KR, Yu JPJ, et al. Methods and challenges in quantitative imaging biomarker development. Acad Radiol. 2015;22:25-32.

92. Jethanandani A, Lin TA, Volpe S, et al. Exploring applications of radiomics in magnetic resonance imaging of head and neck cancer: a systematic review. Front Oncol. 2018;8:131.

93. Kim DW, Jang HY, Kim KW, et al. Design characteristics of studies reporting the performance of artificial intelligence algorithms for diagnostic analysis of medical images: results from recently published papers. Korean J Radiol. 2019;20:405-410.

94. Nagendran M, Chen Y, Lovejoy CA, et al. Artificial intelligence versus clinicians: systematic review of design, reporting standards, and claims of deep learning studies. BMJ. 2020;368:m689.

95. Moons KGM, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. 2015;162:W1-W73.

96. Shukla-Dave A, Obuchowski NA, Chenevert TL, et al. Quantitative Imaging Biomarkers Alliance (QIBA) recommendations for improved precision of DWI and DCE-MRI derived biomarkers in multicenter oncology trials. J Magn Reson Imaging. 2019;49:e101-e121.

97. Zwanenburg A, Vallières M, Abdalah MA, et al. The Image Biomarker Standardization Initiative: standardized quantitative radiomics for high-throughput image-based phenotyping. Radiology. 2020;295:328-338.

98. Liu X, Cruz Rivera S, Moher D, et al; SPIRIT-AI and CONSORT-AI Working Group. Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. Nat Med. 2020;26:1364-1374.

99. Hernandez-Boussard T, Bozkurt S, Ioannidis JPA, et al. MINIMAR (MINimum Information for Medical AI Reporting): developing reporting standards for artificial intelligence in health care. J Am Med Inform Assoc. 2020;27:2011-2015.

100. Mongan J, Moy L, Kahn CE. Checklist for artificial intelligence in medical imaging (CLAIM): a guide for authors and reviewers. Radiol Artif Intell. 2020; 2:e200029.

101. Goble C, Cohen-Boulakia S, Soiland-Reyes S, et al. FAIR computational workflows. Data Intell. 2019;23:108-121.

102. Traverso A, van Soest J, Wee L, et al. The radiation oncology ontology (ROO): publishing linked data in radiation oncology using semantic web and ontology techniques. Med Phys. 2018;45:e854-e862.

103. Holzinger A, Haibe-Kains B, Jurisica I. Why imaging data alone is not enough: AI-based integration of imaging, omics, and clinical data. Eur J Nucl Med Mol Imaging. 2019;46:2722-2730.

Assessment Criteria and Clinical Implications of Extranodal Extension in Head and Neck Cancer

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overview

Tumor breaching the capsule of a lymph node is termed extranodal extension (ENE). It reflects aggressiveness of a tumor, creates anatomic challenges for disease clearance, and increases the risk of distant metastasis. Extranodal extension can be assessed on a pathology specimen, by radiology studies, and by clinical examination. Presence of ENE in a pathology specimen has long been considered a high-risk feature of disease progression and would ordinarily benefit from the addition of chemotherapy to adjuvant radiotherapy. Although the eighth edition of the Union for International Cancer Control/American Joint Committee on Cancer stage classification dichotomizes pathologic ENE according to its presence or absence, emerging evidence suggests that the extent of a pathologic ENE may provide additional value for risk stratification to guide adjuvant therapy. Recent data suggest that the prognostic importance of pathologic ENE is also applicable for HPV-associated head and neck squamous cell carcinoma. In addition, compelling data demonstrate that indisputable radiologic ENE is a powerful risk stratification tool to identify patients at high risk for treatment failure, especially distant metastasis, applicable for both HPV-positive and HPV-negative head and neck squamous cell carcinoma. However, the definition and taxonomy of radiologic ENE requires standardization. The goal of this review is to clarify the contemporary understanding of the prognostic implications of ENE in head and neck squamous cell carcinoma, present the nuances of what is presently known and unknown, and elucidate how to classify ENE pathologically and radiologically with an understanding of the strengths and weaknesses of each approach. Finally, with the development of several risk stratification methods, the relative role of ENE and other prognostic schema will be explored.

INTRODUCTION

Extranodal extension (ENE) is tumor growth beyond the capsule of a lymph node that typically presents a natural barrier for tumor progression. Presence of ENE reflects the aggressiveness of a tumor,[1] creates anatomic challenges for disease clearance, and increases the possibility of tumor cells entering the blood stream, which, in turn, raises the risk of distant metastasis.[2] In locally advanced head and neck squamous cell carcinoma (HNSCC), ENE has long been considered a pathologic high-risk feature, meaning that patients are at increased risk of disease progression and would benefit from the addition of chemotherapy to adjuvant radiotherapy.

This oncologic tenet of HNSCC care along with its underlying prognostic implications have recently been questioned in the context of HPV-associated oropharynx squamous cell carcinomas, which now account for most HNSCCs in North America. The gold standard for assessment of ENE is based on pathologic evaluation of the neck dissection specimen (pENE) and is predicated on receipt of primary surgical therapy. However, the therapeutic paradigm of advanced HNSCCs of select anatomic sites has evolved to also encompass primary radiotherapy as a modality of equivalent oncologic efficacy. Therefore, alternative methods of assessing ENE pretreatment (e.g., radiologic) have been explored.

The goal of this review is to clarify the contemporary understanding of the prognostic implications of ENE, the nuances of what is presently known and unknown, and how to classify ENE pathologically and radiologically with an understanding of the strengths and weaknesses of each approach. Finally, with the development of several risk stratification methods, the relative role of ENE and other prognostic schema will be explored.

BACKGROUND

Historically, HNSCC was a disease caused nearly uniformly by tobacco and alcohol use. Surgery was the mainstay of primary therapy, with radiation and chemotherapy reserved for an adjuvant role. Several pivotal observations in the 1980s to 2000s contributed to a transformation in the care of patients with HNSCC. The first was the landmark Veterans Affairs Laryngeal Study Group that demonstrated that induction chemotherapy preceding primary radiotherapy was oncologically equivalent to surgery and adjuvant radiotherapy

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PRACTICAL APPLICATIONS

- Extranodal extension reflects aggressiveness of a tumor and creates anatomic challenges for disease clearance.
- Pathologic extent of extranodal extension may provide additional prognostic information for patients with head and neck cancer, but additional data are needed.
- Radiologic extranodal extension is a strong prognostic factor in both viral-related and -unrelated head and neck cancer, but standardization of assessment criteria is warranted.
- Extranodal extension has potential in risk stratification and refinement of future TNM N classifications.
- Standardization of taxonomy and criteria for radiologic extranodal extension is warranted.

and resulted in organ preservation.[3] The second was the Intergroup RTOG 91-11 study, which built on the first and demonstrated higher laryngeal preservation in the concurrent chemoradiotherapy than in the radiotherapy alone or induction chemotherapy groups.[4] Several other groups made similar observations for HNSCCs of heterogeneous anatomic sites, including hypopharynx, larynx, oropharynx, and pharynx.[5] The third was the demonstration that patients with locoregionally advanced HNSCC benefited from the addition of chemotherapy to adjuvant radiotherapy in terms of overall survival and recurrence in two synchronous trials in the United States and Europe. In a combined analysis of the two, in the presence of ENE and/or positive margins, chemoradiotherapy was associated with improved prognosis compared with adjuvant radiotherapy alone.[6] With growing appreciation for functional outcomes, oncologic equivalency, and the higher risk of severe and fatal complication rates from surgical approaches from an earlier era,[7] radiation-based therapy emerged as the favored primary approach for many HNSCCs.

In the last 15 years, several innovations, including transoral surgery, the emergence of HPV-related HNSCCs with evolving demographics and improved prognosis, and an improved understanding of functional comorbidities, has led to a re-examination of prior data.

PROGNOSTIC VALUE AND CLINICAL IMPLICATIONS OF MAJOR VERSUS MICROSCOPIC PATHOLOGIC ENE IN HPV-POSITIVE AND HPV-NEGATIVE HNSCC

Early observations of ENE were limited to the prognostic impact of the presence of this pathologic entity, which was associated with higher rates of regional and distant recurrence and worse overall survival and disease-free survival. Although they were not termed microscopic or major ENE, there were descriptions of malignancy replacing a node and minimally overreaching the capsule, being histologically distinct and of better prognosis than malignancy, and not only replacing a node but extending to adjacent soft tissue.[8,9] This literature was based on single-institution case series and comprised heterogenous anatomic sites, consistent with the treatment paradigms of the times. The benefit of these studies is that they provided estimates of survival for ENE alone. They established that ENE reduced survival by 50% and that this pathologic marker more reliably predicted prognosis than staging. Based on this early literature, single-institution and later multi-institution studies showed the prognostic benefit of adjuvant radiation therapy in ENE-positive disease. Building on this understanding, Johnson et al[10,11] showed an incrementally reduced risk of death or recurrence (local, regional, and distant) with the addition of chemotherapy to adjuvant radiation therapy. Our understanding of the prognostic impact of ENE was solidified by the pooled analysis of EORTC 22931 and RTOG 9501.[6] This demonstrated the benefit of the addition of chemotherapy to adjuvant radiotherapy; however, it is important to appreciate that the analysis was not restricted to the prognostic information of ENE alone but rather included ENE and/or positive margins. Yet, this study remains informative with its large sample size, uniformity of treatment, being prospective in nature, and 53% to 57% of each study population having ENE either alone or in combination with positive margins. The pooled risk of locoregional relapse and death across both trials was reduced by chemotherapy by 42% and 30%, respectively.[6]

As the epidemiology of HNSCC has markedly changed in recent decades, the relevance of ENE in HPV-associated oropharynx cancer, a disease of generally good prognosis, has been questioned.[12] Several retrospective studies have evaluated the prognostic impact of ENE as a binary variable (present vs. absent) without accounting for the pathologic nuances. Although some studies have found significant reductions in survival associated with ENE,[13-19] others have not.[20,21] Importantly, in studies that lacked statistical significance, especially smaller ones without ample statistical power to detect differences, the direction and magnitude of the differences have been consistent across studies. Generally, ENE is associated with a two- to eight-fold increased risk of recurrence or death and even in some cases after adjusting for other independent predictors including smoking and positive margins. Notably, these differences have generally been observed in series of patients who have received adjuvant therapy, which improves prognosis for ENE, thereby attenuating differences that would be observed without receipt of adjuvant therapy. Indeed, in

a series of patients who did not receive adjuvant therapy, 8 of 16 with ENE experienced relapse.[22] In the United States, it appears that ENE remains strongly predictive of the receipt of adjuvant chemoradiotherapy.[23] With the recognition of the more nuanced grading of ENE, analyses have shown that prognosis is associated with the grade of ENE; hence, in the current understanding, major ENE and overt clinical signs of ENE are strongly associated with poor prognosis. However, the impact of microscopic ENE may be relatively less influential. Given the limitations in inter- and intrarater classification of microscopic ENE and grades of ENE, interpretation of its impact on prognosis is further restricted.

By contrast, in HPV-negative oropharynx cancer and nonoropharyngeal HNSCC, there is no controversy regarding the prognostic significance of ENE.[24] To reflect this dichotomy, the eighth edition of the Union for International Cancer Control/American Joint Committee on Cancer staging includes ENE in nodal classification for non–HPV-associated HNSCC but excludes it for HPV-associated oropharynx cancers (and Epstein-Barr virus–associated nasopharynx cancers). The presence of ENE effectively upstages nodal disease, thereby reflecting a decrement in prognosis. Also noteworthy is the collection of microscopic ENE ($\leq$ 2 mm) and major ENE ($>$ 2 mm), without inclusion in the staging schema.

ASSESSMENT OF PATHOLOGIC ENE EXTENT

In the seventh edition of the Union for International Cancer Control/American Joint Committee on Cancer stage classification, extent of pENE was quantified simply as macroscopic versus microscopic; however, neither extent nor even presence of ENE was incorporated into the N classification.[25,26] Macroscopic pENE was defined as clinically or grossly apparent (to the naked eye) soft tissue involvement, whereas microscopic disease was defined as only visible histologically.[25] The distinction between macroscopic and microscopic is subjective and imprecise. At least one study attempted to define macroscopic pENE as more than a few layers of tumor cells extending outside the lymph node,[27] but this definition remains vague. Nevertheless, several studies demonstrated a worse prognosis with macroscopic pENE compared with microscopic pENE in laryngo-hypopharyngeal cancer[28] and other HNSCCs.[29] This has not been a universal finding.[30]

Several attempts were subsequently made to more specifically quantify the degree of pENE. Yamada et al[31] categorized pENE extent into types A (few tumor cells outside of the capsule), B (slight invasion of soft tissue with capsular destruction), and C (macroscopic invasion). These definitions are still vague, and only type C was associated with a worse prognosis in oral cavity squamous cell carcinoma (SCC) on multivariate analysis. Lewis et al[32] established a more well-defined grading system (grades 0–4) for pENE. However, Lewis grade 1 (thickened capsule with no extension beyond the capsule) is not considered true ENE (Fig. 1), and the distinction between grades 2 and 3 (cutoff of 1 mm) was arbitrarily determined.[31] Multiple studies[31,33,34] have failed to show significance of this grading system in multivariate analysis for both HPV-positive and HPV-negative tumors.

Direct measurement of pENE in millimeters is a more precise method for quantifying extent of soft tissue invasion by nodal metastases. A continuous variable allows for the

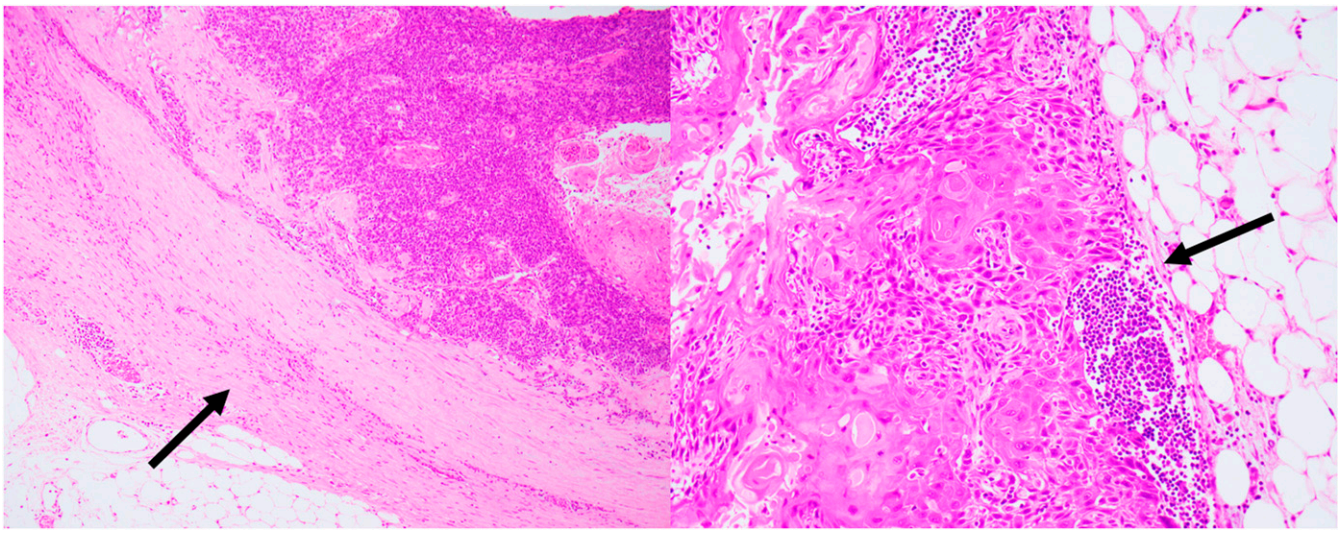

FIGURE 1. Lymph Node Metastases Without Pathologic Extranodal Extension
Lewis grade 1 extranodal extension (left) shows a thickened and obscured lymph node capsule (arrow) without infiltration into the surrounding soft tissue. This pattern is not considered true extranodal extension. For comparison, a lymph node metastasis without a thickened capsule (arrow) is shown (right).

determination of an optimal cutoff point to define clinically relevant ENE. A few earlier studies that examined direct measurement of pENE extent in millimeters were limited by study design. For example, Greenberg et al[35] did not find 2 mm to be a significant cutoff point in oral tongue SCCs; however, the sample size was small (33 patients), and the cutoff point of 2 mm was arbitrary and not empirically derived. In contrast, Kwon et al[36] identified 2 mm or greater as a poor prognostic indicator of cancer-specific survival in multivariate analysis. However, it is difficult to draw conclusions from this study because it included oropharyngeal and nonoropharyngeal sites without information on HPV status.

More recently, direct measurement in millimeters has been carefully investigated in several single-institution retrospective studies (with pathology review) of oral cavity SCC. When directly measured, most lymph nodes with ENE (> 90%) show 5 mm or less of extension beyond the capsule, and the average extent is typically around 2 mm.[37,38] Evidence is emerging that 2 mm may be an important cutoff point, but data are limited and conflicting. Wreesmann et al[39] used receiver operating characteristics curve analysis to determine that 1.7 mm or less of extranodal extension had the same disease-specific survival as no extranodal extension in oral cavity SCC, whereas those with more than 1.7 mm of extranodal extension fared worse, including in multivariate analysis. Based on their data, a cutoff point of 2 mm was included in the latest, eighth edition of the Union for International Cancer Control/American Joint Committee on Cancer staging manual, with major considered as 2 mm or greater and microscopic as 2 mm or less. A more precise measurement such as 1.7 mm was considered unlikely to be reproducible. Although presence/absence of ENE was incorporated into the nodal N staging system, inclusion of extent was only for data collection purposes, because further validation was needed.

Since the publication of the eighth edition of the Union for International Cancer Control/American Joint Committee on Cancer staging manual, attempts to validate the 2-mm cutoff between major and microscopic ENE have been mixed. Mamic et al[40] found a similar cutoff of 1.9 mm by receiver operating characteristics curve analysis to be prognostic in multivariate analysis of oral cavity SCCs, although only patients with clinically occult nodal disease were included in the study. In contrast, a recent examination of ENE in oral cavity SCC[38] found that a 2-mm cutoff was not prognostic; instead, 5 mm imparted worse disease-free and overall survival but only in univariate analysis. Large prospective studies and studies that include nonoral cavity sites and HPV-negative and HPV-positive tumors are needed. Analysis of the ENE data that are now being routinely collected per the American Joint Committee on Cancer guidelines will be helpful.

It is important to keep in mind that measurement of ENE can be challenging in some lymph nodes. If the capsule is effaced, extranodal extent can be estimated by attempting to reconstruct the capsule (Fig. 2). Yet, capsular reconstruction may not be possible in all cases, especially if the lymph node is entirely replaced (soft tissue metastasis). Most cases, even if not directly measurable, can be categorized as major (> 2 mm) or microscopic (≤ 2 mm) despite these limitations. Interobserver agreement studies, which

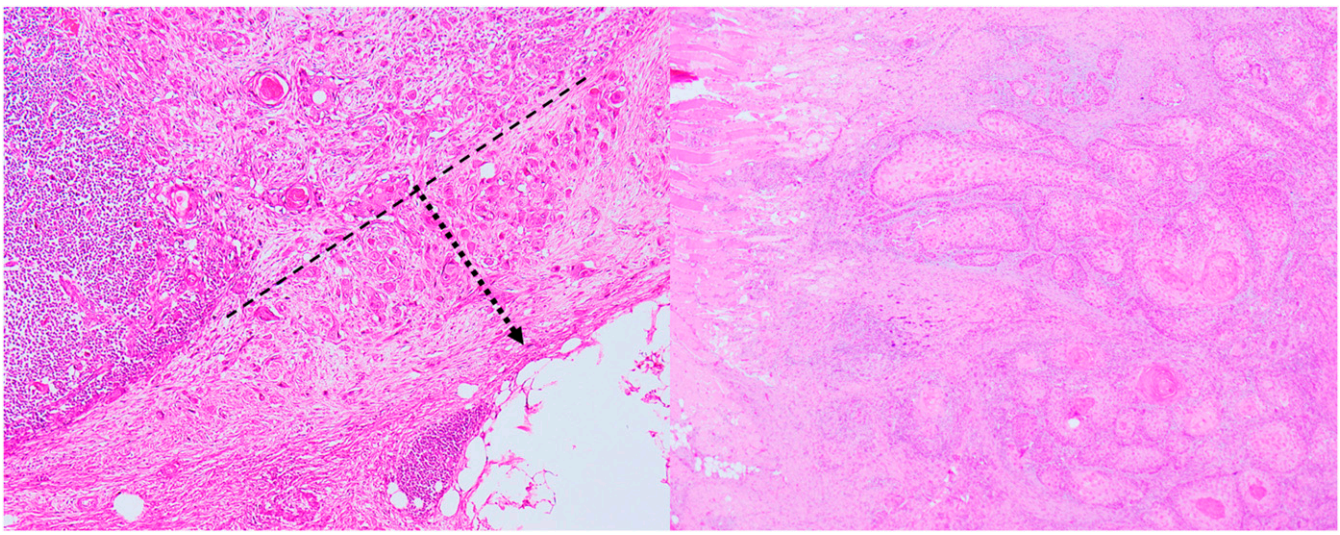

FIGURE 2. Lymph Node Metastases With Pathologic Extranodal Extension
The extent of extranodal extension can be measured when the capsule is focally effaced by perpendicular measurement from a reconstructed capsule (left). A completely effaced capsule in a soft tissue metastasis cannot be reconstructed (right) but is consistent with major (> 2 mm) extranodal extension.

are currently lacking, would be helpful to determine the reproducibility of extranodal extent measurements. Previous studies[41,42] have shown only moderate agreement among pathologists in the dichotomous classification of extranodal extension as either present or absent. Lewis et al[41] found that providing pathologists with precise definitions improved agreement only modestly. Thus, it is unclear whether measurements of ENE are reproducible among pathologists.

Another often overlooked factor that may impact extent of ENE measurement is lymph node sampling. The amount of tissue submitted for histologic evaluation of grossly positive metastases is variable and institution-dependent. No universally accepted standards exist; however, representative sampling of larger metastases is common. Sampling method could impact the extent measurement or even whether ENE is identified at all. Standardization of lymph node processing may increase the accuracy of detecting pENE extent.[43]

ASSESSMENT OF RADIOLOGY STUDIES OF ENE: CRITERIA, PATTERN, AND CORRELATION WITH PATHOLOGIC ENE

As noted earlier, the gold standard for ENE detection is based on pathologic findings, but ENE can also be identified by radiologic assessment (rENE).[44-46] The essence of rENE is based on radiologic signs of tumor breaching through the nodal capsule into and beyond surrounding fat. The early hallmark of rENE would typically be an indistinct nodal margin on anatomic imaging (CT or MRI).[47] The specificity of rENE based on this sign alone for pENE is highly dependent on the threshold adopted by individual radiologists to declare it positive. As tumor breaches the nodal capsule further, the radiologic signs of rENE become more explicit (to eventually be considered indisputable), resulting in a very high specificity ($>$ 90%) of rENE for pENE.[45,47]

Many radiologic features of rENE have been described in the literature, likely reflecting the extent of rENE (Table 1). Huang et al[48] summarized rENE in the following patterns that link to the extent of rENE (Fig. 3): (1) Pattern 1 describes tumor invasion through a single nodal capsule but confined to perinodal fat, characterized as ill-defined nodal borders; (2) Pattern 2 describes tumor invasion through the nodal capsule of two or more lymph nodes but confined to perinodal fat, subdivided into separate disassociated nodes each with rENE (Pattern 2a) or inseparable adjoining nodes exhibiting unambiguous effacement of any component of their internodal plane(s) (implying replacement by tumor) to form a coalescent nodal mass (Pattern 2b); and (3) Pattern 3 describes tumor invasion beyond surrounding nodal fat planes to invade or encase muscles and neurovascular structures. The frequency of Pattern 1 rENE and Pattern 2a is rare ($<$ 3%) in reality.[48] Pattern 3 rENE represents the worst form of rENE, often associated with clinical signs of ENE: invasion of skin (characterized by ulceration, cutaneous tumor nodules, or presence of peau d'orange), infiltration of musculature and adjacent structures (fixation or dense tethering on clinical palpation), or cranial/peripheral nerve dysfunction.[49] Similarly, Lu et al[50] classified rENE extent into three grades: Grade 1 includes infiltration into the surrounding fat only (a combination of Huang's Pattern 1 and Pattern 2a rENE); Grade 2 includes presence of coalescent nodes; and Grade 3 includes invasion into adjacent structures. Ai et al[51] had a similar description of rENE extent except the inclusion of coalescent nodes (Table 2).

A normal lymph node is an isolated structure. However, with tumor invasion, several lymph nodes may aggregate to form a confluent nodal mass. The underlying basis of a confluent nodal mass is tumor intrusion/transgression through the nodal capsule manifested as rENE. Several radiology terms have been used in describing aggregates of lymph nodes that are not clearly delineated from each other (i.e., Pattern 2b rENE). These terms include "conglomerate,"[52] "matted,"[53,54] and "coalescent" lymph nodes.[48,50] A conglomerate nodal mass is an erstwhile term originally intended to indicate multiple juxtaposed nodes that are inseparable from each other (implying the presence of rENE). This concept was introduced by the American Joint Committee on Cancer in the fifth edition staging manual, with a focus on ascertaining the presence/absence of internodal fat.[55] However, the term conglomerate does not emphasize the disappearance of internodal capsules (an important sign of rENE). Matted is another term that has also been used previously to describe Pattern 2b rENE, but it lacks inclusivity with the requirement of three or more involved lymph nodes, because the aggregation of two lymph nodes with partial or complete disappearance of internodal capsules (a sign of rENE) has been shown to attain similar importance.[56] Therefore, the term coalescent may be a more appropriate description of the Pattern 2b rENE.[50,57]

PROGNOSTIC VALUE AND CLINICAL IMPLICATION OF RADIOLOGIC ENE

As described earlier, pENE has long been recognized as a strong prognostic factor for HNSCC. However, the prognostic value of rENE has varied among studies, likely reflecting variation in sample size and the stringency/certainty of rENE assessment. The proportion of patients with pENE rarely approaches 60% in a population with $\geq$ pN1 (Table 1). Considering the limitation of visualization on imaging, it is estimated that about 50% to 60% of pENEs are visible on imaging; the proportion of patients with unambiguous rENE should ordinarily be less than 40% in a normally distributed cohort.

If stringent criteria are used, the prognostic value of rENE is convincing, and its prognostic value may rival that of pENE.[16,45] In fact, emerging data consistently show that

TABLE 1. Radiologic Extranodal Extension and Pathologic Extranodal Extension Concordance in Selected Recent Publications

First Author (yr); Sample Size	Disease Site	Definition of rENE	rENE-pENE Concordance
Url (2013)[66]; 49 patients (cN+: 42; pN+: 49)	HNSCC	Any of the following: • Apparent fat and soft tissue infiltration • Infiltration of muscle, internal jugular vein, or carotid artery	Two observers: • % of pENE+: 17/49 (35%) • % of rENE+: 15/42 (36%) and 16/42 (38%) rENE for pENE: • Sensitivity: 73% and 76% • Specificity: 91% and 91% • Interrater κ: 0.86
Chai (2013)[63]; 100 patients (all cN+)	HNSCC	Capsular contour irregularity, poorly defined nodal margins, and infiltration of adjacent fat planes	Two observers: • % of pENE+: 63/100 (63%) • % of rENE+: 31/100 (31%) vs. 31/100 (31%) % of pENE+ in rENE+: • Likely rENE+: 79% and 61% • Definitely rENE+: 100% and 85%
Prabhu (2014)[70]; 432 patients (cN+ 221; pN+: 203)	HNSCC	Any of the following: • Irregular borders and/or perinodal fat stranding • Invasion of adjacent structures	• % of pENE+: 87/203 (43%) • % of rENE+: 46/221 (21%) rENE for pENE: • Sensitivity: 44% • Specificity: 98%
AiKen (2015)[71]; 111 patients	OSCC	Any of the following: • Irregular borders and/or perinodal fat stranding • Invasion of adjacent structures	• % of pENE+: 28/111 (25%) • % of rENE+: 29/111 (26%) rENE for pENE: • Sensitivity: 68% • Specificity: 88%
Maxwell (2015)[64]; 65 patients	HPV+ OPC	Any of the following: • Nodal capsular contour irregularity • Poorly defined nodal margins • Loss of intervening fat planes • Invasion of adjacent structures	• % of pENE+: 38/65 (58%) • % of rENE+: 19/65 (29%) Two observers: • rENE for pENE: ◦ Sensitivity: 55% and 47% ◦ Specificity: 70% and 85% • % of pENE+ by certainty of rENE+: ◦ Likely rENE+: 62% and 67% ◦ Definitely rENE+: 100% and 100%
Geltzeiler (2017)[72]; 100 patients (cN+: 70; pN+: 70)	HPV+ OPC	Overtly irregular nodal border	• % of pENE+: 39/70 (56%) • % of rENE+: 38/70 (54%) rENE for pENE: • Sensitivity: 21% • Specificity: 100%

(Continued on following page)

TABLE 1. Radiologic Extranodal Extension and Pathologic Extranodal Extension Concordance in Selected Recent Publications (Continued)

First Author (yr); Sample Size	Disease Site	Definition of rENE	rENE-pENE Concordance
Amullar (2018)[45]; 483 patients (cN+: 257; pN+: 262)	OSCC	Unequivocal ill-defined nodal borders	• % of pENE+: 114/262 (44%) • % of rENE+: 55/257 (21%) rENE for pENE: • Sensitivity: 52% • Specificity: 96%
Noor (2019)[65]; 80 patients (all pN+)	HPV+ OPC	Assessing internal characteristics, capsule contour, presence of perinodal fat stranding, and invasion into surrounding structures	Two observers: • % of pENE+: 26/80 (33%) • % of rENE+: 28/80 (35%) rENE for pENE: • Sensitivity: 56.5% and 60.9% • Specificity: 73.3% and 66.7% • Interrater κ for rENE: 0.40 % of pENE+ by certainty of rENE+: • Likely rENE+: 60% and 67% • Definitely rENE+: 85% and 64%
Faraj (2020)[73]; 73 patients (cN+: 67; pN+: 65)	HPV+ OPC	Any of the following seven features: • Indistinct capsular contours • Irregular nodal margins • Perinodal fat stranding • Perinodal fat planes • Nodal necrosis • Intranodal cysts • Nodal matting	• % of pENE+: 32/65 (49%) • Only irregular nodal margins and absence of perinodal fat plane were associated with pENE rENE by irregular nodal margins: • Sensitivity: 45% • Specificity: 94% rENE by absence of perinodal fat plane: • Sensitivity: 87% • Specificity: 50%

Abbreviations: cN+, clinical node−positive; HNSCC, head and neck squamous cell carcinoma; HPV+ OPC, HPV-associated oropharyngeal carcinoma; HPV− OPC, HPV-unassociated oropharyngeal carcinoma; OPC, oropharyngeal carcinoma; OSCC, oral cavity squamous cell carcinoma; pENE, pathologic extranodal extension; pN, pathologic node−positive; rENE, radiologic extranodal extension; yr, year.

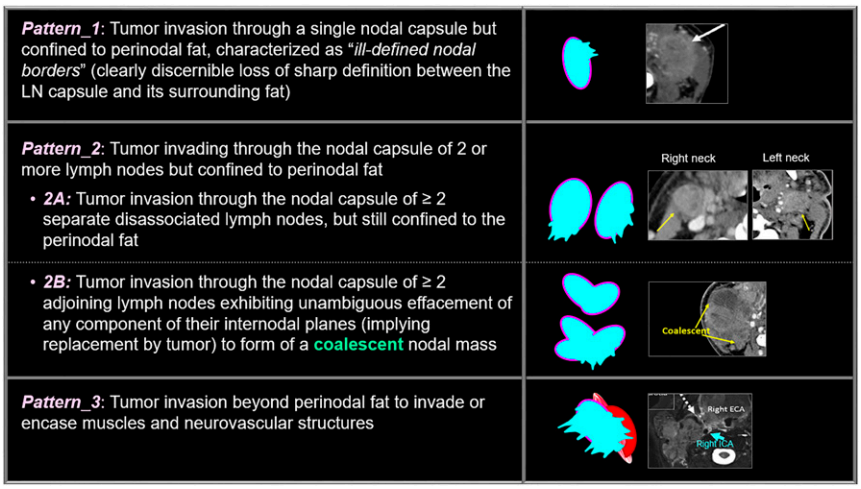

FIGURE 3. Pattern and Extent of Radiologic Extranodal Extension

Abbreviations: ECA, external carotid artery; ICA, internal carotid artery; LN, lymph node.

rENE may be even more powerful than TNM and patient factors in both viral-unrelated[45,57-59] and viral-related head and neck cancer (i.e., nasopharyngeal carcinoma[50,51,56,60,61] and HPV-associated oropharyngeal carcinoma[16,48,53,54,62]). The adverse effect is mainly caused by the increased risk of distant metastasis rather than reduction in locoregional control (Table 2).[16,50,58,62]

Given the strong prognostic value of rENE, it is conceivable that rENE could play an important role in risk stratification and refinement of future staging. In the eighth edition of the Union for International Cancer Control/American Joint Committee on Cancer TNM stage classification, rENE alone was not included for cN classification and risk stratification of nonviral HNSCC because of uncertainty about the reliability of rENE assessment. Similar to pENE, rENE (and clinical ENE) is not included for viral-related HNSCC. However, compelling evidence suggests that rENE can be reliably ascertained if stringent criteria are used. It has the potential to refine the cN classification and facilitate treatment selection in both viral-related and -unrelated HNSCC. Recognizing the prognostic importance of rENE, proposals have been made to include rENE in future cN classification for nasopharyngeal carcinoma[50,60] and HPV-associated[48] and potentially HPV-negative oropharyngeal carcinoma.[58] Lu et al[50] proposed a new cN classification that classifies most overt rENE (i.e., Pattern 3 rENE, tumor invading adjacent structures) to cN3b, while classifying coalescent nodes (i.e., Pattern 2b rENE) one step higher in the cN classification. Huang et al[48] proposed a new N classification for HPV-associated oropharyngeal carcinoma that incorporates rENE as a dichotomized parameter, relocating any case with rENE to N3b. It is important to point out that rENE ascertainment should follow stringent criteria, with only unequivocal/indisputable radiologic evidence being used. Under such a mandate, Pattern 1 and Pattern 2a rENEs are rare, and most rENEs exhibit additional features such as overt nodal coalescence or adjacent structures invasion.[48]

The concerns about using rENE clinically include low sensitivity and the subjectivity of its assessment. Low sensitivity of rENE for pENE is understandable because imaging is not designed to recapitulate findings detectable by the microscope. The literature regarding sensitivity and specificity of the rENE-pENE correlation varies significantly depending on the stringency, certainty, and extent of rENE (Table 1). Similar to pENE measurement, when the radiologic features of rENE are subtle (i.e., with less certainty) or the extent of rENE is minimal, subjectivity of interpretation increases and interrater reliability reduces.[56] In contrast, when rENE is assessed with a higher degree of certainty[63-65] or for greater extensiveness of rENE,[33,66] the presence of rENE almost certainly indicates the presence of pENE (specificity $>$ 90%). The rate of rENE in a study cohort may provide an index of the accuracy of clinically important rENE. In general, for prognostically relevant rENE that may impact the outcome of HNSCC in a cN+ cohort, the proportion of rENE should not exceed 40%, which has been shown consistently in studies over the past decade (Table 1).

Not surprisingly, the sensitivity of rENE for pENE is only modest. It is conceivable that less extensive pENE identified by the microscope will not be readily visible on imaging. However, the modest sensitivity of rENE for pENE does not prevent its use in clinical staging, because staging requires a parameter with high specificity to maintain its prognostic importance. Conversely, if identifying the likelihood of pENE is important for treatment selection, high sensitivity would be desirable. For example, TNM (eighth edition classification) stage I HPV-positive oropharyngeal carcinoma can be treated with either primary surgery or primary radiotherapy. To avoid potential triple modality treatment, using rENE to identify patients with a high likelihood of pENE is important. Therefore, high sensitivity is needed in this setting, because present guidelines for patients who are pENE+ recommend the addition of chemotherapy to adjuvant radiotherapy.

TABLE 2. Prognostic Value of Radiologic Extranodal Extension in Selected Recent Publications

First Author (yr); Sample Size	Disease Site	Definition of rENE	Prognostic Value of rENE
Kann (2014)[74]; 111 patients	cN+ OPC	Any of the following (suspicious or definite): • A thick-walled, enhancing nodal margin • Loss of outer nodal margin definition • Infiltration of the adjacent fat planes around portion of the node	MVA of rENE: • OS: HR, 6.5; 1.5–28.6; p = .014 • PFS: HR, 6.1; 1.8–20.9; p = .026 • DC: HR, 10.3; 1.3–80.4; p = .026 • LRC: NS
Amullar (2018)[45]; 483 patients (cN+: 257; pN+: 262)	OSCC	Unequivocal ill-defined nodal borders	rENE+ vs. rENE−•: • ↓ OS MVA for OS: • rENE: HR, 3.3; p < .001 • pENE: HR, 2.6; p < .001
Tian (2019)[75]; 168 patients	HPV+ OPC	rENE based on initial radiology report including any rENE	• % of rENE+: 88/168 (52%) • Suspicious: 42/168 (25%) • Definite: 46/168 (27%) UVA of OS by rENE: • Definite: HR, 1.4; 0.6–3.7; p = .47 • Suspicious: HR, 1.3; 0.5–3.5; p = .54
Ai (2019)[51]; 546 patients (cN+ 404)	NPC	G of rENE: • G1: Infiltration of surrounding fat • G2: Infiltration of muscle/skin	• G1 rENE: 99/404 (25%) • G2 rENE: 54/404 (13%) • G2 rENE: ↓ DC and OS MVA: • G1 vs. G0: DC (p = .744); OS (p = .062) • G2 vs. G0: DC: p = .001; OS: p = .015
Lee (2019)[76]; 134 patients	cN+ HPV+ OPC	Any of the following: • Enhancement, thickening, and irregularity of the nodal rim • Infiltration of the adjacent fat or other soft tissue planes	• % of rENE+: 70/134 (52%) rENE+ vs. rENE– for PFS: • 3-yr: 84% vs. 95%, p = .023 • MVA: HR, 2.7; 0.7–10.0; p = .141
Lu (2019)[50]; 1,390 patients	NPC	• An involved LN that had an unequivocal ill-defined nodal border (i.e., clearly discernible loss of sharp plane between the nodal capsule and the surrounding fat) • G of rENE: ◦ G1: Infiltration into surrounding fat plane only ◦ G2: Coalescent nodes ◦ G3: Invading into adjacent structures	• % rENE: 826/1,390 (59%) • G1: 18%; G2: 35%; G3: 6% • rENE+ had ↓ OS, DC, and LRC • MVA: rENE+ vs. rENE– • DC: HR, 2.3; 1.7–3.1; p < .001 • OS: HR, 1.6; 1.2–2.1; p < .001 • LRC: NS (p = .228)
Gal (2020)[14]; 4,841 patients: • HPV+: 3,854 • HPV–: 987	cN+ OPC	Not described (NCDB 2010-2015)	• HPV+: % of cENE or rENE: 156/3,854 (4%) • HPV–: % of cENE or rENE: 35/987 (4%) MVA: • cENE/rENE: HR, 1.6; 1.2–2.2

(Continued on following page)

TABLE 2. Prognostic Value of Radiologic Extranodal Extension in Selected Recent Publications (Continued)

First Author (yr); Sample Size	Disease Site	Definition of rENE	Prognostic Value of rENE
Thompson (2020)[77]; 342 patients (cN+: 324)	HPV+ OPC	Any of the following: • A clear loss of the integrity of the nodal capsule with infiltration of tumor into the adjacent fat planes or musculature • Multiple abutting lymph nodes with the loss of intervening fat planes	• % of rENE+: 53/324 (16%) rENE+ vs. rENE–: • ↓ DFS: HR, 2.9; 1.8–4.5 • ↓ OS: HR, 2.2; 1.3–3.6
Benchetrit (2020)[16]; Meta-analysis: 3,603 patients (18 studies)	HPV+ OPC	Not described (meta-analysis)	pENE+ vs. pENE–: • ↓ OS: HR, 1.9; 1.2–3.1 • ↓ DC: HR, 3.2; 1.3–8.3 • LRC (NS): HR, 0.8; 0.2–2.8 rENE+ vs. rENE–: • ↓ OS: HR, 2.4; 1.6–3.6 • ↓ DC: HR, 3.6; 2.0–6.4 • LRC (NS): HR, 1.5; 0.7–3.1
Pilar (2021)[58]; 361 patients (cN+: 264)	HPV– OPC	Any of the following: • An involved LN with an unequivocal ill-defined nodal border (i.e., a clearly discernible loss of the sharp plane between the nodal capsule and the surrounding fat) • Coalescent nodal mass with clear evidence of the disappearance of the intervening fat plane due to replacement by tumor	• % of rENE: 72/264 (27%) rENE+ vs. rENE–: • ↓ OS, DFS, LRC, and DC MVA: • DFS: HR, 1.4; 1.02–2.0; p = .037 • OS: HR, 1.3; 0.9–1.9; p = .140

Abbreviations: cENE, clinical extranodal extension; cN+, clinical node–positive; DC, distant control; DFS, disease-free survival; G, grade; HNC, head and neck cancer; HPV+ OPC, HPV-associated oropharyngeal carcinoma; HPV– OPC, HPV-unassociated oropharyngeal carcinoma; HR, hazard ratio; LN, lymph node; LRC, locoregional control; MVA, multivariable analysis; NCDB, National Cancer Database; NPC, nasopharyngeal carcinoma; NS, not significant; OPC, oropharyngeal carcinoma; OS, overall survival; OSCC, oral cavity squamous cell carcinoma; pENE, pathologic extranodal extension; PFS, progression-free survival; pN, pathologic node–positive; rENE, radiologic extranodal extension; UVA, univariable analysis; yr, year.

Clinical care requires prioritizing sensitivity and specificity depending on the purpose of using this parameter. For TNM staging and risk stratification, high specificity (low false positive) is needed to avoid overcalling that could dilute its prognostic value. In contrast, for screening and treatment decision-making, high sensitivity (low false negative) is desirable to avoid a potential miss in providing optimal care. Radiologic interpretation should address both sensitivity and specificity of rENE and other adverse nodal features to serve different clinical needs. A strategy could be to partner with our medical imaging colleagues to develop guidelines for reporting the presence/absence of adverse nodal features (such as rENE) and the degree of certainty of these features (e.g., likely/suspicious, highly suspicious/unequivocal/definite). In addition, standardization of radiology taxonomy, formalization of radiology reporting templates, and exploration of the potential for artificial intelligence to predict the existence of rENE may improve sensitivity and accuracy.[67-69] Such initiatives may additionally facilitate the clinical utility of the rENE parameter.

CONCLUSION

Convincing evidence has emerged that ENE is one of the strongest prognostic factors for both viral-related and -unrelated HNSCC. Clinical examination of ENE and pENE are new N category modifiers for nonviral HNSCC. Within these subsets defined by such N descriptors, microscopic and major pENE may convey different degrees of clinical importance. rENE also plays a role in risk stratification of HNSCC. rENE may manifest as unequivocal evidence of clearly discernible loss of the sharp definition between the lymph node capsule and its surrounding fat or formation of a coalescent nodal mass characterized as partial or complete disappearance of internodal capsules or invasion of adjacent muscle/neurovascular structures. Standardization of pENE assessment and reporting (especially addressing pENE extent and cutoffs) could further refine the use of the pENE parameter for risk stratification and future staging. Increasing awareness, training, and agreement on rENE assessment criteria among radiologists should increase reliability and accuracy of rENE assessment. Indisputable rENE has the potential to replace clinical examination of ENE for treatment selection, risk stratification, and future stage refinement.

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REFERENCES

1. Bhattacharya P, Mukherjee R. Lymph node extracapsular extension as a marker of aggressive phenotype: classification, prognosis and associated molecular biomarkers. Eur J Surg Oncol. 2021;47:721-731.
2. Pilborough AE, Lambert DW, Khurram SA. Extranodal extension in oral cancer: a role for the nodal microenvironment? J Oral Pathol Med. 2019;48:863-870.
3. Wolf GT, Fisher SG, Hong WK, et al; Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med. 1991;324:1685-1690.
4. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349:2091-2098.
5. Lefebvre JL, Chevalier D, Luboinski B, et al; EORTC Head and Neck Cancer Cooperative Group. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. J Natl Cancer Inst. 1996;88:890-899.
6. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005;27:843-850.
7. Parsons JT, Mendenhall WM, Stringer SP, et al. Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. Cancer. 2002;94:2967-2980.
8. Johnson JT, Barnes EL, Myers EN, et al. The extracapsular spread of tumors in cervical node metastasis. Arch Otolaryngol. 1981;107:725-729.
9. Olsen KD, Caruso M, Foote RL, et al. Primary head and neck cancer. Histopathologic predictors of recurrence after neck dissection in patients with lymph node involvement. Arch Otolaryngol Head Neck Surg. 1994;120:1370-1374.

10. Johnson JT, Myers EN, Schramm VL Jr., et al. Adjuvant chemotherapy for high-risk squamous-cell carcinoma of the head and neck. J Clin Oncol. 1987; 5:456-458.

11. Johnson JT, Wagner RL, Myers EN. A long-term assessment of adjuvant chemotherapy on outcome of patients with extracapsular spread of cervical metastases from squamous carcinoma of the head and neck. Cancer. 1996;77:181-185.

12. Fakhry C, Zevallos JP, Eisele DW. Imbalance between clinical and pathologic staging in the updated American Joint Commission on Cancer staging system for human papillomavirus-positive oropharyngeal cancer. J Clin Oncol. 2018;36:217-219.

13. Freitag J, Wald T, Kuhnt T, et al. Extracapsular extension of neck nodes and absence of human papillomavirus 16-DNA are predictors of impaired survival in p16-positive oropharyngeal squamous cell carcinoma. Cancer. 2020;126:1856-1872.

14. Gal TJ, O'Brien KJ, Chen Q, et al. Clinical vs microscopic extranodal extension and survival in oropharyngeal carcinoma in the human papillomavirus era. Otolaryngol Head Neck Surg. 2020;162:693-701.

15. An Y, Park HS, Kelly JR, et al. The prognostic value of extranodal extension in human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cancer. 2017;123:2762-2772.

16. Benchetrit L, Torabi SJ, Givi B, et al. Prognostic significance of extranodal extension in hpv-mediated oropharyngeal carcinoma: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2020;194599820951176.

17. Miccio JA, Verma V, Kelly J, et al. Impact of contralateral lymph nodal involvement and extranodal extension on survival of surgically managed HPV-positive oropharyngeal cancer staged with the AJCC eighth edition. Oral Oncol. 2019;99:104447.

18. Shevach J, Bossert A, Bakst RL, et al. Extracapsular extension is associated with worse distant control and progression-free survival in patients with lymph node-positive human papillomavirus-related oropharyngeal carcinoma. Oral Oncol. 2017;74:56-61.

19. Bauer E, Mazul A, Chernock R, et al. Extranodal extension is a strong prognosticator in HPV-positive oropharyngeal squamous cell carcinoma. Laryngoscope. 2020;130:939-945.

20. Haughey BH, Sinha P, Kallogjeri D, et al. Pathology-based staging for HPV-positive squamous carcinoma of the oropharynx. Oral Oncol. 2016;62:11-19.

21. Hobelmann KC, Topf MC, Bar-Ad V, et al. AJCC-8ed nodal staging does not predict outcomes in surgically managed HPV-associated oropharyngeal cancer. Oral Oncol. 2018;82:138-143.

22. Routman DM, Funk RK, Tangsriwong K, et al. relapse rates with surgery alone in human papillomavirus-related intermediate- and high-risk group oropharynx squamous cell cancer: a multi-institutional review [correction published in Int J Radiat Oncol Biol Phys. 2018;100(5):P1304]. Int J Radiat Oncol Biol Phys. 2017; 99:938-946.

23. Zhan KY, Puram SV, Li MM, et al. National treatment trends in human papillomavirus-positive oropharyngeal squamous cell carcinoma. Cancer. 2020; 126:1295-1305.

24. Kumar B, Cipolla MJ, Old MO, et al. Surgical management of oropharyngeal squamous cell carcinoma: survival and functional outcomes. Head Neck. 2016; 38 (S1, Suppl 1):E1794-E1802.

25. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th Ed. New York: Springer; 2010.

26. Sobin L, Gospodarowicz M, Wittekind C. UICC: TNM Classification of Malignant Tumours, 7th Ed. Chichester, UK: Wiley-Blackwell; 2010.

27. Huang DT, Johnson CR, Schmidt-Ullrich R, et al. Postoperative radiotherapy in head and neck carcinoma with extracapsular lymph node extension and/or positive resection margins: a comparative study. Int J Radiat Oncol Biol Phys. 1992;23:737-742.

28. Brasilino de Carvalho M. Quantitative analysis of the extent of extracapsular invasion and its prognostic significance: a prospective study of 170 cases of carcinoma of the larynx and hypopharynx. Head Neck. 1998;20:16-21.

29. Carter RL, Bliss JM, Soo KC, et al. Radical neck dissections for squamous carcinomas: pathological findings and their clinical implications with particular reference to transcapsular spread. Int J Radiat Oncol Biol Phys. 1987;13:825-832.

30. Carter RL, Barr LC, O'Brien CJ, et al. Transcapsular spread of metastatic squamous cell carcinoma from cervical lymph nodes. Am J Surg. 1985;150:495-499.

31. Yamada S, Yanamoto S, Otani S, et al. Evaluation of the level of progression of extracapsular spread for cervical lymph node metastasis in oral squamous cell carcinoma. Int J Oral Maxillofac Surg. 2016;45:141-146.

32. Lewis JS Jr., Carpenter DH, Thorstad WL, et al. Extracapsular extension is a poor predictor of disease recurrence in surgically treated oropharyngeal squamous cell carcinoma. Mod Pathol. 2011;24:1413-1420.

33. Prabhu RS, Hanasoge S, Magliocca KR, et al. Extent of pathologic extracapsular extension and outcomes in patients with nonoropharyngeal head and neck cancer treated with initial surgical resection. Cancer. 2014;120:1499-1506.

34. Agarwal JP, Kane S, Ghosh-Laskar S, et al. Extranodal extension in resected oral cavity squamous cell carcinoma: more to it than meets the eye. Laryngoscope. 2019;129:1130-1136.

35. Greenberg JS, Fowler R, Gomez J, et al. Extent of extracapsular spread: a critical prognosticator in oral tongue cancer. Cancer. 2003;97:1464-1470.

36. Kwon M, Roh JL, Lee J, et al. Extranodal extension and thickness of metastatic lymph node as a significant prognostic marker of recurrence and survival in head and neck squamous cell carcinoma. J Craniomaxillofac Surg. 2015;43:769-778.

37. Apisarnthanarax S, Elliott DD, El-Naggar AK, et al. Determining optimal clinical target volume margins in head-and-neck cancer based on microscopic extracapsular extension of metastatic neck nodes. Int J Radiat Oncol Biol Phys. 2006;64:678-683.

38. Arun I, Maity N, Hameed S, et al. Lymph node characteristics and their prognostic significance in oral squamous cell carcinoma. Head Neck. 2021;43:520-533.

39. Wreesmann VB, Katabi N, Palmer FL, et al. Influence of extracapsular nodal spread extent on prognosis of oral squamous cell carcinoma. Head Neck. 2016; 38(suppl 1):E1192-E1199.

40. Mamic M, Lucijanic M, Manojlovic L, et al. Prognostic significance of extranodal extension in oral cavity squamous cell carcinoma with occult neck metastases. Int J Oral Maxillofac Surg. 2020, In press.

41. Lewis JS Jr., Tarabishy Y, Luo J, et al. Inter- and intra-observer variability in the classification of extracapsular extension in p16 positive oropharyngeal squamous cell carcinoma nodal metastases. Oral Oncol. 2015;51:985-990.

42. van den Brekel MW, Lodder WL, Stel HV, et al. Observer variation in the histopathologic assessment of extranodal tumor spread in lymph node metastases in the neck. Head Neck. 2012;34:840-845.

43. Bullock MJ, Beitler JJ, Carlson DL, et al. Data set for the reporting of nodal excisions and neck dissection specimens for head and neck tumors: explanations and recommendations of the guidelines from the International Collaboration on Cancer Reporting. Arch Pathol Lab Med. 2019;143:452-462.

44. Yousem DM, Som PM, Hackney DB, et al. Central nodal necrosis and extracapsular neoplastic spread in cervical lymph nodes: MR imaging versus CT. Radiology. 1992;182:753-759.

45. Almulla A, Noel CW, Lu L, et al. Radiologic-pathologic correlation of extranodal extension in patients with squamous cell carcinoma of the oral cavity: implications for future editions of the TNM classification. Int J Radiat Oncol Biol Phys. 2018;102:698-708.

46. Park SI, Guenette JP, Suh CH, et al. The diagnostic performance of CT and MRI for detecting extranodal extension in patients with head and neck squamous cell carcinoma: a systematic review and diagnostic meta-analysis. Eur Radiol. 2021;50:309-315.

47. Souter MA, Allison RS, Clarkson JH, et al. Sensitivity and specificity of computed tomography for detection of extranodal spread from metastatic head and neck squamous cell carcinoma. J Laryngol Otol. 2009;123:778-782.

48. Huang SH, O'Sullivan B, Su J, et al. Prognostic importance of radiologic extranodal extension in HPV-positive oropharyngeal carcinoma and its potential role in refining TNM-8 cN-classification. Radiother Oncol. 2020;144:13-22.

49. Lydiatt W, Patel S, Ridge JA, et al. Staging Head and Neck Cancers. In Amin M, Edge S, Greene F, et al (eds). AJCC Cancer Staging Manual, 8th Ed. Cham, Switzerland: Springer Nature, 2017;55-65.

50. Lu T, Hu Y, Xiao Y, et al. Prognostic value of radiologic extranodal extension and its potential role in future N classification for nasopharyngeal carcinoma. Oral Oncol. 2019;99:104438.

51. Ai QY, King AD, Poon DMC, et al. Extranodal extension is a criterion for poor outcome in patients with metastatic nodes from cancer of the nasopharynx. Oral Oncol. 2019;88:124-130.

52. Hoang JK, Vanka J, Ludwig BJ, et al. Evaluation of cervical lymph nodes in head and neck cancer with CT and MRI: tips, traps, and a systematic approach. AJR Am J Roentgenol. 2013;200:W17-25.

53. Spector ME, Chinn SB, Bellile E, et al. Matted nodes as a predictor of distant metastasis in advanced-stage III/IV oropharyngeal squamous cell carcinoma. Head Neck. 2016;38:184-190.

54. Vainshtein JM, Spector ME, Ibrahim M, et al. Matted nodes: high distant-metastasis risk and a potential indication for intensification of systemic therapy in human papillomavirus-related oropharyngeal cancer. Head Neck. 2016;38(suppl 1):E805-E814.

55. Fleming I, Cooper J, Henson D, et al. AJCC Cancer Staging Manual, 5th Ed. Philadelphia: Lippincott-Raven; 1997.

56. Hu Y, Lu T, Huang SH, et al. High-grade radiologic extra-nodal extension predicts distant metastasis in stage II nasopharyngeal carcinoma. Head Neck. 2019; 41:3317-3327.

57. Sananmuang T, Yu E, Su J, et al. Pre- and post-radiotherapy radiologic nodal features and oropharyngeal cancer outcomes. Laryngoscope. 2021; 131:E1162-E1171.

58. Pilar A, Yu E, Su J, et al. Prognostic value of clinical and radiologic extranodal extension and their role in the 8th edition TNM cN classification for HPV-negative oropharyngeal carcinoma. Oral Oncol. 2021;114:105167.

59. Moon H, Choi YJ, Lee YS, et al. Value of extranodal extension detected by computed tomography for predicting clinical response after chemoradiotherapy in head and neck squamous cell cancer. Acta Otolaryngol. 2018;138:392-399.

60. Li WF, Sun Y, Mao YP, et al. Proposed lymph node staging system using the International Consensus Guidelines for lymph node levels is predictive for nasopharyngeal carcinoma patients from endemic areas treated with intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys. 2013;86:249-256.

61. Mao Y, Wang S, Lydiatt W, et al. Unambiguous advanced radiologic extranodal extension determined by MRI predicts worse outcomes in nasopharyngeal carcinoma: potential improvement for future editions of N category systems. Radiother Oncol. 2021;157:114-121.

62. Billfalk-Kelly A, Yu E, Su J, et al. Radiologic extranodal extension portends worse outcome in cN+ TNM-8 stage I human papillomavirus-mediated oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2019;104:1017-1027.

63. Chai RL, Rath TJ, Johnson JT, et al. Accuracy of computed tomography in the prediction of extracapsular spread of lymph node metastases in squamous cell carcinoma of the head and neck. JAMA Otolaryngol Head Neck Surg. 2013;139:1187-1194.

64. Maxwell JH, Rath TJ, Byrd JK, et al. Accuracy of computed tomography to predict extracapsular spread in p16-positive squamous cell carcinoma. Laryngoscope. 2015;125:1613-1618.

65. Noor A, Mintz J, Patel S, et al. Predictive value of computed tomography in identifying extracapsular spread of cervical lymph node metastases in p16 positive oropharyngeal squamous cell carcinoma. J Med Imaging Radiat Oncol. 2019;63:500-509.

66. Url C, Schartinger VH, Riechelmann H, et al. Radiological detection of extracapsular spread in head and neck squamous cell carcinoma (HNSCC) cervical metastases. Eur J Radiol. 2013;82:1783-1787.

67. Ariji Y, Sugita Y, Nagao T, et al. CT evaluation of extranodal extension of cervical lymph node metastases in patients with oral squamous cell carcinoma using deep learning classification. Oral Radiol. 2020;36:148-155.

68. Kann BH, Aneja S, Loganadane GV, et al. pretreatment identification of head and neck cancer nodal metastasis and extranodal extension using deep learning neural networks. Sci Rep. 2018;8:14036.

69. Kann BH, Hicks DF, Payabvash S, et al. Multi-institutional validation of deep learning for pretreatment identification of extranodal extension in head and neck squamous cell carcinoma. J Clin Oncol. 2020;38:1304-1311.

70. Prabhu RS, Magliocca KR, Hanasoge S, et al. Accuracy of computed tomography for predicting pathologic nodal extracapsular extension in patients with head-and-neck cancer undergoing initial surgical resection. Int J Radiat Oncol Biol Phys. 2014;88:122-129.

71. Aiken AH, Poliashenko S, Beitler JJ, et al. Accuracy of preoperative imaging in detecting nodal extracapsular spread in oral cavity squamous cell carcinoma. AJNR Am J Neuroradiol. 2015;36:1776-1781.

72. Geltzeiler M, Clayburgh D, Gleysteen J, et al. Predictors of extracapsular extension in HPV-associated oropharyngeal cancer treated surgically. Oral Oncol. 2017;65:89-93.

73. Faraji F, Aygun N, Coquia SF, et al. Computed tomography performance in predicting extranodal extension in HPV-positive oropharynx cancer. Laryngoscope. 2020;130:1479-1486.

74. Kann BH, Buckstein M, Carpenter TJ, et al. Radiographic extracapsular extension and treatment outcomes in locally advanced oropharyngeal carcinoma. Head Neck. 2014;36:1689-1694.

75. Tian S, Ferris MJ, Switchenko JM, et al. Prognostic value of radiographically defined extranodal extension in human papillomavirus-associated locally advanced oropharyngeal carcinoma. Head Neck. 2019;41:3056-3063.

76. Lee B, Choi YJ, Kim SO, et al. Prognostic value of radiologic extranodal extension in human papillomavirus-related oropharyngeal squamous cell carcinoma. Korean J Radiol. 2019;20:1266-1274.

77. Thompson LDR, Burchette R, Iganej S, et al. Oropharyngeal squamous cell carcinoma in 390 patients: analysis of clinical and histological criteria which significantly impact outcome. Head Neck Pathol. 2020;14:666-688.

Barriers to Comprehensive Multidisciplinary Head and Neck Care in a Community Oncology Practice

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Overview

Complex, coordinated, and collaborative care of patients with head and neck cancer can be challenging yet amazingly rewarding and successful. The high symptom burden across multiple functional domains in patients with head and neck cancer, even in early stages of disease, mandates a multidisciplinary team approach that harnesses the combined contributions of physicians and ancillary providers to drive greater patient-centered care, addressing factors that heavily influence morbidity, mortality, and quality of life. Well-organized community-based multidisciplinary teams fulfill this unmet need and benefit patients with conveniently located comprehensive services that are typically found in large academic centers. Equivalent, if not superior, outcomes can be achieved in a unified community-based multidisciplinary team with shared patient-centered and outcomes-based goals. However, implementing true multidisciplinary team care in today's complex health care environment is fraught with challenges and pitfalls. So how have some community-based practices managed to create safe and efficient programs with successful outcomes? The purpose of this review is to discuss barriers to reaching this success and emphasize practical solutions to such challenges.

INTRODUCTION

Contemporary treatment of patients with head and neck cancer is multifaceted and relies on many uniquely qualified professionals. Despite the availability of resources, patients often experience fragmented and uncoordinated care that leads to delays in treatment, compromised outcomes, severe distress in patients and families, and dissatisfaction with care. Patients experience numerous stressors such as severe symptoms due to the disease and the aggressive treatments, body image concerns, loss of speech, difficulty in swallowing, nutritional issues, and respiratory problems that affect their quality of life and ability to function on a day-to-day basis.[1,2] Additionally, patients experience barriers to accessing quality, timely care throughout all stages of the cancer care continuum, from diagnosis through survivorship. This leads to decreased treatment compliance, intensified psychosocial distress, financial hardship, and poor overall outcomes.[3]

A well-coordinated multidisciplinary team (MDT) approach is the present standard-of-care for patients with head and neck cancer. Studies show that an integrated team approach yields better 5-year survival outcomes, increased rates of completion of planned therapy, and higher compliance with speech-language pathologists' recommendations.[4] A recent systematic review of the literature concluded that the improved outcomes are associated with an MDT approach to care.[5] Forming a comprehensive multidisciplinary head and neck cancer team with professionals from multiple specialties that delivers high-quality care is a time- and labor-intensive effort (Fig. 1). A very high level of willingness from the team members to organize and come together in a scheduled fashion is integral to the team's success. All the participants must recognize the inherent value and commit voluntarily to the endeavor. Routine weekly tumor boards, which are the fundamental underpinnings of good multidisciplinary care and exist in most academic centers, are not always freely available in community practices and must be created. The true value of an MDT approach to cancer care in community practice lies in the order-of-magnitude of improvement in benefit to patients, given that more than 80% of all cancer care in the United States is delivered in the community practice setting. However, establishing a fully functional and efficient MDT is fraught with significant challenges and barriers especially in community practices, where the various subspecialists and the ancillary providers reside in geographically disparate locations and do not always have coordinated clinic schedules. These challenges can, however, be surmounted in thoughtful and creative ways. Barriers to multidisciplinary care are broadly categorized and described in the sections below.

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PRACTICAL APPLICATIONS

- Highly successful care of patients with head and neck cancer can be coordinated in the community setting.
- Numerous disease-specific, social, and financial barriers exist, threatening successful outcomes.
- Multidisciplinary teams that meet weekly are essential to overcoming these challenges.
- Identifying and including all necessary subspecialties and key ancillary staff is vital in the short- and long-term success of the team.
- Community-based practices can create safe and efficient head and neck programs with successful outcomes.

PROVIDER-CENTERED BARRIERS

Barrier: Gaps in the "Team" (Provider Identification)

Some of the challenges in providing excellent comprehensive coordinated care of patients with head and neck cancer lies in identifying all of the necessary subspecialists required to create the "team." The National Comprehensive Cancer Network (NCCN) guidelines outline those specialties recommended as part of the team, including head and neck surgery, plastic surgery, medical oncology, radiation oncology, dental oncology, head and neck neuro-radiology, pathology, speech pathology, clinical nutrition, social work, and physical therapy/lymphedema specialist.[6]

Solution

Create an MDT that meets weekly for a multidisciplinary tumor board (in person and/or virtual). It encourages providers to build relationships of trust and hold each other to the standard of care. Be open and transparent in these meetings to discuss areas of accomplishment and concern. Be complimentary and specific about needs or expectations (outcomes, imaging reads, and staging). Expect 100% commitment to the team to the extremes of quality and outcomes. Motivate each other to stay current in their respective fields of interest. Support each other in the toughest of challenges and situations. Invite all specialists with a role on the team. With time, loyalty and teamwork will lead to team success. Treatment of patients with head and neck cancer by a dedicated MDT that meets for tumor boards regularly results in improved survival and can be accomplished in a community setting.[7]

Physical therapy is widely available in most communities. We have worked to establish a good rapport with several physical therapy providers in our community. These provide support during and after treatment as well as spinal accessory nerve rehabilitation after surgery. Commercial companies are also available to provide new treatments for lymphedema management.

Barrier: Availability Patients with head and neck cancer all too often present with symptoms affecting eating, talking, and breathing. Prompt evaluation, work-up, and treatment initiation are necessary.

Solution

Providers should be committed to same-week appointments, even same day in very urgent cases. Be available to help each other and promote efficient and immediate care. Weekly tumor board meetings are key as this facilitates weekly communication and coordination. Be available to help each other. Admit at the same hospital. Be willing to see consults at the hospital (this is a fading art). Have a point of contact for each office with emails and texts to make communication is easier. Encourage the staff at each office to be kind and quick to reply to these requests. Remind them how important they are to the team.

Barrier: Physician Communication

This includes inadequate discussion of the treatment options and shared decision-making, goals of therapy, treatment side effects, and short- and long-term quality of life issues.[8] The resulting erosion of patient trust and confidence in the provider often leads to failure to adhere to the recommendations and poor outcomes.

Solution

Shared decision-making as an ideal and patient perspective and autonomy as guiding goals of care are essential to every physician-patient interaction. Patient empowerment with information about their disease and the applicable treatment options in a balanced manner, to make informed decisions, is critical. Constraints of time in a busy clinical practice must be balanced with making time for communicating with the patient in a fashion that they understand. In some instances, this may mean enlisting the help of family members and providing written information and online resources for review by the patient and their families. Access to translators in minority-prevalent communities where translation is required in their spoken language may be considered to aid in optimizing communication. Physician extenders such as physician assistants and nurse practitioners are effective surrogates to ensure adequate information transfer and to develop a rapport with the patients. Documentation of anticipated short- and long-term outcomes and a survivorship plan must be embedded in the care pathway as a part of every patient's care plan. Lastly, written, informed consent for chemotherapy should be mandatory for every patient before starting a new line of therapy.

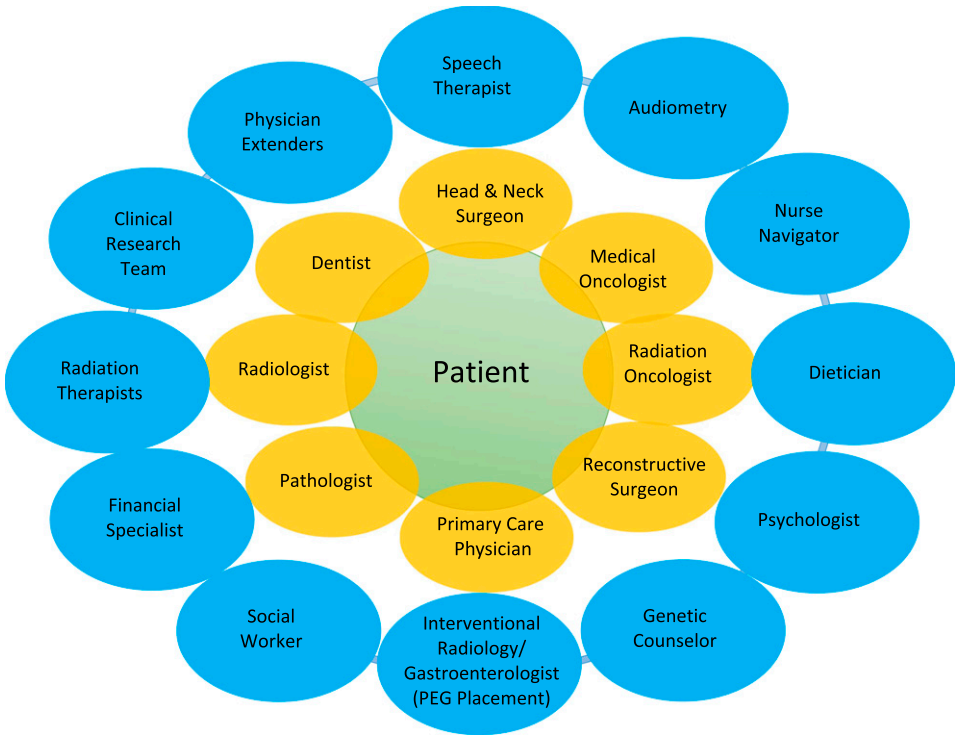

FIGURE 1. Schema of a Multidisciplinary Head and Neck Cancer Care Team
Abbreviation: PEG, percutaneous endoscopic gastrostomy.

Barrier: Variable Adherence to Guidelines

Adherence to clinical practice guidelines such as NCCN, ASCO, and American Society for Radiation Oncology guidelines is variable among surgical, medical, and radiation oncologists and can lead to disparities in care and patient outcomes.

Solution

Standardization of care through development of level 1 pathways powered by national guidelines that are approved by all participants in the MDT is critical. Team members should meet regularly to discuss and provide input toward stratifying the guidelines into pragmatic patient-specific pathways. ASCO criteria for high-quality oncology pathway programs aimed at pathway development, implementation, and use, and analytics should be used as a framework not only to support the measurable delivery of care across participating medical oncologists but also to bring expert opinion to the point of clinical care for the growing number of complexities of cancer therapy.[9] Having a pathway does not ensure its use, usefulness, or production of informative analytics, and as such, deviations from the pathways once developed should be kept to a minimum and explained. Pathway compliance, implementation, and ongoing sustainability should be monitored over time and reported to the MDT.

Barrier: Inadequate Diagnostic Expertise

This includes lack of radiologic and pathologic support, which can delay and compromise patient care.

Solution

Weekly molecular tumor boards, which include a dedicated pathologist familiar with molecular targets in head and neck cancer and salivary gland and thyroid cancers, and a radiologist with expertise in identifying radiographic evidence of extracapsular extension of disease, are essential to the MDT given the complexities of molecularly targeted therapies and rapidly emerging data on clinical significance of extranodal extension. A dedicated radiologist and pathologist should be part of the MDT, and rotation of specialists who do not have a stated interest in head and neck cancer as "fillers" in the tumor board must be minimized.

Barrier: Insurance

This includes lack of insurance, underinsured patients, and that fact that not all providers take insurance.

Solution

This can be a significant challenge if your MDT includes several groups as not all groups participate in the same insurance plans. This is even more complicated with the upcoming governmental insurances that have limited access and require significant referrals. Having more than one medical oncologist and radiation oncologist from two different groups on the team can overcome some of this challenge. If these are on separate sides of the city or have multiple locations, it also serves to overcome some of the travel barriers. Working to navigate the out-of-network system can also be helpful. The team should discuss openly

how to handle situations where the patient is not insured, hopefully creating opportunities to accept and take in these patients through charity support and/or governmental subsidies. We have also found that the hospital will often provide a reduced cost contract or payment plan for surgical services for patients who do not have insurance. The nurse navigator can also play a key role in helping the patients find outside sources of support and charitable resources (see travel section).

The following are cost containment strategies to consider are as follows:

- **Prior authorizations from health insurance companies to determine if a prescribed procedure, service, or medication will be covered:** Significant variations in prior authorization requirements exist at the state level, and it is helpful to have a financial counselor well versed in these issues advise patients of their specific obligations a priori. This can significantly reduce the unanticipated costs of care and enhance patient trust and compliance with the recommended treatment.
- **Step therapy to curtail costs, wherein patients are required to try a lower cost medication or test before a more costly approach is often required by insurance, even when the latter is recommended by their physicians:** Step therapy can delay care and, at times, lead to patients with cancer having to forgo treatments altogether. Added impact of out-of-pocket costs to patients for prescription drugs and diagnostic testing because of the insurance company mandated step therapy requirements must be discouraged when possible.
- **Narrow insurance networks limiting the number of providers within network lead some enrollees to pay high out-of-network costs for cancer care when seeking specialized areas of excellence outside of the network.** The greatest impact of this process is on residents of rural and underserved areas where people have relatively few options for comprehensive cancer care. This should be prevented and regulated at a legislative level by appropriate government agencies.

PATIENT-CENTERED BARRIERS

Barrier: Fear/Anxiety About the Future and Feeling Lonely/Isolated

The very diagnosis of head and neck cancer, sometimes associated with facial disfigurement, has been shown to cause significant anxiety, depression, and fears of social ostracization in patients. This has been shown to cause social withdrawal and failure to seek and receive care.[10]

Solution

Empowering patients with information such that they feel engaged in the treatment plan and can make informed decisions about their care may alleviate some of the fears. An open-ended, transparent discussion of the stage of disease, prognosis, treatment options, goals of therapy, and anticipated outcomes is essential. An important and sometimes challenging aspect of this discussion is the constraint of time in a high-volume practice. The additional time spent during the initial visits to address patients' concerns and fears can significantly impact the subsequent delivery of care. Patients may benefit from information about peer support groups and social gatherings/chat rooms to hear about other patients' experiences. An evaluation from a trained psychologist early in the disease course is invaluable.

Barrier: Family and Social Support, Mental Health Counseling, and Screening for Psychosocial Distress

Patients with head and neck cancers without support of family or close friends lack critical assistance in key areas of need as they receive cancer treatment. Consensus guideline treatment of head and neck cancer is complex and demanding, often involving large time commitments throughout weeks of continuous therapies. Critical needs include transportation, navigating multidisciplinary care and appointments, obtaining prescription and over-the-counter medications for alleviation of acute toxicities, help with care of percutaneous endoscopic gastrostomy tube, and challenges of taking in adequate nutrition. Daily and sometimes twice daily radiotherapy is a significant effort for even the most supported patients over a 6- to 7-week total course of curative radiotherapy. In a validated assessment tool study of community-based care of patients' perception of care coordination in a cross section of cancer types, these factors were significant in a patient's perception of poorer care: the diagnosis of head and neck cancer, the lack of family/friend/relative support, and provider type.[11]

Psychosocial distress often represents the most unmet need for patients with head and neck cancer.[12] The reasons for this are many, including perceived stigma associated with seeking psychiatrist/psychologist evaluation, an acute shortage of qualified practitioners in most communities, and pay-for-services that are not covered by insurers, among others. Patients' resistance to accept help appears multifactorial and includes their perception of self, familial and societal perceptions, and financial constraints of prioritizing essential care among others. Decrease in family support and decline in interpersonal relationships with a diagnosis of head and neck cancer are often a major barrier in patients' ability to travel for their care visits and hence their ability to receive and complete recommended treatment.

Solution

The physician and all team members should emphasize to the patient that it is essential to involve family and friends to prioritize helping the patient from the start of the cancer

journey through to survivorship. This should be a priority. Literature shows strong association between family/friend involvement and success of treatment, decreased use of emergency services, unplanned hospital admissions, test duplication, and satisfaction of patient.[11] It is important to help the patient through various appointments (coordination of care) that sometimes involve multiple health systems, and family and friends can also help patients obtain supplies for percutaneous endoscopic gastrostomy tube and manage acute side effect medications and skin care, provide emotional support, and assist the patient to be accountable to coming every day for treatment despite not feeling well.

Identifying and designating a trained psychologist to be a member of the MDT is one of the greater challenges of creating an MDT in community practice. A psychcologist evaluation of every patient with head and neck cancer at diagnosis should be a standard part of the comprehensive evaluation. Subsequent visits may be tailored based on patient need after the initial evaluation. Transportation assistance to and from the treatment and clinic visits to mitigate the burden on the family can be discussed with each patient during their initial evaluation by the financial counselors or the nurse navigators. Arrangements can be made a priori, especially for patients receiving radiation or concurrent chemoradiation, which require daily visits.

Barrier: Travel

The demands of seeing multiple providers (head and neck surgery, medical oncology, radiation oncology, radiology, etc.) over a short period of time to complete work-up and staging are often overwhelming. Subsequent preparation and coordination of treatment often requiring multiple modalities and visits from ancillary services (speech and swallow, audiology, gastroenterology, and dental, to name a few) only add to the stress. Traditional multi-appointment clinics that are geographically distant can result in delays in initiation of care from diagnosis as patients travel to see the individual specialists on different days.

This is especially true for curative-intent radiotherapy where treatment requirements are significant with one or two daily treatments in courses that last 6 to 7 weeks in duration. It is known that treatment breaks in radiotherapy for head and neck cancers can lower the chance of local control and cure due to accelerated repopulation of cancer cells. Recent literature also suggests that community-based care can differ from academic care institutions in delivery of radiotherapy in important metrics of total dose (Gy), number of delivered fractions of radiotherapy, dose per fraction (Gy), duration of treatment delays, early termination of radiotherapy, and not completing full-course radiotherapy.[13] Analyses by various groups identify travel/transportation issues as a major cause of patients not receiving guideline-adherent radiotherapy in head and neck cancers.[14,15] In a comprehensive root cause analysis of radiotherapy initiation timing in postoperative radiotherapy in head and neck cancers, multiple factors were identified related to communication, process, and social support. Specifically identified in the social support area was the lack of transportation support as a cause of increased time to initiation of postoperative radiotherapy.[15] Delays in receiving postoperative radiotherapy are known to negatively impact overall survival in head and neck squamous cell carcinomas.[14-16]

Solution

Employ a head and neck nurse navigator. These can be helpful in coordination between offices. They can be another reliable contact for patients overwhelmed by the seemingly countless things to get done in preparation to be treated or just the robust schedule of treatment and follow-up for radiation, chemotherapy, or surgery. It is important that the navigator feels like part of the team, be generously available and dependable, understand their role, and serve as a bridge to overcome gaps between offices and not create new ones (i.e., animosity between offices).[17,18] Funding for this position can often be provided by the hospital. Nurse navigator assistance in streamlining patient appointments, such that all essential evaluations can be performed within 24 to 48 hours of the first clinic visit, ensures that patients' treatment starts within 30 days of diagnosis.[19] Admittedly, this is still suboptimal as patients are still required to travel to multiple locations; however, it may mitigate the potential for compromised patient outcomes.

Providers with offices in different areas of the city can also make access for patients easier in larger cities. Two of the authors (M.B. and N.H.) of this review practice in the seventh largest city in the United States. Each has two offices. Though it is a challenge to maintain both, it does make access and travel easier for the patient. A separate group including a medical oncologist and radiation oncologist in the MDT practice on the other side of the city and further assist in overcoming travel challenges. Admissions and inpatient work are coordinated at a single hospital centrally located in the city.

Develop within the MDT a strong social services network of local volunteers, cancer support groups, and church volunteer groups and provide up-to-date information on available city, county, and state resources for patients with head and neck cancer. Low-cost and sometimes free transportation is available through municipal services for a course of treatment or most of a course (i.e., 25–30 trips), as well as vouchers for taxi, Uber, and Lyft and prepaid debit cards for gas.

Barrier: Financial

This includes financial distress due to concerns about high out-of-pocket cost for services, high deductibles, high

premiums, high copay for medications, not enough information to make decisions about insurance, and having to travel long distances to receive care.[20-23]

In surveys where patient opinions were sampled, the reasons for not discussing financial issues included the following: the clinician did not bring it up,[24,25] the patient was embarrassed to discuss personal finances, poor understanding of insurance coverage, visit was too short/rushed, did not want to upset the physician and be seen as a difficult patient, and concerns about receiving low-quality care if cost was discussed.

Solution

Assign a designated financial specialist who can meet with each new patient early in the disease course to develop a rapport, advise the patient about the specific nuances of their insurance, and address the concerns regarding out-of-pocket costs, premiums, and deductibles in a transparent fashion before treatment initiation. Information regarding locally and nationally available foundation grants to offset the cost of treatment can be provided by the specialist to mitigate the anxiety associated with the financial burden of therapy. The patient can work together with the nurse navigator to access a wide range of local and regional resources.

Barrier: Lack of Dietary and Nutritional Counseling

A nutritionist or dietician consultation should be advised pretreatment, and mandatory follow-up visits should be scheduled during and after completion of therapy. Typically, however, most patients are referred during or after treatment. A potential reason for the delay is that patients are overwhelmed with multiple physician appointments, especially when initially diagnosed.[26-28]

Solution

Be creative in finding nutritional support. As percutaneous endoscopic gastrostomy tubes are frequently placed to support patients undergoing treatment, we have found that the durable medical equipment companies that supply the formulas and supplies are often staffed by a clinical nutritionist. They often make home visits, which can be a very creative way to gain nutritional support without additional expense to the team. Certainly, work closely with the hospital clinical nutritionist during the postoperative period while the patient is in the hospital.

Consider a gap analysis to identify best practice care indicators, such as time to treatment with the various modalities including surgery, chemotherapy, and radiation, and supportive care interventions, such as nutrition, speech, and language pathology evaluations. To measure gaps in the metrics against benchmarks, the Agency for Healthcare Research and Quality tool provides a systematic method to compare current practices with best practices, determine the barriers to best practices and feasibility of implementing the recommendations such as ensuring speech pathology, audiometry, and nutritionist/dietitian evaluation pretreatment, during, and post-treatment.[29] Enlisting the support of nurse navigators with knowledge of a clearly defined care pathway for head and neck cancer care in facilitating these evaluations can be invaluable. Establishing a predefined care pathway that all members of the MDT agree upon and follow diligently with each patient encounter can assist in streamlining visits.

Barrier: Dental Care

Dental care is a unique challenge to head and neck cancer. It can be very difficult as it is often very expensive, medical insurance does not cover it, and yet it is a very important part of pretreatment and post-treatment care directly affecting long-term quality of life.

Solution

Invite and motivate a designated dentist to be part of this. Encourage them to seek training with other dental oncologists such that they can provide the detailed cleanings, fluoride treatments, radiation stents, and other comprehensive dental care that is so important to these patients. They can also facilitate obturators and complex dental appliances as needed. Invite them to attend a tumor board. Treat them as a vital part of the team.[30]

SPECIALTY-SPECIFIC BARRIERS

Barrier: Timely Surgery Scheduling

Solution Surgical care for patients with head and neck cancer is often complex and requires coordination of special equipment, specialized operating rooms, and multiple providers. Although there have been advances in surgical care in the last 10 years with greater access now available via robotic and transoral techniques, these often require special robotic rooms at the hospital, laser support, or other specialized equipment that is not often owned by the hospital and has to be brought in or coordinated. Having a designated surgical scheduler/coordinator is key to streamlining these cases.

Complex ablative cases requiring significant reconstruction often necessitate the combined services of a microvascular surgeon, gastroenterologist, and sometimes oral surgery. Access to microvascular free flap reconstruction is becoming more and more available even in the community setting. Coordinating the schedules of multiple busy providers can be difficult. The more these services work together, the more the staff coordinate together, and the easier this gets. Having designated days and times each week that each office can plan predictably for long complex cases can also help. Working toward a steady stream of referrals and cases leads to predictable weekly filling of this time. Providers of each specialty should continually

acknowledge the urgency and importance of timely scheduling to prevent growth and progression of stage between work-up completion and surgical intervention. Sometimes this means compromising and rearranging one's schedule for the benefit of the rest and better outcomes for the patient. Delays in scheduling result in poorer outcomes.

Access to gastroenterology services in the operating room can be a challenge. Not all gastroenterology groups/providers are willing to come to the operating room to place the percutaneous endoscopic gastrostomy tube at the time of ablative surgery. Although avoiding a second anesthetic is ideal, one may consider having the percutaneous endoscopic gastrostomy tube placed prior to the large ablative procedure such to improve nutritional support prior to surgery and to shorten the overall length of a planned lengthy ablative and reconstructive combined surgery. This is often feasible in patients not in airway compromise and often far more appealing to the gastroenterology team.

Barrier: Hospital Support

Solution Not all hospitals are fit or willing to support large ablative and reconstructive surgeries. These are often time, energy, resource, and staff demanding. All the specialized equipment (microscopes, lasers, couplers, and Doppler monitoring devices, etc.) must be available and functioning. If this equipment is lacking, most hospitals with enough notice will work to create a business plan that can budget to acquire them in the future.

Access to a surgical robot can be difficult in some areas. Not all community hospitals have a robot capable of transoral surgery. It is becoming more and more available as robotic procedures in other surgical specialties become more and more common and provide a driving force for access. This can be a two-edged sword, however, as scheduling to use the robot becomes more difficult as other specialties dominate its time. Make it a point to have scheduled robotic block time wherever possible.

Postoperative support is also very important. Given the effects of surgery on breathing and swallow as well as the aggressive flap monitoring and care, necessary early mobilization, and speech and swallowing therapy to name a few, postoperative care is extensive and requires highly trained staff and therapists. Intensive care unit availability can be a challenge in some areas. We have found that most cases, even flaps and tracheostomies, can be managed safely on the surgical floor with continuous pulse oximetry and Doppler monitoring. We have spent a lot of time training a team of nurses to care for these patients who are available and reliable and play a key role in the success of our team. We work hard to be available and are eager to support our nursing team.

Barrier: Preoperative and Postoperative Support

Solution As surgical inpatient stays have shortened over the years, it is important to work closely with the case manager to meticulously arrange postoperative supplies, therapy, and rehabilitation services. Find rehabilitation centers in the area that can be trusted and that understand the special needs of these patients. Understanding the importance of continued care after discharge and recognizing the need for timely discharge so that adjuvant care (postoperative radiation or chemo-radiation) can be started in a timely fashion are both key.

Preoperative and postoperative speech and swallow evaluations and therapy play a very important role in successful long-term outcomes and quality of life.[31] Access to inpatient and outpatient speech services are ideal. Early and aggressive swallowing and voice therapy is vital. Recovery is often a long road that requires patience and ongoing effort.

Support groups (in person or virtual) are a huge source of energy and support for patients at all stages of treatment, recovery, and survival. Participation in these groups has been shown to improve quality of life during and after treatment.[35] These can be easily and inexpensively started in the community setting and can be supported by providers of all specialties. Starting a local chapter of a national society (i.e., Support for People with Oral and Head and Neck Cancer) is simple and very rewarding. These meetings empower patients to support and sustain each other.

Barrier: Timely Postoperative Adjuvant Therapy

Delays in initiation of postoperative radiation therapy of more than 45 to 50 days have been shown to adversely affect overall outcomes and long-term survival.[16]

Solution

Review of each postoperative patient's final surgical pathology the week following surgery at tumor board can facilitate improved communication as to the date of completed surgery and allow for the radiation therapist to plan accordingly. This gives 4 to 5 weeks for the radiation team to successfully coordinate imaging, planning, masking, and treatment initiation.

Coordinating follow-up with the surgeon at 1 to 2 weeks postoperation in the office is also very helpful. An email to the participating radiation oncologist and team, to update them of the patient's postoperative status and to facilitate timely adjuvant therapy, can be helpful.

Barrier: Lack of Infrastructure for Clinical Trials

This represents a major barrier not only in suburban and rural centers but also in large urban clinical practices. A fully functional clinical research unit staffed by personnel

with expertise in various aspects of clinical research, as shown in Fig. 2, can place a significant financial strain on community practices. Additionally, inadequate access to disease-specific clinical trials that encompass early- and late-stage disease and poor accrual to clinical trials remains a concern.

Solution

Partnering with MDTs for other disease types in the community to defray the cost, and pool resources, is a consideration. Alternatively, partnering with a local academic center and referring patients for enrollment in clinical trials where applicable may be considered. Even in community centers where clinical trials are accessible and resources exist, patient enrollment in clinical trials remains poor. Studies have shown an improvement in clinical trial accrual when they are embedded into the pathways for patient care that are routinely used.[33,34] Periodically reviewing the clinical trials open to patient enrollment at multidisciplinary tumor boards and frequent discussion of clinical trials as a therapeutic option where applicable may help enhance patient accrual to clinical trials.

CONCLUSION

Treatment of patients with head and neck cancer is complex and multifaceted. Numerous barriers exist, creating challenges in quality and timely care throughout all stages of the cancer care continuum, from diagnosis through survivorship. Forming a comprehensive multidisciplinary head and neck cancer team with professionals from multiple specialties that delivers high-quality care is time and commitment intensive but is feasible and highly rewarding in the community setting. Weekly tumor boards are the keystone to the group's success. With good communication, hard work, adherence to national guidelines, and creative coordination of community resources, barriers to multidisciplinary care can be overcome, and individualized, personable, and highly successful care can be provided to patients with head and neck cancer in the community setting.

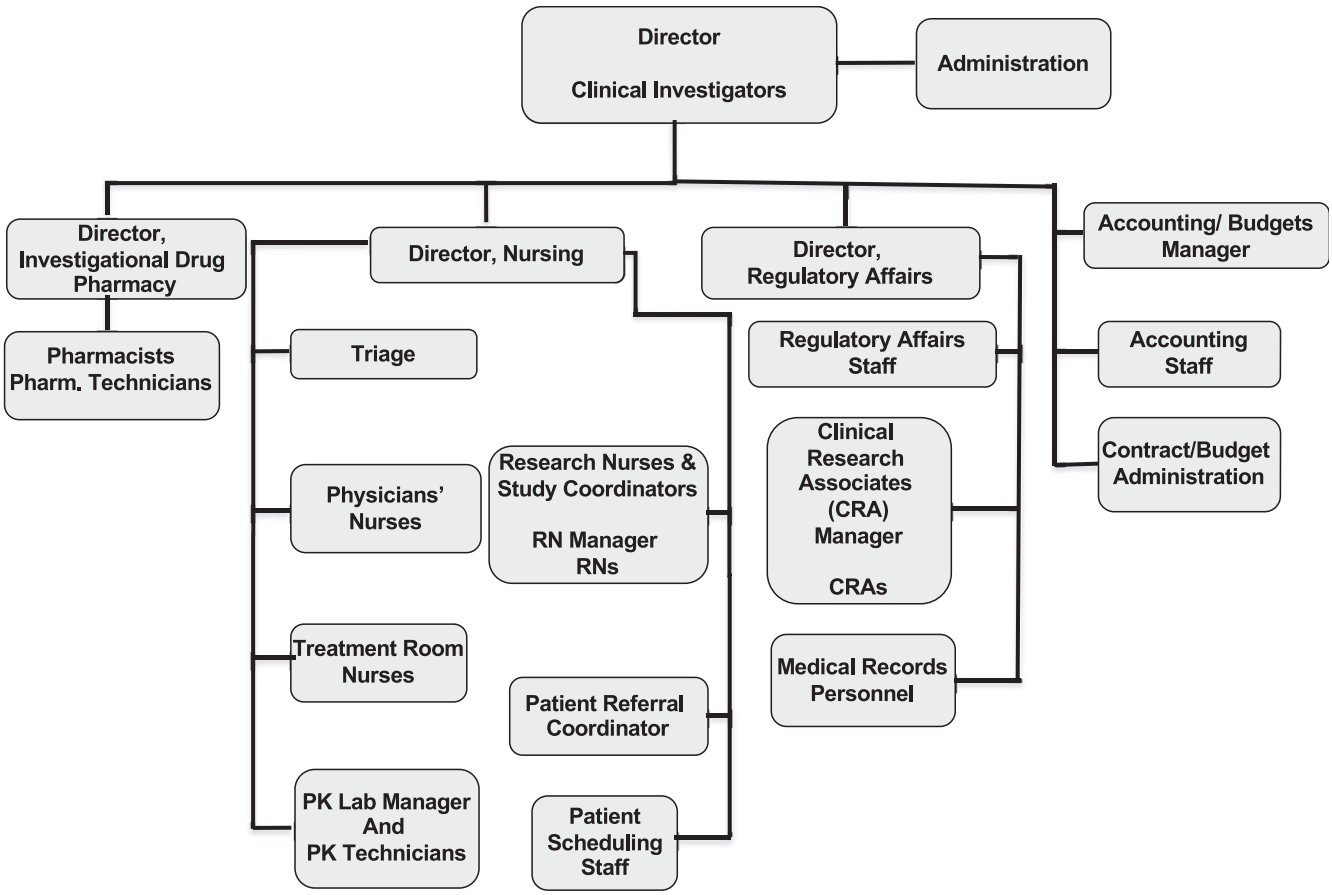

FIGURE 2. Clinical Research Unit Organization Chart
Abbreviations: PK, pharmacokinetics; RN, registered nurse.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Wiederholt PA, Connor NP, Hartig GK, et al. Bridging gaps in multidisciplinary head and neck cancer care: nursing coordination and case management. Int J Radiat Oncol Biol Phys. 2007;69(suppl 2):S88-S91.
2. Dingman C, Hegedus PD, Likes C, et al. A coordinated, multidisciplinary approach to caring for the patient with head and neck cancer. J Support Oncol. 2008; 6:125-131.
3. Neal RD, Tharmanathan P, France B, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. Br J Cancer. 2015;112(suppl 1):S92-S107.
4. Chang YL, Lin CY, Kang CJ, et al. Association between multidisciplinary team care and the completion of treatment for oral squamous cell carcinoma: a cohort population-based study. Eur J Cancer Care (Engl). 2021;30:e13367.
5. Prades J, Remue E, van Hoof E, et al. Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes. Health Policy. 2015;119:464-474.
6. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Head and Neck Cancers Version 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed May 12, 2021.
7. Liu JC, Kaplon A, Blackman E, et al. The impact of the multidisciplinary tumor board on head and neck cancer outcomes. Laryngoscope. 2020;130:946-950.
8. Sandman L, Hofmann B, Bognar G. Rethinking patient involvement in healthcare priority setting. Bioethics. 2020;34:403-411.
9. Zon RT, Frame JN, Neuss MN, et al. American Society of Clinical Oncology Policy Statement on Clinical Pathways in Oncology. J Oncol Pract. 2016;12:261-266.
10. Howren MB, Christensen AJ, Karnell LH, et al. Psychological factors associated with head and neck cancer treatment and survivorship: evidence and opportunities for behavioral medicine. J Consult Clin Psychol. 2013;81:299-317.
11. Okado I, Cassel K, Pagano I, et al. Assessing patients' perceptions of cancer care coordination in a community-based setting. JCO Oncol Pract. 2020; 16:e726-e733.
12. Buzaglo JS, Zaleta AK, McManus S, et al. CancerSupportSource®: validation of a revised multi-dimensional distress screening program for cancer patients and survivors. Support Care Cancer. 2020;28:55-64.
13. George JR, Yom SS, Wang SJ. Combined modality treatment outcomes for head and neck cancer: comparison of postoperative radiation therapy at academic vs nonacademic medical centers. JAMA Otolaryngol Head Neck Surg. 2013;139:1118-1126.
14. Graboyes EM, Halbert CH, Li H, et al. Barriers to the delivery of timely, guideline-adherent adjuvant therapy among patients with head and neck cancer. JCO Oncol Pract. 2020;16:e1417-e1432.
15. Sykes KJ, Morrow E, Smith JB, et al. What is the hold up?-Mixed-methods analysis of postoperative radiotherapy delay in head and neck cancer. Head Neck. 2020;42:2948-2957.
16. Harris JP, Chen MM, Orosco RK, et al. Association of survival with shorter time to radiation therapy after surgery for US patients with head and neck cancer. JAMA Otolaryngol Head Neck Surg. 2018;144:349-359.
17. Kagan SH, Morgan B, Smink T, et al. The oncology nurse navigator as "gate opener" to interdisciplinary supportive and palliative care for people with head and neck cancer. J Oncol Navig Surviv. 2020;11:259-266.
18. Fillion L, de Serres M, Cook S, et al. Professional patient navigation in head and neck cancer. Semin Oncol Nurs. 2009;25:212-221.
19. Schutte HW, Heutink F, Wellenstein DJ, et al. Impact of time to diagnosis and treatment in head and neck cancer: a systematic review. Otolaryngol Head Neck Surg. 2020;162:446-457.
20. Delgado-Guay M, Ferrer J, Rieber AG, et al. Financial Distress and Its Associations With Physical and Emotional Symptoms and Quality of Life Among Advanced Cancer Patients. Oncologist. 2015;20:1092-1098.
21. Fenn KM, Evans SB, McCorkle R, et al. Impact of financial burden of cancer on survivors' quality of life. J Oncol Pract. 2014;10:332-338.
22. Zafar SY, McNeil RB, Thomas CM, et al. Population-based assessment of cancer survivors' financial burden and quality of life: a prospective cohort study. J Oncol Pract. 2015;11:145-50.
23. Barbaret C, Delgado-Guay MO, Sanchez S, et al. Inequalities in financial distress, symptoms, and quality of life among patients with advanced cancer in France and the U.S. oncologist. 2019;24:1121-1127.

24. Schrag D, Hanger M. Medical oncologists' views on communicating with patients about chemotherapy costs: a pilot survey. J Clin Oncol. 2007;25:233-237.
25. Bestvina CM, Zullig LL, Rushing C, et al. Patient-oncologist cost communication, financial distress, and medication adherence. J Oncol Pract. 2014;10:162-167.
26. van den Berg MG, Rasmussen-Conrad EL, Wei KH, et al. Comparison of the effect of individual dietary counselling and of standard nutritional care on weight loss in patients with head and neck cancer undergoing radiotherapy. Br J Nutr. 2010;104:872-877.
27. Granda-Cameron C, DeMille D, Lynch MP, et al. An interdisciplinary approach to manage cancer cachexia. Clin J Oncol Nurs. 2010;14:72-80.
28. Granda-Cameron C, Lynch MP. Clinical Framework for Quality Improvement of Cancer Cachexia. Asia Pac J Oncol Nurs. 2018;5:369-376.
29. Bergamini C, Locati L, Bossi P, et al. Does a multidisciplinary team approach in a tertiary referral centre impact on the initial management of head and neck cancer? Oral Oncol. 2016;54:54-57.
30. Maureen S. The expanding role of dental oncology in head and neck surgery. Surg Oncol Clin N Am. 2004;13:37-46.
31. Perry A, Lee SH, Cotton S, et al. Therapeutic exercises for affecting post-treatment swallowing in people treated for advanced-stage head and neck cancers. Cochrane Database Syst Rev. 2016;2016:CD011112.
33. Shamah CJ, Saphner TJ. Effect on clinical trial participation by integration of a clinical pathway program into an electronic health record (EHR). J Clin Oncol. 2016;34:7s (suppl; abstr 167).
34. Saphner T, Thompson MA, Planton S, et al. Insights from building a new national cancer institute community oncology research program site. WMJ. 2016; 115:191-195.
35. Vakharia KT, Ali MJ, Wang SJ. Quality-of-life impact of participation in a head and neck cancer support group. Otolaryngol Head Neck Surg. 2007;136:405-410.

Making the Best of Limited Resources: Improving Outcomes in Head and Neck Cancer

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overview

The overwhelming majority of head and neck cancers and related deaths occur in low- and middle-income countries, which have challenges related to burden of disease versus access to care. Yet the additional health care burden of the COVID-19 pandemic has also impacted access to care for patients with head and neck cancer in the United States. This article focuses on challenges and innovation in prioritizing head and neck cancer care in Sub-Saharan Africa, the Indian experience of value-added head and neck cancer care in busy and densely populated regions, and strategies to optimize the management of head and neck cancer in the United States during the COVID-19 pandemic.

Head and neck cancer is primarily a disease of low- and middle-income countries, with substantial challenges related to high burden of disease, late presentation, and poor access to care. Low- and middle-income countries account for 67% of head and neck cancer and 82% of head and neck cancer–related deaths.[1] Patients in these countries present with advanced disease; in India, two-thirds of patients present with advanced head and neck cancer,[2] and in Cape Town, South Africa, approximately 50% of laryngectomees require emergency tracheostomy.[3] Only 5% of patients with cancer in Africa and 3% in South Asia have timely access to safe, affordable surgery,[4] and, in 2017, only 24 out of 52 African countries had radiotherapy services.[5] Less than 4% of people in India suffering from chronic pain from cancer have access to morphine,[6] and many African countries do not dispense opioids.

Although the United States provides highly sophisticated cancer care, the additional health care requirements resulting from the COVID-19 pandemic have revealed deficiencies in the health care system and highlighted inequalities to access to care in the United States, including for patients with head and neck cancer.

This article focuses on challenges and innovation in prioritizing head and neck cancer care in Sub-Saharan Africa (Fagan), the Indian experience of value-added head and neck cancer care in busy and densely populated regions (Noronha), and strategies to optimize the management of head and neck cancer in the United States during the COVID-19 pandemic (Graboyes).

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CHALLENGES AND INNOVATION IN PRIORITIZING HEAD AND NECK CANCER CARE IN SUB-SAHARAN AFRICA

Sub-Saharan Africa has more than 1 billion people. Yet it has only 19 fellowship-trained head and neck surgeons, and less than 50% of countries have radiation therapy facilities.[5] Even where radiation is available, old technology is often used, and treatment delays can approach a year.[7] In addition, access to cytology, histopathology, and specialized radiology services are limited, and many patients cannot afford to pay out of pocket for cancer care. Several innovations have been introduced to address these challenges in Sub-Saharan Africa, and are discussed below.

African Head and Neck Surgery Fellowship Training

Two African head and neck fellowship programs have trained 17 head and neck surgeons from 13 African countries. The University of Cape Town has a 1-year hands-on program modeled on North American fellowships. It is funded by Karl Storz Endoscopy and is currently training its 15th fellow. The Pan-African Academy of Christian Surgeons/Johns Hopkins Fellowship is based in Mbingo Baptist Hospital in Cameroon and has a novel outreach fellowship training model with teaching faculty rotating from North American institutions. In an analysis of whether African fellowships have made a sustainable impact on head and neck cancer care in Sub-Saharan Africa, it was reported that all fellows had returned to their countries; all were doing work in public hospitals and hence were involved in transferring surgical skills to trainees; all of those with local radiation therapy services had established head and neck multidisciplinary teams; and there had been a 335% increase in major head and neck surgeries. The authors concluded that high-volume specialized head and neck surgical training was possible in Africa; that training was appropriate in terms of pathology, types of surgery, and affordability; and that the fellowship model made a sustainable change to head and neck practice in Sub-Saharan

PRACTICAL APPLICATIONS

- There are substantial global and region-specific inequities in head and neck cancer care.
- Innovative strategies to prioritize resources and decision trees are presented that optimize and individualize patient care.
- The impact of the COVID-19 pandemic on head and neck cancer care and mitigations are discussed.

Africa by populating it with surgeons and teachers of head and neck surgery, by establishing centers of excellence, by building clinical capacity, and by instituting resource-appropriate management.[7]

African Head and Neck Society

The African Head and Neck Society (https://afhns.org) was established in 2016 by the first 14 African fellowship-trained head and neck surgeons. Its mission is to improve outcomes of patients with diseases of the head and neck in Africa through prevention, clinical excellence, teaching, training, and research and by promoting the highest professional and ethical standards; to coordinate and advance training and education of those engaged in the treatment of patients with diseases of the head and neck in Africa; and to promote friendship and collaboration among those engaged in the treatment of patients with diseases of the head and neck in Africa. It has since held annual conferences and cadaver dissection surgical courses and ultrasound workshops, has published research papers, has served as a link for international otolaryngology and head and neck societies with Africa, runs the African Head and Neck Society Virtual Tumor Board meetings, and has promulgated the African Head and Neck Society Clinical Practice Guidelines for Head and Neck Cancers in Developing Countries and Limited Resource Settings. It is therefore fulfilling a key role in advancing head and neck cancer care and training in Sub-Saharan Africa.

African Head and Neck Society Virtual Tumor Board

With the advent of COVID-19 and development of virtual conferencing software, the African Head and Neck Society introduced a monthly virtual tumor board meeting using Zoom in 2020. It is a free, open-access, multidisciplinary meeting at which interesting clinical cases are presented from around Africa. The second meeting was held in association with the American Academy of Otolaryngology–Head and Neck Surgery. It has attracted more than 150 attendees per meeting and illustrates how virtual conferencing has empowered low- and middle-income countries in terms of knowledge dissemination and networking, and has introduced new opportunities for international collaboration and teaching using virtual platforms.

The African Head and Neck Society Clinical Practice Guidelines for Head and Neck Cancers in Developing Countries and Limited Resource Settings

International head and neck cancer guidelines may be unhelpful, inappropriate, or even harmful when applied in resource-constrained settings, when special investigations, radiotherapy, and complex surgery might not be available or be unaffordable, when management of sequelae of treatment such as hypothyroidism, renal failure, and dysphagia are inadequate, or when cancer surveillance is not possible. The African Head and Neck Society Clinical Practice Guidelines for Head and Neck Cancers (https://afhns.org or https://developingworldheadandneckcancerguidelines.com/) seek to optimize cancer care by tailoring investigations and treatment according to resources available to the individual patient and the treatment center. It reflects the expert opinion of members of the African Head and Neck Society, as well as selected affluent-world surgeons and oncologists. It is directed at local surgeons and oncologists, as well as those undertaking surgical outreach to low- and middle-income countries.

The "Global South" is best qualified to write its own guidelines, as it understands the challenges, constraints, and possibilities of cancer care in limited-resource settings. The promulgation of these guidelines also reflects the Global South's taking ownership, leadership, and responsibility for head and neck cancer practice in low- and middle-income countries. Guidelines have thus far been released for cancers of the thyroid, salivary glands, oral cavity, oropharynx, hypopharynx, and larynx, with guidelines pending for nasopharynx and the unknown primary. In the initial 22 months, the guidelines have been accessed by more than 8,300 visitors with more than 43,000 page views, with the top 10 countries (listed in order of highest to lowest number of visits) being South Africa, the United States, Kenya, India, Nigeria, the United Kingdom, Turkey, France, Italy, and Uganda.

Open Access Atlas of Otolaryngology, Head and Neck Operative Surgery

Accessing educational and scientific material is key to improving head and neck care in low- and middle-income countries. Yet many trainees, practitioners, and researchers in Sub-Saharan Africa cannot afford textbooks and pay-to-view journals, and the content of modern journals and textbooks is often inappropriate for resource-constrained settings. *The Open Access Atlas of Otolaryngology, Head and Neck Operative Surgery* (www.entdev.uct.ac.za/guides/open-access-atlas-of-otolaryngology-head-neck-operative-surgery/) is a free, open-access surgical atlas self-published by Johannes J. Fagan in Cape Town, South Africa. More

than 100 authors from more than 20 countries have contributed, and volunteers have translated chapters into Portuguese, Spanish, and French. The senior authors are mostly international leaders who volunteered to contribute. It provides detailed descriptions of surgical procedures. It includes surgical cancer procedures no longer performed in high-income countries, such as laryngofissure and hemilaryngectomy for early laryngeal cancer, that would not be included in modern textbooks. Being in electronic format, chapters are very detailed, with numerous photographs and video clips. The textbook received the Open Education Consortium 2017 Award for Open Education Excellence, a tribute to its contributors (www.oeconsortium.org/projects/open-education-awards-for-excellence/2017-oe-award-winners-oer-categories/).

Head and Neck Cancer Staging

How head and neck cancers are investigated and managed in high-income compared with low- and middle-income countries is increasingly divergent because of technological, financial, and infrastructural differences. Therefore, having a universal staging system is becoming ever more difficult to achieve. Although anatomic site and tumor extent remain central to defining cancer prognosis and staging, the American Joint Committee on Cancer and Union for International Cancer Control have been incorporating an increasing number of nonanatomic prognostic factors into stage groupings. In the eighth edition of the American Joint Committee on Cancer Cancer Staging Manual, p16 status was included in staging of oropharyngeal cancer. Yet, for 16 out of 17 fellowship-trained head and neck surgeons in 13 Sub-Saharan African countries, p16 testing was not routinely available for their patients with oropharyngeal cancer because of unavailability or unaffordability of the laboratory test.[8] Another challenge that staging bodies must consider is the diversity of the type and quality of therapeutic interventions in high-income versus low- and middle-income countries that might affect outcomes and prognosis. In 2019, only 24 out of 52 African countries had radiotherapy facilities, and treatment could have been delayed for up to 46 weeks.[7] Certain chemotherapy drugs and most targeted agents are also not available to patients in these countries. Such diversity in management might, for instance, invalidate the favorable prognosis for advanced p16+ oropharyngeal cancer reflected in the current staging in such resource-constrained settings. Although the American Joint Committee on Cancer/Union for International Cancer Control should continue to refine staging systems that best reflect prognosis by incorporating nonanatomical factors, anatomically based staging systems must be retained to serve the needs of resource-constrained settings. A model that may be considered is that of a staging system that considers available diagnostic and therapeutic resources, as has been done in the African Head and Neck Society Clinical Treatment Guidelines for Head and Neck Cancer. If the American Joint Committee on Cancer and Union for International Cancer Control do not develop resource-appropriate staging, it would reduce their global relevance and disadvantage most of the world's patients with cancer. This may be an opportunity for the Global South to promulgate its own resource-appropriate staging guidelines.

CHOOSING WISELY: VALUE-ADDED HEAD AND NECK CANCER CARE IN DENSELY POPULATED AND RESOURCE-CONSTRAINED REGIONS—THE INDIAN EXPERIENCE

Head and neck cancer constitutes between 30% and 40% of cancers in India.[9] Oral cavity cancer is the most common cancer in Indian men[10]; one in every 60 Indians will develop cancer of the oral cavity or pharynx during their lifetime.[11] The causative factors for head and neck squamous cell carcinoma in India include smokeless tobacco, smoking, and alcohol; HPV plays a less important etiologic role.[9]

Curative Setting

Resectable oral cancer Patients with resectable oral cancer, both localized and locally advanced, are best treated with surgical resection, followed by adjuvant therapy based on various risk factors.[12] In most centers in India, microvascular free tissue transfer reconstructive surgery is not available, and either primary closure or pedicled flaps are used. Such surgeries can be performed more quickly and more cheaply, thereby facilitating treatment of more patients. The outcomes of patients thus treated match those reported in the global literature, suggesting that even in the absence of a dedicated reconstructive surgical team, good oncologic outcomes are possible.[13]

Until recently, the management of the N0 neck with early-stage oral cancer was controversial. Options range from elective neck dissection to addressing only the oral primary and performing neck dissection for recurrence.[14] In India, watchful waiting is challenging, as patients often travel long distances, and compliance with regular follow-up and radiologic surveillance is poor; this may lead to unsalvageable recurrences. Hence, elective neck dissection is commonly performed. This practice was supported by the N0 trial, which proved that patients with early-stage clinically node-negative oral cancer treated with elective neck dissection had an improved disease-free and overall survival as compared with patients managed with watchful waiting.[15]

Patients with tumors at high risk of recurrence are treated with adjuvant chemoradiotherapy. The standard of care from the landmark trials was high-dose cisplatin administered at 100 mg/m^2 once every 3 weeks during radiation. However, this regimen was difficult to administer in the Indian setting because of patient-related issues (lower body

weight, poorer nutrition, and higher toxicity) and logistic (hospitalization and intravenous hydration) and infrastructure issues (challenges with supportive care). Low-dose cisplatin at 30–40 mg/m^2 administered once a week during radiation was widely introduced even in the absence of level 1 evidence.[16] A subsequent randomized controlled trial comparing high-dose once-every-3-weeks cisplatin to lower-dose once-a-week cisplatin concurrently with radical radiotherapy taught us several important things.[17] First, it is possible to administer high-dose cisplatin in the Indian setting, despite the challenges. Second, high-dose cisplatin led to better locoregional control than weekly cisplatin and should therefore continue as the standard of care. However, overall survival (which was not the primary endpoint of the study) was similar between the two cisplatin schedules, suggesting that low-dose weekly cisplatin could possibly be used, with less toxicity, supportive care, and resource utilization, without compromising overall survival. Recent data from Japan suggest that outcomes are similar between the once-a-week and once-every-3-weeks cisplatin schedules when combined with radical radiotherapy.[18]

Technically unresectable oral cancer A large proportion of our patients present with bulky, extensive oral cancers, which, although localized, are not easily resectable with negative margins. These include buccal mucosa primaries with edema extending up to the zygoma and tumor extension to the infratemporal fossa, primaries of the anterior two-thirds of the tongue extending to the hyoid or posteriorly to the vallecula, or cancers extensively infiltrating skin. Such patients are usually treated conservatively with radiotherapy or concurrent chemoradiotherapy or palliative chemotherapy and have dismal outcomes, with median survival between 2 and 12 months. Induction chemotherapy in an attempt to downstage a tumor, followed by resection, is an exciting approach.[19] In a cohort of 721 patients with technically unresectable oral cancers, we found that with this approach, 43% were able to undergo surgery. The 2-year locoregional control of the entire cohort of patients with technically unresectable oral cancer treated with induction chemotherapy was 21%. Patients who could undergo resection had better outcomes: 2-year locoregional control of 32%, 2-year overall survival of 47%, and a median overall survival of 19.6 months (95% CI, 9.6–25.2) as compared with 15%, 20%, and 8.2 months (95% CI, 7.6–8.6), respectively ($p = .0001$).[20]

Oropharyngeal cancer HPV positivity with oropharyngeal cancer in India is approximately 23%.[21] The availability of robotic surgery is limited. The primary treatment is transoral or open resection or definitive radiotherapy or concurrent chemoradiotherapy depending on disease stage.[22] Patients with stage II and higher disease benefit from the addition of concurrent cisplatin. In a randomized phase II trial, 40 mg/m^2 of cisplatin once a week concurrently with radiotherapy improved oncologic outcomes; the 3-year overall survival and the median overall survival were 62%/not reached versus 42%/27 months (95% CI, 15.2–36.8) in patients treated with concurrent chemoradiotherapy versus radical radiotherapy, respectively.[23] This is a feasible approach in the Indian setting.

Treatment intensification can improve outcomes for patients with HPV-negative oropharyngeal cancer, by addition of the EGFR (epidermal growth factor receptor) antibody nimotuzumab to concurrent cisplatin-based chemoradiotherapy.[24] A subset analysis of a phase III randomized controlled trial showed that nimotuzumab added to weekly cisplatin-based chemoradiotherapy greatly improved locoregional control and progression-free and overall survival. There was an absolute improvement in the 2-year locoregional control of 19%, with 2-year progression-free survival of 26% and 2-year overall survival of 19%. In this trial, 87% of patients were treated with conventional radiation, further emphasizing that oncologic outcomes are not compromised by forgoing intensity-modulated radiotherapy.[25]

Hypopharyngeal/laryngeal cancer A retrospective analysis of 501 patients with locally advanced hypopharyngeal cancer treated with radical radiotherapy or concurrent chemoradiotherapy (30 mg/m^2 of cisplatin once a week) reported a 3-year locoregional control rate of 47.1% and 3-year disease-free survival of 40.9%. As radiotherapy machines are widely available and therefore easily accessible to many Indian patients, this is the usual practice in India.[26] For patients with locally advanced laryngeal tumors, especially without cartilage involvement, induction chemotherapy can result in laryngeal preservation in up to 70% of patients.[27]

Precision-based radiotherapy Both in definitive and adjuvant settings, multiple studies from our institution that used conventional radiotherapy for most patients had similar oncologic outcomes to those reported in international trials.[17,25,28] Thus, conventional radiation remains an important option for our patients and permits treatment of patients in remote areas where teletherapy machines exist. In 2019, there were approximately 545 teletherapy machines in India for an estimated population of 1.35 billion.[29] However, increasing access to therapy and the ability to treat more patients should not come at the cost of poorer oncologic outcomes. Several randomized clinical trials have reported that conventional three-dimensional conformal radiation led to similar locoregional control and survival compared with intensity-modulated radiation therapy, albeit with an increased risk of xerostomia.[30-32]

Palliative Setting

Platinum-sensitive disease Systemic therapy is the standard of care for patients with unresectable recurrent or

metastatic disease. Two approaches that have been shown to prolong survival include the addition of cetuximab to intravenous chemotherapy (i.e., the EXTREME regimen), and immunotherapy, either combined with intravenous chemotherapy or as a single agent, based on the tumor PD-L1 expression. Unfortunately, both of these treatment approaches are unaffordable to 97% of the Indian population. Thus, almost all patients are treated with either intravenous chemotherapy or oral metronomic chemotherapy.

Metronomic chemotherapy is chemotherapy that is administered at low doses on a continuous basis, without breaks. Low-cost oral metronomic chemotherapy consisting of 15 mg/m^2 of oral methotrexate once a week and 200 mg of celecoxib twice daily is widely used in India in the palliative setting. A retrospective analysis of 340 patients treated with oral metronomic chemotherapy reported a median overall survival of 5.1 months (95% CI, 4.6–5.6).[32] A randomized phase II study revealed that an oral metronomic chemotherapy regimen led to a considerable prolongation of median progression-free and overall survival compared with 75 mg/m^2 of intravenous cisplatin once in 3 weeks, and with lower toxicities.[33] We recently reported the results of our phase III noninferiority trial, in which 422 patients with relapsed, recurrent, or newly diagnosed head and neck squamous cell carcinomas were randomly assigned to oral metronomic chemotherapy or intravenous cisplatin. Patients who received oral metronomic chemotherapy had improvement in oncologic outcomes and quality of life. The median overall survival of patients in the oral metronomic chemotherapy arm was 7.5 months (95% CI, 4.6–12.6) versus 6.2 months (95% CI, 3.2–9.6) for patients who received intravenous cisplatin. There were fewer adverse events for patients who received oral metronomic chemotherapy and an improvement in global health-related quality of life.[34]

A phase II study of 114 patients with newly diagnosed locally advanced unresectable incurable nonmetastatic disease evaluated palliative radiotherapy (20 Gy in 5 fractions) compared with palliative radiotherapy with 6 mg/m^2 of daily cisplatin, with reassessment at 4 weeks and completion of radical chemoradiotherapy (70 Gy of a radiobiologically equivalent dose; 40 mg/m^2 of cisplatin once a week added in the chemoradiotherapy arm) for patients who had a partial response. Compared with palliative radiation, patients who received palliative chemoradiotherapy had higher conversion to radical chemoradiotherapy (46.4% vs. 25.5%), prolongation of median survival (10.1 vs. 5.9 months), and improved symptoms and quality of life.[35]

Platinum-refractory disease Patients with disease that relapses within 3 to 6 months of receiving cisplatin-based therapy have very poor outcomes. The standard of care is immunotherapy, which is out of reach for 97% to 99% of Indian patients. Most patients therefore receive various regimens of intravenous or oral metronomic chemotherapy. A retrospective analysis of oral metronomic chemotherapy of 100 patients with platinum-refractory oral cancers revealed only limited efficacy, with median overall survival of 3.6 months (95% CI, 2.8–4.4).[36] This led us to explore the use of triple oral metronomic chemotherapy (i.e., addition of erlotinib to the double oral regimen of 9 mg/m^2 of methotrexate weekly and celecoxib daily). A phase I/II study of 91 patients with platinum-refractory oral cancer showed promising efficacy from the triple oral metronomic chemotherapy regimen; 6-month progression-free survival and 6-month overall survival were 34.5% (95% CI, 23.9–45.3%) and 61.2% (95% CI, 49.2–67.8%), respectively. The median progression-free survival and overall survival were 4.6 months (95% CI, 4.1–5.3) and 7.17 months (95% CI, 5.93–8.10), respectively.[37] Although the data are preliminary, this represents an emerging option for our patients with platinum-refractory oral cancers. An outline of the management of oral cancers is provided in Fig. 1.

Adjunctive Treatments

The primary expectation of patients treated in the palliative setting is prolongation of life in 41.0%, whereas 58.5% of the patients rate symptom relief as either the primary goal or at least of equal importance.[38] Almost 45% of patients experience high distress levels at the start of palliative intent therapy. Counseling by the clinician leads to resolution of distress in 59% of patients; an additional referral to a psychologist leads to resolution of distress in 75%.[39] To maximize quality of life for patients, close attention must be paid to various supportive care measures, including analgesia, management of mucositis, dysphagia, nutritional support, and psychological counseling.

DRIVERS OF OUTCOMES AND STRATEGIES TO OPTIMIZE CARE FOR PATIENTS WITH HEAD AND NECK CANCER IN THE UNITED STATES DURING THE COVID-19 PANDEMIC

Responding to the COVID-19 pandemic in the United States necessitated that health systems urgently reallocate health care resources such as hospital beds, ventilators, health care workers, and personal protective equipment toward the management of COVID-19 and away from other clinical activities.[40] Concurrently, health systems instituted new infection control measures to minimize transmission of the severe acute respiratory syndrome coronavirus 2, which were of particular relevance to head and neck oncology providers because of the risk of acquiring COVID-19 from aerosols generated during a physical examination or procedure of the upper aerodigestive tract.[41] As a result, health systems saw a precipitous decrease in their capacity to care for patients with head and neck cancer and

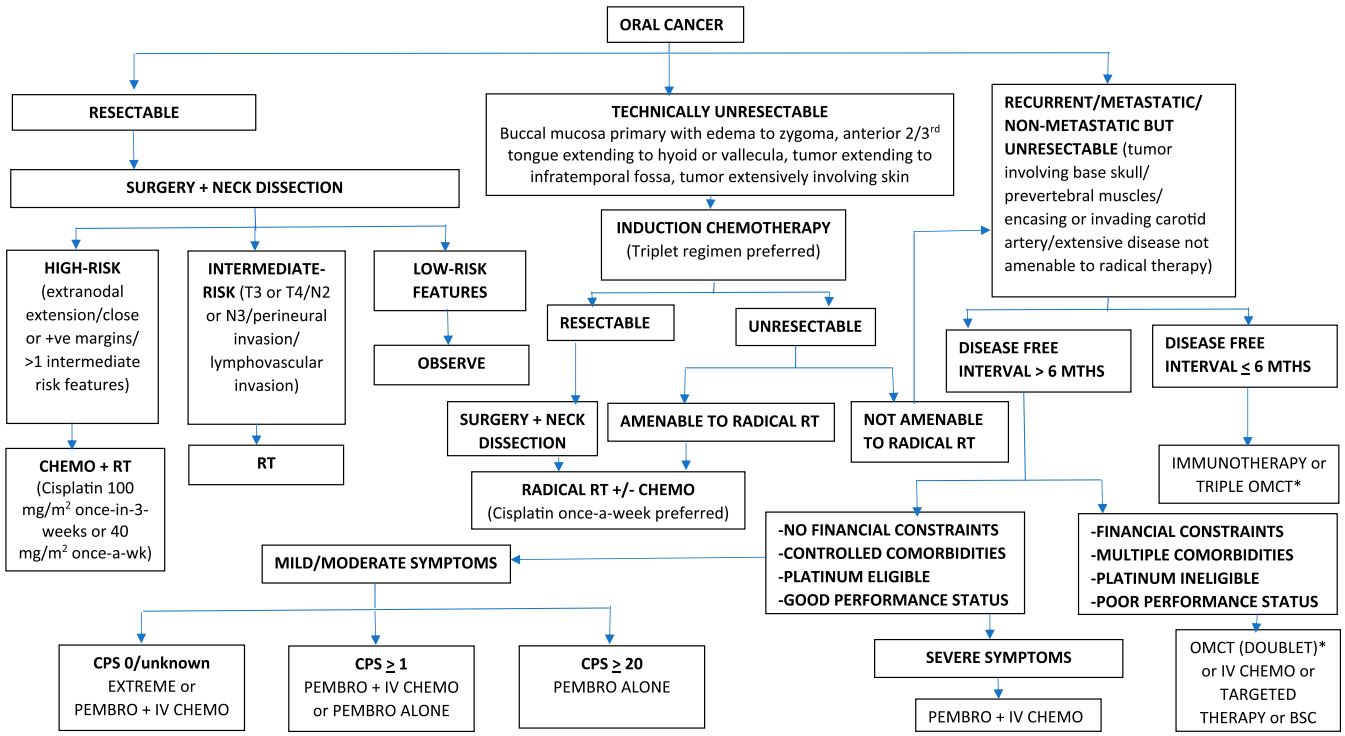

FIGURE 1. An Algorithm Outlining the Suggested Management of Oral Cancers, Based on Resectability and Financial Constraint Considerations

Abbreviations: +ve, positive; MTHS, months; CHEMO, chemotherapy; RT, radiotherapy; wk, week; +/−, with or without; OMCT, oral metronomic chemotherapy; CPS, combined positive score; EXTREME, cetuximab plus combination chemotherapy; PEMBRO, pembrolizumab; IV, intravenous; BSC, best supportive care.

*Preferred for patients with limited financial resources.

substantial reductions in head and neck cancer–related clinical activity.[42,43]

Against the backdrop of hitherto unforeseen resource constraints and the potential for viral transmission, novel methods of head and neck cancer service delivery needed to be developed. Frameworks, protocols, and consensus statements from leading academic centers[44-49] and professional organizations provided recommendations for head and neck cancer surgical,[50] radiation,[51,52] and medical oncologic care.[53] Although diverse in scope, these recommendations shared a common thread of attempting to develop novel care delivery strategies that recognized the oncologic importance of delivering timely treatment that adheres to evidence-based standards of care amid new capacity limitations. The following sections discuss the role of timely treatment and guideline adherence as drivers of outcomes for patients with head and neck cancer in the United States, examine strategies to optimize head and neck cancer care during the COVID-19 pandemic, and explore the ways in which COVID-19–associated care delivery changes may exacerbate existing disparities in access to care and outcomes for patients with head and neck cancer in the United States.

Drivers of Oncologic Outcomes: Delivery of Timely Head and Neck Cancer Care

Because of the robust and consistent association between treatment delays and worse oncologic outcomes for patients with head and neck cancer,[54] strategies to optimize head and neck cancer care delivery in spite of COVID-19 in the United States attempted to ensure timely treatment despite resource constraints and nosocomial infection risks. Across a range of studies, delays in treatment initiation are associated with stage migration,[55] higher rates or recurrence,[56] and worse overall survival.[57] Although precise threshold values for delayed treatment initiation vary,[54] a number of studies suggest that mortality increases precipitously for delays beyond 60 days.[56,57] The association of treatment delay with survival also varies by stage, with an increased hazard of mortality for stages I/II head and neck cancer relative to stages III/IV.[58] Other intervals of timely head and neck cancer care also have a strong and consistent association with recurrence and survival, including initiation of postoperative radiation therapy within 6 weeks of surgery,[54,59,60] the duration of radiation therapy,[60-62] and treatment package time.[63,64] The oncologic impact of treatment delays for patients with head and neck cancer is

extensive; the excess hazard conferred by delayed initiation of postoperative radiation therapy or prolonged radiation duration are comparable in magnitude to the mortality risk associated with adverse features such as positive margins or extranodal extension.[60]

Drivers of Oncologic Outcomes: Delivery of National Comprehensive Cancer Network Guideline-Adherent Treatment

Because of the strong association between the delivery of National Comprehensive Cancer Network guideline-adherent care and oncologic outcomes for patients with head and neck cancer,[65,66] novel head and neck cancer care delivery strategies during the COVID-19 pandemic attempted to balance concordance with evidence-based standards with newly limited capacity and viral transmission risk.[67] Given the clinical equipoise between surgical and nonsurgical management of certain head and neck subsites/stages, nonsurgical management became the preferred treatment modality. However, adherence to National Comprehensive Cancer Network guidelines to treat oral cavity cancer[68,69] and T4a laryngeal cancer[70] with a primary surgical approach is associated with improved survival. Other aspects of National Comprehensive Cancer Network guideline-adherent care for patients with surgically treated head and neck cancer that are associated with improved overall survival include negative-margin resection, adjuvant radiation therapy for pT3–4 or N2–3 disease, adjuvant chemoradiation therapy for extranodal extension or positive margins, and initiation of adjuvant therapy within 6 weeks of surgery.[59,71,72] Designing new head and neck cancer care delivery systems to reflect these drivers of oncologic outcomes was thus an important consideration in attempts to optimize care delivery during the COVID-19 pandemic.

Drivers of Oncologic Outcomes: Social Determinants of Health

As the COVID-19 pandemic unfolded in the United States, the observed racial/ethnic differences in incidence and outcomes served as a magnifying glass for the stark racial/ethnic disparities in outcomes for patients with head and neck cancer.[73] Although the reasons underlying observed racial/ethnic differences in mortality for patients with head and neck cancer are multifactorial, disparities in social determinants of health are major drivers for poor outcomes.[73,74] As health systems massively reoriented strategies to deliver timely, guideline-adherent head and neck cancer care, it became imperative to consider how COVID-19–related changes to health care delivery might exacerbate existing racial/ethnic disparities in access to care and worsen oncologic outcomes for racial/ethnic minority patients with head and neck cancer.[75]

Strategies to Optimize Care: Enhancing Access via Telemedicine

To enhance access to care while minimizing footfall in outpatient clinics, head and neck cancer providers pivoted to direct-to-consumer, telemedicine-based platforms (phone- or video-based) for initial consultations of patients with suspected head and neck cancer and post-treatment follow-up/survivorship care.[76] This forward triage strategy allowed for remote assessment and screening of patients with possible head and neck cancer to protect patients, clinicians, and the community from COVID-19. At the start of the pandemic, there was little experience and a lack of data to guide telemedicine-based evaluation for newly diagnosed head and neck cancer.[77] Nevertheless, initial reports reflected relatively high uptake of telemedicine-based evaluation and treatment of patients with head and neck cancer,[77,78] and it was effective at reducing in-person visits.[79] The efficiency of telemedicine can be further enhanced through the use of risk calculators such as the head and neck cancer risk calculator V.2.[78] Using patient symptoms to calculate a risk of head and neck cancer, the head and neck cancer risk calculator V.2 allows patients with a low predicted risk of primary or recurrent head and neck cancer to be directly discharged or have in-person appointments deferred, thereby minimizing clinic footfall.[78] Despite the publication of practical guides to optimize telemedicine for head and neck cancer,[80] challenges remain because of intrinsic limitations of the physical examination, lack of endoscopic evaluation, and inability to perform biopsies.[76] In addition, disparities in telemedicine usage for patients with head and neck cancer have been reported, as those who were low-income or on Medicaid or uninsured were more likely to complete a telephone visit in lieu of a video-based visit.[81] Nevertheless, it is clear that the COVID-19–inspired shift to telemedicine-based head and neck cancer care delivery will remain in some form long after the COVID-19 pandemic ends.[82]

Strategies to Optimize Care: Prioritization of Head and Neck Cancer Management

In the setting of an instantaneous and precipitous decrement in resource allocation and capacity, providers and health care systems were forced to make difficult but obligatory decisions regarding prioritization of care for patients with head and neck cancer. Because of the considerable risk of virus transmission during transmucosal aerosol-generating procedures of the upper aerodigestive tract as well as the resource intensity of perioperative care, strategies for prioritizing head and neck cancer management focused particularly on triaging patients for head and neck cancer surgery.[44] In general, two triage strategies emerged: (1) general frameworks and (2) prioritization algorithms. General prioritization frameworks were preferred

by some because they facilitate case-by-case decision-making and allow for flexibility and the use of clinical judgment,[45] whereas others favored prioritization algorithms to minimize the logistical challenges, cognitive burden, and inherent bias associated with case-by-case, framework-based decision-making.[83]

Numerous frameworks for ethically triaging and prioritizing head and neck cancer care during the COVID-19 pandemic in the United States were developed from leading academic institutions.[44-49] These frameworks focused on a number of variables, including the acuity and risk of treatment delay, expected oncologic outcomes, risk of viral transmission during surgery, availability of supportive resources, and safety of health care personnel. To help minimize variability and confusion for providers stemming from the massive number of triage frameworks, an international consensus statement from 35 interprofessional societies was developed to help prioritize surgical care for patients with head and neck cancer. The top five factors to consider for triaging patients with head and neck cancer for surgery (from most to least important) were: (1) risk of cancer progression with delay; (2) COVID-19 status of the patient; (3) oncologic prognosis; (4) availability of operative infrastructure; and (5) effectiveness of and availability of alternative treatment modalities.[51]

The Surgical Prioritization and Ranking Tool and Navigation Aid for Head and Neck Cancer is a validated, point-based scoring algorithm to prioritize head and neck cancer surgical care based on 15 variables related to the patient, tumor, treatment, resource availability, and wait time factors.[83] Surgical Prioritization and Ranking Tool and Navigation Aid for Head and Neck Cancer scores range from −17 to 20, with higher scores representing more urgent prioritization for surgical treatment of head and neck cancer.[83] Although the Surgical Prioritization and Ranking Tool and Navigation Aid for Head and Neck Cancer helps prioritize surgical management of head and neck cancer among those diagnosed with head and neck cancer, it does not provide a health care system with guidance for how to prioritize head and neck cancer surgery relative to other surgical procedures. The Medically Necessary, Time-Sensitive scoring system is a surgical scoring system to triage and prioritize surgical cases at the health system level amid the scarce resources of the COVID-19 pandemic, according to 21 variables across three categories (procedure, disease, and patient factors).[84] Cumulative Medically Necessary, Time-Sensitive scores range from 21 to 105, with higher scores suggesting poorer perioperative patient outcomes, increased risk of COVID-19 transmission to the health care team, and/or increased hospital resource use.[84] Each health system can assign upper and lower thresholds for Medically Necessary, Time-Sensitive scores and adjust them dynamically based on evolving resource availability.

CONCLUSION

The prevalence, etiology, and treatment paradigms for head and neck cancer are variable by region. However, diverse health care delivery systems in Sub-Saharan Africa, India, and the United States (during the COVID-19 pandemic) all face substantial challenges related to high burden of disease, late presentation, and inadequate access to care. Importantly, limitations in capacity and resources constrain head and neck cancer care delivery in all three settings. In Sub-Saharan Africa, the challenges of care delivery are primarily driven by the inadequate number of providers and technology. In India, resource constraints reflect the enormous population and the high incidence of head and neck cancer. During the COVID-19 pandemic in the United States, acute resource reallocation, concurrent with a nosocomial infection risk, resulted in a precipitous decrease in capacity to provide head and neck cancer care.

Although the particular strategies adopted by each health system to deliver head and neck cancer care amid resource constraints are variable, their solutions reflect cross-cutting themes and underlying principles that can facilitate and inform care delivery for patients with head and neck cancer more generally. For example, algorithm-based tools and other objective decision aids were used to prioritize and allocate resources in terms of the type and timing of therapy. In each setting, when it was not feasible to deliver internationally accepted guideline-concordant care based on resource constraints, key stakeholders with knowledge and expertise of the local context adapted guidelines to optimize local fit. Technology-enhanced solutions were also key to improving capacity. Finally, attempts were made in all settings of resource constraint to enhance the multidisciplinary evaluation and treatment of patients with head and neck cancer.

In conclusion, the cross-cutting themes described in this article reflect important strategies for how to make the best of limited resources when caring for patients with head and neck cancer. These initiatives help optimize outcomes for individual patients with head and neck cancer, provide value-driven care at a population-level, and minimize disparities in access and outcomes.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_320923.

REFERENCES

1. Patterson RH, Fischman VG, Wasserman I, et al. Global burden of head and neck cancer: economic consequences, health, and the role of surgery. Otolaryngol Head Neck Surg. 2020;162:296-303.
2. Joshi P, Dutta S, Chaturvedi P, et al. Head and neck cancers in developing countries. Rambam Maimonides Med J. 2014;5:e0009.
3. Fagan JJ. Semon Lecture, Royal Society of Medicine: Laryngectomy practice based on personal research. J Laryngol Otol. In press.
4. Alkire BC, Raykar NP, Shrime MG, et al. Global access to surgical care: a modelling study. Lancet Glob Health. 2015;3:e316-e323.
5. Fagan JJ, Zafereo M, Aswani J, et al. Head and neck surgical subspecialty training in Africa: Sustainable models to improve cancer care in developing countries. Head Neck. 2017;39:605-611.
6. Human Rights Watch. Unbearable Pain: India's Obligation to Ensure Palliative Care. https://www.hrw.org/report/2009/10/28/unbearable-pain/indias-obligation-ensure-palliative-care. October 28, 2009. Accessed March 10, 2021.
7. Fagan JJ, Otiti J, Aswani J, et al. African head and neck fellowships: a model for a sustainable impact on head and neck cancer care in developing countries. Head Neck. 2019;41:1824-1829.
8. Fagan JJ, Wetter J, Otiti J, et al. Is AJCC/UICC staging still appropriate for head and neck cancers in developing countries? OTO Open. 2020;4:2473974X20938313.
9. Prabhash K, Babu G, Chaturvedi P, et al. Indian clinical practice consensus guidelines for the management of squamous cell carcinoma of head and neck. Indian J Cancer. 2020;57(Suppl):S1-S5.
10. Shetty R, Mathew RT, Vijayakumar M. Incidence and pattern of distribution of cancer in India: a secondary data analysis from six population-based cancer registries. Cancer Res Stat Treat. 2020;3:678-682.
11. Mathur P, Sathishkumar K, Chaturvedi M, et al; ICMR-NCDIR-NCRP Investigator Group. Cancer statistics, 2020: report from National Cancer Registry Programme, India. JCO Glob Oncol. 2020;6:1063-1075.
12. Chaturvedi P, Prabhash K, Babu G, et al. Indian clinical practice consensus guidelines for the management of oral cavity cancer. Indian J Cancer. 2020;57(Suppl):S6-S8.
13. Nair D, Singhvi H, Mair M, et al. Outcomes of surgically treated oral cancer patients at a tertiary cancer center in India. Indian J Cancer. 2017;54:616-620.
14. Kowalski LP, Sanabria A. Elective neck dissection in oral carcinoma: a critical review of the evidence. Acta Otorhinolaryngol Ital. 2007;27:113-117.
15. D'Cruz AK, Vaish R, Kapre N, et al; Head and Neck Disease Management Group. Elective versus therapeutic neck dissection in node-negative oral cancer. N Engl J Med. 2015;373:521-529.
16. Goyal G, Patil VM, Noronha V, et al. Once-a-week versus once-every-3-weeks cisplatin in patients receiving chemoradiation for locally advanced head-and-neck cancer: a survey of practice in India. Cancer Res Stat Treat. 2018;1:63-67.
17. Noronha V, Joshi A, Patil VM, et al. Once-a-week versus once-every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a phase III randomized noninferiority trial. J Clin Oncol. 2018;36:1064-1072.
18. Kiyota N, Tahara M, Fujii H, et al. Phase II/III trial of post-operative chemoradiotherapy comparing 3-weekly cisplatin with weekly cisplatin in high-risk patients with squamous cell carcinoma of head and neck (JCOG1008). J Clin Oncol. 2020;38 (15 suppl; abstr 6502).
19. Goel A, Singla A, Prabhash K. Neoadjuvant chemotherapy in oral cancer: current status and future possibilities. Cancer Res Stat Treat. 2020;3:51-59.
20. Patil VM, Prabhash K, Noronha V, et al. Neoadjuvant chemotherapy followed by surgery in very locally advanced technically unresectable oral cavity cancers. Oral Oncol. 2014;50:1000-1004.
21. Murthy V, Swain M, Teni T, et al. Human papillomavirus/p16 positive head and neck cancer in India: prevalence, clinical impact, and influence of tobacco use. Indian J Cancer. 2016;53:387-393.
22. Prabhash K, Babu G, Chaturvedi P, et al. Indian clinical practice consensus guidelines for the management of oropharyngeal cancer. Indian J Cancer. 2020;57(Suppl):S12-S15.
23. Sharma A, Mohanti BK, Thakar A, et al. Concomitant chemoradiation versus radical radiotherapy in advanced squamous cell carcinoma of oropharynx and nasopharynx using weekly cisplatin: a phase II randomized trial. Ann Oncol. 2010;21:2272-2277.

24. Noronha V, Patil VM, Joshi A, et al. Nimotuzumab-cisplatin-radiation versus cisplatin-radiation in HPV negative oropharyngeal cancer. Oncotarget. 2020; 11:399-408.
25. Patil VM, Noronha V, Joshi A, et al. A randomized phase 3 trial comparing nimotuzumab plus cisplatin chemoradiotherapy versus cisplatin chemoradiotherapy alone in locally advanced head and neck cancer. Cancer. 2019;125:3184-3197.
26. Gupta T, Chopra S, Agarwal JP, et al. Squamous cell carcinoma of the hypopharynx: single-institution outcome analysis of a large cohort of patients treated with primary non-surgical approaches. Acta Oncol. 2009;48:541-548.
27. Benson R, Mallick S, Rath GK. Neoadjuvant chemotherapy for larynx preservation: has it lost importance? Indian J Med Paediatr Oncol. 2018;39:227-233.
28. Laskar SG, Choukar D, Deshpande M, et al. Phase III randomized trial of surgery followed by conventional radiotherapy (5 fr/Wk) (Arm A) vs concurrent chemoradiotherapy (Arm B) vs accelerated radiotherapy (6fr/Wk) (Arm C) in locally advanced, stage III and IV, resectable, squamous cell carcinoma of oral cavity-oral cavity adjuvant therapy (OCAT): final results (NCT00193843). J Clin Oncol. 2016;34 (suppl; abstr 6004).
29. Munshi A, Ganesh T, Mohanti BK. Radiotherapy in India: history, current scenario and proposed solutions. Indian J Cancer. 2019;56:359-363.
30. Gupta T, Sinha S, Ghosh-Laskar S, et al. Intensity-modulated radiation therapy versus three-dimensional conformal radiotherapy in head and neck squamous cell carcinoma: long-term and mature outcomes of a prospective randomized trial. Radiat Oncol. 2020;15:218.
31. Ghosh-Laskar S, Yathiraj PH, Dutta D, et al. Prospective randomized controlled trial to compare 3-dimensional conformal radiotherapy to intensity-modulated radiotherapy in head and neck squamous cell carcinoma: long-term results. Head Neck. 2016;38(Suppl 1):E1481-E1487.
32. Patil VM, Noronha V, Joshi A, et al. Retrospective analysis of palliative metronomic chemotherapy in head and neck cancer. Indian J Cancer. 2017;54:25-29.
33. Patil VM, Noronha V, Joshi A, et al. A prospective randomized phase II study comparing metronomic chemotherapy with chemotherapy (single agent cisplatin), in patients with metastatic, relapsed or inoperable squamous cell carcinoma of head and neck. Oral Oncol. 2015;51:279-286.
34. Patil V, Noronha V, Dhumal SB, et al. Low-cost oral metronomic chemotherapy versus intravenous cisplatin in patients with recurrent, metastatic, inoperable head and neck carcinoma: an open-label, parallel-group, non-inferiority, randomised, phase 3 trial. Lancet Glob Health. 2020;8:e1213-e1222.
35. Kumar A, Sharma A, Mohanti BK, et al. A phase 2 randomized study to compare short course palliative radiotherapy with short course concurrent palliative chemotherapy plus radiotherapy in advanced and unresectable head and neck cancer. Radiother Oncol. 2015;117:145-151.
36. Patil VM, Noronha V, Joshi A, et al. Metronomic chemotherapy in platinum-insensitive failures and/or early failures postmultimodality management in oral cancers. Indian J Med Paediatr Oncol. 2015;36:161-165.
37. Patil VM, Noronha V, Joshi A, et al. Phase I/II study of palliative triple metronomic chemotherapy in platinum-refractory/early-failure oral cancer. J Clin Oncol. 2019;37:3032-3041.
38. Patil V, Joshi A, Noronha V, et al. Expectations and preferences for palliative chemotherapy in head and neck cancers patients. Oral Oncol. 2016;63:10-15.
39. Patil V, Noronha V, Joshi A, et al. Distress management in patients with head and neck cancer before start of palliative chemotherapy: a practical approach. J Glob Oncol. 2018;4:1-10.
40. Emanuel EJ, Persad G, Upshur R, et al. Fair allocation of scarce medical resources in the time of Covid-19. N Engl J Med. 2020;382:2049-2055.
41. Givi B, Schiff BA, Chinn SB, et al. Safety recommendations for evaluation and surgery of the head and neck during the COVID-19 pandemic. JAMA Otolaryngol Head Neck Surg. 2020;146:579-584.
42. Kiong KL, Guo T, Yao CMKL, et al. Changing practice patterns in head and neck oncologic surgery in the early COVID-19 era. Head Neck. 2020;42:1179-1186.
43. Patil VM, Srikanth A, Noronha V, et al. The pattern of care in head-and-neck cancer: comparison between before and during the COVID-19 pandemic. Cancer Res Stat Treat. 2020;3(Suppl S1):7-12.
44. Topf MC, Shenson JA, Holsinger FC, et al. Framework for prioritizing head and neck surgery during the COVID-19 pandemic. Head Neck. 2020;42:1159-1167.
45. Maniakas A, Jozaghi Y, Zafereo ME, et al; MD Anderson Head and Neck Surgery Treatment Guidelines Consortium; Consortium members. Head and neck surgical oncology in the time of a pandemic: subsite-specific triage guidelines during the COVID-19 pandemic. Head Neck. 2020;42:1194-1201.
46. Ranasinghe V, Mady LJ, Kim S, et al. Major head and neck reconstruction during the COVID-19 pandemic: the University of Pittsburgh approach. Head Neck. 2020;42:1243-1247.
47. Weinstein GS, Cohen R, Lin A, et al. Penn Medicine head and neck cancer service line COVID-19 management guidelines. Head Neck. 2020;42:1507-1515.
48. Shuman AG, Campbell BH; AHNS Ethics & Professionalism Service. Ethical framework for head and neck cancer care impacted by COVID-19. Head Neck. 2020;42:1214-1217.
49. Patil V, Noronha V, Chaturvedi P, et al. COVID-19 and head and neck cancer treatment. Cancer Res Stat Treat. 2020;3(Suppl S1):15-28.
50. Mehanna H, Hardman JC, Shenson JA, et al. Recommendations for head and neck surgical oncology practice in a setting of acute severe resource constraint during the COVID-19 pandemic: an international consensus. Lancet Oncol. 2020;21:e350-e359.
51. Thomson DJ, Palma D, Guckenberger M, et al. Practice recommendations for risk-adapted head and neck cancer radiation therapy during the COVID-19 pandemic: an ASTRO-ESTRO consensus statement. Int J Radiat Oncol Biol Phys. 2020;107:618-627.
52. Sinha S, Laskar SG, Mummudi N, et al. Head-and-neck cancer radiotherapy recommendations during the COVID-19 pandemic: adaptations from the Indian subcontinent. Cancer Res Stat Treat. 2020;3:424-426.
53. European Society of Medical Oncology. ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Head and Neck Cancers. https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/head-and-neck-cancers-in-the-covid-19-era. Accessed December 30, 2020.
54. Graboyes EM, Kompelli AR, Neskey DM, et al. Association of treatment delays with survival for patients with head and neck cancer: a systematic review. JAMA Otolaryngol Head Neck Surg. 2019;145:166-177.

