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ORIGINAL ARTICLE

Development of a novel model for predicting survival of patients with spine metastasis from colorectal cancer

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Abstract

Objective To develop a novel nomogram for predicting survival of patients with spine metastasis from colorectal cancer (SMCRC) based on the clinical characteristics and prognostic factors.

Methods Included in this study were 93 SMCRC patients who received treatments in our institute between 2006 and 2017, whose clinical data were analyzed retrospectively by univariate and multivariate analysis to identify independent variables that could predict prognosis. A nomogram for survival prediction was established on the basis of preoperative independent factors, and then subjected to bootstrap re-samples for internal validation. The discrimination was measured by concordance index (C-index). We used ROC analysis with the corresponding AUROC to compare the prediction accuracy of Changzheng Nomogram with three existing prognostic systems (Tomita, Tokuhashi and Bauer).

Results The high and median degrees of primary tumor differentiation, primary tumor surgery, carcinoembryonic antigen ≤ 5 ng/ml, no visceral metastases and ECOG-PS (0–2) were favorable prognostic factors for CRC metastases in the spine. These five preoperative independent factors were identified and entered into the nomogram with the C-index of 0.786 (0.739–0.833). The calibration curves for probability of 12- and 24-month overall survival (OS) showed good agreement between the predictive risk and the actual risk, and calibration was assessed. Compared with the previous prognostic systems, Changzheng Nomogram reported in this study showed higher accuracy in predicting OS of patients with SMCRC spinal metastases ($p < 0.05$).

Conclusion By using this novel predictive model, clinicians could more precisely estimate the survival outcome of individual patients by evaluating clinical characteristics and identify subgroups of patients who are in need of a specific individual treatment strategy.

Yujie Liu, Minglei Yang and Bo Li have contributed equally to this work.

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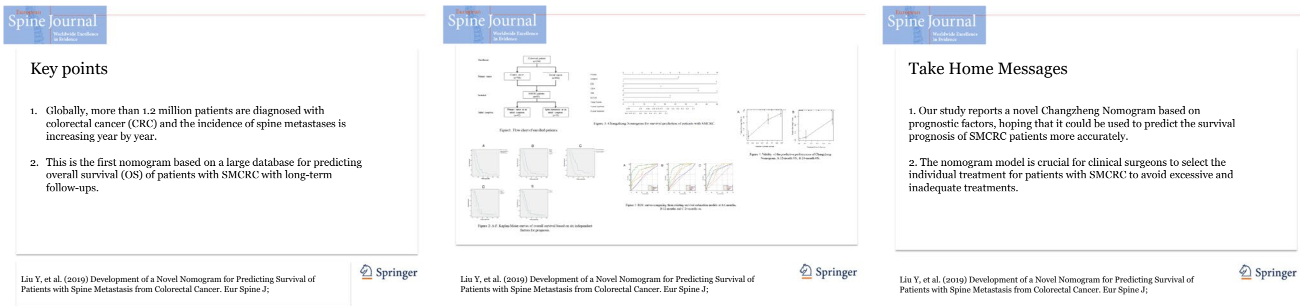
Graphical abstract These slides can be retrieved under Electronic Supplementary Material.



Keywords Colorectal cancer · Spine metastasis · Nomogram · Prognostic factor

Introduction

Globally, more than 1.2 million patients are diagnosed with colorectal cancer (CRC) and more than 600,000 die of the disease every year. The incidence of CRC ranks third among malignant diseases, and the incidence is increasing year by year [1, 2]. With the improved diagnosis and directed therapies for CRC, patients with CRC have a better survival than before. The CRC death rate declined by approximately 2% per year during the 1990s and approximately 3% per year during the past decade [3]. With this trend, more CRC patients experienced spine metastases [4–6]. The decision on selection of conservative therapy, systemic chemotherapy, targeted therapy, radiotherapy, palliative therapy or excisional surgery for the management of spine metastasis depends on various factors, including the estimated life expectancy of the patient in particular [4]. The estimated survival time of the patient should be taken into account in selection of an optimal individualized treatment for each patient.

Several scoring systems have been proposed to assess survival prognosis for spine metastasis [7–12]. However, these scores are designed for patients with spine metastasis in general but not specifically for patients with SMCRC. In addition, the number of CRC patients in these studies is small, making it difficult to draw conclusions on this specific tumor type. Furthermore, some previous and commonly used scoring systems have underestimated the life expectancy of patients with SMCRC due to the increased life expectancy in recent years [3].

