JOURNAL OF THE
ANUS, RECTUM AND COLON
dx.doi.org/10.23922/jarc.2022-060
http://journal-arc.jp

Review Article

# Total Neoadjuvant Chemotherapy in Rectal Cancer: Current Facts and Future Strategies

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**Abstract**

Despite preoperative chemoradiotherapy (CRT) and total mesorectal excision improving the local control for locally advanced rectal cancer (LARC), oncologic outcomes and survival were not significantly improved because the main prognostic factor is distant metastasis. Thus, total neoadjuvant chemotherapy (TNT) as a novel approach has been proposed to improve chemotolerance. Since the first randomized phase II trial of TNT versus standard CRT demonstrated in 2012, many prospective and retrospective studies have been published. The initial consensus from TNT studies was that pathological complete response, pathological response of the main tumor, and local control are more favorable at TNT than at CRT. Furthermore, recent studies such as the PAPIDO trial and PRODIGE 23 trial made a major breakthrough of the treatment of TNT, showing that TNT improves the disease-free survival compared to standard treatment with long-course CRT. In addition, several innovative findings of TNT were clarified by prospective phase II trial. In this review, we summarize the most recent advances in TNT based on the findings of pivotal clinical trials for patients with LARC.

**Keywords**

total neoadjuvant chemotherapy, locally advanced rectal cancer

J Anus Rectum Colon 2023; 7(1): 1-7

## Introduction

The local recurrence in locally advanced rectal cancer (LARC) has significantly reduced by the introduction of total mesorectal excision (TME) with short-course (SRT) or long-course chemoradiotherapy (LC-CRT) at the beginning of 2000s, and the risk is reported to be approximately 10% of overall LARC. The characteristics of this 10% of the high-risk group were clarified. The MERCURY study demonstrated that mesorectal fascia (MRF) involvements < 1 mm, low rectal cancer located within 5 cm from the anal verge, and extramural vascular invasion (EMVI) are risks of local recurrence [1]. In addition, the OCUM study and QuickSilver study presented the same factors. Patients with those factors were at high risk of not only local recurrence but also systemic recurrence and poor survival [2,3]. Therefore, further developing treatment options for those patients are required to improve prognostic outcomes.

The only way in modern modality to reduce the risk of systemic recurrence is via chemotherapy. However, when the patient receives chemoradiotherapy (CRT) for improvement of local control, adjuvant chemotherapy cannot be adminis-

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Received: September 18, 2022, Accepted: October 22, 2022

**Table 1a.** Polish II Trial.

| Year | Author | Patient | Experimental arm | Standard arm | No of patients | Primary endpoint | Outcomes | 3-Year LFS | 3-Year DFS | 3-Year OS |
|---|---|---|---|---|---|---|---|---|---|---|
| 2016 | Polish II trial | Fixed T3 or T4 | 25 Gy + 3 cycles of FOLFOX4 | 50.4 Gy with 5 Fu + Lv | 261 vs. 254 | R0 resection rate | 77% vs. 71%, p = 0.07 | 22% vs. 21%, p = 0.82 | 53% vs. 52%, p = 0.85 | 73% vs. 65%, p = 0.046 |

LFS, local recurrence-free survival; DFS, disease-free survival; OS, overall survival

**Table 1b.** RAPIDO Trial.

| Year | Author | Patient | Experimental arm | Standard arm | No of patients | Primary endpoint | Outcomes | 3-Year LFS | 3-Year DFS | 3-Year OS |
|---|---|---|---|---|---|---|---|---|---|---|
| 2020 | RAPIDO trial | cT3 with N2, EMVI, positive MRF or positive lateral nodes | 25 Gy + 18 weeks of CAPOX or FOLFOX4 | 50 or 50.4 Gy | 462 vs. 450 | 3-Year disease-related failure | 23.7% vs. 30.4%, p = 0.02 | 8.7% vs. 6%, p = 0.10 | | 89.1% vs. 88.8%, p = 0.077 |

LFS, local recurrence-free survival; DFS, disease-free survival; OS, overall survival; EMVI, extramural venous invasion

tered due to the side effects of CRT [4]. These outcomes propose the total neoadjuvant chemotherapy (TNT), and full dose of chemotherapy was sequentially administered as induction or consolidation chemotherapy with SRT or LC-CRT.

Therefore, we obtain high-quality data from previous studies and review the current facts and future strategies.

## Total Neoadjuvant Chemotherapy

There were three phase III trials that investigated the usefulness of TNT for LARC (Table 1).

