



# Pattern of distant metastases and predictive nomograms in colorectal mucinous adenocarcinoma: a SEER analysis

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**Background:** We evaluated the metastatic patterns and explored the prognostic value of distant metastasis pattern in patients with metastatic colorectal mucinous adenocarcinoma (MC) using the Surveillance, Epidemiology, and End Results (SEER) database.

**Methods:** Between 2010 and 2015, newly diagnosed colorectal MC patients were selected using the SEER database. Patient prognosis was compared based on the clinicopathological parameters, treatment method, and the site and number of metastatic organs. Cox analyses were used to identify factors associated with overall survival (OS). A nomogram was built to predict the patient's survival. Harrell's concordance index (c-index) and calibration curves were used to analyze the discriminative ability of the prognostic factors.

**Results:** Of 3,088 patients diagnosed with colorectal MC, the liver was the only metastatic organ in 78.4% (997/1,271) of all liver metastasis cases, the lung was the only metastatic organ in 41.0% (164/400) of all lung metastasis cases, bone was the only metastatic organ in 26.6% (29/109) of all bone metastasis cases, and the brain was the only metastatic organ in 23.5% (4/17) of all brain metastasis cases. Compared with the untreated cases, those treated with chemotherapy, surgery, and radiotherapy had better OS ( $P < 0.001$ ). There were marked OS differences ( $P < 0.001$ ) between patients with and without liver and bone metastases. Patients with bone metastasis had the best survival, while those with brain metastasis had the worst survival ( $P < 0.001$ ). Patients with one metastatic site had better prognosis compared to those with two or three ( $P < 0.001$ ). Patients with liver metastasis had the best survival, while those with bone and brain metastasis had the worst survival ( $P < 0.001$ ). Multivariate analysis showed that age  $< 65$  years, non-black race, grade I, N0 stage, chemotherapy, radiation, surgery, liver metastasis, and bone metastasis were independent prognostic factors. A nomogram was constructed to predict survival probability. The c-index value was up to 0.745. The calibration plot showed that the nomogram was clinically useful.

**Conclusions:** Metastatic MC (mMC) patients had a characteristic distant metastasis pattern. This study constructed a new and sufficiently accurate prognostic model of mMC based on population-based data. These findings can be utilized to predict prognosis and guide mMC patient management.

**Keywords:** Colorectal cancer (CRC); mucinous adenocarcinoma (MC); distant metastases; nomogram; Surveillance, Epidemiology, and End Results (SEER)

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## Introduction

Colorectal cancer (CRC) is a leading cause of morbidity and mortality worldwide (1). There is mounting evidence that the incidence of CRC is increasing, and approximately half of CRC patients develop distant metastasis (2). CRC classification is based on histology. Adenocarcinoma (AC) accounts for 85% of CRCs, while mucinous adenocarcinoma (MC) accounts for 10–15%. MC is characterized by abundant mucus secretion that accounts for at least 50% of tumor volume (3). Mucinous colorectal AC more frequently affects the proximal colon than the rectum or distal colon (4). It is known that relative to non-MC, MC is associated with advanced stage and distant metastases at diagnosis (5). However, the clinicopathological features and metastasis pattern of MC are controversial, which complicates treatment strategy (6–8). Thus, better understanding of the clinicopathological characteristics of MC, especially its metastasis pattern and prognostic factors, is needed.

With the exception of chemotherapy, few studies have examined the treatment of metastatic MC (mMC) with radiotherapy and surgery (9). Moreover, there are no reliable guidelines on mMC management. Thus, it is necessary to study the factors affecting MC treatment.

Based on the Surveillance, Epidemiology, and End Results (SEER) database, we systematically summarized the clinicopathological features and metastasis patterns of mMC patients. We also performed Cox regression analysis of the prognostic factors and subgroup survival analysis of these patients. We then constructed a survival prediction nomogram of the metastasis patterns. We present the following article in accordance with the TRIPOD reporting checklist (available at <https://dx.doi.org/10.21037/jgo-21-824>).

