Risk score model for predicting local control and survival in patients with rectal cancer treated with neoadjuvant chemoradiotherapy

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Abstract. The present study aimed to investigate clinicopathological factors affecting local recurrence and survival in patients with locally advanced rectal cancer (LARC) treated with neoadjuvant chemoradiotherapy (nCRT) and to create a risk-scoring model predicting local control (LC) and survival. The clinical and pathological data of 115 patients who received nCRT for LARC between February 2010 and December 2020 were reviewed retrospectively. A risk-scoring model was developed to predict LC and survival using statistically significant prognostic factors in univariate and multivariate analyses. In the multivariate analysis, the LC rate was improved in patients with a good pathological response to nCRT. By contrast, the disease-free survival (DFS) rate was significantly worse in patients with perineural invasion (PNI). The overall survival (OS) rate was significantly worse in patients who were >60 years of age, who had tumors ≥5 cm, who were PNI-positive and who had pathological N2 stage disease. Patients were grouped to analyze the ability of the scoring system to predict LC and survival. The total score was derived by assigning points to the prognostic factors in univariate and multivariate analyses and was subsequently divided into three groups according to tertile. The median LC times in groups 1-3 were significantly different at 143.6, 97.2 and 93.6 months, respectively. The median DFS times in groups 1-3 were significantly different at 136.1, 108.5 and 67.2 months, respectively, while the median OS times in groups 1-3 were significantly different at 138.3, 87.2 and 64.6 months, respectively. In conclusion, risk score modeling with prognostic factors effectively determined the difference in LC and survival between the groups. Adding effective systemic therapy to nCRT may improve results, especially in patients with multiple poor prognostic factors, including larger tumors, PNI and multiple nodal involvement.

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Key words: rectal cancer, neoadjuvant chemoradiotherapy, prognostic factors, risk score modeling

Introduction

Colorectal cancer is the third-most common cancer in the world and second in terms of cancer-related deaths (1). The disease is widespread in developed countries, but its incidence is increasing in middle- and low-income countries (1). For early-stage rectal cancer, surgery is the main treatment. However, for locally advanced rectal cancer (LARC), total mesorectal excision after neoadjuvant chemoradiotherapy (nCRT) or radiotherapy (RT) is recommended. The neoadjuvant treatment approach effectively reduces the local recurrence rate, and compared to adjuvant treatment, acute side effects are less common (2). There is still no consensus view on the effect of adjuvant chemotherapy (ChT) in patients with rectal cancer (3). The optimal timing of RT and ChT, as well as the type of ChT, is controversial (4).

The identification of prognostic factors with an impact on the survival of patients with rectal cancer may allow individualized treatment and an improvement in the quality of life. TNM stage is the most important known prognostic factor for colorectal cancer (5). However, in patients with the same pathological stage, especially in stages II and III, there are significant differences in clinical outcomes and prognosis (6). For patients with stage IIIA and IIIC, the reported 5-year survival rate varies from 80 to 30% (7). Therefore, in order to improve the accuracy of predicting the prognosis of patients with rectal cancer, it is necessary to identify additional prognostic factors that may allow the treatment to be tailored to the risk profile and preferences of the individual.

Several studies have shown that factors such as CEA level, number of metastatic lymph nodes, response to neoadjuvant therapy, neoadjuvant rectal score (NAR score), lymphovascular invasion (LVI), perineural invasion (PNI) and circumferential resection margin are associated with overall survival (OS) and

disease-free survival (DFS) (8-12). Prognostic factors have been used to manage the follow-up of patients and optimize adjuvant therapy; however, there needs to be more consensus on the factors with the most significant impact (12). It is important to develop accurate models to predict prognosis and identify risk factors, especially for patients at high risk of recurrence or metastasis. For this purpose, various risk-scoring models and nomograms have been developed in the literature. However, risk-scoring models that assess clinical and pathological factors together are uncommon.

The present study aimed to retrospectively analyze the treatment outcomes of patients with LARC treated with nCRT and develop a scoring model that predicts local control (LC) and survival, using clinical and pathological factors affecting prognosis.

Patients and methods

Patient characteristics. A total of 115 patients with LARC who were treated between February 2010 and December 2020 at Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty (Istanbul, Turkey) were included in the present study. The inclusion criteria were as follows: i) Histological confirmation of stage II-III rectal adenocarcinoma, according to the American Joint Committee on Cancer staging system, 8th edition; ii) receipt of nCRT; iii) complete clinicopathological and follow-up data; and iv) no other malignancies. The exclusion criteria were as follows: i) Receipt of postoperative RT; ii) receipt of palliative RT; and iii) missing or incomplete clinical data. All patients were treated with intensity-modulated RT concomitant with ChT followed by total mesorectal excision. Age, sex, clinical tumor (cT) stage, clinical node stage, tumor distance from the anal verge, tumor histological grade, tumor diameter at colonoscopy and MRI, preoperative ChT regimen, postoperative pathological findings [Mandard regression grade (13), pathological tumor (pT), pathological node (pN), resection grade, circumferential resection margin, LVI and PNI], adjuvant ChT and follow-up data (local-regional recurrence and metastasis) were all evaluated retrospectively.