### *1. Polish II trial*

This trial was the first phase III trial of 25 Gy of RT and subsequent 3 cycles of FOLFOX compared with conventional LC-CRT, which enrolled only highly advanced cases as 63% of the experimental arm and 64% of the standard arm were clinical T4 cases [5]. The primary endpoint was R 0 resection rate, which did not reach significance at 77% versus 71% (p = 0.07). This trial was negative regarding primary endpoint. In contrast, 3-year overall survival (OS) was statistically significantly different at 73% versus 65% (p = 0.046). This study found several important points to plan the TNT trial. First, 3 cycles of FOLFOX would be too short to improve the disease-free survival (DFS), and the usefulness of chemotherapy required a longer period. Second, the usefulness of TNT for such very highly advanced cases to improve the DFS and R0 resection rate was further required in the discussion. Finally, this study was not mandatory of taking magnetic resonance imaging (MRI), which would be essential to match the tumor advancements in both regimens and reduce the quality of this study (Table 1a).

### *2. RAPIDO trial*

This trial compared 25 Gy of RT followed by 18 weeks of CAPOX or FOLFOX4 compared with 50 or 50.4 Gy of conventional LC-CRT, which enrolled high-risk patients having those factors as T4, N2, EMVI, positive MRF involvements, or positive lateral nodes [6]. The primary endpoint was 3-year disease-related failure, which reached significance at 23.7% versus 30.4% (p = 0.02). Addition, the pathological response as ypT, ypN, pathological complete response (pCR) rate was statistically significant at experimental arm than standard arm. Additionally, the tolerance to the chemotherapy dose was 85% in the TNT group and 90% in the LC-CRT group of patients who completed preoperative chemotherapy. Moreover, 92% of patients in the TNT group and 89% of those in the LC-CRT group had surgery. These outcomes indicate that TNT is an alternative management for LARC compared with LC-CRT. This is the first phase III study to demonstrate that TNT has a significantly better DFS than LC-CRT for LARC (Table 1b).

### *3. PRODIGE 23 trial*

This trial compared 3 months of mFOLFOXIRI + 50 Gy and 3 months of FOLFOX6 or capecitabine at adjuvant setting versus 50 Gy of LC-CRT and 6 months of FOLFOX6 or capecitabine [7]. The primary endpoint was 3-year DFS, which had a statistically significant difference at 75.7% versus 68.5% (p = 0.034). The patients' characteristics between this trial and previous two studies (Polish II trial and RAPIDO trial) are different as this trial included all T3 and 4 cases. When using FOLFOXIRI, tolerance of dose feasibility is important. This study demonstrated that 3 months of FOLFOXIRI completion rate was 92%, LC-CRT completion

**Table 1c.** PRODIGE 23 Trial.

| Year | Author | Patient | Experimental arm | Standard arm | No of patients | Primary endpoint | Outcomes | 3-Year LFS | 3-Year OS |
|---|---|---|---|---|---|---|---|---|---|
| 2021 | PRODIGE 23 trial | T3, 4 | 3 months of mFOLFOXIRI + 50 Gy + 3 months of FOLFOX6 or Cape | 50 Gy + 6 months of FOLFOX6 or Cape | 231 vs. 230 | 3-Year DFS | 75.7% vs. 68.5%, p = 0.034 | Not reported | 91% vs. 88%, p = 0.59 |

LFS, local recurrence-free survival; DFS, disease-free survival; OS, overall survival; Cape, capecitabine

**Table 2a.** Induction Chemotherapy versus Consolidation Chemotherapy.

| Year | Author | Study design | Patient | N | Study design | Primary endpoint | Outcomes | 3-Year LFS | 3-Year DFS | 3-Year OS |
|---|---|---|---|---|---|---|---|---|---|---|
| 2019 | CAO/ARO/ AIO-12 trial | Phase II | T3, 4 or N+ | 311 | Induction chemotherapy vs. consolidation chemotherapy | pCR | 17% vs. 25% | 94% vs. 95%, p = 0.67 | 73% vs. 73%, p = 0.82 | Not reported |

LFS, local recurrence-free survival; DFS, disease-free survival; OS, overall survival; pCR, pathological complete response

rate was 97%, and surgery was 94%. In contrast, grade 3-4 adverse events occurred at 46%, and 20% of all included patients required G-CSF (Table 1c).

These outcomes demonstrated that TNT is a promising strategy with superior rate of pCR and DFS compared with current standard treatments such as LC-CRT. The outcomes of these studies are incorporated in the latest NCCN guidelines.

Therefore, in this review, we discuss the following points to clarify the usefulness of TNT:

1. Induction chemotherapy versus consolidation chemotherapy
2. Optimal chemotherapy period before surgery
3. Usefulness of molecular target agents
4. Watch-and-Wait approach
5. Immune checkpoint inhibitor with CRT.

