Int. j. adv. multidisc. res. stud. 2025; 5(4):383-389

Received: 26-05-2025
Accepted: 06-07-2025

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Total Neoadjuvant Treatment in Rectal Cancer; A Narrative Review

[1] Alfredo Colombo, [2] Giovanni Piazza, [3] Tiziana Fiorentini, [4] Naida Faldetta, [5] Domenico Miceli, [6] Federico Colombo, [7] Tommaso Sciacchitano, [8] Guido Martorana, [9] Giulia Colombo, [10] Porretto Concetta Maria

[1, 6, 7, 9, 10] Oncology Unit, CDC Macchiarella, Palermo, Italy
[2, 3, 8] Surgery Unit, Ingrassia Hospital, Palermo, Italy
[4] Surgery Unit, CDC Torina, Palermo, Italy
[5] Surgery Unit, CDC Candela, Palermo, Italy

DOI: https://doi.org/10.62225/2583049X.2025.5.4.4605
Corresponding Author: **Alfredo Colombo**

Abstract

Traditional neoadjuvant chemoradiotherapy (CRT) is beginning to give way to total neoadjuvant therapy (TNT), a promising treatment option for locally advanced rectal cancer (LARC). The results of principal study that aided TNT's integration into clinical practice are combined in this review. When compared to normal CRT, it highlights how effective TNT is at enhancing disease-free and metastasis-free survival, pathologic complete response, and, based on current research, a possible improvement in overall survival. We also examines the trend toward individualized medicine using TNT and examines the greater organ preservation produced by TNT. It also investigates whether radiotherapy can be excluded in specific subgroups. The use of TNT in early-stage disease, immunotherapy integration, and identifying the best TNT components—such as the kind of radiotherapy or chemotherapy—are some future prospects.

Keywords: Rectal, Cancer, Radiotherapy, Immunotherapy, Surgery

1. Introduction

With an estimated 153,020 new cases and 52,550 cancer-related deaths per year, colorectal cancer is the third most frequent cancer in the United States [1].

Rectal cancer accounts for one-third of these instances. Neoadjuvant chemoradiotherapy (CRT) alone, followed by surgery and, in certain cases, adjuvant systemic chemotherapy, has been the standard treatment for about 10% of those diagnosed at a locally advanced stage [2]. The results of the Dutch Rectal Cancer Study and the CAO/ARO/AIO-94 trial show that neoadjuvant CRT alone, followed by total mesorectal excision (TME), has significantly reduced local recurrence rates compared to surgery and adjuvant CRT [3, 4]. Preoperative CRT has been correlated to low postoperative adjuvant chemotherapy compliance and has not significantly improved long-term survival or distant metastases. A further weakness of neoadjuvant CRT alone was its poor pathologic complete response (pCR) rates, which ranged from 15 to 20 percent, which limited the applicability of nonoperative management (NOM). During a five-year period, 30 percent of patients attained distant metastases.

To address the drawbacks of the traditional treatment (neoadjuvant CRT alone), particularly the high distant recurrence rates and poor adherence to postoperative adjuvant chemotherapy, total neoadjuvant therapy (TNT), which combines neoadjuvant systemic chemotherapy and chemoradiotherapy (CRT) prior to surgery, has become a viable treatment option for locally advanced rectal cancer (LARC) [6]. Comparing TNT to traditional neoadjuvant CRT, randomized clinical trials like RAPIDO and PRODIGE23 have shown that TNT can improve disease-free survival (DFS) and decrease treatment failure [8, 9]. Moreover, TNT was demonstrated to facilitate organ preservation through Watch & Wait (W&W, a non-operative management strategy involving close surveillance to monitor for tumor regrowth in patients achieving a complete clinical response) protocols that reduce the need for invasive surgeries. These findings were corroborated by early Habr-Gama reports and an expanding body of literature [10]. TNT is now listed as a therapy option for LARC in the NCCN 2024 guideline due to encouraging outcomes, and many institutions employ it in their regular clinical practice based on evidence from benchmark trials [11].

Although TNT includes a number of treatment sequences, its primary components are radiotherapy (RT), either as short-course RT (SCRT) or long-course CRT (LCCRT) in the neoadjuvant setting, and full-dose cytotoxic systemic chemotherapy (a course of oxaliplatin-based chemotherapy). Chemotherapy can be administered either before or after RT in the form of SCRT or LCCRT. Chemotherapy is known as consolidation chemotherapy (CCT) when administered after RT and as induction chemotherapy (ICT) when administered before to RT. Due to encouraging outcomes, TNT has become the new standard for treating LARC. With an emphasis on clinical applications and future directions, this review examines the present management of rectal cancer with a particular focus on TNT. The W&W technique is outside the purview of this analysis because it is a separate field of treatment for rectal cancer with its own strategies and research issues.