## Methods

### Data collection

We used SEER datasets released in November 2016, which included additional treatment fields. Strict quality control is maintained by the SEER Quality Improvement Program, which establishes standards for cancer registries and

maintains them through continual monitoring, assessment, and education. Since SEER is publicly available, the use of its data does not require the informed consent of patients or ethical approval.

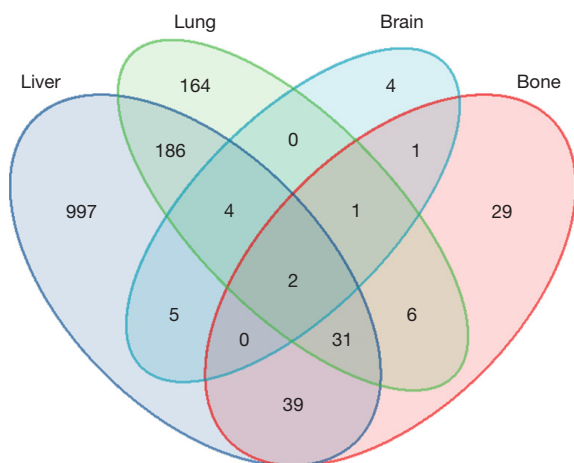
The following criteria were used to identify eligible patients: (I) those diagnosed between 2010 and 2015; (II) primary site was colorectal MC according to the 3<sup>rd</sup> edition of the International Classification of Diseases for Oncology [ICD-O-3/World Health Organization (WHO) 2008]; (III) diagnosis confirmed by histopathology; and (IV) tumor staging performed according to the American Joint Committee on Cancer (AJCC) (7<sup>th</sup> edition). Patients lacking sufficient survival data, those whose first malignant primary tumor was not colon MC, and those with a survival of <1 month were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### Participant variables and outcomes

The following clinicopathological parameters were analyzed: year of diagnosis [2010–2015], age (<65, ≥65 years), gender (female, male), race (black, white, and others), primary site (left-sided colon, right-sided colon, and unknown), grade (grade I/II, grade III/IV, and unknown), AJCC T-stage (T0–4, Tx), N-stage (N0–2, Nx), chemotherapy (no, yes), radiotherapy (no, yes), surgery (no, yes), liver metastasis (no, yes), bone metastasis (no, yes), lung metastasis (no, yes), and brain metastasis (no, yes). Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause or last follow-up.

### Statistical analysis

MC patients were classified by metastases site (liver, bone, lung, and brain). The Chi-square test was used to compare the clinicopathological characteristics among different metastasis sites. Survival analysis was performed using Kaplan–Meier analysis and survival differences between groups were evaluated using the log-rank test. A multivariate Cox proportional hazards model was used to determine the independent prognostic factors, and associated hazard ratios (HRs) with corresponding 95%



**Figure 1** Venn diagrams showing the overlap of the four main types of metastatic organs in MC. MC, mucinous adenocarcinoma.

confidence interval (CI) were generated. A nomogram based on these prognostic factors was then generated for predicting OS. Harrell's concordance-index (C index) was used to evaluate the predictive performance of the nomogram. The nomogram was used to evaluate the consistency of prediction and observation probability. All statistical analyses were performed using R (version 4.0.4, [www.r-project.org](http://www.r-project.org)). Statistical significance was set at two-sided  $P < 0.05$ .

## Results

### Patient characteristics

Of the 3,088 patients diagnosed with MC CRC between 2010 and 2015, 1,636 (53.0%) were <65 years old, 1,504 (48.7%) were male, and 1,584 (51.3%) were female. The primary tumor locations were as follows: 921 (39.8%) had left-side colon cancer, while 1,940 (62.8%) had right-side colon cancer. Also, 1,271 (41.2%) had initial liver metastasis, 400 (13.0%) had initial lung metastasis, 109 (3.5%) had initial bone metastasis, and 17 (0.6%) had initial brain metastasis (Figure 1).

