Updates in the Management of Locally Advanced Rectal Cancer
Presented by Christopher G. Willett, MD

ABSTRACT

A plethora of advancements in the management of locally advanced rectal cancer continue to be developed. Treatment strategies have primarily focused on modifying the current standard paradigm of rectal cancer management—including the complete omission of surgery or radiotherapy, or instead using immunotherapy as first-line treatment in eligible patients. Recommendations for optimal therapeutic strategies, based on a patient’s clinical stage, have been outlined in the NCCN Guidelines for Rectal Cancer.

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“There has been a tremendous amount of activity, clinical research, and translational basic research in rectal cancer and colon carcinoma,” remarked Christopher G. Willett, MD, Chair, Department of Radiation Oncology, Duke Cancer Institute; Mark W. Dewhirst Distinguished Professor of Radiation Oncology, Duke University School of Medicine; and member of the NCCN Guidelines Panel for Rectal Cancer. At the NCCN 2024 Annual Conference, Dr. Willett reviewed the evolution of rectal cancer management strategies since the 1980s (Figure 1), and discussed emerging strategies to “deintensify” the standard treatment paradigm used in this patient population and how they have been incorporated into the updated management guidelines.

Early Management Strategies
Dr. Willett began his discussion with a clinical case. The patient was a 70-year-old female who presented with bright red blood in her rectum. A colonoscopy revealed a fungating, circumferential mass that was 12 to 14 cm from the anal verge. A tissue biopsy showed moderately differentiated adenocarcinoma. A chest/abdomen/pelvis CT was performed for tumor staging, which revealed no evidence of metastasis. Further analysis with a pelvic MRI demonstrated a circumferential mass in the mid-to-upper rectum, with no evidence of enlarged lymph nodes. The mass invaded through the muscularis into the mesorectal fat along the posterior rectum.

“Looking back to 2017, the treatments were pretty straightforward,” Dr. Willett remarked. Typically, patients with locally advanced rectal cancer were given preoperative chemoradiation (CRT) or short-course radiation therapy (SCRT) followed by a resection with total mesorectal excision (TME) and possibly adjuvant chemotherapy. As of 2024, numerous combination management strategies are now available, and optimal management depends on the patient’s TNM clinical stage and microsatellite stability status of the tumor. For example, according to Dr. Willett, patients with T3 or T4 disease—with or without nodal involvement—should be considered for neoadjuvant or adjuvant treatment.

Advances Through the Years in Rectal Cancer Management
“We can see steady progress with improved outcomes for these patients,” commented Dr. Willett, as he discussed the trajectory of rectal cancer treatment advancements. First used in 1986, resection with TME has been a valuable surgical option for these patients. He emphasized the importance of the quality of the excision and its correlation with patient outcomes. A successful TME includes a complete mesorectum with no defects, no evidence of coning, and a smooth, circumferential margin.

“The combination of neoadjuvant treatment and resection with TME has led to a prominent reduction in local failure,” Dr. Willett explained. A series of trials have demonstrated an improvement in local control of disease with the use of both adjuvant and neoadjuvant radiotherapy (RT) and CRT. Additionally, some of the early and pre-TME trials, such as the GITSG 71751 and Swedish Rectal Cancer Trial,2 have shown an improvement in overall survival (OS).

“There has been a lot of discussion about the use of RT between the preoperative and postoperative settings,” remarked Dr. Willett. However, a study conducted by Abraha et al5 demonstrated a profound improvement in local control for patients with locally advanced rectal cancer treated with neoadjuvant RT and resection with TME, suggesting its clinical utility in this patient population.
Dr. Willett further discussed the advancements in the rectal cancer treatment timeline, highlighting the benefit of adjuvant chemotherapy in improving local control and OS. He also mentioned the observed improvements in disease-free survival (DFS) when adjuvant oxaliplatin is added to the therapeutic regimen.

**Total Neoadjuvant Therapy**

“A major development over the past 5 to 10 years is the use of total neoadjuvant therapy [TNT], and importantly, its better compliance and improved outcomes,” stated Dr. Willett. TNT is essentially an intensification of the presurgical treatment. According to Dr. Willett, a number of studies have demonstrated an improvement in DFS, which he speculates “is the result of the systemic control provided by TNT.”

Thus far, the clinical benefits associated with TNT therapy seem promising. Trials comparing TNT and CRT—PRODIGE 23,4 RAPIDO,5 and STELLAR6—have shown significantly improved pathologic complete response rates with TNT therapy. However, additional investigative efforts comparing TNT + TME and the standard paradigm of CRT + TME with or without adjuvant chemotherapy are warranted.

