ORIGINAL RESEARCH

BMI May Be a Prognostic Factor for Local Advanced Rectal Cancer Patients Treated with Long-Term Neoadjuvant Chemoradiotherapy

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Objective: This study aims to develop feasible nomograms to predict the overall survival (OS) and cancer-specific survival (CSS) of the local advanced rectal cancer (LARC) patients who were treated with neoadjuvant chemoradiotherapy (nCRT) and operation.

Methods: A total of 243 LARC patients undergoing nCRT followed by total mesorectal excision (TME) were enrolled. Preoperative clinical features and postoperative pathological characteristics were collected. A Cox regression analysis was performed, and Cox-based nomograms were developed to predict the OS and CSS. We assessed the predictive performance of the nomogram with concordance index and calibration plots.

Results: A total of 243 patients were included with a median follow-up period of 46 months (range from 9 to 86 months). Cox regression analysis showed that low BMI (BMI < 18.5, HR= 21.739, $P < 0.05$), high level of preoperative CA19-9 (HR = 3.369, $P = 0.036$), high ypStage (HR = 19.768, $P < 0.001$), positive neural invasion (HR = 4.218, $P = 0.026$) and no adjuvant chemotherapy (HR = 5.495, $P < 0.001$) were independent predictors of poor OS. Age ≥70 (HR = 2.284, $P <0.001$), low BMI (BMI < 18.5, HR = 3.906, $P < 0.05$), positive preoperative CA19-9 (HR = 1.920, $P = 0.012$), high ypStage (HR = 5.147, $P <0.001$) and positive neural invasion (HR = 2.873, $P = 0.022$) were independent predictors of poor CSS. The predictive nomograms were developed to predict the OS and CSS with a C-index of 0.837 and 0.760. Good statistical performance on internal validation was shown by calibration plots.

Conclusion: In conclusion, this study demonstrated that BMI was an independent prognostic factor for OS and CSS in LARC patients treated with nCRT followed TME. A nomogram incorporating BMI, neural invasion, pre-CA19-9, ypStage, age, and adjuvant chemotherapy could be helpful to predict the OS and CSS.

Keywords: local advanced rectal cancer, neoadjuvant chemoradiotherapy, nomogram, body mass index, prognosis, overall survival, cancer-specific survival

Introduction

In order to improve the local control rate of patients with locally advanced rectal cancer (LARC), National Comprehensive Cancer Network (NCCN) guideline recommends that neoadjuvant chemoradiotherapy (nCRT) combined with radical resection is an ideal treatment.[1–3] However, LARC patients have a wide range of responses to neoadjuvant therapy, so the survival rate is very heterogeneous.[4] At present, the way of predicting the prognosis of LARC patients treated with

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nCRT is still the same as that of patients with surgery only.[5] There are a few studies on the prognosis of LARC patients after nCRT, and most of them are based on AJCC staging, including some improved staging systems, such as T-Plus staging and TNM improved analysis system.[6–8] Nevertheless, the disadvantage of these studies is that they only analyze the prognosis of patients from the tumor pathologico-anatomical point of view. Some biological characteristics of patients are ignored, such as body mass index (BMI), family history of cancer, and the level of serum tumor markers and so on. Another prognosis model is based on high-throughput sequencing of blood or tumor tissue, and constructing the model according to the differential expression of genes or proteins.[9–11] But there were few overlapped genes or proteins between the results of these studies,[12,13] and the results lack of evidence support, so it is difficult to apply them into clinical practice. Moreover, it is too expensive to be suitable for all patients.

Nomogram is a quantitative model to predict the prognosis. It uses the biological characteristics and clinical variables of large samples to calculate a statistical prediction model. This model can calculate the probability of a certain outcome according to the specific clinical and pathological characteristics of patients.[14] This study aimed to develop a feasible nomogram to predict the 3- and 5-years overall survival (OS) and cancer-specific survival (CSS) of the LARC patients who were treated with nCRT and curative resection.

Patients and Methods

Patients

A total of 243 LARC patients were consecutively evaluated from our database. These patients were treated with nCRT followed by total mesorectal excision (TME) from Jan 2010 to Jul 2018 in the Department of Colorectal Surgery, Cancer Hospital Chinese Academy of Medical Sciences. The inclusion criteria were as follows: 1) histopathologically confirmed rectal adenocarcinoma; 2) completed long-term nCRT (45~50Gy/25 fraction) followed by TME and postoperative chemotherapy ±; 3) clinical staging was diagnosed based on preoperative MRI and CT examinations. The exclusion criteria were as follows: 1) serum tumor markers were not detected before nCRT; 2) previous or concurrent malignant tumors; 3) after nCRT, distant

metastasis were found by imaging examination before an operation.

All the available detailed pre-nCRT clinical characteristic and pathological parameters were collected, including age, gender, smoking history, drinking history, chronic disease, family history of cancer, distance from the tumor inferior margin to the anal verge, the level of carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9) before nCRT (named pre-CEA and pre-CA19-9), yield pathologic TNM stage (ypStage), Dworak tumor regression grade (TRG), neural invasion, vascular invasion, nCRT-protocol, adjuvant chemotherapy, and the interval of time between nCRT and operation. According to Dworak tumor regression grade, we define TRG-1 and TRG-2 as poor response, TRG-3 and TRG-4 as good response.

Ethical approval was obtained from the ethics committee of our hospital (ID: NCC2016JZ-06).

Treatment

In brief, a total dose of 45–50Gy (1.8–2.0 Gy/fraction) to the whole pelvis in 25 fractions for 5 weeks, plus 5.4 to 9 Gy (1.8 Gy/fraction) to the tumor volume, with 6 to 15 MV energy photons.[15] Two schemes of concurrent chemotherapy as follows: (i) capecitabine 1650 mg/m^2 daily concurrent with radiotherapy; (ii) oxaliplatin combined with capecitabine (capecitabine 1650 mg/m^2, oxaliplatin 130 $mg/m^2/w$). All the patients received TME surgery for at least four weeks after nCRT treatment.[16]

Follow-Up

All the patients received postoperative reviews every 3 months at our center or local hospital within 2 years, and every 6 months from 3 to 5 years after operation. The postoperative-review examinations included physical examination, peripheral blood tumor markers (eg, CEA, CA19-9), fecal occult blood, chest and abdominal CT, pelvic CT or MRI, and whole-body PET-CT if necessary. Tumor metastasis or recurrence was defined by imaging results or histopathological diagnosis. OS was defined as the time between the date of surgery and the date of death from any cause or the last follow-up. CSS was defined from the date of operation to the date of cancer – related death.

