

Total neoadjuvant therapy in rectal cancer: a review across studies

Research Article

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Abstract: The optimal management of locally advanced rectal cancer (LARC) often presents a therapeutic challenge. Balancing the benefits of treatment against toxicities and reducing the risk for local and distal recurrences are the mainstay of therapeutic approaches. Recently, several studies have compared a more aggressive approach of delivering several cycles of systemic chemotherapy to the established standard of combined chemoradiation. This approach is termed total neoadjuvant therapy and appears to be beneficial, at least for a subset of patients. The results of the main Phase III studies along with their variations in study design are hereby discussed with the goal of extracting useful clinical suggestions for treatment.

Keywords: rectal cancer • total neoadjuvant therapy • Phase III studies • induction • consolidation • organ preservation

1. Introduction

The therapeutic challenge of locally advanced rectal cancer (LARC) is double: to reduce local recurrences and to prevent distant metastases. Total mesorectal excision (TME), the *lege artis* surgical technique, and radiotherapy contribute mainly to the first, improving locoregional control. Radiation is usually given for a dose around 5000 cGy delivered in daily fractions of 200 cGy. Alternatively, a short course of radiation for five daily fractions of 5 Gy is also employed. Chemotherapy (ChT) is usually administered in the form of oral capecitabine during long-course radiation protocols. It is reasonable to assume that this relatively limited ChT intensity is inadequate to successfully treat micrometastases. Oxaliplatin, a drug active when given in combination with fluoropyrimidines, has been tried in the context of neoadjuvant chemoradiotherapy (CRT). It is thought to modestly increase efficacy (remission rates) at a significant increase in morbidity. No overall survival has been recorded with this brief oxaliplatin exposure⁽¹⁾. Postoperative ChT has been a point of contention; albeit debatable, it is increasingly used in full doses aiming at reducing systemic relapse rates in high-risk patients^(2,3).

In general, neoadjuvant systemic treatment for resectable tumors has proven its clinical utility in several cancer types, such as breast, lung, bladder, and stomach^(4–7). With the use of neoadjuvant therapy, downsizing and downstaging of the primary tumor can be achieved, giving the opportunity for a more limited and often more successful surgery. Theoretically, neoadjuvant treatment may offer clinical advantage by treating earlier micrometastatic disease, thus reducing the probability of overt metastasis; however, this statement has not been sufficiently proven. Perhaps more importantly, delivering appropriate ChT and/or radiation before surgery ensures that all patients will be exposed to it, as oftentimes, patients may have poor ChT tolerance postoperatively. All the above arguments could result in increased long-term survival. This hypothesis has to be proven by performing appropriate clinical trials. Based on these premises, full-dose neoadjuvant systemic ChT along with radiation (termed total neoadjuvant treatment [TNT]) has also been tried in localized rectal cancer with considerable success^(8,9). The results of major randomized clinical trials are presented below. As the design of these studies differs considerably, the focus of this review is to extract clinically useful conclusions and recommendations based on the available data.

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2. Clinical trials

Table 1 lists the main randomized controlled trials (RCTs) that tested TNT for LARC, with patient characteristics and results. The Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation (RAPIDO) trial is the first one demonstrating that TNT improves disease-free survival (DFS; 30.4% vs 23.7%, $p = 0.02$) and achieves comparable surgery (92% vs 89%) and ChT (85% vs 90%) completion rates, compared to standard CRT (8). The superiority of TNT in terms of DFS was also confirmed by the “Chemotherapy with FOLFIRINOX and Preoperative Chemoradiotherapy for Patients with Locally Advanced Rectal Cancer” (UNI-CANCER-PRODIGE-23) trial (3-year DFS 75.7% vs 68.5%, $p = 0.034$)⁽⁹⁾. Pathologic complete response (pCR) rates were at least doubled with TNT in both trials (28.4% vs 14.3% in RAPIDO and 27.8% vs 12.1% in PRODIGE-23), but neither of them showed statistically significant benefit in overall survival (OS). The POLISH II trial employed short ChT course and failed to show benefit on DFS (43% vs 41%, hazard ratio [HR] 0.95)

or OS (49% in both arms) compared to standard neoadjuvant therapy at 7-year follow-up⁽¹⁰⁾. The Short-Term Radiotherapy Plus Chemotherapy Versus Long-Term Chemoradiotherapy in Locally Advanced Rectal Cancer (STELLAR) trial comparing TNT with CRT showed an improvement in 3-year OS (86.5% vs 75.1%, HR 0.67) and pCR (21.8% vs 12.3%) rates in favor of the TNT arm⁽¹¹⁾.

