Total Neoadjuvant Therapy Approach in Rectal Adenocarcinoma

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Abstract: The treatment of locally advanced rectal cancer has improved over the years owing to advancements in surgical techniques and chemoradiation, developing into a multidisciplinary approach that has contributed to markedly reduced rates of local recurrence. Despite these advances, however, distant metastatic recurrence continues to be the main cause of rectal cancer–related death. Unfortunately, the former standard of care of neoadjuvant chemoradiation followed by surgery and adjuvant chemotherapy is still associated with significant morbidity and distant relapse rates. Many trials have studied the optimal sequence, timing, and duration of the individual components of treatment, more recently shifting both chemoradiation and systemic chemotherapy to the preoperative setting in an approach termed total neoadjuvant therapy (TNT). Some of the potential advantages of TNT include improved adherence to treatment, early treatment of micrometastases, and tumor downstaging, with the possibility of observation instead of surgery for those patients with a complete clinical response. This review provides the historical context for the shift to TNT in the treatment paradigm and discusses the critical clinical trials supporting the newer strategy. It also addresses the recent focus on the personalization of care that TNT makes possible by allowing the selective omission of radiation therapy and nonoperative management with a watch-and-wait strategy.

Keywords
Rectal cancer, neoadjuvant chemoradiation, total neoadjuvant therapy, watch-and-wait strategy

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death after lung cancer, and the fourth most frequently diagnosed cancer in the United States.[1] An estimated 45,230 new cases of rectal cancer are diagnosed in the United States, and more than 52,000 Americans die of CRC annually.[2] Although CRC mortality has declined overall since the 1990s, the incidence of CRC is increasing in people younger than 50 years, partly because of a disproportionately high increase in the annual rate of rectal cancer (3.9%) among younger people.[3]

Surgery, which is the foundation of curative treatment for rectal cancer, was the sole modality of therapy in the early 1900s. The use of surgery alone made it challenging to effectively treat invasive, locally advanced rectal cancer (LARC), defined as stage II

(T3-4, N0) or stage III (T1-4, N+) disease. The treatment of LARC has since evolved into a multidisciplinary approach; more recent guidelines recommend neoadjuvant chemoradiation therapy (CRT) followed by surgery and adjuvant chemotherapy, whereas standard therapy for early-stage lesions remains surgery with or without adjuvant chemoradiation.[4] The accurate staging of rectal cancer is thus critical, given that the stage can determine whether patients receive neoadjuvant therapy or not. More recently, the preferred imaging modality for staging has shifted from endoscopic rectal ultrasound (ERUS) to magnetic resonance imaging (MRI). Compared with ERUS, MRI can better determine the proximity of the primary tumor to the mesorectal fascia, the presence of extramural vascular invasion, and involvement of the extramesorectal pelvic lymph nodes and anterior peritoneal reflection, all of which are important factors that can upstage tumors.[5-7]

Studies supporting the current standard of care for LARC have demonstrated a significant decrease in local recurrence rates from 25% to less than 10%, but the high rates of distant relapse of approximately 30% indicate a need for the further optimization of treatment.[4] In recent years, a shift has occurred toward intensifying neoadjuvant treatment by delivering adjuvant chemotherapy preoperatively, in a strategy called total neoadjuvant therapy (TNT). This review discusses the evolution of the treatment of rectal cancer, the literature supporting a TNT approach, and the growing data reflecting the trend toward the personalization of rectal cancer treatment, including the selective omission of radiation therapy (RT) and surgery according to individual patient factors.

Adjuvant Therapy

Except for patients who have early-stage rectal tumors that are without high-risk features and amenable to local excision, most patients with LARC require a radical transabdominal procedure (eg, low anterior resection or abdominoperineal resection) in which a total mesorectal excision (TME) technique is used. TME was initially described by Heald in 1987 and has since become the standard surgical technique for modern proctectomy.[8] Around the same time, clinical trials were conducted to examine adjuvant therapies to decrease local recurrence rates (LRRs) and improve survival outcomes by eradicating clinically occult micrometastases. A systematic review of 22 randomized trials showed significantly decreased LRRs but no survival benefit when adjuvant radiation therapy was compared with surgery alone.[9] In contrast, a meta-analysis of 21 trials comparing the outcomes of patients with resected rectal cancer followed by adjuvant chemotherapy vs the outcomes of patients managed with observation demonstrated a significant reduction in risk for disease relapse and death with systemic therapy.[10]