Statistical Analysis

Univariate and multivariate cox regression models were used to identify the factors predicting OS and CSS. Nomograms were constructed based on statistically significant factors identified by the multivariate analysis from the Cox regression model to predict the 3- and 5-years OS and CSS. Kaplan-Meier survival method was used to analyze the 5-years OS and CSS. Log rank tests were employed to assess the statistical significance. Multivariate analyses using Cox proportional hazards models were used to identify the independent prognostic factors for overall survival and cancer-specific survival. Statistical analyses were performed and graphics were created using IBM SPSS Statistics software version 25.0 (IBM Corporation, Armonk, NY, USA). The nomogram analysis was conducted using R version 3.6.3 (https://www.rproject.org/). Statistical significance was set at a two-sided P-value <0.05.

Results

Patient Characteristics

A total of 243 patients were assessed for our study, including 166 males and 77 females. The range of age is from 23 to 82, and the median age is 55 years old. The BMI is (23.8 ± 3.3) kg/m^2. The mean distance from the tumor inferior margin to the anal verge is 4.57 cm. With a median follow-up period of 46 months (range from 9 to 86 months). For details see Table 1.

Univariate and Multivariate Analysis of Prognostic Factors for OS and CSS

Univariate analysis was performed on all the variables, BMI, pre-CA19-9, ypStage, vascular invasion, neural invasion and adjuvant chemotherapy were independently associated with OS in LARC patients treated with nCRT and curative resection. Multivariate Cox regression analysis was performed using the significant prognostic factors identified in univariate analysis. We found that BMI (BMI < 18.5, HR= 21.739, P < 0.05), pre-CA19-9 (pre-CA19-9 $\geq$ 27, HR = 3.369, P = 0.036), ypStage (ypStage = II–III, HR = 19.768, P < 0.001), neural invasion (HR = 4.218, P = 0.026) and no adjuvant

Table 1 Baseline Clinicopathological Characteristics in Patients

Parameters	n
Gender	
Male	166 (68.3%)
Female	77 (31.7%)
Age	
<50	76 (31.3%)
50–59	80 (32.9%)
60–69	44 (18.1%)
≥70	43 (17.7%)
BMI	
<18.5	11 (4.5%)
18.5–23.9	117 (48.1%)
24–27.9	91 (37.4%)
≥28	24 (9.9%)
Smoking history	
No	127 (52.3%)
Yes	11 (47.7%)
Drinking history	
No	138 (56.8%)
Yes	105 (43.2%)
Chronic disease	
No	168 (69.1%)
Yes	75 (30.9%)
Family history of cancer	
No	191 (78.6%)
Yes	52 (21.4%)
Interval time	
4–8 weeks	112 (47.9%)
>8 weeks	122 (52.1%)
TRG	
Poor response	131 (53.9%)
Good response	112 (46.1%)
Pre-CEA	
≤5 ng/mL	202 (83.1%)
>5 ng/mL	41 (16.9%)
Pre-CA19-9	
≤27 U/mL	223 (91.8%)
>27 U/mL	20 (8.2%)
Inferior margin	
≤5cm	174 (71.6%)
>5cm	60 (28.4%)
ypStage	
0 – I	95 (39.1%)
II–III	148 (60.9%)

(*Continued*)

Table 1 (Continued).

Parameters	n
Vascular invasion	
Negative	193 (79.4%)
Positive	50 (20.6%)
Neural invasion	
Negative	229 (94.2%)
Positive	14 (5.8%)
Adjuvant chemotherapy	
No	72 (29.6%)
Yes	171 (70.4%)
nCRT protocol	
Capecitabine	198 (81.5%)
Capecitabine + platinum	45 (18.5%)

Abbreviations: BMI, body mass index; nCRT, neo-chemoradiotherapy; Pre-CA19-9, level of carbohydrate antigen 19–9 (CA19-9) before neo-chemoradiotherapy; Pre-CEA, level of carcinoembryonic antigen (CEA) before neo-chemoradiotherapy; TRG, tumor regression grade; ypStage, yield pathologic TNM stage.

chemotherapy (HR = 5.495, $P < 0.001$) were independent predictors of poor OS. Detailed in Table 2.

Table 3 lists the results of univariate analysis of the prognostic factors for CSS. Age, BMI, TRG, pre-CA19-9, ypStage, vascular invasion and neural invasion were prognostic factors for CSS. All significant parameters in the univariate analysis were entered into the multivariable analysis based on the Cox regression. Age (Age ≥70, HR = 2.2844, $P < 0.05$), BMI (BMI < 18.5, HR = 3.906, $P < 0.05$), pre-CA19-9 (HR = 1.920, $P = 0.012$), ypStage (HR = 5.147, $P < 0.001$) and neural invasion (HR = 2.873, $P = 0.022$) were independent predictors of poor CSS.

Construction of a Nomogram to Predict OS and CSS

We established a nomogram for quantitative prediction of OS (Figure 1A) and CSS (Figure 1B) in LARC patients who received nCRT and TME based on Cox regression analysis results. A total of 5 variables were included. In addition to the 4 same variables such as BMI, neural invasion, pre-CA19-9, and ypStage, there are some subtle differences between the two nomograms. Adjuvant chemotherapy has a major impact on OS, but little effect on CSS. We found that the patients aged ≥70 have a higher risk of tumor recurrence after treatment than other age groups.

Calibration of the Nomogram

Bothnomograms were further validated internally using 2000 bootstrapping resamples. The C-index of the OS and CSS nomograms are 0.837 and 0.760, respectively. The calibration plots demonstrated satisfactory statistical performance upon internal validation between the nomogram prediction and actual observation for the probability of 3- (Figure 2A) and 5-years (Figure 2B) OS, and 3- (Figure 2C) and 5-years (Figure 2D) CSS in internal validation cohort.

Prognosis Value of BMI

In Cox regression analysis, we found that BMI may be related to OS and CSS of LARC patients treated with nCRT. Higher BMI was associated with a higher probability of 5-years OS (Figure 3A) and CSS (Figure 3B). Although only when BMI ≥ 28, its 5-year OS and CSS were significantly higher than BMI < 18.5 ($P = 0.042$ and 0.014), there is a trend that the higher BMI the better OS and CSS for patients.

