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RESEARCH

Optimal waiting period to surgical treatment after neoadjuvant chemoradiotherapy for locally advanced rectum cancer: a retrospective observational study

Khayal Aslanov[1] · Ali Emre Atici[1] · Damlanur Karaman[2] · Emine Bozkurtlar[2] · Şevket Cumhur Yegen[1]

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Abstract

Background The optimal waiting period after neoadjuvant treatment in patients with locally advanced rectal cancers is still controversial. The literature has different results regarding the effect of waiting periods on clinical and oncological outcomes. We aimed to investigate the effects of these different waiting periods on clinical, pathological, and oncological outcomes.

Methods Between January 2014 and December 2018, a total of 139 consecutive patients with locally advanced rectal adenocarcinoma, who were treated in the Department of General Surgery at the Marmara University Pendik Training and Research Hospital, were enrolled in the study. The patients were split into three groups according to waiting time for surgery after neoadjuvant treatment: group 1 ($n = 51$) included patients that have 7 weeks and less (≤ 7 weeks) time interval, group 2 ($n = 45$) 8 to 10 weeks (8–10 weeks), group 3 ($n = 43$) 11 weeks and above (11 weeks $\leq$). Their database records, which were entered prospectively, were analyzed retrospectively.

Results There were 83 (59.7%) males and 56 (40.3%) females. The median age was 60 years, and there was no statistical difference between the groups regarding age, gender, BMI, ASA score, ECOG performance score, tumor location, and preoperative CEA values. Also, we found no significant differences regarding operation times, intraoperative bleeding, length of hospital stay, and postoperative complications. According to the Clavien–Dindo (CD) classification, severe early postoperative complications (CD 3 and above) were observed in 9 patients. The complete pathological response (pCR, ypT0N0) was observed in 21 (15.1%) patients. The groups had no significant difference regarding 3-year disease-free and 3-year overall survival ($p = 0.3$, $p = 0.8$, respectively). Local recurrence was observed in 12 of 139 (8.6%) patients and distant metastases occurred in 30 of 139 (21.5%) patients during the follow-up period. There was no significant difference between the groups in terms of both local recurrence and distant metastasis ($p = 0.98$, $p = 0.43$, respectively).

Conclusion The optimal time for postoperative complications and sphincter-preserving surgery in patients with locally advanced rectal cancer is 8–10 weeks. The different waiting periods do not affect disease-free and overall survival. While long-term waiting time does not make a difference in pathological complete response rates, it negatively affects the TME quality rate.

Keywords Locally advanced rectal cancer · Neoadjuvant chemoradiotherapy · Waiting period · Interval

✉ Ali Emre Atici
ali.emre@marmara.edu.tr

Khayal Aslanov
md.xeyalaslanov@gmail.com

Damlanur Karaman
celiktasdamlanur@gmail.com

Şevket Cumhur Yegen
cumhuryegen@gmail.com

[1] Department of General Surgery, Pendik Education and Research Hospital, Faculty of Medicine, Marmara University, 34899, Pendik, Istanbul, Turkey

[2] Department of Pathology, Pendik Education and Research Hospital, Faculty of Medicine, Marmara University, 34899, Pendik, Istanbul, Turkey

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Introduction

Colorectal cancer is the third most common cancer and one of the most reasons for cancer-related death in the world [1]. The only curative treatment of rectal cancer is complete resection of the primary tumor with the lymphatic network [2]. Several large prospective trials have shown the benefits of chemotherapy, radiation, and surgery for locally advanced rectal cancer [3]. The purpose of preoperative chemotherapy and radiation in locally advanced rectal cancer is to obtain pathological downstaging, provide R0 resection, increase local control, and improve prognosis [4]. Since the Lyon R90-01 randomized trial in 1999, 6–8 weeks has been considered the most appropriate time for surgical treatment after neoadjuvant chemoradiotherapy [5]. Also, European Society of Medical Oncology (ESMO) guidelines have recommended an interval of 6–8 weeks, and National Comprehensive Cancer Network (NCCN) guidelines have recommended 5–12 weeks for better outcomes and improved survival [6]. However, there are still debates about the time to perform surgical therapy after neoadjuvant chemoradiotherapy. While some studies reported that long waiting time has improved oncologic outcomes, local control, disease-free survival, overall survival, and even complete response [7, 8], others reported that it does not affect postoperative results and prognosis [5, 9]. However, in the previous studies, the time interval was divided into two groups a short-interval group and a long-interval group (≤ 6 weeks or 8 weeks ≤). When the patients are divided into two groups like this, those cause more heterogeneous periods because of delays in surgery dates for various reasons, even in the same group. Therefore, it is difficult to decide which time interval is the most appropriate for the waiting period according to prior studies in patients with locally advanced rectal cancer. Even though it is reasonable to think that tumor regression grade may increase from time to time, however, a prospective trial reported that a longer interval time to 11 weeks after neoadjuvant therapy did not raise complete tumor response, whereas this led to higher intraoperative and postoperative morbidity, and also, the patients who have an 11-week waiting period had a worse quality of total mesorectal excision than the 7-week group [5, 10]. Therefore, we thought that if the waiting periods of patients are split into more frequent intervals, a more precise time frame for surgery can be determined in terms of both postoperative short-time outcomes and long-term survival. Unlike studies in the literature, we separated the patients into three groups according to different waiting times before surgery. We aimed to evaluate the effect of waiting time until surgical treatment on clinical, pathological, and oncological outcomes in patients with locally advanced rectal cancer who received long-term neoadjuvant chemoradiotherapy treatment and also to obtain the most optimal waiting period for surgery.

