Total neoadjuvant therapy in patients with locally advanced rectal cancer: A tertiary medical center experience

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Abstract. The current standard of care for locally advanced rectal cancer (LARC) includes preoperative chemoradiation, followed by total mesorectal excision and adjuvant chemotherapy. This multimodality treatment improves local control but is associated with low compliance rates without clear beneficial effects on overall survival (OS) and distant metastasis. In this retrospective study, the charts of patients diagnosed with cT3/4 or cT2-node-positive rectal cancer between January 2011 and June 2019 were reviewed. The chemoradiation therapy (CRT) group received a long course of CRT with capecitabine followed by surgery and adjuvant chemotherapy. The total neoadjuvant therapy (TNT) group received 6 cycles mFOLFOX and a short course of radiation therapy followed by surgery. A total of 81 patients were included, among which 55 (67.9%) received CRT and 26 (32.1%) received TNT. In the CRT group, 15 (27.3%) patients achieved pathologic complete response (pCR) compared with 10 (38.5%) in the TNT group (P=0.22). A total of 19 (35.8%) cases in the CRT group downstaged to pT0N0 or pT1N0 compared with 11 (42.3%) in the TNT group (P=0.33). The 2-year disease-free survival (DFS) rate was 81.0% in the TNT group and 84.0% in the CRT group (P=0.15). Out of 55 patients in the CRT group, 30 patients received adjuvant chemotherapy, 22 (40.0% of CRT cases) of which completed a full course. All 26 patients in the TNT group received neoadjuvant chemotherapy, where 22 (84.6%) patients took a full course (P<0.001). In conclusion, the present study revealed that patients treated with TNT were more compliant to chemotherapy than those treated with CRT. A numerically higher pCR rate, and nodal and tumor downstaging were noted in the TNT group without significance. No difference was noted in the 2-year DFS. Longer follow-up is required.

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Introduction

For the past 3 decades, we have been witnessing dynamic changes in the treatment of locally advanced rectal cancer (LARC) from single modality treatment using surgery alone to multimodality treatment including radiation, chemotherapy and total mesorectal excision (TME). These changes led to an improvement in outcome for stage II and III rectal cancer (1).

TME has made a revolution in the management of rectal cancer as it has shown a decrease in local recurrence from 30-50% to ~5% and allowed the patients to have sphincter preserving surgery (2). The use of adjuvant chemotherapy is advisable, but it is still controversial as studies have not shown an improvement in distant recurrence, overall survival (OS) and disease-free survival (DFS) (3). Compliance to adjuvant treatment has been a major concern in our daily practice and this may have affected the survival outcome. In fact, some studies have shown that a 4-week delay in post-operative treatment correlated with a decrease in OS of ~14% (4-6).

In terms of sequencing, German trial, along with similar trials, showed that preoperative chemo-radiation therapy combined with TME have shown better compliance, less toxicity and less local pelvic recurrence rate as compared to post-operative radiation treatment. Moreover, they detected an increase in pathologic complete response (pCR) rate with chemo-radiation therapy that correlates with better oncologic outcomes and may play an important role in organ preservation strategy (7-11).

Currently, the accepted standard of care for treatment of LARC is neoadjuvant chemo-radiation followed by TME and adjuvant chemotherapy. Despite the improvement in local control resulting from the association of different treatment regimens, the death rate from rectal cancer from distant metastasis is still elevated compared to local failure (12). While this multimodality approach improved local control, no impact was noted on the OS, with distant metastasis remaining the most concerning issue with a cumulative incidence of 30% in 10 years and with an overall DFS of 68% at 10 years (13). Therefore, better systemic control is needed. This could be

potentially achieved by focusing more on micrometastasis early in the course of treatment, hence delivering chemotherapy in pre-operative setting. This regimen, known as total neoadjuvant therapy (TNT), consists of delivering chemotherapy and radiation therapy in neoadjuvant setting. TNT was proposed to treat micrometastasis, increase pCR rate and increase compliance to treatment.

The idea of TNT was developed in the RAPIDO trial that was first launched in 2011 (14). It showed impressive results that were presented at ASCO 2020 and that may lead to a change in standard of care with TNT regimen. In this trial, TNT was associated with lower disease-related treatment failure, distant metastasis rate and doubling of pathologic complete response (pCR) rate compared to standard of care (15).

