

REVIEW ARTICLE

Advances in the treatment of locally advanced rectal cancer

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Abstract

Locally advanced rectal cancer requires multidisciplinary care. In the United States, most patients are treated with neoadjuvant chemoradiation delivered over 25–28 days, total mesorectal excision, and 4 months of adjuvant chemotherapy. While effective, this trimodal approach is arduous. Alternative approaches have emerged to streamline treatment without sacrificing oncologic outcomes. These approaches include preoperative chemotherapy with selective use of radiation, short-course radiotherapy delivered over 5 days, and total neoadjuvant therapy with attempted nonoperative organ-preserving management (watch and wait). Ongoing trials are assessing the efficacies of these approaches in combination with various risk stratification strategies.

KEYWORDS

locally advanced rectal cancer, nonoperative management, total mesorectal excision, total neoadjuvant therapy, watch and wait

1 | INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer worldwide and the fourth leading cause of cancer-related death in the world.¹ Globally, it is estimated that 1.6 million patients are diagnosed with colorectal cancer each year,² with 30% of the tumors located in the rectum.² Historically, locally advanced rectal cancer (LARC), comprising T3 and T4 tumors and/or tumors involving locoregional lymph nodes, has been difficult to cure. The boundaries of the bony pelvis, the proximity to the sphincter, and the need to preserve autonomic nerves have made surgical resection challenging and morbid.

The multimodal treatment approach has improved the rates of local control and sphincter preservation. The widely accepted standard care for LARC consists of neoadjuvant long-course chemoradiotherapy (LCRT) or short-course hypofractionated radiotherapy (SCRT) followed by total mesorectal excision (TME) and adjuvant fluoropyrimidine-based chemotherapy. While this multimodal

approach has led to improvement in the rates of local recurrence, it has not had significant effect on the rates of distant recurrence or overall survival.³

Distant recurrence is the primary cause of treatment failure in LARC patients.⁴ LARC is increasingly recognized as a heterogeneous group of cancers that vary in distance from the anal verge, T and N stages, the size of the circumferential resection margin, the presence of extramural venous invasion, and the tumor's genetic profile, with these variations potentially being responsible for different responses to similar treatments.

As our understanding of tumor-specific prognostic factors improves and our quest to prevent distant recurrence continues, important questions emerge about the benefits (or lack thereof) of each component of the multimodal approach. What is the optimal regimen for neoadjuvant radiotherapy (RT) (LCRT vs SCRT)? Do all patients with LARC need radiation? What is the optimal timing of systemic chemotherapy (neoadjuvant vs adjuvant)? Do all patients need resection, or is nonoperative, organ-preserving

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management appropriate in selected patients with a complete clinical response? In this article, we explore the recent advances and controversies surrounding the management of LARC and describe the importance of an individualized treatment plan based on the tumor's stage, location, genetic profile, and response to neoadjuvant treatment and on the individual patient's quality-of-life goals.

2 | "STANDARD OF CARE": HOW DID WE GET HERE?

Advances in surgical technique and RT have led to significant improvements in the treatment of LARC. TME, the standard surgical approach, entails anatomical resection of the rectum plus the whole enveloping mesorectal fascia by precise dissection along embryological planes. TME facilitates removal of the locoregional lymph nodes while minimizing injury to autonomic pelvic nerves. The adoption of TME led to a significant decline in the rate of local recurrence of resectable rectal cancer.^{5,6} The inclusion of RT in standard treatment of LARC was subsequently challenged, as TME decreased the rates of local recurrence without RT.

