ORIGINAL ARTICLE

Retrospective Study

Delaying surgery after neoadjuvant chemoradiotherapy improves prognosis of rectal cancer

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Data sharing statement: Technical appendix, statistical code and dataset available from the corresponding author at (ekabul@gmail.com). Participants gave informed consent for data sharing. No additional data are available.

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Abstract

AIM
To investigate the prognostic effect of a delayed interval between neoadjuvant chemoradiotherapy (CRT) and surgery in locally advanced rectal cancer.

METHODS
We evaluated 87 patients with locally advanced mid- or distal rectal cancer undergoing total mesorectal excision following an interval period after neoadjuvant CRT at Şişli Hamidiye Etfal Training and Research Hospital, Istanbul between January 2009 and January 2014. Patients were divided into two groups according to the interval

before surgery: < 8 wk (group Ⅰ) and ≥ 8 wk (group Ⅱ). Data related to patients, cancer characteristics and pathological examination were collected and analyzed.

RESULTS

When the distribution of timing between group Ⅰ (n = 45) and group Ⅱ (n = 42) was viewed, comparison of interval periods (median ± SD) of groups showed a significant difference of as 5 ± 1.28 wk in group Ⅰ and 10.1 ± 2.2 wk in group Ⅱ (P < 0.001). The median follow-up period for all patients was 34.5 (9.9-81) mo. group Ⅱ had significantly higher rates of pathological complete response (pCR) than group Ⅰ had (19% *vs* 8.9%, P = 0.002). Rate of tumor regression grade (TRG) poor response was 44.4% in group Ⅰ and 9.5% in group Ⅱ (P < 0.002). A poor pathological response was associated with worse disease-free survival (P = 0.009). The interval time did not show any association with local recurrence (P = 0.79).

CONCLUSION

Delaying the neoadjuvant CRT-surgery interval may provide nodal down-staging, improve pCR rate, and decrease the rate of TRG poor response.

Key words: Rectal carcinoma; Pathological tumor response; Neoadjuvant chemoradiotherapy; Interval timing; Tumor down-staging

Core tip: Delaying the neoadjuvant chemoradiotherapy (CRT)-surgery interval for treatment of locally advanced rectal carcinoma may improve pathological complete response rates by providing nodal down-staging, as well as decreasing the rate of tumor regression grade (TRG) poor response. TRG may be an important predictive factor for disease-free survival. Extending the interval between CRT and surgery may improve the survival through tumor down-staging without increasing the rate of surgical complications.

INTRODUCTION

Locally advanced distal and mid-rectal tumors are commonly treated with preoperative combined chemoradiotherapy (CRT) followed by total mesorectal excision (TME)[1-3]. Previously conducted studies have recommended a treatment interval time between preoperative neoadjuvant CRT and surgery for the treatment of locally advanced rectal cancer[4,5]. The first prospective trial (The Lyon Trial R90-01), which assigned patients randomly to have surgery at two different time intervals following CRT, was conducted in 1999. That trial showed that a 6-8-wk treatment interval between radiotherapy and surgery improved tumor down-staging and yielded a higher pathological response rate compared with a 2-wk interval. Since then, a 6-8-wk interval has been accepted as the appropriate treatment interval between neoadjuvant therapy and surgery[6]. However, a definite definition for an optimum interval period is still lacking in the medical literature. In addition, even though the known effect of an extended interval on pathological complete response (pCR), the impact of pCR on disease-free survival (DFS) and overall survival (OS) has not been clearly described[7].

The aim of this study was to determine whether the interval time between preoperative neoadjuvant CRT and surgery affected the rates of pCR, perioperative surgical complications, sphincter-saving surgery, DFS and OS in locally advanced mid-or distal rectal cancer.

MATERIALS AND METHODS

Patients

This was a retrospective review of a series of 113 consecutive patients who underwent preoperative neoadjuvant CRT followed by radical resection with TME for curative intent of locally advanced mid- or distal rectal cancer between January 2009 and January 2014 at Şişli Hamidiye Etfal Training and Research Hospital, General Surgery and Oncology Departments. The study was approved by the local ethics committee. Written informed consent was obtained from all study participants, or their legal guardian for being included in the study. All patients included in the study (1) were aged ≥ 18 years; (2) had pathological diagnosis of adenocarcinoma of mid-rectal (located between 5 and 10 cm from the anal verge) and distal rectal (situated in the first 5 cm from the anal verge, excluding the anal canal) tumors by endoscopic biopsy; (3) had tumors with T3/T4 stage or N (+) as demonstrated on pelvic phased-array magnetic resonance imaging; and (4) underwent TME after neoadjuvant CRT. Study parameters including interval period between neoadjuvant CRT and surgery, operation time and type, intraoperative and early postoperative morbidity and mortality, and hospital stay were recorded. Reports from pathological examinations were interrogated to extract data on total and metastatic lymph node numbers and surgical margins. Data on local recurrence, organ metastases that occurred during postoperative follow-up period, DFS and OS rates were also recorded. Postoperative anastomotic complications were defined according to severity grading of anastomotic leakage of the International Study Group of Rectal Cancer[8]. Twenty-six patients, including those who had widespread metastasis at the time of diagnosis (n = 3), patients who underwent short-term radiotherapy (5 × 5 Gy)

(n = 7), individuals with synchronized tumors or had treatment due to other malignancies with rectal cancer as secondary (n = 5), patients who could not tolerate neoadjuvant chemotherapy (n = 3), and patients who were lost to follow-up (n = 8) were excluded. The remaining 87 patients constituted the study population. The study patients were divided into two groups according to the interval time between neoadjuvant CRT and surgery: < 8 wk (group Ⅰ) and ≥ 8 wk (group Ⅱ).

