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ORIGINAL ARTICLE

Prognostic factors affecting recurrence and survival in patients with locally advanced rectal cancer

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Summary

Purpose: *This study aimed at investigating the factors that are likely to affect recurrence and survival in patients with locally advanced rectal cancer.*

Methods: *The study included patients treated and followed-up between January 1999 and August 2009. Patient and disease data were retrieved from the patients' hospital charts.*

Results: *A total of 221 patients were evaluated. Their median age was 58 years (range 18-83); 69 (31.2%) patients had clinical stage II and 152 (68.8%) clinical stage III. Median follow-up was 40 months (range 8-136). Median disease-free survival (DFS) was 77 months and median overall survival (OS) 95 months. The factors affecting local recurrence were pathological lymph node involvement (pN+), pathological T4 (pT4) tumors, and postoperative high serum level of carcinoembryonic antigen (CEA). pN (+) tumors, postoperative high serum CEA level, and perineural invasion increased the risk of both local and distant metastasis. The factors affecting mortality were pN+ tumors, pT4 tumors, poor tumor differentiation, high postoperative CEA level, age > 60 years, and no postoperative adjuvant chemotherapy (CT). The factors affecting DFS were pN+ tumors, pT4 tumors, poor tumor differentiation, postoperative high serum CEA level, perineural invasion, and surgical margin positivity. The factors affecting OS were pN+ tumors, postoperative high serum CEA level, poor tumor differentiation, perineural invasion and no adjuvant CT.*

Conclusion: *Some prognostic factors are important in the assessment of prognosis of locally advanced rectal cancer.*

Key words: locally advanced, prognosis, rectal cancer, recurrence, survival

Introduction

Colorectal cancer is a very common neoplastic disease. In the US 148,810 cases are diagnosed annually, 108,070 with colon cancer and the remainder with rectal cancer [1]. It is the third most common type of cancer in both men and women, and it is also the third leading cause of death from cancer. It accounts for 10% of all cancers and 10% for all cancer-related deaths [2]. Surgery is the primary treatment for colorectal cancer. Postoperative adjuvant CT is recommended for stage II colon cancer patients that have some specific risk factors and for all patients with stage III disease. For patients with stage IV disease systemic CT is administered on an individual basis [2-4]. In the treatment of rectal cancer adjuvant or neoadjuvant chemoradiotherapy (CRT) in addition to surgical therapy and adjuvant CT may prolong survival and decrease the local recurrence rate [5,6]. In our clinic patients with locally advanced rectal cancer are treated using CRT.

Although there are many studies on the efficacy of various therapeutic approaches for colon cancer and prognostic factors that affect recurrence and survival [2], it is noteworthy that studies on prognostic factors in rectal cancer are only a few [6]. The prognostic factors commonly highlighted in these studies relate colorectal cancer with the presence of a signet ring cell tumor, poor tumor differentiation, tumor localization in the lower regions of the rectum, lymph node involvement, deep tumor invasion, perineural, lymphatic, and vascular in-

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vasion, surgical margin positivity, obstruction or perforation, high pre- and postoperative CEA level, obesity, and diabetes [2,6-10]. In the presence of poor prognostic factors, administration of CRT and CT in addition to surgery decreased the recurrence rate and prolonged survival [11-15].

The present study aimed at evaluating the prognostic factors that affect recurrence and survival in patients with locally advanced rectal cancer.

Methods

Patients that were treated and followed-up for locally advanced rectal cancer at Dokuz Eylul University, Medical Faculty, Department of Internal Diseases, Medical Oncology Division between January 1999 and August 2009 were reviewed.

The study included patients with stage II and III rectal cancer–staged according to the American Joint Committee on Cancer (AJCC) TNM Staging System, 6th Edition [14]. The pattern of recurrence was categorized in 3 main groups: local recurrence, distant recurrence, and local+distant recurrence. The time between diagnosis and recurrence was considered as DFS, and the time between diagnosis and death was considered as OS. All of the patients underwent preoperative assessment using thoracic, lower, and upper abdominal computed tomography, lower abdominal (pelvic) magnetic resonance imaging (MRI), and endorectal ultrasound (US).