Treatment. Patients were evaluated with a digital rectal examination, routine blood examination, colonoscopy, pelvic MRI, thorax CT and/or positron emission tomography (PET)/CT imaging before treatment. Target volumes [gross tumor volume (GTV) and involved lymph nodes] were identified through fusion with fluorodeoxglucose-PET-CT and/or pelvic MRI. The high-risk clinical target volume (CTV-HR) was created by including the mesorectum and presacral area with a safety margin of 2.5 cm proximal and distal to the GTV. Elective lymphatic areas (internal iliac, external iliac and obturator lymphatic area) were included in the CTV-HR according to tumor stage and location, and the standard-risk CTV (CTV-SR) was created (14). Planning target volumes (PTVs) were generated by expanding the CTVs by 0.7 cm symmetrically. The PTV-SR was delivered a dose of 45 Gy in 25 fractions, and the total dose to the PTV-HR was 50.4 or 54 Gy, with an additional 180 cGy per day administered in 3-5 fractions. Treatment plans for the patients were created using volumetric modulated arc therapy or intensity-modulated RT methods in the Varian's Eclipse v.15.6.3 Treatment Planning System. Target volumes and doses to critical organs were assessed according to the International Commission on Radiation Units and Measurements report number 83 (15). Patient treatments were performed using the Varian brand iX (Rapid Arc) model linear accelerator (Varian Medical Systems, Inc.) at 6 MV photon energy, and quality control of the approved treatment plans was performed. All patients received capecitabine (1,650 mg/m^2/day; 5 days per week for 5-6 weeks) or 5-fluorouracil (225 mg/m^2/day, continuous infusion) concomitant with RT.

Follow-up. Throughout the preoperative CRT period, a weekly evaluation of physical examination and blood parameters was conducted. The tumor response after CRT was evaluated by contrast-enhanced pelvic MRI 6 weeks after treatment. Postoperative follow-up was performed every 3-6 months for the first 2 years, every 6 months for 5 years and annually after 5 years, with a medical history, complete physical examination, laboratory tests and pelvic MRI. A colonoscopy was performed every 6 months for the first 2 years and annually after 2 years.

Developing a risk-score model. Similar to the system used in the study by Morini *et al* (16), points were assigned based on specific parameters that affected LC, DFS and OS. Parameters associated with decreased LC, DFS and OS in multivariate analysis were awarded +2 points, while +1 point was assigned to factors related to LC, DFS and OS in only univariate analysis. A model was created to estimate LC and survival by calculating the total score. In the scoring system, a low score indicates a good prognosis, while a high score indicates a poor prognosis.

Statistical analysis. All analyses were performed using SPSS Statistics version 20 (IBM Corp.). LC time was defined as the time from diagnosis to local recurrence or last follow-up. DFS was defined as the time from diagnosis to local recurrence, metastasis or final follow-up. OS time was defined as the time from diagnosis to death or last follow-up.

Descriptive statistical methods were used for patient characteristics, univariate analysis was used for demographic and clinical characteristics comparisons, the Kaplan-Meier method was used for survival analysis, survival differences were analyzed by log-rank test, and Cox regression analysis was used for multivariate analysis. $P \leq 0.05$ was considered to indicate a statistically significant difference. Using the significant prognostic variables in the univariate and multivariate statistical analyses, a risk-scoring model was developed to estimate LC, DFS and OS. The predictive power of the developed scoring model was evaluated using the receiver operating characteristic (ROC) curve. The study was approved by the Istanbul University-Cerrahpasa Ethics Committee (approval no. E-83045809-064.01.01-626378) and all patients provided informed written consent before treatment.

Results

Clinicopathological and demographic characteristics. A total of 115 patients who received nCRT were evaluated, of whom 81 (70.4%) were male. The median age of all patients

was 57 years (range, 28-85 years). The median tumor diameter was 5 cm (range, 1-16 cm), and 87 patients (75.7%) had tumors ≥5 cm. Tumors were located at a median distance of 6 cm (range, 1-20 cm) from the anal verge, with the majority in the lower rectum (n=54; 47.0%). Most of the patients were classified as cT3N1/2 (79.1%) according to the American Joint Committee on Cancer (8th edition) TNM system (17). A total of 109 patients (94.8%) received 50.4 Gy/28 fractions RT and 95 patients (82.6%) received concurrent capecitabine. The characteristics of the patients, the tumors and the treatment are shown in Table I. In total, 81 patients (70.4%) underwent a low-anterior resection and 34 patients (29.6%) underwent abdominoperineal surgery. A pathological complete response was achieved in 21 patients (18.3%) after nCRT. The median follow-up time was 70 months (range, 6-156 months). A total of 19 patients (16.5%) had locoregional recurrence, and 26 patients (22.6%) had distant metastasis. At 2 and 5 years, the LC rates were 90.2 and 81.6%, the DFS rates were 85.7 and 72.2%, and the OS rates were 94.7 and 70.2%, respectively (data not shown).

Prognostic factors associated with LC, DFS and OS. In the univariate analysis, patients with pathological response Mandard grades 3-5, those positive for LVI and PNI, and those not receiving postoperative ChT were found to exhibit worse LC rates. Similarly, patients with pathological response Mandard grades 3-5, those with a radial circumferential resection margin >1 mm, those positive for LVI and PNI, patients with pN+ disease, and individuals with no postoperative ChT had worse DFS rates. Patients >60 years of age, with a tumor diameter ≥5 cm, a tumor located in the lower rectum, pathological response Mandard grades 3-5, presence of LVI and PNI, and pN+ disease had worse OS rates (P≤0.05) (Table II).

Based on the multivariate analysis findings, it was observed that patients with pathological response Mandard grades 1-2 to treatment exhibited improved LC. However, patients with PNI had a worse DFS rate. In addition, the OS rate was significantly worse in patients over 60 years of age, those with a tumor diameter of 5 cm or more, those with pN2 disease and patients positive for PNI (P≤0.05) (Table III).

