



How Can We Improve the Tumor Response to Preoperative Chemoradiotherapy for Locally Advanced Rectal Cancer?

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Preoperative chemoradiotherapy (pCRT) followed by total mesorectal excision is the accepted standard treatment for patients with locally advanced rectal cancer. The purpose of pCRT is to prevent the spread of viable tumor cells within the local area during surgical procedures. Additionally, pCRT can facilitate the resection of locally advanced tumors that are otherwise challenging to remove, thereby enabling a radical resection. Although a pathologic complete response is observed in fewer than 20% of patients, the reasons for the variability in tumor response to pCRT are not fully understood. Several techniques have been researched with the aim of improving the tumor response to pCRT. These techniques include intensifying or combining chemotherapy, either simultaneously or sequentially, increasing radiation dose, modifying radiation mode or schedule, adjusting the interval between radiation and surgery, and incorporating multiple agents to increase the efficacy of pCRT. This review discusses various strategies that may improve tumor response outcomes following pCRT.

Introduction

Rectal cancer is often diagnosed at a locally advanced stage and ranks as the third most common cancer globally. Despite significant efforts to enhance oncological outcomes for rectal cancer, the mortality rate associated with this disease in South Korea continues to increase [1].

Preoperative chemoradiotherapy (pCRT), followed by total mesorectal excision, is now considered the standard treatment strategy for patients with locally advanced rectal cancer (LARC) [2,3]. The purpose of pCRT is to inhibit the dissemination of locally viable tumor cells during surgery. Additionally, pCRT can facilitate the resection of locally advanced tumors that are difficult to remove, thereby enabling radical resection.

pCRT has become increasingly important in the treatment of tumors, offering a definitive alternative to radical surgery by achieving a complete response in some cases [4,5]. Although a small subset of patients with microsatellite instability has shown promising responses to immunotherapy [6], the response to pCRT remains a critical prognostic factor. Achieving a pathologic complete response (pCR) can significantly reduce the risk of local recurrence and improve both disease-free survival (DFS) and overall survival (OS) [2,4]. However, pCR is achieved in fewer than 20% of patients, and the reasons for the variability in tumor response to pCRT are not fully understood [2,7]. Consequently, further efforts are needed to improve tumor response to pCRT, which could help predict patient prognosis and tailor treatment strategies.

Several strategies have been researched with the goal of improving tumor response outcomes following pCRT, such as intensifying or combining chemotherapy agents either concurrently or sequentially, optimizing the radiation dose, delivery method, or schedule, adjusting the interval between radiation and surgery, or incorporating additional agents to enhance the efficacy of pCRT (Figs. 1, 2) [7–11]. This review investigates different approaches to enhance tumor response outcomes in patients with LARC after pCRT.

Radiotherapy

1. Pathological complete response

pCR is defined as the absence of viable tumor cells upon a gross histopathological examination of the resected specimen, classified as pT0N0M0 [12]. The tumor regression grade (TRG) serves as a method to categorize the primary tumor's response to pCRT by histopathologically assessing residual tumor cells and the extent of tumor regression and replacement. Various TRG classification systems are in use, including those by Mandard (1994), Dworak (1997; modified in 2003), the Memorial Sloan-Kettering Cancer Center (MSKCC) classification (2008), and the Ryan/American Joint Committee on Cancer (AJCC) 7th Edition (2010), as outlined in Table 1 [13–16].

The Mandard system is a TRG system used for esophageal carcinoma and other digestive tract malignancies. The TRGs in the Mandard classification are divided into five grades. Complete regression (CR) is designated as TRG1, characterized by fibrosis throughout multiple layers of the wall with an absence of viable cancer cells. The Dworak system classifies TRGs into four grades and defines CR as TRG4, which is identified by the lack of tumor cells and may include fibrotic masses or pools of cell-free mucus. Another classification system, currently