*1. Induction chemotherapy versus consolidation chemotherapy*

The representative study was the CAO/ARO/AIO-12 trial. A total of 306 stage II or III patients were evaluated for outcomes, including 156 patients who received induction chemotherapy using 3 cycles of mFOLFOX6 before fluorouracil/oxaliplatin CRT (50.4 Gy) or to group B for consolidation chemotherapy after CRT [8,9]. The primary endpoint was pCR rate, and the secondary endpoints were DFS and toxicity. The results show a higher pCR in the consolidation group (25% vs. 17%). In contrast, no differences in long-term outcomes and chronic toxicity or quality of life (QOL) were observed between consolidation chemotherapy and induction chemotherapy. High pCR of consolidation chemotherapy explained that upfront chemotherapy allows the chemotherapeutic agents to reach the primary tumor directly when the vasculature is not disrupted by either radiotherapy or surgery. In addition, pCR was correlated with the duration between completion of radiotherapy to surgery, and consolidation chemotherapy has a longer period than induction chemotherapy. High pCR indicates patients who planned Watch-and-Wait approach or local excision after TNT is better to select consolidation chemotherapy.

Thus; patients who wish to achieve pCR by planning Watch-and-Wait approach or local excision after TNT is better to select consolidation chemotherapy.

One concern of consolidation therapy is chemo-dose feasibility because chemotherapy was administered after CRT. The outcomes of this study demonstrated that 140 of 150 patients could start the chemotherapy after LC-CRT at the consolidation arm, whereas 151 of 156 patients could start LC-CRT after chemotherapy at the induction arm. Thus, acceptable tolerance of consolidation chemotherapy was confirmed (Table 2a).

*2. Optimal chemotherapy period before surgery*

The representative study was conducted by Garcia-Aguilar et al., and they noted whether adding cycles of mFOLFOX6 between LC-CRT and surgery increased the proportion of patients achieving a pCR [10,11]. They divided four groups as LC-CRT alone and 2, 4, and 6 cycles of mFOLFOX6 administered as consolidation chemotherapy after LC-CRT. The pCR rate was 18%, 25%, 30%, and 38%, respectively. They concluded that delivery of mFOLFOX6 after LC-CRT and before surgery has the potential to increase the proportion of patients eligible for less invasive treatment strategies.

The early studies of TNT selected 1 or 2 months of chemotherapy because those were aimed to achieve good local control. However, on the degeneration of micro-metastasis, at least 3 months of oxaliplatin-based chemotherapy is required by the IDEA collaboration trial [12]. In addition, the representative phase III trial of TNT in the RAPIDO trial and PRODIGE 23 trial was administered at 18 or 12 weeks of chemotherapy [2,3]. These results indicate that at least 3 months is required; however, further studies are needed to

**Table 2b.** Optimal Chemotherapy Period before Surgery.

| Year | Author | Study design | Patient | N | Study design | Primary endpoint | Outcomes | 3-Year LFS | 3-Year DFS | 3-Year OS |
|---|---|---|---|---|---|---|---|---|---|---|
| 2015, 2018 | Garcia-Aguilar | Phase II | Stage II–III | 292 | Consolidation chemotherapy with FOLFOX 0, 2, 4, and 6 cycles | pCR | 18%, 25%, 30%, 36% | Not reported | 50%, 81%, 86%, 76%; p = 0.004 | 79%, 92%, 88%, 84%; p = 0.37 |

LFS, local recurrence-free survival; DFS, disease-free survival; OS, overall survival; pCR, pathological complete response

**Table 2c.** Usefulness of Molecular Target Agents. A: Cetuximab.

| Year | Trial | Study design | Patient | N | Study design | Primary endpoint | Outcomes | 3-Year LFS | 3-Year DFS | 3-Year OS |
|---|---|---|---|---|---|---|---|---|---|---|
| 2012 | EXPERT-C | Phase II | High-risk rectal cancer | 165 | CAPOX + cetuximab (4 cycles) vs. CPAOX (4 cycles) | pCR | 9% vs. 11%, p = 1.0 | Not reported | HR, 0.65; p = 0.36 (PFS) | HR, 0.27; p = 0.034 |
| 2018 | SWOG 0713 | Phase II | Stage II–III KRAS-wt rectal cancer | 80 | pCR rate >35% by adding cetuximab | pCR | 27% | Not reported | 72% | Not reported |

LFS, local recurrence-free survival; DFS, disease-free survival; OS, overall survival; pCR, pathological complete response; HR, hazard ratio

clarify whether a longer period of chemotherapy is required.

