RESEARCH ARTICLE

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Is There any Benefit of Addition of Neo-Adjuvant Chemotherapy (FOLFOX4) to Standard Preoperative Treatment of Rectal Cancer? A Randomized Clinical Trial

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Abstract

Background: Total neoadjuvant therapy (TNT) before surgical intervention represents a unique therapeutic approach for the management of locally advanced rectal cancer (LARC) and has witnessed a notable rise in utilization within recent years. However, the efficacy and safety of this treatment remain subjects of ongoing debate and investigation. This randomized controlled trial aimed to evaluate the potential impact of administering induction chemotherapy (IC) before the conventional neoadjuvant concomitant chemoradiotherapy (nCRT) in LARC patients.**Materials & Methods:** patients with resectable stage II-III LARC were randomly allocated to receive either biweekly 6 cycles of FOLFOX4 regimen as IC followed by CRT and total mesorectal excision (TME) (experimental group) or nCRT followed by TME (control group). The primary endpoint was the rate of pathological complete response (pCR). The secondary endpoints encompassed the evaluation of treatment-related adverse events as well as the assessment of survival outcomes. **Results:** 67 patients were enrolled in this study (32 in the experimental group and 35 in the control group). The median age of the patients was 45 years. Stage IIIB was observed in 46.3% of the patients. The patients who underwent induction chemotherapy demonstrated a notably higher rate of achieving pCR in comparison to the control group (28.1% vs 8.6%; P=0.001). There were no statistically significant differences observed in terms of their toxicity profile and survival outcomes. **Conclusions:** Implementation of induction chemotherapy utilizing the FOLFOX4 regimen has demonstrated a notable enhancement in the rate of pathological complete response. However, this improvement does not appear to translate into significant advancements in overall survival outcomes.

Keywords: Induction chemotherapy- pathological complete response- rectal cancer

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Introduction

In recent decades, there has been a significant evolution in the standard of care for locally advanced rectal cancer (LARC). The advancements in surgical methodologies, along with the incorporation of neoadjuvant chemo-radiotherapy (CRT) or short-course radiotherapy (SCRT), have notably diminished the 5-year loco-regional recurrence rate to a range of 5–8%. Additionally, these interventions have yielded a pathological complete response (pCR) rate of approximately 10% - 15% [1]. Despite the notable advancements in treatment modalities, it is important to acknowledge that a significant proportion of patients, approximately 30%, continue to experience the development of distant metastasis. It is crucial to recognize that distant metastasis remains the primary contributor to mortality in individuals with rectal cancer [2]. The attention has been redirected toward the role of neoadjuvant systemic therapy and its optimal timing in the context of preventing local recurrence, enhancing treatment compliance, and reducing distant failure [3]. Nevertheless, the utilization of the total neoadjuvant treatment (TNT) strategy has garnered considerable interest within the medical community [4]. However, its efficacy and overall impact on long-term survival in patients with LARC remains a subject of ongoing debate and controversy. Hence, this study is a single institution, randomized controlled trial designed to assess the effectiveness and safety of the induction FOLFOX4 regimen followed by CRT and total mesorectal excision (TME) in comparison to the standard of care for patients with LARC.

Materials and Methods

Patient selection.

The protocol was approved by the department review board ethics and the committee of our hospital.

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Patients were assigned in a 1:1 ratio to receive induction chemotherapy FOLFOX4 (experimental group) or standard of care (control group).

Patients included in our study were diagnosed with rectal carcinoma and staged with magnetic resonance imaging (MRI) as stage II (cT3-4N0) or stage III (cT(any) cN1-2), aged more than 18 years and less than 70 years with performance status Eastern Cooperative Oncology Group (ECOG) 0-2 and adequate hematologic, hepatic, and renal functions. On the other hand, we excluded patients with local irresectable or metastatic rectal carcinoma, previous pelvic radiotherapy, surgical treatment or chemotherapy, and inflammatory bowel disease.

Randomization and blinding

Upon enrollment in the study, patients were randomized using the sequentially numbered, opaque, sealed envelope technique into two groups (either experiment group or control group). The regimens were administered to patients by the same practitioner (ST), and all assessments were conducted by a blinded oncologist to ensure study blindness.