1.1 Results of main studies

Three main strategies for TNT are suggested by the NCCN guidelines for locally advanced rectal cancer (Fig. 1). The first option is induction chemotherapy, in which patients receive neoadjuvant full-dose systemic chemotherapy first, and then either long-course CRT (LCCRT; 50–50.4 Gy in 25–28 fractions over 5–6 weeks with concurrent chemotherapy) or short-course radiotherapy (SCRT; 25 Gy in 5 fractions over 1 week). The second approach, full-dose systemic consolidation chemotherapy is administered after LCCRT or SCCRT. The third alternative is a chemotherapy-only strategy, in which systemic chemotherapy is given first, followed by selective use of radiation (SCRT or LCCRT) depending on the tumor's response. Depending on the patient's tolerance and risk profile, chemotherapy regimens for all choices usually include 12–16 weeks of FOLFOX, CAPOX, or FOLFIRINOX. (Table 1)

Table 1

Overview of benchmark randomized trials in total neoadjuvant therapy for locally advanced rectal cancer.

Clinical Outcome	POLISH II	STELLAR	RAPIDO		PRODIGE 23		CAO/ARO/AIO-12		OPRA	
Number of Patients	515	599	912		461		311		324	
Inclusion Criteria	cT3/cT4	cStage 2 & 3	cT4, extramural vascular invasion, cN2, mesorectal fascia involvement or lateral lymph node involvement		cT3/T4		cStage 2 & 3		cStage 2 & 3	
Primary Outcome	R0 resection rate	Disease free survival	Disease related treatment failure		Disease free survival		Pathologic complete response rate		Disease free survival	
Median Follow-up	35 mo.	35 mo.	5.6 yrs.		6 yrs.		43 mo.		5.1 yrs.	
Treatment Schema	TNT: SCRT + 3xFOLFOX + surgery	Control: Conventional CRT + surgery	TNT: SCRT + 4xCAPOX + surgery	Control: Conventional CRT + surgery	TNT: SCRT + 6xCAPOX or 9xFOLFOX + surgery	Control: Conventional CRT + surgery	TNT: 6xFOLFIRINOX + LCCRT + surgery	Control: Conventional CRT + surgery	Induction: 3xFOLFOX + LCCRT	Consolidation: LCCRT + 3xFOLFOX	Induction: 8xFOLFOX or 6xCAPOX + LCCRT	Consolidation: LCCRT + 8xFOLFOX or 6xCAPOX
3-yrs DFS, %	53	52	65	62	76	69	76	69	73	73	76	76
5-yrs DFS, %	N/A	N/A	N/A	N/A	72	66	N/A	N/A	N/A	N/A	71	69
3-yrs OS, %	73	65	87	75	89	89	91	88	92	92	N/A	N/A
5-yrs OS, %	N/A	N/A	N/A	N/A	82	80	N/A	N/A	N/A	N/A	88	85
pCR Rate, %	16	12	22	12	28	14	28	12	17	25	N/A	N/A
Organ Preservation Rate, %	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	39	54
Locoregional Recurrence Rate, %	22	21	8	11	12	8	5	8	6	5	6	10
Distant Metastasis Rate, %	30	27	22	23	20	27	21	28	18	16	20	22

TNT, total neoadjuvant treatment; EMVI, extramural venous invasion; LCCRT, long course chemoradiotherapy; MRF, mesorectal fascia; pCR, pathological complete response; SCRT, short course radiotherapy; cT, clinical T