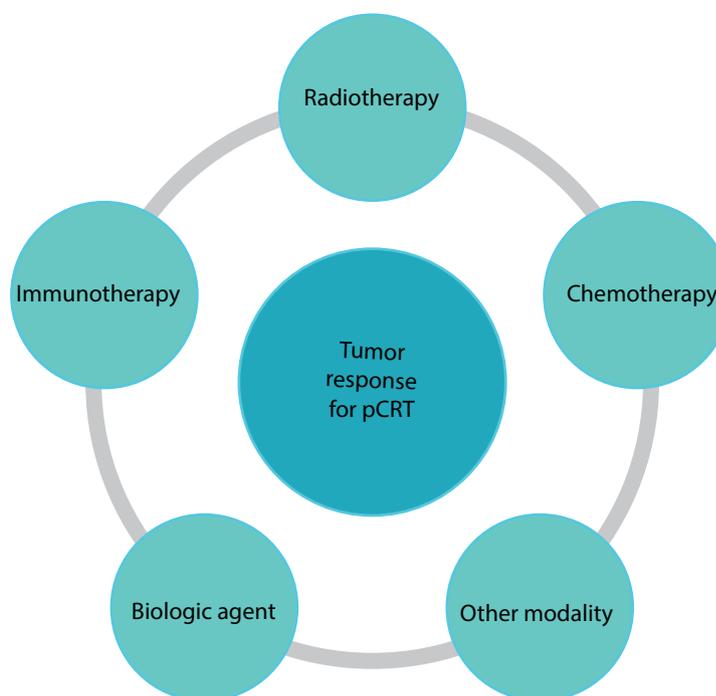


Fig. 1. Various techniques used to improve the tumor response to preoperative chemoradiotherapy. pCRT, preoperative chemoradiotherapy.

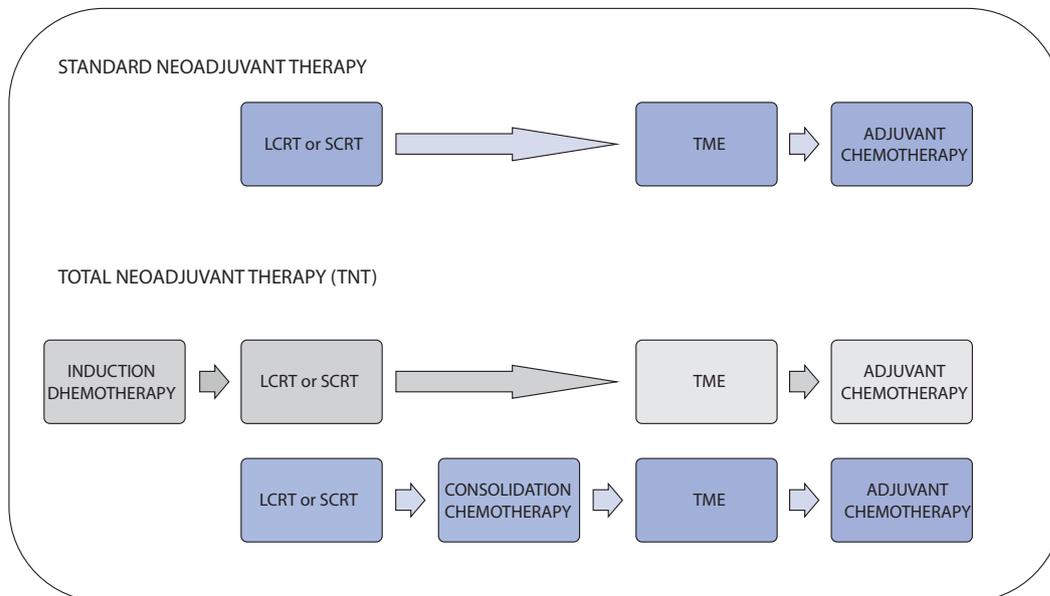


Fig. 2. Schematic overview of regimens for standard neoadjuvant therapy and total neoadjuvant therapy for locally advanced rectal cancer (LARC). LCRT, long-course chemoradiotherapy; SCRT, short-course chemoradiotherapy; TME, total mesorectal excision.

recommended by the AJCC, is the Ryan classification. This system also categorizes TRGs into four grades, with CR defined as TRG0, indicating the complete absence of viable cancer cells. Meanwhile, the MSKCC classification separates tumors into three groups based on the response

Table 1. TRG classification systems

TRG	TRG 0	TRG 1	TRG 2	TRG 3	TRG 4	TRG 5
Mandard		CR, no viable cancer cells, fibrosis extending through the different layers of the wall	Rare residual cancer cells scattered through the fibrosis	Increased number of residual cancer cells, fibrosis predominates	Residual cancer outgrowing fibrosis	Absence of regressive changes
Dworak	No response	Minimal response (dominant tumor mass with obvious fibrosis, vasculopathy); fibrosis <25% of tumor mass	Moderate response (dominant fibrotic changes with a few easy-to-find tumor cells in groups); fibrosis 25%–50% of tumor mass	Near CR (few microscopically difficult-to-find tumor cells in fibrotic tissue with or without mucous substance); fibrosis >50% of tumor mass	CR (no tumor cells, only fibrotic mass or acellular mucin pools)	
Ryan/AJCC	CR, no viable cancer cells	Near-CR, single cells, or rare small groups of cancer cells	Partial response, residual cancer with evident tumor regression but more than single cells or rare small group of cancer cells	Poor or no response, extensive residual cancer with no evident tumor regression		
MSKCC		100% tumor response	86%–99% tumor response	≤85% tumor response		