55. Xiao R, Ward MC, Yang K, et al. Increased pathologic upstaging with rising time to treatment initiation for head and neck cancer: a mechanism for increased mortality. Cancer. 2018;124:1400-1414.
56. Liao DZ, Schlecht NF, Rosenblatt G, et al. Association of delayed time to treatment initiation with overall survival and recurrence among patients with head and neck squamous cell carcinoma in an underserved urban population. JAMA Otolaryngol Head Neck Surg. 2019;145:1001-1009.
57. Murphy CT, Galloway TJ, Handorf EA, et al. Survival impact of increasing time to treatment initiation for patients with head and neck cancer in the United States. J Clin Oncol. 2016;34:169-178.
58. Galloway TJ, Kowalski LP, Matos LL, et al. Head and neck surgery recommendations during the COVID-19 pandemic. Lancet Oncol. 2020;21:e416.
59. Graboyes EM, Garrett-Mayer E, Ellis MA, et al. Effect of time to initiation of postoperative radiation therapy on survival in surgically managed head and neck cancer. Cancer. 2017;123:4841-4850.
60. Ho AS, Kim S, Tighiouart M, et al. Quantitative survival impact of composite treatment delays in head and neck cancer. Cancer. 2018;124:3154-3162.
61. Mazul AL, Stepan KO, Barrett TF, et al. Duration of radiation therapy is associated with worse survival in head and neck cancer. Oral Oncol. 2020;108:104819.
62. Shaikh T, Handorf EA, Murphy CT, et al. The impact of radiation treatment time on survival in patients with head and neck cancer. Int J Radiat Oncol Biol Phys. 2016;96:967-975.
63. Tam M, Wu SP, Gerber NK, et al. The impact of adjuvant chemoradiotherapy timing on survival of head and neck cancers. Laryngoscope. 2018;128:2326-2332.
64. Guttmann DM, Kobie J, Grover S, et al. National disparities in treatment package time for resected locally advanced head and neck cancer and impact on overall survival. Head Neck. 2018;40:1147-1155.
65. Gourin CG, Frick KD, Blackford AL, et al. Quality indicators of laryngeal cancer care in the elderly. Laryngoscope. 2014;124:2049-2056.
66. Lewis CM, Nurgalieva Z, Sturgis EM, et al. Improving patient outcomes through multidisciplinary treatment planning conference. Head Neck. 2016;38(Suppl 1): E1820-E1825.
67. Day AT, Sher DJ, Lee RC, et al. Head and neck oncology during the COVID-19 pandemic: reconsidering traditional treatment paradigms in light of new surgical and other multilevel risks. Oral Oncol. 2020;105:104684.
68. Ellis MA, Graboyes EM, Wahlquist AE, et al. Primary surgery vs radiotherapy for early stage oral cavity cancer. Otolaryngol Head Neck Surg. 2018;158:649-659.
69. Spiotto MT, Jefferson G, Wenig B, et al. Differences in survival with surgery and postoperative radiotherapy compared with definitive chemoradiotherapy for oral cavity cancer: a National Cancer Database analysis. JAMA Otolaryngol Head Neck Surg. 2017;143:691-699.
70. Grover S, Swisher-McClure S, Mitra N, et al. Total laryngectomy versus larynx preservation for T4a larynx cancer: patterns of care and survival outcomes. Int J Radiat Oncol Biol Phys. 2015;92:594-601.
71. Chen MM, Roman SA, Yarbrough WG, et al. Trends and variations in the use of adjuvant therapy for patients with head and neck cancer. Cancer. 2014; 120:3353-3360.
72. Cramer JD, Speedy SE, Ferris RL, et al. National evaluation of multidisciplinary quality metrics for head and neck cancer. Cancer. 2017;123:4372-4381.
73. Jassal JS, Cramer JD. Explaining racial disparities in surgically treated head and neck cancer. Laryngoscope. In press.
74. Graboyes EM, Ellis MA, Li H, et al. Racial and ethnic disparities in travel for head and neck cancer treatment and the impact of travel distance on survival. Cancer. 2018;124:3181-3191.
75. Graboyes E, Cramer J, Balakrishnan K, et al. COVID-19 pandemic and health care disparities in head and neck cancer: scanning the horizon. Head Neck. 2020; 42:1555-1559.
76. Triantafillou V, Rajasekaran K. A commentary on the challenges of telemedicine for head and neck oncologic patients during COVID-19. Otolaryngol Head Neck Surg. 2020;163:81-82.
77. Kang JJ, Wong RJ, Sherman EJ, et al. The 3 Bs of cancer care amid the COVID-19 pandemic crisis: “be safe, be smart, be kind”- a multidisciplinary approach increasing the use of radiation and embracing telemedicine for head and neck cancer. Cancer. 2020;126:4092-4104.
78. Paleri V, Hardman J, Tikka T, et al. Rapid implementation of an evidence-based remote triaging system for assessment of suspected referrals and patients with head and neck cancer on follow-up after treatment during the COVID-19 pandemic: model for international collaboration. Head Neck. 2020;42:1674-1680.
79. Kasle DA, Torabi SJ, Savoca EL, et al. Outpatient otolaryngology in the era of COVID-19: a data-driven analysis of practice patterns. Otolaryngol Head Neck Surg. 2020;163:138-144.
80. Prasad A, Brewster R, Newman JG, et al. Optimizing your telemedicine visit during the COVID-19 pandemic: practice guidelines for patients with head and neck cancer. Head Neck. 2020;42:1317-1321.
81. Tam S, Wu VF, Williams AM, et al. Disparities in the uptake of telemedicine during the COVID-19 surge in a multidisciplinary head and neck cancer population by patient demographic characteristics and socioeconomic status. JAMA Otolaryngol Head Neck Surg. 2021;147:209-211.
82. Khariwala SS, Weinreich HM, McCoul ED, et al. Leveraging COVID-19-inspired changes to advance otolaryngology-here to stay. JAMA Otolaryngol Head Neck Surg. 2020;146:605-607.
83. de Almeida JR, Noel CW, Forner D, et al. Development and validation of a Surgical Prioritization and Ranking Tool and Navigation Aid for Head and Neck Cancer (SPARTAN-HN) in a scarce resource setting: response to the COVID-19 pandemic. Cancer. 2020;126:4895-4904.
84. Prachand VN, Milner R, Angelos P, et al. Medically necessary, time-sensitive procedures: scoring system to ethically and efficiently manage resource scarcity and provider risk during the COVID-19 pandemic. J Am Coll Surg. 2020;231:281-288.

HEMATOLOGIC MALIGNANCIES

CAR T-Cell Therapy in Hematologic Malignancies: Clinical Role, Toxicity, and Unanswered Questions

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overview

At the time of writing, five anti-CD19 CAR T-cell products are approved by the U.S. Food and Drug Administration for seven different indications in lymphoid malignancies, including B-cell non-Hodgkin lymphoma, pediatric B-cell acute lymphoblastic leukemia, and multiple myeloma. CAR T cells for chronic lymphocytic leukemia, acute myeloid leukemia, and less common malignancies such as T-cell lymphomas and Hodgkin lymphoma are being tested in early-phase clinical trials worldwide. The purpose of this overview is to describe the current landscape of CAR T cells in hematologic malignancies, outline their outcomes and toxicities, and explain the outstanding questions that remain to be addressed.

COMMERCIAL CAR T CELLS

The first CAR T-cell product to receive U.S. Food and Drug Administration approval was tisagenlecleucel T for the treatment of patients age 25 or younger with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL). The most recent U.S. Food and Drug Administration approval was for idecabtagene vicleucel to treat patients with relapsed or refractory multiple myeloma. Between these two milestones, there were five other approvals, for axicabtagene ciloleucel, tisagenlecleucel (two separate approvals), brexucabtagene autoleucel, and lisocabtagene maraleucel for aggressive and indolent B-cell non-Hodgkin lymphoma (Table 1). These products are made from autologous cells derived from the patient by leukapheresis and contain a CAR targeting a disease-associated lineage antigen (CD19 for B-cell malignancies, BCMA for multiple myeloma). The CAR transgene is transduced into cells using a replication-incompetent retrovirus (axicabtagene and brexucabtagene) or lentivirus (all others) and contains a costimulatory molecule (CD28 for axicabtagene and brexucabtagene; CD137, also known as 4-1BB, for all others). The U.S. Food and Drug Administration label mandates use of lymphodepleting chemotherapy, consisting of fludarabine and cyclosphosphamide, before infusion (with the exception of tisagenlecleucel in adults with B-cell non-Hodgkin lymphoma, in whom bendamustine may be substituted or chemotherapy may be omitted entirely if the patient's white blood cell count is 1×10^9/L or less in the week before infusion). Lisocabtagene is unique in consisting of a predefined 1:1 ratio of CD4 and CD8 cells.

Remarkably, all these CAR T-cell products received regulatory approval on the basis of modestly sized single-arm studies (92 patients with pediatric ALL, 74–344 patients with non-Hodgkin lymphoma, and 140 patients with multiple myeloma). Subsequent real-world registry reports have largely validated those obtained in the pivotal trials: the complete response (CR) rate for tisagenlecleucel in B-ALL was 81% in the pivotal ELIANA trial and was 86% in 255 patients treated in the real world, and the estimated 12-month event-free survival rates were 50% and 52%, respectively.[1,2] In large B-cell lymphoma treated with axicabtagene, the CR and 12-month progression-free survival were 58% and 44%, respectively, in the pivotal ZUMA-1 trial compared with 64% and 45%, respectively, among 275 patients treated in the real world.[3,4] In large B-cell lymphoma treated with tisagenlecleucel, the CR rate in the pivotal JULIET trial was 40% compared with 40% among 155 real-world patients.[2,5] These results are summarized in Table 2.

To prescribe CAR T cells in the United States, the treating center must be accredited by the Foundation for Accreditation of Cellular Therapy, and the individual physician must have been trained according to a Risk Evaluation and Mitigation Strategy drug safety program that is mandated by the U.S. Food and Drug Administration. Patients must remain within proximity (typically interpreted as up to a 2-hour drive) of the treatment center for at least 4 weeks after administration of the product because of toxicities such as cytokine release syndrome and immune cell–associated neurotoxicity syndrome, which require specific awareness, monitoring, and management. All products other than tisagenlecleucel must be administered in an inpatient setting, and the patient must be monitored at least daily for 7 days. At the time of writing,

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PRACTICAL APPLICATIONS

- Clinical data have led to the regulatory approvals of CAR T cells for B-cell malignancies and multiple myeloma.
- Extensive clinical experience with CAR T cells in lymphoid malignancies provides an important context in which to place the future development of CAR T cells for other diseases.
- The toxicity profile associated with CAR T cells is now well understood and appears broadly similar between different products. The management of cytokine release syndrome is data driven, whereas the management of immune effector cell–associated neurotoxicity syndrome is still poorly standardized.

130 centers were accredited to treat patients with tisagenlecleucel and 35 were accredited to administer lisocabtagene in the United States.

CAR T CELLS IN EARLY CLINICAL TESTING

Multiple CAR T-cell products have been evaluated clinically in settings other than the above-mentioned registration trials in single-center or small multicenter trials (Table 3). Notwithstanding the limitations of cross-trial comparisons, clinical outcomes appear quite reproducible across different products, institutions, and countries. This observation points to the robustness of the CAR T-cell platform and provides some clues regarding the interaction of CAR T cells with disease and patient biology.

In B-ALL, infusion of anti-CD19 CAR T cells uniformly leads to high rates of deep, measurable residual disease–negative CRs. As shown in Table 3, in 322 adults and children across seven different trials, the CR rates were 83% to 93%. Unfortunately, many patients experience relapse, with a relapse-free survival rate of approximately 50% at 12 months. In patients whose CAR T cells persist and remain functional (with demonstration of ongoing B-cell aplasia), relapse largely occurs through loss of CD19.[6,7] CD19 loss occurs through mutations or epigenetic alterations, likely in pre-existing leukemia subclones.[8-10] Inadequate CAR T-cell expansion or persistence after infusion is a less common cause of failure in ALL and may be related to inherent or induced T-cell dysfunction.[11] Factors that appear to protect against relapse include duration of T-cell persistence, low antigen burden, and receipt of a consolidative allogeneic hematopoietic cell transplant.[6,12-14] CAR T cells specific to more than one B-cell antigen may be deployed to mitigate against antigen-negative leukemia escape, either sequentially (e.g., anti-CD22 CAR T cells after failure of prior CD19-specific therapy) or simultaneously (e.g., coinfusion of CART19 and CART22 or using dual-specific CAR platforms).[15,16] Another exciting recent development in B-ALL is the administration of T cells derived from healthy donors, in which the potential for graft-versus-host disease is abrogated by gene knockout of the T-cell receptor. Notably, T-cell expansion and clinical responses appear to require the addition of the highly immunosuppressive anti-CD52 monoclonal antibody, alemtuzumab, to obviate immune rejection of these human leukocyte antigen–disparate cells.[17]

In B-cell non-Hodgkin lymphoma, the CR rates are lower than in B-ALL, but these responses tend to be durable. For example, long-term follow-up of the JULIET trial shows 60% of responders were still in remission at 5 years[18] The mechanisms of failure of CAR T cells are less well understood in B-cell non-Hodgkin lymphoma than in B-ALL. In particular, T-cell expansion or persistence is less well correlated with lymphoma response than in B-ALL.[19,20] Instead, baseline tumor burden, characteristics of the CART19 product (memory state and polyfunctionality), and response to lymphodepletion (elevation in favorable cytokines such as interleukin [IL]-7, IL-15, or monocyte chemoattractant protein-1) appear to be more predictive.[21-26] Interesting recent developments include testing of tandem anti-CD19/CD20 CAR T cells that led to a CR rate of 71% and a 12-month progression-free survival of 64% and the first demonstration of genetically engineered anti-CD19 natural killer cells derived from healthy cord blood stem cells with a CR rate of 64% at early follow-up.[27,28]

Although patients with chronic lymphocytic leukemia were among the first to be treated with CAR T cells, clinical development in chronic lymphocytic leukemia has lagged behind that of ALL or non-Hodgkin lymphoma. In chronic lymphocytic leukemia, the CR rates are lower than in non-Hodgkin lymphoma (approximately 25% by International Workshop on Chronic Lymphocytic Leukemia criteria), although, as with non-Hodgkin lymphoma, those remissions appear to be very durable.[29-31] Sustained remissions are associated with a higher frequency of $CD27^{+}CD45RO^{-}$ CD8 T cells and with other memory and STAT3-related gene signatures in the apheresis sample.[32] Notably, administration of the Bruton's tyrosine kinase inhibitor ibrutinib concurrently with CAR T cells may improve the CR rates.[33,34]

In multiple myeloma, a number of modest-sized trials targeting BCMA have been published. The CR rates appear generally high (45%–86%), and the median progression-free survival in some of the larger studies is 12 to 15 months. However, with relatively short follow-up, there already appears to be little evidence of a survival plateau.[35-38] A novel angle is being pursued using nonviral (transposon/transposase-based) transduction in a process that results in a relative enrichment for T-stem memory cells, leading to slower T-cell

TABLE 1. Commercial CAR T-Cell Products

Name	Indication	Date of FDA Approval	Manufacturer	Trial Data Reported
Tisagenlecleucel	Pediatric and young adult (age ≤ 25) R/R acute lymphoblastic leukemia	August 30, 2017	Novartis	Pivotal ELIANA[1] and real world[2]
Axicabtagene ciloleucel	R/R large B-cell lymphoma (DLBCL, PMBCL, high-grade B-cell lymphoma, transformed FL)	October 18, 2017	Kite Pharma	Pivotal ZUMA-1[3] and real world[4]
Tisagenlecleucel	Adult R/R DLBCL	May 1, 2018	Novartis	Pivotal JULIET[5] and real world[2]
Brexucabtagene autoleucel	Mantle cell lymphoma	July 24, 2020	Kite Pharma	Pivotal ZUMA-2[79]
Lisocabtagene maraleuecel	R/R large B-cell lymphoma	February 5, 2021	Juno Therapeutics	Pivotal TRANSCEND NHL001[51]
Axicabtagene ciloleucel	R/R FL	March 5, 2021	Kite Pharma	Pivotal ZUMA-5[20]
Idecabtagene vicleucel	Multiple myeloma	March 26, 2021	BMS and Bluebird Bio	Pivotal KarMMa (not published)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FDA, U.S. Food and Drug Administration; FL, follicular lymphoma; PMBCL, primary mediastinal B-cell lymphoma; R/R, relapsed/refractory.

expansion kinetics, low rates of CRS, and a 57% overall response rate after a single administration.[39]

CD30 is a validated immunotherapy target in Hodgkin lymphoma. Autologous anti-CD30 CAR T cells in Hodgkin lymphoma were tested in 41 patients in two different centers, and the CR rate for the 32 evaluable patients was 59%. Unfortunately, the progression-free survival at 1 year was 36%.[40]

Conspicuously absent from the published literature are trials of CAR T cells against myeloid malignancies. There are early indications that CAR T cells may have activity against myeloid malignancies; for example, two of five patients with acute myeloid leukemia achieved a CR after infusion of anti-CD123 CAR T cells (published in abstract form).[41] At the time of writing, 24 trials were open to enrollment worldwide for acute myeloid leukemia, seven were not yet recruiting, three were terminated, two were withdrawn, one was active and not recruiting, and only one was completed. The myeloid targets being pursued are CD123, CD33, CLEC12A, or NKG2D ligands using autologous, allogeneic, or universal-donor gene-edited cells.

OPEN QUESTIONS

Having established the response rates, durability, and some parameters that are associated with clinical outcomes, some important questions remain to be addressed.

- Given the occurrence of CD19-negative and CD22-dim relapses in ALL, should all future CAR T-cell platforms incorporate multitargeting, and, if so, which targets (likely CD19 and CD22) should be used and what is the optimal design for such constructs?
- Can patients be retreated with CAR T cells after failure of the first infusion? Patients re-treated with axicabtagene after relapse on ZUMA-1 (aggressive B-cell non-Hodgkin lymphoma) who had evidence of response to the first infusion and no evidence of CD19 loss had limited response to re-treatment.[42] In contrast, patients enrolled in ZUMA-5 (indolent B-cell non-Hodgkin lymphoma) who were re-treated according to similar criteria appeared to benefit from re-treatment.[43] These observations are preliminary and based on a small group of patients and therefore must be viewed with caution.
- When should patients with non-Hodgkin lymphoma be referred for CAR T-cell therapy? Retrospective data suggest a trend to better outcomes if patients receive CAR T cells earlier (i.e., after two lines of chemotherapy or after autologous stem cell transplant that followed two lines of chemotherapy) rather than later (i.e., after at least three lines of chemotherapy or after receipt of additional treatment after autologous stem cell transplant).[44] In a similar vein, an intent-to-treat retrospective comparison of CAR T cells or allogeneic hematopoietic cell transplant for multiply relapsed diffuse large B-cell lymphoma showed, at 12 months, a significantly lower nonrelapse mortality (3% vs. 21%, in favor of CAR T cells; p = .04), whereas differences in relapse rates, progression-free survival, and overall survival were not statistically significant.[45]
- Can CAR T-cell therapy be moved earlier in the treatment of patients with non-Hodgkin lymphoma? A single-center, retrospective, observational study compared the outcomes in 69 patients receiving CAR T cells with 146 historical controls and showed improved CR, progression-free

TABLE 2. Commercial and Advanced CAR T-Cell Outcomes

Name	Reference	Patients	Responses	Survival
Pediatric and Young Adult (≤ 25 years) Patients With R/R Acute Lymphoblastic Leukemia				
Tisagenlecleucel	Pivotal ELIANA[1]	92 enrolled, 75 treated	Per protocol: CR/CRi, 81% at 3 months	Per protocol: EFS, 50%; OS, 76% (12 months)
Tisagenlecleucel	Real world[2]	255 treated	CR, 86%	EFS, 52%; OS, 77% (12 months)
R/R Large B-Cell Lymphoma				
Axicabtagene ciloleucel	Pivotal ZUMA-1[3]	111 enrolled, 101 treated	ORR, 82%; CR, 58%	PFS, 44% (12 months); OS, 52% (18 months)
Axicabtagene ciloleucel	Real world[4]	275 treated	ORR, 82%; CR, 64%	PFS, 45%; OS, 64% (12 months)
Axicabtagene ciloleucel	Real world[50]	122	ORR, 70%; CR 50%	OS, 57% (12 months)
Tisagenlecleucel	Pivotal JULIET[5]	165 enrolled, 93 treated	ORR, 52%; CR, 40%	RFS, 65%; OS, 49% (12 months)
Tisagenlecleucel	Real world[2]	155 treated	ORR, 62%; CR, 40%	PFS, 39%; OS, 71% (6 months)
Lisocabtagene maraleucel	Pivotal TRANSCEND NHL001[51]	344 apheresed, 269 treated, 256 evaluable for efficacy	ORR, 73%; CR, 53%	PFS, 44%; OS, 58% (12 months)
Mantle Cell Lymphoma				
Brexucabtagene autoleucel	Pivotal ZUMA-2[79]	74 enrolled, 68 treated	ORR, 93%; CR, 67%	PFS, 61%; OS, 83% (12 months)
R/R Follicular Lymphoma				
Axicabtagene ciloleucel	Pivotal ZUMA-5[20]	123 treated (follicular lymphoma only)	ORR, 94%; CR, 80%	PFS, 74%; OS, 93% (12 months)
Multiple Myeloma (BCMA)				
Idecabtagene vicleucel	Pivotal KarMMa[115]	140 enrolled, 128 treated (dose escalation)	ORR, 73%; CR, 33%; MRD-ve, 26%	Median PFS, 8.8 months; OS 78% (12 months)

Abbreviations: CR, complete response; CRi, CR with incomplete hematologic recovery; EFS, event-free survival; MRD-ve, minimal residual disease negative; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; R/R, relapsed/refractory.

survival, and overall survival in favor of CAR T cells.[46] This important question will be definitively answered when results from phase III trials of second-line treatment with axicabtagene, tisagenlecleucel, or lisocabtagene versus standard of care (respectively, ZUMA-7, NCT03391466; BELINDA, NCT03570892; or TRANSFORM, NCT03575351) are released. Axicabtagene is being tested in a phase II, multicenter, open-label, single-arm study after two cycles of first-line chemoimmunotherapy in patients with high-risk large B-cell lymphoma (ZUMA-12). Preliminary data from this study showed a CR rate of 74%, underpinned by a higher frequency of $CCR7^{+}CD45RA^{+}$ naïve cells.[47]

- What are the mechanisms and correlates of CAR T-cell response or failure in multiple myeloma? Compared with analyses in ALL and non-Hodgkin lymphoma, the causes of CAR T-cell failure remain relatively opaque to date, with the exception of several preliminary observations. T cells derived from patients early in multiple myeloma therapy exhibit better fitness for CAR T manufacturing than those derived from patients at a later stage of the disease.[48] Dim expression of BCMA expression can be mitigated by gamma secretase inhibitor therapy, and this approach is now being tested in a clinical trial (NCT03502577). Notably, one instance of biallelic loss of BCMA after CAR T-cell therapy was recently identified, suggesting that, at least in this one case, BCMA expression was crucial to multiple myeloma cell survival.[49] CS1-specific CAR T cells are also in clinical trials (NCT03710421, NCT04142619).
- What will be the role of allogeneic products derived from healthy donors? Will their obvious advantages (more streamlined manufacturing and logistics, healthier T cells) be outweighed by their immunogenicity? This approach is currently being tested in the setting of CD19, BCMA, and CD123. What, if any, is the advantage of using effector cells other than α/β T cells (e.g., natural killer cells, natural killer/T cells, γ/δ T cells)?

TABLE 3. Notable Early-Phase Clinical Trials

Name	Citation	Patients	Outcomes	Notes
Acute Lymphoblastic Leukemia				
CART19 (of defined subset composition)	[59]	29 adults	CR, 93%	CD8 T cell–mediated anti-CAR transgene immune responses were seen in some patients. Addition of fludarabine to cyclophosphamide improved persistence and DFS.
CART19 (of defined subset composition)	[6]	43 pediatric	CR, 93%	Duration of T-cell persistence was associated with phenotypic and functional attributes of the T-cell product as well as CD19 antigen load at infusion.
CART19 (long-term follow-up)	[12]	53 adults	CR, 83%; median EFS, 6.1 months; median OS, 12.9 months	Patients with $< 5\%$ marrow blasts before treatment had improved remission duration, toxicity profile, and survival.
CART19 (FHCRC)	[13]	53 adults	CR (MRD-ve), 85%	Described factors predictive of EFS included addition of fludarabine and subsequent alloHCT.
CART19 (Penn)	[14]	35 adults, 20 patients optimized with high-dose fractionated administration schedule	CR, 33% in low-dose group; CR, 90% in high-dose optimized group	Nonrandomized receipt of subsequent alloHCT associated with superior EFS.
CART19 (in B-ALL with high-risk features)	[1]	110 adults and children	CR, 93%; MRD-ve CR, 87%; LFS, 58%; OS, 64% (12 months)	LFS and OS were 77% and 79% in those who received an alloHCT vs. 12% and 32% in those who did not (nonrandomized).
Low-Affinity CART19 (CARPALL)	[116]	14 children	CR (MRD-ve), 86%; EFS, 46%; OS, 63% (12 months)	Based on preclinical data showing superiority of low affinity CD19 binders compared with the canonical FMC63 clone
CAR19 and CAR22 Coinfusion	[15]	51 adults and children	CR (MRD-ve), 96%	Only one antigen-loss relapse (CD19-ve, CD22 dim)
UCART19	[17]	7 children, 14 adults	CR/CRi, 67%; PFS, 27%; OS, 55% (6 months)	Gene-edited, healthy, donor-derived alloCART; responses only seen in patients receiving alemtuzumab in addition to FluCy lymphodepletion.
Nonviral CIK CAR19	[117]	13 adults and children	CR in six of seven patients receiving $> 3 \times 10^6$/kg dose	Nonviral (transposon/transposase) system
CART-22	[16]	58 children and young adults	CR, 70%; median OS, 13.4 months	Of 58 patients, 51 had received prior anti-CD19 therapy. HLH-like manifestations seen in 33% of patients.
R/R Large B-Cell Lymphoma				
CART19 (long-term follow-up)	[118]	43 (DLBCL, PMBCL, FL, and CLL)	Median EFS, 55 months	DOR lasting > 3 years occurred in 51% of treatments. Remissions of up to 9 years are ongoing.
CART19 (after autoSCT)	[119]	15	PFS, 30% (2 years)	High rates of CRS and ICANS
Nonviral CART19 (after autoSCT)	[120]	7	PFS, 71%; OS, 86% (5 years)	Nonviral (transposon/transposase) system
Tandem CAR19/20 China	[28]	33	ORR, 79%; CR, 71%; PFS, 64% (12 months)	Dual-expressing tandem CAR system

(Continued on following page)

TABLE 3. Notable Early-Phase Clinical Trials (Continued)

Name	Citation	Patients	Outcomes	Notes
Tandem CAR19/20 United States	[121]	22 (NHL and CLL)	ORR, 82%; CR, 64%	Dual-expressing CAR system; dose escalation trial, CR 92% at the optimal dose
CB-Derived NK CAR19	[27]	11 (NHL and CLL)	ORR, 73%; CR, 64%	NK cells were manufactured from cord blood stem cells. Transgene included an IL-15 secretion system and an inducible caspase 9 suicide switch.
Chronic Lymphocytic Leukemia				
CART-19 (MSKCC)	[30]	16 treated, 12 evaluable	CR, 25%	Of the three patients who achieved a CR, two were on ibrutinib at leukapheresis and infusion.
CART-19 (Penn)	[31]	38 treated, 32 evaluable	ORR, 44%; CR, 28%; median PFS, 1 month; median OS, 64 months	Randomized to low or high dose of CAR T cells, with no significant difference in outcome.
CART19 (concurrent with ibrutinib; FHCRC)	[34]	19	ORR, 83%; CR (MRD-ve), 61%; PFS, 38% (1 year)	Low CRS severity
Multiple Myeloma				
NCI	[35]	16	ORR, 81%; CR/VGPR, 63%; median EFS, 31 weeks	BCMA expression variable; loss of BCMA found in one patient.
Penn	[122]	25 dose escalation	ORR, 48%; median DOR, 125 days	Residual MM cells had decreased BCMA expression in responders.
Bb2121	[36]	33	ORR, 85%; CR, 45%; median PFS, 11.8 months	Dose escalation from 50 to 800 $\times$ 10^6 CAR T cells. CAR T-cell persistence up to 1 year in some patients
Legend LCAR-B38M	[37]	57	ORR, 88%; CR, 68%; median PFS, 15 months	CAR directed against two distinct epitopes on BCMA
JNJ-4528 (LCAR-B38M)	CARTITUDE-1 (unpublished)	29	ORR, 100%; sCR, 86%	PFS 86% (9 months)
Myeloid Malignancies				
NKG2D (CYAD-01)	[123]	7	ORR, 0%	Dose escalation; NCT03018405 is a follow up dose-escalation study
CAR33	[124]	1	PR	Case report
CAR123	[125]	1		Case report
CAR123	[41]	7	CR in 2/5 patients receiving 2 $\times$ 10^8 CAR T-cells	Abstract
Hodgkin Lymphoma				
Anti-CD30 CAR	[40]	41; 32 evaluable for response	ORR, 72%; CR, 59%; PFS, 36%; OS, 94% (1 year)	First large trial of CAR T cells for HL

Abbreviations: alloCART, allogenic CAR T cell; alloHCT, allogeneic hematopoietic cell transplant; B-ALL, B-cell acute lymphoblastic leukemia; CD19-ve, CD19 negative; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete hematologic recovery; CRS, cytokine release syndrome; DFS, disease-free survival; dim, diminished; DLBCL, diffiuse large B-cell lymphoma; DOR, duration of response; EFS, event-free survival; FL, follicular lymphoma; FluCy, fludarabine/cyclophosphamide; HL, Hodgkin lymphoma; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune cell–associated neurotoxicity syndrome; LFS, leukemia-free survival; MM, multiple myeloma; MRD-ve, minimal residual disease negative; NK, natural killer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; R/R, relapsing/remitting; sCR, stringent complete response; SCT, stem cell transplant; VGPR, very good partial response.

MECHANISMS AND MANAGEMENT OF SHORT- AND LONG-TERM CAR T-CELL TOXICITIES

Short-Term Toxicities of CAR T-Cell Therapy

Cytokine release syndrome and neurologic toxicity: clinical presentation, risk factors, and grading Cytokine release syndrome (CRS) and neurologic toxicity, also known as immune effector cell–associated neurotoxicity syndrome, are considered the main barriers to widespread use of CAR T-cell therapy. Constitutional symptoms and signs associated with CRS include high fevers, chills, rigors, sinus tachycardia, myalgias, and fatigue. More severe toxicities, such as hypotension, hypoxia, arrythmias, depressed cardiac ejection fraction, and other end organ dysfunction, may also occur. Intensive care is needed for toxicity management in an estimated 7% to 47% of patients treated receiving commercially available CAR T-cell products.[1,50,51] Organ toxicities associated with CRS include reversible renal insufficiency, elevation of hepatic enzymes, electrolyte depletion, cytopenias, and coagulopathy. Neurologic toxicity presents in diverse ways, with severity ranging from mild hand tremors or subtle language deficits to aphasia, seizures, and obtundation. Cerebral edema has been reported after CAR T-cell therapy in association with severe neurologico toxicity.[52,53] Frequencies of reported toxicities of commercially available CAR T-cell products are summarized in Table 4. Neurologic toxicity almost always occurs after the onset of fever, although delayed instances have been reported.[7,54,55] However, CAR T-cell toxicity management has improved with time, with an increased understanding of the underlying drivers, and with wider use of tocilizumab and corticosteroids.

Although CAR T-cell expansion is necessary for antimalignancy efficacy and is considered a biomarker of response, increased peak CAR T-cell levels have also been associated with an increased risk of CRS and neurologic toxicity. Many serum cytokines and inflammatory proteins have been implicated in the etiology of CRS and neurologic toxicity, although different proteins have been reported for different CAR T-cell products. These proteins include tumor necrosis factor-α, interferon-γ, IL-2, granzyme B, and granulocyte macrophage colony stimulating factor, which may be produced by the CAR T cells themselves upon interaction with the target antigen; IL-1, IL-6, IL-8, IL-10, IL-5, interferon-γ–induced protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein-α, and nitric oxide, produced by downstream myeloid cells and bystander cells; and ANG2 and von Willebrand factor, produced by activated endothelial cells.[1,54,56-58] The acute-phase reactants ferritin and C-reactive protein are elevated during CRS and can be tracked using readily available laboratory assays. For any given CAR T-cell product, higher cell doses, variations in cell processing techniques, and addition of fludarabine to cyclophosphamide as conditioning chemotherapy may increase the risk of toxicity, although these regimens may also increase the antimalignancy response.[16,59-61] The burden of bone marrow involvement with malignancy has been associated with an increased risk of severe CRS for patients with ALL or non-Hodgkin lymphoma.[61] Both bone marrow malignancy burden for patients with ALL and lymph node disease burden in patients with diffuse large B-cell lymphoma have been associated with a greater risk of severe neurologic toxicity.[24,54] Elevated markers of endothelial activation and disseminated intravascular coagulation have been associated with severe CRS and neurologic toxicity.[54,61,62] The CAR structure has been implicated in the risk for toxicity, with an earlier onset of toxicity and a greater risk of neurologic toxicity reported with CAR constructs that have a CD28 costimulatory domain.[63] Variations in the hinge and transmembrane domains have affected rates of neurologic toxicity, demonstrating that multiple aspects of the CAR structure affect cytokine production and toxicity.[55,64]

Multiple grading scales for CRS and neurologic toxicity have been published,[12,63,65,66] most recently the American Society for Transplantation and Cellular Therapy (i.e., ASTCT) grading scale described by Lee et al,[67] which has been increasingly adopted (Table 5). The use of differing grading systems in clinical trials evaluating the currently commercially available CAR T-cell products makes comparing the toxicity profiles of each product challenging. The ASTCT grading system of CRS has the benefit of being a simplified, user-friendly system that primarily incorporates hemodynamic and respiratory status. It is worth noting that this system does not capture other end organ toxicities. Similarly, the use of the Common Terminology Criteria for Adverse Events, CARTOX CRES grading system, and the immune effector cell–associated neurotoxicity syndrome grading systems may yield differing results in the grading of neurologic toxicity.[63,67,68] The immune cell–associated neurotoxicity syndrome system is increasingly used.

Management of cytokine release syndrome Supportive care for patients experiencing CRS includes the management of constitutional symptoms, typically with antipyretics, fluid resuscitation as needed for insensible losses, and monitoring for hemodynamic changes. Patients who receive a CAR T-cell infusion on an outpatient basis and become febrile or develop new neurologic symptoms should be hospitalized for monitoring.[69,70] Supportive care for hospitalized patients after CAR T-cell infusion is summarized in Table 6. Because tumor lysis syndrome has been observed after CAR T-cell infusion[71,72] even in the absence of chemotherapy,[72] prophylactic use of allopurinol and hydration should be used in patients with a higher disease burden. Cytopenias occurring in the first month after CAR T-cell infusion are common and are at least in part related to conditioning chemotherapy. However, the CAR T cells may

TABLE 4. Reported Adverse Events and Use of Tocilizumab and Corticosteroids in Clinical Trials of U.S. Food and Drug Administration–Approved CAR T-Cell Products

	Tisagenlecleucel for ALL[1]*	Tisagenlecleucel for DLBCL[5]*	Axicabtagene Ciloleucel for DLBCL[3]**	Lisocabtagene Maraleucel for DLBCL[51]**	Brexucabtagene Autoleucel for MCL[78]**	Idecabtagene Vicleucel[115]**
Adverse Events of Interest[65]						
Any CRS (%)	77	58	92	42	91	84
Grade ≥ 3 CRS (%)	46	22	11	2	15	5
Any neurologic toxicity (%)	40	21	67	30	63	18
Grade ≥ 3 neurologic toxicity (%)	13	12	32	10	31	3
Grade ≥ 3 hypotension	20	9	14	3	22	NR
Required supplemental oxygen/hypoxia	44	24	11	10	21	NR
Grade 5 events attributable to treatment (%)	4.0	0	1.9	2.6	2.9	3.1
Grade ≥ 3 infections (%)	27	20	28	12	32	22
Use of Tocilizumab or Corticosteroids for CRS or Neurologic Toxicity						
Tocilizumab	37	14	43	10	59	52
Corticosteroids for CRS	NR	10	NR	10	22	15
Corticosteroids for neurologic toxicity	NR	NR	NR	NR	38	8
Corticosteroids for either CRS or neurologic toxicity	NR	NR	27	NR	58	NR

Abbreviations: ALL, B-cell acute lymphoblastic leukemia; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; NR, not reported.
*CRS graded with Porter et al.[66]
**CRS graded per 2014 criteria as described by Lee et al.[65] Neurologic toxicity graded per the Common Terminology Criteria for Adverse Events, version 4.03, in all trials.

TABLE 5. American Society for Transplantation and Cellular Therapy Consensus Cytokine Release Syndrome Grading

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring vasopressors with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/Or**				
Hypoxia	None	Requiring low-flow† nasal cannula or blow-by	Requiring high-flow† nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Abbreviations: BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome.
*Fever: defined as temperature ≥ 38°C not attributable to any other cause. Fever is no longer required to grade subsequent CRS severity in patients who have CRS and then receive antipyretic or anticytokine therapy. In these cases, CRS grading is determined by hypotension and/or hypoxia.
**CRS grading is determined by the more severe event: hypotension or hypoxia not attributable to other cause.
†Low-flow nasal cannula is defined as oxygen delivery at ≤ 6 L/min. Low flow also includes blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivery > 6 L/min.
Adapted from Lee et al.[65] Reproduced under the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND).

exert a myelosuppressive effect, as cytopenias in the absence of chemotherapy have been observed,[72] and the duration of cytopenias appears to be associated with the severity of CRS.[61,73] Timing of growth factor support for neutropenia is controversial, because growth factors have a hypothetical risk of worsening CRS, but neutropenia carries a clear risk for infection. Administration of granulocyte macrophage colony stimulating factor is contraindicated after CAR T-cell infusion because of the risk of worsening CRS.[70] Delaying growth factor support with filgrastim or pegfilgrastim for 3 weeks after CAR T-cell infusion and until resolution of CRS has been recommended,[70,74] but the approach must be tailored to the risk of infection in the individual patient. Although coagulopathy is a common finding during severe CRS, major hemorrhage is infrequent. Monitoring and replacement of fibrinogen may be especially important in the setting of grade 3 to 4 CRS, in which severe hypofibrinogenemia has been described.[75]

The role of anticytokine and corticosteroid therapy for CRS is continually evolving. Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, is approved by the U.S. Food and Drug Administration for CRS mediated by immune effector cell therapy and is the most commonly given first-line agent for CRS. Corticosteroids are usually reserved for second-line therapy,[63] as per early observations of decreased CAR T-cell expansion after high-dose corticosteroid therapy.[76] There are no universally agreed upon thresholds for administration of anticytokine or corticosteroid therapy in the absence of large randomized trials. Approaches include administering tocilizumab for a predefined list of hemodynamic changes and organ toxicities[69,77] or administration on the basis of CRS grade,[56,63,77] followed by corticosteroid therapy for refractory CRS. Consideration of tocilizumab in cases of grade 2 CRS by ASTCT criteria,[72] with strong consideration given for grade 3 CRS, has been recommended by multiple groups.[56,70] Tocilizumab use has been suggested in cases of persistent fevers refractory to antipyretics.[63] However, there is general agreement that organ toxicities and comorbidities of the individual patient should inform decisions about tocilizumab administration. Retrospective analyses of clinical results for axicabtagene ciloleucel[3] and brexucabtagene autoleucel[78] have shown no clear difference in response rates for patients receiving tocilizumab or corticosteroid therapy for toxicity compared with patients who did not receive these agents; however, greater cumulative doses of corticosteroids, more prolonged duration of use, and earlier use may have deleterious effects on survival outcomes after axicabtagene ciloleucel.[79] Prospective studies have been performed to evaluate various early intervention strategies in small numbers of patients (Table 7). Pre-emptive strategies of administering tocilizumab and/or low-dose corticosteroids for lower grades of CRS compared with various institutional standard approaches have yielded lower rates of severe CRS without clear effects on CAR T-cell expansion or worsening of neurologic toxicity.[80-82] Similarly, prophylactic tocilizumab, given at a defined time interval regardless of toxicity, appears to decrease severe CRS without a clear increase in neurologic toxicity[83,84] or changes in CAR T-cell expansion.[84] Early administration of tocilizumab and/or corticosteroids appears not to decrease response rates or duration,[80-82,84] although no firm conclusions can be drawn from these small sample sizes and nonrandomized designs.

Clinical trial experience with alternative pharmacologic agents to manage CRS remains limited. Siltuximab, anakinra, and etanercept have been used in cases of tocilizumab-refractory CRS, but their optimal use in relation to

TABLE 6. Supportive Care After CAR T-Cell Infusion

Toxicity Type	Monitoring and Supportive Care*
Fever and Constitutional Changes	Baseline and daily CRP, LDH, and ferritin; consider monitoring CPK in cases of high fevers
	Acetaminophen for symptom control
	NSAIDs should be avoided in renal impairment, thrombocytopenia, and coagulopathy
	Cooling blankets/ice packs may be needed for high fevers
	Judicious use of IV fluids to balance insensible losses; monitor for developing hypoxia
Cardiovascular	Baseline echocardiogram or MUGA before CAR T-cell therapy
	Vital sign monitoring every 2–4 hours in hospitalized patients
	Cardiac monitoring for patients with tachycardia or hypotension
	ECG and echocardiogram for patients with persistent tachycardia or hypotension requiring vasopressors
	Initial treatment of mild hypotension with bolus IV fluids
	Consider early ICU transfer for worsening hypotension
	Consider early transition to vasopressors for hypotension to avoid worsening capillary leak to due volume resuscitation
	Standard anti-arrhythmic therapy for arrythmias; caution use of beta blockers in patients with hypotension
Pulmonary	Continuous pulse oximetry if changes in respiratory status
	Chest x-ray and/or chest CT to evaluate new hypoxia
	Supplemental oxygen if needed
	Consider early ICU transfer for worsening hypoxia or increased work of breathing
Renal	Creatinine and electrolyte panel, including magnesium and phosphorus, and a uric acid level at least daily
	Aggressive electrolyte repletion for hypokalemia, hypophosphatemia, hypomagnesemia, and hypocalcemia
	Consider allopurinol +/− IV fluid support for tumor lysis syndrome prophylaxis for patients with high disease burden
	Aggressive hydration and rasburicase for confirmed tumor lysis syndrome
Gastrointestinal	Standard anti-emetics for nausea; avoid corticosteroids
	Evaluate diarrhea for infectious etiologies
Infection Risk	Baseline testing for Hepatitis B, Hepatitis C, HIV, and CMV
	SARS-CoV-2 testing before lymphodepletion chemotherapy
	HSV/VZV and PJP prophylaxis for at least 6 months after cell infusion
	Consider fungal and/or gram-negative bacterial prophylaxis for severe or prolonged neutropenia, prolonged corticosteroid use
	Pharmacologic HBV prophylaxis in patients with detectable HBV DNA, HBsAg+, or HBcAb+
	Blood and urine cultures in febrile patients
	Empirical broad spectrum antibiotics for patients with fever and neutropenia
Cytopenias	At least daily CBC with differential
	Transfusion support as needed. Suggested goals of hemoglobin $\geq$ 8 g/dL and platelets $\geq$ 20 k/μL for febrile patients
	Avoid corticosteroids for transfusion premedication
	The timeline for filgrastim support for neutropenia is controversial
Coagulopathy	At least daily PT/INR, aPTT, D-Dimer, fibrinogen in patients experiencing CRS
	FFP and cryoprecipitate as needed for coagulopathy or hemorrhage

(Continued on following page)

TABLE 6. Supportive Care After CAR T-Cell Infusion (Continued)

Toxicity Type	Monitoring and Supportive Care*
HLH	If suspected, consider evaluation with bone marrow biopsy, fibrinogen, triglycerides, and soluble CD25 level.
	Diagnosis requires ferritin > 10,000 ng/mL and at least two of the following:
	• Grade ≥ 3 bilirubin, AST or ALT increase
	• Grade ≥ 3 creatinine increase, or oliguria
	• Grade ≥ 3 pulmonary edema
	• Presence of histologic hemophagocytosis in bone marrow or organs
	First-line therapy is treating CRS with tocilizumab +/− corticosteroids and ICANS with corticosteroids
	Consider etoposide in refractory cases
Neurologic Toxicity	Baseline neurologic exam and ICE or CAPD score
	Serial ICE or CAPD score at least daily, more frequently if NT present
	Consider prophylactic anti-epileptic medications
	MRI brain to evaluate moderate to severe neurologic toxicity if feasible
	Lumbar puncture may be helpful to rule out infectious etiologies of altered mental status but may be precluded by thrombocytopenia or coagulopathy
	EEG if occult seizures suspected
	Consider consultation with a neurologist if ICANS present
	Treatment of any seizures with anti-epileptic therapy and corticosteroids

Abbreviations: ALT:,Alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CAPD, Cornell Assessment of Pediatric Delirium; CBC, complete blood count; CMV, cytomegalovirus; CPK, creatine phosphokinase; CRP, C-reactive protein; CRS, cytokine release syndrome; ECG, electrocardiogram; EEG, electroencephalogram; FFP, fresh frozen plasma; HBcAb+, hepatitis B virus core antibody positive; HBsAg+, hepatitis B virus surface antigen positive; HBV, hepatitis B virus; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICU, intensive care unit; IV, intravenous; LDH, lactate dehydrogenase; MUGA, multigated acquisition scan; NSAIDs, nonsteroidal anti-inflammatory drugs; NT, neurologic toxicity; PJP, *Pneumocystis jiroveci* pneumonia; PT/INR, prothrombin time/international normalized ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VZV, varicella zoster virus.
*Some recommendations specific to hospitalized patients.

corticosteroids remains unknown.[1,85,86] Cyclophosphamide, antithymocyte globulin, and alemtuzumab have been used for steroid-refractory CRS, but data are limited.[1] Other pharmacologic agents being investigated for CRS prevention or treatment include JAK/STAT pathway targeting agents, such as itacitinib (NCT04071366).[87-89]

Hemophagocytic lymphohistiocytosis is an infrequent complication of CAR T-cell therapy. It is unclear whether hemophagocytic lymphohistiocytosis is a distinct entity with its own pathophysiology or a manifestation of severe CRS. Suggested criteria for CAR T-cell–related hemophagocytic lymphohistiocytosis are a peak serum ferritin level of more than 10,000 ng/mL and at least two additional criteria related to renal, hepatic, and pulmonary function and/or bone marrow findings (Table 6).[63] First-line treatment of hemophagocytic lymphohistiocytosis is treatment of concurrent CRS or neurologic toxicity with tocilizumab and/or corticosteroids. Etoposide has been used in instances of lack of response to tocilizumab and corticosteroids. Successful treatment of hemophagocytic lymphohistiocytosis with anakinra has been reported, although data are limited.[16]

Management of neurologic toxicity Monitoring of neurologic status after CAR T-cell infusion is essential for early recognition and management of neurologic toxicity. Hospitalized patients should have a neurologic assessment at least daily—including a neurologic physical examination and an immune effector cell–associated encephalopathy[67] score or Cornell assessment of pediatric delirium score[67]—or more frequently if neurologic toxicity is present. A brain MRI may be helpful to evaluate neurologic toxicity if the patient's hemodynamic stability and airway status do not preclude MRI, especially in severe cases in which the finding of cerebral edema may influence the escalation of corticosteroid therapy. Lumbar puncture may assist in the evaluation of other etiologies of mental status changes, such as infections, and for measurement of opening pressure. However, thrombocytopenia, coagulopathy, and critical illness may preclude the procedure. Evaluation by

a neurologist may aid in fully assessing neurologic deficits and tracking changes to the examination over time.

Neurologic toxicity appears less responsive to tocilizumab than CRS[54]; therefore, corticosteroids are generally used as the first-line treatment of neurologic toxicity. The concern remains that higher cumulative doses of corticosteroids may impact CAR T-cell efficacy.[79] Optimum thresholds and timing of corticosteroid therapy are not established, although consideration of corticosteroids therapy for grade 2 immune effector cell–associated neurotoxicity syndrome and strong consideration of corticosteroids for grade 3 to 4 immune cell–associated neurotoxicity syndrome have been suggested.[70] In a safety cohort of ZUMA-1, early corticosteroid use after axicabtagene ciloleucel to address grade 1 neurologic toxicity appeared to decrease the frequency of grade 3 or greater neurologic toxicity without compromising efficacy in a small number of patients,[81] but additional investigation is needed. Anakinra has been shown to have preclinical efficacy in treating neurologic toxicity,[90] with limited evidence of clinical efficacy,[91] although its place in a toxicity algorithm and whether it could contribute to a steroid-sparing approach are unknown. There is no defined optimal second-line therapy for steroid-refractory neurologic toxicity. Use of intrathecal corticosteroids and chemotherapy has been reported in this setting,[92] but more investigation is needed. Elevated granulocyte macrophage colony stimulating factor levels are associated with high-grade neurologic toxicity, so prophylactic use of the granulocyte macrophage colony stimulating factor neutralizing antibody lenzilumab to prevent neurologic toxicity and CRS is being investigated.[93] The optimal CAR T-cell design to minimize toxicity, including the integration of suicide genes and pharmacologic on/off switches, is an area of active research.[87,88,94-96]

Long-Term Toxicities of CAR T-Cell Therapy

B-cell aplasia, hypogammaglobulinemia, and infections
Depletion of normal B cells and normal plasma cells is an expected toxicity of anti-CD19 and anti-BCMA CAR T-cell therapies, respectively. B-cell depletion has also been reported after anti-CD22 CART-cell therapy.[97] The resulting hypogammaglobulinemia can be addressed with replacement immunoglobulin therapy. Suggested thresholds for administering immunoglobulin replacement therapy are generally an immunoglobulin G level of less than 400–500 g/dL or the presence of serious or recurrent infection.[70,98] Return of normal B-cell populations has been described in patients receiving anti-C19 CAR T-cell therapy for non-Hodgkin lymphoma,[5,99] although detectable B cells more often appears to be a harbinger of relapse in pediatric and young adult patients receiving tisagenlecleucel for B-cell ALL.[1,7]

Multiple factors may contribute to risk of infection in patients after CAR T-cell therapy. These include depletion of normal B cells or plasma cells caused by direct effect of the CAR T cells, lymphocyte and granulocyte depletion caused by conditioning chemotherapy, anticytokine or corticosteroid therapies given for CRS or neurologic toxicity, and immunocompromise caused by the patient's underlying malignancy. Deaths from infection have been reported after CAR T-cell therapy, and bacterial, viral, and fungal infections have been observed.[16,71,100-103] More severe CRS has been associated with a greater risk of infection in the acute setting.[101,102] The first 28 days after cell infusion may harbor a greater risk of infection than subsequent days, but late infections do occur.[101,104] Cytomegalovirus reactivation has occurred after CAR T-cell therapy[78,101] and is especially a concern after allogeneic off-the-shelf CAR T-cell therapy if anti-CD52 antibody therapy is given to decrease the risk of cell rejection. In a clinical trial of the allogeneic UCART19 product, in which alemtuzumab was administered before CAR T-cell infusion, 24% of patients experienced grade 3 or higher viral infections, including grade 3 cytomegalovirus reactivation in 4.8%.[17] Baseline cytomegalovirus testing and monitoring of the cytomegalovirus viral load after CAR T-cell infusion should be performed in this setting and should be considered in the autologous setting as well, especially if corticosteroids are given to treat toxicity.[103]

Lymphodepletion and CAR T-cell therapy should be delayed if the patient has a serious or uncontrolled active infection.[70,98] Similarly, although some evidence suggests that CAR T-cell therapy may continue safely with appropriate precautions and planning during the SARS-CoV-2 pandemic,[105] SARS-CoV-2 testing should be performed before conditioning chemotherapy begins, and therapy should be delayed if infection is found.[106] Use of prophylactic acyclovir or valacyclovir for viral infections, trimethoprim-sulfamethoxazole or an alternative agent for *Pneumocystis jirovecii* pneumonia, and antifungal agents in cases of severe neutropenia or prolonged corticosteroids have been recommended; gram-negative bacterial prophylaxis can also be considered during periods of neutropenia.[98,103] Recommendations for timing of vaccination for patients who have received anti-CD19 CAR T-cell therapy are available,[98] although the efficacy of vaccination in these patients has not been prospectively evaluated.

PROLONGED CYTOPENIAS

Prolonged cytopenias of more than a 1-month duration, and some instances lasting several weeks to months, have been described after use of CAR T-cell products targeting CD19 and BCMA.[1,36,51,73,104,107,108] Grade 3 or higher cytopenias lasting more than 28 days have been reported in 32% of patients receiving tisagenlecleucel, and the same rate has been reported for children and young adults with ALL as for

TABLE 7. Early Intervention Strategies Using Tocilizumab and/or Corticosteroids in Cytokine Release Syndrome and Neurotoxicity

Publication/ Abstract	Patient Population/CAR Product	Sample Size	Early Intervention Strategy	CRS and ICANS Outcomes	Antimalignancy Response Outcomes
Locke et al, 2017[83] (ZUMA-1, cohort 3)	Adult DLBCL and subtypes/ axicabtagene ciloleucel	31	Tocilizumab on day +2 and levetiracetam on day 0 for all patients in cohort 3	Grade ≥ 3 CRS (Lee 2014 criteria[65]): cohort 3, 3%; cohorts 1-2, 11%. Grade 3–4 NT (CTCAE): cohort 3, 35% plus one death due to cerebral edema; cohorts 1–2, 32%	NR
Topp et al, 2019[126] (ZUMA-1, cohort 4)	Adult DLBCL and subtypes/ axicabtagene ciloleucel	41	Tocilizumab and corticosteroids for grade 1 CRS not resolved after 3 days of supportive care; corticosteroids for grade 1 NT	Grade ≥ 3 CRS (Lee 2014 criteria[65]): cohort 4, 2%; cohorts 1–2, 11%. Grade ≥ 3 NT (CTCAE): cohort 4, 17%; cohort 1–2, 32%	CR rate: cohort 4, 51%; cohorts 1–2, 58%. Ongoing response ≥ 6 months: cohort 4, 54%; cohorts 1–2, 44%
Gardner et al, 2019[80]	Pediatric ALL/SCRI-CAR19v1	20 in cohort; 23 in the DLT cohort*	EI with tocilizumab: fever ≥ 39°C ≥ 10 hours, not responsive to acetaminophen; recurrent hypotension unresponsive to IV fluid bolus within 6 hours; supplemental oxygen; redosing after 48 hours allowed. EI with dexamethasone: 5–10 mg q 6–12 hours: fever ≥ 39°C not responsive to tocilizumab, low-dose vasopressors > 12 hours; higher-dose or second vasopressor, increasing respiratory support needed or concern for intubation	sCRS**: EI group, 15%; DLT group, 30% (p = 0.29). Severe NT**: EI group, 25%; DLT group, 22% (p = 1)	MRD-ve CR rate: EI group, 95%; DLT group, 91%. No difference in LFS or OS between cohorts
Caimi et al, 2020[84]	Adult NHL/anti-CD19 TNFRSF19 CD3z/4-1BB	15 in tocilizumab prophylaxis group; 8 in no-prophylaxis group[82]	Prophylactic tocilizumab given 1 hour before CAR T-cell infusion	Grade ≥ 2 CRS (ASTCT criteria[22,66]): tocilizumab prophylaxis, 20%; no prophylaxis, 62.5% (p = 0.02). NT any grade (CARTOX[17,66]): tocilizumab prophylaxis, 30%; no prophylaxis, 38% (p = 0.30)	CR rate: tocilizumab prophylaxis, 80%; no prophylaxis, 50%

(Continued on following page)

TABLE 7. Early Intervention Strategies Using Tocilizumab and/or Corticosteroids in Cytokine Release Syndrome and Neurotoxicity (Continued)

Publication/ Abstract	Patient Population/CAR Product	Sample Size	Early Intervention Strategy	CRS and ICANS Outcomes	Antimalignancy Response Outcomes
Kadauke et al, 2021[127]	Pediatric ALL/CTL019 (tisagenlecleucel construct)	15 in prospective group with high-burden ALL; 26 in historical cohort with high-burden ALL, treated with standard management†	Early tocilizumab for temperature ≥ 38.5°C two times ≥ 4 hours apart in a 24-hour period in patients with ≥ 40% BM ALL involvement	Grade 4 CRS (Penn criteria): ET group, 27%; historical group, 50% (p = 0.18). Grade ≥ 2 NT (CTCAE): ET group, 53%; historical group, 54% (p > 0.9)	Best ORR: ET group, 87%; historical group, 85% (p > 0.9)

Abbreviations: ALL, acute lymphoblastic leukemia; ASTCT, American Society for Transplantation and Cellular Therapy; BM, bone marrow; CR rate, complete response rate; CRS, cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Events; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; EI, early intervention; ET, early tocilizumab; ICANS, immune effector cell–associated neurotoxicity syndrome; IV, intravenous; LFS, leukemia-free survival; MRD-ve, minimal residual disease negative; NHL, non-Hodgkin lymphoma; NR, not reported in published abstract; NT, neurotoxicity; ORR, overall response rate; OS, overall survival; sCRS, severe CRS; TNFRSF, tumor necrosis factor receptor superfamily.

*DLT cohort received tocilizumab +/− corticosteroids for > 48 hours of related grade 4 toxicity not controlled by medical intervention or > 48 hours of DLT not controlled by medical intervention. This group received corticosteroid therapy for grade ≥ 3 nonhematologic toxicities > 48 hours.

**sCRS defined as vasopressor use, use of inotropes, or intubation. Severe neurotoxicity defined as any grade ≥ 3 neurologic toxicity by CTCAE v4 or any grade 2 seizures.

†By standard management algorithm, indications for tocilizumab were hemodynamic instability despite IV fluids support and moderate to high dose vasopressor support; worsening respiratory status, as indicated by pulmonary infiltrates; increasing oxygen requirement, such as the need for high-flow oxygen or mechanical ventilation; or rapid clinical deterioration.

adults with diffuse large B-cell lymphoma.[1,5] Similarly, grade 3 or higher cytopenias lasting past day 29 were reported in 37% of patients receiving lisocabtagene maraleucel.[51] Grade 3 or higher cytopenias lasting greater than 3 months occurred in 17% of patients with diffuse large B-cell lymphoma who received axicabtagene ciloleucel in ZUMA-1[3] and in 26% of patients receiving brexucabtagene autoleucel for mantle cell lymphoma.[78] The etiology of prolonged myelosuppression is not well understood. Possible risk factors include higher-grade CRS, higher baseline bone marrow involvement with malignancy, lower baseline blood counts, prior stem cell transplant, and CAR construct.[61,73,109,110] Prolonged cytopenias lasting more than a month should be evaluated with bone marrow aspirate and biopsy to rule out progression of malignancy in bone marrow or myelodysplasia. If no other etiology is found, management should include close laboratory monitoring of blood counts, transfusion support, and growth factor support as needed. Use of the thrombopoietin-receptor agonist eltrombopag in patients with severe prolonged cytopenias has been anecdotally reported,[35,110] although whether the medication induced hematopoietic recovery or recovery occurred with time is unclear.

GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease is a potential risk from allogeneic CAR T-cell therapy. Graft-versus-host disease has been described with autologous CAR T cells collected from patients who have full donor engraftment after an allogeneic stem cell transplant,[59,111] after CAR T-cell donor lymphocyte infusions in patients who had a prior allogeneic stem cell transplant,[72] and after infusion of allogeneic off-the-shelf CAR T products.[17] Fortunately, in most cases, graft-versus-host disease was infrequent, occurring at a rate of 0% to 10%.[7,17,59,72,111-114] Graft-versus-host disease was manageable in the setting of recipients who had no or minimal graft-versus-host disease at baseline. Patient selection is important in these scenarios, because severe or uncontrolled baseline graft-versus-host disease in recipients of a prior allogeneic stem cell transplant may preclude CAR T-cell therapy.

SUMMARY

The therapeutic arsenal of CAR T cells for hematologic malignancies is growing rapidly. As experience accrues from clinical trials and from the real world, the next challenge will be to learn, in a systematic and rigorous manner, the appropriate place of CAR T cells among the assortment of chemotherapy, immunotherapies, and small-molecule pathway inhibitors available to our patients. The unique promise of CAR T cells is as a one-and-done treatment with curative potential because of prolonged immunosurveillance, which will likely justify their high initial economic and logistic burdens.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378:439-448.
2. Pasquini MC, Hu Z-H, Curran K, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma [correction published in Blood Adv. 2021;5(4):1136]. Blood Adv. 2020;4:5414-5424.
3. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377:2531-2544.
4. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. J Clin Oncol. 2020;38:3119-3128.
5. Schuster SJ, Bishop MR, Tam CS, et al; JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380:45-56.
6. Finney OC, Brakke HM, Rawlings-Rhea S, et al. CD19 CAR T cell product and disease attributes predict leukemia remission durability. J Clin Invest. 2019;129:2123-2132.
7. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371:1507-1517.
8. Orlando EJ, Han X, Tribouley C, et al. Genetic mechanisms of target antigen loss in CAR19 therapy of acute lymphoblastic leukemia. Nat Med. 2018;24:1504-1506.

9. Jacoby E, Nguyen SM, Fountaine TJ, et al. CD19 CAR immune pressure induces B-precursor acute lymphoblastic leukaemia lineage switch exposing inherent leukaemic plasticity. Nat Commun. 2016;7:12320.
10. Rabilloud T, Potier D, Pankaew S, et al. Single-cell profiling identifies pre-existing CD19-negative subclones in a B-ALL patient with CD19-negative relapse after CAR-T therapy. Nat Commun. 2021;12:865.
11. Singh N, Lee YG, Shestova O, et al. Impaired death receptor signaling in leukemia causes antigen-independent resistance by inducing CAR T-cell dysfunction. Cancer Discov. 2020;10:552-567.
12. Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med. 2018;378:449-459.
13. Hay KA, Gauthier J, Hirayama AV, et al. Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. Blood. 2019;133:1652-1663.
14. Frey NV, Shaw PA, Hexner EO, et al. Optimizing chimeric antigen receptor T-cell therapy for adults with acute lymphoblastic leukemia. J Clin Oncol. 2020; 38:415-422.
15. Wang N, Hu X, Cao W, et al. Efficacy and safety of CAR19/22 T-cell cocktail therapy in patients with refractory/relapsed B-cell malignancies. Blood. 2020; 135:17-27.
16. Shah NN, Highfill SL, Shalabi H, et al. CD4/CD8 T-cell selection affects chimeric antigen receptor (CAR) T-cell potency and toxicity: updated results from a phase I anti-CD22 CAR T-cell trial. J Clin Oncol. 2020;38:1938-1950.
17. Benjamin R, Graham C, Yallop D, et al; UCART19 Group. Genome-edited, donor-derived allogeneic anti-CD19 chimeric antigen receptor T cells in paediatric and adult B-cell acute lymphoblastic leukaemia: results of two phase 1 studies. Lancet. 2020;396:1885-1894.
18. Chong EA, Ruella M, Schuster SJ; Lymphoma Program Investigators at the University of Pennsylvania. Five-year outcomes for refractory B-cell lymphomas with CAR T-cell therapy. N Engl J Med. 2021;384:673-674.
19. Awasthi R, Pacaud L, Waldron E, et al. Tisagenlecleucel cellular kinetics, dose, and immunogenicity in relation to clinical factors in relapsed/refractory DLBCL. Blood Adv. 2020;4:560-572.
20. Jacobson C, Chavez J, Sehgal A, et al. Primary analysis of Zuma-5: a phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL). Blood; 2020;136:40-41.
21. Hirayama AV, Gauthier J, Hay KA, et al. The response to lymphodepletion impacts PFS in patients with aggressive non-Hodgkin lymphoma treated with CD19 CAR T cells. Blood. 2019;133(17):1876-1887
22. Deng Q, Han G, Puebla-Osorio N, et al. Characteristics of anti-CD19 CAR T cell infusion products associated with efficacy and toxicity in patients with large B cell lymphomas. Nat Med. 2020;26:1878-1887.
23. Vercellino L, Di Blasi R, Kanoun S, et al. Predictive factors of early progression after CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma. Blood Adv. 2020;4:5607-5615.
24. Locke FL, Rossi JM, Neelapu SS, et al. Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma. Blood Adv. 2020;4:4898-4911.
25. Rossi J, Paczkowski P, Shen YW, et al. Preinfusion polyfunctional anti-CD19 chimeric antigen receptor T cells are associated with clinical outcomes in NHL. Blood. 2018;132:804-814.
26. Kochenderfer JN, Somerville RPT, Lu T, et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. J Clin Oncol. 2017;35:1803-1813.
27. Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. N Engl J Med. 2020;382:545-553.
28. Tong C, Zhang Y, Liu Y, et al. Optimized tandem CD19/CD20 CAR-engineered T cells in refractory/relapsed B-cell lymphoma. Blood. 2020;136:1632-1644.
29. Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med. 2011;365:725-733.
30. Geyer MB, Rivière I, Sénéchal B, et al. Safety and tolerability of conditioning chemotherapy followed by CD19-targeted CAR T cells for relapsed/refractory CLL. JCI Insight. 2019;5:e122627.
31. Frey NV, Gill S, Hexner EO, et al. Long-term outcomes from a randomized dose optimization study of chimeric antigen receptor modified T cells in relapsed chronic lymphocytic leukemia. J Clin Oncol. 2020;38:2862-2871.
32. Fraietta JA, Lacey SF, Orlando EJ, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia [correction published in Nat Med. 2021;27:561]. Nat Med. 2018;24:563-571.
33. Gill SI, Vides V, Frey N, et al. Prospective clinical trial of anti-CD19 CAR T cells in combination with ibrutinib for the treatment of chronic lymphocytic leukemia shows a high response rate. Blood. 2018;132:298.
34. Gauthier J, Hirayama AV, Purushe J, et al. Feasibility and efficacy of CD19-targeted CAR T cells with concurrent ibrutinib for CLL after ibrutinib failure. Blood. 2020;135:1650-1660.
35. Brudno JN, Maric I, Hartman SD, et al. T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma. J Clin Oncol. 2018;36:2267-2280.
36. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med. 2019;380:1726-1737.
37. Zhao WH, Liu J, Wang BY, et al. A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. J Hematol Oncol. 2018;11:141.

38. Mohyuddin GR, Rooney A, Balmaceda N, et al. Chimeric antigen receptor T-cell therapy in multiple myeloma: a systematic review and meta-analysis of 950 patients. Blood Adv. 2021;5:1097-1101.

39. Costello CL, Cohen AD, Patel KK, et al. Study of the safety and response of P-BCMA-101 CAR-T cells in patients with relapsed/refractory (r/r) multiple myeloma (MM) (PRIME) with novel therapeutic strategies. Blood. 2020 (suppl; abstr 134).

40. Ramos CA, Grover NS, Beaven AW, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory Hodgkin lymphoma. J Clin Oncol. 2020;38:3794-3804.

41. Budde EL. CD123CAR displays clinical activity in relapsed/refractory (R/R) acute myeloid leukemia (AML) and blastic plasmacytoid dendritic cell neoplasm (BPDCN): safety and efficacy results from a phase 1 study. Cancer Immunol Res. (suppl; abstr PR14); 2018.

42. Locke FL, Batlett NL, Jacobson CA, et al. Retreatment (reTx) of Patients (pts) with refractory large B-cell lymphoma with axicabtagene ciloleucel (axi-cel) in ZUMA-1. J Clin Oncol. (suppl; abstr 8012); 2020.

43. Jacobson C, Chavez, JC, Sehgal AR, et al. Primary analysis of ZUMA-5: a phase 2 study of axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL). Blood. 2020 (suppl; abstr 700).

44. Khurana A, Hathcock M, Habermann T, et al. Lines of therapy before autologous stem cell transplant (ASCT) and CAR-T infusion affect outcomes in aggressive non-Hodgkin's lymphoma (NHL). Blood. 2020; 136;29-30.

45. Dreger P, Dietrich S, Schubert M-L, et al. CAR T cells or allogeneic transplantation as standard of care for advanced large B-cell lymphoma: an intent-to-treat comparison. Blood Adv. 2020;4:6157-6168.

46. Sermer D, Batlevi C, Palomba ML, et al. Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies. Blood Adv. 2020;4:4669-4678.

47. Neelapu S, Dickinson M, Ulrickson M, et al. Interim analysis of ZUMA-12: a phase 2 study of axicabtagene ciloleucel (axi-cel) as first-line therapy in patients (Pts) with high-risk large B cell lymphoma (LBCL). Blood. 2020;136; 49.

48. Garfall AL, Dancy EK, Cohen AD, et al. T-cell phenotypes associated with effective CAR T-cell therapy in postinduction vs relapsed multiple myeloma. Blood Adv. 2019;3:2812-2815.

49. Samur MK, Fulciniti M, Aktas Samur A, et al. Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma. Nat Commun. 2021;12:868.

50. Jacobson CA, Hunter BD, Redd R, et al. Axicabtagene ciloleucel in the non-trial setting: outcomes and correlates of response, resistance, and toxicity. J Clin Oncol. 2020;38:3095-3106.

51. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396:839-852.

52. Turtle CJ, Hay KA, Hanafi LA, et al. Durable molecular remissions in chronic lymphocytic leukemia treated with CD19-specific chimeric antigen receptor-modified T cells after failure of ibrutinib. J Clin Oncol. 2017;35:3010-3020.

53. DeAngelo DJ, Ghobadi G, Park JH, et al. Clinical outcomes for the phase 2, single-arm, multicenter trial of JCAR015 in adult B-ALL (ROCKET Study). Presented at: SITC Annual Meeting. National Harbor, MD; 2017. Abstract P217.

54. Santomasso BD, Park JH, Salloum D, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov. 2018;8:958-971.

55. Brudno JN, Lam N, Vanasse D, et al. Safety and feasibility of anti-CD19 CAR T cells with fully human binding domains in patients with B-cell lymphoma [correction published in Nat Med. 2020;26:803]. Nat Med. 2020;26:270-280.

56. Reagan PM, Neelapu SS, How I. How I manage: pathophysiology and management of toxicity of chimeric antigen receptor T-cell therapies. J Clin Oncol. 2021; 39:456-466.

57. Cobb DA, Lee DW. Cytokine release syndrome biology and management. Cancer J. 2021;27:119-125.

58. Giavridis T, van der Stegen SJC, Eyquem J, et al. CAR T cell–induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. Nat Med. 2018;24:731-738.

59. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016;126:2123-2138.

60. Turtle CJ, Hanafi LA, Berger C, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. Sci Transl Med. 2016;8:355ra116.

61. Hay KA, Hanafi LA, Li D, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. Blood. 2017;130:2295-2306.

62. Gust J, Hay KA, Hanafi LA, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. Cancer Discov. 2017;7:1404-1419.

63. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy: assessment and management of toxicities. Nat Rev Clin Oncol. 2018; 15:47-62.

64. Alabanza L, Pegues M, Geldres C, et al. Function of novel anti-CD19 chimeric antigen receptors with human variable regions is affected by hinge and transmembrane domains. Mol Ther. 2017;25:2452-2465.

65. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome [correction published in Blood. 2016; 128(11):1533]. Blood. 2014;124:188-195.

66. Porter D, Frey N, Wood PA, et al. Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel [correction published in J Hematol Oncol. 2018;11:81]. J Hematol Oncol. 2018;11:35.

67. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25:625-638.

68. National Cancer Institute. Common Terminology Criteria for Adverse Events v 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Accessed March 15, 2021.

69. Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: mechanisms, manifestations and management. Blood Rev. 2019;34:45-55.

70. Maus MV, Alexander S, Bishop MR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. J Immunother Cancer. 2020;8:e001511.

71. Porter DL, Hwang WT, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. Sci Transl Med. 2015;7:303ra139.

72. Brudno JN, Somerville RP, Shi V, et al. Allogeneic T cells that express an anti-CD19 chimeric antigen receptor induce remissions of B-cell malignancies that progress after allogeneic hematopoietic stem-cell transplantation without causing graft-versus-host disease. J Clin Oncol. 2016;34:1112-1121.

73. Jain T, Knezevic A, Pennisi M, et al. Hematopoietic recovery in patients receiving chimeric antigen receptor T-cell therapy for hematologic malignancies. Blood Adv. 2020;4:3776-3787.

74. U.S. Food and Drug Administration. Kymriah (Tisagenlecleucel) Package Insert, Version 5/2018. https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert—KYMRIAH.pdf. Accessed March 15, 2021.

75. Buechner J, Grupp SA, Hiramatsu H, et al. Practical guidelines for monitoring and management of coagulopathy following tisagenlecleucel CAR T-cell therapy. Blood Adv. 2021;5:593-601.

76. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014;6:224ra25.

77. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood. 2016;127:3321-3330.

78. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2020;382:1331-1342.

79. Strati P, Ahmed S, Furqan F, et al. Prognostic impact of corticosteroids on efficacy of chimeric antigen receptor T-cell therapy in large B-cell lymphoma. Blood. Epub 2021 Feb 3.

80. Gardner RA, Ceppi F, Rivers J, et al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. Blood. 2019;134:2149-2158.

81. Topp MS, Van Meerten T, Houot R, et al. Earlier steroid use with axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory large B cell lymphoma. Blood. Washington, DC: 2019;134; 243.

82. Kadauke S, Myers RM, Li Y, et al. Risk-Adapted preemptive tocilizumab to prevent severe cytokine release syndrome after CTL019 for pediatric B-cell acute lymphoblastic leukemia: a prospective clinical trial. J Clin Oncol. 2021;39:920-930.

83. Locke FL, Neelapu SS, Bartlett N, et al. preliminary results of prophylactic tocilizumab after axicabtageneciloleucel (axi-cel; KTE-C19) treatment for patients with refractory, aggressive non-Hodgkin lymphoma (NHL). Blood. 2017;130:1547.

84. Caimi PF, Sharma A, Rojas P, et al. CAR-T therapy for lymphoma with prophylactic tocilizumab: decreased rates of severe cytokine release syndrome without excessive neurologic toxicity. Blood. 2020 (suppl; abstr 738).

85. Jatiani SS, Aleman A, Madduri D, et al. Myeloma CAR-T CRS management with IL-1R antagonist anakinra. Clin Lymphoma Myeloma Leuk. 2020;20:632-636.

86. Zhang L, Wang S, Xu J, et al. Etanercept as a new therapeutic option for cytokine release syndrome following chimeric antigen receptor T cell therapy. Exp Hematol Oncol. 2021;10:16.

87. Jan M, Scarfò I, Larson RC, et al. Reversible ON- and OFF-switch chimeric antigen receptors controlled by lenalidomide. Sci Transl Med. 2021;13:eabb6295.

88. Paszkiewicz PJ, Fräßle SP, Srivastava S, et al. Targeted antibody-mediated depletion of murine CD19 CAR T cells permanently reverses B cell aplasia. J Clin Invest. 2016;126:4262-4272.

89. Drent E, Groen RWJ, Noort WA, et al. Pre-clinical evaluation of CD38 chimeric antigen receptor engineered T cells for the treatment of multiple myeloma. Haematologica. 2016;101:616-625.

90. Norelli M, Camisa B, Barbiera G, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. Nat Med. 2018;24:739-748.

91. Strati P, Ahmed S, Kebriaei P, et al. Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. Blood Adv. 2020;4:3123-3127.

92. Shah NN, Johnson BD, Fenske TS, et al. Intrathecal chemotherapy for management of steroid-refractory CAR T-cell-associated neurotoxicity syndrome. Blood Adv. 2020;4:2119-2122.

93. Kenderian SS, Oluwole OO, McCarthy PL, et al. 2103 ZUMA-19: a phase 1/2 multicenter study of lenzilumab use with axicabtagene ciloleucel (Axi-Cel) in patients (Pts) with relapsed or refractory large B cell lymphoma (R/R LBCL). Blood. 2020;(suppl; abstr 2103).

94. Mestermann K, Giavridis T, Weber J, et al. The tyrosine kinase inhibitor dasatinib acts as a pharmacologic on/off switch for CAR T cells. Sci Transl Med. 2019;11:eaau5907.

95. Weber EW, Lynn RC, Sotillo E, et al. Pharmacologic control of CAR-T cell function using dasatinib. Blood Adv. 2019;3:711-717.

96. Maus MV, June CH. Making better chimeric antigen receptors for adoptive T-cell therapy. Clin Cancer Res. 2016;22:1875-1884.

97. Fry TJ, Shah NN, Orentas RJ, et al. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. Nat Med. 2018;24:20-28.

98. Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. Blood. 2020; 136:925-935.

99. Kochenderfer JN, Somerville RPT, Lu T, et al. Long-duration complete remissions of diffuse large B cell lymphoma after anti-CD19 chimeric antigen receptor T cell therapy. Mol Ther. 2017;25:2245-2253.

100. Kochenderfer JN, Dudley ME, Feldman SA, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. Blood. 2012;119:2709-2720.

101. Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood. 2018;131:121-130.

102. Park JH, Romero FA, Taur Y, et al. Cytokine release syndrome grade as a predictive marker for infections in patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with chimeric antigen receptor T cells. Clin Infect Dis. 2018;67:533-540.

103. Gudiol C, Lewis RE, Strati P, et al. Chimeric antigen receptor T-cell therapy for the treatment of lymphoid malignancies: is there an excess risk for infection? Lancet Haematol. 2021;8:e216-e228.

104. Baird JH, Epstein DJ, Tamaresis JS, et al. Immune reconstitution and infectious complications following axicabtagene ciloleucel therapy for large B-cell lymphoma. Blood Adv. 2021;5:143-155.

105. Maurer K, Saucier A, Kim HT, et al. COVID-19 and hematopoietic stem cell transplantation and immune effector cell therapy: a US cancer center experience. Blood Adv. 2021;5:861-871.

106. Bachanova V, Bishop MR, Dahi P, et al; CAR T-cell Consortium. Chimeric antigen receptor T cell therapy during the COVID-19 pandemic. Biol Blood Marrow Transplant. 2020;26:1239-1246.

107. Ali SA, Shi V, Maric I, et al. T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. Blood. 2016; 128:1688-1700.

108. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019;20:31-42.

109. Fried S, Avigdor A, Bielorai B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. Bone Marrow Transplant. 2019;54:1643-1650.

110. Nahas GR, Komanduri KV, Pereira D, et al. Incidence and risk factors associated with a syndrome of persistent cytopenias after CAR-T cell therapy (PCTT). Leuk Lymphoma. 2020;61:940-943.

111. Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. 2017;129:3322-3331.

112. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015;385:517-528.

113. Cruz CRY, Micklethwaite KP, Savoldo B, et al. Infusion of donor-derived CD19-redirected virus-specific T cells for B-cell malignancies relapsed after allogeneic stem cell transplant: a phase 1 study [correction published online in Blood. 2014;123(21):3364]. Blood. 2013;122:2965-2973.

114. Neelapu SS, Munoz J, Lundry Locke F, et al; MJLF. First-in-human data of ALLO-501 and ALLO-647 in relapsed/refractory large B-cell or follicular lymphoma (R/R LBCL/FL): ALPHA study. J Clin Oncol. 2020;38(suppl; abstr 8002).

115. Munshi NC, Anderson LD Jr., Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384:705-716.

116. Ghorashian S, Kramer AM, Onuoha S, et al. Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. Nat Med. 2019;25:1408-1414.

117. Magnani CF, Gaipa G, Lussana F, et al. Sleeping Beauty-engineered CAR T cells achieve antileukemic activity without severe toxicities. J Clin Invest. 2020; 130:6021-6033.

118. Cappell KM, Sherry RM, Yang JC, et al. Long-term follow-up of anti-CD19 chimeric antigen receptor T-cell therapy. J Clin Oncol. 2020;38:3805-3815.

119. Sauter CS, Senechal B, Rivière I, et al. CD19 CAR T cells following autologous transplantation in poor-risk relapsed and refractory B-cell non-Hodgkin lymphoma. Blood. 2019;134:626-635.

120. Srour SA, Singh H, McCarty J, et al. Long-term outcomes of Sleeping Beauty-generated CD19-specific CAR T-cell therapy for relapsed-refractory B-cell lymphomas. Blood. 2020;135:862-865.

121. Shah NN, Johnson BD, Schneider D, et al. Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial. Nat Med. 2020;26:1569-1575.

122. Cohen AD, Garfall AL, Stadtmauer EA, et al. B cell maturation antigen-specific CAR T cells are clinically active in multiple myeloma. J Clin Invest. 2019; 129:2210-2221.

123. Baumeister SH, Murad J, Werner L, et al. Phase I trial of autologous CAR T cells targeting NKG2D ligands in patients with AML/MDS and multiple myeloma. Cancer Immunol Res. 2019;7:100-112.

124. Wang QS, Wang Y, Lv HY, et al. Treatment of CD33-directed chimeric antigen receptor-modified T cells in one patient with relapsed and refractory acute myeloid leukemia. Mol Ther. 2015;23:184-191.

125. Yao S, Jianlin C, Yarong L, et al. Donor-derived CD123-targeted CAR T cell serves as a RIC regimen for haploidentical transplantation in a patient with *FUS-ERG*+ AML. Front Oncol. 2019;9:1358.

126. Topp MS, van Meerten T, Houot R, et al. Earlier steroid use with axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory large B cell lymphoma. Blood. 2019;134(suppl; abstr 243).

127. Kadauke S, Myers RM, Li Y, et al. Risk-adapted preemptive tocilizumab to prevent severe cytokine release syndrome after CTL019 for pediatric B-cell acute lymphoblastic leukemia: a prospective clinical trial. J Clin Oncol. 2021;39:920-930.

Characterize, Optimize, and Harmonize: Caring for Older Adults With Hematologic Malignancies

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overview

With the aging of the population, the number of older adults with hematologic malignancies is growing, and treatment paradigms for these patients are rapidly evolving. Use of allogeneic stem cell transplant has been expanding to include septuagenarians but remains a potentially morbid procedure, creating an opportunity for a geriatric-focused evaluation to improve assessment of the individual's risk in undergoing the procedure. Although age alone should not be the sole determinant for transplant eligibility, geriatric assessment often identifies vulnerabilities that are not captured in assessing performance status and comorbidities alone. Those vulnerabilities may be optimized in an approach employing three sequential steps: characterize resiliency, bolster resilience, and harmonize with patient goals. Data are emerging that show that this approach is associated with lower nonrelapse mortality, shorter length of stay, and better survival after transplant. In older adults with myeloma, treatment recommendations also aim to balance the expected efficacy and toxicity profile and incorporate the patient's goals and preferences. Assessment of frailty allows for more personalized estimates of risk of toxicity. Currently, the European Myeloma Network currently recommends using the International Myeloma Working Group frailty scale as a standard approach to defining frail or at-risk populations with myeloma. In addition to treatment selection, the care of older adults with myeloma must include consideration of other issues, including reducing early mortality with antibiotic prophylaxis, polypharmacy, depression, cognition, and falls. Overall, appreciation of the aging-associated vulnerabilities will allow for the ultimate personalized care and treatment of older adults with hematologic malignancies.

The incidence of hematologic malignancies increases with age. Although increasing age is frequently associated with adverse outcomes, the heterogeneity of aging mandates that clinicians consider that chronologic age alone is simply a surrogate for aging-associated vulnerabilities, and that individualizing cancer treatment decisions and care requires an understanding of the ways to operationalize this heterogeneity using concepts of frailty and geriatric assessment.

Therapeutic trials that have yielded tremendous advances in treatment often focus on younger patients, with increasing intensity of therapy aimed at deepening and prolonging responses. Although some of these approaches, particularly with newer targeted therapies, may be well-tolerated by more vulnerable older adults, other more intense approaches, such as stem cell transplant, require close evaluation to determine the individual's risk in that approach. In this article, we will cover approaches to the care of older adults with blood cancers, which includes addressing the presence of geriatric impairments.

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CONCEPTS OF GERIATRICS IN THE ONCOLOGY CLINIC: GERIATRIC ASSESSMENT AND FRAILTY

Comprehensive geriatric assessment is a multidisciplinary systematic approach to the evaluation and management of "the medical, psychosocial, and functional capabilities and limitations in order to develop an overall plan for treatment and long-term follow-up."[1] In general geriatric populations, comprehensive geriatric assessment improves outcomes in community-dwelling and hospitalized older adults.[2,3] In the geriatric oncology literature, to distinguish from the process of evaluation and subsequent management, the term *geriatric assessment* is commonly chosen when focused on evaluation and identification of domains of impairment.[4] In oncology, identification of geriatric impairments through geriatric assessment has been shown to improve satisfaction with communication with providers and reduces toxicity in older adults with primarily solid tumors.[5,6] The domains of geriatric assessment include physical health (comorbidities and their severity, medications), functional status (activities of daily living and instrumental activities of daily living), psychological status (depression/anxiety and cognition), and social parameters (social needs/resources and environment).

A distinct but related concept is that of frailty. The concept of frailty has clear face validity to clinicians but remains challenging to define rigorously; controversy remains about the optimal way to operationalize the

PRACTICAL APPLICATIONS

- Geriatric assessment and frailty evaluation aim to identify deficits that may impact therapeutic decision-making in older adults with hematologic malignancies and also may be modifiable, particularly in the transplant setting, when the treatment may be delayed or deferred to allow for optimization.
- In the transplant setting, a three-step approach can be used to (1) characterize vulnerabilities/resilience, (2) bolster resilience through intervention recommendations, and (3) harmonize the approach with patient preferences.
- In older adults with myeloma, frailty is widely being assessed using the International Myeloma Working Group frailty scale. However, this scale does not specifically address prevalent and potentially preventable issues, including polypharmacy, falls, depression, and cognition.

concept in research and practice. A Delphi consensus panel of experts in the study of frailty did not reach full consensus on a definition of frailty; however, there was agreement that frailty was a multisystem clinical syndrome "characterized by decreased reserve and diminished resistance to stressors" and a dynamic process.[7] In geriatrics, a systematic review revealed 67 different approaches to operationalizing frailty.[8] The two most widely applied approaches are the phenotypic frailty approach and the accumulation of deficits approach. The phenotypic frailty approach comprises five items, including weakness, exhaustion, slowing, shrinking, and low activity,[9] with patients being categorized as not frail, intermediate, or frail (alternately, as nonfrail, prefrail, and frail). The accumulation of deficits approach identifies the number of a range of potential impairments, and does not require specific items. It is calculated as the quotient of the number of deficits present divided by the potential number of deficits. The result ranges between zero and one. Data from a comprehensive geriatric assessment have been used to calculate a deficits accumulation frailty index in cohorts of older adults with cancer.[10]

Two of the aforementioned facets of the concept of frailty are specifically salient in the management of hematologic malignancies in older adults. First, the concept of frailty resulting in decreased resistance to stressors is relevant when considering the therapeutic options. If we consider cancer treatment as the stressor, it is relevant to consider both the magnitude and duration of the stressor. Second, the concept that frailty is dynamic is important given the high degree of symptom burden that often accompanies a diagnosis of a hematologic malignancy as well as the possibility that it may be reversible with intervention and optimization of individual vulnerabilities.[11]

TRANSPLANT OPTIMIZATION IN OLDER ADULTS WITH HEMATOLOGIC MALIGNANCIES: HOW OLD IS TOO OLD?

Age and Aging: When Is a Patient Too Old?

This section is focused on allogeneic hematopoietic cell transplantation (alloHCT), which may be recommended when there are higher procedural-related complications such as nonrelapse mortality, although the concepts reviewed here could be applied to autologous HCT. Chronologic age is objective and valuable for aggregate data. However, the heterogeneity of health with aging precludes a numeric upper age limit to pursue HCT for an individual patient. In the early 1990s, alloHCT for "older" patients in their fifth decade of life was bold.[12] Thirty years later, the field has honed attention on patients age 70 or older, with 9% of alloHCT in this age range.[13] In "real-world" registry data, 2-year survival was approximately 38% to 39% for hematologic malignancies after alloHCT.[14-16] Yet, 2-year nonrelapse mortality rates of one-third, defined as death after HCT without disease relapse, argue against complacency.

The ninth decade has been a practical upper age limit with U.S. registry data, with approximately 0.01% of alloHCTs (four patients) for this age group from 2008 to 2013.[14] The European registry described no allografts in those age 80 or older for myelodysplastic syndrome and acute myeloid leukemia through 2013 to 2014.[15,16] In a survey, most physicians facilitating HCT reported an upper age limit between age 70 and 80 for reduced-intensity conditioning alloHCT, although 17.7% described no upper age limit.[17] The valid concerns about HCT-associated morbidity, mortality, and quality of life in older age must always be weighed against the unremitting course of hematologic malignancies.[18,19]

Optimization for Hematopoietic Cell Transplantation

Optimization can be broken down into three sequential steps: characterize resiliency, bolster resilience, and harmonize with patient goals.

Characterize resilience The hazy recommendation to consider HCT among "fit" older patients, and not exclude based on age alone, lacks clarity. In addition to higher rates of nonrelapse mortality among older adults, geriatric syndromes such as falls and delirium further complicate alloHCT.[20] Nonolder adult alloHCT engenders loss of function even 3 months after HCT, which may take 1 year to normalize in survivors.[21,22]

Restrictive eligibility criteria (e.g., age younger than 70, low comorbidity) are understandable to attenuate rates of complications; yet these restrictions preclude HCT for older

patients who appear likely to benefit from it.[23,24] Nevertheless, non–age-based institutional HCT criteria remain important. Further profiling of patient resiliency, usually via geriatric assessment and/or other fitness testing, adds value for otherwise eligible older patients. Resiliency reflects the ability to bounce back from a stressor (in this case, after HCT).[11] Geriatric assessment supplements standard clinical parameters of performance status, comorbidity by HCT-comorbidity index, and chronologic age. To appreciate resiliency, geriatric assessment findings must be contextualized to the proposed HCT plan (e.g., autologous vs. allogeneic, myeloablative vs. reduced-intensity conditioning regimen) to inform resilience. Geriatric assessment frequently uncovers health impairments among patients age 50 or older,[25] even among those with good performance status.[26,27] Limitations in geriatric assessment–rated function and cognition track independently with higher nonrelapse mortality after alloHCT.[25,28,29] Autografts, especially for myeloma, have very low rates of nonrelapse mortality for older adults, though geriatric assessment–defined functional limitations are linked to worse disease-free survival.[30,31] Validated prognostic scores incorporating geriatric assessment to risk-stratify may emerge soon (NCT03992352).

Bolster resilience The aging-related changes uncovered by geriatric assessment can be leveraged to bolster resilience. Targeting vulnerabilities found by geriatric assessment (e.g., limitation in function and cognitive impairment) is recommended in cancer treatment.[32] Randomized studies in medical oncology have demonstrated these approaches reduce chemotherapy-induced toxicity.[6,33,34] Data are now emerging through approaches customized to the high-morbidity alloHCT setting.

A prospective quality initiative in Chicago implemented a geriatric assessment–guided optimization program before alloHCT among patients age 60 and older.[11] Patients completed a geriatric assessment and the Fried Frailty Phenotype, followed by a multidisciplinary clinic visit comprising a transplant physician, geriatrics, dietician, social worker, physical or occupational therapist, and infectious disease physician. Provider recommendations entailed further evaluation and/or optimization tailored both to geriatric assessment deficits and the proposed HCT (Table 1). Resiliency-bolstering followed the tenant of "dissimilar redundancy," a process to minimize critical "failures" through independent systems. For example, fall avoidance can be prevented through both physical rehabilitation and caregiver education on ambulating with a patient. Even patients without limitations can be optimized by augmenting their strengths—endurance may be gained even if good function; caregiver support can be intensified beyond minimum HCT requirements; a healthy diet can be proposed even without weight loss.

The optimization program, compared with historic control patients undergoing geriatric assessment without a multidisciplinary clinic, was associated with lower nonrelapse mortality, shorter length of stay, fewer admissions to skilled nursing facilities, and better survival. There appeared to be a learning curve, with best results in the more modern period. Feasibility was high; 97% of eligible patients attended the clinic; 23% of all attendees were age 70 or older. The same approach applied to autologous HCT was associated with low 1-year nonrelapse mortality (0%) in those age 70 or older. A single-center study compared with historical control should be viewed with caution. Nevertheless, multidisciplinary older adult cancer clinics are more prevalent.[35] Preliminary data from The Ohio State group and MD Anderson Cancer Center have reported favorable data without a control in older patients undergoing HCT with geriatric evaluation and treatment or rehabilitation, respectively.[3637]

Continuation Pre-HCT optimization ideally should transition smoothly to immediately after HCT; unfortunately, prospective post-HCT interventions based on resiliency or geriatric assessment deficits are lacking. Current data from the adult HCT population offer the following valuable lessons: education alone starting pre-HCT to continue post-HCT is insufficient to improve quality of life[38]; randomized trials of supervised exercise to enhance physical function or fatigue, primarily after HCT, have had mixed results[39]; and the feasibility of supervised exercise pre-HCT can be challenging.[40,41] More positive findings emerged for palliative care for symptom distress initiated at HCT by 6 months after transplant for patients of all ages.[42] These limitations notwithstanding, communicating the findings and interventions begun pre-HCT to the providers engaged in immediate treatment after HCT is reasonable.[11] Transparency with patients and caregivers (Table 1) may further help bridge the pre- and post-HCT divide.

Harmonize with patient goals Arming physicians and patients with a refined understanding of risk based on the dyad of resilience and proposed HCT promotes shared decision-making. In the Chicago program, three categories of nonbinding recommendations emerged, fusing resilience to patient goals: proceed, defer, and decline. Confirming the advisability of HCT in resilient patients may overcome equivocation resulting from concerns over older age. Objective resilience and patient goals also inform dose modification of preparative regimens, as lowering conditioning intensity for safety based on older age alone predisposes patients to relapse in some diseases. In contrast, deferring HCT in the presence of substantial vulnerabilities that will impact outcome grants time to optimize problems requiring a larger investment (e.g., ongoing weight loss) and/or demanding specialized testing (e.g., imaging and full cognitive testing for an abnormal cognitive screen). Reassessment

TABLE 1. Common Geriatric Impairments and Optimization Hematopoietic Cell Transplantation

GA Limitation	Health Care Provider	Pre-HCT Intervention	Early HCT Continuation
Functional Impairment	Physical therapist	Tailored and safe exercise	Safe walking program
Falls	Occupational therapist or geriatrics	Multifactorial risk assessment and intervention	Educate patient, staff, and caregiver on fall abatement
Thin Social Support	Social worker	Pre-HCT meeting to widen caregiver support	Discrete blocks for selected caregivers
Weight Loss	Dietician	Address reversible causes	Supplements and personalized food choices
Polypharmacy	Geriatrician or pharmacist	De-prescribe	Avoid potentially inappropriate medications
Cognitive Impairment	Geriatrician or neurologist	Further assessment	Delirium avoidance protocol
Comorbid Condition	Specialist	Request "optimization," not clearance	Early specialist follow-up
Any Impairment	HCT physician	Harmonize patient goals with expected HCT trajectory	Periodically revisit patient goals post-HCT
		Assign provider to coordinate optimization	Communicate deficits and optimization to post-HCT team
		Defer HCT until addressed or improved	Require caregiver for hospital stay*
			Increase frequency and/or duration of follow-up visits

Abbreviations: GA, geriatric assessment; HCT, hematopoietic cell transplantation.
*Outpatient hematopoietic cell transplantation may be pursued based on program infrastructure.

after optimization can illuminate situations where no gains occur, prompting more meaningful conversations on the advisability of HCT. In the Chicago program, only approximately 60% of patients proceeded to autologous HCT or alloHCT after initial deferral.[11,30]

Summary

On an individual basis, we should de-emphasize older age alone as a sole criterion for transplant candidacy as HCT at least into the eighth decade of life. A systematic approach to characterizing and bolstering resiliency for HCT in patients age 60 or older may expand access by avoiding "age-only" eligibility determinations, improve outcomes, and foster shared decision-making.

UNIQUE CONSIDERATIONS FOR MANAGEMENT OF MULTIPLE MYELOMA IN OLDER ADULTS

Tightrope of Treatment: Avoiding Undertreatment and Overtreatment in Older Adults

Although the efficacy and tolerability of the treatment of myeloma have, overall, improved survival in patients over age 65,[43] a proportion of older adults with myeloma still receive no treatment, a proportion that increases with age.[44,45] Only half of patients over age 80 received any antimyeloma therapy in one study.[46] Reasons for nontreatment are unexplored in the literature, but presumably center on concerns about toxicity. Conversely, some older patients may experience increased risk of toxicity with aggressive therapy. Clinicians are challenged to walk the line between overtreating or undertreating, providing a treatment recommendation with an expected efficacy and toxicity profile that harmonizes with the patient's goals and preferences.

Over the past 2 decades, there has been a steady progression of trials establishing first-line therapy options for the non–transplant eligible population. A 2020 systematic review of clinical trials examining front-line treatment of transplant-ineligible older adults with myeloma identified 27 phase II and phase III studies.[47] This included 23 different regimens ranging from melphalan and prednisone through quadruplets incorporating multiple novel agents. This review identified the four most effective regimens with regards to progression-free survival: bortezomib/melphalan/prednisone/daratumumab,[48] daratumumab/lenalidomide/dexamethasone,[49] bortezomib/melphalan/prednisone/thalidomide,[50] and bortezomib/lenalidomide/dexamethasone.[51] The authors then examined the toxicity profile of each of the 23 regimens. They concluded that the balance of efficacy with the toxicity profile was most favorable for the combination of daratumumab, lenalidomide, and dexamethasone.

Frailty measures in myeloma As outlined in the introduction, approaches to categorizing frailty vary. In multiple myeloma, a number of approaches and measures have been developed and applied to both clinical trial populations and real-world populations. These include the International Myeloma Working Group Frailty Index, which employs age,

comorbidities, and functional status to yield a composite score that categorizes the patient as fit, intermediate, or frail. A simplified version of the frailty index has been developed, which includes age, performance status, and comorbidities.[52] The Revised Myeloma Comorbidity Index has been developed and validated and incorporates performance status, comorbidities, phenotypic frailty, and laboratory abnormalities. Importantly, patients may be categorized differently using different measures, so stating that a patient is categorized as "frail" must be qualified with which instrument is used.[53,54] The European Myeloma Network currently recommends using the International Myeloma Working Group frailty scale as a standard approach to defining frail or at-risk populations with myeloma.[55] Studies defining the included population using this frailty scale are beginning to emerge. Larocca et al[56] presented a study wherein older adults who were categorized as intermediate-fit were selected for a trial where participants were randomly assigned to either continuous lenalidomide/dexamethasone or nine cycles of induction with the same, followed by lenalidomide maintenance alone. Participants in the lenalidomide maintenance alone arm had a lower rate of treatment discontinuation because of adverse events, with similar progression-free survival.[56] Another ground-breaking study is enrolling patients with myeloma categorized as unfit and frail to the regimen of daratumumab, ixazomib, and dexamethasone.[57] Study designs such as these will provide a solid evidence base for tailoring treatment to the patient's level of frailty.

Considerations beyond myeloma management The treatment of older adults with myeloma requires a comprehensive and wholistic approach to their health to minimize the risk of complications, anticipate intercurrent issues, reduce early mortality, and ensure maintenance of quality of life and independence, and maintain their psychological and cognitive health. Early mortality is a threat to older adults with myeloma. Rates of early mortality are improving overall, but remain substantial, with 10% of patients older than age 65 dying within the first 6 months and 18% within the first year after diagnosis.[45,58,59] The most commonly reported causes of death contributing to early mortality include myeloma, cardiac causes, infection, and renal failure.[58] Given the frequency of infection and immunodeficient state of individuals with newly diagnosed multiple myeloma, a randomized trial aimed to reduce the risk of infection with prophylactic levofloxacin for the first 12 weeks after diagnosis. The patients receiving levofloxacin prophylaxis had a 34% relative reduction in the hazard of febrile episodes or death (19% vs. 27%). Thus, levofloxacin may reduce the risk of infection or death in patients with myeloma, though this benefit must be weighed against the risk of drug-drug interactions and polypharmacy.

Rates of polypharmacy are exceedingly high in older adults with cancer in general, and patients with myeloma are no exception. In geriatrics, taking five or more mediations is a commonly used cutpoint for defining polypharmacy. In older adults with myeloma, the median number of medications is 10.[60,61] Polypharmacy increases the risk of adverse drug reactions and drug-drug interactions. In addition, medications considered potentially inappropriate for older adults increase the risk of falls, delirium, hospitalization, and even death. The presence of polypharmacy also increases the risk for poorer adherence to other medications, of particular concern with orally administered antimyeloma therapy. In a multivariable analysis of older adults with myeloma receiving lenalidomide, increasing the number of concomitant medications was associated with a decreased medication possession ratio, implying poorer adherence to lenalidomide.[61] Of note, in a recent study, patients supervised by physician-pharmacist comanagement had lower rates of polypharmacy and took fewer potentially inappropriate medications, giving insight into the potential benefit of de-prescribing interventions in this population.[62]

Psychosocial wellness is another important and underappreciated burden in older adults with myeloma. In one study of over 500 older adults with myeloma, 30% reported symptoms of depression.[63] The presence of depression is associated with a sixfold increased risk of poor adherence to lenalidomide.[64] More than one in 10 (12.6%) people living with myeloma report suicidal ideation.[65] Longitudinal assessment of symptoms and quality of life demonstrate that, although much of the symptom burden endured by people with myeloma improves over the first year after diagnosis, depression and anxiety remain largely static, with approximately 25% of transplant-ineligible older adults reporting persistent-moderate to severe symptoms of depression and anxiety.[66] This finding implies that these are not transitory symptoms associated with initial diagnosis, but psychological comorbidities that persist and are not adequately controlled. Half of patients with myeloma desired psychosocial interventions, including referrals for counseling or peer support groups, suggesting that patients are open to addressing their psychosocial symptoms.[67]

Falls are another area of particular concern for the treatment of older adults with multiple myeloma. Although common, falls are not considered a normal part of aging. Older adults with myeloma are at even greater risk for falls than matched control patients without cancer.[68] Fatigue, poor overall health, and depression are all associated with increased rate of falls in older adults with myeloma. Chemotherapy-induced peripheral neuropathy increases the risk for falls

in older adults with cancer.[69-71] In older adults with multiple myeloma, receipt of bortezomib is associated with a 36% increased risk of falls, presumably mediated via peripheral neuropathy.[72]

Finally, the cognitive status of older adults with myeloma is an underexplored area. One population-level study from the Swedish cancer registry found that, in a cohort of almost 5,000 patients with myeloma, with a median age of 72, only 1.1% carried a diagnosis of dementia.[73] This likely underestimates the proportion of patients with cognitive impairment, as patients may have cognitive decline without meeting a diagnosis of dementia. Studies using objective tests for cognitive impairment have shown that approximately 10% of older adults with myeloma screen positive for impairment[60] and scores worsen slightly after induction.[74] In a quality-of-life analysis of patients enrolled in the MAIA study,[49] 49.1% of patients treated with lenalidomide/dexamethasone and 57.3% of patients treated with daratumumab/lenalidomide/dexamethasone experienced worsening of self-reported cognitive functioning at any point while receiving treatment, though the duration, persistence, and functional impact of these changes are not reported.[75] There is much work to be done to examine cognition in older adults with myeloma longitudinally and identify those at greater risk for cognitive decline.

Summary

Older adults with myeloma now have a number of therapeutic options that are relatively well-tolerated, and the number of older adults who are untreated is thankfully declining. Incorporating assessment of frailty will aid in stratifying patients for treatment recommendations. Clinical attention to prevalent issues in older adults with myeloma, including polypharmacy, depression, cognition, and falls, may reduce risk for functional decline and adverse drug reactions, while improving the patient's quality of life.

CONCLUSION

The evidence base supporting the utility and benefit of incorporating geriatric assessment and evaluation of frailty/resilience into the treatment of older adults with hematologic malignancies is growing. This approach arguably should become the standard of care in this population. This is not to impugn the clinician's assessment but to recognize the state of the science, the same way that advances in staging and risk stratification based on the biology of the hematologic malignancies are incorporated into treatment paradigms once their prognostic and predictive significance is understood. Appreciation of the aging-associated vulnerabilities in an older adult, coupled with treatment tailored to the individual's disease characteristics, will provide the ultimate personalized care and treatment of older adults with hematologic malignancies.

AFFILIATIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Rubenstein LZ, Stuck AE, Siu AL, et al. Impacts of Geriatric Evaluation and Management Programs on Defined Outcomes: Overview of the Evidence. Hoboken, NJ: John Wiley & Sons; 1991;8S-16S; discussion 17S–18S.
2. Stuck AE, Siu AL, Wieland GD, et al. Comprehensive geriatric assessment: a meta-analysis of controlled trials. Lancet. 1993;342:1032-1036.
3. Ellis G, Gardner M, Tsiachristas A, et al. Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev. 2017;9:CD006211.
4. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol. 2014;32:2595-2603.
5. Mohile SG, Epstein RM, Hurria A, et al. Communication with older patients with cancer using geriatric assessment: a cluster-randomized clinical trial from the National Cancer Institute Community Oncology Research Program. JAMA Oncol. 2020;6:196-204.
6. Mohile S, Mohamed M, Culacova E. A geriatric assessment (GA) intervention to reduce treatment toxicity in older patients with advanced cancer: a University of Rochester Cancer Center NCI community oncology research program cluster randomized clinical trial (CRCT). J Clin Oncol. 2020;38 (suppl; abstr 12009).
7. Rodríguez-Mañas L, Féart C, Mann G, et al; FOD-CC group (Appendix 1). Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci. 2013;68:62-67.

8. Buta BJ, Walston JD, Godino JG, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev. 2016;26:53-61.
9. Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-M156.
10. Cohen HJ, Smith D, Sun CL, et al; Cancer and Aging Research Group. Frailty as determined by a comprehensive geriatric assessment-derived deficit-accumulation index in older patients with cancer who receive chemotherapy. Cancer. 2016;122:3865-3872.
11. Derman BA, Kordas K, Ridgeway J, et al. Results from a multidisciplinary clinic guided by geriatric assessment before stem cell transplantation in older adults. Blood Adv. 2019;3:3488-3498.
12. Ringdén O, Horowitz MM, Gale RP, et al. Outcome after allogeneic bone marrow transplant for leukemia in older adults. JAMA. 1993;270:57-60.
13. D'Souza A, Fretham C, Lee SJ, et al. Current use of and trends in hematopoietic cell transplantation in the United States. Biol Blood Marrow Transplant. 2020; 26:e177-e182.
14. Muffly L, Pasquini MC, Martens M, et al. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. Blood. 2017;130:1156-1164.
15. Ringdén O, Boumendil A, Labopin M, et al. Outcome of allogeneic hematopoietic stem cell transplantation in patients age >69 years with acute myelogenous leukemia: on behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2019; 25:1975-1983.
16. Heidenreich S, Ziagkos D, de Wreede LC, et al. Allogeneic stem cell transplantation for patients age ≥ 70 years with myelodysplastic syndrome: a retrospective study of the MDS Subcommittee of the Chronic Malignancies Working Party of the EBMT. Biol Blood Marrow Transplant. 2017;23:44-52.
17. Mishra A, Preussler JM, Al-Mansour Z, et al. Transplant physicians' attitudes on candidacy for allogeneic hematopoietic cell transplantation (HCT) in older patients: the need for a standardized geriatric assessment (GA) tool. Biol Blood Marrow Transplant. 2020;26:S45-S46.
18. Herold T, Rothenberg-Thurley M, Grunwald VV, et al. Validation and refinement of the revised 2017 European LeukemiaNet genetic risk stratification of acute myeloid leukemia. Leukemia. 2020;34:3161-3172.
19. Vasu S, Kohlschmidt J, Mrózek K, et al. Ten-year outcome of patients with acute myeloid leukemia not treated with allogeneic transplantation in first complete remission. Blood Adv. 2018;2:1645-1650.
20. Lin RJ, Hilden PD, Elko TA, et al. Burden and impact of multifactorial geriatric syndromes in allogeneic hematopoietic cell transplantation for older adults. Blood Adv. 2019;3:12-20.
21. Takekiyo T, Dozono K, Mitsuishi T, et al. Recovery of physical function and quality of life in patients undergoing hematopoietic stem cell transplantation: a 1-year follow-up. Bone Marrow Transplant. 2016;51:1127-1130.
22. Jones LW, Devlin SM, Maloy MA, et al. Prognostic importance of pretransplant functional capacity after allogeneic hematopoietic cell transplantation. Oncologist. 2015;20:1290-1297.
23. Nakamura MN, Corey Cutler MMF. A multi-center biologic assignment trial comparing reduced intensity allogeneic hematopoietic cell transplantation to hypomethylating therapy or best supportive care in patients aged 50-75 with advanced myelodysplastic syndrome: Blood and Marrow Transplant Clinical Trials Network Study. Blood. 2020;136(suppl 1):19-21.
24. Ustun C, Le-Rademacher J, Wang H-L, et al. Allogeneic hematopoietic cell transplantation compared to chemotherapy consolidation in older acute myeloid leukemia (AML) patients 60-75 years in first complete remission (CR1): an alliance (A151509), SWOG, ECOG-ACRIN, and CIBMTR study. Leukemia. 2019; 33:2599-2609.
25. Jayani R, Rosko A, Olin R, et al. Use of geriatric assessment in hematopoietic cell transplant. J Geriatr Oncol. 2020;11:225-236.
26. Muffly LS, Boulukos M, Swanson K, et al. Pilot study of comprehensive geriatric assessment (CGA) in allogeneic transplant: CGA captures a high prevalence of vulnerabilities in older transplant recipients. Biol Blood Marrow Transplant. 2013;19:429-434.
27. Huang L-W, Sheng Y, Andreadis C, et al. Functional status as measured by geriatric assessment predicts inferior survival in older allogeneic hematopoietic cell transplantation recipients. Biol Blood Marrow Transplant. 2020;26:189-196.
28. Olin RL, Fretham C, Pasquini MC, et al. Geriatric assessment in older alloHCT recipients: association of functional and cognitive impairment with outcomes. Blood Adv. 2020;4:2810-2820.
29. Muffly LS, Kocherginsky M, Stock W, et al. Geriatric assessment to predict survival in older allogeneic hematopoietic cell transplantation recipients. Haematologica. 2014;99:1373-1379.
30. Derman BA, Kordas K, Molloy E, et al. Recommendations and outcomes from a geriatric assessment guided multidisciplinary clinic prior to autologous stem cell transplant in older patients. J Geriatr Oncol. 2020;S1879-4068(20)30491-4. Epub 2020 Nov 5.
31. Nawas MT, Andreadis C, Martin TG, et al. Limitation in patient-reported function is associated with inferior survival in older adults undergoing autologous hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2019;25:1218-1224.
32. Mohile SG, Dale W, Somerfield MR, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol. 2018;36:2326-2347.
33. Li D, Sun C-L, Kim H, et al. Geriatric assessment-driven intervention (GAIN) on chemotherapy toxicity in older adults with cancer: a randomized controlled trial. J Clin Oncol. 2020;38(15 suppl):12010.
34. Soo W-K, King M, Pope A. Integrated geriatric assessment and treatment (INTEGERATE) in older people with cancer planned for systemic anticancer therapy. J Clin Oncol. 2020;38 (suppl; abstr 12011).

35. Presley CJ, Krok-Schoen JL, Wall SA, et al. Implementing a multidisciplinary approach for older adults with cancer: geriatric oncology in practice. BMC Geriatr. 2020;20:231-239.
36. Wall SA, Huang Y, Keiter A. Increasing number of geriatric assessment-identified deficits associated with non-receipt of transplant among older adults. Transplant Cellular Ther. 2021;27:S437-S438.
37. Szewczyk N, Neumann JL, Kruse B, et al. Experience with applying and improving feasibility of an enhanced recovery model for allogenic stem cell transplant patients aged 65 and older. Biol Blood Marrow Transplant. 2020;25:S432.
38. Jacobsen PB, Le-Rademacher J, Jim H, et al. Exercise and stress management training prior to hematopoietic cell transplantation: Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0902. Biol Blood Marrow Transplant. 2014;20:1530-1536.
39. Liang Y, Zhou M, Wang F, et al. Exercise for physical fitness, fatigue and quality of life of patients undergoing hematopoietic stem cell transplantation: a meta-analysis of randomized controlled trials. Jpn J Clin Oncol. 2018;48:1046-1057.
40. Wood WA, Weaver M, Smith-Ryan AE, et al. Lessons learned from a pilot randomized clinical trial of home-based exercise prescription before allogeneic hematopoietic cell transplantation. Supportive Care Cancer. 2020;28:5291–5298.
41. Persoon S, ChinAPaw MJM, Buffart LM, et al. Randomized controlled trial on the effects of a supervised high intensity exercise program in patients with a hematologic malignancy treated with autologous stem cell transplantation: results from the EXIST study. PLoS One. 2017;12:e0181313.
42. El-Jawahri A, Traeger L, Greer JA, et al. Effect of inpatient palliative care during hematopoietic stem-cell transplant on psychological distress 6 months after transplant: results of a randomized clinical trial. J Clin Oncol. 2017;35:3714-3721.
43. Turesson I, Bjorkholm M, Blimark CH, et al. Rapidly changing myeloma epidemiology in the general population: Increased incidence, older patients, and longer survival. Eur J Haematol. 2018;101:237-244.
44. Fakhri B, Fiala MA, Tuchman SA, et al. Undertreatment of older patients with newly diagnosed multiple myeloma in the era of novel therapies. Clin Lymphoma Myeloma Leuk. 2018;18:219-224.
45. Mian HS, Seow H, Wildes TM, et al. Disparities in treatment patterns and outcomes among younger and older adults with newly diagnosed multiple myeloma: a population-based study. J Geriatr Oncol. 2020;359:906.
46. Fiala MA, Foley NC, Zweegman S, et al. The characteristics, treatment patterns, and outcomes of older adults aged 80 and over with multiple myeloma. J Geriatr Oncol. 2020;11:1274-1278.
47. Giri S, Aryal MR, Yu H, et al. Efficacy and safety of frontline regimens for older transplant-ineligible patients with multiple myeloma: a systematic review and meta-analysis. J Geriatr Oncol. 2020;11:1285-1292.
48. Mateos M-V, Dimopoulos MA, Cavo M, et al; ALCYONE Trial Investigators. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med. 2018;378:518-528.
49. Facon T, Kumar S, Plesner T, et al; MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med. 2019; 380:2104-2115.
50. Palumbo A, Bringhen S, Larocca A, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival. J Clin Oncol. 2014;32:634-640.
51. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017; 389:519-527.
52. Facon T, Dimopoulos MA, Meuleman N, et al. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial. Leukemia. 2020;34:224-233.
53. Murillo A, Cronin AM, Laubach JP, et al. Performance of the International Myeloma Working Group myeloma frailty score among patients 75 and older. J Geriatr Oncol. 2019;10:486-489.
54. Isaacs A, Fiala M, Tuchman S, et al. A comparison of three different approaches to defining frailty in older patients with multiple myeloma. J Geriatr Oncol. 2020; 11:311-315.
55. Cook G, Larocca A, Facon T, et al. Defining the vulnerable patient with myeloma-a frailty position paper of the European Myeloma Network. Leukemia. 2020; 34:2285-2294.
56. Larocca A, Salvini M, De Paoli L, et al. Efficacy and feasibility of dose/schedule-adjusted Rd-R vs. continuous Rd in elderly and intermediate-fit newly diagnosed multiple myeloma (NDMM) patients: RV-MM-PI-0752 Phase III Randomized Study. Blood. 2018;132(suppl 1):305.
57. Stege CAM, Nasserinejad K, Levin M-D, et al. Efficacy and tolerability of ixazomib, daratumumab and low dose dexamethasone (IDd) in unfit and frail newly diagnosed multiple myeloma (NDMM) patients; first interim safety analysis of the phase II HOVON 143 Study. Blood. 2018;132(suppl 1):596.
58. Kumar V, Ailawadhi M, Dutta N, et al. Trends in early mortality from multiple myeloma: a population-based analysis. Clin Lymphoma Myeloma Leuk. 2020;70:7.
59. Covut F, Driscoll JJ, Cooper B, et al. Racial and age-related disparities in early mortality affect the outcomes of multiple myeloma patients. Leukemia. 2021; 35:250-254.
60. Wildes TM, Tuchman SA, Klepin HD, et al. Geriatric assessment in older adults with multiple myeloma. J Am Geriatr Soc. 2019;67:987-991.
61. Mian H, Fiala M, Wildes TM. Adherence to lenalidomide in older adults with newly diagnosed multiple myeloma. Clin Lymphoma Myeloma Leuk. 2020; 20:98-104.e1.

62. Sweiss K, Calip GS, Wirth S, et al. Polypharmacy and potentially inappropriate medication use is highly prevalent in multiple myeloma patients and is improved by a collaborative physician-pharmacist clinic. J Oncol Pharm Pract. 2020;26:536-542.

63. Alobaidi A, Nabulsi NA, Talon B, et al. Depressive symptoms, mental health-related quality of life, and survival among older patients with multiple myeloma. Supportive Care Cancer. 2020;28:4097–4106.

64. Kim SJ, Kang D, Park Y, et al. Impact of depression on adherence to lenalidomide plus low-dose dexamethasone in patients with relapsed or refractory myeloma. Supportive Care Cancer. Epub 2021 Feb 11.

65. Akechi T, Okuyama T, Uchida M, et al. Factors associated with suicidal ideation in patients with multiple myeloma. Jpn J Clin Oncol. 2020;50:1475-1478.

66. Mian HS, Pond GR, Wildes TM, et al. Symptom burden in transplant ineligible patients with newly diagnosed multiple myeloma: a population-based cohort study. Haematologica. Epub 2020 Dec 23.

67. Lamers J, Hartmann M, Goldschmidt H, et al. Psychosocial support in patients with multiple myeloma at time of diagnosis: who wants what? Psychooncology. 2013;22:2313-2320.

68. Wildes TM, Fiala MA. Falls in older adults with multiple myeloma. Eur J Haematol. 2018;100:273-278.

69. Ward PR, Wong MD, Moore R, et al. Fall-related injuries in elderly cancer patients treated with neurotoxic chemotherapy: a retrospective cohort study. J Geriatr Oncol. 2014;5:57-64.

70. Gewandter JS, Fan L, Magnuson A, et al. Falls and functional impairments in cancer survivors with chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study. Supportive Care Cancer. 2013;21:2059–2066.

71. Tofthagen C, Overcash J, Kip K. Falls in persons with chemotherapy-induced peripheral neuropathy. Supportive Care Cancer. 2012;20:583–589.

72. Schoenbeck KL, Fiala MA, Wildes TM. Bortezomib in first-line therapy is associated with falls in older adults with multiple myeloma. J Geriatr Oncol. Epub 2021 Mar 6.

73. Mohammadi M, Cao Y, Glimelius I, et al. The impact of comorbid disease history on all-cause and cancer-specific mortality in myeloid leukemia and myeloma - a Swedish population-based study. BMC Cancer. 2015;15:850.

74. Roman S, Fanning SR, Chowdhury S, et al. Cognition in multiple myeloma patients. Biol Blood Marrow Transplant. 2019;25:S374-S375.

75. Perrot A, Facon T, Plesner T, et al. Health-related quality of life in transplant-ineligible patients with newly diagnosed multiple myeloma: findings from the phase III MAIA Trial. J Clin Oncol. 2021;39:227-237.

How to Treat High-Risk Myeloma at Diagnosis and Relapse

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overview

Survival in multiple myeloma has improved greatly during the past 2 decades, but this change has primarily benefited patients who have standard-risk disease. Patients with high-risk disease remain a challenge to diagnose and treat. To improve their clinical outcomes, it is imperative to develop tools to readily identify them and to provide them with the most effective available treatments. The most widely used stratification system, the revised International Staging System, incorporates serum β-2 microglobulin, albumin, lactate dehydrogenase, and high-risk chromosomal abnormalities [del(17p), t(4;14), and t(14;16)]. Recent updates have included mutational status and chromosome 1q abnormalities. Plasma cell leukemia, extramedullary disease, circulating plasma cells, renal failure, and frailty are also associated with poor outcome. The treatment approach for a newly diagnosed patient with high-risk multiple myeloma should include induction therapy, autologous stem cell transplantation if appropriate, and maintenance therapy. Triplet therapy with a proteasome inhibitor, immunomodulatory drug, and steroid, with or without an anti-CD38 antibody, should be considered for induction, along with a proteasome inhibitor and/or immunomodulatory drug for maintenance. Aiming for a deep and sustained response is important. Similar principles apply at relapse, with close monitoring of response, especially extramedullary disease and active management of side effects, so that patients can continue therapy and benefit from treatment. Immune-based therapies, including autologous CAR T-cell–based therapies and bispecific antibodies, show promising activity in relapsed disease and are being actively explored in earlier disease settings. As the prognosis for high-risk disease remains poor, the future goal for this patient group is to develop specific clinical trials to explore novel approaches and therapies efficiently.

Survival in multiple myeloma has improved substantially during the past 2 decades as a result of novel treatments. This change has primarily benefited patients with standard-risk disease, who may experience long remission periods, whereas prognosis remains poor for patients with high-risk disease. Most patients receive the same treatment regimen regardless of their underlying risk, even though it is widely known that multiple myeloma is a heterogeneous disease because of its underlying molecular variation.[1-3] It is therefore imperative to develop tools to readily identify patients with high-risk disease and to provide these patients with the most effective available treatments.

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DEFINING HIGH-RISK MULTIPLE MYELOMA

Patients with high-risk disease remain a challenge to diagnose and treat. The definition of high-risk multiple myeloma has evolved over time to incorporate both cytogenetic and clinical biomarkers. Multiple risk stratification tools have attempted to identify patients with high-risk disease, but the nonuniform application and interpretation of the biomarkers results in variable definitions of high-risk disease.[4] Stratification tools tend to split patients into three groups, although the size of each group, the progression-free survival (PFS), the overall survival (OS), and the clinical and genetic heterogeneity within groups vary with each tool.[2] This variance makes it challenging to deliver accurate prognostic information and to make effective clinical decisions for patients. Additionally, because the prognosis for high-risk disease is quite poor, the goal is to develop novel therapies targeted to this high-risk group. However, lack of consensus on which patients are defined as high risk makes it difficult to design and directly compare survival outcomes between risk-adjusted clinical trials. Therefore, it is important to establish clear guidelines on high-risk multiple myeloma features to improve overall outcomes for these patients.

The most simple risk stratification approach, the International Staging System (ISS), uses two readily available laboratory parameters: serum β-2 microglobulin and serum albumin.[5] Elevated serum β-2 microglobulin is associated with reduced renal function and high tumor volume, whereas low serum albumin levels are considered secondary to interleukin-6, various inflammatory cytokines secreted in the myeloma

PRACTICAL APPLICATIONS

- High-risk multiple myeloma remains a challenge to diagnose and to treat. It is necessary to develop tools to readily identify patients with high-risk disease and to provide them with the most effective treatments available.
- The revised International Staging System assigns risk based on serum β-2 microglobulin, serum albumin, serum lactate dehydrogenase, and high-risk chromosomal abnormalities detected by fluorescence in situ hybridization [del(17p), t(4;14), and t(14;16)]. Other important prognostic factors include mutational status and chromosome 1q abnormalities.
- Treatment of high-risk, newly diagnosed disease depends on eligibility for autologous stem cell transplantation. Treatment with a proteasome inhibitor, lenalidomide, and dexamethasone is recommended, followed by maintenance (often with a combination of an immunomodulatory drug and a proteasome inhibitor) until disease progression occurs. The addition of daratumumab to a triplet backbone can also be considered.
- The challenge to managing high-risk relapsed disease is the decrease in effectiveness and shorter durability of response with each successive line of treatment. The most effective treatments should therefore be used early rather than reserving them for later.
- Treatment options for high-risk relapsed disease include three-drug combinations with proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies. Other agents include conventional cytotoxics, anti-BCMA antibody-drug conjugates, and XPO1 inhibitors. Newer CAR T-cell therapies, bispecific antibodies, and novel small molecules look promising.

microenvironment, renal status, and general nutritional status.[6,7] ISS classifies patients into three groups (defined in Table 1), with a median OS of 62 months for stage I, 44 months for stage II, and 29 months for stage III ($p < .001$).[5] Notably, patients are well distributed between groups, with approximately one-third of patients classified as stage III and high risk. However, intragroup heterogeneity exists, which makes the ISS not ideal for the basis of a high-risk treatment decision.

The revised ISS (R-ISS) subsequently incorporated serum lactate dehydrogenase and high-risk chromosomal abnormalities detected by interphase fluorescence in situ hybridization (Table 1).[8] It defined high-risk chromosomal abnormalities as del(17p), t(4;14), and t(14;16), which are associated with more aggressive disease and shorter survival.[1] High serum lactate dehydrogenase levels are also associated with shorter survival and may reflect more aggressive disease, high proliferation rate, and/or the presence of a tumor mass, such as extramedullary and extraosseous disease.[9-11]

Notably, the inclusion of lactate dehydrogenase and high-risk chromosomal abnormalities into the R-ISS changed the risk category for a select group of patients. For 1,171 patients who were previously classified as ISS stage I or low risk, 26% had high-risk chromosomal abnormalities and/or high lactate dehydrogenase levels, which changed their risk category to R-ISS stage III or high risk in the new system. Conversely, for 715 patients with ISS stage III or high-risk disease, 57% had standard-risk chromosomal abnormalities and normal lactate dehydrogenase levels. According to the R-ISS, most patients (62%) were classified as stage II or intermediate risk. Only 10% of patients were considered R-ISS stage III.[8]

Given the suspected heterogeneity of the large R-ISS stage II category, the European Myeloma Network has recently proposed a new additive scoring system (the R2-ISS) to better risk-stratify these patients.[12] Of note, the new system also includes 1q copy number alterations, which were not included in the R-ISS and are a poor prognostic factor in newly diagnosed multiple myeloma.[13-15] The R2-ISS assigns

TABLE 1. Multiple Myeloma Staging According to ISS and R-ISS

Stage	ISS	R-ISS
I	Serum β2M $<$ 3.5 mg/L and serum albumin $\geq$ 3.5 g/dL	ISS stage I, standard-risk[a] CA by iFISH, and normal serum LDH
II	Not ISS stage I or III	Not ISS stage I or III
III	Serum β2M $\geq$ 5.5 mg/L	ISS stage III and either high-risk[b] CA by iFISH or elevated serum LDH

Abbreviations: ISS, International Staging System; R-ISS, revised International Staging System; β2M, β-2 microglobulin; CA, chromosomal abnormalities; iFISH, interphase fluorescence in situ hybridization; LDH, lactate dehydrogenase.
[a]Standard-risk CA: no high-risk CA.
[b]High-risk CA: del(17p), t(4;14), and/or t(14;16).

a prognostic value to each baseline risk feature: ISS stage II (1 point), ISS stage III (1.5 points), del(17p) (1 point), high lactate dehydrogenase (1 point), t(4;14) (1 point), and 1q copy number alterations (0.5 point). Patients are stratified into four risk groups according to the total additive score: low (0 points), low-intermediate (0.5–1 points), intermediate-high (1.5–2.5 points), and high (3–5 points). Half of the patients were considered intermediate-high risk (41.2%) or high risk (8.8%). Additionally, patients classified as stage II by R-ISS (1,372 patients) were reclassified in R2-ISS as low-intermediate risk (517 patients), intermediate-high risk (811 patients), and high risk (44 patients), thus demonstrating the heterogeneity of this large group.[12] The R2-ISS must be confirmed in other data sets, but the incorporation of recently identified prognostic factors (1q copy number alterations) and the increased delineation of intermediate-risk patients are important steps forward.

Much work has been performed to incorporate risk data obtained from more modern molecular technologies, such as next-generation sequencing, into these models. The potential prognostic significance of key myeloma gene mutations is of particular interest. To identify patients at the highest risk for early progression, the Multiple Myeloma Genome Project used a recursive partitioning model for PFS and OS to identify clinical and genomic markers associated with risk. The highest-risk patients, labeled as double-hit and representing 6.1% of all patients, had either biallelic inactivation of *TP53* or ISS stage III with *CKS1B* amplification, which is situated on chromosome 1q. Double-hit patients, compared with intermediate-risk patients, had a significantly shorter median PFS (15.4 months vs. 24.4 months; $p < .01$) and OS (20.7 months vs. not reached; $p < .01$).[4] Additionally, this analysis highlighted the need to revise existing risk stratification systems to incorporate new prognostic information only detected by these technologies. For example, although deletion of 17p (on which the *TP53* gene is located) is considered an adverse risk factor in most staging systems, its presence alone was not prognostic. Rather, biallelic inactivation of *TP53*, as opposed to wild-type or monoallelic inactivation, significantly drives prognosis ($p < .001$).[4] Similarly, gain(1q) has been associated with poor outcomes for a long time, but it is notably missing from the R-ISS.[15,16] Although the consensus is that gain(1q) is a poor prognostic factor, debate exists concerning whether high copy amplification of chromosome 1 confers additional prognostic information.[17] The analysis by the Myeloma Genome Project showed that it is important to distinguish between patients with *CKS1B* amplification (defined as ≥ 4 copies) and those with *CKS1B* gain, given worse outcomes with the former group (18-month PFS, 60% vs. 71%, $p = .06$; OS, 73% vs. 88%, $p = .08$).[4] Other groups have also looked at amp(1q) compared with gain(1q) and found no additional prognostic effect.[18,19] When possible, sequencing panels should be used to detect subtleties in genetic variables to better identify and define a more homogenous high-risk population.

Gene expression profiling can also be used to identify high-risk disease and guide therapeutic decisions for patients. GEP70, initially developed at the University of Arkansas for Medical Sciences and more recently available as MyPRS, is a 70-gene prognostic signature that assigns a risk score for patients with newly diagnosed multiple myeloma. The estimated 1-year survival was 62% for the high-risk group and 97% for the low-risk group ($p < .0001$). Notably, there was over-representation of genes from chromosome 1 in the high-risk prognostic signature. Nearly 50% of the underexpressed genes mapped to chromosome 1p, and 30% of the overexpressed genes mapped to chromosome 1q, which suggests that altered transcriptional regulation of genes mapping to chromosome 1 may contribute to disease progression.[16] The EMC-92-gene signature (marketed as SKY92 MMprofiler) is another example of gene expression profiling that identified a subset of patients (21.7%) with an OS of shorter than 2 years, regardless of transplant eligibility.[20] PROMMIS (NCT02911571) is a prospective, multicenter study that aims to measure the impact of the MMprofiler on treatment intention decisions in patients with multiple myeloma. Preliminary data show that it influenced 40% of treatment intention decisions in clinical high-risk disease and 37% in clinical standard-risk disease.[21] Although there is some crossover from the previously mentioned risk stratification systems in terms of cytogenetic risk, gene expression profiling identifies additional patients at high risk. Unfortunately, it is not widely available or routinely covered by insurance, but it can be considered as an adjunct to other risk stratification systems.

In addition to cytogenetic factors, high-risk multiple myeloma may be defined by clinical features, such as plasma cell leukemia, extramedullary disease, circulating plasma cells, renal failure, and, more recently, frailty. Plasma cell leukemia, defined by at least 2,000 circulating plasma cells/μL and 20% or more plasma cells, is the most aggressive variant of clonal plasma cell disorders. Even in this era of novel agents, plasma cell leukemia carries an extremely poor prognosis. Patients who undergo autologous stem cell transplantation (ASCT) have a 4-year median PFS of 17% and an OS of 28%; similarly, patients who undergo allogeneic SCT have a 4-year median PFS of 19% and an OS of 31%.[22-24] Extramedullary disease, defined as multiple myeloma involving soft tissue or viscera in extraosseous locations at the time of diagnosis, has been shown to be an independent prognostic factor for OS and PFS.[25,26] More recent work using functional imaging techniques (e.g., PET-CT, diffusion-weighted MRI) to assess the extent of myeloma involvement has suggested that, in addition to the site of

disease, the number, size, and activity of focal lesions have prognostic significance.[27,28] High levels of circulating plasma cells ($\geq$ 5 cells/μL) have been known for many years to be a strong, independent, high-risk factor associated with shorter PFS and OS.[29,30] However, the achievement of negative status for minimal residual disease (MRD) can improve poor prognosis in these patients (3-year PFS: 68% MRD negative vs. 32% MRD positive).[31] Renal failure is commonly seen in patients with newly diagnosed multiple myeloma; up to 40% of patients present with moderate or severe renal insufficiency, depending on how it is defined, and up to 10% of patients require dialysis.[32,33] Although outcomes have improved with novel therapies, severe renal impairment (creatinine clearance $<$ 30 mL/min) remains associated with an increased risk of treatment-related toxicity and early death.[32] Frailty, rather than the patient's chronologic age or performance status, has recently been recognized as a high-risk factor. The International Myeloma Working Group proposed a frailty scoring system based on the patient's age, comorbidities, and functional status. It found that frailty is an independent predictor of survival, disease progression, nonhematologic adverse events, and treatment discontinuation regardless of ISS staging, cytogenetic abnormalities, and type of treatment.[34] Additional work in this area has confirmed that, as a patient ages, the influence of genetic risk on clinical outcome decreases.[35]

Although most risk stratification systems assess risk at time of diagnosis, high-risk features may develop later in the disease course at the time of relapse. Outcomes for relapsed disease are significantly worse for R-ISS stage III disease, with a median OS of 4.3, 2.0, and 0.9 years in R-ISS stage I, II, and III, respectively.[36] Acquisition of del(17p) at relapse is associated with a poor prognosis (median PFS, 5.4 months; OS, 18.1 months).[37] At diagnosis, the fraction of cells with del(17p) is important for determining risk and interpreting clinical trials, because the cutoff used for defining del(17p) has varied from any cell to 60%.[38-42] Biallelic inactivation of *TP53* has a very poor prognosis, and gene expression profiling at time of relapse can also be informative.[4,43,44]

A shorter duration of response to prior therapy is consistently a predictor of worse outcomes and can also reliably define high-risk disease. Indeed, the durability, rather than depth, of response was more important in a retrospective analysis of older SWOG trials.[45] Patients who experience early relapse after ASCT ($\leq$ 12 months) had a significantly shorter median OS (26.6 months vs. 90.7 months; $p < .001$).[46] In a more recent analysis of several Intergroupe Francophone du Myelome studies, 18.9% of patients experienced early relapse ($\leq$ 18 months from initial therapy).[47] Early relapse was associated with a worse OS, regardless of cytogenetic risk (HR, 4.4 overall; HR, 2.05 for high risk). Although high-risk cytogenetics, defined as del(17p) or t(4;14), were more common in patients with early relapse (33%), a substantial proportion of early-relapsing disease (67%) had standard-risk cytogenetics. The Myeloma XI trial similarly showed a shorter median OS in patients who experienced relapse within 12 months of ASCT (26 months vs. 91 months); 28.2% of these patients with early relapse had standard-risk cytogenetics.[48] Worse outcomes for patients with early relapse also occur during subsequent therapies. For example, in the ENDEAVOR trial that compared carfilzomib with bortezomib, the median PFS for early relapse ($\leq$ 1 year after the start of most recent line of therapy) was 13.9 months versus 5.7 months for carfilzomib versus bortezomib, compared with 22.2 months versus 10.2 months for the respective treatments in the late-relapse cohort.[49-51]

Similarly, the type of relapse is important for risk assessment. Intuitively, patients with a clinical relapse (e.g., worsening renal function or new bone lesions) have worse outcomes than patients with a biochemical relapse, in whom relapse manifests only as an increase in monoclonal proteins.[52,53] In the ENDEAVOR trial, the outcomes in the biochemical relapse cohort (12.6% of patients) were significantly better (median PFS not reached with carfilzomib vs. 13.7 months with bortezomib; HR, 0.462; 95% CI, 0.232–0.922) compared with patients with symptomatic relapse (17.7 months vs. 8.8 months; HR, 0.539; 95% CI, 0.439–0.662).[53] Extramedullary disease, in which there is increased frequency of *TP53* deletion at the extramedullary site, is also considered high risk.[25,54] In one case series, new extramedullary relapse occurred in 14% of patients at the time of progression, and the median OS after extramedullary relapse was short (5 months).[55] A manifestation of extramedullary disease is circulating plasma cells and, by extension, plasma cell leukemia. In an older series of secondary plasma cell leukemia, the median OS was only 1.3 months.[56] Actively relapsing disease with at least 100 circulating plasma cells per 150,000 events by flow cytometry had a median OS of 12 months, compared with 33 months in patients with fewer than 100 circulating plasma cells.[57]

The definition of risk in multiple myeloma continues to evolve as additional prognostic markers are identified and new treatments are introduced. As discussed in later sections, recent data suggest that more dynamic assessment could be considered, including response to therapy, resolution of imaging findings, and the presence of MRD. Integration of these findings into clinical practice can take time, necessitating the development of a multiparametric risk score that can easily incorporate high-risk cytogenetic and clinical features as they are identified (Fig. 1). Furthermore, it is important for providers to incorporate these biomarkers into the routine diagnostic workup to optimize treatment decisions.

TREATMENT OF HIGH-RISK, NEWLY DIAGNOSED MULTIPLE MYELOMA

The overall treatment approach for a patient with high-risk, newly diagnosed multiple myeloma should include

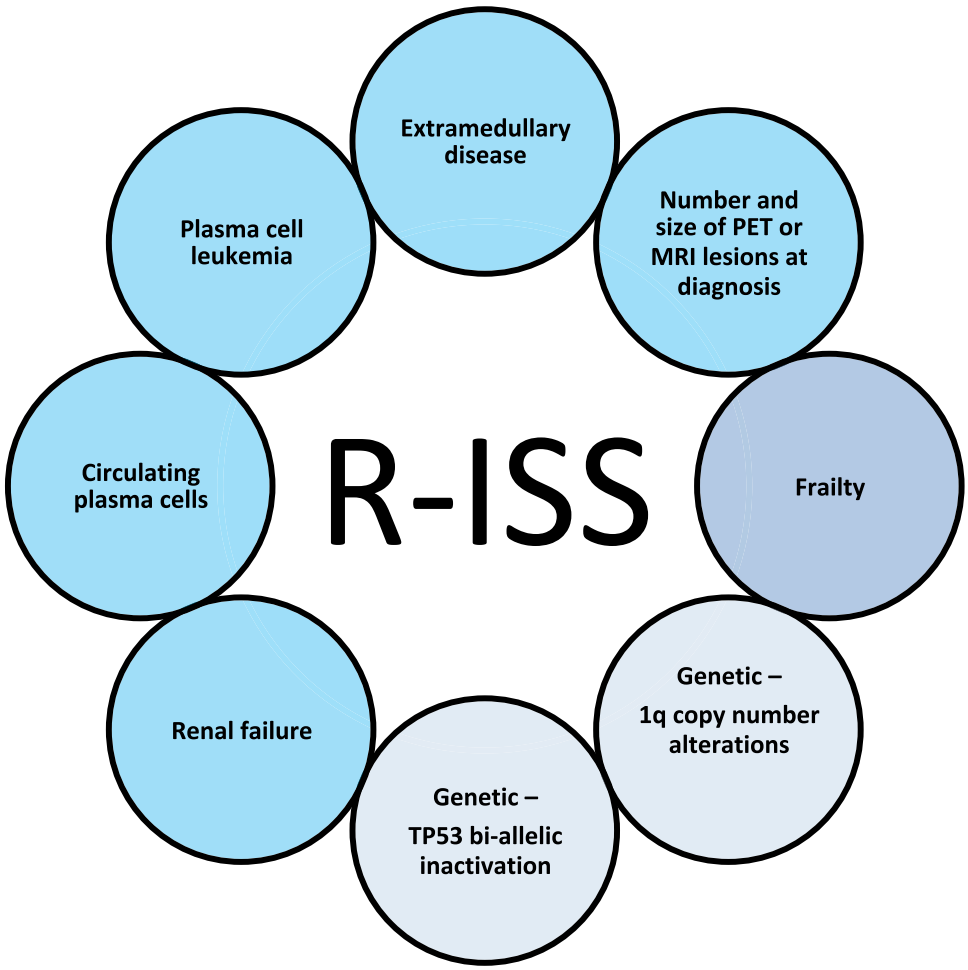

FIGURE 1. Proposed Modifications to Revised International Scoring System to Incorporate Additional High-Risk Features

induction therapy, ASCT if appropriate, and maintenance therapy, with each component being individualized to the patient. Until recently, patients with high-risk disease were included in phase III clinical trials, although they usually constituted less than 15% of all participants and were analyzed ad-hoc as a subgroup. As a result, patients with high-risk disease have historically received the same treatment as patients at standard risk with suboptimal outcomes. More recently, risk-adapted clinical trials (e.g., SWOG-1211 for high-risk disease and ENDURANCE for standard-risk disease) have been developed to help optimize therapy selection.[58,59]

The lack of randomized evidence has resulted in variability of recommendations for high-risk, newly diagnosed multiple myeloma. The National Comprehensive Cancer Network does not suggest a specific preferred regimen for high-risk, newly diagnosed multiple myeloma and recommends different regimens according to transplant eligibility.[60] The International Myeloma Working Group recommends triplet induction therapy with a proteasome inhibitor, lenalidomide, and dexamethasone, followed by ASCT, because studies have shown that lenalidomide and bortezomib can help overcome some high-risk features. The International Myeloma Working Group recommends against thalidomide use and suggests that pomalidomide can overcome some high-risk multiple myeloma features, although it is only approved in the United States for relapsed/refractory disease.[1] The mSMART (Stratification for Myeloma and Risk-Adapted Therapy) guidelines recommend VRd (bortezomib, lenalidomide, and dexamethasone) for 1 year in patients with newly diagnosed multiple myeloma and t(4;14), t(14;16), t(14;20), or del (17p) who are ineligible for transplantation, followed by bortezomib-based maintenance until progression or intolerance develops. For patients who are eligible for transplantation, four cycles of daratumumab/VRd followed by ASCT and bortezomib-based maintenance until progression or intolerance occurs are suggested, with consideration of tandem ASCT.[61]

The addition of daratumumab (an anti-CD38 monoclonal antibody) to backbone regimens has also been explored. A meta-analysis of three randomized clinical trials of newly diagnosed multiple myeloma included 358 patients with

high-risk disease (14%) treated with a daratumumab-containing regimen. The addition of daratumumab was associated with improved PFS (HR, 0.67; 95% CI, 0.47–0.95; p = .02).[62] However, prospective data on the frontline use of daratumumab in high-risk multiple myeloma are lacking. One ongoing study (IFM 2018-04; NCT03606577) is evaluating the addition of daratumumab to KRd (carfilzomib, lenalidomide, and dexamethasone) followed by consolidation therapy and tandem ASCT. Unfortunately, it will be difficult to assess the benefit of more intensive induction with a quadruplet regimen and subsequent tandem ASCT, because this is a single-arm study with no control group.