Discussion

NCCN guideline has recommended nCRT followed by TME as a standard care approach for patients with LARC.[17] Although this treatment can improve the local control rate of tumors, there are still great differences in prognosis among patients.[18,19] However, to the best of our knowledge, there are few studies on the prognosis of these patients. Most studies focused on tumor characteristics, but ignored the characteristics of patients themselves.[20–22]

This study included a large number of LARC patients with clinical history and tumor characteristics. The univariate analysis implies that BMI < 18.50, positive pre-CA19-9, higher ypStage, positive vascular and neural invasion, and no adjuvant chemotherapy were associated with a lower rate of overall survival. Patients aged ≥70, BMI < 18.50, lower TRG (TRG-1 and TRG-2), positive pre-CA19-9, higher ypStage, positive vascular invasion, and neural invasion were associated with a lower rate of cancer-specific survival. We built the nomograms for predicting 3- and 5-years OS and CSS. In these nomograms, we demonstrated that BMI, neural invasion, pre-CA19-9, ypStage, and adjuvant chemotherapy have been integrated to predict OS. And age, BMI, neural invasion, pre-CA19-9, and pStage to predict CSS.

Table 2 Cox Regression Analysis of Prognostic Factors for OS

Factors	Univariate Cox Analysis			Multivariate Cox Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Gender (male/female)	1.698	0.863–3.343	0.125			
Age						
<50	Reference					
50–59	0.860	0.365–2.029	0.730			
60–69	1.541	0.316–3.853	0.356			
≥70	139,918.000	0.344–2.857	0.988			
BMI						
<18.5	Reference			Reference		
18.5–23.9	0.604	0.179–2.043	0.417	0.290	0.123–1.872	0.266
24–27.9	0.433	0.121–1.552	0.199	0.118	0.082–1.326	0.081
≥28	0.145	0.015–0.393	0.044	0.046	0.015–0.961	0.035
Smoking history	0.621	0.307–1.256	0.185			
Drinking history	0.851	0.429–1.685	0.643			
Chronic disease	0.851	0.397–1.824	0.678			
Family history of cancer	0.861	0.375–1.979	0.725			
Inferior margin (≤5 cm/> 5cm)	1.167	0.555–2.453	0.684			
TRG (poor response/good response)	0.516	0.251–1.058	0.062			
Pre-CEA (≤5 ng/mL/>5 ng/mL)	0.651	0.229–1848	0.420			
Pre-CA19-9 (≤27 U/mL/>27 U/mL)	2.100	1.912–5.427	0.026	3.369	1.084–10.472	0.036
ypStage (0-I/II–III)	11.760	2.816–49.070	<0.001	19.768	4.053–96.411	<0.001
Vascular invasion	3.314	1.649–6.661	<0.001	1.223	0.525–2.851	0.640
Neural invasion	7.287	3.306–18.960	<0.001	4.218	1.186–15.008	0.026
Interval time (4–8 weeks/>8 weeks)	1.129	0.574–2.218	0.725			
Neochemoradiotherapy protocol (Capecitabine/Capecitabine + platinum)	1.363	0.653–2.846	0.410			
Adjuvant chemotherapy	0.493	0.250–0.970	0.040	0.182	0.074–0.449	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; nCRT, neo-chemoradiotherapy; Pre-CA19-9, level of carbohydrate antigen 19–9 (CA19-9) before neo-chemoradiotherapy; Pre-CEA, level of carcinoembryonic antigen (CEA) before neo-chemoradiotherapy; TRG, tumor regression grade; ypStage, yield pathologic TNM stage.

Besides pathological TNM stage is a well-known predictor of prognosis, our study has also found several factors. Correlation of CA19-9 but not CEA as a serum biomarker of OS and CSS. These two serum biomarkers are mainly used to monitor the recurrence of the tumor during the re-examination after finishing the whole treatment.[23] If the level of CA19-9 increases after nCRT, it indicates that patients will have worse OS and DFS.[24] The results of previous studies showed that the level of CA19-9 before treatment could predict whether patients could benefit from nCRT.[25,26] In this study, 15 of 20 patients who had a positive CA19-9 before nCRT have no down-staging after nCRT, which is consistent with the above conclusion. It also suggests that we should pay more attention to the

significance of CA19-9 in the prognosis and monitoring of rectal cancer. However, the number of CA19-9 positive patients before treatment in this study was small, which needs further confirmation by expanding the sample size.

The neural invasion (NI) prevalence and neural invasion severity strongly vary within gastrointestinal malignancies.[27] There were 14 patients (5.98%) with NI in this study, which is lower than the previous study.[28] However, most studies demonstrated that neural invasion not only increases the risk of tumor recurrence, but also lead to a poor response to nCRT.[28–30] In current clinical practice, neural invasion is considered to be one of the conditions for adjuvant chemotherapy. In our patient cohort, 4 of 14 patients

Table 3 Cox Regression Analysis of Prognostic Factors for CSS

Factors	Univariate Cox Analysis			Multivariate Cox Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Gender (male/female)	1.373	0.850–2.217	0.195			
Age						
<50	Reference			Reference		
50–59	1.0325	0.308–1.743	0.482	1.148	0.387–2.322	0.907
60–69	1.2269	0.675–2.229	0.502	1.392	0.763–2.541	0.281
≥70	2.2844	1.215–4.296	0.010	3.599	1.836–7.053	<0.001
BMI						
<18.5	Reference			Reference		
18.5–23.9	0.465	0.197–1.113	0.086	0.527	0.210–1.321	0.172
24–27.9	0.5403	0.225–1.299	0.169	0.486	0.194–1.215	0.123
≥28	0.1921	0.048–0.768	0.020	0.256	0.059–0.893	0.047
Smoking history	0.712	0.4420 1.146	0.162			
Drinking history	0.6901	0.426–1.119	0.131			
Chronic disease	1.048	0.633–1.734	0.856			
Family history of cancer	0.8784	0.497–1.554	0.656			
Inferior margin (≤5 cm/>5cm)	1.0579	0.630–1.778	0.832			
TRG (poor response/good response)	0.549	0.337–0.894	0.016	1.044	0.605–1.803	0.876
Pre-CEA (≤5 ng/mL/>5 ng/mL)	1.105	0.605–2.016	0.746			
Pre-CA19-9 (≤27 U/mL/>27 U/mL)	1.437	1.658–3.137	0.036	1.920	1.858–4.299	0.012
ypStage (0-I/II–III)	5.65	2.806–11.380	<0.001	5.147	2.131–12.431	<0.001
Vascular invasion	2.463	1.483–4.089	<0.001	1.386	0.786–2.445	0.259
Neural invasion	4.172	1.886–9.226	<0.001	2.873	1.166–7.076	0.022
Interval time (4–8 weeks/>8 weeks)	0.8217	0.515–1.311	0.410			
Neochemoradiotherapy protocol (Capecitabine/Capecitabine + platinum)	1.017	0.583–1.771	0.954			
Adjuvant chemotherapy	1.428	0.824–2.510	0.201			

