Total Neoadjuvant Therapy Versus Neoadjuvant Chemoradiation in Locally Advanced Rectal Cancer, Who will Gain Maximum Benefit? A Prospective Randomized Study

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Abstract: Colorectal cancer (CRC) is a global health problem as it is a common and lethal disease. Neoadjuvant treatment improves anal sphincter preservation, resectability, and local control. Total neoadjuvant therapy (TNT) [that incorporates chemotherapy with chemoradiotherapy before surgery has been assumed to offer advantages such as enhanced compliance with planned therapy, tumor downstaging, early eradication of occult micrometastases and assessment of chemosensitivity. This prospective phase II randomized study included 70 locally advanced rectal cancer (LARC) patients treated in Tanta University Hospitals throughout the period from January 2022 to April 2025. Thirty-two patients received CRT (Arm A) and 38 patients received TNT (Arm B). The aim was comparison of outcomes and toxicities in stage II and III rectal cancer cases receiving standard neoadjuvant chemoradiation (nCRT) and TNT. The pathological complete response rate was 19.4% in TNT versus 12.5% in CRT and this was statistically insignificant. R0 resection rate was 93.5% versus 87.5% in TNT and CRT respectively. Disease free survival was 54% versus 50% and overall survival (OS) was 86% versus 73% in TNT and CRT respectively with statistically insignificant difference. Toxicity also was comparable between 2 groups and most of reported toxicity was grade 1 and 2 which is easily manageable. TNT resulted in a trend towards improvement in pathologic complete response (PCR), disease free survival (DFS) and OS with comparable manageable toxicity.

Keywords: Neoadjuvant, Rectal, PCR, CRT, TNT, DFS, OS, Toxicity.

INTRODUCTION

Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the second most common cause of cancer-related mortality in both men and women worldwide [1]. Rectal cancer is responsible for approximately 30% of CRC and is linked to a worse clinical outcome [1, 2]. The neoadjuvant chemoradiation (nCRT) is the standard treatment for locally advanced rectal cancer (LARC). This is followed by a complete mesorectal excision to enhance resectability, anal sphincter preservation, and local control. For stage II-III rectal cancer, both short-course radiotherapy (SCRT) and long-course chemoradiotherapy (LCCRT) have been the standard neoadjuvant treatments [3]. Multiparametric functional MRI may be superior to conventional MRI in evaluating the effectiveness of neoadjuvant treatment in locally advanced rectal cancer, enhancing the patient's chances of selecting the optimal further treatment options [4]. Total neoadjuvant therapy (TNT) is a therapeutic approach for LARC that combines chemotherapy with chemoradiotherapy prior to surgery. It has been presumed to provide benefits such as advanced tumor downstaging and improved compliance with intended therapy. Moreover, the assessment of chemosensitivity can be facilitated by exposure to chemotherapy earlier in the disease course, which targets occult micrometastases [5]. In clinical complete responders, TNT can also safely render the patient escape or at least postpone surgery [6]. TNT is particularly effective for higher-risk stage II or III rectal cancer, which includes cT3 lesions with involved or threatened CRM by MRI, cT4 lesions, cN2 disease, extramural venous invasion, and low-lying rectal tumors (≤5 cm from the anal periphery). TNT is also a viable treatment option for medically inoperable or locally unresectable diseases [7]. The aim of this study is comparative analysis of the outcomes of patients who received standard nCRT and TNT, which includes the evaluation of R0 resection rate, pathologic complete response (PCR) rate, adverse events, DFS (disease-free survival), OS (overall survival), and toxicity.

MATERIALS AND METHODS

This prospective randomized study (using simple randomization by coin) was carried out at clinical

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ISSN: 1929-2260 / E-ISSN: 1929-2279/26

oncology department Tanta university hospitals throughout the period from January 2022 to April 2025 and included 70 patients aged more than 18 years old with performance status 0 to 2 according to ECOG (Eastern Cooperative Oncology Group) score with adequate organs' functions diagnosed and histopathologically, radiologically proved clinical stage II or III rectal cancer patients treated with 2 different neoadjuvant treatment strategies. Thirty-two patients received CRT (Arm A) and 38 patients received neoadjuvant TNT (Arm B). Written informed consent was obtained from all participants to participate in the study and for the publication of their data and any related photographs. The study was approved by research ethics committee, Faculty of Medicine, Tanta University, Approval Code: 35464/5/22.

Treatment Details

Patients in arm A received nCRT (50.4Gy in 28 fractions) with capecitabine (825mg/m2 twice daily 5 days per week) followed by total mesorectal excision (TME) after an interval of 7-9 weeks with or without adjuvant chemotherapy (ACT). ACT was delivered as mFOLFOX, CAPOX or capecitabine. Patients in arm B received TNT which is composed of 4 months mFOLFOX6 or CAPEOX followed chemoradiation with capecitabine with the same dose and fractionation as arm A then total mesoractal excision (TME) after an interval of 7-9 weeks TNT arm) (Figure **1**).