Stratification of risk groups. The predictive power of the developed scoring model was evaluated using the ROC curve to give area under the curve (AUC) values as follows: LC, 0.68 (95% CI, 0.57-0.80; P=0.01; Fig. 1); DFS, 0.71 (95% CI, 0.60-0.81; P=0.001; Fig. 2); and OS, 0.68 (95% CI, 0.57-0.79; P=0.001; Fig. 3). The total score of all patients was stratified into three risk groups based on tertiles to assess the ability of the risk scoring model to predict LC, DFS and OS. The scores of groups 1, 2 and 3 for LC were 0-2, 2-4 and 4-5 points, respectively. The scores of groups 1, 2 and 3 for DFS were 0-2, 2-4 and 4-7 points, respectively, while for OS, the scores of groups 1, 2 and 3 were 0-3, 3-6 and 6-11 points, respectively (Table IV). Kaplan-Meier analysis and log-rank tests demonstrated statistically and graphically that the three risk groups differed significantly in terms of LC, DFS and OS. The median LC times for groups 1, 2 and 3 were 143.6, 97.2 and 93.6 months, respectively (P=0.001; Fig. 4). The median DFS times for groups 1, 2 and 3 were 136.1, 108.5 and 67.2 months, respectively (P=0.001; Fig. 5). The median OS times for groups 1, 2 and 3 were 138.3, 87.2 and 64.6 months respectively (P<0.001; Fig. 6). Patients in group 1 had survival rates that were nearly twice as high as those in the group 3. In addition, the study's sub-analysis obtained the following results regarding OS: 86% of patients had a tumor diameter of ≥5 cm, 72% exhibited multiple lymph node involvement radiologically at baseline, 63% had pN+ disease, and 88% showed PNI(+) after neoadjuvant treatment in group 3 (data not shown).

Table I. Patient characteristics.

Variable	No. (%)
Age, years[a]	
≤60	71 (61.7)
>60	44 (38.3)
Sex	
Female	34 (29.6)
Male	81 (70.4)
cT stage	
T2	6 (5.2)
T3	91 (79.1)
T4	18 (15.7)
cN stage	
N0	24 (20.9)
N+	91 (79.1)
Location of the tumor	
Upper rectum	26 (22.6)
Middle rectum	35 (30.4)
Lower rectum	54 (47.0)
Tumor diameter, cm[b]	
<5	28 (24.3)
≥5	87 (75.7)
Tumor grade	
Well-differentiated	64 (55.7)
Undifferentiated	51 (44.3)
RT dose, Gy[c]	
50.4	109 (94.8)
54	6 (5.2)
Concomitant ChT	
Capecitabine	95 (82.6)
5-FU	20 (17.4)

[a]Median age, 57 years; [b]median tumor diameter, 5 cm; [c]median RT dose, 50.4 Gy. RT, radiation therapy; cT, clinical tumor; cN, clinical node; ChT, chemotherapy; 5-FU, 5-fluorouracil.

Discussion

TNM stage is the most important prognostic factor known today in rectal cancer and has been the cornerstone of the associated scoring and nomogram systems (5). However, patient- and tumor-specific factors such as age, sex, tumor diameter, tumor location, lymph node location, tumor response

Table II. Univariate analysis results for LC, DFS and OS rates.

		LC			DFS			OS		
Variable	No.	2 years, %	5 years, %	P-value	2 years, %	5 years, %	P-value	2 years, %	5 years, %	P-value
Age, years				0.400			0.900			0.050
≤60	71	90.0	84.4		84.2	73.7		97.2	78.6	
>60	44	90.6	77.7		88.2	70.2		90.9	57.8	
Sex				0.900			0.200			0.200
Female	34	91.1	80.4		91.1	80.4		96.6	74.4	
Male	81	89.9	82.0		83.3	68.6		93.8	68.4	
cT stage				0.900			0.300			0.200
T2	6	83.3	83.3		66.7	44.4		100.0	100.0	
T3	91	90.0	82.0		85.5	72.4		96.7	68.5	
T4	18	93.3	79.4		93.3	65.0		83.0	70.2	
cN stage				0.900			0.200			0.600
N0	24	95.8	83.1		78.9	64.5		95.7	63.9	
N+	91	92.1	81.2		87.5	74.2		94.5	74.7	
Location of the tumor				0.500			0.400			0.030
Upper rectum	26	84.1	79.7		84.1	79.9		95.3	83.7	
Middle rectum	35	97.1	86.5		91.3	74.4		97.1	77.9	
Lower rectum	54	90.5	78.9		82.8	67.0		94.3	57.8	
Tumor diameter, cm				0.700			0.500			0.030
<5	28	92.7	82.9		85.3	66.3		96.2	72.6	
≥5	87	89.3	81.2		85.8	73.8		94.2	61.4	
Pathological response				0.010			0.010			0.006
Mandard grades 1-2	40	95.0	95.0		92.4	85.3		100	83.0	
Mandard grades 3-5	75	87.5	74.0		82.0	64.7		91.9	63.7	
Circumferential resection margin, mm				0.100			0.010			0.100
<1	19	91.3	83.4		90.4	76.8		96.9	74.4	
≥1	96	83.6	72.0		60.4	48.3		83.9	50.3	
LVI				0.020			0.010			0.006
Negative	56	94.6	90.8		92.8	84.2		100	79.7	
Positive	59	85.7	72.0		78.6	60.0		89.7	91.1	
PNI				0.006			0.001			0.001
Negative	71	95.7	89.4		92.8	83.0		98.6	79.7	
Positive	44	80.9	67.3		73.8	53.1		88.4	53.3	
pT stage				0.070			0.080			0.090
T0	22	100	100		100	100		100	100	
T1	7	95.5	95.5		90.9	90.9		100	85.9	
T2	26	96.2	96.2		92.3	81.1		95.7	71.7	
T3	52	86.2	72.8		80.3	61.1		92.2	64.0	
T4	8	87.5	55.0		87.5	55.0		75.0	57.5	
pN stage				0.060			0.020			0.004
N0	86	92.8	85.7		89.1	77.9		95.3	73.9	
N1-2	29	82.8	69.5		75.9	55.3		92.9	58.4	
Postoperative ChT				0.010			0.006			0.100
No	66	87.6	73.2		84.5	61.8		93.8	68.6	
Yes	49	93.7	93.7		87.3	87.3		95.9	72.5	

cT, clinical tumor; cN, clinical node; LVI, lymphovascular invasion; PNI, perineural invasion; pT, pathological tumor; pN, pathological node; ChT, chemotherapy; LC, local control; DFS, disease-free survival; OS, overall survival.

Table III. Multivariate analysis results for LC, DFS and OS.