Materials and methods

Patient enrollment

This retrospective single-center trial compares three waiting periods after neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer. Between January 2014 and December 2018, 306 consecutive patients with primary rectal adenocarcinoma were treated in the Department of General Surgery at the Marmara University Pendik Training and Research Hospital. After excluding patients who did not meet the study criteria, 139 patients with rectal adenocarcinoma who underwent neoadjuvant therapy followed by radical resection with total mesorectal excision (TME) were enrolled in the study, and their database records were prospectively entered and retrospectively analyzed. The study protocol was approved by Marmara University, Health Sciences Institute, Ethics Committee, and was conducted in accordance with the principles of the Declaration of Helsinki. The inclusion criteria of the study are to be over 18 years old, to be located at the middle or distal rectum, to have locally advanced disease (T3/T4 N0 or any T and N+) according to the American Joint Committee on Cancer (AJCC 8th edition) evaluated by preoperative imaging modalities [11], to receive neoadjuvant chemoradiotherapy followed by radical resection accordingly, the TME, to have no previous or concurrent malignancy, and to have no evidence of distant metastasis on the pretreatment workup. The patients whose histopathological diagnosis is not adenocarcinoma, who have not undergone neoadjuvant chemoradiotherapy or who cannot complete their treatment, who have not been performed by following the TME rule, who have a synchronous tumor in colonoscopy, and who have previously been treated for other organ cancers have been excluded from the study.

The patients were split into three groups according to waiting time for surgery after neoadjuvant treatment: group 1 ($n = 51$) included patients that have 7 weeks and less (≤ 7 weeks) time interval; group 2 ($n = 45$) 8 to 10 weeks (8–10 weeks); group 3 ($n = 43$) 11 weeks and above (11 weeks ≤) (Fig. 1). The patient records including age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, operation and surgical characteristics, early postoperative outcomes, pathological results, the effect of waiting time on surgical quality, disease-free survival (DFS), and overall survival were reviewed retrospectively. To evaluate early postoperative complications, the Clavien–Dindo scoring system was used. In this scoring system, the complications are classified as follows: any

