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Research Article

Total Neoadjuvant Therapy vs. Neoadjuvant Chemoradiotherapy in Locally Advanced Rectal Cancer: A Phase II Randomized Trial

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Abstract
Total neoadjuvant therapy (TNT) is becoming increasingly popular as a systemic treatment for locally advanced rectal cancer (LARC), serving as an alternative to standard neoadjuvant concurrent chemoradiotherapy (CCRT). This study compared TNT versus neoadjuvant CCRT in cases of LARC. This phase II randomized controlled study included 30 patients with LARC (stages T2N1-2, T3, T4), who were randomized into two groups. The TNT group (n=15) received a long-course CCRTH followed by 2 cycles of consolidation chemotherapy with XELOX before surgery. The CRT group (n=15) received a long course of CCRTH followed by surgery. The cumulative dose of radiation in the current chemoradiation therapy was 50.4 Gy. All patients underwent total mesorectal excision (TME). The primary outcome measures were pathologic complete response (pCR) rate and 3-year event-free survival (EFS). The two groups were compared using Pearson's Chi-square test, Fisher's exact test, t-test, or the Mann-Whitney test. Survival analysis was performed using the Kaplan-Meier method, with group comparisons made using the log-rank test. A p-value < 0.05 was considered significant. Five patients in the TNT Group had a pCR compared to none in the CRT group (p=0.042). Moreover, 8 of the remaining 10 patients showed downstaging. In the CRT group, downstaging was observed in 6 patients (40%). Lymph nodes were positive in 3 patients of the TNT group compared to 10 of the CRT group (p=0.010). At 3 years, the overall survival of the TNT group was 86.2% compared to 57% in the CRT group (p=0.034). The event-free survival was 73.3% and 26.7% in the TNT and CRT Groups, respectively (p=0.021). CCRTH toxicity profile was comparable in both groups, mainly in the form of diarrhea, bleeding per rectum, peripheral neuropathy, cystitis, and neutropenia. In patients with LARC, TNT incorporating consolidation chemotherapy after long-course CCRTH before TME is superior to chemoradiation alone. TNT is associated with a higher complete pathological response, reduced local and distant metastases, and enhanced overall and disease-free survival, with a comparable toxicity profile to CRT alone.

Keywords: chemoradiotherapy, consolidation chemotherapy, neoadjuvant therapy, rectal neoplasms, XELOX

1. INTRODUCTION

Rectal cancer is a major global health issue, with around 436,000 new cases documented in 2022. The age-standardized incidence rate (ASR) is approximately 9.1 per 100,000 individuals. Reduced rates are observed in certain areas of Africa and Asia; nonetheless, these regions are witnessing an upward trend attributed to lifestyle modifications and enhanced screening practices [1]. Within the Eastern Mediterranean region, colorectal cancer ranks as the third most prevalent cancer in males and the second most prevalent cancer in females [2]. Meanwhile, the crude rate of rectal cancer was 1.8% in 2022 in Egypt [1].

Locally advanced rectal cancer (LARC) accounts for 5–10% of all rectal cancer cases and it is characterized by tumors that have penetrated the muscularis propria into the outer layers of the rectum (T3), have breached the rectal wall, potentially adhering to adjacent organs or tissues (T4), and/or have nodal involvement [3]. The complexities in managing LARC have led to the implementation of a multimodal therapeutic strategy [4]. The standard of care for these tumors has steadily evolved during the past three decades. Neoadjuvant concurrent chemoradiotherapy (CCRT) has become the preferred option over postoperative chemoradiotherapy due to its superior local control and less toxicity [5]. However, many patients continue to experience distant metastases, and the gain in overall survival is limited [6].

These disadvantages led to the development of novel treatment modalities, culminating in the introduction of total neoadjuvant therapy (TNT) to enhance compliance and systemic management. This method entails the use of 5FU with platinum-

Table 1. Baseline characteristics of the patients and tumors.