Nomograms have been developed in most cancer types in recent years [13–15]. The use of nomograms has compared favorably to the traditional staging systems for many cancers and therefore been proposed as an alternative or even a new standard [16–18]. In the present study, we established a nomogram for predicting the survival of SMCRC patients and compared it with the three existing scoring systems in term of accuracy, in an attempt to help surgeons in evidence-based decision-making process on subsequent individualized treatment of SMCRC patients based on prognostic factors.

Materials and methods

Patients and follow-up strategy

Patients who were diagnosed with SMCRC and received examination and treatments in our institution between January 2006 and October 2017 were reviewed retrospectively. Inclusion criteria: Patients with SMCRC were pathologically confirmed, and spine metastases were demonstrated by X-rays, whole body bone scan (WBBS), CT, MRI or PET-CT. Finally, 93 patients were enrolled in this study. The clinical and operation records, imaging data, blood test results and pathological reports of the patients were reviewed by three researchers independently. Preoperative Frankel Score (evaluated when patients were admitted in our institution) and the Eastern Cooperative Oncology Group performance score (ECOG-PS) [19] were used to evaluate the neurological status and performance status.

All patients were followed up monthly in the first year and at a 3-month interval thereafter on the outpatient basis. The clinical conditions and radiographic findings of the patients were obtained to evaluate the prognosis. Time from primary to metastasis (PoM) was defined as the time period between the date of diagnosis of the primary tumor and the date of spine metastasis based on radiological assessment. Overall survival (OS) was a key endpoint and defined as being from the first day the patient diagnosed as SMCRC until the date of death.

Upon arrival of the SMCRC patients in our institution, blood samples were taken for alkaline phosphatase (ALP) and carcinoembryonic antigen (CEA). ALP was categorized on the basis of our institutional reference values. The cutoff point of CEA was decided according to its reference value and median value in the cohort which was categorized as low-level group (≤ 5 ng/ml) to median-level group (5–10 ng/ml) and high-level group (> 10 ng/ml).

Statistical analysis and model establishment

Quantitative data were described by mean or median, and qualitative data by counts and percentages. Continuous variables are expressed as mean ± standard deviation (SD) and compared using an unpaired, 2-tailed *t* test. Categorical variables were compared using the χ^2 test or Fisher's exact test. The Kaplan–Meier curve was adopted to estimate the cumulative survival rate, with log-rank test to identify the difference.

R project version 3.4.3 (http://www.r-project.org/) was used in the development of the novel model. A nomogram was formulated based on the results of multivariate analysis, by proportionally converting each regression coefficient to a 0- to 10-point scale. The effect of the variable with the highest β coefficient was assigned 10 points. The nomogram was subjected to bootstrap with 1000 re-samples for validation, and the discrimination was evaluated by the concordance index (C-index). Calibration plots were constructed to determine whether the 12- and 24-month prediction conformed to actual observation, and calibration was assessed.

Comparison with the existing scoring systems

To compare the prediction accuracy of Changzheng Nomogram with three existing prognostic systems (Tomita, Tokuhashi and Bauer), we assessed the accuracy for predicting 6-, 12- and 24-month OS in each of the four scoring algorithms and used ROC analysis with the corresponding AUROC using the method reported by DeLong et al.

Results

Research population and characteristics of SMCRC

From January 2006 to January 2017, a total of 1588 patients with primary CRC tumors were treated at Changzheng Hospital. Among them, 786 (49%) patients were diagnosed with colon tumors and 802 (51%) with rectal cancer. Finally, we identified 93 (5.9%) patients who were diagnosed as having SMCRC (Fig. 1).