Both neoadjuvant and adjuvant CRT consisted of the delivery of 45 Gy in 25 fractions at a daily dose of 1.8 Gy, concomitantly with 5-fluorouracil (5-FU) 225 mg/m^2/d continuous infusion for 25 days during RT. Adjuvant CT consisted of modified De Gramont regimen (folinic acid 400 mg/m^2+5-FU 400 mg/m^2 bolus+5-FU 2400 mg/m^2, as a 46-h infusion, given every 14 days) or modified FOLFOX-4 (folinic acid 400 mg/m^2+5-FU 400 mg/m^2 bolus+5-FU 2400 mg/m^2, as a 46-h infusion, in addition to oxaliplatin 85 mg/m^2, given every 14 days).

Statistical considerations

The statistical analysis of the data was done using the Statistical Package for Social Sciences for Windows (SPSS), version 15.0. The means of two groups were analysed using the Student's t-test, independent group ratios were compared using the chi-square test, comparison of predictors, and independent variables or dependent variables was performed using the logistic regression test, DFS and OS were analysed using the Kaplan-Meier method, and two survival curves were compared using the log-rank test. Statistical significance was set at $p < 0.05$.

Table 1. Patient, tumor and treatment characteristics

Characteristics	*N (%)*
Gender	
Female	101 (45.7)
Male	120 (54.3)
Age (years)	
<60	128 (57.9)
>60	93 (44.5)
Stage	
Clinical stage II	69 (31.2)
Clinical stage III	152 (68.8)
Pathological stage 0	18 (8.1)
Pathological stage I	12 (5.4)
Pathological stage II	110 (49.8)
Pathological stage III	81 (36.7)
Rectal localization	
Upper	60 (27.1)
Middle	70 (31.7)
Lower	91 (41.2)
Surgical therapy	
Low anterior resection	133 (60.2)
Abdominoperineal resection	69 (31.2)
Very low anterior resection	19 (8.6)
Total mesorectal excision	221 (100.0)
CRT	
Neoadjuvant	165 (74.7)
Adjuvant	56 (25.3)
Adjuvant CT	198 (89.5)
Modified De Gramont	90 (45.2)
Modified FOLFOX-4	108 (54.8)
None	23 (10.5)
Complete response to neoadjuvant CRT	18 (10.9)
Histopathology	
Adenocarcinoma	183 (82.8)
Mucinous adenocarcinoma	33 (14.9)
Other subtypes	5 (2.2)
Differentiation	
Good	93 (42.1)
Moderate	78 (35.3)
Poor	41 (18.6)
Unknown	9 (4.1)
Perineural invasion	51 (23.1)
Vascular invasion	38 (17.2)
Lymphatic invasion	51 (23.1)
Surgical margin positivity	20 (9.0)
Preoperative CEA >5 ng mL^{-1}	64 (29.0)
Postoperative CEA >5 ng mL^{-1}	22 (10.0)

CRT: chemoradiotherapy, CT: chemotherapy, CEA: carcinoembryonic antigen

Results

A total of 221 patients were evaluated. The median patient age was 58 years (range 18-83). Patients and tumor characteristics are shown in Table 1. Median follow-up was 40 months (range 8-136). Fifty-five (25.9%) patients had died. The median patient DFS and OS were 77 and 95 months, respectively. Survival results according to patients and disease features are shown in Table 2.

All of the patients underwent total mesorectal excision, and 165 (74.7%) patients were given neoadjuvant CRT, 56 (25.3%) were given adjuvant CRT, and 198 (89.5%) were given adjuvant CT in addition to surgical treatment. Eighteen patients (10.9%) that had complete response to neoadjuvant CRT were considered as pathological stage 0.

