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Title: Comparison of Treatment Outcomes in Patients with Rectal Cancer

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Abstract

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

Method: Data of 139 patients with rectal cancer were analyzed retrospectively. However, data of 9 (6%) patients who died during and immediately after treatment and 2 (1%) patients who gave up the treatment were not used in the survival analysis.

Results: Postoperative CRT applied to 57 (44%) patients, preoperative CRT to 47 (37%) patients, and non-operative CRT to 24 (19%) patients. Non-operative CRT patient 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). While a difference determined between the groups regarding median follow-up, the patient group receiving postoperative CRT had the longest median follow-up (p<0.001). A difference 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 group receiving postoperative CRT, 76% and 73% for the group receiving preoperative CRT,

48% and 41% for the group receiving non-operative CRT (p<0.001 and p<0.001, respectively). However, the difference between pre/postoperative CRT regarding overall and disease-free survival was not determined since non-operative CRT group included in survival analysis (p=0.184 and p=0.073, respectively). No difference found between three groups regarding adverse effects of chemoradiotherapy (p>0.050).

Conclusions: While no difference determined in pre/postoperative CRT applications regarding the incidence of local recurrence and distant metastasis, and overall 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 compared to patients receiving operative CRT.

Key Words: Rectal Cancer, Preoperative chemoradiotherapy, Postoperative chemoradiotherapy, Non-operative chemoradiotherapy

Introduction

Primary treatment of rectal cancer is surgery, but local and systemic failure rate increases up to 50% particularly for advanced stage tumors when treated with the surgery alone (1,2). The decreased success of treatment has led researchers to combine treatments such as radiotherapy (RT) and chemotherapy (CT) with surgical treatment. However, studies on how the combination of treatment schemes would be also have been ongoing at present yet. NIH (National Institutes of Health) emphasized in consensus meeting held in 1990 that postoperative chemotherapy and RT have improved local control and survival for locally advanced rectal cancers and combined treatments are required to use in these patients. The use of postoperative RT and CT has become common in the 1990s (3). In a meta-analysis published by Colorectal Cancer Collaborative Group in 2001 (22 randomized studies, 8507 patients), adjuvant RT was revealed to ensure 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 postoperative RT decreased local recurrence by 37%, preoperative RT by 46% (4).

Simultaneous chemoradiotherapy (CRT) in locally advanced rectal cancer has also investigated with large-scale studies. Several studies were indicated that CRT applied following surgery in rectal cancers improved disease-free survival and overall survival rates, and regressed local recurrence rates compared to patients who received only RT treatment (5-10). Preoperative RT and preoperative CRT were compared in the study by Brœndengen et al. (2008), pathological complete response, local control, disease-specific survival were stated to be more advanced for preoperative CRT. However, it was also reported to increase grade 3-4 acute toxicity (8). In EORTC trial22921, it was showed that while tumor down-stating was ensured better with preoperative CRT in early results, improved survival could not be present in long-term results. However, preoperative CRT was indicated to provide an

advantage for local recurrence (9-10). In French FFCD 9203 trial, results were similar to those by EORTC obtained for preoperative CRT (11).

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

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

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

Material and Methods

This study was conducted at the Turkey, by the principles of the Declaration of Helsinki (date: 19/04/2017, a decision no: 2017-04/13). In this study, the data of 139 patients who applied due to rectal cancer and treated between 2007 and 2015 in the Oncology Center were evaluated retrospectively. The patients were examined under three groups including preoperative CRT, postoperative CRT, and non-operative CRT concerning their ways of treatment.

The performance status of the patients was evaluated by the ECOG (Eastern Cooperative Oncology Group) scoring system at the time of the metastases. Pretreatment evaluation was performed by complete counts, 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 by using the above examinations, and pathological staging 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 were received 50,4 Gy RT dose in total consisting of daily 1,8 Gy. Chemotherapies which were administered simultaneously with RT were weekly FUFA, infusional 5FU or capecitabine. Adjuvant chemotherapy was administered as FUFA, FOLFOX6, XELOX, and FOLFİRİ.