In this retrospective study, we assess the difference in pCR rates, compliance to chemotherapy, tumor downstaging and DFS between TNT and chemoradiation therapy (CRT) for LARC at the American University of Beirut Medical Center (AUBMC). We present this article in accordance with the STROBE reporting checklist.

Materials and methods

Study design and patient selection. This study is a retrospective chart review of patients diagnosed with LARC at the American University of Beirut Medical Center between January 1st, 2011, and June 1st, 2019. Patients ≥18 years old and with cT3/4 or cT2-node-positive were included. In total, 81 patients were included in the study and patients' demographics, treatment course and clinical outcomes were recorded. Charlson Comorbidity Index (CCI) was also calculated for every patient. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved via expedited review by the local Institutional Review Board (IRB) committee at AUBMC IRB ID: BIO-2019-0024.

Study objectives. The primary endpoint is the pathologic complete response (pCR) rate between the two different treatment modalities. pCR was defined as the absence of any viable tumor cell within the tumor bed in the setting of chemotherapy effect (16). The secondary endpoints are the compliance to chemotherapy, tumor downstaging and DFS.

Treatment modalities. The change in treatment modalities between patients is due to advancement in the field. Patients included were divided into either TNT or CRT groups. The TNT is defined as short course radiotherapy (5x5 Gy) before or after 6 cycles of mFOLFOX (oxaliplatin, fluorouracil and folinic acid) followed by TME. TME was performed 4 weeks after neoadjuvant therapy in the TNT group. The total duration of treatment between was 16-18 weeks. The CRT is defined as concurrent long course radiotherapy (45 Gy divided in 25 fractions over 5 weeks) and capecitabine followed by TME and adjuvant chemotherapy. TME involves the removal of the rectum together with surrounding mesorectum (lymphovascular fatty tissue) through a precise dissection along the pelvic visceral fascia (17). Treatment modalities were standardized between patients within the same treatment group.

Table I. Patient demographics.

Variables	Treatment modality	
	TNT	CRT
Median age, years (range)	51 (25-75)	60 (34-85)
Sex, n (%)		
Male	16 (61.5)	32 (58.2)
Female	10 (38.5)	23 (41.8)
Tumor differentiation, n (%)		
Well	4 (15.3)	6 (10.9)
Moderate	15 (57.7)	39 (70.9)
Poor	6 (23.1)	1 (1.8)
Not documented	1 (3.9)	9 (16.4)
Clinical stage, n (%)		
T2N1	0 (0.0)	1 (1.8)
T3N0	2 (7.7)	9 (16.4)
T3N1	9 (34.6)	34 (61.8)
T3N2	9 (34.6)	6 (10.9)
T3Nx	1 (3.9)	3 (5.5)
T4N0	0 (0.0)	1 (1.8)
T4N1	2 (7.7)	1 (1.8)
T4N2	3 (11.5)	0 (0.0)
T4Nx	0 (0.0)	0 (0.0)

CRT, chemoradiation therapy; TNT, total neoadjuvant therapy.

Statistical analysis. A biomedical statistician performed the statistical review of the study. Continuous variables were summarized by their median, mean and range. Categorical variables were described by counts and relative frequencies. Crosstabulations in the form of 2x2 tables were plotted to compared and detect differences between the two groups in outcome, downstaging and pathology. DFS curve was plotted using the Kaplan-Meier curve, the log rank was used to check for significant difference between the studied groups. DFS time was defined as the time from initial diagnosis to disease progression or the end of follow-up (censored observations who did not reach the progression event). A value of $P<0.05$ was considered significant in all analyses. All statistical analysis was performed using the SPSS v.25.0 statistical package.

Results

Patient characteristics and distribution. Of the 81 patients diagnosed with LARC, 48 (59.3%) were males and 33 (40.7%) were females with the average age 59 (34-81) and 55 (25-85) years, respectively. Patients were distributed into two treatment groups; 26 patients received TNT and 55 received CRT with the average age 51 and 60 years, respectively (Table I). The median follow-up periods for the TNT and CRT groups were 22.7 and 47.8 months, respectively. The mean CCI was 3.96 in the CRT group and 3.23 in the TNT group ($P<0.05$).