In all, 85 (38.5%) patients recurred, of whom 37

Table 2. Median survival times of the patients according to some characteristics

Characteristics	*DFS (months)*	*3-year DFS (%)*	*5-year DFS (%)*	*OS (months)*	*3-year OS (%)*	*5-year OS (%)*
All patients	77.0	63.1	54.4	95.0	85.6	68.7
Clinical stage						
II	88.0	68.4	58.7	97.0	84.0	71.0
III	76.0	60.8	52.5	94.0	84.2	66.4
CRT						
Neoadjuvant	76.0	62.0	56.7	96.0	82.9	63.7
Adjuvant	78.0	66.5	51.1	94.0	92.2	78.2
CT						
Received	77.0	63.2	57.8	96.0	87.0	69.9
Not received	50.0	61.8	27.5	72.0	74.2	56.0
Pathological N+						
Yes	33.0	47.8	35.9	68.0	76.4	55.6
No	77.0	72.4	65.2	96.0	91.6	78.3
Pathological T4						
Yes	34.0	45.4	35.4	71.0	77.6	54.3
No	78.0	68.5	60.2	96.0	88.5	74.0
Postoperative CEA level						
High	12.0	22.6	00.0	40.0	56.3	35.1
Normal	78.0	67.7	58.2	96.0	89.2	72.9
Surgical margins						
Positive	22.0	45.0	22.5	54.0	74.1	44.6
Negative	77.0	64.8	56.3	95.0	86.8	70.6
Differentiation						
Poor	32.0	38.6	38.6	68.0	75.9	56.0
Moderate/well	77.0	68.6	57.9	96.0	87.9	72.1
Perineural invasion						
Positive	22.0	45.6	37.9	57.0	80.6	46.8
Negative	78.0	70.6	61.0	95.0	85.7	75.5
Age (years)						
< 60	76.0	62.1	54.0	97.0	86.9	73.9
≥ 60	78.0	64.4	54.5	72.0	83.8	62.7
Adjuvant CT						
Yes	77.0	63.2	57.8	96.0	87.0	69.9
No	50.0	61.8	27.5	72.0	74.2	56.0

DFS: disease-free survival, OS: overall survival, CRT: chemoradiotherapy, CT: chemotherapy

(16.7%) with local recurrence, and 48 (83.3%) with distant metastasis and local recurrence+distant metastasis. The median time between diagnosis and first recurrence was 27 months. Recurrence characteristics are shown in Table 3. No significant differences were observed in local recurrence (p=0.321) or distant metastasis (p=0.646) between the clinical stage II and III patients; however, the local recurrence and distant metastasis rates were higher in patients with pathological stage III disease than in those with pathological stage II disease (p=0.005 and p=0.001, respectively).

Prognostic factors that increased the local recurrence rate, local recurrence+distant metastasis rate and mortality rate in univariate and multivariate analysis are shown in Table 4. However, the difference in the number of lymph nodes involved between patients with local recurrence and local recurrence+distant metastasis was not statistically significant (p=0.958 and p=0.132, respectively).

Table 3. Recurrence characteristics

Characteristics	*N (%)*
All recurrences	85 (38.5)
Clinical stage II who recurred	25 (36.2)
Clinical stage III who recurred	60 (39.4)
Pathological stage 0 who recurred	4 (22.2)
Pathological stage I who recurred	2 (16.6)
Pathological stage II who recurred	34 (30.9)
Pathological stage III who recurred	45 (55.5)
Local recurrence	37 (16.7)
Only local recurrence	25 (11.3)
Local recurrence+distant organ metastasis	12 (5.4)
Distant organ metastasis	60 (27.1)
Lung	35 (15.8)
Liver	26 (11.8)
Bone	8 (3.6)
Peritoneal	7 (3.1)
Skin	1 (0.4)
Only distant organ metastasis	48 (21.7)

Table 4. Factors that affected local recurrence, local recurrence plus distant metastasis, mortality, DFS and OS

