The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90, Page 1915-1922

Total Neoadjuvant Therapy Using Short Course Radiotherapy Followed by Chemotherapy in Locally Advanced Rectal Cancer

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ABSTRACT

Background: The most common neoadjuvant therapy for locally advanced rectal cancer is fluoropyrimidine-based chemotherapy combined with radiation (45-50.4 Gy) (LARC). Recently many studies focusing on shifting systemic chemotherapy to preoperative setting to increase pathological complete response rate (pCR).

Patients & Methods: This is a randomized controlled trial (RCT) of stage II-III rectal cancer patients treated from October 2020 to April 2022. They were randomized into: Experimental group: Total neoadjuvant therapy (TNT) with short course radiotherapy (25 Gy) then chemotherapy (Capecitabine and Oxaliplatin) for 6 cycles followed by total mesorectal excision (TME). Control group: Standard long course concurrent chemo radiotherapy (LC-CCRT, 45-50.4Gy) with Capecitabine followed by TME and adjuvant chemotherapy. Primary end points were pathological complete response (pCR) and disease related treatment failure (DrTF). Secondary end points were restricted mean survival time at 12 months (RMST), toxicity and surgical complications. **Results:** High risk criteria as N2 and infiltrated mesorectal fascia (MRF) were statistically higher in TNT group (p=0.005, p= 0.04 respectively). Complete response was achieved radiologically in 11.5% and pathologically in 33.3 % exclusively in TNT group. Restricted mean survival time (RMST) at 12 months was 11.6 months in TNT group and 11.1 months in control group. Pathological complete response was statistically correlated to improvement in DrTF and RMST at 12 months (p =0.01). **Conclusion:** Short course radiotherapy with neoadjuvant chemotherapy is a good alternative to the standard LC-CCRT with less hospital treatment days and cost especially after COVID 19 pandemic.

Keywords: Locally advanced rectal cancer, Total neoadjuvant therapy, Short course radiotherapy.

INTRODUCTION

According to cancer registry report in Egypt, rectal cancer constituted 13% of patients who were experiencing colonoscopy and represent 40% of all colorectal cancer [(1)]. Multimodality treatment including high quality total mesorectal excision (TME) and chemo radiotherapy is the standard of treatment of locally advanced rectal cancer (LARC) and development of neoadjuvant therapy improved the outcomes as regards local and distant failure rate [(2)].

The Swedish Rectal Cancer Trial, showed improved local and survival benefit when used short course radiotherapy (SCRT) (25Gy) [(3)]. While in The Dutch TME trial which used SCRT demonstrate improvement of local control due to high quality TME without survival benefit [(4)]. Expert discussions at the European Organization for Research and Treatment of Cancer (EORTC) St. Gallen conference showed that short course radiotherapy has less short term toxicity with similar late toxicity as long course radiotherapy and no difference in oncological outcomes [(5)].

Systematic review did not show survival benefit of adjuvant fluoropyrimidine-based chemotherapy in adjuvant setting due to poor compliance [(6)]. Shifting of chemotherapy to neoadjuvant setting and hence total neoadjuvant therapy leads to improvement of compliance and decrease distant relapse rate for intermediate and high risk patients defined by MRI features in the MERCURY-trial [(7, 8)]. Using short course radiotherapy with neoadjuvant chemotherapy in resectable metastatic rectal cancer demonstrates high response rate and radical resection in Dutch phase II trial [(9)].This study aimed to compare between total neoadjuvant therapy (TNT) with short course RT followed by preoperative chemotherapy (experimental group) and the long course concurrent chemo radiotherapy (LC-CCRT) (control group) in treatment of non-metastatic stage II-III rectal carcinoma. The primary outcome is to estimate the rate of pathological complete response, disease related treatment failure (DrTF), which was defined as locoregional recurrence, distant metastasis or death. Secondary objectives are restricted mean survival time at 12 months (RMST), toxicity and surgical complications.

PATIENTS AND METHODS

This is a randomized controlled trial that was conducted at Department of Clinical Oncology & Nuclear medicine, Mansoura University Hospitals. It included patients with non-metastatic stage II-III rectal carcinoma. They were randomly assigned to experimental and control groups. The treatment algorithm is presented in CONSORT flow diagram (**figure 1).**

Randomization and stratification were performed using computer generated random tables using stratified blocked randomization in 1:1 ratio. Participants were withdrawn from the Outpatient Clinic until fulfillment of needed sample size (n=26 patient in each arm). The patients were followed for about 2 years post treatment (at least 6 months after enrollment of the last patient).