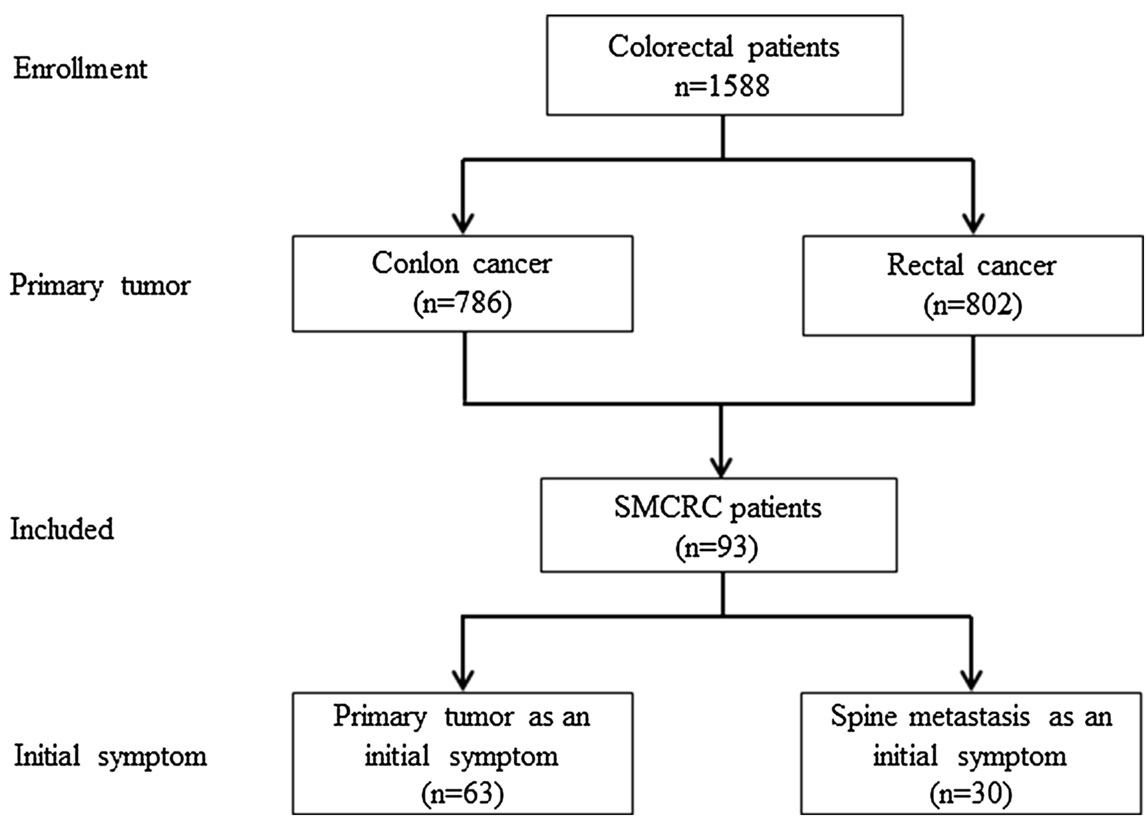


Fig. 1 Flowchart of enrolled patients

Of the 93 SMCRC patients, the median OS after the diagnosis of SM was 15 ± 1.32 months (95% CI 12.42–17.58 months). The demographics and clinical characteristics of these patients are listed in Table 1. Of the 93 SMCRC patients, 71 patients also had other metastases, involving the liver (31%), lung (26%) and other organs (43%). In terms of the diagnostic methods, PET-CT was the most frequently used method for the diagnosis of metastatic lesions ($n = 56$, 60.2%). The most common complaints included nocturnal back pain, extremity numbness and paraplegia. No patient died during the peri-operative period. Surgery, local radiotherapy and chemotherapy remained the mainstay of treatment for the primary tumors in our series, accounting for 75.3%, 48.4% and 48.4%, respectively; 31 (33.3%) patients received targeted therapies. CRC patients received targeted agents including bevacizumab, cetuximab, endostar and sorafenib. Forty patients were diagnosed with solitary spine metastasis. Five of them had tumor en bloc resection, with the median OS of 26 ± 9.86 months (95% CI 6.68–45.32 months). The rest 33 patients had intralesional piecemeal excision, with the median OS of 14 ± 2.84 months (95% CI 9.33–18.67 months).

Table 1 Baseline characteristics of the 93 SMCRC patients

Variable	No. of patients (%)	Univariate analysis *p* value
Sex		
Man/woman	58/35 (62.4/37.6)	0.930
Age		
≤ 55/> 55	39/54 (41.9/58.1)	0.120
Primary tumor		
Colon/rectal cancer	46/47 (49.5/50.5)	0.075
Differentiated degree		
High or median/low	61/32 (65.6/34.4)	< 0.001*
Tumor stage		
I–III/IV	55/38 (59.1/40.9)	0.145
Treatments of primary tumor		
Surgery (yes/no)	70/23 (75.3/24.7)	0.007*
Radiotherapy (yes/no)	45/48 (48.4/41.6)	0.379
Chemotherapy (yes/no)	45/48 (48.4/41.6)	0.395
Targeted therapy (yes/no)	31/62 (33.3/66.7)	0.001*
Initial symptom		
Spine metastasis as an initial symptom/ Primary tumor as an initial symptom	30/63 (32.3/67.7)	0.009*
Visceral metastasis (yes/no)	71/22 (76.3/23.7)	< 0.001*
Loss of weight (yes/no)	32/61 (34.4/65.6)	0.390
Feature of lesions		
Osteoblastic/osteolytic/mixed	14/66/13 (15.1/71.0/13.9)	0.145
Spinal cord compression		
Yes/no	50/43 (53.8/46.2)	0.343
Segments involved		
Single/multiple	40/53 (43.0/57.0)	0.394
VAS score		
≤ 5/> 5	50/43 (53.8/46.2)	0.642
Preoperative Frankel score		
A–C/D–E	52/41 (56.0/46.0)	0.009*
ECOG-PS		
≤ 2/> 2	30/63 (32.3/67.7)	0.022*
Preoperative ALP		
≤ 150/> 150	56/37(60.2/39.8)	0.120
Preoperative CEA		
≤ 5/5–10/> 10	35 (37.6)/14 (15.1)/44 (47.3)	0.001*