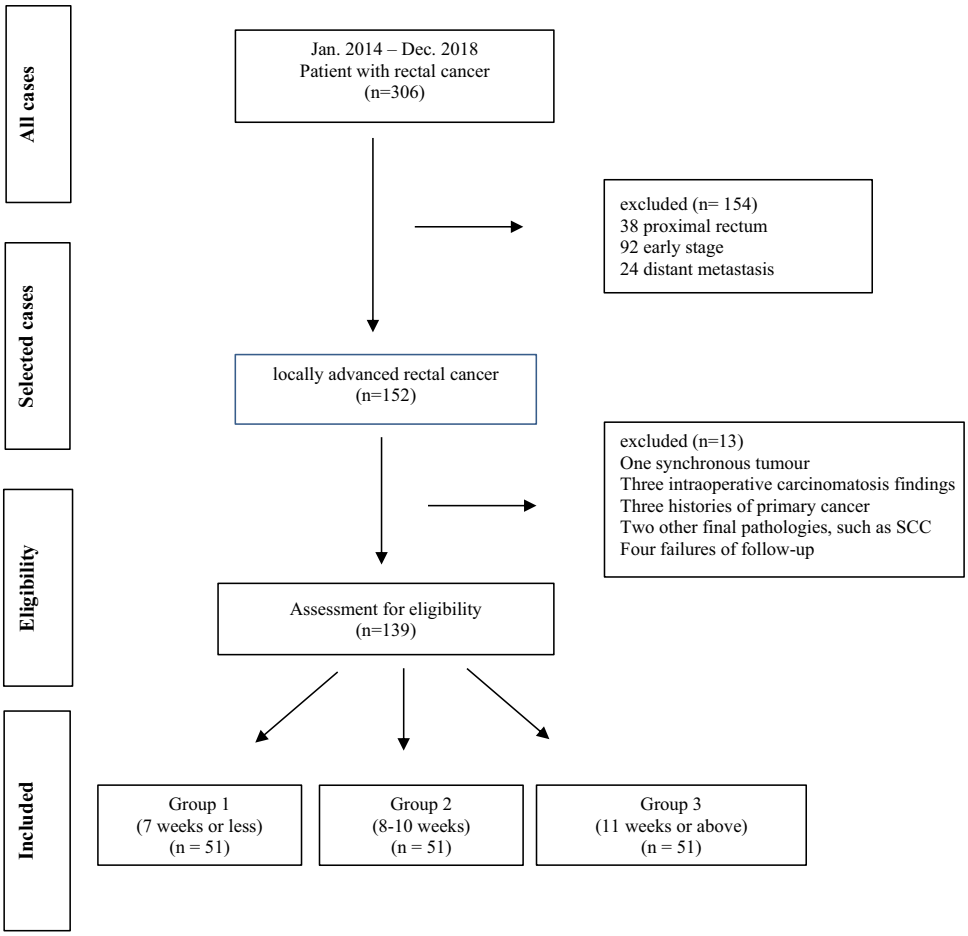

Fig. 1 The study flowchart

deviation from the normal postoperative course without the need for pharmacological treatment, or surgical, endoscopic, and radiological interventions, grade I; requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included, grade II; requiring surgical, endoscopic, or radiological intervention not under general anesthesia, grade IIIa; intervention under general anesthesia, grade IIIb; life-threatening complication (including central nervous system complications) requiring IC/ICU (intensive care unit) management, single organ dysfunction (including dialysis), grade IVa; multiorgan dysfunction, grade IVb; death of a patient, grade V [12].

Neoadjuvant chemoradiotherapy

All patients received long-term chemoradiotherapy treatment. The radiotherapy regimen was completed in 25–28 days as daily fractionated doses (1.8–2.0 Gy) with a total radiation dose of 45–50.4 Gy. In addition, all patients concurrently received capecitabine treatment (825 mg/m^2 twice a day, orally).

Pathological assessment

A single pathologist specializing in the digestive system re-examined the excised specimens of the patients. Tumor histology, lymph node involvement, and perineural and lymphovascular invasion were reported according to the College of American Pathologists (CAP) guidelines [13]. Neoadjuvant therapy response was assessed using the modified Ryan tumor regression score: grade 0, complete response (no cancer cells); grade 1, moderate response (single or small group of cancer cells); grade 2, inadequate response (cancer cells present with fibrosis); grade 3, no response (cancer cells are widely present) [14]. At least a 1-cm distance from the tumor in the intestinal wall was accepted as a clean distal surgical margin. A distance of at least 1 mm or more from the tumor was accepted as a clean circumferential (radial) surgical margin. The mesorectum excision quality (mesorectum integrity) was classified to the M.E.R.C.U.R.Y. classification: complete, partial, and insufficient [15, 16].

Follow-up

The postoperative standardized follow-up protocol involving physical examination that included a digital rectal examination, complete blood count, liver function test, serum carcinoembryonic antigen test (CEA), and chest radiography was performed every 3 months in the postoperative first 2 years and every 6 months after that. The abdominal and pelvic computed tomography was performed every 6 months, and a colonoscopic examination was done during the first year postoperatively, then once every 2 years.

Statistical analysis

Statistical analysis was performed using the SPPS software program version 23.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation and range. Categorical variables are described as frequency and percentage. Chi-squared and Fisher's exact tests were used for categorical variables to compare groups. One-way ANOVA and Kruskal-Wallis were used for continuous variables with regular and without normal distribution, respectively, to compare groups. Student's and Mann–Whitney *U* tests were used for pairwise comparison in continuous variables with normal and without normal distribution, respectively. The Kaplan–Meier survival curve was used to analyze the survival of patients, and a log-rank test was used to compare survival curves. While disease-free survival was defined as the time from the day of operation to the date of first recurrence, overall survival was defined as the time from the day of operation to the day of death or the date of the last follow-up. Statistical significance was defined as $p < 0.05$.

Results

Demographic characteristics

The records of 306 consecutive patients with primary rectal adenocarcinoma were reviewed. After excluding patients who did not meet the study criteria (proximal rectum $n = 38$, early stage $n = 92$, systemic disease $n = 24$, synchronous tumor $n = 1$, intraoperative metastasis $n = 3$, presence of other organ cancer $n = 3$, final pathology squamous cell cancer $n = 2$, insufficient data $n = 4$), a total of 139 patients of rectal adenocarcinoma was enrolled in the study. There were 83 (59.7%) males and 56 (40.3%) females. The median age was 60 years (range 30–90 years) in group 1, 60 years (range 26–80 years) in group 2, and 59 years (range18–77 years) in group 3. There was no statistical difference between the groups regarding age, gender, BMI, ASA score, ECOG performance score, tumor location, and preoperative CEA values ($p > 0.05$). In the preoperative clinical staging, 49 (35.3%) patients had clinical stage II tumors, and 90 (64.7%) patients had clinical stage III tumors. The median interval from completion of neoadjuvant therapy to surgery was 8 weeks (1–57 weeks). There were 51 (36.6%) patients in group 1 (with an interval of 7 weeks and less), 45 (32.3%) patients in group 2 (with an interval of 8–10 weeks), and 43 (30.9%) patients in group 3 (with interval of 11 weeks and above). The demographics were comparable between the three groups, as detailed in Table 1.