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

The Statistical Package for Social Sciences (SPSS) for Windows 14.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis. For descriptive statistics, the mean, standard deviation, frequency, and median were used. Kruskal Wallis test was used for comparing the averages of patients' age and follow-ups. Categorical data were compared statistically by 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

Of 139 patients receiving treatment for rectal cancer, 2 (1%) were not included in survival analysis because they gave up treatment incomplete, 3 (2%) existed during the study (they died due to pulmonary emboli, diabetic coma, heart attack), 6 (4%) were exited following CRT. Survival analysis of remaining 128 patients in total was performed.

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

Low anterior resection (LAR) was applied to 44 (77%) of the patients undergoing postoperative CRT, abdominoperineal resection (APR) to 11 (19%), and transanal resection to 2 (4%) (CRT was applied after resection because these patients did not approve advanced surgery). Metastasectomy was also added along with LAR in 3 (5%) patients. 31 (66%) of the patients receiving preoperative CRT underwent LAR, 15 (32%) underwent APR, and 1(2%) underwent transanal resection. The difference was not determine between the groups regarding surgery type performed (p=0.323). In distal tumors, LAR was applied to 5 (31%) of the patients receiving postoperative CRT (N:16), APR to 9 patients (56%), 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 found in distal tumors regarding surgical treatment (p=0.195). Complete response was determined in 6 (13%) of 47 patients receiving preoperative CRT, partial response in 31 patients (66%), the 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 general characteristics of the disease were examined; the difference was not determine between the groups regarding preoperative T stage, preoperative N condition, type of surgery, extracapsular invasion, surgical limit, and 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. At the postoperative period, the earlier pathological stage was determined in patients undergoing preoperative CRT; whereas, the patients receiving postoperative CRT had a more advanced pathological stage. The presence of LVI and PNI was also observed more in patients undergoing postoperative CRT. Table 2 shows tumor characteristics and surgical treatments of the groups.

In a median 35-month follow-up (range 1-148) for all patients; local recurrence was detected in 3 (5%) of the patients undergoing postoperative CRT, 5 (11%) of the patients undergoing preoperative CRT, and 3 (13%) of the 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%) of the patients undergoing postoperative CRT, 9 (19%) of the patients undergoing preoperative CRT, and 5 (21%) of the patients undergoing non-operative CRT (p=0.312). The difference was not determined between the groups regarding distant metastasis when preoperative CRT and postoperative CRT were compared without including the outcomes of patients undergoing non-operative CRT (p=0.417).

Three-year overall survival and median survivals 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, statistically significant difference was not observed (p=0.184). Three-year disease-free survival 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). A statistically significant difference was not determine when disease-free survival outcomes of postoperative CRT and preoperative CRT were compared without including the patients undergoing non-operative CRT (p=0.073). Table 3 shows mean follow-up, local recurrence, distant metastasis, and survival outcomes of the patient groups. According to the type of treatment, overall survival curves were shown in Figure 1 and, disease-free survival curves were shown in Figure 2.

A significant difference was not determine between every three groups when adverse effects of patients who were evaluated concerning RTOG acute adverse effects were compared. Prevalence of weight loss after the treatment also was similar between the groups. Table 4 shows the comparison of the groups in details regarding adverse effect and weight loss observed after treatment.

Discussion

Rectal cancer is one of the causes leading cancer-related deaths in developed and developing countries and continues to be a crucial health problem. The main objective of multiple use protocols of surgery, chemotherapy, and radiotherapy is to prevent 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). The fact that in postoperative practices pathological stage is determined and the need for adjuvant treatment is known better is an important advantage compared to preoperative practices so that unnecessary treatments/overtreatment are not administered to patients. It was also suggested by some researchers that postoperative CRT could be more effective for determining recurrence and secondary events (26,27). However, postoperative CRT was claimed to result in worse outcomes because of increased adverse effect profile, poor patient tolerance and having RT area with lesser oxygen (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 meant follow-up of these patients was determined to be longer compared to other patient groups. At the beginning of periods

included in the study, postoperative CRT application was higher; the application had a trend towards preoperative treatments as the time progressed to the present day.