Factors	*Univariate analysis (p)*	*Multivariate analysis (p)*	*Log-rank analysis (p)*
Factors that affected local recurrence			
Pathological N+ tumors	0.001	0.019	0.002
Pathological T4 tumors	0.001	0.001	0.001
Administration of adjuvant CRT	0.020	0.538	0.640
High postoperative CEA level	0.001	0.003	0.001
Surgical margin positivity	0.004	0.608	0.003
Factors that affected local recurrence + distant metastasis			
Pathological N+ tumors	0.001	0.009	0.002
Pathological T4 tumors	0.009	0.133	0.109
High postoperative CEA level	0.001	0.004	0.001
Surgical margin positivity	0.040	0.712	0.064
Poor tumor differentiation	0.010	0.169	0.029
Perineural invasion	0.001	0.004	0.002
Perivascular invasion	0.015	0.643	0.159
Invasion of lymph vessels	0.004	0.399	0.007
Factors that affected mortality			
Pathological N+ tumors	0.001	0.004	0.001
Pathological T4 tumor	0.002	0.024	0.050
High postoperative CEA level	0.001	0.002	0.001
Older than 60 years	0.031	0.001	0.065
Poor tumor differentiation	0.007	0.026	0.010
Perineural invasion	0.030	0.168	0.029
Invasion of lymph vessels	0.030	0.895	0.030
Did not receive adjuvant CT	0.001	0.010	0.005
Factors that affected DFS			
Pathological N+ tumors	0.001	0.009	0.001
Pathological T4 tumors	0.009	0.130	0.002
High postoperative CEA level	0.001	0.004	0.001
Poor tumor differentiation	0.010	0.165	0.003
Perineural invasion	0.001	0.003	0.001
Surgical margin positivity	0.040	0.669	0.018
Factors that affected OS			
Pathological N+ tumors	0.001	0.014	0.001
Pathological T4 tumors	0.002	0.035	0.050
High postoperative CEA level	0.001	0.008	0.001
Poor tumor differentiation	0.007	0.014	0.010
Perineural invasion	0.030	0.355	0.029
Did not receive adjuvant CT	0.001	0.003	0.005

CT: chemotherapy, CRT: chemoradiotherapy, CEA: carcinoembryonic antigen, DFS: disease-free survival, OS: overall survival

Prognostic factors that decreased DFS and OS are depicted in Table 4 and Figures 1-12. CRT, whether administered as neoadjuvant or adjuvant therapy, did not significantly affect DFS or OS (p=0.883 and p=0.460, respectively).

Discussion

Studies on prognostic factors in rectal cancer are inadequate in number, and usually derived from data of studies on colon cancer. For this reason in the present study 221 patients with locally advanced rectal cancer were evaluated for prognostic factors determining recurrence and survival.

In the present study the factors associated with poor prognosis were pN+ tumors, pT4 tumors, high postoperative serum CEA level, surgical margin positivity, histopathologically poor tumor differentiation and perineural invasion. We observed that administration of adjuvant CRT instead of neoadjuvant CRT increased the rate of local recurrence, no administration of adjuvant CT decreased OS, and that the mortality rate was higher in patients older than 60 years.

Among the prognostic factors that were evaluated in the present study, lymph node involvement was the most important one. Previous studies showed that pN+ tumors increased the rate of recurrence and decreased survival [9,16-18]. In the present study we found lymph node involvement was an important prognostic factor

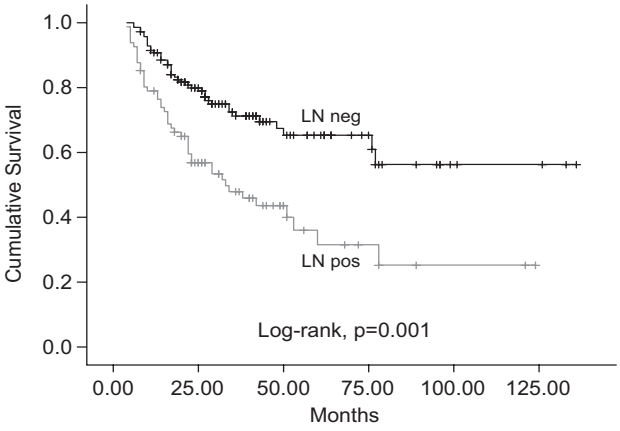

Figure 1. The effect of lymph node (LN) involvement on disease free survival.