The role of elotuzumab (a SLAMF7 monoclonal antibody) has also been evaluated in high-risk, newly diagnosed multiple myeloma. SWOG-1211, a phase II randomized clinical trial for patients with high-risk, newly diagnosed multiple myeloma, evaluated the addition of elotuzumab to VRd induction and maintenance. Unfortunately, there was no improvement in PFS with elotuzumab (33.6 months vs. 31.5 months; p = .45). However, both trial arms had improved PFS compared with statistical estimates, which suggests that continuous maintenance therapy with proteasome inhibitors and immunomodulatory drugs may be beneficial in high-risk, newly diagnosed multiple myeloma.[59]

More intensive quadruplet regimens are also being evaluated in high-risk, newly diagnosed multiple myeloma. The GMMG-CONCEPT trial (NCT03104842) is an ongoing phase II nonrandomized study evaluating isatuximab with carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in high-risk, newly diagnosed multiple myeloma, defined as del(17p), t(4;14), t(14;16), or more than three copies of 1q21 and ISS stage II or III. Patients who were eligible and ineligible for transplantation were enrolled. Interim analysis for 50 patients reported an overall response rate (ORR) of 100%, with 90% achieving a very good partial response or better.[63]

With the exception of SWOG-1211, clinical trials that look specifically into high-risk, newly diagnosed multiple myeloma are lacking. Many large phase III trials still enroll a low number of patients with high-risk disease, which may affect the statistical ability to assess a survival benefit. In the SWOG S0777 trial, the addition of bortezomib to lenalidomide/dexamethasone induction therapy in patients with newly diagnosed multiple myeloma who were ineligible for transplantation showed an improvement in PFS and OS for the overall study population, but there was no statistical benefit observed for patients with high-risk cytogenetics, likely because of the limited number of patients with available data.[64,65] Similarly, other recent trials of newly diagnosed multiple myeloma (including CASSIOPEIA, ALCYONE, MAIA, and GRIFFIN) enrolled relatively low numbers of patients with high-risk disease (< 20% of the study population) and were unable to demonstrate a statistical benefit in the intervention arm for high-risk disease despite showing benefit in the overall population.[66-69] Preliminary reports of the combination of daratumumab, carfilzomib, lenalidomide, and dexamethasone (Dara-KRd) in newly diagnosed multiple myeloma showed promising MRD negativity, though longer follow-up with more data on patients with high-risk multiple myeloma will be needed.[70] Table 2 describes the clinical trials on newly diagnosed multiple myeloma that have included analysis of high-risk disease.

The benefit of ASCT has been established in multiple clinical trials; ASCT helps improve outcomes across all poor-cytogenetic groups in newly diagnosed multiple myeloma.[73,75-78] Transplant eligibility should be determined after confirming the diagnosis and before making a decision on the most appropriate initial treatment. The eligibility criteria differ among institutions and countries. In high-risk multiple myeloma, it is preferable to proceed with ASCT as part of the initial therapy for patients who are transplant eligible.[79,80] The use of tandem ASCT has also been evaluated for high-risk, newly diagnosed multiple myeloma.[1] In a meta-analysis of three phase III studies, tandem ASCT showed a survival benefit compared with single ASCT (5-year OS, 70% vs. 17%; p < .001) for 606 patients with high-risk cytogenetics whose disease failed to achieve a complete response after bortezomib-based induction.[81] The STAMINA trial, which also evaluated the use of both tandem and single ASCT, showed no difference in PFS or OS for patients with high-risk disease at 6 years with an intention-to-treat analysis. However, in the as-treated analysis, patients with high-risk disease who were treated with tandem ASCT had improved PFS compared with those who received single ASCT (43.6% vs. 26%; p = .03).[71,72] In the EMN02/HO95 trial, no difference in 5-year OS was found for patients with high-risk disease when tandem ASCT was compared with single ASCT (61.3% vs. 54.7%; p = .32), but a benefit was seen in a subgroup of patients with del(17p) (80% vs. 57%; p = .066).[73,74] It is important to highlight that the definition of high-risk cytogenetics was different between the STAMINA and EMN02/HO95 trials (Table 2).[73,77] Preliminary reports of the FORTE study indicated that the addition of ASCT to KRd resulted in higher sustained MRD negativity and better PFS when compared with KRd alone, and a benefit was noted for patients with high-risk cytogenetics.[82]

Maintenance therapy, preferably with bortezomib, after induction therapy or ASCT is recommended for high-risk, newly diagnosed multiple myeloma. Bortezomib maintenance administered every other week after ASCT demonstrated improved OS compared with thalidomide maintenance.[80] Bortezomib can be given as a single agent or in combination with lenalidomide and dexamethasone (i.e., VRd). Combining a proteasome inhibitor with an

TABLE 2. Outcomes of Patients in Selected Trials in High-Risk, Newly Diagnosed Multiple Myeloma

Trial	Regimen	Design	Study Definition of High Risk	No. of High-Risk Patients (%)	Primary Study Endpoint	Results for High-Risk Patients
SWOG-1211[59]	Elotuzumab-VRd vs. VRd	Phase II, only high-risk patients, transplant ineligible	High-risk gene expression profile, t(14;16), t(14;20), del(17p), amp(1q21), primary PCL, or elevated serum LDH ($\geq 2 \times$ ULN)	100 (100)	PFS	31.5 vs. 33.6 months, p = .45
SWOG S0777[64,65]	VRd vs. Rd	Phase III, transplant ineligible	t(4;14), t(14;16), or del(17p)	44 (8)	PFS	38 vs. 16 months, p = .19
ALCYONE[67]	Dara-VMp vs. VMp	Phase III, transplant ineligible	t(4;14), t(14;16), or del(17p)	98 (14)	PFS	18 vs. 18.1 months, not significant
MAIA[68]	Dara-Rd vs. Rd	Phase III, transplant ineligible	t(4;14), t(14;16), or del(17p)	92 (12)	PFS	Not estimable, not significant
CASSIOPEIA[66]	Dara-VTd vs. VTd	Phase III, transplant eligible	t(4;14) or del(17p)	168 (15)	sCR at 100 days post-ASCT	24% vs. 28%, not significant
GRIFFIN[69]	Dara-VRd vs. VRd	Phase II, transplant eligible	t(4;14), t(14;16), or del(17p)	30 (14)	sCR at end of post-ASCT consolidation	18.8% vs. 30.8%, not significant
STAMINA[71,72]	ASCT + len maintenance vs. ASCT + VRd consolidation + len maintenance vs. tandem ASCT + len maintenance	Phase III, transplant eligible	β2M > 5.5 mg/L, t(4;14), t(14;20), t(14;16), del(17p), del(13) detected by SC only, or aneuploidy	223 (29)	PFS at 38 months	57.6% vs. 61.6% vs. 62.9%, p value unavailable
EMN02/ HO95[73,74]	VCD, followed by VMp vs. ASCT (single or tandem)	Phase III, transplant eligible	t(4;14), t(14;16), or del(17p)	225 (19)	PFS	20.3 vs. 37.3 months, HR 0.63 (95% CI, 0.46-0.88)

Abbreviations: VRd, bortezomib, lenalidomide, dexamethasone; PCL, plasma cell leukemia; LDH, lactate dehydrogenase; ULN, upper limit of normal; PFS, progression-free survival; Rd, lenalidomide, dexamethasone; Dara, daratumumab; VMp, bortezomib, melphalan, prednisone; VTd, bortezomib, thalidomide, dexamethasone; sCR, stringent complete response; ASCT, autologous stem cell transplantation; len, lenalidomide; β2M, β-2 microglobulin; SC, standard cytogenetics; VCD, bortezomib, cyclophosphamide, dexamethasone; HR, hazard ratio.

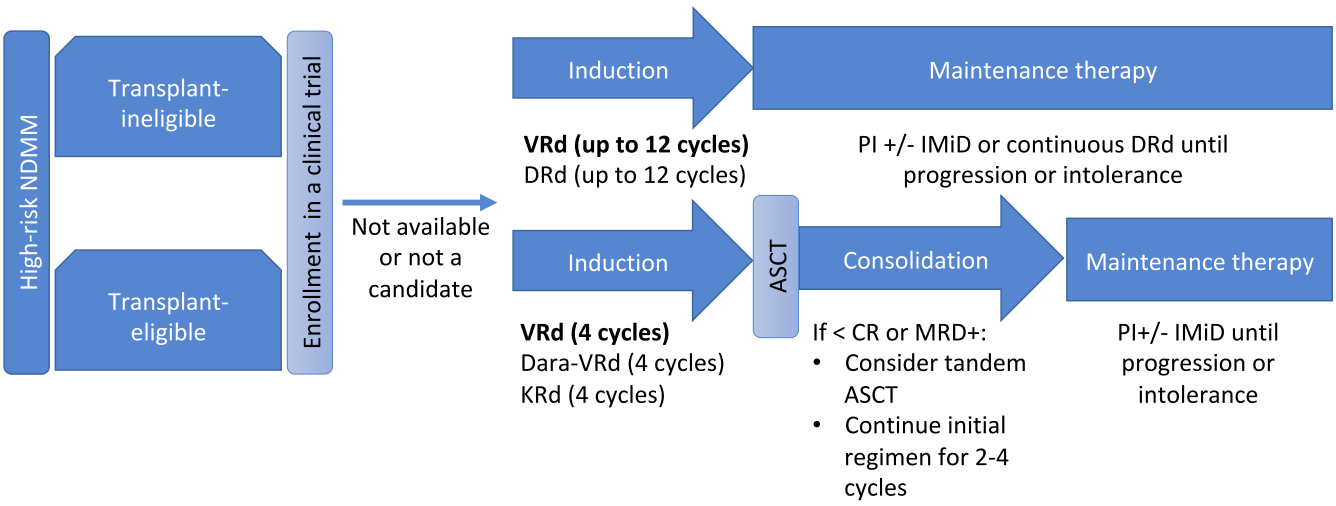

FIGURE 2. Treatment Approach for Patients With High-Risk, Newly Diagnosed Multiple Myeloma

Abbreviations: VRd, bortezomib, lenalidomide, dexamethasone; DRd, daratumumab, lenalidomide, dexamethasone; Dara, daratumumab; KRd, carfilzomib, lenalidomide, dexamethasone; ASCT, autologous stem cell transplantation; CR, complete response; PI, proteasome inhibitor; IMiD, immunomodulatory drug.

immunomodulatory drug as a maintenance approach for patients with high-risk multiple myeloma was beneficial in many previous reports.[83-85] For example, in a single-institution study of 45 patients with high-risk cytogenetics or primary plasma cell leukemia, VRd as a maintenance/consolidation regimen after ASCT led to a median PFS of 32 months and a 3-year OS of 93%.[86] Although oral ixazomib has been beneficial as maintenance therapy, there was no statistical improvement in PFS with its use in high-risk disease after ASCT.[87] An approach for the management of high-risk, newly diagnosed multiple myeloma is summarized in Fig. 2.

The role of immune-based therapies, which were previously only studied in the relapsed/refractory setting, is now gaining interest in high-risk, newly diagnosed multiple myeloma, and these therapies may offer some promising results. Early-phase studies of autologous CAR T-cell therapy in this disease are ongoing. The KARMMA-4 trial (NCT04196491) is a phase I study investigating the role of idecabtagene vicleucel (ide-cel, bb2121), a CAR T-cell therapy that targets BCMA (i.e., B-cell maturation antigen).[88] BCMA is a transmembrane protein that plays a key role in B-cell proliferation and survival as well as maturation and differentiation into plasma cells.[89] Cohort E in the CARTITUDE-2 trial (NCT04133636) will investigate the role of ciltacabtagene autoleucel (cilta-cel), another CAR T-cell therapy targeting BCMA, in high-risk, newly diagnosed multiple myeloma after promising results in the relapsed/refractory setting.[90] As current frontline therapy for high-risk, newly diagnosed multiple myeloma continues to yield poor outcomes, the design and development of clinical trials enriched for patients with high-risk, newly diagnosed multiple myeloma to prospectively study novel therapies and drug combinations are increasing, and the need for these trials is becoming more pressing.

Given the heterogeneity of high-risk multiple myeloma, it is important to consider various patient- and disease-related factors when a treatment plan is established or a change in therapy is required (Table 3). Some examples include patients with poor performance status, frailty, renal insufficiency, extramedullary disease, or plasma cell leukemia.

For all patients with high-risk features, every effort should be made to provide the therapies with the best evidence (triplet-based therapy) when possible. For patients with frailty, a lower dose of lenalidomide and dexamethasone should be considered. If parenteral administration is not possible, ixazomib can be considered instead of bortezomib. For patients presenting with acute renal failure secondary to light-chain cast nephropathy, regimens that act rapidly and can be used safely without major dose adjustments are preferred. For example, lenalidomide should be avoided in the acute stages, because dose reduction is required, and a bortezomib-based doublet or triplet therapy (dexamethasone with or without cyclophosphamide) is preferred.[91,92] There is also some evidence for adding plasmapheresis to bortezomib-based therapy.[93]

For patients who present with extramedullary disease or plasma cell leukemia, rapid disease control with the use of bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (VDT-PACE) is preferable.[84] This combination is usually followed by ASCT and maintenance therapy with a combination of proteasome inhibitors and immunomodulatory drugs. Other initial treatment options that can be considered include bortezomib-based regimens with dexamethasone and either lenalidomide,

TABLE 3. Considerations in Special Scenarios in Patients With High-Risk, Newly Diagnosed Multiple Myeloma

Special Scenarios	Considerations
Patient Related	
Frail patients or poor PS	Geriatric assessment should be performed (age, PS, and frailty do not equate).
	Triplet regimen is better than doublet regimen and should be considered when possible.
	Reconsider switching to a triplet regimen if a doublet regimen was initially chosen and the patient's condition allows.
	Dose attenuation is usually associated with better tolerance. Decrease lenalidomide dose to 15 mg daily (instead of 25 mg) and dexamethasone dose to 20 mg weekly (instead of 40 mg). Additional dose adjustments should be considered according to individual patient needs.
	ASCT after induction therapy is recommended if frailty/PS improves.
	If patient is not eligible for transplantation, consider continuous maintenance with a PI and/or IMiD.
Acute renal failure	Consider initial plasmapheresis.
	Initial therapy with bortezomib-based regimen (VCD) is preferred.
	Take care with drugs that require dose reductions (e.g., lenalidomide).
	Patients should be assessed for ASCT after induction therapy.
Disease Related	
Plasma cell leukemia or extramedullary disease	Initial therapy with VDT-PACE is preferable.
	ASCT after induction therapy is recommended.
	If patient is not eligible for transplantation, consider continuous maintenance with a PI and/or IMiD.

Abbreviations: PS, performance status; ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug; VCD, bortezomib, cyclophosphamide, dexamethasone; VDT-PACE, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide.

cyclophosphamide, or doxorubicin.[94-96] The role of daratumumab is under investigation in this patient group.

TREATMENT OF HIGH-RISK RELAPSED/REFRACTORY MULTIPLE MYELOMA

The concepts that apply to the management of high-risk relapsed disease are similar to those for relapsed disease in general. The challenges of decreasing effectiveness and shorter durability of response with each successive line of treatment build the case for using the most effective treatments early, rather than reserving them for later.[97,98] The importance of this approach is magnified in high-risk disease, in which patient attrition is high. Responses in high-risk disease generally parallel those obtained in standard-risk disease but to a lesser extent in terms of depth and durability of response.

At this time, no regimen is more uniquely suited than another regimen for high-risk disease. Similar to standard-risk disease, treatment regimens at the time of relapse generally include an anti-CD38 monoclonal antibody (daratumumab or isatuximab), carfilzomib, and/or pomalidomide. In the United States, patients are generally on lenalidomide maintenance at the time of relapse and therefore have disease that is refractory to lenalidomide. With this background, multiple triplet regimen options may be considered (Table 4). We can extrapolate from several randomized trials: anti-CD38 antibody with pomalidomide and dexamethasone (daratumumab in APOLLO or isatuximab in ICARIA-MM); anti-CD38 antibody with carfilzomib (daratumumab in CANDOR or isatuximab in IKEMA); daratumumab with bortezomib and dexamethasone in CASTOR; pomalidomide with bortezomib and dexamethasone in OPTIMISMM; daratumumab with lenalidomide and dexamethasone in POLLUX; carfilzomib with lenalidomide and dexamethasone in ASPIRE; and elotuzumab with pomalidomide and dexamethasone in ELOQUENT-3.[42,99-109]

Several practical improvements, such as the availability of subcutaneous daratumumab, have greatly improved the patient experience.[112] We are moving toward weekly carfilzomib dosing based on the ARROW study (e.g., in combination with daratumumab).[113,114] The regimen of carfilzomib, pomalidomide, and dexamethasone can also be useful.[115] The EMN011/HO114 trial evaluated this combination in patients with relapsed disease after participation in the EMN02/HO95 trial.[116] This trial evaluated a higher dose of carfilzomib (36 mg/m^2 twice weekly) than in the prior phase I study and showed an ORR of 87% and a median PFS of 18 months. Because of cardiac adverse events noted with carfilzomib dosing at 70 mg/m^2 in

TABLE 4. Outcomes by Cytogenetic Risk in Selected Trials in Relapsed Disease

Trial (Regimen)	Subset[a]	No. of Patients		PFS (months)		HR (p value or 95% CI)	ORR (%)		Lenalidomide Refractory (%)	Median (range) No. of Prior Treatment Lines
		Novel	Control	Novel	Control		Novel	Control		
BOSTON[110,111] (SVd vs. Vd)	del(17p), 10%	21	16	12.22	5.91	0.38 (p = .008)	76.2	37.5	[b]	2 (1–3)
	t(4;14)	22	27	13.24	8.33	0.7 (p = .18)	90.9	74.1		
	t(14;16)	7	11	4.57	11.89	1.46 (p = .75)	85.7	54.5		
	amp(1q21)	43	39	12.91	8.15	0.63 (p = .07)	76.7	61.5		
	High risk	70	71	12.91	8.61	0.73 (0.47–1.14)	78.6	57.7		
	Standard risk	125	136	16.62	9.46	0.61 (0.42–0.88)	75.2	64.7		
	All	195	207	13.93	9.46	0.7 (0.53–0.93)	76.4	62.3		
IKEMA[104] (isa-Kd vs. Kd)	High risk	42	31			0.724 (0.361–1.451)			32.8	2 (1–4)
	Standard risk	114	77			0.44 (0.266–0.728)				
	All	179	123	NR	19.15	0.531 (0.318–0.889)	86.6	82.9		
CANDOR[102,103] (dara-Kd vs. Kd)	High risk	48	26	15.6	5.6	0.49 (0.26–0.92)			33	2 (1–3)
	Standard risk	107	56	NR	16.6	0.54 (0.32–0.91)				
	All	312	154	28.6	15.2	0.59 (0.45–0.78)	84	75		
APOLLO[99] (dara-Pd vs. Pd)	High risk	39	35			0.85 (0.49–1.44)			80	2 (1–5)
	Standard risk	64	73			0.51 (0.32–0.81)				
	All	151	153	12.4	6.9	0.63 (0.47–0.85)	69	46		
ICARIA[100,101] (isa-Pd vs. Pd)	del(17p), 50%	14	23	9.1	7.4	0.76 (0.3–1.92)	50	22	92.5	3 (2–11)
	t(4;14)	12	14	7.5	2.8	0.49 (0.19–1.31)	50	7		
	High risk	24	36	7.5	3.7	0.66 (0.33–1.28)	50	16.7		
	Standard risk	103	78	11.6	7.4	0.62 (0.42–0.93)	65	42.3		
	All	154	153	11.53	6.47	0.596 (0.436–0.841)	60	35		
ELOQUENT-3[109] (elo-Pd vs. Pd)	High risk	13	14	6.5	2.5	0.52 (0.22–1.25)			87.2	3 (2–8)
	Standard risk	31	27	NR	4.9	0.56 (0.27–1.14)				
	All	60	57	10.3	4.7	0.54 (0.34–0.86)	53%	26		
CASTOR[105] (dara-Vd vs. Vd)	High risk	44	47	11.2	7.2	0.45 (0.25–0.8)	81.8	61.7	20.9[c]	2 (1–10)
	Standard risk	118	131	19.6	7	0.26 (0.18–0.37)	84.7	64.1		
	All	251	247	16.7	7.1	0.31 (0.24–0.39)	83.8	63.2		
OPTIMISMM[106] (PVd vs. Vd)	High risk	61	49			0.56 (0.35–0.9)			70	2 (1–3)
	Standard risk	137	132			0.56 (0.41–0.77)				
	All	281	278	11.2	7.1	0.61 (0.49–0.77)	82.2	50		

(Continued on following page)

TABLE 4. Outcomes by Cytogenetic Risk in Selected Trials in Relapsed Disease (Continued)

Trial (Regimen)	Subset[a]	No. of Patients		PFS (months)		HR (p value or 95% CI)	ORR (%)		Lenalidomide Refractory (%)	Median (range) No. of Prior Treatment Lines
		Novel	Control	Novel	Control		Novel	Control		
POLLUX[107] (dara-Rd vs. Rd)	High risk	28	37	22.6	10.2	0.53 (0.25–1.13)	85.2	66.7	NA[d]	1 (1–11)
	Standard risk	133	113	NR	18.5	0.3 (0.2–0.47)	94.7	82		
	All	286	283	NR	17.5	0.41 (0.31–0.53)	92.9	76.4		
ASPIRE[42,108] (KRd vs. Rd)	del(17p), 60%	13	13	24.5	11.1	NR	76.9	46.2	NA[e]	2 (1–3)
	t(4;14)	30	25	23.1	16.7	NR	80	72		
	High risk	48	52	23.1	13.9	0.703 (0.426–1.16)	79.2	59.6		
	Standard risk	147	170	29.6	19.5	0.656 (0.48–0.897)	91.2	73.5		
	All	396	396	26.3	17.6	0.69 (0.57–0.83)	87.1	66.7		
ENDEAVOR[50,51] (Kd vs. Vd)	del(17p), 20%	40	52	7.6	4.9	0.73 (0.42–1.27)	62.5	50	25.3	2 (1–3)
	t(4;14)	50	61	10.1	6.8	0.63 (0.38–1.02)	78	65.6		
	High risk	97	113	8.8	6	0.646 (0.453–0.921)	72.2	58.4		
	Standard risk	284	291	NE	10.2	0.439 (0.333–0.578)	79.2	66		
	All	464	465	18.7	9.4	0.53 (0.44–0.65)	77	63		

Abbreviations: PFS, progression-free survival; ORR, overall response rate; HR, hazard ratio; SVd, selinexor, bortezomib, dexamethasone; Vd, bortezomib, dexamethasone; NR, not reported; isa-Kd, isatuximab, carfilzomib, dexamethasone; Kd, carfilzomib, dexamethasone; dara-Kd, daratumumab, carfilzomib, dexamethasone; ; dara-Pd, daratumumab, pomalidomide, dexamethasone; Pd, pomalidomide, dexamethasone; isa-Pd, isatuximab, pomalidomide, dexamethasone; elo-Pd, elotuzumab, pomalidomide, dexamethasone; dara-Vd, daratumumab, bortezomib, dexamethasone; PVd, pomalidomide, bortezomib, dexamethasone; dara-Rd, daratumumab, lenalidomide, dexamethasone; NA, not available; KRd, carfilzomib, lenalidomide, dexamethasone; Rd, lenalidomide, dexamethasone.

[a]High risk is defined as del(17p) (with threshold not specified), t(4;14), and t(14;16), unless otherwise specified. In some trials, the threshold for del(17p) was specified, as follows: BOSTON, 10%; IKEMA, 50%; ICARIA, 50%; CASTOR and POLLUX, > 50% by next-generation sequencing; ASPIRE, 60%; ENDEAVOR 20%. BOSTON also included amplification of 1q21 (≥ 4 copies).

[b]Lenalidomide exposed, 38.3%, not refractory.

[c]Refractory as last line of therapy.

[d]Lenalidomide exposed, 17.6% not refractory.

[e]Lenalidomide exposed, 19.8%, not refractory.

combination with lenalidomide, weekly carfilzomib dosing of 56 mg/m^2 is recommended with immunomodulatory combinations.[117]

More intensive four-drug combinations are also under consideration for relapsed high-risk disease. Regimens include elotuzumab in combination with pomalidomide, bortezomib, and dexamethasone as well as daratumumab with carfilzomib, pomalidomide, and dexamethasone (KPd).[118,119] In the trial of KPd, carfilzomib was given twice weekly at doses of 20 mg/m^2 and 27 mg/m^2. For patients with a median of one prior line of treatment, the ORR was 86%, with a 24-month PFS of 76%. A similar trial of daratumumab with KPd is ongoing with weekly carfilzomib (NCT04176718).

Conventional cytotoxic drugs, such as cyclophosphamide, can play a vital part in high-risk relapsed disease. The Spanish Myeloma Group recently evaluated the addition of cyclophosphamide to weekly carfilzomib and dexamethasone in patients who had received one to three prior lines of treatment.[120] Although there was no significant difference in the overall population, a PFS benefit was noted in patients with lenalidomide-refractory disease (26.2 months vs. 9.3 months; p = .02). The Canadian Myeloma Research Group presented findings of daratumumab, cyclophosphamide, and dexamethasone with or without pomalidomide.[94,121] In the four-drug arm, the median PFS was not reached for patients who had received a median of two prior lines (including prior lenalidomide exposure) at a median follow-up of 25.3 months. Finally, in the MAMMOTH study, a retrospective analysis of disease refractory to anti-CD38 antibody, the best outcomes were observed with carfilzomib/cyclophosphamide-based therapy.[122] For patients who are experiencing an aggressive, rapid relapse (e.g., a high burden of extramedullary disease and an urgent need for cytoreduction), a salvage infusion regimen combining traditional cytotoxic drugs may be the best available option. These regimens include DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin) or VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide).[123] For patients who have had stem cells collected and deferred upfront ASCT, relapse with high-risk disease may motivate discussion to move forward with ASCT rather than delay any longer. Allogeneic SCT is also a consideration for select patients, with more benefit seen in high-risk disease, though it is important to consider that clinical trials generally exclude patients with recent allogeneic SCT.[124] Less commonly used drugs can be considered. These include bendamustine in combination with bortezomib, carfilzomib, or lenalidomide as well as the histone deacetylase inhibitor panobinostat in combination with dexamethasone and bortezomib, carfilzomib, lenalidomide, or lenalidomide and bortezomib.[125-132]

Newer, recently approved agents also play an important role in addressing high-risk disease. The STORM trial evaluated the combination of selinexor, an oral inhibitor of XPO1 (i.e., exportin 1), and dexamethasone in disease refractory to an immunomodulatory drug, proteasome inhibitor, and daratumumab.[133,134] The responses compared favorably with historical controls (ORR, 26%; median PFS, 3.7 months; median OS, 8.6 months), but gastrointestinal side effects were noted with selinexor.[135] Like other multiple myeloma treatment agents, the full potential of selinexor may be better achieved in combination, which will allow for lower, less frequent dosing of selinexor to minimize toxicity. With this in mind, the BOSTON study evaluated the addition of selinexor to bortezomib and dexamethasone in patients who had received one to three prior lines of therapy.[110,111] Selinexor and bortezomib were given weekly and showed an improvement in PFS and better tolerability compared with the STORM trial. Selinexor is currently being evaluated in the STOMP trial (NCT02343042) with various partners, such as carfilzomib, pomalidomide, and daratumumab.

As previously mentioned, BCMA is one of the newest and more promising targets in multiple myeloma. For patients with high-risk disease, therapies aimed at BCMA may represent a promising new approach. Belantamab mafodotin (belamaf), an anti-BCMA antibody-drug conjugate with the microtubule inhibitor monomethyl auristatin F, is the first approved drug to target BCMA.[136] The DREAMM-2 study, which led to its accelerated approval, evaluated belamaf in patients with prior anti-CD38 antibody therapy.[137] Patients were randomly assigned to receive 2.5 mg/kg or 3.4 mg/kg given every 3 weeks and had ORRs of 30% and 34%, respectively, and median PFS times of 2.9 and 4.9 months, respectively. As a result of ocular toxicity (a known and unusual but manageable side effect of antibody-drug conjugates), the 2.5-mg/kg dose was selected for future studies. Combinations with belamaf that may allow for less belamaf exposure to reduce toxicity are being explored. The Canadian Myeloma Research Group is evaluating belamaf with pomalidomide and dexamethasone. At a low dose of 1.92 mg/kg every 4 weeks, the median PFS was 14.1 months, and 64% achieved very good partial response or better.[138]

CAR T-cell therapy is another approach to targeting BCMA.[139] The molecule furthest along in development is ide-cel (bb2121).[88] In a pivotal phase II study for patients with three or more prior lines of therapy and prior anti-CD38 antibody, the ORR was 73%, the complete response rate was 33%, and the median PFS was 8.8 months; at the higher dose level of 450 $\times$ 10^6 cells, responses were better, with an ORR of 82%, a complete response rate of 39%, and a median PFS of 12.1 months.[140] Outcomes for patients with high-risk disease approached those for patients without these features.[141] Cilta-cel is following closely in clinical

development. For a similar patient population, recent results of the CARTITUDE-1 trial showed an ORR of 96.9%, a 2-month PFS of 76.6%, and an MRD-negativity rate of 55%.[90] Allogeneic CAR T cells, for which healthy donors provide T cells, may represent the next step forward as an off-the-shelf product.[142] Adverse events common with CAR T-cell therapy include cytokine release syndrome and neurotoxicity, which are manageable with tocilizumab and corticosteroids.

Bispecific antibodies represent another BCMA-targeted modality, with the advantage of direct access and no need to wait for engineered CAR T cells. They also have the risk of cytokine release syndrome and neurotoxicity but to a lesser degree than CAR T-cell therapy. Multiple programs for bispecific antibodies, including CC-93269, teclistamab, AMG 701, REGN5458, TNB-383B, and PF-06863135, are at varying stages of development.[143-148]

One strategy under evaluation is treatment earlier in the disease course, when therapy may be more effective because of less clonal evolution contributing to resistance and the ability to use fitter T cells.[149-151] The KARMMA-2 study (NCT03601078) is evaluating ide-cel for high-risk disease with early relapse ($\leq$ 18 months after start of initial therapy). Similarly, cohort B of the CARTITUDE-2 study is evaluating cilta-cel in patients with relapse no more than 12 months after ASCT or from start of therapy in patients who have not undergone ASCT.

For patients with high-risk disease, another approach is to identify potentially actionable molecular targets, such as t(11;14) and *BRAF* V600E mutation. Venetoclax may be an option for high-risk disease with t(11;14). The BELLINI trial evaluated the addition of venetoclax to bortezomib and dexamethasone in patients who had received one to three prior lines of treatment.[152] Unexpectedly, OS was worse in the venetoclax arm, but, in the subset with t(11;14), there was a marked PFS improvement (median, not reached vs. 9.3 months; HR, 0.09), and OS was not worse.[153] *BRAF* mutations have been reported in approximately 6% of patients with multiple myeloma.[13,150] Extramedullary disease is overrepresented (> 50%) in these patients at the time of relapse.[154] Initial case reports of BRAF inhibition with vemurafenib showed responses in 22.2% of patients, suggesting that these are driver mutations.[154-156] A study of dabrafenib and trametinib for patients with mutations in *KRAS*, *NRAS*, or *BRAF* is ongoing (NCT03091257). Extending on this theme, the Multiple Myeloma Research Foundation is leading the MyDRUG trial (NCT03732703), which is evaluating a mutation-driven approach to high-risk relapsed disease.[157]

Additional promising agents on the horizon may play a part in treating high-risk disease. Melflufen is a prodrug that is converted to melphalan by aminopeptidase N, which is found at higher levels in malignant cells. It was recently approved by the U.S. Food and Drug Administration in February 2021 on the basis of results from the HORIZON phase II study, which evaluated melflufen and dexamethasone for patients with disease refractory to pomalidomide and/or CD38 antibody and showed an ORR of 29%, including an ORR of 24% for patients with extramedullary disease.[158] Cereblon modulators, such as iberdomide (CC-220) and CC-92480, represent a new class of drugs that bind to cereblon.[159-167] Finally, additional cell surface targets under investigation include GPRC5D, targeted by the bispecific antibody talquetamab, and FcRH5, targeted by the bispecific antibody cevostamab.[168,169] Overall, these new therapies are promising, and we await additional studies on how and when to integrate these therapies into the treatment of high-risk disease.

AFFILIATIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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References

1. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016;127:2955-2962.
2. Pawlyn C, Davies FE. Toward personalized treatment in multiple myeloma based on molecular characteristics. Blood. 2019;133:660-675.
3. Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. Nat Rev Cancer. 2012;12:335-348.

4. Walker BA, Mavrommatis K, Wardell CP, et al. A high-risk, double-hit, group of newly diagnosed myeloma identified by genomic analysis. Leukemia. 2019; 33:159-170.
5. Greipp PR, San Miguel J, Durie BGM, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23:3412-3420.
6. Jacobson JL, Hussein MA, Barlogie B, et al; Southwest Oncology Group. A new staging system for multiple myeloma patients based on the Southwest Oncology Group (SWOG) experience. Br J Haematol. 2003;122:441-450.
7. Durie BGM, Kyle RA, Belch A, et al. Myeloma management guidelines: a consensus report from the scientific advisors of the International Myeloma Foundation. Hematol J Off J Eur Haematol Assoc. 2003;4:379-398.
8. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol. 2015;33:2863-2869.
9. Dimopoulos MA, Barlogie B, Smith TL, et al. High serum lactate dehydrogenase level as a marker for drug resistance and short survival in multiple myeloma. Ann Intern Med. 1991;115:931-935.
10. Terpos E, Katodritou E, Roussou M, et al. High serum lactate dehydrogenase adds prognostic value to the international myeloma staging system even in the era of novel agents. Eur J Haematol. 2010;85:114-119.
11. Barlogie B, Smallwood L, Smith T, et al. High serum levels of lactic dehydrogenase identify a high-grade lymphoma-like myeloma. Ann Intern Med. 1989; 110:521-525.
12. D'Agostino M, Lahuerta J-J, Wester R, et al. A new risk stratification model (R2-ISS) in newly diagnosed multiple myeloma: analysis of mature data from 7077 patients collected by European Myeloma Network within harmony big data platform. Presented at: 62nd ASH Annual Meeting and Exposition. San Diego, CA; 2020. Abstract 1329.
13. Walker BA, Boyle EM, Wardell CP, et al. Mutational spectrum, copy number changes, and outcome: results of a sequencing study of patients with newly diagnosed myeloma. J Clin Oncol. 2015;33:3911-3920.
14. Shah V, Sherborne AL, Walker BA, et al. Prediction of outcome in newly diagnosed myeloma: a meta-analysis of the molecular profiles of 1905 trial patients. Leukemia. 2018;32:102-110.
15. Hanamura I, Stewart JP, Huang Y, et al. Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation. Blood. 2006;108:1724-1732.
16. Shaughnessy J. Amplification and overexpression of CKS1B at chromosome band 1q21 is associated with reduced levels of p27Kip1 and an aggressive clinical course in multiple myeloma. Hematology. 2005;10(Suppl):117-126.
17. Sawyer JR, Tian E, Walker BA, et al. An acquired high-risk chromosome instability phenotype in multiple myeloma: jumping 1q syndrome. Blood Cancer J. 2019;9:62.
18. Abdallah N, Greipp P, Kapoor P, et al. Clinical characteristics and treatment outcomes of newly diagnosed multiple myeloma with chromosome 1q abnormalities. Blood Adv. 2020;4:3509-3519.
19. Locher M, Steurer M, Jukic E, et al. The prognostic value of additional copies of 1q21 in multiple myeloma depends on the primary genetic event. Am J Hematol. 2020;95:1562-1571.
20. Kuiper R, Broyl A, de Knegt Y, et al. A gene expression signature for high-risk multiple myeloma. Leukemia. 2012;26:2406-2413.
21. Hari P, Lentzsch S, Siegel DSD, et al. Prospective study to measure the impact of MMprofiler on treatment intention in newly diagnosed multiple myeloma patients (PROMMIS). J Clin Oncol. 2019;37(Suppl; abstr 8030).
22. Tuazon SA, Holmberg LA, Nadeem O, et al. A clinical perspective on plasma cell leukemia: current status and future directions. Blood Cancer J. 2021;11:23.
23. Schinke C, Boyle EM, Ashby C, et al. Genomic analysis of primary plasma cell leukemia reveals complex structural alterations and high-risk mutational patterns. Blood Cancer J. 2020;10:70.
24. Dhakal B, Patel S, Girnius S, et al. Hematopoietic cell transplantation utilization and outcomes for primary plasma cell leukemia in the current era. Leukemia. 2020;34:3338-3347.
25. Bhutani M, Foureau DM, Atrash S, et al. Extramedullary multiple myeloma. Leukemia. 2020;34:1-20.
26. Montefusco V, Gay F, Spada S, et al. Outcome of paraosseous extra-medullary disease in newly diagnosed multiple myeloma patients treated with new drugs. Haematologica. 2020;105:193-200.
27. Rasche L, Angtuaco EJ, Alpe TL, et al. The presence of large focal lesions is a strong independent prognostic factor in multiple myeloma. Blood. 2018; 132:59-66.
28. Hillengass J, Usmani S, Rajkumar SV, et al. International Myeloma Working Group consensus recommendations on imaging in monoclonal plasma cell disorders. Lancet Oncol. 2019;20:e302-e312.
29. Sanoja-Flores L, Flores-Montero J, Pérez-Andrés M, et al. Detection of circulating tumor plasma cells in monoclonal gammopathies: methods, pathogenic role, and clinical implications. Cancers (Basel). 2020;12:1499.
30. Nowakowski GS, Witzig TE, Dingli D, et al. Circulating plasma cells detected by flow cytometry as a predictor of survival in 302 patients with newly diagnosed multiple myeloma. Blood. 2005;106:2276-2279.
31. Bertamini L, Grasso M, D'Agostino M. Poor prognosis of multiple myeloma predicted by high levels of circulating plasma cells is independent from other high-risk features but is modulated by the achievement of minimal residual disease negativity. Blood. 2020;109:12-13.

32. Dimopoulos MA, Delimpasi S, Katodritou E, et al. Significant improvement in the survival of patients with multiple myeloma presenting with severe renal impairment after the introduction of novel agents. Ann Oncol. 2014;25:195-200.

33. Rana R, Cockwell P, Drayson M, et al. Renal outcome in patients with newly diagnosed multiple myeloma: results from the UK NCRI Myeloma XI trial. Blood Adv. 2020;4:5836-5845.

34. Palumbo A, Bringhen S, Mateos M-V, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood. 2015;125:2068-2074.

35. Pawlyn C, Cairns D, Kaiser M, et al. The relative importance of factors predicting outcome for myeloma patients at different ages: results from 3894 patients in the Myeloma XI trial. Leukemia. 2020;34:604-612.

36. Tandon N, Rajkumar SV, LaPlant B, et al. Clinical utility of the revised International Staging System in unselected patients with newly diagnosed and relapsed multiple myeloma. Blood Cancer J. 2017;7:e528.

37. Lakshman A, Painuly U, Rajkumar SV, et al. Impact of acquired del(17p) in multiple myeloma. Blood Adv. 2019;3:1930-1938.

38. An G, Li Z, Tai Y-T, et al. The impact of clone size on the prognostic value of chromosome aberrations by fluorescence in situ hybridization in multiple myeloma. Clin Cancer Res. 2015;21:2148-2156.

39. Thakurta A, Ortiz M, Blecua P, et al. High subclonal fraction of 17p deletion is associated with poor prognosis in multiple myeloma. Blood. 2019; 133:1217-1221.

40. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. Blood. 2007;109:3489-3495.

41. Lonial S, Vij R, Harousseau J-L, et al. Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma. J Clin Oncol. 2012;30:1953-1959.

42. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015; 372:142-152.

43. Nair B, Shaughnessy JD, Zhou Y, et al. Gene expression profiling of plasma cells at myeloma relapse from tandem transplantation trial Total Therapy 2 predicts subsequent survival. Blood. 2009;113:6572-6575.

44. Skerget S, Penaherrera D, Aldrich J, et al. Analysis of sequential patient samples from the MMRF COMMPASS study identifies a high risk progression phenotype. Blood. 2018;132(suppl; abstr 111).

45. Durie BGM, Jacobson J, Barlogie B, et al. Magnitude of response with myeloma frontline therapy does not predict outcome: importance of time to progression in Southwest Oncology Group chemotherapy trials. J Clin Oncol. 2004;22:1857-1863.

46. Kumar S, Mahmood ST, Lacy MQ, et al. Impact of early relapse after auto-SCT for multiple myeloma. Bone Marrow Transplant. 2008;42:413-420.

47. Corre J, Montes L, Martin E, et al. Early relapse after autologous transplant for myeloma is associated with poor survival regardless of cytogenetic risk. Haematologica. 2020;105:e480-e483.

48. Bygrave C, Pawlyn C, Davies F, et al. Early relapse after high-dose melphalan autologous stem cell transplant predicts inferior survival and is associated with high disease burden and genetically high-risk disease in multiple myeloma. Br J Haematol. Epub 10 Jun 2020.

49. Mateos M-V, Goldschmidt H, San-Miguel J, et al. Carfilzomib in relapsed or refractory multiple myeloma patients with early or late relapse following prior therapy: a subgroup analysis of the randomized phase 3 ASPIRE and ENDEAVOR trials. Hematol Oncol. 2018;36:463-470.

50. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016;17:27-38.

51. Chng W-J, Goldschmidt H, Dimopoulos MA, et al. Carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR. Leukemia. 2017;31:1368-1374.

52. Zamarin D, Giralt S, Landau H, et al. Patterns of relapse and progression in multiple myeloma patients after auto-SCT: implications for patients' monitoring after transplantation. Bone Marrow Transplant. 2013;48:419-424.

53. Moreau P, Siegel DS, Goldschmidt H, et al. Subgroup analysis of patients with biochemical or symptomatic relapse at the time of enrollment in the endeavor study. Blood. 2018;132(suppl; abstr 3243).

54. Usmani SZ, Heuck C, Mitchell A, et al. Extramedullary disease portends poor prognosis in multiple myeloma and is over-represented in high-risk disease even in the era of novel agents. Haematologica. 2012;97:1761-1767.

55. Pour L, Sevcikova S, Greslikova H, et al. Soft-tissue extramedullary multiple myeloma prognosis is significantly worse in comparison to bone-related extra-medullary relapse. Haematologica. 2014;99:360-364.

56. Tiedemann RE, Gonzalez-Paz N, Kyle RA, et al. Genetic aberrations and survival in plasma cell leukemia. Leukemia. 2008;22:1044-1052.

57. Gonsalves WI, Morice WG, Rajkumar V, et al. Quantification of clonal circulating plasma cells in relapsed multiple myeloma. Br J Haematol. 2014;167:500-505.

58. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 2020;21:1317-1330.

59. Usmani SZ, Hoering A, Ailawadhi S, et al. Bortezomib, lenalidomide, and dexamethasone with or without elotuzumab in patients with untreated, high-risk multiple myeloma (SWOG-1211): primary analysis of a randomised, phase 2 trial. Lancet Haematol. 2021;8:e45-e54.

60. Kumar SK, Callander NS, Adekola K, et al. Multiple myeloma, version 3.2021: NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2020; 18:1685-1717.

61. Dingli D, Ailawadhi S, Bergsagel PL, et al. Therapy for relapsed multiple myeloma: guidelines from the Mayo Stratification for Myeloma and Risk-Adapted Therapy. Mayo Clin Proc. 2017;92:578-598.

62. Giri S, Grimshaw A, Bal S, et al. Evaluation of daratumumab for the treatment of multiple myeloma in patients with high-risk cytogenetic factors: a systematic review and meta-analysis. JAMA Oncol. 2020;6:1-8.

63. Weisel K, Asemissen AM, Besemer B, et al. Depth of response to isatuximab, carfilzomib, lenalidomide, and dexamethasone (isa-KRd) in front-line treatment of high-risk multiple myeloma: interim analysis of the GMMG-CONCEPT trial. J Clin Oncol. 2020;38(suppl; abstr 8508).

64. Durie BGM, Hoering A, Sexton R, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). Blood Cancer J. 2020;10:53.

65. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017; 389:519-527.

66. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019;394:29-38.

67. Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med. 2018; 378:518-528.

68. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med. 2019;380:2104-2115.

69. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020;136:936-945.

70. Landgren O, Hultcrantz M, Lesokhin AM, et al. Weekly carfilzomib, lenalidomide, dexamethasone and daratumumab (wKRd-D) combination therapy provides unprecedented MRD negativity rates in newly diagnosed multiple myeloma: a clinical and correlative phase 2 study. Blood. 2019;134(Suppl; abstr 862).

71. Hari P, Pasquini MC, Stadtmauer EA, et al. Long-term follow-up of BMT CTN 0702 (STAMINA) of postautologous hematopoietic cell transplantation (autoHCT) strategies in the upfront treatment of multiple myeloma (MM). J Clin Oncol. 2020;38(suppl; abstr 8506).

72. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 trial. J Clin Oncol. 2019;37:589-597.

73. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. Lancet Haematol. 2020;7:e456-e468.

74. Sonneveld P, Beksac M, Van Der Holt B, et al. Consolidation treatment with VRD followed by maintenance therapy versus maintenance alone in newly diagnosed, transplant-eligible patients with multiple myeloma (MM): a randomized phase 3 trial of the European Myeloma Network (EMN02/HO95). Blood. 2020;136(suppl):46-48.

75. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003; 348:1875-1883.

76. Palumbo A, Bringhen S, Petrucci MT, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. Blood. 2004;104:3052-3057.

77. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med. 2014;371:895-905.

78. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. Lancet Oncol. 2015;16:1617-1629.

79. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. N Engl J Med. 2017; 376:1311-1320.

80. Goldschmidt H, Lokhorst HM, Mai EK, et al. Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial. Leukemia. 2018;32:383-390.

81. Cavo M, Salwender H, Rosinol L. Double vs single autologous stem cell transplantation after bortezomib-based induction regimens for multiple myeloma: an integrated analysis of patient-level data from phase III European studies. Blood. 2013;122:767.

82. Gay F, Musto P, Rota Scalabrini D, et al. Survival analysis of newly diagnosed transplant-eligible multiple myeloma patients in the randomized FORTE trial. Blood. 2020;136(suppl):35-37.

83. Joseph NS, Kaufman JL, Dhodapkar MV, et al. Long-term follow-up results of lenalidomide, bortezomib, and dexamethasone induction therapy and risk-adapted maintenance approach in newly diagnosed multiple myeloma. J Clin Oncol. 2020;38:1928-1937.

84. Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of Total Therapy 3. Br J Haematol. 2007;138:176-185.

85. Nair B, van Rhee F, Shaughnessy JD, et al. Superior results of Total Therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with VRD maintenance. Blood. 2010;115:4168-4173.

86. Nooka AK, Kaufman JL, Muppidi S, et al. Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. Leukemia. 2014;28:690-693.

87. Dimopoulos MA, Gay F, Schjesvold F, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2019;393:253-264.

88. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med. 2019;380:1726-1737.

89. Cho S-F, Anderson KC, Tai Y-T, et al. B-cell maturation antigen (BCMA) in multiple myeloma: potential uses of BCMA-based immunotherapy. Front Immunol. 2018;9:1821.

90. Madduri D, Berdeja JG, Usmani SZ, et al. CARTITUDE-1: phase 1b/2 study of ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy, in relapsed/refractory multiple myeloma. Blood. 2020;136(suppl):22-25.

91. Ludwig H, Adam Z, Hajek R, et al. Light chain-induced acute renal failure can be reversed by bortezomib-doxorubicin-dexamethasone in multiple myeloma: results of a phase II study. J Clin Oncol. 2010;28:4635-4641.

92. Sonneveld P, Schmidt-Wolf IGH, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol. 2012;30:2946-2955.

93. Burnette BL, Leung N, Rajkumar SV. Renal improvement in myeloma with bortezomib plus plasma exchange. N Engl J Med. 2011;364:2365-2366.

94. Garderet L, Kuhnowski F, Berge B, et al. Pomalidomide, cyclophosphamide, and dexamethasone for relapsed multiple myeloma. Blood. 2018;132:2555-2563.

95. Pagano L, Valentini CG, De Stefano V, et al. Primary plasma cell leukemia: a retrospective multicenter study of 73 patients. Ann Oncol. 2011;22:1628-1635.

96. Katodritou E, Terpos E, Kelaidi C, et al. Treatment with bortezomib-based regimens improves overall response and predicts for survival in patients with primary or secondary plasma cell leukemia: analysis of the Greek myeloma study group. Am J Hematol. 2014;89:145-150.

97. Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clin Proc. 2004;79:867-874.

98. Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol. 2016;175:252-264.

99. Dimopoulos M, Terpos E, Boccadoro M, et al. Apollo: phase 3 randomized study of subcutaneous daratumumab plus pomalidomide and dexamethasone (D-Pd) versus pomalidomide and dexamethasone (Pd) alone in patients (Pts) with relapsed/refractory multiple myeloma (RRMM). Blood. 2020;136:5-6.

100. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019;394:2096-2107.

101. Harrison S, Richardson P, Alegre-Amor A, et al. Efficacy of isatuximab/pomalidomide/dexamethasone in relapsed/refractory multiple myeloma : ICARIA-MM high-risk cytogenetics subgroup analysis. Clin Lymphoma Myeloma Leuk. 2019;19:E33.

102. Dimopoulos M, Quach H, Mateos M-V, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. Lancet. 2020;396:186-197.

103. Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone in relapsed or refractory multiple myeloma: updated efficacy and safety results of the phase 3 CANDOR study. Blood. 2020;136(Suppl):26-27.

104. Moreau P, Dimopoulos M, Mikhael J, Yong K, Capra M, Facon T. Isatuximab plus carfilzomib and dexamethasone vs. carfilzomib and dexamethasone in relapsed/refractory multiple myeloma (IKEMA): interim analysis of a phase I randomized, open-label study. Presented at: 62nd ASH Annual Meeting and Exposition. San Diego, CA; 2020. Abstract 2316.

105. Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018;103:2079-2087.

106. Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:781-794.

107. Dimopoulos MA, San-Miguel J, Belch A, et al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. Haematologica. 2018;103:2088-2096.

108. Avet-Loiseau H, Fonseca R, Siegel D, et al. Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma. Blood. 2016;128:1174-1180.

109. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. N Engl J Med. 2018;379:1811-1822.

110. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet. 2020;396:1563-1573.

111. Richard S, Chari A, Delimpasi S, et al. Once weekly selinexor, bortezomib, and dexamethasone (SVd) versus twice weekly bortezomib and dexamethasone (Vd) in relapsed or refractory multiple myeloma: high-risk cytogenetic risk planned subgroup analyses from the phase 3 Boston study. Blood. 2020;123(suppl): 35-36.

112. Mateos M-V, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematol. 2020;7:e370-e380.

113. Moreau P, Mateos M-V, Berenson JR, et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R. R.O.W.): interim analysis results of a randomised, phase 3 study. Lancet Oncol. 2018;19:953-964.

114. Chari A, Martinez-Lopez J, Mateos M-V, et al. Daratumumab plus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma. Blood. 2019;134:421-431.

115. Shah JJ, Stadtmauer EA, Abonour R, et al. Carfilzomib, pomalidomide, and dexamethasone for relapsed or refractory myeloma. Blood. 2015;126:2284-2290.

116. Sonneveld P, Zweegman S, Cavo M, et al. Carfilzomib, pomalidomide and dexamethasone (KPd) in patients with multiple myeloma refractory to bortezomib and lenalidomide. the EMN011 trial. Blood. 2018;132(suppl; abstr 801).

117. Biran N, Siegel D, Berdeja JG, et al. Weekly carfilzomib, lenalidomide, and dexamethasone in relapsed or refractory multiple myeloma: a phase 1b study. Am J Hematol. 2019;94:794-802.

118. Yee AJ, Laubach J, Campagnaro EL, et al. A phase II study of elotuzumab in combination with pomalidomide, bortezomib, and dexamethasone in relapsed and refractory multiple myeloma. J Clin Oncol. 2018;36(suppl; abstr 8012).

119. Jasielec J, Zonder J, Derman B, et al. Daratumumab (DARA) plus carfilzomib, pomalidomide, dexamethasone (KPd) in lenalidomide refractory multiple myeloma (MM): a multi-center MMRC study. Blood. 2020;136:50.

120. Mateos MV, Ocio E, Sureda Balari A, et al. Randomized phase 2 study of weekly carfilzomib 70 mg/m2 and dexamethasone plus/minus cyclophosphamide in relapsed and/or refractory multiple myeloma (RRMM) patients (GEM-KyCyDex). Blood. 2020;136:8-9.

121. Sebag M, Bahlis N, Venner C, et al. A randomized phase II, open label, study of daratumumab, weekly low-dose oral dexamethasone and cyclophosphamide with or without pomalidomide in patients with relapsed and refractory multiple myeloma. Blood. 2020;136(Suppl):3121.

122. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. 2019;33:2266-2275.

123. Griffin PT, Ho VQ, Fulp W, et al. A comparison of salvage infusional chemotherapy regimens for recurrent/refractory multiple myeloma. Cancer. 2015; 121:3622-3630.

124. Knop S, Engelhardt M, Liebisch P, et al. Allogeneic transplantation in multiple myeloma: long-term follow-up and cytogenetic subgroup analysis. Leukemia. 2019;33:2710-2719.

125. Ludwig H, Kasparu H, Leitgeb C, et al. Bendamustine-bortezomib-dexamethasone is an active and well-tolerated regimen in patients with relapsed or refractory multiple myeloma. Blood. 2014;123:985-991.

126. Gramatzki M, Guenther A, Offidani M, et al. Carfilzomib, bendamustine, and dexamethasone (KBd) in advanced multiple myeloma: The EMN09-trial. J Clin Oncol. 2018;36(Suppl; abstr 8019).

127. Kumar SK, Krishnan A, LaPlant B, et al. Bendamustine, lenalidomide, and dexamethasone (BRD) is highly effective with durable responses in relapsed multiple myeloma. Am J Hematol. 2015;90:1106-1110.

128. Laubach JP, Schjesvold F, Mariz M, et al. Efficacy and safety of oral panobinostat plus subcutaneous bortezomib and oral dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma (PANORAMA 3): an open-label, randomised, phase 2 study. Lancet Oncol. 2021;22:142-154.

129. Kaufman JL, Mina R, Jakubowiak AJ, et al. Combining carfilzomib and panobinostat to treat relapsed/refractory multiple myeloma: results of a Multiple Myeloma Research Consortium phase I study. Blood Cancer J. 2019;9:3.

130. Manasanch EE, Shah JJ, Lee HC, et al. Phase I/Ib study of carfilzomib and panobinostat with or without dexamethasone in patients with relapsed/refractory multiple myeloma. Haematologica. 2020;105:e242-e245.

131. Chari A, Cho HJ, Dhadwal A, et al. A phase 2 study of panobinostat with lenalidomide and weekly dexamethasone in myeloma. Blood Adv. 2017;1:1575-1583.

132. Laubach JP, Tuchman SA, Rosenblatt JM, et al. Phase 1 open-label study of panobinostat, lenalidomide, bortezomib + dexamethasone in relapsed and relapsed/refractory multiple myeloma. Blood Cancer J. 2021;11:20.

133. Tai Y-T, Landesman Y, Acharya C, et al. CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. Leukemia. 2014;28:155-165.

134. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. N Engl J Med. 2019;381:727-738.

135. Cornell R, Hari P, Tang S, et al. Overall survival of patients with triple-class refractory multiple myeloma treated with selinexor plus dexamethasone vs standard of care in MAMMOTH. Am J Hematol. 2021;96:E5-E8.

136. Tai Y-T, Mayes PA, Acharya C, et al. Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. Blood. 2014;123:3128-3138.

137. Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol. 2020;21:207-221.

138. Trudel S, McCurdy A, Sutherland H, et al. Results of a dose finding study of belantamab mafodotin (GSK2857916) in combination with pomalidomide (POM) and dexamethasone (DEX) for the treatment of relapsed/refractory multiple myeloma (RRMM). Presented at: 62nd ASH Annual Meeting and Exposition. San Diego, CA; 2020. Abstract 725.

139. Shah N, Chari A, Scott E, et al. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. Leukemia. 2020;34:985-1005.

140. Munshi NC, Anderson LD, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384:705-716.

141. Raje N, Siegel D, Jagannath S, et al. Idecabtagene vicleucel (ide-cel, bb2121) in relapsed and refractory multiple myeloma: analyses of high-risk subgroups in the KARMMA study. Presented at: 62nd ASH Annual Meeting and Exposition. San Diego, CA; 2020. Abstract 3234.

142. Mailankody S, Matous J, Liedtke M, et al. Universal: an allogeneic first-in-human study of the anti-BCMA ALLO-715 and the anti-CD52 ALLO-647 in relapsed/refractory multiple myeloma. Blood. 2020;136(suppl):24-25.

143. Costa LJ, Wong SW, Bermúdez A, et al. First clinical study of the B-cell maturation antigen (BCMA) 2+1 T cell engager (TCE) CC-93269 in patients (Pts) with relapsed/refractory multiple myeloma (RRMM): interim results of a phase 1 multicenter trial. Blood. 2019;134(suppl; abstr 143).

144. Garfall A, Usmani S, Mateos MV, et al. Updated phase 1 results of teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody in relapsed and/or refractory multiple myeloma. Blood. 2020;136(suppl):27

145. Harrison S, Minnema M, Lee HC, et al. Phase 1 first in human (FIH) study of AMG 701, an anti-B-cell maturation antigen (BCMA) half-life extended (HLE) BiTE® (bispecific T-cell engager) molecule, in relapsed/refractory (RR) multiple myeloma (MM). Blood. 2020;136(suppl):28-29.

146. Madduri D, Rosko A, Brayer J, et al. REGN5458, a BCMA x CD3 bispecific monoclonal antibody, induces deep and durable responses in patients with relapsed/refractory multiple myeloma. Blood. 2020;136(suppl):41-42.

147. Rodriguez C, D'Souza A, Shah N, et al. Initial results of a phase I study of TNB-383B, a BCMA x CD3 bispecific T-cell redirecting antibody in relapsed/refractory multiple myeloma. Blood. 2020;136(suppl):43-44.

148. Lesokhin A, Levy M, Dalovisio A, et al. Preliminary safety, efficacy, pharmacokinetics, and pharmacodynamics of subcutaneously (SC) administered PF-06863135, a B-cell maturation antigen (BCMA)-CD3 bispecific antibody in patients with relapsed/refractory multiple myeloma. Presented at: 62nd ASH Annual Meeting and Exposition. San Diego, CA; 2020. Abstract 3206.

149. Bolli N, Avet-Loiseau H, Wedge DC, et al. Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. Nat Commun. 2014;5:2997.

150. Lohr JG, Stojanov P, Carter SL, et al. Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. Cancer Cell. 2014;25:91-101.

151. Garfall AL, Dancy EK, Cohen AD, et al. T-cell phenotypes associated with effective CAR T-cell therapy in postinduction vs relapsed multiple myeloma. Blood Adv. 2019;3:2812-2815.

152. Kumar SK, Harrison SJ, Cavo M, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2020;21:1630-1642.

153. Harrison S, Cavo M, De La Rubia J, et al. T(11;14) and high BCL2 expression are predictive biomarkers of response to venetoclax in combination with bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma: biomarker analyses from the phase 3 BELLINI study. Blood. 2019; 134(suppl; abstr 142).

154. Andrulis M, Lehners N, Capper D, et al. Targeting the *BRAF* V600E mutation in multiple myeloma. Cancer Discov. 2013;3:862-869.

155. Sharman JP, Chmielecki J, Morosini D, et al. Vemurafenib response in 2 patients with posttransplant refractory *BRAF* V600E-mutated multiple myeloma. Clin Lymphoma Myeloma Leuk. 2014;14:e161-e163.

156. Raje N, Chau I, Hyman DM, et al. Vemurafenib in patients with relapsed refractory multiple myeloma harboring *BRAF*V600 mutations: a cohort of the histology-independent VE-BASKET study. JCO Precis Oncol. 2018;2:PO.18.00070.

157. Auclair D, Anderson KC, Avigan D, et al. The myeloma-developing regimens using genomics (MyDRUG) master protocol. J Clin Oncol. 2019;37(suppl; abstr TPS8057).

158. Richardson PG, Oriol A, Larocca A, et al. Melflufen and dexamethasone in heavily pretreated relapsed and refractory multiple myeloma. J Clin Oncol. 2021; 39:757-767.

159. Chauhan D, Ray A, Viktorsson K, et al. In vitro and in vivo antitumor activity of a novel alkylating agent, melphalan-flufenamide, against multiple myeloma cells. Clin Cancer Res. 2013;19:3019-3031.

160. Mateos M-V, Oriol A, Larocca A, et al. Clinical activity of melflufen in patients with triple-class refractory multiple myeloma and poor-risk features in an updated analysis of HORIZON (OP-106), a phase 2 study in patients with relapsed/refractory multiple myeloma refractory to pomalidomide and/or daratumumab. Blood. 2019;134(suppl; abstr 1883).

161. Matyskiela ME, Lu G, Ito T, et al. A novel cereblon modulator recruits GSPT1 to the CRL4(CRBN) ubiquitin ligase. Nature. 2016;535:252-257.

162. Chamberlain PP, Cathers BE. Cereblon modulators: low molecular weight inducers of protein degradation. Drug Discov Today Technol. 2019;31:29-34.

163. Matyskiela ME, Zhang W, Man H-W, et al. A cereblon modulator (CC-220) with improved degradation of Ikaros and Aiolos. J Med Chem. 2018;61:535-542.

164. Bjorklund CC, Kang J, Amatangelo M, et al. Iberdomide (CC-220) is a potent cereblon E3 ligase modulator with antitumor and immunostimulatory activities in lenalidomide- and pomalidomide-resistant multiple myeloma cells with dysregulated CRBN. Leukemia. 2020;34:1197-1201.

165. Lonial S, van de Donk NWCJ, Popat R, et al. First clinical (phase 1b/2a) study of iberdomide (CC-220; IBER), a CELMoD, in combination with dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). J Clin Oncol. 2019;37(suppl; abstr 8006).

166. Hansen JD, Correa M, Nagy MA, et al. Discovery of CRBN E3 ligase modulator CC-92480 for the treatment of relapsed and refractory multiple myeloma. J Med Chem. 2020;63:6648-6676.

167. Richardson PG, Vangsted AJ, Ramasamy K, et al. First-in-human phase I study of the novel CELMoD agent CC-92480 combined with dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). J Clin Oncol. 2020;38(suppl; abstr 8500).

168. Chari A, Berdeja J, Oriol A, et al. A phase 1, first-in-human study of talquetamab, a G protein-coupled receptor family C group 5 member D (GPRC5D) x CD3 bispecific antibody in patients with relapsed and/or refractory multiple myeloma. Blood. 2020;136(suppl):40-41.

169. Cohen A, Harrison S, Krishnan A, et al. Initial clinical activity and safety of BFCR4350A, a FcRH5/CD3 T-cell-engaging bispecific antibody, in relapsed/refractory multiple myeloma. Blood. 2020;136(suppl):42-43.

Incorporating Novel Targeted and Immunotherapeutic Agents in the Treatment of B-Cell Lymphomas

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Overview

The introduction of novel targeted agents and immunotherapeutic modalities into the treatment of B-cell lymphomas has drastically shifted the treatment landscape. In diffuse large B-cell lymphoma, recent approvals of CAR T-cell therapy, the antibody-drug conjugate polatuzumab, and the anti-CD19 monoclonal antibody tafasitamab have provided efficacious options for patients with relapsed and refractory disease. These immunotherapies attempt to harness power from the patient's own immune system to eradicate lymphoma. In chronic lymphocytic leukemia, oral targeted kinase inhibitors such as ibrutinib and acalabrutinib (Bruton tyrosine kinase inhibitors) and venetoclax (BCL2 inhibitor) are now favored over chemoimmunotherapy for upfront treatment because of improved progression-free survival across all subgroups (including high-risk subgroups such as unmutated immunoglobulin variable heavy chain and chromosome 17p deletion). In indolent lymphomas, several PI3K inhibitors are approved for treatment of relapsed disease. However, uptake of these agents has been limited because of toxicity concerns. Combination of lenalidomide and rituximab has been a safe and effective immune modality for patients with refractory indolent lymphomas; it is currently being used as a backbone to bring other targeted agents such as tazemetostat (EZH2 inhibitor) into earlier lines of treatment. In this article, we will review novel commercially available agents in the treatment of relapsed/refractory diffuse large B-cell lymphoma, treatment-naïve chronic lymphocytic leukemia, and relapsed/refractory indolent lymphomas. We will evaluate clinical trials that led to their approval and will provide an outlook into the future novel agents currently under investigation in B-cell malignancies.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma, and indolent lymphomas, such as follicular lymphoma and marginal zone lymphoma, are the three most common subtypes of B-cell lymphomas.[1] Although approximately two-thirds of patients with newly diagnosed DLBCL are cured with frontline R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), only a fraction of patients with relapsed disease are eligible for salvage chemotherapy followed by high-dose therapy and autologous stem cell transplant (ASCT) with a minority achieving long-term remission.[2,3] Additionally, patients with refractory disease have a median survival of 6 months, highlighting an urgent need for improvement in therapy.[4] Outcomes with chemoimmunotherapy such as bendamustine/rituximab or fludarabine/cyclophosphamide/rituximab have been poor in patients with CLL with adverse prognostic features such as chromosome 17p deletion and unmutated immunoglobulin variable heavy chain (IGHV) status. These regimens are associated with significant toxicity, especially given the older population of patients. Additionally, fludarabine/cyclophosphamide/rituximab has been associated with a risk of secondary malignancies.[5] And finally, because of the improved life expectancy of patients with indolent lymphomas after the approval of rituximab, there has been a role for targeted therapeutics with durable responses and reduced toxicity.[6]

In the last decade, increasing knowledge of the cellular biology of B-cell receptor signaling paved the way for targeted therapies with Bruton tyrosine kinase (BTK) inhibitors and PI3K inhibitors, ultimately shifting the paradigm for treatment of patients with treatment-naïve and relapsed/refractory CLL. Better understanding of the molecular pathogenesis of lymphoma has resulted in identification and development of therapeutics that target proteins such as BCL2 (B-cell lymphoma 2), EZH2 (enhancer of zeste homolog 2), and XPO1 (exportin-1). Growing insight into the role of the tumor microenvironment in influencing tumor growth has led to development of immune-targeted agents and cell-based therapies that activate systemic immunity against lymphomas. CAR T cells are a prime example of successful adoptive cell–based immunotherapy in

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PRACTICAL APPLICATIONS

- Anti-CD19 CAR T cells can induce durable remissions in patients with refractory diffuse large B-cell lymphoma. Additional efforts to improve the toxicity profile and efficacy of CAR T-cell therapy are in progress.
- Bruton tyrosine kinase inhibitors ibrutinib and acalabrutinib improve progression-free survival when compared with chemoimmunotherapy regimens in patients with chronic lymphocytic leukemia needing upfront treatment, and this benefit extends across all prognostic groups.
- Time-limited therapy with venetoclax results in deep remissions with undetectable minimal residual disease in a high-proportion of treatment-naïve patients with chronic lymphocytic leukemia.
- Several PI3K inhibitors are approved for treatment of patients with relapsed/refractory indolent lymphomas. Because of their specific side-effect profile, a multidisciplinary approach and careful monitoring and management of toxicities are essential. The novel targeted agent tazemetostat, an inhibitor of EZH2, is safe and effective in patients with relapsed/refractory follicular lymphoma.
- CD20 × CD3 bispecific antibodies and CD19-targeting antibody-drug conjugates have a promising future in treatment of both aggressive and indolent lymphomas.

patients with refractory DLBCL. Lenalidomide, antibody-drug conjugates, and bispecific antibodies (bispecifics) are other immune modalities that are active or have a future role in the treatment of B-cell lymphomas.

This article will highlight the clinical data supporting the marketing of the U.S. Food and Drug Administration (FDA)-approved novel agents targeting BTK, PI3K, BCL2, EZH2, and XPO1 and immunotherapeutic agents such as lenalidomide, antibody-drug conjugates, CAR T cells, and bispecifics in the treatment of patients with relapsed/refractory DLBCL, treatment-naïve CLL, and relapsed/refractory indolent lymphomas (follicular lymphoma, marginal zone lymphoma, and Waldenström macroglobulinemia).

TARGETED AGENTS

Bruton Tyrosine Kinase

BTK is a kinase within the TEC family that leads to downstream activation of AKT, extracellular signal–regulated kinase, and nuclear factor-κ light-chain enhancer of activated B-cell pathways important for malignant B-cell's growth and survival.[7-9] Ibrutinib is an irreversible BTK inhibitor that covalently binds to the cysteine-481 amino acid of the BTK enzyme. It has shown significant activity in several B-cell lymphomas including CLL, mantle cell lymphoma, marginal zone lymphoma, and Waldenström macroglobulinemia.[10-14] Second-generation irreversible BTK inhibitors, such as acalabrutinib and zanubrutinib, have greater selectivity for BTK and are designed to limit inhibition of off-target kinases such as TEC, EGFR, and ITK.[15,16] Discovery of acquired mutations to ibrutinib therapy such as mutations in BTK and PLCγ2 has fueled the development of more potent and reversible BTK inhibitors LOXO-305 and ARQ-531 with equal efficacy in patients harboring these resistance mutations.[17-21] Table 1 lists all FDA-approved BTK inhibitors for the treatment of B-cell lymphomas in the frontline and relapsed/refractory settings.

PI3K

PI3K is a lipid kinase with catalytic subunits with four different isoforms referred as p110α, p110β, p110γ, and p110δ.[22] Upon activation by surface receptors, PI3K generates phospholipid second messengers at the cell membrane that activate multiple intracellular enzymes leading to activation of AKT and mTOR pathways important for cellular survival.[23] Idelalisib, a potent and specific inhibitor of PI3Kδ, was the first PI3K inhibitor approved for marketing in treatment of relapsed/refractory CLL and follicular lymphoma.[24,25] In addition to inhibiting PI3Kδ, duvelisib targets PI3Kγ isoform, which potentially contributes to modulation of the tumor microenvironment components such as $CD4^+$ T cells and tumor-associated macrophages.[26] Copanlisib targets both PI3Kδ and PI3Kα isoforms.[27] Umbralisib (combined inhibitor of PI3Kδ and casein kinase-1ε) has a better selectivity for δ isoform and results in fewer immune-mediated toxicities.[28] Table 1 lists all FDA-approved PI3K inhibitors for treatment of B-cell lymphomas in the frontline and relapsed/refractory settings.

BCL2

BCL2 is a prosurvival protein constitutively overexpressed in CLL and other lymphomas; it prevents cell death by inhibiting apoptosis induced by BAX and BAK proteins.[29,30] Proapoptotic BH3-only proteins (such as BIM, BID, BMF) antagonize effects of BCL2. Venetoclax is an oral, highly selective BH3-mimetic, which binds to BCL2, resulting in initiation of apoptosis mediated by BAX and BAK in primed cells.[31] Because of venetoclax's ability to induce high and durable rates of complete responses and undetectable minimal residual disease in combination with an anti-CD20 monoclonal antibody, it has been tested and approved for time-limited therapy in both frontline and relapsed/refractory CLL.[32,33]

EZH2

Among patients with follicular lymphoma, 20%–25% harbor an activating mutation in epigenetic regulator EZH2.[34,35]

TABLE 1. FDA-Approved BTK and PI3K Inhibitors for Marketing in B-Cell Lymphomas

	CLL	FL	WM	MZL	MCL
BTK Inhibitors					
Ibrutinib	Frontline: alone or in combination with rituximab or obinutuzumab[65-68] R/R: 1+[61]		Frontline: alone or in combination with rituximab[84] R/R: alone or in combination with rituximab[12,84]	R/R: 1+[11]	R/R: 1+[14]
Acalabrutinib	Frontline: alone or in combination with obinutuzumab[69] R/R: 1+[93]				R/R: 1+[92]
Zanubrutinib					R/R: 1+[94]
PI3K Inhibitors					
Idelalisib	R/R: 1+: in combination with rituximab 2+: alone[24]	R/R: 2+[25]			
Duvelisib	R/R: 2+[95]	R/R: 2+[86]			
Copanlisib		R/R: 2+[87]			
Umbralisib		R/R: 3+[28]		R/R: 1+[28]	

Abbreviations: FDA, U.S. Food and Drug Administration; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; WM, Waldenström macroglobulinemia; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma; R/R, relapsed/refractory; 1+, after progression on one line of treatment; 2+, after progression on two lines of treatment; 3+, after progression on three lines of treatment.

This mutation results in escape from the normal B-cell clonal selection process and allows GCB cells to survive and proliferate, ultimately resulting in lymphomagenesis.[36] Hence, inhibition of EZH2 with tazemetostat, a first-generation EZH2 inhibitor, has been used as a therapeutic target in lymphomas.[37]

XPO1

XPO1 is an essential nuclear export receptor that is involved in functional inactivation of tumor suppressor proteins (p53, p73, FOXO) and increased translation of oncoproteins such as *BCL2*, *c-MYC*, and *BCL6*.[38] Thus, inhibition of XPO1 with selinexor, a first-in-class selective oral inhibitor of XPO1, has been evaluated in patients with multiple B-cell lymphomas.[39]

IMMUNOTHERAPEUTIC AGENTS

Lenalidomide

Lenalidomide is an immunomodulatory agent that binds to the cereblon E3 ubiquitin ligase complex, resulting in degradation of transcription factors Aiolos and Ikaros, leading to apoptosis of lymphoma cells.[40] It also potentiates the activity of immune effector cells such as $CD8^+$ T cells and natural killer cells.[41] Combining lenalidomide with a monoclonal antibody results in enhanced antibody-dependent cell-mediated cytotoxicity.[42] Because of their synergy, this combination has been very effective in patients with relapsed/refractory follicular lymphoma and marginal zone lymphoma.[43] Recently, lenalidomide was paired with tafasitamab, a novel Fc-engineered, humanized, anti-CD19 monoclonal antibody with enhanced antibody-dependent cell-mediated cytotoxicity in patients with relapsed/refractory DLBCL who were ineligible for ASCT.[44]

Antibody-Drug Conjugates

Antibody-drug conjugates carry a cytotoxic payload directed against tumor antigens in an effort to maximize efficacy and minimize off-target side effects. Polatuzumab vedotin, a CD79b-targeted antibody-drug conjugate that delivers monomethyl auristatin E (a potent microtubule inhibitor), is approved by the FDA for marketing in combination with bendamustine/rituximab in patients with relapsed/refractory DLBCL.[45] Loncastuximab tesirine is humanized CD19-targeted antibody-drug conjugate, which delivers a pyrrolobenzodiazepine dimer as its payload. Loncastuximab tesirine has shown promising activity in patients with relapsed/refractory DLBCL as monotherapy and is currently under investigation with several combinations.[46]

CAR T Cells

CAR T cells are autologous T cells modified to target a specific tumor antigen such as CD19. Lymphocytes are collected from a patient through apheresis and modified using either a lentiviral or retroviral vector containing a CAR-modified product. This CAR product has an extracellular domain (targeting CD19), transmembrane domain, costimulatory domain (typically 4-1BB or CD28), and a CD3ζ intracellular domain.[47] Three anti-CD19 CAR T-cell products, axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel, are FDA approved for marketing in relapsed/refractory DLBCL after progression on two lines of therapy.[48-50] Cytokine release syndrome and neurotoxicity are common side effects with each CAR T-cell construct.

Bispecific Antibodies

Bispecifics are "off-the-shelf" antibody constructs designed to bring T cells in proximity to tumor cells to trigger T-cell–mediated cytotoxicity. There are four different bispecifics targeting CD20 and CD3 that are in development for patients with indolent and aggressive lymphomas: mosunetuzumab, odronextamab, epcoritamab, and glofitamab.[51-54] These agents have shown promising activity even in patients with disease progression after CAR T-cell therapy. Akin to CAR T cells, cytokine release syndrome is a potential adverse event with these agents.

INCORPORATING NOVEL AGENTS INTO THE MANAGEMENT OF RELAPSED DLBCL

Case and Introduction

A 51- or 81-year-old female patient with stage IV nongerminal center DLBCL with an international prognostic index of 2 (stage and lactate dehydrogenase) completed six cycles of R-CHOP with interim and end-of-therapy PET/CT consistent with a complete metabolic response, Deauville 2. Eleven months later, she presented with new cervical lymphadenopathy, biopsy consistent with relapse, and PET/CT showing diffuse hypermetabolic lymphadenopathy.

The standard frontline treatment of DLBCL combines the anti-CD20 monoclonal antibody rituximab with CHOP chemotherapy, providing a cure for approximately 60% of patients.[2] In those patients whose disease is refractory to or relapses after R-CHOP, there is potential for cure with intensive treatment including ASCT, but only approximately 50% will be eligible for this approach and, of those, only approximately 25% of patients will have an outcome of long-term disease-free survival, with outcomes worse in patients with primary refractory disease or relapse within 1 year of R-CHOP.[55]

CAR T Cells

CAR T-cell therapy has changed the treatment landscape for patients with relapsed/refractory DLBCL, providing an effective therapy option for disease not responding to salvage chemotherapy or relapsing after ASCT, where median overall survival (OS) is 6 months.[4] These genetically modified autologous T cells targeting CD19 provide potential curative therapy for patients with chemo-refractory disease. There are three second-generation products approved by the FDA for marketing: axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel. These products provide overall response rates (ORRs) of 52%–83% with complete remission achieved 40%–58% of the time.[48-50] Toxicities of concern include cytokine release syndrome and neurotoxicity that vary by product including 1%–22% grade 3 or greater cytokine release syndrome and 12%–28% grade 3 or greater neurologic dysfunction, generally treatable and reversible but requiring management in an experienced facility. Other differences include manufacturing process, constructs, costimulatory domains, and dose along with differences in eligibility criteria and use of bridging therapy in the pivotal trials. Despite these differences, durable remissions occur in approximately 30%–40% of patients infused with product. Currently, this approach—given the potential for cure—is the preferred treatment of patients requiring third-line therapy, including in select patients who were not considered to be candidates for ASCT because of age or comorbidities. Limitations including proximity to CAR T-cell center, timely referral, central manufacturing of cells, and financial burden have hindered broad accessibility. Despite curative potential, the majority of patients' disease will not respond to or will progress after infusion of the CAR T-cell product. Ongoing research to overcome this resistance includes trials evaluating novel CAR constructs along with rationale combinations, such as combined use of immunomodulatory agents. The efficacy of CAR T-cell therapy has led to clinical trials investigating the use of this approach earlier in the course of treatment, with the potential to further change the therapy landscape for relapsed/refractory DLBCL. Clinical trials randomly assigning patients with high-risk disease, defined by primary refractory to or relapsing within 1 year of completing R-CHOP, to receive standard of care therapy with salvage chemotherapy followed by ASCT versus CAR T-cells are enrolling or have completed accrual with results awaited (NCT03391466, NCT03570892, NCT03575351). Investigation as second-line therapy for patients not considered candidates for ASCT is also ongoing (NCT03483103, NCT04161118), with early indication of safety and efficacy. Patients with disease progression after CAR T-cell therapy represent a challenging population to treat, and as this therapy moves earlier into the treatment algorithm, it will be important to define effective treatment approaches for these patients.

Tafasitamab and Lenalidomide

The immune combination of tafasitamab and lenalidomide is the first FDA-approved therapy for marketing in the

second-line treatment of DLBCL. The combination was approved based on results of the L-MIND study, a phase II trial enrolling 80 patients with relapsed/refractory DLBCL ineligible for ASCT. The trial reported an impressive 60% ORR including 43% achieving a complete response with a median duration of response 21.7 months, median progression-free survival (PFS) of 12.1 months, and median OS not reached.[56] Responses occurred irrespective of cell of origin, with activity seen in patients with both germinal center and nongerminal center DLBCL, and in patients with poor prognostic features including disease refractory to prior therapy. The most common adverse events were hematologic, with neutropenia as the most common grade 3 or greater and overall adverse event, and rash and diarrhea, mostly grade 1–2, as the most common nonhematologic adverse events. With an additional year of follow-up, the median duration of response was 34.6 months and median OS 31.6 months, confirming durability of this immunologic combination.[57] Limitations of the study included the exclusion of patients with certain high-risk disease features including those primary refractory to R-CHOP and heavily pretreated patients as defined by receiving more than three prior therapies. Given the efficacy of this combination, it should be considered as second-line therapy for patients ineligible for ASCT. Although patients with primary refractory disease were excluded from the trial, these patients have limited effective treatment options otherwise. There is theoretical concern regarding the ability to sequence CD19 therapies. There was one patient treated on the L-MIND trial subsequently treated with CAR T-cell therapy; this therapy yielded a complete response in this patient, who was in remission at publication of the trial.[56] More data are needed on the efficacy of tafasitamab both prior to and after CAR T-cell therapy, although emerging data suggest sequencing CD19-directed therapies may not hinder efficacy.[58]

Polatuzumab

Polatuzumab was the first FDA-approved novel therapy in relapsed/refractory DLBCL, approved for marketing in combination with bendamustine/rituximab after two or more prior therapies. This is the only approval based on a randomized study, a phase II trial enrolling 80 patients (40 per arm) resulting in significant improvements in end-of-treatment and best ORR (45.0% vs. 17.5%; 62.5% vs. 25.0%) and complete response (40.0% vs. 17.5%; 50.0% vs. 22.5%) compared with bendamustine/rituximab with a median duration of response, PFS, and OS of 12.6, 9.5, and 12.4 months, respectively, resulting in a survival benefit (12.4 vs. 4.7; p = .002).[45] Efficacy was seen across all risk groups, with activity independent of cell of origin, double expressor status, international prognostic index, refractory status, or number of prior lines of therapy. The addition of polatuzumab resulted in higher rates of grade 3–4 neutropenia without higher rates of infection; grade 1–2 peripheral neuropathy occurred in 44% of patients with improvement/resolution in the majority. This regimen has been used in transplant-ineligible patients for second-line therapy, although different from the label, and as an effective option to bridge patients to a more definitive therapy.

Selinexor

Selinexor is an oral therapy approved for marketing in relapsed/refractory DLBCL after two or more prior therapies. A phase IIb study enrolled 127 patients with disease progressing after two to five prior lines of therapy resulting in a 28% ORR, 12% CR, and median duration of response, PFS, and OS of 9.3, 2.6, and 9.1 months, respectively.[59] Activity was seen in both germinal center (ORR, 34%; CR, 14%) and nongerminal center (ORR, 21%; CR, 10%) subtypes and responses were consistent across risk groups including number of prior therapies and refractory status. The study required 60–98 days since last therapy with a 59-

TABLE 2. Select Ongoing Clinical Trials in Relapsed/Refractory DLBCL With Novel Targeted Therapies or Combinations

Agent	Mechanism	Combination	Phase	Identifier
Loncastuximab tesirine	CD19 antibody-drug conjugate	Single agent	I	NCT03589469
Loncastuximab tesirine	CD19 antibody-drug conjugate	Ibrutinib	I	NCT03684694
Loncastuximab tesirine	CD19 antibody-drug conjugate	Durvalumab	I	NCT03685344
Mosunetuzumab	CD20 × CD3 bispecific antibody	Single agent or combination atezolizumab	I	NCT02500407
Mosunetuzumab	CD20 × CD3 bispecific antibody	Polatuzumab vedotin	I/II	NCT03671018
Odronextamab	CD20 × CD3 bispecific antibody	Single agent	II	NCT03888105
Epcoritamab	CD20 × CD3 bispecific antibody	Single agent	I/II	NCT03625037
Glofitamab	CD20 × CD3 bispecific antibody	Single agent or combination obinutuzumab	I	NCT03075696
Glofitamab	CD20 × CD3 bispecific antibody	Atezolizumab or polatuzumab	I	NCT03533283

Abbreviation: DLBCL, diffuse large B-cell lymphoma.

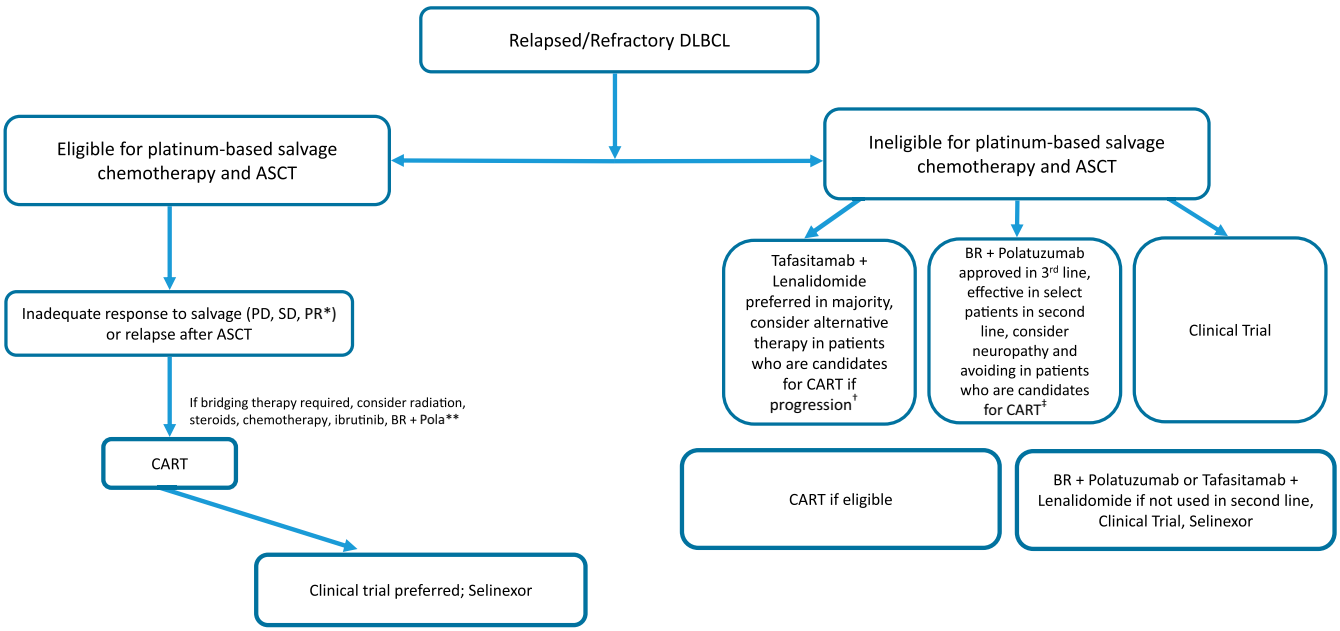

FIGURE 1. Novel Targeted Therapies for Relapsed/Refractory DLBCL

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ASCT, autologous stem cell transplant; PD, progressive disease; SD, stable disease; PR, partial remission; BR, bendamustine/rituximab; Pola, polatuzumab vedotin; CART, chimeric antigen receptor T-cells.

*Some PR appropriate for ASCT.

**Consider factors such as precell or postcell collection, disease burden, timing, and cell of origin.

†Limited data, early evidence to suggest patients response to CART not affected by CD19-directed therapies.

‡Due to concerns for T-cell collection after bendamustine.

day median time from progression on last therapy to signing consent in responding patients, suggesting selection for less proliferative or aggressive disease. The most common toxicities were hematologic, gastrointestinal, fatigue, anorexia, and weight loss with nonhematologic toxicities largely grade 1–2 and most adverse events controlled with scheduled supportive care and dose modifications. Although this single-agent therapy has a limited role, select patients not eligible for or progressing after CAR T-cell therapy may benefit and combination therapies are being evaluated.

Future Direction: Targeted Agents in Relapsed/Refractory DLBCL

There are a number of novel targeted therapies under investigation for the treatment of relapsed/refractory DLBCL both alone and in combination. The most promising therapies at this time include select immunotherapy approaches with an antibody-drug conjugate that targets CD19[58,60] and bispecifics that target CD20 × CD3.[51-54] These agents have shown promising early efficacy including responses in patients whose disease is progressing after CAR T-cell therapy. Select ongoing studies are listed in Table 2.

Case Conclusion

The patient scenario in the clinical case would be approached differently based on the patient age, with a 51-year-old patient receiving standard-of-care salvage chemotherapy followed by ASCT if treatment yields a response to salvage chemotherapy and CAR T-cell therapy with inadequate response to salvage chemotherapy, whereas an 81-year-old patient would have the highest likelihood of response to combination tafasitamab and lenalidomide. Our recommended approach to the treatment of patients with relapsed/refractory DLBCL is summarized in Fig. 1.

INCORPORATING NOVEL AGENTS INTO THE MANAGEMENT OF TREATMENT-NAÏVE CLL

Case and Introduction

Mr. T is a 62-year-old man with treatment-naïve CLL who presents with progressive cytopenias and fatigue. Last year, he had two episodes of severe pneumonia. His prognostic evaluation shows unmutated IGHV and del(11q).

Since the introduction of targeted agents, the standard management of CLL has changed dramatically, especially in the frontline setting. Previously, nonspecific cytotoxic chemotherapies were the norm. The average patient with CLL is older and with multiple medical comorbidities, making these nonspecific cytotoxic chemotherapy regimens difficult to tolerate. Additionally, these standard regimens result in a clear pattern of worse clinical outcomes for patients with high-risk CLL [IGHV unmutated, del(17p), and *TP53*

TABLE 3. Targeted Regimens in Phase III Studies of Frontline Therapy for Patients With Chronic Lymphocytic Leukemia

Study	Targeted Regimen	Comparator	No. of Patients (Targeted Regimen)	ORR of Targeted Regimen, %	CRR of Targeted Regimen, %	uMRD in Targeted Regimen, %	PFS (Targeted Regimen)	OS (Targeted Regimen)	Median Follow-up, months
Ibrutinib									
RESONATE2[65]	Ibrutinib	Ofatumumab	136	92	30	NA	NR; (5-year 70%)	NR; (5-year 83%)	60
iLLUMINATE[66]	Ibrutinib + obinutuzumab	Chlorambucil + obinutuzumab	113	88	19	35	NR; (30-month 79%)	NR; (30-month 86%)	31
E1912[67]	Ibrutinib + rituximab	FCR	354	95	17	8 (276 pts)	NR; (3-year 89%)	NR; (3-year 98%)	48
A041202[68]	Ibrutinib +/− rituximab	BR	Ib = 182	Ib = 93	Ib = 7	Ib = 1	Ib = NR; (2-year 87%)	Ib = NR; (2-year 90%)	38
			Ib + R = 182	Ib + R = 94	Ib + R = 12	Ib + R = 4	Ib + R = NR; (2-year 88%)	Ib + R = NR; (2-year 94%)	
Acalabrutinib									
ELEVATE TN[69]	Acalabrutinib +/− obinutuzumab	Chlorambucil + obinutuzumab	A = 179	A = 87	A = 1	A = 0	A = NR; (2-year 87%)	A = NR; (2-year 95%)	28
			AO = 179	AO = 94	AO = 13	AO = 12	AO = NR; (2-year 93%)	AO = NR; (2-year 95%)	
Venetoclax									
CLL14[33,70,71]	Venetoclax + obinutuzumab	Chlorambucil + obinutuzumab	216	85	50	42	NR; (4-year 74%)	NR; (4-year 85%)	52

Abbreviations: A, acalabrutinib; AO, acalabrutinib/obinutuzumab; BR, bendamustine/rituximab; CRR, complete remission rate; FCR, fludarabine/cyclophosphamide/rituximab; Ib, ibrutinib; Ib + R, ibrutinib/rituximab; NA, not available; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; uMRD, undetectable minimal residual disease.

mutated]. Oral targeted agents such as ibrutinib, acalabrutinib, and venetoclax are highly efficacious and tolerable and have become preferred therapies for patients with CLL.

Ibrutinib

In multiple studies, ibrutinib demonstrated significant efficacy and tolerability in relapsed CLL. Therefore, this drug quickly moved to investigation in the frontline setting.[13,61] The landmark phase II study in which 31 patients with treatment-naïve CLL received continuous ibrutinib therapy now has 8 years of follow-up data supporting the efficacy of ibrutinib in this setting.[62] The estimated 7-year PFS and OS rates were 83% and 84%, respectively. Only 6% of patients discontinued ibrutinib secondary to progressive disease.[62] In this study, the incidence of grade 3 or greater toxicities decreased over time (including infections).[62] The reduction of infections over time supports other data indicating that ibrutinib leads to reconstitution of some of the immune function in patients with CLL.[63,64]

Subsequently, several key phase III studies were initiated using ibrutinib-based therapy in patients with treatment-naïve CLL (Table 3). The RESONATE2 study compared frontline CLL therapy of ibrutinib with chlorambucil.[65] After a median follow-up of 60 months, the ORR was 92% and the complete response rate deepened over time to 30%. The estimated 5-year PFS and OS rates were 70% and 83%, respectively. Remarkably, the estimated PFS was no different in patients with IGHV-mutated or unmutated disease, which is in contrast to shorter PFS demonstrated in patients with unmutated IGHV treated with its chemotherapy comparator [of note, patients with del(17p) were excluded from this study]. Major adverse events and discontinuations secondary to toxicity decreased over time.[65] Data from this study supported the FDA approval of ibrutinib for marketing in frontline CLL. A similar study, the iLLUMINATE study compared frontline CLL therapy of ibrutinib plus the anti-CD20 monoclonal antibody obinutuzumab versus chlorambucil/obinutuzumab.[66] This study comparably demonstrated improved PFS with the ibrutinib-based regimen, which was maintained regardless of CLL risk status, including those with del(17p). Adding obinutuzumab to ibrutinib likely enhanced the speed of response, deepened responses (35% with undetectable minimal residual disease), but increased the risk of infusion-related reactions and cytopenias when compared with patients receiving single-agent ibrutinib on the RESONATE2 study.[65,66] No prospective head-to-head comparisons of ibrutinib versus ibrutinib/obinutuzumab have been done, leaving a question of whether the addition of an anti-CD20 monoclonal antibody is needed to improve the clinical outcomes of ibrutinib unanswered. Regardless, obinutuzumab and ibrutinib were approved by the FDA for marketing in frontline CLL therapy. Both the RESONATE2 and iLLUMINATE studies have been criticized for not using a robust comparator arm (chlorambucil/obinutuzumab).

Eastern Cooperative Oncology Group's E1912 and Alliance's A041202 studies were designed to compare ibrutinib-based regimens with more realistic comparator arms for the frontline treatment of younger patients (< age 65) and older patients (≥ age 65), respectively.[67,68] The E1912 study compared frontline therapy with ibrutinib/rituximab versus fludarabine/cyclophosphamide/rituximab in patients with CLL who were younger than age 65.[67] This study demonstrated both a PFS and OS benefit for patients receiving ibrutinib/rituximab. Notably, the study did not have a single-agent ibrutinib arm and therefore it is unclear if the addition of rituximab is needed to obtain these clinical benefits.[67] The A041202 study compared frontline therapy with ibrutinib versus ibrutinib/rituximab versus bendamustine/rituximab in patients with CLL who were age 65 or older.[68] This study demonstrated a PFS benefit of both ibrutinib-based treatments over bendamustine/rituximab. No clear benefit in survival or response was seen with the addition of rituximab to ibrutinib. The patients on the bendamustine/rituximab arm experienced more cytopenias, and the patients on the ibrutinib-based arms experienced more atrial fibrillation and hypertension.[68] In both the E1912 and A041202 studies, the ibrutinib-containing arms demonstrated similar PFS between patients with IGHV mutated or unmutated disease, in contrast to a shorter PFS for patients with IGHV unmutated CLL demonstrated with the chemotherapy comparators.

Acalabrutinib

The success of ibrutinib in CLL led to the development of the even more selective BTK inhibitor acalabrutinib. The phase III ELEVATE TN study compared frontline CLL therapy with acalabrutinib versus acalabrutinib/obinutuzumab versus chlorambucil/obinutuzumab.[69] The patients who received acalabrutinib-containing therapy had longer PFS than patients receiving chlorambucil/obinutuzumab. This benefit was maintained in the patients with high-risk disease, including IGHV-unmutated disease. Interestingly, there was a not yet significant improvement in PFS for those patients receiving obinutuzumab in addition to acalabrutinib (2-year PFS, 93% vs. 87%), raising the question if obinutuzumab may improve clinical outcomes in combination with acalabrutinib. Adverse events of interest historically seen with ibrutinib were low (≤ 4%) including grade 3 or greater hypertension and any-grade atrial fibrillation. The most common side effect in patients receiving acalabrutinib was headache, seen in up to 40% (almost exclusively low grade).[69] Of note, acalabrutinib requires gastric acid to be properly absorbed and should not be used in combination with proton-pump inhibitors. Based on this study, acalabrutinib

TABLE 4. Select Ongoing Phase III Studies Using Targeted Agents in Frontline Chronic Lymphocytic Leukemia Therapy

Study	Targeted Agent	Potential Benefits	NCT Identifier
Novel Targeted Agents			
SEQUOIA[96,97]	Zanubrutinib (covalent BTKi)	Excellent safety profile	NCT03336333
UNITY-CLL[98]	Umbralisib (PI3Ki) + ublituximab (anti-CD20 monoclonal antibody)	Excellent safety profile; minimal drug interactions (not metabolized by CYP3A)	NCT02612311
Combinations of Targeted Agents			
CAPTIVATE[99,100]	Ibrutinib + venetoclax	MRD-guided potential for time-limited therapy	NCT02910583
GLOW	Ibrutinib + venetoclax	Phase III registration study	NCT03462719
EA9161	Ibrutinib + venetoclax + obinutuzumab	Time-limited therapy	NCT03701282
A041202	Ibrutinib + venetoclax + obinutuzumab	MRD-guided potential for time-limited therapy	NCT03737981
Early Intervention With Targeted Agents			
S1925 EVOLVE	Venetoclax + obinutuzumab	Early intervention in asymptomatic high-risk patients	NCT04269902
CLL12	Ibrutinib	Early intervention	NCT02863718

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; MRD, minimal residual disease; NCT, national clinical trial; PI3Ki, phosphatidylinositol-3-kinase inhibitor.

with or without obinutuzumab was approved for marketing in patients with treatment-naïve CLL.

Venetoclax

Venetoclax, the oral BCL2 inhibitor, has shown substantial efficacy when used in patients with CLL and has some key features that differentiate it from BTK inhibitors. Most notably, venetoclax can lead to deep undetectable minimal residual disease remissions, which allows for patients to take venetoclax for a time-limited course as opposed to the continuous therapy recommended with BTK inhibitor. The phase III CLL14 study compared frontline CLL therapy with venetoclax/obinutuzumab versus chlorambucil/obinutuzumab.[33] Patients who received venetoclax/obinutuzumab had longer PFS than patients receiving chlorambucil/obinutuzumab (74% vs. 35% at 4 years).[70] As with BTK inhibitor therapy, the PFS benefit of venetoclax/obinutuzumab extended across all prognostic groups, including IGHV-unmutated disease.[71] The most common grade 3 or greater adverse events experienced in patients treated with venetoclax/obinutuzumab were hematologic (neutropenia, 53%, and thrombocytopenia, 13%). Patients were given obinutuzumab during a 3-week lead-in period before starting venetoclax and only 1.4% experienced tumor lysis syndrome (laboratory only), which occurred prior to initiation of venetoclax.[33] Based on this study, venetoclax/obinutuzumab was approved for marketing in patients with treatment-naïve CLL.

Future Directions: Targeted Agents in CLL

In addition to the currently approved targeted therapies, many other targeted agents, combinations, and approaches are under active investigation for the frontline therapy of CLL. Select ongoing studies are described in Table 4.

Case Conclusion

As Mr. T. has high-risk disease with unmutated IGHV status, therapy with targeted agents is preferred secondary to improved PFS over multiple studies. As he has a history of severe infections, single-agent continuous ibrutinib was recommended with a goal of effective CLL therapy and a chance of reconstitution of his immune system. Our recommended approach for frontline therapy of a patient with CLL is summarized in Fig. 2.

INCORPORATING NOVEL AGENTS INTO THE MANAGEMENT OF RELAPSED INDOLENT LYMPHOMA

Case and Introduction

A 71-year-old woman was diagnosed with follicular lymphoma grade 2, Ann Arbor stage IV, with high tumor burden per Groupe d'Etude des Lymphomes Folliculaires criteria. She was treated with six cycles of bendamustine/rituximab and was in complete remission. Three years later, she presented with disseminated disease and abdominal pain related to lymph node conglomerate of 6.5 cm × 5 cm with a standardized uptake value of 12. A new biopsy ruled out transformation.

Standard chemoimmunotherapy for frontline treatment of advanced stage follicular lymphoma is bendamustine/rituximab or R-CHOP followed by consideration of maintenance therapy with monoclonal antibody with the caveat that obinutuzumab can result in improved PFS when compared with rituximab.[72,73] The patient in this case did not experience progression of disease with in first 24 months of frontline treatment or an early histologic transformation after treatment with bendamustine/rituximab, both of which are associated with poor survival.[74-76] In the absence of transformation, the role of R-CHOP is not clear in the

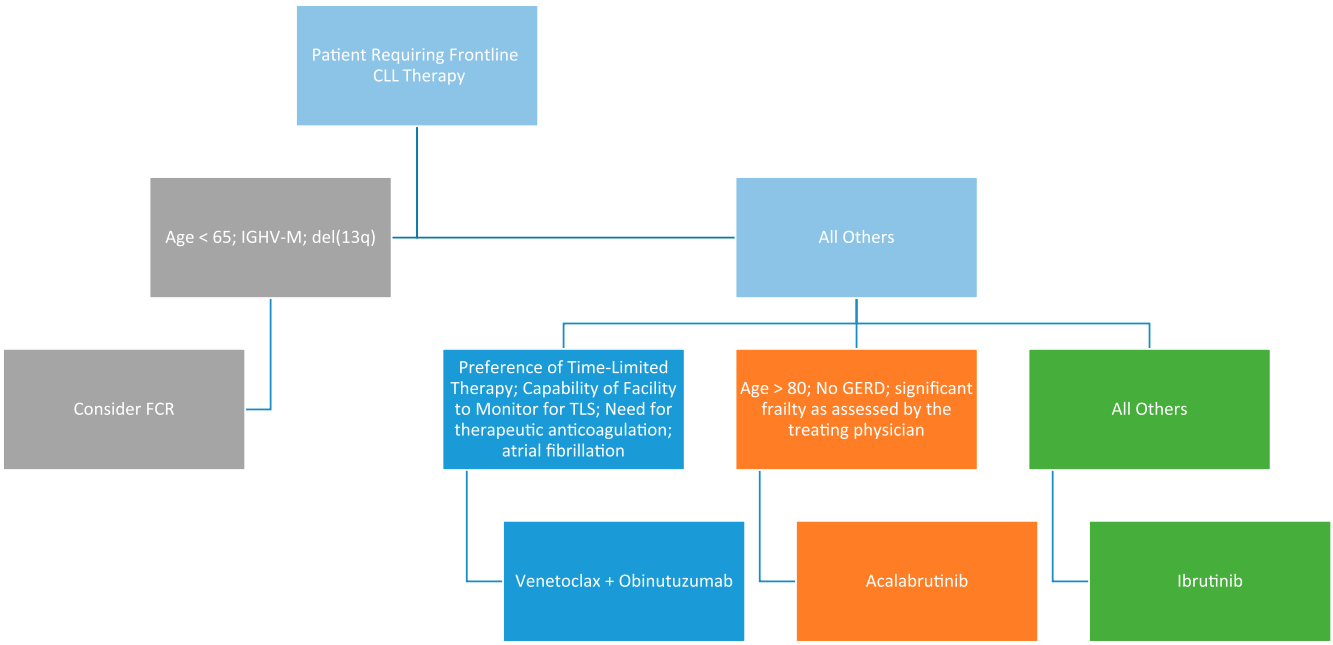

FIGURE 2. Suggested Algorithm for Selection of Frontline Chronic Lymphocytic Leukemia Therapy
Abbreviations: CLL, chronic lymphocytic leukemia; FCR, fludarabine/cyclophosphamide/rituximab; GERD, gastroesophageal reflux disease; IGHV-M, mutated immunoglobulin variable heavy chain; TLS, tumor lysis syndrome.

second-line setting and would result in higher treatment-related mortality.[77] It is important to incorporate novel targeted agents with less toxicity in treatment of patients with indolent lymphomas because of their longer OS, often needing treatment at an older age when comorbidities are high.

Lenalidomide

Follicular lymphoma Combination of lenalidomide/rituximab was compared with chemoimmunotherapy in frontline treatment of follicular lymphoma in the phase III RELEVANCE trial (Table 5).[78] This trial was considered negative as it did not reach its primary objective of superiority of lenalidomide/rituximab (3-year PFS and complete response rates were similar between the two groups). However, the activity of lenalidomide/rituximab combination in this study further supported its investigation in second-line treatment of follicular lymphoma. In the phase III AUGMENT trial of patients with relapsed/refractory follicular lymphoma and marginal zone lymphoma, experimental arm received lenalidomide 20 mg/day for days 1–21 for 12 cycles in combination with rituximab from cycles 1–5, and control arm received placebo and rituximab.[43] Enrolled patients were determined to have rituximab-sensitive disease and were considered appropriate to receive single-agent rituximab. The median PFS was longer (39.4 months vs. 14.1 months) in the lenalidomide/rituximab arm (Table 5). Growth factors were administered to 36% of the lenalidomide/rituximab group, and five patients discontinued lenalidomide because of neutropenia. The study has been criticized for administering longer duration of treatment to the experimental arm (12 months vs. 5 months) and having a weak comparator arm with single-agent rituximab. Nonetheless, lenalidomide/rituximab proves to be a valuable time-limited, effective, and tolerable option for patients with relapsed/refractory follicular lymphoma, and it has been approved for marketing by the FDA in this setting.

Marginal zone lymphoma Multiple phase I and II trials have demonstrated efficacy of lenalidomide/rituximab in frontline and relapsed marginal zone lymphoma.[79,80] In the subgroup analysis of the AUGMENT study, lenalidomide/rituximab did not improve PFS in the patients with relapsed/refractory disease; however, the sample size was small with only 63 patients.[43] Because of the improved ORR of 64% compared with 45% with rituximab alone, lenalidomide/rituximab is also FDA approved for marketing for patients with relapsed/refractory marginal zone lymphoma.

Case: The patient was treated with lenalidomide/rituximab. The dose of lenalidomide was reduced starting at cycle 3 because of skin-related toxicity and neutropenia. The patient had a complete response, but 2 years later, the patient had a relapse requiring treatment.

Bruton Tyrosine Kinase Inhibitors

Follicular lymphoma/marginal zone lymphoma Monotherapy with ibrutinib in patients with relapsed/refractory follicular lymphoma has modest activity.[81] Ibrutinib has

TABLE 5. Key Phase III Trials of Targeted Therapy in Indolent Lymphomas

Trial	Targeted Regimen	Comparator Arm	No. of Patients (Targeted Regimen)	RR of the Targeted Regimen	PFS of the Targeted Regimen	Adverse Events
Lenalidomide in Follicular Lymphoma						
Relapsed/refractory, AUGMENT[43]	R^2	R	178	ORR/CR: 80%/51%	PFS: 39.4 months	More infections (63% vs. 49%), neutropenia (58% vs. 23%), and cutaneous reactions (32% vs. 12%) in patients with R^2
						DVT: 2% of R^2; secondary cancers: 3% of R^2
Frontline, RELEVANCE[78]	R^2	R-chemotherapy (R-CHOP, BR, R-CVP)	513	CR at 120 weeks: 48%	3-year PFS: 77%	Grade $\geq$ 3 neutropenia (50% vs. 32%) and febrile neutropenia of any grade (7% vs. 2%) more common with R-chemotherapy
						Grade $\geq$ 3 cutaneous reactions more common with R^2 (7% vs. 1%)
Ibrutinib in Waldenström Macroglobulinemia						
INNOVATE[84]	Ibrutinib/rituximab	Rituximab	75 (34 TN, 41 R/R)	ORR/major response (CR + VGPR + PR): 92%/72%	30-month PFS: 82%	Grade $\geq$ 3 atrial fibrillation: 12% vs. 1% and grade $\geq$ 3 HTN: 13% vs. 4% (both more common with ibrutinib/rituximab)
						Less IgM flares with ibrutinib/rituximab arm (8% vs. 47%)
Zanubrutinib in Waldenström Macroglobulinemia						
ASPEN[85]	Zanubrutinib	Ibrutinib	102 (19 TN, 83 R/R)	VGPR/major response (CR + VGPR + PR): 28%/77%	18-month PFS: 84%	Grade $\geq$ 3 neutropenia: 20% vs. 8% (more common with zanubrutinib)
						Grade $\geq$ 3 atrial fibrillation: 0% vs. 4%
						Grade $\geq$ 3 HTN: 6% vs. 11%
						Grade $\geq$ 3 PNA: 1% vs. 7% (more common with ibrutinib)

Abbreviations: RR, response rate; PFS, progression-free survival; R^2, lenalidomide/rituximab; R, rituximab; ORR, overall response rate; CR, complete response; PFS, progression-free survival; DVT, deep vein thrombosis; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; BR, bendamustine/rituximab; R-CVP, rituximab/cyclophosphamide/vincristine/prednisone; TN, treatment naive; R/R, relapsed/refractory; VGPR, very good partial response; PR, partial response; HTN, hypertension; IgM, immuoglobulin M; PNA, pneumonia.

been approved for marketing at the dose of 560 mg daily by the FDA in patients with relapsed/refractory marginal zone lymphoma whose disease has progressed on at least one anti-CD20 therapy based on an ORR of 48% and a median PFS of 14.2 months.[11] Zanubrutinib is emerging as a second-generation BTK inhibitor with better efficacy (ORR and complete response of 60% and 15%) and improved toxicity profile in patients with relapsed/refractory marginal zone lymphoma; with the median follow-up of only 6.8 months, PFS is not reached and FDA approval is pending.[82]

Waldenström macroglobulinemia Monotherapy with ibrutinib in relapsed/refractory Waldenström macroglobulinemia illustrated an overall and major response of 90.5% and

TABLE 6. Key Phase II Trials of PI3K Inhibitors in Relapsed/Refractory Follicular Lymphoma

PI3K Inhibitor	Mechanism of Action	Phase	No. of Patients (FL/total)	Response Rates (ORR, CR)	PFS	Grade ≥ 3 Adverse Events	Drug Discontinuation Because of Adverse Event
Idelalisib[25,101]	PI3Kδ	II	72/125	56%/14%*	11 months*	Diarrhea/colitis (16%), pneumonia (7%), hepatotoxicity (13%), and neutropenia (27%)	20%
Duvelisib[86]	PI3Kδ and PI3Kγ	II	83/129	42%/1%*	9.5 months	Diarrhea/colitis (20%), pneumonia (5.4%), hepatotoxicity (5.4%), and febrile neutropenia (9.3%)	24%
Copanlisib[87]	PI3Kδ and PI3Kα	II	104/142	59%/20%*	12.5 months	Transient hyperglycemia (40%), transient hypertension (24%), diarrhea (8.5%), and pneumonia (11%)	26.8%
Umbralisib[28]	PI3Kδ and casein kinase-1ε	II	117/208	45%/5%*	10.6 months*	Neutropenia (11.5%), diarrhea (10.1%), and hepatotoxicity (7.2%)	15%

Abbreviations: FL, follicular lymphoma; ORR, overall response rate; CR, complete response; PFS, progression-free survival.
*Outcomes in cohort of patients with follicular lymphoma histology

79.4% and led to its initial approval for marketing by the FDA.[12,83] The responses deepen overtime with increased very good partial response at 5-year follow-up; additionally, patients with $MYD88^{MT}$- $CXCR4^{WT}$ tend to derive more benefit compared with patients with $MYD88^{MT}$- $CXCR4^{MT}$ (higher major response and very good partial response).[12,83] Addition of rituximab to ibrutinib was compared with placebo plus ibrutinib in the phase III INNOVATE trial in patients with treatment-naïve and refractory Waldenström macroglobulinemia.[84] Ibrutinib/rituximab arm was superior in several response categories (Table 5). Efficacy was similar in patients with and without CXCR4 mutation (major response of 78% vs. 73%) in the ibrutinib/rituximab arm. Based on this study, ibrutinib/rituximab was approved for marketing by the FDA in Waldenström macroglobulinemia in all lines of treatment. In the phase III ASPEN trial of patients with $MYD88^{MT}$ Waldenström macroglobulinemia, zanubrutinib yielded very good partial response in more patients (28% vs. 19%) compared with ibrutinib (p = .09; Table 5).[85] More patients with zanubrutinib had grade 3 or greater neutropenia but fewer had grade 3 or greater atrial fibrillation, hypertension, and pneumonia. In the absence of FDA approval of zanubrutinib for treatment of Waldenström macroglobulinemia, we recommend choosing a BTK inhibitor based on the side effect profile and availability of the drug. For example, in a 75-year-old patient with a history of atrial fibrillation and hypertension, we would prefer zanubrutinib. For a patient with significant underlying

TABLE 7. Select Ongoing Trials of Targeted Therapy in Relapsed/Refractory Indolent Lymphomas

Study	Targeted Agent	Phase	Potential Benefits	NCT Identifier
ZUMA-5[90]	Axicabtagene ciloleucel (anti-CD19 CAR T)	II	High and durable responses with less cytokine release syndrome and neurotoxicity	NCT03105336
GO29781[91]	Mosunetuzumab (CD20 × CD3 bispecific antibody)	I	Fixed duration treatment with robust activity in high-risk subgroups	NCT02500407
NP30179[102]	Glofitamab (CD20 × CD3 bispecific antibody)	I	A novel "2:1" molecular format for the bispecific with greater avidity for CD20 antigen; combined with anti-CD20 mAB	NCT03075696
EZH-302	R^2/tazemetostat vs. R^2/placebo	III	Combination of two active targeted agents	NCT04224493
MAGNIFY[103]	R^2 vs. R maintenance after induction with R^2	III	Novel maintenance strategy in R/R setting	NCT01996865

Abbreviations: NCT, national clinical trial; mAB, monoclonal antibody; R^2, lenalidomide/rituximab; R, rituximab.

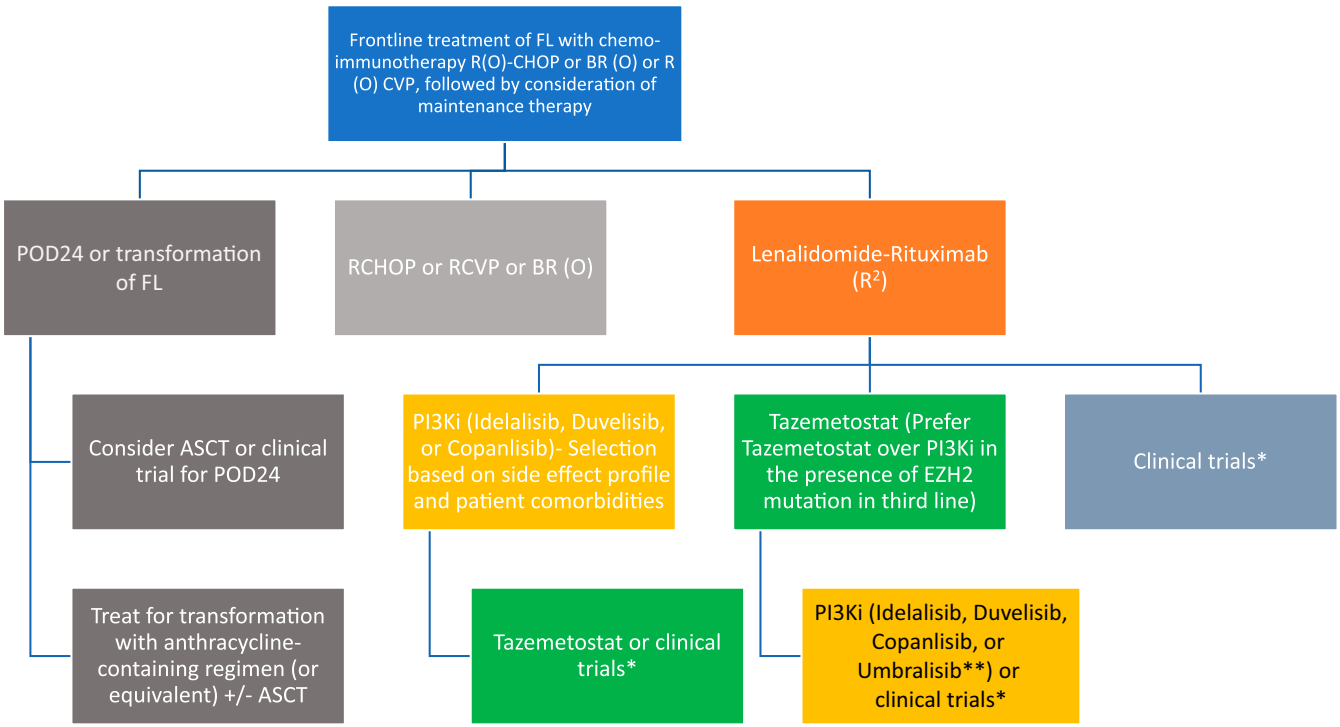

FIGURE 3. Suggested Algorithm for Selection of Therapy in Relapsed/Refractory Follicular Lymphoma

Abbreviations: FL, follicular lymphoma; O, obinutuzumab; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; RCVP, rituximab/cyclophosphamide/vincristine/prednisone; BR, bendamustine/rituximab; POD24, progression of disease in first 24 months; ASCT, autologous stem cell transplant; PI3Ki, PI3K inhibitor.

*Prefer clinical trials with CAR T-cell, CD20 × CD3 bispecific, novel PI3Ki, combination of novel agents.

**Prefer umbralisib over other PI3K inhibitors in fourth line due to better toxicity profile.

neutropenia related to Waldenström macroglobulinemia, we would choose ibrutinib.

PI3K Inhibitors

Follicular lymphoma Idelalisib, duvelisib, and copanlisib are FDA approved for marketing in relapsed/refractory follicular lymphoma after two lines of therapy. Response rates range from 40%–60%, and PFS advantage is modest with each treatment (≤ 1 year; Table 6).[25,86,87] Infections and immune-related adverse events such as colitis and hepatotoxicity result in discontinuation of therapy in a substantial number of patients (up to 25%). Copanlisib also results in grade 3 or greater hyperglycemia and hypertension in more than 25% of patients. Recently, umbralisib was approved for patients with relapsed/refractory follicular lymphoma after progression on three lines of therapy; immune-related adverse events such as colitis and pneumonitis were uncommon (< 1%) and fewer patients discontinued the drug because of adverse events compared with other PI3K inhibitors (Table 6).[28] Selection of a PI3K inhibitor should be done on a case-by-case basis after accounting for a patient's comorbidities. For example, in a patient with type 2 diabetes mellitus requiring insulin or uncontrolled hypertension, it would be prudent to avoid copanlisib. In the fourth line of treatment, we would prefer umbralisib over other PI3K inhibitors because of its better tolerability and reduced immune-related adverse events. Careful management of toxicities of PI3K inhibitors with antimicrobial prophylaxis and multidisciplinary approach is essential.[88]

Marginal zone lymphoma Umbralisib is the only PI3K inhibitor approved for relapsed/refractory marginal zone lymphoma after progression on one line of therapy. In the UNITY-NHL trial, ORR of 49% and complete remission of 16% was observed in 69 patients with relapsed/refractory disease.[28,89] Responses were consistent among all subtypes, and estimated 12-month PFS rate was 64%.

Tazemetostat

In the phase II study evaluating tazemetostat in patients with relapsed/refractory follicular lymphoma, response rates were higher in patients with EZH2 mutation compared with those without (69% vs. 35%); however, median PFS was similar (14 months vs. 11 months).[37] The drug was very tolerable with low grade 3 or greater adverse events of anemia (2%), thrombocytopenia (3%), and leukopenia (3%). Based on these findings, tazemetostat has been

approved by the FDA for marketing for its use in patients with EZH2 mutation after two lines of therapy and for patients without any satisfactory alternative treatment options regardless of the EZH2 mutation.

Future Directions: Novel Agents in Relapsed/Refractory Indolent Lymphomas

In addition to the currently approved targeted therapies, there are at least two promising modalities (anti-CD19 CAR T-cell therapy and CD20 × CD3 bispecific therapy) that are undergoing review by the FDA.[90,91] Select ongoing studies with novel targeted agents, combinations, and unique approaches are described in Table 7.

Case Conclusion

The patient's tumor was tested for EZH2 mutation using an FDA-approved test and was positive. She was started on tazemetostat at the dose of 800 mg twice a day. She is tolerating it well without any significant side effects and has an ongoing partial response. If her disease progresses on this regimen, we would favor treatment with umbralisib over other PI3K inhibitors because of its improved toxicity profile. Our algorithm on how to incorporate novel agents in relapsed/refractory follicular lymphoma is described in Fig. 3.

CONCLUSION

Targeted therapy and immunomodulatory agents have boosted the armamentarium for treatment of B-cell lymphomas. Targeted treatment with BTK inhibitors and venetoclax has supplanted chemo-immunotherapy in frontline treatment of CLL. CAR T-cell therapy has provided a breakthrough treatment option for patients with DLBCL and its role will likely expand to other B-cell lymphomas in the future. Lenalidomide, PI3K inhibitors, and EZH2 inhibitor tazemetostat augment the existing treatment options for patients with relapsed/refractory follicular lymphoma. Further studies are warranted to identify biomarkers of response and toxicity, optimal sequencing, and combinations of these novel agents to yield the greatest benefit to patients with B-cell lymphomas.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_320117.

REFERENCES

1. Al-Hamadani M, Habermann TM, Cerhan JR, et al. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the U.S.: a longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol. 2015;90:790-795.
2. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood. 2010;116:2040-2045.
3. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32:3490-3496.
4. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130:1800-1808.
5. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016;127:208-215.
6. Hiddemann W, Hoster E, Buske C, et al. Rituximab is the essential treatment modality that underlies the significant improvement in short and long term outcome of patients with advanced stage follicular lymphoma - a 10 year analysis of GLSG trials. Blood. 2006;108:483.
7. Craxton A, Jiang A, Kurosaki T, et al. Syk and Bruton's tyrosine kinase are required for B cell antigen receptor-mediated activation of the kinase Akt. J Biol Chem. 1999;274:30644-30650.
8. Petro JB, Rahman SM, Ballard DW, et al. Bruton's tyrosine kinase is required for activation of IkappaB kinase and nuclear factor kappaB in response to B cell receptor engagement. J Exp Med. 2000;191:1745-1754.
9. Tomlinson MG, Woods DB, McMahon M, et al. A conditional form of Bruton's tyrosine kinase is sufficient to activate multiple downstream signaling pathways via PLC gamma 2 in B cells. BMC Immunol. 2001;2:4.

10. Wiestner A. Targeting B-cell receptor signaling for anticancer therapy: the Bruton's tyrosine kinase inhibitor ibrutinib induces impressive responses in B-cell malignancies. J Clin Oncol. 2013;31:128-130.
11. Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood. 2017; 129:2224-2232.
12. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. N Engl J Med. 2015;372:1430-1440.
13. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369:32-42.
14. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369:507-516.
15. Herman SEM, Montraveta A, Niemann CU, et al. The Bruton tyrosine kinase (BTK) inhibitor acalabrutinib demonstrates potent on-target effects and efficacy in two mouse models of chronic lymphocytic leukemia. Clin Cancer Res. 2017;23:2831-2841.
16. Guo Y, Liu Y, Hu N, et al. Discovery of zanubrutinib (BGB-3111), a novel, potent, and selective covalent inhibitor of Bruton's tyrosine kinase. J Med Chem. 2019; 62:7923-7940.
17. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. N Engl J Med. 2014;370:2286-2294.
18. Woyach JA, Ruppert AS, Guinn D, et al. BTK^{C481S}-mediated resistance to ibrutinib in chronic lymphocytic leukemia. J Clin Oncol. 2017;35:1437-1443.
19. Reiff SD, Mantel R, Smith LL, et al. The Bruton's tyrosine kinase (BTK) inhibitor ARQ 531 effectively inhibits wild type and C481S mutant BTK and is superior to ibrutinib in a mouse model of chronic lymphocytic leukemia. Blood. 2016;128:3232.
20. Mato AR, Pagel JM, Coombs CC, et al. LOXO-305, a next generation, highly selective, non-covalent BTK inhibitor in previously treated CLL/SLL: results from the phase 1/2 BRUIN study. Blood. 2020;136(suppl 1):35-37.
21. Woyach J, Stephens DM, Flinn IW, et al. Final results of phase 1, dose escalation study evaluating ARQ 531 in patients with relapsed or refractory B-cell lymphoid malignancies. Blood. 2019;134(suppl 1):4298.
22. Fruman DA, Chiu H, Hopkins BD, et al. The PI3K pathway in human disease. Cell. 2017;170:605-635.
23. Vanhaesebroeck B, Guillermet-Guibert J, Graupera M, et al. The emerging mechanisms of isoform-specific PI3K signalling. Nat Rev Mol Cell Biol. 2010; 11:329-341.
24. Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. J Clin Oncol. 2019;37:1391-1402.
25. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014;370:1008-1018.
26. Peluso M, Faia K, Winkler D, et al. Duvelisib (IPI-145) inhibits malignant B-cell proliferation and disrupts signaling from the tumor microenvironment through mechanisms that are dependent on PI3K-δ and PI3K-γ. Blood. 2014;124:328.
27. Liu N, Rowley BR, Bull CO, et al. BAY 80-6946 is a highly selective intravenous PI3K inhibitor with potent p110α and p110δ activities in tumor cell lines and xenograft models. Mol Cancer Ther. 2013;12:2319-2330.
28. Zinzani PL, Samaniego F, Jurczak W, et al. Umbralisib, the once daily dual inhibitor of PI3Kδ and casein kinase-1ε demonstrates clinical activity in patients with relapsed or refractory indolent non-Hodgkin lymphoma: results from the phase 2 Global Unity-NHL trial. Blood. 2020;136(suppl 1):34-35.
29. Roberts AW. Therapeutic development and current uses of BCL-2 inhibition. Hematology Am Soc Hematol Educ Program. 2020;2020:1-9.
30. Adams JM, Cory S. The Bcl-2 apoptotic switch in cancer development and therapy. Oncogene. 2007;26:1324-1337.
31. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med. 2013; 19:202-208.
32. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2018;378:1107-1120.
33. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med. 2019;380:2225-2236.
34. Bödör C, Grossmann V, Popov N, et al. EZH2 mutations are frequent and represent an early event in follicular lymphoma. Blood. 2013;122:3165-3168.
35. Caganova M, Carrisi C, Varano G, et al. Germinal center dysregulation by histone methyltransferase EZH2 promotes lymphomagenesis. J Clin Invest. 2013; 123:5009-5022.
36. Yang H, Green MR. Harnessing lymphoma epigenetics to improve therapies (article not eligible for CME credit). Hematology Am Soc Hematol Educ Program. 2020;2020:95-100.
37. Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol. 2020;21:1433-1442.
38. Laín S, Xirodimas D, Lane DP. Accumulating active p53 in the nucleus by inhibition of nuclear export: a novel strategy to promote the p53 tumor suppressor function. Exp Cell Res. 1999;253:315-324.
39. Kuruvilla J, Savona M, Baz R, et al. Selective inhibition of nuclear export with selinexor in patients with non-Hodgkin lymphoma. Blood. 2017;129:3175-3183.
40. Gandhi AK, Kang J, Havens CG, et al. Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4(CRBN.). Br J Haematol. 2014;164:811-821.
41. Lagrue K, Carisey A, Morgan DJ, et al. Lenalidomide augments actin remodeling and lowers NK-cell activation thresholds. Blood. 2015;126:50-60.
42. Hernandez-Ilizaliturri FJ, Reddy N, Holkova B, et al. Immunomodulatory drug CC-5013 or CC-4047 and rituximab enhance antitumor activity in a severe combined immunodeficient mouse lymphoma model. Clin Cancer Res. 2005;11:5984-5992.

43. Leonard JP, Trneny M, Izutsu K, et al; AUGMENT Trial Investigators. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol. 2019;37:1188-1199.

44. Horton HM, Bernett MJ, Pong E, et al. Potent in vitro and in vivo activity of an Fc-engineered anti-CD19 monoclonal antibody against lymphoma and leukemia. Cancer Res. 2008;68:8049-8057.

45. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol. 2020;38:155-165.

46. Hamadani M, Radford J, Carlo-Stella C, et al. Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma. Blood. Epub 2020 Nov 19.

47. June CH, Sadelain M. Chimeric antigen receptor therapy. N Engl J Med. 2018;379:64-73.

48. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377:2531-2544.

49. Schuster SJ, Bishop MR, Tam CS, et al; JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380:45-56.

50. Abramson JS, Gordon LI, Palomba ML, et al. Updated safety and long term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL. J Clin Oncol. 2018; 36:15s (suppl; abstr 7505).

51. Hutchings M, Carlo-Stella C, Bachy E, et al. Glofitamab step-up dosing induces high response rates in patients with hard-to-treat refractory or relapsed non-Hodgkin lymphoma. Blood. 2020;136(suppl 1):46-48.

52. Hutchings M, Mous R, Clausen MR, et al. Subcutaneous epcoritamab induces complete responses with an encouraging safety profile across relapsed/refractory B-cell non-Hodgkin lymphoma subtypes, including patients with prior CAR-T therapy: updated dose escalation data. Blood. 2020;136(suppl 1):45-46.

53. Bannerji R, Allan JN, Arnason JE, et al. Odronextamab (REGN1979), a human CD20 x CD3 bispecific antibody, induces durable, complete responses in patients with highly refractory B-cell non-Hodgkin lymphoma, including patients refractory to CAR T therapy. Blood. 2020;136(suppl 1):42-43.

54. Schuster SJ, Bartlett NL, Assouline S, et al. Mosunetuzumab induces complete remissions in poor prognosis non-Hodgkin lymphoma patients, including those who are resistant to or relapsing after chimeric antigen receptor T-cell (CAR-T) therapies, and is active in treatment through multiple lines. Blood. 2019; 134(suppl 1):6.

55. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28:4184-4190.

56. Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol. 2020;21:978-988.

57. Salles GDJ, Duell J, Gonzalez B, et al. Long-term outcomes from the phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma. Presented at: 25th EHA Congress. 2020. Abstract EP1201.

58. Thapa B, Caimi PF, Ardeshna KM, et al. CD19 antibody-drug conjugate therapy in DLBCL does not preclude subsequent responses to CD19-directed CAR T-cell therapy. Blood Adv. 2020;4:3850-3852.

59. Kalakonda N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. Lancet Haematol. 2020;7:e511-e522.

60. Carlo-Stella C, Zinzani PL, Kahl B, et al.Initial results of a phase 2 study of loncastuximab tesirine, a novel pyrrolobenzodiazepine-based antibody-drug conjugate, in patients with relapsed or refractory diffuse large B-cell lymphoma. Presented at: 25th EHA Congress. 2020. Abstract S233.

61. Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371:213-223.

62. Byrd JC, Furman RR, Coutre SE, et al. Ibrutinib treatment for first-line and relapsed/refractory chronic lymphocytic leukemia: final analysis of the pivotal phase Ib/II PCYC-1102 study. Clin Cancer Res. 2020;26:3918-3927.

63. Solman IG, Blum LK, Hoh HY, et al. Ibrutinib restores immune cell numbers and function in first-line and relapsed/refractory chronic lymphocytic leukemia. Leuk Res. 2020;97:106432.

64. Sun C, Tian X, Lee YS, et al. Partial reconstitution of humoral immunity and fewer infections in patients with chronic lymphocytic leukemia treated with ibrutinib. Blood. 2015;126:2213-2219.

65. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med. 2015;373:2425-2437.

66. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:43-56.

67. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med. 2019;381:432-443.

68. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. N Engl J Med. 2018; 379:2517-2528.

69. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet. 2020;395:1278-1291.

70. Al-Sawaf O, Zhang C, Robrecht S, et al. Clonal dynamics after venetoclax-obinutuzumab therapy: novel insights from the randomized, phase 3 CLL14 trial. Blood. 2020;136(suppl 1):22-23.

71. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2020;21:1188-1200.

72. Hiddemann W, Barbui AM, Canales MA, et al. Immunochemotherapy with obinutuzumab or rituximab for previously untreated follicular lymphoma in the GALLIUM study: influence of chemotherapy on efficacy and safety. J Clin Oncol. 2018;36:2395-2404.

73. Rummel MJ, Niederle N, Maschmeyer G, et al; Study Group Indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013; 381:1203-1210.

74. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare study. J Clin Oncol. 2015;33:2516-2522.

75. Freeman CL, Kridel R, Moccia AA, et al. Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma. Blood. 2019;134:761-764.

76. Sarkozy C, Trneny M, Xerri L, et al. Risk factors and outcomes for patients with follicular lymphoma who had histologic transformation after response to first-line immunochemotherapy in the PRIMA trial. J Clin Oncol. 2016;34:2575-2582.

77. Sarkozy C, Maurer MJ, Link BK, et al. Cause of death in follicular lymphoma in the first decade of the rituximab era: a pooled analysis of French and US cohorts. J Clin Oncol. 2019;37:144-152.

78. Morschhauser F, Fowler NH, Feugier P, et al; RELEVANCE Trial Investigators. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. N Engl J Med. 2018;379:934-947.

79. Becnel MR, Nastoupil LJ, Samaniego F, et al. Lenalidomide plus rituximab (R^2) in previously untreated marginal zone lymphoma: subgroup analysis and long-term follow-up of an open-label phase 2 trial. Br J Haematol. 2019;185:874-882.

80. Kiesewetter B, Willenbacher E, Willenbacher W, et al; AGMT Investigators. A phase 2 study of rituximab plus lenalidomide for mucosa-associated lymphoid tissue lymphoma. Blood. 2017;129:383-385.

81. Bartlett NL, Costello BA, LaPlant BR, et al. Single-agent ibrutinib in relapsed or refractory follicular lymphoma: a phase 2 consortium trial. Blood. 2018; 131:182-190.

82. Opat S, Tedeschi A, Linton K, et al. Efficacy and safety of zanubrutinib in patients with relapsed/refractory marginal zone lymphoma: initial results of the MAGNOLIA (BGB-3111-214) trial. Blood. 2020;136(suppl 1):28-30.

83. Treon SP, Meid K, Gustine J, et al. Long-term follow-up of ibrutinib monotherapy in symptomatic, previously treated patients with Waldenström macroglobulinemia. J Clin Oncol. 2021;39:565-575.

84. Dimopoulos MA, Tedeschi A, Trotman J, et al; iNNOVATE Study Group and the European Consortium for Waldenström's Macroglobulinemia. Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia. N Engl J Med. 2018;378:2399-2410.

85. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood. 2020;136:2038-2050.

86. Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: a phase II study of duvelisib (IPI-145) in patients with refractory indolent non-Hodgkin lymphoma. J Clin Oncol. 2019;37:912-922.

87. Dreyling M, Santoro A, Mollica L, et al. Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study. Am J Hematol. 2019;95:362-371.

88. Hanlon A, Brander DM. Managing toxicities of phosphatidylinositol-3-kinase (PI3K) inhibitors. Hematology Am Soc Hematol Educ Program. 2020; 2020:346-356.

89. Fowler NH, Samaniego F, Jurczak W, et al. Umbralisib monotherapy demonstrates efficacy and safety in patients with relapsed/refractory marginal zone lymphoma: a multicenter, open label, registration directed phase II study. J Clin Oncol. 2019;37:15s (suppl; abstr 7506).

90. Jacobson C, Chavez JC, Sehgal AR, et al. Primary analysis of Zuma-5: a phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL). Blood. 2020;136(suppl 1):40-41.

91. Assouline SE, Kim WS, Sehn LH, et al. Mosunetuzumab shows promising efficacy in patients with multiply relapsed follicular lymphoma: updated clinical experience from a phase I dose-escalation trial. Blood. 2020;136(suppl 1):42-44.

92. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet. 2018;391:659-667.

93. Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol. 2020;38:2849-2861.

94. Song Y, Zhou K, Zou D, et al. Treatment of patients with relapsed or refractory mantle-cell lymphoma with zanubrutinib, a selective inhibitor of Bruton's tyrosine kinase. Clin Cancer Res. 2020;26:4216-4224.

95. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood. 2018;132:2446-2455.

96. Brown JR, Robak T, Ghia P, et al. Efficacy and safety of zanubrutinib in patients with treatment-naïve (TN) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with del(17p): follow-up results from arm C of the SEQUOIA (BGB-3111-304) trial. Blood. 2020;136(suppl 1):11-12.

97. Tam CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. Haematologica. Epub 2020 Oct 13.

98. Gribben JG, Jurczak W, Jacobs RW, et al. Umbralisib plus ublituximab (U2) is superior to obinutuzumab plus chlorambucil (O+Chl) in patients with treatment naïve (TN) and relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): results from the phase 3 Unity-CLL study. Blood. 2020;136(suppl 1):37-39.

99. Tam CS, Siddiqi T, Allan JN, et al. Ibrutinib (Ibr) plus venetoclax (Ven) for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): results from the MRD cohort of the phase 2 CAPTIVATE study. Blood. 2019;134(suppl 1):35.

100. Wierda WG, Tam CS, Allan JN, et al. Ibrutinib (Ibr) plus venetoclax (Ven) for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): 1-year disease-free survival (DFS) results from the MRD cohort of the phase 2 CAPTIVATE study. Blood. 2020;136(suppl 1):16-17.

101. Salles G, Schuster SJ, de Vos S, et al. Efficacy and safety of idelalisib in patients with relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study. Haematologica. 2017;102:e156-e159.

102. Dickinson MJ, Morschhauser F, Iacoboni G, et al. CD20-TCB (RG6026), a novel "2:1" format T-cell-engaging bispecific antibody, induces complete remissions in relapsed/refractory B-cell non-Hodgkin's lymphoma. Hematol Oncol. 2019;37(S2):92-93.

103. Andorsky DJ, Coleman M, Yacoub A, et al. MAGNIFY phase IIIb interim analysis of induction R2 followed by maintenance in relapsed/refractory indolent NHL. J Clin Oncol. 2020;38:15s (suppl; abstr 8046).

Navigating Myelodysplastic and Myelodysplastic/Myeloproliferative Overlap Syndromes

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overview

Myelodysplastic syndromes (MDS) and MDS/myeloproliferative neoplasms (MPNs) are clonal diseases that differ in morphologic diagnostic criteria but share some common disease phenotypes that include cytopenias, propensity to acute myeloid leukemia evolution, and a substantially shortened patient survival. MDS/MPNs share many clinical and molecular features with MDS, including frequent mutations involving epigenetic modifier and/or spliceosome genes. Although the current 2016 World Health Organization classification incorporates some genetic features in its diagnostic criteria for MDS and MDS/MPNs, recent accumulation of data has underscored the importance of the mutation profiles on both disease classification and prognosis. Machine-learning algorithms have identified distinct molecular genetic signatures that help refine prognosis and notable associations of these genetic signatures with morphologic and clinical features. Combined geno-clinical models that incorporate mutation data seem to surpass the current prognostic schemes. Future MDS classification and prognostication schema will be based on the portfolio of genetic aberrations and traditional features, such as blast count and clinical factors. Arriving at these systems will require studies on large patient cohorts that incorporate advanced computational analysis. The current treatment algorithm in MDS is based on patient risk as derived from existing prognostic and disease classes. Luspatercept is newly approved for patients with MDS and ring sideroblasts who are transfusion dependent after erythropoietic-stimulating agent failure. Other agents that address red blood cell transfusion dependence in patients with lower-risk MDS and the failure of hypomethylating agents in higher-risk disease are in advanced testing. Finally, a plethora of novel targeted agents and immune checkpoint inhibitors are being evaluated in combination with a hypomethylating agent backbone to augment the depth and duration of response and, we hope, improve overall survival.

INTRODUCTION

Myelodysplastic syndromes (MDS) are a group of clonal myeloid neoplasms characterized by one or more cytopenias, morphologic dysplasia in maturing hematopoietic cells, and varying propensity to progress to acute myeloid leukemia (AML). Although blasts may be increased in some forms of MDS, a historical cutoff of 20% myeloblasts in blood or bone marrow is used to separate MDS from AML. Myelodysplastic syndromes are currently distinguished from premalignant clonal hematopoietic proliferations affecting patients with cytopenia (clonal cytopenia of undetermined significance) by an identification threshold of at least 10% dysplastic forms in at least one hematopoietic cell lineage, although this requirement of morphologic dysplasia has been challenged in some recent studies.[1] The clinical, morphologic, and genetic heterogeneity within MDS is recognized by its division into subtypes in the 2016 World Health Organization (WHO) Classification, based on the presence or absence of ring sideroblasts, increased blasts, and dysplasia involving one versus multiple hematopoietic lineages; in addition, the cytogenetic abnormality del(5q), when occurring in the context of a non-complex karyotype and in the absence of increased blasts, defines a specific MDS subtype.[2] The clinical context—in particular, any prior exposure to cytotoxic chemotherapy/radiotherapy or the presence of pancytopenia—also influences WHO MDS subtyping, and a special MDS subtype, refractory cytopenia of childhood, is recognized in pediatric patients.

As a disease classification scheme, the purpose of the WHO Classification is to recognize entities within MDS that have a distinct biology from one another and are identified by applying specific and mutually exclusive diagnostic criteria. In contrast, prognostic stratification schemes in MDS often share some criteria with classification schemes (e.g., the blast percentage) but merely aim to create categories of disease with different prognoses that predict patient outcome. The most widely used prognostic schemes for MDS include the International Prognostic Scoring System (IPSS), initially proposed in 1997 and updated as a revised form (IPSS-R) in 2012,[3] and the WHO Classification–based

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PRACTICAL APPLICATIONS

- Myelodysplastic syndrome (MDS) classification currently relies mainly on its morphologic features and presence or absence of a del(5q) cytogenetic abnormality; however, recent advances in genetic sequencing have enabled new molecular-based classifications that may better reflect its biologic heterogeneity.
- Mutations in MDS strongly impact its prognosis; incorporation of mutational data improves existing MDS prognostic schemes to better predict patient risk.
- Many novel agents for treating MDS are under study to address transfusion dependence in lower-risk disease after erythropoietic-stimulating agents fail to augment hypomethylating agent response rates and durability and to consider as salvage therapy when hypomethylating agents fail.
- In 2020, two new drugs were approved for MDS: (1) Luspatercept is indicated for the treatment of patients with MDS with ring sideroblasts who are transfusion dependent as second-line therapy after erythropoietic-stimulating agents, and (2) decitabine/cedazuridine is an oral version of the hypomethylating agent decitabine that, in combination with a cytidine deaminase inhibitor, offers pharmacokinetic and pharmacodynamic activity equivalent to intravenous monotherapy.
- MDS/myeloproliferative neoplasm (MPN) overlap neoplasms demonstrate features of MDS and MPN and consist of four adult-onset entities—chronic myelomonocytic leukemia, MDS/MPN with ring sideroblasts and thrombocytosis, atypical chronic myeloid leukemia (*BCR-ABL1* negative), and unclassifiable MDS/MPN—and one pediatric onset entity, juvenile myelomonocytic leukemia.
- Although molecular features are not specific to any of these MDS/MPN overlap neoplasms, relative enrichment of mutations in *ASXL1, TET2, SRSF2*, and *SETBP1* are seen in chronic myelomonocytic leukemia; *SF3B1* and *JAK2*V617F in MDS/MPN with ring sideroblasts and thrombocytosis; *ASXL1, EZH2, ETNK1*, and *SETBP1* in atypical chronic myeloid leukemia; *TP53* in unclassifiable MDS/MPN, and RAS pathway mutations (*PTPN11, CBL, NF1, NRAS,* and *KRAS*) in juvenile myelomonocytic leukemia.

prognostic scoring system.[4] The variables that are used to define disease categories in the WHO Classification and to define prognostic risk strata in the IPSS-R are shown in Table 1.

An important limitation in both the WHO Classification and the current prognostic schemes is their lack of inclusion of mutation data. The karyotype by conventional cytogenetics has been known for decades to have powerful prognostic value in MDS and is incorporated into the IPSS-R scheme.[5] However, in recent years, an accumulation of data has supported the important role that recurring mutations in certain genes play in MDS pathogenesis: specific gene mutations both highlight distinct disease categories and show strong influence on patient prognosis. For example, mutation in the splicing factor *SF3B1* is closely associated with the presence of bone marrow ring sideroblasts in MDS.[6] This genetic-morphologic correlation validated MDS with ring sideroblasts (MDS-RS) as a distinct MDS disease category and led to the separation of MDS-RS with multilineage dysplasia from MDS with multilineage dysplasia that lacks ring sideroblasts in the 2016 WHO Classification, despite their similar prognoses.[2] In this section, the evolving role of genetics in informing both the classification of MDS and its prognostic risk stratification will be reviewed.