Pre-treatment patients' evaluation

Based on the baseline, the patients were assessed by complete medical history, physical examination, and all routine blood tests including the level of CEA and CA19-9. A colonoscopy was done for localization of the tumor and tissue biopsy. The disease was staged with chest and abdominal CTand pelvic MRI before neoadjuvant regimens. All patients underwent nCRT 45 Gy over 25 fractions to the rectum and regional lymph nodes concomitantly with capecitabine 825mg/m² twice daily 5 days/week followed by boost dose 5.4 Gy over 3 fractions to the tumor site. Radiotherapy is delivered with CT-based 3-dimensional conformal treatment planning (3-D CRT) with 10-MV x-rays using a Varian linear accelerator. In addition to CRT, the experimental group received an induction chemotherapy (FOLFOX4) regimen on a bi-weekly schedule for 6 cycles before CRT. Each cycle consists of 85 mg/m² oxaliplatin day 1 only followed by a 200 mg/m² intra venous infusion of leucovorin for 120 min, a 400 mg/m² intravenous bolus of fluorouracil, and a 600 mg/m² continuous infusion of fluorouracil for 22 hours to be repeated on day 2. CRT in the investigational group was delivered approximately 2- 3 weeks after the 6th cycle of the induction chemotherapy.

Treatment response assessment and surgical interference

Following nCRT therapy, all patients had a break for 6–8 weeks, after which they underwent reassessment with proctoscopy, chest and abdomen CT, and pelvic MRI 2–3 weeks before planned TME.

Adjuvant chemotherapy

Adjuvant chemotherapy was delivered with a regimen of (FOLFOX4) approximately 3-4 weeks after TME for 12 cycles in the control group and 6 cycles in the experimental group.

Treatment-related toxicity

Patients were evaluated weekly during the CRT course and every 2 weeks during induction and adjuvant chemotherapy. Toxicities of radiotherapy and chemotherapy were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, 2017.

Follow up

After the end of treatment, all patients underwent follow-up every month for the first 6 months and every 2 months subsequently till the end of the study. Chest, abdomen, and pelvis imaging with contrast, hematological, and tumor markers were done at 3, 6, and 12 months then every 6 months during the 2nd year.

Oncological outcomes

Pathological complete response (pCR) was the primary endpoint. pCR was defined as the absence of viable tumor cells in the resection specimen at both the primary site and at the resected lymph nodes. Survival and toxicity were the secondary endpoints. Disease-free survival (DFS) was calculated from the date of diagnosis to the date of disease relapse. Overall survival (OS) was calculated from the date of diagnosis to the date of death or lost follow-up.

Statistical analysis

The distribution of patients in the two treatment groups according to baseline clinical characteristics, the objective response rate, and the incidence of adverse events were compared using the Chi-square test or Fisher's exact test as appropriate. Cox's proportional hazards modeling was used to calculate hazard ratios (HR) and 95% confidence intervals (CI). The Kaplan-Meier method was used to perform survival analyses and then compared using the log-rank test. The univariate analysis with significance values of $P < 0.05$ was further subjected to a multivariate analysis, which was performed using the Cox proportional hazards model. All data were analyzed and measured by SPSS 22.0 software. The statistical tests were two-sided, and a P value less than 0.05 was considered statistical significance.

Sample size measurement

Based on the hypothesis that the proportion of patients who developed pathological CR after induction chemotherapy followed by concurrent chemoradiation was 38% [5] versus 12% in the standard of care (neoadjuvant CCRTX) [6]. The minimal sample size required to report such a difference in pCR rate was estimated as 60 patients would be required to detect this difference with a power of 90% with an alpha error of 0.05. To account for potential dropouts, we increased the sample size to 67 patients.

Results

Patients' population

Between January 2019 and December 2021, 67 patients (32 in the experimental group and 35 in the control group) were enrolled during the study period. Baseline characteristics for all randomized patients are shown in

Table 1. Baseline Patients' Characters

Variables		Experimental Arm		Control Arm		Total		P-value
		N (32)	%	N (35)	%	N (67)	%	
Age (years)	>40	21	65.6	23	65.7	44	65.7	0.598
	<40	11	34.4	12	34.3	23	34.0	
Gender	Male	16	50	16	45.7	32	47.8	0.458
	Female	16	50	19	54.3	35	52.2	
PS (ECOG)	1	14	43.8	19	54.3	33	49.3	0.269
	2	18	56.3	16	45.7	34	50.7	
Site of Primary tumor	Lower third	14	43.8	14	40	28	41.8	
	Mid third	12	37.5	6	17.1	18	26.9	0.057
	Upper third	6	18.8	15	42.9	21	31.3	
	Bleeding	20	62.5	23	65.7	43	64.2	
Symptoms at presentation	Constipation	7	21.9	6	17.1	13	19.4	0.24
	Intestinal obstruction	2	6.2	3	8.6	5	7.5	
Pathological type	Adenocarcinoma	28	87.5	29	82.9	57	85	
	Mucinous carcinoma	3	9.4	6	17.1	9	13.4	0.389
	Signet ring	1	3.1	0	0.0	1	1.5	
Pathological grade	1	29	90.6	32	91.4	61	91	0.619
	2	3	9.4	3	8.6	6	8.9	
Serum CEA level	<5ng/ml	28	87.5	24	68.6	52	77.6	
	>5ng/ml	4	12.5	5	14.3	9	13.4	0.063
	Not done	0	0.0	6	17.1	6	8.9	
cT staging	T2	9	28.1	8	22.9	17	25.4	
	T3	18	56.3	23	65.7	41	61.2	0.724
	T4a	5	15.6	4	11.4	9	13.4	
cN staging	N0	6	18.8	9	25.7	15	22.4	
	N1	13	40.6	16	45.7	29	43.3	0.536
	N2a	8	25	8	22.9	16	23.9	
	N2b	5	15.6	2	5.7	7	10.4	
c Staging	II A	6	18.8	9	25.7	15	22.4	
	III A	5	15.6	5	14.3	10	14.9	0.314
	III B	13	40.6	18	51.4	31	46.3	
	III C	8	25	3	8.6	11	16.4	