		TNT Group	CRT Group	p-value
		n =15	n=15	
Age	< 50 years	8 (53.3%)	6 (40.0%)	0.464
	≥ 50 years	7 (46.7%)	9 (60.0%)	
Sex	Male/Female	8/7	9/6	0.713
Distance from anal verge	< 10 cm	8 (53.3%)	8 (53.3%)	1.000
	≥ 10 cm	7 (46.7%)	7 (46.7%)	
Pathological grade	G2	12 (80.0%)	10 (66.7%)	0.682
	G3	3 (20.0%)	5 (33.3%)	
cT-stage	T3	10 (66.7%)	12 (80.0%)	0.682
	T4	5 (33.3%)	3 (20.0%)	
cN-stage	N0	5 (33.3%)	4 (26.7%)	
	N1	8 (53.3%)	8 (53.3%)	1.000
	N2	2 (13.3%)	3 (20.0%)	
Stage	Stage II	5 (33.3%)	4 (26.7%)	
	Stage IIIb	9 (60.0%)	11 (73.3%)	1.000
	Stage IIIc	1 (6.7%)	0 (0.0%)	
p53 score	Score 0	2 (28.6%)	2 (25.0%)	
	Score 1	1 (14.3%)	0 (0.0%)	1.000
	Score 2	0 (0.0%)	3 (37.5%)	
	Score 3	4 (57.1%)	3 (37.5%)	
CEA	Negative	13 (86.7%)	11 (73.3%)	0.651
	Positive	2 (13.3%)	4 (26.7%)	

Data are presented as number (%)

based chemotherapy and radiotherapy before surgery, intending to reduce tumor size and minimize the likelihood of local recurrence and the occurrence of occult micrometastases. Recent investigations have shown that TNT surpasses conventional neoadjuvant procedures regarding pathological complete response rates and enhanced long-term oncological outcomes [7][8]. This study aimed to compare a TNT approach incorporating neoadjuvant consolidation chemotherapy after CCTH versus neoadjuvant CCRT alone. Both treatment modalities are followed by surgical resection and then adjuvant chemotherapy according to pathological complete response. Therefore, we can assess the additive effect of consolidation chemotherapy aiming to decrease the distant relapse rate and enhance pathological response.

2. MATERIALS AND METHODS

This phase II randomized controlled parallel group study included 30 patients with pathologically proven locally advanced non-metastatic rectal adenocarcinoma during the period from January 2017 to December 2021. The patients were recruited from the Medical Oncology Department, National Cancer Institute (NCI), Cairo University, Egypt. All patients provided written informed consent for participation in the study after a comprehensive explanation of the benefits and complications of treatment. The study was approved by the ethical committee of the NCI (Approval number: 201617029.3). The inclusion criteria were patients with locally advanced rectal adenocarcinoma (stage T2N1-2, T3, T4), aged ≥ 18 years at diagnosis, and Eastern Cooperative

Oncology Group Performance Status (ECOG-PS) 0 –2. Patients with metastatic or recurrent rectal tumors, extensive growth into the sacrum or the lumbosacral nerve roots, concomitant malignancies, and medical or psychiatric conditions were excluded from the study.

During the baseline visit, clinicopathological characteristics, including the patient's sex, age, tumor size, lymphovascular invasion, and stage, were collected. Full laboratory and radiological investigations were done, including CT chest, abdomen, and pelvis (CT-CAP), and MRI pelvis. Then, randomization was done using the permuted block method to allocate the patients into one of two groups. The TNT group (n=15) received a long course of concomitant chemoradiotherapy (CCRTH) followed after 2–4 weeks by 2 cycles of consolidation chemotherapy with XELOX (capecitabine and oxaliplatin). Surgery was performed 2–4 weeks after the last chemotherapy (CTh) cycle. After surgery, patients with pT0-2N0 were spared adjuvant CTh, while those with higher stages received 4 cycles of XELOX. The CRT Group (n=15) received a long course of CCRTH followed by surgery 8–12 weeks after the end of CCRTH. After surgery, patients with pT0-2N0 did not receive adjuvant CTh, and those with higher stages received 6 cycles of XELOX.