Received: 04/09/2022
Accepted: 07/11/2022

Patient selection was done according to the inclusion and exclusion criteria as follow:

Eligibility criteria: Patients aged ≥18 years. Biopsy proven primary adenocarcinoma of the rectum. No distant metastatic stage II-III disease. MRI with high-risk features including one of the following (cT3-4a-b/ extramural vascular invasion/ N1-N2 /Mesorectal fascia infiltration). ECOG Performance status of 0-2 as determined by Eastern Cooperative Oncology Group (ECOG). Adequate organ function with normal liver, renal and bone marrow functions.

Exclusion criteria: Current or previous history of other malignancy. Inflammatory bowel disease.

Patients' assessment

a- Before enrollment: A complete history & physical examination. Assessment of performance status was done according to Eastern Cooperative Oncology Group (ECOG). Laboratory tests (complete blood picture (CBC), liver and renal function tests (LFT, RFT), alkaline phosphates (ALP), CEA and CA 19-9). Imaging of abdomen and pelvis (MRI or CT), chest X ray (CXR), CT if there is suspicious CXR, and bone scan if there is localized bone pain or elevated ALP. Endoscopy was done for localization of the tumor and biopsy and pathological examination of suspicious lesions.

b- During neoadjuvant treatment: Physical examination, hematological profile and toxicity assessment.

•Experimental group: patients were evaluated during radiotherapy, 2-3 weeks after 25 Gy then every 3 w during neoadjuvant chemotherapy

•Control group: patients were evaluated during the course of neoadjuvant chemo-radiotherapy then one month after surgery followed by a visit every 2-3 w during adjuvant chemotherapy followed by a visit at 3, 6 and 12months.

c- Pre-operative assessment: MRI abdomen and pelvis with contrast was done, endoscopic evaluation and anesthetic fitness.

After the end of treatment and follow-up: Chest, abdomen, pelvis imaging & CBC, LFT, RFT and tumor markers 1-2 months after surgery followed by a visit at 3,6 and 12 months then every 3-6 months during the 2nd year.

We followed the patients up for about 2 years (at least 6 months) after enrollment of the last patient.

Preoperative therapy: Patients meeting the inclusion criteria were randomly allocated into two groups:

- Experimental group: Total neoadjuvant treatment (TNT) with short course radiotherapy followed by TME.
- Control group: Standard long course concurrent chemoradiotherapy (LC-CCRT) followed by TME and adjuvant chemotherapy.

Radiotherapy:

CT planning with contrast if not contraindicated with slices each 3 mm. The rectum was emptied immediately before scanning and treatment with comfortable filled bladder, by educating the patient to empty the bladder immediately before planning and treatment then drinking 500 cc water and waiting for 1 hour to reduce the volume irradiated and doses to normal tissues.

Radiotherapy is delivered with CT-based 3D-conformal treatment planning with a defined clinical target volume (CTV) according to CTV definition, which was defined during the ASTRO meeting held in September 2015 [(10)].

•Experimental (TNT) Patients received short-course radiotherapy with 25/5 treatments over 1 week followed by neoadjuvant chemotherapy after about two weeks from the end of radiotherapy settings. Chemotherapy regimen was Capecitabine (1000 mg/m^2 BID) day 1–14 with Oxaliplatin 130 mg/m2 D1 repeated every 3 weeks for 6 cycles (CAPOX).

•Control (LC-CCRT) patients received LC-CCRT with 45 Gy/25 treatments over 5 weeks, concomitant with Capecitabine (825 mg/m2 BID).

Treatment related toxicity: Toxicity was assessed weekly throughout radiation and every cycle during preoperative and postoperative chemotherapy according to common terminology criteria of adverse events (CTCAE) version 5.0.

Response and resectabilty evaluation: Response evaluation was performed by pelvic MRI using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

• In experimental (TNT): patients underwent interval pelvic MRI after the third cycle of neoadjuvant chemotherapy and after the sixth cycle of chemotherapy before surgery. Surgery and histopathology were performed 2–4 weeks following the last cycle of neoadjuvant chemotherapy.