CEA, Carcinoembryonic antigen; PS (ECOG), performance status (Eastern Cooperative Oncology group)

Table 1. Of 67 patients, 35 (52.2%) were females and the median age of all patients was 45 years (range 18–76 years). However, one-third of patients (34%) were below 40 years. The most prevalent rectal tumor location was the lower third (41.8%) followed by the upper third (31.1%). Stage IIIB was the most frequent stage presented in 46.3% of patients. The clinical characteristics of the eligible participants were balanced among the 2 cohorts with no statistically significant difference between them.

Treatment administration

All patients in the experimental group completed the planned 3 months of induction chemotherapy FOLFOX4 regimen and no dose modification was needed. All patients received CRT with a dose of 50.4 Gy of 28 fractions except one patient didn't complete the CRT course after 45 Gy due to grade 3 proctitis. Only 5(7.4%) patients required treatment breaks during radiotherapy due to grade 3 toxicity. The median duration of the radiotherapy course was 28 days (25-35 days). During adjuvant chemotherapy, 85.7% of patients in the IC group completed 6 cycles of the FOLFOX4 regimen compared to 71.4% of patients in the control arm who received 12 cycles (P=0.001).

Surgical approaches

The median duration between radiotherapy course completion and surgery in both study groups was 8.5 weeks (7-12 weeks). All patients proceeded to surgery after nCRT except 3 (9.3%) patients in the IC group who experienced early distant disease progression and one patient (3.1%) refused surgery after achieving clinical CR proved by EUS, pelvic MRI, and biopsy. According to the type of surgery, a high rate of Low anterior resection (LAR) was performed in the IC group compared to the

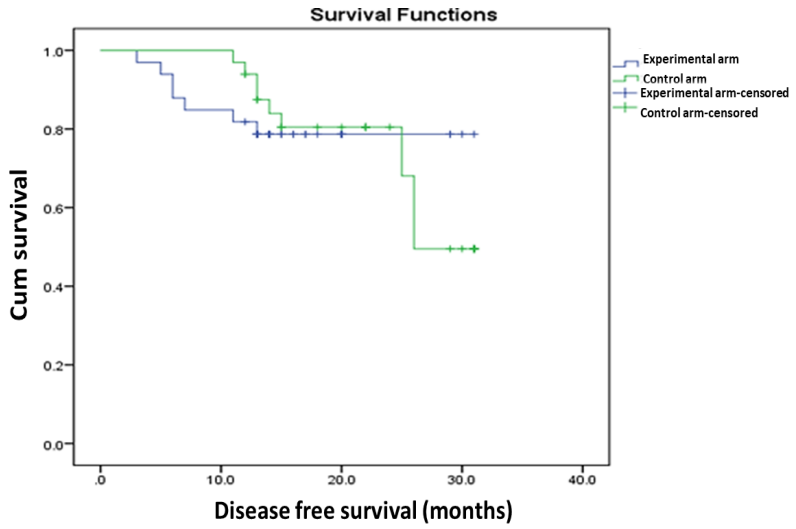

Figure 1. Disease Free Survival for the Two Study Groups

Table 2. Pathological T-stage Response in Both Treatment Arm

Clinical T stage		p T stage										
		No surgery		pT0		pT2		pT3		pT4		P-value
		N	%	N	%	N	%	N	%	N	%	0.001*
Experimental Arm (n=32)	cT2	0	0	2	6.3	5	15.6	2	6.3	0	0	
	cT3	3	9.3	6	18.8	5	15.6	4	12.5	0	0	
	cT4a	0	0	1	3.1	1	3.1	2	6.3	1	3.1	
Total	32	3	9.3	9	28.1	11	34.4	8	25	1	3.1	
Control Arm (n=35)	cT2	0	0	1	2.9	7	20	0	0	0	0	
	cT3	0	0	1	2.9	0	0	21	60	1	2.9	
	cT4a	0	0	1	2.9	0	0	1	2.9	2	5.7	
Total	35	0	0	3	8.6	7	20	22	62.9	3	8.6	