In all patients, tumor localization and pathological diagnosis were made by using procto-sigmoidoscopy and endoscopic biopsy, respectively. Systemic staging was performed using thoracic and abdominal computed tomography (CT), while local staging was performed using phased-array magnetic resonance imaging. Preoperative neoadjuvant CRT was given for a total of 5 wk and it included 45-50.4 Gy radiotherapy (5 × 1.8-2.0 Gy/wk) and concomitant 5-fluorouracil (180 mg/m^2 per day) for 5 d/wk. Surgery was performed in all patients at the earliest interval of 4 wk after neoadjuvant chemotherapy. The interval between neoadjuvant therapy and surgery varied according to logistics and scheduling preferences of the attending surgeon.

Postoperative follow-up protocol was performed every 3-4 mo during the first year, once every 6 mo during the second year, and once every year after the second year. During follow-up, local recurrences were determined using thoracoabdominal CT, positron emission tomography-CT or colonoscopy.

Pathological examination

Histopathological examination of the resected specimens including the mesorectum was performed to identify as many lymph nodes as possible. Evaluation of tumor regression grade (TRG) after CRT in the primary tumor of the rectal wall was performed by experienced pathologists according to the Ryan scheme for tumor regression score[9], which was suggested by the College of American Pathologists protocol. The absence of viable cancer cells or acellular pools of mucin in resected specimens were considered as complete response (TRG 1). Single cells or microscopic foci of cancer cells in samples were assessed as near complete response (TRG 2). Residual cancer outgrown by fibrosis was considered as the minimal response (TRG 3). Minimal or no tumor kill, or extensive residual cancer in specimens were found as a poor response (TRG 4). T stage 0 was considered as complete tumor response in the rectal wall, while near complete, minimal or inadequate responses were examined at any T stage. In the present study, tumoral down-staging or pathological tumor response was expressed by TNM classification, according to American Joint Committee on Cancer, and pCR was defined as T stage 0 in the rectal wall without metastatic lymph node in the mesorectum.

Statistical analysis

Data were analyzed using SPSS for Windows, version 17.0 (SPSS, Chicago IL, United States) by the official biostatistician of the hospital. Continuous variables are represented as mean ± SD and categorical variables as numbers and percentages. Intergroup analyses were performed using Students' t test and Mann-Whitney U test for continuous variables and χ^2 test and Fisher's exact test for categorical variables. The Spearman correlation test was used to investigate the relationship between continuous variables and intervals between CRT and surgery. Paired t and Wilcoxon tests were used to compare dependent groups. Oncological outcomes of patients were classified as 2-year and 5-year DFS and OS. The Kaplan-Meier test, log-rank test, and Cox regression analyses were used to determine the relationship between potential risk factors and DFS and OS. OS was defined as the period between diagnosis of the disease until death that occurred as a result of the disease. DFS was defined as the time between diagnosis of the disease until local recurrence or far-organ metastasis. Patients who died from other causes or died within the early postoperative period were censored. Results were evaluated between 95%CIs, and the level of statistical significance was set at P < 0.05.

RESULTS

A total of 87 patients who had locally advanced mid- or distal rectal cancer underwent surgical resection with TME after neoadjuvant CRT. Of these 45 (group Ⅰ) had a treatment interval < 8 wk and 42 (group Ⅱ) had an interval ⩾ 8 wk. Patient demographics and clinical characteristics were comparable in both groups (Table 1). When the distribution of timing in both groups was viewed, comparison of interval periods (median ± SD) between the groups showed a significant difference; as 5 ± 1.28 (2-7.8) wk in group Ⅰ and 10.1 ± 2.2 (8.2-20.2) wk in group Ⅱ (P < 0.001) (Figure 1).

Effect of interval period on preoperative variables

Statistical analysis did not show any correlation between treatment interval and respective preoperative and postoperative variables (operation time and type, diverting ileostomy dehiscence rate, intraoperative and postoperative complication rate, hospital stay and early postoperative mortality rate) (Table 2). Despite all patients being informed about surgical approach and necessity of diverting stoma, six had not given consent to have a diverting loop stoma. Therefore, 42 patients (93.3%) in group Ⅰ and 39 patients (92.9%) in group Ⅱ were diverted at the time of TME.

