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Original Research

Comparison of Treatment Outcomes in Patients with Rectal Cancer

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ABSTRACT

Objective: The aim of the present study is to evaluate survival results and acute chemoradiotherapy toxicity in patients with rectal cancer who underwent preoperative chemoradiotherapy (CRT), postoperative CRT, and non-operative CRT.

Methods: The records of 139 patients with rectal cancer were analyzed retrospectively. Out of these, the data 9 (6%) patients who died during or immediately after treatment and 2 (1%) patients who gave up the treatment were not used in the survival analysis.

Results: Postoperative CRT was applied to 57 (44%) patients, preoperative CRT to 47 (37%) patients, and non-operative CRT to 24 (19%) patients. Non-operative CRT group was the oldest patient group (median age: 70). There was a difference between the treatment groups regarding tumor localization ($p<0.001$), pathological stage ($p<0.001$), lymphovascular (LVI, $p<0.004$), and perineural invasion (PNI, $p=0.017$). A difference was determined between the groups regarding median follow-up and the postoperative CRT group had the longest median follow-up ($p<0.001$). A difference was also determined between the groups regarding local recurrence and distant metastasis ($p=0.467$ and $p=0.901$, respectively). The three-year overall survival and disease-free survival rates were 78% and 78% for the postoperative CRT group, 76% and 73% for the preoperative CRT group, and 48% and 41% for the non-operative CRT group ($p<0.001$ and $p<0.001$, respectively). However, the difference between preoperative and postoperative CRT regarding overall survival and disease-free survival was not determined since the non-operative CRT group was included in survival analysis ($p=0.184$ and $p=0.073$, respectively). No difference found among the three groups regarding the adverse effects of chemoradiotherapy ($p>0.050$).

Conclusion: While no difference was determined between preoperative and postoperative CRT applications regarding local recurrence and distant metastasis, overall survival and disease-free survival, and adverse effects of treatment, LVI, and PNI determined in earlier pathological stage and lower frequency for the preoperative application. However, overall survival results of patients receiving non-operative CRT were worse as compared to patients receiving operative CRT.

Keywords: Non-operative chemoradiotherapy, postoperative chemoradiotherapy, preoperative chemoradiotherapy, rectal cancer

INTRODUCTION

The primary treatment of rectal cancer is surgery, however, the local and systemic failure rate increases up to 50% particularly for advanced stage tumors when treated with surgery alone (1, 2). The decreased success rate of surgery led researchers to combine treatments such as radiotherapy (RT) and chemotherapy (CT) with surgical treatment. However, at the time, studies on this combination of treatment schemes were also being done. National Institutes of Health emphasized in a consensus meeting held in 1990 that postoperative CT and RT improved local control and survival for locally advanced rectal cancers and that combined treatments are required in such cases. The use of postoperative RT and CT became common in the 1990s (3). In a meta-analysis published by the Colorectal Cancer Collaborative Group in 2001 (22 randomized studies and 8507 patients), it was revealed that adjuvant RT ensured recovery in local control. In survival analyses, this recovery was determined to be on the border (4). It was reported in the same meta-analysis that local recurrence was decreased by 37% in postoperative RT and 46% in preoperative RT (4).

Simultaneous chemoradiotherapy (CRT) in locally advanced rectal cancer has also been investigated in large-scale studies. Several studies indicated that CRT applied following surgery in rectal cancers improved the disease-free survival and overall survival rates, and regressed local recurrence rates as compared to patients who received only RT (5-10). Preoperative RT and preoperative CRT were compared in the study by Braendengen et al. (8) on the basis of complete pathological response, local control, disease-specific survival rate, and preoperative CRT was found to be more advanced. However, it was also reported to increase grade 3–4 acute toxicity. In EORTC trial22921, it was shown that while tumor down-stating was better ensured with preoperative CRT in the early results, improved survival was not seen in long-term results. However, preoperative CRT proved advantageous for local recurrence (9, 10). In French FFCD 9203 trial, results were similar to those by EORTC obtained for preoperative CRT (11).