The problem arising from these studies is that they all used different regimens and duration of ChT, while the type and duration of radiation also varied. Radiotherapy can be given as a short course (SCRT; 5 × 5 Gy) or long course (LCRT; 50 Gy over 5 weeks), while the ChT regimen is commonly leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin (FOLFOX)/capecitabine and oxaliplatin (CAPOX), but in PRODIGE-23, leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, and oxaliplatin (FOLFIRINOX) was used. The timing of ChT is viewed in relation to radiation; when ChT is given before radiation, it is considered as induction and in the converse order, it is considered as consolidation. Higher pCR was achieved in the consolidation arm of the

Table 1: Major total neoadjuvant randomized controlled trials.

Study	Stage	N	Arms	pCR (%)	DFS (%)	OS (%)
RAPIDO	cT4, or EMVI+, CN2, MRF+, or LPLN+	450	Standard: 5FU-CRT→Surgery→ ±FOLFOX(12)/CAPOX(8)	14.3	*DRTF: 30	89
		462	Consolidation: SCRT→FOLFOX(9)/CAPOX(6)→Surgery	28.42	*DRTF: 24 *DRTF:	89
PRODIGE-23	cT3 or cT4	230	Standard: 5FU-CRT→Surgery→mFOLFOX/capecitabine(3)	12.1	62.5	76.1
		231	Induction: FOLFIRINOX(6)→5FU-CRT→Surgery→mFOLFOX/capecitabine(6)	27.8	67.6	81.9
POLISH II	Primary or locally recurrent cT4, or a palpable fixed cT3	254	Standard: 5FU/OX-CRT→Surgery→± ChT	12	43	49
		261	Consolidation: SCRT→FOLFOX(3)→Surgery→± ChT	16	41	49
STELLAR	Primary cT3–4 or N+ in mid to distal rectum	293	Standard: CAPE-CRT→Surgery→CAPOX(6)	12.3	62	75
		298	Consolidation: SCRT→CAPOX(4)→Surgery→CAPOX(2)	21.8	65	87
CAO/ARO/ AIO-12	cT3 if < 6 cm from AV; > cT3b if 6–12 cm from AV; cT4, or LPLN+	156	Consolidation: 5FU/OX-RT→FOLFOX(3)→Surgery	25	73	92
		150	Induction: FOLFOX(3)→5FU/OX-CRT→Surgery	17	73	92
OPRA	AJCC stage III–IV	155	Consolidation: 5FU-CRT→ FOLFOX/CAPOX(4 mo)→Surgery	NR	76	NR
		152	Induction: FOLFOX/ CAPOX(4 mo)→5FU-CRT→Surgery	NR	76	NR

5FU = fluorouracil, AJCC = American Joint Committee on Cancer, AV = anal verge, CAO/ARO/AIO-12 = Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy trial, CAPOX = capecitabine combined with oxaliplatin, CAPE = capecitabine, CRT = chemoradiotherapy, DFS = disease-free survival, DRTF = disease-related treatment failure, EMVI+ = extramural vascular invasion, FOLFIRINOX = leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride and oxaliplatin, FOLFOX = leucovorin calcium (folinic acid), fluorouracil and oxaliplatin, LPLN+ = lateral pelvic lymph node involvement, MRF+ = mesorectal fascia involvement, NR = not reported, OPRA = Organ Preservation of Rectal Adenocarcinoma study, OS = overall survival, OX = oxaliplatin, pCR = pathologic complete response, PRODIGE-23 = Neoadjuvant Chemotherapy with FOLFIRINOX and Preoperative Chemoradiotherapy for Patients with Locally Advanced Rectal Cancer, RAPIDO = Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation trial, SCRT = short-course radiotherapy, STELLAR = Short-Term Radiotherapy Plus Chemotherapy Versus Long-Term Chemoradiotherapy in Locally Advanced Rectal Cancer

Table 2: Disease characteristics of patients enrolled in major TNT RCTs.