• Control (LC-CCRT): Patients underwent pelvic MRI after chemo radiation prior to surgery. Surgery and histopathology were performed 6–8 weeks after the end of chemo radiation.

Surgery was trans-abdominal total mesorectal excision as part of a low anterior resection (LAR) with sphincter preservation or an abdominal perineal resection (APR) after 6-8 weeks from long course of neoadjuvant chemo radiotherapy (45-50 Gy/5.5 weeks) or after 2-4 weeks of the end of TNT.

Adjuvant chemotherapy in control group CAPOX protocol for eight cycles.

Statistical analysis

IBM-SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) was used to enter and evaluate the data. Absolute frequency (N) and percentage (%) were used to convey qualitative data. Shapiro Wilk's test was used to determine the initial normality of quantitative data; if p> 0.050, the data were considered to be normally distributed. Quantitative data were expressed as mean ± standard deviation (normally distributed).

Chi-Square or Fisher's exact test was used to compare nominal data. We compared normally distributed quantitative data by Independent-Samples t-Test or Mann-Whitney U-test if not normally distributed. Restricted mean survival time and reliability for ordinal variables was performed by weighted Kappa using MedCalc Statistical Software version 18.9.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). The DrTF was calculated from the start of randomization till appearance of recurrence or progression or treatment related death or last follow-up visit. The level of significance was considered at 5% (i.e. $P \leq 0.05$). For any of the used tests, results were considered as statistically significant if p value ≤ 0.050. Suitable charts and tables were used to present the results.

Ethics and informed consent: Study protocol was approved by the Institutional Research Board (IRB), Faculty of Medicine, Mansoura University. Informed written consent was obtained from each participant after assuring confidentiality. The work was conducted in accordance with the World Medical Association's code of ethics (Declaration of Helsinki) for human studies.

RESULTS

Between October 2020 and April 2022, 73 patients with pathologically proved rectal adenocarcinoma were randomized from Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospitals. Nine patients were considered ineligible (absence of high-risk features in pelvic MRI), twelve patients refused to participate as shown in CONSORT flow diagram (**figure 1).** In total, 52 patients were included in analysis, 26 in the experimental arm and 26 in the standard arm. Patients and tumor characteristics are reported in **table (1).** There was statistically significant difference in ECOG-PS (P=0.02), clinical TN-status (p=0.02), N2 disease (p=0.005) and infiltrated mesorectal fascia (MRF) (p=0.04).

Compliance and toxicity: In the experimental (TNT) group, all the patients ended five fractions of radiotherapy and chemotherapy without treatment interruption. While in control (LC-CCRT) group, all patients received 45Gy/25 fractions concomitant with Capicitabine 825 mg/m^2 D1-5 orally twice daily with the exception of one patient who received concurrent continuous infusional 5FU 225 mg/m^2 D1-4 +Leucovorine 20 mg/m2 IV push D1-4. Treatment disruption occurred in two patients due to G3 diarrhea and proctitis with dose reduction of Capecitabine. The most common adverse events during radiotherapy in experimental group were diarrhea (34.6%) and perianal pain (34.6%) while neurotoxicity (19.2%) was the commonest during preoperative chemotherapy. The commonest adverse effect during radiotherapy in control group was dysuria (33.7%) while anemia (26.8%) and liver toxicity (19.2%) were the commonest during adjuvant chemotherapy as shown in **table (2).**

Treatment response assessment: Complete response occurred exclusively in experimental group and was detected radiologically in 3 cases (11.5%) and pathologically in 8 cases (33.3%) and two other cases achieved complete clinical response and refused to undergo surgery still on watchful waiting strategy. Partial response was observed in 18 cases radiologically (69.2%) and 9 cases pathologically (37.5%) in experimental group vs. 15 (57.7%) and 11(47.8%) in the control group respectively. **Stable disease** was observed radiologically in 1 case (3.8%) and pathologically in 3 cases (12.5%) in experimental group vs. 10 (38.5%) and 6 (26.1%) cases in the control group respectively**. Progressive disease** was observed radiologically in 4 cases (15.4%) and 4 cases (16.7%) pathologically in experimental group vs. 1 case (3.8%) and 6 cases (26.1%) in the control group respectively with statistically significant difference (p=0.002) (T**able 2).** There was moderate agreement between radiological and pathological response assessment as calculated by weighted Kappa (Kw=0.416).

