Original Article

Prognostic factors and individualized nomograms predicting overall survival in stage IV rectal cancer patients with different metastatic status: a SEER-based study

Heming Ge[1,2,3], Zhongyi Zhou[2,3], Yuqiang Li[1,2,3], Dan Wang[1,2,3], Cenap Güngör[1]

[1]Department of General Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]Department of General Surgery, Xiangya Hospital, Central South University, Changsha, China; [3]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, China

Contributions: (I) Conception and design: H Ge, D Wang; (II) Administrative support: C Güngör, Z Zhou, Y Li; (III) Provision of study materials or patients: H Ge, D Wang; (IV) Collection and assembly of data: C Güngör, Z Zhou; (V) Data analysis and interpretation: Y Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Zhongyi Zhou, MD. Department of General Surgery, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, China. Email: xyzzy_05@163.com.

Background: The prognosis of rectal cancer patients with different metastatic status was significantly different. Our aim was to identify prognostic factors for metastatic rectal cancer (mRC) patients with different metastatic status and to construct specific nomograms to predict overall survival (OS).

Methods: This study retrospectively analyzed mRC patients from 2010 to 2016 in the Surveillance, Epidemiology, and End Results Program database. All patients were ultimately divided into four groups: synchronous liver metastasis, synchronous lung metastasis, synchronous other organs metastasis and synchronous multiple metastases. Univariate and multivariate cox analyses were performed to screen out independent factors for each group. Individualized nomograms were constructed in different metastatic modes. The concordance index (C-index), decision curve analysis (DCA), time-dependent receiver operating characteristic (ROC) curve and calibration curve were performed to verify these nomograms.

Results: Finally, 10,407 mRC patients were included in this study. Age, tumor grade, surgery of primary tumor, and chemotherapy were identified as common independent prognostic factors for each subgroup (all $P<0.05$). Other independent prognostic factors specific to each group included radiotherapy and marital status in the liver metastasis group, race, N stage, and the presence or absence of site-specific metastases in the multiple metastases group (all $P<0.05$). Higher T staging suggested worse OS in the group with liver, lung, and multiple site metastases. Individualized nomograms predicting 1-, 2-, and 3-year OS for each group were constructed by combining all independently significant risk factors in each group. The area under the curve (AUC) values and C-indexes of these nomograms created by each subgroup were greater than 0.7. All calibration curves and DCA curves showed that these nomograms had good clinical application significance.

Conclusions: Individualized prognostic nomograms were constructed for mRC patients with different metastatic status based on different prognostic factors. These nomograms presented satisfactory predictive effects, which helps to provide survival assessment and individualized treatment decision-making for mRC patients with different metastatic status.

Keywords: Metastatic rectal cancer (mRC); nomogram; overall survival (OS); different metastatic status; SEER database

Submitted Feb 21, 2022. Accepted for publication May 30, 2022.
doi: 10.21037/tcr-22-436
View this article at: https://dx.doi.org/10.21037/tcr-22-436

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related death (1). Almost one third of newly diagnosed CRC is rectal cancer (RC), which is equivalent to approximately 730,000 new cases worldwide in 2020 (2). Even worse, synchronous distant metastasis occurred in approximately 20% of RC patients at initial diagnosis (3). The most commonly involved organs of distant metastasis in rectal cancer are the liver and lungs, with incidence of 12.3% and 5.6–7.5%, respectively (3,4).

Despite the rapid development of immunotherapy, chemotherapy and targeted agents, the outcome of metastatic rectal cancer (mRC) is still dissatisfactory in the past few decades (5,6). The 5-year survival rate for RC patients with distant metastases has been reported to be only 14.0% (7). Previous study has confirmed that the location and number of metastases plays an important role in the course of treatment and overall prognosis of RC (8). Accurate identification of metastatic patterns will help clinicians make correct treatment decisions and optimize follow-up strategies. Other prognostic factors affecting stage IV RC patients have been preliminarily investigated in previous studies, such as age at diagnosis, lymph metastasis, tumor size, carcinoembryonic antigen (CEA) levels, resectability and chemoradiotherapy (9-13).

Nomogram quantifies risk by integrating important prognostic factors, on which a model can be built, and the overall probability of specific survival for any individual patient can be calculated by adding up these scores (14). Therefore, it is widely used as a practical tool in clinical oncology. Existing studies (15,16) lack of further stratified analysis on the prognosis of patients with distal metastasis, such as the differences in prognostic factors and models at different sites of metastasis, and the differences between patients with single metastasis and patients with multiple metastasis. What's more, the rectum has embryological origins, anatomy, and functions that differ from the colon. RC is biologically different from colon cancer, leading to differences in clinical treatment and prognosis (17). Hence, individualized nomograms including as many necessary predictors as possible are urgently needed to accurately estimate the current survival of stage IV RC with different metastatic status.

The aim of this study was to determine prognostic factors in RC patients with different metastatic status according to the data from the Surveillance Epidemiology and End Results (SEER) database. Then, based on these prognostic factors, nomograms were constructed to predict overall survival (OS) in different metastatic modes. We present the following article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-436/rc).

Methods

Data extracting and screening

Patients diagnosed with mRC from 2010 to 2016 in the SEER database were retrospectively analyzed. Since the 1970s, the SEER database, part of the National Cancer Center, has been collecting data on all aspects of clinical cancer management, which covers about 30% of the U.S. population. This program began registering information about specific sites of metastasis in 2010. We extracted a total of 12,487 patients with mRC by using the SEER-Stat software (version 8.3.5, http://seer.cancer.gov/seerstat/software/). The ICD-O-3 codes for specific pathological tissue types are as follows: 8140, 8144, 8201, 8210, 8211, 8220, 8221, 8253, 8255, 8260-8263, 8310, 8323, 8480, 8481 and 8490. Exclusion criteria for this study included: (I) the diagnosed at autopsy or death certificate (n=8); (II) survival months is 0 (n=850); (III) M1=NOS, T stage is T0 and blank(s) in AJCC stage (n=736); (IV) The metastatic status of liver, lung, bone and brain is unknown or N/A (n=486). Finally, the patients were divided into four groups according to their different metastatic status: synchronous liver metastasis, synchronous lung metastasis, synchronous other organs metastasis and synchronous multiple metastases. The specific exclusion process of this study can be seen in *Figure 1*.

Our study was a retrospective study, and its data were mainly from the SEER database, so patients' informed consent was not required. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Clinical variables and outcome

The extracted basic demographic indicators were as follows: insurance and marital status, age, gender and race. Insurance and marital status were classified as insured and uninsured, married and unmarried, respectively. Age at diagnosis was divided into three levels: ≤50, 51–65 and >65. Race was categorized into the white, the black and the others.

