Trimodal Therapy Approaches for Localized Rectal Cancer

Presented by Christopher G. Willett, MD

ABSTRACT

Excellent long-term outcomes and manageable toxicity are being achieved with contemporary treatment strategies for rectal cancer. Short-course radiotherapy is now an acceptable standard. Total neoadjuvant therapy (TNT), which incorporates induction or consolidation chemotherapy, has improved the delivery of treatment regiments. TNT is now a standard of care, although the sequencing of radiation and chemotherapy in TNT, appropriate amount of chemotherapy in TNT, and addition of irinotecan to the regimen are still being debated. Nonoperative management of rectal cancer appears to be a safe option for select patients, but it is not yet an NCCN recommendation. In addition, the omission of radiation is being evaluated as a treatment option in some cases.

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Contemporary and future strategies for treating localized rectal cancer aim to provide excellent long-term outcomes while minimizing toxicity, maximizing patient convenience and satisfaction, and, ideally, preserving the sphincter. These strategies include short-course radiotherapy (SCRT), total neoadjuvant therapy (TNT), nonoperative management, and omission of radiotherapy (RT)—topics that were discussed at the NCCN 2020 Virtual Annual Conference by Christopher G. Willett, MD, Professor, and Chair, Department of Radiation Oncology, Duke Cancer Institute.

SCRT Versus Long-Course Chemoradiotherapy

For patients with localized rectal cancer, SCRT is often given as 25 Gy in 5 fractions without concurrent chemotherapy and surgery performed within days of completion. SCRT has economic benefits, and compliance with this approach is excellent, but it does not change the preoperative stage of disease unless the surgery is delayed as in the Stockholm III trial.[1] In addition, there has also been some suggestion that acute toxicity may be less with SCRT than with long-course chemoradiotherapy (LCCRT), he said.[2]

LCCRT typically includes 50.4 Gy given over 5.5 weeks with concurrent 5-FU–based chemotherapy and surgery performed approximately 6 weeks later. LCCRT can result in achievement of pathologic complete response and tumor downstaging, and there may be some reduction in late toxicity compared with SCRT. The treatment, however, involves a much longer commitment from the patient. A watch-and-wait strategy after LCCRT, which avoids surgery altogether in patients whose disease responds, is of emerging interest. LCCRT is usually chosen to optimize sphincter preservation.

The comparative TROG 01.04 study showed that 3-year locoregional recurrence rates were not significantly different between SCRT and LCCRT, nor were rates of distant recurrence, relapse-free survival, and overall survival.[3] "As this trial matures, it will show data on quality-of-life differences, which has become a clinically important issue in assessing the relative merits of these 2 approaches," Dr. Willett said.

The more recent Polish II trial was similar to TROG 01.04 but incorporated neoadjuvant chemotherapy with 4 cycles of FOLFOX (5-FU/leucovorin/oxaliplatin) after SCRT prior to surgery versus LCCRT, surgery, and adjuvant chemotherapy.[4] With SCRT followed by chemotherapy, the rate of R0 resections (primary endpoint) trended favorably (P=.07) and acute toxicity was less (P=.006), but late complications were similar. SCRT also significantly improved overall survival (73% vs 65%; P=.046), although there was no longer a statistical significance in the 2019 update.[5] The Stockholm III trial reported that a longer interval (4–8 weeks) to surgery after SCRT was associated with lower rates of postoperative and surgical complications compared with a shorter interval (3–7 days).[1]

TNT is a Standard of Care for Select Patients

With either approach of LCCRT or SCRT, adjuvant chemotherapy is typically given after surgery. Studies have highlighted potential shortcomings of adjuvant chemotherapy, Dr. Willett continued.

Based on a SEER-Medicare database analysis of 18,491 patients with stage III colon cancer, the study investigators recommended that adjuvant chemotherapy should be ideally given within 8 weeks of surgery.[6]

Each 4-week delay negatively impacted survival and no benefit was seen at all for a delay >20 weeks. "Roughly, the 20-week point appears critical in terms of showing a survival benefit to the use of adjuvant chemotherapy," Dr. Willett commented.

Another limitation with adjuvant chemotherapy is the possibility that patients will not receive it at all. As many as 68% of patients will not receive adjuvant chemotherapy according to an analysis of the National Cancer Database,[7] although rates of nonreceipt appear to be much lower at NCCN Member Institutions.[8] Even for patients who do go on to adjuvant therapy, <50% receive all planned treatments.[9]

TNT: Rationale, Support From Trials

"There are clear challenges associated with the successful administration of adjuvant chemotherapy. To address some of these challenges, there has been the introduction of TNT," Dr. Willett said.