A longer preoperative period is required when using LC-CRT in TNT treatments. In the PRODIGE 23 trial, 12 weeks of chemotherapy, 5 weeks of CRT after 1-3 weeks from the last chemotherapy cycle, and surgery were planned after 6-8 weeks after CRT. Thus, 24-28 weeks (6-7 months) of waiting period from the start of treatment to surgery is required [7]. In contrast, when using SRT in TNT treatments, the preoperative period is shortened to 1.5-2 months (Table 2b).

*3. Usefulness of molecular target agents*

*A: Cetuximab*

Two representative studies included molecular target agents in the TNT. The EXPERT-C trial investigated the effect of adding cetuximab to induction chemotherapy by CAPOX followed by CRT and then again adding cetuximab in adjuvant chemotherapy for high-risk LARC, with having such risk as positive MRF, low rectal cancer, T4 tumor, or EMVI. This study concluded that cetuximab led to a significant increase in response rate and OS in patients with KRAS/BRAF wild-type rectal cancer, but the primary endpoint of improved CR was not met [13].

Another trial, the SWOG 0713 trial, investigated the significance of cetuximab for induction chemotherapy with CAPOX followed by CRT. This study did not meet the targeted pCR rate at 35%; thus, they concluded that cetuximab cannot be recommended outside the clinical setting [14].

This outcome was similar to the treatments of liver metastasis. A study compared the new EPOC trial, which is a multicenter, randomized, and controlled, phase 3 trial to the systemic chemotherapy with or without the use of cetuximab in patients with resectable colorectal liver metastasis and concluded that cetuximab in the perioperative setting in patients with operable disease did not have an oncologic benefit. Thus, cetuximab should not be used in this setting (Table 2c) [15].

*B: Bevacizumab*

AVACROSS was a phase II single-arm study evaluating the effect of bevacizumab to induction chemotherapy with CAPOX followed by CRT. Along with high compliance with the treatment, the pCR rate was as high as 34%, and the R0 resection rate was 98% [16]. However, postoperative morbidity occurred in 58% of patients, and 24% required surgical reintervention. The safety of adding bevacizumab to induction chemotherapy should be addressed. This study is used bevacizumab as induction setting and enough waiting period to surgery has kept. However, bevacizumab-related complications were high.

Another phase II study from Japan investigated the pCR of induction chemotherapy with bevacizumab, CRT, and surgery for poor-risk LARC. The outcomes demonstrated that pCR was 37%, R0 resection was 100%, Clavien-Dindo grade 3-4 complications occurred at 14%, and 3-year DFS was 86% [17]. Thus, the authors concluded that high pCR rate with favorable toxicity and postoperative complications could be achieved (Table 2d).

*4. Organ preservation and Watch-and-Wait approach*

The GRECCAR 2 trial, which is a prospective, randomized, phase 3 trial compared local excision and TME in patients with a good response (residual tumor ≤ 2 cm) after LC-CRT for T2,3 lower rectal cancer [18]. In the local excision group, a completion TME was required if tumor stage

**Table 2d.** Usefulness of Molecular Target Agents. B: Bevacizumab.

| Year | Author | Study design | Patient | N | Study design | Primary endpoint | Outcomes | 3-Year LFS | 3-Year DFS | 3-Year OS |
|---|---|---|---|---|---|---|---|---|---|---|
| 2011 | AVACROSS | Phase II | High-risk rectal cancer | 47 | Feasibility to additional use of bevacizumab | pCR | 36% | 1 of 45 patients had local recurrence | 38 of 45 patients were recurrence free | 3 of 45 patients died |
| 2019 | Konishi | Phase II | Poor-risk low rectal cancer | 43 | Not reported | Not reported | pCR; 37% | 1 of 43 patients had local recurrence | 86% | Not reported |

LFS, local recurrence-free survival; DFS, disease-free survival; OS, overall survival; pCR, pathological complete response

**Table 2e.** Organ Preservation and Watch-and-Wait Approach.

| Year | Author | Study design | Patient | N | Study design | Primary endpoint | Outcomes | 3-Year LFS | 3-Year DFS | 3-Year OS | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2017 | GRECCAR 2 | Phase III | Stage II–III | 186 | Feasibility to assess the local excision after LC-CRT | Oncologic outcomes and mobility | Approximately one-third of patients after local excision required completion TME | 5% vs. 6%, p ≥ 0.05 | 8% vs. 76%, p = 0.45 | 92% vs. 92%, p = 0.92 | Failed to show superiority of local excision |
| 2022 | OPRA trial | Randomized phase II trial | Stage II–III | 324 | Induction chemotherapy vs. consolidation chemotherapy | DFS | 76% vs. 76% | 94% vs. 94% | | 15 vs. 12 deaths, p = 0.39 | TME-free survival; 41% vs. 53% |

