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New Paradigms in Rectal Cancer Multidisciplinary Care: Special Issue Introduction

More than 730,000 cases of rectal cancer worldwide were estimated by GLOBOCAN in 2020, with the incidence in East Asia among the highest.¹ Moreover, early onset colorectal rectal cancer in patients younger than 50 years of age has been an increasingly concerning trend.² Surgery has been the backbone of treatment and, historically, has been followed by post-operative chemoradiation for those patients identified pathologically with T3-T4 or node positive disease. Heald and Ryall reported the initial case series of patients uniformly treated with total mesorectal excision (TME) in 1986, and Heald described the “holy plane” of rectal cancer surgery in 1988.^{3,4} After the introduction of TME, the value of radiation was questioned in the setting of improved surgical technique. The Dutch Colorectal Cancer Group CKVO 95-04 trial reported initial results in 2001 that short-course radiation therapy reduced local pelvic recurrence even with standardized TME.⁵ In 2004, the German CAO/ARO/AIO-94 trial then confirmed the superiority of pre-operative long-course chemoradiation compared to post-operative chemoradiation with respect to both local pelvic control and reduced toxicities.⁶ The publication of the Dutch and German trials led to the wide acceptance of the combined modality treatment paradigm of pre-operative (chemo)radiation followed by TME.

More recently, the landscape of treatment options for rectal cancer has become more complex. As in many other cancer sites, diagnostic and therapeutic advancements have contributed to a drive towards personalized therapy. Therefore, it is an opportune time to highlight these emerging trends in this special issue with perspectives from North America, Asia, and Australia.

Since the publication of the Mercury trial, magnetic resonance imaging (MRI) has supplanted endorectal ultrasound as the primary

staging modality.⁷ Bates et al. review the central role for MRI in both initial staging and post-treatment response evaluation. They emphasize the need for standardization of acquisition techniques and synoptic reporting. Indeed, MRI can be considered an imaging biomarker. The current state of biomarkers in rectal cancer is summarized by Mendis et al.. In addition to MRI, biomarkers include clinical, blood-based, pathological, and molecular and can be incorporated into decision making pre-treatment, post-neoadjuvant chemoradiation, or post-operatively.

Immune checkpoint inhibitors (ICIs) have become integral to the treatment of multiple cancer types. However, their role in rectal cancer remains undefined. Bando et al. update the current state of the science regarding the incorporation of ICIs into the rectal cancer treatment paradigm with an emphasis on the interaction with pre-operative radiation. The authors provide details of ongoing clinical trials as well as potential markers predictive of ICI efficacy in rectal cancer.

Stitzenberg and Barnes review many recent advances in rectal cancer surgery. First, they address the appropriate extent of resection, including the controversial issue of lateral pelvic node dissection. Next, they review advancements in local excision such as transanal excision (TAE), transanal endoscopic microsurgery (TEM), and transanal minimally invasive surgery (TAMIS). Regarding proctectomy, options now include laparoscopic, robotic, and transanal minimally invasive techniques. Finally, the authors acknowledge the potential long-term toxicities of surgery and conclude with a discussion of avoidance of surgery through watch-and-wait strategies.

The poor compliance with post-operative, adjuvant chemotherapy combined with the desire to improve disease-free and overall survival has driven interest in delivering all chemotherapy and radiation prior to surgery, known as total neoadjuvant therapy (TNT). In addition, intensifying pre-operative therapy through TNT has increased opportunities for deferral of surgery for patients with clini-

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cal complete responses in a watch-and-wait approach. Ng et al. review the role of radiotherapy in the current treatment of rectal cancer. Options such as pre-operative vs. post-operative and short course vs. long course are discussed in addition to omission of surgery or omission of radiotherapy in selected patients.

Johnson et al. provide a focused review of TNT from the both the Western and Asian perspectives. The sequencing of chemotherapy and radiation, the chemotherapy agents, and the use of long or short course radiation are all issues that require further data from ongoing clinical trials. Finally, Anker et al. provide a note of caution for overtreatment of some patients with the increased adoption of TNT. The authors emphasize that overall survival and quality of life must be considered the 2 most important endpoints. Incorporating the paradigms of TNT with watch and wait for clinical responders, they introduce the concept to “total definitive therapy (TDT)” for chemotherapy and radiation without surgery. Similarly, with improvements in MRI staging, omission of radiation may be appropriate for more patients. Therefore, the authors conclude that the future of rectal cancer treatment should focus on “one local therapy.”

We hope the reader will appreciate this collection of manuscripts that summarize the current state of the art in the multidisciplinary treatment of rectal cancer and that point the way forward to improvements in both oncologic outcomes and quality of life for our patients.

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