The benefit of chemotherapy in the postoperative setting was evaluated in 3 major trials: GI-7175 from the Gastrointestinal Tumor Study Group, a trial from the North Central Cancer Treatment Group (NCCTG), and NSABP R-01 from the National Surgical Adjuvant Breast and Bowel Project. The GI-7175 trial in 1985 randomly assigned 227 patients with completely resected Dukes stage B2 or C rectal cancer to observation, postoperative RT, chemotherapy, or CRT.[11] The LRRs were significantly lower in the patients treated with CRT than in those who underwent surgery only (33% vs 55%), and the survival outcomes were better at 8-year follow-up.[11,12] The NCCTG trial similarly assigned 204 patients to postoperative RT alone or with concurrent 5-fluorouracil (5-FU), both preceded and followed by 1 cycle of 5-FU and methyl-CCNU, but no surgery-only arm was included in the trial. CRT compared with RT alone resulted in superior LRRs of 13.5% vs 25%, superior distant metastasis rates of 28.8% vs 46%, and a reduction in the overall death rate by 29%, although gastrointestinal and hematologic toxicity was increased with combined therapy.[13] NSABP R-01 also showed better survival with adjuvant chemotherapy (methyl-CCNU, vincristine, and 5-FU) than with surgery alone, but the survival benefit was restricted to male patients.[14] Although these trials used inferior chemotherapy by modern standards, they demonstrated improved survival outcomes with adjuvant chemotherapy, whereas RT alone was associated only with lower local recurrence rates.

Neoadjuvant Therapy

Multiple trials in the 1980s and 1990s studied the optimal sequence of trimodality therapy, shifting postoperative therapy to the preoperative setting.[15-17] The potential benefits of neoadjuvant therapy include downstaging the primary tumor in anticipation of surgical resection and increasing sphincter preservation. A randomized study in 1990 found that preoperative RT, even at lower doses, was more effective than postoperative radiation, although survival rates did not differ.[18] The Swedish Rectal Cancer Trial, which was published in 1997, randomly assigned 1168 patients with resectable rectal cancer to neoadjuvant short-course radiation therapy (SCRT) of 25 Gy in 5 fractions in 1 week followed by surgery or to surgery alone. Neoadjuvant RT, similarly to postoperative RT, resulted in an LRR reduction of more than 50% (11% vs 27%; $P<.001$). Unlike previous studies, this trial was notably the first to demonstrate significantly improved overall survival (OS) with preoperative radiation at 5-year follow-up (58% vs 48%; $P=.004$).[19] In 2001, the Dutch

TME trial was also performed to evaluate the effects of neoadjuvant SCRT in 1861 patients and demonstrated decreased LRRs with preoperative radiation (5.6% vs 10.9%). However, in contrast to the Swedish trial, the Dutch trial standardized TME in its protocol and did not find any difference between OS rates in the 2 treatment groups (64% in both), even at 12-year follow-up.[20,21]

Neoadjuvant Chemoradiation

Besides RT, trials were also conducted to determine the use of chemotherapy in the neoadjuvant setting. The EORTC 22921 trial, published in 2006, evaluated the addition of chemotherapy to preoperative long-course radiation therapy (LCRT) in patients with clinical stage T3 or T4 resectable rectal cancer. The 1011 patients enrolled were divided into groups that received preoperative RT, preoperative RT plus adjuvant 5-FU, preoperative CRT, or preoperative CRT and adjuvant 5-FU. Although the 5-year OS rates did not differ significantly among the 4 groups (65.2%), including between the groups that received preoperative vs postoperative chemotherapy, LRRs were decreased with the addition of chemotherapy (7.6%-9.6% vs 17.1%; *P*=.002). Most importantly, the rate of adherence to chemotherapy was significantly better in the preoperative than in the postoperative setting (82% vs 42.9%).[22] The FFCD 9203 trial also evaluated the benefit of adding chemotherapy (5-FU) to neoadjuvant RT in 733 patients with resectable rectal cancer. Both groups (CRT vs RT) received adjuvant 5-FU/leucovorin. The advantages of CRT were higher pathologic complete response (pCR) rates (11.4% vs 3.6%; *P*<.05) and lower 5-year LRRs (8.1% vs 16.5%; *P*<.05). However, the addition of chemotherapy resulted in higher rates of grade 3 or 4 toxicity (14.6% vs 2.7%; *P*<.05) and failed to improve rates of sphincter preservation or 5-year OS.[23]