TRG, tumor regression grade; CR, complete response; AJCC, American Joint Committee on Cancer; MSKCC, Memorial Sloan-Kettering Cancer Center.

rate and defines CR as TRG1, which corresponds to a 100% tumor response.

2. Dose of radiation

In theory, the effectiveness of pCRT could be enhanced by escalating the radiation therapy (RT) dose through external beam irradiation, brachytherapy, or contact therapy, shortening the overall treatment duration, or administering simultaneous consolidation boosts. Although multiple studies on pathological complete response (pCR) have shown a significant dose-response relationship for tumor regression following pCRT [8,9], randomized trials have not confirmed an increase in pCR rates with higher RT doses within pCRT [10]. A phase 3 randomized trial demonstrated a significant improvement in the primary endpoint, pCR [11], when comparing a novel regimen that included the addition of oxaliplatin and an increase to 50 Gy of external-beam RT, versus the standard pCRT treatment with capecitabine and 45 Gy. Modern RT techniques, including intensity-modulated RT, volumetric arc RT, and image-guided RT, can reduce the involvement of vulnerable organs such as the small bowel, bladder, and femoral head, while precisely targeting the anal sphincter with the radiation dose.

The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) consensus guidelines recommend a radiation dose of 45–54 Gy for the treatment of LARC. However, Appelt et al. [8] have demonstrated a significant dose-response relationship for tumor regression following pCRT for LARC, with radiation doses ranging from 50.4 to 70 Gy. Moreover, LARC patients who received radiation doses of 60 Gy or higher experienced a pCR rate of 20.4%. This rate corresponded with a lower incidence (10.3%) of grade 3 or higher acute toxicity and a high probability (89.5%) of successful surgical resection, as reported in a meta-analysis [9]. These findings suggest that RT exceeding 50 Gy can be clinically beneficial with an acceptable level of toxicity. Nonetheless, there is a lack of large-scale prospective studies investigating doses above 50 Gy. Consequently, additional research is warranted to validate the safety and efficacy of higher dose escalation.

3. Duration of radiation

External beam RT is the primary radiation technique used in pCRT. It delivers radiation to the entire mesorectum and rectal wall, aiming to eradicate tumor deposits within the field. Both preoperative short-course chemoradiotherapy (pSCCRT) and preoperative long-course chemoradiotherapy (pLCCRT) are standard pCRT schedules. Traditional pSCCRT, also known as 5×5 Gy therapy, administers five daily doses of 5 Gy (totaling 25 Gy) and is typically followed by radical resection within one week of completing RT (less than 10 days from the first radiation fraction). Recently, pSCCRT with delayed surgery has emerged as a beneficial alternative to conventional pSCCRT with immediate surgery, demonstrating comparable oncological outcomes and reduced postoperative complications [17]. The pLCCRT regimen administers a daily dose of RT in smaller fractions (approximately 1.8 to 2 Gy) over a longer period of 25 to 28 days. Patients receive a total RT dose ranging from 45 Gy to 54 Gy, which is considered equivalent to a short-course dose of 25 Gy [2]. Research comparing pSCCRT with pLCCRT in early-stage resectable cancer found no significant differences in outcomes [18–20]. However, in more advanced cases, pSCCRT combined with immediate surgery may not allow sufficient time to achieve a significant down-staging response [18,19]. Conversely, if surgery is delayed for an extended period, pSCCRT might be comparable to pLCCRT [21,22]. Nonetheless, it is quite challenging to precisely define the T and N sub-stages that necessitate pSCCRT or pLCCRT [17]. The decision to use pSCCRT versus pLCCRT should be made by a multidisciplinary team, taking into account

the potential for long-term toxicity and the need for preoperative tumor down-staging [23].