MOLECULAR GENETICS IN THE CLASSIFICATION OF MYELODYSPLASTIC SYNDROMES

The current WHO categories of MDS and their typical observed patterns of progression (including progression to AML) are shown in Fig. 1A. MDS-RS in the WHO Classification is an indolent disease subtype that requires the presence of ring sideroblasts in at least 15% of erythroid precursors as well as lack of excess blasts. Mutation in the splicing factor gene *SF3B1* is strongly associated with the presence of ring sideroblasts in MDS, and *SF3B1* is the only mutation in MDS associated with a relatively favorable prognosis.[7] A small subset of *SF3B1*-mutated cases may have less than 15% ring sideroblasts, and these appear to have similar prognosis and clinical presentation to cases with 15% or more ring sideroblasts.[7,8] In recognition of this, the 2016 WHO Classification allows a diagnosis of MDS-RS with only 5% or more ring sideroblasts (instead of $\geq$ 15%) in the presence of an *SF3B1* mutation. However, more recent data suggest that an *SF3B1*-mutated MDS category may be a more biologically meaningful definition than a category based on the presence or absence of ring sideroblasts: an *SF3B1*-based categorization identifies a more homogeneous group based on comutation patterns, clinical features, and patient outcome compared with an RS-based categorization.[9] Of note, approximately 20% of patients with MDS-RS lack an *SF3B1* mutation. These patients have a poorer prognosis versus patients with *SF3B1*-mutated MDS and their disease would optimally be classified separately.[9,10] Moreover, although the WHO currently subdivides the MDS-RS category according to single versus multilineage dysplasia, the latter appears to be accounted for largely by the presence of additional cooperating mutations, such as *TET2*, *DNMT3A*, and *RUNX1*.[10]

TABLE 1. Comparison of Criteria in the WHO Classification and IPSS-R Schemes for Myelodysplastic Syndromes and Potential Refinement by the Addition of Molecular Genetic Features[2,3,17,20,26,147]

Feature	WHO Classification (2016)	IPSS-R (2012)
Morphologic dysplasia	Yes (single vs. multilineage)	Not incorporated
Ring sideroblasts in bone marrow	Yes	Not incorporated
Cytopenias	Yes (only pancytopenia, which impacts classification of lower-risk disease subtypes)	Yes (both the number and depth of cytopenias)
Blast % in blood	Yes	Not incorporated
Blast % in bone marrow	Yes	Yes
Karyotype	Yes [isolated del(5q) is the only defining feature]	Yes (five prognostic groups)
Molecular genetic abnormalities (current)	*SF3B1* (impacts classification of lower-risk subtypes with ring sideroblasts)	Not incorporated
Molecular genetic abnormalities (future)	Potentially useful in defining genomically distinct groups: *SF3B1, TET2, SRSF2, NRAS, KRAS, STAG2, JAK2, BCORL1, RUNX1, ETV6, U2AF1, TP53, DNMT3A, NPM1, FLT3, IDH1*	Favorable: *SF3B1*; unfavorable: *TP53, ASXL1, SRSF2, U2AF1, NRAS, KRAS, IDH1, IDH2, RUNX1, EZH2, STAG2, PHF6, NPM1*

Abbreviations: IPSS-R, International Prognostic Scoring System Revised; WHO, World Health Organization.

At the other end of the spectrum from the *SF3B1* mutation in MDS is the *TP53* mutation, which confers a markedly inferior prognosis to MDS, particularly when it is multihit.[11,12] In the therapy-related setting (which is over-represented in *TP53*-mutated MDS), the outcome of these cases appears to be uniformly poor irrespective of the blast percentage.[13] Yet, *TP53*-mutated MDS can be found across the various WHO MDS subtypes, including MDS with del(5q).[14] The shared genetic signature (complex karyotype) and uniformly poor prognosis advocate for consideration of placing *TP53*-mutated MDS in a single disease category, irrespective of the blast count or relation to therapy. MDS cases with t(3;3) or an inv(3) cytogenetic abnormality also behave similarly irrespective of blast percentage, even if classified as AML.[15] Finally, rare cases with blast counts in the MDS range may bear mutations typically seen in de novo AML, such as *NPM1, FLT3, IDH1,* or *RUNX1*. These cases appear to share more biologic features with de novo AML, exhibiting the same mutations as other MDS, and may be more appropriately classified as such according to their AML-like mutation profile rather than the 20% blast percentage cutoff.[16,17]

Wider application of molecular abnormalities to MDS classification is challenging because most MDS cases bear multiple mutations, and these mutations display complex interactions, patterns of co-occurrence, and hierarchical ontogeny as assessed by their relative variant allele fractions.[18] *TET2* and *SRSF2* comutation in MDS has been associated with relative monocytosis and clinical characteristics and flow cytometry aberrations similar to those of chronic myelomonocytic leukemia (CMML), suggesting that these cases may be more optimally classified together with CMML (so-called oligomonocytic CMML) or at least as a CMML-like type of MDS.[19] Recently, Bayesian machine-learning analyses have been applied to MDS cohorts in an effort to create genomic disease categories in an unsupervised fashion that avoids the bias of a historic classification scheme; such schemes can also take into account the genetic ontogeny by integrating mutation hierarchy and comutation patterns, which are more robust than single-gene analysis.[17,20] In one study, Bersanelli and colleagues used Bayesian analysis to define distinct genomic categories of MDS based on the presence of isolated del(5q) cytogenetic abnormality, *TP53* mutation, *SF3B1* mutation, *SRSF2* mutation, *U2AF1* mutation, or AML-like mutations (*DNMT3A, NPM1, FLT3, IDH1,* and *RUNX1*) or without any of the above genetic aberrations, further refined by additional cooperating mutations or cytogenetic aberrations.[17] These different subtypes showed substantial positive and negative associations with secondary mutations and also correlated with distinctive clinical and pathologic parameters, such as presence of ring sideroblasts, types of cytopenias, excess blasts, and patient survival, yet were heterogeneous in terms of their WHO disease subtype distributions. In another study, Nagata and colleagues applied machine learning to a series of 1,079 patients with MDS and identified six distinct molecular genetic signatures in high-risk MDS (including one strongly enriched in *TP53* mutations) and seven low-risk MDS signatures.[20] Many of these groups correlated with the MDS genomic subtypes identified in the study of Bersanelli et al, which indicates that this approach is applicable across diverse patient cohorts. Again, they found important associations of the specific genetic signatures with morphologic and clinical features that transcended the specific

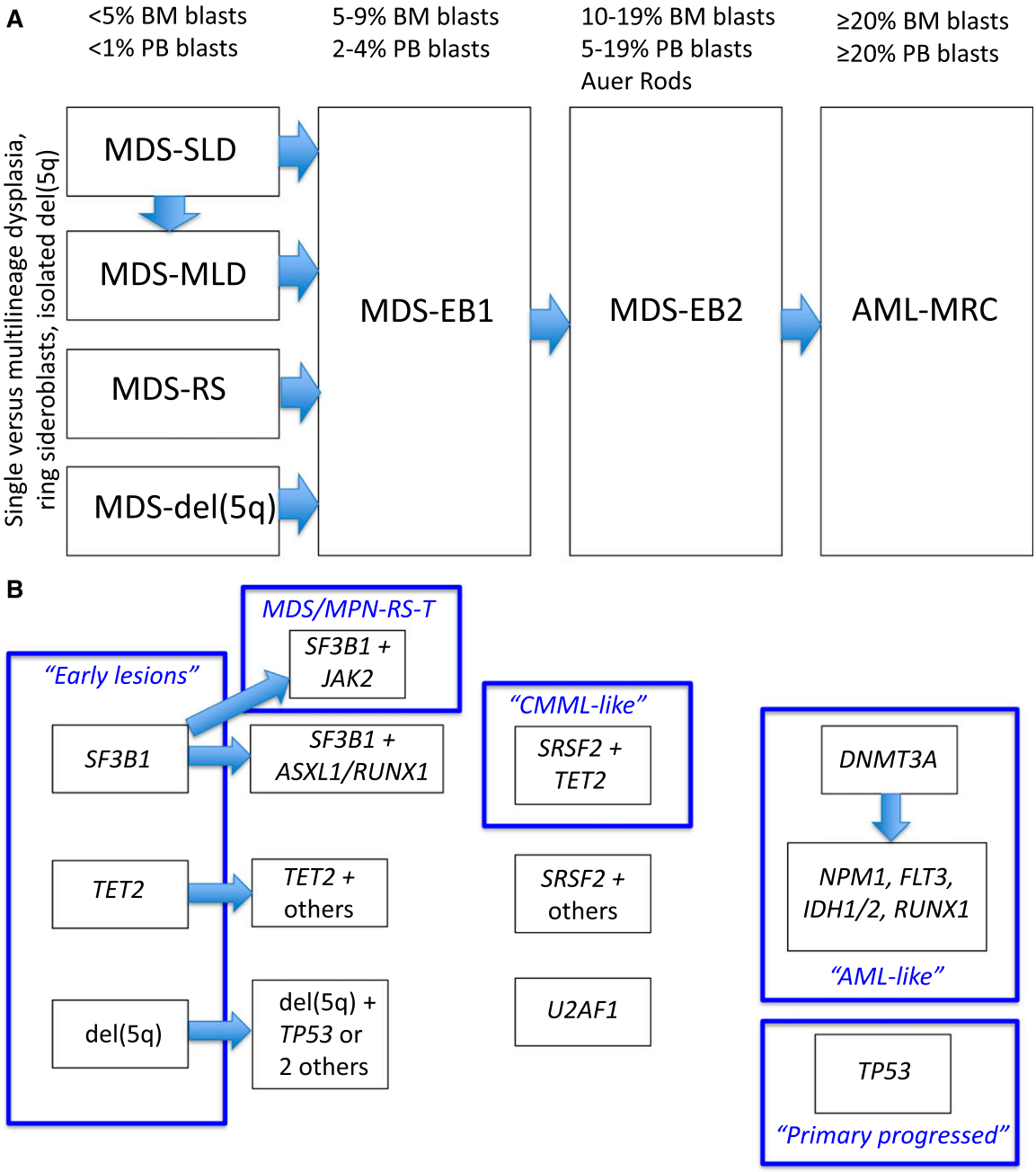

FIGURE 1. Schematic for Current WHO MDS Classification Scheme and Possible Future Genetics-Based MDS Classification
(A) Current (2016) WHO MDS Classification scheme. Typical patterns of progression are indicated by arrows, including progression to AML. Entities with no increase of blasts are classified based on the extent of dysplasia, ring sideroblasts, and isolated del(5q) on karyotype, whereas all cases with increased blasts are classified solely on the basis of their blood and bone marrow blast percentage (and presence or absence of Auer rods). Therapy-related MDS and AML are considered as one entity, irrespective of the blast count or other features. Not shown on this diagram are MDS, unclassifiable, and refractory cytopenia of childhood disease subtypes. (B) A possible genomic grouping scheme for MDS based on unsupervised clustering analyses. Early lesions are typically acquired during the initial phases of MDS development but may acquire secondary genetic events as indicated by arrows. Cases within each genomic entity could be risk stratified based on additional cooperating genetic events and clinical features and the blast percentage. AML-like gene mutations are associated with high blast counts and rapid progression to AML, and CMML-like lesions, with increased monocytes. Primary progressed *TP53*-mutated MDS is highly aggressive even in the absence of increased blasts. Based on data from references [17,20].
Abbreviations: WHO, World Health Organization; MDS, myelodysplastic syndromes; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; SLD, single lineage dysplasia; MLD, multilineage dysplasia; RS, ring sideroblasts; EB, excess blasts; MRC, myelodysplasia-related changes; BM, bone marrow; PB, peripheral blood.

WHO Classification diagnosis assigned to each case.[20] Key gene mutations that influenced genetic signatures in the studies of Nagata et al and Bersanelli et al and represent potential candidates for constructing a genomically based MDS classification are shown in Table 1.

These findings beg the question as to whether morphologic features or the hierarchy of genetic features should define disease classes in MDS; indeed, cytogenetic and, more recently, molecular genetic features have largely superseded morphology in the WHO Classification of AML. Given the increasing use of therapies in MDS that target specific gene products or pathways, moving toward a more genetically based classification akin to that of AML is likely to provide a more clinically meaningful system. Classification systems optimally identify diseases that are stable over time or exhibit similar patterns of clinical and pathologic progression but retain the core ontogeny of their original presentation. This aspect is apparent in the WHO Classification of myeloproliferative neoplasms, in which each disease maintains its unique designation even as it progresses: for example, essential thrombocythemia progresses to post-essential thrombocythemia myelofibrosis, myelofibrosis after essential thrombocythemia in accelerated phase, and myelofibrosis after essential thrombocythemia in blast phase (considered equivalent to AML).[21] However, this practice does not extend to MDS, in which cases of diverse origins are grouped together under a single category of MDS with excess blasts after blasts in blood or bone marrow increase above certain thresholds (Fig. 1A). Retaining the original genetic ontogeny throughout the disease course could facilitate the understanding of unique patterns of progression in specific disease subtypes and also highlight therapeutic strategies based on underlying genetic features that could be effective even in MDS with excess blasts.[22,23] A possible model of such a genomic classification of MDS is shown in Fig. 1B; of course, additional validation of data on large patient cohorts and widespread applicability across varied settings are needed before applying such a scheme to clinical practice.

MOLECULAR GENETICS IN THE PROGNOSTICATION OF MYELODYSPLASTIC SYNDROMES

Prognostic schemes in MDS seek to predict patient outcome (typically measured by overall survival and/or time to transformation to AML) as accurately as possible by considering both disease-related and patient-related factors (Table 1). It should be noted that time to transformation to AML and leukemia-free survival are determined by identifying a blast count of at least 20%. This arbitrary threshold may dictate a change in therapy but does not necessarily reflect a true alteration of the disease biology in all cases.[24] Prognostic models must apply in the real world to patients undergoing treatment, yet many of these studies and scales, such as the IPSS-R, are based on patients who did not receive disease-modifying therapies and are applicable at the time of diagnosis but not necessarily later during the course of disease.[3] These same caveats apply to the integration of molecular genetics into existing prognostic models.

Just as the recent explosive advance in sequencing has allowed mutation data to inform MDS classification, mutation profiles also strongly inform the prognostic modeling of MDS. Importantly, karyotype abnormalities retain their independent prognostic value even in the current era of mutation testing, so mutational analysis does not obviate the need to obtain bone marrow karyotype. In a 2011 study by Bejar et al,[25] mutations in five genes (*TP53, EZH2, ETV6, RUNX1*, and *ASLX1*) were found to negatively impact MDS prognosis independent of the original IPSS patient category. In fact, the presence of any one of these gene mutations was found to have the effect of upstaging the disease to a more adverse prognostic group than suggested by the IPSS alone. As mentioned previously, *SF3B1* appears to be the only gene mutation in MDS associated with a more favorable outcome.[14] In a combined geno-clinical model, Nazha et al[26] found that *EZH2*, *SF3B1*, and *TP53* mutations independently impacted outcome when taking into account clinical, cytogenetic, and blast count covariables. Additionally, the total number of independent mutations has been associated with MDS patient outcome.[14] However, considering mutations as single units may not be optimal: in MDS, as with other myeloid neoplasms such as AML, mutations associate with one another in nonrandom ways and can have different implications depending on the context. For example, multihit *TP53* mutation has much stronger negative prognostic impact than a single *TP53* mutation in the context of a preserved wild-type *TP53* allele.[11] The isolated del(5q) cytogenetic abnormality confers a much better prognosis in a genetically simple background (no mutations or one mutation) than if it is accompanied by two or more somatic mutations.[17] Candidate gene mutations for which current evidence supports possible inclusion in a future MDS prognostic model are shown in Table 1.

Although a purely genetic classification could eventually replace a morphologic classification, morphology will still likely have a role in MDS prognostication. In particular, blast percentage retains strong prognostic power in multiple studies, even in multivariable models that include comprehensive genomic analysis.[17,27] The blast percentage in MDS in a sense could be considered analogous to the clinical stage of a solid tumor: increased blasts reflect progressive hematopoietic maturation arrest as the disease advances. Genes associated with increased blasts in MDS include Ras-pathway genes (*NRAS, KRAS, FLT3*) and *RUNX1*, yet these genetic associations do not obviate the impact of blast percentage on prognostic models.[17] Thus, prognostic models will continue to require an accurate blast percentage to optimally predict patient outcome. Of note, blast percentage in the blood also impacts outcome (and is

reflected in the WHO Classification disease categories) yet is not taken into account in the current IPSS-R scheme; MDS cases with increased blasts in the blood have poorer outcomes, even if marrow blasts are not increased.[28,29]

Accumulative data on the genetics of MDS have the potential to transform both its classification and risk stratification. An optimal future MDS classification will likely be based mainly on the specific portfolio of genetic aberrations in each case. Arriving at such a classification scheme will require studies on large patient cohorts that incorporate advanced computational analysis to create a robust and unbiased scheme; indeed, some such studies have already been published,[17,20] but require additional validation across patient cohorts. Although morphologic dysplasia currently continues to define the disease we call MDS, the distinction between single and multilineage dysplasia (which is often subjective and not always reproducible) and even the presence or absence of ring sideroblasts in MDS subtyping will likely be superseded by the genetic signature in future classification schemes. Even in the setting of detailed genetic analysis, blast percentage remains a critical factor in prognosis and should continue to be incorporated in prognostic schemes. However, its role in classification is uncertain, as it may be more prudent to retain the genetic backbone to classify an MDS case as it progresses through accumulation of blasts rather than using excess blasts as a final common pathway of progressed disease. In terms of prognosis, panels assessing mutations in up to 50 key genes improve existing risk stratification schemes using cytopenias, cytogenetics, and blast percentage.[20] Future MDS prognostic schemes enhanced by mutation data will be more complex than existing schemes but will allow better patient risk stratification and optimization of treatment selection.[30] Determination of the optimal composition of such a panel and how to integrate the many complex mutation–mutation interactions require detailed analysis.

Gazing even further into the future, DNA methylation, microRNA, and/or gene expression profiling may reveal additional associations that are not captured by a purely genomic classification limited to mutations, chromosomal translocations, and copy number gains/losses.[31] The biology of an individual MDS case is likely influenced not only by its hard-wired genetic deviations but also by epigenetic alterations and the bone marrow microenvironment.[32,33] However, incorporating DNA methylation or gene expression profiling into MDS classification is currently limited by the lack of availability of these techniques in routine clinical practice.

UPDATES ON THE MANAGEMENT OF MYELODYSPLASTIC SYNDROMES WITH THE INCORPORATION OF NOVEL AGENTS

The phenotype of MDS includes cytopenias and their resultant complications, such as symptomatic anemia, infections, and bleeding. Iron overload is common in transfused patients, and death from cardiovascular disease (7.7%) is higher than expected.[34] Although two-thirds to three-quarters of patients are considered lower risk using conventional prognostic scoring systems, there is nothing benign about this disease; the life expectancy compared with age-matched controls is reduced by more than 50%, and the majority die prematurely from nonleukemic causes.[35]

Goals of therapy traditionally vary according to risk score; however, there is great overlap in these goals for many disease risk categories, which include the reduction or elimination of transfusion dependence, the amelioration of symptomatic cytopenias, the delay or prevention of progression to AML, and improved overall survival (OS). Cure by allogeneic stem cell transplant is possible in the minority of patients, so improved quality of life is also a ubiquitous goal.

This section will discuss completed and ongoing clinical trials (summarized in Table 2) of novel agents that address the three most pressing problems in MDS: the management of anemia and transfusion dependence in lower-risk disease after erythropoietic-stimulating agents fail to work, the low and brief response rates of hypomethylating agents in use today as monotherapy, and the management of disease after hypomethylating agents fail. Allogeneic stem cell transplant and thrombopoietic agents will not be discussed. With better insights into pathophysiology and mechanisms of response or resistance, there is real potential for more personalized approaches and improved clinical outcomes.

HOW WE TREAT MYELODYSPLASTIC SYNDROMES TODAY

The current (and potentially future) treatment algorithm for MDS is depicted in Fig. 2 (highlighted in red). It is sobering that two large retrospective population studies have not demonstrated improved OS in MDS during 2 decades despite the introduction of the disease-modifying hypomethylating agents and lenalidomide between 2004 and 2006.[36,37]

Patients are traditionally risk stratified into lower- and higher-risk categories, and treatments are geared accordingly.

LOWER-RISK DISEASE

Lower-risk MDS implies lower risk of leukemia and imminent death and typically refers to an IPSS score of less than 1.0 (low and intermediate-1)[38] or an IPSS-R score of 3.5 or lower (very low, low, and part of intermediate).[3] As discussed, some patients with lower-risk disease may be have their disease upstaged with mutational testing,[25] and 65% of patients in the IPSS-R intermediate-risk category have scores higher than 3.5 and survival rates as short as 15.4 months.[39]

Patients who do not experience or lose response to erythropoietic-stimulating agents face treatment challenges, because transfusion dependence and density correlate with shorter survival,[40] and approved treatment options to date have remained limited.

TABLE 2. Summary of Selected Ongoing Clinical Trials in Myelodysplastic Syndromes

Agent	Sponsor	No. of Patients	Phase	Risk	Scenario	Study ID	Primary Endpoints	Mechanism of Action
Roxadustat	Fibrogen	184	III	Lower risk	Lower transfusion burden vs. placebo	NCT03263091	TI × 8 weeks	HIF1α prolyl hydroxylase inhibitor
Luspatercept	BMS/Celgene	350	III	Lower risk	Transfusion dependent vs. placebo	NCT03682536	TI × 24 weeks	TGFβ ligand trap
ASTX727	Astex	160	I/II (randomized)	Lower risk	Lower risk, symptomatically cytopenic	NCT03502668	MTD and HI	Oral HMA
LB-100	Moffitt	47	Ib/II	Low-Int-1	Failed or intolerant of standard therapy	NCT03886662	MTD and ORR	PP2A inhibitor
Imetelstat	Geron	225	II/III	Low-Int-1	Relapsed or refractory to ESAs vs. placebo	NCT02598661	TI × 8 weeks	Telomerase inhibitor
ALX148	ALX Oncology	63	I/II	Higher risk	Phase I: first line, R/R Phase II: first line	NCT04417517	MTD and ORR	Inhibits the CD47-SIRPα signaling pathway
MBG 453	Novartis	500	III	Intermediate-high risk	First-line AZA +/− MBG453	NCT04266301	OS	Anti-TIM3 immune checkpoint inhibitor
Venetoclax	Abbvie	500	III	Higher risk	First line AZA +/− venetoclax	NCT04401748	CR and OS	Pro-apoptotic
Venetoclax	MD Anderson	58	I/II	Higher risk	R/R MDS, CMML, AZA + venetoclax	NCT04550442	MTD and ORR	Pro-apoptotic
Venetoclax + gilteritinib	MD Anderson and NCI	42	I/II	Higher risk MDS or AML *FLT3* mutated	R/R (phase I) First line (phase II)	NCT04140487	MTD + ORR	Pro-apoptotic and FLT3 inhibitor
Venetoclax + trametininb	MD Anderson and NCI	40	II	Higher risk	Cohort A: first-line AML + AZA	NCT04487106	1-yr OS and CR	MEK inhibitor
					Cohort B: R/R AML or higher risk MDS + AZA			
Magrolimab	Gilead	500	III	Higher risk	First-line AZA +/− magrolimab	NCT04313881	CR and CR duration	Anti-CD47 macrophage immune checkpoint inhibitor
AG120	GFM	68	II	Lower and higher risk: *IDH1* mutation	Cohort A: higher risk R/R HMA Cohort B: first-line higher risk + HMA Cohort C: lower risk, R/R ESA	NCT03503409	HI	IDH1 inhibitor
AG 221	GFM	68	II	Lower and higher risk: *IDH2* mutation	Cohort A: higher risk R/R HMA Cohort B: first-line higher risk + HMA Cohort C: lower risk, R/R ESA	NCT03744390	HI	IDH2 inhibitor
Nivolumab and ipilumumab	MD Anderson and NCI	160	II	Lower and higher risk	6 cohorts; previously treated with HMA	NCT02530463	ORR	Immune checkpoint inhibitors
Cusatuzumab	Janssen	170	II	Higher risk and CMML	First-line AZA +/− cusatuzumab	NCT04264806	ORR	Anti-CD70 antibody expressed on LSCs
Pevonedistat	Takeda	454	III	Higher risk and CMML	First-line AZA +/− pevonedistat	NCT03268954	EFS	NEDD8 inhibitor
	Vanderbilt-Ingram and NCI	71	II	Higher risk MDS and MDS/MPN	R/R AZA (5 days) + pevonedistat	NCT03238248	OS	
CPX-351	GFM	65	II I	Higher	First-line, untreated patients: cohort A First-line therapy after HMA failure: cohort B	NCT04273802	MTD and ORR	Cytotoxic
	MD Anderson and NCI	50	II	Higher risk and AML	R/R AML and failed HMA MDS	NCT03672539	Safety and ORR	

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; CMML, chronic myelomonocytic leukemia; EFS, event-free survival; HI, hematologic improvement; HMA, hypomethylating agent; LSCs, leukemia stem cells; ORR, overall response rate; OS, overall survival; MDS, myelodysplastic syndromes; MDS/MPN, myelodysplastic/myeloproliferative neoplasms; MTD, maximally tolerated dose; NCI, National Cancer Institute; R/R, relapsed/refractory; TI, transfusion independence.

WHAT ARE NEW DEVELOPMENTS FOR CURRENTLY APPROVED OPTIONS IN LOWER-RISK DISEASE?

Lenalidomide is indicated for the management of MDS and isolated del(5q) in patients who are transfusion dependent and have experienced failure of erythropoietic-stimulating agents, with expected transfusion independence and cytogenetic response rates of 65% to 70% and 30% to 40%, respectively.[23,41] An ongoing European cooperative group study is assessing the transfusion-free survival benefit afforded by lenalidomide in patients with non–transfusion-dependent MDS with del(5q).[42] Lenalidomide may also be trialed in the 90% of patients with non-del(5q) MDS who are transfusion dependent, but the expected response rates are lower (26%) and shorter (median response duration, 31 weeks), with no categoric clinical or molecular predictors of response yet identified and a high incidence of grade 3 to 4 neutropenia (62%).[43] Despite this, patients with responsive disease may experience improved overall quality of life.[44] Lenalidomide may restore the sensitivity of primitive erythroid precursors to erythropoietin, as evidenced by the superior erythroid response rates observed from the combined use of lenalidomide with erythropoietin alfa compared with lenalidomide alone in a French study[45] and a recently published phase III U.S. intergroup study.[46]

IMMUNOSUPPRESSIVE THERAPY

Immunosuppressive therapy with antithymocyte globulin and or cyclosporine in lower-risk MDS may be effective and induce durable responses in selected younger patients because of the innate and cellular immune dysregulation in the hematopoietic niche of MDS that contributes to disease pathogenesis, ineffective hematopoiesis, and evolution.[47] In the largest international cohort (207 patients), a retrospective study of patients with MDS treated with some form of immunosuppressive therapy, the overall response rate was 49% (complete remission [CR] + partial remission [PR], 16.8%; hematologic improvement, 32%), with 30% achieving red blood cell transfusion independence at a median time after immunosuppressive therapy of 9.4 weeks and lasting 19.9 months. By univariable analysis, the predictors of transfusion independence were hypocellular bone marrow (odds ratio, 3.25) and the receipt of ATG plus cyclosporine (odds ratio, 2.46), and *SF3B1* mutation trended as a negative prognostic factor (odds ratio, 0.17) but was not statistically significant.[48]

Other agents that target the inflammasome-mediated ineffective hematopoiesis in lower-risk disease are under evaluation, including canakinumab (NCT04239157), ibrutinib (NCT02553941), and the Toll-like receptor signaling inhibitor OPN-305.[49]

NEWLY APPROVED: LUSPATERCEPT

Signaling in the SMAD2–SMAD3 pathway is constitutively increased in the bone marrow cells of patients with MDS and exerts an inhibitory effect on red cell maturation. Luspatercept is a recombinant fusion protein that binds select transforming growth factor β superfamily ligands to decrease SMAD2 and SMAD3 signaling, thereby enabling erythroid maturation by means of late-stage erythroblast differentiation.[50] In the double-blind, placebo-controlled, phase III Medalist study, 229 patients with WHO-defined MDS-RS who were transfusion dependent and who had either experienced failure of erythropoietic-stimulating agents or were unlikely to experience a response on the basis of a serum erythropoietin level of more than 200 U/L were randomly selected (2:1) to receive either luspatercept or placebo in escalating doses (1–1.75 mg/kg subcutaneously every 3 weeks). During the first 24 weeks of the trial, 38% and 28% of the patients in the luspatercept group achieved transfusion independence of at least 8 and 12 weeks, respectively, or longer compared with 13% and 8% in the placebo group ($p < .0001$), with the highest response rates observed in the patients with lower transfusion burdens (< 4 U/8 weeks; transfusion independence, 80%) and the lowest in those receiving at least 6 U/8 weeks (9%). The longest median duration of continuous response was 30.6 weeks, and 62% of patients experienced more than one 8-week episode of transfusion independence interspersed by occasional transfusions and the cumulative duration of red blood cell transfusion independence of ≥ 8 weeks of 79.9 weeks. The *SF3B1* mutant allele burden and the total number of baseline somatic mutations were not predictive of response. In the patients treated with luspatercept, the median peak increase in the hemoglobin level was 2.55 g/dL, and they experienced six fewer transfusion visits over 48 weeks compared with placebo. Although there were mildly increased gastrointestinal, asthenia, and nausea symptoms in the luspatercept arm, there were no increased rates of all grade 3 to 4 adverse events compared with placebo.[51] Luspatercept is currently approved in the United States, European Union, and Canada for use in adult patients with transfusion-dependent anemia because of very-low-, low-, and intermediate-risk MDS-RS who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy. Additional data are emerging regarding luspatercept's beneficial impact on ineffective hematopoiesis, as demonstrated by trilineage responses[52] and reductions in serum ferritin.[53] Comparative clinical trials in the first-line setting against erythropoietin are ongoing (COMMANDS, NCT03682536), and earlier-phase studies in combination with lenalidomide are being planned (NCT04539236).

HYPOMETHYLATING AGENTS

The hypomethylating agents azacitidine (AZA) 75 mg/m^2 and decitabine (DEC) 20 mg/m^2, administered in conventional or reduced day schedules (3–5 days) in lower-risk disease, may engender hematologic responses and red blood cell transfusion independence rates ranging from

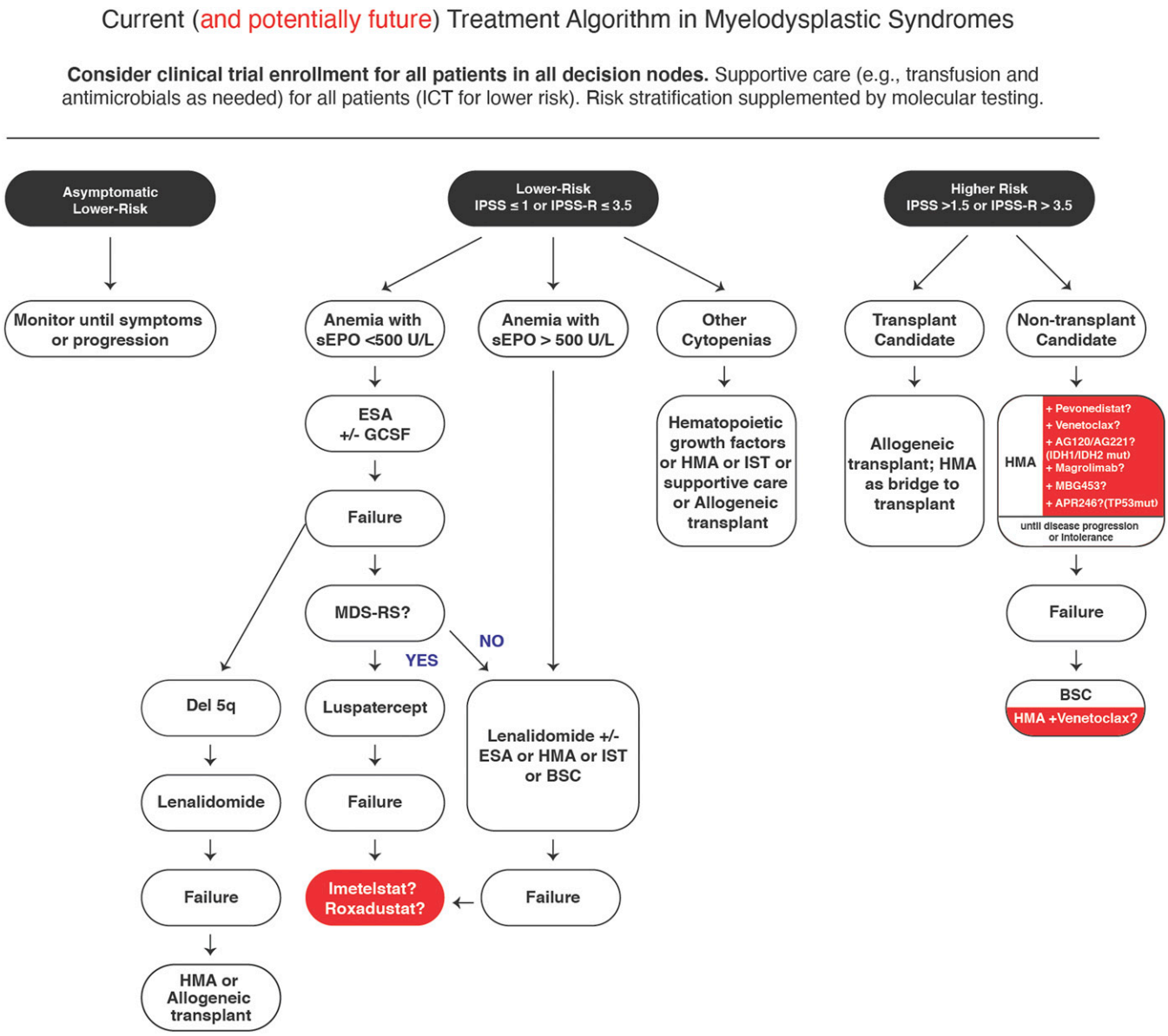

FIGURE 2. Current and Potentially Future Treatment Algorithm for Myelodysplastic Syndromes Stratified by Risk Score

Potentially future treatments are highlighted in red.

Abbreviations: IPSS, International Prognostic Scoring System; IPSS-R, International Prognostic Scoring System Revised; sEPO, serum erythropoietin; ESA, erythropoietic-stimulating agent; MDS-RS, MDS with ring sideroblasts; HMA, hypomethylating agent; AlloSCT, allogeneic stem cell transplant; IST, immunosuppressive therapy; BSC, best supportive care; mut, mutated.

44% to 56% and 50% to 64%, respectively, for AZA[54] and of 49% and 32%, respectively, for DEC.[55] Although cytogenetic responses may be seen in some patients, it is unclear if hypomethylating agents have disease-modifying/life-extending effects in lower-risk disease in the absence of randomized trials in which OS is a primary endpoint. An ongoing, phase II, randomized controlled trial (NCT02269280) comparing DEC (3 days), AZA (3 or 5 days), or best supportive care for patients with transfusion-dependent lower-risk MDS may better clarify their impact.

ORAL HYPOMETHYLATING AGENTS

Newly Approved: Oral Decitabine: Decitabine/Cedazuridine

There is now a convenient marketed oral formulation of DEC with pharmacokinetics and pharmacodynamics equivalent to intravenous DEC by virtue of its combination with cedazuridine, a cytidine deaminase inhibitor.[56] In a phase III, randomized crossover study (ASCERTAIN), DEC/cedazuridine in a fixed oral combination of 35 mg/100 mg for

5 days achieved red blood cell and platelet transfusion independence rates of 49% in 133 patients with MDS, of whom 8.3% had IPSS low-risk disease and 44.4% had intermediate-1 risk disease,[57] so this treatment remains a convenient option in patients with symptomatic MDS with lower-risk disease when a hypomethylating agent is being contemplated.

Oral Azacitidine: CC-486

Despite early closure because of an excess of infectious deaths in the experimental arm, CC-486 met the primary endpoint in the AZA-MDS-003 phase III randomized trial that compared oral AZA for 21/28 days to placebo in 210 patients with IPSS low- and intermediate-1 -risk MDS but with some high-risk disease features that included red blood cell transfusion dependence and/or thrombocytopenia. Thirty-one percent of patients using AZA versus 11% of patients with placebo achieved red blood cell transfusion independence for a median of 11 months and 5 months, respectively, and more patients on AZA achieved hematologic improvement (24% vs. 6%, respectively).[58] Although not powered to assess survival, OS did not differ between the groups but was short (17.3 months vs. 16.2 months, respectively), highlighting this higher lower-risk population. Additional dosing testing and better patient selection will be needed before this version of oral AZA may be endorsed for lower-risk MDS. A newer formulation with cedazuridine (ASTX030) to improve bioavailability is also in early testing (NCT04256317).

Imetelstat

Imetelstat (GRN163L) is a first-in-class competitive inhibitor of telomerase activity under evaluation in myeloid neoplasms. In the first part of a phase II/III study (IMerge, MDS3001), 57 patients with MDS who were heavily red blood cell transfusion dependent and whose disease was ineligible for or relapsed/refractory to erythropoietic-stimulating agents were treated at a dose of 7.5 mg/kg intravenously every 4 weeks and achieved red blood cell transfusion independence rates at 8 and 24 weeks of 37% and 23%, respectively. Overall, 62% of patients who experienced a response had hemoglobin increase by a median of 3 g/dL. Treatment duration was 8.2 months, and the duration of transfusion independence was 86 weeks, with transfusion independence observed across all subgroups evaluated. By virtue of its mechanism of action, imetelstat also demonstrated anticlonal activity with reduction in cytogenetically abnormal clones and mutational allele burden in a small tested subset of patients.

Pharmacodynamic activity of telomerase was observed and correlated with transfusion independence rates. Treatment-emergent adverse events were primarily hematologic and reversible within 4 weeks.[59] A phase III, placebo-controlled, multicenter trial in 225 patients (NCT02598661) is ongoing to clarify the efficacy and safety of this agent in this challenging population (Table 2).

Roxadustat

Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and regulates iron metabolism by simulating hypoxia and is approved for use in China, Japan, and Chile for the treatment of anemia in chronic kidney disease. In the open-label phase of an ongoing, double-blind, placebo-controlled study (NCT03263091), transfusion independence rates of 38% were observed in 24 patients with lower-risk MDS regardless of erythropoietin level, and meaningful reductions in the number of transfusions were also observed (58%) at 1 year. The go-forward dose for phase III testing is 2.5 mg/kg three times weekly (Table 2).[60]

Higher-Risk Disease

Barring allogeneic stem cell transplant, AZA represents the only hypomethylating agent with a proven disease-modifying impact on OS and leukemia-free survival in MDS.[61] However, its effects in the real world[62] or using pooled prospective trial data[63] have not been replicated, in part because of higher rates of early treatment discontinuation[64] and the highly selected patient characteristics of clinical trials. The two randomized clinical trials that compared DEC with conventional care have not demonstrated an OS benefit,[65,66] likely because of suboptimal dose and scheduling, and there are no head-to-head comparisons of AZA with DEC in the higher-risk setting. The best evidence we have for therapeutic equipoise in higher-risk disease comes from a SEER observational study in which the median survival was 12 months for the 523 patients with MDS and excess blasts regardless of the type of hypomethylating agent received.[67] In the ASCERTAIN phase III trial, 43% had higher-risk MDS or CMML and were treated, but the reported CR, transfusion independence, and overall response rates (ORR) rates of 21%, 53%, and 64%, respectively, were not distinguished by risk category,[57] so one cannot discern whether oral DEC achieves comparable clinical efficacy to that of subcutaneous or intravenous AZA in higher-risk MDS. Nevertheless, it can replace intravenous DEC and is a convenient option for patients who cannot receive AZA for logistic or personal reasons and are not candidates for clinical trials.

Combination Approaches

After disappointing results from the S1117 clinical trial in which the addition of either lenalidomide or vorinostat to an AZA backbone failed to improve clinical outcomes in higher-risk MDS and CMML,[68] combination approaches have been or are undergoing testing with hypomethylating agent backbones. The goal is to achieve deeper and longer responses that translate into improved OS and clinical benefit (Table 2).

Pevonedistat

Pevonedistat is a small-molecule inhibitor of neural precursor cell expressing developmentally downregulated 8–activating enzyme that disrupts proteasomal degradation of select proteins and interferes with cell cycle progression and leukemia cell survival. It has been tested in combination with AZA and compared 1:1 with AZA alone in a randomized phase II study (NCT02610777) of 120 patients with higher-risk MDS/CMML or low-blast-count AML. In the intent-to-treat population, event-free survival trended longer in the pevonedistat-plus-AZA arm compared with AZA alone (21 months vs. 16.6 months) and in the 67 patients with higher-risk MDS (event-free survival, 20.2 months vs. 14.8 months). Furthermore, longer median durations of response were observed in combination (34.6 months vs. 13.1 months), as were higher red blood cell transfusion independence rates (69.2% vs. 50%).[69] Reassuringly, the addition of pevonedistat did not appear to increase myelosuppression or serious adverse events. Notable activity was also seen in patients with adverse-risk mutations, including *TP53*.[70] We await the results of the fully accrued Panther trial of similar design (NCT03268954).

Venetoclax

Building on the tremendous success of combination therapy in AML, venetoclax has been combined with AZA in a multicenter, open-label, nonrandomized, phase Ib dose-finding study with the recommended go-forward dose of 400 mg orally daily for 14 days. Enrolled patients had IPSS higher-risk disease and were not eligible for stem cell transplant or intensive chemotherapy. The CR and marrow CR rates were each 39.7%. Complete response was achieved at a median of 2.6 months, and the median duration of response was 12.9 months. Among the 51 patients who received venetoclax 400 mg (the recommended dose), the ORR/CR rates were 84%/35%, which compare favorably with historical data from AZA alone. Sixty-five percent of patients achieved red blood cell or platelet transfusion independence.

At a median follow-up of 16.4 months, the median OS was 27.5 months among all patients and was not reached among those who received venetoclax 400 mg. Participants who achieved CR also experienced clinically meaningful improvements in dyspnea, fatigue, and quality of life.[71] Although extremely promising, results from the phase III Verona trial (NCT04401748), in which CR and OS are primary endpoints, will be needed before implementing this approach as standard of care.

APR246 (Eprenetapopt)

Dysregulation of the tumor suppressor gene *TP53* plays a crucial role in MDS phenotype, treatment response, and risk of AML transformation. *TP53* mutations or deletions are observed in 10% to 28% of patients with MDS and are associated with higher-risk and/or therapy-related disease, complex karyotype, shorter responses to hypomethylating agents, shorter OS,[72,73] and higher relapse rates after allogeneic stem cell transplant.[74] It is now recognized that it is the biallelic loss of *TP53* observed in two-thirds of patients with MDS that conveys this poor prognosis,[75] so the *TP53* variant allele frequency and its cellular/genomic context may correlate with response rates and refine prognosis.[73] APR246 is a novel *TP53* activator prodrug that binds to mutant P53 protein and thermodynamically restores confirmation and reactivates its proapoptotic and cell cycle arrest functions.[76] Two small phase I/II studies conducted in the United States (55 patients)[77] and France (53 patients)[78] combined APR-246 with AZA in patients with MDS and AML and achieved high ORR (71%–75%), CR (44%–56%), and cytogenetic response rates (58%–78%). Complete molecular remissions of *TP53* mutations were observed in 38% to 100% of patients, and treatments were well tolerated without excess myelosuppression compared with AZA alone. The randomized phase III study comparing AZA with AZA plus APR-246 (NCT03745716) in 154 patients with higher-risk *TP53*-mutant MDS completed accrual, but a recent press release by the sponsor, APREA, in December 2020 reported that the trial failed to meet its primary endpoint of significantly superior CR (33% vs. 22%; p = .13). However, secondary endpoints are under evaluation with longer follow-up. It may be that specific subgroups of patients with mutant *TP53* benefit from this agent, so more data are needed.

Splicing Modulators

Heterozygous somatic mutations in the genes encoding RNA splicing factors *SF3B1, U2AF1*, *SRSF2*, or *ZRSR2* induce aberrant splicing in cancer cells and are founder mutations in 50% of patients with MDS.[79] H3B-8800 is an orally available small molecule that binds to the *SF3β* complex and induces alternative splicing changes in cells. A phase I trial of H3B-8800 in patients with AML, CMML, and MDS (84 patients) demonstrated pharmacodynamic activity but no significant objective CR/PR responses, although 14% had reduced transfusion needs.[80] Other spliceosome inhibitors are currently being investigated in MDS, because the inhibition of the remaining functional allele should be preferentially lethal to the spliceosome-mutant cell.[81]

FLT3 Inhibitors

FLT3 mutations are uncommon in MDS (1%)[82] but may be acquired in 7% as a prelude to almost inevitable AML transformation.[83] A number of clinical trials of second- and third-generation *FLT3* inhibitors are underway in combination

with hypomethylating agents in patients with high-risk MDS and AML (NCT04097470, NCT04027309, NCT04140487).

Immune Checkpoint Inhibitors

Hypomethylating agents may increase the expression of immune checkpoints PD-L1 and PD-L2 in MDS and AML cells and compromise the immunostimulatory effects of hypomethylating agents. Combining hypomethylating agents with immune checkpoint inhibitors is therefore a rational strategy.[84] Some of the various immune checkpoint inhibitors being tested in patients with MDS are discussed later.

The immune checkpoint inhibitors pembrolizumab,[85] nivolumab, and ipilumumab[86] alone and in combination with hypomethylating agents are undergoing evaluation in phase I/II clinical trials in both the frontline and relapsed/refractory (R/R) settings. Immune-related adverse events such as colitis, transaminitis, and pneumonitis are not uncommon, and only ipilumumab has modest single-agent activity in R/R MDS.

Magrolimab

CD47 is the dominant-negative macrophage immune checkpoint expressed on cancer cells that acts as a "don't eat me" signal, preventing phagocytosis via its interaction with SIRP-α on macrophages. CD47 has been shown to be upregulated in many cancer types, including myeloid malignancies, and increased expression is associated with inferior OS. In the expansion phase of a single-arm phase I study including 39 patients with MDS and 29 patients with AML (previously untreated), magrolimab 30 mg/kg in two schedules combined with AZA achieved ORR/CR rates of 92%/50% in patients with MDS and 64%/41% in patients with AML. Deep and durable responses were observed, including the achievement of cytogenetic remissions and measurable residual disease negativity, even in some patients with *TP53* mutations. The potential disease-modifying effect of this combination is punctuated by the elimination of $CD34^{+}/CD38^{-}$ leukemia stem cells in 40% of patients experiencing response.[87] The randomized clinical trial comparing AZA versus AZA plus magrolimab in patients with IPSS-R intermediate- to very-high-risk MDS will begin accrual soon (NCT04313881). Some of the most promising immune checkpoint inhibitors under evaluation are discussed later or are included in Table 2.

MBG453 (sabatolimab)

MBG453 is a monoclonal antibody that targets *TIM-3*, which is a key factor in tumor tolerance and leukemic stem cell survival.[88] *TIM-3* is an immune checkpoint that is preferentially expressed on leukemic stem and progenitor cells,[89] so targeting it may limit its toxicity. MBG453 may enhance immune cell–mediated killing of AML cells in vitro.[90] It has modest activity as a single agent in R/R MDS or AML, but a phase I trial that combined MBG453 with AZA or DEC in hypomethylating agent–naïve, higher-risk MDS and AML was well tolerated, with no maximally tolerated dose reached and promising response rates.[91] STIMULUS-2 is comparing the efficacy and safety of MBG453 first line with AZA in higher-risk MDS or CMML-2 in an enrolling phase III study (NCT04266301).

POTENTIAL TREATMENTS FOR HYPOMETHYLATING AGENT FAILURES

The definitions of hypomethylating agent resistance or failure are heterogeneous and sometimes hard to clarify but may be broadly grouped into primary (progression, stable disease without hematologic improvement, pancytopenia, and marrow hypocellularity) or secondary (progression after initial response). The prognosis after the discontinuation of hypomethylating agents in higher-risk disease is very poor[92] in the absence of a clinical trial or allogeneic stem cell-transplant and remains an unmet medical need. Currently, no drugs are approved for this indication, so enrollment in clinical trials is of paramount importance. What are some of the agents under investigation?

Guadecitabine (SGI-110)

Guadecitabine is a dinucleotide of decitabine and deoxyguanosine with similar potency but longer half-life because of resistance to cytidine deaminase degradation. This results in an extended exposure of blasts to its active metabolite, decitabine. Some promising activity was observed in smaller phase I/II studies of higher-risk patients who were experienced R/R disease after other hypomethylating agents.[93,94] However, ASTRAL-3, the large randomized clinical trial of SGI-110 comparing physician's choice in patients previously treated with hypomethylating agents, was recently completed and failed to meet the primary endpoint of improved OS (NCT02907359).

Rigosertib

Although initially promising, intravenous rigosertib, the small-molecule Ras mimetic agent, did not meet the primary endpoint in the ONTIME study of significantly improved OS versus physician's choice of therapy plus best supportive care in patients with MDS with excess blasts or CMML after AZA failure,[95] nor did it achieve this according to topline (yet unpublished) results from the sequential phase III INSPIRE trial (NCT02562443) that was restricted to higher-risk subsets. Phase II results of combined oral rigosertib plus AZA are awaited (NCT01926587).[96]

Venetoclax

In an ongoing phase Ib study, 44 patients with R/R MDS after treatment with hypomethylating agents were treated with escalating doses of venetoclax for 14 days in combination with AZA. The ORR was 39% (marrow CR, 32%; CR, 7%), irrespective of baseline mutational status and risk

score, with the exception of those with *TP53* mutations, who had lower response rates. Importantly, 43% and 57% became independent of red blood cell and platelet transfusions, respectively, and the median OS was 12.3 months; treatment-emergent adverse events were dominated by myelosuppression.[97] Other early-phase trials combining venetoclax with oral and intravenous DEC and other agents in the R/R setting are ongoing, and it will be important to discern whether primary refractory versus relapsed diseases respond differently.

IDH Inhibitors

Unlike AML, mutations involving *IDH1* (3%) and *IDH2* (5%) are uncommon in MDS, but they are associated with higher rates of progression to AML.

Ivosedinib Ivosedinib is an oral targeted inhibitor of mutant isocitrate dehydrogenase 1 (IDH1) enzyme. In the substudy of the phase I study of ivosedinib monotherapy in R/R myeloid cancers, 75% of the 12 patients with MDS experienced a response, and 42% achieved a CR, many of which were durable. Importantly, 75% achieved transfusion independence as well.[98] Treatment was well tolerated, and this agent is undergoing additional testing in an expansion arm of 25 patients with MDS[99] as well as in other trials of patients with R/R and hypomethylating agent–naïve, all-risk MDS with an *IDH1* mutation (NCT030503409) and in combination with other agents.[100]

Enasidinib Enasidinib is a selective oral inhibitor of the mutant IDH2 enzyme with singe-agent activity (ORR, 53%) in a phase I substudy enrolling patients with R/R MDS. Enasidinib has been evaluated in a small phase II study of patients with treatment-naïve, higher-risk MDS (combined with AZA) and in R/R hypomethylating agent-naïve disease. The ORR in patients with treatment-naïve disease and hypomethylating agent failure was 100% and 50%, respectively, with a 38% transfusion independence rate in hypomethylating agent failures.[101] Enasidinib is also undergoing testing in patients with both R/R and hypomethylating agent–naïve higher- and lower-risk MDS with *IDH2* mutations (NCT03744390).

CPX-351 CPX-351 is undergoing testing in patients with relapsed AML and R/R higher-risk MDS after treatment with hypomethylating agents, with promising activity in relapsed AML (NCT03672539).[102]

SUMMARY

We are finally seeing the fruits of decades of research in MDS with the approval of two new agents: luspatercept and decitabine/cedazuridine. Other options to reduce transfusion dependence in lower-risk disease when erythropoietic-stimulating agents fail to work are in late-stage evaluation, and luspatercept is being compared with erythropoietic-stimulating agents in the front line in patients who are transfusion dependent. Many more exciting agents added to the hypomethylating agent backbone are in late-stage phase III studies for higher-risk disease and may improve outcomes. Biomarker interrogation of these trials will be crucial to guide their customized and personalized deployment in the clinic. We are hopeful that these efforts will improve quality of life by reducing transfusion dependence and finally shift the survival curves of patients with MDS to the right in the next decade.[36]

MOLECULAR FEATURES AND MANAGEMENT OF MDS/MPN OVERLAP NEOPLASMS

The MDS/myeloproliferative neoplasms (MPNs) overlap group consists of myeloid neoplasms with overlapping features of both MDS and MPN, with variable ages of onset and outcomes.[2,103] Before 2001, these neoplasms were grouped with either MDS or MPN; however in 2001, the WHO created a new category for these neoplasms, a schema that has since been updated in 2008.[2] Currently, five well-defined entities exist: CMML, juvenile myelomonocytic leukemia, atypical chronic myeloid leukemia that is *BCR-ABL1* negative, MDS/MPN with ring sideroblasts and thrombocytosis, and unclassifiable MDS/MPN (Table 1).[2,104] Of these, juvenile myelomonocytic leukemia is the only pediatric-onset overlap neoplasm; all other entities typically arise in older adults in the context of age-related clonal hematopoiesis.[103,105] With advances in myeloid genomics, it is foreseeable that additional classification of these entities may emerge, especially in the unclassifiable MDS/MPN category.[106]

DIAGNOSES OF AND MANAGEMENT OF INDIVIDUAL MDS/MPN OVERLAP NEOPLASMS

MDS/MPN overlap neoplasms are diagnosed with the help of well-defined morphologic criteria laid out by the WHO and outlined in Table 3. Although there is no substitute to morphology, the advent of next-generation sequencing techniques has defined the molecular landscape of these neoplasms, allowing for molecular integration into diagnostic workflows. It is important to note that there are no gene mutations or karyotypic abnormalities unique to any of these neoplasms; however, in the context of appropriate morphologic changes, these abnormalities can be very supportive and can also help with prognostication and targeted therapeutics.

Chronic Myelomonocytic Leukemia

CMML is characterized by the presence of sustained ($\geq$ 3 months) peripheral blood monocytosis (absolute monocyte count $\geq 1 \times 10^9$/L, with monocytes $\geq$ 10% of white blood count differential) in the absence of known reactive causes of monocytosis or WHO-defined molecular entities associated with monocytosis (*BCR-ABL1, PDGFRA, PDGFRB, FGFR1*, and *PCM1-JAK2* rearrangements), with or without

bone marrow dysplasia, and with a characteristic molecular signature enriched in *ASXL1, TET2, SRSF2*, and *SETBP1* mutations.[107,108] CMML is a disease of aging, with a median age at diagnosis of 73 years, and has a male preponderance.[107,108] CMML can be more specifically classified into CMML-0, -1, and -2 according to the percentage of peripheral blood and bone marrow blast equivalents (which include blasts and promonocytes) and the presence or absence of Auer rods. CMML also can be classified into proliferative CMML and dysplastic CMML subtypes; a white blood cell count of more than 13×10^9/L defines the former.[2] Whole-genome and exome sequencing studies have demonstrated approximately 10 to 15 variants per kilobase of coding region in CMML, with recurrent mutations in *TET2* (60%), *SRSF2* (50%), and *ASXL1* (40%) accounting for more than 75% of these.[109] Clonal architectural studies have demonstrated that CMML usually arises in the context of *TET2*- and/or *SRSF2*-mutated clonal hematopoiesis.[105] The mutational coexpression of *TET2/SRSF2* or biallelic *TET2* mutations skew hematopoiesis toward monocytosis, with subsequent acquisitions of *ASXL1, NRAS, CBL, PTPN11, KRAS,* and *JAK2*V617F mutations giving rise to proliferative CMML and *RUNX1, SETBP1, DNMT3A, SF3B1,* and *ASXL1* mutations giving rise to dysplastic CMML.[103,105] Proliferative-type CMML is associated with MPN-like features, such as leukocytosis, marked monocytosis and splenomegaly, constitutional symptoms (drenching night sweats/bone pain/fatigue), shorter leukemia-free survival, and shorter OS[110] compared with dysplastic type CMML.

Cytogenetic abnormalities are seen in 30% of patients, whereas molecular abnormalities are seen in more than 90%.[111] Among the molecular abnormalities, frame shift and nonsense *ASXL1* mutations are universally detrimental, predicting for inferior OS and leukemia-free survival, and are currently incorporated in all three existing molecularly integrated CMML prognostic models (Mayo Molecular Model, CPSS-Molecular, and the GFM model).[112-114] All three models rely on a combination of clinical and molecular factors, with the CPSS-Molecular integrating a clinical score with a genetic score that is based on cytogenetic abnormalities and mutations involving *ASXL1, RUNX1*, *NRAS*, and *SETBP1*.[112]

Although allogeneic stem cell transplantation is potentially curative, given the late age of onset and frequent comorbidities, less than 10% of patients in general are eligible for allogeneic stem cell transplantation.[115] Recent Mayo Clinic data have demonstrated better outcomes with allogeneic stem cell transplantation in CMML treated before AML transformation compared with CMML that is already progressed to AML, with 5-year OS rates of 50% and 19%, respectively.[115] This survival benefit, however, was offset by a median graft-versus-host disease relapse-free survival of 7 months, highlighting the morbidity associated with allogeneic stem cell transplantation.[115] Hypomethylating agents remain the only U.S. Food and Drug Administration–approved drugs for the management of CMML (azacitidine, decitabine, and decitabine/cedazuridine). These drugs were approved for MDS, and, given that the MDS-predominant registration trials included small numbers of patients with dysplastic-type CMML, approval for CMML was also obtained.[116,117] In CMML, according to phase II and retrospective studies, hypomethylating agents have been associated with an ORR of 40% to 50%, with true CR rates of less than 20%.[108,118,119] Hypomethylating agents epigenetically restore hematopoiesis in a subset of patients with CMML who experience response (through inhibition of DNMT3A); however, they do not alter the mutational allele burdens, and disease progression/loss of response is inevitable.[120] This was recently highlighted by the European DACOTA trial, a prospective, randomized clinical trial comparing hydroxyurea with decitabine in the management of advanced proliferative-type CMML.[121] In this study (170 patients), decitabine did not provide an OS or event-free survival advantage over hydroxyurea, highlighting the inadequacies of hypomethylating agents in CMML. In addition, given the low frequencies of *IDH1, IDH2, FLT3* (all $< 5\%$), and *TP53* (1%) mutations in CMML, conventional targeted therapeutics are in general not applicable to these patients.[103,122]

For several years, therapeutic responses in patients with CMML were assessed using MDS-based response criteria. A major advance in this direction was made in 2015, when the International Working Group proposed MDS/MPN overlap neoplasm response-specific criteria that included proliferative features in the response assessment paradigm.[123] Although these criteria await prospective validation, they have been validated in retrospective studies.[118,124] Future directions in CMML include the discovery of novel therapeutic agents that exploit unique vulnerabilities in MDS and MPN subtypes. Newer targets being explored include cytokine modulation targeting granulocyte macrophage-colonly stimulating factor (lenzilumab),[125] JAK/STAT inhibition,[126] targeting CD123-expressing plasmacytoid dendritic cells,[127] and manipulating IDO1 expression in the CMML microenvironment.[128] Given the high frequency of RAS pathway mutations in proliferative-type CMML (70%) and in CMML transformed to AML (50%), drugs exploiting the RAS/RAF/MEK/ERK pathway are also being investigated.

Atypical CML, *BCR-ABL1* Negative

Atypical CML that is *BCR-ABL1* negative is a rare overlap neoplasm characterized by neutrophilia and dysgranulopoiesis in the absence of peripheral blood monocytosis and basophilia.[2] Along with neutrophilia, immature myeloid cells (promyelocytes/myelocytes/metamyelocytes) comprise 10% or more of the leukocytes. Bone marrow biopsies are classically hypercellular, demonstrating dysgranulopoiesis

TABLE 3. 2017 WHO-Defined MDS/MPN Overlap Syndromes

WHO MDS/MPN Category	Median Age at Presentation (years)	WHO Criteria	Cytogenetics	Molecular Genetics	Genetic Factors Associated With Progression	Median Survival (months)	Treatment Options
Juvenile myelomonocytic leukemia	2	A. Clinical and morphologic criteria (mandatory) PB AMC $\geq$ 1 X10(9)/L PB and BM blasts $<$ 20% Splenomegaly *BCR-ABL1* negative B. Genetics Somatic mutation in *PTPN11, KRAS, NRAS* Germline *CBL* or LOH of *CBL*	Normal: 65% Monosomy: 7%–25%	PTPN11: 35% KRAS/NRAS: 20%–25% CBL: 15% NF1: 11%	*JAK3* *SETBP1* *ASXL1* CN-LOH of *NF1* LOH of *CBL* DNA hypermethylation	10–12	Allogeneic HCTv Spontaneous reversion in germline *CBL* and *PTPN11* mutant cases has been seen.
Chronic myelomonocytic leukemia	71–74	1. Persistent PB AMC $\geq$ 1 $\times 10^9$/L, $\geq$ 10% of WBC 2. Not meeting WHO criteria for CML, ET, PV, or MF 3. Absence of molecularly defined abnormalities* 4. $<$ 20% PB and BM blast equivalents (including promonocytes) 5. Dysplasia in one or more lineages	Normal: 70%–80% Trisomy 8	*TET2*: 60% *SRSF2*: 50% *ASXL1*: 40% *NRAS*: 15%–20% *CBL*: 15% *RUNX1*: 15% *SETBP1*: 15%	*RAS* pathway SCNA	28–32	Hypomethylating agents Allogeneic HCT
Atypical chronic myeloid leukemia	70	1. PB leukocytosis with immature granulocytes $>$ 10% 2. Dysgranulopoiesis 3. Basophils $<$ 2% and monocytes $<$ 10% 4. Negative for *BCR-ABL1, PDGFRA/B, FGFR1*, and *PCM1-JAK2* 5. $<$ 20% PB and BM blasts 6. Not meeting criteria for CML, ET, PV, or MF	Normal: 70%	*ASXL1*: 30% *TET2*: 15% *SETBP1*: 15% *ETNK1*: 15% *EZH2*: 10%	*ASXL1* *RAS* SCNA	22	Hypomethylating agents. Allogeneic HCT
MDS/MPN with ring sideroblasts and thrombocytosis	71–75	1. Anemia associated with erythroid lineage dysplasia, $\geq$ 15% ring sideroblasts, $<$ 1% PB blasts and $<$ 5% BM blasts. 2. Persistent thrombocytosis 3. *SF3B1* mutation typical, but not required. 4. No preceding history of MPN or other MDS/MPN disease type	Normal: 80%	*SF3B1*: 85% *JAK2*V617F: 50% *TET2*: 25% *ASXL1*: 20% *DNMT3A*: 15% *SETBP1*: 10%	*ASXL1* *SCNA*	76	Erythropoiesis stimulating agents Luspatercept Lenalidomide hydroxyurea Aspirin
MDS/MPN-Unclassifiable	70	1. $<$ 20% PB and BM blasts. 2. Clinical and morphologic features of a MDS subtype [except del(5q)] 3. Clinical and morphologic features of MPN; platelets $\geq$ 450 $\times$ 10^9/L or WBC $\geq$ 13.0 $\times$ 10^9/L 4. No *BCR-ABL1, PDGFRA/B, FGFR1*, or *PCM1-JAK2* rearrangements	Normal: 50% Trisomy 8: 14% Monosomy 7: 11%	*ASXL1*: 53% *SRSF2*: 37% *SETBP1*: 20% *JAK2*V617F: 15% *TET2*: 15% *TP53*: 10%	*TP53* *ASXL1* *RAS* SCNA	36	Hypomethylating agents Allogeneic HCT

Abbreviations: AMC, absolute monocyte count; BM, bone marrow; CML, chronic myeloid leukemia; ET, essential thrombocythemia; HCT, hematopoietic cell transplantation; LOH, loss of heterozygosity; MF, myelofibrosis; PB, peripheral blood; PV, polycythemia vera; SCNA, somatic copy number alterations; WHO, World Health Organization.
*Molecularly defined abnormalities include *BCR-ABL1, PDGFRA, PDGFRB, FGFR1*, and *PCM1-JAK2*.

with granulocytic proliferation.[2] Although labeled atypical CML (or aCML), this neoplasm has no overlap with CML, so this label should not be used to annotate CML cases associated with variant *BCR-ABL1* translocations.[2] Outcomes are poor, with a median OS of less than 25 months and high rates of AML transformation (30%–40%).[106,129] Atypical CML often arises on the background of *ASXL1*-mutated, age-related clonal hematopoiesis, and disease evolution occurs because of the acquisition of mutations involving *TET2* (16%), *EZH2* (15%), *NRAS* (15%), *SETBP1* (12%), *RUNX1* (12%), and *ETNK1* (10%).[106,129,130] Among the MDS/MPN overlap neoplasms, atypical CML is relatively enriched in *SETBP1, EZH2*, and *ETKN1* mutations; although prior reports documented a higher prevalence of *CSF3R* mutations, we think that, in the context of accurate morphology, *CSF3R* mutations are extremely uncommon in atypical CML and are relatively specific for the pure MPN entity, chronic neutrophilic leukemia.[131]

Allogeneic stem cell transplantation remains the only curative option for atypical CML. As mentioned previously, this process is fraught with morbidity and mortality.[132] For patients who are not candidates for allogeneic stem cell transplantation, hypomethylating agent therapy has been used to help alleviate cytopenias, transfusion dependence, and proliferative features and to improve progression-free survival.[129] The Mayo Clinic prognostic model risk stratifies patients with atypical CML into low- (zero to one risk factors) and high-risk (at least two risk factors) categories based on age (age 67 or older), hemoglobin levels less than 10 g/dL, and presence of *TET2* mutations; the median OS is 18 months and 7 months, respectively.[122] There is an urgent and unmet need to find better therapeutic options for affected patients.

MDS/MPN With Ring Sideroblasts and Thrombocytosis

MDS/MPN with ring sideroblasts and thrombocytosis was formally recognized as an overlap neoplasm in the 2016 WHO Classification, with diagnostic criteria including anemia with erythroid lineage dysplasia with ring sideroblasts ($\geq$ 15%, and usually accompanied by *SF3B1* mutation), persistent thrombocytosis ($\geq$ 450 $\times$ 10^9/L), and no preceding history of an MPN.[2] The median age of onset is 73, with outcomes being favorable in comparison with other overlap neoplasms (median OS, 76 months), including very low rates of leukemic transformation (1%–2%).[107,133,134] MDS/MPN with ring sideroblasts and thrombocytosis is characterized by the presence of bone marrow ring sideroblasts: erythroid precursors in which, after Prussian blue staining, a minimum of five siderotic granules cover at least a third of the nuclear circumference.[135] In most instances, MDS/MPN with ring sideroblasts and thrombocytosis develops on the background of *SF3B1*- (90%) or *DNMT3A*- (10%) mutated age-related clonal cytopenias, with additional mutations like *TET2, DNMT3A, ASXL1*, and *SETBP1* resulting in evolution to MDS-RS, followed by acquisition of signaling mutations such as *JAK2*V617F (50%), *MPL*, and *SH2B3* (5% each) giving rise to defining proliferative features, including thrombocytosis.[106,135] *SF3B1* mutations are seen in 90% of patients and impact canonical mRNA splicing, resulting in the downregulation of genes such as *ABCB7* and *PPOX*, giving rise to the bone marrow ring sideroblasts.[136]

Although MDS/MPN with ring sideroblasts and thrombocytosis is associated with an increased risk of thrombosis, the risk is lower than that associated with essential thrombocythemia (a pure MPN).[133,137] Because no formal management guidelines exist for MDS/MPN with ring sideroblasts and thrombocytosis, consensus recommendations are based on the management of symptoms that overlap with MDS and MPN. Anemia is usually managed with erythropoiesis-stimulating agents and transforming growth factor β superfamily modulators such as luspatercept,[138] whereas the use of hydroxyurea as a cytoreductive agent is considered in patients at a higher risk for thrombosis (age $>$ 60, history of thrombosis, and presence of the *JAK2*V617F mutation).[51,135] Lenalidomide, an immunomodulatory agent, has been associated with improvements in anemia and thrombocytosis as well as deeper molecular responses in this disease.[139]

Juvenile Myelomonocytic Leukemia

Juvenile myelomonocytic leukemia is the only pediatric-onset overlap neoplasm. It is characterized by peripheral blood monocytosis, is usually associated with poor outcomes, and is considered a bona fide RASopathy syndrome.[140,141] Juvenile myelomonocytic leukemia occurs in early childhood because of germline or somatic RAS pathway mutations, often involving *PTPN11, CBL, KRAS, NRAS*, and *NF1*.[140,141] Most germline cases are related to *PTPN11* (Noonan syndrome), *CBL* (Noonan-like syndrome), or *NF1* (neurofibromatosis) mutations, with germline *PTPN11*- and *CBL*-mutated juvenile myelomonocytic leukemia sometimes demonstrating spontaneous regression.[142] Disease progression often occurs because of the acquisition of mutations involving *ASXL1, SETBP1,* and/or *JAK3*, with *TET2* mutations being uncommon.[143] Patients develop progressive monocytosis, constitutional symptoms, splenomegaly, and thrombocytopenia and have significant organ infiltration. Independent of somatic mutations, unique methylation subtypes exist in juvenile myelomonocytic leukemia, with global DNA hypermethylation being associated with poor outcomes.[144] Allogeneic stem cell transplantation remains the treatment of choice for most patients, with hypomethylating agent and MEK inhibition currently undergoing clinical trial evaluation.

Unclassifiable MDS/MPN

The unclassifiable MDS/MPN subtype consists of a medley of poorly defined MDS/MPN overlap neoplasms not meeting

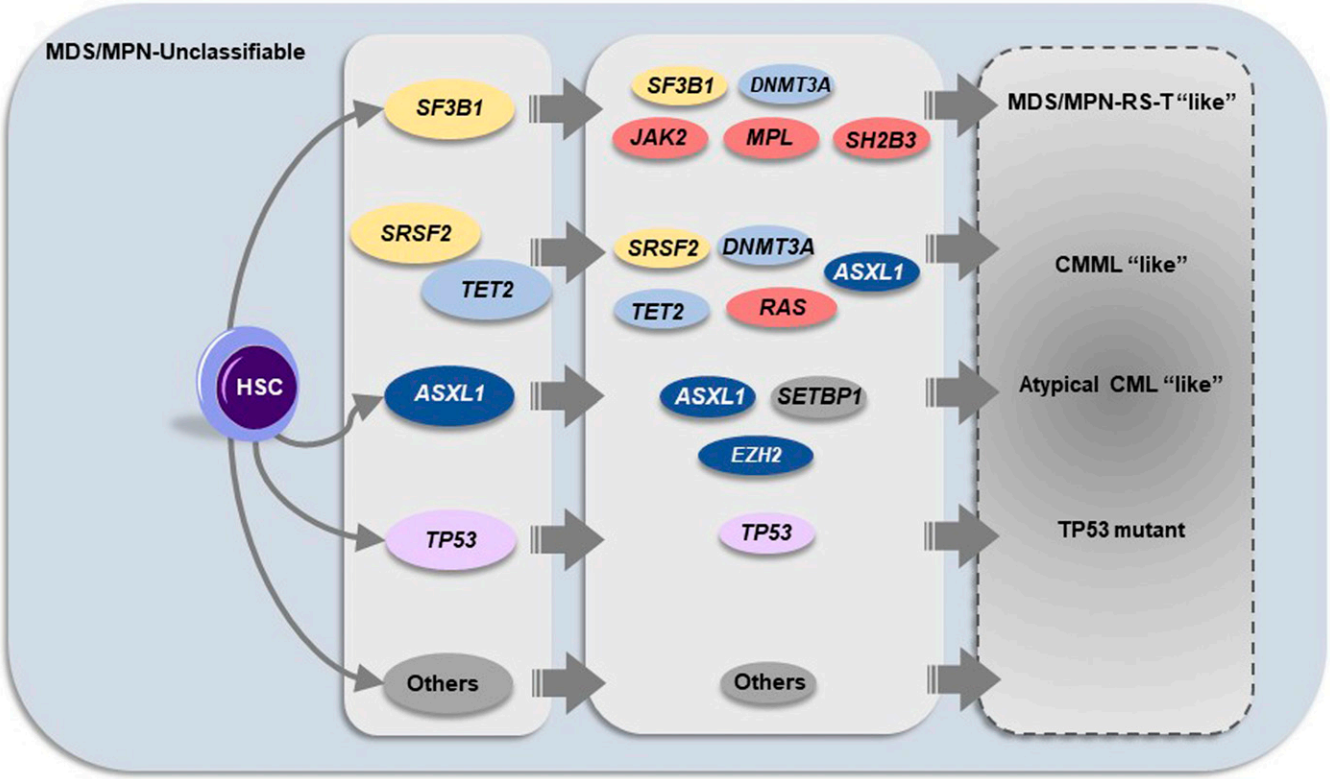

FIGURE 3. Genomic Risk Stratification for MDS/MPN-Unclassifiable Neoplasms Based on Next-Generation Sequencing Results in the Context of Appropriate Disease Morphology

These patients often do not meet strict World Health Organization criteria for defined entities in the MDS/MPN overlap category. In this setting, presence of *SF3B1* mutations with JAK/STAT signaling mutations (*JAK2, SH2B3*, and *MPL*) can define an MDS/MPN-RS-T–like disease. The presence of *SRSF2* with *TET2* mutations can define a CMML-like disease. The presence of *ASXL1* with *SETBP1, EZH2*, or *ETNK1* mutations can define an atypical CML-like disease. The unclassifiable subtype is also enriched in *TP53* mutations that can form their own category. The "others" category reflects a medley of mutations and morphologic subtypes that need clearer definition.

criteria for other well-defined entities in this group, with a median OS of 24 months.[2,145] Frequent mutations encountered include the following: *ASXL1* (30%–50%), *SRSF2* (23%–37%), *SETBP1* (11%–21%), *JAK2* (19%–25%), *NRAS* (10%–15%), and *TET2* (15%–27%), with *TP53* and *CBL* mutations being less frequent (< 10%) but having a negative impact on OS.[106,145,146] Although unclassifiable MDS/MPN does not have a specific prognostic scoring system, two studies have shown that MDS-centered prognostic models can be used to risk stratify affected patients.[145,146] Allogeneic hematopoietic cell transplantation once again remains the only curative option, with hypomethylating agents being palliative and associated with poor response rates (ORR, 20%).[145] Given that this entity contains subtypes with features that overlap with other overlap neoplasms, additional next-generation sequencing–based stratification should be attempted to identify unique subtypes that may influence clinical trial eligibility and outcomes (Fig. 3).

CONCLUSION

In summary, MDS/MPN overlap neoplasms consist of a heterogenous mix of myeloid neoplasms with overlapping features of MDS and MPN. The advent of next-generation sequencing has allowed us to differentiate and classify these neoplasms with greater accuracy, albeit always in the context of an accurate morphologic diagnosis; in particular, accurate interpretation of dygranulopoiesis is important in diagnosing atypical CML, whereas correct estimation of blasts and promonocytes (regarded as blast equivalents) is important in risk-stratifying CMML. Although no gene mutations are specific for any MDS/MPN overlap subtype, the availability of sequencing results aids diagnostic accuracy, helps with risk stratification and, in select cases, helps select targeted therapies. Irrespective of recent advances in disease biology, treatment options remain poor, and rationally derived therapies based on disease biology are much needed.

AFFILIATIONS

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REFERENCES

1. Malcovati L, Gallì A, Travaglino E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. Blood. 2017;129:3371-3378.
2. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia [correction published in *Blood*. 2016;128(3):462-463]. Blood. 2016;127:2391-2405.
3. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120:2454-2465.
4. US Department of Health and Human Services. Surveillance and Mortality Data 1973 to 1977. Washington DC: US Department of Health and Human Services; 1980.
5. Schanz J, Tüchler H, Solé F, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol. 2012;30:820-829.
6. Papaemmanuil E, Cazzola M, Boultwood J, et al; Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. N Engl J Med. 2011;365:1384-1395.
7. Malcovati L, Papaemmanuil E, Bowen DT, et al; Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium and of the Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative. Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. Blood. 2011;118:6239-6246.
8. Patnaik MM, Hanson CA, Sulai NH, et al. Prognostic irrelevance of ring sideroblast percentage in World Health Organization-defined myelodysplastic syndromes without excess blasts. Blood. 2012;119:5674-5677.
9. Malcovati L, Stevenson K, Papaemmanuil E, et al. SF3B1-mutant MDS as a distinct disease subtype: a proposal from the International Working Group for the Prognosis of MDS. Blood. 2020;136:157-170.
10. Malcovati L, Karimi M, Papaemmanuil E, et al. SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. Blood. 2015;126:233-241.
11. Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes [correction published in *Nat Med*. 2021.]. Nat Med. 2020;26:1549-1556.
12. Haase D, Stevenson KE, Neuberg D, et al; International Working Group for MDS Molecular Prognostic Committee. TP53 mutation status divides myelodysplastic syndromes with complex karyotypes into distinct prognostic subgroups. Leukemia. 2019;33:1747-1758.
13. Cleven AH, Nardi V, Ok CY, et al. High p53 protein expression in therapy-related myeloid neoplasms is associated with adverse karyotype and poor outcome. Mod Pathol. 2015;28:552-563.
14. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia. 2014;28:241-247.
15. Rogers HJ, Vardiman JW, Anastasi J, et al. Complex or monosomal karyotype and not blast percentage is associated with poor survival in acute myeloid leukemia and myelodysplastic syndrome patients with inv(3)(q21q26.2)/t(3;3)(q21;q26.2): a Bone Marrow Pathology Group study. Haematologica. 2014;99:821-829.
16. Patel SS, Ho C, Ptashkin RN, et al. Clinicopathologic and genetic characterization of nonacute *NPM1*-mutated myeloid neoplasms. Blood Adv. 2019;3:1540-1545.
17. Bersanelli M, Travaglino E, Meggendorfer M, et al. Classification and personalized prognostic assessment on the basis of clinical and genomic features in myelodysplastic syndromes. J Clin Oncol. Epub 2021 Feb 4.
18. Nagata Y, Makishima H, Kerr CM, et al. Invariant patterns of clonal succession determine specific clinical features of myelodysplastic syndromes. Nat Commun. 2019;10:5386.
19. Calvo X, Garcia-Gisbert N, Parraga I, et al. Oligomonocytic and overt chronic myelomonocytic leukemia show similar clinical, genomic, and immunophenotypic features. Blood Adv. 2020;4:5285-5296.
20. Nagata Y, Zhao R, Awada H, et al. Machine learning demonstrates that somatic mutations imprint invariant morphologic features in myelodysplastic syndromes. Blood. 2020;136:2249-2262.
21. Swerdlow SHCE, Harris NL, Jaffe ES, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed. Lyon, France: International Agency for Research on Cancer; 2017.

22. Giagounidis AA, Germing U, Strupp C, et al. Prognosis of patients with del(5q) MDS and complex karyotype and the possible role of lenalidomide in this patient subgroup. Ann Hematol. 2005;84:569-571.
23. List A, Dewald G, Bennett J, et al; Myelodysplastic Syndrome-003 Study Investigators. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med. 2006;355:1456-1465.
24. Chen X, Othus M, Wood BL, et al. Comparison of myeloid blast counts and variant allele frequencies of gene mutations in myelodysplastic syndrome with excess blasts and secondary acute myeloid leukemia. Leuk Lymphoma. 2020;Dec 19:1-7.
25. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med. 2011;364:2496-2506.
26. Nazha A, Al-Issa K, Hamilton BK, et al. Adding molecular data to prognostic models can improve predictive power in treated patients with myelodysplastic syndromes. Leukemia. 2017;31:2848-2850.
27. Malcovati L, Papaemmanuil E, Ambaglio I, et al. Driver somatic mutations identify distinct disease entities within myeloid neoplasms with myelodysplasia. Blood. 2014;124:1513-1521.
28. Margolskee E, Hasserjian RP, Hassane D, et al. Myelodysplastic syndrome, unclassifiable (MDS-U) with 1% blasts is a distinct subgroup of MDS-U with a poor prognosis. Am J Clin Pathol. 2017;148:49-57.
29. Duong VH, Padron E, Al Ali NH, et al. The prognostic value of circulating myeloblasts in patients with myelodysplastic syndromes. Ann Hematol. 2018; 97:247-254.
30. Shreve J, Nazha A. The evolving landscape of myelodysplastic syndrome prognostication. Clin Hematol Int. 2020;2:43-48.
31. Gerstung M, Pellagatti A, Malcovati L, et al. Combining gene mutation with gene expression data improves outcome prediction in myelodysplastic syndromes. Nat Commun. 2015;6:5901.
32. Calvi LM, Li AJ, Becker MW. What is the role of the microenvironment in MDS? Best Pract Res Clin Haematol. 2019;32:101113.
33. Méndez-Ferrer S, Bonnet D, Steensma DP, et al. Bone marrow niches in haematological malignancies. Nat Rev Cancer. 2020;20:285-298.
34. Brunner AM, Blonquist TM, Hobbs GS, et al. Risk and timing of cardiovascular death among patients with myelodysplastic syndromes. Blood Adv. 2017; 1:2032-2040.
35. Ma X, Does M, Raza A, et al. Myelodysplastic syndromes: incidence and survival in the United States. Cancer. 2007;109:1536-1542.
36. Gangat N, Patnaik MM, Begna K, et al. Survival trends in primary myelodysplastic syndromes: a comparative analysis of 1000 patients by year of diagnosis and treatment. Blood Cancer J. 2016;6:e414-e414.
37. Bernal T, Martínez-Camblor P, Sánchez-García J, et al; Spanish Society of Hematology. Effectiveness of azacitidine in unselected high-risk myelodysplastic syndromes: results from the Spanish registry. Leukemia. 2015;29:1875-1881.
38. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89:2079-2088.
39. Montoro MJ, Ortega M, Villacampa G, et al. A revised international prognostic scoring system of 3.5 points stratifies patients with myelodysplastic syndromes into 2 risk categories. Blood. 2020;136(suppl 1):9-10.
40. de Swart L, Crouch S, Hoeks M, et al; EUMDS Registry Participants. Impact of red blood cell transfusion dose density on progression-free survival in patients with lower-risk myelodysplastic syndromes. Haematologica. 2020;105:632-639.
41. List A, Ebert BL, Fenaux P. A decade of progress in myelodysplastic syndrome with chromosome 5q deletion. Leukemia. 2018;32:1493-1499.
42. Cadenas FL, Lumbreras E, Xicoy B, et al. Phase 3 study of lenalidomide (LEN) vs placebo in non-transfusion dependent (TD) low risk del(5q) MDS patients: interim analysis of the European Sintra-REV Trial. Blood. 2020;132(suppl 1):468.
43. Santini V, Almeida A, Giagounidis A, et al. Randomized phase III study of lenalidomide versus placebo in RBC transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes and ineligible for or refractory to erythropoiesis-stimulating agents. J Clin Oncol. 2016;34:2988-2996.
44. Santini V, Almeida A, Giagounidis A, et al. The effect of lenalidomide on health-related quality of life in patients with lower-risk non-del(5q) myelodysplastic syndromes: results from the MDS-005 study. Clin Lymphoma Myeloma Leuk. 2018;18:136-144.e7.
45. Toma A, Kosmider O, Chevret S, et al. Lenalidomide with or without erythropoietin in transfusion-dependent erythropoiesis-stimulating agent-refractory lower-risk MDS without 5q deletion. Leukemia. 2016;30:897-905.
46. List AF, Sun Z, Verma A, et al. Lenalidomide-epoetin alfa versus lenalidomide monotherapy in myelodysplastic syndromes refractory to recombinant erythropoietin. J Clin Oncol. 2021;39:1001-1009.
47. Wang C, Yang Y, Gao S, et al. Immune dysregulation in myelodysplastic syndrome: clinical features, pathogenesis and therapeutic strategies. Crit Rev Oncol Hematol. 2018;122:123-132.
48. Stahl M, DeVeaux M, de Witte T, et al. The use of immunosuppressive therapy in MDS: clinical outcomes and their predictors in a large international patient cohort. Blood Adv. 2018;2:1765-1772.
49. Garcia-Manero G, Jabbour EJ, Konopleva MY, et al. A clinical study of tomaralimab (OPN-305), a Toll-like receptor 2 (TLR-2) antibody, in heavily pre-treated transfusion dependent patients with lower risk myelodysplastic syndromes (MDS) that have received and failed on prior hypomethylating agent (HMA) therapy. Blood. 2018;132 (suppl 1):798-798.
50. Suragani RNVS, Cadena SM, Cawley SM, et al. Transforming growth factor-β superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. Nat Med. 2014;20:408-414.
51. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. N Engl J Med. 2020;382:140-151.

52. Garcia-Manero G, Mufti G, Fenaux P, et al. Hematologic improvement-neutrophil and -platelet in the MEDALIST Trial: multilineage data from a phase 3, randomized, double-blind, placebo-controlled study of luspatercept to treat anemia in patients with very low-, low-, or intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts (RS) who require red blood cell (RBC) transfusions. Blood. 2019;134(suppl 1):4243.

53. Fenaux P, Santinin V, Mufti G, et al. Effects of luspatercept on serum ferritin in patients (PTS) with lower-risk myelodysplastic syndromes (MDS) with ring sideroblasts (RS) in the phase 3 medalist trial. Poster presented at the EHA25 Virtual Congress; 2020.

54. Lyons RM, Cosgriff TM, Modi SS, et al. Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. J Clin Oncol. 2009;27:1850-1856.

55. Jabbour E, Short NJ, Montalban-Bravo G, et al. Randomized phase 2 study of low-dose decitabine vs low-dose azacitidine in lower-risk MDS and MDS/MPN. Blood. 2017;130:1514-1522.

56. Garcia-Manero G, Griffiths EA, Steensma DP, et al. Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. Blood. 2020;136:674-683.

57. Garcia-Manero G, McCloskey J, Griffiths EA, et al. Pharmacokinetic exposure equivalence and preliminary efficacy and safety from a randomized cross over phase 3 study (ASCERTAIN study) of an oral hypomethylating agent ASTX727 (cedazuridine/decitabine) compared to IV decitabine. Blood. 2019;134(suppl 1): 846-846 .

58. Garcia-Manero G, Santini VAA, Almeida A, et al. A phase III placebo-controlled trial of CC-486 in patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk myelodysplastic syndromes. Presented at: EHA25 Virtual Congress; 2020. Abstract S180.

59. Steensma DP, Fenaux P, Van Eygen K, et al. Imetelstat achieves meaningful and durable transfusion independence in high transfusion-burden patients with lower-risk myelodysplastic syndromes in a phase II study. J Clin Oncol. 2021;39:48-56.

60. Henry DH, Glaspy J, Harrup RA, et al. Oral roxadustat demonstrates efficacy in anemia secondary to lower-risk myelodysplastic syndrome irrespective of ring sideroblasts and baseline erythropoietin levels. Blood. 2020;(suppl 1):29-30.

61. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al; International Vidaza High-Risk MDS Survival Study Group. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009; 10:223-232.

62. Zeidan AM, Stahl M, Sekeres MA, et al. A call for action: Increasing enrollment of untreated patients with higher-risk myelodysplastic syndromes in first-line clinical trials. Cancer. 2017;123:3662-3672.

63. Zeidan AM, Stahl M, DeVeaux M, et al. Counseling patients with higher-risk MDS regarding survival with azacitidine therapy: are we using realistic estimates? Blood Cancer J. 2018;8:55.

64. Mozessohn L, Cheung MC, Fallahpour S, et al. Azacitidine in the 'real-world': an evaluation of 1101 higher-risk myelodysplastic syndrome/low blast count acute myeloid leukaemia patients in Ontario, Canada. Br J Haematol. 2018;181:803-815.

65. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer. 2006;106:1794-1803.

66. Lübbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol. 2011;29:1987-1996.

67. Zeidan AM, Davidoff AJ, Long JB, et al. Comparative clinical effectiveness of azacitidine versus decitabine in older patients with myelodysplastic syndromes. Br J Haematol. 2016;175:829-840.

68. Sekeres MA, Othus M, List AF, et al. Randomized phase II study of azacitidine alone or in combination with lenalidomide or with vorinostat in higher-risk myelodysplastic syndromes and chronic myelomonocytic leukemia: North American Intergroup Study SWOG S1117. J Clin Oncol. 2017;35:2745-2753.

69. Ades L, Watts JM, Radinoff A, et al. Phase II study of pevonedistat (P) + azacitidine (A) versus A in patients (pts) with higher-risk myelodysplastic syndromes (MDS)/chronic myelomonocytic leukemia (CMML), or low-blast acute myelogenous leukemia (LB AML) (NCT02610777). J Clin Oncol. 2020;38 (15 suppl; abstr 7506).

70. Sekeres M, Watts JM, Radinoff A, et al. 653 Efficacy and safety of pevonedistat plus azacitidine vs azacitidine alone in higher-risk myelodysplastic syndromes (MDS) from study P-2001 (NCT02610777). Paper presented at: 62nd ASH Annual Meeting and Exposition; December 2020; All-virtual event.

71. Garcia JS, Wei AH. Borate U eaAPatAAM, December 7, 2020: safety, efficacy, and patient-reported outcomes of venetoclax in combination with azacitidine for the treatment of patients with higher-risk myelodysplastic syndrome: A phase 1b study. Blood. 2020;136(suppl 1):55-57.

72. Bally C, Adès L, Renneville A, et al. Prognostic value of TP53 gene mutations in myelodysplastic syndromes and acute myeloid leukemia treated with azacitidine. Leuk Res. 2014;38:751-755.

73. Montalban-Bravo G, Kanagal-Shamanna R, Benton CB, et al. Genomic context and TP53 allele frequency define clinical outcomes in TP53-mutated myelodysplastic syndromes. Blood Adv. 2020;4:482-495.

74. Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med. 2017;376:536-547.

75. Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes [published correction appears in *Nat Med*. 2021.]. Nat Med. 2020;26:1549-1556.

76. Zhang Q, Bykov VJN, Wiman KG, et al. APR-246 reactivates mutant p53 by targeting cysteines 124 and 277 [correction published in *Cell Death Dis*. 2019:10: 769]. Cell Death Dis. 2018;9:439.

77. Sallman DA, DeZern AE, Garcia-Manero G, et al. Eprenetapopt (APR-246) and azacitidine in *TP53*-mutant myelodysplastic syndromes. J Clin Oncol. Epub 2021 Jan 15.

78. Cluzeau T, Sebert M, Rahmé R, et al. APR-246 combined with azacitidine (AZA) in TP53 mutated myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). A phase 2 study by the Groupe Francophone Des Myélodysplasies (GFM). Blood. 2019;134 (suppl 1):677-677.

79. Boultwood J, Pellagatti A. The impact of spliceosome mutations in MDS. HemaSphere. 2019;3:132-134.

80. Steensma DP, Wermke M, Klimek VM, et al. Results of a clinical trial of H3B-8800, a splicing modulator, in patients with myelodysplastic syndromes (MDS), acute myeloid leukemia (AML) or chronic myelomonocytic leukemia (CMML). Blood. 2019;134 (suppl 1):673-673.

81. Seiler M, Yoshimi A, Darman R, et al. H3B-8800, an orally available small-molecule splicing modulator, induces lethality in spliceosome-mutant cancers. Nat Med. 2018;24:497-504.

82. Daver N, Strati P, Jabbour E, et al. FLT3 mutations in myelodysplastic syndrome and chronic myelomonocytic leukemia. Am J Hematol. 2013;88:56-59.

83. Takahashi K, Jabbour E, Wang X, et al. Dynamic acquisition of FLT3 or RAS alterations drive a subset of patients with lower risk MDS to secondary AML. Leukemia. 2013;27:2081-2083.

84. Daver N, Boddu P, Garcia-Manero G, et al. Hypomethylating agents in combination with immune checkpoint inhibitors in acute myeloid leukemia and myelodysplastic syndromes. Leukemia. 2018;32:1094-1105.

85. Chien KS, Borthakur GM, Naqvi K, et al. Updated preliminary results from a phase II study combining azacitidine and pembrolizumab in patients with higher-risk myelodysplastic syndrome. Blood. 2019;134(suppl 1):4240-4240.

86. Garcia-Manero G, Sasaki K, Montalban-Bravo G, et al. A phase II study of nivolumab or ipilimumab with or without azacitidine for patients with myelodysplastic syndrome (MDS). Blood. 2018;132(suppl 1):465-465.

87. Sallman DA, Asch AS, Kambhampati S, et al. The first-in-class anti-CD47 antibody magrolimab combined with azacitidine is well-tolerated and effective in AML patients: phase 1b results. Blood. 2020;134(suppl 1):569.

88. Asayama T, Tamura H, Ishibashi M, et al. Functional expression of Tim-3 on blasts and clinical impact of its ligand galectin-9 in myelodysplastic syndromes. Oncotarget. 2017;8:88904-88917.

89. Kikushige Y, Shima T, Takayanagi S, et al. TIM-3 is a promising target to selectively kill acute myeloid leukemia stem cells. Cell Stem Cell. 2010;7:708-717.

90. Sabatos-Peyton C, Longmire T, Baker L, et al. 439 Dual modes of action for anti-TIM-3 antibody MBG453 in myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML): preclinical evidence for immune-mediated and anti-leukemic activity. J Immunother Cancer. 2020;8(suppl 3):A267.

91. Brunner AM, Esteve J, Porkka K, et al. Efficacy and safety of sabatolimab (MBG453) in combination with hypomethylating agents (HMAs) in patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (HR-MDS): updated results from a phase 1b study. Blood. 2020;136(suppl 1):1-2.

92. Prébet T, Gore SD, Esterni B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol. 2011;29:3322-3327.

93. Sebert M, Bally C, Peterlin P, et al. Results of a phase II study of guadecitabine (SGI-110) in higher risk MDS, CMML or low blast count AML patients refractory to or relapsing after azacitidine (AZA) treatment. Blood. 2016;128:347-347.

94. Garcia-Manero G, Roboz G, Walsh K, et al. Guadecitabine (SGI-110) in patients with intermediate or high-risk myelodysplastic syndromes: phase 2 results from a multicentre, open-label, randomised, phase 1/2 trial. Lancet Haematol. 2019;6:e317-e327.

95. Garcia-Manero G, Fenaux P, Al-Kali A, et al; ONTIME Study Investigators. Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial. Lancet Oncol. 2016;17:496-508.

96. Navada SC, Garcia-Manero G, OdchimarReissig R, et al. Rigosertib in combination with azacitidine in patients with myelodysplastic syndromes or acute myeloid leukemia: results of a phase 1 study. Leuk Res. 2020;94:106369.

97 Zeidan AM, Pollyea D, Garcia J, et al. A phase 1b study evaluating the safety and efficacy of venetoclax in combination with azacitidine for the treatment of relapsed/refractory myelodysplastic syndrome. *Blood*. 2020;134(suppl 1):565.

98. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med. 2018;378:2386-2398.

99. Foran JM, DiNardo CD, Watts JM, et al. Ivosidenib (AG-120) in patients with IDH1-mutant relapsed/refractory myelodysplastic syndrome: updated enrollment of a phase 1 dose escalation and expansion study. Blood. 2019;134 (suppl 1):4254-4254.

100. Stein EM, Fathi AT, DiNardo CD, et al. Enasidenib in patients with mutant IDH2 myelodysplastic syndromes: a phase 1 subgroup analysis of the multicentre, AG221-C-001 trial. Lancet Haematol. 2020;7:e309-e319.

101. Richard-Carpentier G, DeZern AE, Takahashi K, et al. Preliminary results from the phase II study of the IDH2-inhibitor enasidenib in patients with high-risk IDH2-mutated myelodysplastic syndromes (MDS). Blood. 2019;134(suppl 1):678-678.

102. Ramos Perez JM, Kadia TM, Montalban-Bravo G, et al. Liposomal cytarabine and daunorubicin (CPX-351) in combination with gemtuzumab ozogamicin (GO) in relapsed refractory (R/R) patients with acute myeloid leukemia (AML) and post-hypomethylating agent (post-HMA) failure high-risk myelodysplastic syndrome (HR-MDS). Blood. 2019;134(suppl 1):2642-2642.

103. Patnaik MM, Lasho TL. Genomics of myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes. Hematology (Am Soc Hematol Educ Program). 2020;2020:450-459.

104. Swederlow S, Camp E, Harris NL, et al. WHO Classification of Tumors of the Haematopoietic and Lymphoid Tissue, 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2008.

105. Mason CC, Khorashad JS, Tantravahi SK, et al. Age-related mutations and chronic myelomonocytic leukemia. Leukemia. 2016;30:906-913.

106. Palomo L, Meggendorfer M, Hutter S, et al. Molecular landscape and clonal architecture of adult myelodysplastic/myeloproliferative neoplasms. Blood. 2020; 136:1851-1862.

107. Patnaik MM, Lasho T. Myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes: a focused review. Hematology (Am Soc Hematol Educ Program). 2020;2020:460-464.

108. Patnaik MM, Tefferi A. Chronic myelomonocytic leukemia: 2020 update on diagnosis, risk stratification and management. Am J Hematol. 2020;95:97-115.

109. Ball M, List AF, Padron E. When clinical heterogeneity exceeds genetic heterogeneity: thinking outside the genomic box in chronic myelomonocytic leukemia. Blood. 2016;128:2381-2387.

110. Valent P, Orazi A, Savona MR, et al. Proposed diagnostic criteria for classical chronic myelomonocytic leukemia (CMML), CMML variants and pre-CMML conditions. Haematologica. 2019;104:1935-1949.

111. Wassie EA, Itzykson R, Lasho TL, et al. Molecular and prognostic correlates of cytogenetic abnormalities in chronic myelomonocytic leukemia: a Mayo Clinic-French Consortium Study. Am J Hematol. 2014;89:1111-1115.

112. Elena C, Gallì A, Such E, et al. Integrating clinical features and genetic lesions in the risk assessment of patients with chronic myelomonocytic leukemia. Blood. 2016;128:1408-1417.

113. Itzykson R, Kosmider O, Renneville A, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. J Clin Oncol. 2013;31:2428-2436.

114. Patnaik MM, Itzykson R, Lasho TL, et al. ASXL1 and SETBP1 mutations and their prognostic contribution in chronic myelomonocytic leukemia: a two-center study of 466 patients. Leukemia. 2014;28:2206-2212.

115. Pophali P, Matin A, Mangaonkar AA, et al. Prognostic impact and timing considerations for allogeneic hematopoietic stem cell transplantation in chronic myelomonocytic leukemia. Blood Cancer J. 2020;10:121.

116. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al; International Vidaza High-Risk MDS Survival Study Group. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009; 10:223-232.

117. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol. 2002;20:2429-2440.

118. Coston T, Pophali P, Vallapureddy R, et al. Suboptimal response rates to hypomethylating agent therapy in chronic myelomonocytic leukemia; a single institutional study of 121 patients. Am J Hematol. 2019;94:767-779.

119. Santini V, Allione B, Zini G, et al. A phase II, multicentre trial of decitabine in higher-risk chronic myelomonocytic leukemia. Leukemia. 2018;32:413-418.

120. Merlevede J, Droin N, Qin T, et al. Mutation allele burden remains unchanged in chronic myelomonocytic leukaemia responding to hypomethylating agents. Nat Commun. 2016;7:10767.

121. Itzykson R, Santini V, Chaffaut C, et al. Decitabine versus hydroxyurea for advanced proliferative CMML: results of the Emsco randomized phase 3 Dacota trial. Blood. 2020;136(suppl 1):53-54.

122. Patnaik MM, Barraco D, Lasho TL, et al. DNMT3A mutations are associated with inferior overall and leukemia-free survival in chronic myelomonocytic leukemia. Am J Hematol. 2017;92:56-61.

123. Savona MR, Malcovati L, Komrokji R, et al; MDS/MPN International Working Group. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood. 2015;125:1857-1865.

124. Duchmann M, Yalniz FF, Sanna A, et al. Prognostic role of gene mutations in chronic myelomonocytic leukemia patients treated with hypomethylating agents. EBioMedicine. 2018;31:174-181.

125. Patnaik MM, Sallman DA, Mangaonkar AA, et al. Phase 1 study of lenzilumab, a recombinant anti-human GM-CSF antibody, for chronic myelomonocytic leukemia. Blood. 2020;136:909-913.

126. Padron E, Dezern A, Andrade-Campos M, et al. A multi-institution phase 1 trial of ruxolitinib in patients with chronic myelomonocytic leukemia (CMML). Clin Cancer Res. 2016;22:3746-3754.

127. Lucas N, Duchmann M, Rameau P, et al. Biology and prognostic impact of clonal plasmacytoid dendritic cells in chronic myelomonocytic leukemia. Leukemia. 2019;33:2466-2480.

128. Mangaonkar AA, Reichard KK, Binder M, et al. Bone marrow dendritic cell aggregates associate with systemic immune dysregulation in chronic myelomonocytic leukemia. Blood Adv. 2020;4:5425-5430.

129. Patnaik MM, Barraco D, Lasho TL, et al. Targeted next generation sequencing and identification of risk factors in World Health Organization defined atypical chronic myeloid leukemia. Am J Hematol. 2017;92:542-548.

130. Gambacorti-Passerini CB, Donadoni C, Parmiani A, et al. Recurrent ETNK1 mutations in atypical chronic myeloid leukemia. Blood. 2015;125:499-503.

131. Gotlib J, Maxson JE, George TI, et al. The new genetics of chronic neutrophilic leukemia and atypical CML: implications for diagnosis and treatment. Blood. 2013;122:1707-1711.

132. Sharma P, Shinde SS, Damlaj M, et al. Allogeneic hematopoietic stem cell transplant in adult patients with myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) overlap syndromes. Leuk Lymphoma. 2016;58:872-881.

133. Patnaik MM, Lasho TL, Finke CM, et al. Vascular events and risk factors for thrombosis in refractory anemia with ring sideroblasts and thrombocytosis. Leukemia. 2016;30:2273-2275.

134. Patnaik MM, Lasho TL, Finke CM, et al. Predictors of survival in refractory anemia with ring sideroblasts and thrombocytosis (RARS-T) and the role of next-generation sequencing. Am J Hematol. 2016;91:492-498.

135. Patnaik MM, Tefferi A. Myelodysplastic syndromes with ring sideroblasts (MDS-RS) and MDS/myeloproliferative neoplasm with RS and thrombocytosis (MDS/MPN-RS-T) - "2021 update on diagnosis, risk-stratification, and management. Am J Hematol. 2021;96:379-394.

136. Malcovati L, Della Porta MG, Pietra D, et al. Molecular and clinical features of refractory anemia with ringed sideroblasts associated with marked thrombocytosis. Blood. 2009;114:3538-3545.

137. Jeromin S, Haferlach T, Weissmann S, et al. Refractory anemia with ring sideroblasts and marked thrombocytosis cases harbor mutations in SF3B1 or other spliceosome genes accompanied by JAK2V617F and ASXL1 mutations. Haematologica. 2015;100:e125-e127.

138. Antelo G, Mangaonkar AA, Coltro G, et al. Response to erythropoiesis-stimulating agents in patients with WHO-defined myelodysplastic syndrome/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T). Br J Haematol. 2020;189:e104-e108.

139. Nicolosi M, Mudireddy M, Vallapureddy R, et al. Lenalidomide therapy in patients with myelodysplastic syndrome/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T). Am J Hematol. 2018;93:E27-E30.

140. Niemeyer CM, Flotho C. Juvenile myelomonocytic leukemia: who's the driver at the wheel? Blood. 2019;133:1060-1070.

141. Niemeyer CM. RAS diseases in children. Haematologica. 2014;99:1653-1662.

142. Stieglitz E, Taylor-Weiner AN, Chang TY, et al. The genomic landscape of juvenile myelomonocytic leukemia [correction published in *Nat Genet.* 2016;48:101]. Nat Genet. 2015;47:1326-1333.

143. Stieglitz E, Troup CB, Gelston LC, et al. Subclonal mutations in SETBP1 confer a poor prognosis in juvenile myelomonocytic leukemia. Blood. 2015;125:516-524.

144. Stieglitz E, Mazor T, Olshen AB, et al. Genome-wide DNA methylation is predictive of outcome in juvenile myelomonocytic leukemia. Nat Commun. 2017;8:2127.

145. Mangaonkar AA, Swoboda DM, Coltro G, et al. Clinicopathologic characteristics, prognostication and treatment outcomes for myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U): Mayo Clinic-Moffitt Cancer Center study of 135 consecutive patients. Leukemia. 2020;34:656-661.

146. Bose P, Nazha A, Komrokji RS, et al. Mutational landscape of myelodysplastic/myeloproliferative neoplasm-unclassifiable. Blood. 2018;132:2100-2103.

147. Nazha A, Bejar R. Molecular data and the IPSS-R: how mutational burden can affect prognostication in MDS. Curr Hematol Malig Rep. 2017;12:461-467.

Understanding and Addressing Disparities in Patients With Hematologic Malignancies: Approaches for Clinicians

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Overview

Approximately 185,840 individuals will be diagnosed with hematologic malignancies in the United States in 2020. Disparities in disease incidence, prevalence, burden, mortality, and survivorship have been identified among this patient population. Contributing factors include genetic ancestry, race/ethnicity, sex, socioeconomic status, and geographic region. Historically, these inequities have been understudied. Addressing these disparities requires a systems-level approach, improving access to care and reducing biases in the clinical setting. Additional research is needed to construct comprehensive, multilevel models to explore systematic observational studies and perform strategic intervention trials to overcome these disparities.

BACKGROUND

According to the American Cancer Society, approximately 185,840 individuals will be diagnosed with hematologic malignancies in the United States in 2020, including multiple myeloma and all forms of lymphomas and leukemias.[1] The National Cancer Institute defines cancer disparities as differences in cancer incidence, cancer-related deaths, and cancer-associated health complications across population groups. Observed differences in cancer outcomes predominantly have been described in medically underserved populations, including those with no insurance, Medicaid, lower socioeconomic status (SES), and lower health literacy and those from racial and ethnic minority groups.[2,3] Numerous factors contribute to cancer disparities that interact in complex ways, and these have been described in a multilevel model of disparities occurring in hematologic cancers.[4] These include but are not limited to differences in environmental exposures, diet, lifestyle, cultural beliefs, genetic and biologic factors related to ancestry, SES, and access to health care. Compounding these challenges, patients with hematologic malignancies and other uncommon cancers have received less attention in investigations of these factors. Addressing disparities in cancer incidence, prevalence, burden, mortality, and survivorship requires multilevel models of the interactions between relevant factors and the development of clinical, epidemiologic, and translational research programs to design and evaluate interventions that impact human endpoints.

DISPARITIES IN MYELOMA INCIDENCE AND OUTCOMES

Multiple myeloma is the most commonly diagnosed hematologic malignancy among Black Americans.[5] The incidence of multiple myeloma among Black individuals (15.9 per 100,000) is more than double the incidence among White individuals (7.5 per 100,000).[6] Genome-wide association studies that identified germline genetic variations associated with increased risk of hematologic malignancies have found a higher frequency of loci strongly associated with susceptibility to multiple myeloma among people with African ancestry compared with individuals of European descent.[7,8] The multiple myeloma subtypes involving t(11;14), t(14;16), and t(14;20) were more common among individuals with greater degrees of African ancestry, whereas trisomies and monosomy 13/13q deletion were less common.[8,9] Together, these findings suggest that ancestry may be associated with predisposition for developing specific myeloma subtypes, but additional studies are needed to address potential environmental factors that may contribute to and confound this association. Important observational studies (such as the PROMISE study) evaluating healthy people, including individuals of African ancestry, in higher risk groups for multiple myeloma will provide critical insights in the future to determine the linkages for multiple myeloma risk.

Disparities have also been identified in myeloma treatment and outcomes. An analysis of patients with multiple myeloma in the U.S. Surveillance, Epidemiology, and End Results national database suggests that novel myeloma therapies disproportionately have benefited White patients of higher SES.[10] After the introduction of these therapies, White patients had double the observed survival improvements compared with Black patients. Other data indicate that Black

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PRACTICAL APPLICATIONS

- Eliminating disparities among patients with hematologic malignancies requires clinicians to consider how patients' biologic, clinical, and demographic characteristics interact to affect their prognoses and their access to care.
- By identifying indicators of worse outcomes, clinicians can develop appropriate interventions that can be applied throughout health care systems.

patients in the United States with multiple myeloma were 21% less likely to be treated with bortezomib after it was established as an effective therapy.[11] In a multivariable analysis involving more than 37,000 patients with multiple myeloma, Hispanic patients had significantly worse median overall survival compared with White patients.[11] A single-center study of 453 patients with who underwent autologous stem cell transplantation for multiple myeloma suggests that Black patients may actually have better survival outcomes compared with White patients when receiving the same therapy.[12] Similar to other findings in cancer disparities research, these data suggest that inequalities in access and inequalities in care lead to inequalities in multiple myeloma outcomes. Future efforts should focus on interventions to improve access and delivery of high-quality care to achieve equitable and improved outcomes for all patients with myeloma.

DISPARITIES IN LYMPHOMA INCIDENCE AND OUTCOMES

There are known disparities in incidence, age at diagnosis, and overall survival among patients with Hodgkin lymphoma and non-Hodgkin lymphomas. Most lymphomas, apart from marginal zone and follicular lymphoma, are more common among men.[13] Genome-wide association studies identified susceptibility loci for diffuse large B-cell lymphoma that are more common within Asian populations.[7,8,14-17] In the only study examining ancestry and tumor genomics to date, recurrent somatic mutations in established driver genes, such as *ATM*, *MGA*, *SETD2*, *TET2*, *DNMT3A*, and *MLL3*, were more frequent among patients with African ancestry compared with those of European ancestry.[7] The incidence of lymphoma among patients from racial and ethnic minority groups is lower than the incidence among their White counterparts for most lymphoma subtypes. A counterexample to this occurs in patients with cutaneous T-cell lymphomas, in which Black patients have an increased incidence of mycosis fungoides. These patients often present with a more aggressive course and higher stage, and at an age 10 years younger than White patients.[18,19] No known genetic or environmental exposures have been described to explain these differences. An analysis of the Environmental Protection Agency's National Air Toxics Assessment database for the state of Georgia found that higher rates of cutaneous T-cell lymphoma were geographically clustered in regions with higher levels of benzene and trichloroethylene exposure.[20] Future studies should explore relationships between environmental exposures and disparities in incidence and clinical presentation to define explanatory models and develop interventions for prevention strategies.

Like cutaneous T-cell lymphomas, most subtypes of lymphoma, are diagnosed in Black patients at a younger age and at a more advanced stage, and the lymphomas have higher risk features at initial presentation.[21,22] Across studies, Black patients in the United States with diffuse large B-cell lymphoma were diagnosed at a mean age more than 10 years younger than White patients, more commonly had advanced stage disease, were less likely to be insured, less commonly received standard-of-care therapy, and experienced worse overall survival.[23,24] Studies of patients treated for Hodgkin lymphoma found that Black patients had an increased risk of cardiovascular mortality and anthracycline-associated cardiotoxicity compared with White patients.[25,26] Among patients with follicular lymphoma, women appeared to have improved overall survival compared with men despite being more likely to receive single-agent rituximab as opposed to anthracycline-based chemotherapy.[27] Additionally, patients with Hodgkin lymphoma and lower SES had a higher risk of death compared with patients who had a higher SES.[28] Though each of these findings offers selected insights into the forms of disparities in outcomes observed for patients diagnosed with various lymphoma subtypes, comprehensive models and systematic multilevel research approaches are needed to define clear approaches for improving outcomes.

Across a series of studies, some comprehensive models are now emerging for more common lymphoma subtypes, such as diffuse large B-cell lymphoma. A 2014 study using data from the National Cancer Database found that uninsured patients and patients on Medicaid tended to be younger and were more likely to be members of a racial/ethnic minority group, were more likely to be diagnosed with an advanced stage of diffuse large B-cell lymphoma, and less likely to receive standard-of-care chemoimmunotherapy. Five-year overall survival rates among patients without insurance and patients with Medicaid were lower than survival rates among patients with private insurance.[17] Similar trends have been noted among patients with follicular lymphoma and Burkitt lymphoma but not plasmablastic lymphoma.[9,29] Together, these studies suggest that health insurance may be a key mediator in access to high-quality cancer care that is associated with improved outcomes for lymphomas in which novel therapies have been demonstrated to improve progression-free and overall survival for newly diagnosed

and relapsed disease, as in follicular lymphoma, diffuse large B-cell lymphoma, and Burkitt lymphoma. Insurance status likely was not an independent predictor of survival in plasmablastic lymphoma, because current therapies remain ineffective for most patients.

Ritter and colleagues[30] assessed the relationship among geographic population density (metropolitan, urban, or rural), household income, and overall survival among 83,000 patients with diffuse large B-cell lymphoma and 43,000 patients with follicular lymphoma from the National Cancer Database in the United States. This analysis identified lower overall survival among patients with diffuse large B-cell lymphoma and follicular lymphoma living in rural and urban counties compared with those in metropolitan counties. Compared with their metropolitan counterparts, rural and urban patients were less likely to have private insurance and more likely to have a lower SES. Across all geographic regions, patients with a household income less than $38,000 had worse overall survival.[30] Future studies should identify specific barriers to care and potential interventions to improve access among patients living outside metropolitan areas. Together, these studies of disparities in incidence and outcomes for patients with lymphomas indicate a need for a comprehensive model to describe the interactions of factors that mediate these disparities. Such models can drive the generation of new approaches for addressing these disparities that can be explored in observational studies of large cohorts with biologic samples and tested in population-based interventional studies.

DISPARITIES IN LEUKEMIA INCIDENCE AND OUTCOMES

The incidence of leukemia overall is higher among men compared with women.[31] The age-adjusted incidence of acute myeloid leukemia from 2010 to 2014 was higher among White patients compared with their Black, Asian/Pacific Islander, and Hispanic counterparts.[32] Even though there is a higher prevalence of favorable cytogenetics and a younger mean age of diagnosis among patients from minority groups compared with their White counterparts, a study of 39,000 patients with acute myeloid leukemia in the Surveillance, Epidemiology, and End Results database found that the risk of death increased 12% among Black patients and 6% among Hispanic patients compared with non-Hispanic White patients.[33]

In the United States, the incidence and mortality rate of acute lymphoblastic leukemia are highest among Hispanic Americans. However, a recent review addressed some of the complexities inherent in this association, because there is considerable diversity within the Latinx population and varying methods for defining Hispanic and Latinx groups, which may be associated with distinct environmental factors and variations within the genetic ancestry for Latinx individuals.[34] Data suggest that some of these differences are related to the higher frequency of Philadelphia chromosome–like acute lymphoblastic leukemia and molecular markers associated with Native American ancestry. An analysis of 2,428 patients with acute lymphoblastic leukemia in California, Florida, and New York found that Hispanic patients from continental American countries (populations with higher amounts of Native American ancestry) had worse survival than Hispanic patients from Caribbean countries.[35]

Black patients with chronic lymphocytic leukemia or small lymphocytic lymphoma often present with worse prognostic indicators, such as increased β2-microglobulin levels, worsening anemia, higher Rai stage, and unfavorable cytogenetic markers, compared with White patients.[36] Black patients with chronic lymphocytic leukemia or small lymphocytic lymphoma also tend to present at a younger age and have a decreased event-free survival and overall survival compared with White patients.[36,37] Because diagnoses of leukemia occur less commonly than diagnoses of solid tumors, studies of disparities in these patient groups have been uncommon. Continued exploration of epidemiology and outcomes research across leukemia subtypes is needed to uncover opportunities for additional research and interventions.

DISPARITIES IN STEM CELL TRANSPLANTATION

Stem cell transplantation can be associated with disparities in both access and outcomes for minority populations. Analysis of the California Cancer Registry found that Black and Hispanic patients with acute myeloid leukemia had a decreased likelihood of stem cell transplantation compared with White patients (odds ratio, 0.64; 95% CI, 0.46–0.87; and 0.74; 95% CI, 0.62–0.89, respectively).[38] Another study of autologous stem cell transplantation revealed that age-adjusted relative rates of autologous stem cell transplantation for patients with multiple myeloma were significantly higher in non-Hispanic White patients than in Black, Hispanic, and Asian patients.[39] In another study, Black patients with myeloma were 49% less likely to receive stem cell transplantation than White patients. A study of patients undergoing allogeneic stem cell transplantation found that African ancestry was associated with an increased risk of overall mortality among both transplant recipients (HR, 2.26; 95% CI, 1.28–3.96) and donors (HR, 3.09; 95% CI, 1.7–5.64). This association persisted after adjustment for potential clinical confounders as well as self-reported race/ethnicity.[16,29] Additional studies are needed to explore other factors that may be associated with inequalities in access and outcomes. These disparities in access to stem cell transplantation as a contemporary technology for the management of hematologic malignancies raise considerable concern, particularly with the emergence of

new technologies, such as CAR T cells. Cellular therapy approaches will likely increase in frequency for new indications in hematologic cancers over time and will require the development of population-based interventions and policies to ensure that all patients can appropriately receive the benefits of these innovations when indicated.

POPULATIONS IN WHOM DISPARITIES IN HEMATOLOGIC MALIGNANCIES HAVE BEEN UNDERSTUDIED

Lesbian, gay, bisexual, transgender, and intersex individuals account for approximately 3% to 12% of the population. However, limited data exist regarding disparities in health outcomes, including malignancies, in this population.[40-43] Regrettably, most of the published literature in oncology in the lesbian, gay, bisexual, transgender, and intersex population focuses on associations with HIV and lymphoma and often involves small, observational studies.[40,42] Although there is no universally accepted, all-inclusive term for patients in this community, "sexual and gender minority" has been adopted as an inclusive terminology, and organizations, including ASCO and the American Medical Association, have acknowledged the disparities that exist among sexual- and gender-minority individuals.[44] Sexual- and gender-minority patients with cancer may face unique psychosocial challenges during treatment and in survivorship.[42,43,45] To address this research gap, sexual orientation and gender identity questions were added to the National Health Institute Survey,[46] and the National Cancer Institute has raised studies in sexual- and gender-minority populations as a priority area for research.[47]

APPROACHES FOR CLINICIANS TO ADDRESS DISPARITIES IN HEMATOLOGIC MALIGNANCIES

Research Strategies to Address Cancer Disparities

To eliminate disparities in malignant hematologic outcomes, clinicians and researchers must clearly define demographic and clinical factors that contribute to an increased risk of poor outcomes. Historically, race and ethnicity data were imprecise and often involved limited options that placed a large number of study participants in the "other" category or noted Hispanic ethnicity without documented race.[5] However, since 2005, the Surveillance, Epidemiology, and End Results database and the National Cancer Institute have expanded their race categories to reflect a more diverse population.[48] Likewise, there are issues with correctly quantifying SES and identifying patients with low health literacy. As investigators apply standard definitions of race, ethnicity, and sociodemographic factors in cancer registries and research protocols, future studies may clarify etiologies to explain some of the disparities identified.

Given the myriad biologic, clinical, demographic, and societal factors that contribute to disparities, a multilevel approach is required to create outcomes that are more equitable. However, lack of health care access is a general theme to address across the strategies discussed above. Access can largely be attributed to insurance status. According to the U.S. Census Bureau, 26.1 million Americans (8.0%) were uninsured during 2019,[49] which was a decrease from 42 million (13.4%) in 2013.[50] This increase in insurance coverage resulted from implementation of new provisions of the Affordable Care Act established in January 2014. The largest increase in health insurance coverage was among those with the lowest education and income. Unfortunately, Hispanic and Black Americans continue to be the most likely to be uninsured: 16.7% and 9.6%, respectively, compared with 5.2% of non-Hispanic White Americans and 6.2% of Asian Americans.[49] Uninsured patients are more likely to be diagnosed with cancer at a later stage.[51,52] The information gathered using the strategies above can be shared with stakeholders in real time to inform health policy and encourage increased funding.

DISPARITIES IN CLINICAL TRIAL ENROLLMENT FOR MINORITIES, WOMEN, AND LOW SES, RURAL, AND OTHER POPULATIONS

Barriers to Minority Enrollment in Clinical Trials

Clinical trials are key components of cancer research and continually enhance treatment options for patients across all tumor types. In an analysis by the American Cancer Society Cancer Action Network, the overall trial participation rates averaged 14.8% at academic centers and 6.3% at community centers.[53] Unfortunately, across most studies, Black populations, Hispanic populations, and patients older than age 65 are under-represented in clinical trials. Furthermore, recent studies have found that patients with household incomes less than $50,000 were approximately 30% less likely to participate in trials.[54,55] Equal participation in clinical trials is essential to determine differences in cancer biology, outcomes, safety, and efficacy of new cancer therapeutics across all populations. In specific hematologic malignancies like myeloma, in which the incidence of disease is higher in African Americans, limited participation in clinical trials may mean that new therapies are studied in populations who are dramatically different from those in whom they will be applied. The data presented above regarding the relationships between African ancestry and specific myeloma subtypes accentuate this point. The U.S. Food and Drug Administration has taken note of this issue and recently published guidelines for increasing diversity in clinical trials.[56]

The largest obstacles to enrollment in trials for rural patients seem to be distance and lack of communication between large centers and small clinics, leading to unfamiliarity with clinical trial opportunities. A qualitative study of rural survivors of lymphoma who received treatment at an

academic medical center noted barriers to clinical trial participation, including distance to the academic center, transportation difficulties, and less time with their oncology provider at the academic medical center clinics. However, these patients identified the use of patient portals to improve clinician-patient communication as a notable factor in improving their understanding of clinical trial opportunities.[57] Telemedicine and other strategies that limit patient travel may expand options for clinical trial participation for rural patients. The most common lymphoma subtypes (diffuse large B-cell lymphoma and follicular lymphoma) represent patient subgroups with worse survival and in greater need of clinical trial options. Similar issues may arise for rural patients with other hematologic malignancies when observational studies are performed to examine whether disparities exist for those patient groups.

STRATEGIES FOR IMPROVING MINORITY ENROLLMENT IN CLINICAL TRIALS

The National Institutes of Health Revitalization Act of 1993 required the National Institutes of Health to establish guidelines for inclusion of women and patients from minority groups in clinical research,[58] with the goal that subgroups should be proportionately represented. Published strategies across U.S. cancer centers have analyzed factors that optimize recruitment of patients from minority groups in cancer research. For instance, Regnante and colleagues[59] conducted qualitative research in the form of interviews with multiple U.S. cancer centers that are actively involved in increasing accrual rates for racial and ethnic minority patients. The percentage of minority participations accrued in cancer clinic trials across eight cancer centers studied ranged from 10% to 40% between 2016 and 2018. This study identified five broad themes for increasing participation of women and patients from minority groups in clinical trials. These themes were commitment and center leadership, investigator training and mentorship, community engagement, patient engagement, and operational practices. For example, many trials have strict criteria, such as excluding patients with comorbidities like diabetes and hypertension—comorbidities that are highly prevalent in Black patients. Although these comorbidities are relevant to the treatment being evaluated in trial, these are important exclusions that may require examination of alternative treatments in separate trials for these patient groups. In situations in which these comorbidities are not relevant to the treatment being evaluated, such criteria may inadvertently exclude minority patients and patients with lower SES.

CONCLUSION

Among patients in the United States diagnosed with hematologic malignancies, considerable disparities in disease incidence and outcomes have been identified. Factors attributing to inequities include race/ethnicity, ancestry, gender, SES, and geographic region. These disparities have been understudied in the past but have gained more visibility in recent years. Some approaches that clinicians can apply to address these disparities include increasing systems-level awareness, improving access to care, and reducing biases in clinical setting. Additional research is needed to construct comprehensive, multilevel models; explore systematic observational studies; and perform strategic intervention trials to overcome these disparities.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_320079.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
2. Flowers CR, Glover R, Lonial S, et al. Racial differences in the incidence and outcomes for patients with hematological malignancies. Curr Probl Cancer. 2007;31:182-201.

3. Polite BN, Adams-Campbell LL, Brawley OW, et al. Charting the future of cancer health disparities research: a position statement from the American Association for Cancer Research, the American Cancer Society, the American Society of Clinical Oncology, and the National Cancer Institute. J Clin Oncol. 2017; 35:3075-3082.
4. Flowers CR, Nastoupil LJ. Socioeconomic disparities in lymphoma. Blood. 2014;123:3530-3531.
5. Williams S, Ayers AA, Hildebrandt MT, et al. Strategies for overcoming disparities for patients with hematologic malignancies and for improving enrollment on clinical trials. Oncology (Williston Park). 2020;34:216-223.
6. American Cancer Society. Cancer Facts & Figures for African-Americans 2019-2021. Atlanta, GA: American Cancer Society; 2019.
7. Lee MJ, Koff JL, Switchenko JM, et al. Genome-defined African ancestry is associated with distinct mutations and worse survival in patients with diffuse large B-cell lymphoma. Cancer. 2020;126:3493-3503.
8. Baughn LB, Pearce K, Larson D, et al. Differences in genomic abnormalities among African individuals with monoclonal gammopathies using calculated ancestry. Blood Cancer J. 2018;8:96.
9. Goldstein JS, Switchenko JM, Behera M, et al. Insurance status impacts overall survival in Burkitt lymphoma. Leuk Lymphoma. 2019;60:3225-3234.
10. Fiala MA, Keller J, Stockerl-Goldstein KE, et al. Treatment advances for multiple myeloma have disproportionally benefited patients who are young, white, and have higher socioeconomic status. Blood. 2014;124:555.
11. Fiala MA, Wildes TM. Racial disparities in treatment use for multiple myeloma. Cancer. 2017;123:1590-1596.
12. Bhatnagar V, Wu Y, Goloubeva OG, et al. Disparities in black and white patients with multiple myeloma referred for autologous hematopoietic transplantation: a single center study. Cancer. 2015;121:1064-1070.
13. Teras LR, DeSantis CE, Cerhan JR, et al. 2016 U.S. lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin. 2016;66:443-459.
14. Bassig BA, Cerhan JR, Au WY, et al. Genetic susceptibility to diffuse large B-cell lymphoma in a pooled study of three Eastern Asian populations. Eur J Haematol. 2015;95:442-448.
15. Tan DE, Foo JN, Bei JX, et al. Genome-wide association study of B-cell non-Hodgkin lymphoma identifies 3q27 as a susceptibility locus in the Chinese population. Nat Genet. 2013;45:804-807.
16. Madbouly A, Wang T, Haagenson M, et al. Investigating the association of genetic admixture and donor/recipient genetic disparity with transplant outcomes. Biol Blood Marrow Transplant. 2017;23:1029-1037.
17. Han X, Jemal A, Flowers CR, et al. Insurance status is related to diffuse large B-cell lymphoma survival. Cancer. 2014;120:1220-1227.
18. Imam MH, Shenoy PJ, Flowers CR, et al. Incidence and survival patterns of cutaneous T-cell lymphomas in the United States. Leuk Lymphoma. 2013; 54:752-759.
19. Kudelka MR, Switchenko JM, Lechowicz MJ, et al. Maintenance therapy for cutaneous T-cell lymphoma after total skin electron irradiation: evidence for improved overall survival with ultraviolet therapy. Clin Lymphoma Myeloma Leuk. 2020;20:757-767.e3.
20. Clough L, Bayakly AR, Ward KC, et al. Clustering of cutaneous T-cell lymphoma is associated with increased levels of the environmental toxins benzene and trichloroethylene in the state of Georgia. Cancer. 2020;126:1700-1707.
21. Nabhan C, Byrtek M, Taylor MD, et al. Racial differences in presentation and management of follicular non-Hodgkin lymphoma in the United States: report from the National LymphoCare Study. Cancer. 2012;118:4842-4850.
22. Shenoy PJ, Malik N, Nooka A, et al. Racial differences in the presentation and outcomes of diffuse large B-cell lymphoma in the United States. Cancer. 2011; 117:2530-2540.
23. Flowers CR, Fedewa SA, Chen AY, et al. Disparities in the early adoption of chemoimmunotherapy for diffuse large B-cell lymphoma in the United States. Cancer Epidemiol Biomarkers Prev. 2012;21:1520-1530.
24. Flowers CR, Shenoy PJ, Borate U, et al. Examining racial differences in diffuse large B-cell lymphoma presentation and survival. Leuk Lymphoma. 2013; 54:268-276.
25. Al-Kindi SG, Abu-Zeinah GF, Kim CH, et al. Trends and disparities in cardiovascular mortality among survivors of Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk. 2015;15:748-752.
26. Hasan S, Dinh K, Lombardo F, et al. Doxorubicin cardiotoxicity in African Americans. J Natl Med Assoc. 2004;96:196-199.
27. Nabhan C, Zhou X, Day BM, et al. Disease, treatment, and outcome differences between men and women with follicular lymphoma in the United States. Am J Hematol. 2016;91:770-775.
28. Evens AM, Antillón M, Aschebrook-Kilfoy B, et al. Racial disparities in Hodgkin's lymphoma: a comprehensive population-based analysis. Ann Oncol. 2012; 23:2128-2137.
29. Goldstein JS, Nastoupil LJ, Han X, et al. Disparities in survival by insurance status in follicular lymphoma. Blood. 2018;132:1159-1166.
30. Ritter AJ, Goldstein JS, Ayers AA, et al. Rural and urban patients with diffuse large B-cell and follicular lymphoma experience reduced overall survival: a National Cancer Database study. Leuk Lymphoma. 2019;60:1656-1667.
31. Utuama O, Mukhtar F, Pham YT, et al. Racial/ethnic, age and sex disparities in leukemia survival among adults in the United States during 1973-2014 period. PLoS One. 2019;14:e0220864.
32. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999-2014 Incidence and Mortality Web-based Report. https://apha.confex.com/apha/2017/mediafile/Handout/Paper385940/USCS_FactSheet.pdf/. Accessed February 24, 2021.

33. Kirtane K, Lee SJ. Racial and ethnic disparities in hematologic malignancies. Blood. 2017;130:1699-1705.
34. Quiroz E, Aldoss I, Pullarkat V, et al. The emerging story of acute lymphoblastic leukemia among the Latin American population: biological and clinical implications. Blood Rev. 2019;33:98-105.
35. Shoag JM, Barredo JC, Lossos IS, et al. Acute lymphoblastic leukemia mortality in Hispanic Americans. Leuk Lymphoma. 2020;61:2674-2681.
36. Coombs CC, Falchi L, Weinberg JB, et al. Chronic lymphocytic leukemia in African Americans. Leuk Lymphoma. 2012;53:2326-2329.
37. Shenoy PJ, Malik N, Sinha R, et al. Racial differences in the presentation and outcomes of chronic lymphocytic leukemia and variants in the United States. Clin Lymphoma Myeloma Leuk. 2011;11:498-506.
38. Patel MI, Ma Y, Mitchell B, et al. How do differences in treatment impact racial and ethnic disparities in acute myeloid leukemia? Cancer Epidemiol Biomarkers Prev. 2015;24:344-349.
39. Costa LJ, Huang JX, Hari PN. Disparities in utilization of autologous hematopoietic cell transplantation for treatment of multiple myeloma. Biol Blood Marrow Transplant. 2015;21:701-706.
40. Boehmer U. Twenty years of public health research: inclusion of lesbian, gay, bisexual, and transgender populations. Am J Public Health. 2002;92:1125-1130.
41. Bare MG, Margolies L, Boehmer U. Omission of sexual and gender minority patients. J Clin Oncol. 2014;32:2182-2183.
42. Gibson AW, Radix AE, Maingi S, et al. Cancer care in lesbian, gay, bisexual, transgender and queer populations. Future Oncol. 2017;13:1333-1344.
43. Quinn GP, Sanchez JA, Sutton SK, et al. Cancer and lesbian, gay, bisexual, transgender/transsexual, and queer/questioning (LGBTQ) populations. CA Cancer J Clin. 2015;65:384-400.
44. Griggs J, Maingi S, Blinder V, et al. American Society of Clinical Oncology position statement: strategies for reducing cancer health disparities among sexual and gender minority populations. J Clin Oncol. 2017;35:2203-2208.
45. Kamen C, Mustian K, Johnson MO, et al. Same-sex couples matter in cancer care. J Oncol Pract. 2015;11:e212-e215.
46. Lunn MR, Cui W, Zack MM, et al. Sociodemographic characteristics and health outcomes among lesbian, gay, and bisexual U.S. adults using Healthy People 2020 leading health indicators. LGBT Health. 2017;4:283-294.
47. National Institutes of Health. The Health of Sexual and Gender Minority (SGM) Populations (R01). Bethesda, MD: National Institutes of Health; 2017.
48. Surveillance, Epidemiology, and End Results Program. Race Recode Changes - SEER Documentation. https://seer.cancer.gov/seerstat/variables/seer/race_ethnicity/. Accessed February 24, 2021.
49. Keisler-Starkey K, Bunch LN. Health Insurance Coverage in the United States: 2019. In In U.S. Census Bureau (ed). *Current Population Reports*. Washington, DC: U.S. Government Publishing Office, 2020;60-271.
50. Smith JC, Medalia C. Health Insurance Coverage in the United States: 2013. In U.S. Census Bureau (ed). *Current Population Reports*. Washington, DC: U.S. Government Printing Office, 2014;60-250.
51. Ward E, Halpern M, Schrag N, et al. Association of insurance with cancer care utilization and outcomes. CA Cancer J Clin. 2008;58:9-31.
52. Han X, Yabroff KR, Ward E, et al. Comparison of insurance status and diagnosis stage among patients with newly diagnosed cancer before vs after implementation of the Patient Protection and Affordable Care Act. JAMA Oncol. 2018;4:1713-1720.
53. Unger JM, Vaidya R, Hershman DL, et al. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. J Natl Cancer Inst. 2019;111:245-255.
54. Unger JM, Hershman DL, Albain KS, et al. Patient income level and cancer clinical trial participation. J Clin Oncol. 2013;31:536-542.
55. Unger JM, Gralow JR, Albain KS, et al. Patient income level and cancer clinical trial participation: a prospective survey study. JAMA Oncol. 2016;2:137-139.
56. Food and Drug Administration. Enhancing the Diversity of Clinical Trial Populations: Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry. Silver Spring, MD: U.S. Department of Health and Human Services; 2020.
57. Chen L, Payne JB, Dance KV, et al. Priorities for rural lymphoma survivors: a qualitative study. Clin Lymphoma Myeloma Leuk. 2020;20:47-52.e3.
58. National Institutes of Health. NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. Silver Spring, MD: U.S. Department of Health and Human Services; 2001.
59. Regnante JM, Richie NA, Fashoyin-Aje L, et al. US Cancer Centers of Excellence strategies for increased inclusion of racial and ethnic minorities in clinical trials. J Oncol Pract. 2019;15:e289-e299.

When and How to Treat Relapsed Multiple Myeloma

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overview

The treatment landscape for relapsed multiple myeloma has expanded considerably in recent years, as numerous agents with new mechanisms of action have been introduced, increasing responses even in advanced disease and prolonging survival. The wealth of novel regimens comes with the challenges of balancing toxicities and aligning a regimen with the biology of the myeloma and the nature of the relapse in conjunction with patient treatment history and personal preference. Herein, we provide an overview of treatment options for both early and late relapsing disease as well as a discussion of the role of emerging immune-based therapies.

EARLY-RELAPSING MULTIPLE MYELOMA

Myeloma treatment has evolved during the past decade to include multiple immunomodulatory agents, proteasome inhibitors, and antibodies. This array of choices leads to complexity in designing an optimal regimen for a patient with relapsed myeloma. Herein, we discuss treatment of early relapse. In first or second relapse, the choices are the broadest and can be guided by disease biology, the nature of the relapse (biochemical vs. clinically aggressive), and patient preference.

1. Prior autologous stem cell transplantation. Autologous stem cell transplantation remains a mainstay for patients who elect to defer transplantation[1] as initial therapy. Additionally, a lack of response to standard-dose treatment should not exclude patients from undergoing salvage autologous transplantation.[2]
2. Prior therapies. The main classes of drugs in multiple myeloma include proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies, primarily the CD38-directed monoclonal antibodies (daratumumab and isatuximab) and elotuzumab, which targets SLAMF7 (Table 1). The choice of regimen depends on response to and tolerability of prior therapies; it remains controversial whether a class switch is needed or if one can change to a new agent in the same class at the time of relapse.
3. Aggressiveness of relapse—that is, biochemical versus clinical relapse. Patients who experience a biochemical relapse may be treated by increasing the medication dose if they are on maintenance lenalidomide; reintroducing dexamethasone; and/or adding another agent, such as elotuzumab. However, it is recognized that these responses are not deep or durable. Therefore, patients who develop aggressive relapses, such as those presenting with renal failure or extramedullary disease, may require multiagent therapy with several new agents.
4. Comorbidities. We generally recommend triplet regimens versus doublets except in extremely frail patients. Proteasome inhibitor–containing doublets such as bortezomib/dexamethasone, immunomodulatory agent–containing doublets such as lenalidomide/dexamethasone and pomalidomide/dexamethasone, and single-agent daratumumab can also be used in frail patients or those with poor functional status. See Table 1 for specific considerations while choosing between the different available agents.
5. Psychosocial issues and access to care. Resources, route of administration, drug approvals, and insurance coverage are also important considerations while selecting treatment. Patients with challenges to obtaining transportation may require an oral regimen. Those who do not have insurance coverage for oral medications may prefer an intravenous/subcutaneous medication.

Regimens Used for Early Relapse in Patients With Disease Not Refractory to Lenalidomide

Most patients in the United States experience relapse while on lenalidomide maintenance. If a patient is experiencing a more indolent biochemical relapse on lenalidomide maintenance, it may be reasonable to increase the lenalidomide dose and add a monoclonal antibody or a proteasome inhibitor in combination with dexamethasone (Fig. 1), although with the caveat that most phase III trials do not address this particular scenario. Most regimens used in the United States at first relapse incorporate other classes of drugs, in particular proteasome inhibitors (Table 2) and monoclonal antibodies (Tables 3 and 4). In general, triplet regimens are preferred.

Author affiliations and support information (if applicable) appear at the end of this article.

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PRACTICAL APPLICATIONS

- Patient factors, including prior therapies, aggressiveness of relapse, comorbidities, and access to care, are important considerations in the choice of therapy for relapsed multiple myeloma.
- The combination of multiple drugs has tended to improve response rates and length of survival times, albeit frequently at the cost of increased toxicity, requiring careful clinical management and a consideration of the patient's individual features.
- Optimal sequencing of immunotherapy remains unknown—for example, whether a patient who receives a B-cell maturation antigen CAR T-cell therapy can respond later to a B-cell maturation antigen–bispecific T-cell engager. These questions will become more important as immune therapies are moved to the frontline setting in myeloma.

Regimens Used for Early Relapse in Patients With Disease Refractory to Lenalidomide

With the evolution of myeloma treatment and the approval of multiple novel agents, there are several choices for patients with relapsed disease, especially during early relapse. Although there is no standard algorithm for treating relapsed myeloma, for patients who are lenalidomide refractory, it is common practice to switch to pomalidomide or proteasome inhibitor–based treatment and consider adding a monoclonal antibody (Fig. 1).

Proteasome Inhibitor–Based Regimens for Early Relapse

Bortezomib with pomalidomide and dexamethasone In the phase III OPTIMISMM trial of 559 patients previously treated with lenalidomide (70% were lenalidomide refractory), those receiving bortezomib/pomalidomide/dexamethasone compared with bortezomib/dexamethasone had an improvement in an overall response rate (ORR; 82% vs. 50%) and progression-free survival (PFS; 11 months vs. 7 months; HR, 0.61).[3,4] There was a higher incidence of neutropenia (42% vs. 9%), infection (31% vs. 18%), thromboembolic events (4% vs. < 1% pulmonary embolism), and peripheral sensory neuropathy in the bortezomib/pomalidomide/dexamethasone arm. This trial differed from several other trials in the early relapse setting, in which patients who were lenalidomide refractory generally were excluded[5-8] or represented a much lower proportion of patients.[9-12]

Carfilzomib with lenalidomide and dexamethasone In the phase III ASPIRE trial[8] of 792 patients comparing carfilzomib/lenalidomide/dexamethasone versus lenalidomide/dexamethasone, ORR (87% vs. 67%) and PFS (26 months vs. 17 months; HR, 0.66) improved and, notably, an overall survival benefit (48 months vs. 40 months; HR, 0.79) with carfilzomib was demonstrated.[13] Carfilzomib had less neuropathy compared with bortezomib but had more hypertension; upper respiratory infections; and cardiac, pulmonary, and renal toxicities. The regimen of carfilzomib/

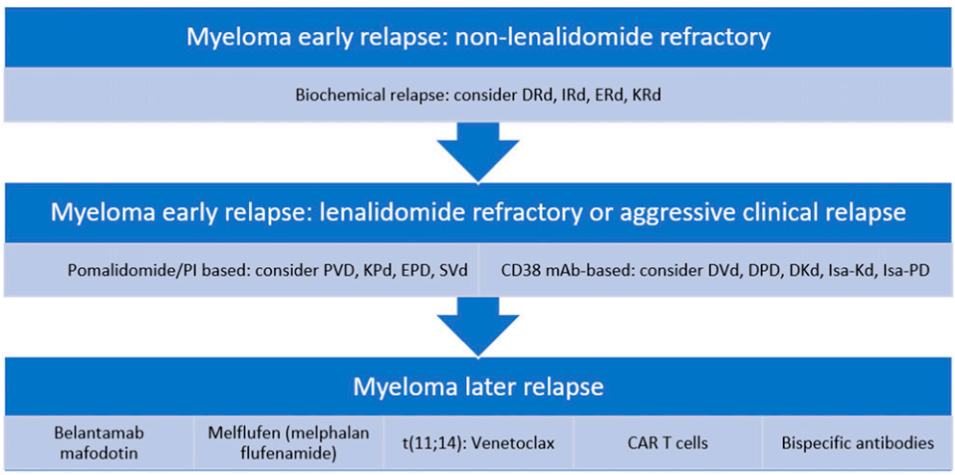

FIGURE 1. Treatment Options Based on Relapse Characteristics

Abbreviations: DKd, daratumumab/carfilzomib/dexamethasone; DPD, daratumumab/pomalidomide/dexamethasone; DRd, daratumumab/lenalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; EPD, elotuzumab/pomalidomide/dexamethasone; ERd, elotuzumab/lenalidomide/dexamethasone. IRd, ixazomib/lenalidomide/dexamethasone; Isa-Kd, isatuximab/carfilzomib/dexamethasone; Isa-PD, isatuximab/pomalidomide/dexamethasone; KPd, carfilzomib/pomalidomide/dexamethasone; KRd, carfilzomb/lenalidomide/dexamethasone; mAb, monoclonal antibody; PVD, pomalidomide/bortezomib/dexamethasone; SVd, selinexor/bortezomib/dexamethasone.

TABLE 1. List of Commonly Used Drugs in Multiple Myeloma

Drugs	Important Considerations
Lenalidomide	• Adjust dose on the basis of renal function
	• Discuss risk of second primary malignancies
	• Thromboprophylaxis
	• Rashes are common, especially with initial use. Consider antihistamine use for the first week.
	• Watch for diarrhea, especially with long-term use. Consider bile acid sequestrants.
Pomalidomide	• More myelosuppressive than lenalidomide, especially in combination with CD38 mAbs
	• Fewer rashes than with lenalidomide
	• Risk of second primary malignancies
	• Thromboprophylaxis
Bortezomib	• Risk of peripheral neuropathy mitigated with subcutaneous once-weekly dosing
	• Avoid in patients with severe existing peripheral neuropathy
	• Higher risk of zoster reactivation, use appropriate prophylaxis
	• No dose adjustment is needed for renal dysfunction
	• Adjust for hepatic dysfunction
Carfilzomib	• Monitor for cardiac, pulmonary, and renal toxicity
	• Hypertension
	• Higher risk of zoster reactivation, use appropriate prophylaxis
	• Less neuropathy than bortezomib
	• Exercise caution in older adults and in those with substantial cardiovascular risk factors
	• No dose adjustment is needed for renal dysfunction
	• Adjust for hepatic dysfunction
Ixazomib	• Monitor for rashes and GI toxicity
	• GI toxicity tends to occur early on
	• Less neuropathy than bortezomib
	• Higher risk of zoster reactivation, use appropriate prophylaxis
	• Food interferes with absorption (i.e., the drug needs to be taken at least 1 hour before or 2 hours after a meal)
mAbs: daratumumab	• Higher rate of infusion reactions with intravenous versus subcutaneous daratumumab
Isatuximab	• No subcutaneous formulation of isatuximab approved yet
Elotuzumab	• Lower rate of infusion reactions from elotuzumab (approximately 10%)
	• Avoid daratumumab and isatuximab use in patients with severe asthma/chronic obstructive pulmonary disease
	• Increased risk of zoster reactivation with all three agents, use appropriate prophylaxis
	• All three antibodies can be detected on SPEP and immunofixation (IgGκ); interference assays available for daratumumab
	• Daratumumab and isatuximab can interfere with blood crossmatching
Selinexor	• GI toxicity
	• Thrombocytopenia
	• Hyponatremia

Abbreviations: GI, gastrointestinal; mAbs, monoclonal antibodies; SPEP, serum protein electrophoresis.

lenalidomide/dexamethasone has been approved for twice-weekly carfilzomib dosing, which may be inconvenient for some patients. Optimal weekly carfilzomib dosing in combination with immunomodulatory agents is yet to be clearly defined. This regimen is appealing for patients who are lenalidomide naïve or lenalidomide exposed but not refractory.

