İstanbul Med J 2019; 20(5): 424-30
DOI: 10.4274/imj.galenos.2019.50133

Delayed Surgical Resection After Long-course Neoadjuvant Chemoradiotherapy in Rectal Cancer: Single Center Experience

Rektum Kanserinde Uzun Süreli Neoadjuvan Kemoradyoterapi Sonrası Gecikmiş Cerrahi Rezeksiyon: Tek Merkez Deneyimi

Özlem Mermut[1], Berrin İnanç[1], Esra Arslan[2], Hasan Bektaş[3], Nevra Dursun[4], Aytul Hande Yardımcı[5]

[1]University of Health Sciences, İstanbul Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
[2]University of Health Sciences, İstanbul Training and Research Hospital, Clinic of Nuclear Medicine, İstanbul, Turkey
[3]University of Health Sciences, İstanbul Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
[4]University of Health Sciences, İstanbul Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey
[5]University of Health Sciences, İstanbul Training and Research Hospital, Clinic of Radiology, İstanbul, Turkey

ABSTRACT

Introduction: The aim of this study was to evaluate whether delayed rectal cancer surgery after long-course neoadjuvant concomitant chemoradiotherapy was effective on pathological complete response (pCR), disease-free survival (DFS), and overall survival (OS).

Methods: A total of 112 patients with rectal carcinoma diagnosed at the Radiation Oncology Clinic between 2011 and 2017 were retrospectively analyzed. We compared the outcomes of patients who were operated on greater than >9 weeks (delayed surgery) and less than <8 weeks (early surgery) after completion of neoadjuvant chemoradiotherapy.

Results: When we compared the delayed and early surgery groups, pCR rate was higher in the Delayed surgery group (18.2% vs. 5.2%, p=0.032). Tumor regression was found to be close to statistical significance in the delayed surgery group (p=0.050). The decrease in postoperative T stage was found to be statistically significant in the delayed surgery group (p=0.007). When the study was completed, the patient group who underwent delayed surgery had a longer life and this was statistically significant (p=0.044). The OS rate (p=0.004) and DFS rate (p=0.003) was statistically significant in the delayed surgery group.

Conclusion: Delaying surgery after neoadjuvant chemoradiotherapy increases the pCR rate, DFS and OS.

Keywords: Rectal cancer, delayed surgery, neoadjuvant long-course radiotherapy, chemotherapy

ÖZ

Amaç: Bu çalışmanın amacı uzun süreli neoadjuvan kemoradyoterapiden sonra gecikmiş rektal kanser cerrahisinin patolojik tam yanıt (pCR), hastalıksız sağkalım (DFS), genel sağkalım (OS) için etkili olup olmadığını değerlendirmektir.

Yöntemler: Retrospektif olarak, 2011-2017 yılları arasında Radyasyon Onkolojisi Kliniğine rektum karsinomu tanısı alan toplam 112 hastadan veri alındı. Neoadjuvan kemoradyoterapinin tamamlanmasından sonra >9 (9-12 hafta) haftadan uzun sürede ameliyat edilen ve <8 (6-8 hafta) haftadan kısa sürede ameliyat edilen hastaların sonuçlarını karşılaştırarak verilerimizi inceledik.

Bulgular: >9 hafta ve <8 hafta tedavi aralığını kıyasladığımızda, hastalarda pCR oranları >9 hafta sonra %5,2 vs %18,2 (p=0,032) daha yüksekti. Ameliyat sonrası >9 hafta içinde tümör regresyonu istatistiksel olarak anlamlılığa çok yakın bulundu (p=0,050). Ameliyat sonrası >9 hafta içinde postoperatif T evresinde azalma istatistiksel olarak anlamlı bulundu (p=0,007). Çalışma tamamlandığında, gecikmiş cerrahi uygulanan hasta grubu daha uzun ömürlü ve bu istatistiksel olarak anlamlı (p=0,044) idi. Gecikmiş cerrahi gurubunda genel OS (p=0,004) ve hastalıksız DFS (p=0,003) istatistiksel olarak anlamlı bulundu.

