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Prediction of cancer-specific survival and overall survival in middle-aged and older patients with rectal adenocarcinoma using a nomogram model

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A B S T R A C T

Objective: To develop a new nomogram tool for predicting survival in middle-aged and elderly patients with rectal adenocarcinoma.

Methods: A total of 6,116 patients were randomly assigned in a 7:3 ratio to training and validation cohorts. Univariate and multivariate Cox proportional hazards regression analyses were used to identify independent prognostic factors associated with overall survival (OS) and cancer-specific survival (CSS) in the training set, and two nomogram prognostic models were constructed. The validity, accuracy, discrimination, predictive ability, and clinical utility of the models were assessed based on the concordance index (C-index), area under the receiver operating characteristics (ROC) curve, time-dependent area under the ROC curve (AUC), Kaplan-Meier survival curve, and decision curve analyses.

Results: Predictors of OS and CSS were identified, and nomograms were successfully constructed. The calibration discrimination for both the OS and CSS nomogram prediction models was good (C-index: 0.763 and 0.787, respectively). The AUC showed excellent predictive performance, and the calibration curve exhibited significant predictive power for both nomograms. The time-dependent AUC showed that the predictive ability of the predictor-based nomogram was better than that of the TNM stage. The nomograms successfully discriminated high-, medium-, and low-risk patients for all-cause and cancer-specific mortality. The decision curve demonstrated that the nomograms are useful with respect to good decision power.

Conclusion: Our nomogram survival prediction models may aid in evaluating the prognosis of middle-aged and older patients with rectal adenocarcinoma and guiding the selection of the clinical treatment measures.

Introduction

The incidence of rectal cancer has exceeded that of gastric cancer and liver cancer, becoming the second most common solid malignancy [1]. The most frequently observed site of colorectal cancer is the rectum, and the main pathological type is adenocarcinoma. Rectal adenocarcinomas mainly affect middle-aged and older patients (aged >45 years) [2]. Therefore, it is important to establish a prognostic model of rectal adenocarcinoma for this population in order to develop effective methods for diagnosis and treatment, as well as to assess prognosis.

The Surveillance, Epidemiology, and End Results (SEER) database, a tumor-related registry database established by the National Cancer Institute in 1973, currently covers 28% of cancer patients. Data are derived from clinical sources, including patients' clinically relevant information, treatment costs, and social information, which provide evidence support and important data for medical research [3]. Nomograms are used to construct survival prediction models that can comprehensively incorporate multiple prognostic indicators and quantify risk with intuitive graphs. They are used as tools for assessing risks and benefits, and they aid in clinical diagnoses and decision-making regarding treatment strategies [4].

Previous clinical survival model studies have used limited numbers of samples and relied on restricted evaluations, reducing their clinical application. At the same time, recent advances in medical technology have affected prognostic outcomes. Thus, it is important to establish a

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method to evaluate the prognostic outcome of middle-aged and older patients with rectal adenocarcinoma in a reasonable and accurate way. Here, we analyzed relevant clinical data of this population registered in the SEER database between 2010 and 2015 to construct a nomogram survival model for predicting patient 3- and 5-year overall survival (OS) and cancer-specific survival (CSS). The nomogram provides a good prediction tool that may help guide physicians in generating more accurate individual diagnoses and treatment plans.

Materials and methods

Patient data collection

Data were obtained from the SEER database (https://seer.cancer.gov/data/). SEER*Stat version 8.3.6 software was used. Permission to access the SEER database was obtained (accession number: 12285-Nov2019).

The inclusion criteria were as follows: (1) registration in the SEER database from 2010 to 2015, (2) diagnosis of rectal adenocarcinoma, (3) surgical treatment, and (4) availability of complete follow-up information. The exclusion criteria were as follows: (1) unclear diagnostic methods; (2) unknown ethnicity; (3) unknown TNM stage; (4) unknown tumor size; (5) unknown histological grade; (6) unknown carcinoembryonic antigen (CEA), circumferential resection margin (CRM), tumor implantation (TD), and perineural invasion (PNI) data; or (7) unknown number of positive lymph nodes and examined lymph nodes.

We collected the following information for each patient: year of diagnosis, age, ethnicity, sex, tumor location, histological grade, clinical stage, CEA, TD, CRM, PNI, tumor size, number of positive lymph nodes, number of examined lymph nodes, metastasis status, histopathological type (malignant behavior based on ICD-O-3), survival time, cause of death, and survival status. Clinical staging was based on the 7th edition of the American Joint Committee on Cancer (AJCC) staging system. The CEA level was determined according to the highest value in the preoperative test results.

Clinical data were obtained from the SEER database for 260,833 patients. A total of 6116 eligible patients were enrolled. The flowchart for the inclusion of patients is shown in Fig. 1. Seventy percent of eligible patients were randomly divided into a training cohort and the remaining 30% into a validation cohort using R software.

Study endpoints

The study endpoints were OS and CSS. Moreover, the 3-year and 5-year survival outcomes were assessed. The validity, accuracy, discrimination, predictive ability, and clinical utility of the nomogram were assessed based on the C-index, receiver operating characteristics (ROC) curve, time-dependent area under the ROC curve (AUC), decision curve, and calibration curve.

OS was defined as the time from diagnosis to death or follow-up [5]. CSS was defined as the time from diagnosis to death or follow-up for rectal cancer [6].

Statistical analysis

The X-tile software was used to divide variables into different basins based on changes in markers and to visualize the optimal cutpoints for creating such segmentations [7]. SPSS software (version 24.0, SPSS Inc., Chicago, USA) and R software (www.r-project.org, version 3.63) were used for statistical analysis. Cox regression analysis was performed using the R package "rms," "foreign," and "survival." The concordance indexes (C-index) and risk score were calculated, and Kaplan-Meier survival curves, decision curves, and cali-
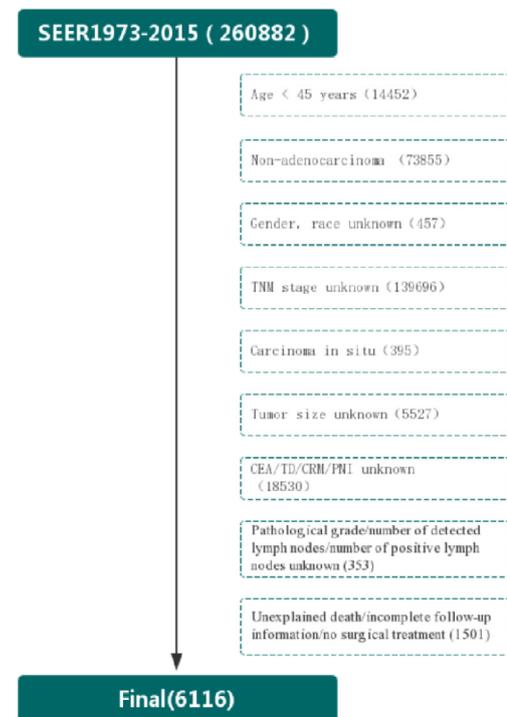
Fig. 1. Flow chart of patient selection.
From the 260,882 patients with rectal cancer in the seer database, a total of 6116 eligible patients were screened.

bration curves were plotted. A nomogram was drawn by the R package "regplot." ROC curve and time-dependent ROC-based AUC were plotted by the R package "timeROC." Statistical tests involved two-way analyses. P values <0.05 were considered to indicate statistical significance.