\Surgery: In experimental (TNT) group, seventeen out of 26 (65.38%) patients underwent curative surgery (TME). Two patients refused surgery due to issue related to permanent colostomy and were on watchful waiting strategy as they achieved complete clinical response, two patients underwent transanal endoscopic mucosal resection (TEMS), and five patients underwent palliative colostomy due to unresectable disease. Of these (n=5), four patients developed local disease progression and still unresectable, so shifted to 2nd line chemotherapy and one patient showed disease regression but still unresectable. As per protocol analysis 41.2% of patients achieved complete pathological response.

In control (LC-CCRT) group, twenty three out of 26 (88.46%) patients underwent curative surgery (TME) as two patients died before TME and one patient refused due to issue related to permanent colostomy. No pathological complete response was achieved, while 47.8% showed partial disease response, 26.1% had stable disease and 26.1% showed disease progression. All received post-operative chemotherapy (CAPOX) for 8 cycles.

Post-operative complications as wound infection and perineal fistula was equally observed in both treatment group (4.2%). Bladder/urethral tear was detected in 8.7% of control group vs 4.2% in experimental group without statistically significant difference (p=0.633). Stoma related complication as herniated loop was detected in 8.7% of patients only in control group with deterioration of quality of life due to severe pain associated that needed narcotics. 4.3% of patients in control group developed adhesive intestinal obstruction that needed hospitalization for management.

Disease related treatment failure (DrTF) was defined in our study as local progression, local recurrence, distant metastasis or death. In control group, DrTF was observed in 6 patients (23.08%), one patient showed disease progression, one patient developed local recurrence [3.8%], 3 patients developed liver metastasis [7.7%] and 2 patients died [7.7%]). While in experimental group, 4 patients (15.4%) showed disease progression (3 patients developed local disease progression [11.5%] and 1 patient developed liver and bone metastasis [3.8%]).

DrTF was detected in 20.51% inpatients who did not achieve pCR while those patients who achieved pCR had no DrTF with statistically significant difference (P value =0.04) **(figure 2).**

Median survival was not reached and restricted mean survival time at 12 month was calculated and was 11.6 months in experimental group and 11.1 months in control group with no statistically significant difference (P=0.374) and HR of experimental group equals 0.74 (0.21-2.63) **(figure 3).**

Table (1): Patients characteristics in both groups

Factors	Experimental (n/26)	Control (n/26)	p-value
Age (years)			0.781
< 50	13 (50%)	14 (53.8%)	
≥ 50	13 (50%)	12 (46.2%)	
Mean ± SD	50.13 ± 13.35	48.38 ± 9.84	
Sex			0.096
Male	10 (38.5 %)	16 (61.5%)	
Female	16 (61.5%)	10 (38.5%)	
BMI (kg/m^2)			1
< 30	15 (57.7%)	15 (57..8%)	
≥ 30	11 (42.3%)	11 (42.3%)	
Mean ± SD	29.34 ± 6.80	29.02 ± 6.47	
ECOG-PS			0.021
0	8 (30.8%)	17 (65.4%)	
1	16 (61.5%)	7 (26.9%)	
2	2 (7.7%)	2 (7.7%)	
Distance from AV (cm)			0.165
< 5	15 (57.7%)	10 (38.5%)	
≥ 5	11 (42.3%)	16 (61.5%)	
Pathological subtype			0.532
Non-mucinous	18 (69.2%)	20 (76.9%)	
Mucinous	8 (30.8%)	6 (23.1%)	
Grade			1
G1	3 (11.5%)	3 (11.5%)	
G2	17 (65.4%)	17 (65.4%)	
G3	6 (23.1%)	6 (23.1%)	
Clinical TN status			**0.024**
cT3N0	6 (23.1%)	16 (61.5%)	
cT2-3N+	13 (50%)	5 (19.2%)	
cT4N0	3 (11.5%)	1 (3.8)	
cT4N+	4 (15.4%)	4 (15.4%)	
T4	9 (34.6%)	5 (19.2%)	0.211
N2	16 (61.5%)	6 (23.1%)	**0.005**
Lateral LNs	12 (46.2%)	7 (26.9%)	0.150
Infiltrated MRF	14 (53.8%)	7 (26.9%)	**0.044**
EMVI	5 (19.2%)	6 (23.1%)	1

Notes: ECOG-PS: Eastern Cooperative Oncology Group performance status. AV: anal verge. MRF: mesorectal fascia. EMVI: extramural vascular invasion.