Sonuç: Neoadjuvan kemoradyoterapi sonrası gecikmiş cerrahi patolojik tam yanıt oranı, hastalıksız sağkalım ve genel sağkalımı artırır.

Anahtar Kelimeler: Rektum kanseri, gecikmiş cerrahi, neoadjuvan uzun süreli radyoterapi, kemoterapi

Address for Correspondence/Yazışma Adresi: Özlem Mermut MD, University of Health Sciences, İstanbul Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
Phone: +90 532 741 39 41 **E-mail:** mermutozlem@gmail.com **ORCID ID:** orcid.org/0000-0002-5449-7361

Cite this article as/Atıf: Mermut Ö, İnanç B, Arslan E, Bektaş H, Dursun N, Yardımcı AH. Delayed Surgical Resection After Long-course Neoadjuvant Chemoradiotherapy in Rectal Cancer: Single Center Experience. İstanbul Med J 2019; 20(5): 424-30.

Received/Geliş Tarihi: 06.05.2019
Accepted/Kabul Tarihi: 27.08.2019

Introduction

Rectal cancer makes up approximately one-fourth of large bowel cancers. Locally advanced rectal tumors are commonly treated with preoperative neoadjuvant concomitant chemoradiotherapy (nCCRT) and followed by total mesorectal excision (TME) (1). nCCRT is employed for locally advanced rectal cancer to downstage size of a tumor and facilitate subsequent R0 resection or sphincter-preserving surgery (SPS) (2,3). Since the results of the Lyons R90-01 study have been published, a 6 to 8-week interval from the completion of nCCRT to surgery has become standard practice (4). The effect of complete pathological complete response (pCR) on disease-free survival (DFS) and overall survival (OS) has not been clearly defined (5,6). In some clinical trials, 50-60% of patients are downsized after nCCRT with 8-20% of patients showing a pCR (7-9).

Our study aimed to analyze the effect of time interval from completion of nCCRT to surgery on oncologic parameters such as pCR, tumor downstaging, distant metastases, local recurrence, DFS and OS.

Methods

We evaluated 112 patients with locally advanced rectal cancer between 2011 and 2017 at İstanbul Training and Research Hospital. Patients were divided into two groups according to the interval after nCCRT to surgery: <8 week (group 1) and >9 week (group 2). The data were analyzed retrospectively.

The nCCRT and surgery range were initially 6-8 weeks. Since 2015, due to the increasing number of publications on the extension of this period, this period has been extended up to 9-12 weeks, thus ensuring organ protection in some patients. Although the onset times of our patients were different, we aimed to compare these two groups retrospectively. Eleven patients in group 2 had delayed surgery due to patient's preference and logistic reasons (9-12 weeks and they were in first group years patients). Three of these 11 patients had a complete pCR and only one patient died. Therefore, our follow-up period was almost the same between the two groups.

All patients included in our study were aged ≥18 years, had pathological diagnosis of rectal carcinoma by endoscopic biopsy, had tumors with T3/4 stage or N0/+ as demonstrated in pelvic magnetic resonance imaging (MRI). The tumor location of the patients before nCCRT was evaluated endoscopically. The first 5 cm was accepted as lower rectum and 5-10 cm was regarded as the middle rectum. All patients underwent blood tests, digital rectal examination, colonoscopy and biopsy, computed thorax tomography or 18-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG PET/CT), and pelvic MRI staging before nCCRT. Preoperative blood tests, colonoscopy and pelvic MRI were performed again. All patients received long-course radiotherapy and underwent TME after nCCRT. Patients were controlled every three months in the first two years and then every six months. The treatment interval was calculated from the end of the CRT to the date of surgery. OS was calculated from the date of diagnosis to the date of death or last follow-up, and DFS as the time to local recurrence or distant metastases.

Ethical Approval

All performed procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol of this retrospective study was approved by the İstanbul Training and Research Hospital Local Ethics Committee in our hospital (approval number: 1655, date: 18.01.2019).