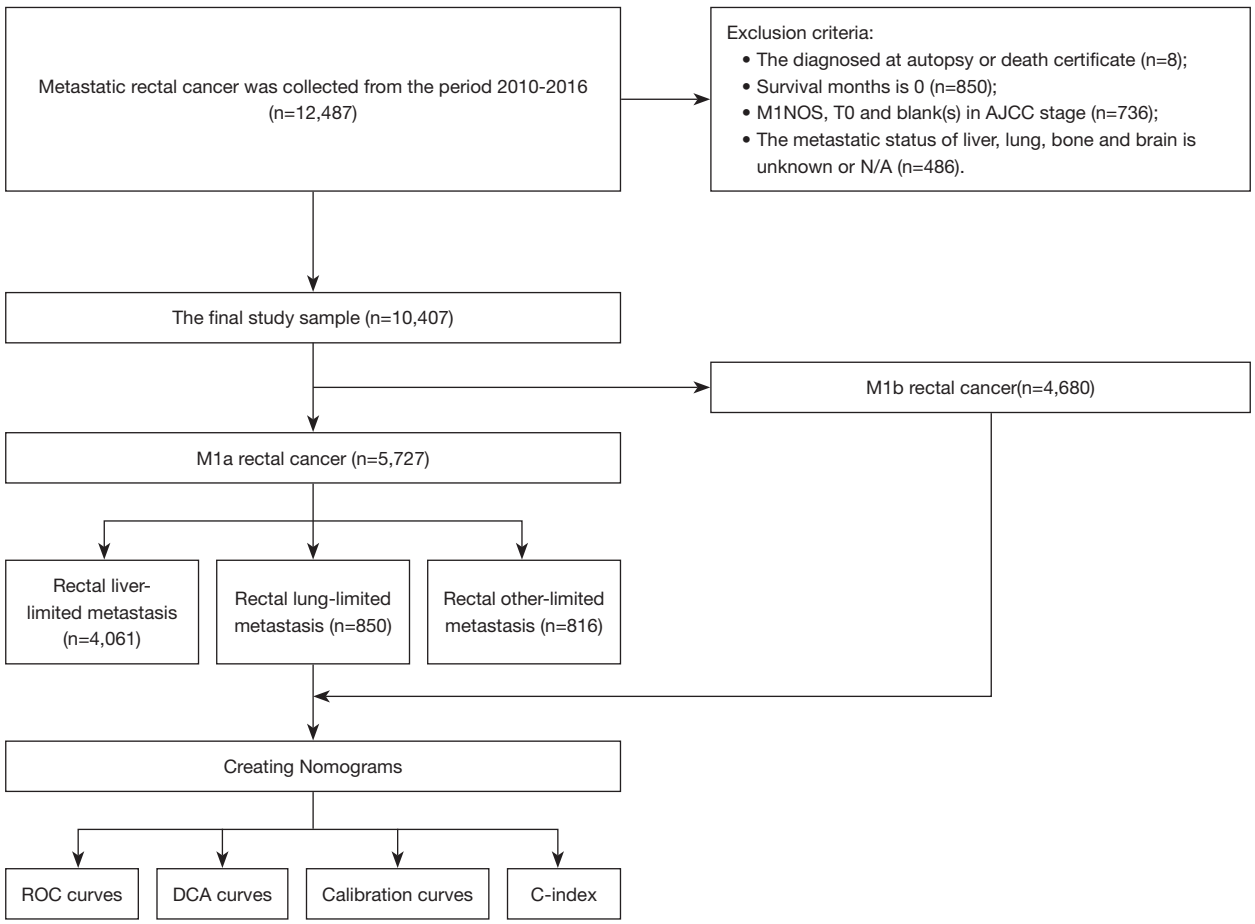

Figure 1 The specific exclusion process of this study. NOS, not otherwise specified; NA, not applicable; ROC, receiver operating characteristic; DCA, decision curve analysis; C-index, concordance index.

The extracted clinicopathological indicators included: tumor grade (Grade I/II: well differentiated/moderately differentiated, Grade III/IV: poorly differentiated/undifferentiated, and unknown), histology [adenocarcinomas and mucinous carcinoma (MCC)/signet ring cell carcinoma (SRCC)], T stage (T1-3, T4 and unknown), N stage (N0, N1 and unknown), M stage (M1a: synchronous liver/lung/other organs metastasis, M1b: synchronous multiple metastases), surgery for primary tumors, regional nodes examined (RNE), chemoradiotherapy (yes and no), sites of metastasis and CEA (negative, positive and unknown). Surgery for primary tumors was classified into standard proctectomy (RNE ≥12), simplified proctectomy (RNE <12) and non-proctectomy [RX Summ--Surg Prim Site (1998+): 0, 90 and 99] according to the number of lymph nodes examined.

The OS, the time from initial diagnosis of rectal cancer to death from all causes, was used as the primary outcome in this study.

Statistical analysis

Subgroups with different metastasis status were randomly divided into training and validation cohorts in a 2:1 ratio. Univariate and multivariate logistic regression analyses were performed to determine predictors, risk ratios (HR) and 95% confidence intervals (CIs) for each group. Variables with P value less than 0.05 in univariate analysis met the criteria for inclusion in multivariate analysis, so as to determine independent prognostic factors. In addition, the Kaplan-Meier (K-M) survival curve was used for survival analysis. Then, based on these independent prognostic factors, nomograms were developed employing the survival package in R. Each of the included predictors has a row

in nomograms, and different prediction quantities are represented by corresponding number of points. The end of nomograms was set with an axis of accumulation points, and the higher total points finally accumulated indicate the worse survival.

In this study, the concordance index (C-index) and receiver operating characteristic (ROC) curve analysis were used to evaluate the discrimination of these nomograms. This means that the larger the area under the curve (AUC) in the ROC curve and the larger the C-index value, indicating that this model has a strong discriminative ability. The calibration capability of nomograms was evaluated using calibration curves. Furthermore, we performed the decision curve analysis (DCA), a new tool for evaluating the clinical application value of nomograms, to evaluate the effect of clinical benefit. All P values in the analysis were two-side and less than 0.05 were defined as statistically significant.

Results

Patient characteristics

Ultimately, 10,407 patients with mRC were included in the research, of which 4,061 (39.02%) had synchronous liver metastasis, 850 (8.17%) had synchronous lung metastasis, 816 (7.84%) had other sites metastasis and 4,680 (44.97%) had synchronous multiple metastases. The total population was mainly composed of patients aged >50 years (78.52%), with a median survival time of 14 months. Briefly, patients who underwent surgery for primary tumors accounted for 45.29% of patients with liver metastasis, 38.12% of patients with lung metastasis, 53.06% of patients with other sites metastasis, and 25.32% of patients with multiple metastases, respectively. In addition, the data of patients receiving radiotherapy in each group were as follows: 32.04% of patients with liver metastasis, 45.88% of patients with lung metastasis, 56.86% of patients with metastasis to other sites, and 29.59% of patients with multiple metastasis. The detailed basic information and clinical characteristics of each group can be seen in *Table 1*.

Effects of different metastatic status on survival

The median OS for mRC patients with liver-limited metastasis, lung-limited metastasis, other sites-limited metastasis and multiple metastases was 24, 26, 29 and 15 months. The K-M survival analysis and Log-rank tests showed significant differences in OS among different metastatic status (P<0.001, *Figure 2*). The 1-, 2- and 3-year OS rates were 72.00% (95% CI: 70.53–73.41%), 49.76% (95% CI: 48.04–51.46%) and 33.01% (95% CI: 31.27–34.75%) in the liver-limited metastasis group, 74.90% (95% CI: 71.69–77.80%), 53.33% (95% CI: 49.45–57.06%) and 37.64% (95% CI: 33.59–41.69%) in the lung-limited metastasis group, 73.92% (95% CI: 70.61–76.93%), 55.03% (95% CI: 51.13–58.75%) and 42.78% (95% CI: 38.73–46.83%) in the other sites-limited metastasis group and 55.43% (95% CI: 53.92–56.91%), 30.09% (95% CI: 28.00–31.58%) and 17.30% (95% CI: 15.99–18.65%) in multiple metastases group , respectively.

Prognostic factors and construction of the nomogram in each group

Univariate and multivariate cox analyses were performed to screen out independent factors for each group. Finally, the following eight factors were associated with OS in the liver-limited metastasis group: marital status, age, tumor grade, T stage, surgery, chemotherapy, radiotherapy and CEA. Only five variables including age, tumor grade, T stage, surgery and chemotherapy were identified as independent prognostic factors in the lung-limited metastasis group. The independent prognostic factors associated with OS in the other sites-limited metastasis group included age, tumor grade, surgery, chemotherapy and CEA. Similarly, we revealed that age at diagnosis, tumor grade, T and N stage, surgery, chemotherapy, CEA, bone metastasis, liver metastasis and brain metastasis were identified as independent risk variables of multiple metastases group. Further details of the Cox analysis for each group were shown in *Table 2*.

Individualized nomograms predicting 1-, 2-, and 3-year OS for each group were constructed by combining all independently significant risk factors in each group (*Figure 3*).