Table (2): Treatment related toxicities in both groups

Toxicities	Experimental			Control			p-value
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	
Dysuria	2 (7.7%)	1 (3.8%)	0	7 (29.9%)	1 (3.8%)	0	0.140
Proctitis	5 (19.2%)	2 (7.7%)	2 (7.7%)	3(11.5%)	1 (3.8%)	2 (7.7%)	0.838
Diarrhea	7 (26.9%)	2 (7.7%)	0	0	4(15.4%)	0	0.014
Perianal pain	7 (26.9%)	2 (7.7%)	0	2 (7.7%)	5(19.2%)	0	0.158
Radiation dermatitis	-	-	-	-	-	-	-
Anemia	5 (19.2%)	-	-	1 (3.8%)	5(19.2%)	1 (3.8%)	0.017
Neutropenia	-	-	2 (7.7%)	-	-	2 (7.7%)	1
Neurotoxicity	4 (15.4%)	1 (3.8%)	-	2 (7.7%)	-	-	0.419
Liver toxicity	5 (19.2%)	-	1 (3.8%)	2 (7.7%)	3(11.5%)	-	0.175

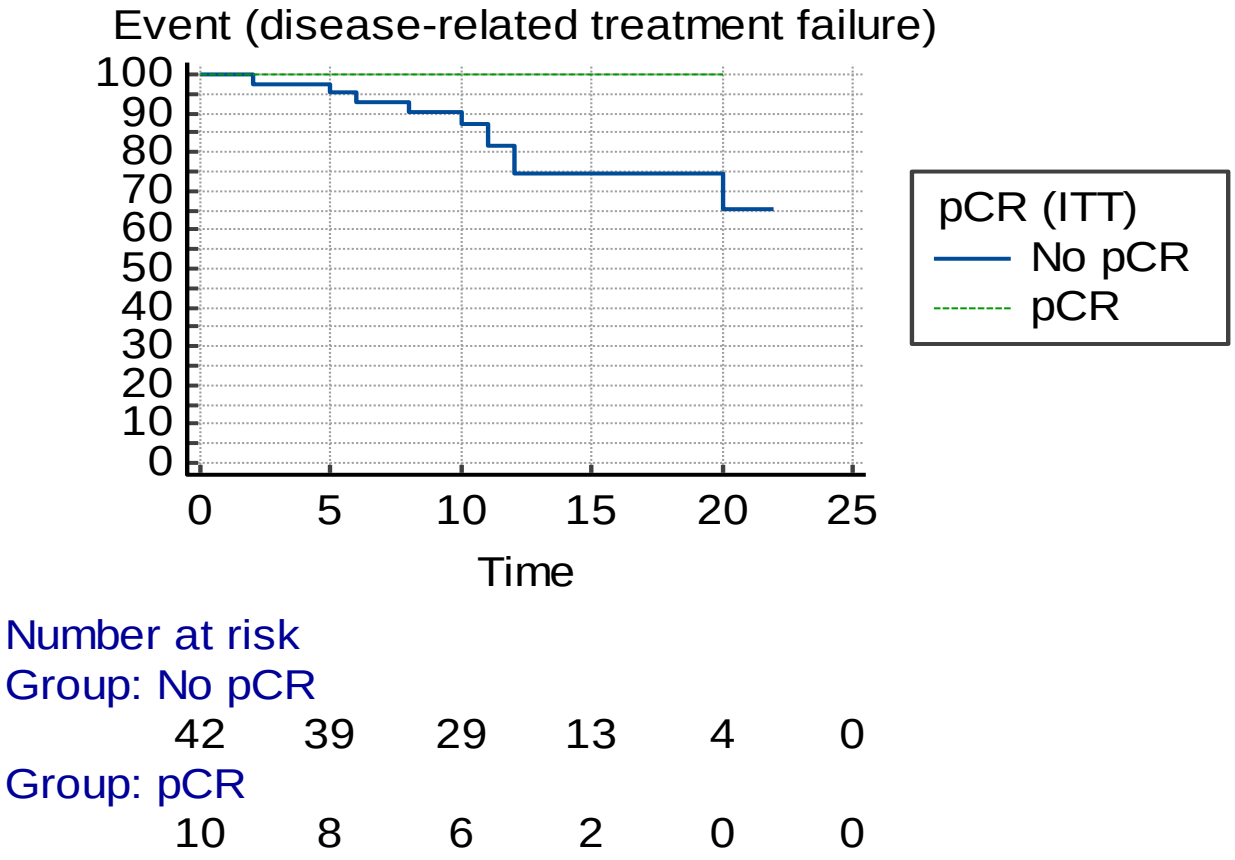

Figure (1): CONSORT Flow diagram of the progress through the phases of a parallel randomized trial of two groups according to CONSORT 2010 updated guidelines