The fact that it provides an opportunity for optimum planning because anatomy is not deformed has more advanced tissue oxygenation and thus cancer tissue is more radiosensitive, and low doses are more efficient, allows surgical resection ensuring advanced cancer to shrink, enables sphincter protecting surgery in distal tumors, and the predictions about that it can result in longer survival rates by allowing relatively better local control have been shown among advantages of preoperative CRT (28,29). 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 in, particularly 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 applications have disadvantages and advantages. In National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 study, 130 patients were evaluated in the preoperative branch, and 137 patients were assessed 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 no statistically significant in the same study, overall survival was also reported to be higher in preoperative CRT branch (30). The study pointing out the position of preoperative CRT compared to postoperative CRT is the study with code CAO/ARO/A10-94 by Dutch Rectal Cancer Group. 823 patients with stage II-III rectal cancer were included in this study and it was reported in early results of study that preoperative CRT provided distinct regression for stage of tumor, local control increased, patient tolerance was better, there were lesser acute-late toxicity and possibly increased sphincter protection rates in distal tumors compared to postoperative treatment (9-14). After publishing data of the study, preoperative CRT was accepted as the standard treatment for locally advanced rectal cancer (9-14). According to results of the same study after a median 11-year follow-up, 10-year overall survival rates were reported to be 59.6% for preoperative CRT and 59.9% for postoperative CRT (p=0.850). Results without a difference regarding overall survival, disease-free survival, and distant metastasis varied for recurrence. While ten-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). 5FU-based chemotherapies were

simultaneously used with RT in both studies above. In the study by Park et al., pre/postoperative CRT was compared using capecitabine simultaneously with RT. In this study, the patient with cT4 or N+ 240 rectal cancer was evaluated, and the difference was not determined between pre/postoperative CRT regarding 3-and 5-year overall survival, disease-free survival, and incidence of cumulative local recurrence as a result of median 52-month follow-up. However, they were also emphasized that rates of sphincter protection be higher in the preoperative application (68% vs. 42%, *p*=0.008) (31). Perineural invasion and lymphovascular invasion were reported to be less frequency pathological characteristics for those undergoing preoperative CRT in this study. In the same study, early stages were determined to be more prevalent in the patient group undergoing preoperative CRT as well. In the present study, on the other hand, there was no difference between preoperative or postoperative applications regarding 3-year overall survival, disease-free survival, local recurrence, and distant metastasis for both applications. However, the location of the tumor played an important role in choosing treatment. The earlier pathological stage was determined in patients undergoing preoperative CRT due to down-staging. Similar to other studies, statistically significant less perineural and lymphovascular invasion were found in this patient group. Even though there was no difference between applications concerning 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 interest in the issue among results of studies about “wait - watch” approach without radical surgery in patients whose clinical complete response following CRT was confirmed via biopsy (27). Habr-Gama et al. were the researchers to conduct the first studies on “wait - 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 to 194 patients with incomplete response after, moreover, they reported that 5-year overall and disease-free survival rate of the patients was 88% and 83% for patients underwent operation, respectively; and 100% and 92% for patients who were followed up (26). In their study with a prospective design, Renehan et al., determined that while 3-year DSF outcome of “wait - watch” group was 88%, these rates were 78% for the group undergoing surgery (*p*=0.043). Three-year overall survival, on the other hand, was observed to be 96% in non-operative CRT group and 87% in the surgery group (*p*=0.024) (27). The pathological complete response was achieved in 13% of the patients in the present study. In the present study, we intended to give also the outcomes of mandatory “wait - watch” group arising from not due to “wait - watch” approach but from the fact that patients could not receive surgical treatment because of various reasons. Most of these patients were the ones who did not accept the treatment due to either permanent colostomy or false believing. When this patient was evaluated

generally, their median ages were observed to be more advanced compared to other patient groups (median age 70). Even though outcomes of preoperative treatment were not evaluated for many patients, 3-year median survival of these patients was 48%, and median survival was 36 months. It was found that 3-year disease-free survival rate of the same patient group was 41% and disease-free median survival was 26 months. When outcomes of these patients were evaluated compared to operated patients, they were observed to have statistically significant worse outcomes regarding both overall survival and disease-free survival. It should be considered about these outcomes that response to treatment after preoperative CRT was required to be evaluated in the patients who were not considered to undergo surgery.