The liver metastasis group was more likely to be >65 years old, black race, have a left side primary tumor, grade II, a lower T stage, and an advanced N stage. A lower proportion of patients with liver metastasis received surgery relative to those with non-liver metastasis. The bone metastasis group was more likely to have left side primary and lower T stage. A higher proportion of those

with bone metastasis received radiotherapy relative to those without bone metastasis. Those with lung metastasis were more likely to be >65 years old, have a left side primary tumor, a lower T stage, and an advanced N stage. A higher proportion of those with lung metastasis received radiation relative to those without lung metastasis. The brain metastasis group was more likely to be Nx tumor stage. A higher proportion of those with brain metastasis received radiation relative to those without brain metastasis (Table 1).

### The pattern of metastases in MC

To explore the proportions of the four main types of metastatic organs, Venn diagrams were used to illustrate the relationship between different co-metastases in mMC patients. Among the 3,088 MC patients, 1,797 patients (58.2%) had other metastasis. The liver was the only metastatic organ in 997/1,271 (78.4%) of all liver metastasis cases. The lung was the only metastatic organ in 164/400 (41.0%) of all lung metastasis cases. The bone was the only metastatic organ in 29/109 (26.6%) of all bone metastasis cases. The brain was the only metastatic organ in 4/17 (23.5%) of all brain metastasis cases. It is worth noting that the liver and lung were the most common co-metastases sites, while bone and brain were the least common co-metastases sites.

### Multivariate analysis

Multivariate analysis showed that being <65 years, being non-black, grade I, N0 stage, chemotherapy, radiation, tumor surgery, and liver and bone metastasis were independent prognostic factors. Compared to those aged <65, patients aged  $\geq 65$  had worse OS (HR =1.53, 95% CI: 1.40–1.67,  $P < 0.001$ ). Furthermore, compared to black race patients, patients with white or other races had better OS (white race: HR =0.87, 95% CI: 0.77–0.98,  $P = 0.023$ ; other race: HR =0.80, 95% CI: 0.66–0.97,  $P = 0.025$ ). Moreover, compared to untreated patients, those treated with chemotherapy, radiotherapy, and tumor surgery had better OS (chemotherapy: HR =0.40, 95% CI: 0.37–0.44,  $P < 0.001$ ; radiotherapy: HR =0.58, 95% CI: 0.46–0.72,  $P < 0.001$ ; surgery: HR =0.36, 95% CI: 0.31–0.42,  $P < 0.001$ ). Compared to non-metastatic patients, those with liver and bone metastases had worse OS (liver: HR =1.46, 95% CI: 1.34–1.60,  $P < 0.001$ ; bone: HR =1.66, 95% CI: 1.34–2.05,  $P < 0.001$ , Table 2).

**Table 1** Baseline clinicopathological features of patients with colorectal mucinous adenocarcinoma stratified by pattern of distant metastases in SEER data sets