Radiotherapy

Radiotherapy was delivered as 3DCRT or IMRT in both arms. Target volumes were defined and contoured according to ASTRO clinical practice guidelines [8]. The clinical target volume (CTV) comprised the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes. External iliac nodes should be included in the evaluation of cases with rectal malignancies that have invaded an anterior organ or structure (e.g., prostate, seminal vesicles, cervix, vagina, and/or bladder). For malignancies that involve the anal canal, it is advisable to include the

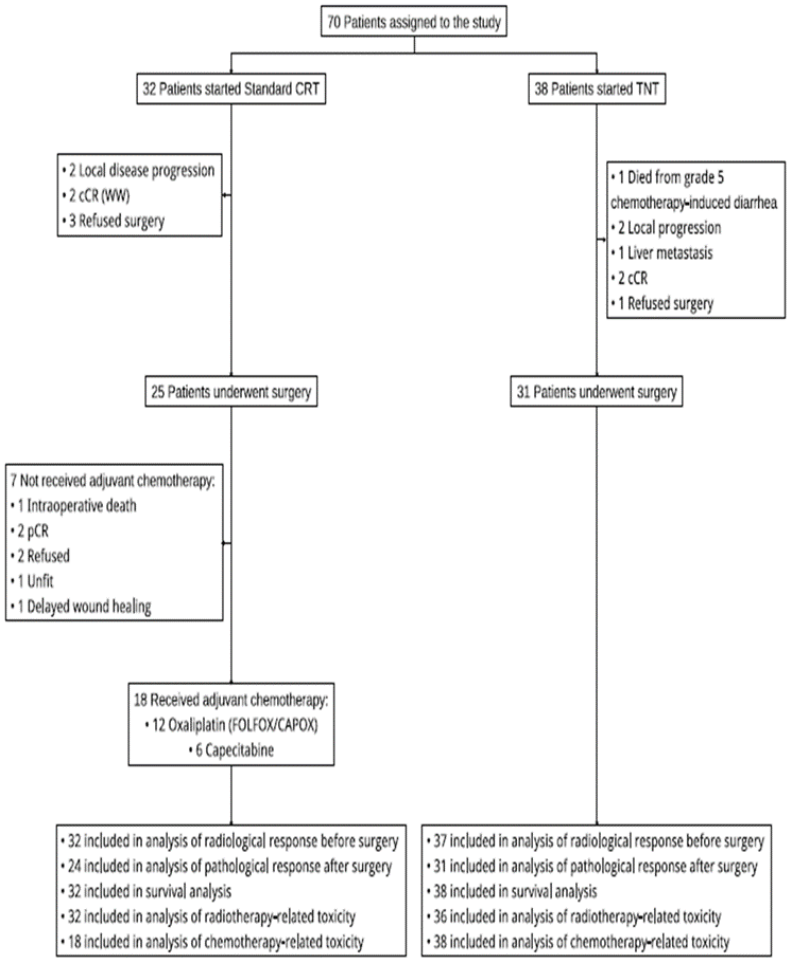

Figure 1: Study profile.

inguinal and external iliac nodes. Organs at risk (OARs), such as the bladder, bowel bag, and femoral heads, were contoured in accordance with the guidelines of the Radiation Therapy Oncology Group (RTOG) [9].

Fertility counselling was done for all patients before starting treatment.

Nutritional consultation and support were done for all patients in both arms during the period of the study at Nutrition Clinic, Tanta University Hospitals.

Response Evaluation

The radiological response was evaluated using RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 [10]. In arm A, radiological assessment was done at least 6 weeks after CRT, after surgery, then every 2 months during adjuvant treatment. In arm B, it was done after 2 months of neoadjuvant chemotherapy, patient was subjected to CRT directly if there was no response to chemotherapy. If there was partial response, the patient completed 4 months neoadjuvant chemotherapy then CRT with assessment of response at least 6 weeks after CRT, then assessment was repeated in postoperative setting.

Pathological response was assessed after total mesorectal excision with reporting of post treatment pathological stage (ypTNM), tumor regression grade (TRG) according to mandard TRG system [11].

Toxicity Evaluation

During treatment, toxicity data were collected from all patients and reported related to the CTCAE version 5.0: Common Terminology Criteria for Adverse Events [12].

Post Treatment Follow-Up

Patients in both arms were followed for 2 years by history, physical examination and serum tumor markers (CEA, CA19.9) every three months, abdomen and chest CT, and rectal MRI every 6 months, colonoscopy 1 year after surgery or when abnormality was detected in MRI. The cases had achieved clinical complete response (cCR) and elected to proceed with non-operative protocol were followed according to the proposed watchful waiting protocol in the OPRA tail [13].

End Points

Primary end points were R0 resection rate in both arms (R0 is defined as resection with microscopically negative margin). The PCR rate in both arms (defined as the absence of residual viable tumor cells in the primary tumor site and regional lymph nodes).

The secondary endpoints were disease-free survival at 2 years, which is defined as the duration from randomization until the first cancer-related event or death from any caused. OS at two years (defined as the period from randomization to mortality from any cause). The frequency and severity of adverse events as determined by the CTCAE version 5.0.

Statistical Analysis

The statistical language R (version 4.5.0; R Core Team, 2025) was used to conduct the analyses. The Shapiro-Wilk test and Q-Q plots were used to investigate the distribution of continuous numerical values. The median, range (low and high values), and interquartile range (IQR, 25th–75th percentiles) were used to characterize variables that did not follow a normal distribution. The range, standard deviation, and mean were used to summarize the continuous variables that followed a normal distribution. For two-group comparisons, we used the Wilcoxon rank sum (Mann-Whitney) test; for three-group comparisons, we used the two-sample T-test/Welch T-test (for normally distributed variables) and the Kruskal-Wallis test (for more than two groups) in the event that the variables were not normally distributed; finally, we used the Dunn test with Bonferroni adjustment for variables that were abnormally distributed. In order to summarize the categorical variables, percentages and counts were used. We used Pearson's Chi-square test for independence of observations (for nominal variables, it was replaced with Fisher's exact test if the expected count in more than 20% of cells was below 5) or the Chi-square test for trend in proportions (for ordinal categorical variables) to test for associations between the treatment arms and categorical variables. The time-to-event outcomes were assessed by survival analysis, which makes use of Kaplan-Meier (KM) curves to estimate the chance of surviving with time. The log-rank test was used to establish differences between the groups. The researchers used hazard ratios (HR) with 95% confidence intervals to measure the impact of each predictor on survival. They used univariable and multivariable Cox proportional hazards regression to do this. The findings of the statistical tests were interpreted using a p-value of 0.05.

