Optimal Neoadjuvant Strategies for Locally Advanced Rectal Cancer by Risk Assessment and Tumor Location

Anurag Saraf, MD1,2; Hannah J. Roberts, MD1,2; Jennifer Y. Wo, MD2; and Aparna R. Parikh, MD, MS3

ABSTRACT

Neoadjuvant therapy is standard of care for locally advanced rectal cancer (LARC). Advancements in multimodality therapy options and sequencing of radiation therapy (RT), surgery, and chemotherapy make decision-making challenging. Traditional treatment of patients with LARC involves neoadjuvant chemoradiation followed by total mesorectal excision and consideration of adjuvant chemotherapy. Advancement in RT has led to trials offering both short-course and long-course RT with good long-term clinical outcomes. Intensification of therapy in high-risk patients has led to studies of total neoadjuvant therapy with chemotherapy and chemoradiation, now standard management for most LARC. De-escalation of therapy in patients with favorable prognosis has led to several considerations, including non–total mesorectal excision management or neoadjuvant chemotherapy only. Several considerations of patient and disease factors can help inform the optimal chemotherapy regimens in different sequencing of neoadjuvant strategies. Finally, novel biomarkers, such as microsatellite instability, has led to utilization of novel therapies, including neoadjuvant immunotherapy, with substantial response. This review attempts to frame the rapidly growing data in LARC in context of disease and patient risk factors, to inform optimal, personalized treatment of patients with LARC.


Although early-stage rectal cancer is primarily treated with surgery, locally advanced rectal cancer (LARC), defined here as T3–4 or N-positive disease, generally involves multimodality therapy with surgery, radiation therapy (RT), and chemotherapy.1 The benefit of multimodality therapy in patients with LARC was established in a number of historical studies, including adjuvant studies of GITSG 7175, NSABP R-01, and NSABP R-02.2-5 Extrapolation from these series in the modern era is limited because most lacked modern surgical technique of total mesorectal excision (TME), which decreases local recurrence from 20% to 5% without adjuvant therapy.6-9 Neoadjuvant therapy trials sought to further improve upon these results in the context of compliance, toxicity, and long-term survival (Table 1).

This review provides an overview of current considerations and approaches to the management of patients with LARC and discusses each treatment modality, including surgical considerations, RT, and chemotherapy, as well as briefly discusses less common considerations, such as patients with microsatellite instability–high (MSI-H) disease and those with inflammatory bowel disease (IBD).

Historical Principles of Neoadjuvant Therapy

The German Rectal Cancer Study Group (GRCSG) trial established the modern neoadjuvant standard-of-care (SoC) management of LARC.10 A total of 823 patients with clinical T3–4 or node-positive rectal cancer by endorectal ultrasonography and CT of the abdomen and pelvis were randomized to receive preoperative chemoradiation (CRT) (5-FU concurrent with 50.4 Gy radiation in 1.8 Gy fractions per day) or postoperative CRT (5-FU concurrent with 55.8 Gy radiation in 1.8 Gy fractions per day). At a median follow-up of 45.8 months, the 5-year overall survival (OS) rate was not significantly different (76% vs 74%; P=.80); however, 5-year local recurrence was decreased in the preoperative arm (6% vs 13%; P=.006). Further, toxicity was lower in the preoperative CRT arm, with improved grade 3–4 acute (27% vs 40%; P=.0001) and late (14% vs 24%; P=.01) toxicity. Given the improvement in local control with fewer adverse effects, neoadjuvant CRT became the SoC for locally advanced rectal tumors.
RTE (Short-Course and Long-Course)

With the GRCSG trial changing the paradigm of neoadjuvant CRT, further consideration was given to the course of RT. RT approach has been a major question in the consideration of neoadjuvant therapy for patients with LARC. The 2 major approaches are short-course RT (SCRT), typically consisting of 25.0 Gy in 5.0 Gy per fraction over 1 to 2 weeks of total treatments, or long-course RT (LCRT), typically consisting of 50.0 to 54.0 Gy in 1.8 to 2.0 Gy per fraction over 5 to 6 weeks of daily treatment. Although higher doses per fraction in SCRT allow for a more convenient treatment schedule, they are also associated with higher rates of acute toxicity, including postoperative complications and anastomotic leaks, and late toxicity, such as long-term bowel, sexual, anorectal, or bladder dysfunction. However, with the lower total SCRT dose of 25.0 Gy, combined with modern techniques such as image-guidance with multiple beams and rigid patient immobilization, rates of late toxicity have been lower than the historical rates with LCRT.