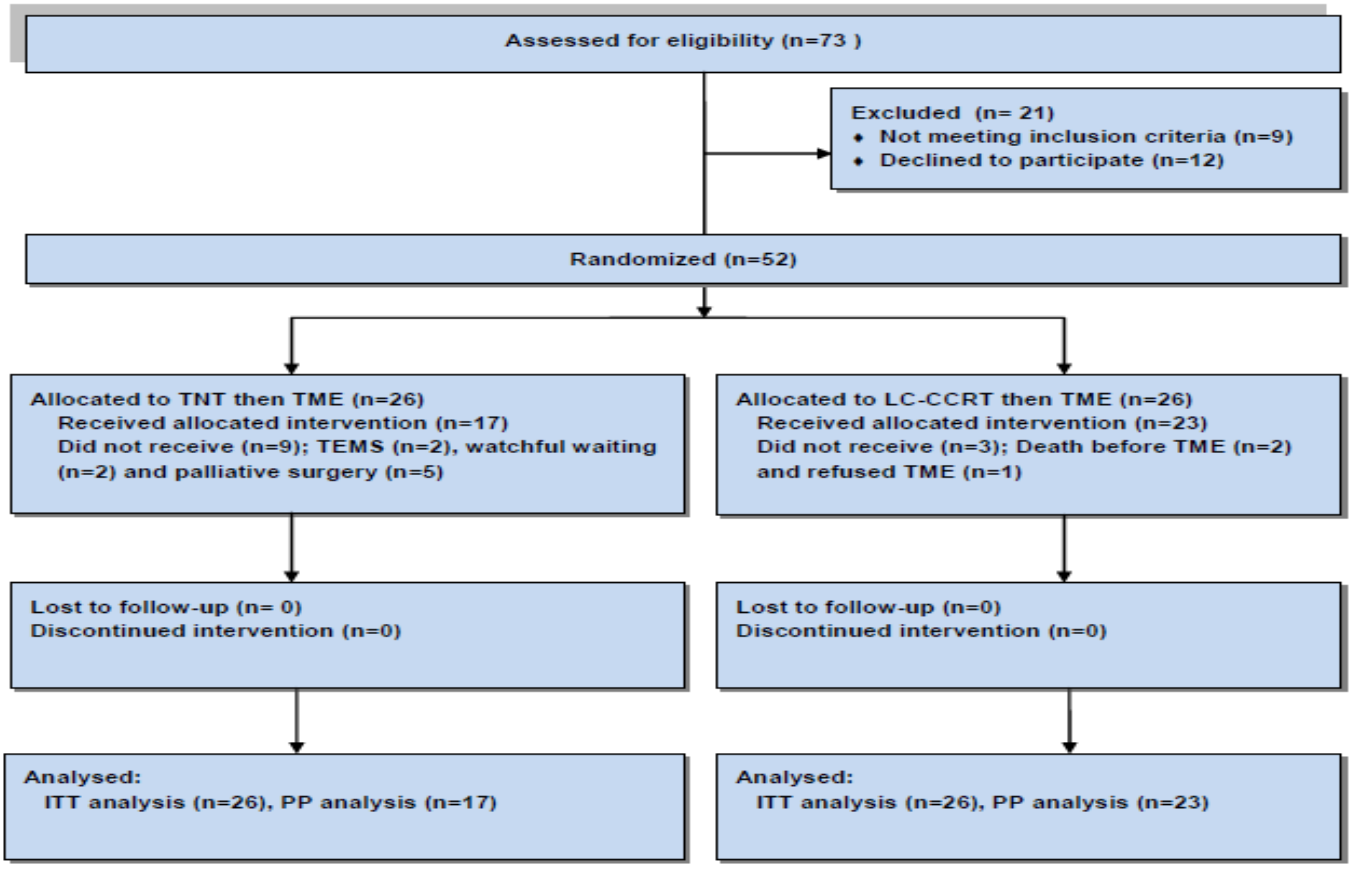

Figure (2): Pathological complete response (pCR) in both groups