RESULTS

The mean age was 57.5 years in CRT arm and 47.5 years in TNT arm. Most patients were nonsmokers in both arms. The mean body mass index at diagnosis was 29.3 in CRT arm and 28.3 in TNT arm. The percentage of positive family history for malignancy was slightly higher in TNT group. The highest was for colon, breast and thyroid. Most patients in both arms were T3. About 75% in CRT arm were clinical node positive versus 97.3% in TNT arm. Most patients in both groups were grade 2. The mean neutrophil lymphocyte ratio (NLR) at diagnosis was 1.7 in CRT arm and 1.6 in TNT arm. As regards primary tumor site, most tumors in both arms were in lower rectum 78.1% and 60.5% in CRT arm and TNT arm respectively. About 40% of tumors in both arms were RAS mutant. Only one patient was RAS wild and BRAF V600E mutant and was in TNT arm (Table **1**).

Tumor Response

Radiological Response

Complete clinical response was achieved in 4 patients (2 in CRT arm "6.3%" and 2 in TNT arm "5.4%"). Partial response was achieved in 62.5% in CRT arm versus 75.7% in TNT arm, but this difference was statistically insignificant (Table **2**).

Pathological Response

PCR was achieved in 12.5% in CRT arm versus 19.4% in TNT arm. The percentage of complete and major pathological response combined (TRG1 plus TRG 2) was 16.7% versus 38.8% in CRT and TNT arms respectively. There was no treatment effect in 16.7% in CRT arm versus 9.7% in TNT arm.

Resection Rate

Resection rate was 87.5% in CRT versus 93.5% in TNT arm, but this difference was statistically insignificant. (Table **3**).

Disease Free Survival

At 2 years, 50% of patients in CRT arm were disease free versus 54% in TNT arm and this difference was statistically insignificant. Univariate analysis of different factors showed that elevated CEA, CA19.9, positive margin and presence of RAS mutation were associated with worse DFS. Also, patients who didn't have surgery had worse DFS, as most of them were due to disease progression or refused surgery despite persistent disease in imaging after neoadjuvant treatment. Multivariate analysis showed that R1 resection and elevated tumor markers adversely affected DFS (Table **2**). There is insignificant difference in pattern of treatment failure in both arms (Table **4**; Figure **2**)

Overall Survival

The 2-year OS was 73% in CRT arm versus 86% in TNT arm and this difference was statistically insignificant. Univariate analysis showed that high CEA, high CA 19.9 and R1 resection were associated with worse OS. Also, patients who didn't undergo surgery had worse survival. Multivariate analysis showed that incomplete resection was the most powerful factor that adversely impacted OS (Table **4**; Figure **3**).

Toxicity

During chemotherapy, the incidence of diarrhea and rectal hemorrhage was significantly higher in CRT arm, but most of these toxicities were grade 1 and 2. There was only one grade 5 diarrhea recorded in TNT arm. The incidence of anemia associated with chemoradiation was significantly higher in TNT arm, but it was grade 1 and 2**.** The rest of gastrointestinal genitourinary and hematological toxicity were comparable in the two arms.

DISCUSSION

The standard management for all cases of LARC was standard chemoradiation followed by surgery with or without ACT according to post-neoadjuvant pathological stage and other patient factors. This treatment strategy provided good local disease control but still a considerable percentage of patients have suboptimal response to CRT and experience local and/or distant failure [14]. TNT has emerged with the aim of decreasing distant failure in LARC. In this study we compared TNT, in the form of oxaliplatin and fluropyrimidine based chemotherapy followed by chemoradiation and total mesorectal excision, to CRT followed by total mesorectal excision.

In this study we tested if further preoperative treatment escalation will lead to improvement in surgical outcomes in the form of R0 resection rates, pathological outcomes in the form of PCR rates and if it will impact patients' survival. In our study, 4 patients (2 in each arm) achieved complete clinical response and opt not to go for surgery due to their preference, and they were followed till the end of the study without any cancer related event. However, radiological response was comparable between the two arms. Regarding

Table 1: Demographic Data and Clinicopathological Characteristics of Studied Population