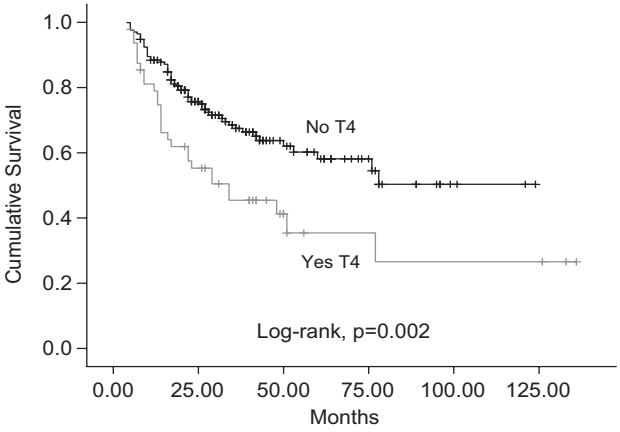

Figure 2. The effect of T stage on disease free survival.

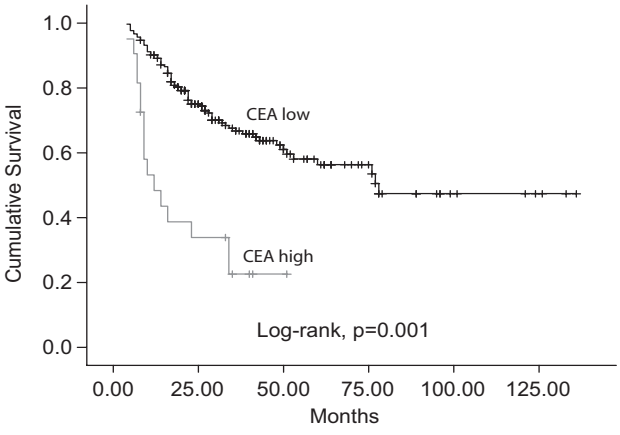

Figure 3. The relationship between postoperative carcinoembryonic antigen (CEA) level and disease free survival.

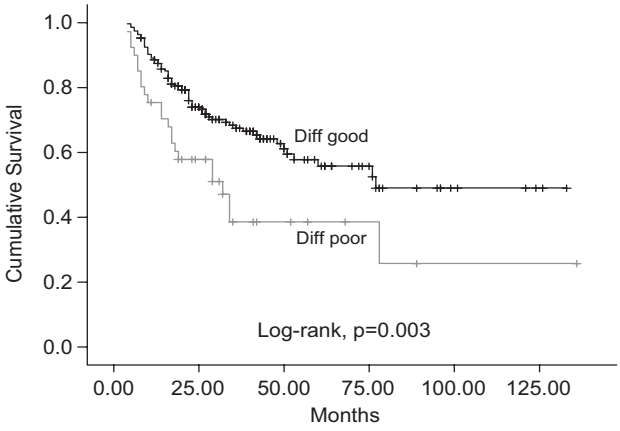

Figure 4. The relationship between tumor differentiation and disease free survival.