Neoadjuvant vs Adjuvant Chemoradiation

Preoperative and postoperative CRT were compared in 3 prospective randomized trials in the 1990s: CAO/ARO/AIO-94 by the German Rectal Cancer Study Group, RTOG 94-01, and NSABP R-03.[24-26] Both the RTOG 94-01 and NSABP R-03 trials were closed early owing to low accrual rates, but NSABP R-03 did show improved disease-free survival (DFS) and a trend toward improved OS in the neoadjuvant CRT group.[24,25] The German study randomly assigned 823 patients with clinical stage T3-4 or N+ disease to receive preoperative CRT with 5-FU followed by TME and adjuvant 5-FU or postoperative CRT. Survival outcomes were similar with neoadjuvant CRT and postoperative therapy; the OS rate was 59% and the distant metastasis rate was 30% in both groups at 5-year follow-up. However, preoperative CRT decreased the LRR (7.1% vs 10.1%; *P*=.048) and was associated with lower rates of treatment-related toxicity.[26,27] The findings from the landmark German trial ultimately established the sequence of trimodality treatment with CRT followed by TME and adjuvant chemotherapy as the standard of care for LARC.

Short-Course vs Long-Course Radiation Therapy

Previous studies had separately shown the benefits of SCRT and conventional LCRT with concurrent chemotherapy, but later studies began to compare the treatments directly. Australian and Polish randomized trials compared neoadjuvant SCRT (5 × 5 Gy) followed by immediate surgery vs LCRT (50.4 Gy with concomitant 5-FU) and delayed surgery. Both trials showed significantly higher pCR rates with LCRT, but they did not demonstrate significant differences in sphincter preservation, survival benefit, or late toxicity.[28,29] To compare SCRT with LCRT and also address the optimal timing of surgery after SCRT, the Stockholm III trial randomly assigned 840 patients to SCRT with immediate surgery within 1 week, SCRT with delayed surgery after 4 to 8 weeks, or LCRT with delayed surgery. Times to local recurrence were similar in all 3 groups. SCRT followed by delayed surgery had increased radiation-induced toxicity but significantly reduced postoperative complications compared with SCRT followed by immediate surgery (41% vs 53%; *P*=.001).[30] Further interim analysis of the Stockholm III trial also found that delayed surgery after SCRT resulted in higher rates of pCR vs immediate surgery after SCRT (11.8% vs 1.7%; *P*<.001), a finding that has been corroborated by other studies.[31-33] Although the trial results suggested that delayed surgery was beneficial for enhancing tumor downstaging and increasing pCR rates, other studies suggested that an even shorter interval (0-3 days) between the end of SCRT and surgery might be preferable because worse treatment-related leukopenia after delayed resection contributed to poorer outcomes.[34,35] Thus, the optimal timing after SCRT is still controversial, with both immediate and delayed SCRT options recommended in the current European Society for Medical Oncology (ESMO) guidelines.[36] LCRT remains the preferred approach in the United States, with SCRT as an alternative in selected patients.