Characteristic	CRT N = 32	TNT N = 38	p-value
Age (years), Mean ± SD (Range)	57.8 ± 14.5 (27.0 - 82.0)	47.5 ± 12.3 (25.0 - 73.0)	0.002*c
Sex, n (%)			0.484d
Female	15 (46.9%)	21 (55.3%)	
Male	17 (53.1%)	17 (44.7%)	
Comorbidity, n (%)			
None	17 (53.1%)	30 (78.9%)	0.100e
Hypertension	11 (34.4%)	3 (7.9%)	0.037*e
Diabetes & hypertension	2 (6.3%)	3 (7.9%)	1.000e
Diabetes mellitus	2 (6.3%)	1 (2.6%)	0.982e
Autoimmune vasculitis	0 (0.0%)	1 (2.6%)	1.000e
Smoking, n (%)			0.130e
No	26 (81.3%)	36 (94.7%)	
Yes	6 (18.8%)	2 (5.3%)	
Family hiatory, n (%)			
Brain	1 (3.1%)	2 (5.3%)	>0.999e
Melanoma	0 (0.0%)	1 (2.6%)	>0.999e
Breast	0 (0.0%)	3 (7.9%)	0.245e
Colon	0 (0.0%)	3 (7.9%)	0.245e
Pancreas	1 (3.1%)	1 (2.6%)	>0.999e
Prostate	1 (3.1%)	0 (0.0%)	0.457e
Thyroid	0 (0.0%)	3 (7.9%)	0.245e
Endometrium	0 (0.0%)	1 (2.6%)	>0.999e
Lung	0 (0.0%)	1 (2.6%)	>0.999e
BMI (Kg/m²), Mean ± SD (Range)	29.3 ± 4.5 (17.3 - 39.8)	28.3 ± 5.2 (18.7 - 41.8)	0.412c
Grade, n (%)			0.007*c
1	5 (15.6%)	2 (5.3%)	
2	27 (84.4%)	29 (76.3%)	
3	0 (0.0%)	7 (18.4%)	
cT stage, n (%)			0.515c
T2	1 (3.1%)	2 (5.3%)	
T3	30 (93.8%)	32 (84.2%)	
T4	1 (3.1%)	4 (10.5%)	
cN stage, n (%)			0.005*c
N0	8 (25.0%)	1 (2.6%)	
N+ve	24 (75.0%)	37 (97.4%)	
NLR, Mean ± SD (Range)	1.7 ± 0.8 (0.4 - 3.5)	1.6 ± 0.7 (0.3 - 3.0)	0.808d
CEA, Median [IQR] (Range)	4.1 [2.1 - 12.0] (1.0 - 205.0)	2.7 [1.6 - 7.3] (0.8 - 415.0)	0.179e
CEA, n (%)			0.557f
Normal	18 (56.3%)	24 (63.2%)	
Elevated	14 (43.8%)	14 (36.8%)	
CA 19.9, Median [IQR] (Range)	21.3 [13.0 - 44.7] (0.7 - 111.0)	20.3 [12.2 - 45.0] (0.5 - 613.0)	0.869e
CA 19.9, n (%)			0.940f
Normal	23 (71.9%)	27 (71.1%)	
Elevated	9 (28.1%)	11 (28.9%)	
Primary site, n (%)			0.114c
Lower	25 (78.1%)	23 (60.5%)	
Middle	6 (18.8%)	12 (31.6%)	
Upper	1 (3.1%)	3 (7.9%)	
RAS, n (%)			0.922f
Mutant	13 (40.6%)	15 (39.5%)	
Wild	19 (59.4%)	23 (60.5%)	
RAF, n (%)			>0.999g
Mutant	0 (0.0%)	1 (4.3%)	
Wild	19 (100.0%)	22 (95.7%)	

Data are presented as mean SD (±) or frequency (%).
*significant as P-value ≤ 0.05.

Table 2: Radiological and Pathological Response, and Site of Disease Recurrence in Both Arms

Characteristic	CRT N = 32	TNT N = 38	p-value
Radiological response before surgery, n (%)			0.554c
CR	2 (6.3%)	2 (5.4%)	
PR	20 (62.5%)	28 (75.7%)	
SD	8 (25.0%)	4 (10.8%)	
DP	2 (6.3%)	3 (8.1%)	
Not recorded	0 (0%)	1 (2.6%)	
Pathological response			
Pathological complete response rate, n (%)	CRT N = 24	TNT N = 31	0.716c
Yes	3 (12.5%)	6 (19.4%)	
No	21 (87.5%)	25 (80.6%)	
Tumor regression grade, n (%)			0.231d
1	3 (12.5%)	6 (19.4%)	
2	1 (4.2%)	6 (19.4%)	
3	7 (29.2%)	4 (12.9%)	
4	9 (37.5%)	12 (38.7%)	
5	4 (16.7%)	3 (9.7%)	
Site of disease progression	CRT N = 15	TNTN = 14	p-value
Site of progression, n (%)			>0.999c
Local	6 (40%)	6 (42.9%)	
Distant	9 (60%)	8 (57.1%)	
Liver, n (%)	4 (26.6%)	2 (14.3%)	>0.999d
Lung, n (%)	1 (6.6%)	4 (28.6%)	0.326d
Bone, n (%)	1 (6.6%)	1 (7.1%)	>0.999d
Brain, n (%)	0 (0.0%)	1 (7.1%)	>0.999d
Abdomen (LN/Omentum), n (%)	3 (20%)	0 (0.0%)	0.222d
Inguinal LNs, n (%)	1 (6.6%)	0 (0.0%)	>0.999d

Table 3: Resection Rate

Characteristic	CRT N = 24	TNT N = 31	p-value *
Residual, n (%)			0.307
R0	21 (87.5%)	29 (93.5%)	
R1	3 (12.5%)	1 (3.2%)	
Missed	0 (0.0%)	1 (3.2%)	

*Significant at p<0.05.

pathological response, TNT achieved 19.4% PCR rate versus 12.5% in CRT. There is numerical improvement in the percentage of cases had achieved major or complete pathological responses (TRG 1 and 2), but this difference was statistically insignificant. This is in accordance with the Spanish Grupo Cáncer de Recto-3 trial, which demonstrated that the pathological complete response rate (14.3%) did not increase than the pathological complete response rate (13.9%) in LARC after 4 cycles of neoadjuvant capecitabine plus oxaliplatin (CAPOX) followed by chemoradiotherapy [15].

Statistically significant improvement was observed in the TNT arm of UNICANCER-PRODIGE 23, with a PCR rate of 27.5% than 11.7% in the standard of care arm. This might be due to the more intensive chemotherapy regimen used in PRODIGE 23 which

Table 4: Univariate and Multivariate Analysis of Disease-Free Survival and Univariate and Multivariate Analysis of Overall Survival