The Swedish Rectal Cancer Trial included 1,168 patients with resectable rectal cancer randomized to preoperative SCRT (25.0 Gy over 5 fractions) followed by surgery within 1 week versus surgery alone. Notably, TME was not mandated. The 5-year local recurrence rate was improved with preoperative RT (11% vs 27%; P<.0001), which translated to a 5-year OS benefit (58% vs 48%; P<.004). Long-term results, with a median follow-up of 13 years, found a persistent OS benefit (38% vs 30%; P=.008) driven by cancer-specific survival (72% vs 62%; P=.03). This suggested a benefit to preoperative SCRT that translated to local recurrence and OS benefit. The Dutch Rectal Cancer Group study similarly found preoperative SCRT and TME resulted in improved local recurrence (2.4% vs 8.2%; P=.001), though it did not translate to OS benefit.

There is currently no evidence that suggests a difference in survival outcomes for SCRT versus LCRT. TROG 01.04 trial randomized 326 patients with T3N0–2 rectal cancer to SCRT (25.0 Gy in 5 Gy/fraction), immediate surgery (within 3–7 days after RT), and adjuvant 5-FU for 6 cycles versus LCRT (50.4 Gy in 1.8 Gy/fraction concurrent with continuous 5-FU), delayed surgery (4–6 weeks after RT), and adjuvant 5-FU for 4 cycles. There was no difference in survival outcomes or late toxicity. Acute adverse effects were higher in the LCRT arm (99.4% vs 72.3%; P<.001), primarily from grade 3–4 dermatitis, proctitis, nausea, and diarrhea. The LCRT arm had more favorable rates of permanent stoma (38.0% vs 29.8%; P= .13) and anastomotic breakdown (7.1% vs 3.5%; P=.26), whereas
the SCRT arm had more favorable rates of perineal wound complications (38.3% vs 50.0%; \( P=.26 \)), though not statistically significant. LCRT also resulted in more downstaging at time of surgery (45% vs 28%; \( P=.002 \)) than SCRT, including increased pathologic complete response (pCR) rates (15% vs 1%), likely because of the increased time to observe a response to RT.

Of note, following SCRT, immediate surgery was performed in these studies because of concern of risk of scarring with prolonged time after the higher RT dose per fraction. However, the Stockholm III trial found lower rates of postoperative complications in SCRT with a 4- to 8-week delay after SCRT versus immediate surgery (odds ratio [OR], 0.61; \( P=.001 \)), and more downstaging with delayed surgery (ypStage 0-I, 39%; ypStage II, 24%) than immediate surgery (ypStage 0-I, 27%; ypStage II, 33%).

When downstaging prior to surgery is needed to facilitate negative margins, guidelines generally recommend multidisciplinary discussion to consider delaying the timing of surgery after SCRT, as well as administering total neoadjuvant therapy (TNT).

### Total Neoadjuvant Therapy

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Rectal Cancer recommend TNT as preferred treatment for most nonmetastatic LARC.