Adjuvant Chemotherapy After Neoadjuvant Therapy

After the focus of treatment had shifted to the preoperative setting, the role of adjuvant chemotherapy after

Table. Major Randomized Trials of Total Neoadjuvant Therapy

Study, Year (No. Pts)	Treatment	Primary Endpoint	pCR, % (*P* value)	LRR, % (*P* value)	DFS, % (*P* value)	OS, % (*P* value)
GCR-3, 2010 (108)	Standard: CRT+CAPOX→ TME→ CAPOX × 3 mo Experimental: CAPOX × 3 mo→ CRT→ TME	pCR	13 vs 14 (.94)	2 vs 5 (.61)	64 vs 62 (.85)	78 vs 75 (.64)
PRODIGE 23, 2021 (461)	Standard: CRT→TME→FOLFOX or cape × 6 mo Experimental: FOLFIRINOX × 3 mo→CRT+cape→TME→–FOLFOX or cape × 3 mo	3-y DFS	12 vs 28 (<.001)	NR	76 vs 69 (.034)	88 vs 91 (.07)
RAPIDO, 2021 (920)	Standard: CRT→TME→FOLFOX or CAPOX × 6 mo (optional) Experimental: SCRT→CAPOX or FOLFOX × 4.5 mo→TME	DRTF	14 vs 28 (<.001)	6 vs 9 (.09)	NR	89 vs 89 (.59)
CAO/ARO/AIO-12, 2019 (306)	Induction: FOLFOX × 3 mo→CRT→TME Consolidation: CRT→ FOLFOX →TME	pCR	17 vs 25 (.21/<.001)	NR	NR	NR
OPRA, 2020 (307)	Induction: FOLFOX or CAPOX × 4 mo→CRT→TME Consolidation: CRT→FOLFOX or CAPOX × 4 mo→TME	3-y DFS vs historical	NR	NR	78 vs 77	NR

cape, capecitabine; CAPOX, capecitabine, oxaliplatin; CRT, chemoradiation therapy; DFS, disease-free survival; DRTF, disease-related treatment failure; FOLFIRINOX, folinic acid, fluoropyrimidine, irinotecan, oxaliplatin; FOLFOX, folinic acid, fluoropyrimidine, oxaliplatin; LRR, local recurrence rate; mo, months; No., number; NR, not reported; OS, overall survival; pCR, pathologic complete response; pts, patients; TME, total mesorectal excision, y, year.

neoadjuvant CRT or SCRT became unclear. The EORTC 22921 trial, as previously mentioned, had failed to show improved OS or DFS with adjuvant chemotherapy after preoperative CRT at 10 years of follow-up.[37] The lack of survival benefit with adjuvant chemotherapy was supported by the I-CNR-RT, PROCTOR-SCRIPT, and CHRONICLE trials, although the latter 2 studies were closed prematurely owing to poor accrual.[38-40] A meta-analysis of these trials by Breugom and colleagues concluded that postoperative fluorouracil-based chemotherapy after neoadjuvant therapy did not decrease distant recurrence or increase DFS and OS, but interestingly it found a significant benefit in outcomes among patients with tumors 10 to 15 cm from the anal verge. Of note, rates of nonadherence to postoperative chemotherapy of approximately 30% to 50% in these studies should be taken into account when the data results are interpreted, so that it is harder to draw conclusions about survival benefit.[41] Although the benefit of adjuvant chemotherapy is not conclusive, it is incorporated in the National Comprehensive Cancer Network guidelines recommending 2 months of fluoropyrimidine-based chemotherapy with concurrent RT followed by surgery and 4 months of adjuvant systemic therapy.[1]

Total Neoadjuvant Therapy

In recent years, TNT has become a more popular approach to further optimize the delivery of trimodality treatment by moving chemotherapy from the postoperative to the preoperative setting. The potential benefits of TNT include better tolerability and adherence to treatment, which allow the administration of full doses of systemic chemotherapy to primary tumors with intact vasculature. Other advantages are downstaging tumors to increase the likelihood of pCR and complete resection, treating micrometastases early, and decreasing the interval between ileostomy and reversal. Possible drawbacks are overtreatment, modification of the tumor biology with subsequent reduced efficacy owing to the selection of resistant clones, and delay of surgery that could allow local progression.[42] To test these theories, multiple contemporary prospective clinical trials have been conducted to evaluate the TNT approach in LARC (Table).