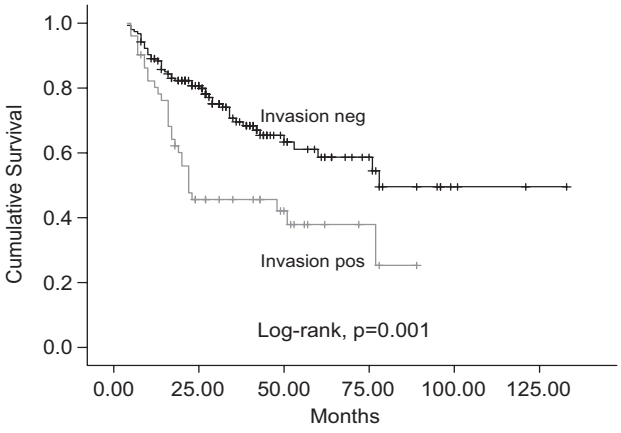

Figure 5. The impact of perineural invasion on disease free survival.

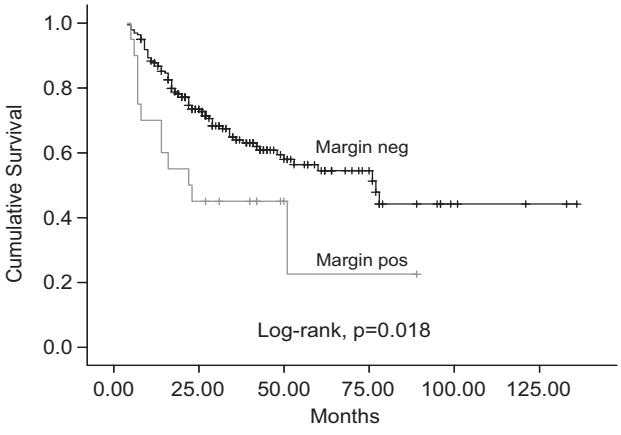

Figure 6. The impact of surgical margin status on disease free survival.

associated with an increase in the recurrence rate, and decreased DFS and OS.

Another important prognostic factor observed in our study was the depth of tumor invasion. Many studies reported that pT4 tumors recurred more frequently and that patients with pT4 tumors had a shorter survival [7-9]. In this study we found patients with pT4 tumors had higher rates of local recurrence and mortality, and significantly decreased DFS and OS.

Serum CEA level is an important marker for the diagnosis and monitoring of patients with colorectal cancer. Elevated preoperative serum CEA level is as-

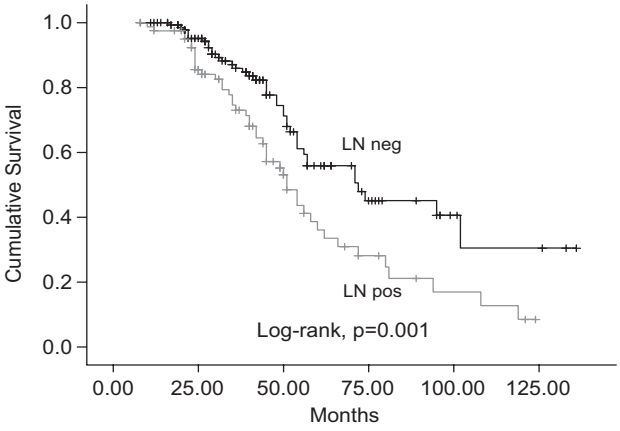

Figure 7. The relationship between lymph node (LN) involvement and overall survival.

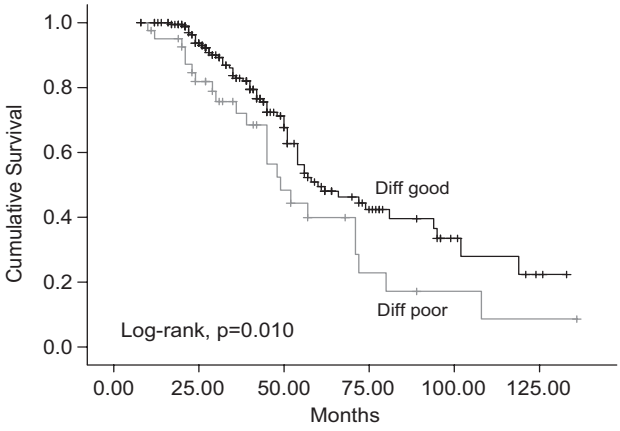

Figure 10. The relationship between tumor differentiation and overall survival.