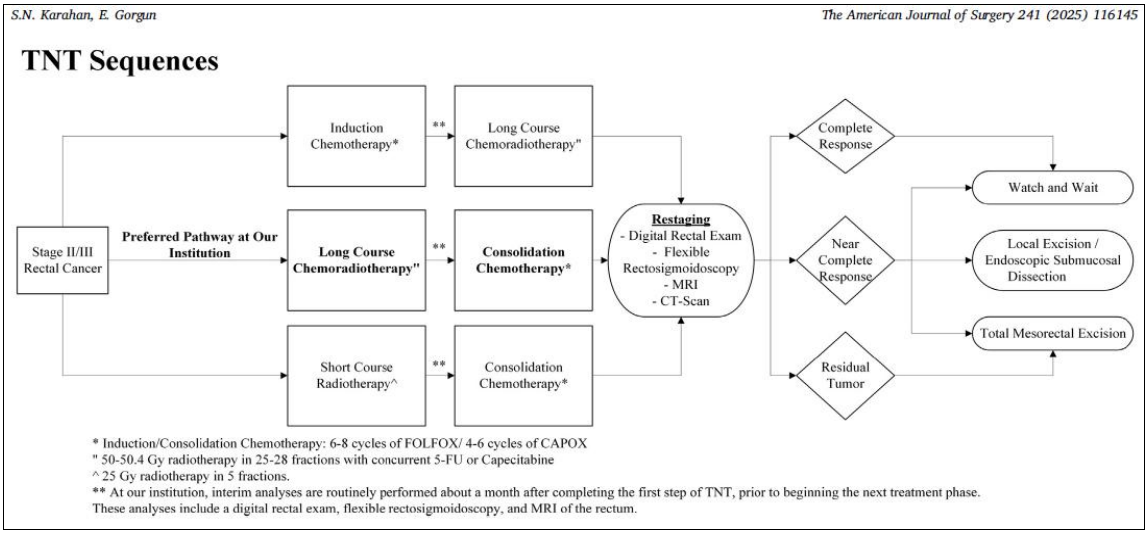

Fig 1: Different schemes of total neoadjuvant therapy for locally advanced rectal cancer

1.1.1 Polish II

In this trial, 541 patients participated, one of the first randomized controlled trials investigating TNT for LARC [12]. Patients with rectal cancer at stage cT3/cT4 were assigned to either conventional neoadjuvant CRT (CRT concurrent with 5-FU and leucovorin, and weekly oxaliplatin) or preoperative TNT, which includes SCRT followed by three cycles (as opposed to the usual eight cycles usually advised in systemic regimens) of consolidation chemotherapy with FOLFOX. Additionally, adjuvant chemotherapy was only administered to 39% of patients in each group. There was no discernible difference in the frequencies of radical resection between the TNT groups (77%) and the traditional neoadjuvant CRT group (71%). The three-year DFS was similar (41 percent for CRT and 43 percent for TNT). Eight-year overall survival (OS) was identical at 49%, despite TNT's superiority in terms of overall survival during the three-year follow-up [13]. The pathological complete response (pCR) rate was comparable, with TNT exhibiting a rate of 16% compared to 12% for conventional neoadjuvant CRT. The TNT group maintained locoregional control in 66% of patients, while the standard neoadjuvant CRT group maintained it at 68%. According to the POLISH II study, TNT—which consists of SCRT followed by chemotherapy—is equivalent to traditional neoadjuvant CRT in terms of pathologic full response, local control, and overall survival. Low DFS and OS, however, may be caused by fewer chemotherapy cycles, a lack of MRI for preoperative staging, the failure to consider nodal disease status when allocating treatment, and poor adherence to adjuvant chemotherapy. These factors also limit the results' wider practical use. Curiously, overall survival rate of POLISH II is comparable to that of the Dutch Rectal Cancer Study, which compared RT after surgery to surgery alone and obtained a 50% OS. This similarity in OS results raises the possibility that the survival advantage anticipated from a full TNT regimen may have been reduced in POLISH II due to the inadequate chemotherapy schedule.

1.1.2 Stellar

The STELLAR trial is a randomized controlled noninferiority study that included 599 patients with LARC [14]. Patients who met the eligibility criteria had cT3-4 and/or regional lymph node metastases. Participants were randomly assigned to either the conventional neoadjuvant CRT (CRT concurrent with capecitabine) or SCRT followed by four cycles of chemotherapy (4 cycles of CAPOX, instead of the standard six cycles typically recommended in systemic regimens) (TNT group). Six to eight weeks following the completion of neoadjuvant treatment, each patient had a total mesorectal excision. The TNT group received adjuvant CAPOX for two cycles, while the traditional neoadjuvant CRT group received adjuvant CAPOX for six cycles. A median follow-up of 35 months was reported. Comparable three-year disease-free survival (DFS) rates of 64.5 and 62.3 percent were reported by the TNT group and the standard neoadjuvant CRT group, respectively. Metastasis-free survival and the risk of locoregional recurrence were similar. The three-year OS rate for the TNT group was 86.5 %, which was significantly higher than that of the standard neoadjuvant CRT group, which was 75.1%. The study's very short median follow-up and inadequate neoadjuvant chemotherapy course, however, restrict how broadly the reported survival improvement may be applied. These results suggest that in LARC, a TNT regimen that includes chemotherapy and SCRT may be employed in place of traditional neoadjuvant CRT.

