Neoadjuvant Chemoradiotherapy in Rectal Cancer: A single Institution Experience from Turkey

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ABSTRACT

Radiotherapy is one of the main treatment modalities for rectal cancer. Neoadjuvant chemoradiotherapy has been accepted as the standard treatment in rectal cancer. Evaluation the treatment results in patients who underwent neoadjuvant chemoradiotherapy were aimed in this study. Between 2009 and 2019, patients with local advanced rectal cancer who underwent neoadjuvant radiotherapy and subsequent surgery in our clinic were retrospectively analyzed. The clinical pathological features, treatment responses and prognostic factors affecting survival of 99 patients were investigated. Radiotherapy dose was 25 Gy in 5 fractions in 11 patients and 50.4 Gy in 28 fractions in 88 patients. Thirty-three of the patients were female and 66 were male and the median age was 60 (30-80). According to tumor locations, 30.3% are located in the upper, 26.3% in the middle, and 43.4% in the distal rectum. The distribution according to clinical radiological stages before radiotherapy were 2% T2, 72.7% T3, 25.3% T4 and 52.5% N0, 47.5% N1-2. Pathological complete response (pCR) was determined in 10.2% of the patients who received long-term chemoradiotherapy. Eight patients developed local recurrence and 12 patients developed distant metastases. Five-year disease-free and overall survival rates were 66% and 76%, respectively. Stage and location of the tumor were found to be effective factors in overall survival. No grade 3 acute or late gastrointestinal and genitourinary system toxicities were observed. Neoadjuvant chemoradiotherapy is an effective treatment for rectal cancer. Determination of clinical pathological prognostic factors in larger series will be effective in treatment selection.

Keywords: Rectal cancer, Neoadjuvant treatment, Short-course radiotherapy, Long-course combined chemoradiation, Prognosis

INTRODUCTION

Colorectal cancer is the 4th most common cause of cancer, and approximately 43000 new cases occurred in the USA in 2020.[1] The main treatment for early-stage rectal cancer is surgery. In locally advanced rectal cancer, the standard of care consists of neoadjuvant chemoradiotherapy followed by surgical resection. The use of neoadjuvant chemoradiotherapy is recommended for all newly diagnosed rectal adenocarcinoma with a clinical stage T3 or T4 based on transrectal endoscopic ultrasound or magnetic resonance imaging (MRI). Neoadjuvant chemoradiotherapy increases the possibility of sphincter preservation surgery and local control in the treatment of rectal cancer.[2,3] It is reported that 10 to 20 percent of patients with locally advanced rectal cancer show pathological complete response (pCR) to neoadjuvant chemoradiotherapy.[4] According to a meta-analysis, pCR was seen in 11.8% of patients with stage 2-3 rectal cancer who underwent surgery after neoadjuvant chemoradiotherapy compared to 3.5% of patients treated with RT alone.[5] Neoadjuvant therapy may comprise of either radiotherapy alone or in combination with chemotherapy.

There are two types of neoadjuvant radiation regimens for resectable rectal cancer: short-course (5 × 5 Gy) radiotherapy alone with immediate surgery and long-course combined chemoradiation (1.8–2 Gy per fraction and a total dose of 45-50.4 Gy) with delayed surgery. In the Dutch Trial was reported that neoadjuvant short-term radiotherapy reduced local recurrences compared to surgery alone group, but did not improve overall survival.[6]

Surgery is applied 4-8 weeks after concurrent chemoradiotherapy in long-term radiotherapy. In the study of the German Rectal Cancer group, patients with T3-4 or node positive rectal cancer were randomized according to neoadjuvant or adjuvant chemoradiotherapy. It was observed that locoregional control and sphincter preservation surgery increased in the group which neoadjuvant chemoradiotherapy was applied, while the frequency of acute and late side effects related to treatment was found to be decreased. However, disease-free and overall survival was similar between the two groups.[3]

In this study, we aimed to examine the clinical features and treatment results of patients with rectal cancer who received neoadjuvant radiotherapy in our clinic.