TNT is an approach to optimize the delivery of trimodality therapy with the incorporation of chemotherapy before or after LCCRT or SCRT and prior to surgery. The 2 approaches are (1) chemotherapy first, followed by LCCRT or SCRT, then surgery, or (2) LCCRT or SCRT first, followed by chemotherapy, then surgery (Figure 1). The relative merit of these approaches is an active area of investigation.

The rationale for using TNT is to improve treatment compliance, offer better tolerability to treatment effects, enhance downstaging of the primary tumor, facilitate organ preservation (through nonoperative management) in select patients, provide earlier treatment of micrometastatic disease, and decrease the interval from ileostomy to reversal. However, potential drawbacks to TNT include delays to resection (possibly potentiating local progression) and development of toxicity that may impact the possibility of definitive resection or lead to worsening performance and nutritional status.

The phase II TIMING trial studied patients with stage II/III rectal cancer within 12 cm of the anal verge.[10] This study evaluated 4 treatment approaches, all of which began with LCCRT, followed by a 4- to 6-week rest; 3 arms then received modified FOLFOX6 for 2, 4, or 6 cycles. Patients then underwent total mesorectal excision (TME). The complete pathologic response rate was highest (38%) for the group who received 6 cycles of modified FOLFOX6 and the longest interval to surgery (20 weeks) after LCCRT and decreased to 18% for those who received no cycles (*P*=.004) and the shortest time to surgery (6 weeks) post FU + RT. The zero-cycle group also experienced significantly inferior disease-free survival (DFS) than the modified FOLFOX6 group. However, overall survival and grade ≥3 surgical complications were not significantly different.

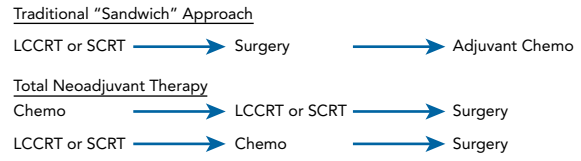

Figure 1. Total neoadjuvant therapy.
Abbreviations: chemo, chemotherapy; LCCRT, long-course chemoradiotherapy; SCRT, short-course radiotherapy.

The sequence of neoadjuvant FOLFOX was also studied in the randomized phase II CAO/ARO/AIO-12 trial.[11] Three cycles were given before or after LCCRT, followed by surgery. The pathologic complete response rate was higher with LCCRT first (27% vs 19%; *P*<.001). There was no difference in R0 resection rate between the treatment arms, Although overall toxicity rates were similar, grade 3/4 toxicity during LCCRT was higher with chemotherapy first (37% vs 27%).

Ongoing and recently completed trials are further evaluating the sequence of treatment strategies, including the randomized phase II Organ Preservation of Rectal Adenocarcinoma (OPRA) trial, NRG GI-002 (which includes novel agents), the Dutch and Nordic RAPIDO trial, and the PRODIGE 23 phase III trial.

At the ASCO 2020 Annual Meeting, the results of 2 randomized trials examining TNT strategies versus standard LCCRT and adjuvant chemotherapy were presented. In the RAPIDO trial,[12] MRI-staged patients with locally advanced rectal cancer with either cT4a/b, extramural vascular invasion, cN2, involved mesorectal fascia, or enlarged lateral lymph nodes were randomly assigned to SCRT with subsequent 6 cycles of CAPOX or 9 cycles of FOLFOX4 followed by TME or LCCRT followed by TME and optional adjuvant chemotherapy. The investigators reported a statistically lower rate of disease-related treatment failure due to a lower rate of distant metastases and a higher pathologic complete response rate in patients randomized to preoperative SCRT followed by chemotherapy + TME compared with conventional LCCRT, TME, and adjuvant chemotherapy.

Also at the ASCO meeting, the PRODIGE 23 investigators examined the role of neoadjuvant modified FOLFIRINOX before preoperative LCCRT with TME surgery and adjuvant modified FOLFOX versus preoperative LCCRT, surgery, and adjuvant modified FOLFOX in patients with stage II and III rectal cancer.[13] Study results demonstrated that neoadjuvant modified FOLFIRNOX and LCCRT were safe and significantly increased complete pathological response rates, DFS, and metastasis-free survival.

How NCCN Guidelines Incorporate TNT

In the NCCN Clinical Practice Guidelines in Oncology for Rectal Cancer,[14] Dr. Willett noted that "You see incorporation of the TNT strategy."

The guidelines were recently updated (version 4.2020) for more advanced disease, as follows:

- For T3, any nodal status, with clear circumferential margins, the 4 main options are: (1) LCCRT,

(2) SCRT, (3) chemotherapy followed by LCCRT, or (4) SCRT followed by 12 to 16 weeks of chemotherapy.