Nomogram construction and performance evaluation

The X-tile software was used to assess the optimal cut-off values for age, tumor size, number of positive lymph nodes, and number of examined lymph nodes. The optimal cut-off values were as follows: age, 60 and 75 years; tumor size, 30 and 60 mm; number of positive lymph nodes, 1 and 4; and number of examined lymph nodes, 10 (Supplementary Fig. 1).

Frequencies and percentages were used to describe the clinical data of the validation cohort and training cohort. The chi-square test was used to determine the difference between the two groups. P <0.05 was considered to indicate statistical significance. Univariate and multivariate Cox regression analyses were used to identify the prognostic factors and calculate hazard ratios (HRs) with 95% confidence intervals (CIs).

A nomogram was constructed using the R software and indicators with statistical significance in the multivariate Cox analysis as predictors. The C-index and AUC were used to assess the predictive effect of the nomogram. The calibration curve was used to evaluate the agreement between actual and predicted results.

Verification of nomogram discrimination

A risk score was calculated for each patient using the "predicted" function of the R software. The X-tile software was used to identify patients in the training set, and the patients were then divided into the low-, medium-, and high-risk groups according to the cut-off optimal

Table 1

Baseline demographic and clinical characteristics of middle-aged and elderly patients with rectal adenocarcinoma.

Variable	Training Cohort (4284)		Validation Cohort (1832)		Overall (6116)		P value
	Quantity	SCALE	Quantity	SCALE	Quantity	SCALE	
Age							0.219
45-60	1957	45.68%	854	46.62%	2811	45.96%	
61-75	1656	38.66%	723	39.47%	2379	38.90%	
> 75	671	15.66%	255	13.92%	926	15.14%	
Race							0.245
Black	317	7.40%	158	8.62%	475	7.77%	
White	3410	79.60%	1433	78.22%	4843	79.19%	
Other	557	13.00%	241	13.16%	798	13.05%	
Sex							0.18
F	1713	39.99%	699	38.16%	2412	39.44%	
M	2571	60.01%	1133	61.84%	3704	60.56%	
Grade							0.933
I/II	3778	88.19%	1617	88.26%	5395	88.21%	
III/IV	506	11.81%	215	11.74%	721	11.79%	
Site							0.134
Rectosigmoid Junction	1495	34.90%	676	36.90%	2171	35.50%	
Rectum	2789	65.10%	1156	63.10%	3945	64.50%	
Stage							0.951
I	675	15.76%	284	15.50%	959	15.68%	
II	1276	29.79%	547	29.86%	1823	29.81%	
III	1874	43.74%	812	44.32%	2686	43.92%	
IV	459	10.71%	189	10.32%	648	10.60%	
Stage_T							0.277
T1	226	5.28%	93	5.08%	319	5.22%	
T2	721	16.83%	296	16.16%	1017	16.63%	
T3	2870	66.99%	1212	66.16%	4082	66.74%	
T4	467	10.90%	231	12.61%	698	11.41%	
Stage_N							0.974
1	2056	47.99%	876	47.82%	2932	47.94%	
2	1582	36.93%	682	37.23%	2264	37.02%	
3	646	15.08%	274	14.96%	920	15.04%	
Stage_M							0.643
M1	3825	89.29%	1643	89.68%	5468	89.40%	
M2	459	10.71%	189	10.32%	648	10.60%	
Tumor size							0.784
<=30	1192	27.82%	525	28.66%	1717	28.07%	
<=60	2233	52.12%	948	51.75%	3181	52.01%	
> 60	859	20.05%	359	19.60%	1218	19.91%	
CEA							0.673
Low	2414	56.35%	1043	56.93%	3457	56.52%	
High	1870	43.65%	789	43.07%	2659	43.48%	
TD							0.262
Neg	3821	89.19%	1616	88.21%	5437	88.90%	
Pos	463	10.81%	216	11.79%	679	11.10%	
CRM							0.023
Neg	1940	45.28%	771	42.09%	2711	44.33%	
Pos	2344	54.72%	1061	57.91%	3405	55.67%	
PNI							0.15
Neg	3685	86.02%	1550	84.61%	5235	85.60%	
Pos	599	13.98%	282	15.39%	881	14.40%	
Number of positive lymph nodes							0.498
0	2605	60.81%	1106	60.37%	3711	60.68%	
<=4	1235	28.83%	550	30.02%	1785	29.19%	
> 4	444	10.36%	176	9.61%	620	10.14%	
Number of lymph nodes examined							0.183
<=10	626	14.61%	292	15.94%	918	15.01%	
> 10	3658	85.39%	1540	84.06%	5198	84.99%	

risk score. The log-rank test was used to assess the differences in survival among the three groups. The Kaplan–Meier survival curves were plotted for OS and CSS based on the risk scores for the validation and training sets.

Evaluation of the predictive power of the nomogram

The time-dependent AUC shows the values of different prediction models of patients at time points of change to further evaluate the accuracy of the constructed nomogram prediction model and that of the TNM stage. Therefore, we used time-dependent AUC to assess the predictive power of the constructed nomogram with that of the TNM stage.

Evaluation of the clinical efficacy of nomograms

Decision curves analytically(DCA) assess clinical utility and net benefit [8]. To test the clinical efficacy of the nomogram, we used the decision curve of the training group versus the validation group.

Table 2
Univariate cox regression analysis of cancer-specific survival and overall survival in the training cohort.