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In a German study comparing the preoperative and postoperative CRT and in an NSABP R-03 trial, the cumulative local recurrence rates were shown to be lower in preoperative CRT patients. Moreover, 5-year disease-free survival (DFS) in the NSABP R-03 trial and grade 3–4 diarrhea in the German study were reported to be increased in preoperative CRT cases (12). Thus, it was indicated that success was achieved in both local-systemic recurrences as well as in survival outcomes of locally advanced rectal cancers with combined treatments. Nevertheless, a standard algorithm has not been created as yet to determine the application time of treatment modalities (13, 14).

The complete response following preoperative CRT can be observed in 8–30% of patients (15-18). Researchers have observed that survival outcomes were better in patients for whom the complete response was observed after preoperative CRT, and have started to develop the "wait and watch" approach after preoperative CRT (19-21).

The aim of the present study was to evaluate the survival outcomes and the level of acute chemoradiotherapy toxicity of patients with rectal cancer who underwent preoperative CRT, postoperative CRT, and non-operative CRT.

METHODS

This study was conducted at the Cumhuriyet University Medical Faculty Hospital, Turkey, in accordance with the principles of the Declaration of Helsinki (date: 19/04/2017, a decision no: 2017-04/13). The data of 139 rectal cancer patients who were treated between 2007 and 2015 at the Oncology Center of Cumhuriyet University Medical Faculty Hospital were retrospectively evaluated. The patients were examined under three groups: preoperative CRT, postoperative CRT, and non-operative CRT.

Table 1. Demographic characteristics of the patients

	Postop CRT n=57 (44%)	Preop CRT n=47 (37%)	CRT n=24 (19%)	p
Gender				
Female	38 (67)	32 (68)	20 (83)	
Male	19 (33)	15 (32)	4 (17)	0.298
Age				
Mean (year)	60.2±1.3	55.6±1.7	72.5±1.9	<0.001
Comorbidity				
No	32 (56)	29 (62)	12 (50)	
Yes	25 (44)	18 (38)	12 (50)	0.631
ECOG PS				
ECOG 0	30 (53)	22 (47)	8 (33)	
ECOG 1	25 (44)	21 (45)	11 (46)	
ECOG 2–4	2 (3)	4 (8)	5 (21)	0.123

ECOG: Eastern Cooperative Oncology Group; PS: performance status; CRT: chemoradiotherapy

The performance status of the patients was evaluated by the ECOG (Eastern Cooperative Oncology Group) scoring system at the time of metastases. Pretreatment evaluation was performed by complete blood count, biochemical profiles, serum CEA (serum carcinoembryonic antigen), colonoscopy with biopsy, abdominopelvic CT scan, EUS (Endoscopic Ultrasound), and chest CT scan. In addition to these examinations, some patients underwent pelvic MR and PET-BT. Clinical staging was performed using the above-mentioned examinations and pathological staging was performed after the surgery. The stage of disease was evaluated according to the 2010 TNM classification developed by the International Union against Cancer and the American Joint Committee on Cancer (22).

Radiotherapy was performed using linear accelerators. Eclipse (version 8.6; Varian Medical Systems, Inc. Palo Alto, CA, USA) was used as the three-dimensional conformal radiotherapy planning software program. All patients received a total RT dose of 50.4 Gy with a daily dose of 1.8 Gy. The chemotherapies administered simultaneously with RT were weekly FUFA, infusional 5FU, or capecitabine. Adjuvant chemotherapy was administered with FUFA, FOLFOX6, XELOX, and FOLFİRİ.

During the course of treatment, the adverse effects of chemoradiotherapy were evaluated weekly based on the RTOG (Radiation Therapy Oncology Groups) scoring. According to the acute radiation morbidity measurement criteria constituted by RTOG, the acute radiation morbidity ranged between grade 0 and 4 (23). Side effects of RT on patients were evaluated based on these criteria once a week during treatment and once every three months during follow-ups and weights. The ECOG performances of patients were also recorded during the evaluation. Weight loss was assessed as loss of 5% of patients' weight during CRT.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Windows 14.0 (SPSS Inc.; Chicago, IL, USA) was used for the statistical analysis. The mean, standard deviation, frequency, and median were used to evaluate descriptive statistics. The Kruskal-Wallis test was used to compare the average of the patients' age and the number of follow-ups. Categorical data were compared statistically using the chi-square test or Fisher's exact test. The survival rates were calculated according to the Kaplan–Meier method. P values of ≤0.05 were accepted as statistically significant.