Ixazomib with lenalidomide and dexamethasone In the phase III TOURMALINE-MM1 trial of 722 patients with relapsed myeloma[7] comparing ixazomib/lenalidomide/dexamethasone versus lenalidomide/dexamethasone, there was improvement in the ORR (78% vs. 72%) and PFS (21 months vs. 15 months; HR, 0.74) in the ixazomib/lenalidomide/dexamethasone

TABLE 2. Phase III Trials Using Proteasome Inhibitor–Based Regimens for Early Relapse

Name of Trial	Regimen	No. of Patients	Regimen	PFS in Months (HR)	ORR (%)	Noteworthy Points
OPTIMISMM	VPd	559	VPd vs. Vd	11 vs. 7 (0.61)	82 vs. 50	• Consider for relapse on lenalidomide
						• Consider for those who received quadruplet induction with a mAb, PI, and lenalidomide
						• More neutropenia, infections, neuropathy, and thromboembolic events in VPd arm
ASPIRE	KRd	792	KRd vs. Rd	26 vs. 17 (0.66)	87 vs. 67	• Approved as twice weekly dosing, which may be inconvenient
						• Showed overall survival benefit (48 vs. 40 months; HR, 0.79)
						• More URIs and hypertension in the KRd arm
TOURMALINE-MM1	IRd	722	IRd vs. Rd	21 vs. 15 (0.74)	78 vs. 72	• Convenient oral regimen
						• Gastrointestinal toxicity and rashes
						• Lower incidence of peripheral neuropathy
BOSTON	SVd	402	SVd vs. Vd	14 vs. 9 (0.7)	76 vs. 62	• More thrombocytopenia and fatigue
						• Less neuropathy in the SVd arm

Abbreviations: HR, hazard ratio; IRd, ixazomib with lenalidomide and dexamethasone; KRd, carfilzomib with lenalidomide and dexamethasone; mAb, monoclonal antibody; ORR, overall response rate; PFS, progression-free survival; PI, proteasome inhibitor; Rd, lenalidomide and dexamethason; SVd, selinexor with bortezomib and dexamethasone; URI, upper respiratory infection; Vd, bortezomib and dexamethasone; VPd, bortezomib with pomalidomide and dexamethasone.

arm. Ixazomib can cause gastrointestinal toxicity and rashes, but it has a lower incidence of peripheral neuropathy. This regimen is an appealing option for patients who are not refractory to lenalidomide, and it has the benefit of being orally administered. It may be ideally suited for older patients or those who are frailer and experience a relatively indolent relapse.

Carfilzomib with pomalidomide and dexamethasone Phase I/II studies[14,15] have shown encouraging responses with the carfilzomib/pomalidomide/dexamethasone regimen, including an ORR of 87%.[16] However, unlike the other regimens, we have no phase III data. Because of the promising response rate and predictable toxicity profile, though, this option remains a regimen of choice for patients who experience progression after CD38 antibodies and who are carfilzomib naïve.

Selinexor with bortezomib and dexamethasone Selinexor is an inhibitor of the nuclear export protein XPO1; as a result of inhibition, cargo is trapped in the nucleus, resulting in cell cycle arrest and apoptosis. The phase III BOSTON trial included 402 patients who were randomly assigned to receive selinexor/bortezomib/dexamethasone or to bortezomib/dexamethasone.[14] There was improvement in the ORR (76% vs. 62%) and PFS (14 months vs. 9 months; HR, 0.7) in the selinexor/bortezomib/dexamethasone arm. More thrombocytopenia and fatigue occurred, but neuropathy was less frequent in the selinexor/bortezomib/dexamethasone arm compared with bortezomib/dexamethasone alone. Although side effects remain a concern from selinexor-containing regimens, an antibody-free approach using this agent may have a role for patients with high-risk cytogenetic abnormalities (especially 17p deletion) and possibly among patients who have received previous therapy with monoclonal antibodies. Additionally, this trial allowed enrollment of patients with cardiac and other major organ dysfunction.

CD38 Monoclonal Antibody–Based Treatment of Early Relapse

The two U.S. Food and Drug Administration–approved CD38 monoclonal antibodies for multiple myeloma are daratumumab and isatuximab. Daratumumab has received U.S. Food and Drug Administration approval in combination with lenalidomide/dexamethasone, bortezomib/dexamethasone, carfilzomib/dexamethasone, and pomalidomide/dexamethasone. Isatuximab is approved by the U.S. Food and Drug Administration in combination with pomalidomide/dexamethasone. Choosing between daratumumab and isatuximab in patients with early relapse is sometimes challenging, because there are no head-to-head comparisons. Practical considerations, such as drug availability and administration, come into play while making these decisions, because both agents have a similar multimodal mechanism of action. With the advent of fixed-dose subcutaneous daratumumab, the daratumumab-containing regimens are very appealing. One of the questions that arises is whether isatuximab is effective in patients who experience progression during daratumumab treatment. In a small (nine patients), single-center, retrospective analysis of a heavily

TABLE 3. Phase III Trials of Daratumumab-Based Regimens for Early Relapse

Name of Trial	Regimen	No. of Patients	Regimen	PFS in Months (HR)	ORR (%)	Noteworthy Points
CASTOR	DVd	498	DVd vs. Vd	17 vs. 7 (0.31)	84 vs. 63	• Favored in patients who are lenalidomide-refractory without significant neuropathy
						• More myelosuppression in the DVd arm
POLLUX	DRd	569	DRd vs. Rd	NR vs. 17 (0.41)	93 vs. 76	• Preferred for relapses on lenalidomide or bortezomib maintenance (nonrefractory to full doses of lenalidomide)
						• More URIs, neutropenia, and diarrhea in the DRd arm
CANDOR	DKd	466	DKd vs. Kd	NR vs. 16 (0.63)	84 vs. 75	• Preferred in younger, fit patients who are double refractory to lenalidomide and bortezomib
						• More respiratory infections with DKd
						• More fatal adverse events in age $\geq$ 65 and intermediate fit
APOLLO	DPd	304	DPd vs. Pd	12 vs. 7 (0.63)	69 vs. 46	• Preferred in patients who are double refractory to lenalidomide and a PI
						• 68% grade $\geq$ 3 neutropenia
						• 5% IRR

Abbreviations: DKd, daratumumab with carfilzomib and dexamethasone; DPd, daratumumab with pomalidomide and dexamethasone; DRd, daratumumab with lenalidomide and dexamethasone; DVd, daratumumab with bortezomib and dexamethasone; HR, hazard ratio; IRR, infusion-related reaction; Kd, carfilzomib and dexamethasone; NR, not reached; ORR, overall response rate; Pd, pomalidomide and dexamethasone; PFS, progression-free survival; PI, proteasome inhibitor; Rd, lenalidomide and dexamethasone; URI, upper respiratory infections; Vd,vortezomib and dexamethasone.

pretreated population with prior pomalidomide and daratumumab exposure, the ORR with isatuximab/pomalidomide/dexamethasone was 55%, suggesting that these two CD38 monoclonal antibodies may have some differences in mechanism of action.[15]

Daratumumab-containing regimens Several randomized trials have shown improvement in PFS and deeper responses from daratumumab-containing combination regimens compared with doublets.[5,9,16-18] The risk of infusion-related reactions is lower[16] with the use of subcutaneous versus intravenous daratumumab (13% vs. 34%), without compromising efficacy.[17]

Daratumumab with bortezomib and dexamethasone In the phase III CASTOR study[9] evaluating daratumumab/bortezomib/dexamethasone versus bortezomib/dexamethasone in 498 patients, there was improvement in the ORR (84% vs. 63%) and PFS (17 months vs. 7 months; HR, 0.31) in the daratumumab/bortezomib/dexamethasone arm.[19] More myelosuppression occurred in the daratumumab/bortezomib/dexamethasone arm, and infusion reactions were associated with daratumumab, but they were generally mild. This regimen is favored in patients who are lenalidomide refractory and do not have notable neuropathy.

Daratumumab with lenalidomide and dexamethasone In the phase III POLLUX study evaluating daratumumab/lenalidomide/dexamethasone versus lenalidomide/dexamethasone in 569 patients, there was improvement in the ORR (93% vs. 76%) and PFS (83% vs. 60%).[5] The median PFS was not reached in the daratumumab/lenalidomide/dexamethasone group versus 17 months in the lenalidomide/dexamethasone group (HR, 0.41).[18] A higher incidence of upper respiratory infections, neutropenia, and diarrhea was noted in the daratumumab/lenalidomide/dexamethasone arm. This regimen is preferred among patients who experience relapse during lenalidomide or bortezomib maintenance, especially for those who are not refractory to full doses of lenalidomide.

Daratumumab with carfilzomib and dexamethasone In the phase III CANDOR study[16] of 466 patients, daratumumab/carfilzomib/dexamethasone led to improvement in the ORR (84% vs. 75%) and PFS (median, not reached vs. 16 months; HR, 0.63), with deeper responses. It is noteworthy that there was a higher incidence of respiratory infections with the daratumumab/carfilzomib/dexamethasone combination compared with carfilzomib/dexamethasone (29% vs. 16%), although the rates of cardiac and acute renal failure were lower in the daratumumab/carfilzomib/dexamethasone arm. It is worth mentioning that patients age 65 and older and those with intermediate fitness experienced more fatal adverse events, mostly because of infection, thereby warranting caution in this population. This regimen is preferred in younger, fit patients who are double refractory to lenalidomide and bortezomib.

Daratumumab with pomalidomide and dexamethasone A nonrandomized trial of daratumumab/pomalidomide/dexamethasone in 103 patients with a median of four prior therapies showed an ORR of 60% and a median PFS of 9 months.[20] Another nonrandomized trial in 112 patients in a less heavily treated population[21] showed an ORR of 78%; the median PFS was not reached. The randomized APOLLO trial[22] comparing daratumumab/pomalidomide/dexamethasone (with subcutaneous daratumumab) and pomalidomide/dexamethasone in 304 patients, presented in abstract form,

TABLE 4. Phase III Trials of Isatuximab- and Elotuzumab-Based Regimens for Early Relapse

Trial Name	Regimen	No. of Patients	Regimen	PFS in Months (HR)	ORR	Noteworthy Points
ICARIA-MM	Isa-Pd	307	Isa-Pd vs. Pd	12 vs. 7 (0.6)	60% vs. 35%	• Option for patients refractory to lenalidomide and a PI
						• Grade ≥ 3 neutropenia in 86% of patients on Isa-Pd (vs. 70%)
						• More G-CSF and dose reductions in Isa arm
						• More URIs and diarrhea in Isa arm
IKEMA	Isa-Kd	302	Isa-Kd vs. Kd	NR vs. 19 months	87% vs. 83%	• Option for patients refractory to lenalidomide and bortezomib
						• Deeper responses in Isa arm (30% vs. 13% MRD negativity)
						• Grade ≥ 3 respiratory infections more frequent in Isa arm (32% vs. 24%)
ELOQUENT-2	ERd	646	ERd vs. Rd	19 vs. 15 (0.71)	79% vs. 66%	• Option for non–lenalidomide-refractory, frailer patients with indolent relapses
						• Improved OS (48 vs. 40 months; HR, 0.78) in the ERd arm
						• More infections in ERd arm
						• IRRs in 10%
ELOQUENT-3	EPd	117	EPd vs. Pd	10 vs. 5 (0.54)	53% vs. 26%	• Option for patients refractory to lenalidomide and PI
						• Similar rates of infections and other adverse events

Abbreviations: EPd, elotuzumab with pomalidomide and dexamethasone; ERd, elotuzumabwith lenalidomide and dexamethasone; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; IRR, infusion-related reaction: Isa-Kd, isatuximab with carfilzomib and dexamethasone; Isa-Pd, isatuximab with pomalidomide and dexamethasone; Kd, carfilzomib and dexamethasone; MRD, minimal residual disease; NR, not reached; ORR, overall response rate; OS, overall survival; Pd, pomalidomide and dexamethasone; PFS, progression-free survival; PI, proteosome inhibitor; Rd, lenalidomide and dexamethasone; URI, upper respiratory infection.

revealed improvement in the PFS (12 months vs. 7 months; HR, 0.63) and ORR (69% vs. 46%) with daratumumab/pomalidomide/dexamethasone versus pomalidomide/dexamethasone. Only 5% of patients developed infusion-related reactions from subcutaneous daratumumab. All three trials showed a high incidence of grade 3 or higher neutropenia, ranging from 63% to 78%, with grade 3 infections in almost a third of patients in one trial.[21]

Isatuximab-Containing Regimens

Isatuximab with pomalidomide and dexamethasone The phase III ICARIA-MM trial[23] evaluated 307 patients who received a median of three prior lines of therapy and randomly assigned them to receive treatment with isatuximab/pomalidomide/dexamethasone versus pomalidomide/dexamethasone. There was improvement in the ORR (60% vs. 35%), and PFS (12 months vs. 7 months; HR, 0.6). Notably, infusion reactions occurred in more than one-third of patients. The incidence of grade 3 or higher neutropenia was 86% (vs. 70%), with a higher proportion of patients requiring granulocyte-colony stimulating factor and dose reductions in the isatuximab-containing arm. Additionally, more upper respiratory infections and diarrhea occurred in the isatuximab-containing arm. This option is available for patients who are refractory to lenalidomide and a proteasome inhibitor.

Isatuximab with carfilzomib and dexamethasone The phase III IKEMA study compared isatuximab/carfilzomib/dexamethasone with carfilzomib/dexamethasone among 302 patients with two prior lines of treatment. This study has been presented in abstract form and showed that the median PFS was not reached for patients treated with isatuximab/carfilzomib/dexamethasone versus 19 months for patients treated with carfilzomib/dexamethasone (HR, 0.53).[24] The ORR was similar (87% vs. 83%), although deeper responses were seen in the isatuximab-containing arm (30% vs. 13% minimal residual disease negativity). Although there was a higher incidence of hematologic toxicity in the isatuximab-containing arm, this immunomodulatory agent–free regimen yielded a relatively low incidence of grade 3 or higher neutropenia in both arms (19% vs. 7%). However, grade 3 or higher respiratory infections were more frequent in the isatuximab-containing arm (32% vs. 24%).

Anti-SLAMF7 Monoclonal Antibody–Containing Regimens for Early Relapse

Elotuzumab with lenalidomide and dexamethasone The phase III ELOQUENT-2 trial[6] included 646 patients who received elotuzumab/lenalidomide/dexamethasone versus lenalidomide/dexamethasone. There was improvement in the ORR (79% vs. 66%), PFS (19 months vs. 15 months;

HR, 0.71), and overall survival (median, 48 months vs. 40 months; HR, 0.78) in the elotuzumab-containing arm, at the cost of more infections.[25,26] Infusion reactions occurred in 10% of patients.[6] This option may be suitable for frailer patients who are not lenalidomide refractory and who have a relatively indolent relapse.

Elotuzumab with pomalidomide and dexamethasone The phase II ELOQUENT-3 trial[27] included 117 patients who were lenalidomide refractory and who were randomly assigned to receive pomalidomide/dexamethasone with or without elotuzumab. Results showed a higher ORR (53% vs. 26%) and improvement in the PFS (10 months vs. 5 months; HR, 0.54) with elotuzumab, with similar rates of infections and other adverse events. This triplet regimen is a possible selection for patients refractory to lenalidomide and a proteasome inhibitor.

DOES ONE SIZE FIT ALL IN RELAPSED MULTIPLE MYELOMA: SEQUENCING NOVEL AGENTS IN LATE-RELAPSED DISEASE

Definition of Late Relapse

The increased use of three- and four-drug combinations described above as first- and second-line therapies for patients with multiple myeloma has dramatically improved patient outcomes. There is an array of combinations, but, in fact, most of the patients who experience relapse after two or three lines of therapy have already been exposed to at least an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. Being exposed does not necessarily mean being refractory, because progression can occur months after treatment has been stopped. When the progression occurs during treatment or within 60 days of the last treatment, it is indeed defined as relapsed and refractory.[28] Clonal evolution explains, from a biologic point of view, the issue of refractoriness. Considering that most of the agents and combinations are now given continuously, most of the patients at second/third relapse are not only exposed but also, more often than not, have relapsed disease that is refractory to at least an immunomodulatory agent and/or a proteasome inhibitor and/or an anti-CD38 monoclonal antibody. These patients, who can be considered triple or quadruple refractory (refractory to one anti-CD38 monoclonal antibody + one proteasome inhibitor + one or two immunomodulatory agents or one anti-CD38 monoclonal antibody + one or two proteasome inhibitors + one immunomodulatory agent), have a median survival of 9.2 months.[29] In later relapse, patients may also be penta exposed or even penta refractory (refractory to one anti-CD38 monoclonal antibody + two proteasome inhibitors + two immunomodulatory agents).

Previous Drug Exposure/Refractoriness

New treatments against different targets or with different mechanisms of action are preferred to obtain disease control in the case of a clone resistant to one or more therapies. In this context, active agents may include the immunomodulatory agent pomalidomide and the proteasome inhibitor carfilzomib, in patients not previously treated with these drugs, on the basis of the preclinical and clinical data proving efficacy in patients refractory to both lenalidomide and bortezomib.[30-35] Unfortunately, optimal treatment after daratumumab progression remains unknown, because most of the phase III trials including pomalidomide/dexamethasone or carfilzomib/dexamethasone backbones did not enroll patients refractory to anti-CD38 monoclonal antibodies.[3,16,22-24]

In the randomized phase II ELOQUENT-3 trial described above, most patients were refractory to lenalidomide and proteasome inhibitors, but very few of them were exposed/refractory to anti-CD38 monoclonal antibodies.[27] One option for these daratumumab progressors is agents with new and different mechanisms of actions. These agents include the clinical XPO-1 inhibitor selinexor, the alkylating agent melphalan flufenamide (melflufen), the anti–BCMA antibody-drug conjugate belantamab mafodotin (belamaf), and venetoclax, which binds to Bcl-2 and displaces proapoptotic proteins. Mechanisms of action for selinexor have been previously discussed. Melflufen is a novel alkylating prodrug that is internalized by cells because of its high lipophilicity and then is hydrolyzed by intracellular aminopeptidases. Hydrolyzation releases the active metabolites of melflufen primarily in multiple myeloma tumor cells[36] because of their high expression of aminopeptidase. Belamaf consists of an anti-BCMA monoclonal antibody conjugated with a microtubule-disrupting compound, MMAF (monomethyl auristatin F). Belamaf shows anti-multiple myeloma activity not only by delivering the proapoptotic MMAF toxin into multiple myeloma cells but also by enhancing immunogenic death through antibody-dependent cellular cytotoxicity and phagocytosis.[37,38]

In triple-class refractory multiple myeloma, an ORR of 27% was reported with the combinations of selinexor/dexamethasone[39] and melflufen/dexamethasone[40]; an ORR of approximately 40% was observed with belamaf as a single agent.[41,42] For a specific subgroup of patients, the efficacy of the anti–Bcl-2 inhibitor venetoclax in patients with t(11;14) or high Bcl-2 (Table 5) seems particularly promising. These agents have been also combined in phase I/II studies with a proteasome inhibitor, immunomodulatory agent, or monoclonal antibody, with preliminary data suggesting improved efficacy (Table 5).

Combination therapies, rather than single agents, are likely the best option to achieve deep and rapid responses, particularly in clinically aggressive disease. On the basis of phase II randomized data, a patient refractory to the anti-CD38 monoclonal antibody daratumumab, the first-generation proteasome inhibitor bortezomib, the second-generation

proteasome inhibitor carfilzomib, and the immunomodulatory agent lenalidomide might benefit from treatment with the anti-CS1 elotuzumab plus the third-generation immunomodulatory agent pomalidomide. Phase I/II data suggest that other options may include pomalidomide plus selinexor or belamaf. A patient refractory to the anti-CD38 monoclonal antibody daratumumab, the first-generation immunomodulatory agent thalidomide, the second-generation immunomodulatory agent lenalidomide, and bortezomib might benefit from the combination of carfilzomib with selinexor or pomalidomide or the combination of carfilzomib with venetoclax if the disease presents with t(11;14) or high Bcl-2. It is extremely difficult to recommend one combination over another because of the lack of randomized comparisons between different treatments and because data are mostly confined to phase II studies, in which specific subgroup analyses (based on prior exposure/refractoriness) have small sample sizes.

The treatment of patients who are penta refractory is more complex and requires two possible treatment choices: first, the rationale of exploiting a potential synergistic effect via the combination of a new agent (e.g., selinexor, belamaf, or—with the presence of t(11;14) or high Bcl-2—venetoclax) with an agent to which the patient is already refractory; second, the use of new agents alone or in combination with dexamethasone. Both options have been evaluated in phase I/II studies with different combinations (Table 5). For instance, in the STOMP trial, the addition of selinexor to pomalidomide led to an ORR of 36% in a small number of patients who were pomalidomide refractory.[44] Nevertheless, the option of re-treatment is more appealing if we consider prior exposure rather than prior refractoriness. This aspect is particularly true in the case of patients who were treated with a proteasome inhibitor as a fixed-duration therapy or who ceased, for reasons other than progression or toxicity, to receive a drug normally given as continuous treatment.

In the event that none of these new agents are available, the options are generally re-treatment with an association of drugs used in prior lines (different combinations of immunomodulatory agents/proteasome inhibitors/monoclonal antibodies or chemotherapy, such as cyclophosphamide, melphalan, and adriamycin).

Patient Characteristics and Prior and Expected Drug Toxicities

Although combination therapies may be optimal to achieve disease control, the potential efficacy needs to be balanced with the possible increase in toxicity. Adverse events may lead to drug discontinuation, thus negatively affecting efficacy, a well-known issue in elderly and intermediate-fit/frail patients[56] as well as in patients with comorbidities. In this scenario, therapy with single agents or doublets with steroids may be preferable. Some comorbidities, if severe, may also limit the selection of suitable drugs. For instance, in patients with cardiovascular disease, carfilzomib should be administered with caution; in patients with neuropathy or with neurologic disease, neurotoxic drugs like bortezomib should be avoided. In patients with chronic obstructive pulmonary disease, the benefit/risk ratio of anti-CD38 monoclonal antibodies should be carefully evaluated, and, in patients with chronic gastrointestinal disorders, the risk of exacerbation with drugs known to have gastrointestinal toxicity (e.g., selinexor) should be carefully assessed. Another issue to consider in the treatment choice at the time of relapse is the toxicity experienced by the patient during prior lines of therapy. Some toxicities can still be present at the time of relapse (i.e., neuropathy related to bortezomib or thalidomide). Other toxicities may be reversible after stopping therapy (e.g., cutaneous toxicity or thrombolytic events with immunomodulatory agents, cardiovascular events with carfilzomib), but, if particularly severe, they may preclude later reuse of these agents. Bone marrow function is also a key factor and is often impaired at the time of late relapse because of the cumulative effect of treatment toxicities, thus limiting the potential use of agents causing neutropenia and thrombocytopenia (i.e., chemotherapy or melflufen). With the use of salvage chemotherapy (e.g., melphalan or multiagent chemotherapy, such as bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide), autologous stem cell reinfusion (if stored cells are available) may be considered to improve bone marrow reconstitution. The main toxicities associated with selinexor, belamaf, melflufen, and venetoclax as single agents or in combinations in late lines are reported in Table 5 and can be helpful in the choice of treatment of a specific patient.

The main adverse events associated with selinexor are gastrointestinal problems (diarrhea and nausea/vomiting), fatigue, and thrombocytopenia. Adverse events related to venetoclax are mainly gastrointestinal and infectious concerns. Melflufen may induce mainly hematologic toxicities. Thrombocytopenia is the main hematologic adverse event with belamaf; the drug is associated with ocular toxicity that can range from blurred vision to keratopathy.

Disease Features: Extramedullary Disease and High Risk

Extramedullary disease is more frequent at relapse and is usually associated with a dismal outcome.[57] Few data are available on efficacy of newer agents in extramedullary disease. Single-agent belamaf showed very low efficacy, with an ORR of 6% to 9% in patients with extramedullary disease compared with approximately 40% in patients without extramedullary disease.[58] In the HORIZON phase II study evaluating melflufen in combination with dexamethasone, 55 of 157 patients had extramedullary disease, defined as the presence of at least one paraskeletal or soft

TABLE 5. Results of New Agents for the Treatment of Late-Relapsed Multiple Myeloma

Compound	Single Use/ Combinations	Trial	Schedule	Phase	No. of Patients	Median (range) No. of Prior Lines	Previous Treatment		Toxicity	Response Rates		Median Survival	
							Exposed	Refractory		ORR	≥ VGPR	PFS	OS
Elo	Combo	ELOQUENT-3[37] NCT02654132	Elo: 10 mg/kg IV D1, 8, 15, 22 for C1–2, 20 mg/kg D1 Pom: 4 mg PO D121 Dex: 40 mg PO/IV (20 mg for pts age > 75) weekly vs. pom-dex	II randomized	117 (randomized 1:1)	3 (2-8)	Bort, 100% Len, 98% Carf, 15% Dara, 2% ASCT, 52%	PI, 78% Len, 90% PI + len, 68%	Grade ≥ 3 AEs: Neutropenia, 13% Thrombocytopenia, 8% Anemia, 10% Lymphopenia, 8% Infections, 13% Pneumonia, 5% Hyperglycemia, 8%	Elo/pom/dex: 53% Pom/dex: 26%	Elo/pom/dex: 20% Pom/dex: 9%	Elo/pom/dex vs. pom/dex: 10.3 vs. 4.7 months; HR, 0.54, 95% CI, 0.34–0.86; p = .008	Elo/pom/dex vs. pom/dex: HR for death, 0.62; 95% CI, 0.30–1.28 (median FU, 9.1 months)
Sel	Single agent	KCP-330-001[43] NCT01607892	Dose escalation from 3 mg/m^2 to 60 mg, 6 to 10 doses of each 28-day cycle	I	57	6 (1–16)	PI, 99% IMiD, 98% Anti-CD38, 6%	NA	Hematologic grade ≥ 3 AEs: Neutropenia, 23% Anemia, 23% Thrombocytopenia, 45% Nonhematologic AEs, any grade/grade ≥ 3: Nausea/vomiting, 75%/2% Fatigue, 70%/13% Anorexia, 64%/4%	4%	0%	NA	NA
Sel/Dex	Combo	STORM[39] NCT02336815	Sel: 80 mg PO D1, 3, 8, 10, 15, 17, 22, 24 of each 28-day cycle Dex: 20 mg PO D1, 3, 8, 10, 15, 17, 22, 24 of each 28-day cycle	IIb	123	7 (3–18)	Penta drug, 100%	Triple class, 100% Penta drug, 68% Carf/pom/dara, 96%	Hematologic grade ≥3 AEs: Neutropenia, 21% Anemia, 44% Thrombocytopenia, 59% Nonhematologic AEs, any grade/grade ≥ 3: Pneumonia, 16%/10% Fatigue, 73%/25% Nausea, 72%/10% Inappetence, 56%/5% Hyponatremia, 37%/22% Vomiting, 38%/3%	26%	7%	3.7 months	8.6 months
Sel/Pom/Dex	Combo	STOMP (arm 1)[44] NCT02343042	Sel: 60 mg* PO D1, 8, 15, 22 Pom: 4 mg PO D1–21 Dex: 40 mg PO D1, 8, 15, 22 of each 28-day cycle	Ib/II	65 (R2PD 20)	3 (1–10)	Bort, 92% Len, 100%/87% Carf, 41% Pom, 29% Dara, 24%	Bort, 49% Len, 87% Carf, 33% Pom, 29% Dara, 24%	Hematologic grade ≥ 3 AEs: Neutropenia, 54% Anemia, 33% Thrombocytopenia, 31% Nonhematologic AEs, any grade/grade ≥ 3: Fatigue, 50%/10% Nausea, 60%/2% Inappetence, 44%/2% Diarrhea, 28%/0% Vomiting, 20%/2%	Overall: NA Pom-naïve/nonrefractory: 58% Pom-refractory: 36%	Overall: NA Pom-naïve/ nonrefractory: 22% Pom-refractory: 7%	Overall: 12.2 months Pom-naïve/ nonrefractory: 12.3 months Pom-refractory: 8.8 months	Overall: NA Pom-naïve/ nonrefractory: 19 months Pom-refractory: 8 months
Sel/Carf/Dex	Combo	STOMP (arm 6)[45] NCT02343042	Sel: 100 mg PO (starting dose, MTD 80 mg) D1, 8, 15, 22 Carf: 20/56 mg/m^2 IV D1, 8, 15 (20 mg/m^2 on C1D1 and 56 mg/m^2 thereafter) Dex: 40 mg PO D1, 8, 15, 22 of each 28-day cycle	Ib/II	24	3 (1–8)	Bort, 100% Len, 96% Pom, 62% Dara, 62% ASCT, 79%	NA	Hematologic grade ≥ 3 AEs: Thrombocytopenia, 54% Anemia, 20% Nonhematologic AEs, any grade/grade ≥ 3: Nausea, 66%/0% Fatigue, 54%/8% Anorexia, 45%/4%	75%	45%	NR (median FU, 4.4 months)	NA
		SINE, IRB14-0033[46] NCT02199665	Sel: dose escalation from 20 to 60 mg PO D1, 3, 8, 10, 15, 17 Carf: 20 mg/27mg/m^2 IV, (20 mg/m^2 in C1D1 and 27 mg/m^2 thereafter) D1, 2, 8, 9, 15, 16 Dex: 20 mg PO D1, 4, 8, 9, 15, 16, 22, 23 of each 28-day cycle	I	21	4 (2–10)	Quad drug, 81% Penta drug, 5%	Dual class, 81% Triple class, 5%	Hematologic grade ≥ 3 AEs: Neutropenia, 33% Thrombocytopenia, 71% Anemia, 33% Lymphopenia, 33% Nonhematologic grade ≥ 3AEs: Infections, 24% Diarrhea, 10% Fatigue, 10%	48%	14%	3.7 months	22.4 months

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TABLE 5. Results of New Agents for the Treatment of Late-Relapsed Multiple Myeloma (Continued)

Compound	Single Use/ Combinations	Trial	Schedule	Phase	No. of Patients	Median (range) No. of Prior Lines	Previous Treatment		Toxicity	Response Rates		Median Survival	
							Exposed	Refractory		ORR	≥ VGPR	PFS	OS
Sel/Dara/Dex	Combo	STOMP (arm 5)[47] NCT02343042	Sel: 60 mg PO twice weekly (D1, 3, 8, 10, 15, 17, 22, 24) or 100 mg once weekly (D1, 8, 15, 22) Dara: 16 mg/kg IV once weekly (D1, 8, 15, 22) Dex: 20 mg PO D1, 2, 8, 9, 15, 16, 22, 23 of each 28-day cycle	Ib/II	34	3 (2–10)	Quad exposed, 23% PI, 100% IMiD, 100% Dara, 6% ASCT, 73% PI + IMiDs, 100%	PI, 85% IMiD, 76% Dara, 6% PI + IMiDs, 74%	Hematologic grade ≥ 3 AEs: Neutropenia, 26% Thrombocytopenia, 47% Anemia, 32% Lymphopenia, 18% Nonhematologic AEs, any grade/grade ≥ 3: Nausea, 70%/9% Fatigue, 62%/18% Anorexia, 35%/0% Diarrhea, 35%/3% Hyponatremia, 33%/12%	Overall: 69% Dara-naïve: 73%	Overall: 34% Dara-naïve: 37%	Overall and dara-naïve: 12.5 months	NA
Ven	Single agent	M13-367[48] NCT01794520	Ven: 300, 600, 900, or 1,200 mg daily in dose-escalation cohorts PO (313 design) of each 21-day cycle	I	66, 30 t(11;14)	5 (1–15)	Bort, 94% Len, 94% Carf, 38% Pom, 59%	Bort, 70% Len, 77% Bort/len refractory, 61% Carf, 38% Pom, 54%	Hematologic grade ≥ 3 AEs: Thrombocytopenia, 26% Neutropenia, 21% Anemia, 14% Lymphopenia, 15% Nonhematologic AEs, any grade/grade ≥ 3: Nausea, 47%/3% Fatigue, 27%/5% Diarrhea, 37%/3% Pneumonia, 8% (SAEs)	Overall: 21% pts with t(11;14) 40%	Overall: 15%; pts with t(11;14), 27%	NA	NA
Ven/Dex	Combo	M13-367[49] NCT01794520 (part 1 dose escalation, part 2 expansion cohort)	Ven: 800 mg PO D1, 8, 15 Dex 40 mg PO (20 mg for pts aged ≥ 75) D1, 8, 15 of each 21-day cycle	I/II	Part 1: 20 + 3 t(11;14) Part 2: 31 t(11;14) NA	Part 1: 3 (1–17) Part 2: 5 (1–9)	Part 1: Bort, 80% Len, 90%/85% ASCT, 85% Part 2: NA	Part 1: Bort, 55% Len, 85% Carf, 20% Pom, 40% Part 2: NA	All grade 3–4 AEs in ≥ 10% of pts: Part 1: Neutropenia, 21% Lymphopenia, 29% Hypophosphatemia, 20% TLS, 10% Part 2: Lymphopenia, 32% Hypophosphatemia, 15% Thrombocytopenia, 11% Hypertension, 10%	Part 1: overall, 65% Bort-refractory: 82% Len-refractory: 71% Part 2: overall, 45%	Part 1: overall, 30% Bort-refractory: NA Len-refractory: NA Part 2: overall, 26%	Part 1: 12.4 months Part 2: NR; 9 months PFS, 57%	Part 1: NA Part 2: NR; 9 months OS, 71%
Ven/Carf/Dex	Combo	M15-538[50] NCT02899052	Cohort 1: Ven, 400 mg/day PO + Carf 27 mg/m^2 IV D1, 2, 8, 9, 15, 16 + dex 40 mg PO D1, 8, 15, 22 Cohort 2 = cohort 1, but Ven 800 mg/day PO Cohort 3: Ven 800 mg/day + Carf 70 mg/m^2 IV D1, 8, 15 + dex 40 mg D1, 8, 15, 22 (expansion cohort) Cohort 4: Ven 800 mg + Carf 56 mg/m^2 IV D1, 2, 8, 9, 15, 16 + dex 40 mg PO D1, 2, 8, 9, 15, 16, 22, 23	II	49, 13 (27%) t(11;14), 22 (45%) high Bcl-2	2 (1–3)	PI, 96% IMiD, 90% PI + IMiD, 86%	PI, 57% IMiD, 71% PI + IMiD, (45%)	All grade ≥ 3 AEs: Neutropenia, 17% Thrombocytopenia, 12% Lymphopenia, 31% Hypertension, 14% Pneumonia, 12%	Overall: 80%, Pts with t(11;14): 92% Pts with t(11;14) or high Bcl-2: 85%	Overall: 65% (≥ CR 41%; 10^{-5} MRD neg, 12%) Pts with t(11;14): 85% (≥ CR 54%; 10^{-5} MRD neg, 15%) Pts with t(11;14) or high Bcl-2: 77%	NA	NA
Ven/Dara/Dex	Combo	M15-654 part 1[51] NCT01794520	Ven: 800 mg/day PO Dex: 40 mg PO (20 mg for pts age ≥ 75) D 1, 8, 15 of each 21-day cycle Dara: 16 mg/kg IV D1, 8, 15, 22 on C1–2; D1, 15 on C3–6; D1 on C ≥ 7	I/II	24, 100% t(11;14)	2 (1–8)	PI, 100% IMiD, 100% PI + IMiD, 100% ASCT, 63%	PI, 46% IMiD, 71% PI + IMiD, 42%	All-grade AEs: Neutropenia, 17% Thrombocytopenia, 4% Hypertension, 25% Diarrhea, 63% Grade ≥ 3 infections, 21% No TLS	96%	96% (≥ CR 54%)	NR, 12 months; PFS, 94%	NA
Ven/Dara/Bort/Dex	Combo	M15-654 part 2[51] NCT01794520	Ven: 800 mg/day PO Dex: 40 mg PO (20 mg for pts age ≥ 75) D1, 8, 15 of each 21-day cycle Dara: 16 mg/kg IV D1, 8, 15 on C1–3; D1, 15 on C4–8; D1 on C ≥ 9 Bort: 1.3 mg/m^2 SC D1, 4, 8, 11 C1–8	I/II	24, 25% t(11;14)	1 (1–3)	PI, 92% IMiD, 71% PI + IMiD, 63% ASCT, 50%	PI, 0% IMiD, 33% PI + IMiD, 0%	All-grade AEs: Neutropenia, 4% Thrombocytopenia, 13% Hypertension, 8% Diarrhea, 50% Grade ≥ 3 infections, 17% No TLS	92%	79% (≥ CR 42%)	NR, 12 months; PFS, 84%	NA

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TABLE 5. Results of New Agents for the Treatment of Late-Relapsed Multiple Myeloma (Continued)

Compound	Single Use/ Combinations	Trial	Schedule	Phase	No. of Patients	Median (range) No. of Prior Lines	Previous Treatment		Toxicity	Response Rates		Median Survival	
							Exposed	Refractory		ORR	≥ VGPR	PFS	OS
Melflufen	Single agent	O-12-M1[52] NCT01897714	Melflufen: 40 mg D1 of each 21-day cycle**	I/II	13	5 (4–6)	ASCT, 85% Dara, 46%	PI + IMiD, 92%	All grade ≥ 3 AEs: Neutropenia, 69% Thrombocytopenia, 61% Anemia, 23% Pneumonia, 8%	8%	0%	4.4 months	15.5 months
Melflufen/Dex	Combo	HORIZON OP-106[40] NCT02963493	Melflufen: 40 mg IV D1 Dex: 40 mg PO (20 mg if pts age ≥ 75) D1, 8, 15, 22 of each 28-day cycle	II	157, 35% EMD	5 (2–12)	PI, 100% IMiD, 100% Anti-CD38, 80% Alkylator, 88%	PI, 92% IMiD, 97% Anti-CD38, 80% Alkylator, 59% Triple class, 79%	All grade ≥ 3 AEs: Neutropenia, 79% Thrombocytopenia, 76% Anemia, 43% Pneumonia, 10% Hypophosphatemia, 10%	Overall: 29%, Triple class–refractory, 26% EMD, 24%	Overall: 12% Triple class refractory: 11% EMD: NA	Overall: 4 months Triple class refractory: 3.9 months EMD: 2.9 months	Overall: 11 months Triple class refractory: 11.2 months EMD: 4.2 months
Melflufen/Bort/Dex	Combo	ANCHOR OP-104[53] NCT03481556	Melflufen: 30 or 40 mg IV D1 Bort: 1.3 mg/m^2 SC D1 4, 18, 11 Dex: 20 mg PO (12 mg if pts age ≥ 75) D1, 4, 8, 11 Dex: 40 mg (20 mg if pts age ≥ 75) D 15 and 22 of each 28-day cycle	I/II	10	2 (1–4)	PI, 90% ASCT, 90%	NA	Grade ≥ 3 AEs: Neutropenia, 60% Thrombocytopenia, 80% Anemia, 40% Pneumonia, 20%	62%	30%	NA	NA
Melflufen/Dara/ Dex	Combo	ANCHOR OP-104[53] NCT03481556	Melflufen: 30 or 40 mg IV D1 Dara: 16 mg/kg IV D1, 8, 15 on C1–3; D1, 15 on C4–8; D1 on C ≥ 9 Dex: 40 mg PO (20 mg for pts age ≥ 75) D1, 8, 15, 22 of each 28-day cycle	I/II	33	2 (1–4)	ASCT, 79%	PI, 45% IMiD, 64% PI/IMiD, 36%	Grade ≥ 3 AEs: Neutropenia, 58% Thrombocytopenia, 55% Anemia, 24%	Overall: 73% 30-mg group: 83% 40-mg group: 70%	Overall 73%, 30-mg group 66%, 40-mg group 36%	11.5 months	NA
Belantamab mafodotin (belamaf, GSK2857916)	Single agent	DREAMM-2[41] NCT03525678	Belamaf 2.5 mg/kg IV D1 of each 21-day cycle vs. belamaf 3.4 mg/kg IV D1 of each 21-day cycle	II	97 + 99 (EMD 18%–23%)	7 (3–21) vs. 6 (3–21)	Belamaf 2.5 mg/kg: Bort, 98% Len, 100% Carf, 76% Pom, 92% Anti-CD38, 100% Belamaf, 3.4 mg/kg Bort, 98% Len, 100% Carf, 65% % Pom, 85% Anti-CD38, 97%	Belamaf 2.5 mg/kg: Bort, 76% Len, 90% Carf, 65% Pom, 87% Anti-CD38, 100% Belamaf, 3.4 mg/kg Bort, 75% Len, 89% Carf, 58% Pom, 78% Anti-CD38, 92%	Grade ≥ 3AEs for belamaf 2.5 mg/kg: Ocular toxicity/keratopathy, 27% Thrombocytopenia, 20% Anemia, 20% Pneumonia, 4% Belamaf 3.4, mg/kg: Ocular toxicity/keratopathy, 21% Thrombocytopenia, 33% Anemia, 25% Pneumonia, 11% Dose reduction, 29% IRR, 15%–18% (mostly grades 1–2)	Belamaf 2.5 mg/kg, 31%, vs. Belamaf 3.4 mg/kg, 30%	Belamaf 2.5 mg/kg, 19% vs. Belamaf 3.4 mg/kg, 20%	Belamaf 2.5 mg/kg, 2.9 months vs. Belamaf 3.4 mg/kg, 4.9 months	NA
Belamaf/Bort/Dex	Combo	DREAMM-6 arm B[54] NCT03544281	Belamaf 2.5 or 3.4 mg/kg IV D1 of each 21-day cycle Bort: 1.3 mg/m^2 SC D1, 4, 8, 11 Dex: 20 mg PO D1, 2, 4, 5, 8, 9, 11, 12	I/II	25	3 (1–11)	NA	NA	Discontinuation from AEs, 28% Grade ≥ 3 AEs: Thrombocytopenia, 67% Keratopathy, 55%	78%	50%	NA	NA
Belamaf/Pom/Dex	Combo	ALGONQUIN[55] NCT03715478	Belamaf 1.92/2.5 mg/kg single IV D1; 2.5/3.4 mg/kg IV split D1, loading 2.5 C1D1 and 1.92 from C2D1, of each 21-day cycle Pom: 4 mg PO D1-21 Dex: 40 mg PO D1, 8, 15, 22	I	37	3 (1–5)	PI, 100% Bort, 97% Carf, 35% Len, 100% Anti-CD38, 43% ASCT, 65%	PI, 81% Len, 89% Anti-CD38, 43% PI/len, 73% PI/len/anti-CD38, 35%	Grade ≥ 3 AEs: Keratopathy, 51% Neutropenia, 40% Thrombocytopenia, 32% Reduced visual acuity, 16% Fatigue, 10% IRR, 5%	Overall: 88% PI/IMiD refractory: 92% PI/IMiD/dara refractory: 100%	Overall 68% PI/IMiD refractory: 75% PI/IMiD/dara refractory: 72%	Overall and PI/IMiD refractory: NR (median FU: 7.8 months); PI/IMiD/dara refractory: 4.9 months	NA

Abbreviations. AEs, adverse events; ASCT, autologous stem-cell transplantation; belamaf, belantamab-mafodotin; bort, bortezomib; C, cycle; carf, carfilzomib; combo, combination; CR, complete response; D, day; dara, daratumumab; dex, dexamethasone; dual class–exposed/refractory, PI and IMiD exposed; elo, elotuzumab; EMD, extramedullary disease; FU, follow-up; HR, hazard ratio; IMiD, immunomodulatory drug; IRR, infusion-related reactions; IV, intravenously; len, lenalidomide; melflufen, melphalan flufenamide; MRD, minimal residual disease; MTD, maximum tolerated dose; NA, not available; neg, negative; NR, not reached; ORR, overall response rate; OS, overall survival; penta drug–exposed, exposed to two PIs, two IMiDs, and anti-CD38; PFS, progression-free survival; PI, proteasome inhibitor; PO, orally; pom, pomalidomide; quad drug–exposed, exposed to bortezomib, carfilzomib, lenalidomide, and pomalidomide; pts, patients; R2PD, recommended phase II dose; SAEs, serious adverse events; SC, subcutaneously; Sel, selinexor; TLS, tumor lysis syndrome; triple class–exposed/refractory, exposed to PI, IMiD, and anti-CD38; ven, venetoclax; VGPR, very good partial response.

*R2PD of selinexor was 60 mg.

**Because enrollment stopped in a low-efficacy single-agent cohort: patients could have dex at 40 mg weekly, added at the discretion of the investigator.

TABLE 6. Selected BCMA-Directed CAR T-Cell Therapies in Relapsed/Refractory Multiple Myeloma

	Idecabtagene Vicleucel (62 patients)[38]	Ciltacabtagene Autoleucel (97 patients)[39]	Orvacabtagene Autoleucel (62 patients)[40]	P-BCMA-101 (53 patients)[41]
Other Names	Ide-cel bb2121 Abecma	Cilta-cel JNJ-4528 LCAR-B38M	Orva-cel JCARH125	
Distinguishing Practical Features	Approved by the FDA in March 2021	Longer time to CRS onset (median 7 days after infusion)	Fully human CAR (may promote cell persistence)	Very low CRS incidence; CAR also includes safety switch
Pertinent CAR Design Features (compared with ide-cel)		Two distinct BCMA binding sites per CAR	CD4 and CD8 T cells expanded separately, then combined 1:1	Transposon-based DNA transfer, hence larger payload
ORR/CR	76%/39%	97%/67%	92%/36%	67%*/N/A
PFS (median follow-up)	8.8 months (14.7 months)	NR (12.4 months)	NR (2.3 months at RP2D)	N/A
Grade 3+ CRS/ICANS**	6%/3%	4%/9%	3%/3%	0%/4%

NOTE: For each CAR T-cell therapy, sample sizes and preliminary results from recent scientific abstracts are shown. Not all BCMA-directed therapies under clinical investigation are listed.

Abbreviations: ASTCT, American Society for Transplantation and Cellular Therapy; BCMA, B-cell maturation antigen; CR, complete response; CRS, cytokine release syndrome; FDA, U.S. Food and Drug Administration; ICANS, immune effector cell-associated neurotoxicity syndrome; N/A, information not yet available; NR, not reached; ORR, overall response rate; PFS, progression-free survival; RP2D; recommended phase II dose.

*With their nanoplasmid-based product (six patients as of December 2020).

**Quantified using ASTCT consensus criteria.[80] However, for cilta-cel, the 9% ICANS figure includes other neurologic toxicities as well.

tissue lesion; 50% of them had soft tissue extraosseous plasmacytoma, and 91% were triple-class refractory. The ORR was 24% in patients with extramedullary disease versus 32% in patients without extramedullary disease, and the median PFS was 2.9 months versus 4.9 months.[59]

Patients treated with novel agents may develop high-risk cytogenetic abnormalities at relapse, which are associated with adverse outcomes.[60,61] Limited data are available on the efficacy of newer agents in high-risk disease. In patients with either t(11;14) or high *BCL2* gene expression, and even in patients with high-risk cytogenetic abnormalities, venetoclax added to the backbone of bortezomib/dexamethasone was associated with better PFS and overall survival rates compared with bortezomib/dexamethasone alone.[62] This finding may support the use of venetoclax in combination with proteasome inhibitors in high-risk patients who also have t(11;14). In general, high risk and extramedullary disease are characterized by high tumor burden/kinetics of replication; therefore, combination therapies are preferred, if tolerable.

EMERGING IMMUNE-BASED STRATEGIES

Selinexor, belantamab, and venetoclax are exciting new agents for relapsed or refractory myeloma, but perhaps the most promise for high response rates lies with immunotherapy, either as dual-body T-cell engagers or engineered T cells. Although allogeneic hematopoietic stem cell transplantation had previously been considered an additional immune-based therapy,[63] its use is uncommon outside of a clinical trial because of the promise of other cellular therapy strategies that may offer lower toxicity.

The bispecific antibodies (known by trademarks such as BiTE or Duobody) can simultaneously bind myeloma cells and native T cells to trigger immune-based tumor cell lysis. Investigational BCMA-binding bispecific antibodies include AMG-701, JNJ-7957 (teclistamab), REGN5458, and TNB-383B.[64-69] Bispecific antibodies targeting other multiple myeloma antigens—for example, FcRH5 (BFCR4350A, cevostamab) and GPRC5D (JNJ-64407564, talquetamab)—have shown promise as well.[67,70-72] Common features of bispecific antibodies include encouraging response rates, often exceeding 60% even in heavily pretreated patients, and generally manageable toxicities. Whereas blinatumomab (a commercially available bispecific antibody for patients with B-cell acute lymphoblastic leukemia) requires continuous 4-week intravenous infusions, some of these bispecific antibody therapies for relapsed/refractory multiple myeloma can be administered as shorter infusions every 3 weeks or even dosed subcutaneously.[69-71]

Although bispecific antibodies may require continued dosing, CAR T-cell therapies offer the promise of deep responses after a one-time infusion of T cells engineered to target BCMA. As shown in Table 6, investigational CAR T-cell therapies in relapsed/refractory multiple myeloma,

TABLE 7. Challenges With BCMA-Directed Immune Therapies

Challenge	Possible Solutions Under Investigation
Lack of durability to responses	• Gamma-secretase inhibitors to prevent plasma cells from creating a "sink" of soluble BCMA[82]
	• Promotion of memory CAR T-cell expansion (e.g., bb21217 manufactured using a phosphoinositide 3-kinase inhibitor)[83]
Two-week period for manufacturing	• Development of universal CAR T cells of allogeneic origin that can be administered off the shelf (e.g., ALLO-715)[84]
	• Development of off-the-shelf CAR natural killer cells with other antimyeloma properties (e.g., FT576)[85]
Risk of CRS in older frailer patients	• Transposon-based DNA transfer allowing for incorporation of a safety switch to shut off CAR T cells (e.g., P-BCMA-101)[76]
	• Preemptive or even prophylactic management of CRS with tocilizumab, an interleukin-6 receptor antagonist[86]
Risk of ICANS in older frailer patients	• Outpatient-based CAR T-cell infusion and monitoring,[74,76] which may lower the risk of hospitalization-induced delirium
	• Administration of anakinra, an interleukin-1 receptor antagonist (possible benefit with CD19-directed CAR T-cell therapy)[87]

Abbreviations: BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

including idecabtagene vicleucel (newly approved by the U.S. Food and Drug Administration in March 2021) and several investigational products, have different "flavors" but uniformly demonstrate deep responses in heavily pretreated patients.[73-76] Compared with CD19-directed CAR T-cell therapies in leukemia and lymphoma; however, studies of BCMA-directed therapies have not yielded long-term plateaus in survival suggestive of durable remission.[77-79] Other broader challenges with current-generation CAR T-cell therapies include the following: (1) a 2-week period between T-cell collection and CAR T-cell infusion needed for CAR T-cell manufacturing, which may limit its feasibility in rapidly progressive disease; and (2) the risk of inflammation-related toxicities, such as cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome. Grade 3 or greater cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome (which can manifest as distributive shock and coma, respectively) occur in fewer than 10% of patients receiving BCMA-directed CAR T-cell therapies, but the need for intensive monitoring and expert management of these unique toxicities limits the feasibility of CAR T-cell therapy outside of the inpatient setting at specialized centers.

Fortunately, several strategies, highlighted in Table 7, are under investigation to address the above challenges with BCMA-directed immune therapies. Other trials are studying immune-based strategies to target several epitopes on myeloma cells simultaneously, for example, bispecific CAR T cells or simultaneous infusions of BCMA-directed and GPRC5D-directed bispecific antibodies.[65,79,81] As clinical experience grows with these immune-based therapies, questions about the optimal sequence of therapies in relapsed/refractory multiple myeloma will become more complex. The ongoing KarMMa-3 and CARTITUDE-4 randomized trials (NCT03651128 and NCT04181827, respectively) will better establish the role of CAR T-cell therapies versus standard-of-care triplet regimens. However, unanswered questions for the field include (1) whether patients with newly relapsed disease should proceed to CAR T-cell therapy versus nonimmune therapies, such as selinexor or salvage autologous stem cell transplantation, and (2) whether patients with prior exposure to BCMA-directed therapy (e.g., the antibody–drug conjugate belantamab mafodotin or the CAR T-cell therapy idecabtagene vicleucel, once commercially available) can develop the same depth of responses with subsequent treatment using a different BCMA-directed therapy.

Emerging Intracellular Strategies

A shared limitation of CAR T cells and bispecific antibodies is their reliance on functional immune effector cells and the presence of extracellular myeloma antigens. As such, other emerging strategies that operate intracellularly may serve as valuable tools for treating relapsed/refractory multiple myeloma as well. Within individual myeloma cells, both proteasome inhibitors and immunomodulatory agents modulate or interfere with the ubiquitin-proteasome system required by these cancerous cells to maintain high rates of protein turnover. (Of note, immunomodulatory agents also work by exerting pleiotropic effects on normal lymphocytes and the bone marrow microenvironment.) Table 8 summarizes investigational agents

TABLE 8. Novel Intracellular Strategies in the Treatment of Relapsed/Refractory Multiple Myeloma

Mechanism	Drug	Mechanism
Protein destruction	PIs (e.g., bortezomib, ixazomib, or carfilzomib)	Prevent UPS-mediated degradation of all proteins, including progrowth proteins
	IMiDs (e.g., lenalidomide or pomalidomide)	Mark progrowth proteins for UPS-mediated degradation
	CELMoDs (e.g., CC-92480 or iberdomide)[72,88-90]	More directly mark progrowth proteins for rapid UPS-mediated degradation
	DUB inhibitors[91,92]	Unmark progrowth proteins to avoid evasion of UPS-mediated degradation
	PROTACs, degronomids[91,92]	Specifically bind preselected progrowth proteins for UPS-mediated degradation
Other types of protein trafficking	SUMOylation inhibitors[92,93]	Prevent modification and recruitment of key proteins involved in DNA repair
	Selective inhibitors of nuclear export (e.g., selinexor)	Prevent nuclear export of progrowth proteins; promote tumor suppressor protein localization within the nucleus

NOTE. For the sake of clarity, certain U.S. Food and Drug Administration–approved drugs (PIs, IMiDs, and selinexor) are also shown; additionally, details about the mechanisms of novel drugs are intentionally simplified.
Abbreviations: CELMoD, cereblon E3 ligase modulation; DUB, deubiquitinating enzymes; IMiD, immunomodulatory drug; PI, proteasome inhibitor; PROTAC, proteolysis targeting chimera proteins; SUMOylation, small ubiquitin-like modifier addition; UPS, ubiquitin-proteasome system.

that modulate protein trafficking intracellularly in relapsed/refractory multiple myeloma, ranging from drugs that target the ubiquitin-proteasome system to small ubiquitin-like modifier inhibitors that interfere with processes such as DNA repair.[65,88-93] Most of these agents remain in preclinical development; however, two studies of cereblon E3 ligase modulation drugs (known by the trademark CELMoD) have demonstrated responses in heavily pretreated patients.[89,90] Although existing immunomodulatory agents similarly exert their effect through cereblon E3 ligase modulation, these newer-generation molecules lead to more rapid and sustained inhibition of downstream progrowth pathways within myeloma cells.[94]

As the evidence for the effectiveness of these novel therapies grows, important considerations will include their activity in triple-class-refractory disease and the choice of synergistic partner agents (for example, iberdomide with bortezomib or small ubiquitin-like modifier addition inhibitors in conjunction with DNA alkylators such as high-dose melphalan).[93,95] Last, even relatively selective inhibitors of intracellular pathways, such as selinexor, can be associated with serious side effects. Although not off target per se, these toxicities compose a key limitation of small-molecule therapies in relapsed/refractory multiple myeloma. Newer innovations in improving small-molecule selectivity include proteolysis-targeting chimera proteins (known by the trademark PROTAC) and degronomids, which, at a fundamental level, seek to accomplish intracellularly what bispecific antibodies seek to accomplish extracellularly.[91,92] In other words, these synthetically engineered drugs are designed to trigger cell destruction through precise interactions between prespecified tumor proteins and regulatory pathways (in this case, the ubiquitin-proteasome system). The extent of activity and durability of these treatments for patients with relapsed/refractory multiple myeloma remains an area of active investigation.

CONCLUSION

The rapidly evolving field of multiple myeloma therapy has been a boon for patients with relapsed disease, but the complex array of treatment options demands a careful consideration of factors that may influence patient outcomes, including prior therapies, aggressiveness of relapse, comorbidities, and access to care. A general pattern that emerges in the sea of data is that the combination of multiple drugs has tended to improve response rates and length of survival times, albeit frequently at the cost of increased toxicity, requiring careful clinical management and a consideration of the patient's individual features (e.g., renal impairment, toxicities from earlier regimens.) We expect immune-based therapies to play an increasingly central role in the setting of relapsed multiple myeloma because of their promising effects, even in heavily pretreated patients. Optimal sequencing of immunotherapy remains unknown—for example, whether a patient who receives a BCMA CAR T-cell therapy can respond later to a BCMA-bispecific T-cell engager. These questions will become more important as immune therapies are moved to the frontline setting in myeloma. Ultimately, the combination of these new therapies in conjunction with standard backbones in the frontline setting will lead us closer to a cure.

AFFILIATIONS

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REFERENCES

1. Attal M, Lauwers-Cances V, Hulin C, et al; IFM 2009 Study. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. N Engl J Med. 2017;376:1311-1320.
2. Giralt S, Garderet L, Durie B, et al; American Society of Blood and Marrow Transplantation, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group. Consensus Conference on salvage hematopoietic cell transplantation in patients with relapsed multiple myeloma. Biol Blood Marrow Transplant. 2015;21:2039-2051.
3. Richardson PG, Oriol A, Beksac M, et al; OPTIMISMM trial investigators. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:781-794.
4. Dimopoulos M, Weisel K, Moreau P, et al. Pomalidomide, bortezomib, and dexamethasone for multiple myeloma previously treated with lenalidomide (OPTIMISMM): outcomes by prior treatment at first relapse. Leukemia. Epub 2020 Sep 7.
5. Dimopoulos MA, Oriol A, Nahi H, et al; POLLUX Investigators. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016; 375:1319-1331.
6. Lonial S, Dimopoulos M, Palumbo A, et al; ELOQUENT-2 Investigators. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med. 2015; 373:621-631.
7. Moreau P, Masszi T, Grzasko N, et al; TOURMALINE-MM1 Study Group. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;374:1621-1634.
8. Stewart AK, Rajkumar SV, Dimopoulos MA, et al; ASPIRE Investigators. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015;372:142-152.
9. Palumbo A, Chanan-Khan A, Weisel K, et al; CASTOR Investigators. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med. 2016; 375:754-766.
10. Dimopoulos MA, Moreau P, Palumbo A, et al; ENDEAVOR Investigators. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016;17:27-38.
11. Moreau P, Joshua D, Chng WJ, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. Leukemia. 2017;31:115-122.
12. San-Miguel JF, Hungria VTM, Yoon S-S, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014;15:1195-1206.
13. Siegel DS, Dimopoulos MA, Ludwig H, et al. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. J Clin Oncol. 2018;36:728-734.
14. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet. 2020;396:1563-1573.
15. Becnel MR, Horowitz SB, Thomas SK, et al. Descriptive analysis of isatuximab use following prior daratumumab in patients with relapsed/refractory multiple myeloma. Blood. 2020;136(suppl):20-21.
16. Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. Lancet. 2020;396:186-197.
17. Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone *versus* bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018;103:2079-2087.
18. Dimopoulos MA, San-Miguel J, Belch A, et al. Daratumumab plus lenalidomide and dexamethasone *versus* lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. Haematologica. 2018;103:2088-2096.
19. Mateos MV, Sonneveld P, Hungria V, et al. Daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone in patients with previously treated multiple myeloma: three-year follow-up of CASTOR. Clin Lymphoma Myeloma Leuk. 2020;20:509-518.
20. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood. 2017; 130:974-981.

21. Siegel DS, Schiller GJ, Samaras C, et al. Pomalidomide, dexamethasone, and daratumumab in relapsed refractory multiple myeloma after lenalidomide treatment. Leukemia. 2020;34:3286-3297.
22. Dimopoulos MA, Terpos E, Boccadoro M, et al. Apollo: phase 3 randomized study of subcutaneous daratumumab plus pomalidomide and dexamethasone (D-Pd) versus pomalidomide and dexamethasone (Pd) alone in patients (Pts) with relapsed/refractory multiple myeloma (RRMM). Blood. 2020;136(suppl):5-6.
23. Attal M, Richardson PG, Rajkumar SV, et al; ICARIA-MM study group. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019;394:2096-2107.
24. Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab plus carfilzomib and dexamethasone vs carfilzomib and dexamethasone in relapsed/refractory multiple myeloma (IKEMA): interim analysis of a phase 3, randomized, open-label study. Blood. 2020;136(suppl; abstr 2316).
25. Dimopoulos MA, Lonial S, Betts KA, et al. Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial. Cancer. 2018;124:4032-4043.
26. Dimopoulos MA, Lonial S, White D, et al. Elotuzumab plus lenalidomide/dexamethasone for relapsed or refractory multiple myeloma: ELOQUENT-2 follow-up and post-hoc analyses on progression-free survival and tumour growth. Br J Haematol. 2017;178:896-905.
27. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. N Engl J Med. 2018;379:1811-1822.
28. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. Leukemia. 2016;30:1005-1017.
29. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. 2019;33:2266-2275.
30. San-Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14:1055-1-66.
31. Lu G, Middleton RE, Sun H, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of ikaros proteins. Science. 2014;343:305-309.
32. Quach H, Ritchie D, Stewart AK, et al. Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. Leukemia. 2010;24:22-32.
33. Siegel DS, Martin T, Wang M, et al. A phase II study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012;120:2817-2823.
34. Hurchla MA, Garcia-Gomez A, Hornick MC, et al. The epoxyketone-based proteasome inhibitors carfilzomib and orally bioavailable oprozomib have anti-resorptive and bone-anabolic activity in addition to anti-myeloma effects. Leukemia. 2013;27:430-440.
35. Kuhn DL, Chen Q, Voorhees PM, et al. Potent activity of carfilzomib, a novel, irreversible inhibitor of the ubiquitin-proteasome pathway, against preclinical models of multiple myeloma. Blood. 2007;110:3281-3290.
36. Mateos M-V, Bladé J, Bringhen S, et al. Melflufen: a peptide–drug conjugate for the treatment of multiple myeloma. J Clin Med. 2020;9:3120.
37. Tai YT, Mayes PA, Acharya C, et al. Novel anti–B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. Blood. 2014;123:3128-3138.
38. Bertamini L, Bonello F, Boccadoro M, et al. New drugs in early development for treating multiple myeloma: all that glitters is not gold. Expert Opin Investig Drugs. 2020;29:989-1004.
39. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor–dexamethasone for triple-class refractory multiple myeloma. N Engl J Med. 2019;381:727-738.
40. Richardson PG, Oriol A, Larocca A, et al. Melflufen and dexamethasone in heavily pretreated relapsed and refractory multiple myeloma. J Clin Oncol. 2021; 39:757-767.
41. Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol. 2020;21:207-221.
42. Trudel S, Lendvai N, Popat R, et al. Antibody-drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: an update on safety and efficacy from dose expansion phase I study. Blood Cancer J. 2019;9:37.
43. Chen C, Siegel D, Gutierrez M, et al. Safety and efficacy of selinexor in relapsed or refractory multiple myeloma and Waldenstrom macroglobulinemia. Blood. 2018;131:855-863.
44. Chen CI, Bahlis NJ, Gasparetto C, et al. Selinexor in combination with pomalidomide and dexamethasone (spd) for treatment of patients with relapsed refractory multiple myeloma (RRMM). Blood. 2020;136(suppl; abstr 726).
45. Gasparetto C, Lipe B, Tuchman SA, et al. Selinexor in combination with carfilzomib and dexamethasone, all once weekly (SKd), for patients with relapsed/refractory multiple myeloma. Blood. 2020;136(suppl; abstr 1366).
46. Jakubowial AJ, Jasielec JK, Rosenbaum CA, et al. Phase 1 study of selinexor plus carfilzomib and dexamethasone for the treatment of relapsed/refractory multiple myeloma. Br J Haematol. 2019;186:549-560.
47. Gasparetto C, Lipe B, Tuchman S, et al. Once weekly selinexor, carfilzomib, and dexamethasone (SKd) in patients with relapsed/refractory multiple myeloma (MM). J Clin Oncol. 2020;38(suppl; abstr 8530).
48. Kumar S, Kaufman JL, Gasparetto C, et al. Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. Blood. 2017; 130:2401-2409.
49. Kaufman JL, Gasparetto CJ, Mikhael J, et al. Phase 1 study of venetoclax in combination with dexamethasone as targeted therapy for t(11;14) relapsed/refractory multiple myeloma. Blood. 2017;130(suppl):3131.

50. Costa LJ, Burwick N, Jakubowiak A, et al. Assessment of minimal residual disease by next-generation sequencing and fluorodeoxyglucose-positron emission tomography in patients with relapsed/refractory multiple myeloma treated with venetoclax in combination with carfilzomib and dexamethasone. Blood. 2020; 136(suppl; abstr 2251).

51. Kaufman JL, Baz RC, Harrison SJ, et al. Updated analysis of a phase I/II study of venetoclax in combination with daratumumab and dexamethasone, +/- bortezomib, in patients with relapsed/refractory multiple myeloma. J Clin Oncol. 2020;38(suppl; abstr 8511).

52. Richardson PG, Bringhen S, Voorhees P, et al. Melflufen plus dexamethasone in relapsed and refractory multiple myeloma (O-12-M1): a multicentre, international, open-label, phase 1–2 study. Lancet Haematol. 2020;7:e395-e407.

53. Ocio EM, Efebera YA, Hájek R, et al. ANCHOR (OP-104): melflufen plus dexamethasone (dex) and daratumumab (dara) or bortezomib (BTZ) in relapsed/refractory multiple myeloma (RRMM) refractory to an IMiD and/or a proteasome inhibitor (PI)—updated efficacy and safety. Blood. 2020;136(suppl; abstr 417).

54. Popat R, Nooka A, Stockerl-Goldstein K, et al. DREAMM-6: safety, tolerability and clinical activity of belantamab mafodotin (Belamaf) in combination with bortezomib/dexamethasone (BorDex) in relapsed/refractory multiple myeloma (RRMM). Blood. 2020;136(suppl; abstr 1419).

55. Trudel S, McCurdy A, Sutherland HJ, et al. Part 1 results of a dose finding study of belantamab mafodotin (GSK2857916) in combination with pomalidomide (POM) and dexamethasone (DEX) for the treatment of relapsed/refractory multiple myeloma (RRMM). Blood. 2020;136(suppl; abstr 725).

56. Larocca A, Dold SM, Zweegman S, et al. Patient-centered practice in elderly myeloma patients: an overview and consensus from the European Myeloma Network (EMN). Leukemia. 2018;32:1697-1712.

57. Bhutani M, Fureau DM, Atrash S, et al. Extramedullary multiple myeloma. Leukemia. 2020;34:1-20.

58. Lee HC, Cohen AD, Chari A, et al. DREAMM-2: single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) and renal impairment. J Clin Oncol. 2020;38(suppl; abstr 8519).

59. Richardson PG, Mateos M-V, Oriol A, et al. HORIZON (OP-106): melflufen plus dexamethasone (dex) in 55 patients (pts) with relapsed/refractory multiple myeloma (RRMM) with extramedullary disease (EMD)—subgroup analysis. Blood. 2020;(suppl):15-17.

60. Merz M, Jauch A, Lielscher T, et al. Longitudinal fluorescence in situ hybridization reveals cytogenetic evolution in myeloma relapsing after autologous transplantation. Haematologica. 2017;102:1432-1438.

61. Oliva S, De Paoli L, Ruggeri M, et al. A longitudinal analysis of chromosomal abnormalities in disease progression from MGUS/SMM to newly diagnosed and relapsed multiple myeloma. Ann Hematol. 2021;100:437-443.

62. Kumar Sk, Harrison SJ, Cavo M, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2020;21:1630-1642.

63. Giralt S, Costa LJ, Maloney D, et al. Tandem autologous-autologous versus autologous-allogeneic hematopoietic stem cell transplant for patients with multiple myeloma: long-term follow-up results from the Blood and Marrow Transplant Clinical Trials Network 0102 Trial. Biol Blood Marrow Transplant. 2020;26:798-804.

64. Shah N, Chari A, Scott E, et al. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. Leukemia. 2020;34:985-1005.

65. Demel I, Bago JR, Hajek R, et al. Focus on monoclonal antibodies targeting B-cell maturation antigen (BCMA) in multiple myeloma: update 2020. Br J Haematol. Epub 2020 Nov 20.

66. Abramson HN. B-cell maturation antigen (BCMA) as a target for new drug development in relapsed and/or refractory multiple myeloma. Int J Mol Sci. 2020; 21:E5192.

67. Caraccio C, Krishna S, Phillips DJ, et al. Bispecific antibodies for multiple myeloma: a review of targets, drugs, clinical trials, and future directions. Front Immunol. 2020;11:501.

68. Cho SF, Lin L, Xing L, et al. BCMA-targeting therapy: driving a new era of immunotherapy in multiple myeloma. Cancers (Basel). 2020;12:E1473.

69. Rodriguez C, D'Souza A, Shah N, et al. Initial results of a phase I study of TNB-383B, a BCMA x CD3 bispecific T-cell redirecting antibody, in relapsed/refractory multiple myeloma. Blood. 2020;136(suppl; abstr 293).

70. Chari A, Berdeja JG, Oriol A, et al. A phase 1, first-in-human study of talquetamab, a G protein-coupled receptor family C group 5 member D (GPRC5D) x CD3 bispecific antibody, in patients with relapsed and/or refractory multiple myeloma (RRMM). Blood. 2020;136(suppl; abstr 290).

71. Cohen AD, Harrison SJ, Krishnan A, et al. Initial clinical activity and safety of BFCR4350A, a FcRH5/CD3 T-cell-engaging bispecific antibody, in relapsed/refractory multiple myeloma. Blood. 2020;136(suppl):42-43.

72. Shah UA, Mailankody S. Emerging immunotherapies in multiple myeloma. BMJ. 2020;370:m3176.

73. Lin Y, Raje NS, Berdeja JG, et al. Idecabtagene Vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy, in patients with relapsed and refractory multiple myeloma: updated results from phase 1 CRB-401 study. Blood. 2020;136(suppl; abstr 131).

74. Madduri D, Berdeja JG, Usmani SZ, et al. CARTITUDE-1: phase 1b/2 study of ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T cell therapy, in relapsed/refractory multiple myeloma. Blood. 2020;136(suppl; abstr 177).

75. Mailankody S, Jakubowiak AJ, Htut M, et al. Orvacabtagene autoleucel (orva-cel), a B-cell maturation antigen (BCMA)-directed CAR T cell therapy for patients (pts) with relapsed/refractory multiple myeloma (RRMM): update of the phase 1/2 EVOLVE study (NCT03430011). J Clin Oncol. 2020; 38 (suppl; abstr 8504).

76. Costello CL, Cohen AD, Patel KK, et al. Phase 1/2 study of the safety and response of P-BCMA-101 CAR-T cells in patients with relapsed/refractory (r/r) multiple myeloma (MM) (PRIME) with novel therapeutic strategies. Blood. 2020;136(suppl):29-30.

77. Grover N, Tschemia N, Dotti G, et al. Extending the promise of chimeric antigen receptor T-cell therapy beyond targeting CD19+ tumors. J Clin Oncol. 2021; 39:499-513.

78. García-Guerrero E, Sierro-Martínez B, Pérez-Simón JA. Overcoming chimeric antigen receptor (CAR) modified T-cell therapy limitations in multiple myeloma. Front Immunol. 2020;11:1128.

79. Mikkilineni L, Kochenderfer JN. CAR T cell therapies for patients with multiple myeloma. Nat Rev Clin Oncol. 2021;18:71-84.

80. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25:625-638.

81. Cronk RJ, Zurko J, Shah NN. Bispecific chimeric antigen receptor T cell therapy for B cell malignancies and multiple myeloma. Cancers (Basel). 2020;12:E2523.

82. Pillarisetti K, Powers G, Luistro L, et al. Teclistamab is an active T cell-redirecting bispecific antibody against B-cell maturation antigen for multiple myeloma. Blood Adv. 2020;4:4538-4549.

83. Alsina M, Shah N, Raje NS, et al. Updated results from the phase I CRB-402 study of anti-BMCA CAR-T cell therapy bb21217 in patients with relapsed and refractory multiple myeloma: correlation of expansion and duration of response with T cell phenotypes. Blood. 2020;136(suppl; abstr 130).

84. Mailankody S, Matous JV, Liedtke M, et al. Universal: an allogeneic first-in-human study of the anti-BCMA ALLO-715 and the Anti-CD52 ALLO-647 in relapsed/refractory multiple myeloma. Blood. 2020;136(suppl; abstr 129).

85. Goodridge JP, Bjordahl R, Mahmood S, et al. FT576: multi-specific off-the-shelf CAR-NK cell therapy engineered for enhanced persistence, avoidance of self-fratricide and optimized mab combination therapy to prevent antigenic escape and elicit a deep and durable response in multiple myeloma. Blood. 2020;136(suppl; abstr FT576).

86. Marsal J, Banerjee R, Huang C, et al. Patterns of tocilizumab use among myeloma patients receiving BCMA-directed therapies: effect on day 30 outcomes. Blood. 2020;136(suppl; abstr 2353).

87. Strati P, Ahmed S, Kebriaei P, et al. Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. Blood Adv. 2020;4:3123-3127.

88. Nadeem O, Tai YT, Anderson KC. Immunotherapeutic and targeted approaches in multiple myeloma. ImmunoTargets Ther. 2020;9:201-215.

89. Wong L, Lamba M, Jiménez Nuñez MD, et al. Dose- and schedule-dependent immunomodulatory effects of the novel celmod agent CC-92480 in patients with relapsed/refractory multiple myeloma. Blood. 2020;136(suppl; abstr 2295).

90. van de Donk NWCJ, Popat R, Larsen J, et al. First results of iberdomide (IBER; CC-220) in combination with dexamethasone (DEX) and daratumumab (DARA) or bortezomib (BORT) in patients with relapsed/refractory multiple myeloma (RRMM). Blood. 2020;136(suppl; abstr 724).

91. Driscoll JJ, Brailey M. Emerging small molecule approaches to enhance the antimyeloma benefit of proteasome inhibitors. Cancer Metastasis Rev. 2017;36:585-598.

92. Wirth M, Schick M, Keller U, et al. Ubiquitination and ubiquitin-like modifications in multiple myeloma: biology and therapy. Cancers (Basel). 2020;12:E3764.

93. Boulanger M, Paolillo R, Piechaczyk M, et al. The SUMO pathway in hematomalignancies and their response to therapies. Int J Mol Sci. 2019;20:E3895.

94. Bjorklund CC, Kang J, Amatangelo M, et al. Iberdomide (CC-220) is a potent cereblon E3 ligase modulator with antitumor and immunostimulatory activities in lenalidomide- and pomalidomide-resistant multiple myeloma cells with dysregulated CRBN. Leukemia. 2020;34:1197-1201.

95. Amatangelo M, Bjorklund CC, Kang J, et al. Iberdomide (CC-220) has synergistic anti-tumor and immunostimulatory activity against multiple myeloma in combination with both bortezomib and dexamethasone, or in combination with daratumumab in vitro. Blood. 2018;132(suppl; abstr 1935).

LUNG CANCER

New Therapies and Biomarkers: Are We Ready for Personalized Treatment in Small Cell Lung Cancer?

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Overview

Small cell lung cancer (SCLC) is an aggressive form of lung cancer with a 5-year survival rate of less than 7%. In contrast to non–small cell lung cancer, SCLC has long been treated as a homogeneous disease without personalized treatment options. In recent years, the incorporation of immunotherapy into the treatment paradigm has brought moderate benefit to patients with SCLC; however, more effective therapies are urgently needed. In this article, we describe the current treatment standards and emerging therapeutic approaches for the treatment of SCLC. We also discuss promising biomarkers in SCLC and the recently discovered four subtypes of SCLC, each with its unique therapeutic vulnerability. Lastly, we discuss the advances in radiation therapy for the treatment of SCLC.

NEW AGENTS IN THE MANAGEMENT OF SMALL CELL LUNG CANCER

Small cell lung cancer (SCLC) is an aggressive high-grade neuroendocrine cancer that arises predominantly in people who smoke, accounting for about 15% of the total number of lung cancers.[1] Although there is the American Joint Committee on Cancer TNM staging system for SCLC,[2] in practice, SCLC is more commonly staged using the U.S. Veterans Administration staging system and is divided into a limited stage (LS-SCLC) and an extensive stage (ES-SCLC).[3] Only one-third of patients with SCLC are diagnosed with LS-SCLC, defined as the presence of tumor in an area that can be treated in one radiation "port."[4] The standard treatment for LS-SCLC remains concurrent chemoradiation with platinum and etoposide plus prophylactic cranial irradiation, although the addition of immunotherapy is being explored in clinical trials. Most patients with SCLC present with ES-SCLC, which confers a poor prognosis with a median survival duration of less than 2 years and a 5-year survival rate of less than 7%.[4,5]

Globally, first-line treatments for ES-SCLC have been platinum-based chemotherapy combinations for decades. However, despite the high initial response rate, almost all patients invariably relapse within 1 year, with a median survival of only 4 to 5 months after relapse.[6] Since 2018, two large randomized phase III trials, IMpower133[7] and CASPIAN,[8] have shown a benefit from adding PD-L1 blockade atezolizumab and durvalumab, respectively. As a result, these two immune checkpoint inhibitors are now incorporated as part of the frontline regimen in the United States and Europe.

In the IMpower133 study, over 400 treatment-naive patients with ES-SCLC were randomly assigned 1:1 to receive atezolizumab plus etoposide/carboplatin (EP) or placebo plus EP as first-line treatment for ES-SCLC. The study demonstrated a considerable improvement in overall survival (OS) with the atezolizumab plus EP combination compared with placebo plus EP. The median OS was 12.3 months in the atezolizumab plus EP group and 10.3 months in the EP plus placebo group (HR, 0.76; 95% CI, 0.60–0.95; p = .0154).[7,9]

In the CASPIAN trial, 805 treatment-naive patients with ES-SCLC were randomly assigned 1:1:1 into one of three treatment arms: durvalumab plus EP with or without a CTLA-4 blockade tremelimumab, followed by durvalumab maintenance, or EP alone with optional prophylactic cranial irradiation. In a planned interim analysis of OS, durvalumab plus EP was associated with a significant improvement in OS (HR, 0.73; 95% CI, 0.59–0.91; p = .0047). Median OS in the durvalumab plus EP group was 13.0 months (95% CI, 11.5–14.8) versus 10.3 months (95% CI, 9.3–11.2) in the EP group.[8] In an updated analysis published in 2020, the addition of tremelimumab to durvalumab plus EP did not significantly improve OS compared with the EP group.[10]

In 2020, another phase III randomized trial, KEYNOTE-604, reported outcomes of adding PD-1 blockade pembrolizumab to EP versus placebo plus EP in the frontline setting for ES-SCLC. The study met its progression-free survival endpoints but missed the OS endpoint (HR, 0.80; 95% CI, 0.64–0.98).[11]

In the second-line setting for the treatment of ES-SCLC, topotecan was the only agent approved by the U.S.

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PRACTICAL APPLICATIONS

- Small cell lung cancer (SCLC) is an aggressive malignancy with dismal prognosis, the treatment of which has been a one-size-fits-all approach.
- Recent incorporation of immunotherapy in addition to platinum-based chemotherapy has brought moderate benefit to patients with SCLC.
- Our understanding of the biology, as well as inter- and intratumoral heterogeneity, of SCLC has propelled development of new therapeutic targets and biomarkers for the treatment of SCLC.
- Four subtypes of SCLC have recently been described, each with its unique vulnerability. For instance, an "inflamed" subtype is found to be particularly sensitive to immunotherapy.
- Radiation therapy remains an important definitive and palliative treatment modality in SCLC.

Food and Drug Administration until the recent introduction of lurbinectedin. Lurbinectedin is an analog of trabectedin. It inhibits active transcription and creates DNA damage in tumor cells, leading to apoptosis.[12,13] In addition, lurbinectedin modifies the tumor microenvironment by reducing tumor-associated macrophages.[14] In 2020, lurbinectedin received accelerated approval from the U.S. Food and Drug Administration based on phase II trial data showing a modest response of 35%.[15] However, the confirmatory phase III ATLANTIS trial comparing lurbinectedin and doxorubicin with physician's choice of topotecan or cyclophosphamide/doxorubicin/vincristine missed its primary endpoint of OS benefit.[16] Continued U.S. Food and Drug Administration approval of lurbinectedin will, therefore, likely be contingent on additional follow-on trials.

In the third-line setting, nivolumab and pembrolizumab were previously approved for SCLC based on the phase I/II CheckMate 032 trial, phase Ib KEYNOTE-028 trial, and phase II KEYNOTE-158 trial.[17-20] In CheckMate 032, nivolumab as monotherapy or nivolumab plus ipilimumab was assessed. Although the objective response rate was higher in nivolumab plus ipilimumab, OS was similar between the two groups: 5.7 months in nivolumab alone compared with 4.7 months in the combination group.[17] Whether or not CTLA-4 blockade has a role in SCLC treatment is still questionable, given the underwhelming results from CheckMate 032 and the lack of benefit from adding tremelimumab to durvalumab in the CASPIAN trial. In March 2021, both manufacturers for pembrolizumab and nivolumab withdrew their indications for SCLC. As such, there continues to be a considerable need for treatment options for patients with relapsed disease, in whom response rates with currently approved agents have ranged from 11% to 35%.

Several novel agents for SCLC, including targeted therapies and new approaches for immune engagement, are being actively studied in clinical trials, including PARP inhibitors (PARPi) talazoparib and olaparib (NCT04170946, NCT04728230, and NCT04334941); antifucosyl-GM1 antibody BMS-986012 (NCT02247349, NCT02815592, and NCT04702880); anti-TIGIT antibody with chemotherapy/immuno-oncology (NCT04256421); liposomal irinotecan (NCT03088813 and NCT04381910); ATR inhibitor BAY1895344 (NCT04514497); Bcl-2/Bcl-xL inhibitor pelcitoclax (NCT03080311 and NCT03387332); anti–delta-like ligand 3 bispecific T-cell engager AMG757 (NCT03319940) and BI764532 (NCT04429087); delta-like ligand 3 CAR T-cell AMG119 (NCT03392064); and anti–GD2-CD3 bispecific T-cell engager nivatrotamab (NCT03860207). For a comprehensive review of new therapeutic targets of interest in SCLC and their rationale, the readers are referred to two excellent reviews by Poirier and colleagues[21] and Rudin and colleagues.[5]

EMERGING BIOMARKERS IN SMALL CELL LUNG CANCER

In stark contrast to non–small cell lung cancer, SCLC has long been treated as a homogeneous disease, with a one-size-fits-all approach. For decades, the standard of care for ES-SCLC was platinum and etoposide combination chemotherapy, with the incorporation of immune checkpoint blockade into frontline treatment only after 2018.[7,8] There has been recent progress in recognizing distinct subtypes of SCLC using transcriptional profiling and multiple novel targeted therapies in trials for ES-SCLC. Although these advances are encouraging, it is reasonable to expect that only a subset of patients with SCLC will benefit from specific targeted or immune therapies, highlighting the need to identify biomarkers that can enhance patient selection and additional therapeutics.

Previously Tested Biomarkers in Small Cell Lung Cancer

In contrast to non–small cell lung cancer, in which numerous drive-gene alterations (e.g., *EGFR*, *ALK*, *BRAF*, *MET*, *RET*, *ROS*, and *NTRK*, etc.) and PD-L1 levels guide personalized therapy for patients with advanced or relapsed disease, it has been a substantial challenge to identify biomarkers and therapeutic targets in SCLC. The SCLC genome exhibits extremely high mutation rates, a pattern indicative of heavy smoking.[22] The prevailing mutations in SCLC are primarily loss of function, involving the tumor suppressor genes *TP53* and *RB1*, which are currently not druggable targets.[22] Also frequent are *MYC* family gene alterations, commonly amplifications, and inactivating mutations in *NOTCH* family genes.[22-24] Other genetic alterations identified include *PTEN* loss,[25] activating *PI3K* mutations,[26,27] and *FGFR1* amplifications.[28,29] In preclinical

studies, *MYC*-amplified SCLC showed vulnerability to aurora kinase inhibitors and CHK1 inhibitors.[30-32] In a phase II trial assessing the aurora A kinase inhibitor alisertib plus paclitaxel compared with paclitaxel alone, median progression-free survival was not significantly better in the alisertib combination group than in the paclitaxel group (3.32 months vs. 2.17 months; p = .113) in an unselected patient population. However, analysis of a prespecified biomarker of c-MYC expression, as determined by immunohistochemistry, indicated that patients with c-MYC–positive SCLC had significantly better progression-free survival with paclitaxel plus alisertib than with paclitaxel alone (HR, 0.29; 95% CI, 0.12–0.72).[33] However, to date, none of these alterations have been prospectively validated as predictive biomarkers or targets in SCLC.

Expression of PD-L1 is a biomarker for immune checkpoint blockade in many solid malignancies. However, PD-L1 was not shown to be a predictive biomarker for first-line immune checkpoint blockade therapy in SCLC. In the updated PD-L1 subgroup analyses of the IMpower133 trial, patients benefitted from adding atezolizumab regardless of PD-L1 or blood-based tumor mutational burden status.[9] In patients with relapsed disease, the predictive potential for PD-L1 is also unclear. In the CheckMate 032 trial, patients with recurrent SCLC received nivolumab monotherapy as third- or later-line treatment, and the response rates were similar among patients regardless of tumor PD-L1 expression.[18] In the KEYNOTE-028 study, PD-L1–positive patients with recurrent or metastatic SCLC were treated with pembrolizumab and achieved an objective response rate of about 33% and median OS of 9.7 months,[34] whereas in the KEYNOTE-158 study, in which patients with recurrent or metastatic SCLC were treated regardless of PD-L1 status, patients achieved an objective response rate of 18.7% and median OS of 8.7 months.[35] Retrospective pooled analyses of combined KEYNOTE-028 and KEYNOTE-158 patients showed that 14 out of 16 patients (88%) with a response had PD-L1–positive tumors, suggesting that patients with relapsed PD-L1–positive SCLC may derive more benefits from immune checkpoint blockade than those with PD-L1–negative disease.[19] Retrospective analysis of CheckMate 032 data also showed that patients with a high tumor mutational burden had improved objective response rate, progression-free survival, and OS compared with those with a low-medium tumor mutational burden, suggesting that tumor mutational burden may be a predictive biomarker for immune checkpoint blockade in SCLC.[36] However, there is no clear standard cutoff for tumor mutational burden as a predictive biomarker.

There is clearly an unmet need for predictive biomarkers to guide therapy selection in SCLC. SLFN11 (protein Schlafen 11), a mediator in DNA damage and cause of irreversible replication block, has been identified as a potentially important biomarker for platinum and PARPi, among other agents in SCLC.

A Promising Biomarker: SLFN11

A preclinical study by Byers and colleagues[37] into the proteomic profile of SCLC identified PARPi and other DNA damage response inhibitors as potential therapeutic targets for SCLC. These findings have led to several clinical trials of PARPi and other agents in SCLC, many of which are ongoing (NCT04170946, NCT04728230, and NCT04334941). Although activity has been seen in a subset of patients with SCLC treated with PARPi, there is a need for biomarkers to identify patients who respond to these agents.[38] SLFN11 is a putative DNA/RNA helicase that blocks replication at stressed replication forks in the presence of DNA damage, leading to cell death. In preclinical studies, SLFN11 has been shown to predict response to multiple DNA-damaging agents, including platinum salts, topoisomerase I/II inhibitors, and PARPi.[39-42]

SLFN11 was first tested clinically as a candidate predictive biomarker in a phase II study comparing temozolomide plus the PARPi veliparib with temozolomide plus placebo in relapsed SCLC (primarily as third-line treatment and in platinum-resistant disease). No OS benefit was seen with the addition of veliparib in the overall cohort.[43] However, in a retrospective subgroup analysis, compared with SLFN11-negative patients, SLFN11-positive patients had significantly longer progression-free survival (5.7 months vs. 3.6 months; p = .009) and OS (12.2 months vs. 7.5 months; p = .014) in the temozolomide plus veliparib combination arm, but no difference was observed in the temozolomide plus placebo arm.[43] This study provided the first clinical trial data supporting SLFN11 as a candidate predictive biomarker for PARPi. Based on these findings supporting SLFN11 as a promising predictive biomarker for PARPi in SCLC, together with preclinical findings that PARPi can activate the innate immune response via the STING pathway to provide a synergic effect of PARPi with immunotherapy,[44-46] a phase II randomized trial of maintenance atezolizumab plus talazoparib versus atezolizumab alone in ES-SCLC was developed by the Southwestern Oncology Group (SWOG 1929; NCT04334941). In this ongoing trial, all patients will receive frontline induction therapy with EP plus atezolizumab. In the meantime, these patients will be prospectively screened for SLFN11 positivity by immunohistochemistry, which is expected in about 50% of ES-SCLC tumors based on previous clinical trial data.[43] If SLFN11 expression by immunohistochemistry is positive, the patient is eligible for random assignment in the maintenance phase to one of two arms: atezolizumab with or without talazoparib. The primary endpoint is to compare progression-free survival between the two arms, with the secondary objectives of comparing OS, objective response

rate, partial response, and adverse events between the two arms.

Many patients with SCLC will not have adequate archival tissue for biomarker testing. Given this paucity of tissue samples, staining for SLFN11 or other biomarkers by immunohistochemistry may not always be feasible. For example, in the veliparib phase II trial,[43] less than 50% of patients had adequate tissue available for the SLFN11 immunohistochemistry assay. Liquid biopsy or circulating tumor cell–based detection could therefore be complementary to tissue biopsy. Zhang and colleagues[47] have recently shown that SLFN11 can be detected in SCLC circulating tumor cells collected from a routine blood draw, and its expression level changes dynamically under treatment pressure: 70% of circulating tumor cells expressed SLFN11 in treatment-naive patients, which was reduced to 25% in patients receiving platinum therapy. This observation suggests SLFN11 level may change over the course of a patient's treatment, and having an easy way to assess the biomarker status at the time of progression, such as a circulating tumor cell–based test, would be useful. One of the potential mechanisms identified for SLFN11 downregulation is hypermethylation on its promoter region.[39,48] In preclinical models, epigenetic modifiers to reverse SLFN11 promotor methylation, such as EZH2 inhibitors, have led to re-expression of SLFN11 and resensitization to DNA-damaging agents.[49] Building on these preclinical findings, a phase I/II trial investigating the combination of EZH1/2 inhibitor DS-3201b and irinotecan in recurrent SCLC is ongoing (NCT03879798). This trial is testing whether EZH1/2 inhibitor could lead to re-expression of SLFN11, therefore enhancing response to chemotherapy or overcoming chemotherapy resistance that may have been acquired in the context of SLFN11 being downregulated as the result of prior lines of therapy.

Identification of Small Cell Lung Cancer Subtypes Opens Possibilities for Biomarker-Driven Clinical Trials

Early studies showed that neuroendocrine differentiation in SCLC is largely driven by key transcription factors, including ASCL1 and NEUROD1,[50] and a non-neuroendocrine, tuft-cell variant of SCLC driven by POU2F3.[51] Recently, Gay and colleagues[52] demonstrated the presence of four major, distinct SCLC subgroups using unbiased clustering of RNA-sequencing data from 81 surgically resected, mostly LS-SCLC tumors and samples from 276 treatment-naive patients with ES-SCLC from the IMpower133 study. Three of the subtypes were characterized by expression of distinct transcription factors: SCLC-A (high ASCL1 expression, 51% of cases), SCLC-N (high NEUROD1, 23% of cases), and SCLC-P (high POU2F3, 18% of cases). In contrast to prior observations, the YAP1 transcription factor did not define a distinct subtype in this unbiased computational approach, and increased YAP1 expression was rare across the SCLC tumors analyzed. This finding was also consistent with recent findings showing only sporadic YAP1 expression in SCLC mouse models and tumor samples.[53,54] The fourth subtype identified by Gay and colleagues[52] was a novel subtype of SCLC that emerged from the transcriptional analysis, which was named the "inflamed" subtype (SCLC-I). SCLC-I tumors lack expression of the ASCL1, NEUROD1, and POU2F3 transcription factors and instead exhibit epithelial-mesenchymal transition and have high expression of genes related to immune cell infiltration and immune checkpoints, HLA genes, and interferon gamma activation. The four subtypes were further validated in cell lines and additional independent patient tumor samples from another cohort of treatment-naive metastatic patients.[52]

More intriguingly, Gay and colleagues[52] identified distinct therapeutic vulnerabilities in each of the four subtypes. For example, the SCLC-A subtype has increased sensitivity to BCL2 inhibitors, the SCLC-N subtype has increased susceptibility to aurora kinase inhibitors, and the SCLC-P subtype is particularly vulnerable to PARPi (independent of SLFN11 expression) and antimetabolites. Each subtype is also associated with unique protein expression patterns, which could serve as drug targets and predictive biomarkers. For example, delta-like ligand 3, an inhibitory Notch ligand, is highly expressed in SCLC-A tumors and virtually unexpressed in SCLC-P and SCLC-I tumors. SLFN11 is also most differentially expressed in the SCLC-A subtype, and, thus, SLFN11 could serve as a secondary biomarker for platinum and PARPi response in patients with SCLC-A. In contrast, the SCLC-N subtype highly expresses a surface protein called SSTR2 (somatostatin receptor 2), which is a well-recognized target of somatostatin analogs such as octreotide, warranting further study in this subtype. SCLC-I cells have high expression of Bruton tyrosine kinase, and these cells are most sensitive to the Bruton tyrosine kinase inhibitor ibrutinib. These findings pave the way for potential biomarker-driven clinical trials and possible basket trials to study each SCLC subtype with its matched therapeutic drug (see an illustrative schema in a recent editorial article by Frese and colleagues[55]).

SCLC-I Subtype Predicts Response to Immunotherapy

Gay and colleagues[52] reported that the SCLC-I subtype responded best to immune checkpoint blockade. This was further demonstrated in the retrospective analyses of IMpower133 data, in which PD-L1 or tumor mutational burden status was not shown to have predictive value for atezolizumab.[9] Comparing IMpower133 survival data between EP plus atezolizumab and EP plus placebo arms stratified by subtype, median OS in patients with the SCLC-I subtype trended higher in the atezolizumab arm (18 months vs. 10 months; HR, 0.572; 95% CI, 0.284–1.15). As

expected, a noteworthy OS benefit was seen for SCLC-I relative to all other tumors in the EP plus atezolizumab arm, but not in the EP plus placebo arm (HR, 0.566; 95% CI, 0.321–0.998). Although many patients with SCLC-I disease had high PD-L1 expression, PD-L1 alone was not a surrogate for defining SCLC-I. SCLC-I tumors, compared with other subtypes, had higher expression of many immune checkpoint molecules such as CD80 and CD86, which encode the ligands that bind to CTLA-4 and other targetable immune checkpoints such as CD38, TIGIT, ICOS, and ALG3.[52] Identification of the SCLC-I subtype is a strong candidate biomarker for benefit from immune checkpoint blockade in SCLC.

Future Directions and Challenges

Lack of SCLC preclinical models and limited patient tumor samples have been a major challenge for the acceleration of personalized therapy in SCLC. The development and use of circulating tumor cell–derived xenografts,[56] in addition to patient-derived xenografts and cell lines, have greatly enhanced research in SCLC. However, intratumoral heterogeneity of SCLC identified in recent studies[52,54] suggests that a repeat biopsy at the time of relapse or progression may be necessary to guide further treatment, although this is not feasible at present. Longitudinal monitoring of SCLC circulating tumor cells and circulating tumor DNA assays could be a potential solution to this prevailing problem. Moreover, defining four major subtypes of SCLC with its unique therapeutic vulnerability provides the potential for biomarker-enriched basket trials.

RADIATION IN SMALL CELL LUNG CANCER

Radiation therapy has historically played an important role in all stages of SCLC, even having a definitional role in separating LS- and ES-SCLC dating back to the Veterans Administration Lung Study Group classification from 1957.[57] Both this definition and the use of radiation therapy in SCLC have continued to evolve over time, but radiation therapy remains an important treatment modality in this disease.

Limited Stage

LS-SCLC is typically treated definitively with surgery and adjuvant chemotherapy, sequential radiation therapy and chemotherapy, or chemoradiation.[58] Surgery has not been standard for most LS-SCLC based on historical data demonstrating inferior OS compared with definitive radiation therapy[59]; however, National Cancer Database data show that in the modern era, surgical utilization has increased,[60] and lobectomy with mediastinal nodal dissection/sampling is recommended by the National Comprehensive Cancer Network in cT1-2N0M0 SCLC.[60] Current American Society for Radiation Oncology and ASCO guidelines recommend adjuvant radiation therapy only in cases of subtotal resection or pathologic N2 involvement.[61] Stereotactic body radiation therapy is similarly increasing in utilization for stage I to II node-negative patients who are not surgical candidates, and retrospective data appear to indicate this treatment is well-tolerated, with clinical outcomes comparable to surgical resection.[62] As with surgery, adjuvant systemic therapy remains necessary following stereotactic body radiation therapy if the patient has adequate performance status.

Most patients with LS-SCLC are not surgical or stereotactic body radiation therapy candidates,[63] and these patients will ideally undergo treatment with definitive concurrent chemoradiation. Multiple historic meta-analyses have demonstrated that the addition of radiation therapy is associated with improved OS compared with chemotherapy alone in this population,[64,65] and since the late 1980s, multiple large clinical trials have sought to optimize the chemoradiation treatment paradigm. The Intergroup 0096 trial established the current standard of care of 45 Gy delivered in 1.5 Gy twice-a-day fractions, with at least a 6-hour interfraction interval to allow for normal tissue repair, by demonstrating superior 5-year OS compared with 45 Gy given daily (9.1% vs. 3.7%).[66] This standard was re-evaluated against dose-escalated daily chemoradiation to 66 Gy in the phase III randomized superiority CONVERT trial, which showed comparable median survival (30 months vs. 25 months) and 2-year OS (56% vs. 51%) between the control and experimental arms, but was not adequately powered to show equivalence.[67] The now-closed CALGB 30610/RTOG 0538 study is similarly comparing 45 Gy two times a day against 70 Gy given daily (a third 61.2 Gy concomitant boost arm closed early based on toxicity analysis), which shows similar toxicity but has not yet published survival outcomes.[68] One additional recently published phase II trial showed promising results with dose-escalated twice-daily radiation to 60 Gy, demonstrating a noteworthy 2-year OS benefit compared with standard-of-care 45 Gy twice-a-day treatment (74.2% vs. 48.1%).[69]

Timing of radiation relative to chemotherapy (i.e., concurrent early start, concurrent late start, or sequential) has also been subject to multiple phase III clinical trials, with mixed data regarding the effect on survival outcomes.[70-75] This has led to several meta-analyses, and, based on their combined results, there is a substantial 5-year OS advantage to "earlier or shorter" thoracic radiation therapy with planned chemotherapy compared with "later or longer" regimens, at the expense of increased acute toxicity.[76] Additionally, meta-analysis of multiple phase III trials has demonstrated that timing of first day of chemotherapy to last day of radiation therapy is another important consideration, with a "package" of 30 days or fewer associated with

improved 5-year OS, again at the expense of increased acute toxicity.[77]

Extensive Stage

Consolidation radiation therapy continues to play a role in select patients with ES-SCLC, typically those who have had good response to initial systemic therapy. Based on historic observation that ES-SCLC has high rates of thoracic relapse after systemic therapy alone, a prospective trial in the former Yugoslavia randomly assigned patients with complete distant response and partial or complete thoracic response from initial chemotherapy to receive either additional standard-dose chemotherapy (four cycles) or two cycles of concurrent hyperfractionated chemoradiation (54 Gy in 36 fractions of 1.5 Gy over 18 days) to residual thoracic disease followed by further chemotherapy (two cycles).[78] This trial demonstrated that consolidation chemoradiation was associated with improved median survival and 5-year OS (9.1% vs. 3.7%), with a trend toward improved local control. A more recent Dutch trial assessing lower dose consolidation radiation (30 Gy in 10 fractions) in patients with any response to four to six cycles of initial systemic therapy failed to show radiation therapy improved its primary endpoint of 1-year OS, but did show improved 6-month progression-free survival (24% vs. 7%), and secondary analysis revealed a 2-year OS benefit (13% vs. 3%).[79] The phase II RTOG 0937 study was designed to detect whether consolidation non-stereotactic body radiation therapy targeting all active sites of disease in oligometastatic patients (i.e., one to four extracranial metastases) in addition to prophylactic cranial irradiation would improve OS compared with prophylactic cranial irradiation alone. Although the trial's OS analysis was underpowered because of low event rate, consolidation radiation did not improve OS, but the 1-year rate of progression did favor consolidation (75% vs. 79.6%).[80]

Prophylactic Cranial Irradiation

Prophylactic cranial irradiation emerged in an era prior to routine brain imaging as part of the SCLC staging workup, and historical data are therefore difficult to extrapolate to the modern day. (The benefits of whole-brain radiation therapy for known metastases are outside the scope of this paper.) Meta-analyzed data from the 1960s through 1990s combining patients with LS- and ES-SCLC demonstrated a 3-year OS benefit associated with prophylactic cranial irradiation (20.7% vs. 15.3%) and continues to influence the recommendation for prophylactic cranial irradiation in patients with LS-SCLC.[81] A more recent European Organisation for Research and Treatment of Cancer phase III study that enrolled patients with ES-SCLC from 2001 to 2006 similarly demonstrated improvement in incidence of symptomatic brain metastases and 1-year OS (27.1% vs. 13.3%), but has been criticized for lacking any required enrollment brain imaging.[82] A follow-up Japanese study that did require absence of metastases on MRI prior to enrollment failed to confirm a survival benefit for prophylactic cranial irradiation to 25 Gy.[83] Hippocampal-sparing prophylactic cranial irradiation has been a topic of interest because of the known cognitive effects of whole-brain radiation therapy, but, unfortunately, recently published phase III data fail to confirm a reduction in cognitive decline.[84]

Current Frontiers

We anticipate the publication of survival outcomes from CALGB 30610/RTOG 0538, which will help to further define optimal radiation dose as part of chemoradiation in LS-SCLC. Additionally, ongoing clinical phase II/III trials are investigating the addition of immunotherapy to chemoradiation in LS-SCLC (NRG-LU005) and to consolidation radiation therapy in ES-SCLC (RAPTOR). Finally, although the results of RTOG 0937 failed to show a survival benefit from metastasis-directed consolidation radiation therapy in oligometastatic SCLC, the publication of the SABR-COMET trial, which demonstrated a histology-neutral OS benefit associated specifically with metastasis-directed stereotactic body radiation therapy, may indicate that further metastasis-directed biologically equivalent dose escalation holds therapeutic potential.[85]

CONCLUSION

Systemic therapy and radiation therapy remain the cornerstones of SCLC treatment, given the early metastatic potential of this aggressive malignancy. Despite the long history of failed attempts to improve outcomes for patients with SCLC, there are reasons to be optimistic about the future. The addition of immunotherapy to the treatment paradigm ushered the treatment of SCLC into the modern era. As our understanding of biologic subtypes and tumor heterogeneity deepens, new therapeutic targets and biomarkers for SCLC are being developed, which brings exciting possibilities of personalized therapy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review (CSR), 1975-2017. National Cancer Institute. https://seer.cancer.gov/csr/1975_2017/. Accessed March 13, 2021.
2. Nicholson AG, Chansky K, Crowley J, et al; Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11:300-311.
3. Davis S, Stanley KE, Yesner R, et al. Small-cell carcinoma of the lung--survival according to histologic subtype: a Veterans Administration Lung Group Study. Cancer. 1981;47:1863-1866.
4. Bernhardt EB, Jalal SI. Small cell lung cancer. Cancer Treat Res. 2016;170:301-322.
5. Rudin CM, Brambilla E, Faivre-Finn C, et al. Small-cell lung cancer. Nat Rev Dis Primers. 2021;7:3.
6. Puglisi M, Dolly S, Faria A, et al. Treatment options for small cell lung cancer - do we have more choice? Br J Cancer. 2010;102:629-638.
7. Horn L, Mansfield AS, Szczęsna A, et al; IMpower133 Study Group. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379:2220-2229.
8. Paz-Ares L, Dvorkin M, Chen Y, et al; CASPIAN investigators. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394:1929-1939.
9. Liu SV, Reck M, Mansfield AS, et al. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). J Clin Oncol. 2021;39:619-630.
10. Goldman JW, Dvorkin M, Chen Y, et al; CASPIAN investigators. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2021;22:51-65.
11. Rudin CM, Awad MM, Navarro A, et al; KEYNOTE-604 Investigators. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. J Clin Oncol. 2020;38:2369-2379.
12. Leal JF, Martínez-Díez M, García-Hernández V, et al. PM01183, a new DNA minor groove covalent binder with potent in vitro and in vivo anti-tumour activity. Br J Pharmacol. 2010;161:1099-1110.
13. Santamaría Nuñez G, Robles CM, Giraudon C, et al. Lurbinectedin specifically triggers the degradation of phosphorylated RNA polymerase II and the formation of DNA breaks in cancer cells. Mol Cancer Ther. 2016;15:2399-2412.
14. Belgiovine C, Bello E, Liguori M, et al. Lurbinectedin reduces tumour-associated macrophages and the inflammatory tumour microenvironment in preclinical models. Br J Cancer. 2017;117:628-638.
15. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol. 2020;21:645-654.
16. Jazz Pharmaceuticals and PharmaMar Announce Results of ATLANTIS Phase 3 Study Evaluating Zepzelca™ in Combination with Doxorubicin for Patients with Small Cell Lung Cancer Following One Prior Platinum-containing Line. https://investor.jazzpharma.com/news-releases/news-release-details/jazz-pharmaceuticals-and-pharmamar-announce-results-atlantis. Accessed December 3, 2020.
17. Ready NE, Ott PA, Hellmann MD, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: results from the CheckMate 032 randomized cohort. J Thorac Oncol. 2020;15:426-435.
18. Ready N, Farago AF, de Braud F, et al. Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. J Thorac Oncol. 2019;14:237-244.
19. Chung HC, Piha-Paul SA, Lopez-Martin J, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: results from the KEYNOTE-028 and KEYNOTE-158 studies. J Thorac Oncol. 2020;15:618-627.
20. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016;17:883-895.
21. Poirier JT, George J, Owonikoko TK, et al. New approaches to SCLC therapy: from the laboratory to the clinic. J Thorac Oncol. 2020;15:520-540.
22. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. Nature. 2015;524:47-53.
23. Peifer M, Fernández-Cuesta L, Sos ML, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet. 2012;44:1104-1110.
24. Sos ML, Dietlein F, Peifer M, et al. A framework for identification of actionable cancer genome dependencies in small cell lung cancer. Proc Natl Acad Sci USA. 2012;109:17034-17039.
25. Yokomizo A, Tindall DJ, Drabkin H, et al. PTEN/MMAC1 mutations identified in small cell, but not in non-small cell lung cancers. Oncogene. 1998;17:475-479.

26. Umemura S, Mimaki S, Makinoshima H, et al. Therapeutic priority of the PI3K/AKT/mTOR pathway in small cell lung cancers as revealed by a comprehensive genomic analysis. J Thorac Oncol. 2014;9:1324-1331.
27. Cardnell RJ, Feng Y, Mukherjee S, et al. Activation of the PI3K/mTOR pathway following PARP inhibition in small cell lung cancer. PLoS One. 2016;11:e0152584.
28. Park JS, Lee JS, Kim EY, et al. The frequency and impact of FGFR1 amplification on clinical outcomes in Korean patients with small cell lung cancer. Lung Cancer. 2015;88:325-331.
29. Schultheis AM, Bos M, Schmitz K, et al. Fibroblast growth factor receptor 1 (FGFR1) amplification is a potential therapeutic target in small-cell lung cancer. Mod Pathol. 2014;27:214-221.
30. Hook KE, Garza SJ, Lira ME, et al. An integrated genomic approach to identify predictive biomarkers of response to the aurora kinase inhibitor PF-03814735. Mol Cancer Ther. 2012;11:710-719.
31. Mollaoglu G, Guthrie MR, Böhm S, et al. MYC drives progression of small cell lung cancer to a variant neuroendocrine subtype with vulnerability to aurora kinase inhibition. Cancer Cell. 2017;31:270-285.
32. Cardnell RJ, Li L, Sen T, et al. Protein expression of TTF1 and cMYC define distinct molecular subgroups of small cell lung cancer with unique vulnerabilities to aurora kinase inhibition, DLL3 targeting, and other targeted therapies. Oncotarget. 2017;8:73419-73432.
33. Owonikoko TK, Niu H, Nackaerts K, et al; C14018 study investigators. Randomized phase II study of paclitaxel plus alisertib versus paclitaxel plus placebo as second-line therapy for SCLC: primary and correlative biomarker analyses. J Thorac Oncol. 2020;15:274-287.
34. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study. J Clin Oncol. 2017;35:3823-3829.
35. Chung HC, Ros W, Delord JP, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol. 2019;37:1470-1478.
36. Hellmann MD, Callahan MK, Awad MM, et al. Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer [published correction appears in *Cancer Cell*. 2019;35:329]. Cancer Cell. 2018;33:853-861.e4.
37. Byers LA, Wang J, Nilsson MB, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. Cancer Discov. 2012;2:798-811.
38. de Bono J, Ramanathan RK, Mina L, et al. Phase I, dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline *BRCA1/2* mutations and selected sporadic cancers. Cancer Discov. 2017;7:620-629.
39. Stewart CA, Tong P, Cardnell RJ, et al. Dynamic variations in epithelial-to-mesenchymal transition (EMT), ATM, and SLFN11 govern response to PARP inhibitors and cisplatin in small cell lung cancer. Oncotarget. 2017;8:28575-28587.
40. Zoppoli G, Regairaz M, Leo E, et al. Putative DNA/RNA helicase Schlafen-11 (SLFN11) sensitizes cancer cells to DNA-damaging agents. Proc Natl Acad Sci USA. 2012;109:15030-15035.
41. Lok BH, Gardner EE, Schneeberger VE, et al. PARP inhibitor activity correlates with SLFN11 expression and demonstrates synergy with temozolomide in small cell lung cancer. Clin Cancer Res. 2017;23:523-535.
42. Polley E, Kunkel M, Evans D, et al. Small cell lung cancer screen of oncology drugs, investigational agents, and gene and microRNA expression. J Natl Cancer Inst. 2016;108:djw122.
43. Pietanza MC, Waqar SN, Krug LM, et al. Randomized, double-blind, phase II study of temozolomide in combination with either veliparib or placebo in patients with relapsed-sensitive or refractory small-cell lung cancer. J Clin Oncol. 2018;36:2386-2394.
44. Jiao S, Xia W, Yamaguchi H, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res. 2017;23:3711-3720.
45. Parkes EE, Walker SM, Taggart LE, et al. Activation of STING-dependent innate immune signaling by S-phase-specific DNA damage in breast cancer. J Natl Cancer Inst. 2016;109:djw199.
46. Sen T, Rodriguez BL, Chen L, et al. Targeting DNA damage response promotes antitumor immunity through STING-mediated T-cell activation in small cell lung cancer. Cancer Discov. 2019;9:646-661.
47. Zhang B, Stewart CA, Gay CM, et al. Detection of DNA replication blocker SLFN11 in tumor tissue and circulating tumor cells to predict platinum and PARP inhibitors response in small cell lung cancer. Presented at: International Association for the Study of Lung Cancer 2021 Targeted Therapies of Lung Cancer Meeting. Virtual; 2021.
48. Nogales V, Reinhold WC, Varma S, et al. Epigenetic inactivation of the putative DNA/RNA helicase SLFN11 in human cancer confers resistance to platinum drugs. Oncotarget. 2016;7:3084-3097.
49. Gardner EE, Lok BH, Schneeberger VE, et al. Chemosensitive relapse in small cell lung cancer proceeds through an EZH2-SLFN11 axis. Cancer Cell. 2017;31:286-299.
50. Gazdar AF, Carney DN, Nau MM, et al. Characterization of variant subclasses of cell lines derived from small cell lung cancer having distinctive biochemical, morphological, and growth properties. Cancer Res. 1985;45:2924-2930.
51. Huang YH, Klingbeil O, He XY, et al. POU2F3 is a master regulator of a tuft cell-like variant of small cell lung cancer. Genes Dev. 2018;32:915-928.
52. Gay CM, Stewart CA, Park EM, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell. 2021;39:346-360.e7.

53. Pearsall SM, Humphrey S, Revill M, et al. The rare YAP1 subtype of SCLC revisited in a biobank of 39 circulating tumor cell patient derived explant models: a brief report. J Thorac Oncol. 2020;15:1836-1843.

54. Baine MK, Hsieh MS, Lai WV, et al. SCLC subtypes defined by ASCL1, NEUROD1, POU2F3, and YAP1: a comprehensive immunohistochemical and histopathologic characterization. J Thorac Oncol. 2020;15:1823-1835.

55. Frese KK, Simpson KL, Dive C. Small cell lung cancer enters the era of precision medicine. Cancer Cell. 2021;39:297-299.

56. Hodgkinson CL, Morrow CJ, Li Y, et al. Tumorigenicity and genetic profiling of circulating tumor cells in small-cell lung cancer. Nat Med. 2014;20:897-903.

57. Kalemkerian GP, Gadgeel SM. Modern staging of small cell lung cancer. J Natl Compr Canc Netw. 2013;11:99-104.

58. National Comprehensive Cancer Network. Small Cell Lung Cancer (Version 2.2021). https://www.nccn.org. Accessed February 16, 2021.

59. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. Lancet. 1973;2:63-65.

60. Stahl JM, Corso CD, Verma V, et al. Trends in stereotactic body radiation therapy for stage I small cell lung cancer. Lung Cancer. 2017;103:11-16.

61. Daly ME, Ismaila N, Decker RH, et al. Radiation therapy for small-cell lung cancer: ASCO guideline endorsement of an ASTRO guideline. J Clin Oncol. 2021;39:931-939.

62. Verma V, Simone CB II, Allen PK, et al. Multi-institutional experience of stereotactic ablative radiation therapy for stage I small cell lung cancer. Int J Radiat Oncol Biol Phys. 2017;97:362-371.

63. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol. 2006;24:4539-4544.

64. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med. 1992;327:1618-1624.

65. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol. 1992;10:890-895.

66. Turrisi AT III, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med. 1999;340:265-271.

67. Faivre-Finn C, Snee M, Ashcroft L, et al; CONVERT Study Team. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol. 2017;18:1116-1125.

68. Bogart J, Wang X, Masters G, et al. Interim toxicity analysis for patients with limited stage small cell lung cancer (LSCLC) treated on the experimental thoracic radiotherapy (TRT) arms of CALGB 30610 (Alliance) / RTOG 0538. Ann Oncol. 2019;30(Suppl 5):v710-v717.

69. Grønberg BH, Killingberg KT, Fløtten Ø, et al. High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial. Lancet Oncol. 2021;22:321-331.

70. Murray N, Coy P, Pater JL, et al; The National Cancer Institute of Canada Clinical Trials Group. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. J Clin Oncol. 1993;11:336-344.

71. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol. 2002;20:3054-3060.

72. Jeremic B, Shibamoto Y, Acimovic L, et al. Initial versus delayed accelerated hyperfractionated radiation therapy and concurrent chemotherapy in limited small-cell lung cancer: a randomized study. J Clin Oncol. 1997;15:893-900.

73. Perry MC, Herndon JE III, Eaton WL, et al. Thoracic radiation therapy added to chemotherapy for small-cell lung cancer: an update of Cancer and Leukemia Group B Study 8083. J Clin Oncol. 1998;16:2466-2467.

74. Spiro SG, James LE, Rudd RM, et al; London Lung Cancer Group. Early compared with late radiotherapy in combined modality treatment for limited disease small-cell lung cancer: a London Lung Cancer Group multicenter randomized clinical trial and meta-analysis. J Clin Oncol. 2006;24:3823-3830.

75. Sun JM, Ahn YC, Choi EK, et al. Phase III trial of concurrent thoracic radiotherapy with either first- or third-cycle chemotherapy for limited-disease small-cell lung cancer. Ann Oncol. 2013;24:2088-2092.

76. De Ruysscher D, Lueza B, Le Péchoux C, et al; RTT-SCLC Collaborative Group. Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis. Ann Oncol. 2016;27:1818-1828.

77. De Ruysscher D, Pijls-Johannesma M, Bentzen SM, et al. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. J Clin Oncol. 2006;24:1057-1063.

78. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. J Clin Oncol. 1999;17:2092-2099.

79. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet. 2015;385:36-42.

80. Gore EM, Hu C, Sun AY, et al. Randomized phase II study comparing prophylactic cranial irradiation alone to prophylactic cranial irradiation and consolidative extracranial irradiation for extensive-disease small cell lung cancer (ED SCLC): NRG Oncology RTOG 0937. J Thorac Oncol. 2017;12:1561-1570.

81. Aupérin A, Arriagada R, Pignon JP, et al; Prophylactic Cranial Irradiation Overview Collaborative Group. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. N Engl J Med. 1999;341:476-484.

82. Slotman B, Faivre-Finn C, Kramer G, et al; EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med. 2007;357:664-672.

83. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18:663-671.

84. Belderbos JSA, De Ruysscher DKM, De Jaeger K, et al. Phase 3 randomized trial of prophylactic cranial irradiation with or without hippocampus avoidance in SCLC (NCT01780675). J Thorac Oncol. Epub 2021 Feb 2.

85. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet. 2019;393:2051-2058.

Tyrosine Kinase Inhibitors, Antibody-Drug Conjugates, and Proteolysis-Targeting Chimeras: The Pharmacology of Cutting-Edge Lung Cancer Therapies

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overview

The number of therapeutic options available for patients with advanced non–small-cell lung cancer has been led by deeper understanding of molecular drivers, immune function, and fundamental biology. In this article, we describe the relevant clinical pharmacologic characteristics of three broad classes of existing and investigational treatments, with a focus on mechanisms of action, adverse event profiles, pharmacokinetic and pharmacodynamic properties, and known and predicted resistance pathways. Specifically, within the kinase inhibitor class, agents directed against the RET, MET, and KRAS pathways are reviewed. Additionally, the first antibody-drug conjugates that target HER2 and HER3 are in trials and will ideally be available for patients soon. Finally, proteolysis-targeting chimeras approach pathway inhibition through enzyme degradation rather than target inhibition and are a promising platform for new agents in non–small-cell lung cancer and across cancer types. Each of these classes requires knowledge of clinical pharmacologic principles in development and use to ensure patient care in clinics and trials is optimized and personalized, including dosing and scheduling strategies, potential drug interactions, use in special populations, and monitoring parameters. Ideally, oncologists will continue to have new agents available across the non–small-cell lung cancer treatment spectrum to offer to a patient group that, until relatively recently, had few options.

The rapid evolution of molecularly directed therapeutics in non–small-cell lung cancer (NSCLC), which was ushered in by EGFR inhibition, has continued to carve the disease into more distinct subtypes. Unlike some other cancers, where genetic and molecular biologic discoveries have led to more scientific and prognostic information than treatments, the diversity and number of agents available as a direct result of a deeper understanding of pathways have altered the field drastically. In addition to EGFR, ALK, ROS1, BRAF, and NTRK inhibitors, new small molecules targeting mesenchymal epithelial transition factor receptor (MET), rearranged during transfection (RET), and Kirsten rat sarcoma viral oncogene homolog (KRAS) have recently been approved or are poised to come to the clinic. Additionally, the first antibody-drug conjugates (ADCs) in NSCLC are in development, signaling the first potential approvals in the disease. Finally, a new construct that targets enzyme degradation as a therapeutic strategy, as opposed to direct or indirect inhibition, has entered trials and has broad potential across multiple cancer types. This article will review the clinical pharmacology of these new and promising treatments as they apply to patients with NSCLC.

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TYROSINE KINASE INHIBITORS

Tyrosine kinase inhibitors competitively inhibit the catalytic domain of a target enzyme, impeding the phosphorylation and downstream signaling that promote cell growth and survival.[1] Various gain-of-function alterations in transmembrane receptor tyrosine kinases precipitate oncogenesis by aberrant activation or overexpression. The number of unique and actionable molecular abnormalities occurring in NSCLC arguably now makes it the most personalized of cancers.[2] It is no longer sufficient to just rule out activating *EGFR* mutations and *ALK* translocations; broad-panel molecular testing is required across the treatment spectrum.[3] In 2020 and 2021, there were four approvals by the U.S. Food and Drug Administration (FDA), which added two new targets, MET and RET, as well as important advances in drugging the prevalent but impervious *KRAS* G12C mutations. A summary of relevant clinical pharmacologic properties of agents outlined here is provided in Table 1.

MET

MET has long been identified as a target in NSCLC, both as a primary driver and as a mediator of acquired resistance to other targeted therapies.[4] Binding of the ligand, hepatocyte growth factor, to MET leads to

PRACTICAL APPLICATIONS

- Drug development of novel agents in NSCLC continues to evolve based on disease subtype identification and new pharmaceutical approaches.
- Molecular alterations in NSCLC that drive cancer growth have led to multiple tyrosine kinase inhibitors with distinct pharmacologic properties.
- Use of small-molecule inhibitors requires knowledge of dosing strategies, drug and food interaction potential, and adverse event profiles to ensure patients are treated optimally.
- Although in use across other cancers, antibody-drug conjugates have not been approved in NSCLC and are showing promise in ongoing trials.
- A new construct of proteolysis-targeting chimeras may be the next wave of oral agents in NSCLC and other cancer types because of the flexibility and potency of the approach.

downstream activation of RAS/ERK/MAPK, PI3K/AKT, and STAT signaling pathways. There are multiple mechanisms by which MET signaling causes dysregulated cell growth, making it a challenge to both identify these alterations and develop effective therapeutics. Increased MET signaling may be mediated through either polysomy (duplication of chromosome 7) or amplification of the *MET* gene via regional duplication.[5,6] Amplification is typically measured via copy-number gains using fluorescence in situ hybridization for MET and CEP7, a centromere protein, with higher ratios of MET to CEP7 indicating increased activity. Such *MET* amplifications mediate resistance to EGFR-targeted therapy, seen in a recent series in 15% of patients experiencing disease progression with osimertinib.[7]

Another class of MET aberrations is the *MET* exon 14 skipping alterations, which are predictive of response to MET-targeted therapy. Here, aberrant splicing removes a juxtamembrane domain that contains the c-Cbl E3 ubiquitin ligase binding site.[8] Receptors that lack this binding site are unable to be tagged by ubiquitination for degradation, thereby leading to sustained overexpression and increased signaling.[9] Oncogenic *MET* exon 14 skipping alterations have been identified in 3% to 4% of patients with NSCLC and are more commonly seen in older patients (mean age > 70) and may be seen in former smokers.[10] Although there has been promising activity of multitarget kinases that inhibit MET, more specific inhibitors have been long awaited.[11-13]

Capmatinib (INCB28060) is a highly potent and selective MET inhibitor that blocks c-MET phosphorylation in lung cancer cell lines at half-maximal inhibitory concentration values of 0.3 to 0.7 nmol/L.[14] In the phase II GEOMETRY mono-1 trial, patients with *MET* exon 14 skipping alterations and various levels of copy-number gain were studied in the first-, second-, and third-line treatment settings.[15] Cohorts with copy-number gain ranging from fewer than four to nine were closed for futility. Optimal efficacy was seen in 28 newly diagnosed patients with *MET* exon 14 skipping alterations who had an objective response rate of 68% (95% CI, 48%–84%), with a median duration of response of 9.7 months.

Tepotinib (EMD1214063) is another specific MET inhibitor studied in the phase II VISION trial.[16] Similar to capmatinib, tepotinib has high potency, with a half-maximal inhibitory concentration ranging from 1.7 to 3 nmol/L.[17] Patients with up to two lines of prior therapy and either *MET* exon 14 skipping alterations or various levels of copy-number gain were included. Initial reports of efficacy in the population with *MET* exon 14 skipping alterations showed an objective response rate by independent review of 46% (95% CI, 36%–57%), with a median duration of 11.1 months.[16]

The two newly approved MET inhibitors have similar clinical pharmacologic profiles (Table 1). Capmatinib requires two tablets twice per day with or without food, whereas tepotinib dosing is two tablets daily with food; these formulation and pill burden differences would not be expected to considerably influence adherence. The common treatment-related adverse events, including fatigue, nausea, and edema as well as the rare but potentially serious interstitial lung disease and hepatotoxicity, are nearly identical. This corresponds to similar dose-reduction and dose-continuation rates seen in the clinical trials. In terms of drug-drug interactions, strong CYP3A4 inducers should be avoided with both agents. Of note, because tepotinib is a P-glycoprotein inhibitor, it has a clinically important interaction with dabigatran, in which coadministration increased dabigatran maximum serum concentration by 40% and area under the curve by 50%, and should be avoided.

RET

The *RET* proto-oncogene encodes a transmembrane receptor tyrosine kinase involved in numerous developmental pathways as well as multiple malignancies, including multiple endocrine neoplasia 2, papillary thyroid cancer, and NSCLC.[18] Binding of one of the family of glial cell line–derived neurotrophic factor ligands leads to downstream activation of MAPK, ERK, PI3K/AKT, and JNK signaling. RET fusion can be found in 1% to 3% of lung adenocarcinomas and are more common in female nonsmokers younger than age 60.[19,20] Although numerous multitarget kinase inhibitors have some RET inhibitory

TABLE 1. Clinical Pharmacologic Characteristics of Selected Tyrosine Kinase Inhibitors

Agent	Target	Dose and Regimen	Metabolism, Transport, and Concurrent Agent Concerns	Adverse Events (> 20%)	Dose Reduction/ Discontinuation Rate (%)	Other
Capmatinib	MET exon 14 skipping	400 mg twice daily with or without food	CYP3A4 and P-gp substrate; CYP1A2 inhibitor; avoid moderate and strong CYP3A inducers	Edema, nausea, fatigue, vomiting, dyspnea, decreased appetite; rare but serious: pneumonitis (4.5%), transaminitis (grade 3-4, 6%)	23/16	No effect of age (up to 90), weight (35-131 kg), or hepatic function on pharmacokinetics
Tepotinib	MET exon 14 skipping	450 mg twice daily with food	CYP3A4 and CYP2C8 substrate; P-gp inhibitor; avoid strong CYP3A inhibitors and inducers; avoid strong P-gp inhibitors and sensitive substrates with narrow therapeutic indices	Edema, fatigue, nausea, diarrhea, musculoskeletal pain, dyspnea; rare but serious: pneumonitis (2.2%), transaminitis (grade 3-4, 4.2%)	30/20	Coadministration with dabigatran (P-gp substrate) increased dabigatran C_{max} by 40% and AUC by 50%; avoid concurrent use
Selpercatinib	RET	160 mg daily if $\geq$ 50 kg; 120 mg if $<$ 50 kg	CYP3A4 and BCRP substrate; CYP2C8, P-gp, and BCRP inhibitor; avoid acid-reducing agents; avoid moderate and strong CYP3A inhibitors and inducers; avoid CYP2C8 and CYP3A substrates or adjust substrate dose per guidance	Dry mouth, diarrhea, constipation, nausea, abdominal pain, hypertension, fatigue, edema, rash, headache; rare but serious: transaminitis (grade 3-4, 8%), hemorrhage (grade 3-4, 2%)	31/5	Give with food if PPI cannot be stopped; give $\geq$ 2 hours before other antacids; no dose reduction for mild or moderate hepatic impairment; hold for at least 7 days before elective surgery and at least 2 weeks after major surgery and until adequate wound healing
Pralsetinib	RET	400 mg daily on empty stomach	CYP3A4 substrate; avoid strong CYP3A inhibitors and inducers	Fatigue, pyrexia, edema, constipation, diarrhea, musculoskeletal pain, hypertension, cough; rare but serious: pneumonitis (10%), transaminitis (grade 3-4, 5.4%), hemorrhage (grade 3-4, 2.5%)	36/15	No dose reduction for mild hepatic impairment; no effect of age (up to 87), weight (29.5-149 kg), or mild/moderate renal impairment on pharmacokinetics; hold for at least 5 days before elective surgery and at least 2 weeks after major surgery and until adequate wound healing
Sotorasib*	KRAS G12C	Recommended phase II dose, 960 mg daily	Not reported	Diarrhea, fatigue, nausea	NR/7	

NOTE. This is a summary of clinically relevant pharmacologic details; please see full prescribing information for dosing guidelines and precautions.
Abbreviations: AUC, area under the curve; Cmax, maximum serum concentration; NR, not reached; P-gp, P-glycoprotein; PPI, proton pump inhibitor.
*Data obtained from U.S. Food and Drug Administration prescribing information, with the exception of sotorasib, which was compiled from Hong et al.[32]

activity, none have been FDA approved to treat *RET*-rearranged NSCLC. Two RET-specific tyrosine kinase inhibitors, selpercatinib and pralsetinib, were approved in 2020 for *RET*-rearranged NSCLC and thyroid cancers.

In the LIBRETTO-001 trial, patients with advanced NSCLC and prior platinum therapy or disease in the first-line setting were treated with selpercatinib (LOXO-292). Selpercatinib is a highly potent and selective inhibitor that competes with ATP binding.[21] Among patients who received prior platinum-based chemotherapy, the objective response rate was 64% (95% CI, 54%–73%; 105 patients), with a median duration of 17.5 months.[22] A higher response rate was seen in patients treated in the first-line setting with selpercatinib (85%; 95% CI, 70%–94%; 39 patients). Preclinical studies showed high central nervous system penetration, and objective central nervous system response was seen in 10 of 11 patients with measurable disease.

Pralsetinib (BLU-667) received accelerated FDA approval based on the phase I/II ARROW data. In RET-driven cancer cell lines, half-maximal inhibitory concentration values ranged from 5 to 10 nmol/L.[23] Again, the NSCLC cohorts included patients previously treated with platinum chemotherapy as well as newly diagnosed patients; response rates were 57% (95% CI, 46%–68%; 87 patients) and 70% (95% CI, 50%–86%; 27 patients), respectively.[24] Duration of response was not reached in the pretreated group and was 9 months in the first-line therapy group.

There are some potentially clinically relevant pharmacologic differences between selpercatinib and pralsetinib (Table 1). Selpercatinib has weight-based dosing, with patients weighing less than 50 kg dosed at 120 mg twice daily (using 40- and 80-mg capsules per dose) and patients weighing more than 50 kg requiring 160 mg twice daily (two 80-mg capsules per dose). Concurrent use of selpercatinib with gastric acid–reducing agents should be avoided, although there are allowances to take with food if a proton pump inhibitor is needed or to precede other antacids by 2 hours. Pralsetinib dosing is four 100-mg capsules once daily, with no food intake for at least 2 hours before and at least 1 hour after the dose. Pralsetinib is a CYP3A4 substrate, whereas selpercatinib is a CYP3A4 and BCRP substrate as well as a CYP2C8, P-glycoprotein, and BCRP inhibitor, with attendant potential drug-drug interactions that should be avoided or require modified dosing. Both selective RET inhibitors have product information warnings about hepatotoxicity, hypertension, and hemorrhage, and both may impair wound healing and should be held perioperatively. Clinicians should note that dose reductions were relatively common, seen in nearly one-third of patients receiving either drug.

KRAS

Mutations in *KRAS* occur in approximately 30% of patients with lung adenocarcinoma and 5% of squamous cell carcinomas of the lung and are commonly seen in smokers.[25] In NSCLC and other affected solid tumors, *KRAS* mutations are associated with poor prognosis. Moreover, there are a variety of different *KRAS* mutations; in lung cancer, the most common are G12C, G12V, and G12D, followed by other G12 and G13 mutations. Despite decades of effort, the molecular mechanism of RAS signaling has impeded targeted inhibition. The transmembrane KRAS receptor tyrosine kinase functions as a switch, cycling from an active GTP-bound state to an inactive GDP-bound state.[26] Mutations that impair the GTPase function increase the proportion of active GTP-bound RAS, leading to oncogenesis.[27] Fortunately, in *KRAS* G12C mutations, the mutant cytosine is physically located near the nucleotide pocket and switch regions, enabling the development of allosteric small-molecule inhbitors.[28] Interestingly, some GTPase activity is required for actively cycling between the two conformations to allow KRAS G12C inhibitors to trap the kinase in an inactive state.[29,30]

Given this large clinical unmet need, there is a great deal of excitement surrounding the clinical development of KRAS G12C inhibitors. In the phase I CodeBreak trial, sotorasib (AMG510) was studied in patients with NSCLC, colorectal cancer, and other solid tumors. In preclinical cell line studies, sotorasib was highly potent, with half-maximal inhibitory concentration values ranging from 9 to 30 nmol/L, effectively inhibiting downstream signaling.[31] Focusing on the lung cohort in which patients had prior platinum-based chemotherapy and/or targeted therapy, an objective response was seen in 32% (19 patients), with a disease control rate of 88.1% (52 patients) and median progression-free survival of 6.3 months.[32] Although the rate of complete or partial response with sotorasib is lower than that with other tyrosine kinase inhibitors in lung cancer, this represents a huge step forward for these patients. An ongoing clinical trial is investigating combination therapy options (NCT04185883), and there is a phase III trial comparing AMG510 with docetaxel for salvage therapy (NCT04303780). Additionally, other KRAS G12C–specific agents in the pipeline include JNJ-74699157/ARS-3284 and MRTX849, and there are ongoing efforts to develop therapy for non-G12C mutant *KRAS* tumors.

Multiple mechanisms of acquired resistance to these and other tyrosine kinase inhibitors in lung cancer have been identified and can be broadly categorized into either within the kinase itself or via activation of alternative pathways. Clinical data regarding acquired resistance to MET and RET inhibitors are awaited after the recent approval of these agents. Capmatinib-resistant NSCLC cell lines showed activation of EGFR signaling as well as PI3K upregulation.[33] In a small study of 18 patients treated with either selpercatinib or pralsetinib, two cases of acquired *RET* G810 mutations,

three cases of *MET* amplification, and one *KRAS* mutation were seen.[34] Resistance to KRAS G12C inhibition potentially looms large, as laboratory data suggest adaptive resistance mechanisms, including increased target production and activation of escape pathways, may occur early after exposure.[35] These data are concerning for lower response durations and support rapid development of combinations with KRAS G12C inhibition to mitigate resistance and extend disease benefit periods.

ANTIBODY-DRUG CONJUGATES

Antibody-drug conjugates combine the specificity of a monoclonal antibody with traditional cytotoxic chemotherapy. The use of precise immune localization significantly increases the therapeutic window by limiting systemic toxicity. Choices of antibody target, linker compound, and payload are critical in determining the safety and efficacy of ADCs. Ideal antigen targets are more highly expressed on tumor than normal tissues, are cell surface antigens, and are often internalized.[36] Advances in antibody development, from first-generation murine to second-generation chimeric/humanized antibodies and now to third-generation fully human monoclonal antibodies, limit immunogenicity and subsequent antidrug antibody development. Despite excellent specificity, bystander killing of adjacent cells without the target antigen can occur via either release of the cytotoxin into the extracellular space directly or internalization and then subsequent release of the drug from the cell membrane.[37] It is important to note that the bystander killing effect may be beneficial, such as in cases where antigen expression is low or lost.

The linkers in ADCs play a key role in determining the release properties of the payload. Noncleavable linkers have stable bonds and require internalization where the monoclonal antibody is degraded in the lysosome, releasing the cytotoxic payload intracellularly.[38] Cleavable linkers that are peptide based and sensitive to specific proteases are the most common, but acid-labile and glutathione-sensitive disulfide linkers are also used.[36] Cytotoxic payloads should be stably bound to the linker and optimally have long half-lives, subnanomolar potency, and low immunogenicity. There are two main categories of payloads: microtubule-disrupting agents and DNA-damaging agents. FDA-approved ADCs with microtubule disruptors include MMAE, an auristatin derivative used in brentuximab vedotin targeting CD30, and DM1, a maytansine derivative used in ado-traztuzumab emtansine targeting HER2.[39,40]

In lung cancer, there are no FDA-approved ADCs, but there are promising ADCs in clinical development that target members of the ErbB family of receptors. *HER2* mutations in the tyrosine kinase domain are seen in 2% to 4% of patients with NSCLC, more often in women and never-smokers. Unlike the more common HER2 protein overexpression or *HER2* gene amplification, mutations seem to be more sensitive to targeted treatments.[41] Per National Comprehensive Cancer Network guidelines, ado-traztuzumab emtansine can be considered for off-label NSCLC salvage therapy. In a small trial, treatment with ado-traztuzumab emtansine resulted in an objective response rate of 44% (95% CI, 22%–66%; 18 patients), with a median duration of response of 4 months.[42] Responses were seen in *HER2* exon 20 insertions and point mutations in the kinase, transmembrane, and extracellular domains and were not associated with HER2 expression by immunohistochemistry. Treatment was well tolerated, with one grade 3 adverse event (anemia) and elevated transaminases, nausea, and thrombocytopenia the most common (> 30%) grade 1 to 2 adverse events.

Trastuzumab deruxtecan (DS-8201a) is a novel ADC-targeting HER2 with a tetrapeptide-based cleavable linker and a topoisomerase I inhibitor payload.[43] Results from a cohort of patients with refractory lung adenocarcinoma and *HER2* mutations treated with salvage trastuzumab deruxtecan were recently reported from the DestinyLung01 phase II trial.[44] The objective response rate by independent central review was 61.9% (95% CI, 45.6%–76.4%; 26 patients), with a disease control rate of 90.5%. Median progression-free survival was 14 months (95% CI, 6.4–14), and duration of response was not reached. Treatment-emergent grade 3 or higher adverse events were seen in 52.4% of patients. Fatigue and nausea led to dose reductions in 11.9% and 9.5% of patients, and neutropenia and lung infection led to dose interruptions in 19.0% and 7.1%, respectively. Ongoing cohorts include patients with HER2 expression (NCT03505710).

Targeting HER3 in patients with *EGFR*-mutant NSCLC is also under active investigation. Patritumab deruxtecan (U3-1402) combines an HER3-targeting antibody with the exactan derivative topoisomerase I inhibitor payload and showed dose-dependent antitumor activity in xenograft models with HER3 expression.[45] In *EGFR*-mutant NSCLC cells with acquired resistance to the EGFR tyrosine kinase inhibitors gefitinib and osimertinib, U3-1402 showed potent antitumor activity; osimertinib-resistant models had nine times greater HER3 surface expression compared with nonosimertinib-resistant cell lines.[46] In a phase I trial including 57 patients treated with U3-1402 at 5.6 mg/kg, the objective response rate was 25% (95% CI, 14.4%–38.4%), and the disease control rate was 70% (95% CI, 55.9%–81.2%).[47] Thrombocytopenia and neutropenia were the most common grade 3 or higher treatment-emergent adverse events at 25% and 16%, respectively. There is currently a phase II trial of patritumab deruxtecan ongoing in patients with *EGFR*-mutant NSCLC refractory to osimertinib and platinum combination chemotherapy (NCT04619004).

Mechanisms of acquired resistance to ADCs have largely been studied in vitro and likely apply across agents regardless of disease or target.[48] First, tumor cells may downregulate target antigen expression. This has been shown in breast cancer cell lines that reduce HER2 expression when treated long term with TDM-1.[49,50] Intracellular processing may be modified, such as raising the pH inside lysosomes, thereby impairing the necessary proteolytic degradation of the ADC complex.[51,52] Lastly, various ATP-binding cassette transporters, also known as drug efflux pumps, may be upregulated to remove the payload from the cytosol. Acquired resistance was shown in breast cancer cell lines upregulating MDR1 and was abrogated with an MDR1 inhibitor.[53] Similar increases in drug efflux pumps have been seen in in vitro models after treatment with gemtuzumab ozogamicin and brentuximab vedotin.[54,55]

PROTEOLYSIS-TARGETING CHIMERAS

Proteolysis-targeting chimeras represent a novel method of reducing kinase function by promoting degradation of the enzyme rather than inhibition, as is the case with tyrosine kinase inhibitors and ADCs. This technology has been under development for 20 years.[56] During normal proteasome degradation, an E3 ubiquitin ligase binds to a target protein. An associated E2-conjugating enzyme carrying ubiquitin transfers the ubiquitin to an accessible lysine residue on the target protein, thereby labeling it for the 26S proteasome.[57] Proteolysis-targeting chimeras are orally delivered large molecular weight engineered molecules that contain three components: a ligand that binds an E3 ubiquitin ligase, a linker protein, and another ligand that binds the target protein of interest.[58] Potential challenges to drug delivery include potential needs to develop novel pharmacokinetic and pharmacodynamic evaluation systems because of the catalytic nature of proteolysis-targeting chimeras, rapid screens for target protein ligands, and prediction of potential off-target effects.[59] Initially this method of coopting proteasome degradation was studied using more accessible intracellular targets. More recently, effective proteolysis-targeting chimeras targeting *EGFR*-mutant cells have been developed using gefitinib or afatinib to bind the mutant EGFR receptor (protein of interest) and couple it to von Hippel-Lindau (an E3 ligase).[60] The authors note this approach led to enhanced inhibition of cell proliferation and downstream signaling reduction compared with tyrosine kinase inhibitors.

This methodology has reached clinical trials for solid tumors. ARV110 is a proteolysis-targeting chimera targeting the androgen receptor that is being studied on a once or twice daily continuous schedule in patients with metastatic castration-resistant prostate cancer (NCT03888612). A phase I clinical trial is also under way using ARV-471, a proteolysis-targeting chimera targeting the estrogen receptor in patients with estrogen receptor–positive/HER2-negative advanced or metastatic breast cancer either alone or in combination with palbociclib (NCT04072952). Although there are currently no lung cancer–specific proteolysis-targeting chimeras in clinical trials, the potential flexibility and potency of this technology have broad implications for anticancer treatment.