Variable	OS			CSS		
	HR	95% CI	P	HR	95% CI	P
Age			< 0.001			< 0.001
45-60						
61-75	1.63	1.36 ~ 1.95	< 0.001	1.38	1.13 ~ 1.69	0.0014
> 75	3.56	2.95 ~ 4.31	< 0.001	2.51	2.01 ~ 3.15	< 0.001
Race			0.02			0.2
Black						
White	0.78	0.61 ~ 1.01	0.0636	0.80	0.59 ~ 1.09	0.1592
Other	0.63	0.45 ~ 0.88	0.0067	0.72	0.49 ~ 1.06	0.0971
Sex			0.01			0.2
F						
M	1.21	1.04 ~ 1.41	0.0148	1.13	0.95 ~ 1.35	0.1680
Grade			< 0.001			< 0.001
I/II						
III/IV	1.85	1.53 ~ 2.23	< 0.001	2.23	1.81 ~ 2.74	< 0.001
Site			0.5			0.6
Rectosigmoid Junction						
Rectum	0.95	0.82 ~ 1.11	0.5340	0.95	0.79 ~ 1.14	0.5690
Stage			< 0.001			< 0.001
I						
II	1.35	1.01 ~ 1.81	0.0443	2.37	1.49 ~ 3.76	< 0.001
III	1.87	1.42 ~ 2.46	< 0.001	3.91	2.52 ~ 6.06	< 0.001
IV	6.10	4.58 ~ 8.14	< 0.001	16.15	10.36 ~ 25.17	< 0.001
Tumor size			< 0.001			< 0.001
<=30						
<=60	1.50	1.24-1.82	< 0.001	1.66	1.31 ~ 2.1	< 0.001
> 60	2.31	1.86 ~ 2.87	< 0.001	2.70	2.08 ~ 3.49	< 0.001
CEA			< 0.001			< 0.001
Low						
High	2.22	1.91 ~ 2.58	< 0.001	2.37	1.98 ~ 2.83	< 0.001
TD			< 0.001			< 0.001
Neg						
Pos	2.10	1.72 ~ 2.56	< 0.001	2.71	2.19 ~ 3.37	< 0.001
CRM			< 0.001			< 0.001
Neg						
Pos	1.36	1.17-1.58	< 0.001	1.47	1.23 ~ 1.76	< 0.001
PNI			< 0.001			< 0.001
Neg						
Pos	2.19	1.83 ~ 2.61	< 0.001	2.62	2.15-3.2	< 0.001
Number of positive lymph nodes			< 0.001			< 0.001
0						
<=4	1.70	1.44 ~ 2.01	< 0.001	2.19	1.79 ~ 2.67	< 0.001
> 4	3.27	2.68 ~ 3.97	< 0.001	4.82	3.86 ~ 6.01	< 0.001
Number of lymph nodes examined			0.001			0.002
<=10						
> 10	0.74	0.62 ~ 0.89	0.0015	0.72	0.58 ~ 0.89	0.0023

Results

Baseline patient characteristics

Except for the CRM, no statistically significant differences were found in the remaining variables between the two groups ($P > 0.05$; Table 1). The results of randomization were satisfactory.

In the univariate Cox regression analysis of OS, other factors, except the tumor site, showed statistical significance ($P < 0.05$). In the univariate Cox regression analysis of CSS, other factors, except sex, race, and tumor location, showed statistical significance ($P < 0.05$; Table 2). Multivariate Cox regression analysis was performed for variables with statistically significant differences. The results of the multivariate Cox regression analysis of OS showed significant statistical differences in all variables, except "White" for race and "<=60" in "II" and "III" tumor sizes ($P < 0.05$). The results of the multivariate Cox regression analysis of CSS showed significant statistical differences in all variables, except "<=60" of tumor size ($P < 0.05$; Table 3).

Determination of predictors and construction of nomogram models

Variables that were not significant or had mild effects were excluded. We used age, ethnicity, sex, histological grade, clinical stage, CEA, TD, CRM, PNI, tumor size, number of positive lymph nodes, and number of examined lymph nodes as predictors of OS models; constructed nomograms; and then plotted the corresponding training set calibration curves. Age, histological grade, clinical stage, tumor size, CEA, TD, CRM, PNI, number of positive lymph nodes, and number of examined lymph nodes were used as predictors of the CSS model; nomograms were constructed; and the corresponding training set calibration curves were plotted (Fig. 2). Specific scores for each predictor in the nomogram are provided in Supplementary Table 2. In the nomogram, the 3-year and 5-year OS/CSS probabilities of middle-aged and older patients with rectal adenocarcinoma could be predicted according to the total score of predictors. The validation cohort's medium-, 3-, and 5-year OS and the calibration curve of the CSS also showed agreement between the actual and predicted clinical outcomes.

Table 3
Multivariate cox regression analysis of cancer-specific survival and overall survival in the training cohort.

Variable	OS			CSS		
	HR	95% CI	P	HR	95% CI	P
Age						
45-60						
61-75	1.83	1.52 ~ 2.18	< 0.001*	1.57	1.28-1.92	< 0.001*
> 75	4.79	3.93 ~ 5.83	< 0.001*	3.54	2.8 ~ 4.46	< 0.001*
Race						
Black						
White	0.82	0.64 ~ 1.07	0.1429			
Other	0.62	0.44 ~ 0.86	< 0.001*			
Sex						
F						
M	1.26	1.08 ~ 1.47	0.0036*			
Grade						
I/II						
III/IV	1.52	1.25-1.84	< 0.001*	1.71	1.38 ~ 2.12	< 0.001*
Stage						
I						
II	1.10	0.81 ~ 1.49	0.5358	1.94	1.21 ~ 3.09	0.0056*
III	1.19	0.84 ~ 1.67	0.3321	2.24	1.36 ~ 3.68	0.0015*
IV	3.30	2.3-4.72	< 0.001*	7.82	4.7 ~ 13	< 0.001*
Tumor size						
<=30						
<=60	1.20	0.98 ~ 1.46	0.0785	1.27	1 ~ 1.62	0.0520
> 60	1.73	1.38 ~ 2.17	< 0.001*	1.91	1.46 ~ 2.49	< 0.001*
CEA						
Low						
High	1.60	1.36 ~ 1.88	< 0.001*	1.44	1.19 ~ 1.74	< 0.001*
TD						
Neg						
Pos	1.36	1.09 ~ 1.69	0.0058*	1.50	1.19 ~ 1.89	< 0.001*
CRM						
Neg						
Pos	1.26	1.08 ~ 1.47	0.0029*	1.35	1.12-1.61	0.0013*
PNI						
Neg						
Pos	1.43	1.18 ~ 1.74	< 0.001*	1.43	1.15 ~ 1.78	0.0013*
Number of positive lymph nodes						
0						
<=4	1.35	1.05 ~ 1.73	0.0185*	1.42	1.08 ~ 1.89	0.0132*
> 4	1.91	1.44 ~ 2.53	< 0.001*	2.14	1.57 ~ 2.92	< 0.001*
Number of lymph nodes examined						
<=10						
> 10	0.70	0.58 ~ 0.84	< 0.001*	0.61	0.49 ~ 0.76	< 0.001*

Note:
* indicates *P* < 0.05.