4. Interval between radiation and surgery

The optimal timing for surgery in patients with LARC following pCRT or pSCCRT remains a contentious issue in clinical trials. It is crucial to find a balance between the acute tissue response and allowing enough time for the maximum effects of CRT to manifest, thereby facilitating safe surgical intervention [17]. This period is designed to enhance tissue response and foster recovery from radiation, while simultaneously preventing radiation-induced tissue fibrosis. The tumor's response to pCRT can fluctuate over time, with peak tumor regression often taking several months to occur. In clinical practice, the timing of surgery post-pCRT can vary significantly (from 4 to 12 weeks) due to a variety of factors, such as recovery from treatment, surgeon preference, and waiting list issues [17–20]. However, retrospective studies have indicated a higher rate of pCR when surgery is postponed following pCRT [24]. A Dutch study corroborated that pSCCRT did not significantly decrease tumor stage when the gap between pCRT and surgery was less than 10 days [25]. Conversely, pSCCRT followed by delayed surgery (5–13 weeks) resulted in a higher rate of pCR (11.8% vs. 1.7%) and a higher rate of Dworak TRG4 (10.1% vs. 1.7%) compared to immediate surgery (within 1–2 weeks) [26]. Given that radiation-induced necrosis requires time to develop, prolonging the interval between CRT and surgery could potentially increase the incidence of pCR.

If the objective is to preserve the sphincter, it is advisable to wait for six weeks after pCRT to initially assess the tumor's response. If the tumor does not respond adequately to pCRT, surgery should be performed within two weeks. In cases where clinical complete regression (cCR) or near cCR is achieved, restaging should be done after six weeks to decide whether to adopt the watch-and-wait treatment approach [27]. The Lyon R 90-01 clinical trial found that pCRT increased the rate of pCR or near-pCR from 10.3% at two-week intervals to 26% at six to eight-week intervals. As a result, the optimal interval between CRT and surgery is currently considered to be six to eight weeks to improve pCR rates and reduce postoperative complications [28,29]. Despite encouraging results from trials that have extended the time between pCRT and surgery, there is still no definitive consensus on the time between the completion of pCRT and surgery, with current studies showing a cautious trend towards delaying surgery.

The impact of the time interval from the completion of pCRT to surgery on pCR rates in rectal cancer remains a topic of ongoing debate [18–32]. The GRECCAR-6 study, however, found no significant difference in pCR occurrence between intervals of 11 and 7 weeks, although patients with an 11-week interval experienced a higher rate of surgical complications [30]. A study using the National Cancer Database (NCDB) sought to identify the optimal timing for surgery following pCRT in patients with stage II–III rectal cancer who received pCRT treatment between 2006 and 2012. This study involved 11,760 participants. The authors found that delaying surgery beyond 8 weeks offered no additional benefit, despite an observed increase in tumor downstaging during the waiting period [31]. A meta-analysis of 13 studies, involving 19,652 patients, showed that patients with a waiting interval of more than 8 weeks between pCRT and surgery had a significantly higher incidence of pCR compared to those with a waiting interval of less than 8 weeks. However, no significant differences were noted in operative time, OS, DFS, local recurrence rate, postoperative complications, or sphincter-sparing surgery [32]. A multicenter study examined outcomes for rectal cancer patients who underwent surgery more than 12 weeks after completing pCRT. The histopathologic examination of resected surgical specimens revealed that the pCR rate was 8.3% for patients who had surgery within 12 weeks and 15.8%

for patients whose surgery was delayed beyond 12 weeks. Moreover, no significant differences were found in morbidity and mortality between the two groups [33]. Another study indicated that patients who underwent surgery after 12 weeks of pCRT therapy, and progressively longer preoperative intervals, had similar postoperative complication rates to patients with a 6-week interval. This study categorized the period between pCRT and surgery into longer intervals of 6, 12, 18, and 24 weeks. Despite the administration of additional systemic chemotherapy to patients who underwent surgery after the longer interval, the group that delayed surgical resection to 20 weeks showed significantly higher pCR rates, with no change in postoperative complications [34].

Chemotherapy

1. Oxaliplatin and irinotecan

Concurrent chemotherapy during pCRT offers a significant advantage in terms of improved tumor regression and local control, compared to RT alone [34]. This is evident in various phase 2 trials involving patients with LARC who underwent preoperative RT alone. These patients exhibited significantly lower rates of pCR (4%–13%) compared to those treated with pCRT (9%–31%). Numerous randomized trials have demonstrated that the addition of concurrent chemotherapy to pSCCRT and pLCCRT enhances local sensitization and systemic control of the disease [27,35,36].