CONCLUSION

Additional agents with established and emerging mechanisms of action and targets will continue to be developed in NSCLC, which is rapidly becoming the most heterogeneous cancer for therapeutics. Relevant clinical pharmacologic information is critical to their use to ensure therapies are chosen wisely, adverse events are predicted and managed, and patient benefit is maximized based on goals. The influx of new treatments is not likely to subside soon; considering that many had deemed the GTP-bound KRAS an undruggable target, new thinking and advances across molecular biology, pharmacology, pharmaceutics, and other aspects of drug development can and will lead to better therapies in the clinic. As an example, if medicinal chemistry, formulation, and production hurdles can be successfully navigated, the promise of proteolysis-targeting chimeras may be substantial in NSCLC and across many other cancer types. These discoveries and novel approaches will continue to be welcomed for a group of patients who, not too long ago, had limited options.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Hartmann JT, Haap M, Kopp HG, et al. Tyrosine kinase inhibitors: a review on pharmacology, metabolism and side effects. Curr Drug Metab. 2009;10:470-481.
2. National Comprehensive Cancer Network. NCCN guidelines (version 3.2020): non-small cell lung cancer. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1462. Accessed February 4, 2021.
3. Imyanitov EN, Iyevleva AG, Levchenko EV. Molecular testing and targeted therapy for non-small cell lung cancer: Current status and perspectives. Crit Rev Oncol Hematol. 2021;157:103194.
4. Drilon A, Cappuzzo F, Ou SI, et al. Targeting MET in lung cancer: will expectations finally be MET? J Thorac Oncol. 2017;12:15-26.
5. Albertson DG, Collins C, McCormick F, et al. Chromosome aberrations in solid tumors. Nat Genet. 2003;34:369-376.
6. Hellman A, Zlotorynski E, Scherer SW, et al. A role for common fragile site induction in amplification of human oncogenes. Cancer Cell. 2002;1:89-97.
7. Leonetti A, Sharma S, Minari R, et al. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. Br J Cancer. 2019;121:725-737.
8. Onozato R, Kosaka T, Kuwano H, et al. Activation of MET by gene amplification or by splice mutations deleting the juxtamembrane domain in primary resected lung cancers. J Thorac Oncol. 2009;4:5-11.
9. Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of met in lung cancer. Cancer Res. 2006;66:283-289.
10. Awad MM, Oxnard GR, Jackman DM, et al. MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and c-Met overexpression. J Clin Oncol. 2016;34:721-730.
11. Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. Cancer Discov. 2015;5:842-849.
12. Drilon A, Clark JW, Weiss J, et al. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. Nat Med. 2020;26:47-51.
13. Jorge SE, Schulman S, Freed JA, et al. Responses to the multitargeted MET/ALK/ROS1 inhibitor crizotinib and co-occurring mutations in lung adenocarcinomas with MET amplification or MET exon 14 skipping mutation. Lung Cancer. 2015;90:369-374.
14. Liu X, Wang Q, Yang G, et al. A novel kinase inhibitor, INCB28060, blocks c-MET-dependent signaling, neoplastic activities, and cross-talk with EGFR and HER-3. Clin Cancer Res. 2011;17:7127-7138.
15. Wolf J, Seto T, Han JY, et al; GEOMETRY mono-1 Investigators. Capmatinib in *MET* exon 14-mutated or *MET*-amplified non-small-cell lung cancer. N Engl J Med. 2020;383:944-957.
16. Paik PK, Felip E, Veillon R, et al. Tepotinib in non-small-cell lung cancer with *MET* exon 14 skipping mutations. N Engl J Med. 2020;383:931-943.
17. Bladt F, Faden B, Friese-Hamim M, et al. EMD 1214063 and EMD 1204831 constitute a new class of potent and highly selective c-Met inhibitors. Clin Cancer Res. 2013;19:2941-2951.
18. Li AY, McCusker MG, Russo A, et al. RET fusions in solid tumors. Cancer Treat Rev. 2019;81:101911.
19. Kohno T, Ichikawa H, Totoki Y, et al. KIF5B-RET fusions in lung adenocarcinoma. Nat Med. 2012;18:375-377.
20. Lin C, Wang S, Xie W, et al. The RET fusion gene and its correlation with demographic and clinicopathological features of non-small cell lung cancer: a meta-analysis. Cancer Biol Ther. 2015;16:1019-1028.
21. Subbiah V, Velcheti V, Tuch BB, et al. Selective RET kinase inhibition for patients with RET-altered cancers. Ann Oncol. 2018;29:1869-1876.
22. Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of selpercatinib in *RET* fusion-positive non-small-cell lung cancer. N Engl J Med. 2020;383:813-824.
23. Subbiah V, Gainor JF, Rahal R, et al. Precision targeted therapy with BLU-667 for *RET*-driven cancers. Cancer Discov. 2018;8:836-849.
24. US Food and Drug Administration. GAVRETO (pralsetinib) capsules for oral use package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213721s000lbl.pdf. Accessed February 11, 2021.
25. Karachaliou N, Mayo C, Costa C, et al. KRAS mutations in lung cancer. Clin Lung Cancer. 2013;14:205-214.
26. Simanshu DK, Nissley DV, McCormick F. RAS proteins and their regulators in human disease. Cell. 2017;170:17-33.
27. Gibbs JB, Sigal IS, Poe M, et al. Intrinsic GTPase activity distinguishes normal and oncogenic ras p21 molecules. Proc Natl Acad Sci USA. 1984;81:5704-5708.
28. Ostrem JM, Peters U, Sos ML, et al. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. Nature. 2013;503:548-551.
29. Lito P, Solomon M, Li LS, et al. Allele-specific inhibitors inactivate mutant KRAS G12C by a trapping mechanism. Science. 2016;351:604-608.
30. Janes MR, Zhang J, Li LS, et al. Targeting KRAS mutant cancers with a covalent G12C-specific inhibitor. Cell. 2018;172:578-589.e17.
31. Canon J, Rex K, Saiki AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature. 2019;575:217-223.
32. Hong DS, Fakih MG, Strickler JH, et al. $KRAS^{G12C}$ inhibition with sotorasib in advanced solid tumors. N Engl J Med. 2020;383:1207-1217.
33. Kim S, Kim TM, Kim DW, et al. Acquired resistance of MET-amplified non-small cell lung cancer cells to the MET inhibitor capmatinib. Cancer Res Treat. 2019;51:951-962.
34. Lin JJ, Liu SV, McCoach CE, et al. Mechanisms of resistance to selective RET tyrosine kinase inhibitors in RET fusion-positive non-small-cell lung cancer. Ann Oncol. 2020;31:1725-1733.
35. Hata AN, Shaw AT. Resistance looms for $KRAS^{G12C}$ inhibitors. Nat Med. 2020;26:169-170.
36. Khongorzul P, Ling CJ, Khan FU, et al. Antibody-drug conjugates: a comprehensive review. Mol Cancer Res. 2020;18:3-19.

37. Staudacher AH, Brown MP. Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required? Br J Cancer. 2017;117:1736-1742.
38. Ducry L, Stump B. Antibody-drug conjugates: linking cytotoxic payloads to monoclonal antibodies. Bioconjug Chem. 2010;21:5-13.
39. Verma S, Miles D, Gianni L, et al; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783-1791.
40. van de Donk NW, Dhimolea E. Brentuximab vedotin. MAbs. 2012;4:458-465.
41. Zhao J, Xia Y. Targeting HER2 alterations in non–small-cell lung cancer: a comprehensive review. JCO Precis Oncol. 2020;4:411-425.
42. Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine for patients with HER2-mutant lung cancers: results from a phase II basket trial [published correction appears in *J Clin Oncol*. 2019;37:362]. J Clin Oncol. 2018;36:2532-2537.
43. Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. Clin Cancer Res. 2016;22:5097-5108.
44. Smit EF, Nakagawa K, Nagasaka M, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer (NSCLC): interim results of DESTINY-Lung01. J Clin Oncol. 2020;38 (suppl; abstr 9504).
45. Hashimoto Y, Koyama K, Kamai Y, et al. A novel HER3-targeting antibody-drug conjugate, U3-1402, exhibits potent therapeutic efficacy through the delivery of cytotoxic payload by efficient internalization. Clin Cancer Res. 2019;25:7151-7161.
46. Yonesaka K, Takegawa N, Watanabe S, et al. An HER3-targeting antibody-drug conjugate incorporating a DNA topoisomerase I inhibitor U3-1402 conquers EGFR tyrosine kinase inhibitor-resistant NSCLC. Oncogene. 2019;38:1398-1409.
47. Yu HA, Baik CS, Gold K, et al. Efficacy and safety of patritumab deruxtecan (U3-1402), a novel HER3 directed antibody drug conjugate, in patients with EGFR-mutated NSCLC. Ann Oncol. 2020;31(suppl 4):S1189-S1190.
48. Drago JZ, Modi S, Chandarlapaty S. Unlocking the potential of antibody-drug conjugates for cancer therapy. Nat Rev Clin Oncol. Epub 2021 Feb 8.
49. Loganzo F, Tan X, Sung M, et al. Tumor cells chronically treated with a trastuzumab-maytansinoid antibody-drug conjugate develop varied resistance mechanisms but respond to alternate treatments. Mol Cancer Ther. 2015;14:952-963.
50. Sung M, Tan X, Lu B, et al. Caveolae-mediated endocytosis as a novel mechanism of resistance to trastuzumab emtansine (T-DM1). Mol Cancer Ther. 2018; 17:243-253.
51. Wang H, Wang W, Xu Y, et al. Aberrant intracellular metabolism of T-DM1 confers T-DM1 resistance in human epidermal growth factor receptor 2-positive gastric cancer cells. Cancer Sci. 2017;108:1458-1468.
52. Ríos-Luci C, García-Alonso S, Díaz-Rodríguez E, et al. Resistance to the antibody-drug conjugate T-DM1 is based in a reduction in lysosomal proteolytic activity. Cancer Res. 2017;77:4639-4651.
53. Li G, Guo J, Shen BQ, et al. Mechanisms of acquired resistance to trastuzumab emtansine in breast cancer cells. Mol Cancer Ther. 2018;17:1441-1453.
54. Chen R, Hou J, Newman E, et al. CD30 downregulation, MMAE resistance, and MDR1 upregulation are all associated with resistance to brentuximab vedotin. Mol Cancer Ther. 2015;14:1376-1384.
55. Walter RB, Gooley TA, van der Velden VH, et al. CD33 expression and P-glycoprotein-mediated drug efflux inversely correlate and predict clinical outcome in patients with acute myeloid leukemia treated with gemtuzumab ozogamicin monotherapy. Blood. 2007;109:4168-4170.
56. Sakamoto KM, Kim KB, Kumagai A, et al. Protacs: chimeric molecules that target proteins to the Skp1-Cullin-F box complex for ubiquitination and degradation. Proc Natl Acad Sci USA. 2001;98:8554-8559.
57. Ciechanover A. Proteolysis: from the lysosome to ubiquitin and the proteasome. Nat Rev Mol Cell Biol. 2005;6:79-87.
58. Schneekloth AR, Pucheault M, Tae HS, et al. Targeted intracellular protein degradation induced by a small molecule: En route to chemical proteomics. Bioorg Med Chem Lett. 2008;18:5904-5908.
59. Gao H, Sun X, Rao Y. PROTAC technology: opportunities and challenges. ACS Med Chem Lett. 2020;11:237-240.
60. Burslem GM, Smith BE, Lai AC, et al. The advantages of targeted protein degradation over inhibition: an RTK case study. Cell Chem Biol. 2018;25:67-77.e3.

MELANOMA/SKIN CANCERS

Current Challenges in Access to Melanoma Care: A Multidisciplinary Perspective

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overview

A diagnosis of melanoma requires multidisciplinary specialized care across all stages of disease. Although many important advances have been made for the treatment of melanoma for local and advanced disease, barriers to optimal care remain for many patients who live in areas without ready access to the expertise of a specialized melanoma center. In this article, we review some of the recent advances in the treatment of melanoma and the persistent challenges around the world that prevent the delivery of the best standard of care to patients living in the community. With the therapeutic landscape continuing to evolve and newer more complex drug therapies soon to be approved, it is important to recognize the many challenges that patients face and attempt to identify tools and policies that will help to improve treatment outcomes for their melanoma.

INTRODUCTION

In recent years, the mortality related to many cancer types has decreased in the United States, in no small measure as the result of a better understanding of the molecular underpinnings of disease, therapeutic targeting of driver mutations, and improved prevention and early detection strategies.[1,2] Perhaps in no malignancy has this been more obvious than in cutaneous melanoma, where the identification and therapeutic manipulation of *BRAF V600* mutations and immune checkpoints in melanomagenesis have led to a substantial reduction in mortality after decades of a contrary trend. Approximately 7,000 deaths from melanoma are predicted in the United States in 2021, which is a decrease of nearly 30% compared with the peak prediction of around 10,000 melanoma deaths in 2016.[1] It is now commonplace to discuss durable disease control and potentially even cure as a worthwhile goal for patients with metastatic melanoma, something that was distinctly uncommon a decade ago. These gains in metastatic melanoma have systematically translated into improvements in adjuvant and neoadjuvant multimodal management for all stages of the disease. Similarly, improved surgical staging with sentinel node (SN) biopsy for early-stage melanoma, as well as the recognition that most patients with primary melanoma found to be SN positive now do not require a therapeutic node dissection with its associated risk of morbidity, have overturned the traditional surgical paradigm of cancer management.

Despite these advances, much work remains to be done. The dominant clinical questions that arise in the melanoma clinic today are summarized below:

1. What is the optimal first-line therapy for metastatic melanoma regardless of molecular profile?
2. How should we treat disease progression upon failure of an anti–PD-1–based regimen, in the metastatic or adjuvant setting?
3. Should patients with macroscopic nodal relapse while on adjuvant therapy for SN-positive disease receive a second (and perhaps different) course of adjuvant treatment after therapeutic node dissection or possibly a different "neoadjuvant" regimen prior to planned therapeutic node dissection?

Although seemingly simple, these questions demonstrate the important challenges that still exist in achieving the optimal, and perhaps most equitable, management of these patients. Limited access to subspecialty melanoma expertise, disparities in clinical trial enrollment, variable management of immune-related adverse events, conundrums of care at academic versus community oncology centers, and financial implications for therapeutic success (who pays, how much, and for how long?) are all pressing issues that we should prioritize as we strive to improve the care of patients with melanoma worldwide.

The 2010 U.S. Census indicated that approximately 17% of the U.S. population lived within a geographic area designated as rural or remote. Within rural America, the corresponding number of physicians and registered nurses remains disproportionately low, at 9% and 16%, respectively. In Australia, data collected by the Australian Bureau of Statistics in 2017 indicated that 29% of the population lived in a remote or rural area; in these areas, medical and nursing services are likewise sparse. In the 2020 Rural Healthy People

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PRACTICAL APPLICATIONS

- The optimal management of melanoma has increasingly become multidisciplinary with expertise required in lymph node scintigraphy for accurate staging, which in turn determines the need for adjuvant therapy.
- Patients living in rural or remote geographic areas are less likely to undergo sentinel lymph node biopsy. Older age and lower socioeconomic status are likely contributing factors.
- Adoptive cellular therapy with autologous tumor-infiltrating lymphocytes is a promising strategy for advanced melanoma that is refractory to immune checkpoint inhibitor therapy. However, the complexity involved with its eligibility and delivery may restrict treatment availability to centralized centers of expertise and preclude widespread access to patients with melanoma who live in rural areas.
- Virtual and digital platforms for delivery of health care may help bridge some of the gaps in access to optimal management in melanoma.

National Survey conducted in the United States, access to health care remained the topmost priority for respondents, a finding similar to that of the original survey conducted in 2010.[3] It is important to note greater diversity within the rural population in 2020, a finding that is likely to have important implications in the allocation and accessibility of resources for cancer care over time. In this educational review, we aim to address selected issues that are pertinent to access to melanoma care and provide a multidisciplinary framework for some possible solutions.

SURGICAL ONCOLOGY SERVICES IN RURAL VERSUS URBAN SETTINGS

In most high-income countries, those who live in cities are able to obtain specialized medical care for whatever ailment afflicts them. However, even in high-income countries, ready access to specialized medical services may not be available to those who live in less populated areas, particularly when the countries are very large, such as the United States, Canada, and Australia.

For patients who develop melanoma, the problem of access to appropriate medical care may loom particularly large for those who live in remote areas, because melanoma treatment has become more highly specialized and multidisciplinary in recent years. This means that family physicians and surgeons serving less-populated areas cannot provide the services that have now been shown to produce the best outcomes. For example, although wide surgical excision of the primary melanoma may be readily performed by a rural surgeon, dermatologist, or even family physician, SN biopsy, which has become the standard method of staging patients who present with primary cutaneous melanomas 1.0 mm or larger in Breslow thickness (and some with T1b tumors) may not be possible. Although the SN biopsy procedure is minimally invasive, it requires considerable surgical expertise and experience, as well as sophisticated nuclear medicine facilities and assessment of the sentinel nodes by an experienced dermatopathologist.

Because of these difficulties, many patients with melanoma who live in remote areas receive suboptimal care. Sentinel node biopsy is not often performed and, as a result, accurate American Joint Committee on Cancer staging is not possible, high-risk patients (who are today likely to benefit from adjuvant systemic treatment) are not identified, and worse survival outcomes are likely to occur. The particular problems associated with access to SN biopsy in rural and remote areas are discussed in more detail below.

Incidence

In general, the incidence of melanoma in high-income countries with predominantly White populations tends to be greater in rural and remote areas than in major cities. In a recent Australian study, there were 32 cases per 100,000 population in rural areas compared with 27 cases per 100,000 in major cities.[4] In New Zealand, which has a mostly White population very similar to that of Australia, the incidence of in situ and invasive melanoma in rural areas was a remarkable four times greater than the national average.[5]

However, in a whole-of-United States study that examined North American Association of Central Cancer Registries data from 2009 to 2013, the incidence of early-stage melanoma diagnosis was lower in rural areas (14.8 per 100,000) compared with urban areas (15.2 per 100,000), a relative risk of 0.97 (95% CI, 0.96–0.98). The fact that the incidence of later-stage melanoma with metastatic spread was substantially higher in rural areas, with a relative risk of 1.15 (95% CI, 1.10–1.19), suggests that many patients with early-stage melanoma in rural areas were not being diagnosed,[6] accounting for the lower early-stage melanoma rate that was actually documented.

Mortality

The results of multiple studies confirm that mortality from melanoma is higher in rural and remote areas compared with cities. In a study published in 2018, the median worldwide age-adjusted mortality for cutaneous melanoma was 5.4 per 100,000 for rural and remote areas, substantially greater than the mortality of 4.6 per 100,000 in major cities.[4] In Australia, the ratio of age-standardized mortality from melanoma for patients living in rural and

remote areas compared with metropolitan areas was 1.15 in men (95% CI, 1.10–1.21) and 1.18 in women (95% CI, 1.10–1.25).[7] A study undertaken in the United States reported a similar increase in the odds ratio for death from melanoma of 1.15 for patients who lived in towns with less than 250,000 residents compared with cities with more than 1,000,000 people.[8] On the other hand, in Scotland, a much smaller country, Murchie et al found no difference in mortality for those living in rural areas compared with urban settings.[9]

The Example of Access to Sentinel Node Biopsy for Melanoma

In Australia, the National Medical Services Advisory Committee suggests limiting SN biopsy procedures for melanoma and breast cancer to centers with appropriate expertise. For patients with melanoma, the Australian melanoma management guidelines[10] also recommend that SN biopsy should be performed at a center with appropriate expertise, although this recommendation is based on low-level evidence (III-3). The Australian guidelines further recommend, as a good practice point, that when SN biopsy is contemplated, patients should be given an opportunity to fully discuss the risks and benefits with a clinician who performs this procedure. These recommendations encourage physicians in rural and remote areas to refer patients to specialist melanoma treatment centers in major urban locations.

Several U.S. studies have shown that patients living in rural areas are less likely to receive a SN biopsy. Using Surveillance, Epidemiology, and End Results Program data, for example, Shah et al reported that the odds ratio for receiving a SN biopsy was 0.87 (95% CI, 0.78–0.97).[11] An earlier survey in Oregon showed that surgeons in rural areas were less likely to perform SN biopsy, and the procedure was less common in smaller hospitals (with $<$ 50 beds).[12]

Another impediment to uptake of SN biopsy by patients is prolonged waiting times, because logistic arrangements associated with coordinating lymphoscintigraphy and surgery are more complex than simply arranging wide surgical excision. In Canada, data from Ontario revealed a waiting time of 24 to 64 days for wide surgical excision of a primary melanoma but 41 to 81 days for wide excision with SN biopsy.[13] Clearly, coordination of bookings is more difficult for all patients with melanoma traveling to major centers for SN biopsy. Although it is no longer the case, complete lymph node dissection was recommended by the National Comprehensive Cancer Network and other national guidelines for all patients found to have a positive sentinel node. However, two U.S. studies found that patients were less likely to have a complete lymph node dissection if they attended a low-volume community hospital.[14,15] It is likely that the same failure to observe current guidelines recommending SN biopsy for T1b and T2 and above melanomas occurs in low-volume community hospitals, which are usually the only hospitals that exist in rural and remote areas.

In Australia, residents of regional and remote areas are generally slightly older than city dwellers and have a lower socioeconomic status.[16] Either or both of these factors are likely to make patients more reluctant to travel long distances to major centers for their melanoma treatment.

The Value of Access to Multidisciplinary Care for Patients With Melanoma

The situation in Australia for patients who live in rural and remote areas differs from that in the United States in some important ways. Australia has a government-funded universal health care system (that runs in parallel with a private health system for those who wish to choose their own medical attendant). Additionally, government-funded financial support for travel and accommodation (the Isolated Patients Travel Assistance Scheme) is available for patients who cannot obtain specialist services locally. With this support, and previously even without it, most patients are remarkably willing to travel to the nearest major city for specialized treatment and even for routine follow-up, even if it means many hours of travel each way and a city stay for one or more nights. This support and general willingness to travel has an effect on treatment, as well as on clinical trial participation, and it is noteworthy that, in a study published in 2014, remoteness of residence and socioeconomic status did not influence the rate of clinical trial participation at a major melanoma treatment center in Sydney (Melanoma Institute Australia), after adjustment for relevant covariates.[17]

However, for some Australian patients, particularly elderly patients, long-distance travel for treatment is not a realistic possibility. It is important to recognize that, even within major cities, patients may prefer to be treated in a community setting for convenience, rather than traveling into the city center to attend a specialized melanoma clinic with an academic affiliation.

The majority of patients with newly diagnosed melanomas have T1a tumors ($<$ 0.8 mm in Breslow thickness); if they live in a remote area, it would seem reasonable for them to be treated as close to home as possible by wide surgical excision, rather than traveling to a specialist center for assessment and treatment. However, for the reasons outlined above, patients with T1b and above melanomas are likely to benefit from the services provided at a specialist center. Today, it is even more important, of course, for patients with stage III or stage IV disease to be offered the multidisciplinary care that is available only in specialist centers, where combined input from surgical oncologists, medical oncologists, radiation oncologists, pathologists,

radiologists, and nuclear medicine physicians, as well as clinical trial staff, is able to be provided.

In the United States, these problems are undoubtedly exacerbated by the less widely available financial support for medical care when patients do not have employer-funded or private health insurance. Thus, patients living in the suburbs of major cities may effectively be just as remote and isolated from specialist care as those who live hundreds of miles from major melanoma treatment centers.

SYSTEMIC THERAPY FOR ADVANCED MELANOMA: PD-1 AND BEYOND

The outlook for patients with stage III or stage IV melanoma has been revolutionized in the past decade by the advent of immune checkpoint agents (targeting PD-1 and CTLA-4) and molecular inhibitors of *BRAF* and *MEK*. Large well-conducted studies have cemented the efficacy and toxicity of these agents administered as monotherapy or in combination. In CheckMate 067, the five-year overall survival for patients with therapy-naive advanced melanoma treated with nivolumab plus ipilimumab was 52%; it was 44% for nivolumab-treated patients and 26% for those who received ipilimumab as monotherapy.[18] It is well known that combination immunotherapy is associated with a higher rate of immune adverse events necessitating discontinuation of therapy. However, this cessation of treatment is not associated with inferior outcomes, as demonstrated in an analysis that pooled data from the CheckMate 069 and CheckMate 067 trials.[19] Similarly, in long-term data from the combined analysis of 563 patients enrolled in the COMBI-d and COMBI-v trials examining the combination of dabrafenib and trametinib for previously untreated patients with BRAF V600E/K–mutant melanoma, the 5-year progression-free survival and overall survival were 19% and 34%, respectively.[20] These mature data clearly highlight gains in melanoma therapy since the approval of ipilimumab in 2011 in the United States. However, they also underscore the fact that a substantial portion of patients still ultimately succumb to the disease.

The role of second-line therapy and beyond for melanoma that is refractory to front-line treatment is yet to be defined, and prospective trials addressing this are ongoing. The addition of low-dose ipilimumab to pembrolizumab in 70 patients with anti–PD-1–refractory advanced melanoma yielded a response rate of 30% and median progression-free survival of 4.7 months.[21] Results from SWOG 1616, a completed phase II randomized study comparing the efficacy of ipilimumab monotherapy with its combination with nivolumab should help to better define the role of combination immune checkpoint inhibitor regimens for this tough-to-treat cohort with anti–PD-1–refractory disease (NCT03033576). This clinical question has become especially important given the widespread use of nivolumab or pembrolizumab as adjuvant therapy for resected stage III or stage IV disease.[22,23]

Immune checkpoint inhibitors have rapidly made their foray into the management of many other malignancies, including other cutaneous cancers such as squamous cell carcinoma (cemiplimab, pembrolizumab), basal cell carcinoma (cemiplimab), and Merkel cell carcinoma (avelumab, pembrolizumab). Ease of outpatient use, predictable toxicity profiles, and favorable reimbursement margins have contributed to an increase in the adoption of their use within the domain of community oncology practice where a large proportion of delivery of oncology care occurs in the United States.[24,25] However, these "real-world" data may not consistently mirror results from clinical trials.[26-28] Undoubtedly, the restrictive nature of clinical trial eligibility plays some role in this discrepancy, but several other factors that are hard to consistently measure, including expertise, volume, supportive services, and access to multidisciplinary care, may also contribute.

In a retrospective study in melanoma using the National Cancer Database, Krimphove et al noted a proportional increase from 14.5% to 37.7% in hospital use treating at least 20% of patients with melanoma with immunotherapy within 90 days of diagnosis when measured from 2011 to 2015.[25] However, there was a considerable variation in the rates of immunotherapy utilization between low-prescribing hospitals and with high-prescribing hospitals (7.8% and 50.8%, respectively). Older patients and those of lower socioeconomic status were more likely to be treated at low-prescribing hospitals which were less often academic centers. Medicaid insurance or being uninsured and the absence of visceral metastases were predictive factors of receipt of care at a low-prescribing hospital, whereas patients who traveled a long distance were less likely to get their therapy at these hospitals. In this study, the vast majority (80%) of hospitals treating the highest proportion of patients with immunotherapy were academic centers; it would follow that these centers were also likely involved in the clinical trials investigating these immunotherapy agents begetting a level of comfort and, thus, a more rapid adoption of these drugs when commercially available. These factors clearly underscore variability in receiving what would conceivably be considered standard of care in melanoma and may propagate inequity of access to health care resources for patients with melanoma.

WHERE DO WE GO FROM HERE? LEVERAGING NEWER TECHNOLOGIES AND DIGITAL HEALTH FOR BETTER PATIENT CARE CLOSER TO HOME

Newer technologies and communication tools can help to bridge the rural–urban and academic–community care gaps for patients with melanoma by creating more innovative access to subspecialty expertise and consistent

standard of care closer to home. Virtual tumor boards or case conferences can help to connect community practices with specialized cancer centers by providing a shared forum for multidisciplinary engagement of all participants involved in the patient's care.[29,30] This model is valuable for achieving consensus and guidance on best practice in the curative treatment setting where multiple subspecialists are part of a patient's melanoma care team, as well as when evaluating therapeutic options for advanced metastatic disease. Here, interpreting genomic tumor information and implementing an applicable treatment plan can be a challenge. Although next-generation sequencing testing is more widely available now in the community, expertise in the ability to translate findings into actionable treatment plans remains varied among general oncology practitioners. Multi-institutional virtual molecular tumor boards can address the need for more in-depth review of genomic tumor information and overcome challenges ranging from guidance to finding effective treatment to connecting patients to applicable later-line clinical trials, which are more often found at urban medical centers.[31,32] Some next-generation sequencing reports provide clinical trial information in the test report itself; however, these are often more algorithmic rather than tailored to a patient's clinical circumstances. Those are usually better considered in the setting of a tumor board in real-time by specialists with access to the patient's clinical history. Some sequencing platforms facilitate enrollment on to clinical trials for patients closer to home by helping their providers open genomic-based trials more seamlessly in the community through centralized trial support within their network of platform users.[33]

The ability to effectively treat patients well between institutions that are separated by considerable distance, and sometimes across state lines, poses several challenges. In the past, simply having limited access to medical records and diagnostic results in real time limited care for patients whose care team members were not all at the same facility. Hand-offs and communication regarding continuity of patient care were poor, with limited effective ways to share information. With the advent of fully digitized patient records, including diagnostics, such as imaging and even histopathology, a major barrier to coordinated expert care has been addressed. In many areas of the Unites States providers now have access to electronic medical record platforms, such as Epic's Care Everywhere Network, that can improve communication between smaller practices and urban cancer centers, making treatment of patients more seamless for primary teams and consultants alike.

Most patients still receive treatment for advanced melanoma in their own community, especially adjuvant therapy or earlier lines of treatment. With multiple drug approvals and effective treatment options now available on and off clinical trial, choosing the optimal treatment for patients can feel daunting to the community practitioner who may not see patients with melanoma frequently. In community or rural settings, where cancer care often still follows a general oncology model, keeping up with practice-changing data can be an important challenge. A more novel practice tool for smaller general oncology clinics can be the use of vetted treatment pathways that incorporate national consensus guidelines. Treatment decisions can be streamlined this way with web-based pathways that incorporate key clinical indicators to guide treatment ordering in real time as patients are seen in the office. Retrospective outcome review in medical groups before and after implementation of such clinical treatment pathways have shown good survival outcomes and even documented cost savings when care can be more standardized this way.[34,35]

With mobile technology more widely available to patients across the country, another strategy to improve care for patients living further away from urban medical centers is to engage them more directly in their care. Patient-centered digital applications that collect symptoms and connect them to supportive treatment algorithms and ancillary staff in real time can be an innovative solution to improve care for patients who live far away from their treatment teams. Electronically collected patient-reported outcomes can help to manage toxicities from treatment early to improve quality of life and decrease health care utilization, avoiding the need for higher levels of care, such as emergency department visits or inpatient admission.[36,37] Immunotherapy is a treatment modality for which timely triage to diagnose and treat immune-related adverse events is critical for better symptom management and safety. Oral targeted therapy for patients with *BRAF*- or *NRAS*-mutated tumors also presents unique management challenges, because patients do not come in as often to have contact with support staff and need more prompting to comply with daily therapy and toxicity. Patient-reported outcome mobile platforms can also provide more accurate assessments of how patients are doing by collecting symptom trends for treating physicians that are more representative of how patients are actually doing on therapy than can be gleaned from less frequent office visits. For patients who live far away from their treatment centers, this newer technology can be a safety net to access medical guidance in real time closer to home, as well as maintain continuity of care if more acute care is needed, because their data can be accessed by providers from different facilities through the digital tool.

Melanoma Care During the COVID-19 Pandemic: Might Telehealth Be Here To Stay?

An unexpected benefit of the current COVID-19 pandemic is that the role of telehealth consultations has been reevaluated. For patients with newly diagnosed melanomas and for those requiring long-term follow-up, telehealth

consultations, ideally with video connection, have proven to be very useful. For patients who live in rural and remote areas, it seems highly likely that they will be keen to continue follow-up, at least, by virtual, rather than face-to-face, consultations. Although most clinicians will be wary of relying on a patient's description, possibly supplemented by photographic images and/or videos and locally arranged imaging studies, rather than undertaking a conventional physical examination, it seems that most problems can be identified without the patient being examined. Those about whom there is any concern can be seen in person for full evaluation at the specialist center, but the majority will be spared the time and expense of a long trip to the city and home again.

In a prospective observational study conducted across the Houston Methodist Cancer Center network, telehealth visits were offered to 1,762 patients, of whom 84% agreed to participate.[38] Patients who elected against participation tended to be older, were from geographically lower-income areas of the catchment, and were less likely to have commercial insurance. Of the 21% of patients who completed their telehealth visit follow-up survey, more than 90% expressed satisfaction with the quality of the visit. Approximately 77% did not require technical support to help with this video visit. Of the 23 hematology and medical oncology providers (fairly evenly distributed between academic and community practitioners), 65% expressed satisfaction with the telemedicine visit. Interestingly, more than half of them indicated their reluctance to use this platform for new patient visits after the COVID-19 pandemic, but this number dropped to 13% for continued follow-up of established patients. The main concerns raised by the physicians included fear of missing relevant physical examination findings, lack of meaningful interaction with the patient, medical liability issues, inability to gather adequate data, and complexity of the process coupled with suboptimal technical support.

This study also highlights an ethical concern previously raised with the rapid expansion of the telemedicine platform, specifically broadening the disparity in access to healthcare between patients with access to the requisite technology and those who lack this functionality. During the initial wave of the pandemic in 2020, the U.S. Congress expanded access to telemedicine for Medicare beneficiaries to allow greater flexibility during the national emergency.[39] Many private insurers followed suit, and regulatory and credentialing requirements previously in place for out-of-state consumers were relaxed. Although this eased delivery of care, it is unlikely that this paradigm will continue with similar momentum within oncology, because previously waived charges for patients have since been reinstated by several commercial payors. Similarly, medical state licensure and credentialing across state lines and distant from the primary state of clinical practice remains a barrier to providers seeking to offer the telemedicine option to patients. Thus, this remains a field in flux that will continue to evolve in the context of oncology care.

WHAT IS THE NEXT FRONTIER IN MELANOMA?

Clearly, immune manipulation as therapy in melanoma is here to stay. This approach continues to be investigated as a means to salvage patients who progress on immune checkpoint therapy. High-dose interleukin-2 (IL-2), a cytokine approved in 1998 for advanced melanoma, induced durable remission in a small minority (16% response rate, including 6% complete response rate) of patients with advanced melanoma.[40] However, its stringent eligibility criteria, need for inpatient administration, and substantial multiorgan toxicity have restricted its use to specialized centers only, with a marked decline in its use for melanoma during the immune checkpoint revolution. In a retrospective review of the high-dose IL-2 PROCLAIM database, Buchbinder et al noted a 23% response rate to high-dose IL-2 after anti–PD-1/PD-L1 therapy, including four patients with complete response.[41] At a median follow-up of 11.2 months, none of the patients with a complete response had progressed, although a longer follow-up will be needed to truly ascertain whether this mirrors the tail of the overall survival curve seen previously with high-dose IL-2. Selective expertise in high-dose IL-2 administration has probably been further diluted by the relative paucity of education in the practical aspects of its delivery and management of toxicity for the next generation of oncologists. In a contemporary review of high-dose IL-2 use in metastatic renal cell carcinoma during the era of expanding targeted therapy for this disease, marked centralization of care toward teaching hospitals was observed, increasing from 24% in 2004 to 89.5% in 2012.[42] If a reincarnation of high-dose IL-2 is envisioned in the present-day management of advanced melanoma, this barrier to access of care must be addressed.

In a similar vein, adoptive cellular therapy using autologous tumor-infiltrating lymphocytes (TILs) expanded ex vivo with IL-2 has shown early success in patients with anti–PD-1–refractory melanoma. This approach was pioneered nearly 4 decades ago at the National Cancer Institute, with the original study, using TILs derived from freshly resected melanoma tumors, reporting an objective response in 60% of patients who had not previously been treated with IL-2.[43] Progressive refinements in the generation of TILs, the appropriate preconditioning lymphodepletion regimen, and the use of high-dose IL-2 after infusion of TILs have been the subject of study over time. In a recent meta-analysis of TIL therapy plus IL-2 (high dose and low dose), the overall response rate in previously treated advanced melanoma was 41% (95% CI, 35–48).[44] The complete response rate was 12%. Among patients receiving TILs with high-dose IL-

2, all but one complete responder maintained their response for the duration of the follow-up. It should be noted that the vast majority of patients included in the reports of this meta-analysis did not receive previous immune checkpoint blockade therapy.

Lifileucel, an autologous TIL product generated from resected melanoma and processed at central Good Manufacturing Practice facilities, was used as salvage therapy in 66 patients with melanoma whose disease had progressed on standard modern-day treatment, including checkpoint blockade and MAPK-targeted therapy (if indicated).[45] In this heavily pretreated population, the overall response rate was 36.4%; the median duration of response was not reached at a median follow-up period of 17 months. The typical lymphodepletion regimen of cyclophosphamide and fludarabine was used, and patients received up to six doses of high-dose IL-2 after the infusion of TILs. This technology has not received regulatory approval in the United States as therapy for melanoma, although it is hoped that this will become a reality. Longer follow-up is required to accurately determine the duration of response. This approach is an example of optimal multidisciplinary cooperation among multiple care teams, including the medical oncologist, surgical oncologists, nurses, tissue procurement personnel, cell therapy facility staff, social workers, the clinical trial team (at least within the current phase of development), and, importantly, the patient's caregiver, who plays a critical role as the patient's confidante and support person during a period of anxiety (awaiting TIL growth after the initial harvest) and physical/emotional stress. This is clearly akin to stem cell transplantation in hematologic disease and will require appropriate investment of resources throughout the supply chain for optimal roll-out, should this be approved for commercial use. Thus, it is likely to be limited to centers of melanoma and immune cellular therapy expertise where high-dose IL-2 therapy can be safely given. Unfortunately, this may also serve as a barrier to access for patients with melanoma who live far from the treatment center or for whom consecutive absenteeism from work is not a realistic option. It would be incumbent on health care systems, government agencies, and payors to strategize about options to overcome these hurdles in a timely manner.

COST OF CARE

It is difficult to obtain an accurate estimate of the cost of melanoma care across various treatments that patients may now be exposed to during their lifetime. At one end of the spectrum is a patient who experiences an excellent response to first-line immunotherapy tantamount to cure and, thus, is spared the need for future treatment. At the other end of this spectrum is a patient with metastatic melanoma that is refractory to all approved agents delivered in a sequential manner who eventually succumbs to the disease. Realistically, most patient scenarios fall somewhere in between. The more expensive initial cost of combination anti–PD-1 plus anti-CTLA4 immunotherapy, along with its higher hospitalization rate for toxicity management, may be offset by a shorter duration of therapy and a lower need for a subsequent line of antimelanoma treatment. Published data typically do not take into account health care costs that are related to long-term toxicity management (e.g., immune-related endocrinopathy [hypothyroidism, adrenal insufficiency, type 1 diabetes mellitus]) requiring replacement therapy, long-term monitoring, and, often, additional subspecialty care.

Let's aim to simplify this by adopting a straightforward uncomplicated case vignette: a patient with *BRAF V600*–mutant metastatic melanoma treated with anti–PD-1 monotherapy (i.e., pembrolizumab) experienced progression after 7 months. He then received ipilimumab at standard dosing for 12 weeks (four doses). Upon confirmed progression, the patient started combination dabrafenib and trametinib therapy for 12 months before receiving palliative care and eventually succumbing to his illness. If one were to use the 2021 payment allowance limit for Medicare Part B drugs from the U.S. Center of Medicare and Medical Services, the estimated drug cost alone for these three courses of drug therapy would approximate $573,000.[46,47] Note that this does not include the costs related to treatment administration, clinic visits, costs for managing toxicity, and laboratory assessment, among other expenses. These financial considerations can result in disparity in access and raise concerns about cost effectiveness, especially within systems in which resources may be limited.

Clinical trials are one strategy that can help to mitigate cost; however, more importantly, they also unify priorities for best care for patients with cancer. Clinical trials can bring newer better treatment options to patients before they are widely available in the community. Treatment on study is also monitored with rigorous oversight, and the best standard of care is written directly into vetted trial protocols. The cooperative groups of the National Cancer Institute are one mechanism through which smaller medical centers can provide access to more novel treatment of patients closer to home. By streamlining Institutional Review Board approval, monitoring, and simplifying eligibility for enrollment, these larger trial networks can provide more patients with access to effective therapy while also providing more representative data outcomes of the patient population at large by gender, age, and race. The National Cancer Institute Community Oncology Research Program is a national network of community oncology centers that is funded to succeed in these priorities. Its mission is to bring clinical trials and care delivery research to patients in their own communities, reaching a more diverse population than is usually seen at academic medical centers. With more effective treatment options available in the

community for melanoma, research trials will benefit from moving more into the community for better patient accrual and more applicable treatment outcomes gathered.

CONCLUSION

Advances in the multimodal management of melanoma have clearly made a positive impact on patients afflicted with this illness. Yet access to optimal care is not assured, with a multitude of factors influencing treatment selection. It is incumbent on policymakers, health systems, insurance payors, health care providers, and patients to make a concerted effort to overcome barriers, so that all patients may benefit from the important accomplishments achieved for this disease.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7-33.
2. Schilsky RL, Nass S, Le Beau MM, et al. Progress in cancer research, prevention, and care. N Engl J Med. 2020;383:897-900.
3. Bolin JN, Bellamy GR, Ferdinand AO, et al. Rural Healthy People 2020: new decade, same challenges. J Rural Health. 2015;31:326-333.
4. Rollin A, Ridout B, Campbell A. Digital health in melanoma posttreatment care in rural and remote Australia: systematic review. J Med Internet Res. 2018; 20:e11547.
5. Townsend T. Diagnosis and management of melanoma in a rural general practice. J Prim Health Care. 2018;10:207-209.
6. Zahnd WE, Fogleman AJ, Jenkins WD. Rural-urban disparities in stage of diagnosis among cancers with preventive opportunities. Am J Prev Med. 2018; 54:688-698.
7. Coory MD, Ho T, Jordan SJ. Australia is continuing to make progress against cancer, but the regional and remote disadvantage remains. Med J Aust. 2013; 199:605-608.
8. Monlezun DJ, Al-Qurayshi Z, Hamner J, et al. Unmasking melanoma mortality disparities by geographic, urban, and insurance trends. J Am Coll Surg. 2016; 223:E188.
9. Murchie P, Adam R, Khor WL, et al. Impact of rurality on processes and outcomes in melanoma care: results from a whole-Scotland melanoma cohort in primary and secondary care. Br J Gen Pract. 2018;68:e566-e575.
10. Cancer Council Australia Melanoma Guidelines Working Party. Clinical practice guidelines for the diagnosis and management of melanoma. https://wiki.cancer.org.au/australiawiki/index.php?oldid=213448. Accessed February 16, 2021.
11. Shah DR, Yang AD, Maverakis E, et al. Assessing rural-urban disparities in the use of sentinel lymph node biopsy for melanoma. J Surg Res. 2013; 184:1157-1160.
12. Garreau JR, Nelson J, Cook D, et al. Geographic variation in sentinel node adaptation by practicing surgeons in Oregon. Am J Surg. 2005;189:616-619, NaN-620.
13. Crawford AB, Nessim C, Weaver J, et al. Wait times for melanoma surgery: is there an association with overall survival? Ann Surg Oncol. 2018;25:265-270.
14. Cormier JN, Xing Y, Ding M, et al. Population-based assessment of surgical treatment trends for patients with melanoma in the era of sentinel lymph node biopsy. J Clin Oncol. 2005;23:6054-6062.
15. Bilimoria KY, Balch CM, Bentrem DJ, et al. Complete lymph node dissection for sentinel node-positive melanoma: assessment of practice patterns in the United States. Ann Surg Oncol. 2008;15:1566-1576.
16. Australian Institute of Health and Welfare. Socioeconomic Group and Mortality 2009-2013. https://www.aihw.gov.au/reports-data/population-groups/rural-remote-australians/overview. Accessed February 16, 2021.
17. Lee JL, Haydu LE, Thompson JF, et al. The impact of socioeconomic status on melanoma clinical trial participation: an observational cohort study from Australia. Melanoma Manag. 2014;1:95-103.
18. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2019; 381:1535-1546.

19. Schadendorf D, Wolchok JD, Hodi FS, et al. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: a pooled analysis of randomized phase II and III trials. J Clin Oncol. 2017;35:3807-3814.
20. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med. 2019;381:626-636.
21. Olson D, Luke JJ, Poklepovic AS, et al. Significant antitumor activity for low-dose ipilimumab (IPI) with pembrolizumab (PEMBRO) immediately following progression on PD1 Ab in melanoma (MEL) in a phase II trial. J Clin Oncol. 2020;38 (15 suppl; abstr 10004).
22. Ascierto PA, Del Vecchio M, Mandalá M, et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. Lancet Oncol. 2020;21:1465-1477.
23. Eggermont AMM, Blank CU, Mandala M, et al. Longer follow-up confirms recurrence-free survival benefit of adjuvant pembrolizumab in high-risk stage III melanoma: updated results from the EORTC 1325-MG/KEYNOTE-054 Trial. J Clin Oncol. 2020;38:3925-3936.
24. Khozin S, Miksad RA, Adami J, et al. Real-world progression, treatment, and survival outcomes during rapid adoption of immunotherapy for advanced non-small cell lung cancer. Cancer. 2019;125:4019-4032.
25. Krimphove MJ, Tully KH, Friedlander DF, et al. Adoption of immunotherapy in the community for patients diagnosed with metastatic melanoma. J Immunother Cancer. 2019;7:289.
26. Khozin S, Carson KR, Zhi J, et al. Real-world outcomes of patients with metastatic non-small cell lung cancer treated with programmed cell death protein 1 inhibitors in the year following U.S. Regulatory Approval. Oncologist. 2019;24:648-656.
27. Hanna GJ, Ruiz ES, LeBoeuf NR, et al. Real-world outcomes treating patients with advanced cutaneous squamous cell carcinoma with immune checkpoint inhibitors (CPI). Br J Cancer. 2020;123:1535-1542.
28. O'Connor JM, Fessele KL, Steiner J, et al. Speed of adoption of immune checkpoint inhibitors of programmed cell death 1 protein and comparison of patient ages in clinical practice vs pivotal clinical trials. JAMA Oncol. 2018;4:e180798.
29. Davis LE, Coleman J, Harnar J, et al. Teleneurology: successful delivery of chronic neurologic care to 354 patients living remotely in a rural state. Telemed J E Health. 2014;20:473-477.
30. Salami AC, Barden GM, Castillo DL, et al. Establishment of a regional virtual tumor board program to improve the process of care for patients with hepatocellular carcinoma. J Oncol Pract. 2015;11:e66-e74.
31. Farhangfar CJ, Morgan O, Concepcion C, et al. Utilization of consultative molecular tumor board in community setting. J Clin Oncol. 2017;35 (15 suppl; abstr 6508).
32. Kato S, Kim KH, Lim HJ, et al. Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. Nat Commun. 2020;11:4965.
33. Suga JM, Thomas SP, Truong T-G, et al. Implementing a genomic oncology program in an integrated health care network with large scale genomic next generation sequencing (NGS) testing of advanced cancers in a community setting. J Clin Oncol. 2020;38 (15 suppl; abstr e19185).
34. Ellis PG, O'Neil BH, Earle MF, et al. Clinical pathways: management of quality and cost in oncology networks in the metastatic colorectal cancer setting. J Oncol Pract. 2017;13:e522-e529.
35. Hertler A, Chau S, Khetarpal R, et al. Utilization of clinical pathways can reduce drug spend within the oncology care model. JCO Oncol Pract. 2020; 16:e456-e463.
36. Basch E, Deal AM, Kris MG, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial [published corrections appear in *J Clin Oncol*. 2016;34:2198 and 2019;37:528]. J Clin Oncol. 2016;34:557-565.
37. Basch E, Deal AM, Dueck AC, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA. 2017;318:197-198.
38. Darcourt JG, Aparicio K, Dorsey PM, et al. Analysis of the implementation of telehealth visits for care of patients with cancer in Houston during the COVID-19 pandemic. JCO Oncol Pract. 2021;17:e36-e43.
39. Royce TJ, Sanoff HK, Rewari A. Telemedicine for cancer care in the time of COVID-19. JAMA Oncol. 2020;6:1698-1699.
40. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol. 1999;17:2105-2116.
41. Buchbinder EI, Dutcher JP, Daniels GA, et al. Therapy with high-dose interleukin-2 (HD IL-2) in metastatic melanoma and renal cell carcinoma following PD1 or PDL1 inhibition. J Immunother Cancer. 2019;7:49.
42. Allard CB, Gelpi-Hammerschmidt F, Harshman LC, et al. Contemporary trends in high-dose interleukin-2 use for metastatic renal cell carcinoma in the United States. Urol Oncol. 2015;33:496.e11-496.e16.
43. Rosenberg SA, Packard BS, Aebersold PM, et al. Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report. N Engl J Med. 1988;319:1676-1680.
44. Dafni U, Michielin O, Lluesma SM, et al. Efficacy of adoptive therapy with tumor-infiltrating lymphocytes and recombinant interleukin-2 in advanced cutaneous melanoma: a systematic review and meta-analysis. Ann Oncol. 2019;30:1902-1913.
45. Sarnaik A, Khushalani NI, Chesney JA, et al. Long-term follow up of lifileucel (LN-144) cryopreserved autologous tumor infiltrating lymphocyte therapy in patients with advanced melanoma progressed on multiple prior therapies. J Clin Oncol. 2020;38 (15 suppl; abstr 10006).
46. Centers for Medicare & Medicaid Services. 2021 ASP Drug Pricing Files. https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2021-asp-drug-pricing-files. Accessed March 14, 2021.
47. IBM Micromedex RED BOOK (electronic version). https://www.micromedexsolutions.com/. Accessed March 15, 2021.

PEDIATRIC ONCOLOGY

PEDIATRIC ONCOLOGY

The Care of Children With Cancer During the COVID-19 Pandemic

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overview

The COVID-19 pandemic has considerably changed health services for children with cancer worldwide by creating barriers throughout the care continuum. Reports available at this time suggest that asymptomatic and mild upper and lower respiratory tract syndromes are the most common presentation of COVID-19 in children with cancer. Nonetheless, severe cases of COVID-19 and deaths secondary to the infection have been reported. In addition to the direct effects of the severe acute respiratory syndrome coronavirus 2, children with cancer have suffered from the collateral consequences of the pandemic, including decreased access to diagnosis and cancer-directed therapy. The COVID-19 pandemic has presented unprecedented challenges to safe and effective care of children with cancer, including their enrollment in therapeutic clinical trials. Data from the Children's Oncology Group and Cancer Research U.K. Clinical Trials Unit show variability in the enrollment of children with cancer in clinical trials during the COVID-19 pandemic. However, the overall effects on outcomes for children with cancer undergoing care during the pandemic remain largely unknown. In this article, we review the current knowledge about the direct and collateral effects of the COVID-19 pandemic, including on clinical trial enrollment and operations.

To date, more than 130 million cases of COVID-19 have been reported worldwide, resulting in more than 2.8 million deaths.[1] Initial reports suggested that patients with comorbidities, including those with cancer, were at higher risk of poor outcomes,[2] causing fear that children with cancer would develop severe disease and have adverse outcomes. This fear was potentiated by an early report of eight pediatric patients with severe COVID-19, including one patient with acute lymphoblastic leukemia.[3]

In addition to the direct consequences of infection, the COVID-19 pandemic has strained health systems and hospitals worldwide, adversely affecting health services for children with cancer by creating barriers throughout the care continuum and presenting an unprecedented challenge to safe and effective care. Unfortunately, the health emergency hit at a time of unprecedented momentum in the field of pediatric oncology, with the launch of the Global Initiative for Childhood Cancer by the World Health Organization. This transformative program seeks to improve the survival of children with cancer to more than 60% across the world by 2030, thereby saving 1 million lives.[4]

Much remains unknown about the epidemiology and clinical spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or COVID-19, infection in children with cancer and the long-term effects of the COVID-19 pandemic. In this article, we review the current knowledge about the direct and collateral effects of the COVID-19 pandemic, including on clinical trial enrollment and operations.

COVID-19 IN CHILDREN WITH CANCER AND POST–HEMATOPOIETIC STEM CELL TRANSPLANTATION

More than 1 year after the start of the COVID-19 pandemic, the frequency of SARS-CoV-2 infection in children with cancer remains uncertain because limited studies have been able to capture population-level incidence for this patient population. Nonetheless, in the areas with high COVID-19 prevalence at the beginning of the pandemic, namely Wuhan and Northern Italy, very few cases of children with cancer and COVID-19 infection were reported.[5] In a single-institution study in New York during the first wave of the pandemic, the rate of asymptomatic SARS-CoV-2 infection among pediatric patients was low, 2.5%.[6]

To describe the natural history of COVID-19 in children with cancer, case series have been published from hospitals and countries around the world.[6-17] Asymptomatic to mild upper and lower respiratory tract syndromes are the most common presentations of COVID-19 in children with cancer (Table 1), and fever and cough are the most common signs. It is important to note that the frequency of asymptomatic patients from these reports is likely to be heavily influenced by institutional testing policies. Nonetheless, most children with COVID-19 do not need admission to a hospital specifically for the management of this infection.[6] In a population-based study from the United Kingdom,

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PRACTICAL APPLICATIONS

- Most children with cancer and COVID-19 will have a mild viral disease course, but a small proportion will have severe disease.
- Risk factors for severe COVID-19 in children with cancer and hematopoietic stem cell transplant are still unknown.
- The pandemic has created additional obstacles for diagnosis and quality care for children with cancer across the world.
- Enrollment in clinical trials during the COVID-19 pandemic has been affected.
- The unintended consequences of the pandemic highlight the pressing need to consider vulnerable populations, such as children with cancer.

85% of patients (46 of 57 patients) did not require admission to a hospital or were admitted for a brief period and discharged after confirmation of SARS-CoV-2 infection.[10]

Although most children with cancer and SARS-CoV-2 will have a mild disease course, severe cases of COVID-19 and deaths secondary to the infection do occur with a wide range of frequency (Table 1). The largest cohort of children with cancer or recipients of hematopoietic stem cell transplantation and COVID-19 is the Global Registry of COVID-19 in Pediatric Cancer, a collaboration between St. Jude Children's Research Hospital and the International Society of Pediatric Oncology.[18] As of April 7, 2021, 1,642 cases from 48 countries are included in this registry. In this cohort, death attributed to SARS-CoV-2 infection is approximately 3.4%. This rate is substantially higher than that reported in the general pediatric population, in whom death attributed to COVID-19 is less than 0.1%.[19] For children with cancer, poorer outcomes are possibly secondary to factors such as immunosuppression, lymphopenia, and existing comorbidities (e.g., malnutrition, lung disease, or cardiac dysfunction). Nonetheless, additional studies are required to define which factors may be linked to a likelihood of worse outcomes in this unique population. When compared with adults with cancer, children with cancer have better outcomes. A registry from the United States with more than 900 cases of adults with cancer and COVID-19 reported a 13% death rate.[20] Additional series have similar death rates.[21,22] In adults, active cancer-directed treatment and lower performance status have been identified as risk factors for death, and these elements could also play a part in the pediatric population.

Recipients of hematopoietic stem cell transplantation who are infected with SARS-CoV-2 may represent a unique patient population, given that they may be more profoundly immunocompromised and have additional comorbidities. A study from Spain reporting eight cases of COVID-19 in children after hematopoietic stem cell transplantation described COVID-19–related symptoms in all patients and death in one (12.5%) of the eight patients.[23] Furthermore, a large international report involving 318 hematopoietic stem cell transplantation recipients, including 29 patients younger than age 20 years, demonstrated a poor overall survival rate.[24]

Months into the pandemic, multisystem inflammatory syndrome in children was described in patients with hyperinflammation and multiorgan involvement and a temporal relation to COVID-19 infection or exposure.[25] A single-institution study described two pediatric patients with cancer and COVID-19 who presented with severe respiratory distress and considerable hyperinflammation requiring intensive care.[26] Although multisystem inflammatory syndrome in children can occur in patients with cancer,[27] the frequency and severity remain unknown. How the immunosuppression of children undergoing cancer therapy plays a role in the development of multisystem inflammatory syndrome in children is unclear.

ADAPTATIONS DURING THE COVID-19 PANDEMIC

The rapidly evolving pandemic has posed many challenges in caring for children with cancer. The rapid spread of information and misinformation presented a public health challenge never seen before, adding complexity to the situation and causing confusion among providers. At the beginning of the COVID-19 pandemic, the global pediatric oncology community moved at great speed to provide support and offer guidance on how to treat children with cancer under these circumstances. For professionals caring for children with cancer, the sharing of experiences from regions that were affected early in the pandemic was essential to formulating initial responses at the local level, and multiple resources were developed as trusted sources of curated information during the pandemic.[28]

Importantly, within weeks of the pandemic being declared, key stakeholders in the treatment of pediatric cancer produced consensus statements to provide insight for frontline providers across the world.[29-31] These publications aimed at offering solutions for the difficulties being faced by medical and nursing professionals caring for children with cancer. The overall recommendation was the continuation of standard care in the diagnosis, treatment, and supportive care for children with cancer whenever possible, with elective modifications to cancer-directed treatment discouraged. Ultimately, these guidance documents sought to provide insight to balance the risk of COVID-19 and the continuation of care for children with cancer. However, the levels of adherence to these recommendations across

TABLE 1. Case Series of Pediatric Patients With Cancer and COVID-19

Reference	Country	No. of Patients	No. Male: Female	No. (%) of Patients With HSCT	No. (%) of Asymptomatic Patients	Most Common Symptoms	No. (%) of Patients With Severe or Critical Disease*	No. (%) of Deaths	No. (%) of Deaths Attributed to COVID-19**
Millen et al[10]	United Kingdom	54	29:25	—	28 (15)	Fever, cough	7 (4)	2 (1)	0 (0)
Montoya et al[9]	Peru	69	44:25	—	54 (37)	Fever, cough	10 (7)	10 (7)	4 (3)
Rouger-Gaudichon et al[17]	France	41	18:19	—	24 (9)	Fever, cough	12 (5)	2 (1)	2 (1)
Arous et al[8]	Algeria	7	3:4	—	0 (0)	Fever, cough	29 (2)	29 (2)	29 (2)
de Rojas et al[11]	Spain	15	14:1	27 (4)	13 (2)	Fever, cough	0 (0)	0 (0)	0 (0)
Kebudi et al[7]	Turkey	51	33:18	12 (6)	37 (19)	Fever, cough	18 (9)	2 (1)	2 (1)
Boulad et al[6]	United States	20	17:3	—	—	—	0 (0)	0 (0)	0 (0)
Lopez-Aguilar et al[12]	Mexico	14	8:6	—	0 (0)	Fever, cough	0 (0)	0 (0)	0 (0)
Bisogno et al[13]	Italy	28	13:16	10 (3)	62 (18)	Fever, respiratory symptoms	0 (0)	0 (0)	0 (0)
Faura et al[14]	Spain	47	34:13	17 (8)	26 (12)	—	23 (11)	4 (2)	4 (2)
Gampel et al[16]	United States	19	15:4	11 (2)	16 (3)	Fever, cough	26 (5)	5 (1)	5 (1)
Madhusoodhan et al[15]	United States	98	69:29	—	33 (32)	Fever, cough	17 (17)	4 (4)	0 (0)
Overall	—	463	297:166	5 (23)	32 (147)	—	13 (60)	4 (19)	2 (10)

Abbreviation: HSCT, hematopoietic stem cell transplantation.

*Patients with severe or critical disease were identified either by the primary reports or as those patients who required transfer to the intensive care unit or intubation.

**Deaths attributed to COVID-19 were defined according to the description in the reports of the ultimate cause of death.

different health care institutions remain unknown. A tertiary referral center in India described the establishment of categories for patient treatment, in which treatment was deferred, reduced, or maintained. These adaptations sought to optimize resources and access to treatment and were implemented with the understanding that they would probably lead to poorer outcomes.[32] Similar situations have been reported around the world.

At the level of hospital and clinic operations, adaptations in the face of the COVID-19 pandemic have been necessary. These adaptations included the implementation of strategies to limit the spread of the virus among patients, families, and staff. Elements such as screening and testing policies and telemedicine were leveraged to this end. Hospitals established screening for COVID-19 in patients, families, and caregivers either by symptom assessment or by SARS-CoV-2 testing.[6,33] Such testing strategies contributed to disease containment and the identification of asymptomatic carriers and enabled a description of the variability of severity of SARS-CoV-2 infection in children with cancer (see above). Furthermore, centers were forced to work with reduced numbers of practitioners, either as a strategy to mitigate the risk of virus spread or as a result of the infection itself, with some centers reporting the cohorting of providers to optimize human resources.[34] Concentrating patients with COVID-19 in one specific area to avoid cross-infection was another frequently implemented action. In addition, limiting the number of caregivers in hospitals was often adopted as an infection-control strategy. Telehealth has been leveraged to provide continued treatment in partnership with satellite centers and to monitor patients after completion of treatment.[35]

Many of the required adaptations to care during the pandemic have brought new challenges, creating a burden on providers, patients, and families. Health care workers have faced numerous challenges during the pandemic, and high levels of burnout and stress have been reported.[36] The relationships between providers and patients and families have also been affected because of the need to don personal protective equipment and the increased use of telemedicine. Patients have suffered from social isolation as activities of distraction, such as playrooms, and schooling have been limited.[37] Because pandemic policies restricted visitors, caregivers have been loaded with additional distress, frequently bearing the burden of difficult conversations and decisions alone. These new limitations have caused increased stress and anxiety for both patients and caregivers.[38]

In addition to the adaptations of cancer-directed therapy and supportive care, psychological support for patients and families has been hindered. Nonetheless, creative solutions have been implemented to continue to provide holistic care whenever possible. Remote access to individual psychotherapy as well as to neuropsychological assessment has been incorporated in addition to the implementation of virtual programs[39] and home-based exercise programs for survivors of cancer to improve fitness.[40]

COLLATERAL EFFECTS OF THE COVID-19 PANDEMIC

Pediatric oncology care relies on prompt evaluation and diagnosis, referral to tertiary centers, multidisciplinary subspecialized teams, timely and coordinated multimodal therapy, and access to supportive care—all of which have been affected by the pandemic. Prioritizing patients with COVID-19, combined with lockdowns and restricted transportation, has contributed to delayed and fragmented attention to children with cancer. It has also been anticipated that the effects of the pandemic on health systems would amplify existing obstacles to caring for children with cancer. In addition, patients and families have been afraid to seek care, adding another barrier during the pandemic. These factors have been reported in both high-income countries and low- and middle-income countries.

Reports have described fewer emergency visits by pediatric patients with cancer and a reduction in outpatient visits, probably influencing the timeliness of diagnoses.[41] Two tertiary referral centers in the United States reported five cases that had delayed cancer diagnoses with grave consequences, including two deaths.[42] These presentations were not commonplace and were influenced specifically by a reluctance to seek care and limitations to accessing full clinical evaluations. Additionally, at the beginning of the pandemic, three patients in Italy arrived in critical condition at the onset of acute lymphoblastic leukemia.[43]

In addition to reports of delayed presentation, reports of lower numbers of new cases of pediatric cancer exist from institutions across the world. A report from Italy described an almost 50% decrease in new cases of pediatric cancer compared with prior years.[44] A tertiary hospital in New York reported a reduction in the number of children with newly diagnosed solid tumors in the area during the height of the pandemic.[45] A decrease in the volume of new cancer diagnoses in children is consistent with what has been observed in adults with cancer. A report from the Dutch population-based cancer registry described a 25% decrease in new cancer cases in the country.[46]

Hospitals and clinics have had to decrease the hours of operation and the volume of patients seen, leading to delays in appointments, ultimately limiting the availability of timely evaluations. Furthermore, families may remain fearful of seeking medical support because of the perceived risks of going to hospitals.[47] Finally, telehealth and the inability to examine a child may limit the diagnostic capacity of health care providers. All these factors, in addition to existing barriers to the diagnosis of pediatric cancer, have probably

contributed to underdiagnosis and delayed and critical presentations. These findings are worrisome, because patients whose cancers are diagnosed later are more likely to present with advanced disease, ultimately leading to poorer outcomes.

EFFECTS OF THE PANDEMIC ON ACCESS TO CARE

The disruption of health services during this pandemic presents a serious challenge to maintaining quality care for children with cancer. Several cross-sectional surveys have sought to evaluate and quantify the indirect effects of the pandemic on access to care and quality of care. A survey carried out in April 2020, collecting data from 20 countries in Latin America, showed that the COVID-19 pandemic had impacted the availability of chemotherapy, cancer surgeries, radiotherapy, and outpatient visits. Importantly, 36% of respondents mentioned that they had to modify chemotherapy regimens because of chemotherapy shortages. These findings were independent of the COVID-19 incidence and fatality rate.[48] A report from the Middle East, North Africa, and the West Asia region described disruptions to essential treatment, including chemotherapy, surgery, and radiotherapy, in between 29% and 44% of institutions. Of note, 24% of centers restricted the acceptance of new patients.[49] A survey from 25 pediatric oncology centers in 15 countries in Africa, which had no reported cases of COVID-19 in children with cancer at the time, graded the impact of the pandemic on cancer treatment as severe.[50] A survey that captured responses from 213 institutions in 79 countries noted that 7% of included centers reported complete closure of services for children with cancer.[51] In addition, almost one-third of centers reported increased treatment abandonment. Unavailability of chemotherapy agents, treatment abandonment, and interruptions in radiotherapy were more frequent at institutions in resource-limited countries.

Although hospitals of all resource levels have suffered as a result of the pandemic, effects have been more frequent and larger in low- and middle-income countries. The phenomenon suggests that the effect of the COVID-19 pandemic on pediatric cancer care reflects the innate strength of health care systems across the world. These unintended consequences of the pandemic highlight the pressing need to consider vulnerable populations, such as children with cancer. Ultimately, the effect of these barriers to quality care on the outcome of children with cancer treated during the pandemic are unknown but are certainly worrisome.

CLINICAL TRIALS DURING THE COVID-19 PANDEMIC

Collaborative clinical trials have been crucial to the continuous improvement in the outcomes of children with cancer during the past decades. In addition to cancer care, pediatric cancer research has been impacted by the COVID-19 pandemic. Delayed opening of new clinical trials and limited accrual of existing trials have been described.[52] Early in the pandemic, health care systems were in danger of being completely overwhelmed by caring for patients with COVID-19 infection. For this reason, regulatory bodies and national agencies provided detailed guidance on managing clinical trials during the pandemic. Although not specific to pediatric oncology, many of the recommendations were very relevant to the care of children with cancer. The advice released by the European Medicines Agency, the U.S. Food and Drug Administration, the U.K. Medicines and Healthcare Regulatory Agency, and other national bodies had several similar recommendations and themes.

The clearest recommendation from the guidance highlighted the importance of placing the safety of trial participants at the forefront of any decision-making, including ensuring data validity. The recommendations can be grouped together as (1) clinical decisions, (2) regulatory requirements, and (3) pharmacovigilance.

Clinical Decisions

For many pediatric patients with cancer who are enrolled in clinical trials, particularly those in phase I/II trials, there may be no effective or proven therapeutic alternatives. The decision to continue treatment for a particular patient must weigh the risks to the patient (and the wider health care system) against the benefits they may be receiving from the study treatment and the availability of alternative therapies.

Many protocols require patients to have regular clinical reviews, and a number of suggestions to manage these reviews during the pandemic exists. When practical, patients may have telephone or video call reviews rather than face-to-face reviews. Alternatively, if they are unable to travel to their treating center because of travel restrictions, monitoring may be able to take place at a local hospital that is not a designated trial site. Patients may also be permitted to have routine investigations (e.g., blood tests and imaging studies) performed at a local hospital and have the results shared with their treating investigator. It is important to ensure that any protocol deviations to accommodate safer clinical pathways be well documented.

Traditionally, patients receiving oral investigational medicinal products would receive these from the pharmacy at their registered trial site. To reduce travel to hospitals, many centers moved to direct delivery of investigational medicinal products to patients and caregivers, either from the pharmacy in question or occasionally directly from the distributor of the medication. Longer supplies of medication (when feasible for shelf life and storage) may also help in this regard. Both the European Medicines Agency and the National Cancer Institute Cancer Therapy Evaluation Program have released specific guidance on this approach.

Regulatory Requirements

Many of the above suggestions would represent protocol deviations, some of which may require amendments to trial protocols. However, the Children's Oncology Group managed this process without the need for amendments to trial protocols specifically for the purpose of COVID-19 accommodation. Both the European Medicines Agency and the U.S. Food and Drug Administration made suggestions so that centers could submit lists of similar protocol violations on a single document rather than having to complete each one individually. Furthermore, the process for protocol amendments was streamlined to facilitate urgent measures introduced to maintain the safety of participants and staff.

Pharmacovigilance

Pharmacovigilance includes, but is not limited to, site initiation visits, monitoring visits, and regular audits of trial sites. Given the need early in the pandemic to prioritize activities essential to the safety of participants and data validity, suggestions were made by many groups that these activities be postponed, cancelled, or moved to remote forms of working. The Children's Oncology Group was up to date on routine institutional audits as of the end of December 2020, although all were carried out remotely.

Although the highlighted steps caused some delay or postponement of vital scrutiny of trial activities, these steps have highlighted the possibility for much of this work to take place remotely, with several potential benefits.

Impact on Pediatric Oncology Trials

The largest published impact of SARS-CoV-2 on pediatric oncology trials is from the Innovative Therapies for Children with Cancer consortium,[53] in an article that focused on the impact during the first wave of the pandemic, between March 1 and April 30, 2020. Trial recruitment was dramatically affected across the Innovative Therapies for Children with Cancer network. A total of 48.5% of phase I trials, 61% of phase II trials, and 64% of molecular platform trials closed to recruitment in at least one site. Worryingly, 16% of sites stopped all clinical trial recruitment for pediatric patients with cancer. Industry-sponsored trials were twice as likely to close to recruitment as academic studies. Overall recruitment across the network was 61% lower than during the corresponding period in 2019. Consistent with the points discussed in the telemedicine section, 20% of patients either had telephone appointments or had their reviews at local hospitals. A total of 58% of sites shipped investigational medicinal products either to local hospitals or directly to patients, and slighly more than 25% provided larger-than-usual quantities of investigational medicinal products to patients. Overall, 77% of units were able to provide remote support for data collection and input. Concerningly, there was a dramatic reduction in site initiation visits and monitoring visits during this time, as 67% of site initiation visits and 64% of monitoring visits were cancelled altogether.

The United Kingdom and the United States have robust clinical research consortia that operate multi-institutional clinical trials. After the impact of COVID-19 during the early months of the pandemic, the second half of 2020 saw a rapid reduction in the proportion of pediatric oncology trials that were suspended across the U.K. National Institutes for Health Research portfolio (Fig. 1). Other data from both the Children's Oncology Group and the U.K. Birmingham Cancer Research U.K. Clinical Trials Unit confirm that recruitment to pediatric oncology trials was robust through the remainder of 2020.

Figure 2 shows data on recruitment to trials run by the Cancer Research U.K. Clinical Trials Unit and the Children's Oncology Group from before and during the pandemic. The total number of trials open per quarter was not dramatically affected by the pandemic (Fig. 2A). Nonetheless, there was a decrease in recruitment in the United Kingdom and a slowdown in Children's Oncology Group trials in the second quarter of 2020, both of which have subsequently improved (Fig. 2B). At its maximum change, recruitment in the United Kingdom was 30% lower than baseline. A reduction in recruitment per clinical trial in the early part of the pandemic, but a robust recovery afterward, was seen both in the United Kingdom and in the Children's Oncology Group trials (Fig. 2C). A more marked reduction in recruitment has been seen for nontherapeutic trials, which has not yet fully recovered to prepandemic levels (Fig. 2D).

Funding

Clinical trials in pediatric oncology are already relatively underfunded compared with other diseases. Estimates suggest that pediatric cancers receive 1% to 4% of total cancer research funding. Before the onset of the pandemic,

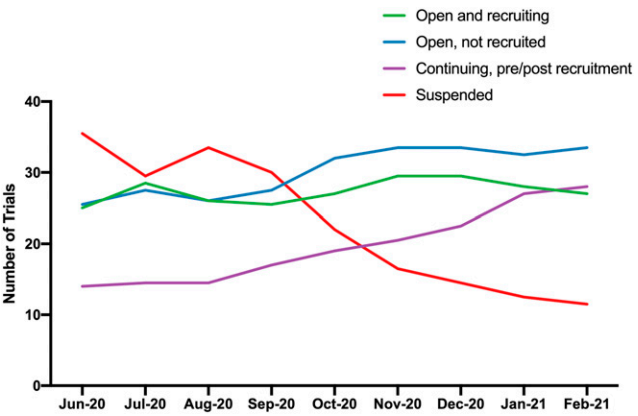

FIGURE 1. Status of Pediatric Oncology Clinical Trials Across the U.K. National Institute for Health Research Portfolio During the Pandemic

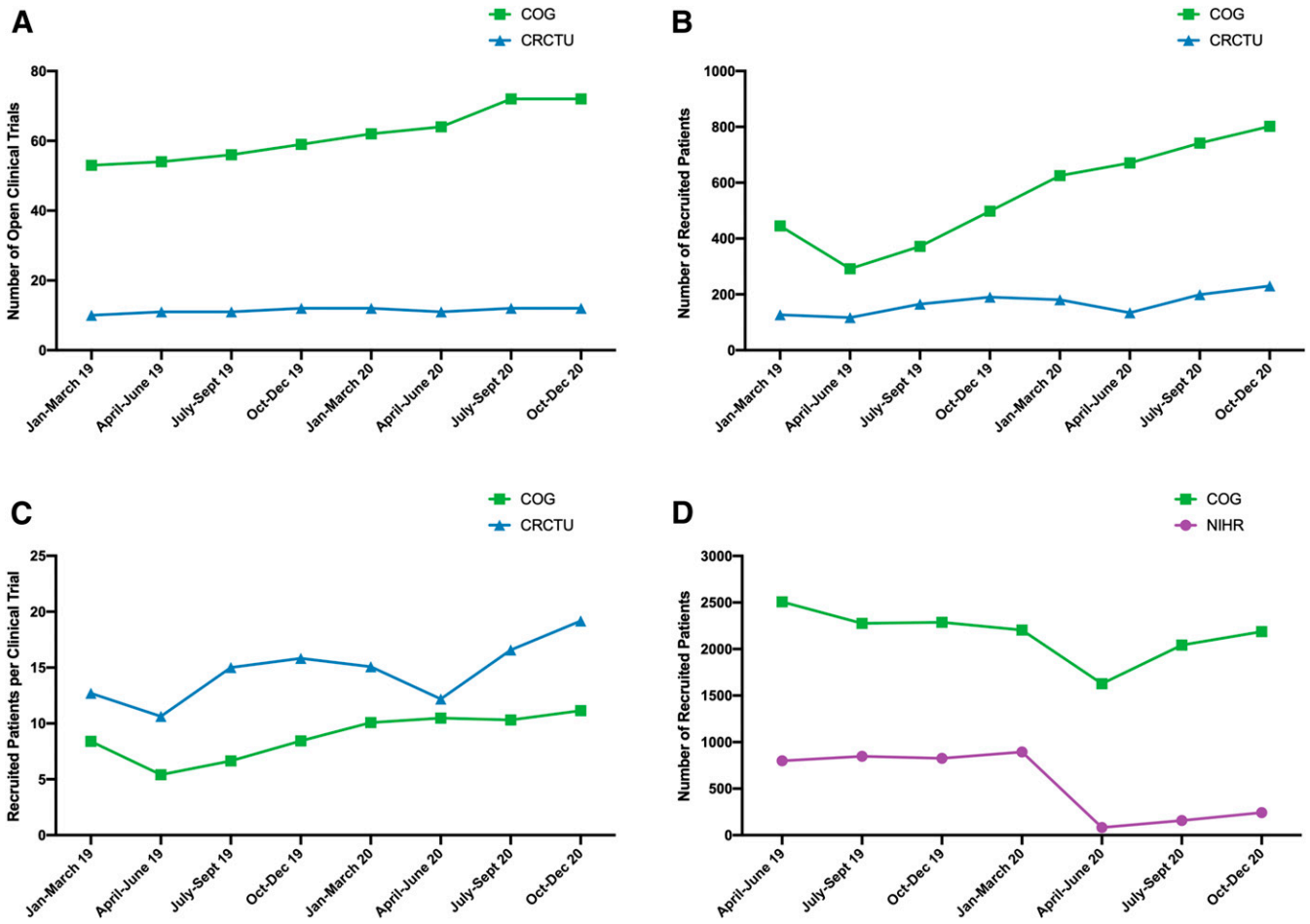

FIGURE 2. Trial Recruitment in Cancer Research U.K. Clinical Trials Unit, National Institute for Health Research, and Children's Oncology Group Trials
Abbreviations: CRCTU, Cancer Research U.K. Clinical Trials Unit; COG, Children's Oncology Group; NIHR, National Institute for Health Research. Open therapeutic trials per quarter (A). Total recruitment to therapeutic trials per quarter (B). Recruitment per open clinical trial per quarter (C). Recruitment to nontherapeutic trials per quarter (D).

there was already a worrying trend toward stagnation or reduction in funding for pediatric oncology.[54] A large proportion of funding for pediatric oncology research comes from philanthropic sources, and 78% originates in the United States. There is also a huge global discrepancy, with researchers in low- and middle-income countries receiving negligible amounts of funding compared with those in the United States and Europe.[55]

It is clear that the COVID-19 pandemic has already had a considerable impact on charitable donations. Cancer Research U.K., the Association of Medical Research Charities, the American Cancer Society, and the Canadian Cancer Society have all indicated notable shortfalls in revenue this year and have indicated that they will need to reduce the level of grants they offer across the entire cancer research sector.[56]

Given the dependency of pediatric oncology trials on charitable funding sources, it is likely that funding for preclinical and translational research, as well as phase I to III trials, will be impacted for many years.

SILVER LININGS

Despite the multiple effects of the COVID-19 pandemic, potential adaptations exist that can be used in the future of pediatric cancer care. Modifications that have been imposed by the pandemic, such as the use of telehealth or changes to the scope of provider responsibilities, have been proven to optimize resources.[51] Furthermore, unparalleled cooperation among industry, regulators, and researchers has shown the possibility for rapid and effective clinical research when there is the political imperative to do so. Additionally, the increasing acceptance and use of remote working and consultations may enable the efficiency of care and clinical trials to be improved, providing a counterpoint to the likely decreased funding going forward.[57] Some benefits to patients and caregivers, such as reduced traveling for evaluations or the increased ability to have some of their trial

treatment carried out more locally, may also be continued in the future.

CONCLUSION

The COVID-19 pandemic has had a substantial effect on pediatric cancer care, presenting an unprecedented global threat to the safe and effective care of children with cancer. The pandemic has disrupted diagnosis, treatment, and follow-up of patients. Although the majority of children with cancer will have mild COVID-19 disease, preliminary reports describe outcomes that are worse than the general pediatric population.[58] Many questions remain unanswered in terms of risk factors for severe disease.

After an initially dramatic reduction in clinical trial recruitment in the spring of 2020, recruitment in the United States and Europe has been robust. However, the medium-term outlook is more concerning, given the likely notable drop-off in funding and the impact this may have on the ability to deliver new trials and translational research.

The impact of the COVID-19 pandemic on the overall survival and outcomes of children with cancer is unclear but worrisome. Although the pandemic has created additional barriers to childhood cancer care, pediatric cancer providers and institutions have proven to be resilient in times with enormous obstacles. There is hope that the effects of the pandemic will subside and the adaptations it has imposed will bring a brighter future for the care of children with cancer. Current international COVID-19 vaccine implementation programs are still focused on the adult population, but there are already suggestions that responses may be less robust in the immune-compromised population with cancer. Once these vaccines are available to young patients, it will be crucial to evaluate their protective value in children with cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_321497.

REFERENCES

1. Johns Hopkins University & Medicine Coronavirus Resource Center. COVID-19 Data in Motion. https://coronavirus.jhu.edu/#covid-19-basics. Accessed March 9, 2021.
2. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21:335-337.
3. Sun D, Li H, Lu XX, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. World J Pediatr. 2020;16:251-259.
4. World Health Organization. Global Initiative Childhood Cancer. https://www.who.int/publications/m/item/global-initiative-for-childhood-cancer. Accessed March 9, 2021.
5. Balduzzi A, Brivio E, Rovelli A, et al. Lessons after the early management of the COVID-19 outbreak in a pediatric transplant and hemato-oncology center embedded within a COVID-19 dedicated hospital in Lombardia, Italy. Estote parati. Bone Marrow Transplant. 2020;55:1900-1905.
6. Boulad F, Kamboj M, Bouvier N, et al. COVID-19 in children with cancer in New York City. JAMA Oncol. 2020;6:1459-1460.
7. Kebudi R, Kurucu N, Tuğcu D, et al. COVID-19 infection in children with cancer and stem cell transplant recipients in Turkey: A nationwide study. Pediatr Blood Cancer. 2021;68:e28915.
8. Arous R, Djillali IS, Rouis NO, et al. High mortality of COVID-19 in children with cancer in a single center in Algiers, Algeria. Pediatr Blood Cancer. 2021;68:e28898.
9. Montoya J, Ugaz C, Alarcon S, et al. COVID-19 in pediatric cancer patients in a resource-limited setting: National data from Peru. Pediatr Blood Cancer. 2021;68:e28610.
10. Millen GC, Arnold R, Cazier JB, et al. Severity of COVID-19 in children with cancer: report from the United Kingdom Paediatric Coronavirus Cancer Monitoring Project. Br J Cancer. 2021;124:754-759.

11. de Rojas T, Pérez-Martínez A, Cela E, et al. COVID-19 infection in children and adolescents with cancer in Madrid. Pediatr Blood Cancer. 2020;67:e28397.
12. López-Aguilar E, Cárdenas-Navarrete R, Simental-Toba A, et al. Children with cancer during COVID-19 pandemic: early experience in Mexico. Pediatr Blood Cancer. 2021;68:e28660.
13. Bisogno G, Provenzi M, Zama D, et al. Clinical characteristics and outcome of severe acute respiratory syndrome coronavirus 2 infection in Italian pediatric oncology patients: a study from the Infectious Diseases Working Group of the Associazione Italiana di Oncologia e Ematologia Pediatrica. J Pediatric Infect Dis Soc. 2020;9:530-534.
14. Faura A, Rives S, Lassaletta Á, et al. Initial report on Spanish pediatric oncologic, hematologic, and post stem cell transplantation patients during SARS-CoV-2 pandemic. Pediatr Blood Cancer. 2020;67:e28557.
15. Madhusoodhan PP, Pierro J, Musante J, et al. Characterization of COVID-19 disease in pediatric oncology patients: the New York-New Jersey regional experience. Pediatr Blood Cancer. 2021;68:e28843.
16. Gampel B, Troullioud Lucas AG, Broglie L, et al. COVID-19 disease in New York City pediatric hematology and oncology patients. Pediatr Blood Cancer. 2020;67:e28420.
17. Rouger-Gaudichon J, Thébault E, Félix A, et al; on behalf of Société Française de Lutte Contre Les Cancers Et Leucémies de l'Enfant Et de L'adolescent Sfce. Impact of the first wave of COVID-19 on pediatric oncology and hematology: a report from the French Society of Pediatric Oncology. Cancers (Basel). 2020;12:3398.
18. The Global COVID-19 Observatory and Resource Center for Childhood Cancer. Global Registry of COVID-19 in pediatric cancer. https://global.stjude.org/en-us/global-covid-19-observatory-and-resource-center-for-childhood-cancer/registry.html. Accessed April 7, 2021.
19. Leeb RT, Price S, Sliwa S, et al. COVID-19 trends among school-aged children - United States, March 1-September 19, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1410-1415.
20. Kuderer NM, Choueiri TK, Shah DP, et al; COVID-19 and Cancer Consortium. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet. 2020;395:1907-1918.
21. Miyashita H, Mikami T, Chopra N, et al. Do patients with cancer have a poorer prognosis of COVID-19? An experience in New York City. Ann Oncol. 2020;31:1088-1089.
22. Mehta V, Goel S, Kabarriti R, et al. Case fatality rate of cancer patients with COVID-19 in a New York hospital system. Cancer Discov. 2020;10:935-941.
23. Vicent MG, Martinez AP, Trabazo Del Castillo M, et al. COVID-19 in pediatric hematopoietic stem cell transplantation: the experience of Spanish Group of Transplant (GETMON/GETH). Pediatr Blood Cancer. 2020;67:e28514.
24. Sharma A, Bhatt NS, St Martin A, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. Lancet Haematol. 2021;8:e185-e193.
25. Ahmed M, Advani S, Moreira A, et al. Multisystem inflammatory syndrome in children: a systematic review. EClinicalMedicine. 2020;26:100527.
26. Stokes CL, Patel PA, Sabnis HS, et al. Severe COVID-19 disease in two pediatric oncology patients. Pediatr Blood Cancer. 2020;67:e28432.
27. Pandrowala A, Panchal H, Mudaliar S, et al. SARS-CoV-2-related multisystem inflammatory syndrome in an immunocompromised child with leukemia. Pediatr Blood Cancer. 2021;68:e28995.
28. Moreira DC, Sniderman E, Mukkada S, et al. The Global COVID-19 Observatory and Resource Center for Childhood Cancer: a response for the pediatric oncology community by SIOP and St. Jude Global. Pediatr Blood Cancer. 2021;68:e28962.
29. Sullivan M, Bouffet E, Rodriguez-Galindo C, et al. The COVID-19 pandemic: a rapid global response for children with cancer from SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI, and St Jude Global. Pediatr Blood Cancer. 2020;67:e28409.
30. Janssens GO, Mandeville HC, Timmermann B, et al. A rapid review of evidence and recommendations from the SIOPE radiation oncology working group to help mitigate for reduced paediatric radiotherapy capacity during the COVID-19 pandemic or other crises. Radiother Oncol. 2020;148:216-222.
31. Verbruggen LC, Wang Y, Armenian SH, et al. Guidance regarding COVID-19 for survivors of childhood, adolescent, and young adult cancer: a statement from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Pediatr Blood Cancer. 2020;67:e28702.
32. Pushpam D, Bakhshi S, Agarwala S. Chemotherapy adaptations in a referral tertiary care center in India for ongoing therapy of pediatric patients with solid tumors during COVID19 pandemic and lockdown. Pediatr Blood Cancer. 2020;67:e28428.
33. Zhang A, Hu Q, Liu A, et al. Prevention of COVID-19 infection in a pediatric oncology ward in Wuhan. Pediatr Blood Cancer. 2020;67:e28424.
34. Schultz L, Link MP, Rheingold S, et al. Summary of COVID-19 clinical practice adjustments across select institutions. Pediatr Blood Cancer. 2020;67:e28411.
35. McLoone J, Wakefield CE, Taylor N, et al. The COVID-19 pandemic: distance-delivered care for childhood cancer survivors. Pediatr Blood Cancer. 2020;67:e28715.
36. Moerdler S, Steinberg DM, Jin Z, et al. Well-being of pediatric hematology oncology providers and staff during the COVID-19 pandemic in the New York and New Jersey epicenter. JCO Oncol Pract. Epub 2021 Feb 17.
37. Ferrari A, Pagani Bagliacca E, Veneroni L, et al. Experiencing social isolation (even in the era of COVID-19 pandemic lockdown): teachings through arts from adolescents with cancer. J Adolesc Young Adult Oncol. Epub 2020 Aug 7.
38. Cakiroglu S, Yeltekin C, Fisgin T, et al. Are the anxiety levels of pediatric hematology-oncology patients different from healthy peers during the COVID-19 outbreak? J Pediatr Hematol Oncol. Epub 2020 Aug 26 .
39. Amicucci M, Ciaralli I, Schiopu AC. Five leisure and training activities to help onco-hematological children to better live hospital isolation during COVID-19. Pediatr Blood Cancer. 2021;68:e28859.

40. Cheung AT, Li WHC, Ho LLK, et al. Health support to pediatric cancer survivors and their families during the COVID-19 pandemic. Pediatr Blood Cancer. 2020; 67:e28441.

41. Lazzerini M, Barbi E, Apicella A, et al. Delayed access or provision of care in Italy resulting from fear of COVID-19. Lancet Child Adolesc Health. 2020;4:e10-e11.

42. Ding YY, Ramakrishna S, Long AH, et al. Delayed cancer diagnoses and high mortality in children during the COVID-19 pandemic. Pediatr Blood Cancer. 2020; 67:e28427.

43. Parasole R, Stellato P, Conter V, et al. Collateral effects of COVID-19 pandemic in pediatric hematooncology: fatalities caused by diagnostic delay. Pediatr Blood Cancer. 2020;67:e28482.

44. Chiaravalli S, Ferrari A, Sironi G, et al. A collateral effect of the COVID-19 pandemic: delayed diagnosis in pediatric solid tumors. Pediatr Blood Cancer. 2020; 67:e28640.

45. Offenbacher R, Knoll MA, Loeb DM. Delayed presentations of pediatric solid tumors at a tertiary care hospital in the Bronx due to COVID-19. Pediatr Blood Cancer. 2021;68:e28615.

46. Dinmohamed AG, Visser O, Verhoeven RHA, et al. Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands. Lancet Oncol. 2020;21:750-751.

47. O'Neill AF, Wall CB, Roy-Bornstein C, et al. Timely pediatric cancer diagnoses: an unexpected casualty of the COVID-19 surge. Pediatr Blood Cancer. 2020; 67:e28729.

48. Vasquez L, Sampor C, Villanueva G, et al. Early impact of the COVID-19 pandemic on paediatric cancer care in Latin America. Lancet Oncol. 2020;21:753-755.

49. Saab R, Obeid A, Gachi F, et al. Impact of the coronavirus disease 2019 (COVID-19) pandemic on pediatric oncology care in the Middle East, North Africa, and West Asia region: a report from the Pediatric Oncology East and Mediterranean (POEM) group. Cancer. 2020;126:4235-4245.

50. Traoré F, Couitchere L, Michon J, et al. Patient management in pediatric oncology during the COVID-19 pandemic: report from francophone Africa. Pediatr Blood Cancer. 2021;68:e28571.

51. Graetz D, Agulnik A, Ranadive R, et al. Global effect of the COVID-19 pandemic on paediatric cancer care: a cross-sectional study. Lancet Child Adolesc Health. 2021;5:332-340.

52. Auletta JJ, Adamson PC, Agin JE, et al. Pediatric cancer research: surviving COVID-19. Pediatr Blood Cancer. 2020;67:e28435.

53. Rubio-San-Simón A, André N, Cefalo MG, et al. Impact of COVID-19 in paediatric early-phase cancer clinical trials in Europe: a report from the Innovative Therapies for Children with Cancer (ITCC) consortium. Eur J Cancer. 2020;141:82-91.

54. Loucaides EM, Fitchett EJA, Sullivan R, et al. Global public and philanthropic investment in childhood cancer research: systematic analysis of research funding, 2008-16. Lancet Oncol. 2019;20:e672-e684.

55. The Lancet Haematology. Childhood cancer: the need to invest in the future. Lancet Haematol. 2020;7:e82.

56. Burki TK. Cuts in cancer research funding due to COVID-19. Lancet Oncol. 2021;22:e6.

57. Bailey C, Black JRM, Swanton C. Cancer research: the lessons to learn from COVID-19. Cancer Discov. 2020;10:1263-1266.

58. Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: a systematic review. EClinicalMedicine. 2020;24:100433.

Disparities in Pediatric Oncology: The 21st Century Opportunity to Improve Outcomes for Children and Adolescents With Cancer

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Overview

Adult cancer disparities have been documented for decades and continue to persist despite clinical advancements in cancer prevention, detection, and treatment. Pediatric cancer survival has improved significantly in the United States for the past 5 decades to over 80%; however, disparate outcomes among children and adolescents with cancer still affect many populations in the United States and globally, including racial and ethnic minorities, populations with low socioeconomic status, and residents of underserved areas. To achieve equitable outcomes for all children and adolescents with cancer, it is imperative that concerted multilevel approaches be carried out to understand and address health disparities and to ensure access to high-quality cancer care. Addressing social determinants of health, such as removing barriers to health care access and ensuring access to social supports, can reduce pediatric cancer disparities. Nevertheless, public health policy, health system interventions, and innovative delivery of evidence-based services are critically needed. Partnerships among patients, caregivers, and health care providers, and among health care, academic, and governmental institutions, have a pivotal role in reducing cancer disparities and improving outcomes in the 21st century.

INTRODUCTION

In the United States, childhood and adolescent cancer is the leading cause of death by disease past infancy, with more than 17,000 children and adolescents younger than age 21 diagnosed annually.[1] Overall survival (OS) has improved tremendously over the past 5 decades,[2] and today, over 80% of U.S. children with cancer will be long-term survivors. These improvements have been driven in large part by multicenter clinical trials conducted by national and international cooperative groups to improve risk stratification, treatment intensity, and supportive care.[3] Despite this highly standardized approach to research and care delivery, underserved children, including those from racial and ethnic minority groups and/or of lower socioeconomic status, experience higher rates of relapse, decreased OS, and inferior psychosocial outcomes compared with their non-Hispanic White or wealthier counterparts.

Although national guidelines[4,5] call for elimination of cancer disparities, research to understand mechanisms driving inferior outcomes for underserved children with cancer is lacking, and few evidence-based interventions to address these disparities have been developed. The pursuit of health equity in pediatric oncology represents an opportunity in this unique political moment when unprecedented attention is being paid to racial and social justice. Moreover, as outcomes for the overall pediatric population with cancer continue to improve, targeting efforts to those who experience persistent inferior outcomes is the best approach to ensure equitable gains in reducing morbidity and mortality. Similar to current approaches to identify patients with high-risk disease characteristics and to allocate more intensive therapy to these patients, it is imperative that underserved patients at risk for inferior outcomes also be identified and their risk be mitigated through targeted interventions.

The National Cancer Institute defines cancer health disparities as adverse differences in cancer incidence, prevalence, burden, mortality, and survivorship that exist among specific U.S. populations.[4] Racial/ethnic and sex/gender disparities are the most frequently studied; however, other factors such as income, education, health insurance coverage, distance to health care facility, cultural dynamics, English proficiency, and health literacy have been found to be relevant as well.[5] For some specific groups, such as gender minorities, the lack of available data makes it difficult to even assess disparities.[6] Underserved populations in low- and middle-income countries are also greatly impacted by health disparities.[7] The worldwide COVID-19 pandemic has laid bare systemic and long-standing inequities and has disrupted access to health care

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PRACTICAL APPLICATIONS

- Cancer health disparities, defined as systematic and avoidable differences in cancer incidence, burden, mortality, and survivorship that adversely affect underserved groups, are prevalent in pediatric cancer, a highly curable disease.
- Disparate outcomes prevail despite advancements in treatment and a high proportion of patients being treated in therapeutic clinical trials. The field of pediatric cancer disparities, although nascent, is growing, and efforts are ongoing to understand and effectively address disparate clinical outcomes and ensure health equity.
- Disparities in pediatric cancer are complex and multifactorial, and involve social determinants of health, as well as inequities in access to high-quality diagnostic procedures and treatments; supportive, psychosocial, and survivorship care; and clinical trials.
- To effectively achieve equitable survival in the United States and globally, domestic and international collaborative research efforts are urgently needed to gain a better understanding of factors underlying disparate outcomes and inform multilevel interventions across patients, caregivers, providers, health systems, and academic and payer organizations.

services; these disruptions disproportionately affect those already facing health disparities within our health care delivery system, making tackling these issues critical.[6]

Black children have consistently experienced worse OS across pediatric cancer diagnoses. In fact, these racial disparities have recently widened for acute myeloid leukemia and neuroblastoma.[8] Hispanic children have a much higher incidence of several cancers, such as leukemia and lymphoma, and poorer 5-year OS than their non-Hispanic White counterparts (74% vs. 81%, respectively).[9-11] The pervasive and escalating nature of these disparities suggests that the underlying mechanisms driving survival disparities across disease groups relate to more complex factors than solely tumor biology,[2,8-10] which certainly varies by type of cancer.

This brief review highlights key disparities along the cancer continuum from access to care through cancer-directed therapy, including enrollment in clinical trials, and summarizes the complex landscape that influences achievement of equitable clinical outcomes for all children with cancer within the United States and globally.

Pediatric Cancer Disparities: Scope of the Problem at the Population-Based Level

ASCO's policy statement on cancer disparities and health equity emphasizes the importance of examining how multiple dimensions of patients' identities intersect to affect health outcomes,[6] including race, ethnicity, and insurance status. Cancer registries present an opportunity to evaluate disparities at the population-based level. These data are essential for generalizability to the broader population in the setting of known disparities in access to specialized cancer centers and disparities in enrollment into clinical trials.[12-14] However, there are also limitations to these data, in that they frequently lack clinical details relevant to prognosis and outcomes, including disease biology and treatment information (Table 1).

Race and ethnicity are social categories constructed based on socioeconomic and political forces and are an imperfect proxy, at best, for genetic ancestry. As oncologists, a considerable proportion of risk stratification and prognosis is based on cancer genomics, and thus, it is tempting to use race as a biologic guidepost for genetic differences among our patients.[15] However, there is mounting evidence that race is not a reliable proxy for genetic differences or the relation between ancestry[16] and genetics. At the very least, we must accept that racial/ethnic groups represent genetically heterogeneous populations that lack clear-cut genetic boundaries.

Racial and Ethnic Disparities

Using the National Cancer Institute's Surveillance, Epidemiology, and End Results database, Kahn et al[17] described notable disparities in survival trends of pediatric and adolescent/young adult patients (defined as age 15 to 39) with hematologic malignancies, including acute lymphoblastic leukemia, acute myeloid leukemia, and Hodgkin lymphoma, over a 4-decade period. Focusing on their data from 2004 to 2007, in acute lymphoblastic leukemia, Hispanic children had worse survival (88% for Hispanic children [95% CI, 85–91] vs. 93% for non-Hispanic White children [95% CI, 91–95]).[17] Among Black children with acute myeloid leukemia, worse survival was observed (54% for Black children [95% CI, 34–70] vs. 71% for non-Hispanic White children [95% CI, 61–79]).[17] In Hodgkin lymphoma, worse outcomes were observed in Black adolescent/young adult patients (92% for Black adolescent/young adults [95% CI, 88–95] vs. 96% for non-Hispanic White adolescent/young adults [95%CI, 95–97]).[17] Care for adolescent/young adult patients with leukemia and brain tumors at specialized cancer centers has been shown to mitigate disparities between adolescent/young adult patients and their younger counterparts[18,19]; however, it is unclear the effect that treatment at such centers similarly has upon racial and ethnic disparities. The Surveillance, Epidemiology, and End Results

TABLE 1. Strengths and Limitations of Data Sources Used to Investigate Disparities

	Cancer Registry Data	Billing/Administrative Data	Clinical Trial Data	Institutional Data
Strengths	Full population-based sample, curated cancer data, and mortality data	Detailed information about medications, procedures, and hospitalizations	Targeted and consistent data collection on disease biology, treatment, and outcomes	Detailed electronic health record data and ease of primary data collections (surveys, interviews, patient-reported outcomes)
Limitations	Detailed clinical and treatment data are lacking	Difficult to identify patients with cancer and lacking clinical details	Selected population who only includes those enrolled in a research study	Limited sample size and generalizability

NOTE. None of these data resources consistently collect individual measures of socioeconomic status.

database was also used to describe survival disparities for common pediatric extracranial solid tumors between 1985 and 2005.[20] Overall, Black and Asian/Pacific Islander children had a higher risk of death compared with non-Hispanic White children (HR, 1.31, and HR, 1.34, respectively; $p < .05$). Black children had a higher risk of death from germ cell tumors, hepatoblastoma, and non-rhabdomyosarcoma soft tissue sarcomas. Interestingly, differences in survival between Hispanic and non-Hispanic children were not observed. For brain tumors, a recent study demonstrated that Hispanic and Black children had substantially higher hazard of death than non-Hispanic White children (Hispanic: HR, 1.25; 95% CI, 1.18–1.31; Black: HR, 1.12; 95% CI, 1.04–1.21).[21] These differences were most prominent among those with high-grade tumors, with no difference observed in diffuse astrocytoma. In a study using the California Cancer Registry to investigate disparities among children with high-grade gliomas, Hispanic children had worse survival than non-Hispanic White children (HR, 1.62; 95% CI, 1.24–2.11).[22]

Health Insurance–Based Disparities

In the United States, health insurance coverage has consistently been demonstrated to be one of the strongest predictors of cancer outcomes.[6,7] Health insurance is often used as a proxy for household income, as child eligibility for public insurance (e.g., Medicaid) is based on state-defined income thresholds. The Patient Protection and Affordable Care Act, enacted in 2010, requires Medicaid coverage for all children up to 133% of the federal poverty line.[23] The 1997 Children's Health Insurance Program was created to subsidize health insurance for children[24] in working families with incomes too high to qualify for Medicaid. In 13 states, the income eligibility threshold for the Children's Health Insurance Program is up to 400% of the federal poverty line.[25] Medicaid and the Children's Health Insurance Program cover more than one in three (37%) of children overall, and over half of Hispanic (52%) and Black children (54%). Among children with cancer, similar differences are observed, with Black children being more likely to have public insurance than non-Hispanic White children (73% vs. 37%).[8] The complementary coverage of these two programs has led to relatively few uninsured children (less than 7%).[23]

Health insurance is also used as a measure of health care access, given that the ability to pay for health services or have them covered is a determinant of the care sought and received.[24] In pediatrics, disruptions in health insurance coverage are associated with reduced access to care.[26] Among adult patients with cancer, a review found that those with disruptions were more likely to present at an advanced stage (odds ratio, 1.2–3.8) and have worse survival (HR, 1.28–2.43) compared with patients without insurance disruptions.[27]

Based on the existing U.S. insurance infrastructure, the adolescent/young adult population is at particular risk for insurance disruptions and is especially vulnerable to the impact of health insurance on health outcomes. In a population of 66,556 patients with cancer in the Surveillance, Epidemiology, and End Results database between 2007 and 2014, noteworthy survival disparities were associated with health insurance status in adolescents with acute lymphoblastic leukemia, acute myeloid leukemia, and Hodgkin lymphoma.[28] Public or no insurance increased the risk of death, and this effect increased with age for most cancer types.

In an attempt to disentangle insurance as a measure of access to care from insurance as a proxy for low-income status, Keegan et al[29] distinguished adolescent/young adult patients with continuous Medicaid coverage prior to diagnosis compared with those who obtained Medicaid coverage at diagnosis using a linkage between the California Cancer Registry with Medicaid enrollment files. Patients with Medicaid insurance had significantly worse survival regardless of when coverage began (Medicaid at diagnosis: HR, 1.51; 95% CI, 1.42–1.61; continuous Medicaid: HR, 1.42; 95% CI, 1.33–1.52; and discontinuous Medicaid: HR, 1.64; 95% CI, 1.49–1.80). Notably, adolescent/young adults who enrolled in Medicaid at diagnosis (and were uninsured prior to diagnosis) were 2.2 to 2.5 times more likely to be diagnosed with later-stage disease (vs. Medicaid discontinuously enrolled, 1.7 to 1.9 times, and Medicaid

continuously enrolled, 1.4 to 1.5 times) compared with those with private insurance.[29] These findings suggest that access to care figures prominently into the impact of health insurance, given that all three study populations qualify for Medicaid based on income.

For patients with acute myeloid leukemia in the Pediatric Health Information System administrative database, the joint effect of Black race and public insurance on induction mortality (HR, 3.91; 95% CI, 1.32–11.6) was greater than expected based on the independent effects, suggesting that the absolute difference between Black and non-Hispanic White patients is larger among publicly insured children.[30]

Taken together, population-based data demonstrate that racial and ethnic minority children and adolescents, and those of lower socioeconomic status, experience consistent disparities in cancer presentation and survival outcomes across diseases.

Minority Underrepresentation in Cancer Research

The National Institutes of Health Revitalization Act of 1993 mandated the inclusion of women and minority populations in clinical trials.[31] However, to date, only 2% of approximately 10,000 National Cancer Institute clinical trials have representative minority participants.[32] By 2060, Hispanic children will comprise 33% of the U.S. childhood population.[33,34] Despite this growth and the National Cancer Institute's efforts to include minority individuals in research,[35] Hispanic and Black adults are severely underrepresented in research participation compared with non-Hispanic White adults (1% to 7% vs. 15% and 67%, respectively).[36] Participation rates in adult cancer clinical trials are even lower, at 0.4% to 2.2% for Hispanic patients and 5.4% for Black patients,[37] even at National Cancer Institute–designated comprehensive cancer centers.[38] In addition, data show that Black and Hispanic adolescent/young adults with acute lymphoblastic leukemia are less likely to be treated at National Cancer Institute–designated comprehensive cancer centers or sites affiliated with the Children's Oncology Group.[19] These patterns of decreased enrollment of patients from minority groups have also been observed in pediatric cancer clinical trials,[39] with Hispanic children being reported as underrepresented in pediatric cancer research.[40] Lower survival rates observed at the population level are at least partially attributable to lower enrollment in clinical trials.[41]

Differences between participants in clinical trials and real-world populations, who ultimately will receive the treatments once they become standard of care, preclude the generalizability of results and equitable translation and assessment of treatment benefits for underrepresented minority groups. Nonrepresentative trial participation in a field that is centered on trial-based cancer discovery perpetuates existing disparities by precluding the ability to assess pharmacogenomics characteristics in metabolism and toxicity in minority populations, which is highly relevant to real-world utilization of cancer-directed therapies. Similarly, patient-level predictors of adherence to complex therapies cannot be evaluated if diverse populations are not represented in clinical trials.

Clinical Trial Participation Inequity in Adolescents With Cancer

Survival disparities among adolescents (age 15 to 21) persist despite overall improvement in survival, morbidity, and quality of life for younger children with cancer in the United States.[42] Evidence shows that participation in clinical trials is associated with better survival outcomes among children and adolescents with cancer;[2,39] however, adolescents have lower clinical trial participation rates compared with younger age cohorts (30% vs. 68%, respectively).[28,38,40] Globally, adolescent enrollment rates into cancer clinical trials are the lowest of any age group.[2] Poor enrollment of adolescents into cancer clinical trials may contribute to inferior survival gains compared with children, beyond differences in tumor biology. For example, in acute lymphoblastic leukemia, the most common pediatric cancer, 5-year survival exceeds 85% in 1 to 14-year-olds and is significantly lower in adolescents at 75%.[3]

Barriers to Clinical Trial Participation in Underserved Groups

Individuals from racial and ethnic minority groups in the United States have a similar level of willingness to enroll in cancer clinical trials compared with non-Hispanic White patients.[38] Nevertheless, multilevel barriers prevent clinical trial enrollment at rates comparable to non-Hispanic White patients.[36] These include structural, clinical, attitudinal, and sociodemographic barriers at the institutional, physician, and patient levels. Structural barriers include clinical trial availability and complexity of trial design, time constraints for proper informed consent and enrollment paperwork, and lack of dedicated research staff to serve minority populations.[43] Clinical barriers related to patient ineligibility due to narrow eligibility criteria in some trials may limit generalizability of results. Sources of funding may impede equitable participation of minority individuals in clinical trials, as an increasing number of pediatric cancer clinical trials are sponsored by the pharmaceutical industry. Lack of diverse representation in clinical trials can be exacerbated when pharmaceutical companies seek a homogenous trial population to minimize confounding patient-related factors, while also attempting to open trials at high-enrolling sites, which tend not to be minority-serving institutions, particularly for adults, and where care appears to be more expensive.[44,45] At the physician level, physician preference has been described as a primary reason for nonenrollment of eligible patients.[36] Physicians play a pivotal role in clinical trial enrollment, because patients may only be aware of

research opportunities and consider enrollment if recommended by their physician. Physicians may not offer a clinical trial if they think it may interfere with the physician-patient relationship. Moreover, racial/ethnic stereotypes may lead to the perception that minority patients are less likely to follow-up with the often-complex requirements of a clinical trial, resulting in the opportunity to participate not being offered. Lastly, patient-level factors include negative misconceptions about research or lack of awareness of clinical trials; fear of side effects, experimental procedures, or random assignment; health literacy, culture, and language barriers; transportation barriers; travel costs; insurance barriers; and unavailability of child care.[46] Moreover, mistrust of the health care and clinical trial systems has been cited by minority patients as a common reason for nonenrollment, particularly by Black individuals who have historically suffered discrimination by the medical system.[47]

Strategies to Increase Enrollment of Minority Populations in Pediatric Cancer Clinical Trials

It is critical that the demographics of patients enrolled in clinical trials of novel cancer therapeutics be comparable to that of the current U.S. pediatric population with cancer. Representative participation in clinical trials that support cancer discovery can ensure investigation of genomics associated with ancestry as well as consideration of health care delivery approaches necessary to maximize cancer care tailored to underserved patients. The U.S. racial/ethnic composition has changed rapidly over the last 50 years and is projected to continue to do so.[48] For instance, in 2010, 16% of the U.S population comprised Hispanic individuals, and by 2065, they are expected to comprise 31%; therefore, efforts to improve enrollment of minority patients are clearly needed, and we must prepare to provide state-of-the-art care to this growing population.[33] Barriers may differ among academic and nonacademic institutions; thus, approaches to optimizing clinical trial enrollment should be tailored to specific settings. Strategies to improve minority enrollment should address structural barriers related to study design and conduct, including informed consent. Decreasing the rigidity of inclusion/exclusion criteria facilitates enrollment of a study population that is a better reflection of patients who are most likely to receive those therapies in the real world. Partnerships between National Cancer Institute–designated comprehensive cancer centers and minority-serving institutions or satellite sites in underserved communities can be established to increase enrollment.[38,49] Additionally, programs at ASCO[50] and the National Cancer Institute, such as the Center to Reduce Cancer Health Disparities,[51] facilitate the training of cancer scientists from diverse backgrounds to address the diversity gap in the pediatric oncology workforce, currently comprising 6.0% Hispanic and 1.5% Black providers.[52]

To overcome provider-level barriers, training focused on patient-provider communication, the use of culturally appropriate tools and medical interpreters, and employment of trained bilingual/bicultural research staff can facilitate minority enrollment. At the patient level, strategies, such as building trust, promoting education and awareness of clinical trials with anticipatory guidance and multimedia, and implementation of health literacy–focused interventions, that are also culturally and linguistically concordant may increase enrollment. Initiatives to address patients' socioeconomic barriers, such as reimbursement for food and/or transportation costs, coupled with allocation of funds to provide additional staff time for minority enrollment, may have a beneficial impact on enrollment and retention of minority individuals.[46]

Barriers and Enablers to Adequate Informed Consent in Minority Parents of Children With Cancer

Research is scarce on the factors that affect informed consent during enrollment of patients from minority groups in pediatric cancer clinical trials.[53,54] Studies indicate that barriers to adequate informed consent limit minority child and adolescent participation in clinical trials.[40,55,56] True informed consent is deemed valid and meaningful if competence, information disclosure, comprehension, and voluntariness are effectively satisfied.[55,57,58] The process involves the consenting provider verifying the participant's understanding of risks, benefits, and alternatives and ensuring patient's decision-making abilities.[59] Voluntariness is defined as the willingness to participate in research without feeling coerced.[60] Federal law requires that children and adolescents have parental informed consent to participate in research, but no mandates ensure voluntariness or comprehension of the information received.[53] Recruitment into pediatric cancer clinical trials often occurs under tremendous emotional stress because of the life-threatening nature of cancer and the need to start treatment promptly. This may hinder comprehension of the informed consent, parental decision-making abilities to weigh the benefits and risks in research, and voluntariness of participation in the clinical trial,[61] particularly in those with limited health literacy.[55,62]

Health literacy is defined as the degree to which individuals are able to process health information to make appropriate health decisions.[63] In the United States, at least one in four adults has limited health literacy skills.[64] Limited health literacy is associated with minority race/ethnicity and poor health outcomes in children.[64,65] Among children with cancer, limited health literacy has been associated with Hispanic ethnicity, Spanish language, low education level, and public insurance coverage.[55] In a recent report, lower perception of voluntariness was associated with limited health literacy among parents of children with newly

diagnosed leukemia who had consented for their child's participation in a therapeutic clinical trial,[55] suggesting that parents with limited health literacy perceive external influences on their decision to enroll their child in a clinical trial. This highlights the potential role of recruitment interventions tailored to the participant's health literacy level to improve comprehension, decision-making abilities, and voluntariness of informed consent in underserved populations.[55] Interventions to increase minority recruitment in clinical trials have focused on communities rather than individuals,[66] with scant information on improving patient-provider communication during recruitment and informed consent procedures. Moreover, research is scarce on interventions to improve clinical trial participation in minority children and adolescents with cancer, particularly parental informed consent comprehension and decision-making self-efficacy. Future areas of research must include evaluating the feasibility and effectiveness of interventions designed to enhance shared decision-making and patient-provider communication during informed consent, including parent advocates and patient navigators and clinical trial education and anticipatory guidance with multimedia.[55]

Racial, Ethnic, and Poverty-Associated Outcome Disparities Persist in the Clinical Trial Setting

Even when treated in multicenter clinical trials, children who are Black, Hispanic, or living in poverty experience higher rates of relapse and lower OS across disease groups.[10,67-70] The persistence of these disparities within the gold-standard setting of trial-delivered care underscores an urgent need to systematically incorporate social determinants of health into clinical trial design while concurrently developing evidence-based interventions to address them.

Acute Leukemia

A review of published trial data from the 1980s to the modern era demonstrates that Black and Hispanic children, and those who were exposed to poverty, experience excess relapse and death when compared with their non-Hispanic White, wealthier counterparts. Among 5,086 children with acute lymphoblastic leukemia enrolled in phase III Pediatric Oncology Group trials from 1981 to 1994, Black and Hispanic children experienced strikingly inferior OS compared with non-Hispanic White children (OS: 68.6% Black, 74.9% Hispanic, and 81.9% non-Hispanic White; $p < .0001$).[71] After adjusting for disease and treatment-era characteristics, Black race (HR, 1.42; 95% CI, 1.12–1.80) and Hispanic ethnicity (HR, 1.33; 95% CI, 1.19–1.49) remained independently associated with increased risk of mortality. A retrospective analysis of 8,762 children with acute lymphoblastic leukemia treated on Children's Cancer Group protocols demonstrated nearly identical survival disparities,[10] recapitulating the independent association of Black race (OS: relative risk, 1.4; 95% CI, 1.1–1.6; event-free survival: relative risk, 1.4; 95% CI, 1.2–1.7) and Hispanic ethnicity (OS: relative risk, 1.4; 95% CI, 1.2–1.6; event-free survival: relative risk, 1.3; 95% CI, 1.2–1.5) with inferior OS and event-free survival in multivariable analyses.

Similar racial and ethnic disparities exist in acute myeloid leukemia, a disease for which treatment is characterized by primarily inpatient chemotherapy and supportive care in contrast to the primarily outpatient cancer therapy used for acute lymphoblastic leukemia. Among 791 children with acute myeloid leukemia treated in CCG-2891 between 1989 and 1995, Black and Hispanic children had inferior OS compared with non-Hispanic White children (OS: Black, $34 \pm 10\%$; $p = .007$; Hispanic, $37 \pm 9\%$; $p = .016$; and non-Hispanic White, $48 \pm 4\%$).[68] These disparities persisted in the subsequent decade in the cohort of 850 children treated in CCG-2961 between 1996 and 2002. Notably, Black and Hispanic children were more likely to experience death during induction ($p = .02$) and die of an infectious complication ($p = .035$) compared with non-Hispanic White children.[68,72]

The impact of socioeconomic status on acute lymphoblastic leukemia outcomes in the clinical trial setting has been less robustly investigated, in part because of historical deficiencies in the systematic collection of measures of socioeconomic status and other social determinants of health in cooperative group trials. A retrospective analysis of 575 children with newly diagnosed acute lymphoblastic leukemia treated in consecutive Dana-Farber Consortium Protocols between 2000 and 2010 demonstrated that children living in high-poverty areas were significantly more likely to experience early relapse (fewer than 36 months in complete remission) compared with those living in low-poverty areas.[67] Specifically, among the cohort of children who relapsed, 92% of those from high-poverty areas experienced early relapse, compared with 48% of those from low-poverty areas ($p = .008$). Black and Hispanic children were significantly more likely to live in high-poverty areas ($p < .0001$).

These retrospective trial data identify striking disparities but are unable to unravel the mechanisms underlying these survival inequities. Specifically, the relative contributions of social determinants of health associated with the social construct of racial/ethnic minority status (e.g., structural racism impacting socioeconomic status, education, access to health care, and basic resource needs) and genetic ancestry–associated pharmacogenomic differences[73,74] that may drive treatment efficacy or toxicity remain unclear. It is notable that similar analyses at St. Jude Children's Research Hospital for acute lymphoblastic leukemia between 1991 and 1998[75] and for acute myeloid leukemia between 1980 and 2002[76] demonstrated no differences in event-free survival or OS for Black or Hispanic children,

perhaps due, in part, to systematic provision of social support in their model of care delivery, regardless of insurance coverage.

Lymphoma

Racial and ethnic disparities have been identified among children treated for Hodgkin lymphoma in the context of both Children's Oncology Group and St. Jude Children's Research Hospital[77] clinical trials, though investigation of trial-based disparities for other lymphomas are limited. Among a cohort of 1,605 patients with Hodgkin lymphoma treated in Children's Oncology Group trials between 2002 and 2012,[69] non-White patients (pooled Black and Hispanic) had a 1.88 (95% CI, 1.06–3.33) times higher risk of mortality in multivariable analyses adjusting for disease-associated characteristics. Among a subcohort of children with relapsed Hodgkin lymphoma, Black and Hispanic children experienced 3.45 (95% CI, 1.46–8.16) and 2.72 times (95% CI, 1.19–6.23) higher risk of postrelapse mortality, respectively, in multivariable analysis adjusting for neighborhood-level poverty. In a St. Jude Children's Research Hospital cohort of 327 patients with Hodgkin lymphoma treated in successive trials between 1990 and 2001,[77] Black children had inferior event-free survival compared with non-Hispanic White children (71 ± 6.1% vs. 84 ± 2.4%; p = .01) and were 3.7 times (95% CI, 1.7–8.0) as likely to relapse 12 months postdiagnosis.

Solid Tumor

Relatively few studies have investigated racial, ethnic, or socioeconomic disparities in clinical trials for pediatric solid tumors. A retrospective analysis of 2,343 children treated in Intergroup Rhabdomyosarcoma Study Group clinical trials between 1984 and 1997 identified no differences in failure-free survival between Black children and non-Hispanic White children.[78] Conversely, a more recent analysis of poverty exposure and survival in high-risk neuroblastoma demonstrated profound survival disparities among children with public insurance and those living in low-income areas. Among 371 children with high-risk neuroblastoma treated in Children's Oncology Group targeted immunotherapy trials ANBL0032 and ANBL0931 from 2005 to 2014, household poverty–exposed children experienced significantly inferior event-free survival (HR, 1.90; 95% CI, 1.28–2.82; p = .001) and OS (HR, 2.79; 95% CI, 1.60–4.79; p < .001) compared with poverty-unexposed children after adjustment for disease and treatment factors.[70] Although neighborhood poverty was not independently associated with survival, dual poverty exposure (household and neighborhood poverty) predicted both inferior event-free survival (HR, 2.21; 95% CI, 1.48–3.30; p < .001) and OS (HR, 3.70; 95% CI, 2.08–6.59; p < .001) in multivariable analyses. Neither race nor ethnicity was independently associated with inferior event-free survival or OS in this cohort; however, Black and Hispanic children were much more likely to be poverty-exposed and thus disproportionately suffered from poverty-associated survival disparities.[70]

Next Steps: Leveraging the Clinical Trial Infrastructure to Investigate and Address Disparities

Although limited to retrospective analyses, these data highlight the stark persistence of racial, ethnic, and socioeconomic disparities in clinical outcomes even in the context of clinical trial–delivered care. More studies are needed to examine differences in outcomes proximal to mortality. For example, among a cohort of 1,240 patients enrolled in Children's Oncology Group trials between 2010 and 2018, Black patients were significantly less likely to receive proton radiation therapy compared with non-Hispanic White patients (odds ratio, 0.35; 95% CI, 0.17–0.72; p = .004) even after adjusting for sociodemographic and disease-associated characteristics.[79] Access to radiotherapy, surgery, and stem cell transplant may impact survival outcomes for underserved children despite enrollment in uniform clinical trials.

That Black, Hispanic, and poor children with cancer are more likely to relapse and die when receiving cancer therapy in multicenter clinical trials highlights the stark reality that access to and equitable enrollment in clinical trials are necessary but not sufficient to eliminate survival disparities in pediatric oncology. More specifically, trial-embedded investigations of structural, sociobehavioral, and biologic mechanisms underlying racial, ethnic, and socioeconomic disparities are essential to inform evidence-based interventions aimed to achieve equity. Reporting of racial/ethnic outcomes in National Institutes of Health–funded trials is very low at approximately 13%, suggesting that National Institutes of Health policies mandating reporting of outcomes by race/ethnicity have not been effective.[32] Recent reports have demonstrated that clinical trial–embedded collection of parent-reported social determinants of health is feasible,[80] a first step in establishing the evidence base necessary to support trial-embedded health equity interventions. Preliminary data from these efforts demonstrate a high frequency of modifiable poverty exposures, including one in three children living with household material hardship (food, heat, housing, or transportation insecurities),[81] which disproportionately impact Black and Hispanic children.[80] Evaluation of a scalable intervention targeting household material hardship as a risk factor for outcome disparities is ongoing.[82]

Global Pediatric Cancer Disparities

Pediatric cancer inequities at the global level are even more striking than those observed in the United States and are essential to acknowledge in any discussion of pediatric oncology disparities. With more than 400,000 new cases of childhood cancer diagnosed annually worldwide,[83] the

survival gap for children with cancer in low- and middle-income countries compared with high-income countries is astounding.[84,85] Unfortunately, in low- and middle-income countries, where 80% of the world's children reside, 5-year OS for children with cancer is 10% to 60%, compared with over 80% in high-income countries.[86] This survival gap reflects the profound disparities that exist in the socioeconomic and health care infrastructures between low- and middle-income countries and high-income countries that hinder access to comprehensive cancer care. Effective management of pediatric cancer involves obtaining accurate epidemiologic data, providing workforce specialty training, developing treatment and supportive care guidelines, ensuring consistent access to medications and equipment, improving patient/family psychosocial and financial support, and facilitating adherence to treatment. Contributing factors to disparate outcomes in low- and middle-income countries include inadequate training for health care providers, high rates of advanced disease at presentation, deficiencies in the referral and diagnostic pathways, malnutrition, high rates of treatment complications and abandonment, and limited access to curative therapies, such as chemotherapy and sophisticated surgical and radiotherapy services.[87-90] Global pediatric cancer programs are desperately needed to reduce survival gaps in low- and middle-income countries. Key components of such programs include financial coverage, accreditation of pediatric cancer centers, mandatory case registration and reporting, and the creation of national standards of care and pediatric cancer–governing bodies.[91] Strategies must focus on overcoming local challenges, leveraging regional opportunities, and engaging in capacity-building through the development of infrastructure, technology, and training for health care professionals to advance their ability to effectively care for underserved children with cancer in low- and middle-income countries.[92,93] Long-lasting improvements in disparate outcomes in low- and middle-income countries will require cohesive global health system planning with multiple stakeholders and establishing partnerships between institutions in high-income countries and low- and middle-income countries aimed at developing large-scale collaborative projects and research that have the potential to change national and international health policy.[86]

CONCLUSION

Pediatric oncology is a success story of modern medicine, with steady improvements in relapse and survival over the past half century ensuring that the great majority of children diagnosed with cancer in this era will be long-term survivors. That our most underserved children—those identified as from racial and ethnic minority groups and those of lower socioeconomic status—remain more likely to relapse and die of cancer is unacceptable. Overcoming pediatric cancer inequities is a moral and ethical imperative.

Pediatric oncology, as a field, is uniquely positioned to achieve the scientific breakthroughs necessary to eliminate outcome disparities by leveraging its robust cooperative group trial infrastructure to systematically identify mechanisms underlying disparities and evaluate health equity interventions to target them. Focusing future efforts on underserved and socially vulnerable children who experience increased morbidity and mortality represents the 21st century opportunity for continued improvements in pediatric cancer survival (Sidebar 1). To understand, address, and reduce disparities, epidemiologic and health outcomes research, including the development of multilevel strategies, is urgently needed within academic, health care, government, and community organizations. As pediatric cancer incidence continues to increase and minority populations continue to grow in the United States, it is time for a paradigm shift to integrate health equity investigation across all domains of pediatric cancer research—from biobanking to clinical trial development—to ensure every child has an equal opportunity for a cure.

SIDEBAR 1. FUTURE AREAS OF FOCUS FOR PEDIATRIC CANCER DISPARITIES RESEARCH

- Health outcomes, cost-effectiveness, quality improvement, and implementation science research to scale up, evaluate, and disseminate evidence-based interventions (e.g., patient navigation and resource equity) to achieve equitable care for underserved children with cancer
- Approaches to raise awareness about pediatric cancer disparities in health care institutions and systems and broader communities, domestically and globally
- Empowerment of patients from minority groups and their caregivers to be active participants in their care and related research
- Dissemination of data to government and private sector health care insurers and policy makers regarding the need for high-quality care for underserved children and for development of health policies to achieve equitable outcomes for all

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7-33.
2. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol. 2012;30:1663-1669.
3. Moke DJ, Oberley MJ, Bhojwani D, et al. Association of clinical trial enrollment and survival using contemporary therapy for pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer. 2018;65:e26788.
4. Polite BN, Adams-Campbell LL, Brawley OW, et al. Charting the future of cancer health disparities research: A position statement from the American Association for Cancer Research, the American Cancer Society, the American Society of Clinical Oncology, and the National Cancer Institute. CA Cancer J Clin. 2017; 67:353-361.
5. Institute of Medicine Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care. In Smedley BD, Stith AY, Nelson AR, (eds). Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC: National Academies Press; 2003.
6. Patel MI, Lopez AM, Blackstock W, et al. Cancer disparities and health equity: a policy statement from the American Society of Clinical Oncology [published correction appears in *J Clin Oncol*. 2020;38:3976]. J Clin Oncol. 2020;38:3439-3448.
7. Peters DH, Garg A, Bloom G, et al. Poverty and access to health care in developing countries. Ann N Y Acad Sci. 2008;1136:161-171.
8. Pui CH, Pei D, Pappo AS, et al. Treatment outcomes in black and white children with cancer: results from the SEER database and St Jude Children's Research Hospital, 1992 through 2007. J Clin Oncol. 2012;30:2005-2012.
9. Winestone LE, Aplenc R. Disparities in survival and health outcomes in childhood leukemia. Curr Hematol Malig Rep. 2019;14:179-186.
10. Bhatia S, Sather HN, Heerema NA, et al. Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. Blood. 2002;100:1957-1964.
11. Wang L, Gomez SL, Yasui Y. Racial and ethnic differences in socioeconomic position and risk of childhood acute lymphoblastic leukemia. Am J Epidemiol. 2017; 185:1263-1271.
12. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. Br J Cancer. 2014;110:551-555.
13. Chamberlain LJ, Pineda N, Winestone L, et al. Increased utilization of pediatric specialty care: a population study of pediatric oncology inpatients in California. J Pediatr Hematol Oncol. 2014;36:99-107.
14. Alvarez E, Keegan T, Johnston EE, et al. Adolescent and young adult oncology patients: Disparities in access to specialized cancer centers. Cancer. 2017; 123:2516-2523.
15. Vyas DA, Eisenstein LG, Jones DS. Hidden in plain sight - reconsidering the use of race correction in clinical algorithms. N Engl J Med. 2020;383:874-882.
16. Yudell M, Roberts D, DeSalle R, et al. Taking race out of human genetics. Science. 2016;351:564-565.
17. Kahn JM, Keegan TH, Tao L, et al. Racial disparities in the survival of American children, adolescents, and young adults with acute lymphoblastic leukemia, acute myelogenous leukemia, and Hodgkin lymphoma. Cancer. 2016;122:2723-2730.
18. Wolfson J, Sun C-L, Kang T, et al. Impact of treatment site in adolescents and young adults with central nervous system tumors. J Natl Cancer Inst. 2014; 106:dju166.
19. Wolfson J, Sun CL, Wyatt L, et al. Adolescents and young adults with acute lymphoblastic leukemia and acute myeloid leukemia: impact of care at specialized cancer centers on survival outcome. Cancer Epidemiol Biomarkers Prev. 2017;26:312-320.
20. Johnson KA, Aplenc R, Bagatell R. Survival by race among children with extracranial solid tumors in the United States between 1985 and 2005. Pediatr Blood Cancer. 2011;56:425-431.

21. Haizel-Cobbina J, Spector LG, Moertel C, et al. Racial and ethnic disparities in survival of children with brain and central nervous tumors in the United States. Pediatr Blood Cancer. 2021;68:e28738.
22. Cooney T, Fisher PG, Tao L, et al. Pediatric neuro-oncology survival disparities in California. J Neurooncol. 2018;138:83-97.
23. Rudowitz RSA, Arguello R. Children's health coverage: Medicaid, CHIP and the ACA. Kaiser Family Foundation. https://www.kff.org/health-reform/issue-brief/childrens-health-coverage-medicaid-chip-and-the-aca/. Accessed April 28, 2021.
24. Saloner B, Hochhalter S, Sabik L. Medicaid and CHIP premiums and access to care: a systematic review. Pediatrics. 2016;137:e20152440.
25. Gresenz CR, Edgington SE, Laugesen MJ, et al. Income eligibility thresholds, premium contributions, and children's coverage outcomes: a study of CHIP expansions. Health Serv Res. 2013;48:884-904.
26. Guevara JP, Moon J, Hines EM, et al. Continuity of public insurance coverage: a systematic review of the literature. Med Care Res Rev. 2014;71:115-137.
27. Yabroff KR, Reeder-Hayes K, Zhao J, et al. Health insurance coverage disruptions and cancer care and outcomes: systematic review of published research. J Natl Cancer Inst. 2020;112:671-687.
28. Colton MD, Goulding D, Beltrami A, et al. A U.S. population-based study of insurance disparities in cancer survival among adolescents and young adults. Cancer Med. 2019;8:4867-4874.
29. Keegan THM, Parsons HM, Chen Y, et al. Impact of health insurance on stage at cancer diagnosis among adolescents and young adults. J Natl Cancer Inst. 2019;111:1152-1160.
30. Winestone LE, Getz KD, Miller TP, et al. The role of acuity of illness at presentation in early mortality in black children with acute myeloid leukemia. Am J Hematol. 2017;92:141-148.
31. National Institutes of Health. NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm. Accessed April 28, 2021.
32. Geller SE, Koch AR, Roesch P, et al. The more things change, the more they stay the same: a study to evaluate compliance with inclusion and assessment of women and mnorities in randomized controlled trials. Acad Med. 2018;93:630-635.
33. University of California Berkeley. Sociodemographic Profile of Latinos in the United States. Fact Sheet. 2017. https://hiaucb.files.wordpress.com/2017/04/demographic-profile-of-latinos-english.pdf. Accessed April 28, 2021.
34. Batalova J, Hanna M, Levesque C. Frequently Requested Statistics on Immigrants and Immigration in the United States. Migration Policy Institute. https://www.migrationpolicy.org/article/frequently-requested-statistics-immigrants-and-immigration-united-states-2020. Accessed April 28, 2021.
35. Nazha B, Mishra M, Pentz R, et al. Enrollment of racial minorities in clinical trials: old problem assumes new urgency in the age of immunotherapy. Am Soc Clin Oncol Educ Book. 2019;39:3-10.
36. Wallington SF, Dash C, Sheppard VB, et al. Enrolling minority and underserved populations in cancer clinical research. Am J Prev Med. 2016;50:111-117.
37. Guerrero S, López-Cortés A, Indacochea A, et al. Analysis of racial/ethnic representation in select basic and applied cancer research studies. Sci Rep. 2018;8:13978.
38. Barrett NJ, Rodriguez EM, Iachan R, et al. Factors associated with biomedical research participation within community-based samples across 3 National Cancer Institute-designated cancer centers. Cancer. 2020;126:1077-1089.
39. Winestone LE, Getz KD, Rao P, et al. Disparities in pediatric acute myeloid leukemia (AML) clinical trial enrollment. Leuk Lymphoma. 2019;60:2190-2198.
40. Aristizabal P, Singer J, Cooper R, et al. Participation in pediatric oncology research protocols: Racial/ethnic, language and age-based disparities. Pediatr Blood Cancer. 2015;62:1337-1344.
41. Strahlendorf C, Pole JD, Barber R, et al. Enrolling children with acute lymphoblastic leukaemia on a clinical trial improves event-free survival: a population-based study. Br J Cancer. 2018;118:744-749.
42. Murphy CC, Lupo PJ, Roth ME, et al. Disparities in cancer survival among adolescents and young adults: a population-based study of 88,000 patients. J Natl Cancer Inst. Epub 2021 Jan 23.
43. Durant RW, Wenzel JA, Scarinci IC, et al. Perspectives on barriers and facilitators to minority recruitment for clinical trials among cancer center leaders, investigators, research staff, and referring clinicians: enhancing minority participation in clinical trials (EMPaCT). Cancer. 2014;12(Suppl 7):1097-1105.
44. Wolfson JA, Bhatia S, Ginsberg J, et al. Expenditures among young adults with acute lymphoblastic leukemia by site of care. Cancer. 2021;127:1901-1911 Epub 2021 Jan 19.
45. Loree JM, Anand S, Dasari A, et al. Disparity of race reporting and representation in clinical trials leading to cancer drug approvals from 2008 to 2018. JAMA Oncol. 2019;5:e191870.
46. Unger JM, Cook E, Tai E, et al. The role of clinical trial participation in cancer research: barriers, evidence, and strategies. Am Soc Clin Oncol Educ Book. 2016;35:185-198.
47. Penner LA, Dovidio JF, Hagiwara N, et al. An analysis of race-related attitudes and beliefs in black cancer patients: implications for health care disparities. J Health Care Poor Underserved. 2016;27:1503-1520.
48. Scheurer ME, Lupo PJ, Schüz J, et al. An overview of disparities in childhood cancer: report on the Inaugural Symposium on Childhood Cancer Health Disparities, Houston, Texas, 2016. Pediatr Hematol Oncol. 2018;35:95-110.
49. Russo C, Stout L, House T, et al. Barriers and facilitators of clinical trial enrollment in a network of community-based pediatric oncology clinics. Pediatr Blood Cancer. 2020;67:e28023.

50. Winkfield KM, Flowers CR, Mitchell EP. Making the case for improving oncology workforce diversity. Am Soc Clin Oncol Educ Book. 2017;37:18-22.
51. National Institutes of Health, National Cancer Institute. NCI Center to Reduce Cancer Health Disparities (CRCHD). https://www.cancer.gov/about-nci/organization/crchd. Accessed March 12, 2021.
52. Frugé E, Lakoski JM, Luban N, et al. Increasing diversity in pediatric hematology/oncology. Pediatr Blood Cancer. 2011;57:147-152.
53. Aristizabal P. Diverse populations and enrollment in pediatric cancer clinical trials: challenges and opportunities. Pediatr Blood Cancer. 2020;67:e28296.
54. Ford JG, Howerton MW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer. 2008;112:228-242.
55. Aristizabal P, Ma AK, Kumar N, et al. Assessment of factors associated with parental perceptions of voluntary decisions about child participation in leukemia clinical trials. JAMA Netw Open. 2021;4:e219038.
56. Nooka AK, Behera M, Lonial S, et al. Access to Children's Oncology Group and Pediatric Brain Tumor Consortium phase 1 clinical trials: racial/ethnic dissimilarities in participation. Cancer. 2016;122:3207-3214.
57. Kadam RA. Informed consent process: a step further towards making it meaningful!. Perspect Clin Res. 2017;8:107-112.
58. Lantos J. Informed consent. The whole truth for patients? Cancer. 1993;72(9 Suppl):2811-2815.
59. Tait AR, Voepel-Lewis T, Malviya S. Do they understand? (part I): parental consent for children participating in clinical anesthesia and surgery research. Anesthesiology. 2003;98:603-608.
60. Appelbaum PS, Lidz CW, Klitzman R. Voluntariness of consent to research: a conceptual model. Hastings Cent Rep. 2009;39:30-39.
61. Kupst MJ, Patenaude AF, Walco GA, et al. Clinical trials in pediatric cancer: parental perspectives on informed consent. J Pediatr Hematol Oncol. 2003;25:787-790.
62. Simon C, Zyzanski SJ, Eder M, et al. Groups potentially at risk for making poorly informed decisions about entry into clinical trials for childhood cancer. J Clin Oncol. 2003;21:2173-2178.
63. Institute of Medicine (US) Committee on Health Literacy. In Nielsen-Bohlman L, Panzer AM, Kindig DA, (eds). Health Literacy: A Prescription to End Confusion. Washington, DC: National Academies Press; 2004.
64. Yin HS, Johnson M, Mendelsohn AL, et al. The health literacy of parents in the United States: a nationally representative study. Pediatrics. 2009;124(Suppl 3):S289-S298.
65. Sentell T, Braun KL. Low health literacy, limited English proficiency, and health status in Asians, Latinos, and other racial/ethnic groups in California. J Health Commun. 2012;17(Suppl 3):82-99.
66. Nipp RD, Hong K, Paskett ED. Overcoming barriers to clinical trial enrollment. Am Soc Clin Oncol Educ Book. 2019;39:105-114.
67. Bona K, Blonquist TM, Neuberg DS, et al. Impact of socioeconomic status on timing of relapse and overall survival for children treated on Dana-Farber Cancer Institute ALL Consortium protocols (2000-2010). Pediatr Blood Cancer. 2016;63:1012-1018.
68. Aplenc R, Alonzo TA, Gerbing RB, et al; Children's Oncology Group. Ethnicity and survival in childhood acute myeloid leukemia: a report from the Children's Oncology Group. Blood. 2006;108:74-80.
69. Kahn JM, Kelly KM, Pei Q, et al. Survival by race and ethnicity in pediatric and adolescent patients with Hodgkin lymphoma: a Children's Oncology Group Study. J Clin Oncol. 2019;37:3009-3017.
70. Bona K, Li Y, Winestone LE, et al. Poverty and targeted immunotherapy: survival in Children's Oncology Group clinical trials for high-risk neuroblastoma. J Natl Cancer Inst. 2021;113:282-291.
71. Pollock BH, DeBaun MR, Camitta BM, et al. Racial differences in the survival of childhood B-precursor acute lymphoblastic leukemia: a Pediatric Oncology Group Study. J Clin Oncol. 2000;18:813-823.
72. Winestone LE, Getz KD, Bona KO, et al. Area-based socioeconomic disparities in survival of children with newly diagnosed acute myeloid leukemia: a report from the Children's Oncology Group. Blood. 2019;134(Suppl 1):703.
73. McClain CA, Bernhardt MB, Berger A, et al. Pharmacogenetic association with neurotoxicity in Hispanic children with acute lymphoblastic leukaemia. Br J Haematol. 2018;181:684-687.
74. Yang JJ, Cheng C, Devidas M, et al. Ancestry and pharmacogenomics of relapse in acute lymphoblastic leukemia. Nat Genet. 2011;43:237-241.
75. Pui CH, Sandlund JT, Pei D, et al. Results of therapy for acute lymphoblastic leukemia in black and white children. JAMA. 2003;290:2001-2007.
76. Rubnitz JE, Lensing S, Razzouk BI, et al. Effect of race on outcome of white and black children with acute myeloid leukemia: the St. Jude experience. Pediatr Blood Cancer. 2007;48:10-15.
77. Metzger ML, Castellino SM, Hudson MM, et al. Effect of race on the outcome of pediatric patients with Hodgkin's lymphoma. J Clin Oncol. 2008;26:1282-1288.
78. Baker KS, Anderson JR, Lobe TE, et al. Children from ethnic minorities have benefited equally as other children from contemporary therapy for rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group. J Clin Oncol. 2002;20:4428-4433.
79. Bitterman DS, Bona K, Laurie F, et al. Race disparities in proton radiotherapy use for cancer treatment in patients enrolled in Children's Oncology Group trials. JAMA Oncol. 2020;6:1465-1468.
80 Koch V, Blonquist T, Cole P, et al. Feasibility of poverty screening in a multi-center therapeutic clinical trial for pediatric ALL. Presented at: American Society of Pediatric Hematology/Oncology (ASPHO). New Orleans, LA; May 1–4, 2019. Poster #026.

81. Frank DA, Casey PH, Black MM, et al. Cumulative hardship and wellness of low-income, young children: multisite surveillance study. Pediatrics. 2010; 125:e1115-e1123.

82. NCT03638453. Pilot Feasibility of the Pediatric Cancer Resource Equity (PediCARE) Intervention. https://clinicaltrials.gov/ct2/show/NCT03638453. Accessed March 12, 2021.

83. Ward ZJ, Yeh JM, Bhakta N, et al. Global childhood cancer survival estimates and priority-setting: a simulation-based analysis. Lancet Oncol. 2019;20:972-983.

84. Rodriguez-Galindo C, Friedrich P, Morrissey L, et al. Global challenges in pediatric oncology. Curr Opin Pediatr. 2013;25:3-15.

85. Farmer P, Frenk J, Knaul FM, et al. Expansion of cancer care and control in countries of low and middle income: a call to action. Lancet. 2010;376:1186-1193.

86. Atun R, Cavalli F. The global fight against cancer: challenges and opportunities. Lancet. 2018;391:412-413.

87. Friedrich P, Ortiz R, Fuentes S, et al; Central American Association of Pediatric Hematologists and Oncologists (AHOPCA). Barriers to effective treatment of pediatric solid tumors in middle-income countries: can we make sense of the spectrum of nonbiologic factors that influence outcomes? Cancer. 2014; 120:112-125.

88. Aristizabal P, Fuller S, Rivera R, et al. Improving pediatric cancer care disparities across the United States-Mexico border: lessons learned from a transcultural partnership between San Diego and Tijuana. Front Public Health. 2015;3:159.

89. Jabeen K, Ashraf MS, Iftikhar S, et al. The impact of socioeconomic factors on the outcome of childhood acute lymphoblastic leukemia (ALL) treatment in a low/middle income country (LMIC). J Pediatr Hematol Oncol. 2016;38:587-596.

90. Ceppi F, Antillon F, Pacheco C, et al. Supportive medical care for children with acute lymphoblastic leukemia in low- and middle-income countries. Expert Rev Hematol. 2015;8:613-626.

91. Ramirez O, Aristizabal P, Zaidi A, et al; VIGICANCER Working Group. Implementing a childhood cancer outcomes surveillance system within a population-based cancer registry. J Glob Oncol. 2018;4:1-11.

92. Aristizabal P, Fuller S, Rivera-Gomez R, et al. Addressing regional disparities in pediatric oncology: results of a collaborative initiative across the Mexican-North American border. Pediatr Blood Cancer. 2017;64:e26387.

93. Aristizabal P, Burns LP, Kumar NV, et al. Improving pediatric neuro-oncology survival disparities in the United States-Mexico border region: a cross-border initiative between San Diego, California, and Tijuana, Mexico. JCO Glob Oncol. 2020;6:1791-1802.

CANCER PREVENTION, RISK REDUCTION, AND GENETICS

A Case-Based Approach to Understanding Complex Genetic Information in an Evolving Landscape

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Overview

The rapid integration of highly sensitive next-generation sequencing technologies into clinical oncology care has led to unparalleled progress, and yet these technological advances have also made genetic information considerably more complex. For instance, accurate interpretation of genetic testing for germline/inherited cancer predisposition syndromes and somatic/acquired pathogenic variants now requires a more nuanced understanding of the presence and incidence of clonal hematopoiesis and circulating tumor cells, with careful evaluation of pathogenic variants occurring at low variant allele frequency required. The interplay between somatic and germline pathogenic variants and awareness of distinct genotype-phenotype manifestations in various inherited cancer syndromes are now increasingly appreciated and can impact patient management. Through a case-based approach, we focus on three areas of particular relevance to the treating clinician oncologist: (1) understanding clonal hematopoiesis and somatic mosaicism, which can be detected on germline sequencing and lead to considerable confusion in clinical interpretation; (2) implications of the detection of a potentially germline pathogenic variant in a high-penetrance cancer susceptibility gene during routine tumor testing; and (3) a review of gene-specific risks and surveillance recommendations in Lynch syndrome. A discussion on the availability and difficulties often associated with direct-to-consumer genetic testing is also provided.

INTRODUCTION

Roughly 5% to 10% of cancers have an underlying hereditary component. Thus, germline genetic testing for the evaluation of familial cancer syndromes represents an essential component of oncology care. These tests have implications for the optimal treatment of the index patient and also have potential downstream effects related to preventative approaches for affected family members. The advent and integration of next-generation sequencing technology has led to unparalleled advances in clinical oncology. The ability of multigene germline panels to rapidly identify informative cancer-related pathogenic variants (PVs) has enabled real-time decision-making for individualized treatments, as well as timely identification of hereditary cancer syndromes.[1-5] Furthermore, minimally invasive technology that now allows for identification and deep sequencing of circulating tumor-derived material from peripheral blood (i.e., liquid biopsy or cell-free analysis) has led to an improved ability to detect minimal residual disease and obtain genomic information for therapy selection without the need for more invasive biopsy methods and may lead to improved screening and early-detection approaches.

Yet, these technological advances have also made the field of genetic testing considerably more complex for clinical oncologists. Accurate interpretation of clinical germline testing, somatic sequencing, and liquid biopsy analyses now requires an understanding of nuanced factors such as clonal hematopoiesis (i.e., the presence of tissue-specific acquired/somatic mutations arising within the hematopoietic system), the interplay between somatic and germline PVs, and knowledge about genotype-phenotype manifestations in these various inherited cancer syndromes. In this article, we present three cases and discussions that elucidate the science and management strategies relevant to these important topics.

CASE 1: CLONAL HEMATOPOIESIS

A 43-year-old gravida 2, para 2 female is diagnosed with a stage IA, cT1b cN0 cM0, right-sided breast-invasive ductal carcinoma, grade 2, with estrogen receptor/progesterone receptor–positive and *HER2/neu*-negative status. An additional focus of atypical ductal proliferation of the right lower breast is detected, along with a stage 0, cTis, cN0, cM0 left-sided ductal carcinoma in situ. She has a 20 pack-year remote smoking history. Her maternal aunt was diagnosed with breast cancer at age 45. She received neoadjuvant anastrozole during the COVID-19 pandemic followed by bilateral surgical excision and right-sided

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PRACTICAL APPLICATIONS

- Clinical germline testing can identify pathogenic variants that may not be truly germline and may instead represent clonal hematopoiesis. Distinguishing true germline variants from mosaic germline variants and clonal hematopoiesis can be challenging but has significant implications for screening and familial counseling.
- Somatic next-generation tumor sequencing can identify pathogenic variants that may actually be germline variants. The identification of such variants on somatic testing should prompt formal germline evaluation, as these can have significant implications for patients and their at-risk family members.
- The treatment and counseling of individuals with certain inherited cancer susceptibility syndromes is moving away from one-size-fits-all risk assessment approaches. In Lynch syndrome, specifically, prospective data have shed important light on sex-, gene-, and age-specific considerations that influence an individual's future cancer risk.

sentinel lymph node biopsy. Bilateral breast radiation for risk reduction is planned.