PATIENTS and METHODS

In this study, 99 patients with T3-4 or lymph node positive biopsy proven rectal cancer who received neoadjuvant chemoradiotherapy between 2009 and 2019 were retrospectively analyzed. Clinical and pathological characteristics of the patients and treatment responses were evaluated, prognostic factors effective in survival were investigated. Physical examination, rectal examination, complete blood count, blood biochemistry, rectosigmoidoscopy, colonoscopy and tumor biopsy were performed in all cases. Patients were staged with pelvic magnetic resonance imaging (MRI) and/or positron emission tomography computed tomography (PET-CT) before treatment. The part from the anal verge to 5 cm was defined as the lower rectum, the middle rectum between 6 and 10 cm, and the upper rectum more than 10 cm. The clinical target volume consisted of the tumor with mesorectal fat, iliac, obturator and presacral nodes. Radiotherapy was delivered as three-dimensional conformal radiotherapy or intensity modulated radiotherapy with 6 MV, 10 MV or 18 MV photons. Surgery was planned for patients who received short-term radiotherapy within 1 week after radiotherapy. In patients planned for chemoradiotherapy, 5FU or capecitabine chemotherapy was administered concurrently with radiotherapy. Response evaluation was made with pelvic MRI and/or PET-CT 4-6 weeks after chemoradiotherapy, and surgical resection was planned 6-8 weeks after the last fraction of radiotherapy. Low anterior resection was performed in patients who could undergo sphincter preservation surgery, and abdominoperineal resection was performed in other patients. The absence of any cancer cells in the resection material (ypT0N0) was considered as pCR. Tumor regression in T and N stages was considered as partial response. After treatment, local and regional recurrences, distant metastases and survival rates were evaluated and factors affecting survival were investigated. Since the number of patients who received short-term radiotherapy was small, survival analyzes were performed only for patients who received long-term chemoradiotherapy.

Acute gastrointestinal system (GIS) and genitourinary system (GUS) toxicities were assessed by using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Late toxicity was assessed by using RTOG/EORTC Late Radiation Morbidity Scoring Schema.

This study was approved by the Akdeniz University Faculty of Medicine Clinical Research Ethic Committee (No: KAEK-59; Date: 08.01.2020).

Statistical Analysis

SPSS 22.0 program was used for statistical analysis. Kaplan Meier analysis was used to evaluate disease-free and overall survival and chi-square test was used to compare factors that may affect pathological response. Values below the p value of 0.05 were considered significant.

RESULTS

Thirty-three of the patients were female and 66 were male, and the median age was 60 (30-80).

Table 1. Patients' characteristics

Variable	Number (%)
Gender	
Female	33 (33.3)
Male	66 (66.7)
Weight Loss (10% reduction in 6 months)	
Yes	19 (19.2)
No	80 (80.8)
Performance status (ECOG)	
0-1	79 (79.8)
2-3	20 (20.2)
Comorbidity	
Yes	55 (55.6)
No	44 (44.4)
Localization of the tumor	
Upper rectum	30 (30.3)
Middle rectum	26 (26.3)
Lower rectum	43 (43.4)
T stage	
T2	2 (2)
T3	72 (72.7)
T4	25 (25.3)
Lymph node stage	
N0	52 (52.5)
N1-2	47 (47.5)
Radiotherapy scheme	
Short-term	11 (11.1)
Long-term	88 (88.9)
Radiotherapy Techniques	
IMRT	53 (53.5)
3D-CRT	46 (46.5)

Seventy-nine patients had a European Cooperative Oncology Group (ECOG) performance status of 0-1. Among the 99 enrolled patients, 44 (44.4%) had comorbidities. It was found that 30.3% of the patients were located in the upper, 26.3% in the middle and 43.4% in the lower rectum. The distribution according to clinical stages before radiotherapy were 2% T2, 72.7% T3, 25.3 % T4 and 52.5% N0, 47.5% N1-2. Fifty-three of patients were treated with intensity modulated radiotherapy (IMRT) and 46 with three-dimensional conformal radiotherapy (3D-CRT). Eleven patients received 25 Gy short-term radiotherapy, 88 patients received long-term chemoradiotherapy at a dose of 45 Gy in 25 fractions, followed by a boost of 5.4 Gy to the primary tumor. In 85 of 88 patients scheduled for chemoradiotherapy, concurrent chemotherapy was completed as planned. Neoadjuvant chemotherapy was applied to 31 patients before chemoradiotherapy. Surgery was performed in a median of 55 days after completion of neoadjuvant radiotherapy. Surgery was performed as low anterior resection in 72 patients, abdominoperineal resection in 27 patients, and the sphincter was preserved in 72.7%. Demographic and tumor characteristics for 99 patients included in the study are shown in Table 1.