RESULTS

Out of the 139 patients who received treatment for rectal cancer, 2 (1%) were not included in survival analysis because they gave up the treatment, 3 (2%) expired during the study (death due to pulmonary emboli, diabetic coma, and heart attack), and 6 (4%) were excluded following CRT. Total survival analysis of the remaining 128 patients was performed.

Postoperative CRT was applied to 57 (44%) patients, preoperative CRT to 47 (37%), and non-operative CRT to 24 (19%). There was a statistical difference in the mean age of the patients ($p<0.001$), where the mean age of the patients undergoing non-operative CRT was observed to be higher as compared to the other groups. Demographic characteristics of the patients were summarized in Table 1.

Table 2. Characteristics of the disease

	Postop CRT n=57 (44%)	Preop CRT n=47 (37%)	CRT n=24 (19%)	p
Rectal localization				
Proximal	18 (32)	2 (4)	1 (4)	
Medial	23 (40)	17 (36)	9 (38)	
Distal	16 (28)	28 (60)	14 (58)	<0.001
Preop. T stage				
T2	–	1 (2)	1 (4)	
T3	–	13 (28)	11 (46)	
T4	–	33 (70)	12 (50)	0.245
Preop. N stage				
Nod negative	–	20 (43)	10 (42)	
Nod positive	–	27 (57)	14 (58)	0.945
Surgery				
Low anterior resection	44 (77)	31 (66)	–	
Abdominoperineal resection	11 (19)	15 (32)	–	
Transanal resection	2 (4)	1 (2)	–	0.323
Postop. Stage				
Complete response	–	6 (13)	–	
Stage I	2 (4)	11 (23)	–	
Stage II	21 (37)	15 (32)	–	
Stage III	33 (58)	15 (32)	–	
Stage IV	3 (5)	–	–	<0.001
Extracapsular invasion				
No	41 (79)	35 (88)	–	0.278
Yes	11 (21)	5 (12)		
Surgical margin				
Negative	52 (91)	42 (89)	–	
Positive	5 (9)	5 (11)	–	0.542
Lymphovascular invasion				
No	30 (58)	31 (86)	–	
Yes	22 (42)	5 (14)	–	0.004
Perineural invasion				
No	30 (58)	30 (81)	–	
Yes	22 (42)	7 (19)	–	0.017
Grade				
Grade 1	8 (15)	10 (28)	3 (43)	
Grade 2	38 (72)	21 (58)	4 (57)	
Grade 3	7 (13)	5 (14)	–	0.244

CRT: chemoradiotherapy

Low anterior resection (LAR) was performed on 44 (77%) patients undergoing postoperative CRT, abdominoperineal resection (APR) on 11 (19%) patients, and transanal resection on 2 (4%) patients (CRT was applied after resection because these patients did not consent to advanced surgery). Metastasectomy was also added along with LAR in 3 (5%) patients. 31 (66%) patients receiving preoperative CRT underwent LAR, 15 (32%) underwent APR, and 1 (2%) underwent transanal resection. The between-group difference was not determined regarding the type of surgery performed (p=0.323). In distal tumors, LAR was applied to 5 (31%) patients receiving postoperative CRT (N=16), APR to 9 patients (56%), and transanal resection to 2 patients (13%); whereas, LAR was applied to 16 (57%) of the patients receiving preoperative CRT (N=28), APR to 11 (39%), and transanal resection to 1 (4%). No difference was found in distal tumors regarding surgical treatment (p=0.195). Complete response was determined in 6 (13%) out of 47 patients receiving preoperative CRT, partial response in 31 patients (66%), stable response in 9 patients (19%), and response to progress in 1 (2%). Table 2 shows tumor characteristics and surgical treatments of the groups.