Surgical characteristics and early postoperative results

Most of the patients (79.1%) were performed by open surgery. A total of 65 patients underwent low anterior resection, 23 (45.1%) patients in group 1, and 24 (55.3%) patients and 18 (41.9%) patients in group 2 and group 3, respectively. There were no significant differences among groups regarding sphincter-preserving surgery ($p = 0.07$). A total of 58 (41.7%) patients underwent abdominoperineal resection, 26 (51%) patients in group 1, and 14 (31.1%) patients and 18 (41.9%) patients in group 2 and group 3, respectively. Although there were no significant differences among groups, the number of patients who performed abdominoperineal resection was much more in group 1 than in others. Protective stoma was performed in 42 (64.6%) patients who underwent low anterior resection, and there were no significant differences among groups regarding diverting stoma ($p = 0.92$). The early postoperative complications were graded according to the Clavien–Dindo classification (CD). In the operative findings and early postoperative period data, including operation times, intraoperative bleeding, the length of hospital stay, and postoperative complications, there was no statistically significant difference between the groups ($p = 0.3$, $p = 0.1$, $p = 0.6$, $p = 0.09$, respectively). The CD classification observed severe early postoperative complications (CD 3 and above) in 9 patients. Three of these patients have CD 3a, 4 have CD 3b, one has CD 4a, and the other has CD 5. A total of 20 patients (15.1%) were readmitted to the hospital in the early postoperative period due to various problems. Nine of these 21 patients were in group 1: wound infection ($n = 2$), abdominal collections ($n = 2$), ileus ($n = 3$), dehydration ($n = 2$). Seven of the 20 patients were in group 2: pulmonary thromboembolism ($n = 1$), ileus ($n = 2$), anastomotic leakage ($n = 1$), pelvic abscess ($n = 1$), rectovaginal fistula ($n = 1$), hemorrhage from the ostomy edge ($n = 1$); and 4 patients in group 3: wound infections ($n = 3$), ileus ($n = 1$). A total of 3 patients were dead in the early postoperative period. Two of these patients were from group 1, and the causes of death were sepsis and pulmonary thromboembolism, respectively. The other patient who died was from group 2, and the reason for death was cardiac arrest.

Table 1 Demographics and clinical characteristics

	Overall ($n = 139$)	Group 1 (≤ 7 weeks) $n = 51$ (%)	Group 2 (8–10 weeks) $n = 45$ (%)	Group 3 (11 weeks ≤) $n = 43$ (%)	p-value
Sex					0.377
Male	83 (59.7)	33 (64.7)	28 (62.2)	22 (51.2)	
Female	56 (40.3)	18 (35.3)	17 (37.8)	21 (48.8)	
Age (years, mean ± SD)	58.9 ± 12	60 ± 13	59 ± 11	58 ± 12	0.716
Mean BMI (kg/m^2)	27.6 ± 4.7	27.6 ± 4.4	28.3 ± 4.3	26.9 ± 5.3	0.420
ASA grading					0.382
1	21 (15.1)	7 (13.7)	6 (13.3)	8 (18.6)	
2	105 (75.5)	36 (70.6)	38 (84.4)	31 (72.1)	
3	12 (8.6)	7 (13.7)	1 (2.2)	4 (9.3)	
4	1 (0.7)	1 (2.0)	0	0	
Tumor location					0.241
0–5 cm	71 (51.1)	23 (45.1)	25 (55.6)	23 (16.5)	
6–10 cm	54 (38.8)	25 (49.0)	16 (35.6)	13 (9.4)	
11–15 cm	14 (10.1)	3 (5.9)	4 (8.9)	c	
ECOG grading					0.821
0	105 (75.5)	37 (72.5)	34 (75.6)	34 (79.1)	
1	30 (21.6)	13 (25.5)	10 (22.2)	7 (16.3)	
2	3 (2.2)	1 (2.0)	1 (2.2)	1 (2.3)	
3	1 (0.7)	0	0	1 (2.3)	
Clinic stage					0.039
II	49 (35.3)	19 (37.3)	21 (46.7)	9 (20.9)	
III	90 (64.7)	32 (62.7)	24 (53.3)	34 (79.1)	
Preoperative CEA	1.51 (.00–63.70)	1.43 (.00–57.0)	2 (.00–63.7)	1.18 (.00–23.6)	0.118
Waiting period (week)	8 (1–57)	7 (1–7)	8 (8–10)	13 (11–57)	< 0.001

BMI body mass index, *ASA* American Society of Anesthesiologists, *CEA* carcinoembryonic antigen, *ECOG* Eastern Cooperative Oncology Group

Surgical characteristics and early postoperative results are shown in detail in Table 2.

Pathologic results

Pathological complete response (pCR, ypT0N0) was observed in 21 (15.1%) patients. Although there was no difference among groups ($p = 0.46$), there was much more pathologic complete response in group 3 than in others. The rate of pCR in group 1 was minimal. When the groups were compared pairwise, any significant differences were not detected between groups regarding pCR. There was no statistical difference between the groups regarding histopathologic tumor grade, median tumor diameters, ypT stage, ypN stage, and lymphovascular and perineural invasion. Pathological results are shown in Table 3.