*, Significant

control group (71.4% vs 56.1%, respectively). In contrast, abdominoperineal resection (APR) was the predominant surgical type in 43.9% of patients in the control group compared to 25% of patients in the IC group. One patient (3.6%) in the IC group underwent palliative colostomy after the detection of malignant peritoneal nodules during surgery. However, no significant difference was seen between the groups regarding the type of surgical approach

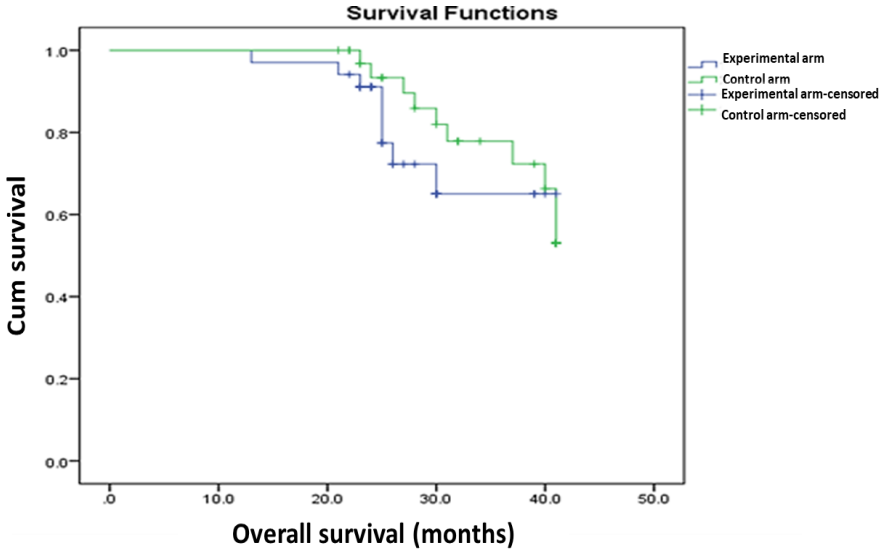

Figure 2. Overall Survival for the Two Study Groups

Table 3. Pathological Nodal-Stage Response in both Treatment Arms.

Clinical N stage		pN stage										P-value
		No surgery		p N0		p N1		p N2a		p N2b		
		N	%	N	%	N	%	N	%	N	%	0.001*
Experimental Arm (n=32)	cN0	0	0	6	18.8	0	0	0	0	0	0	
	cN1	2	6.3	8	25	3	9.4	0	0	0	0	
	cN2a	0	0	4	12.5	1	3.1	3	9.4	0	0	
	cN2b	1	3.1	2	6.3	0	0	0	0	2	6.3	
Total	32	3	9.4	20	62.5	4	12.5	3	9.4	2	6.3	
Control Arm (n=35)	cN0	0	0	8	22.8	0	0	1	2.9	0	0	
	cN1	0	0	6	17.1	10	28.5	0	0	0	0	
	cN2a	0	0	1	2.9	1	2.9	6	17.1	0	0	
	cN2b	0	0	1	2.9	0	0	1	2.9	0	0	
Total	35	0	0	16	45.7	11	31.4	8	22.9	0	0	

*, Significant

Table 4. Treatment-Related Grade 3 Toxicities

Adverse Events	Experimental arm (32)		Control arm (35)		P-value
	N	%	N	%	
During chemotherapy					
Neutropenia	1	3.1	2	5.6	0.28
Nausea/Vomiting	1	3.1	1	2.8	
Diarrhea	1	3.1	0	0	
Paresthesia	2	6.2	2	5.6	
During chemoradiotherapy					
Diarrhea	3	9.3	0	0	0.8
Proctitis	4	12.5	2	5.6	
Total	12	37.5	7	20	0.11

N, number

(P=0.1) and R0 resection (P=0.1). Although patients with a tumor in the lower rectum part in the IC group have a higher rate of sphincter preservation compared to the control group (13.8% vs 2.9% respectively) the difference between the two groups was not statistically significant (p = 0.07).

Treatment efficacy

At the final pathological analysis, the pCR was observed in 9 (28.1%) of the patients receiving induction therapy compared to 3 (8.6%) patients in the control group (p=0.04). Downstaging of the T-category was achieved in 19 (59.4%) patients in the IC group compared to 4 (11.5%) patients in the control group (p=0.001) and downstaging of the N-category was achieved in 15 (46.8%) patients in IC group on compared to 10 (28.7%) patients in the control group (p=0.03). The histopathological results are summarized in Table 2, 3. However, stable disease was observed in 9 (28.1%) patients in the IC group compared to 25 (71.4%) patients in the control group (p=0.001). By univariate analysis, no clinicopathological factors correlate significantly with the pCR rate.