A, LC

Variable	RR	95% CI	P-value
Pathological response			0.028
Mandard grades 1-2	Reference		
Mandard grades 3-5	5.18	1.19-22.47	
PNI			0.338
Negative	Reference		
Positive	0.53	0.14-1.93	
LVI			0.903
Negative	Reference		
Positive	0.91	0.21-3.86	
Postoperative ChT			0.181
No	2.16	0.69-6.73	
Yes	Reference		

B, DFS

Variable	RR	95% CI	P-value
Pathological response			0.902
Mandard grades 1-2	Reference		
Mandard grades 3-5	0.61	0.17-2.18	
PNI			0.006
Negative	Reference		
Positive	2.93	1.36-6.29	
LVI			0.974
Negative	Reference		
Positive	1.02	0.24-4.28	
pN stage			0.085
N0	Reference		
N1	0.02	0.06-0.85	
N2	0.28	0.07-1.10	
Circumferential resection margin, mm			0.118
<1	2.07	0.83-5.19	
≥1	Reference		
Postoperative ChT			
No	2.35	0.65-8.45	0.189
Yes	Reference		

C, OS

Variable	RR	95% CI	P-value
Age, years			0.030
≤60	Reference		
>60	2.08	1.07-4.04	
Tumor diameter, cm			0.010
<5	Reference		
≥5	2.46	1.20-5.04	
Location of the tumor			0.393
Upper rectum	Reference		
Middle rectum	1.35	0.15-11.63	
Lower rectum	0.62	0.29-1.32	
Pathological response			0.936
Mandard grades 1-2	Reference		
Mandard grades 3-5	0.688	0.17-2.67	
PNI			0.009
Negative	Reference		
Positive	2.55	1.26-5.16	
LVI			0.985
Negative	Reference		
Positive	0.990	0.340-2.881	
pN stage			0.030
N0	Reference		
N1	1.50	0.70-3.22	
N2	4.55	1.44-14.36	

RR, relative risk; PNI, perineural invasion; pN, pathological node; LC, local control; DFS, disease-free survival; OS, overall survival.

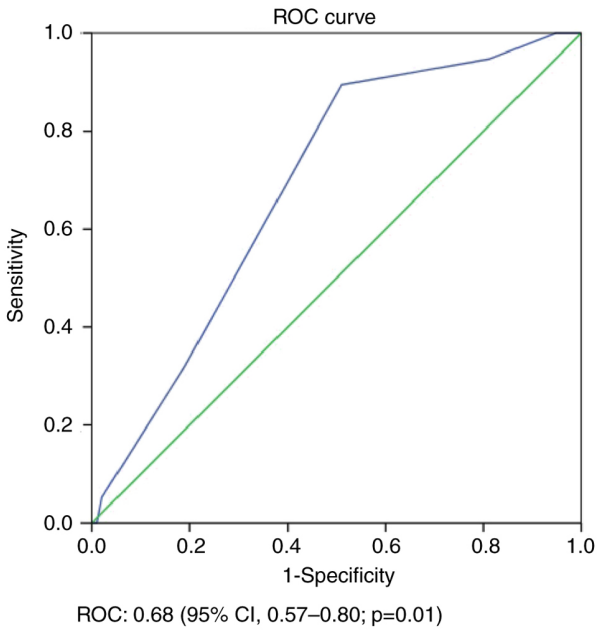

Figure 1. ROC curve of the risk score model for local control. ROC, receiver operating characteristic.

degree, peripheral circumferential margin, LVI, PNI and other stages have been found to affect LC and survival (18-20). For this reason, the present study developed a prognostic risk-scoring model using clinical and pathological factors to determine the prognosis and predict LC, DFS and OS in patients with LARC.

Several risk scoring or nomogram systems have been developed to predict prognosis or decide on adjuvant treatment

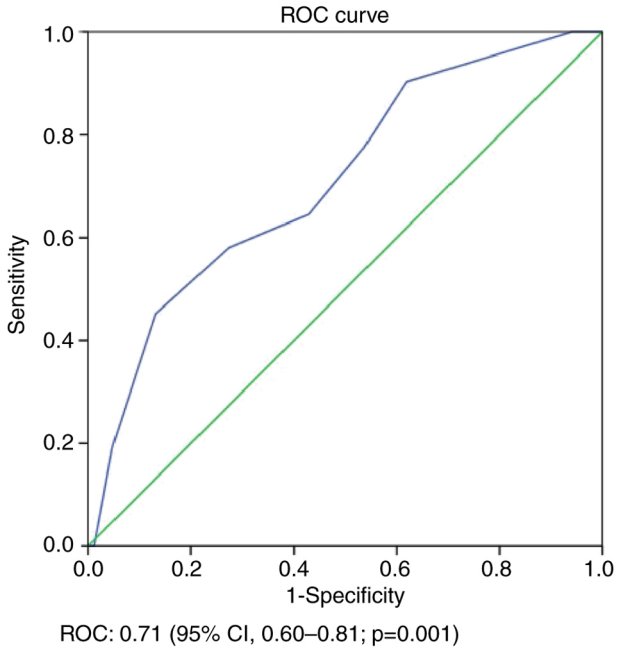

Figure 2. ROC curve of the risk score model for disease-free survival. ROC, receiver operating characteristic.