In the postoperative pathological evaluation, pCR was observed in 9.1% of the patients, and partial response was observed in 59.6% of the patients. Pathological complete response was not obtained in any of the 11 patients who received short-term radiotherapy and pCR was obtained in 9 (10,2%) of 88 patients who received long-term chemoradiotherapy. Complete response rates were found higher in patients who had no lymphovascular involvement (p= 0.04). However, no significant correlation was found between gender, tumor location, stage, surgical method, radiotherapy technique, time between radiotherapy to surgery, circumferential margin, histopathological grade and tumor response (Table 2).

Sphincter preservation surgery could be performed in 44 of 60 patients with complete or partial response to neoadjuvant chemoradiotherapy and in 18 of 28 patients who did not respond to neoadjuvant therapy. In 7 of the 40 patients with tumors located in the lower rectum who received neoadjuvant chemoradiotherapy, a complete pathological response was obtained and sphincter preservation surgery was performed in 23 patients. Postoperative adjuvant chemotherapy was applied to 60.6% of the patients. After a median follow-up period of 42 (4-196) months, local recurrence developed in 8 (8.1%) patients and distant metastasis developed in 12 (12.1%) patients.

Five-year disease-free and overall survival rates were 66% and 76%, respectively. T stage and location of the tumor were found to be effective factors in overall survival and disease-free survival. Patients with advanced T stage had significantly higher risks of poorer disease-free survival and poorer overall survival. It has been shown in Figure 1 that overall survival is worse in upper rectal

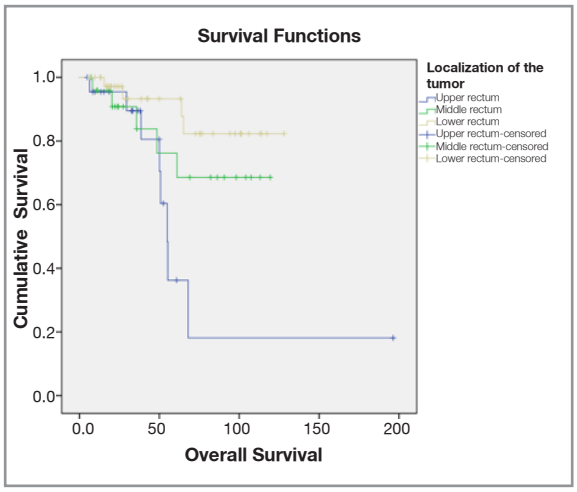

Figure 1. Overall survival according to the tumor location in patients received chemoradiotherapy

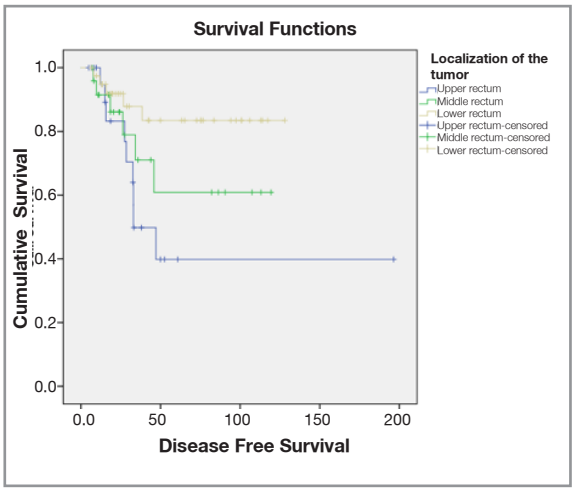

Figure 2. Disease free survival according to the tumor location in patients received chemoradiotherapy

cancers. Disease-free survival was also found to be worse in patients with upper rectal cancer. It is shown in Figure 2.

Age at diagnosis, gender, pCR, time between radiotherapy and surgery, histopathological features (grade, lymphovascular involvement, circumferential margin), and radiotherapy technique did not predict disease-free survival or overall survival.

