Special Series: Advances in GI Cancer

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Worldwide, 14 million people are diagnosed with cancer annually, and more than a quarter of these are GI cancers (more than 4 million new cases each year).¹ Of the 8.2 million people who die as a result of cancer each year in the world, 2.7 million (33%) die as a result of GI malignancies. The total new cases of GI cancer are greater than breast (1.6 million) and lung (1.8 million) cancers combined, with 22% more deaths annually. GI cancers represent at least 10 distinct diseases (depending on how the diseases are grouped or differentiated). To some extent, many of these tumors share similar characteristics (eg, staging, and thus prognosis, for tumors in the alimentary tract considers the extent of invasion through the bowel wall as opposed to the size of the tumor, and the extent of nodal involvement), and nearly all of the GI tumors are responsive to either single-agent fluoropyrimidine or combination therapy with a fluoropyrimidine. Conversely, the biology of these tumors is distinct, as evidenced by emerging data on molecular signatures as well as variable response to treatments, particularly targeted therapies. For some GI cancers, great strides have occurred in the last 10 to 15 years in terms of understanding biology as well as expanding treatment options and improving prognosis (eg, median survival for metastatic colorectal cancer has lengthened from 1 year to nearly 3 years); however, in other GI cancers, advances have been slow and minimal in affecting the course of the disease (eg, survival for metastatic pancreatic cancers remains < 1 year, and fewer than 5% of patients are long-term survivors). Our goal in this Special Series issue of *Journal of Clinical Oncology* is to update readers on the current state of the science for most GI cancers, break down the successes and failures, and look ahead to the potential opportunities to further advance our understanding and treatment of these diseases. In addition, we have several overview articles that have implications for multiple GI (and other) cancers and discuss issues that are critical to patient treatment.

After decades of clinical trials of cytotoxic therapies that targeted rapidly dividing cells (which included a wide variety of healthy as well as cancerous cells), in the early 2000s, the era of so-called biologic or targeted therapy entered the GI cancer arena. The blockbuster development of imatinib for GI stromal tumors (GISTs) was and remains the seminal event in targeted therapies (we consider GIST a GI cancer rather than sarcoma, and it is featured in the article by Cioffia and Maki).² Beyond cKIT, the focus has been on two pathways: angiogenesis via the vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR). Initial trials in colorectal cancer were promising. In an era when clinical trials for metastatic colorectal cancer were powered to detect median overall survival improvement of as little as 2 months, Hurwitz et al³ presented eye-opening data on

VEGF inhibition at the American Society of Clinical Oncology 2003 Annual Meeting: the addition of bevacizumab to standard cytotoxic chemotherapy improved median overall survival by nearly 5 months. Unfortunately, the magnitude of the initial results was never replicated and the expected promise of this pathway has not been realized; subsequent trials in colorectal cancer have shown only modest improvements⁴ while demonstrating a frustrating lack of efficacy in multiple other GI cancer types.^{5,6} Nonetheless, the VEGF pathway continues to be a valid target in GI cancers, with data emerging for other agents and other GI cancers (eg, ramucirumab and gastric cancer⁷).

The approach to a subset of lung cancers has been revolutionized with the detection of specific, targetable mutations that are drivers of cancer in some patients.⁸ Unfortunately, in GI cancers other than GIST, we have not been able to achieve such results. Nonetheless, our understanding of the molecular basis of GI cancers has expanded greatly, and it is hoped that these results will lead to a better understanding of how to characterize and treat by molecular subtypes. Data recently reported by Bass et al⁹ that have emerged from the Cancer Genomic Atlas Network have revolutionized our understanding of the pathways that lead to the development of gastric cancer, with four molecularly defined subtypes: Epstein-Barr virus positivity, microsatellite instability, chromosomal instability, or genomic stability. Similarly, the Cancer Genomic Atlas data confirmed the classification of colon and rectal cancers as emerging from either the hypermutated pathway (through high microsatellite instability, hypermethylation, *MLH1* silencing, or somatic mismatch-repair gene and polymerase ϵ [*POLE*] mutations) or the nonhypermutated pathway (through chromosomal instability), as well as the concept that colon and rectal cancers are nearly indistinguishable molecularly.¹⁰ With these data, the hope is that progress in selecting the right therapy (or likely therapies) for tumors on the basis of molecular analyses may accelerate.