In four out of five randomized phase 3 trials evaluating the addition of oxaliplatin as a radiation enhancer to preoperative fluoropyrimidine-based CRT (STAR-01, ACCORD 12/0405-Prodige 2, NSABP R-04, PETTAC-6), the oxaliplatin chemoradiotherapy arm led to a significant increase in grade 3–4 toxicity, up to approximately 25%. However, there was no notable benefit in terms of complete response, R0 resection, local control, or survival [11,35,36]. In the CAO/ARO/AIO-04 study, the group treated with oxaliplatin demonstrated a significantly higher pCR rate than the control group, but without substantial increases in toxicity [35]. There was also a minor advantage in 3-year DFS [36]; however, despite the slight increase in pCR (17%–13%), there was no difference in R0 resection. Given the increased toxicity without a clear benefit in outcomes, the addition of oxaliplatin to fluoropyrimidine-based CRT is currently not recommended outside of clinical trials. The primary question is whether adding oxaliplatin at a full systemic dose (85–130 mg/m²) to pCRT can improve pCR rates and oncological outcomes, including DFS and OS. Although most trials show little or no difference in response rates between the two groups, patients receiving oxaliplatin experienced more severe toxicities and adverse events [36].

Irinotecan is a promising radiosensitizer that has been evaluated in multiple published phase 2 trials. The CinClare study confirmed that adding irinotecan to pCRT could increase the pCR rates when compared to the standard pCRT group (30.0% vs. 15.0%) [37]. Some studies [38,39] have reported increased rates of acute toxicities in the irinotecan arm, but did not identify any significant differences in pCR or tumor regression between treatments. Conversely, a handful of non-randomized phase 2 studies suggested that the integration of irinotecan into standard fluoropyrimidine-based CRT could boost response rates to roughly 14% to 22% [39]. Currently, there is insufficient evidence to propose that irinotecan effectively increases the pCR rate, and further research is required to confirm its potential as a radiosensitizer.

2. Total neoadjuvant therapy

Despite the significant improvement in outcomes for rectal cancer patients treated with

pCRT, there is still a 25%–30% risk of recurrence within 5 years [19]. The creation of more intensive neoadjuvant strategies has facilitated the progression of all systemic therapies to total neoadjuvant therapy (TNT). It is hypothesized that TNT can decrease the risk of distant recurrence by providing early treatment and eliminating systemic micrometastases, thereby improving OS. Furthermore, administering chemotherapy and RT prior to surgery, as opposed to post-surgery recovery, results in a significantly higher completion rate of the full dose and schedule. The RAPIDO trial, a phase 3 randomized controlled study, compared pSCCRT followed by systemic chemotherapy with FOLFOX or CAPOX (capecitabine, oxaliplatin) for 18 weeks before surgery to conventional pCRT in high-risk patients (T4, N2, epidural vascular invasion, positive mid-rectal fascia, positive side nodes) [40]. After 5 years, the study showed a doubling of the pCR rate from 13.8% to 27.7%, and a 6.7% decrease in disease-related treatment failure. However, the 5-year update on the RAPIDO trial revealed a statistically significant increase in local recurrence (8% vs. 12%, $P=0.07$) and breached mesorectum (4% vs. 21%, $P=0.048$) in the experimental arm [41]. Contrary to mid-term results, this raised concerns that short-course TNT might lead to inferior surgical quality, which could offset the benefits of an increased pCR rate with short-course TNT.

Another recent phase 3 trial, PRODIGE 23, explored the efficacy of TNT in treating T3 or T4 rectal cancer. This trial differed from the RAPIDO trial in that it included both T3 and T4 rectal cancer. The experimental group demonstrated a higher pCR rate (27.5% vs. 11.7%, $P<0.001$), coupled with a 7.2% rise in 3-year DFS. Furthermore, the experimental group showed superior metastasis-free survival. Surgical morbidity rates were comparable in both groups [42].

Targeted Agents

Numerous phase 1 and 2 trials have reported a range of outcomes concerning pCR rates and safety when integrating angiogenic inhibitors or epidermal growth factor receptor (EGFR) inhibitors into pCRT using 5-fluorouracil (5-FU) for LARC treatment [43,44,45]. The pairing of bevacizumab with pCRT has shown tolerable toxicity in some trials [46,47,48], while other studies have consistently indicated more severe toxicity, increased surgical morbidity, and unfavorable healing outcomes [43,44]. Sorafenib has shown promising results, but its use is still limited to small cohorts and phase I studies [49]. Despite veliparib and capecitabine-based CRT achieving a pCR rate of only 28%, the potential radiosensitizers in this category are cause for concern. Further research is essential to clarify their role in rectal cancer treatment [49].