For patients who had distally located tumors, sphincter-saving surgery was performed in 17 (64.7%) in group Ⅰ and 11 (63.6%) in group Ⅱ (P = 0.86). Intraoperative complications occurred in four patients from group Ⅰ, left ureter injuries in two patients (4.4%), and presacral significant bleeding in the other two (4.4%). In group Ⅱ, there was right ureter injuries in two patients (4.7%) and bladder injury in one patient (2.3%) (P = 0.48). During
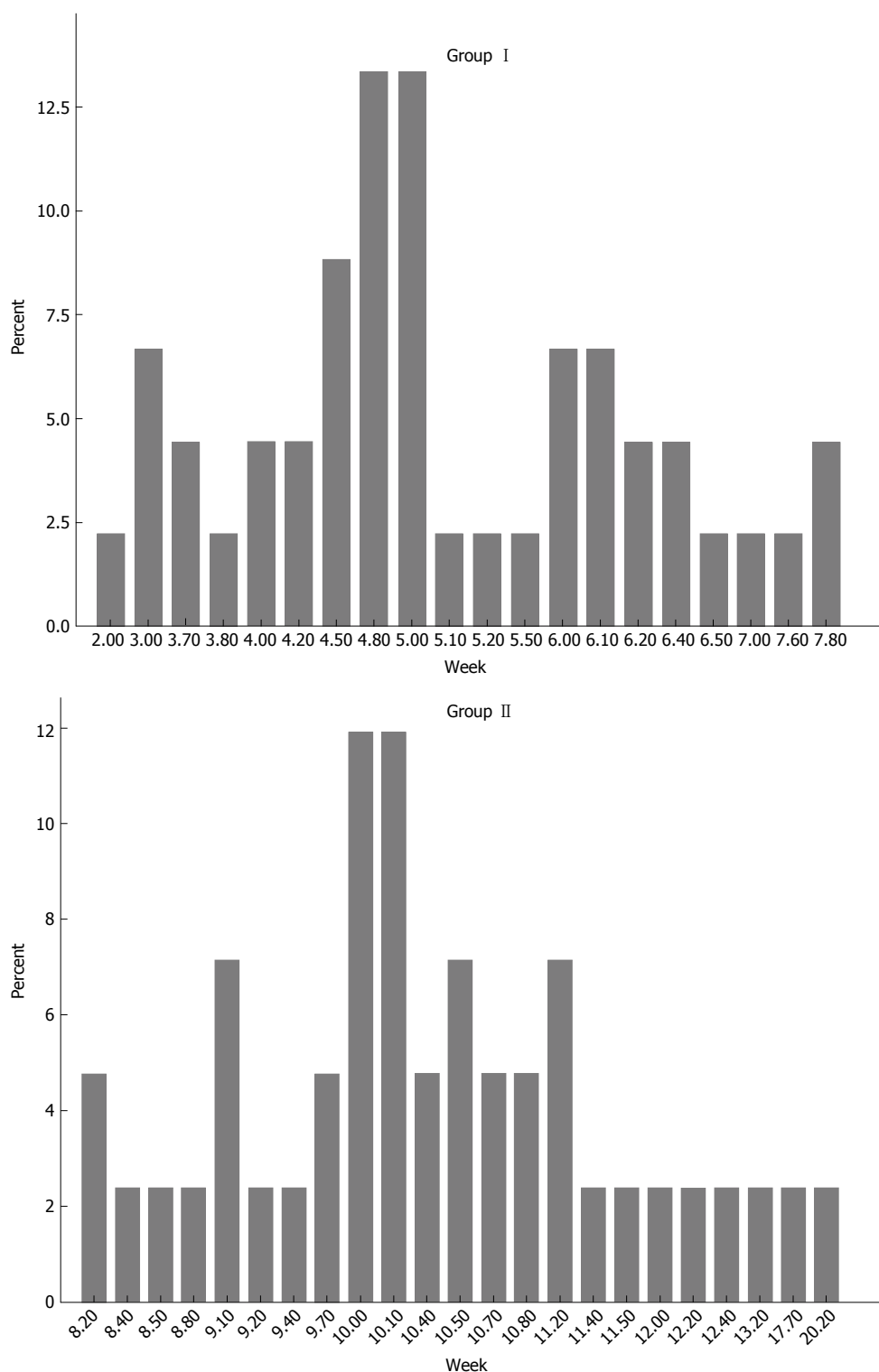
Figure 1 Distributions of groups with regard to interval time between neoadjuvant therapy and surgery. Median interval periods ± SD were 5 ± 1.28 (2-7.8) wk in group Ⅰ and 10.1 ± 2.2 (8.2-20.2) wk in group Ⅱ ($P < 0.001$).

the postoperative period, complications occurred in 13 patients (28.9%) in group Ⅰ and 11 patients (26.1%) in group Ⅱ. Complications that occurred in group Ⅰ were anastomotic leakage in five patients (11.2%) and wound infection in eight (17.8%). Surgical complications in both groups were comparable ($P = 0.42$).

Anastomotic complications were classified based

on the severity grading of anastomotic complications of the International Study Group of Rectal Cancer. In group Ⅰ, three cases with diverting stoma developed perianastomotic abscess in the pelvis. These were classified as Grade B anastomotic complications, and managed successfully with percutaneous abscess drainage and antibiotics. Two cases that were not

Table 1 Demographic and clinical characteristics of patients			
	Group Ⅰ (*n* = 45)	Group Ⅱ (*n* = 42)	*P* value
Age (mean ± SD)	53.7 ± 13.4	58 ± 13.2	0.82
Sex (male/female)	32/13	31/11	0.62
Localization of tumor from the anal verge (cm) (mean ± SD)	5.6 ± 3	6.1 ± 2.8	0.39
T stage (2-4)	8/28/9	6/32/4	0.56
Stage (Ⅱ/Ⅲ)	4/41	5/37	0.53
Preoperative radiation dose (Gy) (mean)	49.5 ± 1.99	49.5 ± 2	0.78
Follow-up time (mo) (mean ± SD)	37.2 ± 19.6	31.1 ± 20.7	0.51

Table 2 Effect of interval time on the perioperative variables *n* (%)			
	Group Ⅰ (*n* = 45)	Group Ⅱ (*n* = 42)	*P* value
Procedure type			
LAR	28 (62.2)	31 (73.8)	0.06
ULAR	11 (24.4)	7 (16.7)	0.09
APR	6 (13.3)	4 (9.5)	0.50
Diverting ileostomy	42 (93.3)	39 (92.9)	0.90
Operative time (min) (mean ± SD)	134.2 ± 19.9	133.4 ± 23.5	0.62
Intraoperative complications	8 (8.9)	3 (7.1)	0.48
Postoperative complications	13 (28.9)	11 (26.1)	0.42
Early postoperative mortality	1 (2.3)	2 (4.7)	0.37
Hospital stay (d) (mean ± SD)	11 ± 10.5	10 ± 9.3	0.32

APR: Abdominoperineal resection; LAR: Low anterior resection; ULAR: Ultralow anterior resection.

diverted at the time of TME required reoperation for Grade C anastomotic leakages. Mortality occurred in 1 (2.3%) of the patients who had Grade C anastomotic leakage on postoperative day 18.

In group Ⅱ, anastomotic leakage was observed in 8 patients (19%), wound infection in 3 (7.1%) and mortality in 2 (4.7%). Mortality was due to postoperative pulmonary emboli and myocardial infarction. Grade A anastomotic complications appeared in four patients with diverting ileostomy who were treated with antibiotics, without the need for invasive interventions or surgical procedures. Grade B anastomotic complications occurred in three cases, and one of them did not have a diverting stoma. These patients underwent percutaneous abscess drainage and were treated with antibiotics. One patient who was not diverted with a stoma at the time of TME developed Grade C anastomotic leakage, and surgery was performed in this case. There was no mortality associated with anastomotic leakage in group Ⅱ patients. There were no significant differences between the groups in terms of anastomotic complications or early postoperative mortality (*P* = 0.07 and *P* = 0.37, respectively).