*These values are statistically significant at a p value of < 0.05

Statistical analysis of potential independent factors

The results of univariate prognostic analysis are demonstrated in Table 1. Based on the inclusion criterion of $p < 0.05$, eight potential factors were submitted into the Cox regression model (Table 2). High and median differentiations of primary tumors ($p < 0.001$), no visceral metastases ($p < 0.001$), receiving primary tumor surgery ($p = 0.011$), lower levels of preoperative CEA ($p < 0.001$) and ECOG-PS (0–2) ($p = 0.012$) were independent and favorable prognostic factors. Independent factors affecting the OS rate as identified by the Kaplan–Meier Method are illustrated in Fig. 2.

Table 2 Results of multivariate analysis of potential prognostic factors

Factors	Overall survival	
	HR (95% CI)	*p* value
Differentiated degree	3.302 (1.967–5.544)	< 0.001*
Primary tumor surgery	0.509 (0.302–0.859)	0.011*
Targeted therapy	–	0.138
Initial symptom	–	0.517
Visceral metastasis	3.169 (1.718–5.845)	< 0.001*
Preoperative Frankel score	–	0.417
ECOG-PS	1.799 (1.136–2.849)	0.012*
Preoperative CEA	1.619 (1.265–2.072)	< 0.001*

*These values are statistically significant at a *p* value of < 0.05

Development and validation of the nomogram

The finally identified five independent variables were included to develop this survival estimation nomogram (Fig. 3). The score of each significant variable is shown in Table 3. Each point was determined by drawing a line straight upward from each predictor to the point axis, and the total points were then calculated by summing each point. The 12- and 24-month OS was determined by drawing a line straight down from the total point axis. For clinical use of the model, the estimated incidence of each patient was calculated based on the nomogram. Internal validation showed the nomogram demonstrated good accuracy in estimating the survival of patients with SMCRC, with a C-index of 0.786 (95% CI, 0.739–0.833). In addition, calibration plots presented a good agreement between the nomogram prediction and actual observation for 12- and 24-month OS (Fig. 4).

Comparison with the existing scoring systems

ROC and AUROC were compared between Changzheng Nomogram and the three existing models (Tomita, Tokuhashi and Bauer) for 6-, 12- and 24-month OS prediction.