Evaluation of the predictive power and usefulness of the model

The C-indexes of the OS and CSS nomograms of the training set were 0.763 (95% CI 0.745–0.781) and 0.787 (95% CI 0.765–0.80), respectively. The AUCs of the 3- and 5-year survival rate in the OS prediction model of the training set were 0.773 and 0.768, respectively, and those of the CSS prediction model were 0.802 and 0.790, respectively. The prediction model showed good predictive power. Time-dependent AUC curves were not only used to evaluate the predictive power of the nomogram, but also used to compare the predictive ability of TNM stage. The curve in Fig. 3 shows that the AUC value of the OS/CSS nomogram is significantly higher than that of the TNM stage at 0–60 months, and the predictive ability of the nomogram is better than that of the TNM stage.

Validation of the discrimination capability of the predictive model

A risk score was calculated for each patient using the "predicted" function of the R software. The optimal OS and the CSS risk score cut-off values obtained by the X-tile software were 1.2 and 3.5, 1.4 and 4.1, respectively. Patients were divided into three groups according to the optimal cut-off value: low-, intermediate-, and high-risk groups. Kaplan–Meier survival curves were plotted. We found significant survival differences between the training cohort and all three groups of patients in the validation cohort (Fig. 4). Therefore, the OS nomogram can successfully distinguish all-cause mortality in high- and medium-risk patients, and the CSS nomogram can successfully distinguish cancer-specific mortality in high-, medium-, and low-risk patients.

Evaluation clinical efficacy of nomograms

Decision curves of the OS and CSS nomograms were constructed at a threshold probability of <88% and <80% at 3 years, respectively (Fig. 5). The OS and CSS nomograms provided a net benefit over the "all treatment" or "no treatment" strategy. In addition, similar results were obtained in the validation set, when the threshold probabilities were <88% and <82% at 3 years, respectively. Therefore, the presented nomogram displays good, clinically relevant decision power.
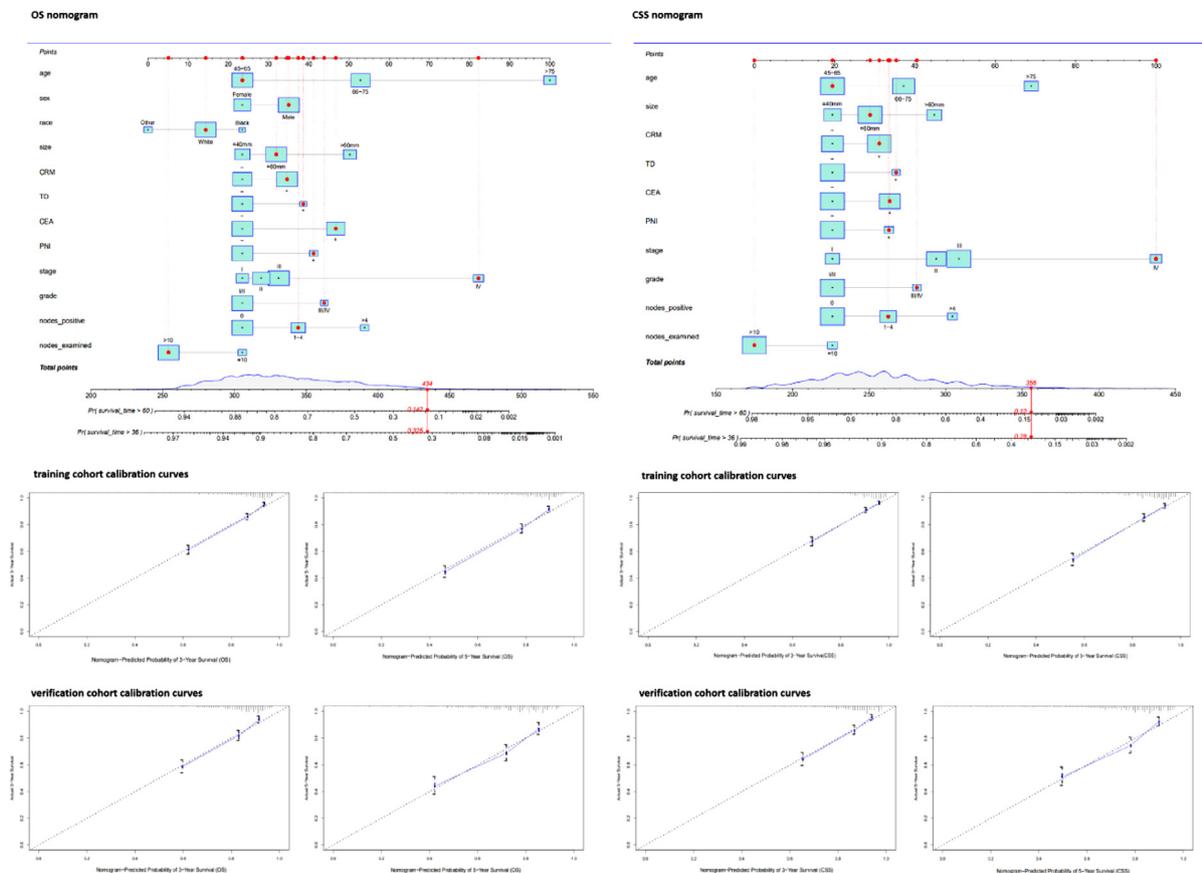
Fig. 2. OS and CSS nomograms and calibration curves.

The total score obtained by summing the individual scores of the predictors was used to predict the 3- and 5-year survival rates of the patients. The calibration curves showed a high degree of agreement between the predicted and actual values of the OS nomogram and the CSS nomogram. Example: A 50-year-old male Caucasian patient with rectal adenocarcinoma, tumor size 50 mm, CRM (+), TD(+), CEA (+), PNI (+), clinical stage V, grade: poorly differentiated, number of positive postoperative lymph nodes: 3, number detected: 11. The red indicator line in the figure represents the score of patients: OS total score 434, 3-year OS survival: 0.325, 5-year OS survival: 0.142; CSS total score 356, 3-year CSS survival: 0.26, 5-year CSS survival: 0.12.