The Dutch Colorectal Cancer Group Trial played a crucial role in determining the benefits of preoperative RT in combination with TME. The trial found that patients who underwent TME alone for resectable rectal cancer (including LARC) had a higher rate of local recurrence than patients who underwent SCRT (25 Gy over 5 days) plus TME (8.2% vs 2.4%), with no significant difference in overall survival at 2 years (81.8% vs 82.0%, respectively) or the rate of distant recurrence at 2 years (16.8% vs 14.8%, respectively). Univariate subgroup analysis showed that among patients with tumors in the middle rectum, those who underwent preoperative SCRT plus TME had a lower rate of local recurrence at 2 years than those who underwent TME alone (1% vs 10.1%; $P < .001$). A difference was also seen for patients with tumors in the lower rectum (5.8% vs 10%; $P = .05$) but not in patients with tumors in the upper rectum. Other than higher blood loss and more perineal wound complications in the SCRT-TME group, there was no significant difference in morbidity or mortality.⁷ The finding of no significant difference in overall survival or the rate of distant recurrence and a lower rate of local recurrence in SCRT-TME patients was confirmed with median follow-up of 6 years (local recurrence, 5.6% vs 10.9%; $P < .001$).⁸

In contrast, the earlier Swedish Rectal Cancer Trial did find a higher 5-year rate of overall survival in patients who had undergone preoperative SCRT plus surgery than in patients who had undergone surgery alone (58% vs 48%; $P = .004$).⁹ The rate of local recurrence in patients who had undergone SCRT plus surgery was 9%, compared with 23% in patients who underwent surgery alone. It is worth noting that the surgical approach in the Swedish trial did not comply with the principles of TME, which probably explains the very high rate of local recurrence. The survival benefit was not reproducible in other trials.^{8,9}

Subsequent trials that focused on LARC and various RT regimens, with or without concurrent chemotherapy in the preoperative or postoperative period, obtained results consistent with the findings of the Dutch study.¹⁰⁻¹⁴ In a trial conducted by the German Rectal Cancer Study Group, preoperative chemo-RT consisting of LCRT (50.4 Gy over 5 weeks) and fluorouracil was compared with postoperative chemo-RT. As reported by Sauer et al,^{10,11} the trial found lower rates of grade 3 or 4 acute and long-term toxicities and better 5-year local control in patients who received preoperative chemo-RT than in patients who received postoperative chemo-RT (6% vs 13%; $P = .006$), with no significant difference in overall survival (74% vs 76%), disease-free survival (68% vs 65%), or the rate of distant recurrence (36% vs 38%) at 5 years. Importantly, the rate of compliance with chemotherapy and RT and the rate of sphincter preservation were higher in patients who received chemo-RT before surgery. This trial was pivotal in establishing preoperative chemo-RT as the standard of care for LARC.

The benefits of preoperative chemo-RT were further revealed in the FFCO 9203 trial, a multicenter trial comparing preoperative RT and preoperative chemo-RT in patients with T3 or T4 tumors in the middle rectum or lower rectum (>5 or ≤5 cm from the anal verge, respectively). Patients who had undergone preoperative chemo-RT had a 50% lower rate of local recurrence at 5 years (8.1% vs 16.5%) and a higher rate of pathologic complete response (pCR; 11.4% vs 3.6%).¹²

In an effort to establish a standard of care for LARC, the EORTC trial 22921 compared preoperative RT, preoperative chemo-RT, preoperative chemo-RT with adjuvant chemotherapy, and preoperative RT with adjuvant chemotherapy. No significant difference in overall survival was observed. The rate of local recurrence was lowest in patients who received preoperative chemo-RT and postoperative chemotherapy (7.6%) and highest in patients who received preoperative RT only (17.1%). The authors concluded that fluorouracil-based chemotherapy helped reduce the likelihood of local recurrence.^{13,14}

Some trials have investigated alternative agents for neoadjuvant radiosensitizing chemotherapy. The NSABP-R04 trial demonstrated the noninferiority of capecitabine to fluorouracil. Oxaliplatin combined with neoadjuvant fluorouracil has not been consistently beneficial in multiple trials and is associated with higher toxicity. Fluorouracil remains the recommended agent for neoadjuvant chemo-RT.^{4,6} While preoperative chemo-RT and TME are widely accepted as the standard of care, the relative advantages of SCRT and LCRT are a subject of ongoing debate.