Surgical quality

The complete total mesorectal excision (TME) was observed in 44 of 139 (31.7%) patients. Moreover, 68 of 139 (48.9%) patients were identified as partial, and 27 of 139 (19.4%) patients were detected with incomplete mesorectal excision. Although there was no difference among groups ($p = 0.064$), when the groups were compared pairwise, there was a significant difference between group 2 and group 3 ($p = 0.013$) regarding total mesorectal excision. TME quality was better than group 3. The circumferential resection margin was positive in 9 patients (6.5%); 2 were in group 1, 3 were in group 2, and 4 were in group 3. The distal surgical margin was positive in only two patients; one was in group 1, and the other was in group 3. The median number of lymph nodes removed was 14 (0–44), and the median positive lymph node was 5 (0–16); there were no significant differences between the groups regarding both extracted total number of lymph nodes and the number of positive lymph nodes. The effect of the waiting period on surgical quality is shown in Table 4.

Oncological outcome

The median follow-up period was 49.5 months (1–90 months). There were no differences among groups regarding

Table 2 Surgical characteristics and early postoperative results

	Overall ($n = 139$)	Group 1 (≤ 7 weeks) $n = 51$ (%)	Group 2 (8–10 weeks) $n = 45$ (%)	Group 3 (11 weeks $\leq$) $n = 43$ (%)	p-value
Surgical procedure					0.071
Low anterior resection	65 (46.7)	23 (45.1)	24 (53.3)	18 (41.9)	
Hartman	16 (11.5)	2 (3.9)	7 (15.6)	7 (16.3)	
Abdominoperineal resection	58 (41.7)	26 (%51)	14 (31.1)	18 (41.9)	
Surgical technic					0.771
Open	110 (79.1%)	42 (82.4)	35 (77.8)	33 (76.7)	
Laparoscopic	29 (20.9%)	9 (17.6)	10 (22.2)	10 (23.3)	
Diverting ostomy (for just low ant. resect. $n = 65$)					0.922
Yes	42 (64.6)	16 (69.6)	16 (66.7)	10 (55.6)	
No	23 (33.3)	7 (30.4)	8 (33.3)	8 (44.4)	
Median operative time (min)	150 (60–360)	150 (80–300)	130 (60–350)	150 (60–360)	0.300
Median intraoperative blood loss (mL)	200 (100–2500)	180 (100–2500)	175 (100–1000)	200 (100–900)	0.146
Median time in hospital after the operation	5 (3–19)	5 (3–19)	4 (3–13)	5 (3–16)	0.675
Postoperation complications					0.099
Yes	50 (36)	24 (47.1)	12 (26.7)	14 (32.6)	
No	89 (64)	27 (52.9)	33 (73.3)	29 (67.4)	
Wound infection	8 (16)	3 (12.5)	2 (16.6)	3 (21.4)	
Urinary retention	6 (12)	5 (20.8)	0	1 (7.1)	
Anastomotic leakage	2 (4)	1 (4.1)	0	1 (7.1)	
Ileus	18 (36)	11 (45.8)	4 (33.5)	4 (28.5)	
Cardiopulmonary	6 (12)	1 (4.1)	3 (25.0)	1 (7.1)	
Abdominal infection	1 (2)	0	1 (8.3)	0	
Blood transfusion	9 (18)	3 (12.5)	2 (16.6)	4 (28.5)	
Clavien–Dindo					0.217
1	94 (67.6)	30 (58.8)	33 (73,3)	31 (72.1)	
2	36 (25.9)	16 (31.4)	9 (20.0)	11 (25.6)	
3a	3 (2.2)	2 (3.9)	1 (2.2)	0	
3b	4 (2.9)	2 (3.9)	1 (2.2)	1 (2.3)	
4a	1 (0.7)	1 (2.0)	0	0	
4b	0	0	0	0	
5	1 (0.7)	0	1 (2.2)	0	
30-day readmission					0.441
Yes	20 (14.3)	9 (17.6)	7 (15.5)	4 (9.3)	
No	119 (85.6)	42 (82.4)	38 (84.4)	39 (90.7)	
30-day mortality					0.427
Yes	3 (2.1)	2 (3.9)	1 (2.2)	0	
No	136 (97.8)	49 (96.1)	44 (97.8)	43 (100)	

follow-up time. The 1-year disease-free survival was 93% ± 3 in group 1, 97% ± 2 in group 2, and 95% ± 3 in group 3. The 3-year disease-free survival was 91% ± 0.4 in group 1, 87% ± 0.5 in group 2, and 80% ± 0.6 in group 3. There was no significant difference between the groups regarding 3-year disease-free survival ($p = 0.35$, $p = 0.3$ respectively) (Fig. 2a). The 1-year overall survival was 95% ± 3 in group 1, 97% ± 2 in group 2, and 97% ± 2 in group 3. The 3-year overall survival was 88% ± 0.4 in group 1, 84% ± 0.5 in group 2, and 78% ± 0.6 in group 3. The groups had no significant difference regarding 1-year and 3-year overall survival ($p = 0.83$, $p = 0.8$ respectively) (Fig. 2b). Local recurrence was observed in 12 of 139 (8.6%) patients during the follow-up period; 4 were in the first group, four were in the second group, and the other four were in the third group. Distant metastases occurred in 30 of 139 (21.5%)