Effect of interval period on stage and pathological response
In both groups, there were no significant differences in terms of postoperative T stage (*P* = 0.17). However, histopathological examination of TME specimens showed different nodal complete response in both groups (46.7%

vs 81%, *P* = 0.001) (Table 3). The pathological tumor down-staging was found to be related to a decreased number of metastatic lymph nodes in the mesorectum. Tumor down-staging rate was 57.4%, as the pCR [Stage 0 (T0N0)] rate was 13.8%. In group Ⅰ, tumor down-staging occurred in 22 patients (48.9%), while no down-staging was obtained in 23 patients (51.1%); of whom 22 patients had Stage 3 disease and the remaining one had Stage 2 disease. The pCR rate in group Ⅰ was 8.9%. In group Ⅱ, 33 patients (78.5%) developed tumor down-staging and nine (21.4%) showed no down-staging. Eight of the patients who showed no down-staging had Stage 3 disease and the other one had Stage 2 disease. The pCR rate in group Ⅱ was 19%. A significant decrease in postoperative stage was seen in patients who had a longer interval period. Patients in group Ⅱ had significantly higher rates of pCR than their counterparts in group Ⅰ (19% *vs* 8.9%, *P* = 0.002).

Significant predictors of pathological response such as age, gender, tumor localization, preoperative stage, preoperative T stage, and interval time were investigated by univariate and multivariate analyses. Except for pathological TRG and interval time, no positive correlation was noted between other predictive factors and pathological response. However, while rate of poor response TRG (TRG-4) was found to be 44.4% in group Ⅰ, it was 9.5% in group Ⅱ (*P* < 0.002). Although, an extended interval between CRT and surgery was found to increase rates of complete or near-complete TRG response, this rate was not significant when both groups were compared (Table 4).

A total of 60 patients who were diagnosed with Stage 2 or 3 disease after histopathological examination of TME specimens, including 30 patients in each group, were recommended for postoperative adjuvant therapy. However, 57 patients eventually received adjuvant therapy after surgery due to early postoperative mortality in three patients.

Factors predicting local recurrence, DFS and OS
The median follow-up period for all patients was 34.5 (9.9-81) mo. Median follow-up time for group Ⅰ was 37.5 (9.9-74.5) mo and group Ⅱ was 31.2 (10.7-81) mo. Median follow-up was comparable in both groups (*P* = 0.59).

Analysis of OS in group Ⅰ showed median survival duration of 62.8 (95%CI: 55.8-69.7) mo, and a 24-mo

Table 3 Comparison of pre- and post-treatment stages in both groups _n_ (%)

	Group Ⅰ (_n_ = 45)		Group Ⅱ (_n_ = 42)		Comparison of groups Ⅰ and Ⅱ
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	_P_ value
T stage					0.17
T0	-	9 (18.9)	-	8 (19)	
T1	-	2 (4.4)	-	2 (4.8)	
T2	8 (17.8)	14 (31.7)	6 (14.3)	14 (33.4)	
T3	28 (62.2)	19 (42.8)	32 (76.2)	16 (38.1)	
T4	9 (20)	1 (2.2)	4 (9.5)	2 (4.8)	
Stage					0.002
Stage 0	-	4 (8.9)	-	8 (19)	
Stage 1	-	11 (24.4)	-	15 (35.7)	
Stage 2	4 (8.9)	8 (17.8)	2 (11.9)	11 (26.2)	
Stage 3	41 (91.1)	22 (48.9)	37 (88.1)	8 (19)	
Postop LN without metastasis	21 (46.7)		34 (81)		0.001

Table 4 Analysis of the effect of factors on pathological tumor regression grade

TRG	Relationship between demographics and TRG (p) and OR with 95%CI					Distribution and comparison of TRG rates in both groups		
	Age	Sex	Tumor localization	Preop T stage	Preop stage	Group Ⅰ (_n_ = 45) %	Group Ⅱ (_n_ = 42) %	_P_ value
Complete response	(0.46)	(0.84)	(0.17)	(0.24)	(0.48)	(_n_ = 4)	(_n_ = 8)	0.36
	2.19, 95%CI:	0.54, 95%CI:	0.66, 95%CI:	1.00, 95%CI:	1.21, 95%CI:	8.9	19	
	0.55-8.72	0.12-2.29	0.15-2.92	0.90-1.50	0.12-11.8			
Near complete response	(0.91)	(0.79)	(0.38)	(0.75)	(0.80)	(_n_ = 9)	(_n_ = 14)	0.35
	1.02, 95%CI:	1.11, 95%CI:	1.93, 95%CI:	0.50, 95%CI:	0.36, 95%CI:	20	33.3	
	0.37-2.79	0.36-3.38	0.64-5.8	0.12-2.57	0.10-1.51			
Minimal response	(0.79)	(0.59)	(0.12)	(0.66)	(0.38)	(_n_ = 12)	(_n_ = 16)	0.15
	0.67, 95%CI:	1.25, 95%CI:	0.45, 95%CI:	2.25, 95%CI:	2.02, 95%CI:	26.7	38.1	
	0.25-1.76	0.43-3.63	0.16-1.20	0.36-13.8	0.37-10.9			
Poor response	(0.48)	(0.95)	(0.11)	(0.19)	(0.70)	(_n_ = 20)	(_n_ = 4)	0.002
	0.98, 95%CI:	0.94, 95%CI:	1.65, 95%CI:	3.22, 95%CI:	1.34, 95%CI:	44.4	9.5	
	0.35-2.76	0.31-2.82	0.56-4.84	0.92-11.2	0.23-7.62			

$P < 0.05$ is statistical significance. OR: Odds ratio; TRG: Tumor regression grade.

survival rate of 91.5%, and 60-mo survival rate of 79.1%. For group Ⅱ, the median OS was 77.9 (95%CI: 72-81) mo. Twenty-four-month survival rate was 100%, and 60-mo survival rate was 94.4%. OS showed a significant difference when both groups were compared ($P = 0.02$). The median DFS duration in group Ⅰ was 50.8 (95%CI: 43.4-58.2) mo. DFS rates were 76.4% at 24 mo and 55.3% at 60 mo. For group Ⅱ, median DFS was 71.2 (95%CI: 63.1-79.2) mo. DFS rate was 85.1% at 24 mo and remained unchanged at 85.1% until 60 mo in group Ⅱ. DFS rates differed significantly when both groups were compared ($P = 0.01$) (Figure 2).