When the general characteristics of the disease were examined; the between-group difference was not determined regarding preoperative T stage, preoperative N condition, type of surgery, extracapsular invasion, surgical limit, and tumor grade. A difference was determined between the groups regarding localization of disease (p<0.001), postoperative disease stage (p<0.001), LVI (p=0.004), and PNI (p=0.017). The patients undergoing preoperative CRT and non-operative CRT were observed to have more distal rectum localization. In the postoperative period, the earlier pathological stage was determined in patients undergoing preoperative CRT, whereas the patients receiving postoperative CRT reached a more advanced pathological stage. The LVI and PNI were also increased in patients undergoing postoperative CRT.

Table 3. Survival of the patients

	Postop CRT n=57 (44%)	**Preop CRT n=47 (37%)**	**Non-opere CRT n=24 (19%)**	**p**
Median follow-up (month)	55.4±3.8	41.5±3.4	27.7±3.4	<0.001
Local Recurrence				
No	54 (95)	42 (89)	21 (87)	
Yes	3 (5)	5 (11)	3 (13)	0.467
Local Recurrence				
No	54 (95)	42 (89)	–	
Yes	3 (5)	5 (11)	–	0.256
Distant Metastasis				
No	44 (77)	38 (81)	19 (79)	
Yes	13 (23)	9 (19)	5 (21)	0.901
Distant Metastasis				
No	44 (77)	38 (81)	–	
Yes	13 (23)	9 (19)	–	0.417
Overall Survival				
The 3-year OS	78%	76%	48%	
Median survival	Not yet	75 month	36 month	0.001
Overall Survival				
The 3-year OS	78%	76%	–	
Median survival	Not yet	75 month	–	0.184
Disease-free survival				
The 3-year DFS	78%	73%	41%	
Median survival	101 month	64 month	26 month	<0.001
Disease-free survival				
The 3-year DFS	78%	73%	–	
Median survival	101 month	62 month	–	0.073

CRT: chemoradiotherapy; DFS: disease free survival

Table 2 shows tumor characteristics and surgical treatments of the groups.

In a median 35-month follow-up (range: 1–148 months) for all patients, local recurrence was detected in 3 (5%) patients undergoing postoperative CRT, 5 (11%) patients undergoing preoperative CRT, and 3 (13%) patients undergoing non-operative CRT (p=0.467). When preoperative CRT and postoperative CRT were compared without including outcomes of the patients undergoing non-operative CRT, no difference was determined between the groups regarding local recurrence (p=0.256). Distant metastasis was determined in 13 (23%) patients undergoing postoperative CRT, 9 (19%) patients undergoing preoperative CRT, and 5 (21%) patients undergoing non-operative CRT (p=0.312). The between-group difference regarding distant metastasis was not determined when preoperative CRT and postoperative CRT were compared without including the outcomes of patients undergoing non-operative CRT (p=0.417).

Table 4. Side effects of chemoradiotherapy

	Postop CRT n=57 (44%)	Preop CRT n=47 (37%)	CRT n=24 (19%)	p
Upper Gastrointestinal System				
Grade 0	37 (65)	34 (72)	18 (75)	
Grade 1–2	20 (35)	13 (28)	6 (25)	0.580
Lower Gastrointestinal System				
Grade 0	19 (33)	12 (25)	3 (13)	
Grade 1–2	35 (62)	29 (62)	20 (83)	
Grade 3–4	3 (5)	6 (13)	1 (4)	0.161
Genitourinary System				
Grade 0	35 (61)	29 (62)	15 (63)	
Grade 1–2	21 (37)	18 (38)	9 (37)	
Grade 3–4	1 (2)	–	–	0.868
White blood cell				
Grade 0	46 (82)	38 (81)	16 (67)	
Grade 1–2	11 (19)	8 (17)	8 (33)	
Grade 3–4	–	1 (2)	–	0.357
Neutrophil				
Grade 0	52 (91)	41 (87)	21 (88)	
Grade 1–2	5 (9)	6 (13)	3 (12)	0.780
Platelet				
Grade 0	55 (97)	44 (94)	22 (92)	
Grade 1–2	2 (3)	3 (6)	2 (8)	0.644
Hemoglobin				
Grade 0	49 (86)	34 (87)	20 (83)	
Grade 1–2	8 (14)	13 (28)	4 (17)	0.202
Hematocrit				
Grade 0	55 (92)	43 (92)	22 (92)	
Grade 1–2	4 (8)	4 (8)	2 (8)	0.517
Loss in weight[1]				
No	52 (91)	41 (87)	20 (75)	
Yes	5 (9)	6 (13)	4 (25)	0.144