Pathologic and survival outcomes. Of the 26 patients that received TNT, 10 (38.5%) patients had a pCR, while of the

Table II. Treatment outcome.

Variables	Treatment modality	
	TNT	CRT
Pathologic response		
Complete response (TRG 0)	10 (38.5)	15 (27.3)
Near complete response (TRG 1)	3 (11.5)	5 (9.1)
Other response (TRG 2 and 3)	13 (50.0)	35 (63.6)
Pathologic staging		
ypT0N0	10 (38.5)	15 (27.3)
ypTisN0	0 (0.0)	1 (1.8)
ypT1N0	1 (3.9)	3 (5.5)
ypT2N0	2 (7.7)	3 (5.5)
ypT3N0	6 (23.1)	16 (29.1)
ypT1N1	2 (7.7)	0 (0.0)
ypT2N1	0 (0.0)	5 (9.1)
ypT3N1	1 (3.9)	6 (10.9)
ypT3N2	1 (3.9)	3 (5.5)
ypT4N1	1 (3.9)	1 (1.8)
ypT4N2	2 (7.7)	1 (1.8)
ypTxN1	0 (0.0)	1 (1.8)

CRT, chemoradiation therapy; TNT, total neoadjuvant therapy; TRG, tumor regression grade.

55 patients that received CRT, 15 (27.3%) patients had a pCR (P=0.22). On the other hand, 7 (26.9%) patients from the TNT group and 17 (30.9%) patients from the CRT group had a pathologic node-positive (P=0.46). Moreover, downstaging to pT0N0 and pT1N0 was achieved in 11 (42.3%) and 19 (35.8%) patients in the TNT and CRT groups, respectively (P=0.33) (Table II). The 2-year DFS rate was 81 and 84% in the TNT and CRT groups, respectively (P=0.15) (Fig. 1).

Compliance to chemotherapy. Of the 55 patients that received CRT, 30 (54.5%) patients received any number of cycles of adjuvant chemotherapy and 22 (40%) of which received a full course of chemotherapy. All of the 26 patients in the TNT group received neoadjuvant chemotherapy with 22 (84.6%) of which receiving a full course (P<0.01). None of CRT patients and 1 patient from the TNT group had a dose reduction.

Discussion

Clinical outcomes in patients with LARC have improved markedly especially significant decrease in local failure with the development in treatment regimens. Sauer *et al* (13) proved in a randomized trial that neoadjuvant chemoradiation was significantly superior in local control in comparison to adjuvant chemoradiation, but with no difference in OS or DFS. Then, in the phase III randomized trials, EORTC22921 and I-CNR-RT, the addition of adjuvant fluorouracil and folinic acid to preoperative chemoradiation did not improve OS and DFS in comparison to regular surveillance post-surgery (18,19). Moreover, the PETACC-6 phase III trial compared neoadjuvant chemoradiation with capecitabine followed by 6 cycles of adjuvant capecitabine with or without oxaliplatin, before and after surgery. This trial also showed that the addition of oxaliplatin to capecitabine did not improve OS and DFS (20). Finally, in the German CAO/ARO/AIO-04 phase III trial, the addition of oxaliplatin to preoperative chemoradiation and adjuvant fluorouracil and folinic acid, led to a significant improvement in DFS and OS, even though the addition of oxaliplatin to capecitabine-based chemoradiation is not the standard of care (21). Furthermore, the compliance rates to adjuvant chemotherapy were low. In a multicenter retrospective review, only 44.1% received adjuvant chemotherapy after neoadjuvant chemoradiation and rectal surgery and, of those, only 56% were compliant to treatment (22). In comparison, in our cohort, 54.5% of the patients in the CRT group received adjuvant chemotherapy and 40% of which were compliant to treatment. While on the other hand, 100% of the patients in the TNT group received neoadjuvant chemotherapy and 84% were compliant to treatment (P<0.01).

Furthermore, in a phase II trial, Marco *et al* (23) showed that giving mFOLFOX6 after chemoradiation and before surgery was associated with better compliance and DFS rates. Indeed, in another phase II trial, delaying the surgery by giving up to 6 cycles of mFOLFOX after chemoradiation was associated with superior pCR rates in comparison to patients not receiving neoadjuvant chemotherapy (24). Similar to the findings in previous studies, the main causes of noncompliance in our patients were post-operative complications, drug-related toxicities and patients' preferences.