When potential factors affecting OS and DFS were analyzed, nodal down-staging was found to have a positive correlation with OS and DFS (Table 5). OS and DFS were better in patients who achieved nodal down-staging (OS: 78% _vs_ 52.1%, $P = 0.001$; DFS: 72.3% _vs_ 43.1%, $P = 0.001$) (Figure 3).

After investigating the correlation between survival rates and pathological TRG, lower and moderate pathological regression grades (TRG 1-3) provided similar survival benefit, but only a poor pathological response (TRG 4) was associated with worse DFS

($P = 0.009$). However, TRG scores did not show any association with OS and local recurrence ($P = 0.06$ and $P = 0.39$, respectively) (Figure 4).

Local recurrence was found to be 8.9% after a mean duration of 71.1 ± 2.3 mo in group Ⅰ. Group Ⅱ had a local recurrence rate of 7.1% after a mean duration of 72.4 ± 4.6 mo. The interval time did not show any association with local recurrence ($P = 0.79$) (Figure 5).

DISCUSSION

Since the initial description of the TME technique for rectal cancer by Heald, TME has become the standard surgical treatment for mid- and distal rectal cancer[10-12]. Previous prospective studies have shown that surgery alone is not sufficient for local disease control, but its combination with preoperative CRT reduces local recurrence and increases DFS[3,13-19]. The Lyon R90-01 Trial was the first randomized prospective study to compare the effects of short and long intervals after neoadjuvant therapy on pathological tumor down-staging, and found that a 6-8-wk treatment interval between radiotherapy and surgery improved tumor

Table 5 Effect of factors on overall survival and disease-free survival

	OS		DFS	
	P value	HR with 95%CI	*P* value	HR with 95%CI
Sex	0.61	0.97, 95%CI: 0.19-4.99	0.69	0.50, 95%CI: 0.46-4.46
Age	0.57	1.01, 95%CI: 0.95-1.08	0.60	1.00, 95%CI: 0.94-1.06
Tumor localization	0.53	0.97, 95%CI: 0.72-1.30	0.88	1.17, 95%CI: 0.80-1.70
Pre-treatment stage	0.94	0.77, 95%CI: 0.80-7.50	0.45	0.90, 95%CI: 0.80-1.50
Pre-treatment T stage	0.59	1.08, 95%CI: 0.21-5.48	0.39	0.39, 95%CI: 0.15-3.02
Post-treatment stage	0.01	18.07, 95%CI: 0.60-53.9	0.007	0.82, 95%CI: 0.10-6.23
Post-treatment T stage	0.13	0.62, 95%CI: 0.34-11.3	0.07	0.25, 95%CI: 0.19-8.54
Postoperative metastatic lymph node (+)	0.001	0.91, 95%CI: 0.69-1.20	0.001	1.25, 95%CI: 0.93-1.67
Pathologic TRG	0.11	0.90, 95%CI: 1.28-6.35	0.04	1.19, 95%CI: 0.17-8.41

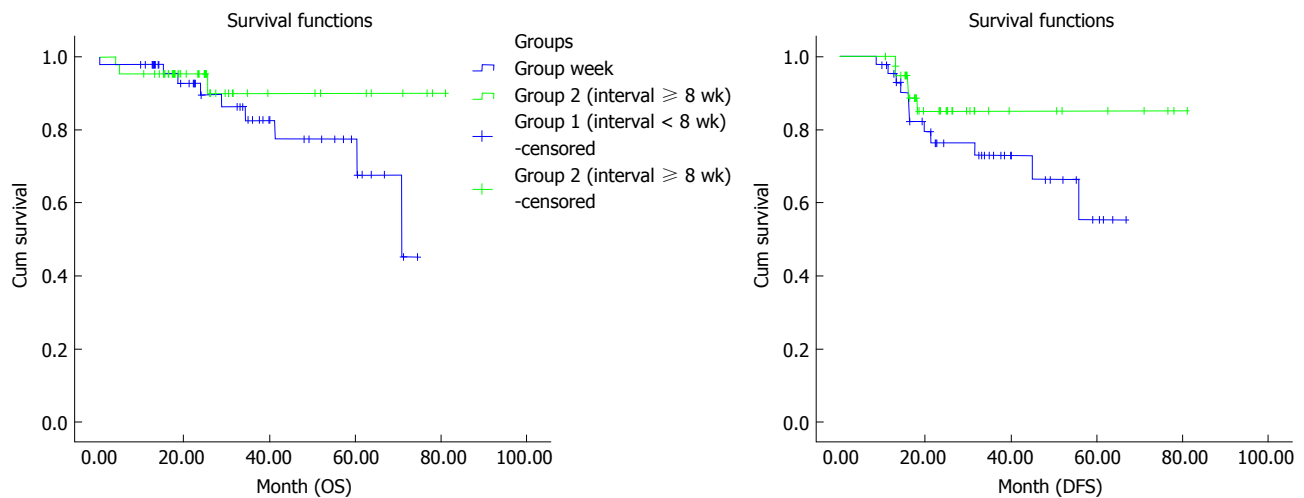DFS: Disease-free survival; OS: Overall survival; TRG: Tumor regression grade.