The benefits of TNT include improved response, higher completion rates of neoadjuvant therapy, improved systemic control, and the possibility of organ preservation for low-lying rectal tumors (Figure 1, Table 2). A phase II study by Fernández-Martos et al.\(^2\) investigated 108 patients with LARC randomized to SoC concurrent CAPOX (capecitabine/oxaliplatin) and RT, surgery, and adjuvant CAPOX versus TNT with CAPOX for 4 cycles, concurrent CAPOX and RT, and surgery, and found no difference in pCR but improved chemotherapy compliance with TNT (49% vs 94%; \( P=.0001 \)) and decreased grade 3–4 toxicity during chemotherapy with TNT (54% vs 19%; \( P=.0004 \)). This was validated in a retrospective study at Memorial Sloan Kettering Cancer Center (MSKCC), which found patients who received higher average doses of 5-FU, fewer dose reductions, and a greater likelihood of receiving \( \geq \) 6 cycles. Additionally, they found a higher pCR or sustained complete clinical response (cCR) rate of 35.7% versus 21.3% with TNT.\(^2\)

The UNICANCER-PRODIGE 23 trial studied the benefit of further intensifying the TNT regimen.\(^2\) This phase III multicenter randomized controlled trial randomized 461 patients with cT3-cM0 LARC to standard neoadjuvant CRT, surgery, and adjuvant FOLFOX (folinic acid/5-FU/oxaliplatin) for 12 cycles versus TNT with neoadjuvant FOLFIRINOX (folinic acid/5-FU/irinotecan/oxaliplatin) for 6 cycles, CRT, surgery, and adjuvant FOLFOX for 6 cycles. At a median follow-up of 46.5 months, the primary endpoint of 3-year disease-free survival (DFS) was improved in TNT versus SoC (76% vs 69%; \( P=.034 \)), primarily driven by 3-year metastasis-free survival (79% [95% CI, 73%–84%] vs 72% [95% CI, 65%–77%]). Rates of pCR were also increased in the TNT arm (28% vs 12%; \( P<.0001 \)). Compliance rates were excellent, with 92% of patients in the TNT arm completing 6 cycles of FOLFIRINOX, >95% completing CRT in both arms, and >75% completing adjuvant chemotherapy in both arms. The authors note the decrease in toxicity within FOLFIRINOX arm, such as grade 3–4 neutropenia (17% vs historical rates of 85%), likely due to a restriction of patients aged <75 years, removal of bolus 5-FU, and targeted use of granulocyte colony-stimulating factor. This study is criticized for asking about both the sequencing chemotherapy and the effect of FOLFIRINOX versus FOLFOX, making it difficult to determine what is driving the benefit. It remains unclear whether FOLFIRINOX can be sequenced after LCRT. Overall, this did suggest a reasonable option of intensification of therapy for healthy patients with excellent performance status and high-risk disease.

The RAPIDO trial also investigated TNT versus SoC using SCRT (25 Gy over 5 treatments).\(^2\) A total of 920 patients were randomized to SoC LCRT, surgery, and adjuvant chemotherapy versus TNT with SCRT, CAPOX for 6 cycles/FOLFOX for 9 cycles, and surgery. The inclusion criteria required at least one higher-risk feature of cT4a/b, extramural venous invasion (EMVI)–positive, cN2, mesorectal fascia involvement, or enlarged lateral nodes. Among enrolled patients, more than half had either mesorectal fascia involvement or cN2 disease, with 60% having \( \geq 2 \) high-risk factors and 30% having \( \leq 3 \) high-risk factors. The primary endpoint of 3-year disease-related treatment failure was improved in TNT versus SoC (23.7% vs 30.4%; \( P=.019 \)), whereas pCR rates were higher with TNT (28% vs 14%; \( P<.0001 \)). The most significant preoperative grade 3–4 toxicity was diarrhea (18% TNT vs 9% SoC) and the most significant adjuvant grade 3–4 toxicity was neuropathy (9%), otherwise serious adverse effects were not significantly different between arms. Limitations of the study include that adjuvant chemotherapy was not mandatory in the SoC arm, making comparison difficult; there was a change of primary endpoint during study enrollment; and there was no central imaging review.