Discussion

In this study, we constructed a nomogram based on the data of 6,116 middle-aged and older patients with rectal adenocarcinoma. We included patient demographic and clinicopathologic data and sought a suitable new cut-off for our model. We found significant prognostic factors associated with the OS and CSS and constructed nomograms for middle-aged and older patients with rectal adenocarcinoma.

Most previous studies presenting prediction models for colorectal cancer-related survival had limited samples and included data from a single center. The included predictors were limited, or the evaluation indicators were not easy to obtain, greatly limiting the clinical application of these models [9,10]. In addition, the study endpoint was limited to a single prediction of CSS or OS for some studies [11,12], and few studies have been constructed to predict both. Middle-aged and older patients are at a high risk of rectal adenocarcinoma; however, studies comprehensively analyzing its predictors and the construction of visual nomogram models are limited. With the advancement of medical care, the clinical outcomes of patients with rectal adenocarcinoma have changed. Therefore, new, more comprehensive, and practical indicators are required for constructing clinical prediction models to effectively determine the prognosis of patients.

Our constructed nomogram prediction models for OS and CSS clearly displayed the effects of various predictors on middle-aged and older patients with rectal adenocarcinoma and provided accurate scores. We found 12 independent prognostic variables associated with OS and 10 with CSS. Of note, sex and ethnicity were predictive of OS in the study population, with men having a poorer prognosis than women, and black and white participants having poorer prognosis than other ethnic groups. These findings are similar to those of Brenner et al. [13] and Wen et al. [14].

We found that the age of the included population was associated with a poorer prognosis. The pathological grade was "poorly differentiated," and the prognosis of patients with undifferentiated grade was poorer than those with "moderately differentiated" and "well-differentiated" grades, which was also confirmed by Julien et al. [15]. Among the clinicopathological features, although no significant differences were found in the scores of stage II and III patients, the scores of stage I and IV patients were significantly different. We believe that lymph node metastasis and distant metastasis are important factors in the prognosis of patients with rectal adenocarcinoma.

Several factors, including CEA, TD, CRM, and PNI have been demonstrated to be associated with poor prognosis [16–19]. CEA is a tumor marker used in the differential diagnosis and detection of colorectal
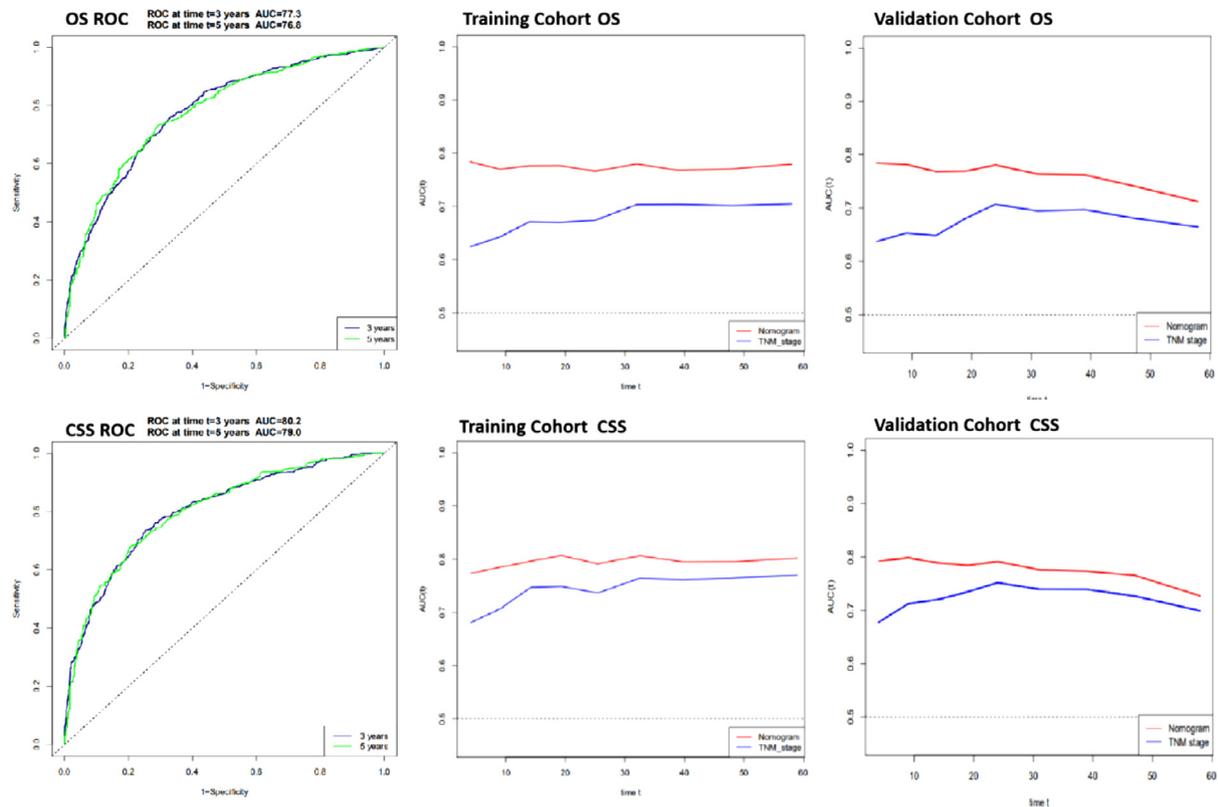
Fig. 3. ROC and time-dependent AUC.
ROC values for the training cohort are shown in the figure. AUC values of nomogram versus TNM stage based on temporal changes are shown. In the training and validation cohorts, the AUC of nomogram was higher than that of TNM stage.

cancer [20]. TD is defined as one or more satellite peritumoral nodules in the adipose tissue surrounding the colorectum of the primary cancer, and histological evidence does not support residual lymph nodes or identifiable vascular or neural structures [21]. CRM positivity is defined as the presence of tumor cells within 1 mm of the inner CRM [22]. PNI is a metastatic modality associated with an aggressive cancer phenotype that exhibits poor survival as well as an increased risk of local and distant recurrence, occurring through invasion of the intraneural or extramural plexus independent of lymphatic invasion [23]. These critical predictors provided important predictive power and proportion of scores in our nomogram prediction model. The nomogram showed that preoperative CEA levels were higher than normal, and that TD, PNI, and CRM were positive, all of which indicate a poor prognosis.