Characteristic	Liver metastasis, N [%]		Bone metastasis, N [%]		Lung metastasis, N [%]		Brain metastases, N [%]	
	No	Yes	No	Yes	No	Yes	No	Yes
Age								
<65 years	1,024 [56]	612 [48]	1,580 [53]	56 [51]	1,474 [55]	162 [40]	1,627 [53]	9 [53]
≥65 years	793 [44]	659 [52]	1,399 [47]	53 [49]	1,214 [45]	238 [60]	1,444 [47]	8 [47]
Gender								
Male	860 [47]	644 [51]	1,447 [49]	57 [52]	1,305 [49]	199 [50]	1,498 [49]	6 [35]
Female	957 [53]	627 [49]	1,532 [51]	52 [48]	1,383 [51]	201 [50]	1,573 [51]	11 [65]
Race								
White	1,456 [80]	985 [77]	2,361 [79]	80 [73]	2,135 [79]	306 [76]	398 [13]	1 [6]
Black	199 [11]	200 [16]	379 [13]	20 [18]	337 [13]	62 [16]	398 [13]	1 [6]
Other	162 [9]	86 [7]	239 [8]	9 [8]	216 [8]	32 [8]	247 [8]	1 [6]
Site of the primary								
Left	455 [25]	466 [37]	876 [29]	45 [41]	747 [28]	174 [44]	916 [30]	5 [29]
Right	1,236 [68]	704 [55]	1,890 [63]	50 [46]	1,762 [66]	178 [44]	1,929 [63]	11 [65]
Large intestine NOS	126 [7]	101 [8]	213 [7]	14 [13]	179 [7]	48 [12]	226 [7]	1 [6]
Grade								
Grade I	304 [17]	86 [7]	386 [13]	4 [4]	363 [14]	27 [7]	388 [13]	2 [12]
Grade II	658 [36]	594 [47]	1,221 [41]	31 [28]	1,086 [40]	166 [42]	1,248 [41]	4 [24]
Grade III	311 [17]	195 [15]	488 [16]	18 [17]	456 [17]	50 [13]	502 [16]	4 [24]
Grade IV	95 [5]	60 [5]	153 [5]	2 [2]	142 [5]	13 [3]	154 [5]	1 [6]
Unknown	449 [25]	336 [26]	731 [25]	54 [50]	641 [24]	144 [36]	779 [25]	6 [35]
T stage								
T0	23 [1.3]	15 [1.2]	34 [1.1]	4 [3.7]	28 [1.0]	10 [2.5]	37 [1.2]	1 [5.9]
T1	60 [3.3]	60 [4.7]	107 [3.6]	13 [11.9]	94 [3.5]	26 [6.5]	119 [3.9]	1 [5.9]
T2	18 [1.0]	25 [2.0]	41 [1.4]	2 [1.8]	33 [1.2]	10 [2.5]	42 [1.4]	1 [5.9]
T3	332 [18.3]	412 [32.4]	727 [24.4]	17 [15.6]	630 [23.4]	114 [28.5]	740 [24.1]	4 [23.5]
T4	1,087 [59.8]	522 [41.1]	1,575 [52.9]	34 [31.2]	1,473 [54.8]	136 [34.0]	1,604 [52.2]	5 [29.4]
TX	297 [16.3]	237 [18.6]	495 [16.6]	39 [35.8]	430 [16.0]	104 [26.0]	529 [17.2]	5 [29.4]

**Table 1** (continued)



**Table 2** Univariable and multivariate Cox regression analysis for OS in patients with colorectal mucinous adenocarcinoma

Variables	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age						
<65 years	–	–		–	–	
≥65 years	1.81	1.66, 1.97	<0.001	1.53	1.40, 1.67	<0.001
Gender						
Female	–	–		–	–	
Male	1.13	1.04, 1.23	0.003	1.08	0.99, 1.17	0.094
Race						
Black	–	–		–	–	
Other	0.80	0.66, 0.97	0.020	0.80	0.66, 0.97	0.025
White	0.86	0.76, 0.97	0.014	0.87	0.77, 0.98	0.023
Site of the primary						
Large intestine	–	–		–	–	
Left	0.63	0.53, 0.73	<0.001	0.92	0.77, 1.10	0.300
Right	0.46	0.39, 0.53	<0.001	0.80	0.68, 0.95	0.011
Grade						
Grade I	–	–		–	–	
Grade II	2.18	1.85, 2.57	<0.001	1.73	1.45, 2.05	<0.001
Grade III	3.06	2.56, 3.66	<0.001	2.11	1.75, 2.56	<0.001
Grade IV	2.41	1.90, 3.05	<0.001	1.87	1.46, 2.40	<0.001
Unknown	3.45	2.91, 4.09	<0.001	1.57, 2.31	1.57, 2.31	<0.001
T stage						
T0	–	–		–	–	
T1	1.01	0.66, 1.54	0.97	1.28	0.83, 1.99	0.300
T2	0.74	0.44, 1.25	0.26	1.25	0.73, 2.15	0.400
T3	0.76	0.52, 1.11	0.15	1.04	0.70, 1.57	0.800
T4	0.72	0.49, 1.04	0.082	1.32	0.89, 1.97	0.200
TX	1.21	0.82, 1.77	0.34	1.14	0.77, 1.68	0.500
N stage						
N0	–	–		–	–	
N1	1.60	1.43, 1.79	<0.001	1.66	1.47, 1.87	<0.001
N2	2.03	1.83, 2.26	<0.001	2.57	2.26, 2.91	<0.001
NX	2.03	1.75, 2.35	<0.001	1.15	0.98, 1.35	0.089
Chemotherapy						
No	–	–		–	–	
Yes	0.48	0.44, 0.52	<0.001	0.40	0.37, 0.44	<0.001