In a randomized trial, Ngan *et al* (25) compared the local recurrence rates between short-course radiotherapy (25 Gy in 5 fractions) and long-course chemoradiation (50.4 Gy in 28 fractions). No difference was noted between the 3-year local recurrence rates, OS, distant recurrence rate or late toxicity, all in favor of considering short-course radiotherapy to decrease the treatment time without any change in clinical outcomes (25).

Moreover, the Stockholm III trial compared by randomization short-course radiation immediately before surgery, short-course radiation with delayed surgery and long-course radiotherapy (50 Gy in 25 fractions) with delayed surgery. It showed that postoperative complications were significantly less in the group receiving short-course radiotherapy with delayed surgery, making this regimen practical (26). On the other hand, the Polish II randomized trial showed no difference, after 8 years, between short-course radiotherapy followed by neoadjuvant chemotherapy and upfront chemoradiotherapy in OS or DFS (27).

In an effort to truly assess the potential of neoadjuvant chemotherapy, Fokas *et al* (28) compared, in a randomized phase II trial, neoadjuvant chemotherapy given before or after chemoradiation followed by surgery. Chemoradiation followed by neoadjuvant chemotherapy and surgery was associated with superior pCR rates and better compliance with chemoradiation but worse compliance with chemotherapy (28). Most recently, in a randomized trial, short-course radiotherapy followed by neoadjuvant chemotherapy then by TME was compared to long-course radiotherapy followed by TME and optional adjuvant chemotherapy. The RAPIDO trial showed that the TNT treatment modality was significantly superior in pCR

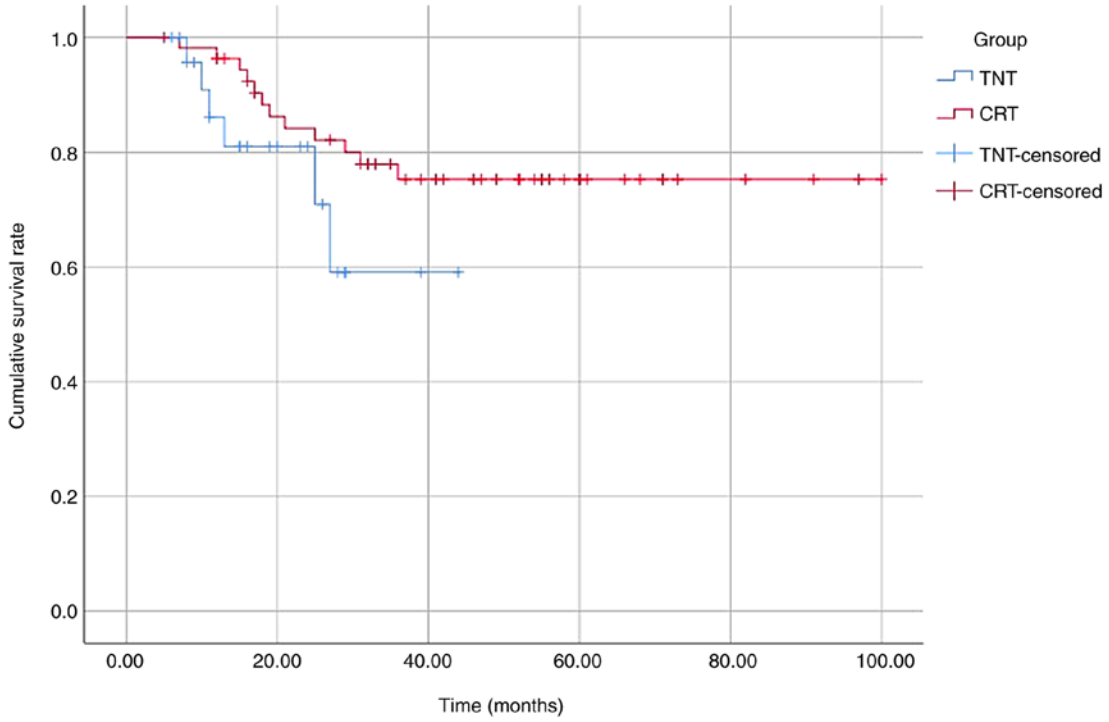

Figure 1. Two-year DFS in the TNT and CRT groups. The 2-year DFS rate was 81 and 84% in the TNT and CRT groups, respectively (P=0.15). DFS, disease-free survival; CRT, chemoradiation therapy; TNT, total neoadjuvant therapy.