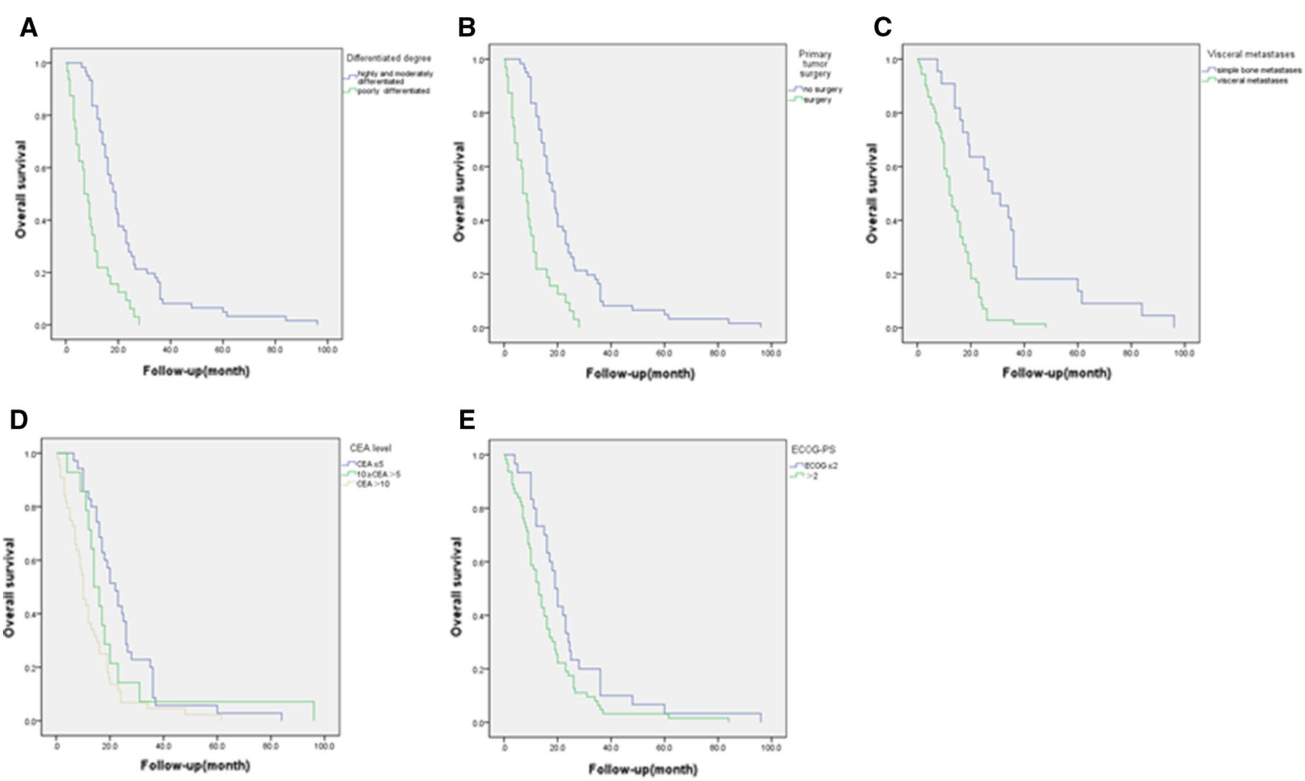


Fig. 2 **a–e** Kaplan–Meier curves of overall survival based on five independent factors for prognosis

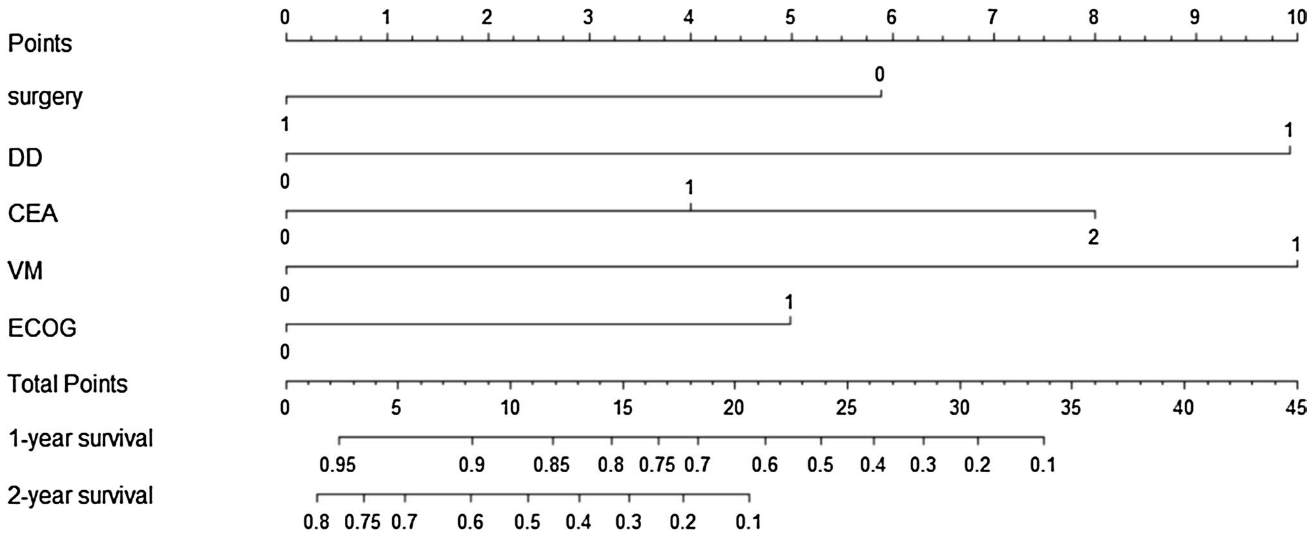


Fig. 3 Changzheng Nomogram for survival prediction of patients with SMCRC. *Surgery* primary tumor surgery; *DD* primary tumor differentiated degree; *CEA* preoperative carcinoembryonic antigen; *VM* visceral metastasis; *ECOG* ECOG-PS

Table 3 Point assignment and prognostic scores of the SMCRC patients

Prognostic factors	Score
Primary tumor surgery	
Yes	0
No	6
Differentiated degree	
High or median	0
Low	10
Preoperative CEA	
≤5	0
5–10	4
>10	8
Visceral metastasis	
No	0
Yes	10
ECOG-PS	
0–2	0
3–5	5

The results showed that our new nomogram had significantly better accuracy than that of the above three models for 6-, 12- and 24-month OS prediction ($p<0.05$; Table 4; Fig. 5).