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; nCRT, neo-chemoradiotherapy; Pre-CA19-9, level of carbohydrate antigen 19–9 (CA19-9) before neo-chemoradiotherapy; Pre-CEA, level of carcinoembryonic antigen (CEA) before neo-chemoradiotherapy; TRG, tumor regression grade; ypStage, yield pathologic TNM stage.

had not received adjuvant chemotherapy, and recurrence occurred in 3 patients (75%), the earliest tumor recurrence occurred at two months after surgery, and all 3 patients had passed away when we did the survival analysis. In the present study, we found neural invasion had a negative correlation with both OS and CSS, indicating that it was a prognostic factor of LARC patients treated with nCRT.

Interestingly, BMI might have a negative correlation with the prognosis. In our study, the patients whose BMI more than 28.0 had the best OS and CSS. It seems to become a common sense that obesity means a high risk of cancer.[31,32] However, the relationship between high BMI and prognosis seems to be controversial. Sweigert et al showed a positive correlation

between obesity and the incidence of postoperative complications.[33] Several studies had also found that higher BMI may be related to a better prognosis of rectal cancer.[34–36] And other studies demonstrated that BMI does not seem to be related to prognosis or even contrary.[36–38]

Visceral fat area (VFA) and skeletal muscle area (SMA) are two obesity-associated parameters.[39] They can assess the role of fat in the treatment in more detail. Visceral obesity (VO) was considered as a metabolic risk factor that negatively impacts surgical outcome in colon cancer.[40] At present, VO is thought to be related to the incidence of postoperative complications and poor prognosis.[41–44] But this is a controversial view.[45,46] In our study, the patients were divided into four groups
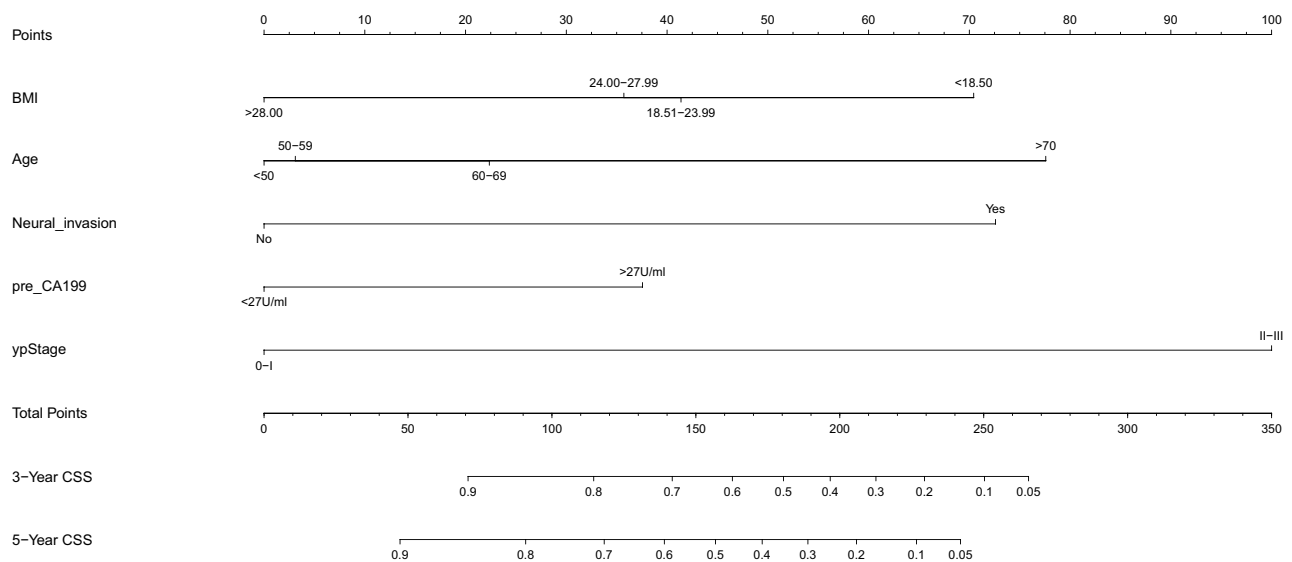
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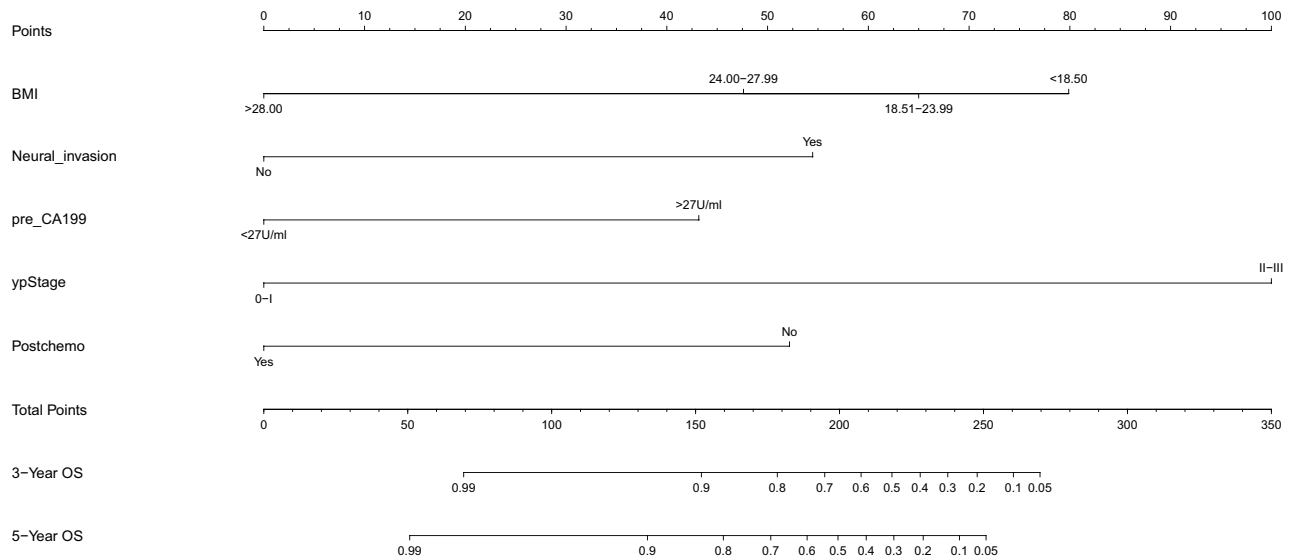
B