[1]Loss in weight during chemoradiotherapy
CRT: chemoradiotherapy

Figure 1. Treatment-based overall survival curves

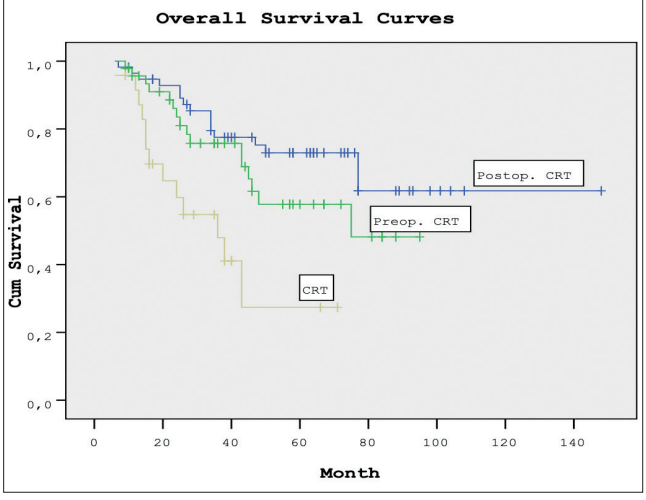
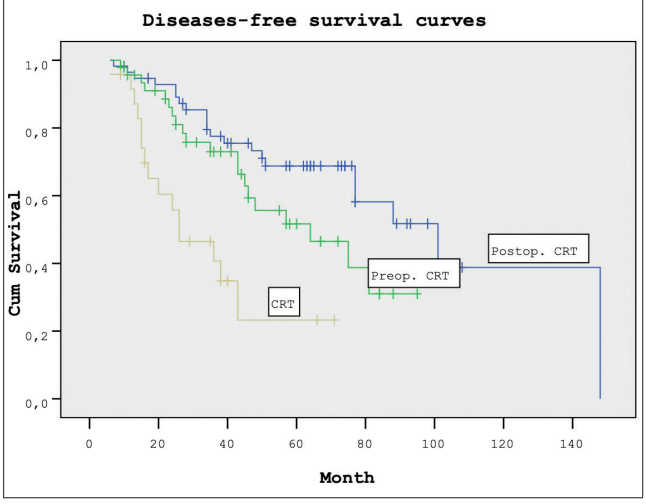


Figure 2. Treatment-based disease-free survival curves



The 3-year overall survival and median survival rates were 78% and no median survival in patients undergoing postoperative CRT, 76% and 75 months in patients undergoing preoperative CRT, and 48% and 36 months in patients undergoing non-operative CRT, respectively (p=0.001). When survival outcomes of postoperative CRT and preoperative CRT were compared without including patients undergoing non-operative CRT, no statistically significant difference was observed (p=0.184). The 3-year DFS and disease-free median survival were determined to be 78% and 101 months in postoperative CRT, 73% and 64 months in preoperative CRT, and 41% and 26 months in non-operative CRT (p<0.001). No statistically significant difference was determined when DFS outcomes of postoperative CRT and preoperative CRT were compared without including the patients undergoing non-operative CRT (p=0.073). Table 3 shows the mean follow-up, local recurrence, distant metastasis, and survival outcomes of all patient groups. According to the type of treatment, overall survival curves are shown in Figure 1 and, DFS curves are shown in Figure 2.

No significant difference was determined between the three groups when the adverse effects of patients who were evaluated with RTOG were compared. Prevalence of weight loss after the treatment also was similar between the groups. Table 4 shows the comparison of the groups regarding adverse effect and weight loss observed after treatment.

DISCUSSION

Rectal cancer is one of the leading causes of cancer-related deaths in developed and developing countries and continues to be a crucial health problem. The main objective of multiple treatment protocols of surgery, chemotherapy, and radiotherapy is to prevent a loco-regional recurrence, increase survival, and preserve the quality of life via primary tumor resection (5).