Radiation therapy was delivered by external beam photon radiation with a 3D conformal technique. Radiation treatment was provided once a day at 1.8 Gy/day, 5 days/week for 5 weeks (45 Gy in 25 fractions), followed by a minimum boost of 5.4 Gy. The cumulative dose within the tumor volume to the prescription point (or PTV) of 50.4 Gy. Concomitant capecitabine was given starting from the 1st day of radiotherapy in a dose of 825 mg/m^2 twice daily for 5 days per week**.** XELOX regimen comprised oxaliplatin 130 mg/m^2 IV over 2 h on day 1 and capecitabine 1000 mg/m^2 twice daily, days 1–14 every 21 days. In patients with low absolute neutrophilic count after the 1st cycle of CTh (neoadjuvant or adjuvant), granulocyte colony-stimulating factor (G-CSF) was used in subsequent cycles to avoid schedule delays. In cases of unacceptable toxicity or withdrawal of consent, therapy was stopped. All patients underwent total mesorectal excision (TME) with a minimum surgical distal margin of 5 cm for upper-third rectal tumors and 2 cm for middle and lower-third tumors.

2.1. Follow-up

Follow-up visits were scheduled every 3 weeks during CCRTH (3 visits) and with every cycle of neoadjuvant and adjuvant CTh. During these visits, thorough examinations and investigations were done in addition to evaluations for adverse events. The subsequent follow-up visits were scheduled every three months during the 1st two years and every 6 months thereafter. During these visits, manifestations of disease relapses were examined. CT scan of chest, abdomen, and pelvis (CT-CAP) and pelvic MRI with or without contrast were done every 6 months for 2 years, then annually or if indicated by symptoms or laboratory abnormality. Other radiological imaging was done if indicated by symptoms or lab abnormalities. Colonoscopy was done within the 1st year after surgery, and according

Table 2. Toxicity grading after neoadjuvant concurrent chemoradiotherapy.

		TNT Group	CRT Group	p-value
		n =15	n=15	
Diarrhea	Grade 1	5 (33.3%)	7 (46.7%)	0.795
	Grade 2,3	7 (46.7%)	8 (53.3%)	
Bleeding per rectum	Grade I	7 (46.7%)	10 (66.7%)	0.211
	Grade 2	2 (13.3%)	0 (0.0%)	
Neuropathy	Grade I	9 (60.0%)	14 (93.3%)	0.080
Cystitis	Grade I	9 (60.0%)	11 (73.3%)	0.253
	Grade 2	0 (0.0%)	3 (20.0%)	
Abdominal pain and/or neutropenia		9 (60.0%)	15 (100%)	0.017

Data are presented as number (%)

Table 3. Surgical results.

Pathological Finding		TNT Group n =15	CRT Group n=15	p-value
pT	T0	5 (33.3%)	0 (0.0%)	
	T1	5 (33.3%)	4 (26.7%)	
	T2	2 (13.3%)	3 (20.0%)	*
	T3	2 (13.3%)	6 (40.0%)	
	T4	1 (6.7%)	2 (13.3%)	
pN	Negative	12 (80.0%)	5 (33.3%)	0.010
	Positive	3 (20.0%)	10 (66.7%)	
Stage	Stage 0	5 (33.3%)	0 (0.0%)	
	Stages I, II	7 (46.7%)	5 (33.3%)	0.009
	Stage III	3 (20.0%)	10 (66.7%)	
Negative surgical margins		15 (100.0%)	10 (66.7%)	0.042
Pericolic fat invasion		2 (13.3%)	4 (26.7%)	0.651
Lymphovascular invasion		1 (6.7%)	8 (53.3%)	0.014
Perineural invasion		1 (6.7%)	10 (66.7%)	0.001

Data are presented as number (%); * No p-value due to the small number of cases in subgroups

to the standard guidelines.