**Table 2** (continued)

Table 2 (continued)

Variables	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Radiation						
No	–	–		–	–	
Yes	0.59	0.47, 0.73	<0.001	0.58	0.46, 0.72	<0.001
Surgery						
No	–	–		–	–	
Yes	0.43	0.39, 0.47	<0.001	0.36	0.31, 0.42	<0.001
Liver metastasis						
No	–	–		–	–	
Yes	1.63	1.50, 1.78	<0.001	1.46	1.34, 1.60	<0.001
Bone metastasis						
No	–	–		–	–	
Yes	2.12	1.73, 2.60	<0.001	1.66	1.34, 2.05	<0.001
Lung metastasis						
No	–	–		–	–	
Yes	1.61	1.44, 1.81	<0.001	1.09	0.96, 1.23	0.200
Brain metastases						
No	–	–		–	–	
Yes	1.88	1.13, 3.13	0.015	1.79	1.06, 3.01	0.028

OS, overall survival; HR, hazard ratio; CI, confidence interval.

site metastases. Our findings confirmed that MC predominantly metastasizes to the liver, followed by the lung, while the incidence of bone and brain metastases was much lower. Previous studies have also reported that the incidence of bone and brain metastases is 10–15% and 1–3%, respectively, in CRC patients (10,11). In this study, we observed a lower incidence of brain metastasis incidence (0.55%).

MC patients have been reported to have higher rates of right/transverse colon cancer (12), which is consistent with our results. Moreover, we found that right side primary MC patients had a higher incidence rate of liver, lung, bone, and brain metastases. Numerous studies have shown significant epidemiological, clinical, and histological differences in left versus right CRC (13). Comprehensive analysis of the four metastasis sites showed that metastasis was more likely to be low T stage and advanced N stage. We speculate that advanced N stage indicates an increased risk of metastasis.

We also found statistically significant differences in race

distribution for liver metastases, and age distribution for liver and lung metastases. Race differences may be explained by disparities in access to health care, while the impact of age may be due to differences in baseline physical condition and comorbidities (14).

