Neoadjuvant Treatment Approaches for Stage II–III Rectal Cancer

Presented by Steven Nurkin, MD, MS

ABSTRACT

Excellent long-term outcomes are being achieved with contemporary treatment strategies for localized rectal cancer. A “watch-and-wait” nonoperative strategy seems to be a safe option for patients experiencing a complete clinical response. Total neoadjuvant therapy (TNT) has shown many advantages over standard chemoradiotherapy, although the optimal sequencing—with induction or consolidation chemotherapy—is still debated. The use of FOLFIRINOX can boost the benefit of TNT. Of note, in the small subset of patients whose tumors have mismatch repair deficient (dMMR) tumors, checkpoint inhibition has led to responses in most patients, eliminating the need for further treatment.

Contemporary strategies for treating localized rectal cancer are seeking to provide excellent long-term outcomes while minimizing toxicity, maximizing patient convenience and satisfaction, and, ideally, preserving the sphincter. These approaches currently include total neoadjuvant therapy (TNT), nonoperative management (“watch and wait”), and checkpoint inhibition in patients with mismatch repair–deficient (dMMR) tumors. The application of these approaches was described at the NCCN 2023 Annual Conference by Steven Nurkin, MD, MS, Chief, Colorectal Surgery, Associate Professor of Surgery, Roswell Park Comprehensive Cancer Center.

“For a patient with newly diagnosed rectal cancer there are several factors to think about. One of the most important things to focus on is the ‘who,’ which is more about the art of management than the science of it. It’s critical to engage patients and their caregivers in this discussion, to know their goals, and what they are trying to achieve with treatment. Then, we can tailor treatment based on that,” Dr. Nurkin said, adding that a multidisciplinary team should be involved from the start (Figure 1).

These tailored treatments largely center on the most effective contemporary management approaches of watch and wait and TNT. Dr. Nurkin described the evidence for these and other strategies.

Watch-and-Wait Approach

In 2004, Brazilian investigators reported the first results of a watch-and-wait approach in patients achieving a complete clinical response (cCR) to neoadjuvant chemoradiation (CRT).1 The 5-year overall and disease-free survival (DFS) rates were 88% and 83%, respectively, in the resection cohort and 100% and 92%, respectively, in the observation cohort. The investigators concluded that watch and wait was a potentially curable strategy, deferral of surgery was safe, and surgical salvage, when necessary, was effective.

Thereafter, the International Watch & Wait Database Consortium began collecting data and has reported over time a stable local tumor regrowth rate of around 24%.2 Of note, the phase II OPRA trial showed, for the first time in a randomized controlled trial, that a watch-and-wait strategy can be offered safely to patients with a similar regrowth rate.3 This has changed many conversations, Dr. Nurkin said.

“Newly diagnosed patients are terrified… They fear surgery and the probability of a permanent colostomy,” he said. For those who achieve a cCR and are offered watch-and-wait, “it’s a very emotional visit.” They are avoiding the potential complications of total mesorectal excision (TME), including surgical morbidities, permanent stoma, urinary and fecal incontinence, and sexual dysfunction. This strategy must involve an optimal preoperative regimen, comprehensive assessment of tumor response, and intensive surveillance, ideally as part of a clinical trial protocol, he emphasized. Optimal assessment includes a digital rectal examination, endoscopic evaluation, and MRI.1 If used alone, each tool has significant limitations, but if used in combination, the risk of missing a residual tumor is just 2%, according to one study,4 Dr. Nurkin said.

“We now have a high level of evidence supporting watch and wait, so we have included more guidance on this approach in the NCCN Guidelines,” he added.

Outcomes With TNT

The optimal way to achieve a cCR is with TNT, in which both chemotherapy and RT are given preoperatively. There are 2 approaches: chemotherapy first followed by CRT...
analysis of OPRA, patients were followed for >2 years. Results of this analysis showed that the probability of patients not needing TME was 78% for those who achieved a clinical complete response, 45% for those with a near-complete response, and 7% for those with an incomplete response ($P<.0001$). He said the difference likely reflects the “better biology” of tumors able to respond completely. The analysis also showed the benefit of waiting longer to determine response. In patients with a near-complete response at 8 to 10 weeks, 90% converted to a complete response 6 to 12 weeks later. Extended waiting increased the proportion of patients on the watch-and-wait approach by 43% in this series.