Trial	T2	T3	T4	N0	MRF+	EMVI	LLN
RAPIDO	3	66	31	9	61	30	15
POLISH II	3	34	64	NS	NS	NS	NS
STELLAR	3	84	14	15	56	48	NS
Prodige-23	0	83	17	10	22	NS	10
CAO/AIO/ARO-12	4	71	15	10	27	NS	NS
OPRA	10	77	13	29	NS	NS	NS

PRODIGE-23 = Neoadjuvant Chemotherapy with FOLFIRINOX and Preoperative Chemoradiotherapy for Patients with Locally Advanced Rectal Cancer, RAPIDO = Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation trial, STELLAR = Short-Term Radiotherapy Plus Chemotherapy Versus Long-Term Chemoradiotherapy in Locally Advanced Rectal Cancer, OPRA = Organ Preservation of Rectal Adenocarcinoma study, CAO/ARO/AIO-12 = Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy trial, EMVI = extramural vascular invasion, MRF = mesorectal fascia involvement, LLN = Lateral Lymph Node

“Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy” (CAO/ARO/AIO-12) study without any difference in terms of OS⁽¹²⁾. Although the “Organ Preservation of Rectal Adenocarcinoma” (OPRA) study did not show difference in DFS and metastasis-free-survival (MFS) between induction and consolidation groups, organ preservation rate was higher in the consolidation arm⁽¹³⁾. Thus, direct comparison of the results across studies has to be made with caution and in respect to the treatment protocols.

3. Which Patients are considered?

LARC is defined as clinical T3–T4 or N-positive disease. However, the characteristics of patients included in each TNT study are different. RAPIDO enrolled 912 patients with especially high-risk factors defined as T4, N2, extramural vascular invasion (EMVI) positive, mesorectal fascia (MRF) involvement, or positive lateral nodes⁽⁸⁾. PRODIGE-23, with 461 participants, used a broader definition of LARC and included all T3/T4 cases⁽⁹⁾. Most patients enrolled in the POLISH II trial (328/515) had T4 tumors, as eligibility criteria permitted T4 or fixed T3 stage⁽¹⁰⁾. Participants in OPRA and CAO/ARO/AIO-12 trials (307 and 306, respectively) had T3–T4 or N-positive disease (the latter with restrictions regarding the distance from the anal verge)^(12,13). STELLAR enrolled 591 patients with the same characteristics, whose tumors were located only in the mid or distal rectum⁽¹¹⁾.

4. Which ChT regimen and duration?

Neoadjuvant ChT, as part of TNT, differed among trials in both the selected regimen and duration of

treatment. In most studies, ChT in the experimental arms of TNT consisted of FOLFOX/CAPOX, except for PRODIGE-23. The latter trial compared 3 months of mFOLFOXIRI and fluorouracil (5-FU)-CRT preoperatively, followed by 3 months of FOLFOX6 or capecitabine at an adjuvant setting versus long-course chemoradiotherapy (LC-CRT) plus 6 months of adjuvant FOLFOX6 or capecitabine⁽⁹⁾. The intention then was for both arms to receive 6 months of perioperative therapy, but intensified in the experimental arm. In RAPIDO, patients of the TNT arm were given SCRT followed by six cycles CAPOX (maintenance) or nine cycles of FOLFOX4 in the experimental arm compared to conventional LC-CRT⁽⁸⁾. Similarly, POLISH II compared SCRT followed by FOLFOX, but with only three cycles, versus conventional LC-CRT⁽¹⁰⁾; the brevity of the systemic treatment may account for the failure of this study to show TNT superiority. OPRA and CAO/ARO/AIO-12 were designed to evaluate whether induction or consolidation ChT is superior. In the former, 4 months FOLFOX/CAPOX and 5-FU-CRT were used, while in the latter, three cycles of FOLFOX and 5-FU/OX-RT were used^(12,13). Lastly, STELLAR compared SCRT and four cycles CAPOX (maintenance) plus two cycles of adjuvant CAPOX versus capecitabine-CRT + six cycles of adjuvant CAPOX⁽¹¹⁾.

5. What is the radiation timing and schedule?

Radiotherapy dosage, schedule, and sequencing in relation to ChT varied among TNT trials. RAPIDO, POLISH II, and STELLAR used radiation-first approach (ChT as “consolidation”), employing the short-course schedule (5 x 5 Gy over a maximum of 8 days)^(8,10,11).

On the other hand, in PRODIGE-23, patients underwent ChT first (induction) and LCRT (50 Gy over 5 weeks) thereafter⁽⁹⁾. OPRA and CAO/ARO/AIO-12 used LC-CRT^(12,13). It should be noted that there are no data from the above trials exploring SCRT after induction ChT; it is doubtful that the benefit of SCRT would be maximized by the time of surgery if this sequence were to be elected.