Characteristic		DFS probability (95% CI) at 2 Y	p-value	Hazard ratio (95% CI)	p-value
Univariate and Multivariate analysis of disease-free survival					
Overall		52 (41, 67)	-	-	-
Groups	Arm A	50 (35, 72)	0.664	-	-
	Arm B	54 (39, 75)		-	-
Sex	Female	47 (33, 69)	0.750	-	-
	Male	57 (42, 79)		-	-
Smoking	No	54 (42, 70)	0.182	-	-
	Yes	38 (15, 92)		-	-
Comorbidities	No	52 (39, 70)	0.701	-	-
	Yes	51 (32, 82)		-	-
Grade	1	57 (30, 100)	0.583	-	-
	2	54 (42, 70)		-	-
	3	24 (4.5, 100)		-	-
cT stage	T2	100 (100, 100)	0.371	-	-
	T3	49 (38, 65)		-	-
	T4	53 (21, 100)		-	-
cN stage	N0	51 (26, 100)	0.979	-	-
	N+ve	52 (40, 68)		-	-
CEA	Normal	68 (54, 85)	0.006*	—	
	Elevated	30 (16, 56)		2.665 (1.281, 5.543)	0.009*
CA 19.9	Normal	67 (55, 83)	<0.001*	—	
	Elevated	19 (7.3, 48)		3.866 (1.881, 7.946)	<0.001*
ypT stage	T0	100 (100, 100)	0.007*	-	-
	T1	0 (—, —)		-	-
	T2	41 (19, 91)		-	-
	T3	54 (37, 79)		-	-
	T4	33 (6.7, 100)		-	-
ypN stage	N0	74 (58, 94)	0.052	-	-
	N+ve	42 (26, 67)		-	-
Primary site	Lower	50 (36, 68)	0.909	-	-
	Middle	59 (40, 88)		-	-
	Upper	38 (8.4, 100)		-	-
RAS	Mutant	39 (23, 65)	0.031*	—	
	Wild	60 (46, 79)		0.460 (0.223, 0.947)	0.035*
RAF	Mutant	100 (100, 100)	0.616	-	-
	Wild	60 (46, 78)		-	-
Residual	R0	63 (49, 79)	<0.001*	—	
	R1	0 (—, —)		13.711 (3.947, 47.635)	<0.001*
Underwent surgery	No	40 (20, 79)	0.040*	—	
	Yes	55 (43, 72)		0.435 (0.193, 0.983)	0.045*

(Table 4). Continued.

Characteristic		DFS probability (95% CI) at 2 Y	p-value	Hazard ratio (95% CI)	p-value
Univariate and multivariate analysis of Overall survival					
Overall	79 (69, 90)				
Groups	Arm A	73 (58, 91)	0.323		
	Arm B	86 (75, 98)			
Sex	Female	82 (70, 96)	0.590		
	Male	76 (61, 94)			
Smoking	No	80 (70, 92)	0.812		
	Yes	73 (47, 100)			
Comorbidities	No	79 (67, 92)	0.852		
	Yes	80 (64, 100)			
Grade	1	67 (38, 100)	0.463		
	2	82 (72, 94)			
	3	69 (40, 100)			
cT stage	T2	100 (100, 100)	0.401		
	T3	76 (66, 89)			
	T4	100 (100, 100)			
cN stage	N0	76 (52, 100)	0.756		
	N+ve	79 (69, 91)			
CEA	Normal	90 (82, 100)	0.033*	—	
	Elevated	64 (47, 87)		3.341 (1.027, 10.867)	0.045*
CA 19.9	Normal	88 (79, 99)	0.007*	—	
Elevated	59 (40, 86)		4.157 (1.359, 12.712)	0.012*	
pT stage	T0	100 (100, 100)	0.003*		
	T1	100 (100, 100)			
	T2	81 (60, 100)			
	T3	95 (87, 100)			
	T4	33 (6.7, 100)			
ypN stage	N0	89 (75, 100)	0.803		
	N+ve	89 (78, 100)			
Primary site	Lower	79 (67, 92)	0.918		
	Middle	82 (65, 100)			
	Upper	75 (43, 100)			
RAS	Mutant	67 (50, 89)	0.044*	—	
	Wild	87 (76, 98)		0.336 (0.109, 1.030)	0.056
RAF	Mutant	100 (100, 100)	0.781		
	Wild	86 (76, 98)			
Residual	R0	98 (94, 100)	<0.001*	—	
	R1	0 (—, —)		70.025 (7.605, 644.770)	<0.001*
Underwent surgery	No	42 (21, 84)	<0.001*	—	
	Yes	88 (79, 98)		0.161 (0.054, 0.482)	0.001*

*Significant as P-value ≤ 0.05. CI = Confidence Interval, HR = Hazard Ratio.