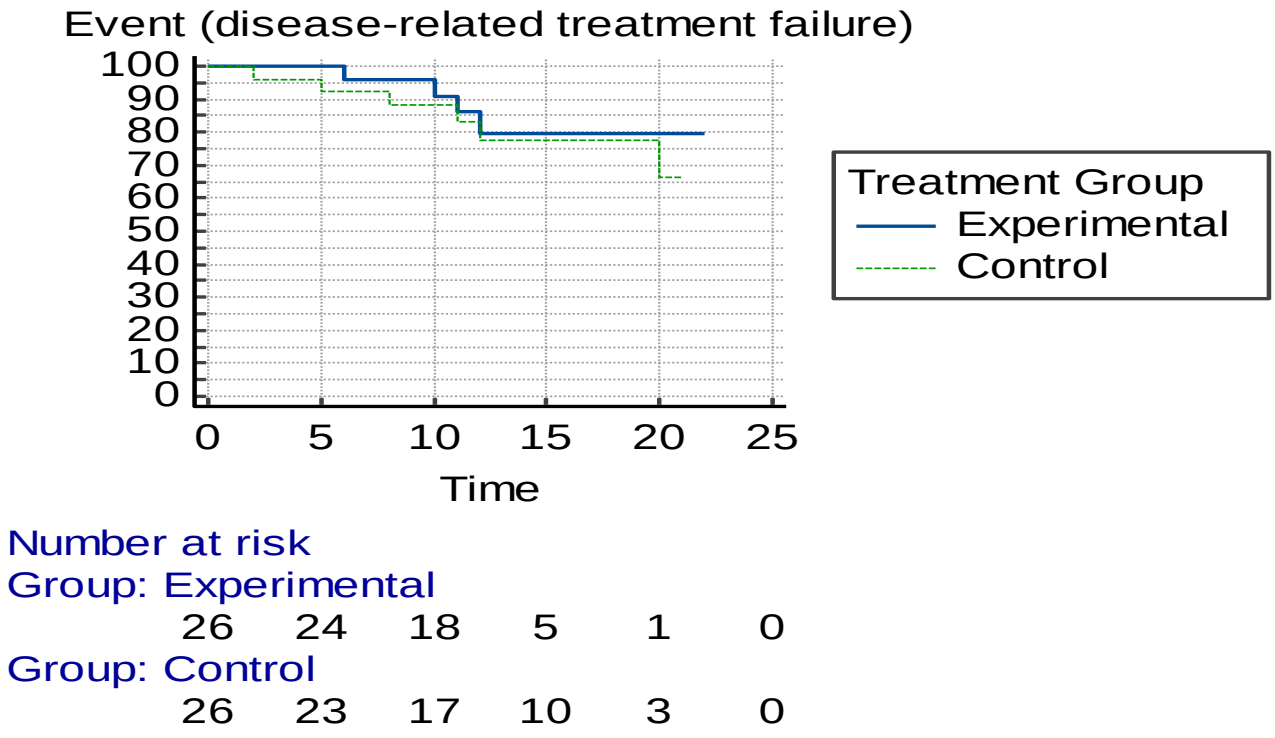

Figure (3): Disease related treatment failure in both groups.