Figure 2 Comparison of overall survival and disease-free survival between the groups by Kaplan–Meier curves. The median DFS duration in group Ⅱ was better than in group Ⅰ (*P* = 0.01). DFS: Disease-free survival; OS: Overall survival.
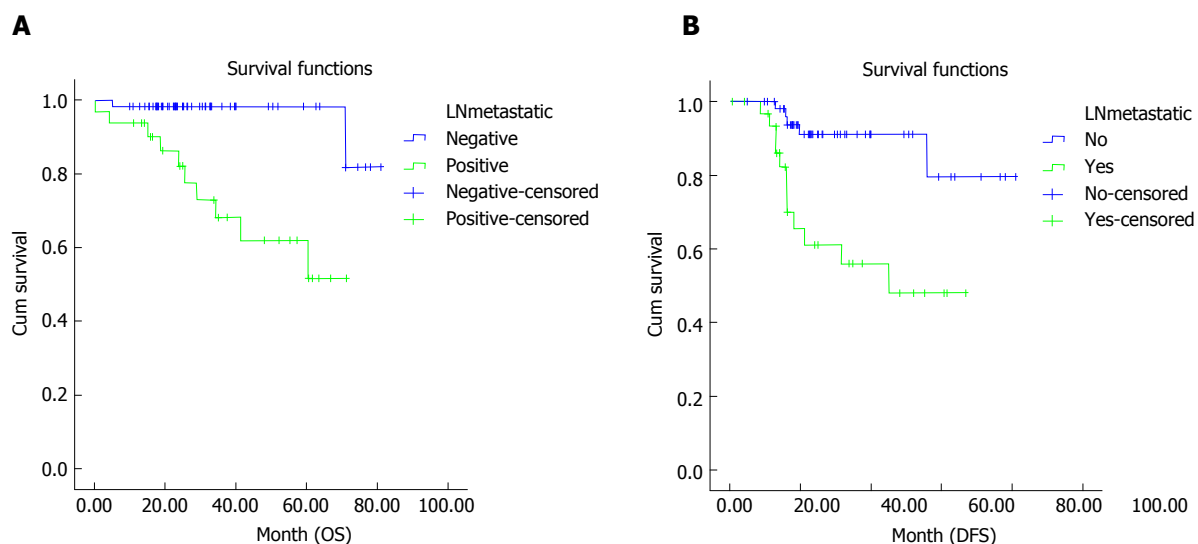

Figure 3 Effect of presence of tumor in lymph nodes and its correlation with overall survival (A) and disease-free survival (B). Survival rates were better in patients who achieved nodal down-staging (*P* = 0.001). OS: Overall survival; DFS: Disease-free survival.

down-staging and pCR. Since then, a 6-8-wk interval has been accepted as an appropriate interval between preoperative neoadjuvant therapy and surgery[6].

In contrast, there have been rising concerns among surgeons regarding radiation-induced pelvic fibrosis that may occur as a result of a longer waiting period.

Table 6 Studies comparing the effects of the interval periods between neoadjuvant therapy and surgery on oncological outcome in locally advanced rectal cancer

Ref.	Total no. of patients	Design	Interval time (wk)	pCR	Local recurrence	OS
Francois *et al*[6]	201	Prospective, randomized	2/6-8	7%/14%[2]	13%/10%[2]	69%/66%[2]
Wolthuis *et al*[20]	356	Retrospective	≤ 7/> 7	16%/28%[2]	6%/3%[2]	NA
Kalady *et al*[21]	306	Prospective	< 8/≥ 8	16.3%/28%[2]	NA	NA
Garcia-Aguilar *et al*[22]	136	Prospective, nonrandomized	6/11	18%/25%[2]	NA	NA
de Campos-Lobato *et al*[23]	177	Retrospective	< 8/≥ 8	16.5%/30.8%[2]	1.2%/10.5%[2]	NA
Tulchinsky *et al*[24]	132	Retrospective	≤ 7/> 7	17%/35%[2]	6%/4%[1]	81%/93%[2]
Sloothaak *et al*[25]	1593	Prospective	< 13/13-14/15-16	10%/13%/18%[1]	NA	NA
Saglam *et al*[31]	153	Prospective, randomized	4/8	19.7%/14.3%[2]	11.8%/10.3%[2]	76.5%/74.2%[2]
Rödel *et al*[36]	385	Prospective	> 6	10.4%	3%	85%
Kerr *et al*[42]	189	Retrospective	Median 76 d (6-215 d)	15.9%	21%	NA

[1]Significant difference statistically; [2]Not significant difference statistically. pCR: Pathological complete response; NA: Not available; OS: Overall survival.
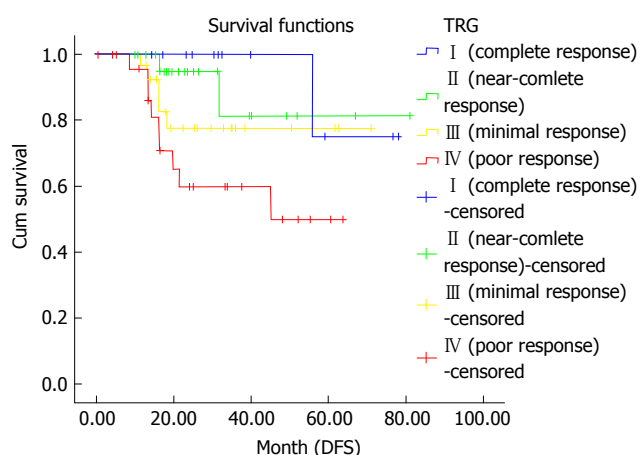

Figure 4 Correlation between level of the pathological tumor responses and disease-free survival. Only a poor pathologic response (TRG 4) was associated with worse DFS (*P* = 0.009). TRG: Tumor regression grade; DFS: Disease-free survival.

Figure 5 Local recurrences were similar in both interval groups. The interval duration did not show any association with local recurrence (*P* = 0.79).

This is because fibrosis may cause operative difficulty and lead to an increased rate of surgical complications. Therefore, the issue of surgical timing has encouraged further studies to investigate the optimal interval time for surgical treatment in terms of oncological outcomes.