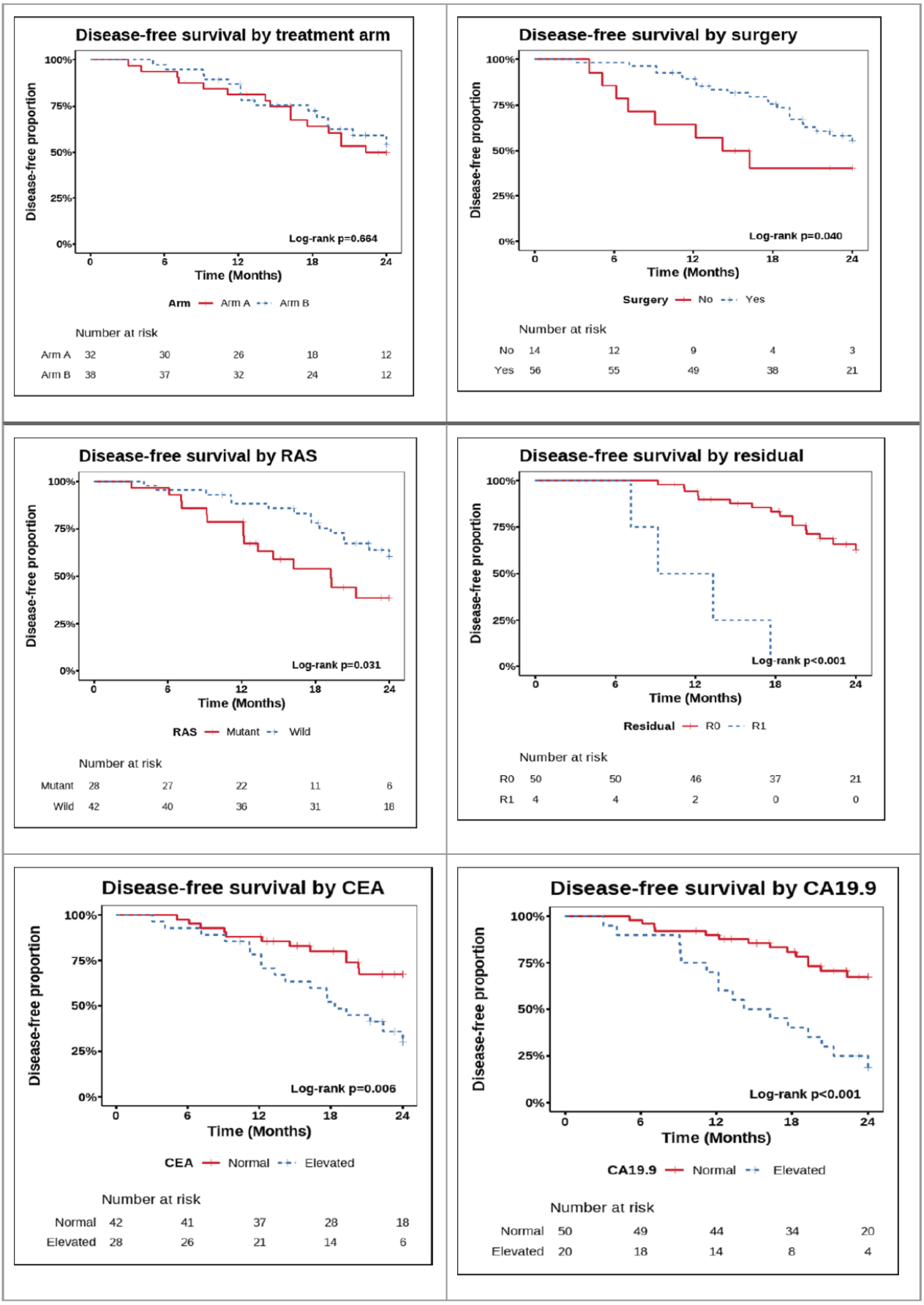

Figure 2: Disease- free survival.

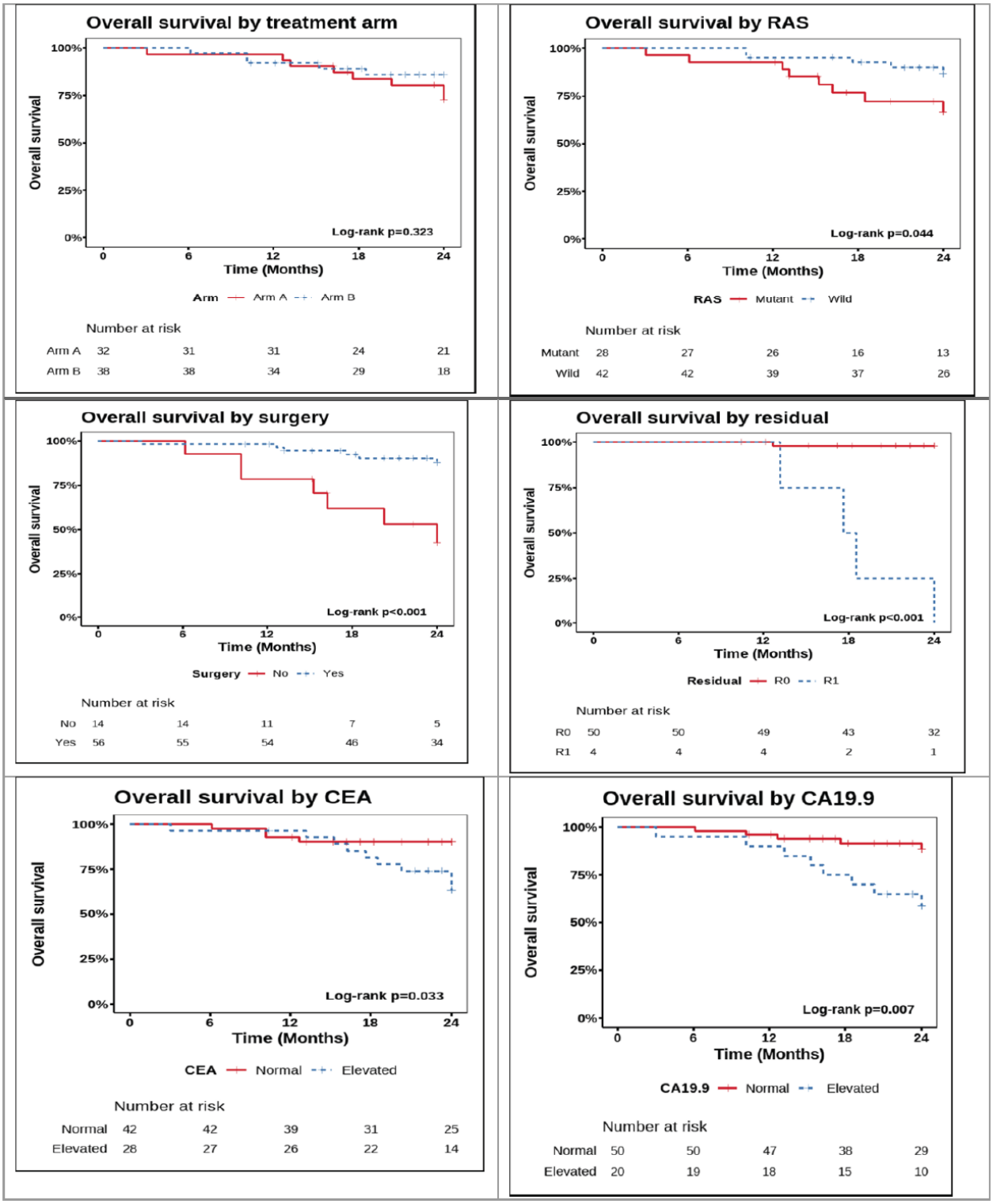

Figure 3: Overall survival (OS).

was the FOLFIRINOX triplet instead of FOLFOX or CAPOX [16]. In the RAPIDO trail, PCR rate was 28.4% in TNT versus 14.3% in the standard arm. This is nearly equal to the PCR achieved in PROGIGE 23 with FOLFIRINOX triplet. The increased PCR rate in RAPIDO may be related to the timing between radiotherapy and surgery which was scheduled approximately 24 weeks after the radiotherapy start as patients in this trail received chemotherapy after short course radiotherapy [17].