Toxicity and Adverse Events

An overview of adverse events is provided in Table 4. During chemotherapy, all patients experienced grade 1-2 toxicity and were manageable. Overall, grade 3 adverse events occurred in 37.5% of patients in the induction group compared with 20% of patients in the control group with no statistically significant difference.

Survival outcomes and recurrence

Disease-free survival

The median follow-up period was 25 months (13 - 39 months). Five (7.4%) patients experienced local recurrence, 12 (17.9%) patients developed distant metastasis, and one (1.4%) patient simultaneously developed distant metastasis and pelvic regrowth with

Table 5. Pattern of Treatment Failure among Treatment Arms

		Experimental arm (N=32)		Control arm (N=35)		
Type of failure	Site	N	%	N	%	P-value
Loco-regional recurrence	Pelvic	1	3.1	4	11.4	0.27
Total 5 (7.4%)		1	3.1	4	11.4	
Distant metastases	Peritoneum	1	3.1	1	2.9	0.40
	Skin	1	3.1	0	0	
	Liver	1	3.1	4	11.4	
	Bone	1	3.1	1	2.9	
	Lung	0	0	2	5.7	
Total 12 (17.9%)		4	12.5	8	22.8	

N, number

Table 6. Univariate and Multivariate Analysis of Predictive Factors for Survival

DFS				OS			
Univariate							
Variables		Mean (95% CI)	P-value	Variables		Mean (95% CI)	P-value
Pathological response	pCR	29.7 (27.6 - 31.8)	0.001*	Pathological response	pCR	30.7 (30.3 - 31.1)	0.001*
	pPR	26.6 (23.8 - 29.5)			pPR	28.5 (24.8 - 32.3)	
	pSD	26.9 (26.9 - 29.7)			pSD	27.3 (24.5 - 30.1)	
	pDP	16.6 (12.3 - 21.0)			pDP	20.0 (17.5 - 22.4)	
Tumor stage	pT0	29.7 (27.6 - 31.8)	0.001*	Metastasis	No	28.5 (26.6 - 30.5)	0.001*
	pT2	26.9 (23.4 - 30.4)			Yes	21.3 (16.7 - 25.9)	
	pT3	25.0 (21.9 - 28.1)		Local recurrence	No	27.6 (25.7 - 29.4)	0.004*
	pT4	22.0 (14.7 - 29.2)			Yes	22.6 (17.2 - 28.0)	
Multivariate							
Variables		(95% CI)	P-value	Variables		(95% CI)	P-value
Pathological response		0.207 - 0.996	0.04*	Pathological response		0.1 - 0.78	0.012*
				Distant metastasis		2.0 - 17.9	0.001*

DFS, Disease-free survival; OS, Overall survival; CI, Confidence interval; pCR, Pathological complete response; pPR, Pathological partial response; pSD, Pathological stationary disease; pDP, Pathological disease progression; *, Significant

no statistically significant difference between treatment arms regarding local recurrence and distant metastasis Table 5. As regards treatment type, there was no statistically significant difference in the mean DFS of the experimental arm compared to the control group (25.9 vs 25.8 months) (P=0.8). Two-year DFS was 78.5% in the experimental group versus 82.5% in the control group (P=0.3) Figure 1.

By univariate analysis, DFS was significantly prolonged in the patients who achieved pCR 29.7 months (95% CI: 25.2 - 30.7) and pathological PR 26.6 months (95% CI: 22.1 - 27.3) versus 16.6 months in the patients who experienced pathological disease progression (P=0.001). Pathological T4 stage appeared to be associated with worse mean DFS at 22 months (95% CI 14.7 - 29.2; P = .001). By multivariate analysis, only pathological response (95% CI: 0.2-0.9; P=0.04) was an independent prognostic factor for DFS. Other patients and tumor characteristics were not significantly correlated to prolonged DFS.

Overall survival (OS)

At the end of the study, 17 (25.4%) patients had died, including 6 (9%) patients in the induction group and 11 (16.4%) patients in the control group. The mean OS was similar for patients who received induction chemotherapy compared to standard of care (35.3 (95% CI: 31.9 – 38.6) months versus 37.7 (95% CI: 35.4 – 39.9) months respectively) with no significant statistical difference (p=0.3). No clinically meaningful difference in the 2-year OS rates was observed between the groups (94.3% vs 94.6% for IC patients and control patients respectively). Figure 2.