Pathological Response Assessment

After surgery, samples were analyzed histopathologically by an experienced gastrointestinal system pathologist. Tumor regression grading (TRG) was assessed according to the Modified Ryan Classification. The TRGs were as follows: TRG0 was a pCR, no visible tumor cells; TRG1 was very few or small groups of tumor cells, TRG2 was a residual tumor in fibrotic tissue, TRG3 was residual tumor without any signs of destroyed tumor cells (10).

Radiotherapy/Chemotherapy Definitions

Bladder, femoral heads, small bowels and pelvic bones were contoured as critical organs. The gross tumor volume (GTV) was defined based on 18-FDG PET/CT and MRI images of the tumoral lesion in the rectum and the fixed lymph nodes. The clinical target volume (CTV) included mesorectum, presacral space, internal iliac lymph nodes and GTV. The planning target volume was CTV plus a 1 cm margin above the sacral promontory. 3D conformal RT (3DCRT) was applied with box technique. 6-18 MV photon energy was used. Preoperative long-course radiation therapy of 45 Gy/25 fractions was delivered to the pelvis, followed by a 5.4 Gy/3 fractions boost to a primary tumor using Varian DHX Linear accelerator machine. The median radiation dose applied was 45-50.4 Gy. During radiation therapy, all patients were examined weekly to examine toxicity. Chemotherapy was given concurrently with radiotherapy and the regimen continued with 5-fluorouracil (180 mg/m^2 per day for 7 d/w) intravenous infusion or orally 5-FU derived capecitabine (850 mg/m^2 twice a day) for five days of radiotherapy (11). Patients were referred to the medical oncology clinic for adjuvant treatment with postoperative pathological results.

Statistical Analysis

Statistical analysis for group comparisons was performed using Pearson's x^2 test, Mann-Whitney U test depending on the nature of the data. A p value less than 0.05 was considered statistically significant. Survival curves were constructed using Kaplan-Meier analyses. All statistical tests were performed using IBM SPSS version 18.0 (IBM Co., Armonk, NY, USA).

Results

Of the patients, 36 were female and 76 of them were male. The median age was 61 years and the tumors were most often located in the distal rectum. The follow-up period in group 1 was 54.6 months and was 67.2 months in group 2. Histopathology was mucinous adenocarcinoma in eight patients (14%) in group 1 and six patients (10.9%) in group 2. All other patients had adenocarcinoma. The general characteristics of all patients are shown in Table 1.

The localization was middle rectum in 30 patients (52.6%) in group 1 and in 25 patients (45.5%) in group 2. The tumor was located in the distal rectum in 27 patients (47.4%) in group 1 and in 30 patients (54.5%) in group 2. There was no statistically significant difference between the groups (p=0.448). Preoperative tumor grade, preoperative T/N stage, chemotherapy protocol, the type of surgery, the presence of lymphovascular invasion/perineural invasion were not statistically significant between the two groups. Postoperative N stage regression was not statistically significant (p=0.519).

Local recurrence was observed in four patients (3.5%) in group 1 and in one patient (0.9%) in group 2 (p=0.326). Distant metastasis was present

Table 1. General characteristics of all patients

		Minimum-maximum	Median	Median ± SD (n %)
Age		27.0-86.0	61.0	60.5±12.1
Gender	Female			36 (32.1%)
	Male			76 (67.9%)
Surgery time (week)		6.0-12.0	8.0	8.8±2.2
Follow-up (month)		6.0-60.0	19.5	26.5±16.6
Preoperative CEA		0.1-123.0	2.8	8.5±18.1
Preoperative CA19-9		0.6-417.0	8.9	22.7±52.6
Surgery	LAR			69 (61.6%)
	Miles			43 (38.4%)
	Middle			55 (49.1%)
Localization	Lower			57 (50.9%)
Preoperative stage	T3			87 (77.7%)
	T4			25 (22.3%)
Histology	Adenocarcinoma			98 (87.5%)
	Mucinous			14 (12.5%)
LVI	(-)			68 (69.4%)
	(+)			30 (30.6%)
PNI	(-)			70 (71.4%)
	(+)			28 (28.6%)
Tumor regression	Grade 0			13 (11.6%)
	Grade 1			27 (24.1%)
	Grade 2			55 (49.1%)
	Grade 3			17 (15.2%)
Complete response	Present			13 (11.6%)
	Absent			99 (88.4%)
Chemotherapy	5-FU intravenous			28 (25.0%)
	Capesitabine			84 (75.0%)
Locally recurrence (month)		9.0-60.0	12.0	22.0±21.4
Distant metastases (month)		4.0-38.0	12.0	12.9±7.4
Distant metastases	Absent			93 (83.0%)
	Present			19 (17.0%)
	Lung			11 (9.8%)
	Liver			6 (5.3%)
	Brain			1 (0.9%)
	Bone			1 (0.9%)
	Local recurrence			5 (4.4%)
	Exitus			23 (20.5%)
	Alive			89 (79.5%)