3 | SCRT VS LCRT

Preoperative SCRT consists of 25 Gy given over 5 days and is followed by surgery within 7 days, while LCRT consists of 45-50.4 Gy over 5-6 weeks, with concurrent sensitizing fluoropyrimidine-based chemotherapy and surgery 8-12 weeks later. Preoperative SCRT is more commonly used in European countries and is

considerably less expensive, less time-consuming, and more convenient for patients than LCRT. While the tumor-killing capacity of SCRT is equivalent to that of LCRT, the shorter time to surgery decreases the potential for tumor downstaging and adequate pathologic response.^{9,15-17}

In a clinical trial conducted in Poland, Bujko et al¹⁵ compared preoperative SCRT followed by surgery within 7 days with LCRT followed by surgery in 4-6 weeks. The oncologic outcomes (overall survival, disease-free survival, and local recurrence) at 4 years were similar between the two groups, indicating that SCRT is a reasonable alternative to LCRT. However, patients who received LCRT had a higher rate of pCR (16.1% vs 0.7%) and a lower likelihood of a positive circumferential margin (4.4% vs 12.9%; $P = .017$).

A clinical trial conducted by the Trans-Tasman Radiation Oncology Group¹⁶ compared preoperative SCRT and LCRT in patients with T3 rectal tumors within 12 cm from the anal verge, regardless of nodal status. The two groups of patients did not differ significantly in overall survival, local-recurrence-free survival, or distant-recurrence-free survival, but SCRT patients had a somewhat higher rate of local recurrence (7.5% vs 4.4%). This trend may have stemmed from the fact that the SCRT group had a higher proportion of patients with tumors in the lower rectum (30% vs 19%). The rate of pCR was higher in the LCRT group (15% vs 1%), but the rates of positive circumferential margin were comparable (4% vs 5%). The authors concluded that LCRT may be more effective in terms of local control.

Optimal dosing and time to surgery for preoperative RT were investigated in the Stockholm III noninferiority trial, in which 840 patients with resectable rectal cancer underwent either SCRT with immediate surgery, SCRT with surgery 4-6 weeks later, or LCRT with surgery 4-6 weeks later. Disease outcomes did not differ significantly between the three groups, but patients who underwent SCRT with surgery 4-6 weeks later had a lower rate of postoperative complications, greater tumor regression, and a higher rate of pCR (11.8% vs 1.7%) than patients who underwent SCRT with immediate surgery. The authors concluded that SCRT with delayed surgery is a viable alternative to LCRT.¹⁷

Although these trials have not definitively answered the question of whether SCRT or LCRT leads to better tumor control, they have demonstrated the potential benefit of delaying surgery after RT to maximize tumor response.

4 | SELECTIVE RT

Other than the Swedish Rectal Cancer Trial,⁹ no study has demonstrated a survival benefit of RT in patients with rectal cancer. In a pooled analysis of multiple phase III trials in North America, Gunderson et al¹⁸ found that in LARC patients with intermediate risk of local recurrence (T1/2N1 or T3N0), the addition of RT did not reduce the likelihood of local recurrence or increase survival. In addition, a subgroup analysis of data from the trial conducted by the Dutch Colorectal Cancer Group did not find a benefit of RT in

patients with tumors confined to the upper rectum.⁸ Trimodal treatment regimens may in fact be excessive in some patients with rectal cancer, with the associated toxicities (such as pelvic fibrosis; autonomic nerve injury causing sexual, bladder, or bowel dysfunction; and depletion of pelvic bone marrow leading to reduced tolerance of chemotherapy and compromising functional outcomes, especially in cases of low anastomosis) potentially outweighing the benefit. The use of neoadjuvant chemotherapy alone allows systemic chemotherapy to be delivered earlier, which may induce tumor downstaging, eliminate micrometastases, prevent distant relapse, and benefit overall survival.^{6,19}