By univariate analysis, the mean OS was significantly longer for patients with pCR (P=0.001), who didn't develop local recurrence (P=0.004), and patients who didn't have distant metastasis (P=0.001). By multivariate analysis, the mean OS is significantly longer for patients who had a pathological response (95%CI, 0.13-0.78; P=0.012) and didn't have distant metastasis (95%CI, 2.03-17.97; P=0.001) Table 6.

Discussion

The present research investigated the efficacy and potential adverse effects of administering the induction FOLFOX4 regimen before the standard of care regimen in patients diagnosed with LARC. It is worth mentioning that the median age of the patients in our research was 45 years, which is comparatively lower than the median age reported in a recent meta-analysis done by Lin et al. Specifically, the median age of patients in the six trials included in their investigation ranged from 54 to 68 years [7]. Furthermore, it is worth noting that approximately 33% of the individuals included in our study were aged 40 years or younger. This observation aligns with the growing trend of higher incidence rates of rectal cancer among individuals below the age of 50. This phenomenon can potentially be attributed to various behavioral risk factors, including but not limited to obesity, cigarette smoking, alcohol consumption, high consumption of red or processed meat, and a lack of physical activity [8]. In our research, the key endpoint used to assess the efficacy of neoadjuvant induction chemotherapy in comparison to conventional CRT is pCR. The results indicate that induction chemotherapy has a significantly higher incidence of pCR (28.1% vs 8.6%, respectively; P=0.001). The present study aligns with the outcomes of a comprehensive analysis undertaken by Zaborowski et al, which included 10 prospective studies including 648 patients who received TNT. The overall rate of pCR was found to be 21.8%, with a range of 10% to 40% [9].

The present study shows comparable results, which align with the outcomes described in a previous meta-analysis done by Petrelli et al. including 28 trials and a total of 3579 patients. Among these patients, 2688 received TNT, whereas 891 had conventional CRT. According to Petrelli et al., the rate of pCR achieved with the use of

TNT was found to be 22.4% (95% confidence interval [CI] 19.4–25.7, p < 0.001) [10].

Remarkably, the present investigation yielded a pCR rate that closely approximated the pCR rate observed in the PRODIGE 23 trial (27.5%). To achieve this outcome, the researchers employed a more intense treatment regimen involving the administration of six cycles of modified FOLFIRINOX (mFOLFIRINOX), followed by nCRT, surgical intervention, and an additional three-month course of chemotherapy using either FOLFOX or capecitabine [11].

We were unable to identify any predictive variables in the present investigation that were connected to the pCR rate. According to Ceelen et al., the primary determinants of oncological outcomes in individuals diagnosed with CRC are tumor and nodal involvement [12]. In the present research, it was seen that the use of induction chemotherapy resulted in significant reductions in tumor and nodal staging, with percentages of 59.4% and 46.8% respectively, in contrast to the standard of care arm which exhibited lower percentages of 11.4% and 28.7% respectively. The results of our investigation were consistent with the findings of Schrag et al., who conducted a study on the use of preoperative mFOLFOX6/ Bevacizumab and selective radiotherapy for LARC. Their study demonstrated notable rates of pCR and downstaging of the T-category, with percentages of 25% and 72% respectively [13]. In the research conducted by Markovina et al., it was shown that the rates of pCR and tumor downstaging were 28% and 75% in the TNT group, whereas, in the CRT group, these rates were 16% and 41% respectively [14].

On the other hand, the Spanish GCR-3 phase II study did not observe a statistically significant difference in the rate of pCR between the induction therapy with CAPOX and the usual nCRT, with rates of 14.3% and 13.5%, respectively. The authors postulate that this result might be attributed to inherent dissimilarities in patient attributes between the two cohorts under treatment, such as a greater proportion of patients in the neoadjuvant chemotherapy group exhibiting a compromised circumferential margin [15]. A recent meta-analysis conducted by Lin et al. examined 6 studies involving 12,812 patients. The objective was to compare the outcomes of neoadjuvant chemotherapy alone (NACT) versus nCRT in LARC. The study included 677 patients in the NACT group and 12,135 patients in the nCRT group. The researchers observed that there were no notable distinctions between the two cohorts concerning the pCR rate. The pCR rate was 8.0% in one group and 11.8% in the other group, with an odds ratio (OR) of 0.62 and a 95% confidence interval (CI) ranging from 0.27 to 1.41 [7].