In locally advanced rectal cancers, the use of postoperative CRT improves both local control and survival (24, 25). In postoperative treatment, the pathological stage is determined after surgery and the need for adjuvant treatment is better known, which is an important advantage compared to preoperative practices and avoids unnecessary treatment or overtreatment. It was also suggested by some researchers that postoperative CRT could be more effective in determining recurrence and secondary events (26, 27). However, postoperative CRT was found to result in worse outcomes because of increased adverse effect profile, poor patient tolerance, and lesser oxygen in RT area (27). Postoperative CRT was applied to 44% of patients in the present study. Only 28% of patients receiving postoperative CRT had distal rectum localization and the follow-up of these patients was determined to be longer as compared to other patient groups. At the beginning of periods included in the study, postoperative CRT application was higher; the application tended toward preoperative treatments as time progressed.

The preoperative treatment provides an opportunity for optimum planning because the anatomy is not deformed and has more advanced tissue oxygenation, because of which the cancer tissue is more radiosensitive and low doses are more efficient. This allows surgical resection to shrink advanced cancers and enable sphincter protecting surgery in distal tumors. The predictions about it resulting in longer survival rates by allowing relatively better local control have been shown among the advantages of preoperative CRT (28, 29). A preoperative CRT treatment option that allows sphincter protection in distal and central tumors and provides an opportunity for life without colostomy should be primarily preferred. When applying preoperative CRT to 47% of patients in the present study, 60% of these were observed to have a distal rectal tumor. Preoperative treatments were recorded as preferred treatments, particularly in distal tumors.

Combination of surgical intervention along with chemoradiotherapy in rectal cancer is an accepted method of treatment. However, there is no consensus yet about the preoperative or postoperative use of CRT because both applications have disadvantages and advantages. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 study, 130 patients were evaluated in the preoperative branch, and 137 patients were evaluated in the postoperative branch. While early results of this

study reported that elevated complete pathological response was obtained with preoperative CRT application, it was also stated in reports published in 2009 that 5-year DFS was more improved in patients undergoing preoperative CRT (64.7% vs. 53.4%, p=0.011). Even though it was not statistically significant in the same study, overall survival was also reported to be higher in preoperative CRT branch (30).

A study by the Dutch Rectal Cancer Group (code: CAO/ARO/A10-94) shows the position of preoperative CRT compared to postoperative CRT. A total of 823 patients with stage II-III rectal cancer were included in this study and the early results reported that preoperative CRT provided distinct regression of the tumor, increased local control and patient tolerance, reduced acute-late toxicity, and possibly increased sphincter protection rates in distal tumors compared to postoperative treatment (9-14). After publishing the data of the study, preoperative CRT was accepted as the standard treatment for locally advanced rectal cancer (9-14). According to the results of the same study after a median 11-year follow-up, the 10-year overall survival rates were reported to be 59.6% for preoperative CRT and 59.9% for postoperative CRT (p=0.850). Results showed no difference in overall survival or DFS and distant metastasis varied for recurrence. While the 10-year cumulative recurrence ratio was 7.1% in patients undergoing preoperative CRT, it was determined to be 10.1% in patients undergoing postoperative CRT (p=0.048) (12). The 5FU-based chemotherapies were simultaneously used with RT in both the above-mentioned studies.

In a study by Park et al. (31), preoperative and postoperative CRT was compared using capecitabine simultaneously with RT. Patients with cT4 or N+ 240 rectal cancer were evaluated, and no difference was determined between preoperative or postoperative CRT regarding 3-and 5-year overall survival, DFS, and incidence of cumulative local recurrence as a result of median 52-month follow-up. However, the study also emphasized that rates of sphincter protection were higher in the preoperative application (68% vs. 42%, p=0.008). Perineural invasion and lymphovascular invasion were reported to be less frequent as pathological characteristics for those undergoing preoperative CRT. Further, early stages were determined to be more prevalent in the patient group undergoing preoperative CRT. In the present study, on the other hand, there was no difference between preoperative or postoperative applications regarding 3-year overall survival, DFS, local recurrence, and distant metastasis for both applications. However, the location of the tumor played an important role in choosing the treatment. The early pathological stage was determined in patients undergoing preoperative CRT due to down-staging. Similar to other studies, statistically significant decreased levels of perineural and lymphovascular invasion were found in this patient group. Even though there was no difference between applications with respect to the type of surgery, APR surgery was performed in distal tumors in 39% of patients undergoing preoperative CRT and 56% of patients undergoing postoperative CRT.