SD: standard deviation, LAR: lower anterior resection, LVI: lymphovascular invasion, PNI: perineural invasion, CEA: corcinoembryonic antigen

Table 2. Comparison of group 1 and group 2

	6-8 week Patient number (%)	9-12 week Patient number (%)	p
Gender			
Female (n=36, 32%)	17 (29.8)	19 (34.5)	0.593[a]
Male (n=76, 78%)	40 (70.2)	36 (65.5)	
Age			
Median (minimum-maximum-SD)	62 (27-86) 62.11±12.60	58 (31-80) 58.85±11.40	0.156[b]
Localization			
Middle (55)	30 (52.6)	25 (45.5)	0.448[a]
Distal (57)	27 (47.4)	30 (54.5)	
Histology			
Adenocarcinoma (98)	49 (86.0)	49 (89.1)	0.617[a]
Mucinous carcinoma (14)	8 (14.0)	6 (10.9)	
Preoperative stage			
T3N+ (85)	48 (84.2)	37 (67.3)	
T4N+ (22)	7 (12.3)	15 (27.3)	0.105[a]
T3/4N0 (5)	2 (3.5)	3 (5.5)	
Chemotherapy protocol			
5-FU intravenously (26)	14 (24.6)	12 (21.8)	0.731[a]
Capesitabine orally (86)	43 (75.4)	43 (78.2)	
Operation type			
LAR (69)	33 (57.9)	36 (65.5)	0.411[a]
Miles (43)	24 (42.1)	19 (34.5)	
Lymphovascular invasion			
Absent (69)	40 (70.2)	29 (52.7)	
Present (30)	14 (24.6)	16 (29.1)	0.060[a]
pCR (13)	3 (5.3)	10 (18.2)	
Perineural invasion			
Absent (70)	37 (64.9)	33 (61.8)	
Present (28)	17 (29.8)	11 (20)	0.076[a]
pCR (13)	3 (5.3)	10 (18.2)	
Postoperative T stage			
T0 (16)	5 (8.8)	11 (20)	
T1 (7)	7 (12.3)	-	
T2 (30)	20 (35.1)	10 (18.2)	0.007[a]
T3 (48)	21 (36.8)	27 (49.1)	
T4 (11)	4 (7)	7 (12.7)	
Postoperative N stage			
N0 (70)	36 (63.2)	34 (61.8)	
N1 (36)	18 (31.6)	18 (32.7)	0.989[a]
N2 (6)	3 (5.3)	3 (5.5)	
TRG			
TRG0 (complete response, 13)	3 (5.3)	10 (18.2)	
TRG1 (27)	11 (19.3)	16 (29.1)	0.050[a]
TRG2 (55)	34 (59.6)	21 (38.2)	
TRG3 (17)	9 (15.8)	8 (14.5)	
Response			
Partial response (99)	54 (94.7)	45 (81.8)	0.033[a]
Complete response (13)	3 (5.3)	10 (18.2)	