Validation of nomograms

For the liver metastasis patients, the C-indexes for the nomogram to predict OS were 0.742 (95% CI: 0.729–0.754) and 0.739 (95% CI: 0.720–0.757) in the training and the verification cohort (*Table 3*). The AUCs of 1-, 2- and 3-year OS were 81.05%, 78.79% and 76.49% in the training group. The AUC values of 1-, 2- and 3-year survivals were 81.51%, 76.60% and 77.28% in the verification group (*Figure 4A,4B*).

Table 1 The characteristics of mRC patients in the total population and each subgroup

Characteristics	Entire population (N=10,407), n (%)	Synchronous liver metastasis, n (%)			Synchronous lung metastasis, n (%)			Synchronous other organs metastasis, n (%)			Synchronous multiple metastases, n (%)		
		Total (N=4,061)	Training group (N=2,707)	Validation group (N=1,354)	Total (N=850)	Training group (N=567)	Validation group (N=283)	Total (N=816)	Training group (N=544)	Validation group (N=272)	Total (N=4,680)	Training group (N=3,120)	Validation group (N=1,560)
Insurance status													
Insured	9,708 (93.28)	3,808 (93.77)	2,542 (93.90)	1,266 (93.50)	788 (92.71)	528 (93.12)	260 (91.87)	763 (93.50)	509 (93.57)	254 (93.38)	4,349 (92.93)	2,895 (92.79)	1,454 (93.21)
Uninsured/NOS	699 (6.72)	253 (6.23)	165 (6.10)	88 (6.50)	62 (7.29)	39 (6.88)	23 (8.13)	53 (6.50)	35 (6.43)	18 (6.62)	331 (7.07)	225 (7.21)	106 (6.79)
Marital status													
Married	5,237 (50.32)	2,150 (52.94)	1,409 (52.05)	741 (54.73)	405 (47.65)	279 (49.21)	126 (44.52)	402 (49.26)	284 (52.21)	118 (43.38)	2,280 (48.72)	1,537 (49.26)	743 (47.63)
Unmarried/NOS	5,170 (49.68)	1,911 (47.06)	1,298 (47.95)	613 (45.27)	445 (52.35)	288 (50.79)	157 (55.48)	414 (50.74)	260 (47.79)	154 (56.62)	2,400 (51.28)	1,583 (50.74)	817 (52.37)
Age at diagnosis (years)													
≤50	2,235 (21.48)	899 (22.14)	601 (22.20)	298 (22.01)	120 (14.12)	75 (13.23)	45 (15.90)	178 (21.81)	122 (22.43)	56 (20.59)	1,038 (22.18)	695 (22.28)	343 (21.99)
51–65	4,343 (41.73)	1,742 (42.90)	1,153 (42.59)	589 (43.50)	319 (37.53)	195 (34.39)	124 (43.82)	313 (38.36)	216 (39.71)	97 (35.66)	1,969 (42.07)	1,306 (41.86)	663 (42.50)
>65	3,829 (36.79)	1,420 (34.96)	953 (35.21)	467 (34.49)	411 (48.35)	297 (52.38)	114 (40.28)	325 (39.83)	206 (37.86)	119 (43.75)	1,673 (35.75)	1,119 (35.86)	554 (35.51)
Race													
White	8,170 (78.50)	3,236 (79.69)	2,154 (79.57)	1,082 (79.91)	671 (78.94)	446 (78.66)	225 (79.51)	636 (77.94)	419 (77.02)	217 (79.78)	3,627 (77.50)	2,442 (78.27)	1,185 (75.96)
Black	1,182 (11.36)	416 (10.24)	281 (10.38)	135 (9.97)	96 (11.29)	67 (11.82)	29 (10.25)	100 (12.25)	66 (12.13)	34 (12.50)	570 (12.18)	363 (11.63)	207 (13.27)
Other/NOS	1,055 (10.14)	409 (10.07)	272 (10.05)	137 (10.12)	83 (9.77)	54 (9.52)	29 (10.24)	80 (9.81)	59 (10.85)	21 (7.72)	483 (10.32)	315 (10.10)	168 (10.77)
Sex													
Female	4,003 (38.46)	1,344 (33.10)	904 (33.39)	440 (32.50)	393 (46.24)	263 (46.38)	130 (45.94)	353 (43.26)	221 (40.63)	132 (48.53)	1,913 (40.88)	1,276 (40.90)	637 (40.83)
Male	6,404 (61.54)	2,717 (66.90)	1,803 (66.61)	914 (67.50)	457 (53.76)	304 (53.62)	153 (54.06)	463 (56.74)	323 (59.37)	140 (51.47)	2,767 (59.12)	1,844 (59.10)	923 (59.17)
Grade													
Grade I/II	6,397 (61.47)	2,699 (66.46)	1,785 (65.94)	914 (67.50)	561 (66.00)	375 (66.14)	186 (65.72)	495 (60.66)	325 (59.74)	170 (62.50)	2,642 (56.45)	1,796 (57.56)	846 (54.23)
Grade III/IV	1,694 (16.28)	574 (14.13)	383 (14.15)	191 (14.11)	103 (12.12)	71 (12.52)	32 (11.31)	178 (21.82)	117 (21.51)	61 (22.43)	839 (17.93)	563 (18.05)	276 (17.69)
NOS	2,316 (22.25)	788 (19.41)	539 (19.91)	249 (18.39)	186 (21.88)	121 (21.34)	65 (22.97)	143 (17.52)	102 (18.75)	41 (15.07)	1,199 (25.62)	761 (24.39)	438 (28.08)
Histology													
Adenocarcinomas	9,829 (94.45)	3,945 (97.14)	2,630 (97.16)	1,315 (97.12)	813 (95.65)	542 (95.59)	271 (95.76)	746 (91.42)	502 (92.28)	244 (89.71)	4,325 (92.41)	2,881 (92.34)	1,444 (92.56)
MCC/SRCC	578 (5.55)	116 (2.86)	77 (2.84)	39 (2.88)	37 (4.35)	25 (4.41)	12 (4.24)	70 (8.58)	42 (7.72)	28 (10.29)	355 (7.59)	239 (7.66)	116 (7.44)
T stage													
T1-3	5,404 (51.93)	2,399 (59.07)	1,591 (58.77)	808 (59.68)	520 (61.18)	355 (62.61)	165 (58.30)	450 (55.15)	306 (56.25)	144 (52.94)	2,035 (43.48)	1,347 (43.17)	688 (44.10)
T4	2,050 (19.70)	604 (14.87)	398 (14.71)	206 (15.21)	167 (19.64)	103 (18.17)	64 (22.61)	242 (29.66)	159 (29.23)	83 (30.51)	1,037 (22.16)	707 (22.66)	330 (21.15)
Tx	2,953 (28.37)	1,058 (26.06)	718 (26.52)	340 (25.11)	163 (19.18)	109 (19.22)	54 (19.08)	124 (15.19)	79 (14.52)	45 (16.55)	1,608 (34.36)	1,066 (34.17)	542 (34.75)
N stage													
N0	3,599 (34.58)	1,462 (36.00)	1,010 (37.31)	452 (33.38)	326 (38.35)	218 (38.45)	108 (38.16)	254 (31.13)	168 (30.88)	86 (31.62)	1,557 (33.27)	1,051 (33.69)	506 (32.44)
N+	5,630 (54.10)	2,178 (53.63)	1,417 (52.35)	761 (56.21)	446 (52.47)	296 (52.20)	150 (53.00)	517 (63.36)	351 (64.52)	166 (61.03)	2,489 (53.18)	1,659 (53.17)	830 (53.20)
Nx	1,178 (11.32)	421 (10.37)	280 (10.34)	141 (10.41)	78 (9.18)	53 (9.35)	25 (8.84)	45 (5.51)	25 (4.60)	20 (7.35)	634 (13.55)	410 (13.14)	224 (14.36)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Entire population (N=10,407), n (%)	Synchronous liver metastasis, n (%)			Synchronous lung metastasis, n (%)			Synchronous other organs metastasis, n (%)			Synchronous multiple metastases, n (%)		
		Total (N=4,061)	Training group (N=2,707)	Validation group (N=1,354)	Total (N=850)	Training group (N=567)	Validation group (N=283)	Total (N=816)	Training group (N=544)	Validation group (N=272)	Total (N=4,680)	Training group (N=3,120)	Validation group (N=1,560)
Surgery													
Standard proctectomy	2,747 (26.40)	1,398 (34.43)	926 (34.21)	472 (34.86)	227 (26.71)	149 (26.28)	78 (27.56)	300 (36.76)	209 (38.42)	91 (33.46)	822 (17.56)	563 (18.04)	259 (16.60)
Simplified proctectomy	1,034 (9.94)	441 (10.86)	293 (10.82)	148 (10.93)	97 (11.41)	70 (12.35)	27 (9.54)	133 (16.30)	81 (14.89)	52 (19.12)	363 (7.76)	256 (8.21)	107 (6.86)
Non-proctectomy	6,626 (63.66)	2,222 (54.71)	1,488 (54.97)	734 (54.21)	526 (61.88)	348 (61.37)	178 (62.90)	383 (46.94)	254 (46.69)	129 (47.42)	3,495 (74.68)	2,301 (73.75)	1,194 (76.54)
Radiation													
Yes	3,540 (34.02)	1,301 (32.04)	859 (31.73)	442 (32.64)	390 (45.88)	256 (45.15)	134 (47.35)	464 (56.86)	312 (57.35)	152 (55.88)	1,385 (29.59)	914 (29.29)	471 (30.19)
No	6,867 (65.98)	2,760 (67.96)	1,848 (68.27)	912 (67.36)	460 (54.12)	311 (54.85)	149 (52.65)	352 (43.14)	232 (42.65)	120 (44.12)	3,295 (70.41)	2,206 (70.71)	1,089 (69.81)
Chemotherapy													
Yes	8,175 (78.55)	3,294 (81.11)	2,205 (81.46)	1,089 (80.43)	654 (76.94)	423 (74.60)	231 (81.63)	641 (78.55)	422 (77.57)	219 (80.51)	3,586 (76.62)	2,390 (76.60)	1,196 (76.67)
No	2,232 (21.45)	767 (18.89)	502 (18.54)	265 (19.57)	196 (23.06)	144 (25.40)	52 (18.37)	175 (21.45)	122 (22.43)	53 (19.49)	1,094 (23.38)	730 (23.40)	364 (23.33)
CEA													
Negative	1,372 (13.18)	503 (12.39)	332 (12.26)	171 (12.63)	175 (20.59)	117 (20.63)	58 (20.49)	177 (21.69)	119 (21.88)	58 (21.33)	517 (11.05)	358 (11.47)	159 (10.19)
Positive	6,245 (60.01)	2,474 (60.92)	1,663 (61.43)	811 (59.50)	428 (50.35)	292 (51.50)	136 (48.06)	378 (46.32)	256 (47.06)	122 (44.85)	2,965 (63.35)	1,943 (62.28)	1,022 (65.51)
NOS	2,790 (26.81)	1,084 (26.69)	712 (26.31)	372 (27.47)	247 (29.06)	158 (27.87)	89 (31.45)	261 (31.99)	169 (31.06)	92 (33.82)	1,198 (25.60)	819 (26.25)	379 (24.30)