This *JCO* Special Series issue begins with broad reviews of four topics that relate to multiple GI cancers: genetic screening, imaging, radiation therapy, and immunotherapy. We begin with Stoffel¹¹ reviewing the role of genetics in GI cancer, discussing the variety of germline mutation syndromes that increase the risk of GI cancers, reviewing the past, current, and future methods to identify patients with genetic predispositions, and outlining the limited potential preventative strategies for high-risk patients. By intent, certain important broad-based topics that are applicable across GI cancers are not included because they have been incorporated into other *JCO* Special Series issues in the recent past, including Survivorship (September 2012),¹² Pain Management (June 2014),¹³ and Geriatric Oncology

(August 2014).¹⁴ In addition, a full series on Radiation Therapy (September 2014)¹⁵ expands on topics included in the review by Hajj and Goodman.¹⁶

Although a day does not pass without an oncologist ordering imaging of patients—for staging, observing treatment benefit, and surveillance—there are often misunderstandings and confusion about the various modalities of imaging. Bentley-Hibbert and Schwartz¹⁷ provide an excellent overview of the benefits and limitations of each type of imaging. As targeted therapies have been increasingly integrated into the treatment of GI cancers, we have learned that not all therapeutics can be assessed with RECIST criteria, and consideration of the use of positron emission tomography and other functional imaging for response assessment is discussed.

Hajj and Goodman¹⁶ begin their review on radiotherapy in GI cancers with discussions on the growing assortment of treatment options (intensity-modulated radiation therapy, stereotactic beam radiation therapy, image-guided radiation therapy, intraoperative radiation therapy, and proton therapy), noting the advantages and limitation of each technique and the potential role in therapy. The authors also tackle the shifting role of radiation by disease site and when to integrate radiation therapy in the treatment course, as well as describing controversies about usage. The final broad-based review in this issue focuses on the hot topic of immunotherapy. Wang et al¹⁸ present their case for why the immune system is relevant to GI cancers and then provide a comprehensive review of the hits and misses in therapeutics ranging from vaccines to antibodies targeting tumor antigens, costimulatory molecules, and immune checkpoints (including the programmed death pathway). Although immunotherapy has been an active area of research for decades, including in GI cancers, the recent excitement generated by these new inhibitory molecules has us at a critical crossroads in the realization of immune-based opportunities, and the authors discuss the limitations of these strategies and the future directions.

There are 12 reviews on individual disease sites. Our prompt to the authors was not to provide a trial-by-trial history lesson that led to current management practices but rather a brief roadmap of how we got to where we are today and, just as important, where we are going. Their mandate was to focus on hot topics for each disease. As the reader will appreciate, in some areas there are natural overlaps across disease sites (eg, the limited role of precision medicine to date across many GI cancers), but, obviously, there are specific areas of focus within individual diseases (eg, the role of adjuvant therapy after chemoradiotherapy in locally advanced esophageal cancer).

There are two reviews on esophageal and gastric cancer: Cohen and Leichman¹⁹ focus on local and locally advanced disease, whereas Shah²⁰ reviews metastatic disease. As Cohen and Leichman describe, esophageal and gastric cancer management has evolved from a so-called lumping approach, in which both diseases and various subtypes of each disease are treated in similar fashions, to more of a so-called splitting strategy, in which the different etiologies, molecular biology, and patterns of recurrence dictate more individualized approaches. In addition to providing a discussion of current management, they focus on the multiple unanswered questions in treating these diseases and how the field is moving to answer these issues. Shah's review of metastatic esophageal and gastric cancer describes how for metastatic disease, lumping has been the overriding strategy, although increasing understanding of potential actionable targets has started to shift the field. In addition to the known suspects, human epidermal growth

factor receptor 2 and VEGF, other targets are emerging that may play a key role in the future treatment of these two cancer types, including immune checkpoint targets and the MET/hepatocyte growth factor receptor.

In geographic proximity to the stomach but with different biology, pancreatic cancer is featured in two thoughtful articles in this issue. Heestand et al²¹ focus on nonmetastatic disease, whereas Ko²² reviews the approach to patients with distant disease. Although fewer than 20% of pancreatic cancers are considered resectable, controversy and inconsistency exist with respect to the strategy for such patients, and these authors focus much of their review on the various approaches to the patient with resectable and borderline resectable disease, discussing the current options and emerging areas of research. In the second half of their article, the authors review approaches to locally advanced disease, the treatment of which previously focused on local control but is evolving to therapy that is more systemic in nature. Ko provides a summary of current treatments for metastatic pancreatic cancer but devotes most of the review to potential future opportunities, focusing on three promising areas: stromal depleting agents, immunotherapy, and novel signal transduction inhibitors. He discusses how disappointments in the past will hopefully inform promising new therapies in the future in a disease that continues to be one of the most difficult to treat in oncology.

We have four review articles that are focused on colorectal cancer. Dienstmann et al²³ review nonmetastatic colon cancer. After providing the data that support current recommendations for adjuvant therapy in stage II and III colon cancer, they focus attention on how molecular features can, and hopefully will, inform discussion and decisions on adjuvant therapy in the future. Smith and Garcia-Aguilar²⁴ provide a comprehensive review of the various components of trimodality therapy for locally advanced rectal cancer, including staging strategies, surgical options, role and timing of radiation, and chemotherapy options with radiation and as adjuvant therapy. There is growing controversy on use of all three modalities, particularly in certain substages, and Smith and Garcia-Aguilar tackle this topic in a section of the review entitled, "Less May Be More." Fakhri²⁵ reviews current management of metastatic colorectal cancer, focusing on emerging areas, including incorporation of all-RAS testing for use of EGFR inhibitors, first-line therapy with an EGFR inhibitor versus a VEGF inhibitor, and the growing area of research in *BRAF*-mutated tumors (a subtype of colorectal cancers that carry a significantly worse prognosis but for which there are emerging areas of research on potential opportunities). Finally, Van Blarigan, with one of us (J.A.M.),²⁶ has reviewed the emerging data on the role of diet and lifestyle in colorectal cancer survivors. Although this field lacks randomized trials, patients ask about diet and exercise, and the consistency found in the prospective observational cohorts has reinforced the importance of this area of research.