Lymph node dissection is the focus of surgery, and the prognostic survival of patients is closely related to the degree of lymph node dissection [24]. An increased number of positive lymph nodes often indicates a high chance of recurrence and metastasis and a poor prognosis [25]. The AJCC proposes that the detection of ≥12 lymph nodes can improve the accuracy of postoperative staging of colorectal cancer and help determine the presence or absence of lymph node metastasis [26]. Therefore, the number of lymph nodes should be accurately assessed to provide a basis for clinical staging and diagnosis, as well as treatment [27]. Chang et al. [28] found that with the increase in the number of detected lymph nodes, the 5-year survival rate of patients increases. Although the SEER database did not have accurate information on the number of lymph nodes, our survival model did evaluate patients based on lymph node

number. The cut-off number for node positivity and examined nodes was 1 or 4, and 10, respectively. We found that the number of positive lymph nodes was negatively correlated with patient prognosis, while the number of examined lymph nodes was positively correlated with patient prognosis.

Here, we comprehensively analyzed the effect of predictive factors on the prognosis of patients with rectal cancer and constructed a prognostic factor-based nomogram to assess the 3-year and 5-year OS and CSS of patients. Both the C-index and AUC of ROC suggest that the model has excellent predictive ability. Both the training and validation cohort survival curves showed good discrimination ability of the prediction model. The use of time-dependent AUC in the training and validation cohorts confirmed that our prediction model was consistently superior to traditional TNM staging for 5-year survival prediction. The DCA indicated that the prediction model may have good clinical decision power, which needs further validation in clinical practice, and the correction curves of both cohorts showed that the prediction value was highly consistent with the actual value. OS has been considered the gold standard primary endpoint for assessing the effect of cancer treatment, and it provides meaningful evidence for clinical benefit [29,30]. Differences in CSS can reflect changes in treatment quality and are influenced by patient characteristics [31,32]. The nomogram constructed in this study can simultaneously predict the survival rates for CSS and OS using patient-independent clinical data, and may, therefore, be beneficial in guiding the clinical decision-making of physicians.

This study included many patients, had a long overall observation time, and evaluated the effect of multiple factors on rectal adenocar-
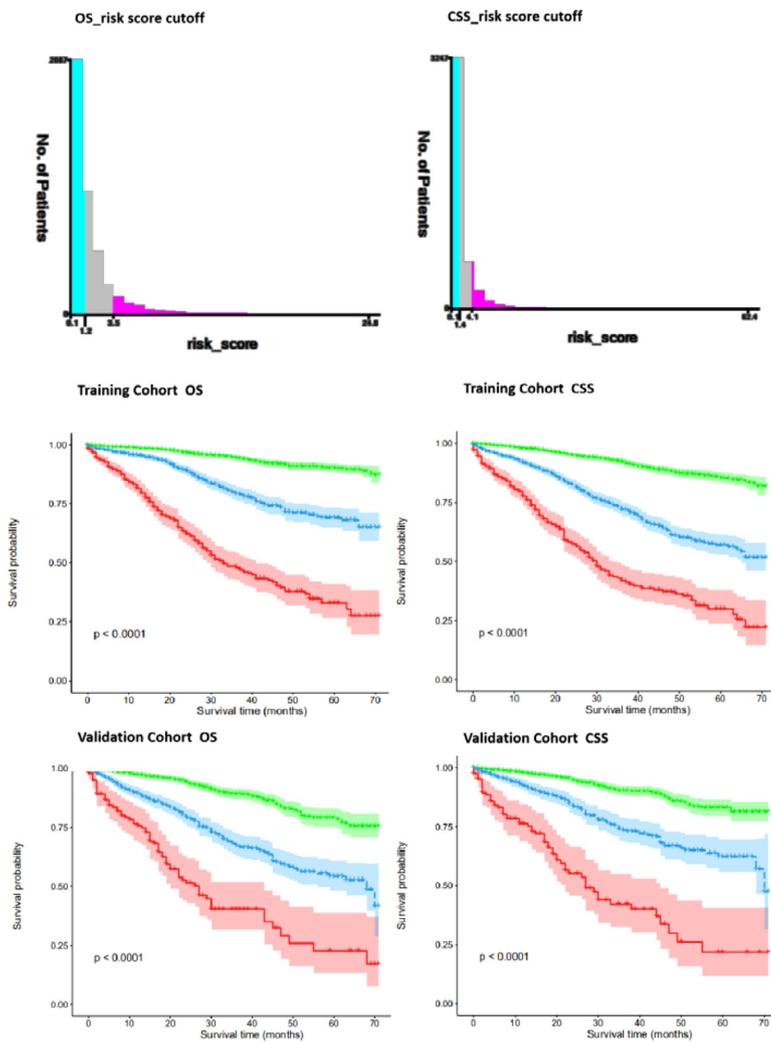
Fig. 4. Kaplan–Meier survival curves for low-, medium-, and high-risk groups based on risk scores. The optimal OS risk score cut-off was 1.2, 3.5. CSS risk score cutoffs were 1.4, 4.1. Significant differences in OS, CSS were observed among the low-risk, intermediate-risk, and high-risk patients in the training and validation cohorts.

cinoma in middle-aged and older patients. With the validation cohort, the constructed model may provide significant value for clinical diagnosis and treatment. Our model has some evaluation advantages. First, the proposed prognostic model is indicated for middle-aged and older patients with rectal adenocarcinoma and can better reflect the characteristics of this population. Second, our nomogram is based on patient demographic characteristics and clinicopathological related data, which are key indicators easily obtained in clinical practice, and the nomogram has good clinical utility. Third, studies have reported that the tumor size, number of dissected lymph nodes, and number of detected lymph nodes are important predictors. We found that the optimal cut-off values of these three factors were different from those defined in the most current data, which reminded us to establish the cut-off values of relevant indicators in middle-aged and older patients with rectal adenocarcinoma, rather than using the universal cut-off values for patients with colorectal cancer.

There are some limitations to our study. First, this study was retrospective, and patients were screened based on strict inclusion and ex-

clusion criteria; therefore, potential selection bias may have occurred. Second, the SEER database does not specify procedures, operators, and other such factors, and bias may exist owing to different experience levels of operators and pathologists. Third, we could not analyze the 8- or 10-year survival rates due to the length of follow-up for the included population data. Additional databases could be used for further evaluation. Finally, unrecorded clinical characteristics may affect patient outcomes, such as complications, nutritional status, and detailed chemoradiotherapy information.