The addition of cetuximab to 5-FU-based chemoradiation regimens has produced disappointing results, with complete remission rates of less than 10% for the combined regimen, according to a pooled analysis of existing studies. This is in contrast to standard 5-FU regimens, which have shown rates of 15%–30%. Moreover, the combined regimen has shown unacceptably high levels of toxicity. Numerous phase 1-2 trials involving the addition of cetuximab to chemoradiation with fluoropyrimidines have generally led to more instances of diarrhea, without significantly increasing pCR rates or survival [44]. In the only randomized phase 2 trial (EXPERT-C), adding cetuximab to the induction neoadjuvant chemotherapy with capecitabine and oxaliplatin, or to the capecitabine chemoradiotherapy regimen, did not result in a significant improvement in pCR rates (18% vs. 15%) or DFS or OS. This was also the case in the subgroup with *RAS* or *BRAF* wild-type tumors [45]. EGFR inhibitors, including panitumumab and cetuximab, are approved for treating wild-type metastatic colorectal cancer involving *RAS*. However, their effectiveness in treating LARC remains uncertain. Only a handful of phase 2 trials using panitumumab have been

published. The authors concluded that adding panitumumab to pCRT did not achieve the expected primary endpoint of pCR due to additional toxicity [49]. Therefore, currently, there is no role for EGFR-targeted agents as radiosensitizers in the treatment of LARC.

Immunotherapy

Currently, immunotherapy is evolving from a post-diagnosis treatment for metastatic cancers to a primary treatment option. It is also being incorporated into adjuvant and neoadjuvant therapies for early-stage cancers. Patients in the neoadjuvant phase are generally healthier but are at a higher risk of experiencing side effects from the treatment. In the context of neoadjuvant therapy for rectal cancer, immunotherapy has shown remarkable results in patients with high microsatellite instability or deficient mismatch repair. Researchers at MSKCC reported that administering PD-1 monotherapy to individuals with high microsatellite instability/deficient mismatch repair LARC resulted in a complete clinical response (cCR) of 100% (14/14) [50]. Many researchers are investigating the promising results of combining PD-1/PD-L1 inhibitors with chemoradiotherapy for patients with microsatellite-stable LARC.

The addition of immunotherapy has led to more promising results in the modern era. At present, the reported findings are primarily from small-scale phase 2 studies. However, studies with similar designs corroborate these results. In trials based on pCRT, the CR rate can surpass 30% when combined with immunotherapy, as evidenced by Voltage-A, NSABP FR-2, and PANDORA [51–53]. Therefore, the combination of pCRT and PD-1 monoclonal antibodies can attain CR rates that are comparable to those of the TNT model.

Conclusion

The field of surgical treatment for rectal cancer has consistently evolved with the introduction of new techniques such as laparoscopic, robotic, transanal robotic/laparoscopic total mesorectal excision, and image-guided surgery. These advances have not only improved oncological outcomes but also highlighted the importance of functional preservation [3,54–58]. However, despite these developments, complications related to surgery and the onset of postoperative bowel dysfunction [59,60]—often viewed as an unavoidable result of rectal resection—remain significant concerns in rectal cancer surgery.

In light of these considerations, there has been a growing interest in recent years in increasing the rates of pCR and cCR achieved through pCRT, with the ultimate goal of preserving the rectum. The refinement of pCRT, which includes intensifying concurrent chemotherapy, increasing the frequency of interval chemotherapy, and implementing TNT, has gradually improved tumor regression effectiveness in patients. Research suggests that the TNT model can significantly boost the rate of pCR to over 30%. In instances where a high likelihood of achieving pCR is initially assessed, a treatment approach involving local excision may be considered. This is akin to the management of early-stage cancer, although the complications of local excision after pCRT should not be overlooked [34,60]. Furthermore, a watch-and-wait strategy can be adopted by more patients with cCR to enhance organ preservation and improve quality of life. The use of this strategy is also anticipated to reduce the incidence of distant metastases and improve long-term survival. Therefore, the focus of pCRT for LARC is shifting from the traditional approach, which primarily aimed to control local recurrence, to a new approach that emphasizes enhancing tumor regression, preserving organs, and promoting long-term survival.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Ethics Approval and Consent to Participate

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