The fact that outcomes of treatment approaches are similar necessitates treatment toxicity to be evaluated for every alternative treatment. All studies comparing preoperative and postoperative CRT also reported acute side effects while giving early results of 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. It was 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., to compare pre-postoperative CRT using capecitabine, there was no difference between the groups regarding acute adverse effects (31). Similar to two surveys above, the difference was not determined between the groups regarding treatment-related acute adverse effects in the present study as well. Again, 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.

As a result of the present study, it was found that while no difference was determined between pre/postoperative CRT applications regarding local recurrence and distant metastasis prevalence, overall and disease-free survival, and adverse effects of treatment, 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 compared to operated patients. Non-operative CRT seems far from being an option of sufficient treatment particularly in patients without complete response.

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Table 1. Demographic characteristics of the patients

	Postop CRT N=57 (%44)	Preop CRT N=47 (%37)	CRT N=24 (%19)	*p* value
Gender				
Female	38 (67)	32 (68)	20 (83)	0,298
Male	19 (33)	15 (32)	4 (17)	
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)	0,631
Yes	25 (44)	18 (38)	12 (50)	

ECOG PS				
ECOG 0	30 (53)	22 (47)	8 (33)	0,123
ECOG 1	25 (44)	21 (45)	11 (46)	
EGOG 2-4	2 (3)	4 (8)	5 (21)	

Table 2. Characteristics of the disease

	Postop CRT N=57 (%44)	Preop CRT N=47 (%37)	CRT N=24 (%19)	*p* value
Rectal localization				
Proximal	18 (32)	2 (4)	1 (4)	**<0,001**
Medial	23 (40)	17 (36)	9 (38)	
Distal	16 (28)	28 (60)	14 (58)	
Preop. T stage				
T2	-	1 (2)	1 (4)	0.245
T3	-	13 (28)	11 (46)	
T4	-	33 (70)	12 (50)	
Preop. N stage				
Nod negative	-	20 (43)	10 (42)	0.945
Nod positive	-	27 (57)	14 (58)	
Surgery				
Low anterior resection	44 (77)	31 (66)	-	
Abdominoperineal resection	11 (19)	15 (32)	-	0.323
Transanal resection	2 (4)	1 (2)	-	

Postop. Stage				
Complete response	-	6 (13)	-	
Stage I	2 (4)	11 (23)	-	
Stage II	21 (37)	15 (32)	-	**<0,001**
Stage III	33 (58)	15 (32)	-	
Stage IV	3 (5)	-	-	
Extracapsular invasion				
No	41 (79)	35 (88)	-	0,278
Yes	11 (21)	5 (12)		
Surgical margin				
Negative	52 (91)	42 (89)	-	0,542
Positive	5 (9)	5 (11)	-	
Lymphovascular invasion				
No	30 (58)	31 (86)	-	**0,004**
Yes	22 (42)	5 (14)	-	
Perineural invasion				
No	30 (58)	30 (81)	-	**0,017**
Yes	22 (42)	7 (19)	-	
Grade				
Grade 1	8 (15)	10 (28)	3 (43)	0,244
Grade 2	38 (72)	21 (58)	4 (57)	
Grade 3	7 (13)	5 (14)	-	

Table 3. Survival of the patients

	Postop CRT N=57 (44%)	Preop CRT N=47 (37%)	Non-opere CRT N=24 (19%)	*p* value
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)	0,467
Yes	3 (5)	5 (11)	3 (13)	
Local Recurrence				
No	54 (95)	42 (89)	-	0.256
Yes	3 (5)	5 (11)	-	
Distant Metastasis				
No	44 (77)	38 (81)	19 (79)	0,901
Yes	13 (23)	9 (19)	5 (21)	
Distant Metastasis				
No	44 (77)	38 (81)	-	0.417
Yes	13 (23)	9 (19)	-	
Overall Survival				
The 3-year OS	78%	76%	48%	**0.001**
Median survival	Not yet	75 month	36 month	

Overall Survival				
The 3-year OS	78%	76%	-	0.184
Median survival	Not yet	75 month	-	
Disease-free survival				
The 3-year DFS	78%	73%	41%	**<0.001**
Median survival	101 month	64 month	26 month	
Disease-free survival				
The 3-year DFS	78%	73%	-	0.073
Median survival	101 month	62 month	-	