LFS, local recurrence-free survival; DFS, disease-free survival; OS, overall survival; LC-CRT, long-course chemoradiotherapy

was ypT2-3. The primary endpoint was oncologic outcomes and morbidity. The results demonstrated that the oncologic outcomes between two groups were not different; however, approximately one-third of patients after local excision required completion TME, increasing the morbidity and side effects. Thus, better patient selection to avoid unnecessary completion TME is required to expand this strategy.

The most recent trial of the Watch-and-Wait approach is the OPRA trial, which was a prospective, randomized phase II trial [19]. Stage II or III rectal cancer was treated with induction chemotherapy followed by LC-CRT or LC-CRT followed by consolidation chemotherapy and either TME or Watch-and-Wait on the basis of tumor response. The primary endpoint was DFS, and the secondary endpoint was TME-free survival. The outcomes demonstrated that DFS was not different between two groups (76% vs. 76%). The 3-year TME-free survival was 41% and 53%, indicating that consolidation chemotherapy is better when aimed at the Watch-and-Wait approach than induction chemotherapy.

pCR is essential for this approach, and several studies were conducted to predict pCR. Ishioka et al. used narrow-band imaging to chromoendoscopy for the evaluation of tumor response to LC-CRT [20]. In addition, Khakoo et al. demonstrated MRI tumor regression grade and circulating tumor DNA as complementary tools to assess response and guide therapy adaptation in rectal cancer. Those studies contribute to making personalized care decision for LARC (Table 2e) [21].

*5. Immune checkpoint inhibitor with or without CRT*

Mismatch repair-deficient colorectal cancer is responsive to programmed death 1 (PD-1) blockade in the context of metastatic disease, and checkpoint blockade could be effective in patients with mismatch repair-deficient LARC [22]. A prospective phase 2 study of single-agent dostarlimab, which is an anti-PD-1 monoclonal antibody, was conducted where it was administered every 3 weeks for 6 months in patients with mismatch repair-deficient stage II or III rectal cancer. A total of 12 patients had completed treatment with dostarlimab and had undergone at least 6 months of follow-up. All 12 patients had a clinical CR.

In contrast, Bando et al. demonstrated the pCR after sequentially combined CRT, 5 cycles of nivolumab, and radical surgery [23]. A pCR was centrally confirmed in 30% (11/37) and 60% (3/5) of the microsatellite stable and microsatellite instability-high (MSI-H) patients, respectively. While immune-related severe adverse events were observed in three patients, no treatment-related deaths were observed.

Further discussion is required to identify the optimal cycles of PD-1 blockade, longer follow-up period, and the follow-up approach. However, 9% of rectal cancer was diag-

**Table 2f.** Immune Checkpoint Inhibitor with or without CRT.

| Year | Author | Study | Patient | N | Study design | Primary endpoint | Outcomes |
|---|---|---|---|---|---|---|---|
| 2022 | Cerek | Phase II | Stage II or III rectal cancer | 12 | Anti-PD-1 monoclonal antibody for MSI-H | pCR | 100% |
| 2022 | Voltage study | Phase II | Stage II or III rectal cancer | 42 | Anti-PD-1 monoclonal antibody with CRT | Feasibility | pCR was 30% in MSS and 60% in MSI-H |

CRT, chemoradiotherapy; PD-1, programmed death 1; MSI-H, microsatellite instability-high; MSS, microsatellite stable

nosed as MSI-H, and those patients would dramatically change their treatment strategies (Table 2f).

## Conclusion

TNT has a chance to deliver full dose of chemotherapy with good compliance for micro-metastasis, and which has the potential to reduce the risk of overall recurrence and improve the survival in LARC. Because the QOL after TME was significantly decreased, organ preservation and Watch-and-Wait approach should be discussed thoroughly. For those strategies, TNT is promising managements due to expect high pCR. Addition, selected patients have great advantage by using anti-PD-1 monoclonal antibody. Multiple ongoing and future trials will assist the clinical decision that will improve the survival with preserving the QOL.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

N Beppu: conception and design of the study; acquisition, analysis, and interpretation of the data; drafting of the article.

K Kataoka, K Kimura, Y Nakamoto, R Okamoto: acquisition of the clinical data.

M Uchino, H Ikeuchi, M Ikeda, H Yanagi: acquisition of the data, drafting or critical revision of the article for important intellectual content, final approval.

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