Table 2 contiuned

	6-8 week Patient number (%)	9-12 week Patient number (%)	p
Last situation Exitus (23) Alive (89)	 16 (28.1) 41 (71.9)	 7 (12.7) 48 (87.3)	0.044[a]
Distant metastases Absent (89) Present (19)	 43 (80.7) 11 (19.3)	 46 (85.5) 8 (14.5)	0.503[a]
Local recurrence Absent (108) Present (4)	 54 (94.7) 3 (5.3)	 54 (98.2) 1 (1.8)	0.326[a]
Overall survival Median (month)	54.62 (44.41±64.83) %95 CI	67.24 (55.73±78.75) %95 CI	0.004[c]
Disease free survival Median (month)	49.14 (38.62±59.65) %95 CI	61.19 (50.71±71.67) %95 CI	0.003[c]
Nausea Absent (97) Present (15)	 49 (86) 8 (14)	 48 (87.3) 7 (12.7)	0.839[a]
Diarrhea Absent (47) Present (65)	 25 (43.9) 32 (56.1)	 22 (40) 33 (60)	0.679[a]
Cystitis Absent (106) Present (6)	 54 (94.7) 3 (5.3)	 52 (94.5) 3 (5.5)	0.964[a]
Proctitis Absent (68) Present (44)	 36 (63.2) 21 (36.8)	 32 (5.2) 23 (41.8)	0.590[a]
Fatigue Absent (104) Present (8)	 52 (91.2) 5 (8.8)	 52 (94.5) 3 (5.5)	0.496[a]

[a]: chi-square, [b]: T-test [c]: Mann-Whitney U test, SD: standard deviation, pCR: pathological complete response, TRG: tumor regression grade, CI: confidence interval

in 11 patients (19.3%) in group 1 and in eight patients (14.5%) in group 2 (p=0.503). Distant metastasis and local recurrence were more common in group 1, but it did not reach statistical significance. Sixteen patients (28.1%) died in group 1 and seven patients (12.7%) died in group 2 (p=0.044).

The rate of SPS was 33.3% (n=9) in group 1 and 43.3% (n=13) in group 2. The decrease in postoperative T stage was higher in group 2 (p=0.007). TRGs were found to be almost significant between the two groups (p=0.050). pCR was significantly higher in group 2 (p=0.032). DFS during follow-up was 80.7% in group 1 and 85.5% in group 2 (p=0.003) (Figure 1). OS was 71.9% in group 1 and 87.3% in group 2 (p=0.004) (Figure 2). Comparison of general characteristics of group 1 and group 2 are shown Table 2.

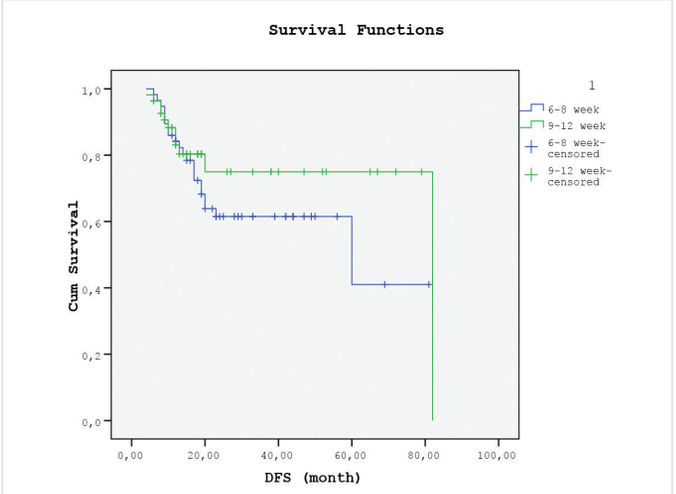

Figure 1. Disease-free survival time in both groups

Side Effects

Diarrhea was the most common side effect and was observed in 65 patients (58%) (p=0.679). Proctitis was observed in 44 patients (39.2%)