mRC, metastatic rectal cancer; NOS, not otherwise specified; CEA, carcinoembryonic antigen; MCC, mucinous carcinoma; SRCC, signet ring cell carcinoma.

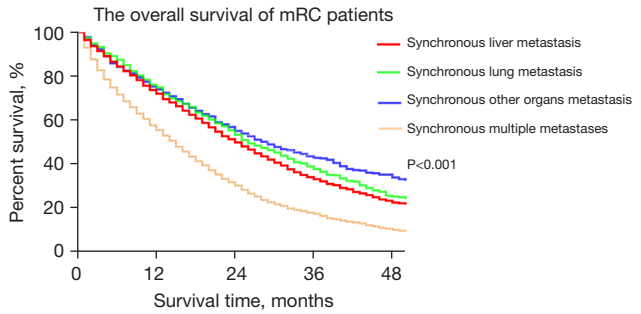

Figure 2 The K-M survival analysis of OS among different metastatic status. mRC, metastatic rectal cancer; K-M, Kaplan-Meier; OS, overall survival.

The C-indexes of the nomogram for lung metastasis patients were 0.742 (95% CI: 0.713–0.771) in the training and 0.716 (95% CI: 0.671–0.761) in the verification group. In addition, the AUCs for 1-, 2- and 3-year OS were 76.19%, 77.95%, 77.17% (the training cohort) and 74.41%, 76.29%, 72.23% (the verification cohort) (*Figure 4C*,*4D*).

The C-indexes of the OS nomogram for other sites metastasis were 0.722 (95% CI: 0.689–0.755) and 0.735 (95% CI: 0.691–0.779) in the training and verification cohort, respectively. The AUCs were 76.96%, 72.09%, 74.93% the training group and 84.47%, 76.79%, 74.81% in the verification group (*Figure 4E*,*4F*).

Similarly, for patients with multiple metastases, the C-indexes were 0.710 (95% CI: 0.699–0.722) and 0.713 (95% CI: 0.696–0.730) in the training and verification group. The AUCs for the nomogram in predicting 1-, 2- and 3-year OS were 75.33%, 75.18%, 73.04% the training group and 76.86%, 73.48%, 75.85%% in the verification cohort (*Figure 4G*,*4H*).

All calibration curves were close to the 45-degree line, indicating good calibration capability (*Figure 5*). Moreover, the DCA curves of these nomograms created in this study indicated superior net benefits, which demonstrating good clinical application significance (*Figure 6*).

Discussion

RC and colon cancer are usually studied as one entity. However, primary RC and colon cancer require different stages and different neoadjuvant therapies (for example, neoadjuvant radiotherapy or chemoradiotherapy is only used for rectal cancer), due to differences in anatomy and prognosis (17). Moreover, RC patients are more likely to have extra-abdominal metastases than patients with colon cancer because of venous drainage from the rectum into the systemic circulation (18). Most importantly, study has shown that there are significant differences in the prognosis of mRC patients with different metastatic status (8). Our research, consistent with previous studies (19,20), showed that the most common metastatic site of RC is the liver (39.02%), followed by the lung (8.17%). Similarly, the present study revealed that survival outcomes of mRC patients varied according to the metastatic status. Versus the patients with liver metastasis, the patients with isolated lung metastases manifested a significantly better OS. Also, an obviously worse OS was identified for the patients with multiple organ involvement compared with patients with a single metastatic site. So, this study explored the prognostic factors for mRC patients with different metastatic status and established the corresponding individualized prognostic nomograms.

In this study, a number of variables were identified as independent prognostic factors shared by each subgroup, including age at diagnosis, tumor grade, surgery for primary site and chemotherapy. The current treatment for mRC is mainly chemotherapy, and the improvement of chemotherapy has extended the survival time of mRC patients (8). The OS rate in CRC patients with and without chemotherapy was 62.1% and 40.4% in a retrospective study of stage IV CRC after therapeutic resection (13). Chemotherapy was the most sensitive predictor for the liver-limited metastasis group and the other sites-limited metastasis group in the current study. Even the 3-year OS of triple chemotherapy plus bevacizumab is only 40% (21), so chemotherapy alone seems to be insufficient. Our study indicated that surgery for the primary tumor is another independent prognostic variable for all mRC. Similarly, in a previous study, the status of no surgery was related with a 2.807-fold increased risk of death (22). Moreover, adequate lymph node removal seems to yield better survival outcomes than tumor removal alone. Combined with previous study (23), these findings suggested that patients with metastatic CRC should also try R0 resection and radical lymphadenectomy, if possible. However, the predictive sensitivity of surgery in each prognostic model was different. In patients with non-hepatic isolated metastases, especially isolated lung metastases, surgery is the most sensitive predictor in the current study. Lung metastases grow more slowly than liver metastases, which may provide a relatively sufficient time gap for patients to undergo surgery on the primary tumor and achieve a better