The primary outcome measures were pathologic complete response (pCR) rate, defined as the absence of viable tumor cells in the primary tumor and the lymph nodes (ypT0N0), and 3-year event-free survival (EFS). A moderate response was defined by the presence of only small clusters or single cancer cells. Minimal response means remaining residual cancer with predominant fibrosis, while poor response was defined as extensive residual cancer [9]. EFS was calculated from the date of randomization till the date of relapse, death, or last follow-up. The secondary outcome measures were overall survival (OS), radiological response by MRI before surgery, short and long-term toxicity, and surgical complications. OS was calculated from the date of diagnosis till the date of death or last follow-up.

2.2. Sample Size Estimation

Previous studies indicate that the failure rate among controls is 0.13 [10][11]. If the true failure rate for TNT is 0.667, 12 per group were needed to be able to reject the null hypothesis that the failure rates for the two groups are equal with probability (power) 0.8. The type I error probability associated with the test of this null hypothesis is 0.05. The number was increased to a total sample size of 30 (15 in each of the two groups) to allow for losses of around 25%. The sample size was calculated using G*Power program (University of Düsseldorf, Düsseldorf, Germany).

2.3. Statistical Methods

Statistical analysis was done using IBM SPSS® Statistics version 26 (IBM® Corp., Armonk, preNY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data was expressed as frequency and percentage. Pearson's Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables. Data were tested for normality using the Shapiro-Wilk test. A comparison of quantitative variables between two groups was done using the t-test for normally distributed data or the Mann-Whitney test for not normally distributed numerical data. Survival analysis was done using the Kaplan-Meier method, and a comparison between two survival curves was done using the log-rank test. All tests were two-tailed. A p-value < 0.05 was considered significant.

3. RESULTS AND DISCUSSIONS

The patients' characteristics are outlined in Table 1. The two groups were comparable regarding age, sex, and all tumor characteristics. The mean age of the TNT group was 48.9±14.2 years, and that of the CRT was 52.1±12.3 (p=0.514). Tumor markers (CEA) were not elevated in about 80% of patients. cT3 stage accounted for more than 70% of patients. About half of the patients (53.3%) in both groups had cN1 stage, and 16.7% had cN2. Clinical stage III accounted for 70% of patients in both groups.

3.1. Preoperative Radiological Assessment

After CCRTH, the radiological assessment revealed comparable results between both groups. Moderate/marked regressive courses were recorded in 7 patients (46.7%) in the TNT group and 9 (60%) in the CRT group (p=0.464). In the TNT group, additional 2 patients showed a complete response during preoperative CT/MRI.

3.2. CCRTH Toxicity

The toxicity profile after CCRTH was comparable in both groups, mainly in the form of diarrhea, bleeding per rectum, peripheral neuropathy, cystitis, and neutropenia (Table 2). Grade I neuropathy was common in the CRT group and occurred in 93.3% of patients compared to 60% of patients in the TNT group. Despite the neuropathy numerical difference, no significant statistical difference was found (p=0.080). Abdominal pain and/or neutropenia occurred in 60% of patients in the TNT group and all patients in the CRT group (p=0.017).

3.3. Postoperative Pathological Features

Five patients did not have any residual tumor tissue in the TNT Group (T0), and one patient had T4 disease. Moreover, 8 of the remaining 10 patients showed downstaging. In the CRT Group, none achieved a complete response, and two had T4 disease. Downstaging was observed in 6 patients (40%). Lymph nodes were positive in 3 patients of the TNT group compared to 10 of the CRT group (p=0.010). Thus, five patients in the TNT group had a pathologic complete response (ypT0N0) compared to none in the CRT group (p=0.042). A moderate therapy effect was noticed in 10 patients in both groups, while 5 patients of the CRT group had a poor therapy effect. All the TNT group patients had negative surgical margins compared to 10 of the CRT group (p=0.042). Lymphovascular and perineural invasion as well as invasion of the pericolic fat, are shown in Table 3.