Figure 1 Nomograms for predicting 5-years OS (**A**) and CSS (**B**) of patients with LARC treated by nCRT and curative resection.
Abbreviations: BMI, body mass index; OS, overall survival; Pre-CA19-9, level of carbohydrate antigen 19–9 (CA19-9) before neo-chemoradiotherapy; CSS, cancer-specific survival; ypStage, yield pathologic TNM stage.

according to BMI. Although only patients with BMI ≥ 28.0 had significantly higher OS and CSS than patients with BMI < 18.5, the disadvantage of this study is that the proportion of the two groups in the patients' cohort is relatively small, which is 4.5% (BMI < 18.5) and 9.9% (BMI ≥ 28.0) respectively. However, we can find a trend that the higher BMI the better prognosis. The reason might be that the change of

SMA in the course of nCRT is little and the decrease of SMA content may have an adverse effect on the prognosis.[47,48] Some studies even found that SMA increased after treatment with nCRT.[41] Although our study did not measure VFA and SMA in patients, this issue is still worthy of further study.

There were still several shortcomings in our study. First, this is a single-center retrospective study, and these
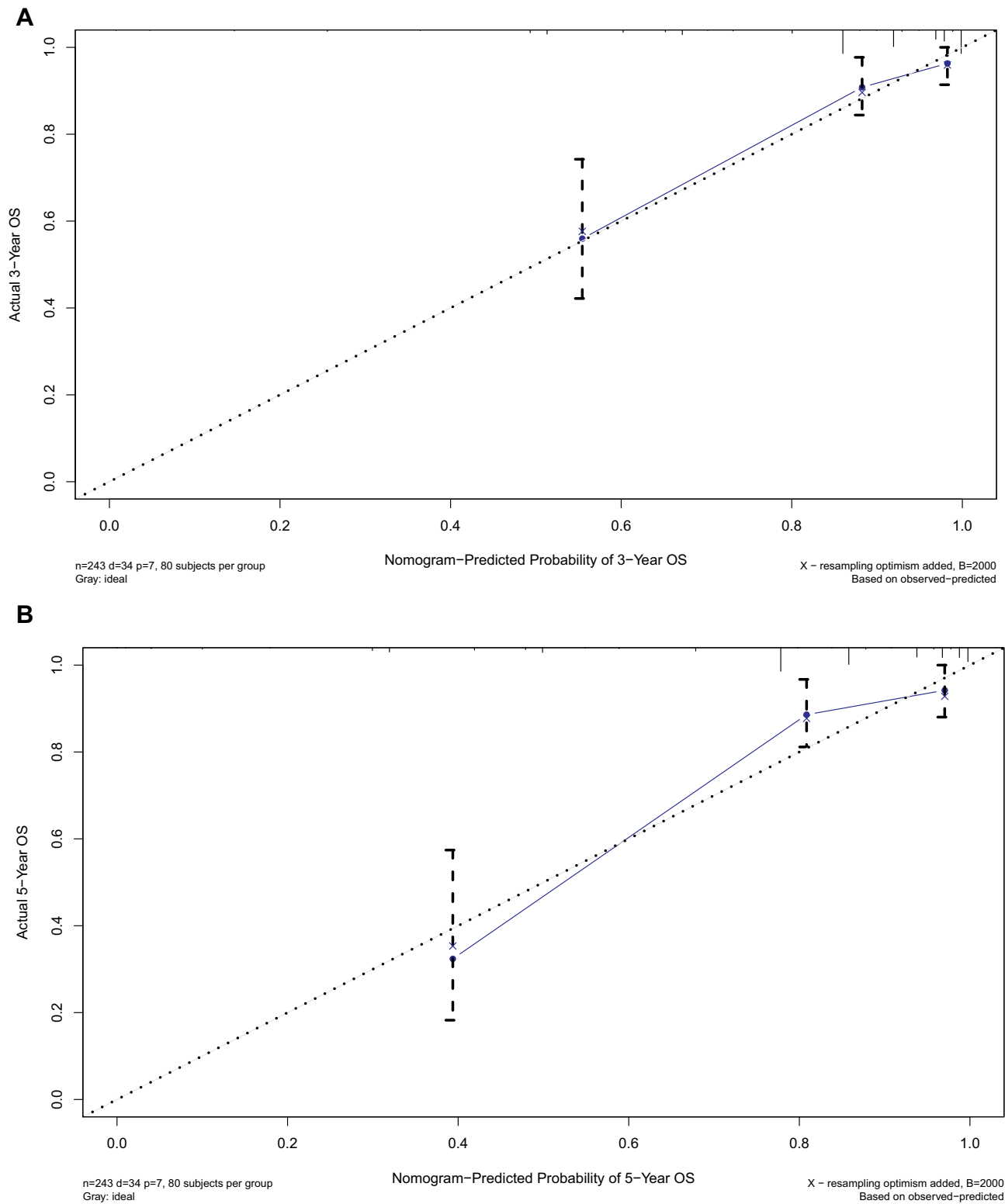
A

n=243 d=34 p=7, 80 subjects per group
Gray: ideal

Nomogram−Predicted Probability of 3−Year OS

X − resampling optimism added, B=2000
Based on observed−predicted

B

n=243 d=34 p=7, 80 subjects per group
Gray: ideal

Nomogram−Predicted Probability of 5−Year OS

X − resampling optimism added, B=2000
Based on observed−predicted

Figure 2 Continued.

findings should be corroborated by multi-center prospective studies. Second, only 24 patients with BMI ≥ 28.0, it is impossible to confirm whether or not in obese patients, the higher the BMI, the better the prognosis. A range of BMI should be clearly defined to explore the significance in survival.