Table 2 Univariate and multivariate Cox regression model analysis of the nomograms of predicted OS for each group

Characteristics	Synchronous liver metastasis			Synchronous lung metastasis			Synchronous other organs metastasis			Synchronous multiple metastases		
	Univariable analysis	Multivariable analysis		Univariable analysis	Multivariable analysis		Univariable analysis	Multivariable analysis		Univariable analysis	Multivariable analysis	
	P	HR (95% CI)	P	P	HR (95% CI)	P	P	HR (95% CI)	P	P	HR (95% CI)	P
Insurance status	0.824	NA		0.021		0.106	0.022		0.226	0.426	NA	
Insured					Reference	1		Reference	1			
Uninsured/NOS					1.478 (0.920–2.374)	0.106		1.310 (0.846–2.027)	0.226			
Marital status	<0.001		<0.001	<0.001		0.091	0.054	NA		<0.001		0.089
Married		Reference	1		Reference	1					Reference	1
Unmarried/NOS		1.212 (1.098–1.339)	<0.001		1.227 (0.968–1.554)	0.091					1.076 (0.989–1.171)	0.089
Age at diagnosis	<0.001		<0.001	<0.001		<0.001	<0.001		0.005	<0.001		<0.001
≤50		Reference	1		Reference	1		Reference	1		Reference	1
51–65		1.094 (0.953–1.255)	0.202		0.920 (0.614–1.378)	0.685		1.224 (0.852–1.758)	0.275		1.143 (1.020–1.280)	0.021
>65		1.554 (1.350–1.789)	<0.001		1.605 (1.099–2.346)	0.014		1.670 (1.168–2.388)	0.005		1.470 (1.308–1.652)	<0.001
Race	0.022		0.690	0.354	NA		0.439	NA		0.003		0.018
White		Reference	1								Reference	1
Black		1.036 (0.888–1.208)	0.653								1.201 (1.056–1.366)	0.005
Other/NOS		0.943 (0.795–1.118)	0.496								1.059 (0.921–1.218)	0.420
Sex	0.613	NA		0.518	NA		0.652	NA		0.059	NA	
Female												
Male												
Grade	<0.001		<0.001	0.030		0.037	<0.001		<0.001	<0.001		<0.001
Grade I/II		Reference	1		Reference	1		Reference	1		Reference	1
Grade III/IV		1.742 (1.517–1.999)	<0.001		1.547 (1.099–2.177)	0.012		1.940 (1.458–2.582)	<0.001		1.671 (1.496–1.866)	<0.001
NOS		1.087 (0.959–1.232)	0.191		1.001 (0.748–1.340)	0.994		1.165 (0.840–1.615)	0.359		1.152 (1.039–1.278)	0.007
Histology	0.882	NA		0.467	NA		0.691	NA		0.069	NA	
Adenocarcinomas												
MCC/SRCC												
T stage	<0.001		<0.001	<0.001		<0.001	0.001		0.362	<0.001		0.036
T1-3		Reference	1		Reference	1		Reference	1		Reference	1
T4		1.324 (1.147–1.528)	<0.001		1.862 (1.366–2.537)	<0.001		1.188 (0.902–1.564)	0.220		1.153 (1.032–1.289)	0.012
Tx		1.125 (0.991–1.277)	0.068		1.214 (0.876–1.683)	0.245		1.213 (0.823–1.788)	0.330		1.077 (0.970–1.195)	0.163

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Synchronous liver metastasis			Synchronous lung metastasis			Synchronous other organs metastasis			Synchronous multiple metastases		
	Univariable analysis	Multivariable analysis		Univariable analysis	Multivariable analysis		Univariable analysis	Multivariable analysis		Univariable analysis	Multivariable analysis	
	P	HR (95% CI)	P	P	HR (95% CI)	P	P	HR (95% CI)	P	P	HR (95% CI)	P
N stage	<0.001		0.445	<0.001		0.833	0.003		0.674	<0.001		0.005
N0		Reference	1		Reference	1		Reference	1		Reference	1
N+		1.007 (0.900–1.128)	0.899		1.024 (0.780–1.344)	0.866		1.094 (0.830–1.443)	0.524		1.056 (0.959–1.164)	0.268
Nx		1.110 (0.943–1.307)	0.209		1.134 (0.753–1.709)	0.547		1.228 (0.716–2.107)	0.455		1.245 (1.092–1.420)	0.001
Surgery	<0.001		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001		<0.001
Standard proctectomy		Reference	1		Reference	1		Reference	1		Reference	1
Simplified proctectomy		1.116 (0.928–1.341)	0.245		1.415 (0.898–2.230)	0.135		1.483 (1.015–2.167)	0.041		1.368 (1.136–1.647)	0.001
Non-proctectomy		2.360 (2.066–2.696)	<0.001		2.690 (1.913–3.783)	<0.001		2.294 (1.693–3.110)	<0.001		1.873 (1.640–2.138)	<0.001
Radiation	<0.001		0.004	0.007		0.279	0.005		0.653	0.001		0.457
Yes		Reference	1		Reference	1		Reference	1		Reference	1
No		1.179 (1.053–1.319)	0.004		1.139 (0.900–1.442)	0.279		1.063 (0.815–1.387)	0.653		1.037 (0.942–1.142)	0.457
Chemotherapy	<0.001		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001		<0.001
Yes		Reference	1		Reference	1		Reference	1		Reference	1
No		2.644 (2.341–2.985)	<0.001		1.762 (1.360–2.283)	<0.001		2.178 (1.621–2.926)	<0.001		2.711 (2.456–2.991)	<0.001
CEA	<0.001		<0.001	0.541	NA		0.001		0.002	<0.001		0.001
Negative		Reference	1					Reference	1		Reference	1
Positive		1.512 (1.265–1.807)	<0.001					1.885 (1.330–2.672)	<0.001		1.322 (1.144–1.528)	<0.001
NOS		1.363 (1.125–1.651)	0.002					1.674 (1.165–2.404)	0.005		1.242 (1.063–1.451)	0.006
Bone metastasis		NA			NA			NA		<0.001		<0.001
No											Reference	1
Yes											1.416 (1.252–1.601)	<0.001
Brain metastasis		NA			NA			NA		<0.001		<0.001
No											Reference	1
Yes											1.833 (1.409–2.383)	<0.001
Liver metastasis		NA			NA			NA		0.007		0.017
No											Reference	1
Yes											1.134 (1.023–1.256)	0.017
Lung metastasis		NA			NA			NA		<0.001		0.117
No											Reference	1
Yes											1.074 (0.982–1.174)	0.117

OS, overall survival; NOS, not otherwise specified; mRC, metastatic rectal cancer; CEA, carcinoembryonic antigen; MCC, mucinous carcinoma; SRCC, signet ring cell carcinoma; CI, confidence interval; HR, hazard ratio; NA, not applicable.