3.4. Adverse Events of Adjuvant Chemotherapy

Adjuvant chemotherapy was administered for 10 patients in the TNT group (4 cycles) and all patients in the CRT group (6 cycles) (Table 4). Diarrhea was a common side effect with higher frequency and grades in the CRT group (80%) who received 6 cycles compared to the TNT group (40%) who received 4 cycles only (p=0.635). Diarrhea led to treatment interruption in 3 patients in the CRT group. Grade 2 neuropathy was more common in the CRT group (40%), but no dose modification or treatment interruption was needed. Abdominal pain and colic were very common side effects, but with mild to moderate degrees in both groups. Moderate to severe nausea and vomiting were observed more

Table 4. Adverse events of adjuvant chemotherapy.

	TNT Group	CRT Group
	n =15	n=15
Adjuvant chemotherapy	10 patients	all patients
Number of cycles	4	6
Diarrhea frequency	40%	80%, with higher frequency and grades
Diarrhea treatment interruption	0	3 patients
Grade 2 neuropathy (%)		40%, dose modification/interruption was not needed
Mild to moderate abdominal Pain/colic	Very common	Very common
Nausea/vomiting (%)	33.3%	40.0%
Grade I neutropenia (%)	46.7%	93.3%

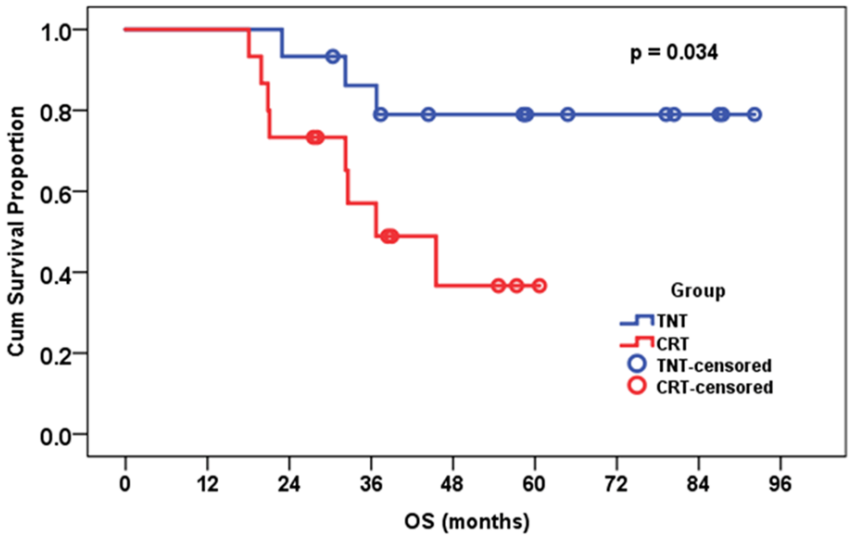

Figure 1. Overall survival in the two groups studied.

in the CRT group (40%) than in the TNT group (33.3%, p=0.052). Other side effects, including grade I neutropenia, were more common in the CRT group (93.3%) compared to 46.7% in the TNT group (p=0.014).

3.5. Follow-up Assessment with Imaging (MRI/CT) and Colonoscopy

At the end of adjuvant therapy, none of the TNT group and one in the CRT group had local recurrence after 3 months. Local hyperemic and inflammatory changes were common in both groups (40% vs. 60%, respectively, p=0.273). At 3 months, one patient in the TNT group and 4 in the CRT group developed distant metastases (p=0.241). One more patient in the TNT group developed distant metastases after 6 months. During the 12-month assessment, two patients in the TNT group had distant metastasis, and one had local recurrence compared to 6 and 4 patients in the CRT group, respectively.

The most common site of recurrence in both groups was abdominal recurrence in lymph node recurrence and peritoneal nodules (n=9), followed by liver (n=8), bone (n=6), and lung (n=5), while rectal recurrence occurred in 3 patients. Metastases to multiple sites were common. All patients with recurrent disease (n=15) received the FOLFIRI protocol (Irinotecan 180 mg/m^2, calcium folinate (Leucovorin) 50 mg, fluorouracil 400 mg/m^2 IV push, fluorouracil 2,400 mg/m^2 continuous IV via pump over 46 h every 14 days) as a second line, and 5 patients (16.7%) received palliative radiotherapy to the bone. Nine out of the 15 patients (60%) had progressive disease after 2nd-line Cth.