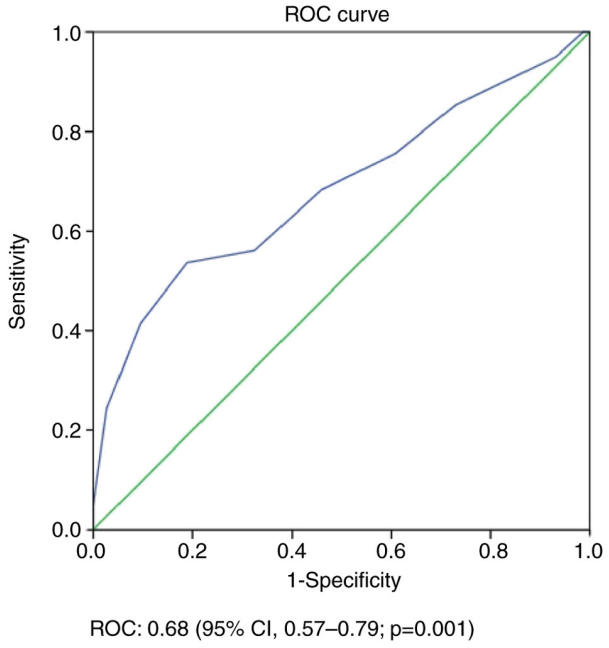

Figure 3. ROC curve of the risk score model for overall survival. ROC, receiver operating characteristic.

for rectal cancer (10,11,21,22). One of the scoring systems is the NAR score, based on the TNM staging system. The NAR score is calculated using the cT, ypT (yield pathological T) and ypN (yield pathological N) stages. Baek *et al* (10) compared the NAR scoring system with tumor regression grade and pathological TNM staging, and showed that the most important factor influencing survival was the ypTNM stage (10). Calculating the NAR score using the TNM staging system is practical and easy. However, this scoring system does not consider a number of important clinical and pathologic

Table IV. Risk score points awarded.

Assessed parameters	Point score awarded
LC	
Mandard grades 3-5	2
LVI(+)	1
PNI(+)	1
Postoperative ChT(-)	1
DFS	
PNI(+)	2
Mandard grades 3-5	1
LVI(+)	1
pN(+)	1
CRM <1 mm	1
Postoperative ChT(-)	1
OS	
Age >60 years	2
Tumor diameter ≥5 cm	2
PNI(+)	2
pN(+)	2
Lower rectum	1
Mandard grades 3-5	1
LVI(+)	1

LVI, lymphovascular invasion; PNI, perineural invasion; pN, pathological node; ChT, chemotherapy; CRM, circumferential resection margin; LC, local control; DFS, disease-free survival; OS, overall survival.

prognostic factors, such as age, performance score, tumor location, tumor diameter, tumor regression grade, LVI and PNI.

The degree of tumor response to neoadjuvant therapy is one of the prognostic factors that has been discussed in risk score models and nomograms in the literature over the last 10 years (10,12,16). In some studies, the degree of tumor response to neoadjuvant therapy is one of the determinants of local recurrence risk and even OS. Various tumor regression grading systems have been developeDd to classify the pathological response to nCRT in patients with LARC (13,23). Mandard *et al* (24) developed a five-category tumor regression system to assess tumor response to CRT in patients with oesophageal cancer by quantitatively evaluating residual tumor cells versus inflammatory fibrosis. In subsequent studies, the Mandard system was shown to be an effective classification system for evaluating tumor response to nCRT and predicting prognosis in patients with LARC (23,25). A meta-analysis of patients with a pathological complete response to neoadjuvant treatment found that local recurrence rates were low (1.6%) at a median follow-up time of 46.4 months, and that the 5-year DFS and OS rates were 85 and 90%, respectively (26). The present study classified the degree of tumor response to neoadjuvant treatment according to the Mandard system. The LC rate was statistically significantly lower in the Mandard grades 3-5 patient group compared with that in the Mandard grades 1-2 patient group. In the pathological T0N0 group, local recurrence was