The variability observed in the rate of pCR in previous studies can be attributed to the utilization of diverse systemic treatment regimens, variations in the timing of chemotherapy administration, differences in the number of treatment cycles administered, and variations in the interval between chemotherapy and surgical intervention. Another objective in the utilization of neoadjuvant chemotherapy is to enhance the probability of sphincter preservation, particularly for individuals diagnosed with lower LARC. Our study reveals that the sphincter preserving rate among patients diagnosed with lower rectal tumors was observed to be relatively higher in the group that underwent induction chemotherapy, as compared to the control group (13.8% vs 2.9% respectively; P=0.07). However, it is important to note that this difference did not reach statistical significance. The findings of Anup Kasi's meta-analysis, in which three trials examined sphincter preservation rate, indicate that there is no statistically significant distinction in sphincter preservation rate between the TNT group and the standard CRT group (OR, 1.06; 95% CI, 0.73-1.54) [3]. Furthermore, it is worth noting that Zhao Y et al. observed a sphincter preservation rate of 79.6% in the TNT group compared to 66.2% in the nCRT group (p = 0.06). It is important to acknowledge that this difference did not reach statistical significance, indicating that the observed disparity may not be clinically meaningful [16]. The PRODIGE-23 trial findings were consistent with the absence of significant variation in surgical procedures performed between the two groups, as indicated by a p-value of 0.303. Most patients underwent low anterior resection, with 78.9% in the TNT arm and 74.4% in the control arm. Abdominoperineal resection was the subsequent most common procedure, with rates of 14.1% and 14.0% in the TNT and control arms, respectively. Inter-sphincteric resection was performed in 7.0% of patients in the TNT arm and 10.7% in the control arm [11].

Likewise, the incidence of achieving R0 resection was found to be similar in both cohorts under investigation (P=0.1). The observed results align with the findings of four trials examined by Liu et al, indicating that there is no statistically significant distinction in the R0 resection rate between TNT and standard nCRT (odds ratio [OR], 1.04; 95% confidence interval [CI]: 0.71-1.53; p=0.85) [17]. The meta-analysis conducted by Kasi et al. included six randomized controlled trials (RCTs) that provided information regarding the specific type of resection performed. R0 resection was successfully achieved in 86.2% of patients in the experimental arm, while in the standard group, it was achieved in 84.3% of patients. Furthermore, the study conducted by Kasi et al. did not reveal any noteworthy disparities between the two cohorts [3].

Despite significant advancements in the tri-modality treatment of LARC, it is important to acknowledge that local failure can still manifest and remains a primary contributor to morbidity and the development of debilitating conditions in affected patients. Furthermore, it is important to note that distant metastasis remains the primary factor contributing to treatment failure in approximately 20% to 30% of patients [2]. As expected, the rates of local and distant failures demonstrated improvement in patients who underwent TNT compared to those who received standard treatment. Regrettably, the study conducted by Kim et al. did not reveal any significant clinical disparities in the rates of local recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) (p=0.92 and p=0.11 respectively). This observation was made when comparing the group of patients (n = 313) who received 4 months of mFOLFOX6

or CAPOX as induction chemotherapy followed by chemoradiotherapy, known as the TNT group, with the standard nCRT group (n = 311) treated at Memorial Sloan Kettering Cancer Center [18]. Furthermore, it is noteworthy to mention that the Spanish GCR-3 phase 2 trial did not yield evidence indicating a significant disparity in the 5-year local recurrence rate (2% vs 5%; P=0.61) and distant metastasis rate (21% vs 23%; P=0.79) between the cohort that underwent the conventional treatment and the TNT group [15].

Our study further elucidates that the incidence of local recurrence and distant disease failure exhibited a favorable outcome in the induction chemotherapy cohort, with rates of 3.1% and 12.5% respectively. In contrast, the nCRT group displayed higher rates of 11.4% and 22.8% respectively, although these disparities did not reach statistical significance. This observation potentially indicates that neoadjuvant chemotherapy exhibits comparable efficacy to the postoperative adjuvant approach in mitigating the likelihood of long-term recurrence. In contrast, the meta-analysis performed by Liu et al. revealed that TNT demonstrated a favorable outcome in terms of DMFS when compared to standard CRT (HR = 0.81, 95% confidence interval [CI]: 0.68 to 0.95, p = 0.012). The study conducted by Liu et al. in 2021 found that there was no statistically significant difference in LRFS between the two groups (HR=1.19, 95% CI: 0.94 to 1.51, P = 0.151) [17]. Survival results serve as crucial indicators for assessing the effectiveness of TNT. Multiple clinical studies and meta-analyses have shown enhancements in DFS and OS after TNT in comparison to CRT [17]. The PRODIGE-23 phase III study used the mFOLFIRINOX regimen as a kind of induction chemotherapy before chemoradiotherapy. The trial's findings, as published by Conroy et al., indicated a significant enhancement in the 3-year DFS rate and the 3-year rate of survival without metastasis [11].

A comparative study of seven studies revealed that patients who were administered TNT exhibited improved DFS (HR 0.75, 95%, CI 0.52–1.07, p = 0.11) and OS (HR 0.73, 95% CI 0.59–0.9, p = 0.004) in comparison to those who received just conventional nCRT [10].