The Spanish GCR-3 phase 2 randomized trial assigned 108 patients with middle-third or distal T3-4 and/or N+ tumors either to preoperative CRT with concurrent capecitabine and oxaliplatin (CAPOX) followed by surgery and 4 cycles of postoperative CAPOX or to

TNT with 4 cycles of CAPOX followed by CRT and surgery. Rates of pCR (approximately 14%), R0 resection, downstaging, and tumor regression were similar in the 2 arms. At 5-year follow-up, no significant differences were found in LRR (2% vs 5%; *P*=.61), distant metastasis rate (21% vs 23%; *P*=.79), DFS rate (64% vs 62%; *P*=.85), and OS rate (78% vs 75%; *P*=.64) between the group that received the standard sequence of care and the TNT group. However, the TNT arm experienced significantly less grade 3 to 4 toxicity (19% vs 54%; *P*=.004) with better adherence to chemotherapy (91% vs 54%; *P*<.001).[43,44] The promising results of this study were later supported in phase 3 trials.

Like the GCR-3 study, the PRODIGE 23 trial compared the standard treatment paradigm with neoadjuvant chemotherapy, but the systemic therapy regimen was more intensive: triplet therapy with 5-FU/leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX).[43-45] The 461 patients with T3-4 tumors in the high, middle, or low third of the rectum were assigned either to neoadjuvant FOLFIRINOX for 3 months followed by CRT with concurrent capecitabine, TME, and adjuvant FOLFOX or capecitabine for 3 months, or to standard care with CRT, TME, and adjuvant chemotherapy for 6 months. Although no significant improvement in OS was observed with TNT (91% vs 88%), neoadjuvant systemic therapy significantly improved the primary endpoint of 3-year DFS (76% vs 69%; *P*=.034) and 3-year metastasis-free survival (78.8% vs 71.7%) vs standard therapy at a median follow-up of 46.5 months. Despite the more intensive chemotherapy regimen, neoadjuvant FOLFIRINOX was generally well tolerated, with a 92% adherence rate. By contrast, only 78% of patients in either group received any adjuvant chemotherapy owing to reasons including investigator decision, postoperative complications, and consent withdrawal. Upfront chemotherapy did not significantly impede adherence to CRT, although slightly more patients discontinued capecitabine during CRT for at least 2 days (8% vs 3%). Patients in the neoadjuvant chemotherapy group also notably had a pCR rate more than twice as high (28% vs 12%), less neurotoxicity, and fewer serious adverse events during postoperative therapy.[45]

Another phase 3 trial, RAPIDO, randomly assigned 920 patients either to TNT with SCRT followed by 4.5 months of CAPOX or FOLFOX then TME and adjuvant chemotherapy or to CRT with capecitabine followed by TME and optional adjuvant treatment for 6 months with CAPOX or FOLFOX.[46] Unlike the PRODIGE study, this trial recruited only patients with at least one of 5 high-risk features on baseline pelvic MRI: cT4, cN2, extramural vascular invasion, involved mesorectal fascia, or enlarged lateral lymph nodes. Whether the RAPIDO approach can be applied to low-risk stage III tumors and, conversely, whether the PRODIGE strategy should be limited to higher-risk tumors will need to be determined.[45,46] At 3 years, the RAPIDO trial also met its primary endpoint of disease-related treatment failure (defined as first occurrence of locoregional failure, distant metastasis, new primary colorectal tumor, or treatment-related death), which was 23.7% in the TNT arm vs 30.4% in the standard-care arm (hazard ratio [HR], 0.75; *P*=.019). Most cases of disease-related treatment failure were caused by distant metastasis in both groups.[46] Like the results of the PRODIGE trial, the RAPIDO results showed that TNT doubled the pCR rate (28% vs 14%) and led to an absolute reduction of about 7% in the risk for 3-year distant metastasis (20% vs 26.8%).[45,46] No significant differences were found in the LRR (although it was higher with TNT, at 8.7% vs 6%; *P*=.09), 3-year OS rate (89% in each), or the rate of perioperative complications. Regarding toxicity, the rate of grade 3 or higher adverse events was higher in the TNT group than in the standard-care group (48% vs 25%), but the latter group also had an additional 35% of grade 3 or higher adverse events during adjuvant therapy.[46]