Recent results from the STELLAR study have further supported the use of SCRT in TNT.\(^2\) A total of 599 patients with LARC were randomized to SCRT with CAPOX for 2 cycles, TME, and adjuvant CAPOX for 4 cycles versus LCRT concurrent with capecitabine, TME, and adjuvant CAPOX for 2 cycles. SCRT was noninferior in the primary endpoint of 3-year DFS (64.5% vs 62.3%; \( P<.001 \) for non-inferiority), although grade 3–4 toxicity was higher in the TNT arm (26.5% vs 12.6%; \( P<.001 \)). Although 3-year OS was improved in TNT (86.5% vs 75.1%; \( P=.033 \)), there was no difference in metastasis-free survival or interestingly,
locoregional recurrence, and there was no difference in outcomes in subgroup analysis; long-term results may further clarify these results. Baseline characteristics were similar to patients in PRODIGE; however, grade 3–4 toxicity was significantly lower (20% in STELLAR vs 40% in PRODIGE).25,27 Because no direct comparison of regimens has been studied, both SCRT and LCRT are reasonable TNT strategies that should be considered in a multidisciplinary setting.

High-Risk LARC

Rectal tumors with T4 or N2 disease are at high risk for local and distant relapse and may warrant intensification of therapy.10,28 Other high-risk features associated with worse outcomes include threatened or involved circumferential resection margin and mesorectal fascial involvement on imaging, EMVI, or involvement of lateral nodes.29–31 RAPIDO consisted of patients with high-risk features, including T4 or N2 disease, whereas >80% of patients in STELLAR had cT3 disease and >65% had cN0–1 disease, which may suggest a DFS benefit but higher grade 3–4 toxicity in RAPIDO for high-risk patients.26–27 RAPIDO added evidence to NCCN Guidelines recommendations that TNT is a preferred strategy for LARC with high-risk factors. Results of recent studies investigating alternative strategies are encouraging, and future studies are focused on challenges in personalizing treatment strategy from an array of options in treatment modalities as well as sequence and timing of treatments.

De-escalation of Neoadjuvant Therapy

Nonoperative Management

Given the significant morbidity and quality-of-life impact of TME, there is also a growing interest in the nonoperative management of LARC in patients with a good response to neoadjuvant therapy. Habr-Gama et al32 investigated nonoperative management in a pioneering study following patients after CRT with strict follow-up, finding 49% complete clinical response (cCR) overall and 26 of 28 patients with pelvic recurrence successfully salvaged.

The phase II OPRA trial assessed the safety and feasibility of TNT for nonoperative management compared with historical control rates.33 OPRA randomized patients with stage II–III distal rectal cancer to receive induction chemotherapy before CRT or CRT before consolidation chemotherapy, followed by a strict watchful waiting protocol in those with a cCR, or TME in those without cCR. Consolidation chemotherapy after CRT was associated

<table>
<thead>
<tr>
<th>First Therapy</th>
<th>Secondary Therapy</th>
<th>Adjuvant Therapy</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT 50.4 Gy/28 fx with FOLFOX</td>
<td>None</td>
<td>TME</td>
<td>German Rectal Cancer Study Group</td>
</tr>
<tr>
<td>Chemotherapy FOLFIRINOX x 6 cycles</td>
<td>CRT 50.4 Gy/28 fx with Cape</td>
<td>TME</td>
<td>FOLFOX x 3 mo</td>
</tr>
<tr>
<td>SCRT 25 Gy/5 fx</td>
<td>Chemotherapy CAPOX x 6 cycles or FOLFOX x 9 cycles</td>
<td>TME</td>
<td>CAPOX or FOLFOX4</td>
</tr>
<tr>
<td>Chemotherapy FOLFOX x 8 cycles/ CAPOX x 6 cycles</td>
<td>CRT 50.4 Gy/28 fx with 5-FU/Cape</td>
<td>TME</td>
<td>None</td>
</tr>
<tr>
<td>CRT 50.4 Gy/28 fx with 5-FU/Cape</td>
<td>Chemotherapy FOLFOX x 8 cycles/ CAPOX x 6 cycles</td>
<td>TME</td>
<td>None</td>
</tr>
<tr>
<td>CRT 50.4 Gy/28 fx with FOLFOX</td>
<td>Chemotherapy FOLFOX x 3 cycles</td>
<td>TME</td>
<td>None</td>
</tr>
</tbody>
</table>