Panel-based germline genetic testing for hereditary breast cancer syndromes was performed and returned with a *TP53* PV, specifically c.733G>T (p.Gly245Cys), with a report suggesting mosaic Li-Fraumeni syndrome. Additional details are requested from the clinical testing laboratory, and the consideration of a mosaic variant was suggested due to the presence of the *TP53* PV at a subheterozygous frequency with variant allele frequency (VAF) of 25%.

Clinical Questions

Does this patient have mosaic Li-Fraumeni syndrome? Does this *TP53* PV represent clonal hematopoiesis? What else could this *TP53* PV represent?

Germline *TP53* Pathogenic Variants and Li-Fraumeni Syndrome

Li-Fraumeni syndrome is a rare familial cancer syndrome, occurring in fewer than one in 5,000 individuals.[6] Men with germline *TP53* PVs are estimated to have a 75% chance of developing cancer by age 60, and nearly 100% of women present with a first malignancy by age 60.[7] Due to this heighted malignancy risk, individuals with Li-Fraumeni syndrome are offered an extensive cancer surveillance program typically starting at age 20, including annual whole-body and brain MRI, annual skin check, esophagogastroduodenoscopy/colonoscopy every 2 to 5 years, clinical breast examination, and breast MRI for females.[8] In females, breast cancer is the most common presenting malignancy of Li-Fraumeni syndrome, often with *HER2/neu* overexpression.[9,10] Importantly for our patient, if a diagnosis of Li-Fraumeni syndrome was confirmed, then the risk of a radiation-induced therapy-related malignancy would potentially offset the benefit of bilateral breast irradiation, amplifying the importance of accurate diagnosis.

Notwithstanding the rarity of Li-Fraumeni syndrome, most contemporary germline hereditary cancer panels include assessment of *TP53*. Yet *TP53* is a gene that is also recurrently somatically mutated in nearly all tumor types, including clonal hematopoietic processes. Thus, the detection of a *TP53* PV during genetic testing represents an excellent example of the many challenges of variant interpretation.

Germline/Hereditary Genetic Variants Are Typically Heterozygous

The frequency of any gene variant in question is typically referred to as the VAF and represents the fraction of alleles at any particular locus that carry that specific variant. Although an inherited heterozygous variant should have a true VAF of 50%, due to technical considerations with next-generation sequencing platforms, a range of anywhere from 40% to 60% (or even 30% to 70%) can be seen with a heterozygous variant.[11]

At present, most clinical germline testing laboratories do not provide the VAF of identified variants within the clinical report, although most testing companies will highlight variants that fall below a certain threshold (often 25% or 30%) as a comment provided in the interpretation or comments section.[12] The importance of this should not be understated, especially when considering *TP53* annotation, as one recent analysis determined that 20% of "positive" *TP53* PVs on a germline multigene panel occurred at VAF less than 25%,[13] and an even more remarkable recent study reported that 39% of *TP53* PVs identified on a germline multigene panel were most likely somatic in origin.[14]

When to Consider Mosaicism

The term "mosaicism" is traditionally used in the field of genetics to describe a disease-causing variant that occurs early in embryogenesis (i.e., postzygotic mosaicism). It is important to note that variants can also develop later, in a more organ- or tissue-specific manner, such as what occurs in the hematopoietic system and is now commonly referred to as clonal hematopoiesis, or clonal hematopoiesis of indeterminate potential (CHIP).

Cultured skin fibroblasts are often recommended for genetic testing to evaluate for mosaic patterns of inheritance and are also considered the gold standard for confirmatory germline testing. For instance, if a PV was present throughout the

mesoderm, as would be seen in a classic postzygotic mosaic pattern, it would likely be present in both the peripheral blood as well as in fibroblast analysis.

Batalini et al[12] recently described four patients with breast cancer and a *TP53* variant with less than 30% VAF on genetic testing. Confirmatory skin fibroblast analysis demonstrated that one patient had the variant also present in the cultured skin fibroblasts, confirming classic mosaicism.[12] A challenge with management of genetic disorders in patients with postzygotic mosaicism is the inability to be certain which tissue layers harbor the PV. With mosaic Li-Fraumeni syndrome, patients are offered augmented cancer surveillance mirroring that of classic Li-Fraumeni syndrome.

What Is Clonal Hematopoiesis/Clonal Hematopoiesis of Indeterminate Potential?

The ongoing and lifelong division of hematopoietic stem cells within the bone marrow is associated with occasional replication errors, leading to the acquisition of PVs. Occasionally, acquired variants confer a survival advantage that over time leads to clonal expansion, often without initial development of overt hematopoietic malignancy. This process is known as CHIP, also termed age-related clonal hematopoiesis, and occurs in more than 10% of patients over age 65 (when a VAF threshold of 2% or higher is used; note that the rate of CHIP is much higher when even more sensitive VAF cutoffs are used).[15,16]

Approximately two dozen genes comprise the majority of CHIP-associated somatic variants. The most common variants occur in *DNMT3A*, *TET2*, and *ASXL1*, epigenetically relevant genes that are frequently mutated in hematopoietic malignancies and rare in most solid tumors. Thus, identification of these variants at low VAF in peripheral blood analyses can be rather straightforwardly attributed to CHIP. Other CHIP variants that are identified more universally in tumors, such as *TP53*, and also *CHEK2* and *ATM*, can complicate genetic testing interpretation.[14,17] Although CHIP variants are most often present at low VAFs, large pathogenic CHIP variants in the absence of overt hematologic malignancy are well described. For example, in nearly 25,000 of patients with cancer evaluated across a wide range of primary tumor types, 30% of patients were identified to have CHIP, with a median VAF of 4.7%, but with a surprisingly large VAF range (2% to 87%).[18]

A history of malignancy, particularly the receipt of prior cytotoxic chemotherapy or radiation, is associated with an increased risk of CHIP; a recent analysis from the MSK-IMPACT panel identified clonal hematopoiesis in 30% of 24,146 patients with solid tumors.[18] In these patients, *TP53*, *PPM1D*, *CHEK2*, and *ATM* were frequently mutated and significantly associated with receipt of prior chemotherapy or radiation therapy in a dose-dependent fashion. The specific treatment received was also relevant; CHIP was most strongly associated with prior exposure to topoisomerase II inhibitors and platinum agents (carboplatin more than cisplatin or oxaliplatin) and not targeted therapy or immunotherapy. Increasing age and prior tobacco use was also associated with higher prevalence of CHIP. Pathogenic variants in DNA damage repair genes were most frequent in patients with ovarian and endometrial cancer, especially patients with prior receipt of platinum-based therapy.[13,19]

The presence of CHIP is associated with an increased risk of hematologic malignancy development, as well as cardiovascular disease and all-cause mortality.[15] Analogous to the incidence of developing multiple myeloma in an individual with monoclonal gammopathy of undetermined significance, an estimated 1% of patients with CHIP will progress to a hematologic malignancy per year. In a patient with CHIP, current recommendations include routine complete blood count monitoring and consideration of hematology referral for ongoing surveillance, including a baseline bone marrow evaluation to rule out underlying hematopoietic malignancy.

Although there are currently limited data on the association of therapy-related myeloid neoplasms in patients with solid tumors and CHIP, an important recent analysis[18] of patients with breast cancer suggests that in the most high-risk populations (including patients with *TP53* clonal hematopoiesis at VAF 10% or higher), the risk of a therapy-related myeloid neoplasm (myelodysplastic syndromes or acute myeloid leukemia) can increase by up to 9% in the setting of adjuvant cytotoxic chemotherapy, which may in fact exceed the projected benefit of adjuvant chemotherapy. The effect of local radiation therapy is estimated to be very low.

Could This Represent Circulating Tumor?

Cell-free DNA or other liquid biopsy approaches for tumor detection are increasingly used for measurement of residual disease and to identify optimal treatment of advanced disease with simultaneous avoidance of multiple or high-risk biopsies. A key advantage associated with cell-free analyses is the ability to capture molecular heterogeneity.[20] Yet without paired germline evaluation, an identified variant may represent circulating solid tumor or may instead represent clonal hematopoiesis. This can be seen especially with *TP53*, but additional actionable variants of therapeutic relevance, such as variants in *IDH1* and *IDH2*, are described as a part of clonal hematopoiesis and could impact treatment decisions if misattributed to the solid tumor under evaluation.

Although circulating tumor DNA could certainly confound germline testing, the VAF of PVs from circulating tumor are typically far below standard reporting levels.[20] In our patient without apparent residual tumor after definitive surgical management, a *TP53* PV present at 20% VAF is unlikely to come from circulating tumor.

Case 1: Follow-up and Summary

Genetic testing on cultured skin fibroblasts failed to identify the *TP53* PV that had been identified on germline panel testing, suggesting this variant was indeed of hematopoietic origin. The patient was referred to hematology and noted to have mildly abnormal complete blood count indices (macrocytic anemia with elevated red blood cell distribution width). A bone marrow aspirate and biopsy were performed, which confirmed a normocellular bone marrow with trilineage maturation and no evidence of a hematologic neoplasm or metastatic tumor. An 81-gene myeloid panel demonstrated both a *DNMT3A* c.2598-1G>A variant (VAF 25%) and the known *TP53* variant (VAF 18%). The diagnosis of Li-Fraumeni syndrome was thus excluded, and augmented Li-Fraumeni syndrome–specific preventative cancer screening was not required. She received her planned radiation therapy, which was well-tolerated, and she is now followed in both the breast center and hematology center for ongoing cancer surveillance, given the increased lifetime risk of hematologic malignancy associated with CHIP.

CASE 2: INTERGRATING SOMATIC AND GERMLINE SEQUENCING DATA

Ms. S is a 49-year-old woman who was recently found to have metastatic breast cancer who presents to you for a second opinion. She has a history of cT3N1 triple-negative breast cancer diagnosed 2 years ago, treated with neoadjuvant dose-dense doxorubicin and cyclophosphamide followed by weekly paclitaxel. Lumpectomy and axillary lymph node dissection performed after chemotherapy revealed 2 cm of residual disease in the breast and one out of 17 positive axillary nodes, with treatment effect seen in three additional nodes. She then received adjuvant radiation followed by capecitabine. Three months after completing capecitabine, she noted back pain, and imaging revealed new mixed lytic/blastic lesions in the lumbar and cervical spine and iliac wing and additional disease in the liver and lung. Biopsy of a liver lesion confirmed metastatic breast cancer, estrogen receptor/progesterone receptor–negative, *HER2/neu*-negative. A sample from the recent biopsy was sent for genomic testing and PD-L1 immunohistochemistry, which revealed:

- PD-L1 status: negative
- Tumor mutational burden: 5 mutations/megabase
- Microsatellite status: microsatellite-stable
- Somatic genomic findings detected: *BRCA1* c.1576C>T; *TP53* splice site c.559+1G>A

The patient is of Latinx origin. She has a paternal aunt who died of ovarian cancer in her 50s and a paternal grandfather with a history of prostate cancer. The patient states that she "did gene testing at home and does not have the breast cancer gene." On further questioning, the patient explained that she took a home DNA test several years ago to learn more about her ancestry, and that report stated that she did not have genetic predisposition to breast cancer.

Clinical Questions

Does the *BRCA1* PV seen on tumor testing represent a germline or somatic finding? What are the treatment implications of each? How should a negative result on a direct-to-consumer genetic test be interpreted?

Somatic Versus Germline Pathogenic Variants

When performing next-generation sequencing on a tumor to identify genomic abnormalities that could guide treatment, it is important to be able to distinguish between germline and somatic variants. Both physicians and patients should be aware of the possibility of finding a germline variant when undertaking somatic tumor sequencing.[21] Germline testing for variants associated with a hereditary predisposition to cancer traditionally involves pre- and post-test genetic counseling; this may not be feasible (or necessary) when the intent is to identify somatic variants that will inform treatment. However, it is important for providers to discuss with patients the potential for identification of a germline variant. This discussion should outline the consequences of a germline finding for the patient and the relevance and potential benefits and risks of the information for the patient's members.

Treatment Implications of a Germline *BRCA1/2* Pathogenic Variant in Metastatic Breast Cancer

Currently, two PARP inhibitors, olaparib and talazoparib, are approved by the U.S. Food and Drug Administration (FDA) for the treatment of breast cancers in patients with germline *BRCA1/2* PVs. For both drugs, selection of patients for therapy should be based on an FDA–approved companion diagnostic assay. Olaparib is approved by the FDA for the treatment of metastatic breast cancer in patients with a known germline PV in *BRCA1* or *BRCA2* who have previously received chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.[22] The approval of olaparib was based on the OlympiAD trial, in which 302 patients with germline *BRCA1/2* PVs by local or central testing were randomly assigned to receive either olaparib or single-agent chemotherapy of the physician's choice (eribulin, capecitabine, or vinorelbine). Median progression-free survival was 7.0 months in patients receiving olaparib compared with 4.2 months in those receiving chemotherapy (HR, 0.58; 95% CI, 0.43–0.80; $p < .001$).[23] Objective response rates were 59.9% in the olaparib group and 28.8% in chemotherapy group. Anemia and neutropenia were the most common side effects in both treatment arms (grade 3 or higher anemia: 16.1% for olaparib and 4.4% for chemotherapy; grade 3 or higher neutropenia: 9.3% vs. 26.4%, respectively). Nausea and vomiting were both more frequent

with olaparib, but there were no grade 3 or higher occurrences.

Talazoparib has FDA approval for the treatment of locally advanced or metastatic breast cancer in patients with a known or suspected germline PV in *BRCA1* or *BRCA2*.[24,25] In the EMBRACA trial, 431 such patients were randomly selected to receive talazoparib or physician's choice single-agent chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Median progression-free survival was 8.6 months with talazoparib versus 5.6 months with chemotherapy (HR, 0.54; 95% CI, 0.41–0.71; $p < .001$), and the objective response rate was higher for talazoparib (objective response rate, 62.6% vs. 27.2%; odds ratio, 5.0; $p < .001$). Common adverse events with talazoparib included anemia, fatigue, and nausea. Grade 3 or 4 hematologic adverse events occurred in 55% of patients in the talazoparib group (primarily anemia) and 38% of patients in the standard treatment group. Patient-reported outcomes favored talazoparib.

Although there are FDA approvals for PARP inhibitors to treat patients with ovarian and prostate cancer with somatic *BRCA1/2* PVs, there are currently no such approvals at this time in breast cancer. Two recent studies have evaluated PARP-inhibitor treatment in patients with breast cancer with somatic *BRCA1/2* PVs. TBCRC 048 was a single-arm study of olaparib in patients with germline PVs in a non-*BRCA1/2* homologous recombination-related gene or a somatic PVs in *BRCA1/2* or a homologous recombination-related gene.[26] Sixteen patients had a somatic *BRCA1/2* PV (6 *BRCA1* and 10 *BRCA2*). Among these patients, the objective response rate was 50% (90% CI, 28–72), and median progression-free survival was 6.3 months. SWOG S1416 was a placebo-controlled trial of veliparib in combination with cisplatin in three groups of patients: those with germline *BRCA1/2* PVs (37 patients) and those classified as "*BRCA*-like" (99 patients) and "non–*BRCA*-like" (110 patients).[27] Patients in the *BRCA*-like group included those with a somatic *BRCA1/2* PV, a homologous recombination deficiency genomic instability score of 42 or higher on the Myriad myChoice assay, *BRCA1* promoter methylation, or a germline PV in a non-*BRCA1/2* homologous recombination-related gene on the BROCA-HR assay. Eight percent of patients in the *BRCA*-like group had somatic *BRCA1/2* PVs, all of whom also had a homologous recombination deficiency score of 42 or higher. In this group, median progression-free survival was 5.9 months in patients who received veliparib and cisplatin versus 4.2 months in patients who received cisplatin and placebo (HR, 0.53; 95% CI, 0.34–0.83; $p = .006$).

As these trials include only small numbers of patients with somatic *BRCA1/2* PVs, additional data are needed to determine whether patients with breast cancer with *BRCA1/2* PVs benefit from PARP-inhibitor treatment. At this time, standard of care for a patient with metastatic breast cancer and a somatic PV in *BRCA1/2* does not include a PARP inhibitor. Thus, differentiating between a somatic and germline PV has therapeutic implications for patients with breast cancer.

Recommendations for Germline *BRCA1/2* Pathogenic Variant Carriers With Early-Stage Breast Cancer

Although not pertinent in this case, as the patient now has metastatic disease, in a newly diagnosed patient with early-stage breast cancer and a germline *BRCA1/2* PV, discussion of local treatment should include counseling regarding risk of contralateral breast cancer and increased risk of an ipsilateral new primary breast cancer. Ipsilateral therapeutic mastectomy and contralateral risk-reducing mastectomy can be considered in this context. Discussion regarding surgical management should include assessment of additional risk factors, including age at diagnosis, family history of breast cancer, overall prognosis of this and other cancer, ability to undergo appropriate breast surveillance, comorbidities, and life expectancy.[28] However, it is important to note that the risk of local recurrence does not appear to be elevated in women with a *BRCA1/2* PV, and patients who undergo breast-conserving therapy do not appear to have worse breast-cancer specific or overall survival compared with those who undergo mastectomy.[29-31] Therefore, a germline *BRCA1/2* PV should not preclude breast-conserving therapy in a patient who is otherwise eligible for and desires breast conservation. *BRCA1/2* PV carriers who do not have bilateral mastectomy should undergo high-risk screening of remaining breast tissue with annual mammogram and breast MRI.

Cancer Risk Management in *BRCA1/2* Pathogenic Variant Carriers

First-degree relatives of an individual with a germline *BRCA1/2* PV each have a 50% chance of carrying the same PV. Family members of an individual with a germline *BRCA1/2* PV should be counseled regarding their risks and offered the opportunity for genetic counseling and testing. A recent study showed that fewer than 20% of individuals with a family history of breast or ovarian cancer who met established criteria for genetic testing received appropriate testing.[32] Both a thorough family history for nonaffected individuals and counseling of an affected individual regarding implications for their family members are essential for the identification of family members at risk for cancer. Cancer screening recommendations for men and women with *BRCA1/2* PVs are summarized in Table 1.

Direct-to-Consumer Genetic Testing

In recent years, the introduction and evolution of next-generation sequencing technology has led to widespread availability of genomic testing without the need for an

TABLE 1. Cancer Screening Recommendations for Women and Men With Pathogenic Germline *BRCA1/2* Variants

Women		Men	
Starting Age (Years)	**Intervention**	**Starting Age (Years)**	**Intervention**
18	Breast awareness	35	Breast self-examination training and education; yearly clinical breast examination
25	Clinical breast examination every 6–12 months; annual breast MRI	40	Recommend prostate cancer screening with PSA and DRE for *BRCA2*; consider prostate cancer screening for *BRCA1*
30	Annual mammogram with consideration of tomosynthesis	50	Consider annual mammogram screening if gynecomastia present (age 50 or 10 years prior to earliest known male breast cancer in family)
	Discuss option of risk-reducing mastectomy	**Women and Men**	
30–35	Consider transvaginal ultrasound and CA-125 in patients who have not undergone RRSO	50	Consider pancreatic cancer screening with annual contrast-enhanced MRI/MRCP and/or EUS (begin at age 50 or 10 years prior to earliest known pancreatic cancer case in family, whichever is earliest)*
35–40	Recommend RRSO (upon completion of childbearing); discuss risks and benefits of concurrent hysterectomy		

Abbreviations: RRSO, risk-reducing salpingo-oophorectomy; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasound.
*Screening typically recommended only if there is a known family history of pancreatic cancer.

ordering physician. Most commonly available tests look at single nucleotide polymorphisms in specific areas of the human genome. These tests generate information on ancestry and on susceptibility to certain diseases based on the presence of specific variants, with varying amounts of clinical data to support their claims.[33] There were concerns raised early on regarding both the quality and clinical validity of these widely available tests. In 2010, the FDA notified several companies offering direct-to-consumer genetic tests of their intent to regulate the tests. In 2013, the FDA ordered one company (23andMe) to stop marketing their test in its current form, citing concern about the public health consequences of inaccurate test results.[21] In 2018, the FDA granted authorization to 23andMe for their direct-to-consumer genetic test for *BRCA1/2* PVs, which assesses for three *BRCA1/2* PVs that are commonly found in people of Ashkenazi Jewish descent. These PVs occur in about 2% of women of Ashkenazi Jewish descent but in less than 0.1% in other populations; a negative result may be falsely reassuring, particularly if the person taking the test is not of Ashkenazi Jewish descent.[34] This test also does not assess for the more than 1,000 additional known PVs in *BRCA1* and *BRCA2*, nor does it assess for variants in other genes that are associated with increased susceptibility to breast cancer, such as *ATM*, *CHEK2*, *PALB2*, *PTEN*, *TP53*, and *CDH1*, all of which have associated screening recommendations.[35] The 23andMe test itself carries a disclaimer stating that the results should be confirmed in a clinical setting.[36] A negative 23andMe result should not be equated with a negative test on a more comprehensive hereditary risk panel, particularly in a patient with a known cancer and/or a positive family history. Additionally, as these tests are not accompanied by pre- or post-test genetic counseling as is recommended with physician-ordered tests, the limitations of the testing may not be accurately communicated with the patient.

Several companies now offer what has been referred to as "physician-mediated direct-to-consumer genetic testing." In this model, either the patient's own physician or a company-provided physician orders the hereditary cancer test.[37] These tests provide more comprehensive hereditary cancer risk panels and contain a varying number of genes with different degrees of penetrance. The information received is often complex and may have nuanced clinical implications. Thus, there are concerns regarding the adequacy of the informed consent process and the timing of genetic counseling offered in conjunction with these tests.[37] In the traditional model of genetic counseling and testing by a clinician, patients receive pretest counseling to explain what test is being used and the possible implications of different findings. With the physician-mediated direct-to-consumer model, the patient may not undergo the informed consenting process until after they have ordered and paid for a test. Counseling can range from online videos that are available on the website to access to a genetic counselor. Because test results are provided directly to the patient, there may not be a health professional involved in disclosure of results. Thus, physicians must be prepared to discuss test results and provide referral to a genetics professional for posttest counseling if necessary.

Case 2: Follow-up and Summary

You confirmed with the patient that her prior test included only the three Ashkenazi Jewish founder mutations and referred her to Medical Genetics. After pretest counseling, a multigene panel test was ordered and confirmed the presence of a germline *BRCA1* PV, c.1576C>T, which has been described in patients of Latinx descent.[38] The patient began treatment with talazoparib. Her 25-year-old daughter also saw a genetic counselor and tested positive for a *BRCA1* PV; she initiated breast cancer screening with yearly breast MRI.

This case highlights the importance of distinguishing between a somatic and germline *BRCA* PV; in this patient, the results impacted both the patient's cancer therapy and screening recommendations for a family member. Additionally, it raises the importance of awareness of both the risks and limitations of direct-to-consumer genetic testing. The patient's family history and triple-negative breast cancer diagnosis were highly suspicious for a familial cancer syndrome and warranted genetic testing with a comprehensive panel. Direct-to-consumer tests commonly used for ancestry should not be equated with the more comprehensive panels that are available through either clinical testing or physician-mediated testing. Pre- and post-test counseling are valuable in educating patients on the appropriate tests and clinical implications of a PV.

CASE 3: GENE-SPECIFIC CANCER RISKS IN LYNCH SYNDROME

Ms. B is a 38-year-old woman with no remarkable past medical history presenting for genetic evaluation due to her family history of suspected Lynch syndrome. Her father had a history of transitional cell carcinoma of the ureter at age 44 and died of advanced microsatellite instability-high colon cancer diagnosed at age 47. Her paternal grandmother had endometrial cancer at age 54 and two separate colon cancers at ages 58 and 68. Her paternal aunt had colon cancer at age 42 and reportedly has a diagnosis of Lynch syndrome, but she is not willing to share her germline testing results. Another paternal aunt is age 68 and cancer free. $PREMM_5$ risk assessment (http://premm.dfci.harvard.edu)[39] indicates that Ms. B has a 12.8% likelihood of harboring a pathogenic germline variant in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*. Germline testing is ordered.

Clinical Questions

If Ms. B is diagnosed with Lynch syndrome, what will her future risks of cancer be? How could these risks differ, based on the Lynch syndrome gene involved? What are appropriate risk-reduction strategies for Ms. B?

Cancer Risks and Personalized Management in Lynch Syndrome

Lynch syndrome is caused by pathogenic germline variants in one of the DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) or *EPCAM* and is characterized by high lifetime risks of colorectal and endometrial cancers, as well as significantly increased risks of ovarian, gastric, urinary tract (ureter, renal pelvis, bladder, and possibly kidney cancers), small bowel, pancreatic, biliary tract, and brain malignancies, as well as cutaneous sebaceous neoplasms. Tumor testing with immunohistochemistry for the DNA mismatch repair proteins and/or polymerase chain reaction–based microsatellite instability analysis is now considered standard of care for all individuals with colorectal cancer or endometrial cancer to screen for Lynch syndrome, given that Lynch-associated cancers are almost universally mismatch repair deficient with high-level microsatellite instability.[40] For individuals who are cancer unaffected or for whom tumor tissue is unavailable for such testing, the $PREMM_5$ risk assessment model can be used to efficiently quantify an individual's likelihood of underlying Lynch syndrome using one's personal and family history data.[39] Germline testing is recommended for individuals with 2.5% or greater likelihood of Lynch syndrome by $PREMM_5$ assessment.[39,40]

Until recently, clinical practice guidelines recommended the same risk-reducing management for all individuals with Lynch syndrome, regardless of gene or family history. All carriers of Lynch syndrome were recommended to initiate colonoscopic surveillance every 1 to 2 years beginning at age 20 to 25, and female carriers of Lynch syndrome were recommended to pursue hysterectomy and salpingo-oophorectomy at the completion of childbearing to reduce risk of endometrial and ovarian cancers. Recommendation for other Lynch syndrome–associated gastrointestinal cancers, in contrast, have been variable due in large part to a lack of data demonstrating any benefit to such screening as well as the relatively uncommon nature of such cancers in Lynch syndrome.

Numerous recent studies, however, have demonstrated considerable sex- and gene-specific variability in Lynch syndrome–associated cancer risks and are setting the stage for personalized risk-assessment and risk-management strategies. The most notable example of this has been *PMS2*-associated Lynch syndrome, which is now recognized as the most attenuated form of Lynch syndrome. Longitudinal data from the Prospective Lynch Syndrome Database have identified individuals with *PMS2*-associated Lynch syndrome to have 10.4% and 12.8% cumulative risks of colorectal cancer and endometrial cancer, respectively, by age 75, compared with 46.6% to 57.1% and 37.0% to 48.9% for *MLH1*- and *MSH2*-associated Lynch syndrome.[41] Furthermore, data have strongly suggested that *PMS2*-associated Lynch syndrome may not confer significantly increased risks of ovarian, gastric, urinary tract, or any other cancers beyond colorectal and endometrial cancer.[42] Curiously, such Prospective Lynch Syndrome

Database data have confirmed the observation from other prior studies that *MSH6*-associated Lynch syndrome likewise confers a relatively attenuated risk of colorectal cancer (18.2% to 20.3% cumulative risk to age 75), whereas risks of *MSH6*-associated gynecologic malignancies (cumulative 41.1% and 10.8% risk of endometrial and ovarian cancer, respectively, to age 75) are on par with those from *MLH1*- and *MSH2*-associated Lynch syndrome.[41]

Such data have led to the evolution of clinical practice guidelines[40,43-45] that now largely feature age- and gene-specific recommendations for colonoscopic surveillance and risk-reducing gynecologic surgery in Lynch syndrome carriers. For example, guidelines from the National Comprehensive Cancer Network continue to recommend that individuals with *MLH1*- and *MSH2*-associated Lynch syndrome undergo colonoscopic surveillance every 1 to 2 years beginning at age 20 to 25, but recommend waiting until age 30 to 35 for *MSH6*- and *PMS2*-associated Lynch syndrome, unless there is a family history of a particularly early-onset colorectal cancer. Clinical practice guidelines from the European Hereditary Tumour Group and the European Society of Coloproctology similarly recommend an earlier age for colonoscopic initiation for *MLH1*- and *MSH2*-associated Lynch syndrome (age 25) versus *MSH6*- and *PMS2*-associated Lynch syndrome (age 35), but recommend that those with *PMS2*-associated Lynch syndrome consider colonoscopies only once every 5 years due to the particularly attenuated phenotype.[43] Similarly, such guidelines have softened their recommendations for risk-reducing gynecologic cancer surgery in females with *PMS2*-associated Lynch syndrome, now advising hysterectomy be considered and highlighting that there are insufficient data to recommend salpingo-oophorectomy.[40,46]

Data from the Prospective Lynch Syndrome Database and others have also begun to shed light on sex- and gene-specific considerations for other less common Lynch syndrome–associated cancers. Specific examples include the finding that *MSH2*-associated Lynch syndrome confers disproportionately high risks for urinary tract cancers (7.9% to 12.8% and 17.6% to 18.7% cumulative risks of bladder and ureter/kidney cancer, respectively, to age 75) and that male Lynch syndrome carriers have significantly higher risks of any upper gastrointestinal tract cancer compared with female carriers. Furthermore, other recent studies have demonstrated that a family history of gastric cancer[47] and urinary tract cancer[48] may identify Lynch syndrome carriers with increased risks of these cancers, independent of gene-, sex-, and age-specific considerations. Data remain unclear, however, on the ideal approaches for reducing risk of these less common Lynch syndrome–associated cancers, which is a critically important need for these individuals given that such cancers tend to have significantly worse prognoses than Lynch-associated colorectal, endometrial, and ovarian cancers.[49]

To help incorporate such practice-changing data into routine clinical care and guide personalized management of individuals with Lynch syndrome, the Prospective Lynch Syndrome Database investigators have developed a free online tool to estimate a Lynch syndrome carriers' future risk of various Lynch-associated cancers based on the individual's age, sex, and the affected mismatch repair gene (www.plsd.eu). Other investigators have developed a similar tool, All Syndromes Known to Man Evaluator, or ASK2ME (www.ask2me.org), which can be used for individuals with Lynch syndrome or other forms of inherited cancer risk.

Case 3: Follow-up and Summary

Germline testing revealed that Ms. B harbors a pathogenic germline variant in *MSH2*, thus confirming a diagnosis of *MSH2*-associated Lynch syndrome. Risk prediction from the Prospective Lynch Syndrome Database calculator (rounding her age up to 40; www.plsd.eu) estimated that her colorectal cancer risk to age 75 is 42.7% and that her risk over the next 10 years is 10.8%. Similarly, her 10-year risk of endometrial cancer is 15.5%, and risk to age 75 is 47.7%. Risks of other cancers to age 75 years included 12.8% for upper gastrointestinal cancers (gastric, duodenal, biliary, and pancreatic cancers combined), 15.6% for ovarian cancer, 7.3% for bladder cancer, 18.7% for ureter/kidney cancers, and 2.2% for brain cancers. She initiated colonoscopic surveillance, as recommended by clinical practice guidelines, and was found to have two 10-mm tubular adenomas. She plans to repeat this in 1 year. She also started taking daily aspirin, given compelling data demonstrating a marked reduction in colorectal cancer incidence from daily aspirin use.[50] She opted to defer risk-reducing hysterectomy and salpingo-oophorectomy until at least age 40. She had a baseline esophagogastroduodenoscopy with biopsy for *Helicobacter pylori*, which is negative. Given the disproportionately elevated risk of urinary tract cancers in *MSH2*-associated Lynch syndrome plus her father's history of urinary tract cancer, she opted to pursue annual urinalysis screening, even though data[51] have demonstrated that such screening has an exceedingly high rate of "false positives" in Lynch syndrome and is not routinely endorsed by clinical practice guidelines. By identifying the specific *MSH2* pathogenic germline variant responsible for her family history of cancer, germline testing has thus allowed Ms. B to have a more specific understanding of her own future cancer risks and is also now being used to help facilitate site-specific germline testing for her children, siblings, and other at-risk paternal relatives.

DISCUSSION AND CONCLUSION

The incorporation of multigene testing panels with impressive detection sensitivity has led to the increased

identification of hereditary cancer syndromes, leading to improved patient management. However, care must be taken with interpretation of genetic testing, and, through a case-based approach, we have provided diagnostic considerations to improve clinical interpretation of complex genomic information. Key elements and points to consider include the awareness from Case 1 that PVs identified from the peripheral blood do not always represent true germline variants. Indeed, no standards currently exist for the detection or reporting of CHIP on multigene panels, and PVs arising from CHIP can be erroneously classified as tumor-derived or germline in origin, so the index of suspicion of the clinician must remain high. Careful evaluation of variants with low VAFs for underlying clonal hematopoiesis (CHIP) or circulating tumor, in addition to mosaic presentations, must be considered during the genetic evaluation for cancer predispositions. In Case 2, we underscore the importance of distinguishing between somatic and germline PVs, with important implications pertaining to both the patient's cancer there and screening recommendations for family members. Additionally, we discussed the increasing use of direct-to-consumer genetic testing and awareness of both risks and limitations of these services. Lastly, in Case 3, we emphasize the evolving, more nuanced understanding of inherited cancer syndromes based on gene-specific risks. We highlight Lynch syndrome, in which there is now a growing understanding of factors that contribute to an individual's personalized risks of various malignancies, including the underlying mismatch repair gene in which they harbor a pathogenic germline variant. The growing body of such prospectively obtained, longitudinal data has led to the adoption of gene-specific approaches to clinical Lynch syndrome management, and we expect that further efforts to personalize patient care in hereditary cancer risk are likewise forthcoming.

Advances in genetic-sequencing technologies have helped push germline genetic testing into mainstream clinical oncologic care. Data from germline testing are increasingly being used to guide therapeutics and prognostication for individuals with a wide array of malignancies, and such data remain invaluable at identifying individuals and families with inherited cancer predisposition so that they can then pursue evidence-based interventions to mitigate such risk. As our knowledge about germline factors in cancer risk and biology continues to grow, so too will the additional complexities and nuances inherent to germline analysis continue to deepen. In spite of such challenges, however, these intricacies ultimately help expand our understanding of cancer biology while also moving the field incrementally closer to truly personalized and genetically driven cancer care.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_321041.

REFERENCES

1. Tung N, Lin NU, Kidd J, et al. Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer. J Clin Oncol. 2016;34:1460-1468.
2. Yurgelun MB, Kulke MH, Fuchs CS, et al. Cancer susceptibility gene mutations in individuals with colorectal cancer. J Clin Oncol. 2017;35:1086-1095.
3. Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci USA. 2011;108:18032-18037.
4. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med. 2016;375:443-453.
5. Yurgelun MB, Chittenden AB, Morales-Oyarvide V, et al. Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med. 2019;21:213-223.
6. Lalloo F, Varley J, Ellis D, et al; Early Onset Breast Cancer Study Group. Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. Lancet. 2003;361:1101-1102.
7. Kratz CP, Achatz MI, Brugières L, et al. Cancer screening recommendations for individuals with Li-Fraumeni syndrome. Clin Cancer Res. 2017;23:e38-e45.
8. National Comprehensive Cancer Network. Clinical Practice Guidelines - Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (Version 2. 2021). https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Accessed April 13, 2021.

9. Melhem-Bertrandt A, Bojadzieva J, Ready KJ, et al. Early onset HER2-positive breast cancer is associated with germline TP53 mutations. Cancer. 2012; 118:908-913.
10. Mester JL, Jackson SA, Postula K, et al. Apparently heterozygous TP53 pathogenic variants may be blood limited in patients undergoing hereditary cancer panel testing. J Mol Diagn. 2020;22:396-404.
11. DiNardo CD, Routbort MJ, Bannon SA, et al. Improving the detection of patients with inherited predispositions to hematologic malignancies using next-generation sequencing-based leukemia prognostication panels. Cancer. 2018;124:2704-2713.
12. Batalini F, Peacock EG, Stobie L, et al. Li-Fraumeni syndrome: not a straightforward diagnosis anymore-the interpretation of pathogenic variants of low allele frequency and the differences between germline PVs, mosaicism, and clonal hematopoiesis. Breast Cancer Res. 2019;21:107.
13. Weitzel JN, Chao EC, Nehoray B, et al. Somatic TP53 variants frequently confound germ-line testing results. Genet Med. 2018;20:809-816.
14. Coffee B, Cox HC, Bernhisel R, et al. A substantial proportion of apparently heterozygous TP53 pathogenic variants detected with a next-generation sequencing hereditary pan-cancer panel are acquired somatically. Hum Mutat. 2020;41:203-211.
15. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371:2488-2498.
16. Genovese G, Kähler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014; 371:2477-2487.
17. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood. 2015; 126:9-16.
18. Bolton KL, Ptashkin RN, Gao T, et al. Cancer therapy shapes the fitness landscape of clonal hematopoiesis. Nat Genet. 2020;52:1219-1226.
19. Swisher EM, Harrell MI, Norquist BM, et al. Somatic mosaic mutations in PPM1D and TP53 in the blood of women with ovarian carcinoma. JAMA Oncol. 2016; 2:370-372.
20. Corcoran RB, Chabner BA. Application of cell-free DNA analysis to cancer treatment. N Engl J Med. 2018;379:1754-1765.
21. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol. 2015;33:3660-3667.
22. Lynparza (olaparib) prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s001lbl.pdf. Accessed March 13, 2021.
23. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a grmline BRCA mutation. N Engl J Med. 2017;377:523-533.
24. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med. 2018;379:753-763.
25. Talzenna (talazoparib) prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211651s000lbl.pdf. Accessed March 13, 2021.
26. Tung NM, Robson ME, Ventz S, et al. TBCRC 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. J Clin Oncol. 2020;38:4274-4282.
27. Sharma P, Rodler E, Barlow WE, et al. Results of a phase II randomized trial of cisplatin +/– veliparib in metastatic triple-negative breast cancer (TNBC) and/or germline BRCA-associated breast cancer (SWOG S1416). J Clin Oncol. 2020;38 (15_suppl; abstr 1001).
28. Tung NM, Boughey JC, Pierce LJ, et al. Management of hereditary breast cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology guideline. J Clin Oncol. 2020;38:2080-2106.
29. Nilsson MP, Hartman L, Kristoffersson U, et al. High risk of in-breast tumor recurrence after BRCA1/2-associated breast cancer. Breast Cancer Res Treat. 2014; 147:571-578.
30. Pierce LJ, Phillips KA, Griffith KA, et al. Local therapy in BRCA1 and BRCA2 mutation carriers with operable breast cancer: comparison of breast conservation and mastectomy. Breast Cancer Res Treat. 2010;121:389-398.
31. van den Broek AJ, Schmidt MK, van 't Veer LJ, et al. Prognostic impact of breast-conserving therapy versus mastectomy of BRCA1/2 mutation carriers compared with noncarriers in a consecutive series of young breast cancer patients. Ann Surg. 2019;270:364-372.
32. Childers CP, Childers KK, Maggard-Gibbons M, et al. National estimates of genetic testing in women with a history of breast or ovarian cancer [published correction appears in *J Clin Oncol*. 2018;36:432]. J Clin Oncol. 2017;35:3800-3806.
33. Horton R, Crawford G, Freeman L, et al. Direct-to-consumer genetic testing. BMJ. 2019;367:l5688.
34. Gill J, Obley AJ, Prasad V. Direct-to-consumer genetic testing: the implications of the US FDA's first marketing authorization for BRCA mutation testing. JAMA. 2018;319:2377-2378.
35. Shah PD, Domchek SM. The contemporary landscape of genetic testing and breast cancer: Emerging issues. Breast J. 2020;26:1549-1555.
36. 23andMe. 23andMe BRCA1/BRCA2 (Selected Variants) Frequently Asked Questions (FAQs). https://permalinks.23andme.com/pdf/faqs.pdf. Accessed March 13, 2021.
37. Kilbride MK, Domchek SM, Bradbury AR. Ethical implications of direct-to-consumer hereditary cancer tests. JAMA Oncol. 2018;4:1327-1328.
38. Zayas-Villanueva OA, Campos-Acevedo LD, Lugo-Trampe JJ, et al. Analysis of the pathogenic variants of BRCA1 and BRCA2 using next-generation sequencing in women with familial breast cancer: a case-control study. BMC Cancer. 2019;19:722.
39. Kastrinos F, Uno H, Ukaegbu C, et al. Development and validation of the $PREMM_5$ model for comprehensive risk assessment of Lynch syndrome. J Clin Oncol. 2017;35:2165-2172.
40. National Comprehensive Cancer Network. National Comprehensive Cancer Network Clinical Practice Guidelines - Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2020). https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Accessed April 13, 2021.

41. Dominguez-Valentin M, Sampson JR, Seppälä TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database [published correction appears in *Genet Med*. 2020;22:1569]. Genet Med. 2020;22:15-25.

42. Ten Broeke SW, van der Klift HM, Tops CMJ, et al. Cancer risks for PMS2-associated Lynch syndrome [published correction appears in *J Clin Oncol*. 2019;37:761]. J Clin Oncol. 2018;36:2961-2968.

43. Seppälä TT, Latchford A, Negoi I, et al. European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender. Br J Surg. Epub 2020 Sep 21.

44. Monahan KJ, Bradshaw N, Dolwani S, et al; Hereditary CRC guidelines eDelphi consensus group. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). Gut. 2020;69:411-444.

45. Stjepanovic N, Moreira L, Carneiro F, et al; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Hereditary gastrointestinal cancers: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30:1558-1571.

46. Crosbie EJ, Ryan NAJ, Arends MJ, et al; Manchester International Consensus Group. The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. Genet Med. 2019;21:2390-2400.

47. Kim J, Braun D, Ukaegbu C, et al. Clinical factors associated with gastric cancer in individuals with Lynch syndrome. Clin Gastroenterol Hepatol. 2020;18:830-837.e1.

48. Wischhusen JW, Ukaegbu C, Dhingra TG, et al. Clinical factors associated with urinary tract cancer in individuals with Lynch syndrome. Cancer Epidemiol Biomarkers Prev. 2020;29:193-199.

49. Møller P, Seppälä TT, Bernstein I, et al; Mallorca Group. Cancer risk and survival in *path_MMR* carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database [published correction appears in *Gut*. 2020;69:e4]. Gut. 2018;67:1306-1316.

50. Burn J, Sheth H, Elliott F, et al; CAPP2 Investigators. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. Lancet. 2020;395:1855-1863.

51. Myrhøj T, Andersen MB, Bernstein I. Screening for urinary tract cancer with urine cytology in Lynch syndrome and familial colorectal cancer. Fam Cancer. 2008;7:303-307.

State of the Science: Screening, Surveillance, and Epidemiology of HPV-Related Malignancies

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overview

Oropharyngeal, cervical, vulvar, and anal cancers share a common risk factor of HPV infection. HPV vaccination is currently recommended at age 11 or 12 to prevent new HPV infections for all genders with catch-up vaccination recommened up to age 26. Despite the known effectiveness of HPV vaccination to prevent HPV-related cancer, there is continued low uptake in the United States; only 40% of eligible persons were vaccinated in 2018, though rates are 70% among teenagers. Current American Cancer Society cancer screening guidelines recommend cervical cancer screening, but do not have specific recommendations for screening for other HPV-related cancers. Oropharyngeal cancer precursors have yet to be identified, and there are currently no routine screening tests for oropharyngeal cancer recommended by the U.S. Preventive Services Task Force. The U.S. Preventive Services Task Force and American Cancer Society recommend cervical cancer screening for women at average risk up to age 65, and screening guidelines do not currently differ by HPV vaccination status. Primary HPV DNA testing was first approved for cervical cancer screening in 2016 and was shown to be superior for cervical cancer prevention. Vulvar and anal cancer precursors have been identified, but optimal screening remains unclear. Examination of the anal canal and perianus is best performed by trained clinicians using high-resolution anoscopy, and effectiveness of using high-resolution anoscopy to detect and treat anal high-grade squamous intraepithelial lesions to prevent cancer is actively being researched. Current multistep approaches to control HPV-related malignancies include HPV vaccination coupled with cervical cancer screening or surveillance for oropharyngeal, vulvar, and anal cancers.

INTRODUCTION

Current Rate of HPV-Related Cancers in the United States

In the United States currently, there are about 45,000 new HPV-associated cancers occurring in the cervix, vagina, vulva, anus, oropharynx, and penis diagnosed each year. Among these cancers, the percentage attributed to HPV is estimated as 90% of cervical and anal cancers and 70% of oropharyngeal, vaginal, vulvar, and penile cancers.[1]

From 2013 to 2017, each year there were around 25,400 HPV-related cancers in women and 19,900 HPV-related cancers in men in the United States.[1] This includes approximately 20,000 oropharyngeal cancers among men and women, approximately 12,000 cervical cancers among women, approximately 7,000 anal cancers among men and women, and smaller numbers of vaginal, vulvar, and penile cancers.[1] Men have a higher incidence of oropharyngeal cancer than women, but women have a higher incidence of anal cancers than men. Women also have cervical and vulvar cancers, so overall incidence of HPV-related cancers remains higher in women than men in the United States. Rates of HPV-related cancers were highest among the White population and lowest among the Asian/Pacific Islander population (Fig. 1).[1]

HPV Vaccination in the United States

If given prior to exposure, vaccination with GARDASIL 9 HPV 9-valent prevents approximately 92% of HPV-related cancers.[2] Advisory Committee on Immunization Practices recommended routine HPV vaccination for female patients in 2006 and for male patients in 2011. HPV vaccination is currently recommended at age 11 or 12 to prevent new HPV infections and HPV-associated cancers, with catch-up vaccination of all persons through age 26 who are not adequately vaccinated.[3] Since then, HPV vaccination rates have increased steadily, but uptake remains lower than other recommended vaccines. The HPV vaccine was originally introduced as a three-dose regimen, but in 2016, the Advisory Committee on Immunization Practices recommendation was updated to a two-dose schedule for girls and boys who receive the vaccine at ages 9 through 14; the three-dose recommendation was maintained for those initiating vaccination at ages 15 to 26 and for immunocompromised persons.[4] The 2019 Advisory Committee on Immunization Practices guidelines extended vaccination to those up to age 45. Specifically, the guidelines state that for adults ages 27

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PRACTICAL APPLICATIONS

- HPV vaccination is currently recommended at age 11 or 12 for all genders, to prevent new HPV infections and HPV-associated cancers, with catch-up vaccination recommended for all persons through age 26 who are not vaccinated.
- Updated cervical cancer screening recommendations apply to asymptomatic women with intact cervix, starting at age 21 or 25 to age 65, based on U.S. Preventive Services Task Force or American Cancer Society guidelines; three different strategies continue to be offered including cytology only, cotesting, or primary HPV testing.
- The incidence of oropharyngeal and anal cancer has consistently increased over the past 20 years, but optimal screening is still unclear.
- High-resolution anoscopy, performed by specially trained providers, is the best way to detect anal cancer precursors and may have a considerable benefit in the management of superficially invasive squamous cell carcinoma of the anus or perianus. Access is currently limited by the small number of trained providers.

to 45, the "public health benefit of HPV vaccination in this age range is minimal; shared clinical decision-making is recommended because some persons who are not adequately vaccinated might benefit."[3] However, the American Cancer Society does not recommend vaccination for anyone older than age 26.[5]

In 2019, 71.5% of 13- to 17-year-old individuals had received at least one dose of the HPV vaccine, with similar uptake in female (73%) and male (70%) adolescents, compared with 89% to 91% vaccination rates for other vaccines recommended for those ages, such as tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; meningococcal; and measles, mumps, and rubella vaccines (Fig. 2).[6] Among adults still within the recommended catch-up ages for vaccination (ages 18 to 26), the proportion who received at least one dose of the HPV vaccine has been increasing, but is still low, with only 40% vaccinated in 2018 (up from 22% in 2013) and with higher vaccination rates seen in women than men (54% vs. 37%).[7] Vaccine completion rates are even lower, with only 21.5% of those age 18 to 26 receiving all of the recommended number of doses of the HPV vaccine in 2018.[6] As health care providers, we must support universal and widespread HPV vaccination as the best way to eradicate HPV-related cancers.

SCREENING FOR HPV-RELATED CANCERS

Current American Cancer Society cancer screening guidelines recommend cervical cancer screening, but do not have specific recommendations for screening for other HPV-related cancers.[8,9] The incidence of invasive cervical cancer has decreased in the United States due to successes in screening to detect and eradicate the cervical cancer precursors. In contrast, the incidence of oropharyngeal and anal cancer has consistently increased over the past 20 years, but optimal screening for noncervical cancers is still debated. Oropharyngeal cancer precursors have yet to be identified, whereas vulvar and anal precursors, known as high-grade squamous intraepithelial lesions, have been identified; guidelines for prevention are lacking or unsubstantiated. The following sections describe the state of the science for oropharyngeal, cervical, vulvar, and anal cancers.

Oropharyngeal Cancer Screening

Risk for oral HPV infection and HPV-related oropharyngeal cancer is higher in men than women, associated number of lifetime partners performed oral sex on, and increased with tobacco use. Despite increasing oropharyngeal cancer rates, risk of oropharyngeal cancer for most people remains low,[10] and current biomarkers have low sensitivity or very low prevalence such that large numbers would need to be screened to detect a single case.[11] There are currently no routine screening tests for oropharyngeal cancer recommended by the U.S. Preventive Services Task Force.[12] The U.S. Preventive Services Task Force concluded in 2013 that there is inadequate evidence that oral screening examination accurately detects oral cancer or improves morbidity or mortality. "The evidence for screening for oral cancer remains insufficient; therefore, the U.S. Preventive Services Task Force is unable to make a recommendation in favor of or against screening."[12]

The most common oral cancer screening technique is a visual examination by a dentist, doctor, or dental hygienist or self-examination, which sometimes identifies areas of concern to biopsy, although the oropharynx can be difficult to see.[13] The American Dental Association has recommended routine visual examination by a dentist for oral cancer screening for many years and expanded this recommendation in 2019 to suggest this routine visual and tactile examination for evaluation of both oral and oropharyngeal cancer, highlighting dentists' current critical role in oral cancer screening.[14] Similarly, the American Academy of Oral Medicine recommends visual and tactile oral mucosal examination as part of the standard visit by oral health care providers for all patients.[15]

Usually oropharyngeal cancers do not cause symptoms until they have grown or spread, although they can cause symptoms such as toothache, ear pain, and swollen lymph nodes.[16] Recent evidenced-based guidelines by the American Dental Association concluded there were "no

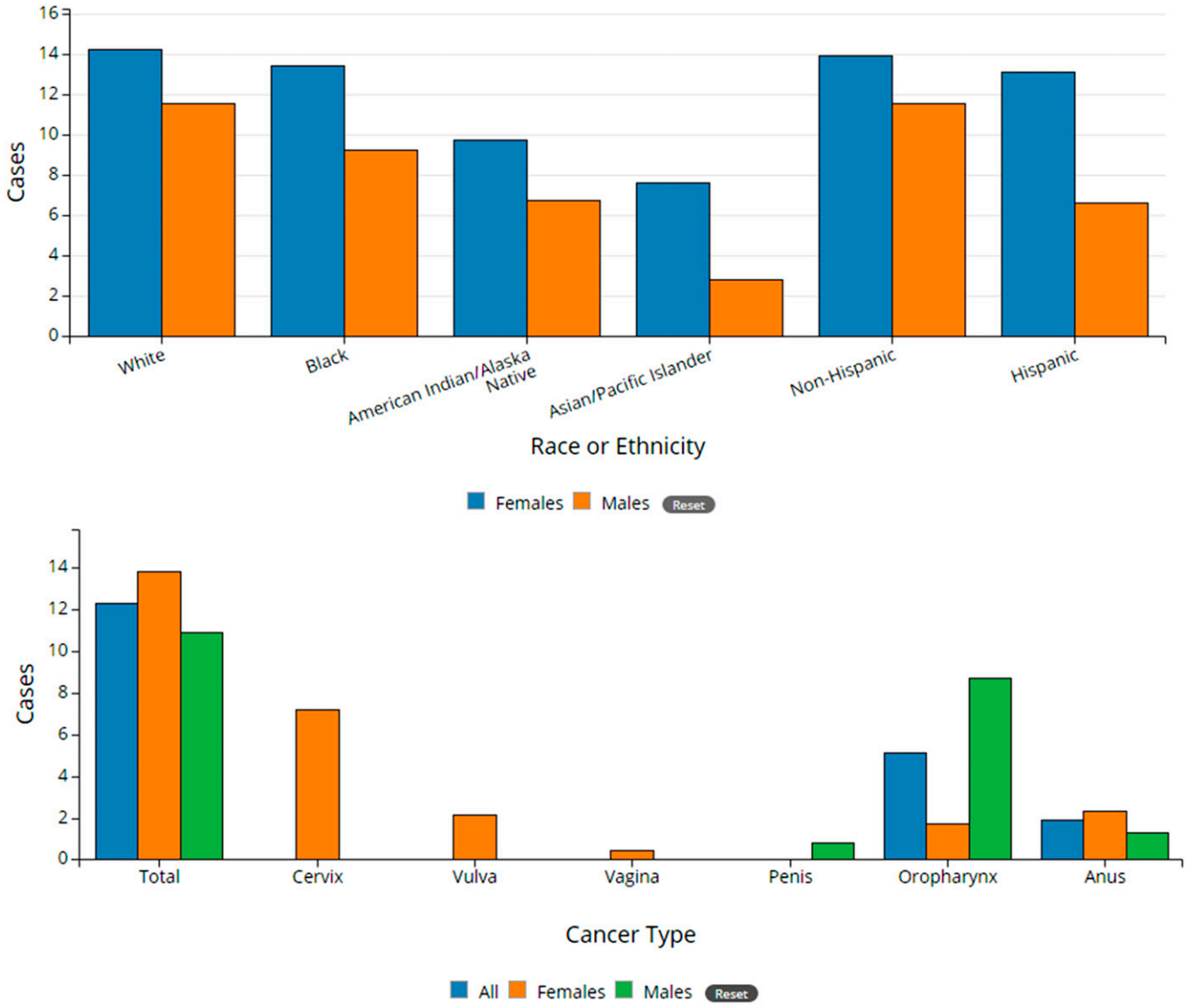

FIGURE 1. Annual Incidence of New HPV-Associated Cancers per 100,000 by Sex and Race/Ethnic Group (top) and Sex and Cancer Type (bottom)[1]
Figure is from Centers for Disease Control and Prevention data that are in the public domain and may be used and reprinted with special permission.

available adjuncts that demonstrated sufficient diagnostic accuracy to support their routine use as triage tools for lesions in the oral cavity"; this included review of salivary and light-based adjuncts (including salivary HPV tests), which were not recommended for use in screening or evaluation of lesions for malignancy.[17] There is currently limited evidence to support screening for oropharyngeal cancer; however, visual oral examination is a noninvasive, inexpensive method and is currently recommended by some groups.

Cervical Cancer Screening

The future of cervical cancer screening is HPV-based testing. The increasing uptake in HPV vaccination rate and the introduction of new technologies and new approaches to cervical cancer screening, such as HPV self-testing, are shifting the historical approach to cervical cancer screening. The natural evolution of testing that has now occurred is an expansion of the use of primary HPV-based testing that can account for HPV vaccination status and provide a risk stratification based on previous screening history. This transition away from previous cytology only–based screening has led to current national cervical cancer screening guidelines for the general risk population that continue to present multiple strategies for screening as acceptable, both that include cytology with HPV cotest or sequential testing, without differentiation based on HPV vaccination history.

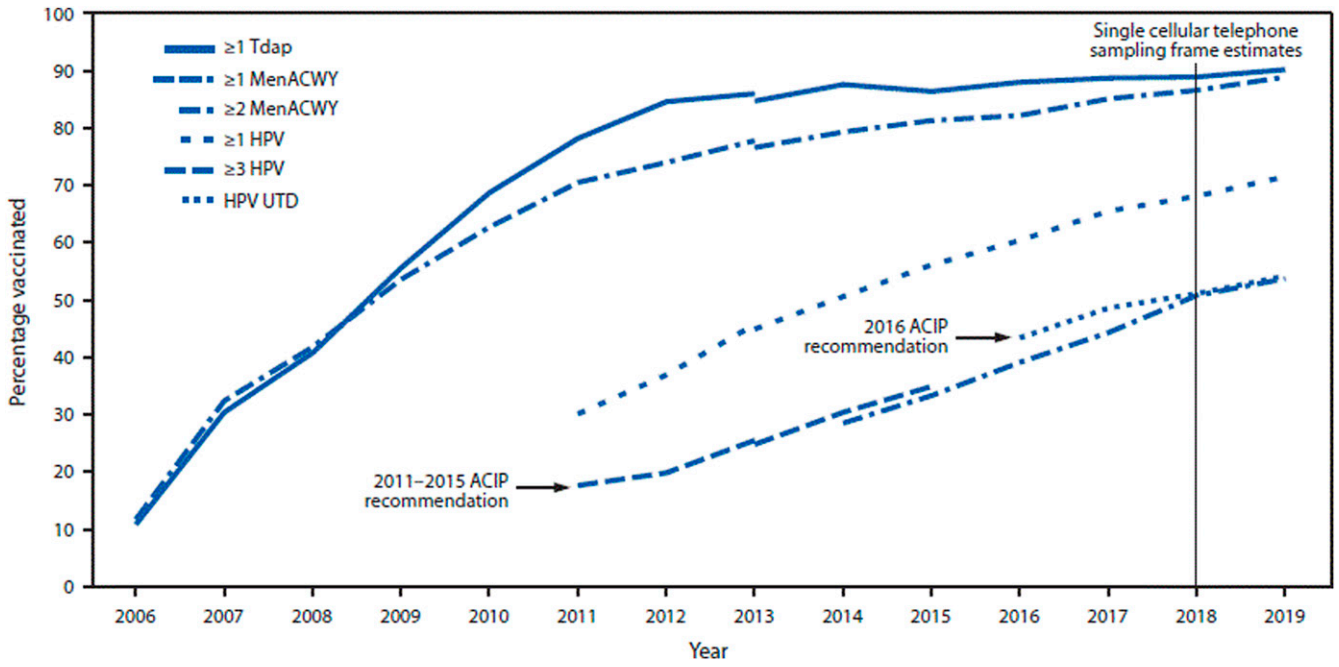

FIGURE 2. Estimated Vaccination Coverage With Selected Vaccines and Doses Among Adolescents Age 13–17 in the United States Between 2006 and 2019, by Survey Year and Advisory Committee on Immunization Practices Recommendations

Figure is from the *MMWR* series that is in the public domain and may be used and reprinted with special permission. Data from the National Immunization Survey-Teen.[6]

Abbreviations: ACIP, Advisory Committee on Immunization Practices; MenACWY, quadrivalent meningococcal conjugate vaccine; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; UTD, up to date.

The enormously successful, secondary prevention of cervical cancer is well established, exemplified by increased mortality in countries without access to screening and treatment of cervical cancer precursors known as cervical high-grade squamous intraepithelial lesions (HSIL). The population benefit that cytology-based screening has had historically cannot be overstated; since its first introduction in the 1950s, death attributed to cervical cancer in the United States has substantially decreased. Although most cervical cancers in the United States are now prevented from screening, not all are. In 2020, an estimated 13,800 women will develop invasive cervical cancer, with an estimated 4,290 deaths.[18] Current cervical cancer screening guidelines seek to balance the benefit of cancer prevention with risk of multiple rounds of testing and overtreatment to the patient. Recommendations for screening consensus guidelines are based on comparative effectiveness studies that determine the benefit of reduction in cervical cancer via measurement of a secondary endpoint, histologic diagnosis of cervical intraepithelial neoplasia grade 3/HSIL or higher.[19,20] Evaluation of an abnormal screening test may require colposcopy with targeted biopsy, excisional procedure of the cervix, hysterectomy for adenocarcinoma in situ, and follow-up surveillance. Potential harm of screening includes unnecessary colposcopy and biopsy to evaluate false-positive screen results, psychological stress, anxiety, and preterm birth.[21,22]

Historical context for cervical cancer screening The goal of cervical cancer screening is to reduce the incidence, mortality, and treatment-associated morbidity from cervical cancer. In poorly screened populations or in countries without a national screening program, cervical cancer screening can provide a secondary benefit of early detection. HPV infection is common and occurs early in sexual debut, but the risk of progression is low, as most infections and low-grade cervical dysplasia will regress in younger women.[23-25] Persistent infection with high-risk HPV, primarily HPV 16 and 18, continues to be the leading cause of cervical cancer.[26,27]

Population-based studies of cervical cancer screening have documented the benefit of cervical cancer screening through diagnosis and treatment of high-grade cervical dysplasia.[28,29] In the 1920s, two discoveries occurred that made cervical cancer prevention possible. Colposcopy was invented, which uses a bright light and magnification to identify precancerous changes on the cervix that appear after applying acetic acid, along with the Papanicolau test, or use of scraping and staining of cells to identify HSIL, now supplemented by direct molecular testing for high-risk HPV.

Colposcopy is performed by gynecologists and some family medicine practitioners. The success of cervical cancer screening is directly linked to compliance with secondary diagnostic testing with colposcopy and directed biopsy. Thus, screening strategies must also consider the burden of screening on the patient and determine risk of failure to follow-up on abnormal screening test.

Screening targets by age group Guidelines for the general population at average risk for cervical cancer applies to all asymptomatic women with an intact cervix and established cervical cancer screening history (Table 1). The 2018 U.S. Preventive Services Task Force recommendation set the target age to start screening at 21, irrespective of sexual history.[30] Women ages 21 to 29 should undergo cytology only–based screening every 3 years; due to high risk of transient high-risk HPV infection in younger women,[23,25] high-risk HPV-based screening was deemed potentially clinically harmful for younger women. From ages 30 to 65, there are three available strategies: cytology alone, cytology and high-risk HPV testing (cotesting), or primary HPV test alone. Women with symptoms of abnormal vaginal bleeding or discharge should be referred for appropriate diagnostic workup. Specific population guidelines for special groups, including women with immunocompromised status, are listed in Table 1.[30,31]

The American Cancer Society in the updated 2020 cervical cancer screening guideline raised the age to start screening

TABLE 1. Recommendations for Cervical Cancer Screening[a]

	2018 U.S. Preventive Service Task Force[30]	2020 American Cancer Society[31]
Target Age Group	Ages 21 to 65	Ages 25 to 65
Screening Interval	Ages 21 to 29: cytology only every 3 years	Option 1: primary HPV testing alone every 5 years (preferred)
	Ages 30 to 65:	Option 2: cotesting[b] every 5 years
	Option 1: primary HPV testing alone every 5 years	Option 3: cytology alone every 3 years
	Option 2: cotesting[b] every 5 years	
	Option 3: cytology alone every 3 years	
Discontinue Screening	**Discontinue If:**	
	Older than age 65 with negative screening in the prior 10 years AND no history of CIN2 or higher dysplasia in past 25 years	
	At any age with limited life expectancy	
	After total hysterectomy[c] AND no history of CIN2+ in past 25 years	
Immunocompromised Persons	**Persons With HIV Infection**	
	Begin within 1 year of sexual activity and if normal repeat annually for 3 years then every 3 years	
	Starting age 30: cytology only every 3 years	
	Lifetime: cytology alone or cotesting every 3 years	
	Other Immunosuppressed Groups That Follow HIV-based Guidelines	
	Solid organ transplant recipients (if transplant < age 21, start screening within 1 year of sexual activity)	
	Allogeneic hematopoietic stem cell transplantation	
	If new or chronic genital graft vs. host disease resume annual cytology for 3 years; then, if normal, every 3 years for lifetime.	
	Other Immunosuppressed Groups That Follow General Population Guidelines	
	Type 1 diabetes	
	Autoimmune disease not on immunosuppressant	
	Autoimmune disease on immunosuppressant (start screening before age 21 if on immunosuppressant)	
	Cytology preferred before age 30, if normal repeat annually for 3 years then every 3 years	
	Cotesting is preferred after age 30, repeat every 3 years for lifetime	

Abbreviation: CIN, cervical intraepithelial neoplasia.
[a]HPV vaccination status is not a factor in screening guideline.
[b]Cotesting refers to HPV testing in combination with cytology.
[c]Total hysterectomy: confirm surgical procedure to document both uterus and cervix were removed; recommendation excludes women who underwent supracervical hysterectomy.

to 25.[31] Based on modeling analysis, starting high-risk HPV testing at age 25 was deemed the most efficient strategy using the number of tests (cytology or high-risk HPV) performed per life year gained. In addition, when compared with cytology alone starting at age 21, this strategy showed a 7% gain in cervical cancer deaths prevented, with only a 9% increase in colposcopies.[20] The American Cancer Society in its 2020 report also clearly signaled a long-term strategy to move toward primarily HPV-based screening because of its increased sensitivity, by stating "the use of co-testing or cytology alone for cervical cancer screening will be eliminated from future guidelines."[31] Multiple factors, including updated comparative effectiveness studies, will ultimately determine broader adoption of primary HPV-based screening as a standard approach to cervical cancer screening in the United States.

The upper age limit for cervical cancer screening is set at 65, a consensus within U.S. Preventive Services Task Force and American Cancer Society guidelines. There are no current randomized trials or large population screening trials that can directly answer the question of what the ideal age is to stop cervical cancer screening. Modeling studies have explored the risk and benefit of stopping screening between ages 55 and 75.[20,32] The U.S. Preventive Services Task Force in 2018 in its modeling study determined the harm, as measured by the number of colposcopies required to achieve an additional year of life gained, outweighs the benefit.[20] Despite concerns raised around HPV risk due to new sexual partners or possible role of HPV reactivation, the risk of infection leading to cancer is exceedingly low in this age group, and thus, resuming screening is not recommended with a new partner.[20,31] Women with poor screening history at age 65 should continue to be screened. In an analysis of women with established health insurance and newly diagnosed cervical cancer, more than 70% of those older than age 65 with new cervical cancer were documented to have failure of screening.[33]

Primary HPV screening Recent advances in cervical cancer screening include the U.S. Food and Drug Administration approval of primary HPV testing, which subsequently led to the inclusion of primary HPV screening in the U.S. Preventive Services Task Force 2018 and American Cancer Society 2020 guidelines. In a pooled analysis of four randomized trials (176,464 women) of high-risk HPV cervical cancer screening versus cytology only, with a median follow-up of 6.5 years, high-risk HPV was superior to cytology for prevention of cervical cancer.[34] The difference can be attributed to increased detection of cervical intraepithelial neoplasia grade 3+ at first round of screening (years 2–5) and superior performance of high-risk HPV over cytology at detecting precursors to invasive adenocarcinoma of the cervix.[19,34] The evidence in support of high-risk HPV-based testing compared with cytology is clear, although challenges to wider adoption of primary HPV-based cervical cancer screening exist. Among the potential barriers include acceptance of the extended 5-year screening interval by patients and clinicians, lag in dissemination of technology, limitation in laboratory capacity, and financial cost associated in conversion away from cytology-based screening. The American Society for Colposcopy and Cervical Pathology continues to provide guidelines for follow-up of abnormal cervical cancer screening based on patient age, screening history, and screening test performed.[35]

Currently, cervical cancer screening guidelines in the United States do not support a change in the recommendation based on HPV vaccination status. It is anticipated that an increasing HPV vaccination uptake and aging of vaccinated cohort will impact screening strategies in the future. Analysis of a Swedish birth cohort, 1989 to 1993, documented a remarkable decline in the positive predictive value of cytology-based screening for diagnoses of cervical intraepithelial neoplasia grade 2+ among the vaccinated cohort, highlighting the need for additional studies to determine optimal screening and diagnostic strategies for the HPV-vaccinated women.[36] Based on meta-analysis of high-income countries after the introduction of the HPV vaccine, among girls who were vaccinated at ages 13 to 19, the prevalence of HPV 16 and 18 decreased by 83%, with a reduction by 51% in diagnosis of cervical HSIL/cervical intraepithelial neoplasia grade 2+ and 67% in anogenital warts.[37] In the United States, in the setting of ongoing barriers to improve vaccination uptake, it is not certain at what level and time herd immunity may be achieved. However, initial models based on HPV vaccine uptake suggest cervical cancer incidence will be substantially reduced in the next 20 years.[38] The most effective age to initiate screening and interval for screening is yet to be determine for the HPV-vaccinated groups.

Other screening considerations The burden of cervical cancer is highest among women who have never been screened or do not undergo routine screening. Lack of access to cervical cancer screening is a recognized barrier. Cervical cancer disparity persists for women from racial and ethnic minority populations, those residing in rural regions, and those who are disadvantaged based on gender or socioeconomic status. Hispanic women and non-Hispanic Black women continue to experience higher cervical cancer incidence and mortality,[18] underlining the importance of continued efforts to improve access to screening and HPV vaccination. Screening options such as HPV self-sampling and immediate see and treat are alternative strategies to increase uptake and treatment in underscreened populations.[39]

Cell-mediated immunity is important for the control of HPV infection. Specifically, immunocompromised persons including those living with HIV infection, solid organ transplant, allogenic hematopoietic stem cell transplant, chronic graft versus host disease, systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease on chronic immunosuppressive therapies have decreased capacity to clear new HPV infections and warrant closer observation. Cervical cancer screening guidelines are most clearly defined for persons living with HIV and are extrapolated for other immunocompromised populations based on expert opinion (Table 1).[40] Data from a multicohort prospective study on women living with HIV reported an elevated incidence of invasive cervical cancer; women living with HIV with a $CD4^+$ T-cell count of 200–349 had three times the incidence of cervical cancer compared with women not living with HIV.[41] Cervical cancer screening for women living with HIV is best positioned within a comprehensive HIV care setting with optimal antiretroviral therapy. Among persons infected with HIV, screening should start within 1 year of acquiring HIV via sexual exposure and no later than age 21. Due to the high HPV prevalence, cytology-only screening should be used until age 30. After age 30, screening can be continued with cytology alone or cotesting every 3 years for the person's lifetime.[42]

Vulvar Cancer Screening

There are no recommended population-based guidelines for the screening of vulvar cancer, and an estimated 6,120 cases will be diagnosed in 2020 in the United States.[18] Vulvar HSIL (70%) is more commonly known as vulvar intraepithelial neoplasia or usual-type vulvar intraepithelial neoplasia, commonly associated with carcinogenic genotypes of HPV, and it occurs among younger women in their 40s. Available HPV vaccinations are effective at decreasing the risk of vulvar HSIL, and thus, the benefit of preventing vulvar condyloma and vulvar cancer should be discussed. Differentiated vulvar intraepithelial neoplasia representing approximately 30% of precancerous vulvar lesions is often not associated with HPV but frequently occurs in the background of chronic vulvar inflammation in older women or dermatologic conditions of the vulvar such as lichen sclerosus.[43] Women may present with symptoms of vulvar pruritus, pain, and new raised or flat lesions. An ulcerative lesion is more indicative of vulvar cancer and warrants immediate biopsy. An examination of the vulva to detect a new lesion can be enhanced with application of 3% to 5% acetic acid to the skin for several minutes to detect changes. Although not required, colposcopy may detect more subtle change. Vulvar punch biopsy is recommended for dense new lesions, lesions with atypical borders or vasculature, and for older patients or those with known immunosuppression. Patients with both usual-type vulvar intraepithelial neoplasia and differentiated vulvar intraepithelial neoplasia require more definitive treatment, including excision or ablative surgical procedure and ongoing closer follow-up for recurrence. Those with usual-type HPV-related vulvar intraepithelial neoplasia should be considered for screening for anal cancer.

ANAL CANCER SCREENING

Until HPV vaccination of children prior to sexual debut becomes widespread and those age cohorts approach the ages of usual cancer onset, there will be a substantial population of HPV-infected men and women susceptible to cancer.[44] This section presents the current data on risk-reduction strategies for anal cancer. Men who have sex with men have a high prevalence of anal HPV and anal HSIL and, consequently, high rates of anal cancer (as high as cervical cancer among unscreened women). Anal cancer incidence is even higher among men who have sex with men immunocompromised by HIV,[45] with an incidence of approximately 131 per 100,000.[46] Likewise, men who have sex with men living with HIV have a high prevalence of anal HSIL, exceeding 50% in some studies performed by experienced anoscopists. Solid organ transplant recipients and women with a prior history of lower genital tract HPV-related neoplasia are also at increased risk of anal cancer.[47-49] Among older women age 65 to 74 and older than age 75, the incidence of anal or vulvar cancer is greater than cervical cancer.[50]

Historical Context for Anal Cancer Screening

Techniques developed for cervical cancer screening have been adapted for anal cancer screening. Analogous to colposcopy used to visualize the cervix in cervical cancer screening, the colposcope was adapted in the early 1990s to examine the anal canal and perianus, now known as high-resolution anoscopy.[51] The University of California San Francisco Anal Neoplasia Clinic, Research, and Education Center became the world's first clinic dedicated to anal neoplasia in approximately 1995.[52] The International Anal Neoplasia Society inaugural scientific meeting was in 2013. This historical context indicates that high-resolution anoscopy is not taught regularly in medical schools or in residency programs; there are a limited number of trained and experienced providers worldwide.

There are less effective methods that might be considered for anal cancer screening when high-resolution anoscopy is not available. Colonoscopy is not an effective procedure for evaluating anal neoplasia, although occasionally findings during this procedure diagnose anal neoplasia. Retroflexed views of the anus are not routinely performed and are likely to miss anal lesions. Simple anoscopy may reveal warts or macroscopic lesions, but most precancerous HSIL and superficially invasive cancers will not be seen. Although digital anorectal examination is an accepted method of screening for anal cancer, it is often not performed or well

performed in patients with early symptoms, often delaying diagnosis.[53] But for screening, there are insufficient data on digital anorectal examination sensitivity and specificity; however, in areas without other screening options, it has been shown to have some utility in anal cancer screening.[54] High-resolution anoscopy requires performing more than 100 examinations in patients at risk to become proficient.[55] The American Society of Colon and Rectal Surgeons provides a tepid recommendation for high-resolution anoscopy because it has yet to be shown that identification and treatment of anal HSIL prevents anal cancer.[56]

The ANCHOR trial In 2014, the ANCHOR (Anal Cancer HSIL Outcomes Research) study (U01CA121947), funded by the U.S. National Cancer Institute, began enrollment of a planned 5,058 persons over age 35 living with HIV and diagnosed with anal HSIL who were randomly assigned in a 1:1 ratio to either close follow-up or treatment of their HSIL. The ANCHOR study has been conducted in over 15 centers across the United States, creating a network of trained high-resolution anoscopy providers. If a noteworthy reduction in anal cancer is demonstrated in the treatment group in this challenging group of patients at particularly high risk of anal cancer, then it will provide the evidence to make this the standard of care for all persons at risk for anal cancer. Initial effectiveness data from the ANCHOR trial are expected in 2026.[57] Although the American Society of Colon and Rectal Surgeons practice parameters acknowledge that high-resolution anoscopy effectively identifies HSIL, a major shortcoming is they do not recommend its use routinely to help facilitate the early diagnosis of anal cancer prior to it becoming palpable or often visible, also known as superficially invasive squamous cell carcinoma (SISCCA), and/or its use in surveillance of patients treated for anal cancer, particularly with excision alone.

Management of early-stage anal cancer Staging of anal cancer uses the TNM system; T1 for tumors 2 cm or less and T2 for tumors larger than 2 cm but 5 cm or less.[58] Determination of T stage is primarily through clinical evaluation, known as a digital anorectal examination, because smaller cancers are below the resolution of common imaging techniques. In 2012, the Lower Anogenital Squamous Terminology standardization project consensus conference convened a group of major stakeholders worldwide that recommended a new pathologic entity known as an SISCCA.[59] These early cancers are usually not palpable, detected serendipitously during surgical excisions for benign anorectal disorders or using high-resolution anoscopy. Superficially invasive squamous cell carcinoma are defined as fully excised squamous carcinoma of the anal canal or perianus with clear margins with a depth of invasion 3 mm or less and 7 mm or more in horizontal extent. To date, no specific recommendation has been made to indicate SISCCA within the American Joint Committee on Cancer staging system other than as a T1. The significance of SISCCA is that patients may be able to be treated with excision alone.

Current management of T1 anal cancers is debatable and not well studied. The National Comprehensive Cancer Network currently recommends chemotherapy and radiation for T1 anal canal cancers with the exception that complete excision of SISCCA "may be adequate treatment."[58] It is well established that T1N0 perianal cancers may be treated with excision; however, what is not widely known is that approximately 75% of perianal cancers will have concomitant precancerous HSIL within the anal canal. Because high-resolution anoscopy is not widely available or routinely performed and is the best way to identify these lesions, patients treated with excision of perianal cancers are at significantly increased risk for second anal cancers. Although SISCCA is pathologically defined, it must be placed in clinical context. Anal biopsies can be quite small, sampling only a minor aspect of a larger lesion or mass. A true SISCCA is a cancer that has been completely excised with a margin clear of cancer.[60]

Historically, patients with T1 anal cancers were excluded from the major clinic trials, such as RTOG 9811 (cisplatin vs. mitomycin and neoadjuvant therapy) and RTOG 0529 (intensity-modulated radiation therapy).[61,62] In ACT II (like RTOG 9811 but evaluated maintenance therapy), T1 cancers represented 10% of the 940 patents enrolled, but results were combined with patients with T2 cancers, and these patients were excluded from the maintenance arm.[63] Contributing to further confusion are recent reports analyzing large cancer databases such as Surveillance, Epidemiology, and End Results, Medicare claims, and the National Cancer Center Database that show increasing use of local excision of early cancers.[64-66] It is encouraging that these studies do not show any notable differences in the survival rates for patients treated with excision compared with those treated with chemotherapy and radiation, but limitations such as the inability to analyze results by tumor location (anal canal or perianus), size, especially SISSCA or greater, and locoregional failure as opposed to survival preclude a strong recommendation of this alternative.[67] Although it is understandable and desirable to avoid the lifelong effects of radiation therapy, this approach has not been rigorously validated by prospective clinical trials. Each of these reports recommends further study to define the role of excision.

Some database and cohort series demonstrate unacceptable rates of local recurrence, particularly for tumors located within the anal canal, providing support for not recommending this approach.[68-71] The difference in outcome may relate to how these patients treated with excision were followed. Anal cancer is a result of persistent high-risk HPV

TABLE 2. Clinical Trials in Progress Evaluating Management Strategies in Early Anal Cancer

Study Name, Identifier, Reference	Accrual Goal	Strategy
PLATO ACT 3, ISRCTN88455282[73]	90 patients with excision of T1 cancers (United Kingdom)	Chemotherapy and decreased radiation following excision if margin is < 1 mm vs. observation (if anal canal, must be SISCCA); no HRA follow-up
EA2182, NCT04166318[74]	252 patients (United States)	Randomization following excision of T1–T2 < 4 cm tumors in a 1:2 ratio of standard radiation vs. reduced radiation given with standard chemotherapy (excludes T1 perianal cancers with clear margins)
AMC 092, NCT02437851[75]	28 anal canal (United States) 28 perianus (United States)	Feasibility study of excision of SISCCA in patients living with HIV with HRA follow-up and ablation of any HSIL

Abbreviations: SISCCA, superficially invasive squamous cell carcinoma; HRA, high-resolution anoscopy; HSIL, high-grade squamous intraepithelial lesions.

infection producing a field effect across the entire anogenital tract; the impact of the field effect explains why women with prior cervical or vulvar HSIL/cancer are at increased risk for anal cancer. Using high-resolution anoscopy to examine patients newly diagnosed with either anal cancer or SISCCA reveals that nearly all have concomitant visible HSIL. Following chemotherapy and radiation, both the cancer and these precancerous HSIL resolve. One mechanism for local recurrence following chemotherapy and radiation is persistence of HSIL that, if unrecognized and untreated, may progress to cancer. Our approach at the University of California, San Francisco, in treating patients who underwenth excision of SISCCA is to use high-resolution anoscopy to follow and treat any remaining HSIL.[52,60] A recent study published from the United Kingdom that used high-resolution anoscopy in follow-up of patients surgically treated for anal cancer yielded excellent results and demonstrated that these patients are at high risk for not only recurrent precancerous HSIL but also recurrent SISCCA, especially when they have not received chemotherapy and radiation.[72] Early detection and treatment of this HSIL and SISCCA is then easily treated, such that most patients do not require chemotherapy and radiation. See Table 2[73-75] for a list of current clinical trials in progress to optimize treatment of early anal cancer.

To summarize, the increase in diagnosis of earlier-stage anal cancers can be attributed to a combination of the increased incidence of anal cancer, increased awareness of anal cancer, and, most importantly, the increased screening of patients at risk for anal cancer. There is now a formal definition for SISCCA that will facilitate pathologic homogeneity and allow more accurate comparison of outcomes. As local excision is being used more frequently, these patients will be seeking professional guidance on whether they can avoid chemotherapy and radiation. Unfortunately, well-designed clinical trials have yet to be performed demonstrating the effectiveness of this approach. It is imperative that patients and providers understand that this is not standard of care, and, if chosen, they must be followed carefully by someone experienced in managing anal neoplasia surgically, ideally with high-resolution anoscopy.

CONCLUSION

Widespread vaccination of children and adolescents has the potential to eradicate HPV-related cancers in the future, but in the meantime, a substantial amount of people remain at risk for cancer. No effective risk-reduction or screening strategy has yet been documented for oropharyngeal cancer. Cervical cancer screening has been very successful, but older women remain at increased risk for noncervical HPV-related cancers such as vulvar and anal cancer. Effectiveness of treating anal HSIL to prevent cancer is actively being researched but not yet established and, if proven effective, will require acceptance of and training of more providers in high-resolution anoscopy. Patients treated for early anal cancer with excision alone should be referred to experienced providers for surveillance due to a higher risk of recurrence.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_325319.

REFERENCES

1. Centers for Disease Control and Prevention. Cancers Associated with Human Papillomavirus, United States—2013–2017. USCS Data Brief, no 18. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 2020. https://www.cdc.gov/cancer/uscs/about/data-briefs/no18-hpv-assoc-cancers-UnitedStates-2013-2017.htm. Accessed January 11, 2021.
2. Senkomago V, Henley SJ, Thomas CC, et al. Human papillomavirus-attributable cancers - United States, 2012-2016. MMWR Morb Mortal Wkly Rep. 2019;68:724-728.
3. Meites E, Szilagyi PG, Chesson HW, et al. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2019;68:698-702.
4. Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination - updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2016;65:1405-1408.
5. Saslow D, Andrews KS, Manassaram-Baptiste D, et al; American Cancer Society Guideline Development Group. Human papillomavirus vaccination 2020 guideline update: American Cancer Society guideline adaptation. CA Cancer J Clin. 2020;70:274-280.
6. Elam-Evans LD, Yankey D, Singleton JA, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years - United States, 2019. MMWR Morb Mortal Wkly Rep. 2020;69:1109-1116.
7. Boersma P, Black LI. Human papillomavirus vaccination among adults aged 18-26, 2013-2018. NCHS Data Brief. 2020;354:1-8.
8. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2017: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2017;67:100-121.
9. American Cancer Society. American Cancer Society Guidelines for the Early Detection of Cancer. https://www.cancer.org/healthy/find-cancer-early/cancer-screening-guidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer.html. Accessed January 7, 2021.
10. D'Souza G, McNeel TS, Fakhry C. Understanding personal risk of oropharyngeal cancer: risk-groups for oncogenic oral HPV infection and oropharyngeal cancer. Ann Oncol. 2017;28:3065-3069.
11. D'Souza G, Clemens G, Troy T, et al. Evaluating the utility and prevalence of HPV biomarkers in oral rinses and serology for HPV-related oropharyngeal cancer. Cancer Prev Res (Phila). 2019;12:689-700.
12. Moyer VA; U.S. Preventive Services Task Force. Screening for oral cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160:55-60.
13. Mabry-Hernandez I, Chu K. Screening for oral cancer. Am Fam Physician. 2015;91:387-388.
14. American Dental Association. ADA expands policy on oral cancer detection to include oropharyngeal cancer. https://www.ada.org/en/publications/ada-news/2019-archive/september/ada-expands-policy-on-oral-cancer-detection-to-include-oropharyngeal-cancer. Accessed January 15, 2021.
15. American Academy of Oral Medicine. Clinical Practice Statement: Oral Cancer Screening. https://www.aaom.com/clinical-practice-statement–oral-cancer-screening. Accessed January 15, 2021.
16. American Cancer Society. Can Oral Cavity and Oropharyngeal Cancers Be Found Early? https://www.cancer.org/cancer/oral-cavity-and-oropharyngeal-cancer/detection-diagnosis-staging/detection.html. Accessed January 15, 2021.
17. Lingen MW, Abt E, Agrawal N, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity: a report of the American Dental Association. J Am Dent Assoc. 2017;148:712-727.e10.
18. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
19. Melnikow J, Henderson JT, Burda BU, et al. Screening for cervical cancer with high-risk human papillomavirus testing: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2018;320:687-705.
20. Kim JJ, Burger EA, Regan C, et al. Screening for cervical cancer in primary care: a decision analysis for the US Preventive Services Task Force. JAMA. 2018;320:706-714.
21. Habbema D, Weinmann S, Arbyn M, et al. Harms of cervical cancer screening in the United States and the Netherlands. Int J Cancer. 2017;140:1215-1222.
22. Weinmann S, Naleway A, Swamy G, et al. Pregnancy outcomes after treatment for cervical cancer precursor lesions: an observational study. PLoS One. 2017;12:e0165276.
23. Ho GY, Bierman R, Beardsley L, et al. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med. 1998;338:423-428.
24. Bekos C, Schwameis R, Heinze G, et al. Influence of age on histologic outcome of cervical intraepithelial neoplasia during observational management: results from large cohort, systematic review, meta-analysis. Sci Rep. 2018;8:6383.
25. Moscicki AB, Shiboski S, Hills NK, et al. Regression of low-grade squamous intra-epithelial lesions in young women. Lancet. 2004;364:1678-1683.

26. Schiffman M, Doorbar J, Wentzensen N, et al. Carcinogenic human papillomavirus infection. Nat Rev Dis Primers. 2016;2:16086.
27. Castle PE, Fetterman B, Poitras N, et al. Variable risk of cervical precancer and cancer after a human papillomavirus-positive test. Obstet Gynecol. 2011; 117:650-656.
28. Andrae B, Andersson TM, Lambert PC, et al. Screening and cervical cancer cure: population based cohort study. BMJ. 2012;344:e900.
29. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. N Engl J Med. 2009;360:1385-1394.
30. Curry SJ, Krist AH, Owens DK, et al; US Preventive Services Task Force. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;320:674-686.
31. Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin. 2020;70:321-346.
32. Malagón T, Kulasingam S, Mayrand MH, et al. Age at last screening and remaining lifetime risk of cervical cancer in older, unvaccinated, HPV-negative women: a modelling study. Lancet Oncol. 2018;19:1569-1578.
33. Leyden WA, Manos MM, Geiger AM, et al. Cervical cancer in women with comprehensive health care access: attributable factors in the screening process. J Natl Cancer Inst. 2005;97:675-683.
34. Ronco G, Dillner J, Elfström KM, et al; International HPV screening working group. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet. 2014;383:524-532.
35. Perkins RB, Guido RS, Castle PE, et al; 2019 ASCCP Risk-Based Management Consensus Guidelines Committee. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis. 2020;24:102-131.
36. Lei J, Ploner A, Lehtinen M, et al. Impact of HPV vaccination on cervical screening performance: a population-based cohort study. Br J Cancer. 2020; 123:155-160.
37. Drolet M, Bénard É, Pérez N, et al; HPV Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet. 2019;394:497-509.
38. Laprise JF, Chesson HW, Markowitz LE, et al. Effectiveness and cost-effectiveness of human papillomavirus vaccination through age 45 years in the United States. Ann Intern Med. 2020;172:22-29.
39. Arbyn M, Smith SB, Temin S, et al; Collaboration on Self-Sampling and HPV Testing. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. BMJ. 2018;363:k4823.
40. Moscicki AB, Flowers L, Huchko MJ, et al. Guidelines for cervical cancer screening in immunosuppressed women without HIV infection. J Low Genit Tract Dis. 2019;23:87-101.
41. Abraham AG, D'Souza G, Jing Y, et al; North American AIDS Cohort Collaboration on Research and Design of IeDEA. Invasive cervical cancer risk among HIV-infected women: a North American multicohort collaboration prospective study. J Acquir Immune Defic Syndr. 2013;62:405-413.
42. Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/human-papillomavirus-disease. Accessed January 21, 2021.
43. Alkatout I, Schubert M, Garbrecht N, et al. Vulvar cancer: epidemiology, clinical presentation, and management options. Int J Womens Health. 2015;7:305-313.
44. Beachler DC, Kreimer AR, Schiffman M, et al; Costa Rica HPV Vaccine Trial (CVT) Group. Multisite HPV16/18 vaccine efficacy against cervical, anal, and oral HPV infection. J Natl Cancer Inst. 2015;108:djv302.
45. Palefsky JM, Holly EA, Ralston ML, et al. Anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual and bisexual men: prevalence and risk factors. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;17:320-326.
46. Wang CJ, Palefsky JM. HPV-associated anal cancer in the HIV/AIDS patient. Cancer Treat Res. 2019;177:183-209.
47. Madeleine MM, Finch JL, Lynch CF, et al. HPV-related cancers after solid organ transplantation in the United States. Am J Transplant. 2013;13:3202-3209.
48. Saleem AM, Paulus JK, Shapter AP, et al. Risk of anal cancer in a cohort with human papillomavirus-related gynecologic neoplasm. Obstet Gynecol. 2011; 117:643-649.
49. Moscicki AB, Darragh TM, Berry-Lawhorn JM, et al. Screening for anal cancer in women. J Low Genit Tract Dis. 2015;19(Suppl 1):S27-S42.
50. Deshmukh AA, Suk R, Shiels MS, et al. Incidence trends and burden of human papillomavirus-associated cancers among women in the United States, 2001-2017. J Natl Cancer Inst. Epub 2020 Aug 24.
51. Jay N, Berry JM, Hogeboom CJ, et al. Colposcopic appearance of anal squamous intraepithelial lesions: relationship to histopathology. Dis Colon Rectum. 1997; 40:919-928.
52. Berry-Lawhorn JM. Improved anal cancer outcomes: is there light at the end of the tunnel? Dis Colon Rectum. 2020;63:1343-1346.
53. Hillman RJ, Berry-Lawhorn JM, Ong JJ, et al; International Anal Neoplasia Society. International Anal Neoplasia Society guidelines for the practice of digital anal rectal examination. J Low Genit Tract Dis. 2019;23:138-146.
54. Nyitray AG, D'Souza G, Stier EA, et al. The utility of digital anal rectal examinations in a public health screening program for anal cancer. J Low Genit Tract Dis. 2020;24:192-196.

55. Hillman RJ, Cuming T, Darragh T, et al. 2016 IANS International Guidelines for practice standards in the detection of anal cancer precursors. J Low Genit Tract Dis. 2016;20:283-291.

56. Stewart DB, Gaertner WB, Glasgow SC, et al; Prepared on Behalf of the Clinical Practice Guidelines Committee of the American Society of Colon and Rectal Surgeons. The American Society of Colon and Rectal Surgeons clinical practice guidelines for anal squamous cell cancers (revised 2018). Dis Colon Rectum. 2018;61:755-774.

57. ClinicalTrials.gov. Topical or Ablative Treatment in Preventing Anal Cancer in Patients With HIV and Anal High-Grade Squamous Intraepithelial Lesions (ANCHOR). https://clinicaltrials.gov/ct2/show/NCT02135419. Accessed January 23, 2021.

58. Benson AB, Venook AP, Al-Hawary MM, et al. Anal carcinoma, version 2.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018; 16:852-871.

59. Darragh TM, Colgan TJ, Cox JT, et al; Members of LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 2012;136:1266-1297.

60. Berry-Lawhorn JM, Palefsky JM. Progression of anal high-grade squamous intraepithelial lesions to anal squamous cell carcinoma and clinical management of anal superficially invasive squamous cell carcinoma. Semin Colon Rectal Surg. 2017;28:91-96.

61. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA. 2008;299:1914-1921.

62. Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys. 2013;86:27-33.

63. James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial. Lancet Oncol. 2013;14:516-524.

64. Deshmukh AA, Zhao H, Das P, et al. Clinical and economic evaluation of treatment strategies for T1N0 anal canal cancer. Am J Clin Oncol. 2018;41:626-631.

65. Chai CY, Tran Cao HS, Awad S, et al. Management of stage I squamous cell carcinoma of the anal canal. JAMA Surg. 2018;153:209-215.

66. Gao X, Goffredo P, Kahl AR, et al. Chemoradiation versus local excision in treatment of stage I anal squamous cell carcinoma: a population-based analysis. Eur J Surg Oncol. 2020;46:1663-1667.

67. Renehan AG, Muirhead R, Sebag-Montefiore D. Limitations of the National Cancer Data Base to evaluate early-stage anal cancer treatment outcomes. JAMA Surg. 2018;153:691.

68. Leon O, Hagberg O, Johnsson A. Primary surgery with or without postoperative radiotherapy in early stage squamous cell carcinoma in the anal canal and anal margin. Acta Oncol. 2018;57:1209-1215.

69. Maccabe TA, Parwaiz I, Longman RJ, et al. Outcomes following local excision of early anal squamous cell carcinomas of the anal canal and perianal margin. Colorectal Dis. Epub 2020 Nov 3.

70. Renehan AG, Muirhead R, Berkman L, et al; PLATO trial management group. Early stage anal margin cancer: towards evidence-based management. Colorectal Dis. 2019;21:387-391.

71. Arana R, Fléjou JF, Si-Mohamed A, et al. Clinicopathological and virological characteristics of superficially invasive squamous-cell carcinoma of the anus. Colorectal Dis. 2015;17:965-972.

72. Cappello C, Cuming T, Bowring J, et al. High-resolution anoscopy surveillance after anal squamous cell carcinoma: high-grade squamous intraepithelial lesion detection and treatment may influence local recurrence. Dis Colon Rectum. 2020;63:1363-1371.

73. Cancer Research UK. Identifier ISRCTN88455282, PLATO - PersonaLising Anal cancer radioTherapy dOse - Incorporating Anal Cancer Trials (ACT) ACT3, ACT4 and ACT5. https://www.isrctn.com/ISRCTN88455282. Accessed January 18, 2021.

74. ClinicalTrials.gov. NCT04166318, Lower-Dose Chemoradiation in Treating Patients With Early-Stage Anal Cancer, the DECREASE Study. https://clinicaltrials.gov/ct2/show/NCT04166318. Accessed January 18, 2021.

75. ClinicalTrials.gov. NCT02437851, Surgery in Treating Patients With Early Stage Anal Canal or Perianal Cancer and HIV Infection. https://www.clinicaltrials.gov/ct2/show/NCT02437851. Accessed January 18, 2021.

PROFESSIONAL DEVELOPMENT AND EDUCATION ADVANCES

Creating a Blueprint of Well-Being in Oncology: An Approach for Addressing Burnout From ASCO's Clinician Well-Being Taskforce

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overview

Optimizing the well-being of the oncology clinician has never been more important. Well-being is a critical priority for the cancer organization because burnout adversely impacts the quality of care, patient satisfaction, the workforce, and overall practice success. To date, 45% of U.S. ASCO member medical oncologists report experiencing burnout symptoms of emotional exhaustion and depersonalization. As the COVID-19 pandemic remains widespread with periods of outbreaks, recovery, and response with substantial personal and professional consequences for the clinician, it is imperative that the oncologist, team, and organization gain direct access to resources addressing burnout. In response, the Clinician Well-Being Task Force was created to improve the quality, safety, and value of cancer care by enhancing oncology clinician well-being and practice sustainability. Well-being is an integrative concept that characterizes quality of life and encompasses an individual's work- and personal health–related environmental, organizational, and psychosocial factors. These resources can be useful for the cancer organization to develop a well-being blueprint: a detailed start plan with recognized strategies and interventions targeting all oncology stakeholders to support a culture of community in oncology.

CASE PRESENTATION

Dr. N had always been an enthusiastic, devoted medical oncologist and a successful clinical trial investigator. At the age of 38, he was fatigued, cynical, and lonely. Dr. N's resentment was originally directed at the health care system for the perceived coercion to see more patients per week in less time. His frustrations surrounded the limited clinical time he can spend with patients with advanced cancer who require detailed information pertaining to disease, prognosis, and treatment. As a result, Dr. N became irritable as he cared for patients for what he views to be increasingly demanding, yet expected, needs because of their role as patients with advanced cancer. He detested the hours devoted to electronic medical records and clerical administration, which he believes contributes to his loss of identity, autonomy, and values. Although Dr. N's relationships with patients once thrived, they no longer provided the same level of satisfaction. Now, in the midst of the COVID-19 pandemic, he continually worries about the risk of viral infection to his immunocompromised patients, trying to protect those in routine cancer care at every level. His electronic medical record documentation time has only increased with the additional burden of telemedicine visits. The joy of oncology practice that he relished is a distant memory. Even his treasured discussions with his supportive wife have not relieved these feelings of intense isolation and pessimism. As he meets with peer colleagues, Dr. N reports feeling cynical regarding his future career and presents the following question to them: "Is any of this worth it?"

INTRODUCTION

Prioritizing oncology clinician well-being has never been more critical. The role of the cancer clinician is a rewarding experience, yet the complexity of care provided to seriously ill patients in an ever-evolving health care environment places substantial demands on the individual clinician and workforce. It is the clinical ethics framework of medicine–patient autonomy, respect for patient welfare, avoidance of harm, and the provision of justice that serves as a model for action in the delivery of optimal oncology care and further solidifies the clinician's obligation to the patient. However, mounting clinical care responsibilities, coupled with increasing administrative and electronic medical record demands on clinical time, productivity, loss of autonomy, and the evolving medical landscape,

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PRACTICAL APPLICATIONS

- The COVID-19 pandemic has evolved during a time of previously established intensified burnout substantially impacting the well-being of oncologists and oncology team members and overall practice health.
- It is imperative that oncology clinicians and cancer organizations have direct access to resources to address team burnout, thereby improving the quality of patient care and workforce sustainability.
- The mission of ASCO's Clinician Well-Being Task Force is to improve the quality, safety, and value of cancer care by enhancing the well-being of oncology clinicians and oncology practice sustainability.
- Empowerment of the oncology team is critical to find a path forward in the face of an evolving oncology clinical landscape and to rise above pandemic-related adversity.
- Organizations should consider developing a blueprint (a detailed immediate start plan with recognized strategies and interventions targeting all oncology stakeholders) to support a culture of community that prioritizes initial programs, culture transformation, research, and practice sustainability.

both directly and indirectly, compromise the clinician's obligation to the patient. This places the dutiful oncologist, Dr. N, at notable risk for occupational stress in the form of burnout syndrome. Burnout arises, intensifying, when clinicians realize their professional and personal values are not shared by their organization. Moreover, as Dr. N finds it increasingly difficult to repeatedly translate his decisions to ethical action, especially in the presence of the COVID-19 pandemic, moral distress develops. When clinicians experience burnout and moral distress, their well-being is placed in jeopardy. Thus, enhancing oncology clinician well-being is vital to initiating and maintaining the clinician–patient relationship and simultaneously improves the overall quality of cancer care, organizational success, workforce sustainability, and professional fulfillment. Here, the authors, members of the ASCO Clinician Well-Being Task Force, will present an update on the prevalence, contributors, and consequences of burnout for the oncologist; the ASCO Clinician Well-Being Task Force roadmap, mission, and vision; focus group study data on the oncologist's personal and professional experiences during the COVID-19 pandemic; evidence on burnout for oncology team members, including advanced practice providers; ASCO's Quality Training Program initiatives to prepare teams to design and implement well-being interventions; how leadership's empowerment of the clinician and recognition of well-being improves the business of oncology; and a blueprint for cancer organizational strategies to promote oncology clinician well-being.

THE BURNOUT EXPERIENCE IN ONCOLOGISTS: PREVALENCE, CONTRIBUTORS, CONSEQUENCES

The burnout syndrome was first identified in the mid-1970s by psychologist Dr. Herbert Freudenberger as a syndrome arising as occupational stressors coupled with additional life pressures exceed the ability to thrive, resulting in physical and mental distress.[1,2] Today, in the most comprehensive study of oncologist burnout to date, 45% of U.S. ASCO member medical oncologists have reported experiencing emotional exhaustion and/or depersonalization symptoms related to burnout.[3] Burnout has been empirically defined as an occupational-related syndrome characterized by signs of physical and emotional exhaustion, cynicism and depersonalization (sense of detachment/disengagement), and a low sense of professional accomplishment.[1] These three-dimensional burnout domains exist along a continuum distinguished by distinct symptoms and an overlap of symptoms. For example, the symptoms of physical and emotional exhaustion include chronic fatigue, cardiovascular issues, cognitive dysfunction, insomnia, gastrointestinal complaints, and affective and behavioral distress (anger, depression, anxiety). Cynicism and depersonalization are characterized by signs of pessimism/depression, isolation, demoralization, and detachment. A low sense of personal accomplishment leads to a sense of inefficacy, decreased productivity, and work–life balance dissatisfaction. Initial physical and emotional symptoms develop slowly, insidiously, over the course of 1 year, becoming chronic.[1-4] Burnout is not a formal medical or mental health disorder, because it has been primarily recognized as an occupational-related condition by the World Health Organization.[5] It is presently incorporated in the International Classification of Diseases 11th Revision with a recently expanded, comprehensive definition under the category "Problems related to employment or unemployment" (QD85 Burnout) resulting from chronic workplace stress that has not been addressed, adversely impacting the individual's health.[2,5]

In addition to prior empirically defined individual and organizational contributors to burnout in oncologists, consideration of a new combination of factors impacting well-being in oncology must be considered (Sidebar 1).[6] The evolving medical landscape and practice demands have greatly affected care delivery, documentation, and reimbursement, contributing to clinician stress across practice areas. Oncologists encounter patients and families in a potential state of crisis, medical or psychological, at any point across the cancer trajectory. Repeated exposure to life-threatening

illness, limited treatment options, and treatment failure place oncologists at risk for distress and burnout.[7,8] The increasing prevalence of elderly and long-term survivors of cancer with chronic health conditions pose unique treatment and care challenges.[9,10] Finally, oncologists encounter ethically challenging situations related to differences in patient, family, and colleague values and end-of-life preferences. Dr. N grew pessimistic toward his role as an oncologist because of mounting cumulative institutional demands, resulting in overall decreased productivity and an increased clinical and administrative workload that has intensified since the COVID-19 pandemic. Increasingly, these signs and contributors adversely impact Dr. N's well-being, potentially leading to key adverse consequences for both oncologist and organization (Sidebar 1). For the oncologist, consequences include a negative impact on physical and emotional health; career dissatisfaction; and early retirement. The primary consequences for the organization include substantial effects on practice, resulting in turnover.[11] Recent evidence revealed that, nationally, $4.6 billion in yearly costs associated with physician turnover, shortages, and absenteeism can be attributed to burnout.[11] For the organization, the annual economic cost associated with burnout-related turnover and reduced clinical hours is $7,600 per employed physician, resulting in lost revenue and also diminished patient satisfaction.[11]

A CALL FOR INDIVIDUAL AND ORGANIZATIONAL CHANGE TO ADDRESS ONCOLOGIST BURNOUT

Before the pandemic, oncology clinicians were at risk for burnout because of the increasing demands on clinical time, productivity, and the evolving medical landscape, with limited autonomy and control over daily responsibilities and endless electronic medical record documentation. Thus, there is a need for both individual and organizational change to address burnout in oncology.[6] As reported in recent recommendations for addressing burnout and moral distress in oncology, key evidence-based individual and organizational interventions are illuminated as options to reduce burnout.[6] For example, individual interventions include mindfulness training, education/awareness to identify burnout symptoms in self and others, and communication skills training. Organizational well-being interventions involve modification of organizational culture and policy; provision of resources to reduce administrative burden (e.g., electronic medical record support, scribes); infrastructure improvement; and addressing stigma associated with requesting mental health assistance. Evidence has consistently found that burnout can be greatly reduced by a combination of these evidence-based individual and organizational interventions, yet it is the organization-level interventions that can be far more efficacious and should be adopted.[12]

In response, given the identification of these burnout contributors in oncologists and the oncology team, the call for action to address burnout, and the emergence of the COVID-19 pandemic that remains widespread with repetitive phases of outbreaks, recovery, and response, optimizing oncology clinician well-being has never been more important. It is imperative that oncology clinicians and cancer organizations have direct access to resources to address team burnout, thereby improving the quality of cancer care and workforce sustainability. A Well-Being Task Force within ASCO was needed to provide guidance to committees, initiatives, members, and the cancer organization on addressing burnout in oncology.

CLINICIAN WELL-BEING TASK FORCE

ASCO's Clinician Well-Being Task Force was created in May 2020 as a cross-committee collaborative effort between the Ethics and Clinical Practice Committees as a 5-year charter. This Well-Being Task Force was identified as a major recommendation in response to the burnout crisis in oncology.[6] It will serve as a nexus between committees and ASCO initiatives to address burnout and well-being. The Well-Being Task Force directly meets ASCO's strategic goals, centered on meeting member needs and increasing the quality of care and practice health. It is led by two co-chairs (F.J.H. and P.S.) and comprises 16 ASCO members with expertise in oncology, psychology/psychiatry, nursing/advanced practice; burnout/well-being; and professional/organizational development, ethics, and cancer administration. As the professional society of oncologists, ASCO is uniquely positioned to understand why burnout is experienced by oncologists and how to address well-being. The Well-Being Task Force is tackling burnout and seeking to make ASCO a central part of the solution to assist colleagues and cancer organizations.[13,14]

Oncology clinician well-being is formally defined as an integrative concept that characterizes quality of life, encompassing an individual's work- and personal health–related environmental, organizational, and psychosocial factors.[13,14] The experience of well-being involves satisfaction with clinical work, finding joy and meaning in that work, and experiencing professional growth and fulfillment. Our mission is to improve the quality, safety, and value of cancer care by enhancing oncology clinician well-being and practice sustainability. We have developed a 5-year plan, a roadmap, with the goals of promoteing clinician well-being across all ASCO activities, broadening well-being resources, and promoting research that identifies the clinician and practice needs for optimal well-being (Fig. 1). Eventually, the ultimate goal is for cancer care delivery in clinical and research environments where patients, clinicians, and practices thrive. All oncology colleagues, clinicians, trainees, and leadership are encouraged

SIDEBAR 1. CONTRIBUTORS TO AND CONSEQUENCES OF BURNOUT SPECIFIC TO ONCOLOGY

CONTRIBUTORS

- Evolving medical and oncology landscape
- Psychological and medical crisis for many patients
- Changing patient demographics
- Moral distress
- Compassion fatigue
- Repeated exposure to death and dying
- Increased administrative demands
  - Electronic medical records
  - Negotiations with patient insurance
  - Payment incentives
  - Reimbursement
- Increased caseloads
- Staff turnover
- Workflow inefficiencies
- Stigma and consequences of seeking help
- Financial stress

CONSEQUENCES

- Effects on physician
  - Physical health
  - Mental health (including depression, anxiety, suicide)
  - Attrition (leaving the practice of oncology and early retirement)
- Effects on practice: $4.6 billion per year cost to practices
  - Medical errors
  - Staff turnover and physician shortages
  - Lost revenue
  - Decreased patient satisfaction

to visit our new resource webpage for a webinar, news, education, research, and additional external resources.[13,14]

EVIDENCE ON THE IMPACT OF BURNOUT, MORAL STRAIN, AND COVID-19 ON ONCOLOGIST WELL-BEING

The COVID-19 pandemic evolved during a time of previously established intensified occupational stress and has had a notable impact on the well-being of oncologists and oncology team members.[15] Early reports revealed that clinicians were at an increased risk of burnout and poor mental health because of immediate and long-term delayed pandemic-related stressors.[16-19] In oncology, the direct effects of COVID-19 are acutely experienced given that the risk of viral infection, complications, and mortality are greater in older, immunocompromised patients with cancer compared with the average patient with COVID-19.[6] To protect patients in routine cancer care from COVID-19 infections, oncologists had to modify cancer care delivery, including delays in surgeries or chemotherapy administrations, suspension of clinical trial enrollment, and initiation of telehealth visits.[15] Oncologists encountered daily life and death decision-making while simultaneously encountering the potential risk and fears of viral exposure to self, patients, and families. Despite this evidence, limited information exists on the experiences of the oncologist's occupational and personal well-being caring for seriously ill patients with cancer. In response, the Well-Being Task Force conducted a focus group study to describe the COVID-19 consequences on U.S. oncologist well-being and overall patient care. Our objectives were to describe the sources of occupational and personal stressors impacting oncologists treating patients with cancer during the COVID-19 pandemic; explore how sources impact patient care; and identify interventions (e.g., organizational, individual) that support oncologists coping with the current COVID-19 pandemic and beyond.

We conducted four virtual focus groups with 25 U.S. ASCO member oncologists from September to November 2020: the median age was 47.7 (range, 35–69); 52% were women 52% were members of a minority group; 76% were medical oncologists; 64% were married; they saw 51.5

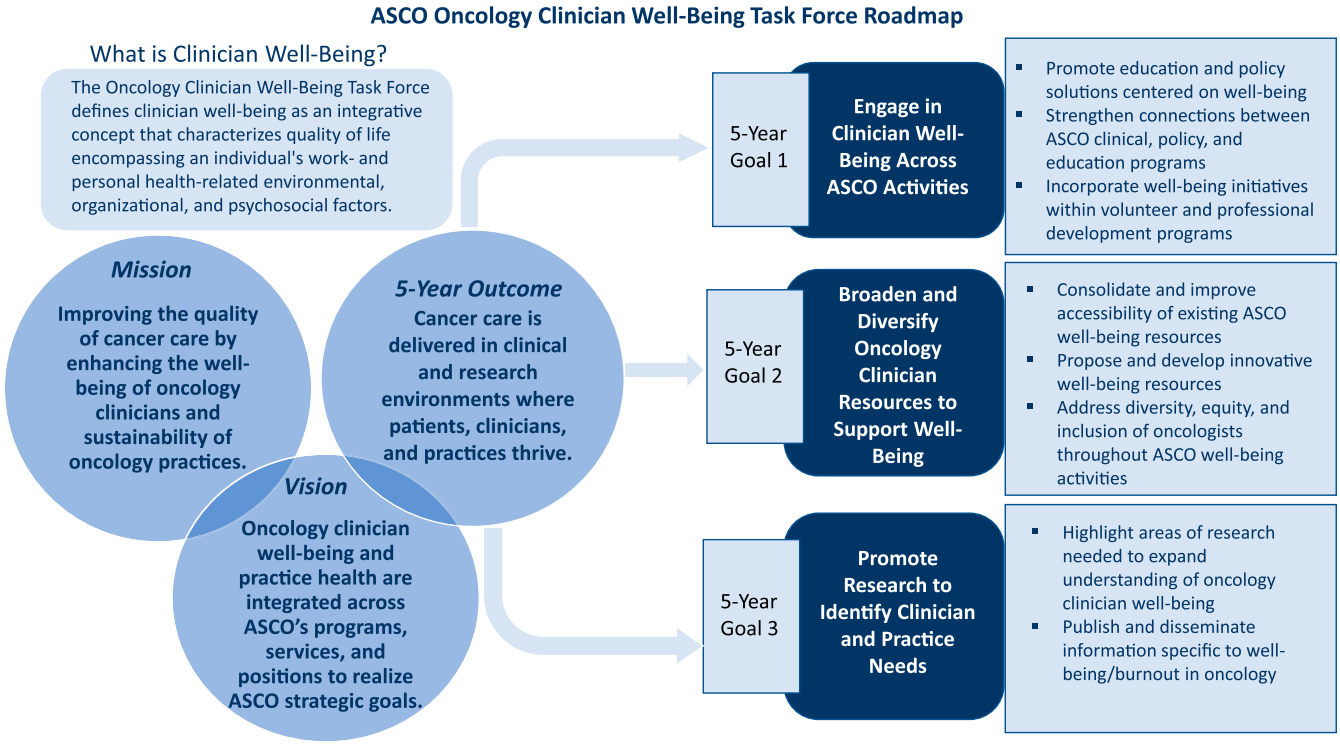

FIGURE 1. ASCO Oncology Clinician Well-Being Task Force Roadmap

patients/week (range, 20–120); and 36% had a practice in the Mid-Atlantic United States. Oncologists discussed various COVID-19 pandemic thematic consequences, including pre–COVID-19 burnout, occupational/professional consequences, personal implications, future cancer care, and workforce departures. Underlying oncologist burnout was exacerbated, creating stress associated with disruptions in care, education, research, financial practice health, and telemedicine. Personal familial stressors related to COVID-19 exposure fears and loss of social support were noted. However, COVID-19 offered opportunity for growth and resilience. The workforce was adversely impacted, resulting in part-time status and early retirement. Many feared delays in cancer screening, diagnosis, and treatment. Recommendations for organizational well-being interventions included psychological/peer support resources and flexible time off. For many, ASCO and state oncology societies held a duty to develop care guidelines, well-being resources, and mental health advocacy. Our study provides an understanding of the implications of the COVID-19 pandemic on oncologist burnout, fulfillment, practice health, cancer care, and workforce. It illuminates how professional organizations could play a larger role in oncologist well-being. A manuscript detailing these data has currently been submitted for peer review, with the goals of subsequent publication.[20]

THE ONCOLOGY TEAM

J is a diligent highly successful, midcareer, oncology physician assistant (PA) who works with Dr. N on the inpatient solid tumor service. J not only is responsible for the essential decision-making responsibilities in the care of patients but also serves as a manager of the inpatient advanced practice providers. She worries about the well-being of her young staff who are initiating careers in oncology and for those who worked on COVID-19 units during the early pandemic. J reported feeling ineffective in recent months, despite working long hours and receiving positive reviews from colleagues and staff.

Clinician well-being efforts ideally incorporate the entire oncology team, who delivers care to patients with cancer across the cancer trajectory. This includes physicians, trainees (especially fellows in training), nurse clinicians, advanced practice nurses (nurse practitioners [NPs] and clinical nurse specialists), pharmacists, PAs, radiation therapists, social workers, and all other team members. Focusing on the well-being of team members such as J is crucial. Studies suggest that the prevalence of burnout and compassion fatigue can be substantial and has potential negative consequences for patient care, professional oncology team member functioning, and individual clinicians (Table 1).[7,21-24]

TABLE 1. Consequences of Oncology Team Members' Burnout

Organizational	Professional	Personal
↓ Patient safety	Erosion in teamwork	↑ Substance abuse
↑ Errors	↓ Sense of professional accomplishment	↑ Symptoms fatigue, gastrointestinal disturbances, headache
↑ Infection	Work disengagement	↑ Family discord
↑ Turnover	Poor team communication	Altered sleep
↑ Patient mortality	↑ Occupational injury	Impaired concentration
↓ Patient satisfaction	↑ Absenteeism	Altered eating patterns
↑ Patient length of stay	Poor patient communication	↓ Social interaction
↑ Costs	Incivility potential	↑ Anger, cynicism, blaming
↑ Malpractice claims	Suboptimal performance	↑ Depression, suicide

Scope of Burnout in the Oncology Team

In 2015, oncology NP and PA burnout was initially examined in two independent cross-sectional studies.[25,26] Burnout was defined by high scores on the Maslach Burnout Inventory subscales of emotional exhaustion or depersonalization.[27] The estimated rate of burnout was 31.3% and 34.8%, respectively, for each profession, with similar levels of emotional exhaustion, depersonalization, and personal accomplishment. Despite the high level of burnout in PAs, career and specialty satisfaction remained high, and few PAs planned to pursue a different career or specialty (3.6%) or retire (2.0%). For NPs, the impact of burnout was more concerning, with 21.9% reporting an intent to leave the profession altogether or the hematology/oncology specialty. NPs' intention to leave correlated with high levels of emotional exhaustion ($r = .459$, $p < .001$) and depersonalization ($r = .276$, $p < .001$) but not personal accomplishment ($r = -.117$, $p = .99$).

Recently, in 2019, a significant increase in the burnout rate for PAs was reported, with 48.7% of PAs reporting burnout (odds ratio for burnout in 2019 vs. 2015, 1.92; 95% CI, 1.40–2.65; $p < .001$).[28] The highest rate of burnout was seen in the medical oncology subspecialty, with 53.3% of PAs reporting burnout, followed by surgical oncology (46.2%) and radiation oncology (8.3%). The increase in burnout remained significant despite adjustments for age, sex, relationship status, practice setting, subspecialty, practice type, and hours worked.

Although data on oncology pharmacists and technicians are limited, a survey conducted across multiple professional groups examined burnout incidence and associated factors among clinicians specializing in hematopoietic stem cell therapy settings.[28] Among 95 pharmacists studied, 53% exhibited burnout using the same definitions as used for NPs and PAs. Pharmacists exhibited the highest burnout rates across all the six groups studied. Similarly, the mean moral distress score was highest among pharmacists.

Factors Associated With Oncology Team Burnout

Numerous stressors in the oncology setting contribute to burnout (Table 1).[7,21-24] Organizational context and job fit have been identified as important factors associated with burnout and/or intent to leave for NPs and PAs in oncology. The Areas of Work Life Survey was used to assess six domains of work life, workload, control, reward, community, fairness, and values in a study of 201 oncology NPs and another study of 234 oncology PAs.[26,28] Consistent with the theoretical model for the Areas of Work Life Survey, as the level of congruence (job fit) between the oncology NP or PA and the job decreases for each domain, the burnout level or intent to leave their job increases. In addition to organizational context, role and team-based factors associated with higher burnout rates for oncology PAs include spending a higher percentage of time on indirect patient care, practicing below the full extent of education and training, and relationship with collaborating physician dissatisfaction. Last, age, hours worked per week, and satisfaction with compensation have been associated with oncology PA burnout.

Among a small sample of 95 pharmacists working in hematopoietic stem cell therapy settings, multivariable analyses identified factors associated with increased likelihood of reported emotional exhaustion.[29] Significant factors included inpatient or inpatient plus outpatient work settings (vs. solely outpatient setting), adult patient populations (vs. pediatric or pediatric and adult populations), and lower hematopoietic stem cell therapy (< 50 transplants/year). No personal factors were significantly associated with emotional exhaustion or depersonalization.

Oncology pharmacy services often use a team model comprising pharmacists and technicians. Turnover rates for technicians are high, often increasing the workload of

pharmacists to assume additional duties and train new personnel.[30] As cancer drug therapies become increasingly complex, cancer care teams require the skill and pharmacist expertise with oncology fellowship training.[31]

Contribution of COVID-19 to Stress in Oncology Teams

Throughout the COVID-19 pandemic trajectory, there has been a notable and wide-ranging impact on all oncology team members (Sidebar 2).[32-34] In a 2020 national study, 31.7% of PAs across all specialties reported that they worked without necessary personal protection equipment, 3.6% had been infected with COVID-19, and 72.4% were at least somewhat concerned about their health or their family's health.[35] The pandemic has also impacted the well-being of PAs. By August 2020, 76% were as stressed or more stressed compared with reports 6 months earlier in which 35% reported burnout symptoms.[36]

Similarly, in May 2020, a national study of NPs was conducted by the American Association of Nurse Practitioners. Nearly one-quarter (24%) identified the lack of personal protection equipment as a top barrier to treating patients with COVID-19; 79% had reused personal protection equipment. Related consequences on the NP workforce entailed 65% reporting a change in work hours and 36% noting a reduction in pay. In August 2020, the American Association of Nurse Practitioners follow-up survey revealed that 17% of NPs had been furloughed, 40% experienced a decrease in income, and 31% described a reduction in hours worked.

During pandemics, most clinical pharmacists cannot work virtually to oversee the medication administration processes; rather, their onsite presence is required. Additionally, pharmacists may be redeployed to support other essential medication functions. Constant role changes and demand for intensive medication management services, coupled with staffing shortages, may exacerbate pharmacists' burnout and its consequences.[37]

Interventions to Address Oncology Team Well-Being

Opportunities exist to reduce work-related stress and prevent or mitigate burnout while concurrently enhancing professional well-being (Sidebar 3).[38-48] Numerous organizations developed resources to provide assistance and support in this realm of practice (Sidebar 4). For oncology NPs and PAs, a focus on role-specific factors is critical. This entails ensuring that NPs and PAs are practicing to the top of their license, degree, and training. Optimizing this capacity may provide the greatest opportunity to not only reduce the risk of NP and PA burnout but also increase work engagement. This is ideally accomplished when NPs and PAs, oncologists, and other team members collaborate on outlining team-based role expectations and strategize to minimize burdensome administrative tasks. A similar example has been described by the University of North Carolina Medical Center's oncology advanced practice providers' role delineation review and modification. The NP and PA roles were expanded to allow for modification of chemotherapy orders and supportive medications. A comprehensive educational, training, and privileging process was implemented to support this role expansion. Five years after the program's initiation, outcomes were explored by implementing participating oncologists, NPs, and PAs. NPs and PAs reported the training was adequate (94%), and their privileges were used often (82%) and were beneficial (94%). Physicians had a similar impression of the program, reporting that having NPs and PAs modify orders was efficient (87%) and beneficial (94%). This experience highlights the opportunity to enhance the NP and PA role in oncology in a structured and streamlined process that ensures quality cancer care is provided. Similar efforts to enhance oncology NP and PA scope of practice has the potential to not only improve practice efficiency and cost-effectiveness but also favorably influence clinician well-being and restore "joy in work."[49]

SIDEBAR 2. ONCOLOGY TEAM MEMBER WORKPLACE STRESSORS

- Role ambiguity
- Administrative barriers to optimal autonomous practice
- Reduced time in direct patient care
- Dissatisfaction with collegial relationships
- Lack of respect from colleagues
- Inadequate resources (fiscal or otherwise)
- Chaotic work environment
- Nonrecognition of contributions
- Overwhelming workload
- Focus on performance metrics vs. quality of care
- Documentation (i.e., electronic health record) time demands
- Regulatory and payer requirements

SIDEBAR 3. COVID-19–SPECIFIC FACTORS CONTRIBUTING TO ONCOLOGY TEAM MEMBER STRESS

- Ongoing changes in data/evidence, policies, and supplies (i.e., testing, social distancing, quarantine, personal protective equipment) requiring ongoing adaptability to change
- Increased complexity in monitoring and differentiating symptoms associated with cancer or its treatment from COVID-19[9]
- Altered hours/schedule/workloads
- Concern about impaired job performance
- Need to respond to patient worries about treatment interruptions, delayed surgery, postponement of adjuvant therapy, altered radiation therapy protocols, and pharmacy access
- Infusion area space modifications and staffing alterations related to such
- Educating and supporting families when their presence is contraindicated or minimized
- Added support required when patients continue or complete treatment alone
- Added surveillance requirements of older patients with cancer, comorbidity, and a positive COVID-19 status
- Feeling ill-equipped to respond to mental health concerns of patients
- Providing emotional support to new survivors (months after treatment completion)
- Intensified and diverse subtypes of moral anguish (i.e., moral distress, uncertainty, dilemmas, conflicts, suffering, outrage)
- Cross training of nursing staff and use of temporary staff
- Death of coworker, family, or friend
- Concern about potential transmission of COVID-19 to one's family[10-15]

Recommendations targeting oncology pharmacy personnel include careful workload assessment and adjustment of staffing levels to match anticipated service demands. Such interventions have been shown to quantify the reduction of costly pharmacy technician turnover in one comprehensive cancer center. Also, the 2019 National Consensus Conference to Enhance Well-Being and Resilience among the Pharmacist Workforce identified 50 action steps at the individual and organizational level. Key among these are mandatory, scheduled, uninterrupted breaks for all pharmacy personnel with support from cancer center leadership.[50]

GAPS IN CURRENT KNOWLEDGE REGARDING ONCOLOGY TEAM WELL-BEING

Robust longitudinal surveys of cancer care team members are necessary to enhance understanding of the interplay between team members, burnout, and the quality of patient care. These analyses would yield important insights about the incidence of suboptimal clinician well-being, inclusive of

SIDEBAR 4. WORK SETTING OPPORTUNITIES TO REDUCE STRESS AND POTENTIAL BURNOUT AMONG ADVANCED PRACTICE NURSES, PHYSICIAN ASSISTANTS, AND PHARMACISTS

SELF-FOCUSED

- Take time out, engage in brief mediation and deep breathing
- Access personnel support with planning for self-care measures
- Pay ongoing attention to physical and emotional well-being

RELATIONAL-FOCUSED

- Make a concerted effort to connect with coworkers and peers at breaks and lunch
- Lobby for improved division/organizational team communication

JOB-FOCUSED

- Regularly de-brief difficult scenarios
- Provide ongoing emotional support
- Ensure access to confidential employee assistance programs
- Facilitate administrative rounding that incorporates recognition and appreciation
- Discuss role expectations and potential role ambiguity with members of the interdisciplinary team
- Improve access to, and advocate for, ongoing professional education; topics could include awareness of symptoms and characteristics associated with compassion fatigue and burnout, time management, communication skills training specific to conflict resolution, work-life balance, self-care planning

personal and organizational factors contributing to such. Results could then be shared with organizational leaders, with the intent of lobbying for additional resources, both people and programmatic in nature. The efficacy of existing well-being enhancements in the work setting requires additional study, including their impact on work engagement, job fulfillment, and turnover, as well as patient satisfaction. Given the contemporary emphasis on team-based cancer care, insight into potential future strategies that effectively improve the well-being of the entire care team are mandated. Key variables to consider include the consistent use of validated burnout measures and job satisfaction over time; identification of personal, professional, and organizational variables hypothesized to be associated with clinician well-being; and improved understanding of team dynamics that ultimately influence the delivery of high-quality patient care.[51] To improve the rigor of this area of research, oncology professional organizations could collaborate on high-quality longitudinal studies using sensitive metrics of role functioning and intradisciplinary collaboration that integrate the unique corollaries of caring for a patient cohort with a potential life-limiting diagnosis.

EMPOWERING THE ONCOLOGY LEADER TO FOSTER AN ENVIRONMENT OF WELL-BEING

S is a cancer center administrator who is well informed of the benefits of incorporating well-being programs for his staff. However, he is unsure how best to implement an effective well-being plan. Oncologist and clinician team well-being relies on the collective environment and group initiatives to a greater extent than individual temperance or resilience.[6] The oncology workplace environment is crucial to workflow, quality, well-being, and patient experience. Choices matter for self and others. Leadership comes from knowing how to manage oneself well, especially in the context of environment. Yet, the oncologist must be empowered to do so.

This section reviews several ways in which oncology clinicians can empower themselves to create and foster well-being throughout their careers. Empowerment as a source of well-being is increasingly important as workplace factors in oncology are continually changing from the COVID-19 pandemic to hospital mergers and practice changes to unclear reporting structures, or career trajectories, with mounting pressure to maintain work–life balance. Empowerment stems from self-efficacy, defined by Albert Bandera as a person's belief in their capacity to perform successfully, which leads not only to persistence and hard work in the face of adversity but also the ability to let go when needed or take a participatory approach fostering self-efficacy, empowerment, and well-being of others in the group.[52] Understanding the importance of agency in the promotion of well-being may help oncologists negotiate roles, boundaries, and goals in the spirit of becoming our best selves: As stated in Emerson's work *Self-Reliance,* "Trust thyself: every heart vibrates to that iron string."[53] Trust and empowerment allow us to internalize those sagacious adages we encounter throughout our training and career experiences like the following: "You can have it all, but maybe not all at the same time"; "Careers have seasons"; "Someone needs to have your back"; "Get a work/life mentor and advocate." Empowerment ultimately lies within self but also in the interaction with one's environment and requires negation. External circumstances that may lead to empowerment, and greater well-being, are obtained through advocacy (e.g., institutional), reflection (introspection), managing expectations for self and others, and clarifying role descriptions.

The role of the administrator, such as S, in supporting provider practices and ensuring provider well-being is paramount.[54] Clinicians often do not receive specific training or mentoring on optimizing work–life balance, addressing complex organizational dynamics, or engaging in crucial conversations. The growing challenges of the modern clinical environment, including increasing administrative tasks and workplace inefficiencies that distract from patient care, exacerbate clinicians' stress. In this context, the administrative and clinical dyad partnership is pivotal to supporting providers in a meaningful way. Support can take many forms, including monitoring for the signs of burnout, listening to clinicians' concerns, and supporting well-being initiatives. Perhaps of greatest importance is supporting oncology clinicians in setting boundaries, having space to express their vulnerabilities, and partnering with them to create a positive work environment and a culture of well-being. Administrative leaders can take a pro-active role in ensuring clinicians have the resources necessary to manage clinical workflows optimally (e.g., scribes, clinical support staff, patient relations services, flexible scheduling). Administrative leaders often have access to organizational resources and training not readily available to clinicians, making the administrative leader's role critical to establishing an environment of well-being and balance.

Oncology professionals should incorporate positive behaviors, such as reflection, self-compassion, and reasonable expectation setting, as proactive strategies to prevent burnout and build resilience. Deliberate attention to these personal tactics, alongside modeling of such behaviors for colleagues and mentees, creates a culture of openness and group validation around issues that all professionals face within taxing work responsibilities and complex work environments. For example, many liken a professional career to being more like a marathon than a sprint. This analogy applies on many levels, because the pace of tasks and accomplishments should vary among different phases of a career, particularly emphasizing the need not to expend all one's physical, emotional, and spiritual energy at the

beginning, only to fall short toward the latter stages. Reminding one self that pursuing several short-term sacrifices to one's spirit in lieu of a longer-term view of thriving should be a philosophy to deprioritize. This is when the role of a "work/life mentor" can be valuable. Such a mentor is a colleague who understands and values your total self, particularly the nonprofessional areas of joy and fulfillment. Additionally, oncology professionals often face the greatest pressures to meet near-impossible perfection from themselves, with their own expectations far outstripping what others may expect of them. Moments of self-compassion, when we take a moment to remember and congratulate ourselves for doing our best, regardless of the perceived missteps, are high-value practices. Reflecting on positive aspects of one's day, as a necessary distraction from a tendency to focus on the negative, can be achieved through regular journaling of simple gratitude. Last, reasonable expectation setting for ourselves and our team is critical to avoiding predictable senses of failure when implicit goals of explicit expectations are unreasonable. A common adage, "You can have it all, just not all at the same time," applies well here. It is tempting to believe that, without sacrifice to one's well-being, all hopes and dreams can be accomplished in a short period. However, for most in oncology, careers are measured in decades, and short- and long-term goals serve as milestones along the way. Few, if any, accomplish all they set out to be, achieve, and know in one setting, within one job, in a short period of time. To address this, we recommend creating "storyboards" for professional careers that map out one's career over years and decades, inclusive of milestones in currency important to that career. For example, three important currencies for academic physicians are deliverables (e.g., publications), resources (e.g., grants), and relationships (e.g., collaborations). When goals in these areas are placed carefully over timelines measured in years, one gains perspective that widens the vision of the current moment and immediate future to a longer-term view. Altogether, these three behaviors of regular reflection, self-compassion, and reasonable expectation provide a concerted plan to achieve one's professional dreams without sacrificing the needed emotional and spiritual energy to get there.

Defining one's role is crucial for well-being and ultimately supporting one's work–life balance. Without a proper definition, it is too easy for work-related boundaries to become blurred and take on work that may not be central to one's purpose. It should also be clear that roles can be negotiated and change over time. Reassessing these responsibilities with an eye toward the future can help not only in career advancement but also in reaching personal goals. Making priorities explicit is a good way to maintain accountability with colleagues, family, and friends. Every oncologist has different needs when it comes to promoting or enhancing well-being. Empowerment centralizes one's sense of agency and should realign priorities toward what is manageable while letting go of other issues that siphon off energy.

CHARTING THE COURSE FOR ONCOLOGY TEAM WELL-BEING: ASCO'S QUALITY TRAINING PROGRAM EXPERIENCE

ASCO's Quality Training Program is a 6-month experiential learning course developed by oncologists and cancer care specialists designed to educate and train in improvement science, team building, and leadership.[55] Multidisciplinary team participants will have a better understanding of process analysis, rapid cycle improvement, quantitative/qualitative methods, and effective management of teams through didactics, coaching, and simulation. At the end of 6 months, teams will have successfully identified a structured improvement project, tested solutions, and developed a framework for ongoing improvement.

In alignment with the Well-Being Task Force Roadmap, ASCO, in partnership with the American Medical Association, launched its first thematic Quality Training Program on Burnout in July 2019. As Efficiency of Practice is a domain influencing wellness, the focus of this themed session was to address the impact of the system challenges and issues on clinical well-being. The goal for each participating team was to design, implement, and lead successful quality improvement activities in their own practices to improve practice efficiency, reduce physician workload, enhance physician autonomy, and/or increase physician time spent with patients. The session goal was to favorably impact clinician burnout.

Several teams, including Saudi Arabia and Spain, participated, with a majority makeup of physicians (62%), nurses (25%), and other (13%). ASCO collaborated with the American Medical Association to provide teams with institution-wide burnout assessments, reports and analyses, faculty and coach experts, and intervention tools. The final institutional projects included 1) Mitigating Provider Burnout Because of Infusion Center Delays: Analysis of Sustainability; 2) Reducing Burnout Among University of Virginia Hematology/Oncology Fellows; and 3) Is Burnout Syndrome a Problem Among Oncology Workers? Incidence and Effective Tools to Achieve Improvement.[56-58] The final presentations were shared in publications (*JCO Global Oncology* and *JCO Oncology Practice*) and presentations (ASCO Annual Meeting and Quality of Care Symposium).

CREATING A BLUEPRINT FOR ORGANIZATIONAL STRATEGIES TO PROMOTE THE WELL-BEING IN ONCOLOGY

Cancer organizations, including cancer centers and community practices, should consider developing a blueprint: a detailed immediate start plan with recognized strategies and interventions targeting all oncology stakeholders to support a culture of community.[59,60] For many

SIDEBAR 5. RESOURCES TO SUPPORT ONCOLOGISTS AND ONCOLOGY TEAM MEMBERS

ASCO

- Recognizing Burnout and Promoting Well-Being: https://practice.asco.org/practice-support/staff-well-being-development/recognizing-burnout-promoting-well-being
- ASCO Oncology Clinician Well-Being Task Force Roadmap: http://practice.asco.org/asco-oncology clinician-well-being
- ASCO Webinar on Burnout and Oncology Clinician Well-Being: https://practice.asco.org/asco-webinar-burnout-and-oncology-clinician-well-being

AMERICAN MEDICAL ASSOCIATION

- Physician Burnout: https://www.ama-assn.org/topics/physician-burnout

AMERICAN ACADEMY OF PHYSICIAN ASSISTANTS

- https://www.aapa.org
- PA Burnout and Well-Being: https://www.aapa.org/career-central/pa-burnout/
- Burnout Webinar Series: https://cme.aapa.org/local/catalog/view/product.php?productid=407

ADVANCED PRACTITIONER SOCIETY FOR HEMATOLOGY AND ONCOLOGY

- https://www.ashp.org/
- Statement on Oncology APs During COVID-19: https://www.apsho.org/news/news.asp?id=510993&hhSearchTerms=%22burnout%22

AMERICAN PHARMACISTS ASSOCIATION

- https://www.pharmacist.com/
- Enhancing Well-Being and Resilience Among the Pharmacist Workforce: A National Consensus Conference (2019): https://www.pharmacist.com/enhancing-well-being-and-resilience-among-pharmacist-workforce-national-consensus-conference

AMERICAN SOCIETY OF HEALTH SYSTEM PHARMACISTS

- https://www.ashp.org/
- Clinician Wellbeing Website: https://wellbeing.ashp.org/The Road to Resilience: Develop Your Map to Navigate Burnout (for Pharmacy Technicians):
- The Road to Resilience: Develop Your Map to Navigate Burnout (for Pharmacy Technicians): https://elearning.ashp.org/products/8231/the-road-to-resilience-develop-your-map-to-navigate-burnout-pharmacytech-ce-free-trial%E2%80%8B

END-OF-LIFE NURSING EDUCATION CONSORTIUM

- https://www.aacnnursing.org/ELNEC
- Self-Care Strategies to Deal With Moral Distress & Compassion Fatigue: https://www.aacnnursing.org/ELNEC/COVID-19
- Infographic: Meditation/Mindfulness Apps: https://www.aacnnursing.org/Portals/42/ELNEC/PDF/Meditation-and-Mindfulness-Apps.pdf

NATIONAL COMPREHENSIVE CANCER NETWORK

- https://www.nccn.org/
- Self-Care and Stress Management During the COVID-19 Crisis: Toolkit for Oncology Health Care Professionals: https://www.nccn.org/covid-19/pdf/Distress-Management-Clinician-COVID-19.pdf

ONCOLOGY NURSING SOCIETY

- www.ons.org
- Nursing Self-Care Learning Library: www.ons/learning-libraries/self-care-nurses
- Compassion Fatigue and Burnout Articles: https://www.ons.org/explore-resources?topic=916&subtopic=936&display=results&sort_by=created&items_per_page=50

Abbreviations: APs, advanced practitioners; PA, physician assistant.

SIDEBAR 6. DRAFT PLAN FOR ASSESSMENT AND IMPLEMENTATION OF INSTITUTIONAL WELL-BEING PROGRAMS

1. Assessment of oncologist needs, burnout, and moral distress
2. Proactive engagement of leadership and oncology in collaborative action planning
3. Establishment of well-being programs for oncology
4. Implementation of empirical well-being interventions
5. Reassessment of oncologist needs, burnout, and moral distress
6. Modification of intervention plan to address evolving needs

organizations, implementation of interventions can be challenging, so an effective approach with specific tactics is required. Shanafelt et al[59] recently reported that such a blueprint requires strategies with effective tailored initiatives designed to tackle specific organizational challenges to meet its mission. In fact, they assert that any strategy to promote well-being must be tailored to meet the cancer organization's goals and challenges. Here, leadership needs to adopt a model addressing initial, formative programs; culture transformation; research; and practice sustainability. Interventions can promote the oncology clinician's well-being to thrive and ultimately flourish. Research has consistently found that burnout can be greatly reduced by a combination of evidence-based individual and organizational interventions, yet it is the organization-level interventions that should be adopted.[12]

Optimal organizational resilience programs share common elements and strategies previously identified to promote clinician engagement and enhance well-being.[6,60,61] These programs are founded on a shared mission and mutual collaboration between leadership and clinicians to improve well-being through education, training, research, and peer support. Routine, longitudinal self-assessment of clinician burnout, satisfaction, and engagement using validated self-reported screening tools (e.g., Maslach Burnout Inventory,[27] Physician Well-Being Index[62]) is a key step. Education of leaders and staff regarding prevalence of burnout, signs, and contributors is also essential. Specific identification of the unique organizational challenges (e.g., electronic medical record inefficiency) in the oncology clinical work environment or inpatient units helps in the development of tailored interventions. Promoting flexibility and a balanced work–personal life is also paramount. Physician champions who can lead this process and speak for peers and the oncology team are imperative. Implementation of virtual evidence-based well-being sessions (e.g., mindfulness-based stress reduction or cognitive behavioral therapy) should be considered. For the oncology fellow, early adoption of formal well-being curriculum and programs are not only required by the Accreditation Council for Graduate Medical Education but also vital for the trainee to learn about and prepare to address burnout during training and in the long term as practicing oncologists.[63-65] Fostering peer support, including virtual support, enhances professional and personal development, especially now during the pandemic when social connections have been lost. Finally, reducing the stigma associated with burnout and COVID-19 pandemic–associated stressors by providing clinician access for mental health resources to aid coping is vital (Sidebar 5). Consequently, once the blueprint is developed, the cancer organization should consider preparation, planning, assessment, and implementation to foster a supportive culture and ethical work climate. A sample plan for organizational strategies toward assessment and intervention to promote well-being is included in Sidebar 6.

CONCLUSION

Oncology clinician well-being has never been more important than right now. The COVID-19 pandemic evolved during a time of previously established intensified burnout and has had a substantial impact on oncologists and oncology team well-being. Yet, there is hope and room for optimism. Empowering the oncology team is crucial to setting a path forward for clinicians to thrive, flourish, and have continued organizational success. The cancer organization should consider developing a blueprint including a detailed immediate organization-specific start plan, with recognized strategies and interventions targeting all oncology stakeholders to support a culture of community. Now is the time, more than ever.

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REFERENCES

1. Freudenberger HJ. Staff burnout. J Soc Issues. 1974;30:159-165.
2. Bahrer-Kohler S, (ed). Burnout for Experts: Prevention in the Context of Living and Working. Berlin: Springer; 2014.
3. Shanafelt TD, Gradishar WJ, Kosty M, et al. Burnout and career satisfaction among US oncologists. J Clin Oncol. 2014;32:678-686.
4. Schaufeli WB, Leiter MP, Maslach C. Burnout: 35 years of research and practice. Career Dev Int. 2009;14:204-220.
5. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, 11th ed. Geneva: 2020.
6. Hlubocky FJ, Taylor LP, Marron JM, et al. A call to action: ethics committee roundtable recommendations for addressing burnout and moral distress in oncology. JCO Oncol Pract. 2020;16:191-199.
7. National Academies of Sciences, Engineering, and Medicine: Taking Action Against Clinician Burnout: A Systems Approach to Professional Well-Being. Washington, DC: The National Academies Press; 2019.
8. Shanafelt T, Dyrbye L. Oncologist burnout: causes, consequences, and responses. J Clin Oncol. 2012;30:1235-1241.
9. Hurria A, Lichtman SM, Gardes J, et al. Identifying vulnerable older adults with cancer: integrating geriatric assessment into oncology practice. J Am Geriatr Soc. 2007;55:1604-1608.
10. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019;69:363-385.
11. Han S, Shanafelt TD, Sinsky CA, et al. Estimating the attributable cost of physician burnout in the United States. Ann Intern Med. 2019;170:784-790.
12. Panagioti M, Panagopoulou E, Bower P, et al. Controlled interventions to reduce burnout in physicians: A systematic review and meta-analysis. JAMA Intern Med. 2017;177:195-205.
13. American Society of Clinical Oncology. ASCO Oncology Clinician Well-Being Task Force Roadmap. https://www.asco.org/practice-policy/policy-issues-statements/asco-in-action/oncology-clinician-well-being-roadmap. Accessed March 5, 2021
14. American Society of Clinical Oncology. ASCO Webinar on Burnout and Oncology Clinician Well-Being. https://www.asco.org/practice-policy/policy-issues-statements/asco-in-action/free-webinar-burnout-and-oncology-clinician. Accessed March 5, 2021
15. Hlubocky FJ, Symington BE, McFarland DC, et al. Impact of the COVID-19 pandemic on oncologist burnout, emotional well-being, and moral distress: considerations for the cancer organization's response for readiness, mitigation, and resilience. JCO Oncol Pract. 2021;17:OP2000937.
16. Wu Y, Wang J, Luo C, et al. A comparison of burnout frequency among oncology physicians and nurses working on the frontline and usual wards during the COVID-19 epidemic in Wuhan, China. J Pain Symptom Manage. 2020;60:e60-e65.
17. Rossi R, Socci V, Pacitti F, et al. Mental health outcomes among frontline and secondline health care workers during the Coronavirus disease 2019 (COVID-19) pandemic in Italy. JAMA Network Open. 2020;3:e2010185.
18. Preti E, Di Mattei V, Perego G, et al. The psychological impact of epidemic and pandemic outbreaks on healthcare workers: rapid review of the evidence. Curr Psychiatry Rep. 2020;22:43.
19. Lai J, Ma S, Wang Y, et al. factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. JAMA Netw Open. 2020;3:e203976.
20. Hlubocky FJ, Back AL, Shanafelt TD. The Occupational and personal consequences of the COVID-19 pandemic on U.S. oncologist burnout and well-being: a study from the ASCO Clinician Well-Being Task Force. JCO Oncol Pract. In press.
21. Boyle DA, Bush NJ. Reflections on the emotional hazards of pediatric oncology nursing: four decades of perspectives and potential. J Pediatr Nurs. 2018;40:63-73.
22. Cañadas-De la Fuente GA, Gómez-Urquiza JL, Ortega-Campos EM, et al. Prevalence of burnout syndrome in oncology nursing: a meta-analytic study. Psychooncology. 2018;27:1426-1433.
23. Kelly LGP, Butler R. Impact of nurse burnout on organizational and position turnover. Nurs Outlook. 2021;69:96-102.
24. Boyle DSM. Emotional hazards of nurses' work: a macro perspective for change and a micro framework for intervention planning. J Infus Nurs. 2021;44:78-93.