Several studies that have examined the effect of different intervals after neoadjuvant CRT on tumor response, pCR, local tumor control and survival have reported conflicting results (Table 6). Our study showed a higher rate of pCR among patients who had an interval > 8 wk. pCR was associated with a decreased number of metastatic lymph nodes in the mesorectum, which led to tumor down-staging. The only factor providing nodal down-staging was found to be interval period. In contrast, a shorter or longer interval time did not show any effect on T stage of the rectal wall. Specifically, a longer interval time was associated with a significant reduction in TRG 4 (poor response) rates. High TRG 4 rate (44%) in the shorter interval group in our study may be explained by performing surgery at 5 wk after neoadjuvant CRT in most patients.
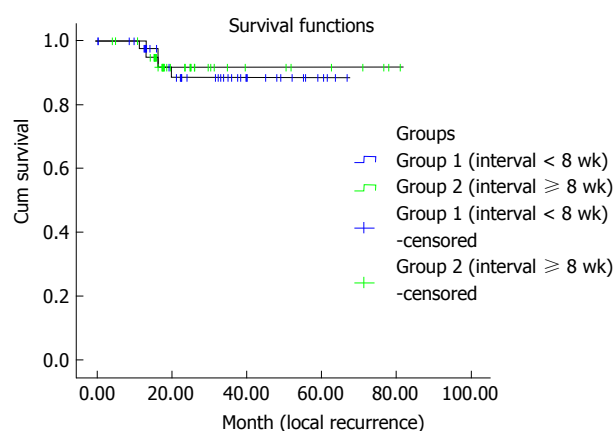
It is questionable whether the poor tumor response

also reduces DFS, while pCR is assumed as an indicator of improved DFS. Our findings established a negative correlation between TRG 4 (poor response) and DFS; an outcome that has not been mentioned in previous studies. Its clinical significance represents poor prognosis in terms of disease recurrence. Thus, the possibility of early recurrence of the disease should be considered in follow-up of patients who had TRG 4.

In a retrospective study by Wolthuis *et al*[20], patients who underwent surgery after a treatment interval > 7 wk showed better pathological tumor response. However, pathological response in this study was evaluated based on the final pathological T staging of the rectal wall. In the Lyon R90-01 Trial by Francois *et al*[6], despite the exclusion of preoperative chemotherapy, a longer interval time was again associated with better clinical tumor response. In another study, Kalady *et al*[21] reported a pCR of 31.8% among patients who waited for > 8 wk before surgery and 16% in patients who had an interval < 8 wk. The authors further documented that an extended interval between completion of neoadjuvant therapy and surgery was the single most important determinant of better tumor response regarding final T stage in rectal wall as well as lymph nodes. Garcia-

Aguilar *et al*[22] in their prospective multicenter study investigated the effect of an extended interval between CRT and surgery on tumor response, CRT-related toxicity, and surgical complications. The authors also examined the impact of intense chemotherapy that was given during this interval period on pCR rates. They found that intense CRT in addition to increasing the time interval between neoadjuvant therapy and surgery may increase the pCR rate without significantly increasing CRT-related complications, operative difficulty or postoperative complications. Similarly, de Campos-Lobato *et al*[23] found an interval > 8 wk to be associated with a higher rate of pCR. In a recent study of predictive factors affecting pCR by Tulchinsky *et al*[24], neoadjuvant-surgery interval time was an independent predictive factor of tumor down-staging. In the largest and one of the most recent studies by the Dutch Surgical Colorectal Audit, a longer CRT–surgery interval of approximately 11 wk was related to the highest chance of pCR[25]. Also, meta-analyses of several studies confirmed that an interval > 8 wk before surgery resulted in more tumor regression[26,27].

In contrast, there have been studies reporting no correlation between duration of treatment interval and pCR. Findings from these studies have associated pCR with the longer period needed for a CRT response[5,19,28-32]. In a study by Pucciarelli *et al*[33], tumor response was associated with preoperative chemotherapy regimen. A surgical interval > 6 wk was identified as a favorable prognostic factor for OS, although no differences were observed in pCR or DFS.

Our rates of tumor responses were lower than in the other studies. This was because of failure of tumor down-staging in half of the patients in group Ⅰ. However, the longer interval group still had a better pCR than the shorter interval group had in the present study, and pCR rate was 19%, which was comparable with other studies. In the present study, tumor down-staging was related to a decrease in metastatic lymph nodes in the mesorectum, and a longer interval was needed for nodal down-staging.

A pCR is deemed to increase the chances of sphincter-saving surgery, decreases local recurrence, and has a positive prognostic impact on survival. Our study showed a positive correlation between pathological tumor response and OS and DFS. Patients who had an extended interval time had higher OS and DFS rates. These findings are in agreement with the study of Yeo *et al*[34]. In their multicenter retrospective study, which examined mesorectal nodal status in patients with T0 stage in the rectal wall after neoadjuvant therapy, nodal status was the most efficient independent prognostic factor for DFS and OS. Similarly, Abdul-Jalil *et al*[35] reported that pCR and nodal status after neoadjuvant therapy were important predictive factors for survival. Pucciarelli *et al*[33] showed that preoperative T staging was the only independent prognostic factor of DFS and OS; however, they reported that pathological tumor response did not affect survival. In the study by Francois *et al*[6] an extended interval time did not have any effect

on local recurrence and short-term survival. Also, in our study, rate of poor response TRG (TRG 4) was found to have negative effect on DFS, and was significantly lower in patients who had an extended interval before surgery. This shows the contribution of the prolonged interval to longer DFS. However, these factors were not associated with local recurrence. Similarly, Rödel *et al*[36] found that poor TRG was associated with worse DFS rate (63%), but not with local recurrence. In contrast, they found an association between TRG and presence of residual tumors in lymph nodes, but not between TRG and interval before surgery[36]. In another study by Abdul-Jalil *et al*[35], TRG had no prognostic effect on survival.