In retrospective research conducted by Zhao et al., a total of 49 patients diagnosed with LARC were treated with the TNT regimen, which included two cycles of CAPOX administered before and after nCRT. In comparison, 71 patients got the usual treatment. The research conducted by Zhao et al. did not demonstrate any significant advantages in DFS between the two groups, with rates of 84.8% and 73.2% (p = 0.26) respectively [16]. Similarly, there were no significant differences in OS between the groups, with rates of 89.8% and 79.4% (p = 0.21) respectively. In our research, while there was an increase in both the rate of pCR and adherence to induction neoadjuvant chemotherapy, this did not result in a significant improvement in survival outcomes. There was no significant improvement seen in the 2-year DFS and 2-year OS rates between the induction chemotherapy group and the control group (78.5% vs 82.5%; p=0.3) and (94.3% vs 94.6%; p=0.9), respectively. Nevertheless, the presence of pCR was identified as a significant independent factor linked to an extended duration of DFS with a confidence interval (CI) of 0.2-0.9 and a p-value of 0.04. Similarly, pCR was also shown to relate to a prolonged overall survival (OS) with a 95% CI of 0.13-0.78 and a p-value of 0.012. The results of this study align with other research indicating comparable survival outcomes between targeted therapy and conventional care. The bad outcomes in terms of DFS or OS may be attributed to the limited duration of the follow-up period.

A more rigorous neoadjuvant chemotherapy treatment in the TNT groups led to a higher incidence of high-grade adverse effects being recorded. Only 5 (15.6%) of the patients in our research developed grade 3 toxicity during induction treatment, and no grade 4 toxicity was detected. There was no requirement for a reduction in drug dosage or withdrawal of the patient. Our findings agree with the meta-analysis that incorporated 8 trials, led by Liu et al. The authors observed that patients who received TNT experienced a range of grade 3-4 acute toxicities, varying from 9% to 41%, whereas the standard treatment group reported a lower incidence of 2% to 29% [17].

The administration of adjuvant chemotherapy after nCRT has become an established component of the tri-modality approach in the comprehensive care of LARC. Nevertheless, there exists a divergent interpretation of the available data regarding the potential advantages of adjuvant chemotherapy, which has sparked considerable deliberation regarding its practical implementation in clinical settings. Furthermore, it is imperative to consider the potential toxicity associated with adjuvant chemotherapy regimens. Ensuring optimal compliance becomes paramount as inadequate completion of the prescribed dose intensity may pose significant challenges. In our study, it was observed that patients who underwent induction chemotherapy demonstrated a higher likelihood of receiving all cycles of adjuvant chemotherapy, as compared to those who received nCRT (85.7% vs 71.4% respectively, P=0.001). Our observation aligns with the observation made in the Spanish GCR-3 study, where it was noted that 91% of patients successfully adhered to the study protocol in the induction chemotherapy group, while only 54% were able to do so in the nCRT/adjuvant chemotherapy group (p <0.001) [15].

A recently published retrospective study comprised a cohort of 81 patients diagnosed with LARC. Among these patients, 26 individuals underwent TNT, which involved receiving a short course of radiotherapy (5x5 Gy) either before or after completing six cycles of mFOLFOX chemotherapy. The remaining 55 patients underwent standard nCRT. The compliance rate demonstrated a statistically significant advantage in favor of TNT, with a rate of 84.6% compared to 40% in the respective control group (p<0.01), as reported by ElHusseini et al. [19]. In conclusion, the findings of our study indicate that the utilization of induction chemotherapy in combination with conventional chemo-radiotherapy holds promise as a viable approach to enhance the rate of pCR and preserve sphincter function in patients diagnosed with LARC while maintaining manageable levels of treatment-related toxicities. Long-term surveillance is imperative to ascertain whether the timely initiation of

systemic chemotherapy can enhance overall survival rates. The present investigation is constrained by its relatively modest sample size and abbreviated duration of follow-up. Further investigation through larger-scale prospective studies is warranted to validate the findings we have obtained.

Author Contribution Statement

All patients were submitted randomly in each arm by Heba Ashraf Hosni Mohamed, they were followed up by Hussein Mohamed Metwally and Hanan Selim Mosallum. Omar Elfarouk Osman Zaki revised all data.

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If it was approved by any scientific Body/ if it is part of an approved student thesis

The research protocol was approved by Kasr Elainy department of oncology congress in 2019. Also, this research project is an approved part of PhD thesis.

Availability of data

Patients records are available at Kasr Elainy Oncology department.

How the ethical issue was handled (name the ethical committee that approved the research)

The study was approved by the department review board ethics and the committee of our hospital ``Kasr Elainy Hospitals``, Cairo University, Egypt in 2019.

Conflict of interests

There is no conflict of interest for all authors.

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