Although OPRA showed higher rectal-sparing rates with consolidation chemotherapy, Dr. Nurkin cautioned against overinterpreting this difference between the TNT approaches. NCCN has not recommended one approach over the other, but the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Rectal Cancer, Version 1.2023, do offer a discussion of this debate, he said.

“The main purpose of the OPRA trial was to show that if the patient does achieve a cCR—based on digital rectal examination, endoscopic evaluation, and MRI—and then undergoes intensive surveillance, they can safely be offered watch and wait; if the tumor recurs, this patient can be salvaged without harm,” he added.

**Short- Versus Long-Course Radiation for TNT**

Can the radiation course be shortened? The RAPIDO study evaluated an experimental short course of CRT as part of TNT. This involved RT with 5 × 5 Gy over a maximum of 8 days followed by 6 cycles of CAPOX (capecitabine/oxaliplatin) or 9 cycles of FOLFOX4 (oxaliplatin/leucovorin/fluorouracil), followed by TME. At 3 and 5 years follow-up, short-course CRT resulted in higher rates of pCR and lower rates of treatment failure and distant metastases compared with the standard longer course, but locoregional failures increased by 61% (10.2% vs 6.1%).

**Figure 1. Rectal cancer management—who, what, where, when, and how?**

Abbreviations: dMMR, deficient mismatch repair; DRE, digital rectal examination; RT, radiotherapy; TNT, total neoadjuvant therapy.
“The jury, therefore, is still out” as to whether short-course CRT is a good substitute for standard RT, according to Dr. Nurkin. The German ACO/ARO/AIO-18.1 trial is currently evaluating the RAPIDO short-course regimen hypothesizing that long-course chemoradiation will increase organ preservation rates compared with short-course RT (ClinicalTrials.gov identifier: NCT04230759).

Is More Chemotherapy Better?
“We are also looking to determine whether we can further improve tumor response, and thus be able to offer watch and wait to more patients by giving more chemotherapy prior to the response assessment,” stated Dr. Nurkin. The recent PRODIGE 23 study not only upheld the benefits of TNT but also showed that the use of intensified chemotherapy—FOLFIRINOX—may further boost efficacy. The experimental arm received neoadjuvant chemotherapy with FOLFIRINOX (fluorouracil/leucovorin/irinotecan/oxaliplatin) for 6 cycles, CRT, TME, and 3 months of adjuvant chemotherapy with modified FOLFOX6 or capecitabine. The standard-of-care group received CRT, TME, and 6 months of adjuvant chemotherapy. TNT with FOLFIRINOX significantly improved the pCR rate (P<.001), DFS (hazard ratio [HR], 0.69; P=.034), and metastasis-free survival (HR, 0.64; P=.017) in patients with cT3 or cT4 M0 rectal cancer.

“PRODIGE 23 showed that by adding irinotecan, we can improve outcomes; we are considering this especially for big, bulky, aggressive, high-risk tumors,” noted Dr. Nurkin. The currently enrolling randomized phase II Janus Rectal Cancer Trial will evaluate FOLFIRINOX versus FOLFOX/CAPOX in locally advanced tumors with cCR as the primary endpoint (ClinicalTrials.gov identifier: NCT05610163).

Immunotherapy Changes Clinical Practice for Some Patients
A major advance in curative-intent therapy is the use of PD-1 blockade in dMMR locally advanced rectal cancer. “It’s really quite tremendous, where we are going with immunotherapy,” Dr. Nurkin commented. “Without RT, we see some patients achieving a cCR and not needing surgery. It’s quite a game-changer.”
This excitement stems from a small 2022 study in which all of the patients with stage II–III tumors (n=16) were treated with 6 months of preoperative dostarlimab-gxly (and with 6 months of follow-up) and achieved a cCR. This resulted in the patients being able to forgo CRT and surgery.\textsuperscript{13} At the time of publication, none had experienced disease progression or recurrence.

The NCCN Guidelines have been updated to reflect these data, with recommendations for treating patients according to MMR status (Figure 2). “We have changed the algorithm to reflect dMMR vs MMR-proficient tumors, and we have completely different guidelines based on those data,” he noted.

Disclosures: Dr. Nurkin has disclosed serving as a consultant for Merck & Co., Inc.

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References