The pathologic complete response can be ensured in 8–20% of cases after preoperative CRT (16-20). Researchers have started to evaluate the results of the "wait and watch" approach without radical surgery in patients whose clinical complete response following CRT was confirmed via biopsy (27). Habr-Gama et al. (26) conducted the first studies on "wait and watch" approach in patients with complete response. In their study including 365 patients, they followed-up 71 patients with complete response after preoperative CRT, performed surgery on 194 patients with incomplete response and reported that 5-year overall and DFS rate of the patients was 88% and 83% for patients underwent operation, respectively and 100% and 92% for patients who were followed-up. In their prospective study, Renehan et al. (27) determined that while the 3-year DSF outcome of "wait and watch" group was 88%, it was 78% for the group undergoing surgery (p=0.043). The 3-year overall survival was observed to be 96% in the non-operative CRT group and 87% in the surgery group (p=0.024). In the present study, the pathological complete response was achieved in 13% of the patients. We intended to also show the outcomes of the mandatory "wait and watch" group arising not from the "wait and watch" approach but from the fact that patients could not receive surgical treatment because of various reasons. Most of these patients did not accept the treatment due to either permanent colostomy or false belief. When these patients were evaluated generally, their median ages were observed to be higher as compared to other patient groups (median age: 70). Even though outcomes of preoperative treatment were not evaluated for many patients, the 3-year median survival of these patients was 48%, and median survival was 36 months. It was found that the 3-year DFS rate of the same patient group was 41% and disease-free median survival was 26 months. When outcomes of these patients were evaluated as compared to operated patients, they were observed to have statistically significant worse outcomes regarding both overall survival and DFS. However, it is important to consider that the response to treatment after preoperative CRT was required to be evaluated in the patients who were not scheduled for surgery.

Since the outcomes of treatment approaches are similar, the treatment toxicity should be evaluated for every treatment modality. All studies comparing preoperative and postoperative CRT also reported acute side effects while reporting early results of the treatment. In a German study, the existence of any grade 3–4 toxicity and side effect diarrhea were observed to be more prevalent in postoperative CRT and were found to be statistically significant (13). In this study, grade 3–4 toxicity was determined to be 27% in patients undergoing preoperative CRT and 40% in patients undergoing postoperative CRT (13). Acute toxicities generally associated with the treatment were determined to be similar for both groups in the NSABP R-03 trial (30). In the study conducted by Park et al. (31) that compared pre-postoperative CRT using capecitabine, there was no difference between the groups regarding acute adverse effects. Similar to the two surveys above, the between-group difference was not determined regarding treatment-related acute adverse effects in the present study as well. Similarly, even though patients undergoing non-operative CRT had the highest weight loss regarding weight loss during the treatment, no statistical difference was obtained for all three groups.

CONCLUSION

As a result of the present study, it was found that while no difference was determined between preoperative and postoperative CRT applications regarding local recurrence and distant metastasis prevalence, overall and DFS, and adverse effects of treatment, the earlier pathological stage and less frequent LVI and PNI was determined for the preoperative application. However, all survival outcomes of the patients undergoing non-operative CRT gave worse results as compared to operated patients. Non-operative CRT seems far from being an option of sufficient treatment, particularly in patients without complete response.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Cumhuriyet University School of Medicine (date: 19.04.2017, no: 2017-04).

Informed Consent: Due to the retrospective design of the study and some of the patients died, informed consent was not taken.

Author Contributions: Concept – E.E.; Design – E.E.; Supervision – E.E.; Resources – E.E.; Materials – B.Y.; Data Collection and/or Processing – E.E.; Analysis and/or Interpretation – B.Y.; Literature Search – E.E.; Writing Manuscript – E.E.; Critical Review – E.E.

Conflict of Interest: The authors have no conflicts of interest to declare.

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