3.6. Survival Analysis

During the period of the study, 11 patients died. The median follow-up period was 38 months (range: 18–92 months). The cumulative overall survival (OS) at 3 years was 72%. At 3 years, the OS of the TNT group was 86.2% compared to 57% in the CRT Group (p=0.034, Figure 1). At 3 years, 15 patients had local and/or distant metastases. The EFS was 73.3% and 26.7% in the TNT and CRT groups, respectively (p=0.021, Figure 2). However, surgical margin and postoperative nodal status were the only independent variables affecting OS and EFS. Factors affecting survival are shown in Tables 5 and 6.

3.7. Discussion

We treat LARC with neoadjuvant long-course chemoradiotherapy, followed by surgery and adjuvant chemotherapy, to enable tumor downstaging and pCR. Recent studies highlight TNT as a promising strategy for improving local and systemic control. This phase II trial aims to compare the oncological outcomes of TNT versus standard chemoradiation. This study found that TNT was superior to CCRT in terms of more tumor downstaging, fewer lymph node positivities, more negative surgical margins, and better survival outcomes. TNT achieved downstaging in 87% of

the patients, with pCR in 5 patients (33.3%), compared to 40% of the patients in the CRT group reached tumor downstaging with no cases of pCR. Positive lymph nodes are significantly fewer in the TNT group (p=0.010). Besides, all patients in the TNT Group had negative surgical margins compared to 10 of the CRT group (p=0.042). None of the patients in the TNT group showed poor therapy effects. In terms of survival, TNT resulted in significantly higher cumulative EFS (p=0.021) and OS (p=0.034) at 3 years.

Two TNT sequences, induction chemotherapy followed by chemoradiation and chemoradiation followed by consolidation chemotherapy, show enhanced efficacy compared to regular CRT and TME in previous randomized trials [12]. However, the optimum TNT sequence is still a subject of controversy and may be influenced by various pretreatment circumstances or treatment objectives [13]. The CAO/ARO/AIO-12 randomized phase 2 clinical trial compared the two sequences [14]. Long-term analysis of its results has shown that consolidation chemotherapy following CRT resulted in elevated rates of pCR without adversely affecting disease-free survival, chronic toxicity, overall health status, quality of life, or stool incontinence when compared to induction chemotherapy followed by CCRT and TME [12]. However, using either regimen, TNT can be more effective in eliminating micro-metastatic disease than adjuvant chemotherapy delayed following surgery [15]. Moreover, TNT may circumvent the tolerant milieu for tumor proliferation induced by surgery and diminish tumor cell dissemination [16].

In the current study, we adopted the sequence of CCRT followed by consolidation chemotherapy, which is intended to optimize tumor response and may enhance the achievement of pCR [17]. This regimen prioritizes the treatment of local disease to avert local progression; then, administering consolidation chemotherapy has the additional benefit of extending the time between surgery and radiotherapy, perhaps enhancing the pathological response [18]. The pCR rate was 33.3% in the TNT group, while none of the patients in the CRT group reached pCR. Many previous studies investigated the efficacy of TNT with pCR as the primary endpoint. A recent meta-analysis of 14 RCTs involving 2,217 patients reported a pooled estimate of pCR of 23.6% (95% CI: 20.3–27.2) [19]. This meta-analysis involved 6 studies employing the consolidative strategy, in which the pCR was 20% (95% CI: 13.9–27.8%). However, the type of consolidation chemotherapy used in these studies was heterogeneous.