In comparison with the other trials, the NRG-GI002 phase 2 study differs in its parallel, noncomparative platform trial design, which allows multiple experimental arms to be added. Patients who have high-risk, distal, or bulky tumors are enrolled and randomly assigned either to FOLFOX for 4 months, CRT with capecitabine, then TME surgery or to the same regimen with a novel radiosensitizing agent added to chemoradiation. The primary endpoint is the neoadjuvant rectal (NAR) score, which is a prognostic tool used to measure the pathologic response to TNT.[47-49] Thus far, the novel agents included in the study are the poly(ADP-ribose) polymerase inhibitor veliparib and the immune checkpoint inhibitor pembrolizumab (Keytruda, Merck).[47,48] We await a longer follow-up for survival data in all of these trials.

Induction vs Consolidation Neoadjuvant Chemotherapy

Within the TNT approach, 2 treatment strategies emerged: induction chemotherapy followed by CRT and CRT followed by consolidation chemotherapy. Both CAO/ARO/AIO-12 and OPRA were phase 2 randomized trials designed to compare induction vs consolidation TNT.[50,51] In the CAO/ARO/AIO-12 trial, 306 patients with T3-4 or N+ tumors were randomly assigned preoperatively either to induction chemotherapy with 3 cycles of FOLFOX followed by CRT with 5-FU plus oxaliplatin or to consolidation chemotherapy after CRT. In a pick-the-winner design, the pCR rate was higher in the consolidation chemotherapy group than in the induction arm

(25% vs 17%, respectively), and the consolidation group was the only group that fulfilled the predefined statistical hypothesis. Rates of CRT-related grade 3 or 4 toxicity were lower in the consolidation group (27% vs 37%) and adherence to CRT was better, but adherence to chemotherapy was worse in the consolidation arm than in the induction arm.[50] In the OPRA study, 307 patients were randomly assigned either to induction with 4 months of FOLFOX or CAPOX followed by CRT with capecitabine or 5-FU or to consolidation chemotherapy after CRT. Notably, the primary endpoint was a comparison of the 3-year DFS rates of patients with the historical data for each individual treatment arm (single-stage study), not a comparison between the 2 treatment arms. At 8 to 12 weeks after finishing TNT, the patients were restaged with a combination of physical examination, imaging, and endoscopic surveillance methods. If they had achieved a clinical complete response (cCR), defined as the absence of residual tumor after nonoperative therapy determined by clinical restaging, then they were offered a watch-and-wait (WW) strategy, whereas those with an incomplete response underwent TME. Although the study had a noncomparative design, no differences in the 3-year DFS rates (78% vs 77%) and rates of adherence to systemic chemotherapy (81% vs 82%) were seen between the induction and consolidation groups. Rates of WW and organ preservation were higher in the consolidation arm (58% vs 43%), which is important to note, given the growing interest in nonoperative management strategies.[51]

Watch-and-Wait Strategy

The WW approach is an attractive alternative to surgery, given the risks for surgical complications and perioperative mortality, which increase with age, as well as potential postoperative morbidity (eg, urinary and sexual dysfunction), which can significantly affect quality of life. Currently, no randomized control trials directly comparing surgery with observation in patients who achieved cCR have been published, but increasing numbers of reports have described favorable outcomes with WW. In 2004, Habr-Gama and colleagues introduced a WW strategy for 71 patients (27% of the study population) with rectal cancer who had achieved protocol-defined cCR after neoadjuvant CRT. The surveillance protocol was strict, requiring follow-up visits for physical and digital rectal examination, endoscopy with biopsy, measurement of serum tumor markers, and radiographic imaging every 6 months during the first year. At more than 4 years after the completion of CRT, local recurrence had developed in 2 patients (2.8%), which was successfully managed with salvage surgery. Compared with the patients who had pCR after resection, the observed patients had similar distant recurrence rates and survival outcomes at a mean follow-up of 55 months. It should be noted that approximately 20% of the study patients had T2N0 tumors, which may have contributed to the favorable outcomes with observation. Nevertheless, this study described a promising WW approach with regimented monitoring to avoid surgery.[52]