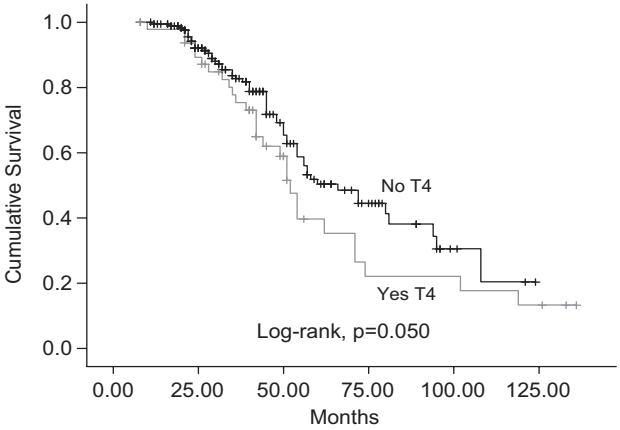

Figure 8. The impact of T stage on overall survival.

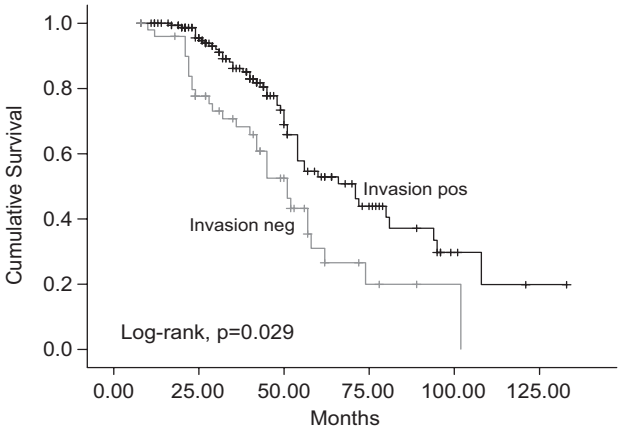

Figure 11. The impact of perineural invasion on overall survival.

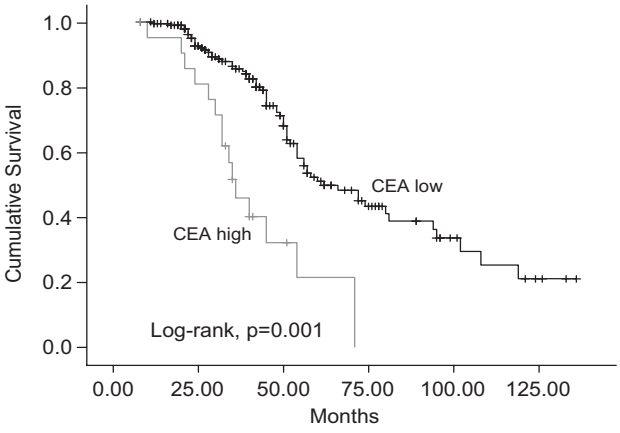

Figure 9. The relationship between postoperative carcinoembryonic antigen (CEA) level and overall survival.

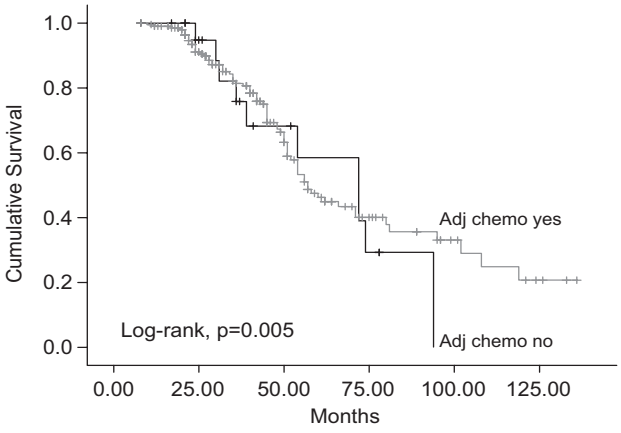

Figure 12. The impact of adjuvant chemotherapy on overall survival.