Although it is suggested that neoadjuvant CRT increases the chances of sphincter-saving surgery, the benefit of extending the interval time from neoadjuvant therapy to surgery in reducing rates of abdominoperineal resection is controversial. Most studies investigating sphincter preservation rates by neoadjuvant therapy-surgery interval have reported no correlation between them[5,6,22,24-26,29-31,37,38]. Our sphincter-saving surgery rates were similar in both groups, indicating no influence of neoadjuvant therapy-surgery interval. Also, its rate of 64% was comparable with the results of the other studies[2,24,39].

One of the major concerns regarding extending the interval after neoadjuvant CRT is radiotherapy-induced fibrosis, which can lead to operative difficulty and an increased risk of intraoperative and postoperative morbidity. Current data on the effect of interval time and perioperative morbidity have varied. Buie *et al*[40] in their retrospective study of 246 patients, who underwent TME after neoadjuvant CRT, noted a significant increase in the rate of pelvic sepsis. In contrast, Martel *et al*[41] reported factors such as smoking, difficult anastomosis, and anastomosis located in the first 4 cm from the anal verge as significant predictors of pelvic sepsis, and not neoadjuvant CRT. In a recent prospective randomized study by Saglam *et al*[31], although overall surgical complication rate was higher in the short interval group, similar individual postoperative complications in both groups were observed. Similar findings were reported by Kerr *et al*[42] in another retrospective study that included 189 patients. Postoperative complication rates in that study were higher in patients operated on after < 8 wk delay, while the interval was not related to mortality. In contrast, several studies have shown no significant increase in postoperative complications by delaying surgery after neoadjuvant CRT[6,20,22-24,30,32,43-45]. The findings of the present study have also shown similar postoperative complication rates in both short and long neoadjuvant therapy-surgery interval. Besides, we report a surgical complication rate of 26%-28%, which is considerably lower than the 40%-43% that previously reported[24,39]. Our short-interval group had an anastomotic leakage rate of 11.1% compared with 19% in the long-interval group. The overall anastomotic complication rate in the present study was 14%, and did not differ significantly between the short- and

long-interval groups (11.1% and 19%, respectively). These findings were comparable with the results of other studies reporting an anastomotic leakage rate of 10%-20%[4,6,24,40,46]. Our early postoperative morbidity rates also showed no significant difference between the groups.

The current study had several limitations. First, the retrospective nature of the study did not allow a comprehensive appraisal of the reported findings, and may account for the significant effect of the interval time on poor response TRG (TRG 4) and its effect on DFS. The other limitation was that the study did not allow a full analysis of long-term oncological results in all patients, because of the patients who did not complete the 5-year follow-up period.

The findings of the present study suggest that delaying the neoadjuvant CRT-surgery interval provides nodal down-staging and improves pCR rates, as well as decreasing the rate of TRG poor response. TRG may be an important predictive factor for DFS. Extending the interval between CRT and surgery may improve survival through tumor down-staging without increasing the rate of surgical complications. Studies investigating the optimal time between neoadjuvant CRT and surgery and its effect on pre- and postoperative outcomes should be encouraged for better oncological outcomes and lowest morbidity.

COMMENTS

Background

Today, locally advanced distal and mid-rectal tumors are commonly managed with preoperative combined chemoradiotherapy (CRT) followed by a waiting time before total mesorectal excision (TME). Previous studies have shown that a 6-8-wk interval between CRT and surgery improves tumor down-staging and provides a higher pathological response rate. However, the optimum interval is still lacking in the medical literature. In addition, even though the effect of an extended interval on pathological complete response (pCR) is known, the impact of pCR on disease-free survival (DFS) and overall survival (OS) has not been clearly described. Thus, interval before surgery is important in terms of tumor response and survival. The aim of this study was to determine whether the interval time between preoperative neoadjuvant CRT and surgery affects the rates of pCR, perioperative surgical complications, sphincter-saving surgery, DFS and OS in locally advanced mid- or distal rectal cancer.

Research frontiers

Although the concept of interval between CRT and surgery in the management of locally advanced rectal cancer is generally accepted, a clear and explicit waiting period before surgery is not defined. However, previous studies have shown that an extended interval time between CRT and surgery improve survival and tumor response rates without increasing surgical complications. Based on the current results, there is a trend towards extension of the interval to > 8 wk before surgery for locally advanced rectal cancer.

Innovations and breakthroughs

In this study, longer interval time was related to nodal down-staging and better pathological tumor response. pCR rate was 19% in the longer-interval group, comparable with other studies. Also, patients who had an extended interval had higher OS and DFS rates. However, in this study, poor response tumor regression grade (TRG) 4 had a negative effect on DFS and was significantly lower in patients who had an extended interval before surgery. This finding emphasizes the importance of the negative effect of poor TRG on DFS.

Applications

The present study suggests that an interval > 8 wk between CRT and surgery provides tumor down-staging and higher tumor response rates, and improves survival. Poor TRG is associated with shorter interval before surgery and related to worse DFS. If a patient has TRG 4 in his/her histopathological examination of the resected specimen, the possibility of early recurrence should be considered in follow-up of the patient.

Terminology

TME is a gold standard surgical technique for treatment of rectal cancer, first described by Bill Heald in 1982. A significant length of the bowel around the tumor together with mesorectum involving metastatic lymph nodes is removed *en bloc*. Neoadjuvant CRT is the administration of chemotherapeutic agents before surgery for locally advanced rectal cancer. The goals of neoadjuvant CRT are to reduce tumor size before radical surgical intervention, and provide local control of the disease. DFS is the length of disease-free time until the first relapse of the disease after curative treatment. OS is the length of time that patient is still alive, from the date of diagnosis or the start of treatment. TRG is a scoring system evaluating the response of the primary tumor of the rectal wall to CRT in resected specimens.

Peer-review

The authors have concluded that studies investigating the optimal time between neoadjuvant CRT and surgery and its effect on pre and postoperative outcomes should be encouraged for better oncological outcomes and lowest morbidity.

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