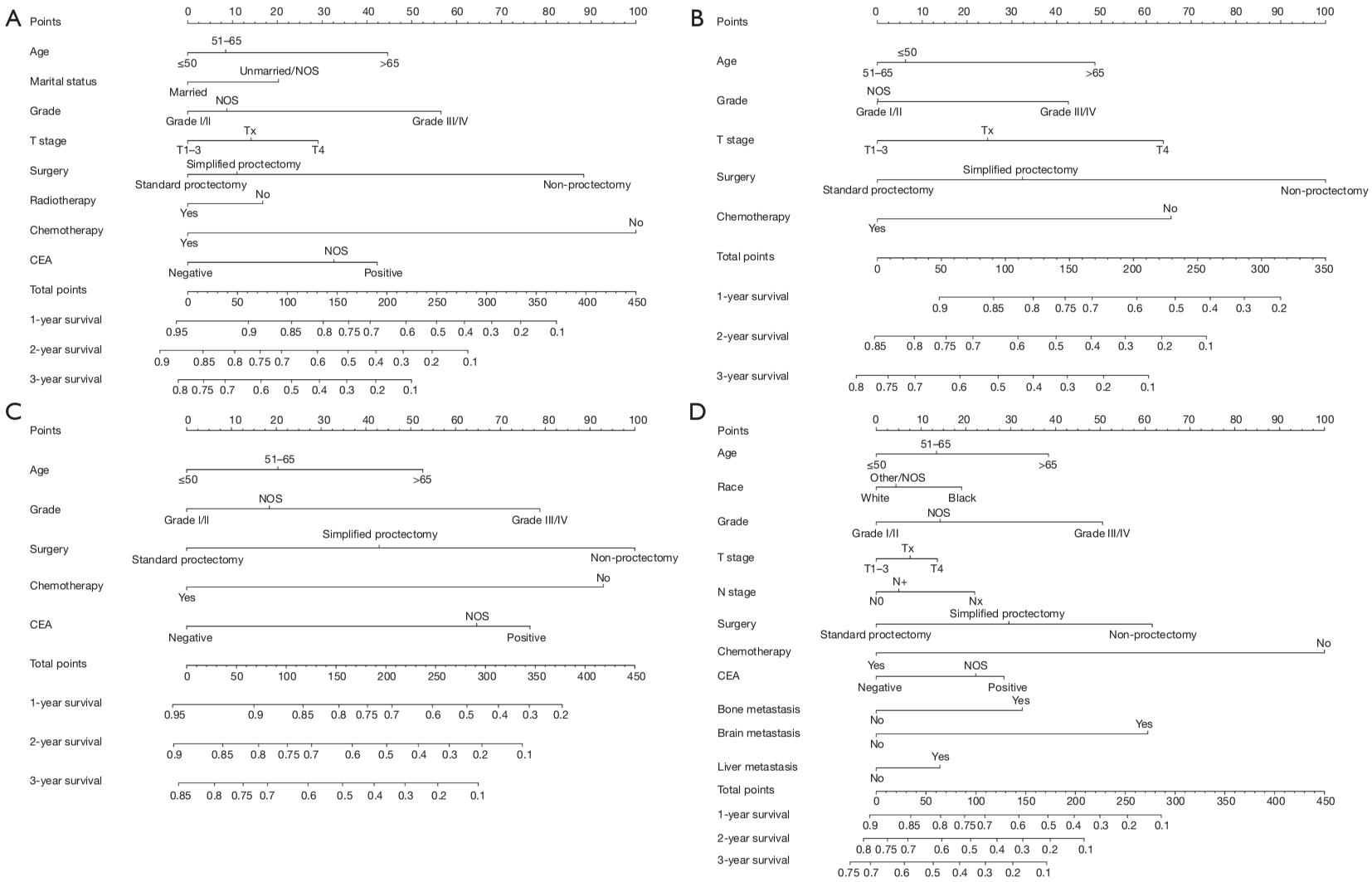

Figure 3 The nomograms predicting OS for mRC patients with different metastatic status. (A) Liver-limited metastasis group; (B) lung-limited metastasis group; (C) other sites-limited metastasis group; (D) multiple metastases group. CEA, carcinoembryonic antigen; NOS, not otherwise specified; OS, overall survival; mRC, metastatic rectal cancer.

Table 3 The C-indexes for predicting OS in each group

Groups	OS	
	C-index	95% CI
Synchronous liver metastasis		
Training group	0.742	0.729–0.754
Validation group	0.739	0.720–0.757
Synchronous lung metastasis		
Training group	0.742	0.713– 0.771
Validation group	0.716	0.671–0.761
Synchronous other organs metastasis		
Training group	0.722	0.689–0.755
Validation group	0.735	0.691–0.779
Synchronous multiple metastases		
Training group	0.710	0.699–0.722
Validation group	0.713	0.696–0.730

OS, overall survival; C-index, concordance index; CI, confidence interval.

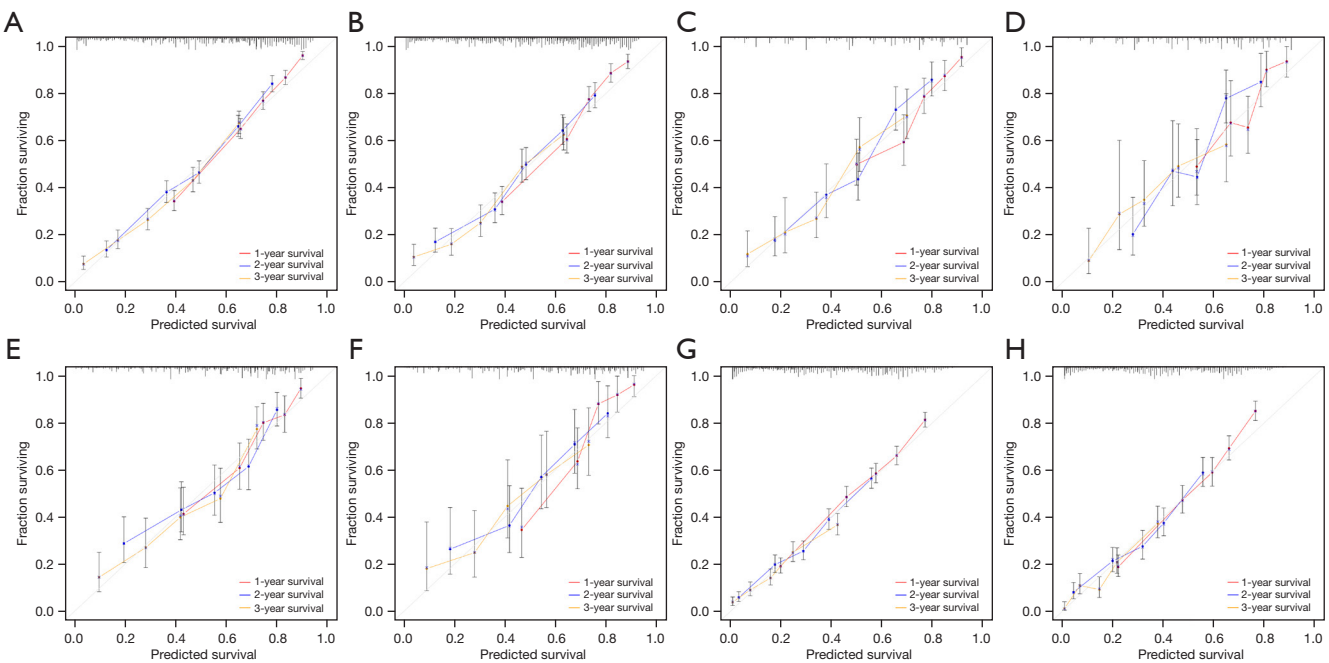

Figure 4 The calibration curves regarding the nomograms. (A) The training group of liver-limited metastasis; (B) the verification group of liver-limited metastasis; (C) the training group of lung-limited metastasis; (D) the verification group of lung-limited metastasis; (E) the training group of another sites-limited metastasis; (F) the verification group of another sites-limited metastasis; (G) the training group of multiple metastases; (H) the verification group of multiple metastases.