Table 3 Pathologic results

	Overall ($n = 139$)	Group 1 (≤ 7 weeks) $n = 51$ (%)	Group 2 (8–10 weeks) $n = 45$ (%)	Group 3 (11 weeks ≤) $n = 43$ (%)	p-value
Histological grade					0.926
Low	124 (89.2)	45 (88.2)	40 (88.9)	39 (90.7)	
High	15 (10.8)	6 (11.8)	5 (11.1)	4 (9.3)	
Median tumor diameter (cm)	1.6 (0–10.5)	1.7 (0–8)	1.5 (0–10.5)	1.5 (0–6)	0.819
ypT stage					0.880
T0	23 (16.5)	7 (13.7)	7 (15.6)	9 (20.9)	
T1	12 (8.6)	6 (11.8)	3 (6.7)	3 (7)	
T2	40 (28.8)	17 (33.3)	13 (28.9)	10 (23.3)	
T3	63 (45.3)	20 (39.2)	22 (48.9)	21 (48.8)	
T4	1 (0.7)	1 (2.0)	0	0	
yp N stage					0.867
N0	100 (71.9)	36 (70.6)	32 (71.1)	32 (74.4)	
N1	30 (21.6)	10 (19.6)	11 (24.4)	9 (20.9)	
N2	9 (6.5)	5 (9.8)	2 (4.4)	2 (4.7)	
TRG (Ryan)					0.506
Complete	21 (15.1)	5 (9.8)	7 (15.6)	9 (20.9)	
Moderate	38 (27.3)	17 (33.3)	14 (31.1)	7 (16.3)	
Low	56 (40.3)	18 (35.3)	20 (44.4)	18 (41.9)	
No response	24 (17.3)	11 (21.6)	4 (8.9)	9 (20.9)	
Pathologic complete response (ypT0N0)					0.463
pCR	21 (15.1)	5 (%9.8)	7 (15.6)	9 (20.9)	
Perineural invasion					0.804
Yes	25 (18.0)	9 (17.6)	7 (5.0)	9 (20.9)	
No	114 (82.0)	42 (82.4)	38 (27.3)	34 (79.1)	
Lymphovascular invasion					0.584
Yes	47 (33.8)	15 (29.5)	15 (15.6)	17 (39.5)	
No	92 (66.2)	36 (70.5)	30 (84.4)	26 (60.5)	

TRG tumor regression grade, *pCR* complete pathological response

Table 4 The effect of interval on surgical quality

	Overall ($n = 139$)	Group 1 (≤ 7 weeks) $n = 51$ (%)	Group 2 (8–10 weeks) $n = 45$ (%)	Group 3 (11 weeks ≤) $n = 43$ (%)	p-value
CRM					0.571
Positive	9 (6.5)	2 (3.9)	3 (6.7)	4 (9.3)	
Negative	130 (93.5)	49 (96.1)	42 (93.3)	39 (90.7)	
Distal margin					0.609
Positive	2 (1.4)	1 (2.0)	0	1 (2.3)	
Negative	137 (98.6)	50 (98.0)	45 (100)	42 (97.7)	
TME					0.064
Complete	44 (31.7)	15 (29.4)	14 (31.1)	15 (34.9)	
Near complete	68 (48.9)	24 (47.1)	28 (62.2)	16 (37.2)	
Incomplete	27 (19.4)	12 (23.5)	3 (6.7)	12 (27.9)	
Total lymph nodes	14 (0–44)	13 (0–44)	13 (1–28)	13.5 (1–29)	0.457
Positive lymph nodes	5 (0–16)	3 (0–13)	3 (0–16)	3 (0–10)	0.838