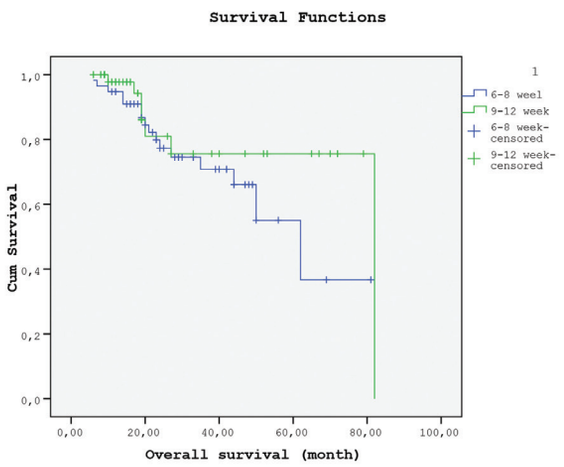

Figure 2. Overall survival time in both groups

patients (p=0.590). Nausea was observed in 15 patients (13.3%) (p=0.839), cystitis was reported in six patients (5.3%) (p=0.964) and fatigue was observed in eight patients (7.1%) (p=0.496). Side effects were similar in both groups and difference was not statistically significant.

Discussion

Rectal cancer makes up approximately one-fourth of colon cancers. Treatment includes radiation therapy, chemotherapy and surgery. nCCRT is generally used in patients with clinical locally advanced rectal cancers. In the literature, long-term results of nCCRT and patients who achieved a pCR after curative surgery have been reported (12,13). The Lyon R90-01 trial showed that a longer interval of 6 to 8 weeks between preoperative irradiation and surgery, compared with two weeks, increased tumor down-staging (26% versus 10%), but did not affect 5-year survival rates (14).

Mihmanlı et al. (15) showed that a longer interval before surgery was associated with high pCR rates, lymph nodal downstaging, decreased rate of TRG poor response and improved DFS and OS. In our study, pCR rates were significantly higher in group 2 (p=0.033), with a rate of 18.2%. Also, in our study, TRG response rate was found to be near significant (p=0.050) and DFS was found to be significant (p=0.003). The decrease in T stage was statistically significant in group 2 compared to the total number of patients (p=0.007). In our study, we observed statistical significance between the two groups in terms of OS and DFS. However, local recurrence and distant metastasis were not statistically significant in both groups. The regression in TRG was near significant between the two groups (p=0.050). In subgroup analysis, we found that local recurrence and distant metastasis were observed in patients with no regression in TRG. Long surgery time increases the number of patients who can respond fully pathologically. We believe that the pathology and molecular pattern of the tumor causes TRG to remain without regression. The number of patients in this group was almost equal in both groups. We believe that the excess in the group positively affects DFS and OS, which the decline in TRG will increase as the number of patients undergoing delayed surgery increases, and that this will reduce local recurrence and distant metastasis and contribute positively to OS and DFS.

Increased chance of SPS with nCCRT has been reported. Randomized trials have shown that nCCRT increases the chance of achieving SPS by approximately 60% (3,4,16). In our study, there were 27 patients (47.4%) in the lower rectum in group 1 and 30 patients (54.5%) in group 2. SPS was performed in 10 patients (37%) in group 1 and 14 patients (46.6%) in group 2. In conclusion, in the absence of nCCRT, SPS could be performed in 42.1% of patients who were planned to undergo APR. This shows lower rates than the literature. We think that the reason for this is that T and N stages of our lower rectum tumors were higher than the others.

In a study by Tulchinsky et al. (16), patients who were operated seven weeks after surgery showed a statistically significant increase in the complete response rate compared to those who were operated seven weeks before surgery. They also showed better DFS rates in patients who were operated seven weeks after CRT. However, contribution to OS has not to be shown. In our study, pCR rates, DFS and also OS were found to be significantly higher in group 2 (p=0.033, p=0.003, p=0.004, respectively).

De Campos-Lobato et al. (17) reported that more than 8 weeks interval between completion of CRT and surgical procedure was associated with significant improvement in pCR rate (30.8% vs. 16.5%, respectively, p=0.03). In the same study, they reported decreased 3-year local recurrence rate (1.2% vs. 10.5%, respectively, p=0.04). In our study, no statistically significant difference was found between two groups in terms of local recurrence (p=0.326).

Patel et al. (18) have shown that patients with <4 cm tumors were less likely to have pCR. In our study, the tumor was found to be T4 stage in three patients (23%) and T3 stage in ten patients (77%), and the mean tumor diameter was 5.4 cm in pCR patients.