A single-institution phase II trial with 32 patients demonstrated that selective elimination of preoperative RT might be feasible in patients with chemosensitive LARC and a low risk of local recurrence. In that trial, Schrag et al²⁰ evaluated neoadjuvant chemotherapy in patients with stage II or III LARC (cT3N- or cT2/3N+) who were candidates for sphincter-preserving TME. The protocol consisted of six cycles of FOLFOX with bevacizumab, followed by immediate TME in responders or preoperative RT and then TME in patients with stable or progressive disease. Interestingly, all patients had a clinical response and proceeded to TME without preoperative RT. In addition, all patients had a negative circumferential resection margin, with sustained local control at 4 years. The rate of pCR was 25%, which is in the range of pCR rates achieved with preoperative RT. Disease-free survival at 4 years was 84%.

PROSPECT, a large multicenter phase II/III trial, is currently investigating selective RT in patients with intermediate-risk LARC (T1/2N1, T3N0, or T3N1) and a nonthreatened circumferential resection margin who are eligible for sphincter-preserving treatment.²¹ In the standard arm, the patients receive standard care in the form of preoperative fluorouracil- or capecitabine-based LCRT, followed by TME and then eight cycles of adjuvant FOLFOX. In the selective arm, patients receive six cycles of neoadjuvant FOLFOX followed by response evaluation with proctoscopy and magnetic resonance imaging (MRI). Those with a $\geq 20\%$ tumor response based on endoscopy and MRI proceed to TME, followed by adjuvant FOLFOX, while those with $< 20\%$ response undergo neoadjuvant chemo-RT, followed by TME and two cycles of adjuvant chemotherapy. Patients in the latter group who have a positive circumferential resection margin also receive postoperative chemo-RT.¹⁹ The trial has completed accrual and is awaiting data maturation.²¹ The results of this trial will help determine whether some patients can avoid preoperative RT without compromising local control or adequate surgical resection.

5 | TNT

A relatively new approach to multimodal management of LARC involves neoadjuvant use of systemic chemotherapy. This approach is known as total neoadjuvant therapy (TNT). In TNT, neoadjuvant chemotherapy can be given either before (induction) or after (consolidation) chemo-RT but prior to curative surgical resection. Preoperative administration of systemic chemotherapy has several

potential advantages. It facilitates tumor downstaging, tackles micrometastatic disease up front, and has the potential to prevent distant recurrence, a common cause of death in patients with rectal cancer. Administering systemic chemotherapy in the neoadjuvant setting improves compliance with treatment and minimizes treatment-related complications. For example, after a proctectomy, patients often experience treatment delays and/or receive suboptimal dosing while they are recovering from major surgery and postoperative complications. In the EORTC 22921 trial, up to 27% of patients did not receive adjuvant chemotherapy at all, and less than 43% of patients randomized to postoperative chemotherapy received treatment within the scheduled time interval.¹⁴ Similarly, only 58% of patients randomized to adjuvant chemotherapy in the Italian I-CNR-RT Trial received all six planned cycles of adjuvant chemotherapy.²²

Patients who receive neoadjuvant chemotherapy and undergo restorative proctectomy with a diverting loop ileostomy do not have to receive chemotherapy while the stoma is in place, minimizing stoma-related morbidity and the gastrointestinal toxicity of systemic chemotherapy. In a study of 61 LARC patients who received induction chemotherapy followed by chemo-RT or immediate TME, Cercek et al²³ found that 36% of patients had either a pCR ($n = 13$) or a clinical complete response ($n = 9$). All patients had an R0 resection, and no side effects resulting in treatment interruption occurred. The investigators concluded that the TNT approach results in excellent tumor regression with minimal toxicity. In another study, patients with LARC who received neoadjuvant chemotherapy had a higher rate of completion (91% vs 54%) and lower incidence of toxicity (19% vs 54%) than patients who received chemotherapy after the surgery.²⁴