CRM circumferential resection margin, *TME* total mesorectal excision

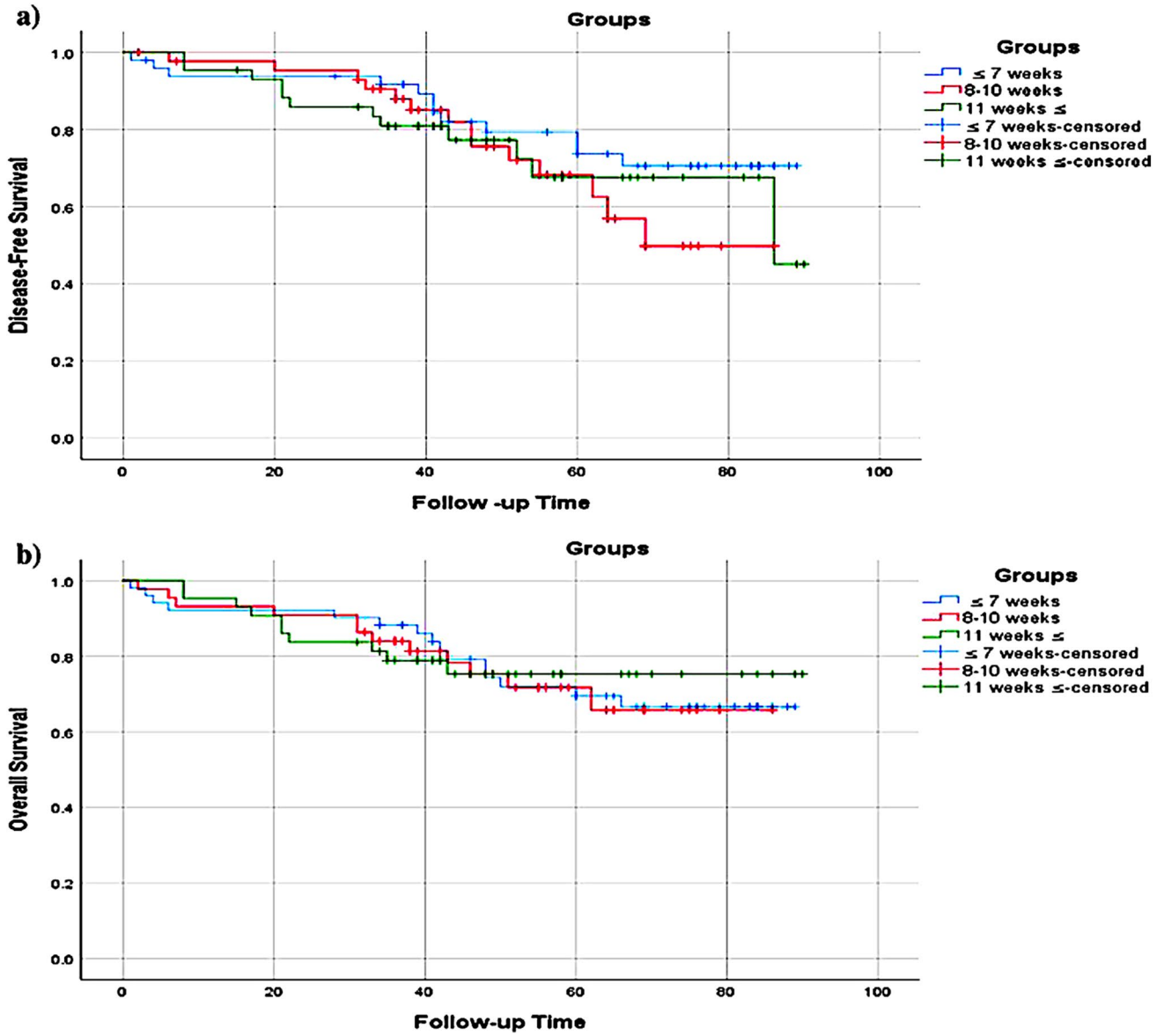

Fig. 2 **a** Comparison of disease-free survival between the groups by Kaplan–Meier curves. **b** Comparison of overall survival between the groups by Kaplan–Meier curves

patients. Eight of them (15.6%) occurred in the first group, 12 of them (26.6%) occurred in the second group, and 10 of them (23.2%) occurred in the third group. There was no significant difference between the groups in terms of both local recurrence and distant metastasis ($p = 0.98$, $p = 0.43$, respectively).

Discussion

In current guidelines, neoadjuvant chemoradiotherapy for patients with locally advanced rectal cancer is accepted as the standard treatment before surgical treatment. The essential advantages of neoadjuvant chemoradiotherapy are regressions in tumor size and stages that cause increased sphincter-sparing surgery and better local disease control. However, the most appropriate waiting time between neoadjuvant chemoradiotherapy and surgery is still controversial since the first randomized controlled trial study, Lyon R90-01, was published in the literature [5]. The studies published after this date were primarily retrospective, and patients were evaluated in two groups according to the waiting period determined by the authors. This type of choice causes heterogeneity among the patients due to the wide range of waiting periods, such as patients with 7 weeks and those with 12 weeks in the

same group. We evaluated our patients in three groups based on their waiting time to determine the most appropriate time interval. The first group had 7 weeks and less waiting period, the second group had an 8–10-week waiting period, and the third group had 11 weeks and above waiting period.

Despite the hypothesis that preoperative radiotherapy impairs intraoperative and postoperative early outcomes due to its chronic inflammation-fibrosis forming effect, most studies had no adverse effect on intraoperative and early postoperative results [5, 7, 17]. In another prospective randomized controlled study, the early postoperative complication rate was statistically significantly higher in the patients with a more extended waiting period. However, when the complications were classified according to the Clavien–Dindo classification, the authors reported no significant difference between the groups [10, 18]. Our early postoperative results aligned with the literature, and we found no significant difference between our three study groups. Nevertheless, when the groups were compared pairwise, we found that the complication rates in group 1 were significantly higher than in group 2. When the complications were analyzed, most included clinical situations that do not require an intervention that affects outcomes, such as postoperative ileus and urinary retention. These complications may be due to radiotherapy treatment which can affect small intestines that enter the treatment area and its possible edematous effect on the genitourinary nerves, respectively. Also, it can be affected by pelvic dissection and aggressive surgery because of abdominoperineal resection rate being higher in group 1 than in other groups. There was no significant difference between the groups regarding the amount of intraoperative bleeding, operation time, postoperative hospital stay, readmission in the first 30 days, and 30-day morbidity-mortality rates ($p > 0.05$).

