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ORIGINAL ARTICLE

Survival-effective prognostic factors of rectal cancer patients receiving neoadjuvant chemoradiotherapy

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Abstract

Objective: Our aim in this study is to investigate the survival-effective prognostic factors of rectal cancer patients receiving neoadjuvant chemoradiotherapy.

Methods: A total Data from 102 patients who underwent surgery due to rectal cancer at the Gastroenterology Surgery Clinic of Koşuyolu High Specialization Training and Research Hospital, Health Sciences University, between January 2013 and October 2019 were retrospectively reviewed. Two patients who underwent total proctocolectomy, nine patients with distant organ metastasis, and seven patients who did not receive neoadjuvant therapy and had fewer than 12 lymph nodes removed were excluded from the study. A total of 84 patients, including 54 who received neoadjuvant CRT and 30 who did not, were included in the study. The study end date was set as July 30, 2020.

Results: 84 patients were included in our study. Of these patients, 40 were male(47%) and 44 were female(53%). The patients were followed for an average of 44 months. Neoadjuvant chemoradiotherapy treatment was applied to 64.3% of the 84 patients who underwent surgery for rectal cancer. According to Kaplein Meier long rank test analysis, no statistical difference was found in the survival Deciency between the two groups (p=0.115). It was found that the presence of positive lymph nodes within the excised lymph nodes serves as a prognostic factor in patients receiving neoadjuvant chemotherapy (p=0.005).

Conclusion: The incidence of rectal cancer is still high today. Neoadjuvant CRT at the local advanced stage is a standard treatment approach. In our study, the most important prognostic factor effective survival after neoadjuvant CRT was found to be the presence of lymph node metastasis after surgery.

Keywords: Rectum cancer; neoadjuvant cemoradioterapy; lymph node

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Introduction

Although the diagnosis and treatment of rectal cancer have improved dramatically over the past decade, its incidence has also been steadily increasing. The universal acceptance of the total mesorectal excision (TME) technique and improved imaging with magnetic resonance imaging (MRI) have provided better selection of high-risk patient groups, and neoadjuvant chemoradiotherapy (CRT) treatment before surgery has become a standard treatment method in these patient groups[1]. The benefits of preoperative CRT for rectal cancer are well known in terms of reduction to pathological complete response, increased sphincter-protective surgery, and a significant reduction in local relapses[2]. The use of neoadjuvant chemoradiotherapy with clinical stage T3 or T4 based on transrectal endoscopic ultrasound (EUS) or MRI is recommended for all patients with newly diagnosed rectal adenocarcinoma. Neoadjuvant therapy, radiotherapy can be alone or in combination with chemotherapy[3].

Low anterior resection(LAR) or abdominoperineal resection(APR) combined with total mesorectal excision is the standard surgical treatment for rectal cancer surgical treatment, and these methods have significant disadvantages, including a 2% risk of perioperative mortality, an 11% risk of anastomosis leakage, a 5% risk of re-surgery for complications, and a risk of sexual and urinary dysfunction[4]. It is important to note that not every patient responds positively to radiation therapy, and there may be toxicity related to treatment, which may negatively affect the overall and health-related quality of life of patients. Moreover, neoadjuvant radiotherapy can cause excessive tissue payoff, which can lead to the loss of surgical plans, which can pose an increased surgical difficulty, especially in the narrow male pelvis[5].

Our aim in this study will be to investigate the survival-effective prognostic factors of rectal cancer patients receiving neoadjuvant CRT.

Material and Method

A total Data from 102 patients who underwent surgery due to rectal cancer at the Gastroenterology Surgery Clinic of Koşuyolu High Specialization Training and Research Hospital, Health Sciences University, between January 2013 and October 2019 were retrospectively reviewed. Two patients who underwent total proctocolectomy, nine patients with distant organ metastasis, and seven patients who did not receive neoadjuvant therapy and had fewer than 12 lymph nodes removed were excluded from the study. A total of 84 patients, including 54 who received neoadjuvant CRT and 30 who did not, were included in the study. The study end date was set as July 30, 2020. Patients were divided into two groups, those who received neoadjuvant CRT and those who did not, and their clinicopathological features and overall survival were compared. Additionally, prognostic factors affecting survival in patients receiving neoadjuvant CRT were examined.

