In this issue of JAMA Network Open, Kasi et al report the results of a systematic review and meta-analysis comparing the use of total neoadjuvant therapy (TNT) followed by surgery vs standard chemoradiotherapy (CRT) followed by surgery and adjuvant chemotherapy for patients with locally advanced rectal cancer. In their meta-analysis, which included 6 prospective trials with more than 1500 patients, a TNT approach was associated with higher rates of pathologic complete response (PCR) at the time of surgery and with improved disease-free survival (DFS) in the 3 studies that reported DFS. None of the 6 studies they analyzed provided data on overall survival (OS), and thus, the authors correctly conclude that longer follow-up of these studies is required to better understand the association between PCR, DFS, and eventual OS in patients with locally advanced rectal cancer. However, as more studies continue to complete accrual and present their results, the preponderance of evidence appears to support a TNT approach.

The treatment of locally advanced rectal cancer has evolved substantially during the last 3 decades. Along with improvements in preoperative staging and surgical techniques—in particular total mesorectal excision (TME)—the use of preoperative radiation or chemoradiation has helped to decrease local recurrence rates compared with surgery alone or surgery followed by adjuvant chemoradiation. For several decades, the standard of care for patients with clinically staged T3 or T4 or node-positive disease was to start treatment with concurrent CRT or short-course radiotherapy followed by TME and adjuvant chemotherapy. With this focus on local-regional neoadjuvant treatment options, local recurrences occur less often than with upfront surgery so that now distant failures have become the primary cause of morbidity and mortality for patients with locally advanced tumors. Therefore, the goal of many recent studies has been to improve rectal cancer outcomes by improving either systemic agents or the way systemic agents are given. It is important to note that after rectal surgery (either low-anterior or an abdomino-perineal resection) not every patient will be able to undergo postoperative adjuvant therapy, which is critical for systemic tumor control. Changing the order in which therapy is given, ie, giving systemic chemotherapy before surgery, either before or after radiotherapy or CRT, has been investigated in several studies to shift the standard of care away from the traditional approach of CRT followed by TME and adjuvant chemotherapy.

Delivering chemotherapy before surgery has several theoretical benefits that could conceivably optimize patient outcomes. First, delivering systemic therapy prior to surgery helps to improve the delivery of chemotherapy agents, with several studies showing greater than 90% compliance with preoperative chemotherapy. Second, many patients have fast and significant symptom relief shortly after starting systemic chemotherapy, which helps to further improve their ability to tolerate therapy. Third, the use of systemic agents in the neoadjuvant setting allows for the potential testing of novel systemic agents that could lead to improvements in surgical outcomes and ultimately distant failures and survival. Fourth, and most importantly, delivering systemic treatment to an intact tumor allows for potential preoperative assessment of response and either escalation or deescalation of therapy. Thus, the TNT approach is increasingly allowing a more personalized approach to the treatment of individual patients with locally advanced rectal cancer.

There is now no longer a single standard-of-care approach to the treatment of locally advanced rectal cancer. The inclusion of a TNT approach has allowed for the personalization of treatment based on several factors. The location of the patient's primary tumors (distal vs proximal) and magnetic
resonance imaging to evaluate whether the circumferential margin for TME is threatened can affect both the surgical approach and radiation decisions (ie, short course vs long course). Microsatellite instability of a tumor could affect the decision to begin treatment with chemoradiation rather than systemic fluorouracil-based therapy. Patient symptoms, such as bleeding, tenesmus, proctitis, or near obstruction, can affect the decision whether to start with systemic therapy or local/regional treatment. With the results of the Organ Preservation in Rectal Adenocarcinoma trial, a potential nonoperative management can affect the decision to use systemic therapy even in patients with node-negative disease. The results of the Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME trial may eventually also affect the decision to use or omit neoadjuvant radiotherapy in patients who respond to systemic chemotherapy and are willing to undergo surgery.

The use of preoperative systemic therapy has ushered in an era of increased personalization in the treatment of locally advanced rectal cancer and thus should be considered a component of the individualized standards of care. Although maturation of some of the ongoing and recently completed studies is needed to better understand the consequences of this approach on overall survival and quality of life, allowing a more personalized approach with either escalation or deescalation as warranted, represents by itself an improvement in clinical management. Future studies, which incorporate patient choice, personalized treatment approaches, and predictive as well as on-treatment biomarkers of response, such as circulating tumor DNA, will help to further define the best approaches to care for individual patients with locally advanced rectal cancer. We are no longer just standing on the threshold of the next frontier in the treatment of rectal cancer. The TNT approach has allowed us to open the door and enter the foyer of the future of locally advanced rectal cancer care.

ARTICLE INFORMATION
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REFERENCES