Table 4. Side effects of chemoradiotherapy

	Postop CRT N=57 (%44)	Preop CRT N=47 (%37)	CRT N=24 (%19)	*p* value
Upper Gastrointestinal System				
Grade 0	37 (65)	34 (72)	18 (75)	0,580
Grade 1-2	20 (35)	13 (28)	6 (25)	
Lower Gastrointestinal System				
Grade 0	19 (33)	12 (25)	3 (13)	0,161
Grade 1-2	35 (62)	29 (62)	20 (83)	
Grade 3-4	3 (5)	6 (13)	1 (4)	
Genitourinary System				
Grade 0	35 (61)	29 (62)	15 (63)	0,868
Grade 1-2	21 (37)	18 (38)	9 (37)	
Grade 3-4	1 (2)	-	-	
White blood cell				
Grade 0	46 (82)	38 (81)	16 (67)	
Grade 1-2	11 (19)	8 (17)	8 (33)	0,357
Grade 3-4	-	1 (2)	-	
Neutrophil				
Grade 0	52 (91)	41 (87)	21 (88)	0,780
Grade 1-2	5 (9)	6 (13)	3 (12)	
Platelet				
Grade 0	55 (97)	44 (94)	22 (92)	0,644
Grade 1-2	2 (3)	3 (6)	2 (8)	

Hemoglobin				
Grade 0	49 (86)	34 (87)	20 (83)	0.202
Grade 1-2	8 (14)	13 (28)	4 (17)	
Hematocrit				
Grade 0	55 (92)	43 (92)	22 (92)	0.517
Grade 1-2	4 (8)	4 (8)	2 (8)	
Loss in weight[1]				
No	52 (91)	41 (87)	20 (75)	0,144
Yes	5 (9)	6 (13)	4 (25)	

[1]Loss in weight: during chemoradiotherapy

Figure 1. Treatment based overall survival curves

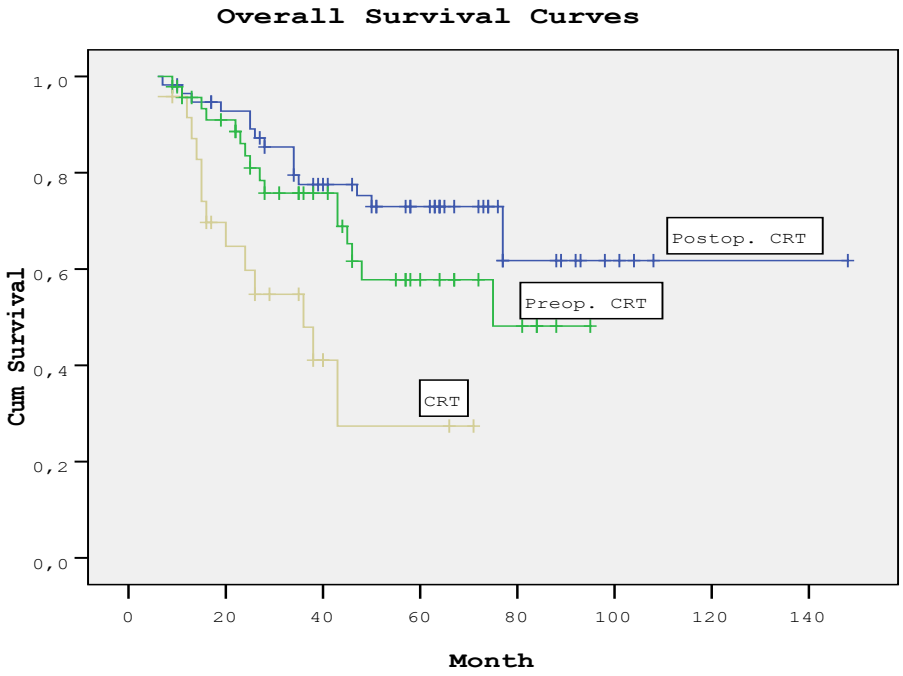

Figure 2. Treatment based disease-free survival curves