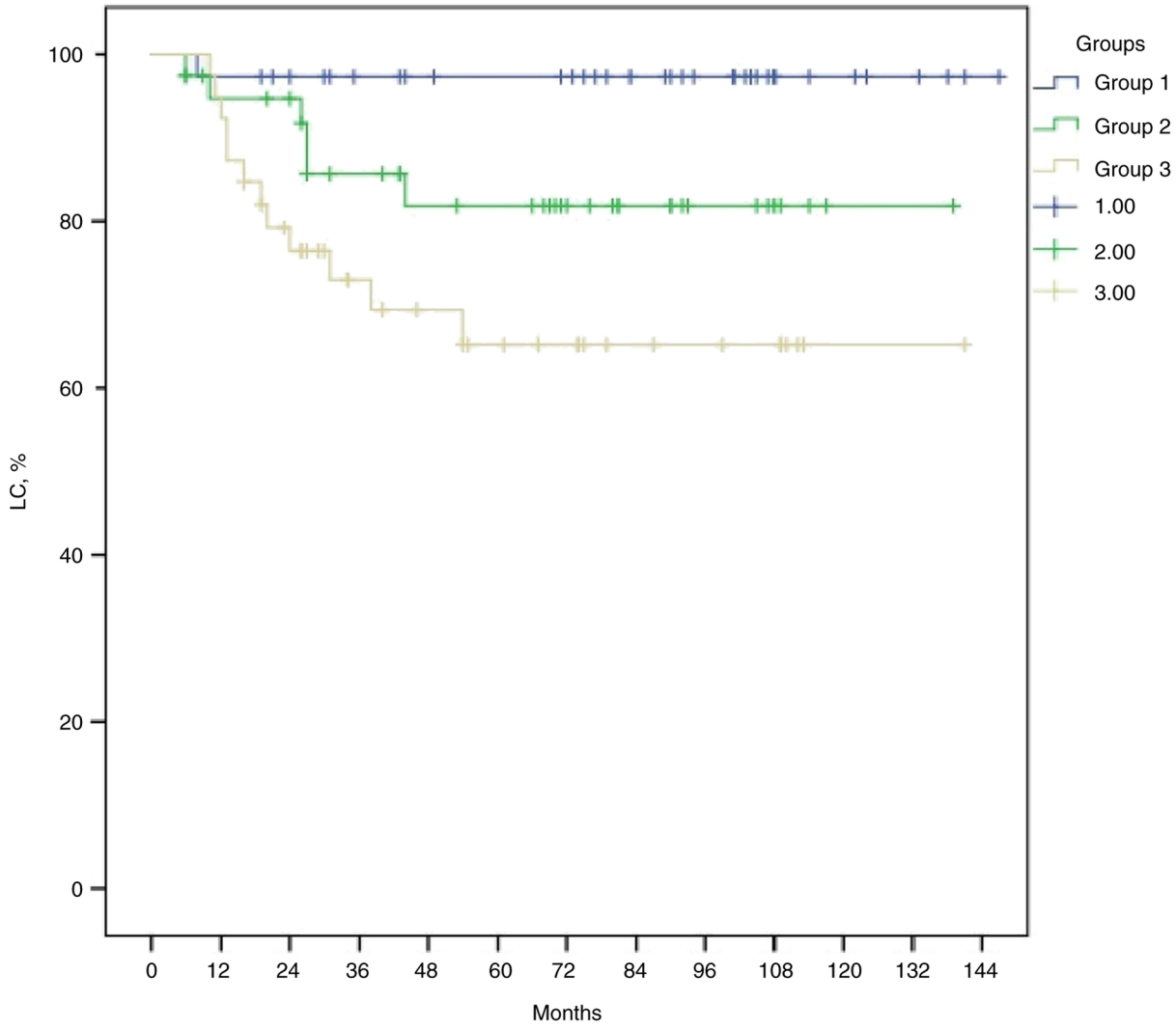

Figure 4. LC curves based on groups. LC, local control.

observed in only 1 out of 21 patients at a median follow-up time of 70 months, which is likely to be due to a larger tumor (>5 cm) . Complete pathological response was not a prognostic factor in the risk score model due to the small number of patients with complete pathological responses (pT0N0) after neoadjuvant therapy.

Another prognostic factor that should be more broadly discussed in risk score models and nomograms is PNI. PNI refers to the invasion of nerves by tumor cells. Tumor cells can grow into, around or through the three layers of nerves (endoneurium, perineurium and epineurium). Therefore, there are different definitions in the literature. The most commonly used definition is that >33% of the nerve periphery is surrounded by tumor cells (20). The incidence of PNI reported in the literature varies between 9 and 30% (20,27). The incidence increases in advanced-stage disease. In one study, it was reported to be ~10% in stage I-II, 30% in stage III and 40% in stage IV disease (20). In the present study, the rate of PNI was 38.3%. In a meta-analysis of 22,900 patients with colorectal cancer, PNI, depth of tumor invasion, tumor grade, lymph node metastasis and extramural invasion were shown to be prognostic factors. In addition, OS and DFS rates were lower in patients with PNI (28). Similarly, in the present study, both DFS and OS rates were significantly lower in patients with PNI.

Data from 2,795 patients in five large randomized trials comparing preoperative CRT versus preoperative RT or postoperative CRT/ChT have been used to develop nomograms to predict local recurrence, distant metastases and OS. In addition to pathological and clinical TNM staging as prognostic factors, sex, age, tumor location, RT dose, concurrent and adjuvant ChT, and surgical procedure were included in the analysis. The pathological stage was found to be the most critical factor for the accurate prediction of survival outcomes. In multivariate analysis, the rates of LC and OS were higher, while distant metastasis rates were lower in patients with low anterior resection, pT0, pN0 and adjuvant ChT (11). Weiser *et al* (22) also found that postoperative pathological staging was more critical than clinical staging in terms of prediction outcomes in patients receiving neoadjuvant therapy to evaluate response to treatment and to choose appropriate treatment (22). In the univariate and multivariate analyses in the present study, clinical T and N stages were not found to be prognostic factors for LC, DFS and OS. However, pathological N stage was a prognostic factor for DFS and OS in univariate and multivariate analysis, and OS was higher in