Statıstıcs Analysıs: Evaluation between patients receiving and not receiving neoadjuvant CRT was evaluated using Student T test, Mann Whitney U test, Fisher Exact test and Chi square test. Survival analysis between the two groups was checked with the Kaplan-Meier test and whether there was a difference was evaluated with the longrank test. Prognostic factors affecting survival of patients receiving neoadjuvant CRT were evaluated with Cox regression analysis.

Results

84 patients were included in this study. 40 of these patients were male (47%) and 44 were female (53%). Patients were followed for an average of 44 (+/-12 months) months. Neoadjuvant chemoradiotherapy treatment was applied to 64.3% of 84 patients who underwent surgery for rectal cancer. Patients were divided into two groups according to neoadjuvant chemoradiotherapy status: those who did not receive treatment and those who received it. In the clinicopathological evaluation of the two groups, there was no statistically significant difference between

the treatment response rates of men and women (p = 0.434). This suggests that gender is not a determining factor on response to treatment. There is no significant relationship between pre-treatment T stage and surgery type after neoadjuvant chemoradiation (p=0.681). Lymph node positivity can be considered as a factor affecting response to treatment. However, there is no statistically significant relationship between lymph node positivity and surgical outcomes after neoadjuvant chemoradiation (p=0.712). There is no statistically significant relationship between the cancer stage before treatment and the type of surgery after neoadjuvant chemoradiotherapy (p = 0.322). This suggests that cancer stage is not a direct determinant in surgical planning. There is a significant relationship between the type of surgery (LAR or APR) and protective ileostomy (p<0.001). This demonstrates the nature of the surgical procedure and its impact on overall survival. The effect of lymphovascular and perineural invasion on treatment outcomes was examined. However, neither showed a statistically significant association with surgical outcomes (p=0.173 and p=0.230, respectively). The incidence of anastomotic leakage after surgery is low and does not show that neoadjuvant chemoradiotherapy has a significant effect on this complication (p = 0.875). There is no statistically significant difference in surgical outcomes between patients' ages and body mass indexes (BMI) (p=0.128 and p=0.374, respectively). The total number of lymph nodes removed after neoadjuvant chemoradiation is associated with the type of surgery and lymph node positivity (p<0.001). This highlights the effect of neoadjuvant chemoradiotherapy on lymph node dissection. Surgery time is related to surgery type and complexity, but there is no statistically significant difference (p = 0.118) (Table 1).

According to Kaplein Meier long rank test analysis, no statistical difference was found in the survival comparison between the two groups (p = 0.115) (Figure 1). While the average life expectancy of patients who received neoadjuvant chemoradiotherapy was 66.713±4.833 months, it was 76.665±4.443 months in patients who did not receive neoadjuvant treatment .

Prognostic factors affecting survival in rectal cancer patients receiving neoadjuvant chemoradiotherapy were investigated by Cox regression analysis. It was found that age, gender, depth of tumor wall invasion, development of anastomotic leakage, presence of lymphovascular invasion and perineural invasion had no prognostic significance. Positive lymph node involvement within the lymph node removed after neoadjuvant chemoradiotherapy was found to be a poor prognostic factor on survival (p = 0.005) (Table 2).