One of the other significant effects of neoadjuvant chemoradiotherapy is increased rates of sphincter-sparing surgery. The radiotherapy-induced tumor cell death and regression take time [19, 20]. This reality led to the idea that a longer waiting period might increase rates of sphincter-sparing surgery. However, studies did not support this idea, and most authors reported that long waiting times do not increase the rates of sphincter-sparing surgery [5, 10, 20]. There can be different factors regarding tumor regression. Our study showed no statistically significant difference among the three groups regarding sphincter-sparing surgery rates. When the groups were analyzed pairwise comparison, the rate of sphincter-sparing surgery in group 2 was statistically significantly higher than in group 1. This finding was convenient with another randomized controlled trial published by Terzi et al. in the literature. The authors reported that tumor regression was more in patients with an 8-week waiting period than in patients with 11 weeks and above waiting period. Also, the authors said they could not explain the result [20].

The complete pathological response was observed in 21 patients in our study. Although there were no significant differences among the groups, we found that the pathologic response rates increased from the first group patients with the shortest waiting period to the third group patients with the most prolonged. The lack of statistically significant differences may be due to the small number of patients in our study groups. Similar to our results, a randomized controlled study published in the literature reported that the pathological complete response rate was statistically significantly higher in patients with 12-week waiting periods than in patients with 8 weeks [20]. Unlike these findings, there was no significant difference between the two study groups regarding complete pathological response in the Lyon study [5]. Another multicenter randomized controlled study reported that they did not find significant differences among their study groups concerning complete pathological response [10]. The fact that most of the studies that reported a long-term waiting time increased complete pathological response was designed retrospectively, and the waiting times are variable and heterogeneous. Therefore, it is relatively easy to interfere with the complete pathological response [7, 17, 21].

The quality of surgical treatment is one of the most important prognostic factors that directly affect patient survival. Some criteria to assess the surgical technic, such as whether the mesorectum has been wholly removed, provide a clean circumferential resection margin and remove an adequate number of lymph nodes. The failure to meet these surgical technic criteria causes increasing local recurrence rates [22]. Pelvic tissue edema and local inflammation after radiotherapy treatment lead to fibrosis in time and make pelvic dissection more difficult [5, 10]. Therefore, a longer waiting period may negatively affect the total mesorectal excision quality. Lefevre et al. reported a negative effect of longer waiting time, especially 11 weeks and above, on total mesorectal excision [10].

On the other hand, Terzi et al. reported that they found better results in patients who had 12-week waiting period for complete mesorectal excision in their randomized controlled study [20]. We did not find significant differences among our study groups regarding mesorectum quality. However, when the groups were compared pairwise, TME quality was significantly lower in both group 3 and group 1. Our results suggest that the best schedule for mesorectum quality are 8–10-week waiting period. The lack of statistical difference may be related to the low number of patients. Our study groups had no statistical difference in the circumferential (radial) surgical margin, distal surgical margin, and the number of excised lymph nodes. Although several studies reported a negative correlation between a

positive circumferential margin and a short waiting period, other studies have not provided evidence of a longer waiting period to achieve a negative circumferential margin [7, 10].

With the widespread use of neoadjuvant chemoradiotherapy, several studies reported that local recurrence rates decrease in patients with extended waiting periods. De Campos-Lobato et al. reported a significant reduction in 3-year local recurrence rates with long-term waiting time; however, no relationship was observed between waiting periods and disease-free survival in their study [8]. Tulchinsky et al. reported that long waiting times improved disease-free survival rates but did not affect overall survival [23]. In the GRECCAR 6 randomized controlled trial published by Lefevre et al., the authors reported increased local recurrence in patients with an 11-week waiting period [10]. Albeit there is no clear evidence, there is serious concern regarding a long waiting period. Because it is not clear whether or not it causes the progression of the disease because of taking no treatment during the waiting period [24, 25]. Therefore, there is a paradigm shift from neoadjuvant therapy toward a total neoadjuvant therapy regimen. A recent meta-analysis reported that a longer waiting period does not affect 5-year disease-free survival and overall survival [4]. In our study, the local recurrence rates were similar in the groups, and the distant metastasis rates were lower in group 1. We have not found any significant differences among our study groups regarding local recurrence rates and distant metastasis rates. When the groups were compared, 3-year disease-free survival and overall survival rates were similar.

This study has some limitations. First, this is a retrospective, single-center study; therefore, it can cause selection bias. Second, the number of patients in groups and the total were low. Third, the absence of clinical re-staging after neoadjuvant therapy can be considered one of the shortcomings of this study. Finally, there were a lot of censored data in survival analysis, and there was no record concerning whether the patients received standardized adjuvant chemotherapy treatment in the postoperative period. For these reasons, it is challenging to conclude over survival analysis.

Conclusion

In patients with locally advanced rectal cancer, the optimal time for postoperative complications and sphincter-preserving surgery is a waiting period of 8–10 weeks. A long-term waiting period does not affect pathological complete response rates but negatively affects the TME quality rate. Well-designed prospective randomized controlled trials with different waiting times are needed to determine the optimal time.

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Declarations

Conflict of interest The authors declare no competing interests.

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