A retrospective cohort analysis of 628 patients at Memorial Sloan Kettering Cancer Center²⁵ found that the rate of complete response (both pathologic and clinical) was significantly higher in patients who received induction chemotherapy than in patients who received adjuvant chemotherapy (41% vs 27%), and 78% of patients who received induction chemotherapy completed eight cycles of chemotherapy (including oxaliplatin), compared with only 41% of patients who received adjuvant chemotherapy. Similarly, a pooled analysis of data from the European phase II clinical trials EXPERT and EXPERT-C²⁶ found that patients with high-risk LARC (tumor location < 1 mm from the mesorectal fascia, category cT3c/d or T4, or involvement of pelvic floor musculature) benefited from induction chemotherapy followed by chemo-RT. The rate of pCR was 20%, and T and N downstaging occurred in 56% and 43% of patients in the two trials. Although the trials lacked a chemo-RT control group, they did demonstrate sustained tumor regression in a high-risk population.

The multicenter Timing trial conducted by Garcia Aguilar et al²⁷ demonstrated good tolerance of consolidation chemotherapy (given after chemo-RT and prior to surgery), with pCR in 36% of patients after six cycles of FOLFOX. Although it is not clear whether this high rate of tumor regression was due to delaying surgery for several months after chemo-RT, the findings provide additional evidence that TNT promotes tumor downstaging. In addition to tumor downstaging, newly published results from two phase III trials, RAPIDO and

PRODIGE 23, demonstrate the benefit of neoadjuvant chemotherapy in decreasing risk of distant recurrence.^{28,29} In the international RAPIDO trial, 920 patients with high-risk LARC, including patients with cT4 tumors, cN2 disease, threatened mesorectal margin, or enlarged lateral pelvic lymph nodes, were randomized to either SCRT followed by consolidation systemic chemotherapy and TME surgery or traditional LCRT followed by TME surgery.²⁸ Patients in the TNT arm achieved a higher rate of pCR (28% vs 14%) and a lower 3-year rate of distant recurrence (20% vs 27%). The PRODIGE 23 trial randomized patients with LARC to either six cycles of FOLFIRINOX followed by chemoradiation and then surgery and 3 months of adjuvant chemotherapy or neoadjuvant chemoradiation followed by surgery and 6 months of adjuvant chemotherapy.²⁹ Patients in the TNT arm had a higher rate of pCR (28% vs 12%) and a higher rate of disease-free survival at 3 years (76% vs 69%). The ability to reduce the risk of systemic recurrence is a unique advantage to the TNT approach. In addition, the increasing rates of pCR and clinical complete response with TNT have opened opportunities for organ preservation in selected patients.

6 | WATCH AND WAIT

Although TME has been a cornerstone in management of rectal cancer for several decades, between one-quarter and one-third of patients who receive neoadjuvant chemo-RT are found to have a pCR when they undergo TME.^{30,31} Patients with pCR have excellent oncologic outcomes, with local recurrence rates of <1% and 5-year overall survival of up to 95%.^{32,33} Can surgery, and possible colostomy, be avoided in patients with no clinical evidence of disease following neoadjuvant therapy? The challenge of nonoperative management of rectal cancer is how to accurately identify complete response.

Nonoperative management, or watch and wait, has been studied most extensively by A. Habr-Gama's group in Sao Paulo, Brazil.³⁴⁻³⁶ In one study, patients with resectable distal rectal cancer (≤ 7 cm from the anal verge) were offered strict surveillance if they had a complete clinical response based on MRI and endoscopy 1 year after completion of chemo-RT.³⁴ A sustained complete clinical response was found in 27% of the patients, and those patients were able to avoid TME. Endoluminal recurrence was found in 5% of those patients, all of whom underwent successful salvage with either local excision or TME. The rate of systemic recurrence in patients who underwent nonoperative management was equivalent to the rate in patients who were found to have a pCR when they underwent TME.