In rectal cancer, the response to nCCRT is different among patients. While there is a partial response in approximately 40% of patients, pCR is achieved after surgery in 8-20% of patients. Some of the tumors (~20%) exhibit resistance to nCCRT, demonstrating either progression or only minimal regression or stable disease (19-22). In our study, similar to the literature, 11 patients (19.3%) in group 1 and nine patients (16.4%) in group 2 did not downstage (p=0.685).

In pathological specimens, tumor differentiation, mucinous tumor histology and macroscopic ulceration are related to the low response rate to nCCRT (23-27). In our study, pCR was not observed in any patient with mucinous histology. One (7.1%) of 14 patients had local recurrence and three patients (21.4%) had lung metastasis with mucinous histology. In these patients, two (14.2%) had a tumor downstaging, three (21.4%) remained at the same stage, and nine (64.2%) did not downstage. No pCR was observed in mucinous carcinomas.

We did not evaluate surgical complications in our study because we focused on predicting the effects of prolonged surgical intervals on pCR, DFS and OS.

Conclusion

nCCRT and curative surgery remain the standard treatment for patients with locally advanced rectal cancer. Delaying surgery by 9 to 12 weeks after the end of nCCRT increases pCR rate. Moreover, it reduces the T

stage of the tumor and decreases the TRG. Our findings seem to support the benefit of a longer time interval between chemoradiotherapy and surgery in rectal cancer in terms of pCR. There was no local recurrence or distant metastasis or death in any patient with a pCR. These results suggest that longer preoperative intervals support ongoing tumor necrosis and regression. Based on this, we think that OS and DFS reach statistical significance.