Acute Grade 1-2 GIS and GUS toxicity rates were 67.7% and 12%, respectively. Late Grade 1-2 GIS and GUS toxicity rates were 3% and 1%, respectively. No grade 3 acute or late gastrointestinal and genitourinary system toxicity were observed during the follow-up of the patients. Acute toxicity was higher in the conformal radiation technique than IMRT (p= 0.031).

DISCUSSION

Neoadjuvant chemoradiotherapy followed by surgery is the current standard of care for locally advanced rectal carcinoma. The results of important randomized controlled trials comparing preoperative chemoradiation against postoperative chemoradiation have demonstrated improved local control and reduced toxicities with neoadjuvant chemoradiation.[7,8] In a recent retrospective study comparing surgery after neoadjuvant chemoradiotherapy and surgery alone, it was reported that 5-year overall survival was 75.42% in the group receiving neoadjuvant therapy and 72.76% in the group not receiving neoadjuvant therapy. Five-year disease-free survival was reported to be 74.25% in the group receiving neoadjuvant chemoradiotherapy and 70.13% in the group not receiving neoadjuvant chemoradiotherapy.[9] In our study, 88 patients received neoadjuvant chemoradiotherapy and five-year disease-free and overall survival rates were 66% and 76%, respectively. These results are comparable to published data.[2,9] In a study by Hee Jeong Chu et al, it was reported that pathological T, N stage, and the presence of lymphovascular and perineural invasion after neoadjuvant treatment were effective factors in disease-free survival and overall survival.[10] It has been reported that adjuvant chemotherapy improves survival in patients with locally advanced rectal cancer, even if there is a pCR after neoadjuvant therapy.[11]

The pCR to neoadjuvant treatment is an important outcome for rectal cancer. The pCR rate of 10.1% in our study was comparable to those of other published trials.[12] In a study evaluating 6555 patients with nonmetastatic rectal cancer who received neoadjuvant therapy, 3-year overall survival was reported as 92.4% in patients with pathological complete response, while overall survival was reported as 88.2% in patients without pathological complete response.[13] In a study in which 580 patients were evaluated retrospectively, 23.7% of patients with

Table 2. Response rates according to the tumor characteristics in patients receiving long-term chemoradiotherapy.

Characteristic	Complete Response (n) (%)	Partial Response (n) (%)	No Response (n) (%)
Gender			
Female	7 (77.8)	15 (29.4)	8 (28.6)
Male	2 (22.2)	36 (70.6)	20 (71.4)
Localization			
Upper rectum	0	16 (31.4)	7 (25)
Middle rectum	2 (22.2)	15 (29.4)	8(28.6)
Lower rectum	7 (77.8)	20 (39.2)	13 (46.4)
T Stage			
T2	0	2 (3.9)	0
T3	6 (66.7)	38 (74.5)	21(75)
T4	3 (33.3)	11 (21.6)	7 (25)
N Stage			
N0	6 (66.7)	27 (52.9)	13 (46.4)
N1-2	3 (33.3)	24 (47.1)	15 (53.6)
Grade			
Unknown	6 (66.7)	34 (38.6)	21 (75)
Grade 1	2 (22.2)	7 (7.9)	0
Grade 2	1 (11.1)	9 (17.6)	7 (25)
Grade 3	0	1 (2)	0
Lymphovascular involvement			
Yes	0	4 (7.8)	7 (25)
No	9 (100)	47 (92.2)	21 (75)
Circumferenential Margin			
Yes	0	1 (2)	0
No	9 (100)	50 (98)	28 (100)
Surgery type			
LAR	8 (88.9)	36 (70.6)	18 (64.3)
APR	1 (11.1)	15 (29.4)	10 (35.7)
Time between RT and surgery (median days)	56	58	53

rectal cancer who received neoadjuvant treatment had a pathological complete response. 5-year disease-free survival was determined as 92.5% in pathological Stage 0 disease, 85.1% in Stage I, 72.2% in Stage II and 54.3% in Stage III. 5-year overall survival was determined as 94.5% in pathological Stage 0 disease, 91% in Stage I, 83.1% in Stage II, and 69.3% in Stage III.[14]

In a meta-analysis in which patients with rectal cancer who underwent surgery after neoadjuvant chemoradiotherapy, it is concluded that a pCR following neoadjuvant chemoradiotherapy is associated with improved long-term survival, with low rates of local recurrence and distant failure.[15] The pCR appears to be associated with a very favorable prognosis. However, our results showed that pCR after preoperative chemoradiotherapy (CRT) did not improve disease-free survival or overall survival in our patients. In our group, all patients with complete pathological response after CRT were alive, and 88.9% of patients with complete response were followed up without recurrence.