sociated with an increase in the likelihood of advanced stage tumors, poor prognosis, and recurrence, and that normal CEA levels after treatment are indicative of therapeutic response. Furthermore, CEA levels that were not lower after treatment or increased following an initial decrease were associated with a poor prognosis [17,19]. We observed that in the cases in which the CEA level did not decrease to <5 ng/mL after surgery, the rates of local and distant metastasis were higher, and DFS and OS were shorter. As such, we believe that high postoperative CEA level is a poor prognostic factor.

Infiltration of the surgical margin is considered an

important cause of recurrence, and it has been reported that survival was shorter in such patients [20,21]. In our study, especially in patients with surgical margin positivity, DFS was shorter and local recurrence rate was higher.

It has also been reported that the degree of histopathological tumor differentiation was important and that poorly differentiated tumors had a high recurrence rate [7,8]. Moreover, poor tumor differentiation is a factor that must be considered when deciding to administer adjuvant CT in stage II colon cancer patients [2-4]. In our study patients with poorly differentiated tumors had high mortality rates and shorter DFS and OS.

Another important prognostic factor is perineural invasion of the tumor. Perineural invasion is associated with early recurrence, metastasis, and shorter survival [20,21]. In our study patients with perineural invasion had a higher rate of distant metastasis, and shorter DFS and OS.

Due to advancements in neoadjuvant and adjuvant therapies, as well as surgical techniques, patient age has lost its importance and survival outcomes have become almost identical in elderly and young patients [22]. We observed a higher mortality rate in patients older than 60 years in our study. It is a reality that patients of advanced age are closer to death and have shorter survival. Another explanation for the higher mortality rate in these patients may be the fact that elderly patients are less able to tolerate the therapy, especially CT, and are not given therapies such as adjuvant CT, or that CT is administered with reduced dosage to old patients. For this reason, we believe that old age in rectal cancer is a poor prognostic factor.

Multimodal therapy used to treat rectal cancer may decrease the rate of local recurrence and the likelihood of distant metastasis, and may prolong survival. An important component of this method is adjuvant CT. Results of relevant studies are inconsistent; some report that adjuvant CT prolongs DFS and OS [14], whereas others report that it does not [23]. In the present study, patients that did not receive adjuvant CT had a higher rate of mortality and shorter OS. This may be attributed to the fact that adjuvant CT was primarily administered to patients with a good general health status; therefore, it is not possible to comment about the efficacy of adjuvant CT based on the present study's findings.

CRT, especially when administered as neoadjuvant therapy, has led to better results [24,25] and a complete response rate of approximately 15% [26,27]; therefore, many researchers suggest that CRT should be administered as neoadjuvant rather than as adjuvant therapy [11-13]. In our study patients that received adjuvant CRT had a higher rate of local recurrence; however, the patients in this study were not randomized and adjuvant CRT was generally administered to patients with surgical margin positivity and high likelihood of local recurrence. As such, we think it is difficult to reach a definitive conclusion about the timing of administration and efficacy of CRT based on the present study's findings.

As the present study was retrospective, it has some limitations specific to retrospective studies; however, we think that it will make a beneficial contribution to the rectal cancer literature, despite its use of retrospective data. The strengths of the study include the surgical and medical therapies employed, patient follow-up supervised by a staff experienced in rectal cancer, and the number of patients enrolled.

In conclusion, patients with pN+ tumors, pT4 tumors, high postoperative CEA levels, surgical margin positivity, older than 60 years of age, without adjuvant CT, poorly differentiated tumors and perineural invasion had poorer prognosis. We think that different and more efficient therapeutic methods added to surgery are needed to increase both local and systemic control and survival in these patients. Furthermore, patients with such unfavorable prognostic factors must be followed-up carefully.

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