A retrospective case series analyzed the outcomes of 113 patients who achieved cCR after completing neoadjuvant therapy and agreed to a WW strategy vs those of 136 patients who underwent TME and were found to have pCR at resection. The patients in the WW group were on average 10 years older, had lower primary tumors (median height from the anal verge, 5.5 vs 7 cm), and received predominantly induction and consolidation chemotherapy vs CRT only in the pCR group. All 22 local recurrences in the WW arm were found on routine surveillance and treated with salvage surgery, whereas no pelvic recurrences developed in the pCR arm. Rectal preservation was achieved in 82% of the WW group. Unfortunately, the patients managed with WW had significantly worse rates of 5-year OS (72% vs 94%) and DFS (75% vs 92%), and those with local recurrence had higher rates of distant metastasis (36% vs 1%).[53] These data suggest that WW allows organ preservation and a better quality of life by avoiding surgery-related morbidity. Patients need to be selected carefully, however, with better risk stratification used to identify appropriate candidates for nonoperative management. Larger prospective studies are needed to verify long-term outcomes.

Neoadjuvant Chemotherapy and TME With Omission of Radiation

Reflective of the trend toward tailoring therapy, questions were raised about whether radiation could be omitted in a selected group of patients without compromising outcomes. Although RT has significantly decreased LRRs in LARC, it has not been shown to improve survival outcomes and is associated with significant toxicity, including bowel and genitourinary dysfunction and loss of fertility in younger patients. The Chinese FOWARC phase 3 trial randomly assigned 495 patients to neoadjuvant CRT with 5-FU/leucovorin, CRT with FOLFOX, or FOLFOX alone to evaluate the potential benefit of oxaliplatin. The preliminary results of the study showed significantly higher pCR rates in the group that received CRT with FOLFOX (27.5%) than in the group that received standard CRT (14%) and the group that received chemotherapy alone (6.6%).[54,55] However, after a median follow-up of 45.2 months, the 3-year DFS rates were roughly equivalent, with values of 72.9%, 77.2%, and 73.5% (P=.709 by log-rank test) in the CRT with 5-FU,

CRT with FOLFOX, and FOLFOX arms, respectively. Also, no significant differences were found in 3-year OS rates.[55] The ongoing PROSPECT phase 2/3 randomized trial is comparing standard-care CRT followed by TME and adjuvant chemotherapy vs neoadjuvant FOLFOX followed by the selective use of CRT, depending on the treatment response, in patients with good prognostic pathologic features (eg, proximal, nonbulky tumors). If at least a 20% decrease in the tumor has occurred after neoadjuvant chemotherapy, then the patients will proceed directly to TME, whereas if the decrease has been less than 20%, they will receive neoadjuvant CRT before surgery.[56] This trial was based on data from a pilot study that enrolled 32 patients who received preoperative FOLFOX with bevacizumab and selective CRT according to whether they had stable or progressive disease on repeat imaging. Thirty patients completed neoadjuvant chemotherapy without radiation, resulting in tumor regression, followed by TME. The pCR rate after chemotherapy alone was 25%, the 4-year LRR was 0%, and the 4-year DFS rate was 84%.[57] The PROSPECT trial will help validate these promising results to determine if selected patients with a favorable treatment response according to specific criteria can be spared pelvic radiation without compromising treatment outcomes.[56] Similarly, the phase 3 NORAD01-GRECCAR16 trial will help evaluate whether preoperative chemotherapy (FOLFIRINOX) without radiation can be used as an alternative to CRT.[58]

Conclusion

Over the past few decades, the treatment of LARC has evolved into a trimodality approach, so that multidisciplinary teams are essential for effective patient care. Neoadjuvant CRT followed by TME and adjuvant chemotherapy has been the standard of care for many years, but this treatment paradigm is actively changing. Numerous studies have evaluated the sequence of treatment components, and more recently systemic therapy has been shifted to the preoperative setting in a TNT approach to address the shortcomings of standard care in preventing distant relapse and mortality. A TNT approach allows an assessment of the tumor response after neoadjuvant therapy and provides opportunities for the selective omission of RT and nonoperative management through a WW strategy. The results of ongoing trials are eagerly awaited to determine strategies that personalize care and improve survival outcomes in LARC.

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