1.1.3 Rapido

There were 912 patients with stage 2 and stage 3 rectal cancer in the RAPIDO trial. Unlike to other studies, the RAPIDO trial only included high-risk patients who met at least one of the following criteria: cT4a, cT4b, extramural vascular invasion, cN2, or mesorectal fascia involvement. They were randomized to receive either conventional neoadjuvant CRT (Long-course chemoradiotherapy) or a preoperative regimen of short-course radiotherapy followed by consolidation chemotherapy of six cycles of CAPOX or nine cycles of FOLFOX and TME.

When compared to conventional neoadjuvant CRT, TNT dramatically decreased the rate of distant metastases (20 % vs. 26.8%), raised the pathologic complete response (pCR) (28.4 % vs. 14.3 %), and decreased the disease-related treatment failure rate (23.7 % vs. 30.4%) at three years. Conversely, patients in the TNT arm were more likely to experience treatment drop-out (15 % vs. 9 %) and significant adverse events (48 % vs. 25 %). With a median follow-up of 5.6 years, the updated results revealed similar 5-year OS rates (81.7 vs. 80.2%), but the TNT group experienced higher locoregional recurrence (12 vs. 8%).15 Higher local recurrence rates in the TNT arm may raise questions about non-operative management. Nonetheless, it is important to consider variations in radiation schedules (SCRT in the TNT group versus LCCRT in the typical neoadjuvant CRT group). It is difficult to determine if the increased locoregional failure in the TNT group in the RAPIDO trial is attributable to SCRT or the TNT strategy itself, because there is no direct comparison of radiation schedules in the context of TNT. Additional information will be provided by the ongoing ACO/ARO/AIO-18 trial, which compares the results of LCCRT and SCRT with a consolidation scheme in the TNT regimen. The RAPIDO study highlights how crucial it is to strike a balance between local and systemic control. The higher rates of local recurrence underscore the necessity of a suitable mix of chemotherapy and radiation therapy, even though TNT (SCRT and chemotherapy) prevents distant metastases. This is particularly true for high-risk patients whose advanced tumor characteristics may have contributed to the observed outcomes.

1.1.4 Prodige 23

461 patients with clinical stage 2 and stage 3 rectal adenocarcinomas participated in the PRODIGE-23 randomized controlled study. The TNT arm was given adjuvant FOLFOX for six cycles, along with FOLFIRINOX, LCCRT, and TME. The traditional neoadjuvant CRT arm, on the other hand, received LCCRT, TME, and adjuvant either eight cycles of capecitabine or twelve cycles of FOLFOX.

Three-year DFS (76 vs. 69 percent), pCR rate (27.8 vs. 12.1%), and three-year metastasis-free survival rates (79 vs. 72 percent) were all higher in the TNT group. 92% of the TNT was completed. In comparison to conventional neoadjuvant CRT, quality of life assessments revealed a significantly lower rate of impotence in men treated with TNT (37 % vs. 58 %) [16]. The updated results, after a seven-year follow-up period, showed that TNT showed significantly superior DFS (67.6 % vs. 62.5 %) and OS (82 % vs76 %) along with similar local recurrence rates [17].

PRODIGE23 showed that TNT with induction chemotherapy of FOLFIRINOX results in better long-term oncologic outcomes.

It's unclear, though, if the PRODIGE 23 study's survival advantage was due to FOLFIRINOX or the TNT strategy. The current JANUS trial intends to evaluate FOLFIRINOX vs FOLFOX [18], despite the fact that there are no direct comparisons of chemotherapeutic drugs in the setting of TNT in the literature.

1.1.5 CAO/ARO/AIO-12

There is still disagreement over the optimal sequence for administering CRT and chemotherapy in TNT. Consolidation chemotherapy is superior in terms of complete response and organ preservation, according to the CAO/ARO/AIO 12 and OPRA trials [19, 21]. The CAO/ARO/AIO-12 trial included 311 patients with stage 2/3 rectal cancer. Induction chemotherapy (INCT) followed by LCCRT and chemoradiotherapy followed by consolidation chemotherapy (CNCT) were contrasted in this study. In comparison to the INCT group, the CNCT group had a greater rate of pCR (25 % vs. 17 %). Similar three-year DFS (73%) and OS (92%) rates were shown by both groups. Additionally, quality of life outcomes, chronic toxicity rates, and locoregional recurrence rates were similar (6 %in the INCT and 5% in the CNCT).