A group in the Netherlands investigated outcomes after nonoperative management in 21 patients with rectal cancer who met the criteria of complete clinical response after chemo-RT.³⁷ With mean follow-up of 25 ± 19 months, one patient developed a small endoluminal recurrence with no nodal disease and underwent complete excision of the recurrent tumor by transanal endoscopic microsurgery. In a study at Memorial Sloan Kettering, 32 patients with stage I-III rectal cancer who had a clinical complete response

after neoadjuvant chemo-RT underwent nonoperative management.³⁸ With median follow-up of 28 months, six patients (19%) had a local recurrence. All six underwent a successful salvage TME, with no further recurrence. As in previous studies, the rate of systemic recurrence in patients who underwent nonoperative management was not significantly different from the rate in patients who underwent TME and were found to have a pCR. While all these studies demonstrated high rates of rectum preservation and successful salvage of local (mostly endoluminal) recurrences, they were limited by small sample sizes, the heterogeneity of the study populations, and relatively short follow-up. Retrospective analysis of an international database of about 1000 rectal cancer patients managed with a watch-and-wait approach similarly showed that 25% of patients had a local regrowth after a median follow-up of 3 years; 88% of regrowths were diagnosed within the first 2 years, and 97% of the local regrowths were within the bowel wall.³⁹

A follow-up study reported by Memorial Sloan Kettering⁴⁰ analyzed 5-year follow-up data from patients who underwent watch-and-wait management after a clinical complete response to neoadjuvant therapy. Of the 113 patients, 22 (20%) developed local regrowth at a median of 11 months. All 22 patients underwent salvage surgery, including two patients who underwent transanal excision as definitive salvage treatment. Thus, the rectum was preserved in 82% of the patients. A concerning finding from the study is the significantly higher rate of distant recurrence in patients with local regrowth than in patients without regrowth (36% vs 1%; $P < .001$). Eight of the nine patients who developed distant recurrence had local regrowth. In comparison, in patients found to have a pCR when they underwent TME, the rate of distant recurrence was 4%. Causality cannot be determined, but these observations raise the question of whether deferral of surgery predisposes some patients to distant metastasis. Better risk stratification is needed for nonoperative management.^{41,42} Molecular subtyping and analysis of circulating tumor DNA may help identify appropriate candidates among patients.

While many studies provided evidence that the TNT approach offers an improvement in the rate of pCR, very few studies assessed the role of this approach in achieving organ preservation within a watch-and-wait protocol. The OPRA trial is the first trial to address the effect of the sequence of neoadjuvant treatment within a TNT approach on the rate of organ preservation.⁴³ In this multicenter randomized control trial by Garcia Aguilar et al, patients with clinical stage II or III rectal cancer were randomized to 4 months of FOLFOX or CAPEOX before (induction) or after (consolidation) LCRT. A watch-and-wait approach was pursued if clinical complete response, based on digital rectal exam, endoscopy, and MRI, was achieved. After a median follow-up of 2.1 years, preliminary results showed that 58% of patients in the consolidation chemotherapy arm were able to achieve organ preservation compared to only 43% of patients in the induction chemotherapy arm.⁴³ There was no difference in disease-free survival or distant metastasis-free survival between the two groups. While the results are very promising, it is

important to await the final and long-term follow-up results of the study to understand the complete oncologic outcomes.

7 | SUMMARY

Locally advanced rectal cancer is a complex disease that requires multidisciplinary care. While local control has been improved by combining TME, RT, and chemotherapy, systemic recurrence remains a concern. Recent advances include TNT, which can reduce the likelihood of distant metastasis by delivering effective systemic chemotherapy early in the course of treatment. Nonoperative management of distal tumors and selective use of RT for tumors in the middle or upper rectum can reduce treatment morbidity without compromising oncologic outcomes. The results of recently reported trials including RAPIDO, PRODIGE 23, and OPRA will hopefully lead to an individualized approach to treatment of rectal cancer, based on tumor characteristics, genomics, and patient preferences.

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