- For T3 disease, any nodal status and involved or threatened circumferential radial margin; T4 disease with any nodal status; and locally unresectable or medically inoperable tumors, the options are: (1) LCCRT, with restaging 6 weeks after completion of RT. For patients with involved circumferential radial margins or bulky residual disease, chemotherapy is advised for 12 to 16 weeks followed by restaging; (2) chemotherapy for 12 to 16 weeks followed by LCCRT; or (3) SCRT followed by 12 to 16 weeks of chemotherapy (Figure 2).

Watch-and-Wait Nonoperative Management

A nonoperative approach termed "watch and wait" involves treating the disease with LCCRT, and then evaluating response. Pivotal early studies showed local recurrence-free rates of 69%, 85%, and 85%,[15–17] and DFS rates of 68% to 81%. Of particular importance is a more recent study from Memorial Sloan Kettering Cancer Center (MSKCC).[18] "A total of 93 patients had rectal preservation with the watch-and-wait strategy, and the disease-specific survival was approximately 95% at 4 years. This analysis and others show us that select patients having a complete clinical response can be followed with watch-and-wait strategies," Dr. Willett said.

A number of phase II watch-and-wait trials are underway, including the OPRA trial evaluating both nonoperative management and TNT sequencing. This trial randomized patients with stage II and III rectal cancer to either induction chemotherapy followed by LCCRT, or LCCRT followed by consolidation chemotherapy and either TME (incomplete response) or nonoperative management (complete response).[19] Preliminary results of the OPRA trial were reported at the ASCO 2020 Annual Meeting.[20] Upfront LCCRT followed by consolidation chemotherapy resulted in a numerically higher watch-and-wait rate (58%) compared with induction chemotherapy followed by LCCRT (43%). More follow up and larger numbers of patients treated within properly controlled prospective studies are needed to validate the "watch-and-wait" approach.[21]

Role of Local Excision, Organoids

The recent GRECCAR-2 trial evaluated the role of local excision versus TME in 148 patients with T2/3 low rectal cancers <4 cm and have ≤2-cm residual tumors after CRT.[22] At 5 years there were no statistically significant differences between local excision and TME in terms of local recurrence (7% vs 7%), metastatic disease (19% vs 18%), or overall survival (82% vs 84%). These findings suggest that after LCCRT, local excision may be an alternative to radical resection for good responders, Dr. Willett said.

Such responses may eventually become more predictable, if research into patient-derived organoids is successful. The organoids, grown from the patient's tumor, can predict sensitivity to radiation and treatment. Yao et al[23] recently reported high accuracy (84%) between the organoid response and the clinical response to CRT in a phase III trial, confirming that rectal cancer organoids closely recapitulate the pathophysiology and genetic changes of corresponding tumors. "We're seeing really excellent correlation between clinical responses and the results of the organoid studies," Dr. Willett observed. "Clearly, these are very promising data that may allow us to identify which patients respond to neoadjuvant treatment."

Omission of Radiation

Ongoing studies are also evaluating the omission of radiation therapy in select patients. A pilot study from MSKCC enrolled 32 patients with stage II/III rectal cancers and

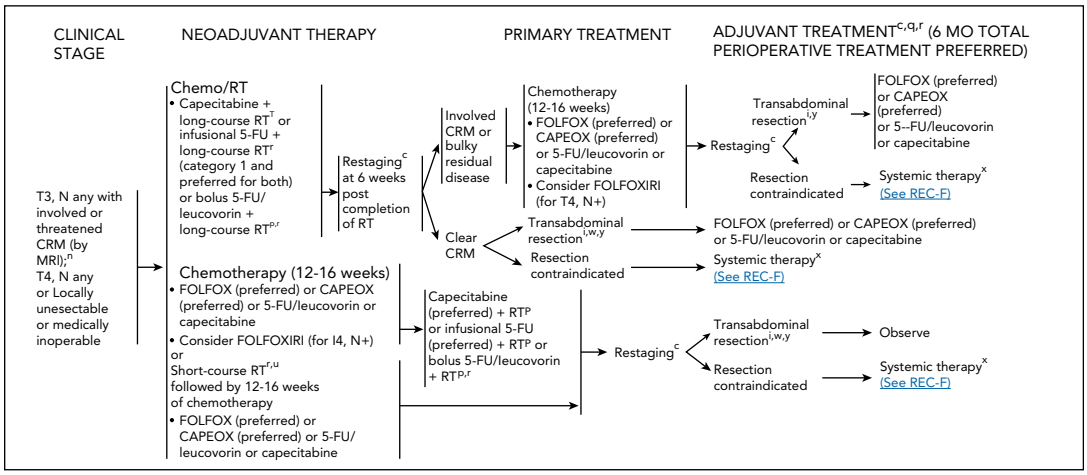

Figure 2. TNT for rectal cancer: 2020 standard of care. From the NCCN Guidelines for Rectal Cancer. Version 2.2020.

nonthreatened circumferential margins whose treatment goal was sphincter preservation.[24] After 6 cycles of FOLFOX + bevacizumab, the R0 resection rate was 100%, pathologic complete response rate was 25%, 4-year local recurrence rate was 0%, and 4-year DFS rate was 84%. In addition, 91% of patients were alive at 4 years. "These were very interesting data showing a quite satisfactory outcome in selected patients, without CRT," he commented.