Discussion

Colorectal cancer is the third leading cause of cancer-related deaths, with over 50,000 deaths during 2014 alone in the USA [1, 20]. The incidence is on the rise both in China and the USA [21]. With the improved diagnosis and directed therapies for CRC, more patients with CRC have a better survival than before but at the same time more CRC patients experienced spine metastases [4–6]. In recent years, there is an increase in the number of publications to analyze CRC patients with bone metastasis [22–24]. Nevertheless, previous studies seldom paid attention to establish a predictive model and analyze prognostic factors in SMCRC patients before decision making of the therapeutic approaches. Therefore, the aim of this study was to make a comprehensive evaluation on the clinical features and prognostic risk factors for the sake of establishing a novel predictive model called Changzheng Nomogram for predicting survival of patients with SMCRC. Individualized treatment approaches are often based on the life expectancy of the patient as estimated with the help of significant prognostic factors and scoring systems. To the best of our knowledge, this is the first nomogram model based on a large database for predicting overall survival (OS) of patients with SMCRC with long-term follow-ups.

The current study demonstrated that the degree of primary tumor differentiation, primary tumor surgery, serum CEA level, visceral metastasis and ECOG-PS were independent prognostic factors. To the best of our knowledge, only few studies have focused on the degree of primary tumor differentiation for CRC with spine metastasis [25]. Effective medical and surgical treatment of primary neoplasm has rendered prolonged survival in cancer patients [26]. In other words, effective disposal of the primary CRC and high or moderate differentiation render a better prognosis. Radiotherapy is a remarkable modality to oligometastatic colorectal liver and lung metastases in patients not amenable to surgery or other ablative treatments [27]. However, patients who received radiotherapy on the primary tumors did not seem to gain significant benefits in terms of OS ($p=0.379$). Chemotherapy is an important treatment for

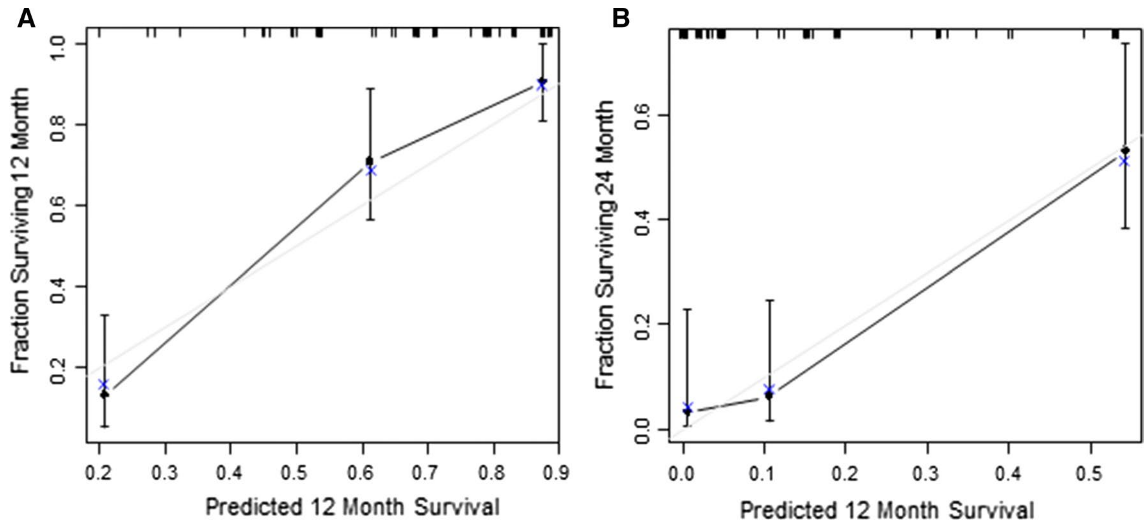


Fig. 4 Validity of the predictive performance of Changzheng Nomogram. **a** 12-month OS; **b** 24-month OS

patients with metastatic CRC, and some newer therapeutic regimens developed in recent years have been shown to improve survival in patients with metastatic CRC [28–31]; however, in our study it did not seem to render significant benefits to OS of the patients. Of course, more high-quality prospective randomized cohort studies are needed to validate this potential factor. In our study, patients benefited from targeted therapy in terms of OS ($p = 0.001$). Several studies [5, 6, 32] showed that the use of molecular-targeted drugs such as cetuximab and bevacizumab improved OS of patients who underwent incomplete cytoreductive surgery. Moreover, more accurate and effective targeted medicines should be explored and validated for CRC patients.