The final four reviews in this series cover GI cancers that are less common (at least in the United States); significant strides have been made with two cancer types (GIST and neuroendocrine/carcinoids tumors), whereas two others (hepatocellular carcinoma [HCC] and biliary cancers) continue to present challenges insofar as changing the natural history of the disease. Knox et al²⁷ begin with an overview of the surgical and other localized therapy options for patients with localized HCC. Then, they focus on the challenges in treating incurable disease, reviewing the disappointments in targeted therapies beyond sorafenib and providing insight into next steps to crack HCC, the

sixth most common cancer worldwide. Chan and Berlin²⁸ provide a review of the current limited options to treat biliary cancers and then discuss a potentially exciting development: the growing understanding of potential targetable mutations that will be the focus of studies in the upcoming years. Cioffi and Maki² discuss the exciting breakthrough history of treatments for GIST, starting with what they describe as the Big Bang of imatinib and the continuous research on the biology of these tumors to find the next agents to use on resistance. Finally, Kunz²⁹ reviews the burgeoning field of research in carcinoid and neuroendocrine tumors, which have variable natural histories and aggressiveness. The growing number of treatments for these tumors is proof that understanding the biology of the tumor can lead to therapeutic options.

Given limitations in length, we could not cover every GI cancer. Small bowel and appendiceal adenocarcinomas and anal cancer are not covered in this series, primarily since, unfortunately, these cancer types have had few new studies in the last decade. The advances in treatment of anal cancer were remarkable three decades ago, but recent changes have been small and have focused with some success on means to decrease radiation toxicity. Research is desperately needed to advance our knowledge and subsequent management of small bowel, appendiceal, and anal cancer. Finally, the spectrum from pseudomyxoma peritonei to peritoneal carcinomatosis is treated with much variability, and large-scale studies are greatly needed to guide management of these challenging problems.

If this series had been published 15 years ago, each of the reviews would be purely focused on trial after trial of cytotoxic chemotherapies and the limited options available beyond fluoropyrimidines. Median survival for metastatic colorectal cancer would be reported as 12 months,³⁰ median survival for metastatic gastric cancer as 7 months,³¹ and median survival for metastatic pancreatic cancer as 5 to 6 months.³² These survivals have increased in the last 15 years, most dramatically for metastatic colorectal cancer (30 months),³³ but also for selected patients with gastric cancer (human epidermal growth factor receptor 2 positive, 13 months)³⁴ and pancreatic cancer (good performance status, 11 months).³⁵ We finally are starting to understand the biology of these cancers, with the realization that, except for GISTs, there is not a single driver mutation causing GI cancers to form, grow, and metastasize. The same cancer type does not develop the same way in each patient and thus personalization of therapy will be essential. However, to reach this goal, we have a long way to go. As you read these review articles, we urge you to think about patients under your care and potential opportunities to enroll them onto clinical trials that may allow us to turn these cancers into chronic (and one day, curable) diseases.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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American Society of Clinical Oncology

NCI-ASCO Teams in Cancer Care Delivery Project: Call for Participants

The National Cancer Institute (NCI) and American Society of Clinical Oncology (ASCO) are collaborating to illustrate models of team-based care at a workshop and in *JOP* content. Teamwork involves delineating roles and responsibilities for multidisciplinary care across many settings. At a time of increasing expectations and pressure to demonstrate value in oncology care, this project will explore how oncology care can provide an effective model.

Goal: Illustrate in presentations and manuscripts effective approaches to delivering coordinated, patient-centered cancer care and apply the evidence for effective cancer care teams

Who: Approximately 10 writing groups will be formed with the following participants:

- Clinicians (physicians, nurse practitioners, physician assistants, and nurses)
- Patient advocates
- Researchers studying team effectiveness in health care (not only oncology) in the United States or Canada

What: Groups including clinicians, patient advocates, and team researchers will develop a presentation and manuscript applying principles of team-based care to a case within the cancer care continuum (prevention, screening, diagnosis, active treatment of curable and incurable disease, survivorship, end of life).

Important Dates:

- Applications due: June 15, 2015
- Selection of teams: July 17, 2015
- In-person meeting at ASCO offices, Alexandria, VA: August 28, 2015
- Presentations at NCI-ASCO Workshop: February 25, 2016

Apply as individuals or teams at www.ASCO.org/Teams

Questions: teams@asco.org

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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