This PCR rate was also achieved with consolidation chemotherapy in trail comparing it with induction chemotherapy as a part of TNT in LARC, 25% in

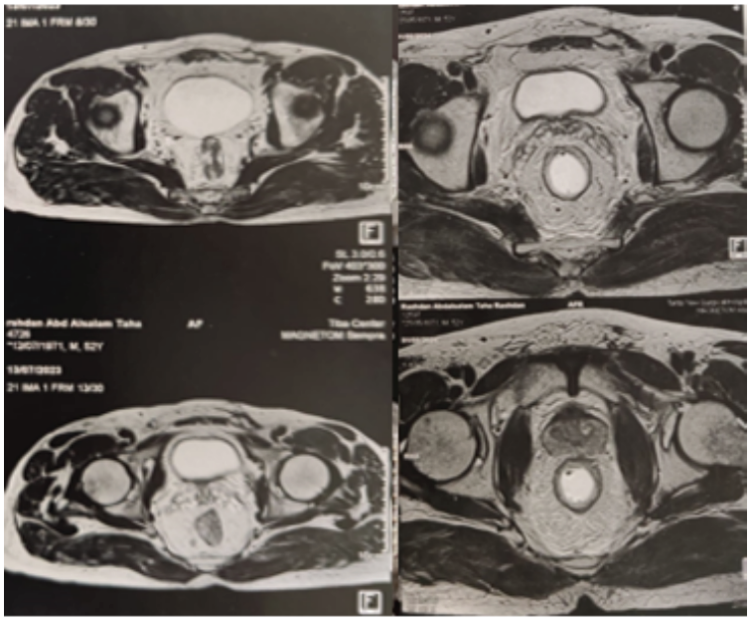

Figure 4: MRI showing response after TNT.

CAO/ARO/AIO-12 trail [18]. In our study, 93.5% in TNT arm achieved R0 resection versus 87.5% in CRT arm with statistically insignificant difference. This is consistent with R0 resection rate in PROGIGE 23 which was 95% in TNT arm and in CAO/ARO/AIO-12 trail which was 92% and 90% in induction and consolidation chemotherapy arms respectively. R0 resection rate was 90% in both arms of RAPIDO. Our 2-year disease-free survival results in both arms were 54% and 50% in TNT and CRT respectively. In PRODIGE 23, 3-year DFS was the primary end point, and it was 76% in TNT arm and 69% in standard arm with significant P value and HR of 0.69. This improvement in DFS in PRODIGE 23 may be due to the use of FOLFIRINOX instead of doublet chemotherapy in our study. Also, it is possible that the small sample size and relatively brief follow-up period are contributing factors.

In RAPIDO, the primary end point was three years disease related treatment failure, and it was 77.1% in TNT arm versus 71.8% in standard arm with significant P value and HR of 0.79 and this was also higher than recorded in our study. However, our results were slightly consistent with a Chinese (STELLAR) phase 3 tail with a study design similar to that of RAPIDO trail as used SCRT followed by consolidation chemotherapy. In this trial 3-year The DFS was 64.5% in TNT arm versus 62.3% in standard arm with only a modest improvement [19].

In our study, DFS rates were significantly affected by refusal of curative surgery, elevated tumor markers, presence of RAS mutation and presence of R1 resection. The 2-year OS in our study was 86% in TNT arm versus 73% CRT arm with statistically insignificant improvement, and this is consistent with the results of STELLAR Chinese trail as 3-year OS was 86.5% in TNT and 84.1% in standard arm with a HR of 0.79. In PRODIGE 23, 3- year OS was 91% in TNT versus 88% in standard arm with a significant improvement. The significant improvement in PRODIGE 23 trail may be due to the use of more intensive regimen (FOLFIRINOX triplet) which lead to improvement in PCR rates and metastasis free survival which in turn affects OS. In RAPIDO trail, 3- year OS was 89.1% in TNT versus 88.8% in standard ram and 5-year OS was 77.4% versus 71.6% with only trend toward improvement. In our study, OS was significantly affected by refusal of curative surgery, elevated tumor markers and presence of R1 resection.

Most of the reported toxicity were grade 1 and 2. Grade 3 or more toxicities were low in both arms and were comparable with similar trails. There was no grade 5 toxicity except in one patient in TNT arm who developed fatal diarrhea and mucositis with the first cycle of chemotherapy. The most frequently reported toxicity during chemotherapy was peripheral neuropathy in TNT arm and diarrhea in CRT arm. The most frequently reported toxicities during chemoradiation were rectal pain and proctitis. Most of the toxicities were low grade and adequately managed. Our study is a single-institution study with a comparatively brief follow-up period and a restricted number of patients. More comprehensive trials with large sample sizes are required to establish these

results. Moreover, we see that disease-related treatment failure is a more suitable end point to be used in neoadjuvant trails than DFS.

COMPETING INTERESTS

Nil.

FUNDING

Nil.