A retrospective study showed that bone metastasis occurred later than metastasis in other sites in their 256 CRC patients who received PET-CT examination [22]. However, there were still 30 patients in our series who presented with spinal cord compression or back pain as the initial clinical sign that led to the diagnosis of SMCRC. The observed median PoM time in our series was different from that in other published studies. Santini et al. [23] reported a median PoM time of 11 months (95% CI 4.7–13.1 months), but 17 ± 3.30 months (95% CI 10.53–23.47 months) in our series. An explanation could be that primary tumor stages between the studied populations were different.

Visceral metastases have been reported as a fatal factor with a long survival rate below 5% [33]. It was also found to be strongly associated with poor OS (median OS 12 ± 1.40 months, 95% CI 9.25–14.75) in our study. In addition, we have found in our clinical work that the survival of patients without visceral metastases was considerably longer than expected (median OS 28 ± 5.28 months, 95% CI 17.66–38.34, $p < 0.001$). Likewise, Nozue et al. [34] showed that CRC patients with bone metastasis alone had a better prognosis than those with combined bone metastasis and visceral metastasis. Similar findings have also been observed in other cancers. In patients with breast cancer, Harries et al. reported that the median survival time after the diagnosis of bone metastasis was 2.3 years versus less than one year in patients with both bone and visceral metastases [35]. The possible reason might be as follows: The primary tumors might have been in their late stage in these CRC patients, and their performance status might be influenced by other visceral metastases and might have more complications than those with spine metastasis alone. Another explanation could lie in the metastatic process and efficiency that differ according to the tumor biology [36].

In particular, comprehensive laboratory examinations including ALP and CEA that are seldom included as variables in other systems are also considered in our risk system. High-level CEA is a poor prognostic factor for CRC in some studies [37–39]. The serum CEA level is an indication of the total tumor mass and the ability of tumor cells to express CEA, which is involved in intracellular recognition and attachment, and might promote tumor–tumor cell and tumor–host cell adhesions [40]. High CEA levels might reflect a large tumor burden and thus be associated with shorter survival [41]. The usefulness of measuring the serum CEA level in the diagnosis, prognosis prediction and management of CRC after resection has been previously described [42, 43]. Based on survival analysis, we determined that a normal CEA level measured at the time of diagnosis of spine metastasis was significantly and independently associated with a good prognosis in CRC patients with spine metastasis. A high serum CEA level was associated with a poor prognosis in CRC patients with spine metastasis, and this finding was also observed in previous studies [40]. Thus,

Table 4 AUC comparison for the current nomogram with Tomita, Bauer and Tokuhashi score from ROC analysis

Prediction time	AUC										
	Changzheng Nomogram	95% CI	Tomita score	*p* value	95% CI	Tokuhashi score	*p* value	95% CI	Bauer score	*p* value	95% CI
6 months	0.92	0.845–0.966	0.755	0.0017*	0.655–0.839	0.677	0.0049*	0.572–0.771	0.515	<0.0001*	0.409–0.620
12 months	0.904	0.825–0.955	0.721	0.0001*	0.618–0.809	0.733	0.0023*	0.631–0.819	0.543	<0.0001*	0.436–0.646
24 months	0.888	0.805–0.944	0.735	0.0194*	0.634–0.821	0.718	0.0042*	0.615–0.807	0.74	0.0266*	0.639–0.826

*Compared with Changzheng Nomogram, these values are significant at a two-tailed *p* value of <0.05. All values are given as the AUC, with the 95% CI in parentheses

CEA is a useful tumor marker and a significant prognostic factor not only for CRC but for CRC with spine metastasis.

Good performance status was a robust predictor of survival in patients with spinal metastasis from non-small-cell lung cancer [44, 45]. In our research, ECOG-PS was also found to be an independent factor. ECOG-PS is a standard criterion to comprehensively measure and evaluate the living ability of a patient. Relevant studies have also demonstrated that ECOG-PS is a possible independent factor in other types of spine metastases [8]. In our study, ECOG-PS (0–2) of patients had a better initial life performance that we thought; it was critical to enable patients to withstand the impact of surgery and the adjuvant therapies, such as chemotherapy.