C

n=243 d=71 p=8, 80 subjects per group
Gray: ideal

Nomogram−Predicted Probability of 3−Year CSS

X − resampling optimism added, B=2000
Based on observed−predicted

D

n=243 d=71 p=8, 80 subjects per group
Gray: ideal

Nomogram−Predicted Probability of 5−Year CSS

X − resampling optimism added, B=2000
Based on observed−predicted
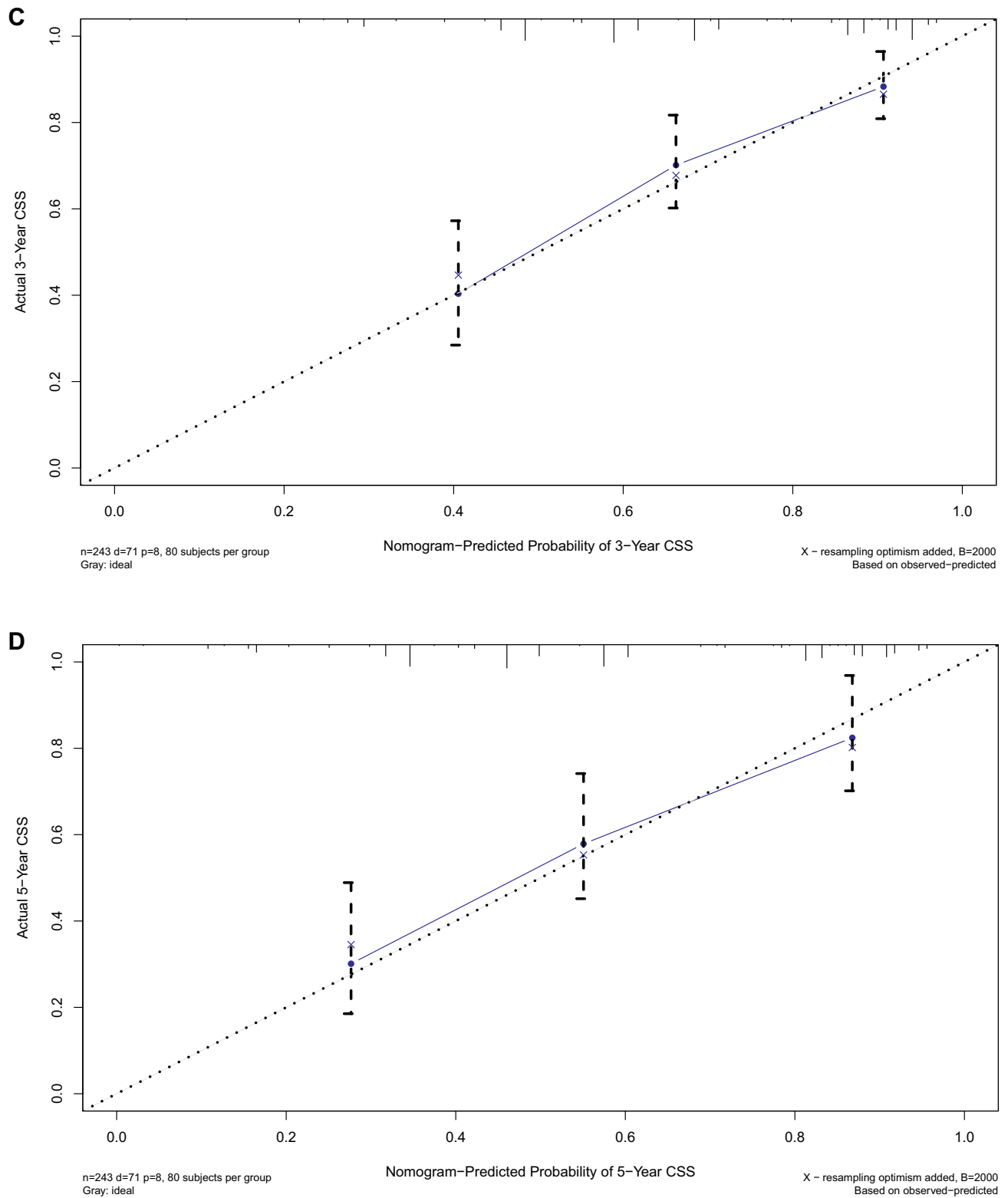
Figure 2 Calibration plots for 3- (**A**) and 5-years (**B**) OS and 3- (**C**) and 5-years (**D**) CSS in internal validation cohort.
Abbreviations: OS, overall survival; CSS, cancer-specific survival.

A

B
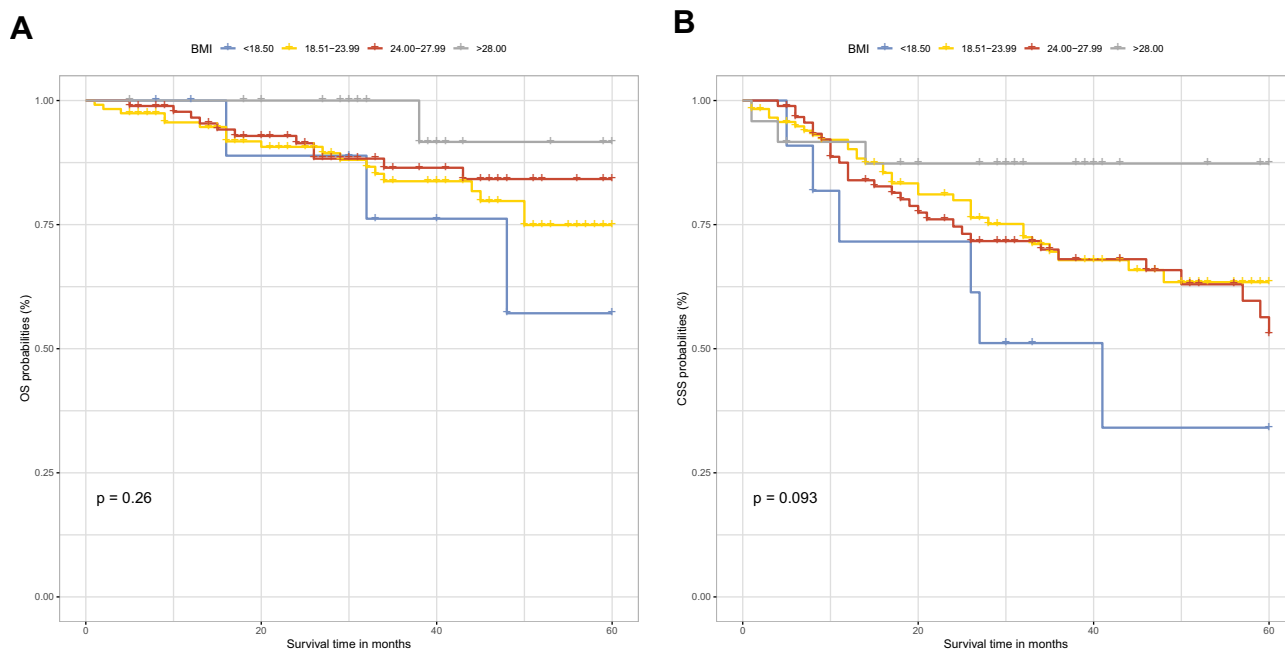
Figure 3 Kaplan–Meier curves showed higher BMI was associated with a higher probability of 5-years OS (**A**) and CSS (**B**).
Abbreviations: BMI, body mass index; OS, overall survival; CSS, cancer-specific survival.