1.1.6 Opra Trial

In OPRA trial, a phase II study, 324 patients with stage 2 and 3 distal rectal cancer were included. Patients who received eight cycles of FOLFOX or five cycles of CAPOX either before (induction) or after (consolidation) LCCRT had their outcomes compared with those of patients who underwent induction vs consolidation chemotherapy in conjunction with LCCRT. Patients with an incomplete clinical response were administered TME, whilst those with cCR or near cCR were offered WW. A subsequent study published follow-up data for five years, whereas the initial study reported follow-up data for three years [22]. The CNCT and INCT groups had comparable survival rates at three and five years. The CNCT group had a greater organ preservation rate (60 % vs. 47 % at 3 years; 54 % vs. 39 % at 5 years). The rates of sphincter preservation were comparable. Whether TME was performed in response to tumor regrowth or after restaging, there were no appreciable changes in disease-free survival after TME. The results of the CAO/ARO/AIO-12 study were confirmed by the greater organ preservation rate in the consolidation scheme, which resulted in a change in global practice favoring consolidation chemotherapy.

1.2 Radiotherapy used selectively

It has been demonstrated that radiotherapy lowers long-term quality of life, particularly when it comes to gastrointestinal function. These side effects raise concerns about lowering the dose of radiation therapy or avoiding it in some patients for better results [23]. The Swedish Rectal Cancer Trial has shown that high-dose radiation causes deteriorated bowel function, which is characterized by increased frequency, incontinence, and urgency.

1.2.1 Fowarc

In the FOWARC trial, 495 patients with stage II and III rectal cancer were randomly assigned to one of three treatment groups: CRT with concurrent 5-fluorouracil, CRT concurrent with FOLFOX, or four cycles of FOLFOX alone. The study examined the effects of excluding RT from TNT procedures in patients with LARC.

Overall survival, locoregional recurrence, and disease-free survival did not vary after a median follow-up of 45.2 months. These three-year OS rates were 91.3 %, 89.1 %, and 90.7 %, whereas the three-year DFS rates were 72.9 %, 77.2 %, and 73.5 %. The corresponding locoregional recurrence rates were 8%, 7%, and 8.3%. The functional benefit of skipping radiation was one of the FOWARC trial's most significant conclusions. Stool incontinence, high Wexner scores, and the frequency of daily bowel movements were all lower in patients who did not receive radiation treatment (FOLFOX alone). These practical advantages raise the possibility of better quality of life for people who are spared radiation. According to this experiment, some patients may benefit from chemotherapy alone, which could lessen radiation-related toxicities. In the future, a customized strategy that uses radiotherapy sparingly may also be an option.

1.2.2 Prospect

The PROSPECT trial compared neoadjuvant FOLFOX with selective CRT (tumor size < 20% reduction) in 1194 patients with LARC with normal neoadjuvant CRT. Each group received TME [25]. Patients with locally advanced rectal cancer who were clinically staged as T2 node-positive, T3 node-negative, or T3 node-positive were included in this study. Tumors that were T4 or N2 were not included. Following 58 months, the FOLFOX group's five-year DFS was 80.8%, whereas the CRT group's was 78.6%. The FOLFOX group's five-year OS rates were 89.5%, whereas the CRT group's were 90.2%. Additionally comparable were the local recurrence rates (1.8% and 1.6%). Just 9% of patients in the TNT arm needed selective CRT after their tumors shrank by less than 20%. Results for both sexual and gastrointestinal function were better for patients in the FolFOX group.

Particularly for low-risk patients, the PROSPECT study advocates de-escalating treatment (neoadjuvant chemotherapy alone), saving CRT for nonresponders. This strategy can lead to a more individualized approach by lowering toxicity and enhancing functional results.

1.2.3 Convert

In the CONVERT trial, 663 patients with locally advanced rectal cancer who had uninvolved mesorectal fascia were enrolled [26]. Neoadjuvant CRT with capecitabine (nCRT) and neoadjuvant CAPOX alone (nCT) were compared. Adjuvant chemotherapy and TME were administered to all patients. Patients in the nCT group received CRT if they experienced progression or mesorectal fascia involvement. The three-year local recurrence-free survival was comparable at a median follow-up of 48 months (96.3% for nCT vs. 97.4% for nCRT) [26].