Among 40 patients diagnosed with solitary spinal metastasis in our study, five of them received tumor en bloc resection with relatively longer median OS, compared to those having intralesional piecemeal excision. Different surgical strategies were studied and practiced in the treatment of spinal metastasis [8]. En bloc resection can remove the tumor completely and reduce the residual. The study of Matsumoto et al. [46] showed that en bloc resection of spinal metastasis was effective in the local control and in preserving the neurological functions. Chataigner et al. [47] also suggested en bloc resection because of the risk of recurrence, especially when the primary tumor is of slow or moderate growth. However, its complication might be relatively high [48]. Piecemeal resection and decompressive surgery can also improve the functional status and decrease narcotic requirements in patients with spinal metastasis, while adjuvant radiotherapy is needed to reduce the local recurrence [49, 50]. There is no consensus whether en bloc resection could prolong the survival of spinal metastasis patients. And we cannot make this conclusion in our study. These five patients receiving en bloc resection had no visceral metastasis, high differentiation of primary tumor, less neurological deficits and lower CEA, which also contributed to their better prognosis.

Personalization of cancer therapy has penetrated into the sphere of oncology in recent decades [51]. Individual strategies are particularly crucial for patients with SMCRC, and life expectancy of patients with SMCRC is increased due to the development of surgery technic and novel targeted medicine [52]. Compared with the previous prognostic systems, Changzheng Nomogram reported in this study showed higher accuracy in predicting OS of patients with SMCRC spinal metastases and therefore could be used to help apply optimal and better individualized treatment for SMCRC patients with spinal metastases. Unlike those previous scoring systems, our nomogram is specifically for those patients with SMCRC. Particularly, CEA level was added into this model establishment which was a crucial indicator in metastatic gastrointestinal tumor such as colorectal cancer with spine metastasis in our

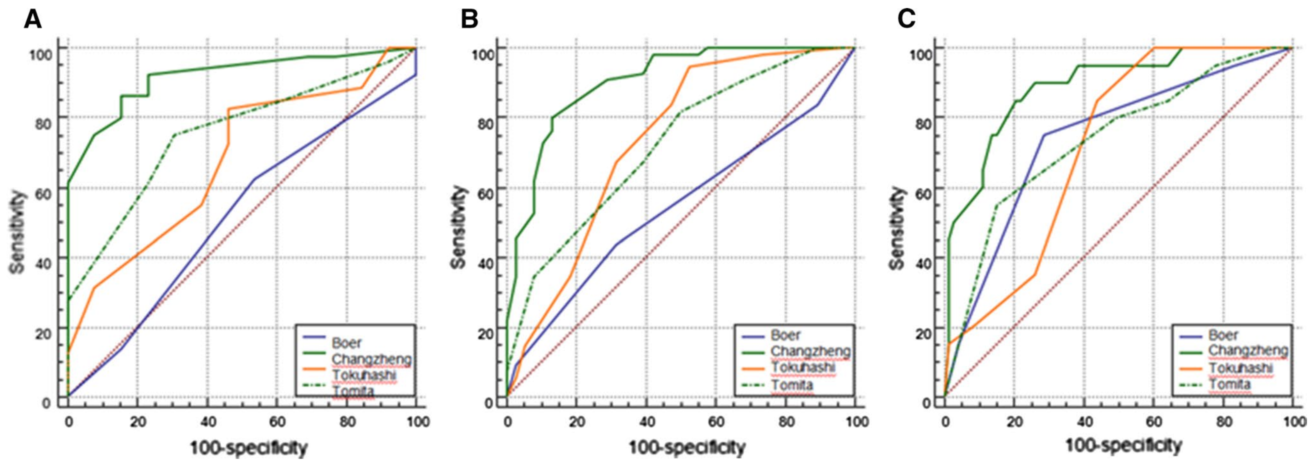


Fig. 5 ROC curves comparing three existing survival estimation models at **a** 6 months, **b** 12 months and **c** 24 months OS

nomogram model whereas not included in those scoring systems. This model based on statistical approach is more suitable and accurate for Chinese population group.

However, there are several limitations of this study. First, this Changzheng Nomogram model was established based on the database obtained from a single center in China. Second, the current study is a retrospective study and might introduce recall bias, and therefore more prospective studies are required to testify its accuracy and reliability. Third, we do not evaluate the local progression of patients after surgery or radiotherapy, and local recurrence was not selected as an endpoint. Moreover, this nomogram is developed based on the patients with colorectal cancer and spinal metastatic disease. It cannot be applied for patients with spinal metastasis from other cancers.

In conclusion, the present study reports a novel Changzheng Nomogram based on prognostic factors, hoping that it could be used to predict the survival prognosis of SMCRC patients more accurately. The nomogram model is crucial for clinical surgeons to select the individual treatment for patients with SMCRC to avoid excessive and inadequate treatments. Additional studies are required to verify whether it can be applied to other patient groups.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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