25. Tetzlaff ED, Hylton HM, DeMora L, et al. National study of burnout and career satisfaction among physician assistants in oncology: implications for team-based care. J Oncol Pract. 2018;14:e11-e22.
26. Bourdeanu L, Pearl Zhou Q, DeSamper M, et al. Burnout, workplace factors, and intent to leave among hematology/oncology nurse practitioners. J Adv Pract Oncol. 2020;11:141-148.
27. Maslach C, Jackson SE, Leiter MP. Maslach Burnout Inventory Manual. Palo Alto, CA: Consulting Psychologists Press; 1996.
28. Tetzlaff ED, Ruth K, et al. Burnout among oncology physician assistants (PAs) from 2015 to 2019. J Clin Oncol. 2020;38:15s (suppl; abstr 11009).
29. Neumann JL, Mau LW, Virani S, et al. Burnout, moral distress, work–life balance, and career satisfaction among hematopoietic cell transplantation professionals. Biol Blood Marrow Transplant. 2018;24:849-860.
30. Trinh LD, Wong JT, Sullivan PA, et al. Impact of a chemotherapy workload and productivity dashboard on pharmacy technician turnover. Am J Health-System Pharm. 2019;76:992-997.
31. Holle LM, Segal EM, Jeffers KD. The expanding role of the oncology pharmacist. Pharmacy (Basel). 2020;8:130.
32. Klein CJ, Weinzimmer LG, Cooling M, et al. Exploring burnout and job stressors among advanced practice providers. Nurs Outlook. 2020;68:145-154.
33. Kapu AN, Borg Card E, Jackson H, et al. Assessing and addressing practitioner burnout: results from an advanced practice registered nurse health and well-being study. J Am Assoc Nurse Pract. 2019;33:38-48.
34. Han RM, Carter P, Champion JD. Relationships among factors affecting advanced practice registered nurses' job satisfaction and intent to leave: a systematic review. J Am Assoc Nurse Pract. 2018;30:101-113.
35. American Academy of Physician Assistants. COVID-19 and the PA Workforce: Trends and Implications for PAs. https://www.aapa.org/download/65014/. Accessed April 21, 2021.
36. American Academy of Physician Assistants. AAPA Data Dose: PA Experiences During COVID-19 Six Months Into the Pandemic. https://www.aapa.org/download/77125/. Accessed April 21, 2021.
37. Johnston K, O'Reilly CL, Cooper G, et al. The burden of COVID-19 on pharmacists. J Am Pharm Assoc (2003). 2020;61:e61-e64.
38. Miaskowski C, Paul SM, Snowberg K, et al. Oncology patients' perceptions of and experiences with COVID-19. Support Care Cancer. 2021;29:1941-1950.
39. Paterson C, Gobel B, Gosselin T, et al. Oncology nursing during a pandemic: critical reflections in the context of COVID-19. Semin Oncol Nurs. 2020;36:151028.
40. Johnston MG. Coping with moral distress during COVID-19. Nursing. 2021;51:55-58.
41. Shah M, Roggenkamp M, Ferrer L, et al. Mental health and COVID-19: the psychological implications of a pandemic for nurses. Clin J Oncol Nurs. 2021;25:69-75.
42. Banerjee SLK, Murali K, Hardy C, et al. The impact of COVID-19 on oncology professionals: results of the ESMO resilience taskforce survey collaboration. ESMO Open. 2021;6:1-10.
43. Cipriano PF, Boston-Leary K, Mcmillan K, et al. The US COVID-19 crises: facts, science and solidarity. Int Nurs Rev. 2020;67:437-444.
44. Johnston PA, Kitchens JL, LaBree K, et al. Kuban D. COVID-19 and oncology: operationalizing best practices across collaborative health systems. Clin J Oncol Nurs. 2020;24:444-447.
45. Bouchard L. Compassion fatigue in advanced practice registered nurses: why don't we know more? Nurs Clin North Am. 2019;54:625-637.
46. Klein CJ, Dalstrom MD, Weinzimmer LG, et al. Strategies of advanced practice providers to reduce stress at work. Workplace Health Saf. 2020;68:432-442.
47. Klein CJ, Dalstrom M, Lizer S, et al. Advanced practice provider perspectives on organizational strategies for work stress reduction. West J Nurs Res. 2020;42:708-717.
48. Pastores SM, Kvetan V, Coopersmith C, et al. Workforce, workload, and burnout among intensivists and advanced practice providers: a narrative review. Crit Care Med. 2019;47:550-557.
49. Institute for Healthcare Improvement. What Matters to You? Conversation Guide for Improving Joy in Work. https://hcifonline.org/wpcontent/uploads/2018/04/Balik_IHITool_ImprovingJoyinWork_WhatMatterstoYouConversationGuide.pdf. Accessed April 21, 2021.
50. American Pharmacists Association. Enhancing Well-Being and Resilience Among the Pharmacist Workforce: A National Consensus Conference. https://www.tnpharm.org/wp-content/uploads/APhA_Well_Being_Resilience_Report_0719.pdf. Accessed April 21, 2021.
51. Sinsky CA, Mallick A, Dopp AL, et al. Organizational Evidence-Based and Promising Practices for Improving Clinician Well-Being. National Academy of Medicine. https://nam.edu/organizational-evidence-based-and-promising-practices-for-improving-clinicianwell-being/. Accessed April 21, 2021.
52. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev. 1977;84:191-215.
53. Emerson R. Self-Reliance. Create Space Independent Publishing; 2017.
54. Rosenstein AH. Hospital administration response to physician stress and burnout. Hosp Pract (1995). 2019;47:217-220.
55. American Society of Clinical Oncology. ASCO Practice Central: Quality Training Program. https://practice.asco.org/quality-improvement/quality-programs/quality-training-program. Accessed March 5, 2021.
56. American Society of Clinical Oncology. ASCO Quality of Care Symposium Session, Posters and Abstracts on Clinician Well-Being and Burnout. https://practice.asco.org/sites/default/files/drupalfiles/2021-01/2020-QCS-Sessions.pdf. Accessed March 5, 2021.
57. Sewaralthahab S, Thorne S, King L. Mitigating provider burnout due to infusion center delays: analysis of sustainability. J Clin Oncol. 2020;38:29s (suppl; abstr 235).

58. Cunquero Tomas AJ, Ortega I, Gomez A, et al. Is burn-out-syndrome a problem among oncology workers? Incidence and effective tools to achieve improvement. J Clin Oncol. 2020;38:15s (suppl; abstr 11016).

59. Shanafelt T, Stolz S, Springer J, et al. A blueprint for organizational strategies to promote the well-being of health care professionals. NEJM Catalyst. 2020;1.

60. Shanafelt TD, Noseworthy JH. Executive leadership and physician well-being: nine organizational strategies to promote engagement and reduce burnout. Mayo Clin Proc. 2017;92:129-146.

61. Handley NR, Tomescu O, Lopez AM. Well-being during a time of crisis and beyond: supporting a culture of mindfulness in oncology practices. JCO Oncol Pract. 2020;16:713-717.

62. Dyrbye LN, Satele D, Sloan J, et al. Utility of a brief screening tool to identify physicians in distress. J Gen Intern Med. 2013;28:421-427.

63. Richardson DR, Winzelberg G, Rosenstein DL, et al. Development of an Art of Oncology Curriculum to Mitigate Burnout and Foster Solidarity Among Hematology/Oncology Fellows. JCO Oncol Pract. 2020;16:384-394.

64. Accreditation Council for Graduate Medical Education. Milestones. https://www.acgme.org/What-We-Do/Accreditation/Milestones/Overview. Accessed March 6, 2021.

65. Shanafelt TD, Raymond M, Horn L, et al. Oncology fellows' career plans, expectations, and well-being: Do fellows know what they are getting into? J Clin Oncol. 2014;32:2991-2997.

SARCOMA

SARCOMA

Breast Sarcomas, Phyllodes Tumors, and Desmoid Tumors: Epidemiology, Diagnosis, Staging, and Histology-Specific Management Considerations

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overview

Breast sarcomas arise from connective tissues of the breast and account for fewer than 1% of all breast malignancies. They can be subclassified as primary breast sarcomas, which arise de novo and are histologically diverse, and secondary breast sarcomas, which arise as a result of radiation or lymphedema and are most commonly angiosarcomas. Two other connective tissue neoplasms that occur within the breast include phyllodes tumors and desmoid tumors, which exhibit a spectrum of behaviors. Malignant phyllodes tumors are biologically similar to primary breast sarcomas, whereas desmoid tumors are technically benign but often locally aggressive. Patients with breast sarcomas often present with a rapidly growing mass or, in cases of radiation-associated angiosarcoma, violaceous cutaneous lesions. Core needle biopsy is generally required to confirm the diagnosis of sarcomas. Staging workup includes MRI and chest imaging, although these are not required in the case of benign phyllodes or desmoid tumors. In general, localized breast sarcomas should be resected, with the extent of resection tailored to histologic subtype. Radiation and chemotherapy can be used in the neoadjuvant or adjuvant setting, but data are limited, so treatment decisions should be made on an individualized basis. Systemic therapy options for metastatic disease and refractory breast desmoids mimic those used for the same histologies when present in other sites. Given the rarity and heterogeneity of breast sarcoma, as well as limited literature describing these entities, expert multidisciplinary evaluation is crucial for optimal decision making.

INTRODUCTION

In 2020, the most common new cancer diagnosis in the United States was breast cancer, with almost 280,000 new cases of invasive disease[1] and almost 49,000 cases of noninvasive (in situ) disease.[2] The vast majority of these were breast carcinomas derived from epithelial tissues, with fewer than 1% arising in the connective tissue of the breast. Here, we review the epidemiology, diagnosis, staging, prognosis, and management of these rare and distinct mesenchymal neoplasms: breast sarcoma, phyllodes tumors, and desmoid tumors. We highlight unique aspects of their biology and clinical behavior, as well as the differing prognoses and treatment strategies.

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EPIDEMIOLOGY AND RISK FACTORS

Breast sarcomas are rare and account for fewer than 1% of all breast malignancies[3] and fewer than 5% of soft tissue sarcomas from all anatomic locations.[4] The vast majority of breast sarcomas occur in women, with an estimated incidence of 45 cases per 10 million women in the United States,[5] although 1.5% of cases do occur in men.[6] Median age at diagnosis ranges from age 47 to 50.[7,8]

Breast sarcomas can be subcategorized into primary and secondary tumors, with primary breast sarcomas arising de novo from the breast parenchyma. There are no known risk factors specifically associated with primary breast sarcomas, but certain genetic syndromes, such as Li-Fraumeni syndrome[9] and hereditary retinoblastoma,[10] as well as environmental exposures, such as phenoxyacetic acid–containing herbicides,[11] have been associated with an increased risk for soft tissue sarcomas in general. Secondary breast sarcomas occur after breast or chest wall radiation or in the setting of chronic lymphedema. As such, they most commonly occur in women who have been treated for invasive or in situ breast cancer. To be considered radiation associated, a secondary breast sarcoma must occur within the irradiated field, be of a different histology than the initial tumor, and occur after a prolonged latency period (more than 4 years by Cahan's initial definition[12] or more than 2 years by other modified definitions[13]). A study using the Surveillance, Epidemiology, and End Results database from

PRACTICAL APPLICATIONS

- Patients with suspected breast sarcoma should have a diagnostic mammogram and undergo core needle biopsy, as opposed to fine needle aspiration, for diagnosis, followed by breast MRI and, at a minimum, chest CT for treatment planning and staging.
- Locoregional management is highly histology dependent, ranging from observation for stable desmoid tumors to radical surgery for radiation-associated angiosarcomas.
- Unlike for patients with invasive breast carcinoma, axillary sampling is generally not necessary for patients with breast sarcoma.
- Metastatic breast sarcomas and malignant phyllodes tumors are managed similarly to metastatic soft tissue sarcomas arising from other anatomic sites, often utilizing first-line doxorubicin-based chemotherapy.
- Given the rarity and heterogeneity of breast sarcomas, data are limited primarily to small retrospective studies, and management decisions should be made on an individual patient basis in a multidisciplinary setting.

1973 to 2003 found an in-field sarcoma incidence of 12 per 100,000 person-years in patients who had previously received breast radiation, with a median latency period of 7 years.[14] There is also a well-described association between chronic lymphedema and angiosarcomas. Stewart and Treves initially described six patients who developed angiosarcoma in the setting of postmastectomy lymphedema in 1948,[15] and subsequent studies have supported an association between lymphedema and angiosarcoma in other clinical settings.[16,17] Lymphedema-associated angiosarcomas are much rarer than radiation-associated sarcomas, so patients with the latter disease make up the vast majority of the study population in contemporary series. Compared with patients with primary breast sarcomas, those with secondary breast sarcomas tend to be older, likely reflecting the older average age of patients with breast cancer. In one series of patients with breast angiosarcoma, the median age for patients with primary angiosarcoma was 30 years younger than that of patients with secondary radiation-associated angiosarcoma.[18]

Phyllodes tumors are fibroepithelial breast tumors with a broad range of behavior. These tumors are histologically classified as benign, borderline, or malignant (Table 1),[19] with benign lesions behaving similarly to fibroadenomas and malignant lesions behaving similarly to other breast sarcomas. As a result, malignant phyllodes tumors are variably included in breast sarcoma studies,[7] whereas benign or borderline tumors are typically excluded. In an epidemiologic study from Los Angeles County, the incidence of phyllodes tumors was 2.1 cases per million women, with a peak in the age range from age 45 to 49.[20] Li-Fraumeni syndrome appears to increase the risk of developing phyllodes tumors.[21] There is also some evidence from genomic sequencing[22,23] and small case reports[24] that phyllodes tumors may arise from malignant degeneration of fibroadenomas, but this is not clearly established, and many phyllodes tumors arise in patients without preexisting fibroadenomas.[25]

As with soft tissue sarcomas in other anatomic regions of the body, primary breast sarcomas are highly histologically heterogenous. In one series of 78 patients with primary breast sarcomas, the most common subtypes were malignant phyllodes tumors (41%), stromal sarcoma (18%), and angiosarcoma (10%).[7] In another series of 90 patients with primary breast sarcomas, malignant fibrous histiocytoma (70%) and angiosarcoma (10%) were the most common subtypes.[8] Of note, it is difficult to make between-study comparisons of the relative incidence of different histologic subtypes because of the small sample sizes and the fact that some subtypes, such as stromal sarcoma or malignant fibrous histiocytoma, have subsequently been reclassified. In contrast, for secondary breast sarcomas, angiosarcoma consistently appears to be the most common histologic subtype.[26,27]

Desmoid tumors, a rare mesenchymal tumor with an incidence of two to four cases per million people for all anatomic locations,[28] can also occur in the breast (Fig. 1). Although they similarly arise within connective tissue, they are distinct from soft tissue sarcoma because they are locally aggressive with rare reports of metastatic potential.

TABLE 1. Histologic Classification of Phyllodes Tumors

Histologic Feature	Benign	Borderline	Malignant
Stromal atypia	Mild	Moderate	Marked
Mitoses per 10 HPF	< 5	5–9	> 9
Tumor margin	Well defined	Well defined or focally infiltrative	Infiltrative
Stromal overgrowth	Absent	Absent or focal	Present

Abbreviation: HPF, high-powered field.
Adopted from *Breast Tumours. WHO Classification of Tumors, 5th edition.*[19]

Desmoid tumors can be associated with familial adenomatous polyposis,[29] pregnancy,[30] and antecedent trauma.[31] Up to 44% of patients with breast desmoid tumors have had prior breast surgery,[32] which supports the hypothesis that trauma predisposes to desmoid tumorigenesis, but desmoid tumors are not typically considered "treatment associated."

CLINICAL FEATURES, DIAGNOSIS, AND IMAGING

Primary breast sarcomas typically present as unilateral large painless and firm breast masses. They often exhibit rapid growth and are usually larger than breast carcinomas at the time of diagnosis, with a median tumor diameter of 5 to 6 cm.[7,8] Of note, it can be difficult to distinguish breast sarcomas with chest wall involvement from chest wall sarcomas invading or displacing the breast (Fig. 2), although management still depends primarily on the tumor's histologic subtype and relationship to the surrounding structures rather than its organ of origin. Secondary breast angiosarcomas often present as skin lesions that are characterized by skin discoloration and erythema that can be mistaken for bruising or cellulitis (Fig. 3).[33]

Although patients who present with breast masses often initially undergo diagnostic mammography and breast ultrasound, these modalities are inadequate for characterizing breast sarcomas.[34,35] Breast MRI with contrast is the study of choice, because it can delineate the extent of involvement of the surrounding skin, fascia, and muscle, which is critical for surgical and radiation treatment planning. However, it should be noted that MRI may underestimate skin involvement, especially for cutaneous angiosarcomas. Unlike breast carcinomas,[36] breast sarcomas are typically T2-hyperintense (Fig. 2A) and often appear as irregularly

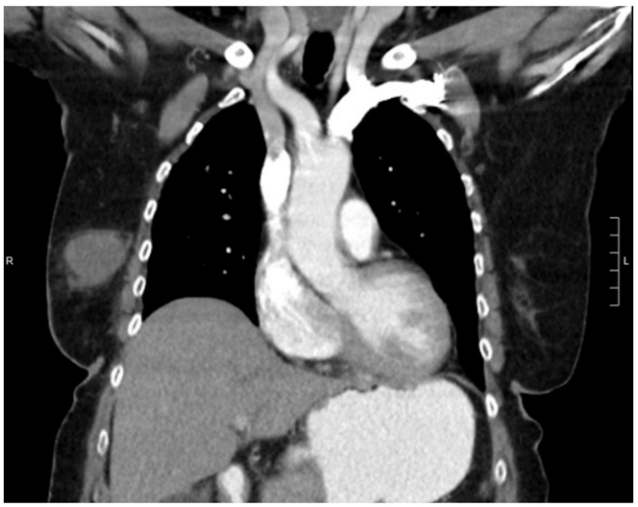

FIGURE 1. Chest CT Scan of a Patient With a Right Breast Desmoid Tumor

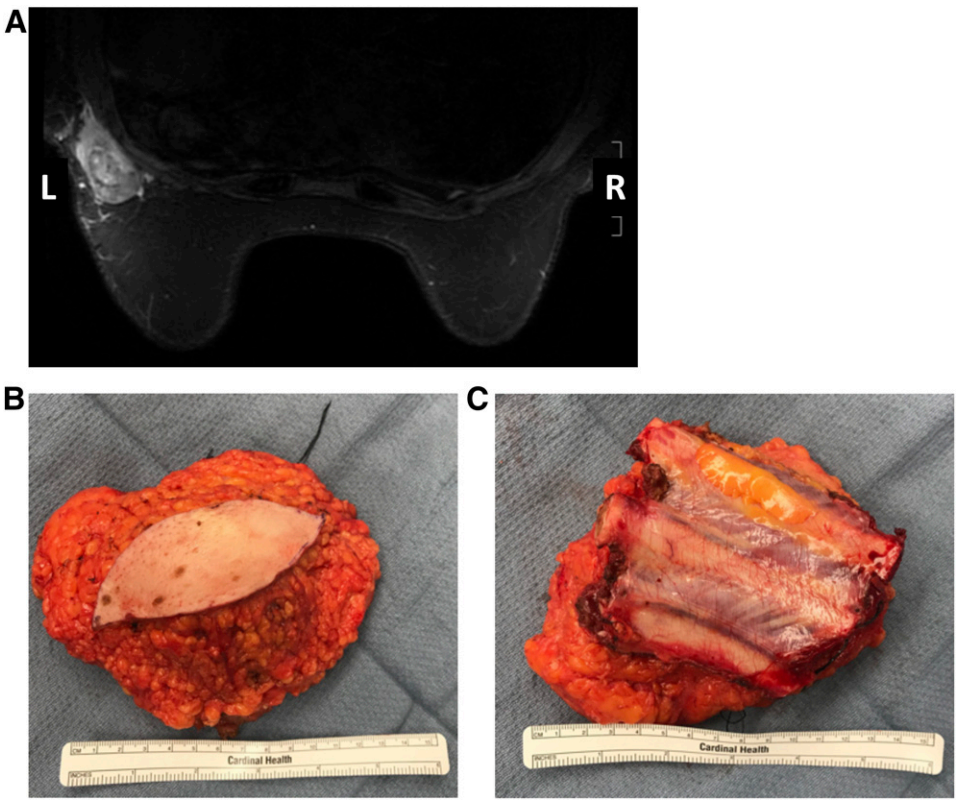

FIGURE 2. Extraskeletal Osteosarcoma of the Left Breast.

(A) Breast MRI showed a heterogeneous T2-hyperintense lesion in the lower outer quadrant of the left breast (L) with chest wall abutment in a patient who presented with a growing palpable left breast mass. (B) The patient received neoadjuvant radiation followed by wide excision of the tumor with partial mastectomy and en bloc chest wall resection. The anterior view of the surgical specimen is shown. (C) Posterior view of the surgical specimen. R, right breast.

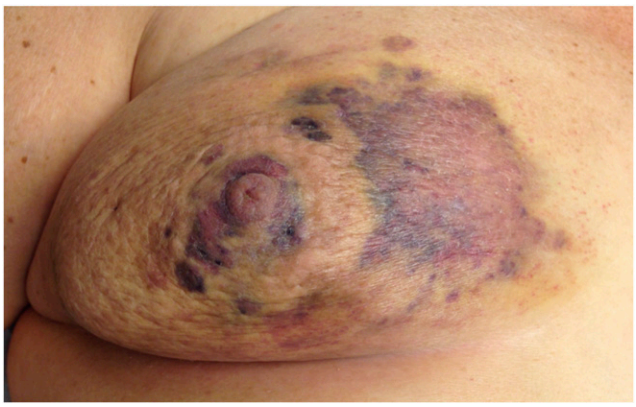

FIGURE 3. Secondary Radiation-aAsociated Angiosarcoma of the Right Breast

bordered oval masses with heterogenous rapid contrast enhancement.[37]

However, diagnosis cannot be made on imaging alone, and tissue biopsy is required. Fine needle aspiration should not be performed for suspected sarcoma, because histologic subtype and grade cannot be determined accurately on fine needle aspiration specimens. Core needle biopsy is the preferred initial approach, but if it is indeterminant, then an incisional or excisional biopsy should be performed depending on lesion size. Cutaneous radiation-associated breast angiosarcomas can be diagnosed with a punch biopsy. Patients with benign and borderline phyllodes tumors and desmoid tumors generally do not require further radiographic staging, because these tumors have little to no distant metastatic potential. All other patients diagnosed with breast sarcoma should undergo a CT scan of the chest, because the lungs are the most common site of metastasis. Additional imaging, including CT scan of the abdomen and pelvis and bone scan, can be considered in patients with angiosarcoma given their propensity for liver and bone metastases as well. These additional imaging studies can also be helpful to identify patients with a history of breast cancer who have concurrent breast sarcoma with locoregional or distant metastasis from their breast cancer.

STAGING

Breast sarcomas are staged according to the combined American Joint Committee on Cancer/Union for International Cancer Control system, which takes into account the primary tumor characteristics, regional lymph node involvement, presence or absence of distant metastases, and histologic grade (Sidebar).[38] Primary tumor stage is based solely on tumor size. Unlike carcinomas, sarcomas rarely spread to regional lymph nodes, and the presence of regional lymph node metastases is considered stage IV disease. Histologic grade is based on the degree of differentiation, mitotic rate, and degree of necrosis.

Phyllodes tumors are histologically classified as benign, borderline, or malignant, and these classifications have strong implications for prognosis and management. Classification is based on four characteristics: degree of stromal cellular atypia, mitotic activity, whether the tumor margin is well-defined versus infiltrative, and whether there is stromal overgrowth (Fig. 4).[19,39] Characteristics of benign, borderline, and malignant phyllodes tumors, as defined by the World Health Organization, are outlined in Table 1.

Desmoid tumors are excluded from the American Joint Committee on Cancer/Union for International Cancer Control soft tissue sarcoma staging system because they do not have any propensity for regional nodal or distant spread. There is no widely accepted staging system for desmoid tumors, and prognosis and management decisions are primarily driven by tumor location and feasibility of resection.

PROGNOSTIC FACTORS

For patients with localized primary breast sarcoma, 10-year disease-free survival is approximately 40% to 50%, and 10-year overall survival is approximately 60%.[7,8] Larger tumor size and higher histologic grade have been consistently associated with worse survival.[8,40,41] Angiosarcomas also seem to be associated with a worse prognosis compared with other histologic subtypes in many,[8,26,42] but not all,[43] series, although, interestingly, the prognosis of angiosarcomas does not appear to be associated with histologic grade.[44] Patients with benign or borderline phyllodes tumors have an excellent prognosis, with low rates of local recurrence and only rare reports of distant metastases,[45] whereas patients with malignant phyllodes tumors have prognoses similar to patients with other breast sarcomas, with a 5-year overall survival between 60% and 80%.[26,45] Patients with breast desmoid tumors may experience local recurrence rates as high as 29%,[32] but death from disease in this location is rare.

Patients with secondary breast sarcomas appear to have more aggressive disease and poorer outcomes than do those with primary breast sarcomas, with a median overall survival of approximately 3 years.[18,46] However, angiosarcomas also make up a much higher proportion of secondary breast sarcomas, so it is not entirely clear whether histology, radiation exposure, or both are the key drivers of worse prognosis. Some evidence suggests that the effect of radiation on prognosis is independent of tumor histology; a large study including soft tissue sarcomas at any anatomic site found that radiation-associated sarcomas were associated with worse disease-specific survival compared with sporadic sarcomas, independent of histologic subtype.[47] However, another study of 55 patients with primary (32

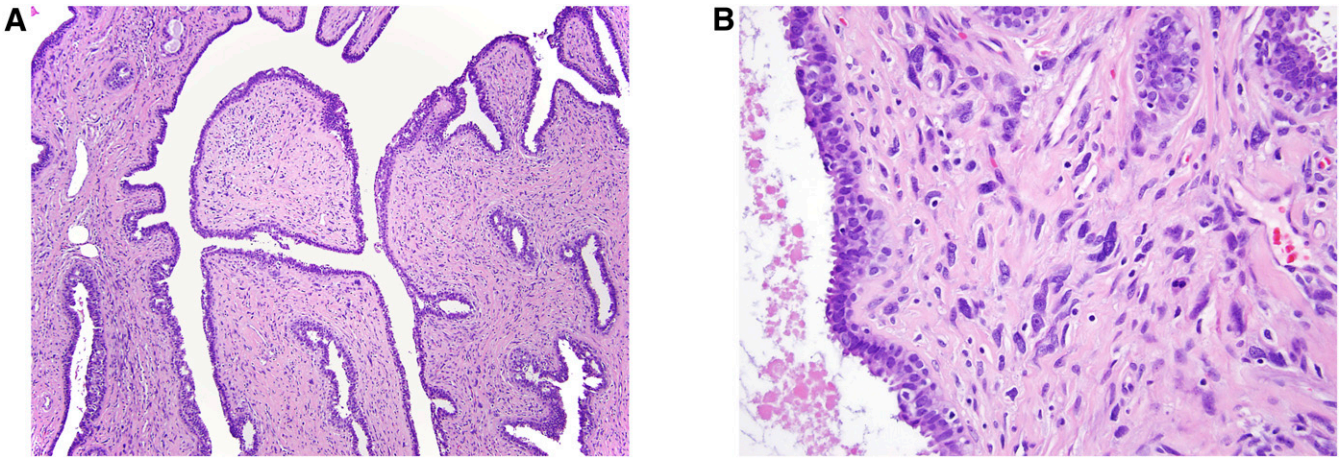

FIGURE 4. Histologic Appearance of Phyllodes Tumors
(A) Phyllodes tumor has a well-defined biphasic pattern consisting of irregular epithelial-lined spaces and cellular stromal elements. (B) The degrees of cellularity and atypia vary among phyllodes tumors. This high-power micrograph illustrates a malignant phyllodes tumor containing pleomorphic hyperchromatic stromal cells. Images were stained with hematoxylin and eosin at a magnification of 20x (A) and 400x (B). Both images are courtesy of David Lucas (Department of Pathology, University of Michigan).

patients) or secondary (23 patients) radiation-associated breast angiosarcomas did not find a substantial difference in overall survival between these two groups.[18]

MANAGEMENT

General Approach

Surgery is the mainstay of therapy for localized breast sarcomas. These tumors should generally be resected to negative margins, because margin status of first surgery appears to be predictive of survival,[48] although the margin widths and extent of surgery should be tailored to histology and prior radiation exposure (Table 2). In general, with the exception of primary and secondary angiosarcomas, there is no difference between breast-conserving surgery and mastectomy as long as negative margins can be achieved. Patients with chest wall involvement may require more extensive resection, including underlying muscle and ribs (Fig. 2C). Unlike for breast carcinomas, axillary surgery is generally not recommended for breast sarcomas unless there is disease identified on imaging studies confirmed on biopsy or direct extension of the primary tumor into the axilla, because breast sarcomas rarely metastasize to regional nodes.[49] Local recurrences should be resected if possible, because this can still result in the potential for long-term disease control.[8,48]

Adjuvant radiation can be used to treat primary breast sarcomas to reduce the risk of local recurrence. Data are conflicting and all are retrospective, with some series not showing any association between adjuvant radiation and local recurrence rates[50,51] and other series showing an association between adjuvant radiation and improved outcomes.[7,52] Studies on the use of adjuvant radiation are summarized in Table 3. Radiation therapy is even more controversial for secondary sarcomas because of concern for cumulative tissue toxicity with repeat radiation.

There are few data to guide the use of neoadjuvant chemotherapy and/or radiation, but these modalities can be used in an attempt to convert an unresectable locally advanced tumor into a resectable one or to decrease the potential morbidity of surgery. Neoadjuvant or adjuvant chemotherapy can also be considered to help reduce the risk of metastases for patients with high-risk breast sarcoma and excellent functional status. However, similar to soft tissue sarcomas in other anatomic sites, this approach

TABLE 2. Summary of Surgical Management Recommendations for Localized Breast Sarcoma

Histology	Recommendation
Phyllodes Tumor	
Benign	Grossly complete excision*
Borderline	Excision* to 1-cm margins
Malignant	Excision* to 1-cm margins
Angiosarcoma	
Primary	Mastectomy
Radiation associated	Mastectomy with resection of all irradiated skin
Desmoid Tumor	Excision* to negative margins
Other Histology	Excision* to negative margins

*Partial or total mastectomy is acceptable as long as adequate margins can be achieved.

TABLE 3. Summary of Studies of Adjuvant Radiation for Breast Sarcomas

Study	Population	Treatment Groups	Local Recurrence	Survival Outcomes
Johnstone et al, 1993[52]	10 patients:	Surgery + XRT (10 patients)	0%	5-year DFS, 68%
	4 angiosarcoma			
	2 MFH			
	4 other			
Barrow et al, 1999[50]	59 patients:	Surgery + XRT (17 patients)	5 patients (29%)	Not reported for subgroups
	32 MFH, fibrosarcoma, and stromal sarcoma	Surgery only (42 patients)	16 patients (38%)	
	17 angiosarcoma			
	10 other			
McGowan et al, 2000[7]	78 patients:	Surgery + XRT (26 patients):	5-year LRFS	5-year DSS
	7 fibrosarcoma	> 48 Gy (11 patients)	91%	91%
	14 stromal sarcoma	≤ 48 Gy (12 patients)	55%	50%
	8 angiosarcoma	(3 excluded for gross residual disease)		
	32 malignant phyllodes tumors	Surgery only (52 patients)	74%	50%
	17 other			
	17 other			
Bousquet et al, 2007[51]	103 patients:		5-year LRFS	5-year DFS
	42 angiosarcoma	Surgery + XRT (51 patients)	65%	48%
	14 MFH	Surgery only (52 patients)	55%	40%
	12 fibrosarcoma			
	35 other			

Abbreviations: MFH, malignant fibrous histiocytoma; XRT, radiation; DFS, disease-free survival; LRFS, local recurrence-free survival; DSS, disease-specific survival.

remains highly controversial and is best undertaken only after careful discussion of the risks and benefits of therapy and ideally in the context of a clinical trial. Decisions should be made on a case-by-case basis in a multidisciplinary setting.

The treatment of patients with metastatic breast sarcoma is similar to that of patients with metastatic soft tissue sarcoma from other sites. Patients generally receive doxorubicin-based chemotherapy in the first-line setting, often as a single agent or in combination with ifosfamide. Although combination regimens do not yield superior overall survival rates, they are associated with higher objective response rates and longer progression-free survival compared with single-agent doxorubicin.[53,54] Patients with therapy-related sarcoma often have had prior exposure to doxorubicin for antecedent breast malignancies; thus, additional doxorubicin use may be limited by the risk of cardiotoxicity with higher cumulative doses. Other systemic regimens commonly used in breast sarcoma are often histology specific and include gemcitabine and docetaxel,[55] pazopanib,[56] trabectedin (leiomyosarcoma and liposarcoma),[57] taxanes (angiosarcoma),[58,59] and eribulin (liposarcoma).[59] Emerging evidence also suggests a potential role for checkpoint inhibition for certain sarcoma histologies, including angiosarcoma (Table 4).[60-62] Patients with isolated or limited lung metastases who are good surgical candidates should undergo wedge resections of these lesions, because 5-year overall survival is as high as 40%, even in older series.[63,64]

Phyllodes Tumors

Patients with phyllodes tumors should undergo excision, although the extent of surgery depends on histologic classification. For borderline and malignant phyllodes tumors, resection margins should be at least 1 cm.[65] In a retrospective series of 48 patients with malignant phyllodes tumors, a margin of less than 1 cm was associated with an increased risk for local recurrence, although the local recurrence rate for patients with margins wider than 1 cm was still quite high (39%).[66] In contrast, a meta-analysis of 54 studies found that a positive margin was

TABLE 4. Select Reports of Systemic Therapies in Metastatic Malignant Phyllodes Tumors, Angiosarcoma, and Desmoid Tumors

Systemic Therapy	No. of Patients	Outcomes	Study type	Study
Malignant Phyllodes Tumor				
Doxorubicin	6	PR, 4	Case series	Mitus et al, 2016[106]
	13	PR, 5; mPFS, 3.2 mo	Case series	Parkes et al, 2021[107]
Ifosfamide	3	CR, 1; PR, 1,	Case series	Hawkins et al, 1992[108]
	4	PR, 1; NR, 3	Case series	Mitus et al, 2016[106]
	8	PR, 2; mPFS, 2.3 mo	Case series	Parkes et al, 2021[107]
Doxorubicin + cisplatin	5	PR, 4; NR, 1	Case series	Mitus et al, 2016[106]
Doxorubicin + ifosfamide	1	CR=1	Case series	Hawkins et al, 1992[108]
	3	CR=1, PR, 2	Case series	Mitus et al, 2016[106]
	19	PR=10, mPFS, 9.1 mo	Case series	Parkes et al, 2021[107]
Gemcitabine-based treatment	13	PR=3, mPFS, 3.1 mo	Case series	Parkes et al, 2021[107]
Angiosarcoma (Various Anatomic Sites)				
Paclitaxel	75	ORR, 53%; mPFS, 5.8 mo	Case series	Italiano et al, 2012[109]
	24	ORR, 50%; mPFS, 6.6 mo	Phase II	Ray-Coquard et al, 2015[110]
Doxorubicin	42	ORR, 29.5%; mPFS, 3 mo	Case series	Italiano et al, 2012[109]
Gemcitabine	25	ORR, 68%; mPFS, 7 mo	Case series	Stacchiotti et al, 2012[111]
Sorafenib	37	ORR, 13.5%; mPFS, 3.8 mo	Phase II	Maki et al, 2009[112]
	41	ORR, 14.6%	Phase II	Ray-Coquard et al, 2012[113]
Checkpoint inhibitor based	7	PR, 5	Case series	Florou et al, 2019[61]
Desmoid Tumors (Various Anatomic Sites)				
Methotrexate + vinblastine	20	ORR, 25%; mPFS, NR	Randomized phase II	Toulmonde et al, 2019[100]
Sorafenib	50	ORR, 33%; mPFS, NR	Phase III	Gounder et al, 2018[91]
Pazopanib	48	ORR, 37%; mPFS, NR	Randomized phase II	Toulmonde et al, 2019[100]
Nirogacestat	17	ORR, 29%	Phase II	Kummar et al, 2017[105]

Abbreviations: PR, partial response; mPFS, median progression-free survival; CR, complete response; NR, not reached; ORR, overall response rate (PR+CR).

predictive of local recurrence for malignant phyllodes tumors but not for benign or borderline tumors. Pooled local recurrence rates in this analysis were 8%, 13%, and 18% for benign, borderline, and malignant phyllodes tumors, respectively.[67] In fact, some evidence suggests that even a positive margin for benign tumors is not associated with an increased local recurrence risk. A retrospective study that included 216 patients with benign phyllodes tumors, of whom 102 underwent excision with positive margins, did not find any substantial difference in local recurrence rates between patients with negative margins and those with positive margins, with an overall local recurrence rate of 2% after a median follow-up of 3 years.[68] A recent multicenter analysis of 550 patients (70% had benign phyllodes tumors) from 11 institutions further supports the concept that wide margins are not needed for benign phyllodes tumors, and re-excision for positive margins is rarely warranted. Of 75 patients with positive margins (60 benign, 12 borderline, three malignant), only two patients (one benign, one borderline; 2.7%) had local recurrences; for the entire cohort, margin width or margin status was not associated with local recurrence.[69] Thus, for benign phyllodes tumors, a grossly complete excision is acceptable, regardless of microscopic margin status, according to National Comprehensive Cancer Network guidelines.[65] This makes re-excision of benign phyllodes tumors unnecessary when they are mistaken for fibroadenomas on core biopsy and excised with narrow margins or enucleated, as long as no gross tumor is left behind. Axillary staging is not indicated, because phyllodes tumors rarely metastasize to regional lymph nodes.[70] There also does not appear to be a difference in local recurrence rates between partial and total mastectomy as long as margins are negative.[70] For large or rapidly growing phyllodes, a margin-negative resection may require a mastectomy.

Adjuvant radiation can be used for malignant phyllodes tumors to try to improve local control, especially if the patient was treated with breast-conserving surgery. In a series of 46 patients with borderline or malignant phyllodes tumors who underwent partial mastectomy followed by adjuvant breast radiation, there were no local recurrences, although two patients died of distant metastases.[71] A meta-analysis of eight studies of borderline and malignant tumors also showed that adjuvant radiation was associated with decreased local recurrence, but not with overall survival, in patients undergoing partial mastectomy.[72] Data on the use of adjuvant radiation for patients undergoing total mastectomy are weaker; the same meta-analysis showed that adjuvant radiation was not associated with a marked decreased in local recurrence for patients undergoing total mastectomy, although there was a trend in that direction. Because only a minority of adjuvant radiation studies included patients with borderline phyllodes tumors,[72] adjuvant radiation is not offered to these patients at some centers. Adjuvant radiation is uniformly not recommended for benign phyllodes tumors because of the low local recurrence rates achieved with surgery alone, even in the setting of positive margins.

Patients with locally recurrent phyllodes tumors can be treated with repeat surgery, with or without radiation, or with palliative radiation if the disease is unresectable.[73] Most recurrent tumors are usually the same histologic grade as the initial tumor; however, up to 20% of patients will have higher-grade tumors at the time of recurrence, suggesting the potential for malignant transformation over time.[67,74]

Phyllodes tumors also spread distantly, most commonly to the lung. The vast majority of metastatic tumors have malignant histology, although a very small percentage of patients with benign phyllodes tumors subsequently develop distant metastases.[45] Approximately 20% of patients with malignant phyllodes tumors develop metastases, and they are treated with similar systemic agents as those with soft tissue sarcomas originating in other anatomic sites (Table 4).[66] In general, data on systemic therapy are limited to small case reports and series that tend to emphasize favorable outcomes. In practice, patients seem to derive less benefit from chemotherapy with relatively short durations of response compared with those with more common sarcoma histologies. Malignant phyllodes tumors do not respond to hormonal or endocrine therapies.[75] Although estrogen receptors are often expressed on the epithelial portions of the tumor, they are not expressed on the stromal portions of the tumor, which are thought to be the actual contributors to malignant behavior. There is also no clear evidence to support the use of adjuvant chemotherapy. A small retrospective study included 28 patients with malignant phyllodes tumors treated with surgery, of whom 17 received adjuvant doxorubicin plus dacarbazine. There was no substantial difference in overall or recurrence-free survival, but the small size and retrospective nature of the study limit the applicability of these findings.[76] Similar to soft tissue sarcoma, adjuvant chemotherapy for malignant phyllodes, typically using doxorubicin and ifosfamide, should only be considered after consultation at a center with sarcoma expertise, recognizing that the data are even more controversial compared with soft tissue sarcomas originating at other anatomic sites.

Angiosarcomas

Patients with localized primary breast angiosarcomas should undergo resection. Although these tumors most commonly present as discrete palpable breast masses, they are unencapsulated and display highly infiltrative growth patterns on histologic examination.[44] As a result, mastectomy is usually required to achieve adequate negative margins, although local recurrence rates are still 15% to 24% after approximately 2 years of follow-up.[44,77] Partial mastectomy may be considered on a case-by-case basis (e.g., for a woman with a small lesion on MRI and ample uninvolved breast tissue). Patients who develop local recurrences may still achieve prolonged disease-free intervals with repeat surgery.[78]

Adjuvant radiation has been used after surgery to try to improve local control, although it is not significantly associated with reduced local recurrence rates in several small series.[79,80] However, because the data are limited and solely retrospective, adjuvant radiation is applied in practice on a case-by-case basis using clinical judgment. Furthermore, patients with primary breast angiosarcoma frequently develop metastatic disease, with distant recurrence rates of 37% to 59% after local therapy.[44,77] Patients with metastatic disease are often candidates for systemic chemotherapy, which may offer palliation and prolonged tumor control (Table 4). Unlike other histologic subtypes, angiosarcomas are uniquely sensitive to paclitaxel.[58,81] A phase II trial of weekly paclitaxel in 30 patients with unresectable angiosarcomas (including 10 with breast angiosarcoma) demonstrated a 74% progression-free survival at 2 months, although progression-free survival was only 45% by 4 months, suggesting that tumor response is only temporary. However, three patients in this study had a partial response sufficient to allow for their tumors to become resectable,[58] which suggests that chemotherapy can also be applied in a neoadjuvant setting in select cases. Like most other sarcomas, angiosarcomas are sensitive to doxorubicin, and it is not clear whether one agent is superior to the other for these patients.[82]

In contrast to primary breast angiosarcomas, which arise from breast parenchyma, secondary radiation-associated angiosarcomas actually arise from the overlying dermis; therefore, they are technically “cutaneous” and not “breast”

sarcomas.[83] They tend to be multifocal and diffusely infiltrative, despite sometimes presenting clinically as one or more small discrete skin lesions. Furthermore, resection specimens frequently contain multifocal islands of atypical vascular lesions, which are postradiation vascular changes thought to be precursors to angiosarcoma.[84] Historically, conservative excisions to negative margins have been performed for patients with localized disease, but reported local recurrence rates in retrospective studies ranged from 52% to 75%.[33,46,85] We instead recommend a cutaneous-oriented surgical approach consisting of mastectomy with en bloc radical resection of all irradiated skin (Fig. 5), given the multifocality and diffuse infiltrative nature of most of these tumors. The assessment of the extent of the irradiated breast skin for an individual patient can be challenging if access to the original radiation planning is not readily available. Therefore, we tend to rely on standard anatomic landmarks to guide the extent of skin resection: clavicle as superior margin, superior border of rectus sheath as inferior margin, midsternum as medial margin, and anterior border of latissimus dorsi as lateral margin.[33,86] Evidence suggests that this approach is associated with improved local control and disease-specific survival. In a retrospective series of 76 patients with secondary radiation-associated breast angiosarcomas, patients undergoing radical skin resections had a higher 5-year disease-specific survival compared with those undergoing more conservative resections (86% vs. 46%; $p < .01$) and a lower 5-year crude cumulative incidence of local recurrence (23% vs. 76%, $p < .01$). Radical skin resection was also an independent predictor of disease-specific survival after controlling for margin status.[86] Complete resection of the breast skin is critical. Although the radiation-associated angiosarcoma only extends into the breast parenchyma in 60% of cases, mastectomy is typically performed given the extent of skin resection (with appropriate deep margin) required. Muscle resection may be performed selectively based on clinical or radiographic assessment, although direct pectoralis major involvement is rare and occurs in only 6% of cases.[86]

Given the amount of skin that needs to be excised, almost all patients require complex reconstruction. In a study[87] of 35 women who had undergone mastectomy with radical skin resection for secondary radiation-associated breast angiosarcoma, the median surface area of the wound defect was 700 cm^2. Twenty-five patients underwent an abdominal advancement flap, followed by split-thickness skin grafting. Ten patients had exposed cartilage or bone in the wound bed that was not completely covered with an abdominal advancement flap alone. Seven of these patients underwent an omental flap, and three underwent a pedicled latissimus dorsi flap to cover cartilage and bone, after which all 10 patients underwent split-thickness skin grafting. Six patients (17%) developed wound healing or infectious complications requiring operative revision, highlighting the morbidity of these large complex wounds.

Radiation for secondary breast angiosarcomas is controversial. Some groups have reported good outcomes,[88] but concern exists about cumulative radiation toxicity, in particular rib fracture, pneumonitis, and tissue fibrosis.[89] Treatment of metastatic radiation-associated angiosarcoma is similar to that of primary angiosarcoma discussed

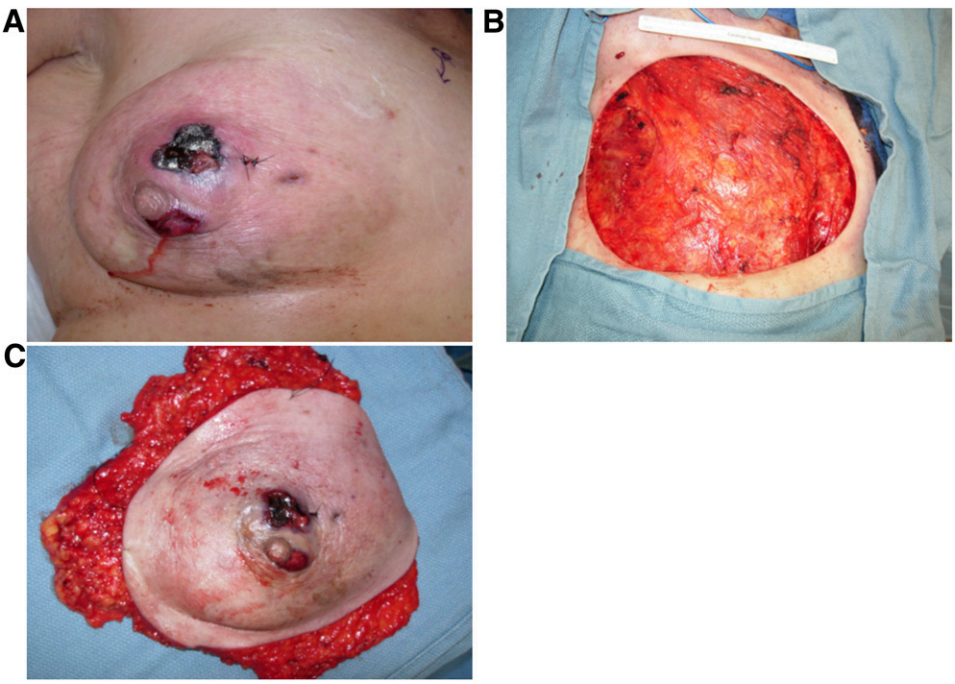

FIGURE 5. Secondary Radiation-Associated Angiosarcoma of the Right Breast in a Patient Who Had Undergone Breast-Conservation Therapy for Invasive Carcinoma Several Years Prior

(A) Preoperative photograph shows a peri-areolar erythematous ulcerative lesion. (B) The patient underwent a mastectomy with radical resection of all irradiated skin from the clavicle to the superior border of the rectus abdominis, as well as from the sternum to the anterior border of the latissimus dorsi. The resection bed is depicted here. (C) Anterior view of the surgical specimen.

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previously (Table 4). Although systemic therapies for localized disease are again controversial, a neoadjuvant approach for locally advanced and borderline resectable tumors can be considered after multidisciplinary evaluation to help facilitate surgery of advanced tumors.

Desmoid Tumors

Desmoid tumors of the breast are managed similarly to other extra-abdominal desmoid tumors. These tumors do not have any metastatic potential, but they can be locally aggressive and difficult to control. Some "breast" desmoids actually arise deep to the breast parenchyma in the underlying chest wall, and MRI of the breast can help to discern whether the tumor is arising in the breast parenchyma or from the underlying pectoralis muscle with displacement of the breast anteriorly. Initial observation is a reasonable approach for patients with stable asymptomatic desmoid tumors based on direct and indirect observations from several studies, because some tumors may partially spontaneously regress over time. In a series of 102 patients with abdominal wall desmoid tumors undergoing observation, 28% experienced some degree of spontaneous tumor regression, and only 16% underwent surgery for progression or symptoms by 3 years. Size larger than 7 cm was identified as a risk factor for progressing to surgery.[90] Furthermore, in a phase III trial comparing sorafenib with placebo in 87 patients with desmoid tumors at any site, 2-year progression-free survival was 36% in the 37-patient placebo arm; there was also a 20% objective response rate in this arm, suggesting that these tumors had spontaneously regressed.[91]

For patients with progressing or symptomatic lesions, surgery remains the mainstay of therapy. Historically, widely negative margins were mandated, even if this meant substantial postoperative morbidity, because local recurrence rates were found to be as high as 27%, even with negative margins.[92] A smaller study of 32 patients with only breast desmoid tumors also found a 56% recurrence rate with margin-positive resection compared with a 16% recurrence rate with margin-negative resection after a median follow-up of 54 months, although it was underpowered to detect a statistically significant difference.[32] However, other data suggest that local recurrence rates may not be as dependent on margin status as initially believed. In a series of 426 patients with extra-abdominal desmoid tumors, of which 119 were truncal, 110 patients underwent R0 resection (negative microscopic margins) and 107 underwent R1 resection (negative gross margins but positive microscopic margins); there was no significant difference in 5-year progression-free survival between these patient groups (R0, 62.5% vs. R1, 60.5%; p = .867).[93] Furthermore, another study of 177 patients with desmoid tumors undergoing macroscopically complete (R0 or R1) resections showed that, although R0 margin status was an independent predictor of progression-free survival, those with an R1 resection still had a 10-year progression-free survival of 52%.[94] Grossly margin-positive (R2) resections are not recommended, because 2-year and 10-year progression-free survival are as low as 43% and 22%, respectively.[93] Taking all of the data from desmoid tumors of any site into consideration, if surgery is deemed warranted after multidisciplinary discussion for a tumor originating in the breast, we recommend an R0 resection if technically feasible; however, an R1 resection is reasonable to consider if it will help to spare the patient excessive morbidity, such as an extensive chest wall resection.

Radiation can be used as alternative primary local therapy to surgery for patients who are not surgical candidates or for those with unresectable disease. A study of 44 patients with desmoid tumors treated with radiation alone found that 91% of patients had stable or responsive disease at 3 years; some of these patients experienced prolonged responses to radiation beyond 3 years.[95] Adjuvant radiation does not seem to be associated with improved local recurrence rates after R0 resection,[96] but data on adjuvant radiation after R1 resection is somewhat conflicting. One retrospective study of 189 patients with desmoid tumors found 10-year local recurrence rates of 27% in 78 patients with R0 resections, 54% in 40 patients with R1 resections, and 31% in 33 patients with R1 resections plus adjuvant radiation. Margin positivity was a predictor of local recurrence in the surgery-only group but not in the surgery-plus-radiation group, which the investigators argued indicated that radiation helped to offset the increased risk of local recurrence in patients with R1 resections.[92] However, another study of 105 patients with truncal or extremity desmoid tumors treated with surgery alone (74 patients) or with surgery plus adjuvant radiation (31 patients) did not find a significant difference in local recurrence rates (23% for both groups; p = .82), and this remained true after controlling for margin positivity.[97]

A wide range of systemic therapies can be used to treat unresectable breast desmoid tumors or those that recur locally, despite both radiation and surgery. Options include nonsteroidal anti-inflammatory agents,[98] hormone therapy (e.g., tamoxifen),[99] tyrosine kinase inhibitors (e.g., sorafenib[91] or pazopanib),[100] or cytotoxic chemotherapy (e.g., doxorubicin alone[101] or in combination with dacarbazine[102] or methotrexate-based combinations; Table 4).[103] Novel agents targeting the Wnt/β-catenin and Notch pathways, such as Wnt inhibitors[104] and gamma-secretase inhibitors,[105] show promise for management and are under investigation. In general, cytotoxic chemotherapy is reserved for fast-growing symptomatic tumors, whereas noncytotoxic therapies, such as hormone therapy or tyrosine kinase inhibitors, are used for more indolent tumors.

SIDEBAR. AMERICAN JOINT COMMITTEE ON CANCER/UNION FOR INTERNATIONAL CANCER CONTROL STAGING FOR SOFT TISSUE SARCOMAS OF THE EXTREMITIES AND TRUNK, 8TH EDITION

T (PRIMARY TUMOR)

- Tx = Cannot be assessed
- T0 = No evidence of primary tumor
- T1 = Tumor $\leq$ 5 cm in greatest dimension
- T2 = Tumor $>$ 5 cm and $\leq$ 10 cm in greatest dimension
- T3 = Tumor $>$ 10 cm and $\leq$ 15 cm in greatest dimension
- T4 = Tumor $>$ 15 cm in greatest dimension

N (REGIONAL LYMPH NODES)

- N0 = No regional lymph node metastasis or unknown lymph node status
- N1 = Regional lymph node metastasis

M (DISTANT METASTASIS)

- M0 = No distant metastasis
- M1 = Distant metastasis

G (GRADE)

- GX = Cannot be assessed
- G1 = Total grade score of 2–3
- G2 = Total grade score of 4–5
- G3 = Total grade score of 6–8

GRADE SCORING

Differentiation

- 1: Sarcomas closely resembling normal adult mesenchymal tissue
- 2: Sarcomas for which histologic typing is certain
- 3: Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumors of soft tissue

MITOTIC COUNT

- 1: 0–9 mitoses per 10 HPF
- 2: 10–19 mitoses per 10 HPF
- 3: $\geq$ 20 mitoses per 10 HPF

Necrosis

- 0: No necrosis
- 1: $<$ 50% tumor necrosis
- 2: $\geq$ 50% tumor necrosis

STAGING

- IA = T1, N0, M0, GX or G1
- IB = T2-4, N0, M0, GX or G1
- II = T1, N0, M0, G2–3
- IIIA = T2, N0, M0, G2–3
- IIIB = T3-4, N0, M0, G2–3
- IV = Any T, N1 or M1

Abbreviation: HPF, high-powered field.

Adapted from AJCC Cancer Staging Manual, 8th ed.[38]

CONCLUSION

Breast sarcomas are rare entities that share more in common with soft tissue sarcomas of other sites than breast carcinomas. Similar to sarcomas of other anatomic sites, diagnosis generally requires a core needle biopsy and MRI of the affected area (breast), and staging should be performed with a CT scan of the chest, with the exception of desmoid tumors or benign phyllodes tumors. Treatment of localized disease generally involves surgical resection to negative margins if feasible, but it is highly histology dependent, because stable desmoid tumors may be observed, whereas even small secondary angiosarcomas may require mastectomy with radical skin resection. Although surgery is the cornerstone of management for most localized breast sarcoma and phyllodes tumors, the benefit of adjuvant radiation and chemotherapy is controversial and highly dependent on histology and prior therapies. Metastatic breast sarcoma is treated similarly to other metastatic soft tissue sarcomas with systemic chemotherapy, palliative radiation, and pulmonary metastasectomy for select patients with resectable isolated lung metastases. Novel approaches with immunotherapy and targeted therapy are also being investigated. More prospective data are needed to help guide and improve the care of patients with breast sarcomas, although multiinstitutional collaboration and thoughtful trial designs will be needed given the rarity and heterogeneity of this disease.

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REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2017. https://seer.cancer.gov/csr/1975_2017. Accessed February 6, 2021.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
3. Adem C, Reynolds C, Ingle JN, et al. Primary breast sarcoma: clinicopathologic series from the Mayo Clinic and review of the literature. Br J Cancer. 2004;91:237-241.
4. Moore MP, Kinne DW. Breast sarcoma. Surg Clin North Am. 1996;76:383-392.
5. May DS, Stroup NE. The incidence of sarcomas of the breast among women in the United States, 1973-1986. Plast Reconstr Surg. 1991;87:193-194.
6. Al-Benna S, Poggemann K, Steinau HU, et al. Diagnosis and management of primary breast sarcoma. Breast Cancer Res Treat. 2010;122:619-626.
7. McGowan TS, Cummings BJ, O'Sullivan B, et al. An analysis of 78 breast sarcoma patients without distant metastases at presentation. Int J Radiat Oncol Biol Phys. 2000;46:383-390.
8. Zelek L, Llombart-Cussac A, Terrier P, et al. Prognostic factors in primary breast sarcomas: a series of patients with long-term follow-up. J Clin Oncol. 2003;21:2583-2588.
9. Li FP, Fraumeni JF Jr., Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. Cancer Res. 1988;48:5358-5362.
10. Kleinerman RA, Tucker MA, Abramson DH, et al. Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. J Natl Cancer Inst. 2007;99:24-31.
11. Hardell L, Eriksson M. The association between soft tissue sarcomas and exposure to phenoxyacetic acids. A new case-referent study. Cancer. 1988;62:652-656.
12. Cahan WG, Woodard HQ, Higinbotham NK, et al. Sarcoma arising in irradiated bone; report of 11 cases. Cancer. 1948;1:3-29.
13. Bjerkehagen B, Smeland S, Walberg L, et al. Radiation-induced sarcoma: 25-year experience from the Norwegian Radium Hospital. Acta Oncol. 2008;47:1475-1482.
14. Mery CM, George S, Bertagnolli MM, et al. Secondary sarcomas after radiotherapy for breast cancer: sustained risk and poor survival. Cancer. 2009;115:4055-4063.
15. Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphedema; a report of six cases in elephantiasis chirurgica. Cancer. 1948;1:64-81.

16. Offori TW, Platt CC, Stephens M, et al. Angiosarcoma in congenital hereditary lymphoedema (Milroy's disease)--diagnostic beacons and a review of the literature. Clin Exp Dermatol. 1993;18:174-177.

17. Woodward AH, Ivins JC, Soule EH. Lymphangiosarcoma arising in chronic lymphedematous extremities. Cancer. 1972;30:562-572.

18. Vorburger SA, Xing Y, Hunt KK, et al. Angiosarcoma of the breast. Cancer. 2005;104:2682-2688.

19. WHO Classification of Tumours Editorial Board. Breast Tumours. WHO Classification of Tumours. Vol. Volume 2, 5th edition. Lyon: International Agency for Research on Cancer; 2019.

20. Bernstein L, Deapen D, Ross RK. The descriptive epidemiology of malignant cystosarcoma phyllodes tumors of the breast. Cancer. 1993;71:3020-3024.

21. Birch JM, Alston RD, McNally RJ, et al. Relative frequency and morphology of cancers in carriers of germline TP53 mutations. Oncogene. 2001;20:4621-4628.

22. Noguchi S, Yokouchi H, Aihara T, et al. Progression of fibroadenoma to phyllodes tumor demonstrated by clonal analysis. Cancer. 1995;76:1779-1785.

23. Piscuoglio S, Geyer FC, Burke KA, et al. Massively parallel sequencing analysis of synchronous fibroepithelial lesions supports the concept of progression from fibroadenoma to phyllodes tumor. NPJ Breast Cancer. 2016;2:16035.

24. Abe M, Miyata S, Nishimura S, et al. Malignant transformation of breast fibroadenoma to malignant phyllodes tumor: long-term outcome of 36 malignant phyllodes tumors. Breast Cancer. 2011;18:268-272.

25. Pareja F, Geyer FC, Kumar R, et al. Phyllodes tumors with and without fibroadenoma-like areas display distinct genomic features and may evolve through distinct pathways. NPJ Breast Cancer. 2017;3:40.

26. Confavreux C, Lurkin A, Mitton N, et al. Sarcomas and malignant phyllodes tumours of the breast--a retrospective study. Eur J Cancer. 2006;42:2715-2721.

27. Yap J, Chuba PJ, Thomas R, et al. Sarcoma as a second malignancy after treatment for breast cancer. Int J Radiat Oncol Biol Phys. 2002;52:1231-1237.

28. Reitamo JJ, Häyry P, Nykyri E, et al. The desmoid tumor. I. Incidence, sex-, age- and anatomical distribution in the Finnish population. Am J Clin Pathol. 1982; 77:665-673.

29. Fallen T, Wilson M, Morlan B, et al. Desmoid tumors -- a characterization of patients seen at Mayo Clinic 1976-1999. Fam Cancer. 2006;5:191-194.

30. Fiore M, Coppola S, Cannell AJ, et al. Desmoid-type fibromatosis and pregnancy: a multi-institutional analysis of recurrence and obstetric risk. Ann Surg. 2014; 259:973-978.

31. Lopez R, Kemalyan N, Moseley HS, et al. Problems in diagnosis and management of desmoid tumors. Am J Surg. 1990;159:450-453.

32. Neuman HB, Brogi E, Ebrahim A, et al. Desmoid tumors (fibromatoses) of the breast: a 25-year experience. Ann Surg Oncol. 2008;15:274-280.

33. Morgan EA, Kozono DE, Wang Q, et al. Cutaneous radiation-associated angiosarcoma of the breast: poor prognosis in a rare secondary malignancy. Ann Surg Oncol. 2012;19:3801-3808.

34. Liberman L, Dershaw DD, Kaufman RJ, et al. Angiosarcoma of the breast. Radiology. 1992;183:649-654.

35. Yang WT, Muttarak M, Ho LW. Nonmammary malignancies of the breast: ultrasound, CT, and MRI. Semin Ultrasound CT MR. 2000;21:375-394.

36. Mann RM, Cho N, Moy L. Breast MRI: state of the art. Radiology. 2019;292:520-536.

37. Smith TB, Gilcrease MZ, Santiago L, et al. Imaging features of primary breast sarcoma. AJR Am J Roentgenol. 2012;198:W386-393.

38. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67:93-99.

39. Hawkins RE, Schofield JB, Fisher C, et al. The clinical and histologic criteria that predict metastases from cystosarcoma phyllodes. Cancer. 1992;69:141-147.

40. McGregor GI, Knowling MA, Este FA. Sarcoma and cystosarcoma phyllodes tumors of the breast--a retrospective review of 58 cases. Am J Surg. 1994; 167:477-480.

41. Terrier P, Terrier-Lacombe MJ, Mouriesse H, et al. Primary breast sarcoma: a review of 33 cases with immunohistochemistry and prognostic factors. Breast Cancer Res Treat. 1989;13:39-48.

42. Blanchard DK, Reynolds CA, Grant CS, et al. Primary nonphylloides breast sarcomas. Am J Surg. 2003;186:359-361.

43. Gutman H, Pollock RE, Ross MI, et al. Sarcoma of the breast: implications for extent of therapy. The M.D. Anderson experience. Surgery. 1994;116:505-509.

44. Nascimento AF, Raut CP, Fletcher CD. Primary angiosarcoma of the breast: clinicopathologic analysis of 49 cases, suggesting that grade is not prognostic. Am J Surg Pathol. 2008;32:1896-1904.

45. Chaney AW, Pollack A, McNeese MD, et al. Primary treatment of cystosarcoma phyllodes of the breast. Cancer. 2000;89:1502-1511.

46. Billings SD, McKenney JK, Folpe AL, et al. Cutaneous angiosarcoma following breast-conserving surgery and radiation: an analysis of 27 cases. Am J Surg Pathol. 2004;28:781-788.

47. Gladdy RA, Qin LX, Moraco N, et al. Do radiation-associated soft tissue sarcomas have the same prognosis as sporadic soft tissue sarcomas? J Clin Oncol. 2010; 28:2064-2069.

48. Pandey M, Mathew A, Abraham EK, et al. Primary sarcoma of the breast. J Surg Oncol. 2004;87:121-125.

49. Gullett NP, Delman K, Folpe AL, et al. National surgical patterns of care: regional lymphadenectomy of breast sarcomas. Am J Clin Oncol. 2007;30:461-465.

50. Barrow BJ, Janjan NA, Gutman H, et al. Role of radiotherapy in sarcoma of the breast--a retrospective review of the M.D. Anderson experience. Radiother Oncol. 1999;52:173-178.

51. Bousquet G, Confavreux C, Magné N, et al. Outcome and prognostic factors in breast sarcoma: a multicenter study from the rare cancer network. Radiother Oncol. 2007;85:355-361.

52. Johnstone PA, Pierce LJ, Merino MJ, et al. Primary soft tissue sarcomas of the breast: local-regional control with post-operative radiotherapy. Int J Radiat Oncol Biol Phys. 1993;27:671-675.

53. Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol. 1993;11:1276-1285.

54. Edmonson JH, Ryan LM, Blum RH, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J Clin Oncol. 1993;11:1269-1275.

55. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected] [published correction appears in *J Clin Oncol*. 2007;25:3790]. J Clin Oncol. 2007;25:2755-2763.

56. van der Graaf WT, Blay JY, Chawla SP, et al; PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379:1879-1886.

57. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol. 2016;34:786-793.

58. Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. J Clin Oncol. 2008;26:5269-5274.

59. Demetri GD, Schöffski P, Grignani G, et al. Activity of eribulin in patients with advanced liposarcoma demonstrated in a subgroup analysis from a randomized phase III study of eribulin versus dacarbazine [published correction appears in J Clin Oncol. 2018;36(4):432]. J Clin Oncol. 2017;35:3433-3439.

60. D'Angelo SP, Mahoney MR, Van Tine BA, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol. 2018;19:416-426.

61. Florou V, Rosenberg AE, Wieder E, et al. Angiosarcoma patients treated with immune checkpoint inhibitors: a case series of seven patients from a single institution [published correction appears in J Immunother Cancer. 2019;7(1):285]. J Immunother Cancer. 2019;7:213.

62. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol. 2017;18:1493-1501.

63. Choong PF, Pritchard DJ, Rock MG, et al. Survival after pulmonary metastasectomy in soft tissue sarcoma. Prognostic factors in 214 patients. Acta Orthop Scand. 1995;66:561-568.

64. Vogt-Moykopf I, Bülzebruck H, Merkle NM, et al. Results of surgical treatment of pulmonary metastases. Eur J Cardiothorac Surg. 1988;2:224-232.

65. Gradishar WJ, Anderson BO, Balassanian R, et al. Breast Cancer, Version 4.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16:310-320.

66. Kapiris I, Nasiri N, A'Hern R, et al. Outcome and predictive factors of local recurrence and distant metastases following primary surgical treatment of high-grade malignant phyllodes tumours of the breast. Eur J Surg Oncol. 2001;27:723-730.

67. Lu Y, Chen Y, Zhu L, et al. Local recurrence of benign, borderline, and malignant phyllodes tumors of the breast: a systematic review and meta-analysis. Ann Surg Oncol. 2019;26:1263-1275.

68. Moo TA, Alabdulkareem H, Tam A, et al. Association Between recurrence and re-excision for close and positive margins versus observation in patients with benign phyllodes tumors. Ann Surg Oncol. 2017;24:3088-3092.

69. Rosenberger LH, Thomas SM, Nimbkar SN, et al. Contemporary Multi-Institutional Cohort of 550 Cases of Phyllodes Tumors (2007-2017) Demonstrates a Need for More Individualized Margin Guidelines. J Clin Oncol. 2021;39:178-189.

70. Macdonald OK, Lee CM, Tward JD, et al. Malignant phyllodes tumor of the female breast: association of primary therapy with cause-specific survival from the Surveillance, Epidemiology, and End Results (SEER) program. Cancer. 2006;107:2127-2133.

71. Barth RJ Jr., Wells WA, Mitchell SE, et al. A prospective, multi-institutional study of adjuvant radiotherapy after resection of malignant phyllodes tumors. Ann Surg Oncol. 2009;16:2288-2294.

72. Zeng S, Zhang X, Yang D, et al. Effects of adjuvant radiotherapy on borderline and malignant phyllodes tumors: a systematic review and meta-analysis. Mol Clin Oncol. 2015;3:663-671.

73. Mangi AA, Smith BL, Gadd MA, et al. Surgical management of phyllodes tumors. Arch Surg. 1999;134:487-492, NaN-493.

74. Barrio AV, Clark BD, Goldberg JI, et al. Clinicopathologic features and long-term outcomes of 293 phyllodes tumors of the breast. Ann Surg Oncol. 2007;14:2961-2970.

75. Telli ML, Horst KC, Guardino AE, et al. Phyllodes tumors of the breast: natural history, diagnosis, and treatment. J Natl Compr Canc Netw. 2007;5:324-330.

76. Morales-Vásquez F, Gonzalez-Angulo AM, Broglio K, et al. Adjuvant chemotherapy with doxorubicin and dacarbazine has no effect in recurrence-free survival of malignant phyllodes tumors of the breast. Breast J. 2007;13:551-556.

77. Scow JS, Reynolds CA, Degnim AC, et al. Primary and secondary angiosarcoma of the breast: the Mayo Clinic experience. J Surg Oncol. 2010;101:401-407.

78. Lahat G, Dhuka AR, Lahat S, et al. Outcome of locally recurrent and metastatic angiosarcoma. Ann Surg Oncol. 2009;16:2502-2509.

79. Rosen PP, Kimmel M, Ernsberger D. Mammary angiosarcoma. The prognostic significance of tumor differentiation. Cancer. 1988;62:2145-2151.

80. Sher T, Hennessy BT, Valero V, et al. Primary angiosarcomas of the breast. Cancer. 2007;110:173-178.

81. Fata F, O'Reilly E, Ilson D, et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. Cancer. 1999;86:2034-2037.
82. Skubitz KM, Haddad PA. Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. Cancer. 2005;104:361-366.
83. Brenn T, Fletcher CD. Postradiation vascular proliferations: an increasing problem. Histopathology. 2006;48:106-114.
84. Brenn T, Fletcher CD. Radiation-associated cutaneous atypical vascular lesions and angiosarcoma: clinicopathologic analysis of 42 cases. Am J Surg Pathol. 2005;29:983-996.
85. Fodor J, Orosz Z, Szabó E, et al. Angiosarcoma after conservation treatment for breast carcinoma: our experience and a review of the literature. J Am Acad Dermatol. 2006;54:499-504.
86. Li GZ, Fairweather M, Wang J, et al. Cutaneous radiation-associated breast angiosarcoma: radicality of surgery impacts survival. Ann Surg. 2017;265:814-820.
87. Mella JR, Ross KM, Li GZ, et al. Cutaneous breast radiation-associated angiosarcoma: anterior chest wall reconstruction options following extra-radical resection. Plast Reconstr Surg Glob Open. 2018;6:e1938.
88. Palta M, Morris CG, Grobmyer SR, et al. Angiosarcoma after breast-conserving therapy: long-term outcomes with hyperfractionated radiotherapy. Cancer. 2010;116:1872-1878.
89. Sheth GR, Cranmer LD, Smith BD, et al. Radiation-induced sarcoma of the breast: a systematic review. Oncologist. 2012;17:405-418.
90. Bonvalot S, Ternès N, Fiore M, et al. Spontaneous regression of primary abdominal wall desmoid tumors: more common than previously thought. Ann Surg Oncol. 2013;20:4096-4102.
91. Gounder MM, Mahoney MR, Van Tine BA, et al. Sorafenib for advanced and refractory desmoid tumors. N Engl J Med. 2018;379:2417-2428.
92. Ballo MT, Zagars GK, Pollack A, et al. Desmoid tumor: prognostic factors and outcome after surgery, radiation therapy, or combined surgery and radiation therapy. J Clin Oncol. 1999;17:158-167.
93. Salas S, Dufresne A, Bui B, et al. Prognostic factors influencing progression-free survival determined from a series of sporadic desmoid tumors: a wait-and-see policy according to tumor presentation. J Clin Oncol. 2011;29:3553-3558.
94. Mullen JT, Delaney TF, Kobayashi WK, et al. Desmoid tumor: analysis of prognostic factors and outcomes in a surgical series. Ann Surg Oncol. 2012;19:4028-4035.
95. Keus RB, Nout RA, Blay JY, et al. Results of a phase II pilot study of moderate dose radiotherapy for inoperable desmoid-type fibromatosis--an EORTC STBSG and ROG study (EORTC 62991-22998). Ann Oncol. 2013;24:2672-2676.
96. Spear MA, Jennings LC, Mankin HJ, et al. Individualizing management of aggressive fibromatoses. Int J Radiat Oncol Biol Phys. 1998;40:637-645.
97. Merchant NB, Lewis JJ, Woodruff JM, et al. Extremity and trunk desmoid tumors: a multifactorial analysis of outcome. Cancer. 1999;86:2045-2052.
98. Nishida Y, Tsukushi S, Shido Y, et al. Transition of treatment for patients with extra-abdominal desmoid tumors: nagoya university modality. Cancers (Basel). 2012;4:88-99.
99. Kinzbrunner B, Ritter S, Domingo J, et al. Remission of rapidly growing desmoid tumors after tamoxifen therapy. Cancer. 1983;52:2201-2204.
100. Toulmonde M, Pulido M, Ray-Coquard I, et al. Pazopanib or methotrexate-vinblastine combination chemotherapy in adult patients with progressive desmoid tumours (DESMOPAZ): a non-comparative, randomised, open-label, multicentre, phase 2 study. Lancet Oncol. 2019;20:1263-1272.
101. de Camargo VP, Keohan ML, D'Adamo DR, et al. Clinical outcomes of systemic therapy for patients with deep fibromatosis (desmoid tumor). Cancer. 2010;116:2258-2265.
102. Patel SR, Evans HL, Benjamin RS. Combination chemotherapy in adult desmoid tumors. Cancer. 1993;72:3244-3247.
103. Azzarelli A, Gronchi A, Bertulli R, et al. Low-dose chemotherapy with methotrexate and vinblastine for patients with advanced aggressive fibromatosis. Cancer. 2001;92:1259-1264.
104. Jimeno A, Gordon M, Chugh R, et al. A first-in-human phase I study of the anticancer stem cell agent ipafricept (OMP-54F28), a decoy receptor for Wnt ligands, in patients with advanced solid tumors. Clin Cancer Res. 2017;23:7490-7497.
105. Kummar S, O'Sullivan Coyne G, Do KT, et al. Clinical activity of the γ-secretase inhibitor PF-03084014 in adults with desmoid tumors (aggressive fibromatosis). J Clin Oncol. 2017;35:1561-1569.
106. Mituś JW, Blecharz P, Walasek T, et al. Treatment of patients with distant metastases from phyllodes tumor of the breast. World J Surg. 2016;40:323-328.
107. Parkes A, Wang W-L, Patel S, et al. Outcomes of systemic therapy in metastatic phyllodes tumor of the breast [published online ahead of print 11 Feb 2021]. Breast Cancer Res Treat.
108. Hawkins RE, Schofield JB, Wiltshaw E, et al. Ifosfamide is an active drug for chemotherapy of metastatic cystosarcoma phyllodes. Cancer. 1992;69:2271-2275.
109. Italiano A, Cioffi A, Penel N, et al. Comparison of doxorubicin and weekly paclitaxel efficacy in metastatic angiosarcomas. Cancer. 2012;118:3330-3336.
110. Ray-Coquard IL, Domont J, Tresch-Bruneel E, et al. Paclitaxel given once per week with or without bevacizumab in patients with advanced angiosarcoma: a randomized phase II trial. J Clin Oncol. 2015;33:2797-2802.
111. Stacchiotti S, Palassini E, Sanfilippo R, et al. Gemcitabine in advanced angiosarcoma: a retrospective case series analysis from the Italian Rare Cancer Network. Ann Oncol. 2012;23:501-508.
112. Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. J Clin Oncol. 2009;27:3133-3140.
113. Ray-Coquard I, Italiano A, Bompas E, et al; French Sarcoma Group (GSF/GETO). Sorafenib for patients with advanced angiosarcoma: a phase II Trial from the French Sarcoma Group (GSF/GETO). Oncologist. 2012;17:260-266.

Disparities in Cancer Care: The Example of Sarcoma—In Search of Solutions for a Global Issue

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Overview

Disparities in health care have an adverse effect on the outcome of disadvantaged patients with cancer. Patients may be at a disadvantage because of geographic isolation; insurance status; or racial, ethnic, or other factors. In this article, we examine how disparities affect the care of patients with sarcoma in the United States, Canada, and the Asia-Pacific region. Because of the rarity of sarcomas and their challenging diagnosis and complex treatment patterns, some professional or national guidelines stipulate that patients with sarcoma should be treated at centers of expertise by multidisciplinary teams. This recommendation, based on published evidence, is not always applicable because of various sociopolitical or patient-related factors. We are proposing solutions to overcome these obstacles in a practical and patient-centered way while acknowledging that disparities exist among countries as well as within any country.

INTRODUCTION

Sarcomas are rare cancers arising from mesenchymal tissue. Bone and soft tissue sarcomas encompass at least 175 distinct histologic subtypes, with varying clinical behaviors and oncologic outcomes. Their rarity and histologic heterogeneity pose a great challenge in diagnosis and management.[1] For instance, although patients diagnosed with extremity sarcoma present relatively early in the disease process, those diagnosed with retroperitoneal sarcoma present later, because the course of disease is indolent and involves marked growth before notable symptoms. These diseases require an approach by a multidisciplinary team "with extensive expertise and experience in the treatment of sarcoma," according to the National Comprehensive Cancer Network.[2] This recommendation comes from data that fairly consistently show improved sarcoma outcomes at a center with expertise,[3,4] although studies are hampered by accounting for case mix and confounding variables and by trouble defining expertise. In this article, we review disparities in sarcoma care in North America (Canada and the United States) and provide some remarks about the Asia-Pacific region.

Referral Centers and Regionalization of Care

Given the challenges in the diagnosis of sarcoma and the complexity of its treatment, it is crucial to obtain the input of experienced radiologists, pathologists, surgeons, medical oncologists, and radiation oncologists in the setting of a multidisciplinary tumor board. Sarcomas should ideally be treated at a high-volume referral center with the expertise to provide such care.[5] Multiple analyses of the National Cancer Database found that, in the United States, there were significantly improved oncologic outcomes in patients with soft tissue sarcoma undergoing treatment at high-volume centers,[6-8] even when this care necessitated travel.[9] Most studies have used case volume as a surrogate for expertise.[10] The definition of high-volume sites has varied; it is sometimes defined as sites in the 99th percentile for volume, but it generally includes sites that see more than five to 20 (de novo, surgical) cases per year. Regionalization of care and the establishment of clear guidelines are associated with improved outcomes in European countries, such as France.[11]

In Canada, there are established referral centers in each province to which all patients have access, and mandates in most provinces regionalize and establish corridors of care. Because of the oversight by provincial agencies, the care provided in these centers tends to be uniform, evidence based, and consensus driven. Moreover, thanks to organizations such as the Canadian Cancer Trials Group, many regional centers offer patients enrollment in high-quality trials, facilitating access to cutting-edge treatments.

However, access to treatment can be geographically and economically challenging, especially in Canada, where distance traveled to a referral center is extremely variable. In the United States, where centralized sarcoma care is not mandated, most patients with sarcoma are still treated at low-volume sites. National Cancer Database analyses estimate this proportion to be between 83% and 95% (depending on the sarcoma

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PRACTICAL APPLICATIONS

- Because not all patients with sarcoma can be treated at centers of expertise, it is necessary to find creative ways for them to benefit from these centers when they have no access.
- Benefits can be achieved by improving utilization of centers of expertise or improving decentralized care through collaboration.
- Telemedicine can be used as a tool to enhance national or international collaboration.

subtype and the definition of high-volume center).[12] Because the National Cancer Database only includes patients treated at Commission on Cancer–affiliated sites (approximately 30% of cancer cases), the percentage seen at high-volume sites is almost assuredly even lower. The concept of distance decay (i.e., the oncologic outcomes of patients decrease the farther away they live from a referral center) has been shown for several malignancies, including sarcoma.[13] If care and outcomes are better at specialized, regionalized centers of excellence, then patients with sarcoma who reside a distance from these sites are disadvantaged, either because they are less likely to travel for that care, or, if they do travel, because they will bear greater associated financial and psychosocial burdens. Clearly, issues remain with regard to ensuring access and receipt of care at these centers. To remove this disparity, two approaches can be taken.

Improve Utilization of Centers of Excellence

Clarify definition of centers of excellence Given the low number of sites that meet the criteria of high volume, there is opportunity to clarify and expand the definition of centers of excellence. The Sarcoma Alliance for Research through Collaboration has 85 U.S. institutions that are deemed centers with expertise, but there has been no assessment of whether treatment at one of these centers results in improved outcomes or whether they are accessible to a majority of the population. The sarcoma advocacy and professional communities should work together to analyze geographic disparities, such as has been done in France,[14] and creatively develop incentives that would create more accessible options for centralized high-quality care. In addition, efforts to further define and accredit centers of expertise may clarify guidelines that encourage referral, similar to the development of the Foundation for the Accreditation of Cellular Therapy in blood and marrow transplantation centers.

Educate primary care physicians about diagnosis and referral There is no screening test for sarcoma, so the timeliness of diagnosis depends on initial medical providers recognizing and appropriately working up the condition. Occurring in various forms throughout the body, sarcoma can present nonspecifically; the first symptoms are often misattributed to other musculoskeletal conditions or benign lesions (e.g., lipomas). Educating primary care providers to recognize the symptoms of sarcoma and to refer appropriately is a daunting task, given the number and variety of providers that patients with sarcoma may first see with symptoms. In the United Kingdom, a national sarcoma advocacy group has developed a provider awareness campaign and sponsored the development of an open-access training module.[15]

Promote patient awareness and study patient-reported barriers It is likely that many patients with sarcoma are never made aware of the possible differential outcome benefits of care at a center of excellence, although it is not clear that this knowledge overcomes preference for local care. A few studies in the United States have presented hypothetical vignettes to patients, asking whether they would be willing to travel to improve outcomes; the results suggest that factors other than raw outcome differences are considered.[14,16,17] Receipt of care in a distant site requires financial and other costs that can be considered unaffordable: travel time and expense, possible need for lodging and food, reliable transportation, additional time away from work, and additional time away from childcare responsibilities. These burdens may be prohibitive or, even if overcome, may leave the remote patient with unequal financial hardship, not to mention other psychosocial stress. In the United Kingdom, where guidelines have increasingly mandated centralization of care, a 2015 patient experience study,[18] in which 90% of patients were treated by a sarcoma specialist team and half of patients had to travel more than 20 miles for treatment, found that 90% of patients did not mind traveling. However, a robust survey of patients with sarcoma who have not traveled to be treated by specialists would be required to fully understand the patient values and preferences needed to overcome logistic and financial issues. Programs offered by charities, such as the Canadian Cancer Society, help Canadian residents with transportation and housing while they receive lengthy chemotherapy and radiotherapy treatments away from home.

Improve Decentralized Care to Those Who Do Not Travel

The disparities noted here can be mitigated by strengthening the seamless transfer of care of patients with sarcoma. Constant communication with primary care physicians, as well as access to telemedicine, can improve access to care even more and limit the pecuniary burden of care in referral centers.

There is a need to improve care when the patient does not physically receive all care at the center of expertise. Although this approach may be perceived as mixed

messaging, because guidelines promote centralized care, it is a reality that, given the substantial and real barriers, not all patients will be able or willing to receive any or all of their care at these centers, and efforts should be made to minimize compromised outcomes. The most practical approach in these cases is to pursue a hybrid approach, finding a way to support the patient by delivering the most important components of care at the center of excellence and facilitating the quality delivery of remaining therapy closer to home. An important finding of one study, by Bagaria et al,[19] in extra-abdominal soft tissue sarcoma was that, although high-volume hospitals more often adhere to treatment guidelines (significantly so for stage III tumors), low-volume hospitals that followed national guidelines achieved comparable outcomes.

Centralized pathology review Many studies have identified difficulties with accurate pathologic diagnosis in sarcomas. On expert review, up to 40% of cases were considered incorrectly diagnosed[2,20]; errors involved underestimating and overestimating the malignant nature, resulting in the risk of inadequate treatment. National Comprehensive Cancer Network guidelines recommend that "pathologic assessment of biopsies and resection specimens should be carried out by an experienced sarcoma pathologist."[2] Centralized or expert pathology review is a relatively feasible procedure that does not require patient travel and is likely cost saving.[21] Barriers include insurance coverage or out-of-pocket cost for uninsured patients, delay in the start of treatment, and pathologist reluctance, but other countries can be models of successfully overcoming these barriers. In addition to the French experience, England has established designated Specialized Sarcoma Pathologists who take part in external quality-assurance schemes and have an informal network for slide and peer review.[22]

Centralized surgery for appropriate cases Because appropriate surgical resection is such a powerful predictor of outcome for soft tissue sarcoma, it is not surprising that patients having surgery at low-volume sites have worse outcomes.[11] Studies have shown that rates of complete (R0) resection are lower at remote or low-volume centers. Soft tissue sarcoma can be resected by a variety of general and specialty surgeons. Fewer than 10% of suspicious lumps will be malignant; if all these were initially referred to a sarcoma surgeon, the burden on the patients and the specialist would be onerous. Some studies have been done to delineate an algorithm that would appropriately flag likely malignant soft tissue tumors (size $>$ 5 cm, rapid increase in size, location deep to fascia, pain). Efforts should be made to improve, disseminate, and test the efficacy of such diagnostic algorithms for community surgeons. It is unclear whether there is a threshold of cost savings or patient outcomes that would influence practice policy or changes to insurance coverage in the United States or other countries.

Support and education of local oncologists Care and case discussion via a multidisciplinary team or a tumor board are believed to be essential to sarcoma outcomes.[23,24] Improving the expertise and comfort of remote oncologists is likely best accomplished with ongoing, case-based support. The wider acceptance of telemedicine and teleconferencing in the last year, as a result of the restrictions imposed by the COVID-19 pandemic, should open large doors for remote dissemination of sarcoma expertise,[25] especially because the benefit has already been proven in other settings. In the United States, the Extension for Community Healthcare Outcomes,[26] which was initially developed to support remote physicians treating hepatitis through monthly case conferences and education by a centralized expert gastroenterologist, has now been expanded and proven effective in multiple other fields and settings and could be the platform for supporting sarcoma care in remote areas.

Psychosocial support and resources for remote patients Sarcoma therapy may be offered or attempted locally, but the patient may not have access to appropriate psychosocial support to start or complete therapy. Multiple studies have shown that geographic barriers disproportionately affect patients of low socioeconomic status, racial minorities, or those who lack private insurance—so those with perhaps the greatest needs cannot access the support services of a tertiary center.[27] Without multidisciplinary ancillary services, such as social work, therapists, and navigators, patients may not be aware of or access resources that would make treatment financially, pragmatically, or emotionally feasible. Efforts to provide decentralized psychosocial support to patients with sarcoma have been successful in England and Australia by placement of remote "key workers" or nurse navigators.[28] Some ancillary services, such as fertility preservation or prosthetic shops, are also centralized; presumably, remote patients with sarcoma have less access to these services that can improve quality of life. Again, the COVID-19 pandemic has resulted in increased availability of technology benefiting remote patients with cancer, including access to telepsychiatry and an enormous increase in the utilization of online support groups. This availability should dramatically increase access to the resources and support needed to complete therapy.

Ethnic and Racial Disparities

Multiple population studies in the United States based on the Surveillance, Epidemiology, and End Results program or the National Cancer Database have identified racial disparities in sarcoma-specific survival and other oncologic endpoints. In Canada, given the rarity of these tumors and the comparatively smaller population, racial and ethnic disparities have not been identified in the context of sarcoma care specifically. However, disparities and health inequities have been identified in high-risk populations with

regard to other, more common cancers, such as lung, breast, and ovarian cancers,[22] and they are likely present for sarcomas as well. Indeed, the Indigenous population has decreased access and utilization of health care services, leading to decreased survival in 14 of the 15 most common cancers, even after accounting for socioeconomic status and rurality.[28] Community partnerships are key in improving these outcomes; Ontario, for example, has established a three-phased Aboriginal Cancer Strategy to improve cancer-control strategies with tailored programs.

Another high-risk health disparity group is immigrants, who, as an example, constitute approximately 20% of the Canadian population and significantly underutilize the health care system, especially cancer-screening programs, with an impact on cancer survival.[29,30] This underutilization can be due to a language barrier, education level, or poor socioeconomic status. Additional research must address these issues in sarcoma care in Canada and elsewhere.

INSURANCE STATUS

In countries with a predominance of privately insured care, patient outcomes can vary according to insurance status. A recent study of the Surveillance, Epidemiology, and End Results program database of patients with extremity sarcoma identified that disparities in insurance status were associated with an increased risk for metastatic stage at diagnosis, decreased rate of limb-salvage procedures, and decreased disease-specific survival.[31] The Canadian health care system is based on universal access for all Canadian citizens and permanent residents, free of charge. Health care is a provincial mandate; thus, each province allocates resources and establishes its own guidelines in terms of resource management. Yet, disparities can occur when it comes to access of novel systemic treatments that are not provincially reimbursed and, thus, must be covered by the patient's medication insurance, which is mandatory in many provinces.

The great advantage of such a health care system is the improved access to treatment and to optimal care independent of the patient's age, employment status, or financial situation. Although one might be concerned about the delays that can be incurred at every step of the diagnosis in a fully public-funded system, provincial health agency requirements ensure that each component of care is performed within a timely fashion according to pre-existing guidelines.

THE ASIA-PACIFIC REGION

The Asia-Pacific region, comprising 45 countries, is the most diverse and populous on earth. Much of this diversity is relevant to health outcomes, including cancer. The following data were extracted from the World Health Organization[32] and the World Bank.[33] It is critical to note that the quality of data collection varies by country. For example, there are no data recorded on gross domestic product for the World Bank for Afghanistan between 1982 and 2002 or from North Korea at all.

The Asia-Pacific region comprises more than 4.2 billion people, or 54% of the global population. The subregions range in population size from 11,650 people (Tuvalu) to 1.4 billion (China). Population growth in the region has been among the highest on the planet, and the Asia-Pacific region contains the three largest populations globally: China, India, and Indonesia. Populations vary in size as well as in ethnicity. Government types vary from autocracy through single-party systems to parliamentary democracies. The per capita gross domestic product also varies strikingly across the Asia-Pacific region from low-income Micronesia (US $631) and Nepal (US $1,071) to middle-income India (US $2,099), Papua New Guinea (US $2,434), and China (US $10,261) and high-income Singapore, Australia, Japan, and South Korea (more than US $44,671; 2017 data).

These demographic, political, and economic features are immediately relevant to health outcomes, which also vary enormously across the region. In 2018, life expectancy in Papua New Guinea was 64.3 years, compared with 83.1 years in Singapore. Among low-income countries, life expectancy is 63.5 years, compared with 80.7 years for nations with high-income status. However, life expectancy is changing rapidly, increasing in Nepal from age 62.3 in 2000 to age 70.5 in 2018. Unsurprisingly, the contribution of cancer to health outcomes and life expectancy also varies enormously. Among low-income countries, six of the top 10 causes of death are infectious (HIV, tuberculosis, malaria), whereas communicable, maternal, and perinatal causes of death account for 65% of mortality. Cancer is not in the top 20 causes of death; it accounts for 3.9% of deaths. Among high-income countries, cancer accounts for four of the top 10 causes of death (lung, bowel, breast, and stomach), and infectious illness (lower respiratory tract infections) accounts for only one of the top 10 causes. Communicable, maternal, and perinatal causes account for 6.6% of deaths in higher-income countries, whereas cancer accounts for 25% of deaths. Indeed, cancer is now the leading cause of death in high-income countries.[34] These factors determine the priorities for health systems in addressing the challenge of cancer.

The patterns of cancer vary strikingly across the Asia-Pacific region, as determined by poorly understood genetic and environmental differences. For example, although breast, bowel, and lung cancers are among the leading types of cancer in Australia and New Zealand, in the Western Pacific region, liver and stomach cancers are important causes of cancer mortality. Many cancers associated with infectious diseases are more common and more lethal in the

Asia-Pacific region; examples include nasopharyngeal cancer (Epstein-Barr virus), liver cancer (hepatitis B and C viruses), bladder cancer (schistosomiasis), and cervical cancer (HPV). In Papua New Guinea, cervical cancer is more common than breast cancer as a leading cause of death in women younger than age 50.[35] This fact reflects social determinants of the transmission of HPV, the absence of public health measures (Papanicolaou screening, vaccination), and limited resources for cancer treatment. Other distinctive cancer patterns appear genetically determined. For example, *EGFR* mutation–positive non–small cell lung cancer in young, nonsmoking Asian women appears linked to distinct loci in genome-wide association studies.[36]

Disparities in cancer outcomes exist within countries in the Asia-Pacific region as well as between them. Within Australia, a high-income nation with excellent overall cancer outcomes, Indigenous populations are 40% more likely to die from cancer than are non-Indigenous Australians.[37] In New Zealand, Maori populations have poorer outcomes for 23 of 24 of the most common causes of cancer death.[38] The excess mortality is partially attributed to persistent social disadvantage, despite the efforts of the relevant health systems.

Rare cancers, including sarcomas, represent particularly problematic challenges to health care, including in the Asia-Pacific region.[39] Concentrated expertise in diagnosis, imaging, surgery, radiotherapy, and systemic therapy for sarcomas are essential for optimal outcomes. Molecular pathology and genomics are only partially accessible in high-income countries. In countries such as Papua New Guinea, simple histologic diagnosis of osteosarcoma is performed by a limited number of laboratories for the entire country, often not in a timeframe consistent with optimal treatment. Volume-dependent, sarcoma-specific surgical expertise, including the intraoperative, anesthetic, and postoperative support resources to perform limb-salvage procedures, is limited by context in low-income countries. Low-income countries have limited access to linear accelerators and may depend on older cobalt machines, without access to advanced planning and simulation. The affordability of systemic therapies is a persistent issue, driving the use of generic agents and affecting the choice of agents. In addition, the ability to record outcomes accurately is a key feature of quality-driven outcomes and is likely limited by income status. In countries without single-payer, government-supported health care, access to optimal care may be affordable privately, creating issues of equity of access. The global trend for rare cancers toward personalized medicine, with its progressive dependence on genomics and access to targeted therapies, is likely to exacerbate differences between countries in the Asia-Pacific region in particular.

Research is fundamental to state-of-the-art care for patients with sarcoma. There are active cooperative clinical research organizations focused on sarcoma in the Asia-Pacific region, including the Australian and New Zealand Sarcoma Association and the Asian Sarcoma Consortium, which have broad membership of oncologists from higher-income countries in the Asia-Pacific region.[40]

Economic and population growth in the Asia-Pacific region will dominate the global landscape in the 21st century. Among global giants, China has increased its per capita gross domestic product more than 10-fold since 2000, and India's has increased almost 4.8-fold. Health is a fundamental human good; as the per-capita wealth of countries expands, it will likely drive investment from and engagement with the global pharmaceutical industry. However, this engagement is also determined by politics and international law. Economic and population growth may increase the likelihood of major conflicts in the Asia-Pacific region, which will have adverse effects on health systems. Drug development globally depends on international patent law and trade agreements. Low- and middle-inome countries have to balance protecting intellectual property rights and satisfying the health needs of their populations. An example of this balance was the Indian patent office's rejection of the Novartis patent for imatinib, a decision upheld by the Indian Supreme Court in 2013.[41] This balance will shift as the economic development of countries, such as India and China, incorporates vibrant pharmaceutical and high-tech industries.

CONCLUSION

Improvement in cancer-treatment outcomes requires increasingly complex diagnostic and treatment procedures, which have variable availability between countries and even within countries. The best outcomes are obtained through treatment given by multidisciplinary teams in centers of expertise, especially for rare tumors, such as sarcomas. This ideal model is not always possible because of sociopolitical or patient-related reasons, whether in high-income or low-income areas. Even in countries with uniform universal health care and accessible regional centers, disparities in care can still occur secondary to distance, education, and socioeconomic status as well as racial and ethnic factors. Several solutions have been tested in different countries and can be applied to help patients take advantage of that expertise, even partially, to reduce disparities. The current trend of telemedicine could facilitate these exchanges at a national or an international level.

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REFERENCES

1. Dumitra S, Gronchi A. The diagnosis and management of retroperitoneal sarcoma. Oncology (Williston Park). 2018;32:464-469.
2. von Mehren M, Randall RL, Benjamin RS, et al. Soft tissue sarcoma, version 2.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16:536-563.
3. Sandrucci S, Trama A, Quagliuolo V, et al. Accreditation for centers of sarcoma surgery. Updates Surg. 2017;69:1-7.
4. Derbel O, Heudel PE, Cropet C, et al. Survival impact of centralization and clinical guidelines for soft tissue sarcoma: a prospective and exhaustive population-based cohort. PLoS One. 2017;12:e0158406.
5. Trans-Atlantic RPS Working Group. Management of recurrent retroperitoneal sarcoma (RPS) in the adult: a consensus approach from the Trans-Atlantic RPS Working Group [published correction appears in Ann Surg Oncol. 2017;24(suppl 3):688-689]. Ann Surg Oncol. 2016;23:3531-3540.
6. Villano AM, Zeymo A, McDermott J, et al. Regionalization of retroperitoneal sarcoma surgery to high-volume hospitals: missed opportunities for outcome improvement. J Oncol Pract. 2019;15:e247-e261.
7. Bagaria SP, Neville M, Gray RJ, et al. The volume-outcome relationship in retroperitoneal soft tissue sarcoma: evidence of improved short- and long-term outcomes at high-volume institutions. Sarcoma. 2018;2018:3056562.
8. Lazarides AL, Kerr DL, Nussbaum DP, et al. Soft tissue sarcoma of the extremities: what is the value of treating at high-volume centers? Clin Orthop Relat Res. 2019;477:718-727.
9. Schmitz R, Adam MA, Blazer DG III. Overcoming a travel burden to high-volume centers for treatment of retroperitoneal sarcomas is associated with improved survival. World J Surg Oncol. 2019;17:180.
10. Venigalla S, Nead KT, Sebro R, et al. Association between treatment at high-volume facilities and improved overall survival in soft tissue sarcomas. Int J Radiat Oncol Biol Phys. 2018;100:1004-1015.
11. Blay JY, Honoré C, Stoeckle E, et al. Surgery in reference centers improves survival of sarcoma patients: a nationwide study. Ann Oncol. 2019;30:1407.
12. Adam MA, Moris D, Behrens S, et al. Hospital volume threshold for the treatment of retroperitoneal sarcoma. Anticancer Res. 2019;39:2007-2014.
13. Reddy VK, Jain V, Venigalla S, et al. Radiotherapy remains underused in the treatment of soft-tissue sarcomas: disparities in practice patterns in the United States. J Natl Compr Canc Netw. Epub 8 Feb 2021.
14. Fayet Y, Coindre JM, Dalban C, et al. Geographical accessibility of the referral networks in France. Intermediate results from the IGéAS Research Program. Int J Environ Res Public Health. 2018;15:2204.
15. BMJ Learning. Lumps, Bumps, and Sarcomas: A Guide. https://new-learning.bmj.com/course/10050381. Accessed February 9, 2021.
16. Bühn S, Holstiege J, Pieper D. Are patients willing to accept longer travel times to decrease their risk associated with surgical procedures? A systematic review. BMC Public Health. 2020;20:253.
17. Finlayson SR, Birkmeyer JD, Tosteson AN, et al. Patient preferences for location of care: implications for regionalization. Med Care. 1999;37:204-209.
18. Sarcoma UK. The National Sarcoma Survey 2015. https://sarcoma.org.uk/sites/default/files/resources/sarcoma_uk_patient_survey_report_digital_version_0.pdf. Accessed February 9, 2021.
19. Bagaria SP, Chang YH, Gray RJ, et al. Improving long-term outcomes for patients with extra-abdominal soft tissue sarcoma regionalization to high-volume centers, improved compliance with guidelines or both? Sarcoma. 2018;2018:8141056.
20. Rupani A, Hallin M, Jones RL, et al. Diagnostic differences in expert second-opinion consultation cases at a tertiary sarcoma center. Sarcoma. 2020; 2020:9810170.
21. Perrier L, Rascle P, Morelle M, et al. The cost-saving effect of centralized histological reviews with soft tissue and visceral sarcomas, GIST, and desmoid tumors: the experiences of the pathologists of the French Sarcoma Group. PLoS One. 2018;13:e0193330.
22. National Institute for Health and Clinical Excellence. Improving Outcomes for People With Sarcoma. www.nice.org.uk/guidance/csg9/documents/improving-outcomes-for-people-with-sarcoma-all-recommendations2. Accessed February 9, 2021.
23. Siegel GW, Biermann JS, Chugh R, et al. The multidisciplinary management of bone and soft tissue sarcoma: an essential organizational framework. J Multidiscip Healthc. 2015;8:109-115.

24. Blay JY, Soibinet P, Penel N, et al. Improved survival using specialized multidisciplinary board in sarcoma patients. Ann Oncol. 2017;28:2852-2859.
25. Rajasekaran RB, Whitwell D, Cosker TDA, et al. Will virtual multidisciplinary team meetings become the norm for musculoskeletal oncology care following the COVID-19 pandemic? Experience from a tertiary sarcoma centre. BMC Musculoskelet Disord. 2021;22:18.
26. The University of New Mexico School of Medicine. Project ECHO. https://hsc.unm.edu/echo/. Accessed February 9, 2021.
27. Keung EZ, Chiang Y-J, Cormier JN, et al. Treatment at low-volume hospitals is associated with reduced short-term and long-term outcomes for patients with retroperitoneal sarcoma. Cancer. 2018;124:4495-4503.
28. Ahmed S, Shahid RK. Disparity in cancer care: a Canadian perspective. Curr Oncol. 2012;19:e376-e382.
29. Withrow DR, Pole JD, Nishri ED, et al. Cancer survival disparities between First Nation and non-Aboriginal adults in Canada: follow-up of the 1991 Census Mortality Cohort. Cancer Epidemiol Biomarkers Prev. 2017;26:145-151.
30. Wang AMQ, Yung EM, Nitti N, et al. Breast and colorectal cancer screening barriers among immigrants and refugees: a mixed-methods study at three community health centres in Toronto, Canada. J Immigr Minor Health. 2019;21:473-482.
31. Smartt AA, Jang ES, Tyler WK. Is there an association between insurance status and survival and treatment of primary bone and extremity soft-tissue sarcomas? A SEER database study. Clin Orthop Relat Res. 2020;478:527-536.
32. World Health Organization. Global Health Estimates: Life Expectancy and Leading Causes of Death and Disability. www.who.int/data/gho/data/themes/mortality-and-global-health-estimates. Accessed January 20, 2021.
33. The World Bank. GDP Per Capita (current US$). https://data.worldbank.org/indicator/NY.GDP.PCAP.CD. Accessed January 20, 2021.
34. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. Epub 2021 Feb 4.
35. International Agency for Research on Cancer. Cervix Uteri. http://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf. Accessed February 10, 2021.
36. Seow WJ, Matsuo K, Hsiung CA, et al. Association between GWAS-identified lung adenocarcinoma susceptibility loci and EGFR mutations in never-smoking Asian women, and comparison with findings from Western populations. Hum Mol Genet. 2017;26:454-465.
37. Australian Institute of Health and Welfare. Cancer in Aboriginal & Torres Strait Islander People of Australia. www.aihw.gov.au/reports/cancer/cancer-in-indigenous-australians/contents/table-of-contents. Accessed February 10, 2021.
38. Gurney J, Stanley J, McLeod M, et al. Disparities in cancer-specific survival between Māori and non-Māori New Zealanders, 2007-2016. JCO Glob Oncol. 2020;6:766-774.
39. Lewin J, Puri A, Quek R, et al. Management of sarcoma in the Asia-Pacific region: resource-stratified guidelines. Lancet Oncol. 2013;14:e562-e570.
40. Poon E, Quek R. Soft tissue sarcoma in Asia. Chin Clin Oncol. 2018;7:46.
41. Global Health & Human Rights Database. Novartis AG v. Union of India. www.globalhealthrights.org/pdf.php?ID=3755. Accessed February 10, 2021.

SYMPTOMS AND SURVIVORSHIP

Telehealth Strategies to Support Patients and Families Across the Cancer Trajectory

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overview

Effective delivery of cancer care via telehealth requires a planned care system that accounts for myriad patient, provider, and practice/cancer center resources before, during, and after the care episode. Telehealth is broadly defined as a method to have virtual, bidirectional communication between patients and providers. Telehealth can include methods such as audio-only, video-consultation, and tele-monitoring, which can occur in a synchronous, asynchronous, or blended format. The purpose of this review is to present common foundational principles for providing clinical cancer care via telehealth, followed by an overview of three distinct examples of comprehensive telehealth programs that have been developed to meet the needs of patients and families across the cancer trajectory, including survivorship, rehabilitation, and palliative care phases. The programs described are exemplars that were developed and implemented prior to the coronavirus pandemic, so they reflect many years of planning and evidence. Lessons learned include the need for ongoing patient support, clinician training, and cancer health system/practice programmatic considerations such as billing, scheduling, reimbursement, software, and hardware/platform security. Although the COVID-19 pandemic produced an explosive shift in regulations and implementation, sustainability of these changes may not be long-term. Nevertheless, a permanent shift in cancer care to include telehealth is likely here to stay.

The novel coronavirus pandemic caused major shifts from in-person care to telehealth in oncology practices—described by one health care executive as "weeks where decades happen."[1] These practice changes were motivated by the need for social distancing rather than a desire to create an organized, patient- and family-centered telehealth program. Practices, patients, and oncology professionals learned quickly that telehealth is more than providing an office visit by phone or video-conferencing. Rather, effective delivery of telehealth requires a planned care system that accounts for myriad patient, provider, and practice/cancer center resources before, during, and after the care episode.[2] In cancer, many diagnostic and anticancer treatment activities cannot be performed remotely. However, in the diagnostic realm, a notable exception has been telepathology, where a joint program was developed between the American Society of Clinical Pathology and organizations in Africa to improve cancer diagnosis.[3] Nevertheless, a significant proportion of evidence-based cancer care can and has been safely and successfully provided in a virtual format.[4]

Telehealth is broadly defined as a method to have virtual, bidirectional communication between patients and providers. Telehealth can include methods such as audio-only, video-consultation, and tele-monitoring, which can occur in a synchronous, asynchronous, or blended format.[5] Figure 1 illustrates considerations in clinical care via telehealth with three examples. The vertical axis reflects the spectrum of audio-only (e.g., telephone) to more sophisticated applications inclusive of video and tele-monitoring platforms. The horizontal axis reflects the timing of the contact from proactive (e.g., focused psychoeducation while patients are stable), to planned (e.g., a scheduled visit), to reactive (e.g., in response to a problem).

In Fig. 2, Educate, Nurture, Advise, Before Life Ends (ENABLE), described in detail later, is shown as an example of a proactive, audio-only palliative care approach that is initiated when patients are newly diagnosed with an advanced cancer.[6] Resolution Care is an example of a program that provides planned telehealth visits to patients with known problems and issues and offers multiple platforms and home monitoring to track patients' symptoms.[7] Finally, telephone triage has been commonplace in oncology care for decades. In response to the pandemic, a novel telehealth program, known as PATCH-24 (PAlliaTive Care Help line), provided palliative care telephonic support to emergency department providers across New York City to help educate them in palliative care–focused communication skills and symptom management. Ultimately, PATCH-24 palliative care

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PRACTICAL APPLICATIONS

- High-quality supportive care for persons with cancer has been provided by telehealth for decades; however, the COVID-19 pandemic created a paradigm shift within weeks that increased widespread telehealth application and acceptability.
- Cancer care by telehealth is not simply replacing an in-person visit with an audio or video contact; it requires comprehensive program planning and proactive training of patients, professionals, and practices.
- Survivorship care via telehealth requires coordination, electronic health record–based survivorship care plan templates, and follow-up to maintain high-quality and safe care.
- The COPE and electronic health record–facilitated E2C2 trials offer use cases that highlight the capabilities that make "telerehabilitation" more accessible and potentially more effective than conventional center-based care.
- Despite the "high-touch" bias, early palliative care telehealth models such as Educate, Nurture, Advise, Before Life Ends for patients newly diagnosed with advanced cancer and Cornerstone for family caregivers have been able to improve quality of life, boost mood, and reduce caregiver burden.

specialists were able to speak to patients directly, thus alleviating the burdens of having goals of care conversations with the overwhelming number of patients and families coming into the emergency department in acute crisis.[8]

This purpose of this article is to present some of the overall issues for health care providers to consider while providing clinical cancer care via telehealth and an overview of three distinct examples of comprehensive telehealth programs that have been developed to meet the needs of patients and families across the cancer trajectory, including survivorship, rehabilitation, and palliative care phases. The programs described are exemplars that have been developed and implemented prior to the coronavirus pandemic, so they reflect many years of planning and evidence. After a brief program description, phase-specific issues of using telehealth are described, including lessons learned and actual or potential dissemination strategies.

TELEHEALTH PROGRAM BASICS FOR CANCER CARE

Program development of telehealth programs for cancer care, regardless of the phase in which it is being used, have common and important considerations.[9] The first step is to

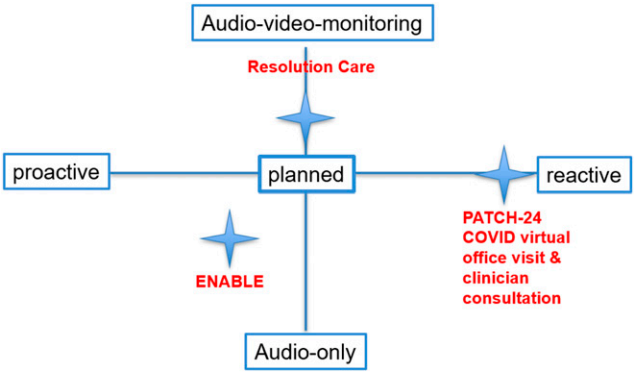

FIGURE 1. The Spectrum of Telehealth With Examples
Abbreviations: ENABLE, Educate, Nurture, Advise, Before Life Ends; PATCH-24, Palliative Care Help.

do comprehensive planning to address the needs of the patients, providers, populations, and health systems.[10] Assessment of patient needs must include those who may provide care for them (e.g., caregivers, families, and local community providers). In this realm is their familiarity and comfort with technology, health literacy, language considerations, availability of broadband (in the case of video visits), and safety concerns. This assessment should recognize that 20% to 40% of patients, depending on the setting, are digitally illiterate and unable to participate in telehealth. Much work is needed in this area to reduce care inequity. Prospective systems must be in place to assess and assist the patient to properly participate in the visit. Clinicians must be able to assess whether the patient is able to speak freely, discern who else may be present, and have the capacity to assess whether an in-person visit may be needed and how that would be provided.[11] Coordination with local community primary care providers is an additional consideration, especially if local in-person care may be needed in response to issues identified in a telehealth visit.

Clinicians require education, time, and space to perform telehealth visits. Telehealth etiquette does not come naturally to patients and providers.[11] Workflow and scheduling considerations for telehealth are unique; telehealth visits are not well suited to be performed during a busy in-person clinic. Scheduling systems must clearly communicate to patients whether the visit is in-person or telehealth. Hence, best practice recommendations are for clinicians to have specific times for telehealth clinics. Typically, a nurse or technician must contact the patient and prepare them for the visit, perhaps being placed in a virtual waiting space until the clinician can join. Mechanisms must be in place for follow-up examinations, prescriptions, and referrals to local, community, and home-based support services to supplement when needed.

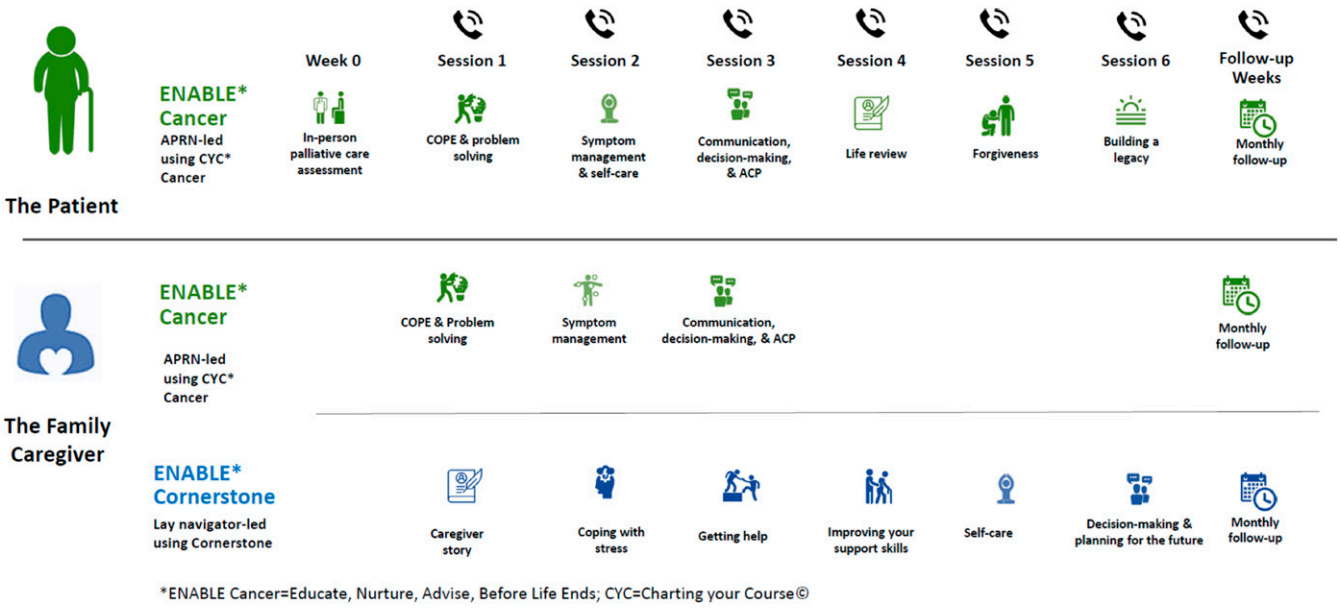

FIGURE 2. Educate, Nurture, Advise, Before Life Ends and Cornerstone Telehealth Sessions
Abbreviations: ACP, advance care planning; APRN, advanced practice registered nurse; CYC, Charting Your Course; ENABLE, Educate, Nurture, Advise, Before Life Ends.

The health system or cancer practice should conduct a financial assessment of developing telehealth support to determine staffing, billing, scheduling, interactivity with the medical record, reimbursement, and issues related to return on investment.[10,12] With the advent of the COVID-19 pandemic and declaration of a public health emergency, modifications were made in public and private insurance allowances for billing, reimbursement, relaxation of regulations for using Health Insurance Portability and Accountability Act–compliant technology, and professional barriers to allow care to be provided across states.[2,13,14] It remains to be seen how these regulations will be maintained following the public health emergency to continue to facilitate the delivery of high-quality cancer care via telehealth.

TELEHEALTH CARE DURING THE SURVIVORSHIP PHASE

Prior to the COVID-19 pandemic, clinical care delivery via telehealth accounted for 0.4% of total Medicare professional fee services spending.[15] Seemingly overnight, the COVID-19 pandemic abruptly altered cancer care and patient provider communications.[16] At Massachusetts General Hospital Cancer Center, telehealth visits accounted for half of all visits during the COVID-19 pandemic surge, and now, post-surge, account for 25% of all ambulatory oncology visits. With this shift in care, we identified the need to define and provide guidance for our cancer center clinicians regarding best practices for optimal telehealth survivorship care.

We defined telehealth for our providers as a means of interacting with patients in real time and asynchronously, including virtual clinic visits by telephone or video platform, embedded educational videos, real-time support groups, and asynchronous written e-consults that do not require a patient visit.[2] Recognizing the real differences in care delivery from an in-person visit to a virtual visit, we developed guidelines for etiquette and cadence for all visits for adult survivors of solid tumor malignancies, using published literature and local experience.[17-19]

We recognized the difference between usual in-person clinic visits and telehealth visits was most often familiarity and comfort navigating a video platform, on the part of both providers and patients.[20,21] Provider educational videos were developed and on-demand tip sheets to troubleshoot common problems while using virtual care were developed. We recognized that the provider conducting the virtual visit became the de facto "help desk" during the visit and as such needed training. Both patients and providers require a confidential and quiet environment to conduct a video or telephone visit. Establishing this etiquette requires planning. A video visit in a busy clinic workroom between in-person visits was not recommended after our early experience and is no longer scheduled in this manner.

The choice of platform requires clear communication at the time of scheduling and a backup plan if the connection is problematic. We use a Zoom-embedded electronic health record platform that is pushed to the patient through the established electronic portal and use the phone-based Doximity video platform as backup. Telephone visits are the last option to communicate if a video option is not

available. Recognizing that many patients cannot use a video-based platform because of limited device or internet access, telephone visits remain an important way to connect with patients in lieu of in-person visits, especially when physical examination is not the focus of the encounter, as we find with many survivorship visits.

Clinic staff set visit expectations with patients regarding all modalities of telehealth visits. In addition to having the visit in a quiet place, patients are encouraged to invite family members when appropriate, both in-person or as a linked video or telephone visit. We ask that the patient have their medication list available and updated for the visit and have any questions prepared in advance of the visit. Patients are apprised that these are provider visits and as such are billed in accordance with Medicare rules.

Patients followed for long-term survivorship care are uniquely well-suited for telehealth visits, especially if they are also following regularly with their primary care and other providers, such as the surgeon or radiation oncologist in addition to medical oncology.[19] Telehealth visits are ideal after completion of therapy for patients who may not require frequent physical examinations for surveillance or who are dependent on imaging for follow-up. A plan for alternating care among providers to avoid duplication of follow-up after combined modality therapy was in place prior to the pandemic and helped facilitate the transition to virtual visits for patients in keeping with their expectations of follow-up in person.

A survivorship care template for facilitating a virtual discussion, embedded into the electronic health record and available to the provider in real time, was developed. This document addresses the domains of survivorship when providing long-term care for patients who have completed definitive therapy. Additionally, for cancer survivors who are on long-term endocrine or targeted therapy, this document is also used. The purpose is to address several domains of survivorship care, including the following: late and long-term complications of all modalities of therapy, cancer screening and surveillance for recurrence, secondary prevention, psychosocial issues after a cancer diagnosis, assessing and addressing coping behaviors, sexual health, financial toxicity, and lifestyle/exercise recommendations. Additional services such as disease-specific support groups, mind-body programs, and exercise programs were transitioned to virtual meetings both in real time and on demand for patients in survivorship. Educating providers to instruct patients where to access these programs allowed patients to continue the supportive services they expect after cancer-directed therapy. During a telehealth visit is an ideal time to introduce virtual resources for a patient.

A Successful Survivorship Telehealth Visit

LS is a 50-year-old White woman who is 3 months post-completion of therapy for stage II triple-negative breast cancer. She received neoadjuvant chemotherapy, including both a taxane and an anthracycline, and had a complete pathologic response at the time of mastectomy. She underwent reconstruction at the time of surgery and has completed post-mastectomy radiation. She saw the plastic surgeon 2 weeks ago and reports that she is healing well and had a negative examination. At this time, she states her energy is improving, her hair is growing back, and she is adjusting to her new body image. She continues to have neuropathy in her feet but thinks this is improving. She is experiencing menopausal symptoms after chemotherapy but is managing well and is not interested in medication for these symptoms at this time. She has some anxiety about how to know her cancer is gone. She has questions about her recurrence risk, her cardiac risk after chemotherapy, her risk of complications from COVID-19, and her eligibility for a vaccine. She is a teacher and is concerned about returning to work. She denies any financial toxicity from her therapy or time away from work. She has no insurance issues. She is sleeping well, and she feels secure and happy in her relationship with her partner of 20 years, who accompanies her to this visit. Her children are overall doing well, but she is worried about her 12-year-old, as "he doesn't say much," and his grades are lower than what she would expect.

This patient had a routine scheduled in-person visit that was converted to a video telehealth visit because of visitor restrictions, which would have required she come to the clinic alone. All of her questions were answered using the telehealth platform embedded in the electronic health record. The note was documented in real time by the oncologist during the visit. After review, a referral to onco-cardiology as an e-consult was agreed and placed in the record. The e-consult will allow the cardiologist to review the patient's chart without an in-person visit and make suggestions for follow-up and testing and will provide a written summary of interventions the patient can make in her life to reduce her risk of late cardiac events. The patient and her partner were provided information about virtual support groups for herself and her family, and as a couple after breast cancer. She was directed to the embedded videos for exercise and self-care after completion of therapy. She and her partner were happy to learn of the resources available if they need them. As the patient was recently examined by her surgical team, an in-person follow-up visit in 6 months was scheduled. The patient was happy not to duplicate visits across the team. The patient and her partner were happy to be able to have their questions answered and concerns addressed from their own home, avoiding the risks of COVID. They both expressed how surprised they were at how easy the visit was and how the care was coordinated across the cancer center team, and they expressed satisfaction at the ease of accessing additional resources when and if needed.

Survivorship Telehealth: Lessons Learned

This example of virtual care is ideal. Models for accessing survivorship care by telehealth were available prior to the COVID pandemic for survivors of adult cancer. These primarily focused on a single intervention.[22] Coordinating care across the spectrum of medical needs is now accepted and expected by patients. Operationalizing this coordination is a challenge but a key component of providing high-quality survivorship care.[23] Most prior interventions demonstrated that virtual synchronous and asynchronous visits improved convenience and personalized care, and provided remote reassurance. Reassuring patients that the provider is available and listening remains the common key to any successful visit. Some issues will continue to require in-person visits. Having the ability to convert a telehealth visit to an in-person visit, either scheduled in the near future or urgently, is important. For this reason, we discourage telehealth visits at times when the clinic is closed and schedulers are not available to coordinate an in-person visit in real time.

Telehealth can be provided to the cancer survivor in their own language and in a setting that provides comfort and support from family members or others living in their homes. Language itself is not a barrier to telehealth but does require advanced planning to schedule and coordinate translation services, help the translator and patient navigate the variety of electronic platforms available, and coordinate follow-up.

As we move forward, telehealth is here to stay.[24] Telehealth has been demonstrated to provide both patient convenience and satisfaction for the survivor of adult cancer. The cognitive care provided to patients in survivorship is ideally suited to a telehealth platform. The lessons we are learning now will continue to inform best practice in the future.

TELEHEALTH FOR PATIENTS IN THE REHABILITATION PHASE

Telecare has proven uniquely effective in surmounting long-standing barriers to the delivery of individualized rehabilitation services to patients with cancer. The need for such services is well established, as functional decline affects virtually all patients with late-stage cancer. The severity and magnitude of these losses are as heterogeneous as the cancer populations are diverse. Nonetheless, these losses exact a uniformly high monetary and human toll. The COPE[25,26] and electronic health record–facilitated E2C2[27] trials use cases that highlight the capabilities that make "tele-rehabilitation" more accessible and potentially more effective than conventional center-based care. These include the ability to: (1) remotely assess patients' functional status; (2) asynchronously deliver individually targeted education and motivational materials; (3) engage local, generalist rehabilitation providers to match care with patient need; (4) monitor and advance function-directed programming; (5) scale standardized, high-fidelity evidence-based care; and (6) track high-need patients who are vulnerable to precipitous, even catastrophic, disablement.

Tele-Rehabilitation Exemplars

In brief, the COPE trial tested whether a collaborative care model–based intervention could improve function, quality of life, and pain relative to enhanced usual care. Similar to prior collaborative telecare interventions trialed in cancer populations,[28] the COPE intervention coupled patient-reported outcome measure monitoring with evidence-based care coordination by a physical therapist, partnered with a physician. The COPE intervention significantly improved function and pain relative to the control condition while significantly reducing health care utilization and costs.[26,29] The population-based, pragmatic E2C2 trial is ongoing and draws heavily from COPE in its collaborative care model–based telecare delivery.[27] The E2C2 trial intervention targets a total of five symptoms and functional decline, and spans all cancer stages.

In contrast, the COPE intervention was delivered to patients with late-stage cancer and mild to moderate disability. The flexibility of the COPE intervention, due in large part to the telecare capabilities enumerated below, allowed for its facile expansion to address the broad range of functional limitations experienced by patients in the E2C2 trial, spanning disease-free survivorship to hospice care. Highlighting the integration of these telecare capabilities in rehabilitation service delivery is warranted, as collectively they achieved a remarkable, and much needed, adaptability in meeting patient-specific needs.

Program Characteristics

Remote, longitudinal assessment of patients' functional status Both the COPE and E2C2 trials demonstrated the feasibility and acceptability of patient-reported outcome measure–based functional monitoring to direct tele-rehabilitation care delivery, even among patients with far advanced cancer. The trials' lean, parsimonious patient-reported outcome measure assessment strategies proved nonburdensome and sufficiently responsive for longitudinal assessments. Patient-reported outcome measure scores were used to remotely determine the type and intensity of initial rehabilitative care, and to define needed care plan refinements. Patient-reported outcome measure scores were also used to identify instances of precipitous functional decompensation, which in many cases were markers of impending severe neuromuscular decompensation.

Asynchronous delivery of individually targeted education and motivational materials Patient education has proven to be a critical need for effective cancer rehabilitation, as many patients believe functional decline is inevitable and are unaware of its potential reversal.[30] Convincing patients of likely benefits is often a necessary initial step to engage

them in the rehabilitation process. Such education can be time-consuming and prohibitively costly when provided one-on-one by clinicians. Telecare offers the potential not only to asynchronously deliver high-quality, standardized education, but also to target material to patient need based on patient-reported outcome measure scores, cancer type/stage, and other characteristics. Tele-rehabilitation in the E2C2 trial leverages algorithms, branching logic, and other electronic health record capabilities for patient-specific targeting.

Engaging local, generalist rehabilitation providers to match care with patient need Tele-rehabilitation offers the opportunity to engage local generalist rehabilitation providers and thereby obviate the requirement for patients to travel to specialty centers. Rehabilitation service providers practicing outside of cancer and tertiary centers are generalists with limited experience in caring for patients with cancer. These providers benefit from asynchronous information delivery—in this case, guidelines, protocols, and guidance in managing cancer-specific concerns (e.g., bone and brain metastases). Both the COPE and E2C2 trials capitalized on this capability by creating web content for local rehabilitation service providers. In addition, both trials relied on telephonic communication between cancer center–based specialists and local physical and occupational therapy generalists.

Monitoring and advancing rehabilitation programming Telecare allows for low-burden, almost real-time monitoring of patients' adherence and progress in function-directed programming. This offers the potential for timely, remote, data-directed advancement of patients' programs. Because most rehabilitation interventions are behavioral in nature and require ongoing daily performance, such adherence can understandably be challenging for patients with cancer as they navigate often heavy symptom burdens and treatment requirements. Problem-solving and motivation become critical. Remote telecare adherence monitoring enables rehabilitation service providers to recognize when a patient's adherence flags and to gently intervene to help them address barriers and problem-solve ways to continue their rehabilitation program.

Scaling standardized, high-fidelity evidence-based cancer rehabilitation Telecare allows for low-cost scaling of high-fidelity, evidence-based cancer rehabilitation services. Both the COPE and E2C2 trials aggressively leveraged this capability. In the COPE trial, the robustly validated Rapid, Easy Strength Training and First Step programs were made available to patients in print, DVD, web, and smartphone formats.[31-33] These programs were designed for benefit and safety among fit and frail individuals. The Rapid, Easy Strength Training program was additionally designed to accommodate individual modifications, making it an effective springboard for creating highly tailored and targeted treatment programs. Individualized Rapid, Easy Strength Training modifications were performed remotely by cancer and local generalists with center-based therapists serving as an expert resource.

Tracking Patients Who Are Vulnerable to Precipitous AND Potentially Catastrophic Disablement

The telecare platforms used by both the COPE and the E2C2 trials enabled close monitoring of high-risk subpopulations, specifically those whose bone metastases posed a high risk of fracture or neural compromise. The E2C2 intervention uses electronic health record functionalities to identify and remotely track these patients. This approach has led to the early detection of impending spinal cord compression among multiple patients when their neural deficits were modest but evolving. Tele-surveillance and early intervention allow rehabilitation service providers to become more proactively involved in preserving patients' function—a capability that significantly improved outcomes and reduced costs in the COPE trial.[29]

Broad implementation of the success achieved with the COPE trial will require closer collaboration between oncologic and rehabilitation providers than has been the norm. Fortunately, robust tele-rehabilitation platforms are widely available. Their clinical application awaits interdisciplinary partnerships to specify, implement, and troubleshoot them.

TELEHEALTH FOR PROVIDING PALLIATIVE CARE

Despite typical assessment of palliative and supportive care as a "high-touch" specialty, this care has been provided to persons with cancer and their families successfully for decades.[6,34] In the United States, most palliative care telehealth use prepandemic was provided for patients in rural areas; however, this is no longer the case. In many low-income areas, palliative care tele-consultation and tele-education through programs like Project Echo (Extension of Community Healthcare Outcomes) have brought much needed expertise to rural and low-income areas. Project Echo is a tele-mentoring program that links health care experts with local clinicians in a "hub" (expert) and "spokes" (community facilities in need) model.[35,36] A case, evidence, and program description illustrate the use of telehealth to carry out a comprehensive cancer plan for a patient with advanced disease.

Telehealth Palliative Care: Case Study

James is a 70-year-old Black male and retired steel worker with a new diagnosis of an inoperable glioblastoma. He lives with his wife Jackie in the rural southern United States; they are both devout Baptists and regularly attend religious services and activities. They have three children, seven grandchildren, and three great-grandchildren, all of whom live more than a 2-hour drive away. Aside from occasional

visits to a local primary care doctor, they have had very little interaction with the health care system. James' primary care doctor sends him to the academic cancer center 50 miles away for further diagnostic work-up and treatment recommendations. The academic oncologist shares a poor prognosis, and James and Jackie decide they will speak with their pastor and pray about the best decision. They are referred to the palliative and supportive care program, which has a comprehensive telehealth supportive care program. The program includes an initial in-person comprehensive assessment and structured telehealth phone support sessions for the patient by a specially trained palliative care nurse and for the family by a lay navigator telehealth coach.

The telehealth sessions begin the following week. James and Jackie feel well-supported and learn decision-making skills that are based on their values and preferences. James decides that it is too burdensome and expensive to return to the cancer center for further evaluation, especially given their understanding of the poor prognosis of his cancer. After consulting with their local physician, pastor, and prayer, they decline the recommended radiation and chemotherapy treatments. The palliative care nurse coach and lay navigators continue their separate sessions with James and Jackie so that they each have opportunities to address their concerns in a confidential manner. Because James does not want to return to the cancer center for the in-person comprehensive consultation with a palliative care specialist, the nurse coach organizes for James to have a video visit through the Tele-Pal Virtual Visit Program when their daughter Vanessa is visiting. Vanessa has a laptop computer with a camera and a wi-fi hotspot so that other family can join the visit remotely on a secure Zoom platform. The palliative care specialist assesses symptoms and prescribes steroids, antiepileptics, and antidepressants for anticipated symptoms and works closely with James' primary care physician and the local hospice agency to mobilize support when needed and arrange for home medications that do not require an oral route if needed in the event of a symptom crisis.

James' family and congregation rally support for the family, providing prayer, meals, and help with chores as needed. James continues to enjoy a moderately good quality of life with some mild speech and balance issues. The nurse coach reviews important topics with James and Jackie via weekly calls, covering topics of problem-solving, self-care, symptom assessment and management, communication, and advance care planning. She also addresses issues of spirituality and meaning through life review and legacy-building activities. The family provides James and Jackie with a simple tablet and cellular plan so they can have weekly video chats with the extended family in between visits. When James can no longer attend church services/activities, parishioners visit and make provisions so James can attend church services virtually. One day his symptoms of headache, nausea, and vomiting become severe, and the nurse coach is able to talk them through initiating non-oral symptom medications and arranges for an urgent video visit with the cancer center palliative care specialist who did the initial consult. The specialist suggests they initiate home hospice, and the primary care clinician, who is also the hospice medical director, does a home visit. James' virtual specialty care allows him to die peacefully in his home with the assistance of local community, congregation, family, and hospice support.

Providing Evidence-Based Palliative Care via Telehealth

Providing comprehensive cancer care via telehealth to patients with advanced cancer requires a prospective and coordinated approach.[11,37,38] Although the case example highlights the special challenges of providing palliative care in a rural environment, similar technology-aided care can be equally well-suited to patients with cancer and their families who have transportation, financial, illness-related, or other issues that compromise their ability to access high-quality cancer care.

ENABLE was developed as a nurse-led early palliative care telehealth program for patients with advanced cancer in rural New England.[39-41] As presented in the case, patients with advanced cancer who are newly diagnosed are provided with a comprehensive palliative care assessment, and this is followed by structured phone sessions for the patient and the family that cover topics of problem-solving, symptom and self-care, communication, decision-making, and life review.

We found that we could increase scalability while maintaining high-quality support for family caregivers using a lay navigation model of telehealth support. Dionne-Odom and colleagues[42-47] developed Project ENABLE Cornerstone based on a series of studies examining cancer family caregivers' needs, especially in Black and rural underserved populations. In Cornerstone, trained lay navigators are overseen by specialist palliative care clinicians and provide family care partners with a series of brief in-person and telehealth sessions focusing on stress management and coping, caregiving skills and organization, getting help, self-care, and preparing for the future/advance care planning. This tailored caregiver support provided by lay navigators has demonstrated great promise, and studies in progress will provide additional evidence and opportunities for dissemination.

Although audio-only phone support has proven beneficial, the in-person consultation has been difficult to implement in the rural southern United States. In a study of patients with heart failure, only 50% were able to attend the in-person component of ENABLE. Hence, a study of video consultation is underway to provide this care via video visit.[48] However, the

University of Alabama at Birmingham Community-based (Virtual) Access to Palliative Expertises program has a clinical video-visit program that enables patients to have this consultation in the comfort of their homes, though prior to relaxation of telehealth regulations, these visits were only possible to conduct at local area health departments where there was a clinician present at the originating site. Hence, patients like James are now able to get high-quality palliative care in their rural local community, where this care does not often exist.

FUTURE DIRECTIONS

Providing high-quality cancer care across the cancer trajectory via telehealth is a reality, evidence-based, and likely here to stay. The exemplars presented provide evidence of the variety of strategies, lessons learned, and innovations that are available to serve patients with cancer and their family and friends across the supportive care trajectory. There is evidence that this care can reduce costs, while maintaining patient and clinician satisfaction. Although the COVID-19 pandemic provided an opportunity to accelerate widespread use of telehealth in cancer care, it also revealed that telehealth programs require planning for patients, providers, and practices to be fully functional. Additional critical lessons learned included the importance of providing local community care in a culturally responsive way. This requires early and ongoing community stakeholder engagement to fashion the approach in ways that will be acceptable to community members.[49] Finally, though telehealth on the surface appears to improve equity in health care access, many of the same issues related to poverty, underinsurance, low technology and broadband availability, and health literacy have left many low-income areas with ongoing difficulties in achieving equitable health care access.[12,50,51]

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REFERENCES

1. Pifer R. "Weeks where decades happen": Telehealth 6 months into COVID-19. HealthcareDive. 2020. https://www.healthcaredive.com/news/telehealth-6-months-coronavirus/581447/. Accessed January 1, 2021.
2. Mulvey TM, Jacobson JO. COVID-19 and cancer care: ensuring safety while transforming care delivery. J Clin Oncol. 2020;38:3248-3251.
3. Orah N, Rotimi O. Telepathology in low resource African settings. Front Public Health. 2019;7:264.
4. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; National Cancer Policy Forum. Cancer Care in Low-Resource Areas: Cancer Treatment, Palliative Care, and Survivorship Care: Proceedings of a Workshop. Washington, DC: The National Academies Press; 2017.
5. Sirintrapun SJ, Lopez AM. Telemedicine in cancer care. Am Soc Clin Oncol Educ Book. 2018;38:540-545.
6. Allen Watts K, Malone E, Dionne-Odom JN, et al. Can you hear me now? Improving palliative care access through telehealth. Res Nurs Health. 2021;44:226-237.
7. Calton B, Abedini N, Fratkin M. Telemedicine in the time of coronavirus. J Pain Symptom Manage. 2020;60:E12-E14.
8. Ankuda CK, Woodrell CD, Meier DE, et al. A beacon for dark times: palliative care support during the coronavirus pandemic. NEJM Catal Innov Care Deliv. Epub 2020 May 12.
9. Cooley L. Fostering human connection in the Covid-19 virtual health care realm. NEJM Catal Innov Care Deliv. Epub 2020 May 20.
10. Silvers A, Lustbader D, Fratkin M. Telehealth and Palliative Care: Toolkit, Vol. Vol. 2021. New York: Center to Advance Palliative Care; 2020.
11. Calton BA, Rabow MW, Branagan L, et al. Top ten tips palliative care clinicians should know about telepalliative care. J Palliat Med. 2019;22:981-985.
12. Lee S, Black D, Held ML. Factors associated with telehealth service utilization among rural populations. J Health Care Poor Underserved. 2019;30:1259-1272.
13. Portnoy J, Waller M, Elliott T. Telemedicine in the era of COVID-19. J Allergy Immunol Pract. 2020;8:1489-1491.
14. Thota R, Gill DM, Brant JL, et al. Telehealth is a sustainable population health strategy to lower costs and increase quality of health care in rural Utah. JCO Oncol Pract. 2020;16:e557-e562.

15. Koonin LM, Hoots B, Tsang CA, et al. Trends in the use of telehealth during the emergence of the COVID-19 pandemic — United States, January–March 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1595-1599.
16. Jhaveri K, Cohen JA, Barulich M, et al. "Soup cans, brooms, and Zoom:" Rapid conversion of a cancer survivorship program to telehealth during COVID-19. Psychooncology. 2020;29:1424-1426.
17. Merz V, Ferro A, Piras EM, et al. Electronic medical record-assisted telephone follow-up of breast cancer survivors during the COVID-19 pandemic: a single institution experience. JCO Oncol Pract. 2021;17:e44-e52.
18. Cox A, Lucas G, Marcu A, et al. Cancer survivors' experience with telehealth: a systematic review and thematic synthesis. J Med Internet Res. 2017;19:e11.
19. Denis F, Yossi S, Septans AL, et al. Improving survival in patients treated for a lung cancer using self-evaluated symptoms reported through a web application. Am J Clin Oncol. 2017;40:464-469.
20. Moore MA, Coffman M, Jetty A, et al. Only 15% of FPs report using telehealth; training and lack of reimbursement are top barriers. Am Fam Physician. 2016; 93:101.
21. Lai AM, Kaufman DR, Starren J, et al. Evaluation of a remote training approach for teaching seniors to use a telehealth system. Int J Med Inform. 2009; 78:732-744.
22. Strasser F, Blum D, von Moos R, et al; Swiss Group for Clinical Cancer Research (SAKK). The effect of real-time electronic monitoring of patient-reported symptoms and clinical syndromes in outpatient workflow of medical oncologists: E-MOSAIC, a multicenter cluster-randomized phase III study (SAKK 95/06). Ann Oncol. 2016;27:324-332.
23. Park ER, Peppercorn J, El-Jawahri A. Shades of survivorship. J Natl Compr Canc Netw. 2018;16:1163-1165.
24. Duffy S, Lee TH. In-person health care as option B. N Engl J Med. 2018;378:104-106.
25. Cheville AL, Moynihan T, Basford JR, et al. The rationale, design, and methods of a randomized, controlled trial to evaluate the effectiveness of collaborative telecare in preserving function among patients with late stage cancer and hematologic conditions. Contemp Clin Trials. 2018;64:254-264.
26. Cheville AL, Moynihan T, Herrin J, et al. Effect of collaborative telerehabilitation on functional impairment and pain among patients with advanced-stage cancer: a randomized clinical trial. JAMA Oncol. 2019;5:644-652.
27. Finney Rutten LJ, Ruddy KJ, Chlan LL, et al. Pragmatic cluster randomized trial to evaluate effectiveness and implementation of enhanced EHR-facilitated cancer symptom control (E2C2). Trials. 2020;21:480.
28. Kroenke K, Theobald D, Wu J, et al. Effect of telecare management on pain and depression in patients with cancer: a randomized trial. JAMA. 2010;304:163-171.
29. Longacre CF, Nyman JA, Visscher SL, et al. Cost-effectiveness of the Collaborative Care to Preserve Performance in Cancer (COPE) trial tele-rehabilitation interventions for patients with advanced cancers. Cancer Med. 2020;9:2723-2731.
30. Cheville AL, Dose AM, Basford JR, et al. Insights into the reluctance of patients with late-stage cancer to adopt exercise as a means to reduce their symptoms and improve their function. J Pain Symptom Manage. 2012;44:84-94.
31. Cheville AL, Kollasch J, Vandenberg J, et al. A home-based exercise program to improve function, fatigue, and sleep quality in patients with Stage IV lung and colorectal cancer: a randomized controlled trial. J Pain Symptom Manage. 2013;45:811-821.
32. Cheville AL, Girardi J, Clark MM, et al. Therapeutic exercise during outpatient radiation therapy for advanced cancer: feasibility and impact on physical well-being. Am J Phys Med Rehabil. 2010;89:611-619.
33. Tudor-Locke C. Promoting lifestyle physical activity: experiences with the First Step Program. Am J Lifestyle Med. 2009;3(suppl 1):508-548.
34. Stockdill ML, Barnett MD, Taylor R, et al. Telehealth in palliative care: communication strategies from the COVID-19 pandemic. Clin J Oncol Nurs. 2021; 25:17-22.
35. Burpee E. A Progress Report: Expanding Palliative Care with Project ECHO. In CAPC: Health Equity, Vol. Vol. 2021. New York: Center to Advance Palliative Care; 2019.
36. Arora S, Byers EL. Leveraging local expertise to improve rural cancer care outcomes using Project ECHO: A response to Levit et al. JCO Oncol Pract. 2020; 16:399-403.
37. Bakitas MA, El-Jawahri A, Farquhar M, et al. The TEAM approach to improving oncology outcomes by incorporating palliative care in practice. J Oncol Pract. 2017;13:557-566.
38. Beasley A, Bakitas MA, Edwards R, et al. Models of non-hospice palliative care: a review. Ann Palliat Med. 2019;8(suppl S1):S15-S21.
39. Bakitas M, Lyons KD, Hegel MT, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. JAMA. 2009;302:741-749.
40. Bakitas M, Stevens M, Ahles T, et al; Project Enable Co-Investigators. Project ENABLE: a palliative care demonstration project for advanced cancer patients in three settings. J Palliat Med. 2004;7:363-372.
41. Bakitas MA, Tosteson TD, Li Z, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. J Clin Oncol. 2015;33:1438-1445.
42. Dionne-Odom JN, Azuero A, Lyons KD, et al. Family caregiver depressive symptom and grief outcomes from the ENABLE III randomized controlled trial. J Pain Symptom Manage. 2016;52:378-385.
43. Dionne-Odom JN, Demark-Wahnefried W, Taylor RA, et al. The self-care practices of family caregivers of persons with poor prognosis cancer: differences by varying levels of caregiver well-being and preparedness. Support Care Cancer. 2017;25:2437-2444.

44. Dionne-Odom JN, Ejem D, Azuero A, et al. Factors associated with family caregivers' confidence in future surrogate decision making for persons with cancer. J Palliat Med. 2018;21:1705-1712.

45. Dionne-Odom JN, Ejem D, Wells R, et al. How family caregivers of persons with advanced cancer assist with upstream healthcare decision-making: a qualitative study. PLoS One. 2019;14:e0212967.

46. Dionne-Odom JN, Williams GR, Warren PP, et al. Implementing a clinic-based telehealth support service (FamilyStrong) for family caregivers of individuals with grade IV brain tumors. J Palliat Med. 2021;24:347-353.

47. Hendricks BA, Lofton C, Azuero A, et al. The project ENABLE Cornerstone randomized pilot trial: Protocol for lay navigator-led early palliative care for African-American and rural advanced cancer family caregivers. Contemp Clin Trials Commun. 2019;16:100485.

48. Watts KA, Gazaway S, Malone E, et al. Community Tele-pal: a community-developed, culturally based palliative care tele-consult randomized controlled trial for African American and white rural southern elders with a life-limiting illness. Trials. 2020;21:672.

49. Elk R, Emanuel L, Hauser J, et al. Developing and testing the feasibility of a culturally based tele-palliative care consult based on the cultural values and preferences of southern, rural African American and white community members: a program by and for the community. Health Equity. 2020;4:52-83.

50. Watanabe SM, Fairchild A, Pituskin E, et al. Improving access to specialist multidisciplinary palliative care consultation for rural cancer patients by video-conferencing: report of a pilot project. Support Care Cancer. 2013;21:1201-1207.

51. Yabroff KR, Han X, Zhao J, et al. Rural cancer disparities in the United States: a multilevel framework to improve access to care and patient outcomes. JCO Oncol Pract. 2020;16:409-413.

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