Additionally comparable were the three-year DFS and OS rates (DFS: 89.2% vs. 87.9%; OS: 95.0% vs. 94.1%). The pCR rates for nCT and nCRT were 11.0% and 13.8%, respectively. The nCT group saw lower rates of grade 2 long-term toxicity (15.7% vs. 24.7%) and perioperative distant metastases (0.7% vs. 3.1%).

Similar to the low rate of RT necessity in the PROSPECT trial, only a small minority (1.2%) of nCT patients needed CRT because of progression. The CONVERT trial reduces radiation-related toxicities in low-risk, chosen patients by recommending neoadjuvant CAPX as a substitute for CRT, hence supporting the de-escalation therapy intensity.

1.3 Future perspective

1.3.1 Early-stage rectal cancer

Although the use of TNT is being researched because of the difficulties and functional impairments associated with surgery, TME remains the conventional treatment indicated by recommendations for stage I rectal cancer. The ACOSOG Z6041 trial demonstrated a 50% pCR rate in T2N0 patients in the setting of CRT [27]. Another study examined patients who chose TNT for stage I rectal cancer in the past. This includes patients who opted for TNT after transanal excision or after receiving an initial diagnosis. The percentage of organ preservation was 86%, while the rate of complete response was 100%. Except for one patient who developed a rectovaginal fistula, neither group experienced any regrowth, local recurrence, or distant metastases during the median follow-up period of 19 months [28]. These findings point to the possible effectiveness of TNT in treating early-stage rectal cancer. It is anticipated that the continuing TOWARD trial will provide additional details regarding the function of TNT in early-stage rectal cancer and assess if TNT combined with a watch-and-wait strategy can serve as a substitute for drastic surgery in these patients [29].

1.3.2 Immunotherapy

About 5% of rectal cancers have high microsatellite instability (MSI-H), which results in a poor response to fluorouracil-based chemotherapy [30, 33]. Conventional neoadjuvant regimens like TNT and CRT that use fluorouracil-based chemotherapies have trouble treating these cases. A phase 2 trial, published in 2022, examined the use of neoadjuvant immunotherapy (dostarlimab, an anti-PD-1 monoclonal antibody) for 6 months in 12 patients with MSI-H stage II and III rectal cancer [34]. Even without radiotherapy, the trial produced impressive results, with a pCR rate of 100%. Cercek *et al*.'s retrospective study revealed that MSI-H patients had higher rates of progression under TNT, highlighting the need for distinct treatment options for this particular subgroup. At ASCO 2024 were presented the trial updated results, which included 41 patients [35]. Every patient had a complete response. All of these had a sustained full clinical response, and 20 of them had follow-up times longer than 12 months. Although bigger sample numbers and longer follow-up are required, these initial findings are encouraging. The most recent NCCN guidelines suggest neoadjuvant immunotherapy for patients with MSI-H.11 in light of these findings.

1.3.3 Queries that Need more Research

Even if TNT results have improved recently, certain important questions remain. The best course of action for each patient is yet unknown because TNT includes a variety of therapy techniques for a diverse set of people. The OPRA and CAO/ARO/AIO-12 studies examined the treatment sequence (induction versus consolidation) and found that consolidation improved pCR and organ preservation rates while overall survival rates were similar. Since these studies lacked subgroup analyses to investigate which patients would benefit more from each strategy, it is still unclear which order is best for specific patients. The optimal sequence and the categories most likely to gain from induction or consolidation require more investigation. The difference between SCRT and LCCRT in radiation is still up for debate, although it should be clarified by ongoing trials like ACO/ARO/AIO-18.1. Results from the ENSEMBLE and JANUS studies are expected [18, 36]. The ENSEMBLE trial is a randomized phase III trial that compares the effectiveness of a triplet chemotherapy regimen (irinotecan, capecitabine, and oxaliplatin, CAPOXIRI) with a doublet chemotherapy regimen (capecitabine and oxaliplatin, CAPOX). Additionally, there is currently no evidence comparing triplet chemotherapy regimens (FOLFIRINOX, CAPOXIRI) with doublet regimens (CAPOX, FOLFOX). Disease-free survival is the primary end point. Another phase II/III trial that compares a triplet chemotherapy treatment (FOLFIRINOX) and a doublet regimen (FOLFOX or CAPOX) as consolidation therapy is JANUS trial. Phase-specific primary end point vary, with phase III evaluating DFS and phase II concentrating on cCR. Finally, although there are some prognostic indicators for TNT response, they are not yet sufficiently proven to have a substantial impact on patient selection and clinical decision-making. In some patients, omitting radiation was found to be safe; however, the results of ongoing trials such as GRECCAR 14 are still pending [37]. The GRECCAR 14 is a randomized phase II-III non-inferiority study that looks into a customized approach to TNT for patients with high-risk features and mid-to-low-LARC. Patients undergo MRI to evaluate tumor response after six course of high-dose FOLFIRINOX treatment. R0 resection rates in phase II and 3-year DFS in phase III are the main end point for good responders (tumor volume reduction of ≥60%) who are randomized to either CRT or direct surgery. To determine which patients will benefit most from treatment regimens, radiation, or chemotherapy, more validation is required.