Previous study used the same regimen as the current study, i.e., 2 cycles of XELOX (capecitabine and oxaliplatin) [20]. The authors reported pCR in 13.6% and downstaging in 36.4% of the consolidation group. The STELLAR trial found a 16.6% pCR rate with 4 courses of XELOX [21]. The RAPIDO trial, a phase 3 study comparing

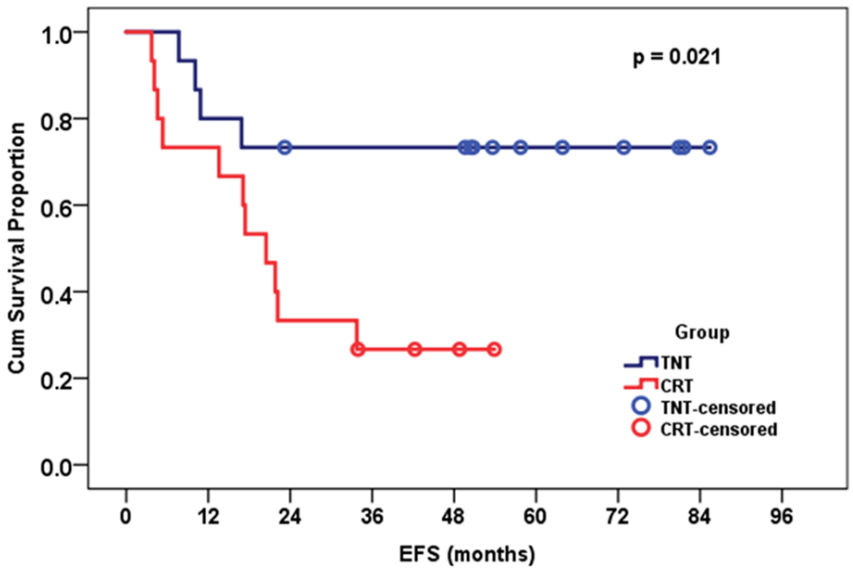

Figure 2. Event-free survival in the two studied groups.

Table 5. Overall survival and its relation to clinicopathological factors.

	n	n Events	Cumulative Survival at 3 Years (%)	p-value
Whole group	30	11	72.0	
Treatment group				
TNT	15	3	86.2	0.034
CRT	15	8	57.0	
Age				
< 50 years	14	5	70.1	84.9
≥ 50 years	16	6	73.9	
Sex				
Male	13	7	51.3	0.021
Female	17	4	87.5	
Distance from anal verge				
< 10 cm	16	5	80.0	0.308
≥ 10 cm	14	6	64.3	
Clinical Stage				
Stage 2	9	3	77.8	0.706
Stage 3	21	8	68.6	
Surgical Margins				
Negative	25	6	86.9	<0.001
Positive	5	5	0.0	
Nodal Status				
Negative	17	2	93.8	<0.001
Positive	13	9	41.0	
cT Stage				
T3	22	8	66.5	0.870
T4	8	3	87.5	
cN Stage				
N0	9	3	77.8	0.014
N1	16	4	84.6	
N2	5	4	20.0	
Pathological Response				
Poor or mild effect	12	7	47.6	0.044
Marked/moderate effect	13	4	83.1	
Complete therapy effect	5	0	100.0	

short-course radiotherapy followed by chemotherapy and delayed surgery to standard preoperative CCRT, compared TNT in the form of short-course CCRT followed by consolidation therapy of 6 cycles of with long-course CCRT [8]. They reported a significantly higher pCR rate in the TNT arm compared to CCRT (28% vs. 14%).

The CAO/ARO/AIO-12 trial reported a 25% rate of pCR after 3 cycles of FOLFOX [14]. In another study, 3 cycles of fluorouracil-based consolidation chemotherapy did not improve the pCR rate compared to standard chemoradiation [22]. A recent systematic review and network meta-analysis of 27 RCTs confirmed the high benefit of long-course CCRT + consolidation chemotherapy compared to CCRT alone (RR: 1.96; 95% CI, 1.25–3.06) [23].