6. What are the major endpoints (PCR – DFS – OS)?

In general, TNT improves outcomes in LARC patients, but some trials failed to show benefit for certain endpoints. In the initial PRODIGE-23 study, 3-year DFS (76% vs 69%, HR 0.69, $p = 0.034$) and pCR (27.8% vs 12.1%, $p < 0.001$) favored TNT, while no benefit in 3-year OS was proven (91% vs 88%). Of patients treated with TNT, 81% completed ChT and 94% received surgery, compared to 75% and 89% in the standard arm, respectively⁽⁹⁾. Recently, an update of PRODIGE-23 with 7-year results was presented in ASCO 2023; all survival endpoints appeared better for the TNT arm, including OS: DFS (67.6% vs 62.5%, HR 0.80, 95% confidence interval [CI] 0.58–1.11), MFS (73.6% vs 65.4%, HR 0.73, 95% CI 0.51–1.02), and OS (81.9% vs 76.1%, HR 0.73, 95% CI 0.48–1.09)⁽¹⁴⁾. Although not conclusively proven, these results may suggest that induction therapy with mFOLFOXIRI for three cycles + LC-CRT followed by three cycles of adjuvant FOLFOX is a valid option in terms of long-term outcomes.

RAPIDO used a novel primary outcome, “disease-related treatment failure” (DRTF), defined as the first occurrence of locoregional failure, distant metastasis, new primary colorectal tumor, or treatment-related death. The 3-year probability of DRTF in the TNT arm was lower than in the experimental one (23.7% vs 30.4%, HR 0.75, $p = 0.019$), while 3-year OS did not differ between the two arms (89.1% vs 88.8%) (8). pCR rates were doubled with TNT (28% vs 14%, OR 2.37 [95% CI 1.67–3.37], $p < 0.0001$), patients were similarly likely to proceed to surgery (92% vs 89%, $p = 0.086$), while ChT completion rates seemed lower in the experimental arm (85% vs 90%), mainly due to toxicity. This trial shows that SCRT followed by 18 weeks of CAPOX/FOLFOX4 could be considered as the standard treatment for patients with high-risk LARC. Further follow-up may provide long-term survival data.

Although POLISH II had promising results at the first analysis, 8-year data concerning endpoints were negative⁽¹⁰⁾. The primary endpoint was R0 resection rate, which barely missed the significance threshold (77% vs

71%, $p = 0.07$). Upon first publication, the 3-year OS advantage was statistically significant (73% vs 65%, $p = 0.046$), while DFS was not (53% vs 52%, $p = 0.85$)⁽¹⁵⁾. However, long-term results of the trial failed to confirm the OS benefit (49% in both arms) and confirmed the absence of DFS benefit (43% vs 41%, HR 0.95, 95% CI 0.75–1.19, $p = 0.65$)⁽¹⁰⁾. The trial updated existing knowledge regarding TNT, even though it was negative. It is clear that three cycles of FOLFOX are inadequate for the treatment of LARC with high-risk features; such patients require a more aggressive approach.

STELLAR 3-year results showed similar DFS rates between the experimental and standard arms (64.5% vs 62.3%) and no significant difference in MFS (77.1% vs 75.3%)⁽¹¹⁾. In that sense, it differed from RAPIDO, perhaps due to the addition of adjuvant ChT in the conventional arm. Despite these, there was a benefit in favor of the TNT arm in both OS (86.5% vs 75.1%, HR = 0.67, 95% CI 0.46–0.97) and pCR (21.8% vs 12.3%, $p = 0.002$)⁽¹¹⁾. It should be noted that POLISH II had similar results in an early analysis, which disappeared in the long-term follow-up⁽¹⁰⁾. The percentages of patients who proceeded to and completed ChT did not differ between the two groups (78.5% vs 78.9% and 58% vs 59% in the TNT and standard arms, respectively), supporting the administration of SCRT plus six cycles of CAPOX (four neoadjuvant and two adjuvant) as a reasonable option for LARC treatment⁽¹¹⁾.

Although in general, TNT shows benefit in outcomes, it is unclear whether a specific sequence of CRT and ChT is optimal. This is the question that the CAO/ARO/AIO-12 trial intended to address. It showed the consolidation arm (CRT first followed by ChT) achieved higher pCR rates than the converse (25% vs 17%), while 3-year DFS and OS were similar in both groups (73% and 92%, respectively)⁽¹²⁾. The 3-year cumulative incidence of locoregional recurrence (6% vs 5%) and distant metastases (18% vs 16%, $p = 0.52$) were not significantly different. An issue that deserves consideration is whether patients can complete ChT courses after CRT and vice versa. Results from the study confirmed that 140 of 150 patients could start ChT after LC-CRT in the consolidation arm. Treatment intensity was also maintained in the induction arm, as 151 of 156 patients could start LC-CRT after ChT. It can be concluded that either schedule is well tolerated and provides equivalent long-term survival.