rate (28 vs. 14%) and had a 7% decrease in disease-related treatment failure (14). In our cohort, the pCR rate was numerically higher for the TNT group without statistical significance, which can be due to the small sample size. On the other hand, in a systemic review comparing the two treatment modalities, the pooled pCR rates were found to be 32.4 and 22.3%, while in our cohort the rates were 38.5 and 27.3% in the TNT and CRT groups, respectively (29). Moreover, the difference in the 2-years DFS rates between the two modalities was not significant, while only one study showed an improved DFS in the TNT group (29). In fact, the RAPIDO trial showed that the 3-year OS rate was the same in both groups (14). Furthermore, our data showed that the TNT group had a numerically higher rate of tumor downstaging than the CRT group but without statistical significance. Chapman *et al* (30) compared the neoadjuvant rectal score between the two treatment modalities and showed that TNT is superior to the standard CRT in tumor downstaging between clinical and pathologic stage.

Furthermore, organ preservation has been advocated with the elevated rates of complete response reached with TNT. Patients in the OPRA trial were randomized into neoadjuvant chemotherapy before or after chemoradiation, and then patients with complete or near-complete response were offered watchful waiting. It showed that patients receiving upfront chemoradiation followed by neoadjuvant chemotherapy resulted in a significantly superior rates of organ preservation (31).

Currently, a clinical trial is the assessing the efficacy and toxicity of short-course radiation concurrently with 5-fluorouracil infusion for the treatment of LARC (NCT04370418) (32). Moreover, Zhang *et al* (33) are evaluating the efficacy and safety of dose escalation of short-course radiotherapy, from 25 to 40 Gy in 5 fractions, followed by chemotherapy and surgery. Additionally, immune checkpoint inhibitors have been gaining a great deal of attention lately. The VOLTAGE trial is assessing nivolumab (anti-programmed death-1) monotherapy after chemoradiation followed by surgery in LARC patients. The preliminary results showed a promising 30 and 60% pCR rates in microsatellite stable and unstable patients, respectively (34). Also, the DUREC trial is assessing the addition of durvalumab (anti-programmed death-ligand 1) to induction chemotherapy and short-course radiotherapy or long-course chemoradiation followed by surgery (35). Moreover, in a phase II trial, avelumab (anti-programmed death-ligand 1) was combined with neoadjuvant mFOLFOX after short-course radiotherapy followed by surgery. The preliminary results showed a promising 25% pCR rate and 50% major response rate (36).

There are several limitations facing this study. First, this is a retrospective chart review with a small sample size, therefore more patients are needed with extended follow up periods to compare 5-year DFS and OS. In addition, there is some inhomogeneity within the TNT group as some patients received chemotherapy before radiotherapy unlike others who received radiotherapy before chemotherapy. In addition, the 2 groups were different in terms of comorbidity index which makes the comparison challenging. Moreover, the short median follow-up period for the TNT group is due to the novelty of this modality which has only been used recently.

In conclusion, our data show that TNT is superior to CRT in chemotherapy compliance. In addition, the pCR and tumor downstaging rates in the TNT group were numerically higher than the CRT group. No difference was noted in the 2-year DFS rates between the two treatment modalities. Finally, more studies are needed to truly compare the disease-free and OS rates between the two treatment modalities.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to the IRB restrictions but are available from the corresponding author on reasonable request.

Authors' contributions

AS conceived and designed the study. MAD and MC provided administrative support. AS provided study materials or patients. ZEH, YH, YB and MK collected and assembled data. ZEH, YH, YB, MK, DM, ST, MAD, MC and AS analyzed and interpreted data. All authors wrote the manuscript. AS and MC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved via expedited review by the Biomedical Institutional Review Board Committee of the American University of Beirut Medical Center (IRB ID, BIO-2019-0024; Beirut, Lebanon). In this retrospective study, the IRB previously granted a waiver of the requirement to obtain informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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