DISCUSSION

Colorectal cancer (CRC) is the third most common malignancy worldwide, and is the second leading cause of cancer deaths. According to cancer registry report in Egypt, rectal cancer constituted 13% of patients who experienced colonoscopy and represent 40% of all colorectal cancer [(1)]. Most of cases presented with locally advanced stage is due to lack of screening and delay in diagnosis because anorectal bleeding that represents 45% of symptoms of CRC is initially thought to be due to hemorrhoids [(11)]. Management of locally advanced rectal cancer is crucial to achieve better survival rate as survival of CRC is highly depended on stage at presentation, in Egypt the median overall survival is 2 years (stage I 44 months; stage IV 8 months) [(12)]. The role of multimodality treatment in LARC is to decrease recurrence rate and improve survival [(13)]. Shifting of systemic treatment to neoadjuvant setting is addressed in several clinical trials to decrease distant relapse rate, improve patients compliance and reduce toxicity [(14,7,15)] [(14)] [(7)] [(15)]. Stockholm III trial done on 840 patients diagnosed with rectal adenocarcinoma ,showed a non-inferiority regarding local recurrence when short course radiotherapy is followed by delayed surgery [(16)].

Clinical staging and high risk criteria were statistically higher in TNT group than standard group and this was in contrast to that reported by RAPIDO and PRODIGE 23 trials showing a well-balanced two arms both in patients and tumor characteristics involved in the study [(17)].

In our study, clinical stage IIC-IIIA was higher in TNT group (61.5%), however stage IIA was statistically higher in control group (61.5%) (p =0.02). Also, high risk criteria as N2 (p=0.005) and infiltrated MRF was statistically higher in TNT group (p= 0.04). ECOG-PS 1 was statistically higher in TNT group (61.5%) than in control group (26.9%) (p=0.02).

Preoperative chemotherapy also provides information about tumor sensitivity and hence can decide the next step accordingly. In our study 15.4% showed disease progression in interval radiological assessment in TNT group and so shifted to 2nd line chemotherapy as being unresectable disease with molecular testing of mismatch repair (MMR), KRAS and BRAF. This gives an opportunity for further analysis of tumor biology.

Despite radiological progression in control group was 3.8% but there was higher incidence of pathological progressive disease in control group 26.1% as well as stable disease 26.1%. This is similar to what is reported in the **Cecerk *et al.*** [(18)] study, which showed that there were 29% disease progression following neoadjuvant treatment with deficient mismatch repair mechanism (dMMR). This may indicate tumor resistance to neoadjuvant therapy in those patients' group and hence incorporation of recent therapy including immune check points inhibitor (ICI) in neoadjuvant therapy in this patients' group.

Most of recent studies focus on predictors for pCR to guide non-surgical management for those who achieved PCR. We need for further genetic assessment of those who progressed on neoadjuvant therapy for possibility of tailoring treatment and if possible for treatment intensification to reach maximum tumor response and better outcome.

In our study we compared standard (LC-CCRT) treatment versus total neoadjuvant therapy (TNT) using short course radiotherapy. Complete response was achieved radiologically in 11.5% and pathologically in 33.3 % exclusively in TNT group. This is similar as in RAPIDO trial (pCR 28.4%)which used SCRT and preoperative chemotherapy CAPOX 6 cycles and PRODIGE 23 trial (pCR 27.8%), which used mFOLFORINOX and CRT in preoperative setting [(19,20)].

Restricted mean survival time at 12 month was 11.6 in TNT group and 11.1 months in control group. DrTF in our study defined as local progression, local recurrence, distant metastasis and death was 15.4 % in TNT group versus 19.23% in control group (HR 0.74-p= 0.374), while in RAPIDO trial loco regional failure was 8.3% versus 6% at 3 years and distant metastasis was 20% versus 26.8% [(17)]. Pathological complete response was statistically correlated to improvement in DrTF and in RMST at 12 months (P=0.01). DrTF was 50.51% in non PCR group versus 0% in PCR group.

CONCLUSION

Total neoadjuvant therapy (TNT) is a good choice for multimodality treatment of locally advanced rectal cancer patients with reasonable toxicity profile and post-operative complications compared to standard long course concurrent chemo-radiotherapy. Despite this study did not prove statistically advantage of survival of TNT over standard LC-CRT, however pathological complete response (pCR) rate was recorded only in TNT and associated with better disease related treatment failure rate. This indicate that PCR is a major surrogate for survival and further follow up of those patients is needed for more evaluation. Short course radiotherapy with neoadjuvant chemotherapy is a good alternative to the standard LC-CCRT with less hospital treatment days and cost especially after COVID 19 pandemic and subsequent development of new strategy for radiotherapy free protocol to reduce toxicity.

Conflict of interest: None.
Financial support: None.

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