Important data will be forthcoming from phase III trials, such as the Alliance PROSPECT study (ClinicalTrials.gov identifier: NCT01515787), which is evaluating the selective use of neoadjuvant FOLFOX and sphincter preservation surgery versus standard CRT, sphincter preservation surgery, and adjuvant chemotherapy.

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References

1. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol 2017;18:336–346.
2. Bujko K, Mowacki M, Nasierowska-Guttmejer A, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2004;72:15–24.
3. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827–3833.
4. Bujko K, Wyrwicz L, Rutkowski A, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol 2016;27:834–842.
5. Ciseł B, Pietrzak L, Michalski W, et al. Long-course preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: long-term results of the randomized Polish II study. Ann Oncol 2019;30:1298–1303.
6. Gao P, Huang XZ, Song YX, et al. Impact of timing of adjuvant chemotherapy on survival in stage III colon cancer: a population-based study. BMC Cancer 2018;18:234.
7. Xu Z, Mohile SG, Tejani MA, et al. Poor compliance with adjuvant chemotherapy use associated with poorer survival in patients with rectal cancer: an NCDB analysis. Cancer 2017;123:52–61.
8. Khrizman P, Niland JC, ter Veer A, et al. Postoperative adjuvant chemotherapy use in patients with stage II/III rectal cancer treated with neoadjuvant therapy: a National Comprehensive Cancer Network analysis. J Clin Oncol 2013;31:30–38.
9. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014;15:184–190.
10. Marco MR, Zhou L, Patil S, et al. Consolidation mFOLFOX6 chemotherapy after chemoradiotherapy improves survival in patients with locally advanced rectal cancer: final results of a multicenter phase II trial. Dis Colon Rectum 2018;61:1146–1155.
11. Fokas E, Allgäuer M, Polat B, et al. Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12. J Clin Oncol 2019;37:3212–3222.
12. Hospers G, Bahadoer RR, Dijkstra EA, et al. Short-course radiotherapy followed by chemotherapy before TME in locally advanced rectal cancer: the randomized RAPIDO trial [abstract]. Presented at the ASCO 2020 Annual Meeting; May 29–31, 2020; Chicago, Illinois. Abstract 4006.
13. Conroy T, Lamfichekh N, Etienne PL, et al. Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: final results of the PRODIGE 23 phase III trial, a UNICANCER GI trial [abstract]. Presented at the ASCO 2020 Annual Meeting; May 29–31, 2020; Chicago, Illinois. Abstract 4007.
14. Benson AB III, Venook AP, Al-Hawary MM, et al. NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer. Version 2.2020. Accessed March 3, 2020. Available at NCCN.org
15. Habr-Gama A, Gama-Rodrigues J, São Julião GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys 2014;88:822–828.
16. Martens MH, Maas M, Heijnen LA, et al. Long-term outcome of an organ preservation program after neoadjuvant treatment for rectal cancer. J Natl Cancer Inst 2016;108:djw171.
17. Appelt AL, Pløen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol 2015;16:919–927.
18. Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. JAMA Oncol 2019;5:e185896.
19. Smith JJ, Chow OS, Gollub MJ, et al. Organ Preservation in Rectal Adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management. BMC Cancer 2015;15:767.
20. Garcia-Aguilar J, Patil S, Kim J, et al. Preliminary results of the OPRA trial [abstract]. Presented at the ASCO 2020 Annual Meeting; May 29–31, 2020; Chicago, Illinois. Abstract 4008.
21. Gynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow up. Ann Oncol 2017;28(Suppl 4):iv22–40.
22. Rullier E, Vendrely V, Asselineau J, et al. Organ preservation with chemoradiotherapy plus local excision for rectal cancer: 5-year results of the GRECCAR 2 randomised trial. Lancet Gastroenterol Hepatol 2020;5:465–474.
23. Yao Y, Xu X, Yang L, et al. Patient-derived organoids predict chemoradiation responses of locally advanced rectal cancer. Cell Stem Cell 2020;26:17–26.
24. Schrag D, Weiser MR, Goodman KA, et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 2014;32:513–518.