AUTHOR'S CONTRIBUTIONS

Conceptualization: S.G.B. & F.G., methodology: S.G.B. & F.G., Formal analysis and investigation: F.G. & M.H.A., Writing—original draft preparation: S.G.B., Writing—review and editing: M.H.A., A.M.E., supervision, validation and final editing: S.G.B., A.M.E. & H.T., all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

Nil.

ETHICS APPROVAL

This prospective randomized study (using simple randomization by coin) was carried out at clinical oncology department Tanta university hospitals throughout the period from January 2022 to April 2025. The study was approved by research ethics committee, faculty of medicine, Tanta University, approval code: 35464/5/22.

CONSENT TO PARTICIPATE DECLARATION

An informed and written consent was taken from each patient. Confidentiality was respected.

AVAILABILITY OF DATA AND MATERIAL

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

CONSENT FOR PUBLICATION

Written informed consent was obtained from all participants for the publication of their data and any related photographs.

REFERENCES

[1] Bailey CE, Hu CY, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM, *et al*. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States. JAMA Surg 2015; 150: 17-22. https://doi.org/10.1001/jamasurg.2014.1756

[2] El-Bolkainy TN, Sakr MA, Nouh AA, El-Din NH. A comparative study of rectal and colonic carcinoma: demographic, pathologic and TNM staging analysis. J Egypt Natl Canc Inst 2006; 18: 258-63.

[3] Liscu HD, Miron AI, Rusea AR, Oprea AN, Mitre R, Herdea A, *et al*. Short-Course Radiotherapy versus Long-Course Radio-Chemotherapy as Neoadjuvant Treatment for Locally Advanced Rectal Cancer: Meta-Analysis from a Toxicity Perspective. Maedica (Bucur) 2021; 16: 382-8. https://doi.org/10.26574/maedica.2021.16.3.382

[4] Tawfik MMA, Gheida UES, Khedr RA, Khadrah RSA. Multiparametric MRI in the assessment of the response of locally advanced rectal cancer to neoadjuvant chemoradiotherapy. Tanta Med J 2025; 53(2): 161-70. https://doi.org/10.4103/tmj.tmj_84_24

[5] Kasi A, Abbasi S, Handa S, Al-Rajabi R, Saeed A, Baranda J, *et al*. Total Neoadjuvant Therapy vs Standard Therapy in Locally Advanced Rectal Cancer: A Systematic Review and Meta-analysis. JAMA Netw Open 2020; 3: 97-9. https://doi.org/10.1001/jamanetworkopen.2020.30097

[6] van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, *et al*. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet 2018; 391: 2537-45. https://doi.org/10.1016/S0140-6736(18)31078-X

[7] Hofheinz RD, Fokas E, Benhaim L, Price TJ, Arnold D, Beets-Tan R, *et al*. Localised rectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2025; 36: 1007-24. https://doi.org/10.1016/j.annonc.2025.05.528

[8] Wo JY, Anker CJ, Ashman JB, Bhadkamkar NA, Bradfield L, Chang DT, *et al*. Radiation Therapy for Rectal Cancer: Executive Summary of an ASTRO Clinical Practice Guideline. Pract Radiat Oncol 2021; 11: 13-25. https://doi.org/10.1016/j.prro.2020.08.004

[9] Gay HA, Barthold HJ, O'Meara E, Bosch WR, El Naqa I, Al-Lozi R, *et al*. Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy Oncology Group consensus panel atlas. Int J Radiat Oncol Biol Phys 2012; 83: 353-62. https://doi.org/10.1016/j.ijrobp.2012.01.023

[10] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47. https://doi.org/10.1016/j.ejca.2008.10.026

[11] Kim SH, Chang HJ, Kim DY, Park JW, Baek JY, Kim SY, *et al*. What Is the Ideal Tumor Regression Grading System in Rectal Cancer Patients after Preoperative Chemoradiotherapy? Cancer Res Treat 2016; 48: 998-1009. https://doi.org/10.4143/crt.2015.254

[12] Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. Actas Dermosifiliogr (Engl Ed) 2021; 112: 90-2. https://doi.org/10.1016/j.ad.2019.05.009

[13] Garcia-Aguilar J, Patil S, Gollub MJ, Kim JK, Yuval JB, Thompson HM, *et al*. Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy. J Clin Oncol 2022; 40: 2546-56. https://doi.org/10.1200/JCO.22.00032

[14] Smith HG, Nilsson PJ, Shogan BD, Harji D, Gambacorta MA, Romano A, *et al*. Neoadjuvant treatment of colorectal cancer: comprehensive review. BJS Open 2024; 8: 87-98. https://doi.org/10.1093/bjsopen/zrae038

[15] Fernández-Martos C, Pericay C, Aparicio J, Salud A, Safont M, Massuti B, *et al*. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010; 28: 859-65. https://doi.org/10.1200/JCO.2009.25.8541

Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N, *et al*. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021; 22: 702-15. https://doi.org/10.1016/S1470-2045(21)00079-6

[16] Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM, *et al*. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021; 22: 29-42. https://doi.org/10.1016/S1470-2045(20)30555-6

[17] Fokas E, Schlenska-Lange A, Polat B, Klautke G, Grabenbauer GG, Fietkau R, *et al*. Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Patients With Locally Advanced Rectal Cancer: Long-term Results of the CAO/ARO/AIO-12 Randomized Clinical Trial. JAMA Oncol 2022; 8: 21544-5 https://doi.org/10.1001/jamaoncol.2021.5445

[18] Jin J, Tang Y, Hu C, Jiang L-M, Jiang J, Li N, *et al*. Multicenter, randomized, phase III trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR). Journal of Clinical Oncology 2022; 40: 1681-92. https://doi.org/10.1200/JCO.21.01667

Received on 24-05-2026 Accepted on 27-06-2026 Published on 25-07-2026

https://doi.org/10.30683/1929-2279.2026.15.19