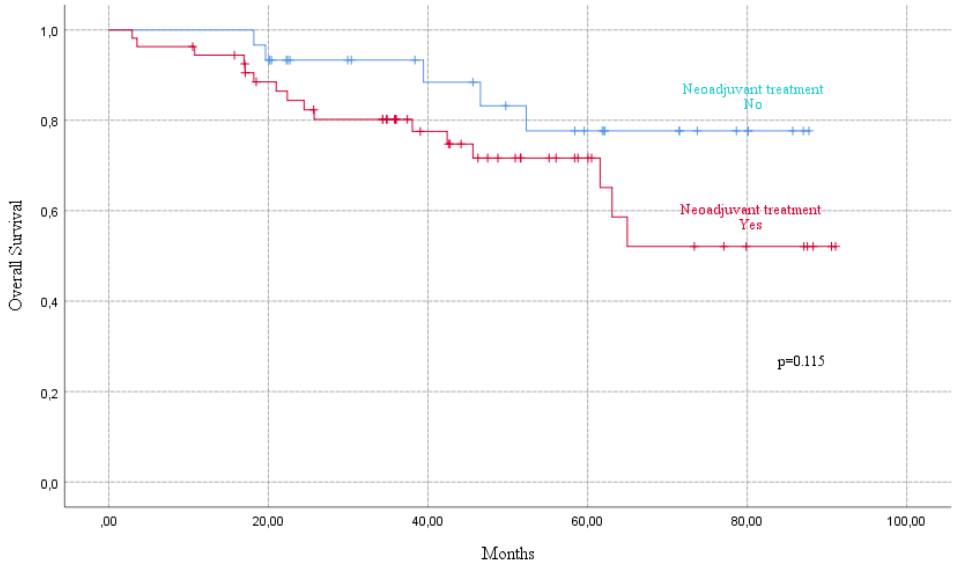

Figure 1: Comparison of Patient Survival According to Neoadjuvant Treatment Status

Table 1. Clinical and Histopathological Features of Rectal Tumors with and without Neoadjuvant Chemoradiotherapy

Neoadjuvant Chemoradiotherapy Status						
		No		Yes		
		n	%	n	%	p
Sex	Male	16	53,3%	24	44,4%	0.434
	Female	14	46,7%	30	55,6%	
T	T1	3	10,0%	2	4,1%	0.681[a]
	T2	6	20,0%	13	26,5%	
	T3	17	56,7%	29	59,2%	
	T4	4	13,3%	5	10,2%	
Lymph Node	Negative	23	76,7%	35	72,9%	0.712
	Positive	7	23,3%	13	27,1%	
Stage	Stage I	8	26,7%	7	17,9%	0.322
	Stage II	12	40,0%	12	30,8%	
	Stage III	10	33,3%	20	51,3%	
Operation Type	LAR	29	96,7%	41	75,9%	0.015*
	APR	1	3,3%	13	24,1%	
Loop İleostomy	No	20	66,7%	3	5,6%	p<0.001**
	Yes	9	33,3%	37	94,4%	
Lymphovascular Invasion	Negative	22	73,3%	42	85,7%	0.173
	Positive	8	26,7%	7	14,3%	
Perineural Invasion	Negative	25	83,3%	35	71,4%	0.230
	Pozitive	5	16,7%	14	28,6%	
Anastomotic Leak	No	27	90,0%	48	88,9%	0.875
	Yes	3	10,0%	6	11,1%	
		Median	(IQR)	Median	(IQR)	
Age		64	58-70	61	48-68	0.128
BMI		27,95	25,30-31,30	29,25	25,50-32,90	0.374[b]
Total Number of Lymph Nodes Removed		18	15-33	12	9-19	p<0.001**
Operation Time		238	180-280	248	230-300	0.118

*[a] Likelihood Ratio, [b]Student T test, Ki Kare test, Mann Witney U test, *p<0.05, **p<0.001*

LAR:Low Anterior Rezection APR:Abdominoperineal Rezection BMI;Body-Mass Index

Table 2: Multivariate Cox Regression Analysis of Prognostic Factors Affecting Survival in Rectal Cancer Patients Receiving Neoadjuvant Chemoradiotherapy

	OR	95,0% CI		p
Gender	1,710	,425	6,880	0.450
Age	,964	,915	1,016	0.174
T stage				0.963
T1	,957	,077	11,863	0.973
T2	,927	,075	11,399	0.953
T3	,539	,018	16,575	0.723
T4				
Lymph Node Involvemen	15,520	2,272	106,024	0.005*
Lymphovascular Invasion	,278	,041	1,901	0.192
Perineural Invasion	,483	,126	1,848	0.288
Anastomotic Leak	3,300	,471	23,121	0.229

Discussion

Neoadjuvant chemoradiotherapy is increasingly used in the treatment of rectal cancer, and much research is being conducted on the clinical effectiveness of this treatment regimen. This study aimed to evaluate the effects of neoadjuvant chemoradiotherapy on surgical outcomes and survival in rectal cancer patients. Our findings have helped us better understand the effects of neoadjuvant chemoradiation on specific clinical and pathological factors.