2. Conclusion

Total neoadjuvant treatment is a major advancement in the treatment of locally advanced rectal cancer thatimproves organ preservation disease-free and potentially overall, survival. Studies like OPRA, PRODIGE 23, and RAPIDO have shown the benefits of TNT. Individualized therapies are emphasized through the use of immunotherapy and targeted radiation. For the best use of TNT, better response prediction and patient selection are required. To determine the best radiation schedule, the best chemotherapeutic agents and sequences, and the best methods for treating early-stage rectal cancer, more study are necessary.

3. Funding

This research received no external funding.

4. Conflicts of Interest

The authors declare no conflict of interest.

5. References

1. Siegel RL, Miller KD, Wagle NS. Cancer statistics, 2023. CA: A Cancer J Clin. 2023; 73:17-48.
2. Daprà V, Airoldi M, Bartolini M. Total neoadjuvant treatment for locally advanced rectal cancer patients: Where do we stand? Int J Mol Sci, Jul 29, 2023; 24.
3. Sauer R, Liersch T, Merkel S. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years J Clin Oncol, Jun 1, 2012; 30:1926-1933.
4. Van Gijn W, Marijnen CA, Nagtegaal ID. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the

multicentre, randomised controlled TME trial. Lancet Oncol, Jun 2011; 12:575-582.
5. Mari GM, Maggioni D, Crippa J. Compliance to adjuvant chemotherapy of patients who underwent sur gery for rectal cancer: Report from a multi-institutional research network. World J Surg. 2019; 43:1.
6. Ngan SY, Burmeister B, Fisher RJ. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-tasman radiation oncology group trial 01.04. J Clin Oncol. 2012; 30:3827-3833.
7. Gambacorta MA, Masciocchi C, Chiloiro G. Timing to achieve the highest rate of PCR after preoperative radiochemotherapy in rectal cancer: A pooled analysis of 3085 patients from 7 randomized trials. Radiother Oncol, Jan 1, 2021; 154:154-160.
8. Bahadoer RR, Dijkstra EA, Van Etten B. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): A randomised, open-label, phase 3 trial. Lancet Oncol, Jan 2021; 22:29-42.
9. Conroy T, Bosset JF, Etienne PL. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol, May 2021; 22:702-715.
10. Habr-Gama A, Perez RO, Nadalin W. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: Long-term results. Ann Surg. Oct 2004; 240:711-717; discussion 717-8.
11. Network NCC. NCCN clinical practice guidelines in oncology (NCCN Guidelines®): Rectal cancer, Mar 5, 2024. https://www.nccn.org Date: April 30, 2024.
12. Bujko K, Wyrwicz L, Rutkowski A. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: Results of a randomized phase III study Ann Oncol.
13. Ciseł B, Pietrzak L, Michalski W. Long-course preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: Long-term results of the randomized Polish II study Ann Oncol, Aug 1, 2019; 30:1298-1303.
14. Jin J, Tang Y, Hu C. Multicenter, randomized, phase III trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally.
15. Dijkstra EA, Nilsson PJ, Hospers GAP. Locoregional failure during and after short-course radiotherapy followed by chemotherapy and surgery compared with long-course chemoradiotherapy and surgery: A 5-year follow-up of the RAPIDO.
16. Bascoul-Mollevi C, Gourgou S, Borg C. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER PRODIGE 23): Health-related quality of life longitudinal analysis Eur J Cancer, Jan 6, 2023; 186:151-165.
17. Conroy T, Etienne P-L, Rio E. Total Neoadjuvant Therapy with mFOLFIRINOX versus Preoperative Chemoradiation in Patients with Locally Advanced Rectal Cancer: 7-year Results of PRODIGE 23 Phase III Trial, A UNICANCER GI Trial American Society of Clinical Oncology, 2023.
18. Smith JJ, Dasari A, Shi Q. Alliance A022104/NRG-GI010: A randomized phase II trial testing the efficacy of triplet versus doublet chemotherapy to achieve clinical complete response in patients with locally advanced rectal cancer. The Janus Rectal Cancer trial J Clin Oncol. 2023; 41:TPS3640.