In addition to comparing induction to consolidation ChT, the OPRA trial tried to assess if the wait-and-watch (WW) approach is a reasonable option for LARC patients who achieve remission⁽¹³⁾. Patients were assessed for treatment response at 8–12 weeks after completion of TNT. Patients who achieved a complete

or near-complete response after finishing TNT were offered WW, while those with incomplete response were recommended to undergo TME. The primary endpoint of 3-year DFS was 76% for both induction and consolidation arms; furthermore, there was no difference between groups in local recurrence-free survival, distant MFS, or OS. Long-term results at 5 years, as recently published, confirmed the absence of survival superiority of one schedule compared to the other. However, TME-free survival was significantly higher for the consolidation arm in both 3 years (55% vs 41%) and 5 years (54% vs 39%), concluding that consolidation ChT is a better option when WW approach is planned. This is probably due to the delayed response induced by radiation, which was not fully developed in the induction arm. The LCRT-first followed by consolidation ChT arm allowed more time for radiation to act and can be considered as a better surgery-sparing approach. It appears that a treatment plan consisting of TNT and WW or TME, depending on whether a pCR is achieved, allows organ preservation in almost half of the patients with LARC without an apparent adverse impact on oncologic outcomes.

7. Omission of radiotherapy?

Although radiation therapy is included in the established treatment plan for LARC, short- and long-term toxicity raises the question of whether it can be omitted or not. The PROSPECT trial, whose results were recently announced in ASCO 2023, tried to clarify that dilemma comparing the use of ChT (mFOLFOX6) with selective use – depending on the percentage of tumor regression – of CRT (LCRT with either capecitabine or 5-FU) to CRT for neoadjuvant treatment of LARC⁽¹⁶⁾. The trial enrolled 1128 patients with cT2N+, cT3N-, or cT3N+ rectal cancers, while those with distal, T4 tumors, threatened radial margins, or more than four enlarged lymph nodes were excluded. The 5-year results showed that ChT with selective use of CRT was noninferior to CRT in terms of DFS (80.8% vs 78.6%, HR = 0.92, $p = 0.0051$), OS (89.5% vs 90.2%, HR = 1.04, $p = 0.84$), and pCR (21.9% vs 24.3%, $p = 0.35$). Similarly, results from the CONVERT trial that compared ChT to CRT in LARC patients with uninvolved MRF showed similar 3-year DFS (89.2% vs 87.9%, HR = 0.88) and OS (95% vs 94.1%, HR = 0.86) rates between the two arms⁽¹⁷⁾. Thus, in certain LARC patients who are not characterized as high risk, ChT alone seems to be a reasonable option with promising results.

8. Administration of adjuvant ChT?

There are limited data considering the use of adjuvant ChT with TNT, as the concept of the latter is to move full-dose ChT preoperatively. In RAPIDO, CAO/ARO/AIO-12, and OPRA trials, adjuvant ChT was not included in the schedule of experimental arms, while in POLISH II, it was left to the discretion of treating physicians, without more information provided^(8,10,12,13). STELLAR treatment plan included six cycles of CAPOX in both arms: two cycles adjuvant–four cycles neoadjuvant in the experimental arm and six cycles adjuvant in the standard one⁽¹¹⁾. Of patients who received adjuvant ChT ($n = 351$), 108 patients (60%) in the TNT group and 82 patients (48.3%) in the CRT group completed the planned cycles of the schedule, while the incidence of grade III–IV toxicities with adjuvant ChT was less in the TNT group compared to the CRT group (3.3% vs 11.8%). However, despite the good tolerability and adherence to therapy, it is unknown whether additional cycles of the same as neoadjuvant or another ChT regimen would be beneficial in terms of DFS/OS or not. In PRODIGE-23 trial, adjuvant ChT with mFOLFOX or capecitabine was given for 3 months in the TNT group and 6 months in the standard-of-care group, while the former had been treated with neoadjuvant FOLFIRINOX for 3 months⁽¹⁴⁾. Interestingly, of the patients who received adjuvant ChT, 35 of 160 (22%) patients in the TNT group and 80 of 158 (51%) patients in the standard-of-care group received at least 80% of the planned doses during the first 3 months of adjuvant treatment. However, the standard-of-care group developed more frequently grade 3 or worse adverse events than the experimental group (120/158 [76%] vs 73/162 [45%] patients), had significantly more treatment delays or modifications, and received a lower oxaliplatin cumulative dose overall. It appears that completion of full-course ChT postoperatively is problematic. Hence, when administration of full-course ChT is desired, the neoadjuvant approach is clearly preferable.