In conclusion, we constructed a nomogram model of CSS and OS to determine the 3- and 5-year survival rates of middle-aged and older patients with rectal adenocarcinoma. The results showed that the prediction model had satisfactory prognostic discrimination ability and survival prediction ability, as well as good clinical decision-making power. This nomogram can be used to individualize the survival prediction for middle-aged and older patients with rectal adenocarcinoma, providing a good tool for gastrointestinal surgeons to accurately assess a patient's condition.
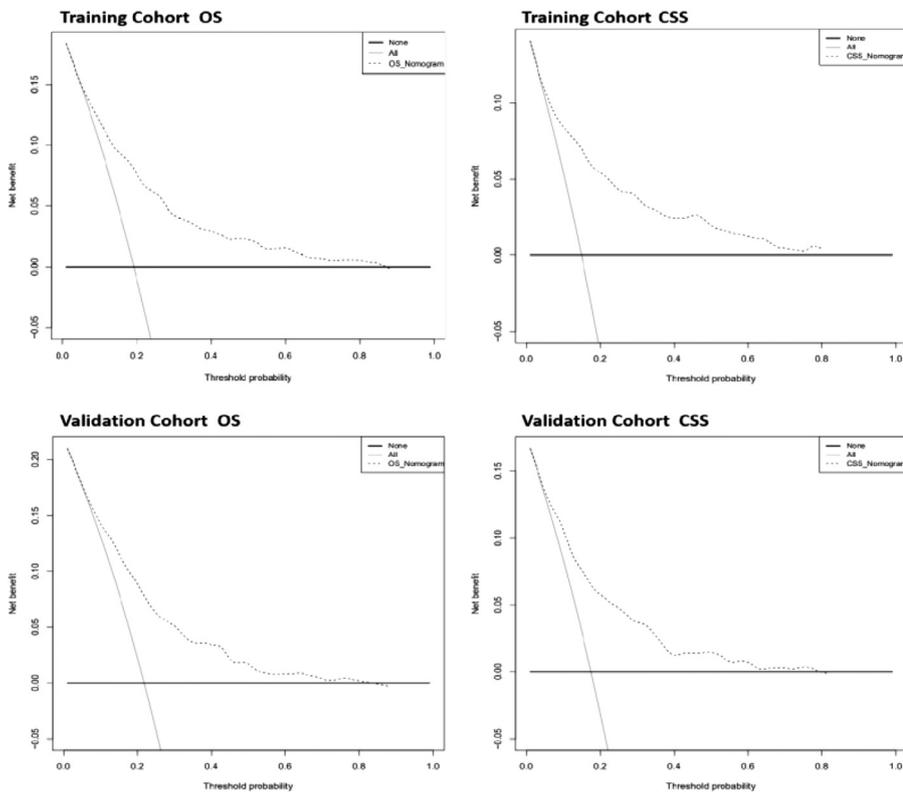
Fig. 5. Decision curve analysis. Plot net benefit versus threshold probability.
The net benefit was calculated by subtracting the proportion of all false-positive cases from the proportion of true-positive cases, weighing the relative harm of abandoning treatment against the adverse consequences of unnecessary treatment. The gray and black lines indicate the net benefit of treating all patients and no patient strategies, respectively. Dashed lines represent nomograms. The results showed that the nomogram had good decision power in the training cohort and the validation cohort.

Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing, others, who have contributed in other ways should be listed as contributors.

Author	study design	data collections	data analysis	writing	final approval of manuscript
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Jun Jiang Zhao	√		√		√
Bo Liu	√	√			√
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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2020.100938.

References

[1] G. Artaş, H.I. Ozercan, The expression of STAT3, BCL-XL and MMP-2 proteins in colon adenocarcinomas and their relationship with prognostic factors, Turk Patoloji Derg. 30 (3) (2014) 178–183, doi:10.5146/tjpath.2014.01269.
[2] J.Y. Kim, E.S. Jang, S.Y. Park, et al., Distinct characteristics of colorectal cancer and frequency of right colon cancer in elderly patients of Korea, J. Korean Geriatrics Soc. (2010).
[3] M.A. Duggan, W.F. Anderson, S. Altekruse, L. Penberthy, M.E. Sherman, The surveillance, epidemiology, and end results (SEER) program and pathology: toward strengthening the critical relationship, Am. J. Surg. Pathol. 40 (12) (2016) e94–e102, doi:10.1097/PAS.0000000000000749.
[4] V.P. Balachandran, M. Gonen, J.J. Smith, R.P. DeMatteo, Nomograms in oncology: more than meets the eye, Lancet Oncol. 16 (4) (2015) e173–e180 PMID:25846097PMCID: PMC4465353, doi:10.1016/S1470-2045(14)71116-7.
[5] M.Y. Polley, K.R. Lamborn, S.M. Chang, N. Butowski, J.L. Clarke, M. Prados, Conditional probability of survival in patients with newly diagnosed glioblastoma [published correction appears in J Clin Oncol. 2011 Dec 20;29(36):4847], J. Clin. Oncol. 29 (31) (2011) 4175–4180, doi:10.1200/JCO.2010.32.4343.
[6] X. Guan, W. Chen, Z. Jiang, et al., Exploration of the optimal minimum lymph node count after colon cancer resection for patients aged 80 years and older, Sci. Rep. 6 (2016) 38901 Published 2016 Dec 12, doi:10.1038/srep38901.
[7] R.L. Camp, M. Dolled-Filhart, D.L. Rimm, X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization, Clin. Cancer Res. 10 (21) (2004) 7252–7259, doi:10.1158/1078-0432.CCR-04-0713.

[8] Z. Hijazi, J. Oldgren, J. Lindbäck, et al., A biomarker-based risk score to predict death in patients with atrial fibrillation: the ABC (age, biomarkers, clinical history) death risk score, Eur. Heart J. 39 (6) (2018) 477–485, doi:10.1093/eurheartj/ehx584.

[9] F. Pan, T. Chen, X. Sun, et al., Prognosis prediction of colorectal cancer using gene expression profiles, Front Oncol. 9 (2019) 252 Published 2019 Apr 9, doi:10.3389/fonc.2019.00252.

[10] J. Liu, X. Huang, W. Yang, et al., Nomogram for predicting overall survival in stage II-III colorectal cancer, Cancer Med. 9 (7) (2020) 2363–2371, doi:10.1002/cam4.2896.