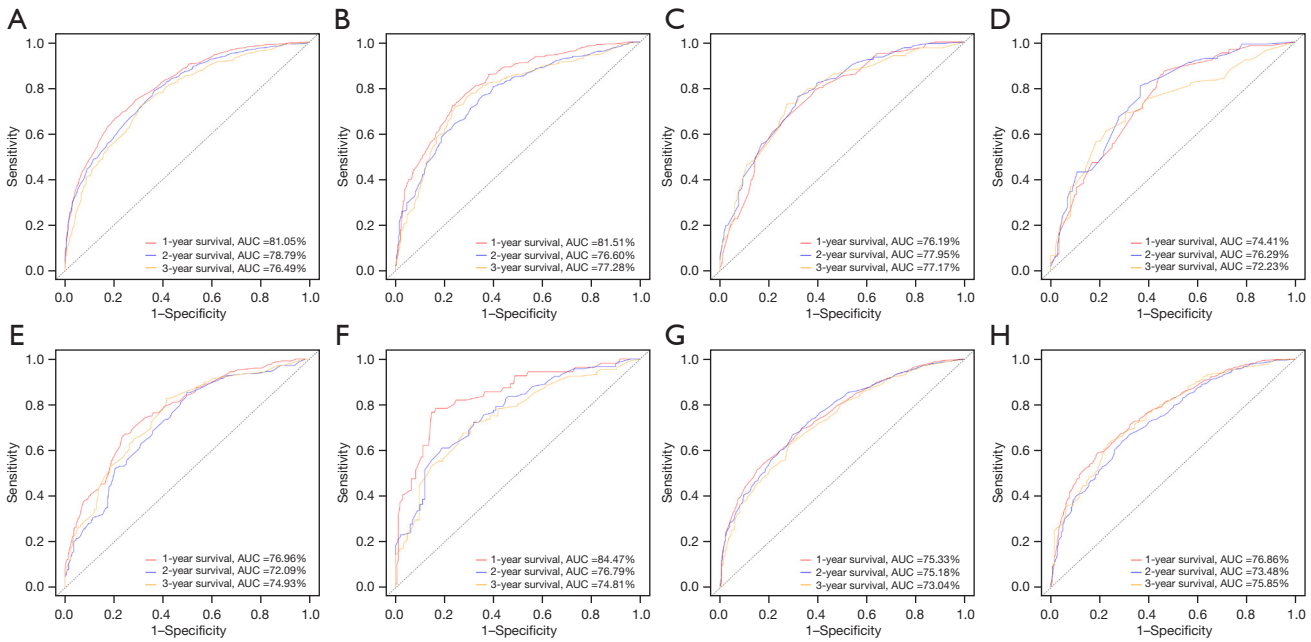

Figure 5 The AUC values of ROCs of the nomograms. (A) The training group of liver-limited metastasis; (B) the verification group of liver-limited metastasis; (C) the training group of lung-limited metastasis; (D) the verification group of lung-limited metastasis; (E) the training group of another sites-limited metastasis; (F) the verification group of another sites-limited metastasis; (G) the training group of multiple metastases; (H) the verification group of multiple metastases. AUC, area under the curve; ROC, receiver operating characteristic.

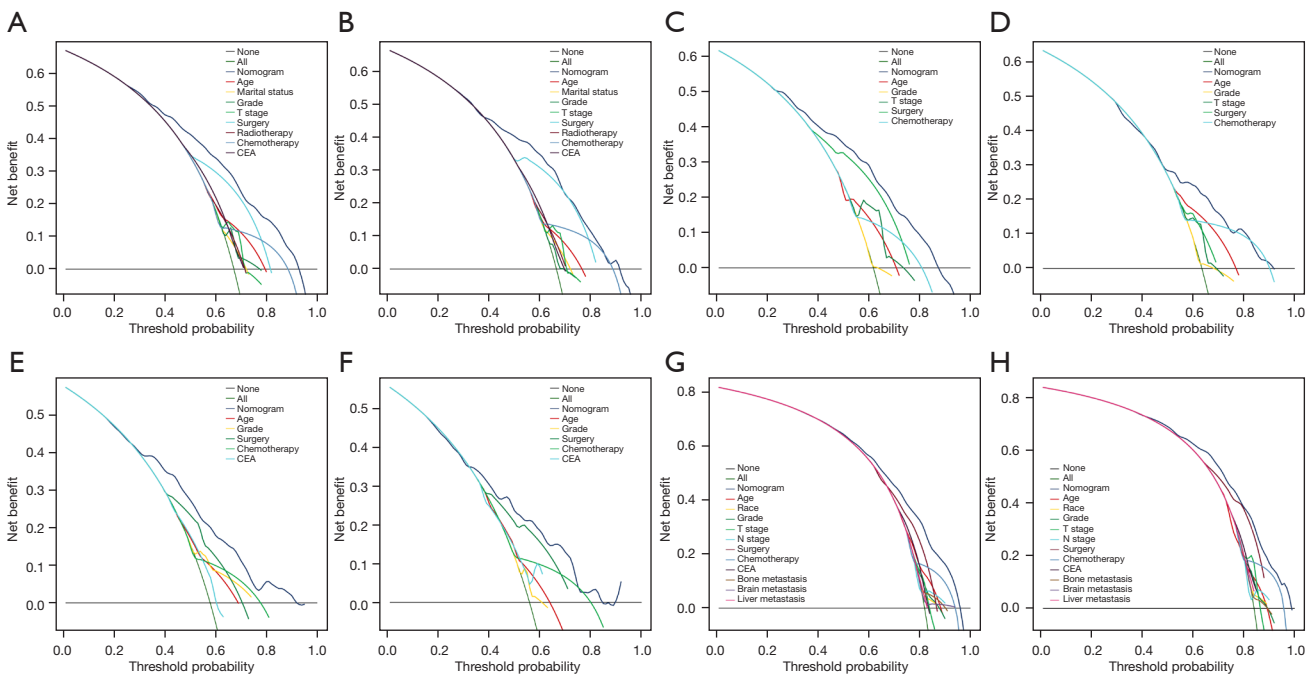

Figure 6 Decision curve analysis regarding the nomograms. (A) The training group of liver-limited metastasis; (B) the verification group of liver-limited metastasis; (C) the training group of lung-limited metastasis; (D) the verification group of lung-limited metastasis; (E) the training group of another sites-limited metastasis; (F) the verification group of another sites-limited metastasis; (G) the training group of multiple metastases; (H) the verification group of multiple metastases. CEA, carcinoembryonic antigen.

prognosis (24). Additionally, research confirmed surgical resection of CRC appears to be useful for distant metastases beyond the liver or lungs (25).

Radiotherapy and marital status were unique independent prognostic factors in patients with liver metastasis. Our study was the first to demonstrate that radiotherapy is an independent predictor of prognosis in patients with RC with liver metastasis and to include it in a predictive model. Systemic chemotherapy following short-term radiotherapy was demonstrated to be an effective and safe regimen in a retrospective study of RC patients with liver metastases in the Netherlands (26). Thus, multimodal therapy is associated with better survival in patients with liver metastasis. In addition, study confirmed that depression and stress are strongly associated with cancer-related deaths. Unmarried patients who are diagnosed with advanced cancer are more likely to develop depression and stress, leading to a poor prognosis (27). Some previous studies have reported that elevated CEA levels usually indicated a poor prognosis and were included in the prognosis model of CRC patients (28,29). In the present study, CEA was closely correlated with the prognosis of mRC patients in the other three groups except the lung metastasis group. In addition, consistent with other nomograms (30,31), higher T staging suggested worse OS in the group with liver, lung, and multiple site metastases.

Factors specific to the prognosis of mRC patients with multiple metastases included race, N stage, and the presence or absence of site-specific metastases. Previous study also confirmed that the black race seems to be associated with poorer OS compared to the white race (32). Similarly, higher N staging predicted worse survival (33). Furthermore, in the multi-site metastasis group, patients with brain metastasis had the worst prognosis, followed by patients with bone metastasis and liver metastasis.

Although previous models have been created to predict the prognosis of stage IV CRC, these nomograms have shortcomings. Firstly, most of these studies have been conducted in relatively small populations, such as fewer than 1,000 cases in both Liang's (34) and Beppu's nomograms (35). Secondly, previous nomograms for the mCRC patients after liver metastases resection were presented, but the C-index was relatively low (about 0.6) (28). Most important, the remaining studies missed important variables and did not stratify prediction models by metastatic status specifically for RC (15,16,36). Our study, to compensate for the above deficiencies, estimated more prognostic factors based on the SEER database with a larger sample size to reduce selection bias. Furthermore, specific nomograms for RC patients based on different metastatic status were tested by a variety of methods in this study. The C-index and AUC values of all the queues were greater than 0.7, indicating that the model had strong discrimination ability. The calibration curves and DAC curves proved that the model had good clinical practicability.