9. Impact of age on outcome?

Although most studies do not have an upper age limit requirement for enrollment, it is possible that relatively younger patients were preferentially directed to the studies. In OPRA, it was reported that participants had a median age of 59 years (range 51–68)⁽¹³⁾. The enrollees in CAO/ARO/AIO-12 had a median age of 60 years⁽¹²⁾. STELLAR excluded patients >70 years: patients had a median age of 55 years (11). In the experimental arm of

PRODIGE-23, the enrolled patients had a median age of 60 years (range 34–76)⁽¹⁴⁾. In PROSPECT, patients had a median age of 57 years⁽¹⁶⁾. Because of the intensity of TNT, it is not surprising that the median age of patients enrolled in TNT studies is below the average age of patients diagnosed with rectal cancer in the general population⁽¹⁸⁾. Therefore, patients over 60 years should be selected for TNT with caution.

10. Discussion

The optimal treatment of a patient with rectal cancer is often challenging. Accurate preoperative staging is essential for defining the most appropriate treatment strategy because it can drive the sequence of treatments and defer surgery. Patients with early tumors (T1 or T2 and N0) can proceed to upfront surgery. More advanced tumors should be discussed in a multidisciplinary context for consideration of neoadjuvant treatment. The question of TNT becomes more relevant when considering organ preservation. Most randomized studies did, in fact, document the beneficial effect of TNT in the studied populations⁽¹⁹⁾. However, the inclusion criteria and the end points used in each study differed. It is, therefore, difficult to derive firm conclusions from the totality of the studies. Despite this, certain plausible statements can be extracted that may be useful in clinical practice.

All patients with rectal cancer should be carefully staged, preferably with magnetic resonance imaging (MRI), to delineate the extent of the tumor and, more importantly, possible involvement of lymphatics or adjacent tissue, assuming the absence of distant metastases⁽²⁰⁾. A positive emission tomography (PET) scan may be additionally useful in this manner⁽²¹⁾. Clearly, most patients with stage III disease can also be treated according to a TNT protocol; selected patients with low T3 N0 can be considered for TNT, as in the OPRA study, 30% of the patients were cN0⁽¹³⁾. This has to be balanced with the risk of overtreating patients with stage II disease, hence the inclusion of such patients should be entertained with caution.

The different protocols cannot be compared based on the rate of complete pathologic response achieved, as this outcome is related not only to the effectiveness of therapy but also to the temporal distance to the radiation delivered⁽²²⁾. In either schedule, it appears that there is no long-term difference between induction and consolidation ChT. In terms of long-term reduction of distal metastasis, it appears that ChT intention matters. Therefore, either a full course of at least 4 months of oxaliplatin-based treatment or a shorter course of more intense (FOLFOXIRI) regimen in fit patients should be recommended^(8,14). The type of radiation, that is, either 5 x 5 or long course, does not seem to impact the final outcome^(8,11–15). However, if organ preservation is a goal of the treatment, long-course radiation is preferable⁽¹³⁾. To date, there are no available data to support the use of short-course radiation to achieve this goal. It also makes sense to administer ChT as consolidation after CRT to ensure the maximum rate of CR⁽²³⁾. Several studies provisioned for postoperative ChT, a practice that cannot be fully supported if an adequate course of ChT is administered preoperatively, unless the PRODIGE treatment plan is followed, lest four cycles of FOLFOXIRI are not adequate to maximally control distant micrometastases⁽⁹⁾.

In conclusion, TNT represents a novel paradigm shift in the treatment of LARC. Recently, results of the PROSPECT study showed equivalence of full-course neoadjuvant ChT to standard CRT in patients with intermediate risk LARC⁽¹⁶⁾. Clearly, this offers another therapeutic option for certain patients, although organ preservation was not an aim. In addition, immunotherapy presents another excellent option for appropriate patients; it seems that it may be also beneficial for microsatellite stable (MSS) rectal tumors in the context of TNT^(24,25). Longer follow-up and results of ongoing studies will help reshape a new and exciting landscape for the treatment of LARC.

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