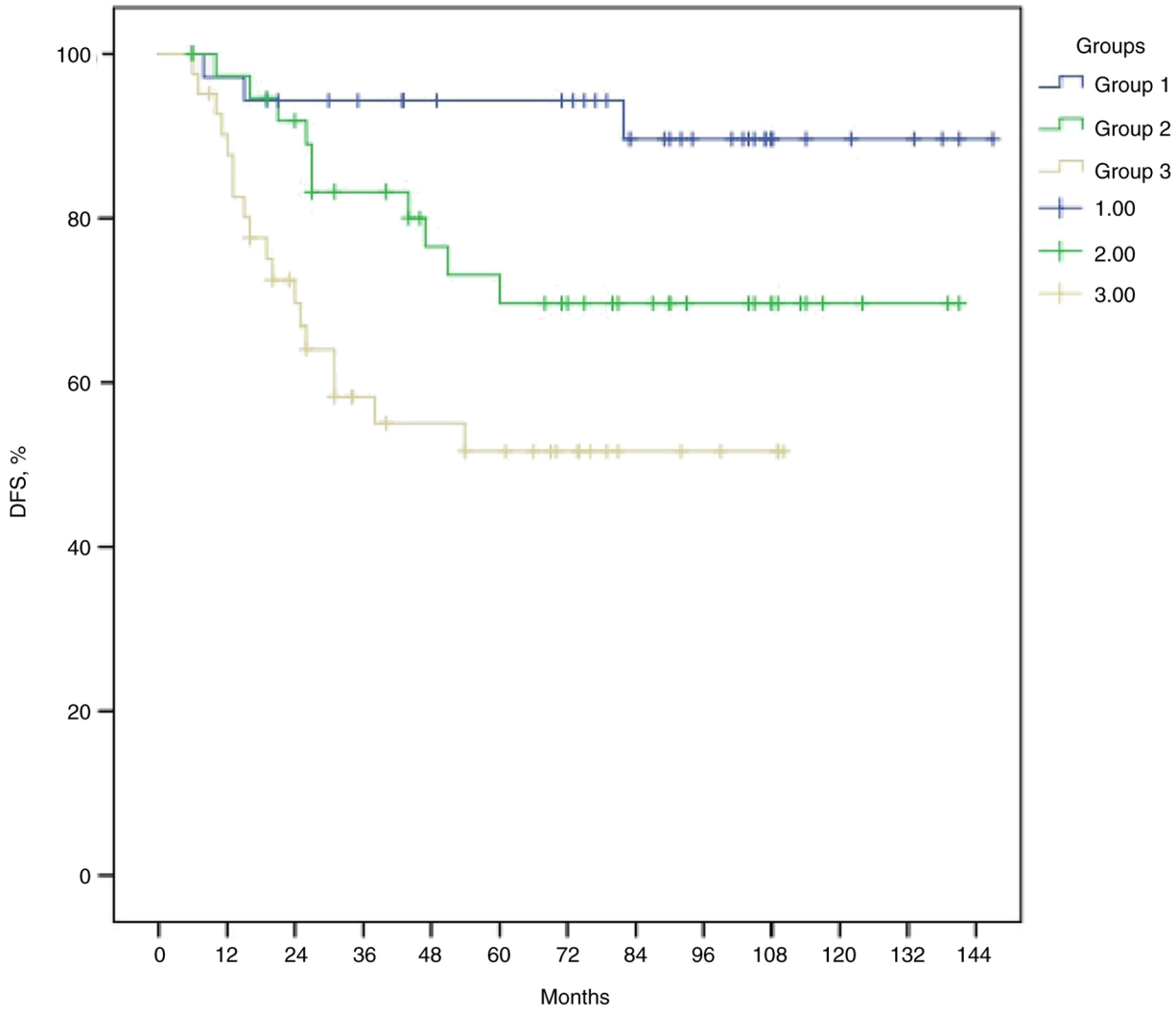

Figure 5. DFS curves based on groups. DFS, disease-free survival.

pN0 patients (P=0.03). Therefore, effective postoperative ChT is needed, especially in patients with ypN2 disease, to improve survival rates.

Lin's nomogram evaluated patients with stage II-III rectal cancer, and ethnicity, sex, age, marital status, T stage, tumor grade, tumor size, positive lymph node involvement rate, CEA level and postoperative ChT were all factors found to be affecting OS (29). For the first time, a study reported that a tumor size >7 cm was an independent prognostic factor for patients undergoing neoadjuvant CRT treatment (23). There is a lack of consensus among international guidelines regarding the specific cutoff value for tumor size. A few studies have reported that a tumor size of 4 cm is a prognostic cut-off (30-32). In the present study, multivariate analysis found that a tumor diameter of ≥5 cm was significantly associated with a decreased OS rate. Although tumor size may not represent the actual tumor volume or burden, it is a convenient and rapid method to estimate tumor volume in clinical practice. In the literature, the prognostic significance of tumor volume has been investigated, and some studies have reported that a small tumor volume is more important than the size of the tumor (33,34). In addition, Yeo *et al* (35) showed that the decrease in tumor volume after neoadjuvant treatment was a prognostic factor.

Weiser *et al* (22) developed a clinical risk calculation model to determine recurrence-free survival and OS in patients without a pathological complete response who were treated with nCRT. Besides the TNM staging system and the NAR score, the clinical risk calculation model included the number of positive lymph nodes, the distance to the anal margin, VI and PNI as predictors of relapse-free survival. For OS, age was also evaluated. Recurrence-free survival and OS rates were lower in patients with <5 cm distance to the anal verge, pathologically advanced T stage, positive lymph node count >1, VI and PNI. In addition, advanced age negatively affected survival. The study also compared their scoring system with the NAR score and TNM staging system. The recurrence probability and survival were predicted with greater accuracy using their system compared with using the TNM staging system and NAR score (22). In the present risk score model, OS was significantly worse in patients aged >60 years, with lower rectal tumors, pathological lymph node involvement and PNI.

More accurate treatment outcome predictions can be obtained when patient and tumor-specific clinical and pathological factors other than the TNM staging system are added to the model. In the present study, when patients in