Ethics Committee Approval: The protocol of this retrospective study was approved by the İstanbul Training and Research Hospital Local Ethics Committee in our hospital (approval number: 1655, date: 18.01.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - A.H.Y.; Concept - Ö.M., N.D.; Design - Ö.M., B.İ., H.B.; Data Collection and/or Processing E.A., A.H.Y.; Analysis and/or Interpretation - N.D., A.H.Y.; Literature Search - B.İ., E.A.; Writing Manuscript - Ö.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Guillem JG, Chessin DB, Cohen AM, Shia J, Mazumdar M, Enker W, et al. Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. Ann Surg 2005; 241: 829-36.
2. Lim CS, Mehigan BJ, Hartley JE, Monson JRT. Neoadjuvant therapy in the treatment of high risk rectal carcinoma. Surg Oncol 1999; 8: 1-11.
3. Marks G, Mohiuddin M, Masoni L, Montori A. High-dose preoperative radiation therapy as the key to extending sphincter-preservation surgery for cancer of the distal rectum. Surg Oncol Clin North Am 1992; 1: 71-86.
4. Francois Y, Nemoz CJ, Baulieux J, Vignal J, Grandjean JP, Partensky C. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R- 90-01 randomized trial. J Clin Oncol 1999; 17: 2396-402.
5. Bujko K. Timing of surgery following preoperative therapy in rectal cancer: there is no need for a prospective randomized trial. Dis Colon Rectum 2012; 55: e31.
6. Ryan R, Gibbons D, Hyland JM, Treanor D, White A, Mulcahy HE, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology 2005; 47: 141-6.
7. Al Sukhni E, Attwood K, Mattson DM, Gabriel E, Nurkin SJ. Predictors of pathologic response following neoadjuvant chemoradiotherapy for rectal cancer. Ann Surg Oncol 2016; 23: 1177-86.
8. Wheeler JM, Dodds E, Warren BF, Cunningham C, George BD, Jones AC, et al. Preoperative chemoradiotherapy and total mesorectal excision surgery for locally advanced rectal cancer: correlation with rectal cancer regression grade. Dis Colon Rectum 2004; 47: 2025-31.
9. Park IJ, You YN, Agarwal A, Skibber JM, Rodriguez-Bigas MA, Eng C, et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. J Clin Oncol 2012; 30: 1770-6.
10. Ryan R, Gibbons D, Hyland JM, Treanor D, White A, Mulcahy HE, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology 2005; 47: 141-6.
11. Wang L, Li ZY, Li ZW, Li YH, Sun YS, Ji JF, et al. Efficacy and safety of neoadjuvant intensity-modulated radiotherapy with concurrent capecitabine for locally advanced rectal cancer. Dis Colon Rectum 2015; 58: 186-92.
12. Han YD, Kim WR, Park SW, Cho MS, Hur H, Min BS, et al. Predictors of pathologic complete response in rectal cancer patients undergoing total mesorectal excision after preoperative chemoradiation. Medicine (Baltimore) 2015; 94: e1971.
13. Yeo SG, Kim DY, Kim TH, Chang HJ, Oh JH, Park W, et al. Pathologic complete response of primary tumor following preoperative chemoradiotherapy for locally advanced rectal cancer: long term outcomes and prognostic significance of pathologic nodal status (KROG 09-01). Ann Surg 2010; 252: 998-1004.
14. Glehen O, Chapet O, Adham M, Nemoz JC, Gerard JP. Long-term results of the Lyons R90-01 randomized trial of preoperative radiotherapy with delayed surgery and its effect on sphincter- saving surgery in rectal cancer. Br J Surg 2003; 90: 996-8.
15. Mihmanlı M, Gürbulak EK, Akgün İE, Celayir MF, Yazıcı P, Öz A, et al. Delaying surgery after neoadjuvant chemoradiotherapy improves prognosis of rectal cancer. World J Gastrointest Oncol 2016; 8: 695-706.
16. Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M. An interval of >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. Ann Surg Oncol 2008; 15: 2661-17.
17. De Campos-Lobato LF, Geisler DP, da Luz Moreira A, Stocchi L, Dietz D, Kalady MF. Neoadjuvant therapy for rectal cancer: the impact of longer interval between chemoradiation and surgery. J Gastrointest Surg 2011; 15: 444-50.
18. Patel SV, Roxburgh CS, Vakiani E, Shia J, Smith JJ, Temple LK, et al. Distance to the anal verge is associated with pathologic complete response to neoadjuvant therapy in locally advanced rectal cancer. J Surg Oncol 2016; 114: 637-41.
19. Park IJ, You YN, Agarwal A, et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. J Clin Oncol 2012;30:1770–1776.
20. Silberfein EJ, Kattepogu KM, Hu CY, Skibber JM, Rodriguez-Bigas MA, Feig B, et al. Long-term survival and recurrence outcomes following surgery for distal rectal cancer. Ann Surg Oncol 2010; 17: 2863-9.
21. Smith KD, Tan D, Das P, Chang GJ, Kattepogu K, Feig BW, et al. Clinical significance of acellular mucin in rectal adenocarcinoma patients with a pathologic complete response to preoperative chemoradiation. Ann Surg 2010; 251: 261-4.
22. Ryan JE, Warrier SK, Lynch AC, Heriot AG. Assessing pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: A systematic review. Colorectal Dis 2015; 17: 849-61.
23. Bitterman DS, Resende Salgado L, Moore HG, Sanfilippo NJ, Gu P, Hatzaras I, et al. Predictors of complete response and disease recurrence following chemoradiation for rectal cancer. Front Oncol 2015; 5: 286.
24. Zeng WG, Liang JW, Wang Z, Zhang XM, Hu JJ, Hou HR, et al. Clinical parameters predicting pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. Chin J Cancer 2015; 34: 468-74.
25. Huh JW, Kim HR, Kim YJ. Clinical prediction of pathological complete response after preoperative chemoradiotherapy for rectal cancer. Dis Colon Rectum 2013; 56: 698-703.
26. Qiu HZ, Wu B, Xiao Y, Lin GL. Combination of differentiation and T stage can predict unresponsiveness to neoadjuvant therapy for rectal cancer. Colorectal Dis 2011; 13: 1353-60.
27. McCawley N, Clancy C, O'Neill BD, Deasy J, McNamara DA, Burke JP. Mucinous rectal adenocarcinoma is associated with a poor response to neoadjuvant chemoradiotherapy: A systematic review and meta-analysis. Dis Colon Rectum 2016; 59: 1200-8.