19. Fokas E, Schlenska-Lange A, Polat B. Chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for patients with locally advanced rectal cancer: Long-term results of the CAO/ARO/AIO-12 randomized clinical trial JAMA Oncol. 2022; 8:e215445.
20. Garcia-Aguilar J, Patil S, Gollub MJ. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy J Clin Oncol. 2022; 40:2546-2556.
21. Fokas E, Allgäuer M, Polat B. Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12.
22. Verheij FS, Omer DMR, Williams H. Sustained organ preservation in patients with rectal cancer treated with total neoadjuvant therapy: Long-term results of the OPRA trial. J Clin Oncol. 2023; 41:3520.
23. Dahlberg M, Glimelius B, Graf W. Preoperative irradiation affects functional results after surgery for rectal cancer: Results from a randomized study. Dis Colon Rectum. 1998; 41(5):543-549.
24. Deng Y, Chi P, Lan P. Neoadjuvant modified FOLFOX6 with or without radiation versus fluorouracil plus radiation for locally advanced rectal cancer: Final results of the Chinese FOWARC trial. J Clin Oncol. 2019; 37:3223-3233.
25. Schrag D, Shi Q, Weiser MR. Preoperative treatment of locally advanced rectal cancer. N Engl J Med. 2023; 389:322-334.
26. Ding PR, Wang XZ, Li YF. LBA26 Neoadjuvant chemotherapy with CAPOX versus chemoradiation for locally advanced rectal cancer with uninvolved mesorectal fascia (CONVERT): Final results of a phase III trial Ann Oncol, Jan 10, 2023; 34:S1267-S1268.
27. Garcia-Aguilar J, Shi Q, Thomas Jr, CR. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: Preliminary results of the ACOSOG Z6041 trial Ann Surg Oncol, Feb 2012; 19:384-391.
28. Erozkan K, Miller J, Schabl L. Is there a role for total neoadjuvant treatment in EARLYSTAGE rectal cancer Gastroenterology. 2024; 166.
29. Hashimoto T, Tsukamoto S, Murofushi K. Total neoadjuvant therapy followed by a watch-and-wait strategy for patients with rectal cancer (TOWARd): Protocol for single-arm phase II/III confirmatory trial (JCOG2010). BJS Open, Nov 1, 2023; 7.
30. Ishikubo T, Nishimura, Y, Yamaguchi K. The clinical features of rectal cancers with high-frequency microsatellite instability (MSI-H) in Japanese males. Cancer Lett, Aug 12, 2004; 216:55-62.
31. Hong SP, Min BS, Kim TI. The differential impact of

microsatellite instability as a marker of prognosis and tumour response between colon cancer and rectal cancer. Eur J Cancer, Jan 5, 2012; 48:1235-1243.
32. Alex AK, Siqueira S, Coudry R. Response to chemotherapy and prognosis in metastatic colorectal cancer with DNA deficient mismatch repair Clin Colorectal Cancer, Sep 2017; 16:228-239.
33. Cercek A, Dos Santos Fernandes G, Roxburgh CS. Mismatch repair-deficient rectal cancer and resistance to neoadjuvant chemotherapy. Clin Cancer Res, Jul 1, 2020; 26:3271-3279.
34. Cercek A, Lumish M, Sinopoli J. PD-1 blockade in mismatch repair–deficient, locally advanced rectal cancer N Engl J Med. 2022; 386:2363-2376.
35. Cercek A, Sinopoli JC, Shia J. Durable complete responses to PD-1 blockade alone in mismatch repair deficient locally advanced rectal cancer J Clin Oncol. 2024; 42:LBA3512.
36. Watanabe J, Kagawa Y, Kotani D. Ensemble study: A multicenter, randomized, phase III trial to test the superiority of consolidation irinotecan, capecitabine and oxaliplatin vs capecitabine and oxaliplatin following short course radiotherapy as total neoadjuvant therapy in patients with locally advanced rectal cancer. J Clin Oncol. 2023; 41:TPS276.
37. Rouanet P, Castan F, Mazard T. Greccar 14 - A multicentric, randomized, phase II-III study evaluating the tailored management of locally advanced rectal carcinoma after a favourable response to induction chemotherapy: Study protocol Colorectal Dis, Oct 2023; 25:2078-2086.