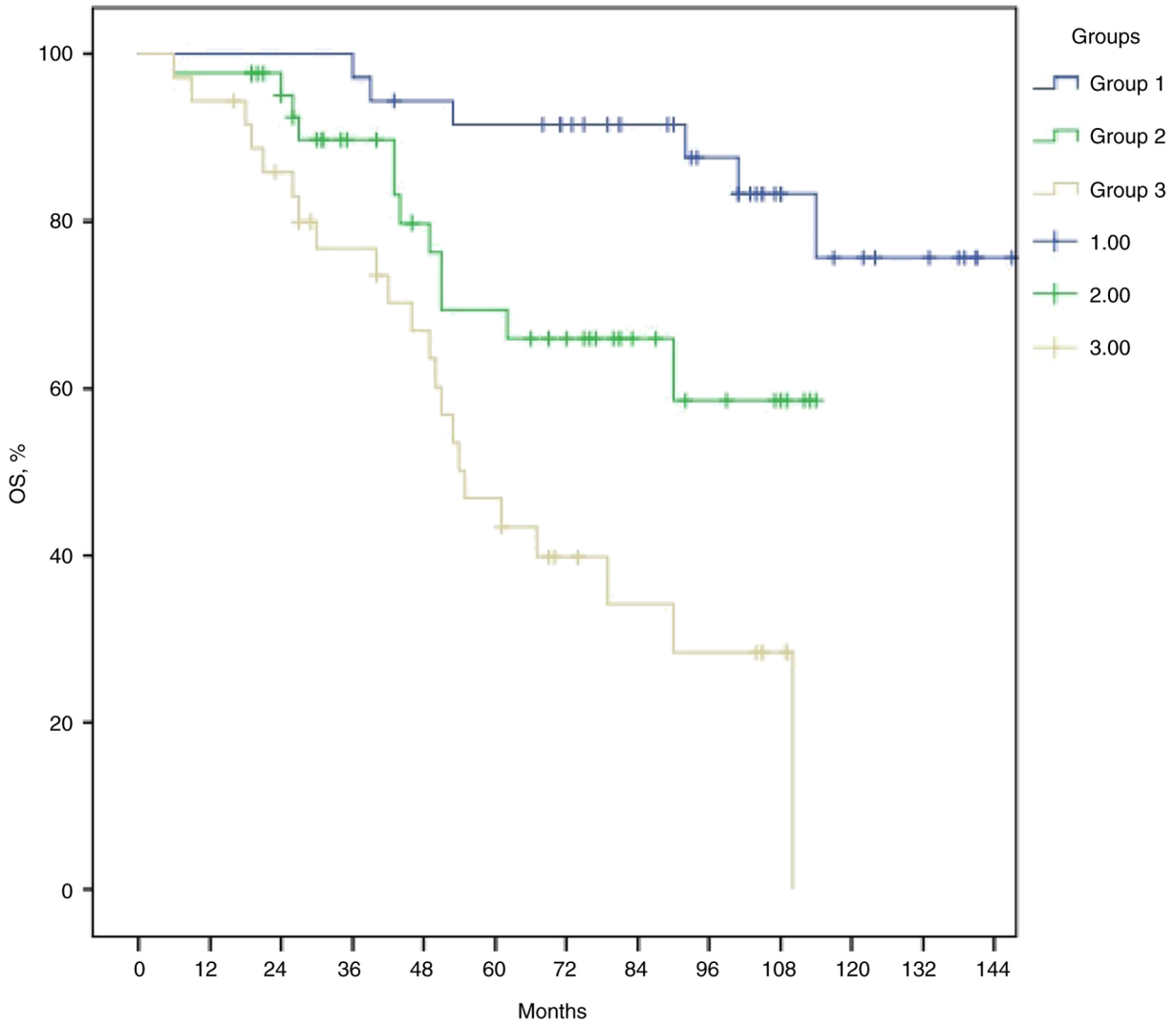

Figure 6. OS curves based on groups. OS, overall survival.

the group 3 were examined in terms of OS according to the scoring system, 86% had a tumor diameter ≥5 cm, 72% had radiological multiple lymph node involvement at baseline, 63% had pN+ disease and 88% had PNI after neoadjuvant treatment. The median survival time of these patients in the group 3 was significantly lower than that of patients in the group 1 and 2 (median OS times for groups 1, 2 and 3 were 138.3, 87.2 and 64.6 months, respectively; P<0.001). The addition of ChT to neoadjuvant RT has a radiosensitizing role and has been proven to have positive effects in terms of local recurrence (36). However, it has been less effective for OS. In particular, one of the novel treatment strategies, total neoadjuvant treatment with maximal oncological treatment before surgery, has been investigated in relation to the effect on survival. Furthermore, the STELLAR study demonstrated an OS benefit (4,37). Previous studies have shown that total neoadjuvant treatment, in which systemic treatment is intensified in the neoadjuvant period in distally located tumors with clinical T4, N2 and extra mesorectal lymph node involvement, contributes to DFS (38-40). In the present study, a significant number of patients in the high-risk category had PNI, multiple lymph node involvement or large tumors. With standard neoadjuvant therapy, the survival rate for this group was poor. The advances in medical treatment and RT have not significantly influenced DFS and OS rates, and systemic metastases are seen in up to 30% of high-risk cases (8). Total neoadjuvant therapy (TNT) approaches that have proven effective can be used in these patients.

Clinical prediction models can help determine the surveillance of patients with rectal cancer and aid risk stratification in clinical trials. In the present study, the discriminative potential of the score model was measured by ROC curves, and the AUCs were calculated. The risk scoring modeling had reliable AUC values [LC, 0.68 (95% CI, 0.57-0.80; P=0.01); DFS, 0.71 (95% CI, 0.60-0.81; P=0.001); and OS, 0.68 (95% CI, 0.57-0.79; P=0.001)]. These levels are suitable for clinical decision-making but not optimal. These factors may help develop novel models. Model accuracy can be improved by adding novel molecular factors related to tumor biology to risk score modeling. The present study has certain limitations, namely, it was a retrospective, single center study, does not represent the general population, and the number of patients was small. Additionally, novel molecular information, such as microsatellite instability, was not included in the

scoring system. Since the scoring system consists of patients treated with standard nCRT, it does not include total neoadjuvant treatment. It was not possible to establish a training and validation cohort in the present study, as there was an insufficient number of patients, despite the fact that such a cohort has been established in the relevant literature for some studies (22,29,41). However, positively, the present study consists of a homogeneous group of patients treated with the same RT dose, technique and ChT regime by the same experienced team. The present scoring system was similar to that of Morini *et al* (16). However, Morini's scoring system investigated the effect of tumor regression, grading and LVI on survival in patients with stage II-III rectal cancer, while the present scoring system investigated a greater number of clinical and pathological factors.

The present risk-scoring modeling determined the difference between groups in terms of LC, DFS and OS. This may help in decision-making for patient selection for different treatment approaches and clinical trials, and it may provide a rationale for individualized follow-up and treatment in high-risk patients. Especially in patients with tumor size >5 cm, those with PNI and those with multiple poor prognostic factors such as multiple lymph node involvement, the addition of effective systemic therapy to RT may lead to improved treatment outcomes and could be evaluated in existing large randomized trials of TNT or adjuvant ChT for rectal cancer. However, the external validation of the present risk score model using large-scale prospective studies is required.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

Study conception and design was performed by TKC and DCO. Data collection was performed by TKC and IFD. TKC and IFD confirm the authenticity of all the raw data. Analysis and interpretation of results were completed by TKC, GC and SAE. The draft manuscript was prepared by TKC and DCO. All authors have read and approved the final version of the manuscript

Ethics approval and consent to participate

The present retrospective analysis was performed with appropriate approval by Istanbul University-Cerrahpasa Ethics Committee (dated Feburary 22, 2023; approval no. E-830458 09-064.01.01-626378). Informed written consent was obtained from all individual participants included in the study.

Patient consent for publication

The authors affirm that human research participants provided informed written consent for publication.

Competing interests

The authors declare that they have no competing interests.

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