Although our research has certain advantages, it also has certain limitations inevitably. First, as a large retrospective study, there must be an inherent selection bias. Secondly, the SEER database does not provide the specific regimen, quantity and toxic and side effects of chemotherapy and radiotherapy. Moreover, the database only provides the site of metastases, and there is no specific data on the number of metastases. Therefore, it is impossible to determine whether it is oligometastatic cancer, which is of great significance for clinical treatment. Additionally, the expression status of several important biomarkers closely associated with rectal cancer metastasis, such as MSI, RAS, and BRAF, could not be obtained from the SEER database.

Conclusions

Individualized prognostic nomograms were constructed for mRC patients with different metastatic status based on different prognostic factors. These nomograms presented satisfactory predictive effects, which helps to provide survival assessment and individualized treatment decision-making for mRC patients with different metastatic status.

Acknowledgments

The authors acknowledge the efforts of the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of this database.
Funding: Dan Wang has received funding from the China Scholarship Council.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-436/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.

com/article/view/10.21037/tcr-22-436/coif). DW reports funding from China Scholarship Council. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Approval from the ethical board for this study was not required because of the public nature of all the data.

References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer Statistics, 2021. CA Cancer J Clin 2021;71:7-33.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
3. Qiu M, Hu J, Yang D, et al. Pattern of distant metastases in colorectal cancer: a SEER based study. Oncotarget 2015;6:38658-66.
4. Nordholm-Carstensen A, Krarup PM, Jorgensen LN, et al. Occurrence and survival of synchronous pulmonary metastases in colorectal cancer: a nationwide cohort study. Eur J Cancer 2014;50:447-56.
5. Riley JM, Cross AW, Paulos CM, et al. The clinical implications of immunogenomics in colorectal cancer: A path for precision medicine. Cancer 2018;124:1650-9.
6. Lee RM, Cardona K, Russell MC. Historical perspective: Two decades of progress in treating metastatic colorectal cancer. J Surg Oncol 2019;119:549-63.
7. Provenzale D, Gupta S, Ahnen DJ, et al. NCCN Guidelines Insights: Colorectal Cancer Screening, Version 1.2018. J Natl Compr Canc Netw 2018;16:939-49.
8. Luo D, Liu Q, Yu W, et al. Prognostic value of distant metastasis sites and surgery in stage IV colorectal cancer: a population-based study. Int J Colorectal Dis 2018;33:1241-9.
9. Yang L, Yang X, He W, et al. Comparisons of metastatic patterns of colorectal cancer among patients by age group: a population-based study. Aging (Albany NY) 2018;10:4107-19.
10. Sudo M, Furuya S, Shimizu H, et al. Long-term outcomes after surgical resection in patients with stage IV colorectal cancer: a retrospective study of 129 patients at a single institution. World J Surg Oncol 2019;17:56.
11. Sato H, Maeda K, Morise Z, et al. Clinical outcomes of stage IV colorectal cancer after R0 resection: a multi-institutional retrospective analysis. Int J Clin Oncol 2017;22:297-306.
12. Suthananthan AE, Bhandari M, Platell C. Influence of primary site on metastatic distribution and survival in stage IV colorectal cancer. ANZ J Surg 2018;88:445-9.
13. Huh JW, Lee WY, Park YA, et al. Prognostic factors associated with primary cancer in curatively resected stage IV colorectal cancer. J Cancer Res Clin Oncol 2014;140:435-41.
14. Bonnett LJ, Snell KIE, Collins GS, et al. Guide to presenting clinical prediction models for use in clinical settings. BMJ 2019;365:l737.
15. Liu Z, Xu Y, Xu G, et al. Nomogram for predicting overall survival in colorectal cancer with distant metastasis. BMC Gastroenterol 2021;21:103.
16. Ge Y, Xiang R, Ren J, et al. A Nomogram for Predicting Multiple Metastases in Metastatic Colorectal Cancer Patients: A Large Population-Based Study. Front Oncol 2021;11:633995.
17. Tamas K, Walenkamp AM, de Vries EG, et al. Rectal and colon cancer: Not just a different anatomic site. Cancer Treat Rev 2015;41:671-9.
18. Hugen N, van de Velde CJH, de Wilt JHW, et al. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. Ann Oncol 2014;25:651-7.
19. Bhullar DS, Barriuso J, Mullamitha S, et al. Biomarker concordance between primary colorectal cancer and its metastases. EBioMedicine 2019;40:363-74.
20. Zong Z, Zhou TC, Tang FX, et al. Impact of Site-Specific Metastases on Surgical Value and Survival among Metastatic Colorectal Cancer Patients. Am Surg 2020;86:220-7.
21. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as

first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol 2015;16:1306-15.
22. Ge H, Yan Y, Xie M, et al. Construction of a nomogram to predict overall survival for patients with M1 stage of colorectal cancer: A retrospective cohort study. Int J Surg 2019;72:96-101.
23. Matsui S, Okabayashi K, Hasegawa H, et al. Effect of high ligation on survival of patients undergoing surgery for primary colorectal cancer and synchronous liver metastases. BJS Open 2020;4:508-15.
24. Prasanna T, Karapetis CS, Roder D, et al. The survival outcome of patients with metastatic colorectal cancer based on the site of metastases and the impact of molecular markers and site of primary cancer on metastatic pattern. Acta Oncol 2018;57:1438-44.
25. Naito A, Kagawa Y, Kawai K, et al. Surgical Resection of Colorectal Cancer With Distant Metastases to Other than Liver or Lung. In Vivo 2019;33:1605-8.
26. Kok END, Havenga K, Tanis PJ, et al. Multicentre study of short-course radiotherapy, systemic therapy and resection/ablation for stage IV rectal cancer. Br J Surg 2020;107:537-45.
27. Guan NC, Termorshuizen F, Laan W, et al. Cancer mortality in patients with psychiatric diagnoses: a higher hazard of cancer death does not lead to a higher cumulative risk of dying from cancer. Soc Psychiatry Psychiatr Epidemiol 2013;48:1289-95.
28. Kawai K, Ishihara S, Yamaguchi H, et al. Nomograms for predicting the prognosis of stage IV colorectal cancer after curative resection: a multicenter retrospective study. Eur J Surg Oncol 2015;41:457-65.
29. Das V, Kalita J, Pal M. Predictive and prognostic biomarkers in colorectal cancer: A systematic review of recent advances and challenges. Biomed Pharmacother 2017;87:8-19.
30. Zhang ZY, Luo QF, Yin XW, et al. Nomograms to predict survival after colorectal cancer resection without preoperative therapy. BMC Cancer 2016;16:658.
31. Kobayashi H, Kotake K, Sugihara K. Prognostic scoring system for stage IV colorectal cancer: is the AJCC sub-classification of stage IV colorectal cancer appropriate? Int J Clin Oncol 2013;18:696-703.
32. Zhang J, Gong Z, Gong Y, et al. Development and validation of nomograms for prediction of overall survival and cancer-specific survival of patients with Stage IV colorectal cancer. Jpn J Clin Oncol 2019;49:438-46.
33. Wang X, Mao M, Xu G, et al. The incidence, associated factors, and predictive nomogram for early death in stage IV colorectal cancer. Int J Colorectal Dis 2019;34:1189-201.
34. Liang JY, Lin HC, Liu J, et al. A novel prognostic nomogram for colorectal cancer liver metastasis patients with recurrence after hepatectomy. Cancer Med 2021;10:1535-44.
35. Beppu T, Sakamoto Y, Hasegawa K, et al. A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a Project Study for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci 2012;19:72-84.
36. Li M, Li X, Guo Y, et al. Development and assessment of an individualized nomogram to predict colorectal cancer liver metastases. Quant Imaging Med Surg 2020;10:397-414.

Cite this article as: Ge H, Zhou Z, Li Y, Wang D, Güngör C. Prognostic factors and individualized nomograms predicting overall survival in stage IV rectal cancer patients with different metastatic status: a SEER-based study. Transl Cancer Res 2022;11(9):3141-3155. doi: 10.21037/tcr-22-436