In conclusion, the present study demonstrated that BMI was an independent prognostic factor for LARC patients treated with nCRT, and nomograms incorporating clinical characteristics we built could be helpful to predict the survival outcome.

Ethical Approval Statement

Our study was approved by Cancer Hospital, Chinese Academy of Medical Sciences; National GCP Center for Anticancer Drugs; The Independent Ethics Committee (approval no. NCC2016JZ-06). All patients were informed of the purpose of the study at follow-up and received oral consent. Ethics committee approved the verbal informed consent process, and that this study was conducted in accordance with the Declaration of Helsinki.

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Disclosure

References

1. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol*. 2009;27(31):5124–5130. doi:10.1200/JCO.2009.22.0467
2. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomized controlled TME trial. *Lancet Oncol*. 2011;12(6):575–582. doi:10.1016/S1470-2045(11)70097-3
3. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized Phase III trial after a median follow-up of 11 years. *J Clin Oncol*. 2012;39(16):1926–1933. doi:10.1200/JCO.2011.40.1836
4. Kong JC, Guerra GR, Warrier SK, et al. Prognostic value of tumour regression grade in locally advanced rectal cancer: a systematic review and meta-analysis. *Colorectal Dis*. 2018;20(7):574–585. doi:10.1111/codi.14106
5. Wei J, Huang R, Guo S, et al. ypTNM category combined with AJCC tumor regression grade for screening patients with the worst prognosis after neoadjuvant chemoradiation therapy for locally advanced rectal cancer. *Cancer Manag Res*. 2018;10:5219–5225. doi:10.2147/CMAR.S179151
6. Li J, Yi CH, Hu YT, et al. TNM staging of colorectal cancer should be reconsidered according to weighting of the T stage: verification based on a 25-year follow-up. *Medicine (Baltimore)*. 2016;95(6):e2711. doi:10.1097/MD.0000000000002711

7. Gunderson LL, Jessup JM, Sargent DJ, et al. Revised TN categorization for colon cancer based on national survival outcomes data. *J Clin Oncol*. 2010;28(2):264–271.

8. Hashiguchi Y, Hase K, Kotake K, et al. Evaluation of the seventh edition of the tumour, node, metastasis (TNM) classification for colon cancer in two nationwide registries of the United States and Japan. *Colorectal Dis*. 2012;14(9):1065–1074. doi:10.1111/j.1463-1318.2011.02917.x

9. Ji D, Yi H, Zhang D, et al. Somatic mutations and immune alternation in rectal cancer following neoadjuvant chemoradiotherapy. *Cancer Immunol Res*. 2018;6(11):1401–1416. doi:10.1158/2326-6066.CIR-17-0630

10. Lee IH, Kang K, Kang BW, et al. Genetic variations using whole-exome sequencing might predict response for neoadjuvant chemoradiotherapy in locally advanced rectal cancer. *Med Oncol*. 2018;35(11):145. doi:10.1007/s12032-018-1202-8

11. Tweedle EM, Khattak I, Ang CW, et al. Low molecular weight heat shock protein HSP27 is a prognostic indicator in rectal cancer but not colon cancer. *Gut*. 2010;59(11):1501–1510. doi:10.1136/gut.2009.196626

12. Ryan JE, Warrier SK, Lynch AC, et al. Predicting pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a systematic review. *Colorectal Dis*. 2016;18(3):234–246. doi:10.1111/codi.13207

13. Redalen KR, Sitter B, Bathen TF, et al. High tumor glycine concentration is an adverse prognostic factor in locally advanced rectal cancer. *Radiother Oncol*. 2016;118(2):393–398.

14. Balachandran VP, Gonen M, Smith JJ, et al. Nomograms in oncology: more than meets the eye. *Lancet Oncol*. 2015;16(4):e173–180. doi:10.1016/S1470-2045(14)71116-7

15. Roels S, Duthoy W, Haustermans K, et al. Definition and delineation of the clinical target volume for rectal cancer. *Int J Radiat Oncol Biol Phys*. 2006;65(4):1129–1142. doi:10.1016/j.ijrobp.2006.02.050

16. Deng X, Liu P, Jiang D, et al. Neoadjuvant radiotherapy versus surgery alone for stage II/III mid-low rectal cancer with or without high-risk factors: a prospective multicenter stratified randomized trial. *Ann Surg*. 2019. doi:10.1097/SLA.0000000000003649

17. Benson AB 3rd, Venook AP, Al-Hawary MM, et al. Rectal cancer, version 1.2019, NCCN clinical practice guidelines in oncology, 2019. *J Natl Compr Canc Netw*. 2019.

18. Keller DS, Berho M, Perez RO, et al. The multidisciplinary management of rectal cancer. *Nat Rev Gastroenterol Hepatol*. 2020.

19. Huang MY, Huang CW, Wang JY. Surgical treatment following neoadjuvant chemoradiotherapy in locally advanced rectal cancer. *Kaohsiung J Med Sci*. 2020;36(3):152–159. doi:10.1002/kjm2.12161

20. Sun Y, Huang Z, Chi P. An inflammation index-based prediction of treatment response to neoadjuvant chemoradiotherapy for rectal mucinous adenocarcinoma. *Int J Clin Oncol*. 2020.