In a study evaluating neoadjuvant short-course radiotherapy and long-course chemoradiotherapy

in patients with rectal cancer, it was shown that both schemes provided similar local recurrence, distant metastasis and survival.[16] However long course chemoradiotherapy has a better pathologic complete response rate than short course radiotherapy.[17,18] In our series, no complete response was achieved in any of the patients who received short course radiotherapy.

The size of the tumor, the clinical T and N stage, the distance of the tumor from the anal canal, the Carsino Embryonic Antigen (CEA) levels in the blood at the time of diagnosis, the time between neoadjuvant chemoradiotherapy and surgery affect the response of neoadjuvant therapy. In addition, pathological tumor differentiation, mucinous component of the tumor, and the presence of macroscopic ulceration are factors affecting the response of the disease to neoadjuvant chemoradiotherapy.[19,20] In our study, complete response rates were found higher in patients who had no lymphovascular involvement. Apart from these factors, it was observed that chemotherapy administration before neoadjuvant chemoradiotherapy did not change pathological complete response rates.

One of the determinants of pathological response is the interval from completion of chemoradiation to surgery. In a meta-analysis in which 13 studies were evaluated, it was observed that the interval between preoperative chemoradiotherapy and surgery ≥8 weeks provided a better pathological complete response compared to less than 8 weeks. It has been reported that there is no difference in overall survival, disease-free survival, local recurrence and postoperative complications.[21] In another meta-analysis, they reported that most surgeons underwent surgery 6 weeks after neoadjuvant therapy was completed, but surgery performed in the 6–8-week period after neoadjuvant therapy increased pathological complete response rates.[22] In our study, the median time between neoadjuvant therapy and surgery is 55 days. When the pathological response rates were compared within 6 weeks and 6 weeks after neoadjuvant therapy, no difference was observed.

In a review published by Yi Li et al, it was stated that patients with middle and lower rectal cancer benefit more from neoadjuvant chemoradiotherapy than patients with upper rectal cancer.[23] In addition, in middle and lower rectal cancers, local recurrences are seen more commonly than upper rectal cancers due to heterogeneity of their lymphatic drainage.[24] Mathis K. L. et al reported in their study that tumor location did not make a significant difference in local recurrence.[25] In our study, it was found that local recurrence was not associated with tumor localization, but survival was worse in upper rectal cancer. It is may be due to percentage of patients diagnosed with T4 cancer are higher in the upper rectal cancers than the ones with lower rectal cancers; 23.3% and 18.6%, respectively.

Treatment of the upper third of the rectum remains controversial. There is controversy as to whether surgery alone is sufficient or whether neoadjuvant radiotherapy and/or chemotherapy should be administered to the upper rectal cancer patients with locally advanced disease. According to a review analysis by Popek et al., neo-adjuvant treatment for locally advanced rectal cancer (T3N0) located at 10-15 cm from the anal verge is not likely to offer additional benefit, whilst treatment of T4N0 upper rectal tumors should be individualized.[26] Based on tumor location, several authors suggest that the majority of tumors with their lower border above the anterior peritoneal refection should be treated with upfront surgery, avoiding neoadjuvant treatment.[27] Park et al. also suggested that upper rectum cancers have better prognosis because their treatment approach is similar with colon cancers surgically.[28] However, there are several studies supporting the view that upper rectal cancers should be treated as rectal cancer and neo-adjuvant treatment is recommended in case of high-risk upper rectal tumors.[29]

Our study was limited by the relatively small number of patients studied compared to other larger landmark trials. However, we were able to show that a neoadjuvant chemoradiotherapy followed by surgery for locally advanced rectal cancer had comparable outcomes in our local population.

In conclusion, it is observed that neoadjuvant chemoradiotherapy is effective in providing local control and survival in patients with locally advanced rectal cancer.

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