Figure 1. Total neoadjuvant therapy strategies for locally advanced rectal cancer. Abbreviations: Cape, capecitabine; CAPOX, capecitabine/oxaliplatin; CRT, chemoradiation; FOLFIRINOX, folinic acid/5-FU/irinotecan/oxaliplatin; FOLFOX, folinic acid/5-FU/oxaliplatin; fx, fractions; SCRT, short-course radiation therapy; TME, total mesorectal excision.
with increased organ-preservation rates (53% vs 43%) with no difference in 3-year DFS (76% vs 76%), local recurrence-free survival, distant metastasis-free survival, or OS. Patients who developed regrowth during follow-up had similar DFS to those who did not have cCR. Younger patients and patients with distal tumors should be encouraged to consider clinical trials assessing nonoperative management.

The CAO/ARO/AIO-12 study also supported a CRT-first approach. In this study, 311 patients were randomized to receive either FOLFOX followed by CRT or CRT followed by FOLFOX. The primary endpoint of pCR was higher in patients who received CRT first (25% vs 17%), with no difference in surgical morbidity. Some hypothesize that this may be due to a higher risk of accelerated repopulation of cancer cells during a prolonged time to surgery if starting with a less-definitive local therapy. Compliance rates were similar in both arms, with patients more likely to complete whichever therapy started first, and long-term follow-up found no difference in DFS, locoregional recurrence, distant metastasis, OS, or toxicity.

The Janus Rectal Cancer Study is currently under development between the SWOG, NRG, and Alliance groups to randomize patients with high-risk LARC (including T4, N1, or EMVI) in mid/low rectum to LCRT and FOLFOX or LCRT and FOLFIRINOX, with organ preservation as the primary endpoint (JJ Smith, email, 2022). We caution the standard use of TNT for the intent of nonoperative management outside of a clinical trial at this time, and suggest that this treatment be performed in centers with experience and the vigilance required to monitor these patients.

### Preoperative Chemotherapy With Selective Omission of RT

As chemotherapy and surgery have each improved, there has been an interest in omission of RT in select patients. A pilot study from MSKCC of 32 patients with stage II–III LARC who were candidates for TME received FOLFOX with bevacizumab for 4 cycles followed by FOLFOX for 2 cycles and surgery, and only patients with stable/progressive disease then received neoadjuvant RT. No patients experienced disease progression after 6 cycles of chemotherapy, 25% achieved pCR, and 4-year DFS was 84% (95% CI, 67%–94%) with no local recurrences. Noting that some patients may have a complete response with chemotherapy alone, the phase III randomized controlled PROSPECT trial has closed pending mature results to test the efficacy of omitting RT in neoadjuvant therapy in highly selected patients (ie, those with T2N1, T3N0, T3/N1 disease without involvement of the circumferential resection margin and candidates for