[11] P. Zheng, C. Lai, W. Yang, J. Guo, S. Xiao, Z. Chen, Nomogram predicting cancer-specific survival in elderly patients with stages I-III colon cancer, Scand. J. Gastroenterol. 55 (2) (2020) 202–208, doi:10.1080/00365521.2020.1720280.

[12] J.P. Pei, C.D. Zhang, Y. Liang, et al., Novel nomograms individually predicting overall survival of non-metastatic colon cancer patients, Front Oncol. 10 (2020) 733 Published 2020 May 6, doi:10.3389/fonc.2020.00733.

[13] O. Purim, N. Gordon, B. Brenner, Cancer of the colon and rectum: potential effects of sex-age interactions on incidence and outcome, Med. Sci. Monit. 19 (2013) 203–209 Published 2013 Mar 20, doi:10.12659/MSM.883842.

[14] W.J. Fu, Racial-sex disparities–a challenging battle against cancer mortality in the USA, J. Racial. Ethn. Health Disparities 2 (2) (2015) 158–166, doi:10.1007/s40615-014-0059-6.

[15] J. Langrand-Escure, P. Diao, M.A. Garcia, et al., Outcome and prognostic factors in 593 non-metastatic rectal cancer patients: a mono-institutional survey, Sci. Rep. 8 (1) (2018) 10708 Published 2018 Jul 16, doi:10.1038/s41598-018-29040-2.

[16] Y. Gao, J. Wang, Y. Zhou, S. Sheng, S.Y. Qian, X. Huo, Evaluation of serum CEA, CA19-9, CA72-4, CA125 and ferritin as diagnostic markers and factors of clinical parameters for colorectal cancer, Sci. Rep. 8 (1) (2018) 2732 Published 2018 Feb 9, doi:10.1038/s41598-018-21048-y.

[17] F. Liu, J. Zhao, C. Li, et al., The unique prognostic characteristics of tumor deposits in colorectal cancer patients, Ann. Transl. Med. 7 (23) (2019) 769, doi:10.21037/atm.2019.11.69.

[18] S.H. Baik, N.K. Kim, Y.C. Lee, et al., Prognostic significance of circumferential resection margin following total mesorectal excision and adjuvant chemoradiotherapy in patients with rectal cancer, Ann. Surg. Oncol. 14 (2) (2007) 462–469, doi:10.1245/s10434-006-9171-0.

[19] I. Kazutsugu, S. Toshihiro, T. Shin, et al., Evaluation of perineural invasion in rectal cancer as a prognostic factor, Jpn. J. Gastroenterol. Surg. 46 (9) (2013) 635–646.

[20] H. Hu, J. Huang, P. Lan, et al., CEA clearance pattern as a predictor of tumor response to neoadjuvant treatment in rectal cancer: a post-hoc analysis of FOWARC trial, BMC Cancer 18 (1) (2018) 1145 Published 2018 Nov 20, doi:10.1186/s12885-018-4997-y.

[21] K.A. Mirkin, A.S. Kulaylat, C.S. Hollenbeak, E. Messaris, Prognostic significance of tumor deposits in stage III colon cancer, Ann. Surg. Oncol. 25 (11) (2018) 3179–3184, doi:10.1245/s10434-018-6661-9.

[22] N.J. O'Farrell, C.L. Donohoe, C. Muldoon, et al., Lack of independent significance of a close (<1 mm) circumferential resection margin involvement in esophageal and junctional cancer, Ann. Surg. Oncol. 20 (8) (2013) 2727–2733, doi:10.1245/s10434-013-2899-4.

[23] C.H. Kim, S.S. Yeom, S.Y. Lee, et al., Prognostic impact of perineural invasion in rectal cancer after neoadjuvant chemoradiotherapy, World J. Surg. 43 (1) (2019) 260–272, doi:10.1007/s00268-018-4774-8.

[24] M. Numata, T. Yamaguchi, Y. Kinugasa, et al., Index of estimated benefit from lateral lymph node dissection for middle and lower rectal cancer, Anticancer Res. 37 (5) (2017) 2549–2555, doi:10.21873/anticanres.11598.

[25] J. Yang, Q. Chen, J. Li, Z. Song, Y. Cheng, Short-term clinical and oncological outcome of prolonging operation interval after neoadjuvant chemoradiotherapy for locally advanced middle and low rectal cancer, Cancer Manag. Res. 12 (2020) 2315–2325 Published 2020 Mar 27, doi:10.2147/CMAR.S245794.

[26] C.C. Compton, F.L. Greene, The staging of colorectal cancer: 2004 and beyond, CA Cancer J. Clin. 54 (6) (2004) 295–308, doi:10.3322/canjclin.54.6.295.

[27] W. Kelder, B. Inberg, M. Schaapveld, et al., Impact of the number of histologically examined lymph nodes on prognosis in colon cancer: a population-based study in the Netherlands, Dis. Colon. Rectum. 52 (2) (2009) 260–267, doi:10.1007/DCR.0b013e3181979164.

[28] G.J. Chang, M.A. Rodriguez-Bigas, J.M. Skibber, V.A. Moyer, Lymph node evaluation and survival after curative resection of colon cancer: systematic review, J. Natl. Cancer Inst. 99 (6) (2007) 433–441, doi:10.1093/jnci/djk092.

[29] M. Shimokawa, T. Kogawa, T. Shimada, et al., Overall survival and post-progression survival are potent endpoint in phase III trials of second/third-line chemotherapy for advanced or recurrent epithelial ovarian cancer, J. Cancer 9 (5) (2018) 872–879 Published 2018 Feb 16, doi:10.7150/jca.17664.

[30] R.C. Nie, X.B. Zou, S.Q. Yuan, et al., Disease-free survival as a surrogate endpoint for overall survival in adjuvant trials of pancreatic cancer: a meta-analysis of 20 randomized controlled trials, BMC Cancer 20 (1) (2020) 421 Published 2020 May 14, doi:10.1186/s12885-020-06910-5.

[31] C.S. McArdle, D.J. Hole, Outcome following surgery for colorectal cancer: analysis by hospital after adjustment for case-mix and deprivation, Br. J. Cancer 86 (3) (2002) 331–335, doi:10.1038/sj.bjc.6600120.

[32] C.R. Ling, R. Wang, M.J. Wang, J. Ping, W. Zhuang, Prognosis and value of preoperative radiotherapy in locally advanced rectal signet-ring cell carcinoma, Sci. Rep. 7 (2017) 45334 Published 2017 Mar 27, doi:10.1038/srep45334.