Fan and colleagues showed that female gender and younger age are associated with better prognosis[6]. However, when the patients were examined in terms of their response to neoadjuvant chemoradiotherapy in our study, no statistically significant difference was found. This result shows that gender is not a determining factor on response to treatment in rectal cancer treatment.

It has been shown that T stage has a significant impact on the long-term survival of rectal cancer patients[7]. It is known that stage T3 patients have lower long-term survival and recovery probabilities compared to patients in T1[8]. Many studies have reported that T stage plays an important role in determining survival and that the recurrence rate is higher in T3 tumors than in T1 tumors [9]. In our study, no significant relationship was found between tumor stage and survival after neoadjuvant chemoradiotherapy. This suggests that the stage of cancer is not a determinant.

One study, the largest of its kind to date, examined patients undergoing LAR and APR and found that LAR produced higher overall survival rates compared to APR, but disease-free survival rates were similar[10]. We found significant differences between surgical procedures depending on whether patients received neoadjuvant chemoradiation. In particular, in the comparison between low anterior resection (LAR) and abdominoperineal resection (APR), a significant relationship was observed between the type of surgery and protective ileostomy. This highlights the nature of the surgical procedure and its implications for the risk of complications.

Caricato et al. [11] analyzed the effect of preoperative CRT on lymph node (LN) status in 28 patients who underwent surgical treatment. Complete response was seen in the LNs of 18 patients (51%), while the others showed variable or no response. Due to the low number of cases, no prognostic evaluation was made. Lindebjerg et al.[12] examined a cohort of 135 patients who responded to CRT (major + complete response = 66%). They found a significantly lower survival rate in patients with post-treatment LN metastases than in LN-negative patients. However, in our own study, no statistically significant relationship was found between lymph node positivity and surgical outcomes after neoadjuvant chemoradiotherapy. However, an important finding showing the effect of neoadjuvant chemoradiotherapy on lymph node dissection is that the total number of lymph nodes removed after neoadjuvant chemoradiotherapy is associated with the type of surgery and lymph node positivity. Additionally, a lower incidence of anastomotic leak was observed in patients receiving neoadjuvant chemoradiation, although this was not statistically significant.

Data from randomized trials have demonstrated better tumor control and reduced toxicity with preoperative (versus postoperative) chemo-radiotherapy, leading to widespread acceptance of the preoperative approach as the preferred treatment sequence[13]. Preoperative concurrent chemo-radiotherapy has also been associated with tumor regression and resulted in an improvement in pathological tumor stage[14]. Since the number of cases was high in the sample group in both studies, a statistically significant difference was detected between patients who received neoadjuvant CRT and those who did not. On the other hand, since the number of patients in this study was smaller, it shows that no statistically significant difference was found between patients who received neoadjuvant chemoradiotherapy and those who did not. However, it has been determined that the average life expectancy of patients receiving neoadjuvant chemoradiotherapy is lower compared to those who do not receive neoadjuvant treatment. Evaluation of prognostic factors by Cox regression analysis revealed that positive lymph node involvement within the lymph node removed after neoadjuvant chemoradiation was a poor prognostic factor.

There were some limitations in this study. The limitations of our study are that it was conducted with a small sample group, was retrospective, and was planned as a single center.

Conclusion

In conclusion, this study examined the effects of neoadjuvant chemoradiotherapy on clinical and pathological factors in rectal cancer patients. Our findings highlight the effect of neoadjuvant chemoradiotherapy on lymph node dissection and show that positive lymph node involvement is a poor prognostic factor. However, the prognostic significance of other clinical and pathological factors should be further investigated, and the effects of this treatment regimen on surgical outcomes and survival should be evaluated more comprehensively.

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Conflict of Interest: None of the authors have a conflict of interest.

Ethical Approval: The study was approved by the Clinical Research Ethics Committee Koşuyolu Yuksek Ihtisas Research and Training Hospital, and adhered to the ethical standards expected for medical research involving human participants.

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