### Table 2. Chemotherapy Dosing for Total Neoadjuvant Therapy Regimens

<table>
<thead>
<tr>
<th>Trial</th>
<th>First Therapy</th>
<th>Second Therapy</th>
<th>Adjuvant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAO/ARO/AIO-12²⁵</td>
<td>Continuous infusion of 5-FU, 250 mg/m² on days 1–14 and 22–35 of RT and oxaliplatin, 50 mg/m² on days 1, 8, 22, and 29 of RT, concurrent with long-course RT</td>
<td>FOLFOX ×3 cycles (oxaliplatin, 100 mg/m² administered as a 2-h infusion, followed by a 2-h infusion of folinic acid, 400 mg/m², followed by a continuous 46-h infusion of 5-FU, 2,400 mg/m², repeated on day 15 for a total of 3 cycles)</td>
<td>None</td>
</tr>
<tr>
<td>UNICANCER-PRODIGE 2³²⁵</td>
<td>mFOLFOX ×6 cycles (oxaliplatin, 85 mg/m²; irinotecan, 180 mg/m²; folinic acid, 400 mg/m²; and 5-FU, 2,400 mg/m² continuous infusion every 14 days for 6 cycles)</td>
<td>Capecitabine, 800 mg/m² twice daily orally, concurrent with long-course RT</td>
<td>3 months of mFOLFOX (oxaliplatin, 85 mg/m²; folinic acid, 400 mg/m²; and 5-FU, 400 mg/m² bolus followed by 46-h continuous infusion at 2,400 mg/m² every 14 days) or capecitabine (1,250 mg/m² orally twice daily on days 1–14 every 21 days)</td>
</tr>
<tr>
<td>RAPIDO²⁶</td>
<td>Short-course RT</td>
<td>CAPOX ×6 cycles (capecitabine, 1,000 mg/m² orally twice daily on days 1–14; oxaliplatin, 130 mg/m² on day 1, every 21 days) or FOLFOX ×9 cycles (oxaliplatin, 85 mg/m² on day 1; folinic acid, 200 mg/m² on days 1 and 2; followed by bolus 5-FU, 400 mg/m² and 5-FU, 600 mg/m² for 22 h on days 1 and 2, every 14 days)</td>
<td>CAPOX or FOLFOX per physician discretion hospital policy</td>
</tr>
</tbody>
</table>

Abbreviations: CAPOX, capecitabine/oxaliplatin; FOLFIRINOX, folinic acid/5-FU/irinotecan/oxaliplatin; FOLFOX, folinic acid/5-FU/oxaliplatin; mFOLFIRINOX, modified FOLFIRINOX; mFOLFOX, modified FOLFOX; RT, radiation therapy.
sphincter-preserving surgery (ClinicalTrials.gov identifier: NCT01515787).

**Distal Tumors (<5 cm From Anal Verge)**

Neoadjuvant therapy strategies have been a particular area of research for distal rectal tumors, in which co-loanal anastomosis or abdominal perineal resection may result in poor bowel function or permanent os-tomy creation. Distal tumors have been shown to have higher rates of local failure.19-40 Although tumors <5 cm from the anal verge were historically not considered candidates for sphincter preservation, some studies suggest that a 1-cm distal resection margin may be sufficient.41-43 Neoadjuvant therapy allows for tumor downstaging and improved rates of sphincter-preserving surgery.10

Neoadjuvant CRT followed by local excision has been investigated with the goal of sphincter preservation. The phase III randomized controlled GRECCAR-2 trial enrolled 186 patients with T2–3N0 distal tumors ≤8 cm from the anal verge who received neoadjuvant therapy (50 Gy in 2.0 Gy/fraction concurrent with CAPOX) and good response (scan ≤2 cm) randomized to local excision versus TME; 26 of 74 patients with ypT2–3 or R1 underwent completion TME.44 In modified intention-to-treat analysis, there was no difference in 2-year composition endpoint of death, recurrence, morbidity, or adverse effects (56% vs 48%; P=.43), which did not meet superiority.44-45 These results were supported by other robust studies, in which up to 50% to 70% of highly selected patients with early-stage LARC were candidates for sphincter preservation with neoadjuvant therapy, with high local control rates up to 70% to 90%.46-49