21. Sun Y, Zhang Y, Huang Z, et al. Prognostic implication of negative lymph node count in ypn+ rectal cancer after neoadjuvant chemoradiotherapy and construction of a prediction nomogram. *J Gastrointest Surg*. 2019;23(5):1006–1014. doi:10.1007/s11605-018-3942-3

22. Sun Y, Zhang Y, Wu X, et al. Prognostic significance of neoadjuvant rectal score in locally advanced rectal cancer after neoadjuvant chemoradiotherapy and construction of a prediction model. *J Surg Oncol*. 2018;117(4):737–744. doi:10.1002/jso.24907

23. Gao XH, Yu GY, Gong HF, et al. Differences of protein expression profiles, KRAS and BRAF mutation, and prognosis in right-sided colon, left-sided colon and rectal cancer. *Sci Rep*. 2017;7(1):7882. doi:10.1038/s41598-017-08413-z

24. Zhang LN, OuYang PY, Xiao WW, et al. Elevated CA19-9 as the most significant prognostic factor in locally advanced rectal cancer following neoadjuvant chemoradiotherapy. *Medicine (Baltimore)*. 2015;94(45):e1793. doi:10.1097/MD.0000000000001793

25. Yılmaz Rakıcı S, Bedir R, Hatipoğlu C. Are there predictors that can determine neoadjuvant treatment responses in rectal cancer? *Turk J Gastroenterol*. 2019;30(3):220–227. doi:10.5152/tjg.2018.18179

26. Song J, Huang X, Chen Z, et al. Predictive value of carcinoembryonic antigen and carbohydrate antigen 19-9 related to downstaging to stage 0-I after neoadjuvant chemoradiotherapy in locally advanced rectal cancer. *Cancer Manag Res*. 2018;10:3101–3108. doi:10.2147/CMAR.S166417

27. Liebl F, Demir IE, Mayer K, et al. The impact of neural invasion severity in gastrointestinal malignancies: a clinicopathological study. *Ann Surg*. 2014;260(5):900–907. doi:10.1097/SLA.0000000000000968

28. Nikberg M, Chabok A, Letocha H, et al. Lymphovascular and perineural invasion in stage II rectal cancer: a report from the Swedish colorectal cancer registry. *Acta Oncol*. 2016;55(12):1418–1424. doi:10.1080/0284186X.2016.1230274

29. Peng J, Sheng W, Huang D, et al. Perineural invasion in pT3N0 rectal cancer: the incidence and its prognostic effect. *Cancer*. 2011;117(7):1415–1421. doi:10.1002/cncr.25620

30. Bacha D, Talbi G, Ben Slama S, et al. Predictive factors for histological response to neo-adjuvant treatment in rectal cancers. *Tunis Med*. 2019;97(11):1284–1290.

31. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569–578. doi:10.1016/S0140-6736(08)60269-X

32. Garcia H, Song M. Early-life obesity and adulthood colorectal cancer risk: a meta-analysis. *Rev Panam Salud Publica*. 2019;43:e3. doi:10.26633/RPSP.2019.3

33. Sweigert PJ, Chen C, Fahmy JN, et al. Association of obesity with postoperative outcomes after proctectomy. *Am J Surg*. 2020;S0002-9610(20)30185–9.

34. Abdel-Rahman O. Effect of body mass index on 5-FU-based chemotherapy toxicity and efficacy among patients with metastatic colorectal cancer; a pooled analysis of 5 randomized trials. *Clin Colorectal Cancer*. 2019;18(4):e385–e393. doi:10.1016/j.clcc.2019.07.005

35. Kalb M, Langheinrich MC, Merkel S, et al. Influence of body mass index on long-term outcome in patients with rectal cancer – a single centre experience. *Cancers (Basel)*. 2019;11(5):E609. doi:10.3390/cancers11050609

36. Shahjehan F, Merchea A, Cochuyt JJ, et al. Body mass index and long-term outcomes in patients with colorectal cancer. *Front Oncol*. 2018;8:620. doi:10.3389/fonc.2018.00620

37. Zhang X, Wu Q, Gu C, et al. The effect of increased body mass index values on surgical outcomes after radical resection for low rectal cancer. *Surg Today*. 2019;49(5):401–409. doi:10.1007/s00595-019-01778-w

38. Lino-Silva LS, Aguilar-Cruz E, Salcedo-Hernández RA, et al. Overweight but not obesity is associated with decreased survival in rectal cancer. *Contemp Oncol (Pozn)*. 2018;22(3):158–164.

39. Clark W, Siegel EM, Chen YA, et al. Quantitative measures of visceral adiposity and body mass index in predicting rectal cancer outcomes after neoadjuvant chemoradiation. *J Am Coll Surg*. 2013;216(6):1070–1081. doi:10.1016/j.jamcollsurg.2013.01.007

40. Rickles AS, Iannuzzi JC, Mironov O, et al. Visceral obesity and colorectal cancer: are we missing the boat with BMI? *J Gastrointest Surg*. 2013;17(1):133–143. doi:10.1007/s11605-012-2045-9

41. Heus C, Cakir H, Lak A, et al. Visceral obesity, muscle mass and outcome in rectal cancer surgery after neo-adjuvant chemo-radiation. *Int J Surg*. 2016;29:159–164. doi:10.1016/j.ijsu.2016.03.066

42. Goulart A, Malheiro N, Rios H, et al. Influence of visceral fat in the outcomes of colorectal cancer. *Dig Surg*. 2019;36(1):33–40. doi:10.1159/000486143

43. Lee KH, Kang BK, Ahn BK. Higher visceral fat area/subcutaneous fat area ratio measured by computed tomography is associated with recurrence and poor survival in patients with mid and low rectal cancers. *Int J Colorectal Dis*. 2018;33(9):1303–1307. doi:10.1007/s00384-018-3065-z

44. Zhou CJ, Cheng YF, Xie LZ. Metabolic syndrome, as defined based on parameters including visceral fat area, predicts complications after surgery for rectal cancer. *Obes Surg*. 2020;30(1):319–326. doi:10.1007/s11695-019-04163-1

45. Tokunaga R, Nakagawa S, Miyamoto Y, et al. The clinical impact of preoperative body composition differs between male and female colorectal cancer patients. *Colorectal Dis*. 2020;22(1):62–70. doi:10.1111/codi.14793

46. Yu H, Joh YG, Son GM, et al. Distribution and impact of the visceral fat area in patients with colorectal cancer. *Ann Coloproctol*. 2016;32(1):20–26. doi:10.3393/ac.2016.32.1.20

47. De Nardi P, Salandini M, Chiari D, et al. Changes in body composition during neoadjuvant therapy can affect prognosis in rectal cancer patients: an exploratory study. *Curr Probl Cancer*. 2019;100510.

48. Takeda Y, Akiyoshi T, Matsueda K, et al. Skeletal muscle loss is an independent negative prognostic factor in patients with advanced lower rectal cancer treated with neoadjuvant chemoradiotherapy. *PLoS One*. 2018;13(4):e0195406. doi:10.1371/journal.pone.0195406