The median follow-up period in the present study was 38 months (range: 18–92 months). TNT was associated with a survival advantage compared to the conventional CCRT in both EFS and OS. The 3-year EFS was 73.3% and 33.3% in the TNT and CRT Groups, respectively (p=0.021). Only the RAPIDO trial indicated that the cumulative risk of disease-related treatment failure at 3 years was 23.7% in the TNT group versus 30.4% in the standard-of-care group (p=0.019) [8][24]. On the other hand, a non-significant disease-free survival (DFS) advantage was reported in the STELLAR trial (64.5% in the TNT group compared to 62.3% in the control group) [21][25], and the CAO/ARO/AIO-12 (73% in both groups) [12]. This was confirmed in a meta-analysis that found a pooled estimate of 3-year DFS of 70.6% (95% CI: 62.5%–77.7%).

The OS was significantly higher in the TNT group in the current study compared to the CRT group (86.2% vs. 57%, respectively, p=0.034). The OS rate in the STELLAR trial was 86.5% compared to 75.1% in the control group [21][26]. The OS was similar in the induction and consolidation groups in the CAO/ARO/AIO-12 trial [12][27]. The pooled estimate of 3-year OS following TNT was 93% (95% CI: 80.8%–97.7%) in a meta-analysis of 14 RCTs [19][28]. The toxicity profile after CCRTH was comparable in both groups in the present study, mainly in the form of diarrhea, bleeding per rectum, peripheral neuropathy, cystitis, and neutropenia. In addition, 5 patients in the TNT group (33.3%) who achieved pCR were spared from adjuvant chemotherapy. In the CAO/ARO/AIO-12 trial [12][29]. The consolidation sequence was associated with lower CRT-related grade 3–4 toxicity (37% vs. 27%) and higher compliance with CRT. In concordance with the current study, the most common grade 3 or 4 adverse event in the RAPIDO trial in the two groups was diarrhea [8][30]. In the present study, grade 2 neuropathy was more common in the CRT group (40%) following adjuvant chemotherapy. The RAPIDO trial reported a 9% neurological toxicity during adjuvant chemotherapy in the standard of care group [8][31]. An obvious limitation of this study is the small sample size. However, this is attributed to the exploratory nature of the study, which aims to examine a relatively novel strategy in our institution. Another limitation is the relatively short follow-up period. Nonetheless, the results of the present study align with many randomized studies indicating that TNT yields better rates of pCR, reduced distant metastases, and enhanced DFS [32]. The available studies in the literature utilized multiple TNT regimens, yet no definitive reference treatment has been established.

4. CONCLUSIONS

The TNT approach for treatment of LARC, incorporating a two-cycle consolidation chemotherapy with XELOX after long-course concomitant chemoradiotherapy before total mesorectal excision, was superior to chemoradiation alone. TNT led to a complete pathological response in one-third of patients, decreased local and distant metastases, and enhanced overall and disease-free survival. Adjuvant chemotherapy was avoided in 33.3% of the patients receiving TNT. TNT was associated with a comparable toxicity profile to CRT alone.

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Table 6. Event-free survival and its relation to clinicopathological factors.

	n	n Events	Cumulative Survival at 3 Years (%)	p-value
Whole group	30	15	53.3	
Treatment group				
TNT	15	4	73.3	0.021
CRT	15	11	26.7	
Age				
< 50 years	14	5	64.3	0.260
≥ 50 years	16	10	43.8	
Sex				
Male	13	8	38.5	0.057
Female	17	7	64.7	
Distance from anal verge				
< 10 cm	16	7	62.5	0.242
≥ 10 cm	14	8	42.9	
Clinical Stage				
Stage 2	9	4	55.6	0.747
Stage 3	21	11	52.4	
Surgical Margins				
Negative	25	10	64.0	<0.001
Positive	5	5	20.0	
Nodal Status				
Negative	16	4	81.3	0.001
Positive	14	11	21.4	
cT Stage				
T3	22	10	59.1	0.437
T4	8	5	37.5	
cN Stage				
N0	9	4	55.6	0.154
N1	16	7	62.5	
N2	5	4	20.0	
Pathological response				
Poor or mild effect	5	4	20.0	0.033
Marked/moderate effect	20	11	50.0	
Complete therapy effect	5	0	100.0	

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Conflicts of Interest

The authors declare no conflict of interest.

DECLARATION OF GENERATIVE AI

Not applicable.

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