**Other Considerations (MSI-H, IBD, Younger Patients)**

MSI is now a part of routine testing for patients with CRC, but those with MSI-H disease are still relatively rare.50-54 Immunotherapy is standard for MSI-H metastatic CRC given marked responses, and now neoadjuvant immunotherapy is being explored in LARC with impressive responses.1,55-57 In the exploratory NICHE study, neoadjuvant single-dose ipilimumab and 2 doses of nivolumab in early-stage CRC was associated with major pathologic response (MPR; <10% residual viable tumor) in 31 of 32 patients with MMR-deficient tumors versus 7 of 30 patients with MMR-proficient tumors, and pCR in 22 of 32 patients with MMR-deficient tumors and 3 of 30 patients with MMR-proficient tumors.58,59 An ECOG-ACRIN phase II study is planned for neoadjuvant ipilimumab/nivolumab and SCRT in advanced rectal cancer to validate these findings (ClinicalTrials.gov identifier: NCT04751370). A phase II study of 12 patients with mismatch repair-deficient stage II-III LARC found neoadjuvant single-agent dostarlimab (PD-1 blockade) was associated with 100% (95% CI, 74%-100%) clinical complete response after at least 6 months of follow-up. No patients have undergone CRT or surgery at last follow-up, and there have been no cases of progression or recurrence (follow-up 6–25 months), results that may revolutionize treatment in MSI-H LARC pending further validation and longer follow-up.60 Further molecular and genomic testing, such as PI3K and circulating tumor DNA (ctDNA), may provide additional biomarkers of patients at high risk of worse clinical outcomes and help to further personalize neoadjuvant strategies.19,61,62

Another consideration that warrants comment is IBD, which is associated with a 60% increase in risk of developing CRC, and these patients have a standardized mortality rate of 2.0 to 2.3 above the general population with CRC.63 IBD historically was a contraindication for RT due to risk of inciting significant flare.64,65 However, modern techniques have allowed for more favorable radiation dose distribution, with one series from Massachusetts General Hospital finding that late toxicity was significantly decreased with specialized modern techniques (73% vs 23%; P=.02).66 A Dutch registry of patients with IBD who received neoadjuvant therapy for rectal cancer found a slight increase in acute grade 3 toxicity in LCRT (1 case of perianal abscess formation) and concurrent CRT (1 case of sepsis/ICU admission, 4 cases of radiation cystitis, and 3 cases of diarrhea/anorectal infection) versus SCRT (P=.004).67 Although limited by retrospective study design and small sample size, these results do not suggest excessive toxicity. Further, the results do not comment on the status of IBD at time of treatment, and caution should be exercised in patients with ongoing/frequent flares.

There is an increasing incidence of young adults with rectal cancer, with rates almost quadrupled over the past few decades (41.5% in 1995–2014 vs 9.8% in 1973–1994).68 Younger patients tend to present with more advanced disease and high-risk prognosis; however, treatment intensification can be associated with significant late toxicity.69 Further studies should investigate the optimal treatment strategy in younger patients.

**Conclusions**

A neoadjuvant approach, particularly TNT, is the standard of care for LARC. Rectal cancer can serve as a paradigm for personalized oncology, where the optimal strategy should be tailored to the individual patient. Although the optimal TNT strategy is under investigation, biomarkers such as microsatellite instability or ctDNA may soon further guide the LARC paradigm toward a more personalized approach to patient management, with careful consideration of which treatment modalities each patient may or may not require.
Neoadjuvant Therapy for Rectal Cancer

Submitted April 24, 2022; final revision received July 4, 2022; accepted for publication August 8, 2022.

Disclosures: Dr. Roberts has disclosed having a spouse whose company owns stock in Oxford Biomedica. Dr. Wo has disclosed receiving grant/research support from Genentech. Dr. Parikh has disclosed having equity in Oxford Biomedica. Dr. Roberts has disclosed having a spouse whose company owns stock in Oxford Biomedica. Dr. Wo has disclosed receiving grant/research support from Genentech. Dr. Parikh has disclosed having equity in Oxford Biomedica.

References


Correspondence: Apama R. Parikh, MD, MS, Department of Medical Oncology, Massachusetts General Hospital, 55 Fruit Street, Yawkey Center, Suite 7E, Boston, Massachusetts 02114. Email: Apama.Parikh@mgz.harvard.edu

JNCCN.org | Volume 20 Issue 10 | October 2022 1183

 research funding from PureTech, PMV Pharmaceuticals, Plexixon, Takeda, Bristol-Myers Squibb, Mirati, Novartis, Genentech, Natera, and Daichi Sankyo. Dr. Saraf has disclosed not having any financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.