“The findings of these studies provide an opportunity for nonoperative management,” suggested Dr. Willett.

**Strategies to Deintensify Rectal Cancer Treatment**

Dr. Willett discussed emerging opportunities to “de-intensify” treatment options for locally advanced rectal cancer. These strategies include considering nonoperative management, limiting the use of RT, and adopting the novel approach of immunotherapy.

**Selective Surgical Omission**

The OPRA trial randomly assigned patients with clinical stage II or III rectal cancer to receive induction chemotherapy followed by CRT or CRT followed by consolidation chemotherapy.7 Patients who achieved a near-complete or complete response after therapy were offered watch-and-wait surveillance protocols, whereas those with an incomplete response were advised to undergo resection with TME. This study revealed comparable DFS, OS, and rates of distant metastases in both treatment groups.

Dr. Willett then discussed the clinical parameters necessary for a complete response and incomplete response based on digital rectal and endoscopic examination, chest/abdomen CT scans, and pelvic MRI. “These types of studies are important in determining the recommendations toward the next steps in treatment,” he emphasized.

Furthermore, comparative analyses performed in patients managed with watch-and-wait surveillance protocols demonstrated increased rates of tumor regrowth in those treated with induction chemotherapy followed by CRT. Similarly, these patients had reduced rates of TME-free survival (41%) compared with patients treated with CRT followed by consolidation chemotherapy (53%).7

“One of the important requirements for watch and wait is the surveillance policies,” remarked Dr. Willett. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Rectal Cancer offer detailed surveillance guidelines with specific follow-up evaluations, which include history and physical examination, digital assessment, rectal MRI, chest and abdominal CT scan, and colonoscopy. Moreover, the NCCN Guidelines now include nonoperative management in potential treatment algorithms, according to Dr. Willett.
Selective Omission of RT

The need for RT in patients with low-risk, locally advanced rectal cancer is an ongoing topic of discussion, noted Dr. Willett, particularly in patients who can be managed with standard surgery-based treatment algorithms. Studies have attempted to resolve this question by omitting RT in the therapeutic approach and assessing DFS, OS, and the extent of local control.

The phase III FOWARC trial evaluated the clinical outcomes in patients with stage II or III rectal cancer who did and did not receive RT. Patients were randomly assigned to 1 of 3 treatment strategies: neoadjuvant fluorouracil with RT, modified FOLFOX6 [fluorouracil, leucovorin, oxaliplatin] with RT, or modified FOLFOX6 without RT. This study did not reveal any significant differences in DFS between the arms; thus, omitting RT as a therapeutic strategy may prove to be of clinical use. Although this study was deemed inconclusive given its limitations, it is “promising for recommending radiation omission in this patient population,” Dr. Willett noted.

The PROSPECT trial randomly assigned 1,194 patients (candidates for sphincter-preserving surgery) to receive CRT or modified FOLFOX6 therapy. Patients treated with modified FOLFOX6 who had a >20% tumor response had CRT omitted before surgery. No significant differences in DFS or OS were observed between treatment groups, suggesting similar clinical outcomes despite the omission of RT. Of note, both treatment groups demonstrated evidence of local tumor control rates >98%.

The PROSPECT trial also reported on patient-reported outcomes. This revealed an increased number of acute treatment-related adverse events associated with modified FOLFOX therapy in the neoadjuvant setting. However, a larger number of adverse events were reported by the patients treated with CRT 12 months after surgery. Despite these differences, the overall health-related quality of life remained equivalent between the groups.

According to Dr. Willett, additional factors should be considered before completely omitting RT. Of note, these decisions should be incorporated into a multidisciplinary, collaborative assessment and patient priorities to optimize the best clinical outcomes for the patient.

Immunotherapy

“These very preliminary findings lend optimism to molecular personalized approaches,” commented Dr. Willett, in reference to the role of immunotherapy in the management of rectal cancer. A study conducted by Cercek et al evaluated the PD-1 inhibitor dostarlimab-gxly in patients with locally advanced rectal cancer with microsatellite instability. All 12 patients demonstrated a clinical complete response, with evidence of durable disease control at follow-up.

“Unfortunately, the probability of the tumors being mismatch repair–deficient is only 5% to 10%,” explained Dr. Willett. “So this is an unusual clinical situation.”

References


Disclosures: Dr. Willett has disclosed no relevant financial relationships. Correspondence: Christopher G. Willett, MD, Duke Cancer Institute, 30 Duke Medicine Circle, Room 05143 Morris, Box 3085, Durham, NC 27710. Email: christopher.willett@duke.edu