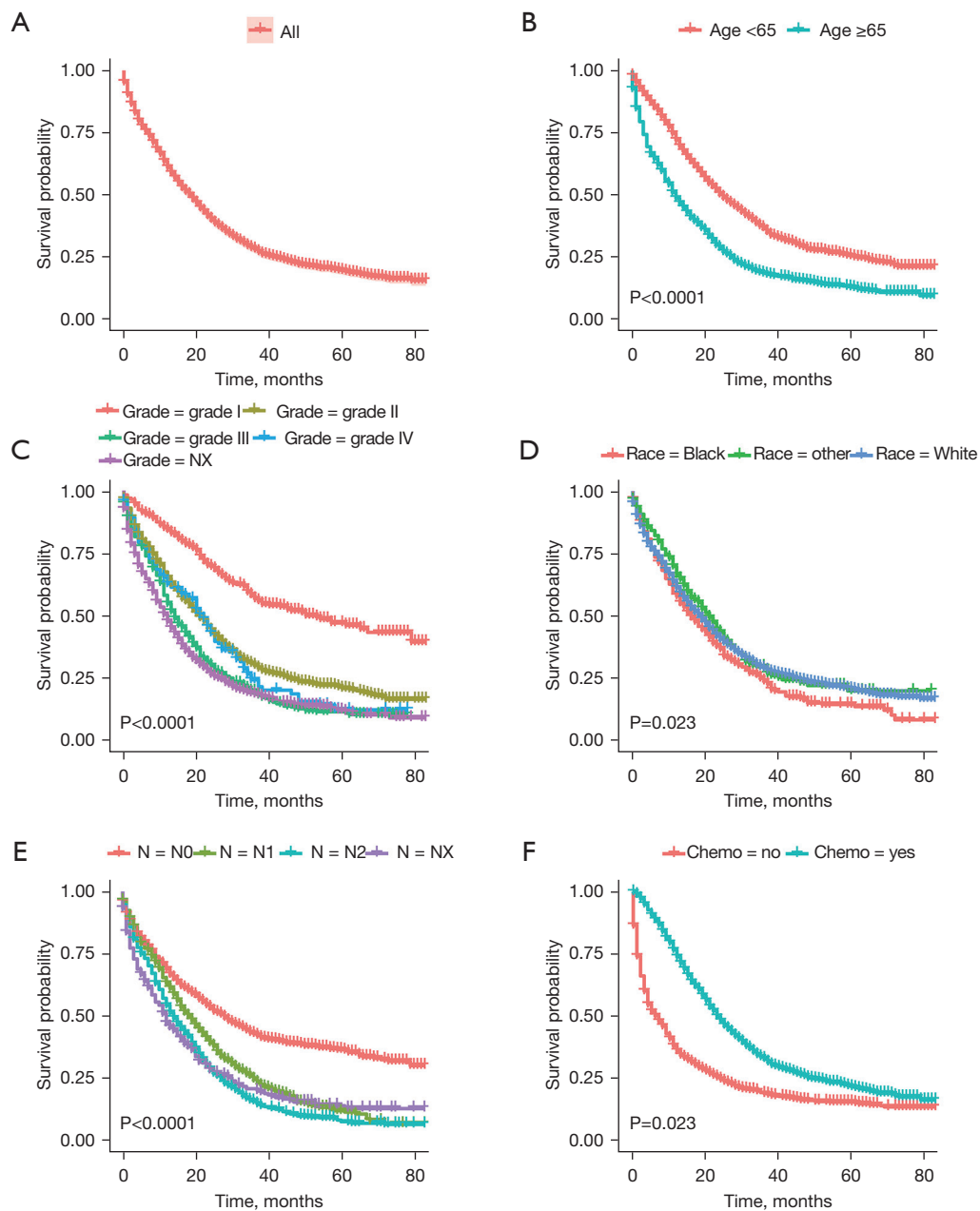
Chemotherapy is the main treatment for mMC, although surgical resection and radiotherapy are also used (9). Ott *et al.* proposed that combined chemotherapy protocols are effective for patients with mMC (15). In this subtype, mucus around the tumor cells may be a physical barrier to drugs. Additionally, there is a protective layer of extracellular mucin around metastatic foci in advanced MC patients. Furthermore, a large amount of mucus around the tumor causes abnormal microvascular development, which may reduce drug delivery. Moreover, compressive force (solid stress) from the giant mucinous tumor on the vascular system may further reduce drug delivery to the tumor. The development of chemotherapeutic agents that overcome these may improve MC treatment outcomes. For instance,

nanoparticle drug carriers that can cross the mucosal barrier may improve the efficacy of chemotherapy against MC (16). Drugs targeting the mucus layer itself may also provide another effective choice for systemic therapy (17).

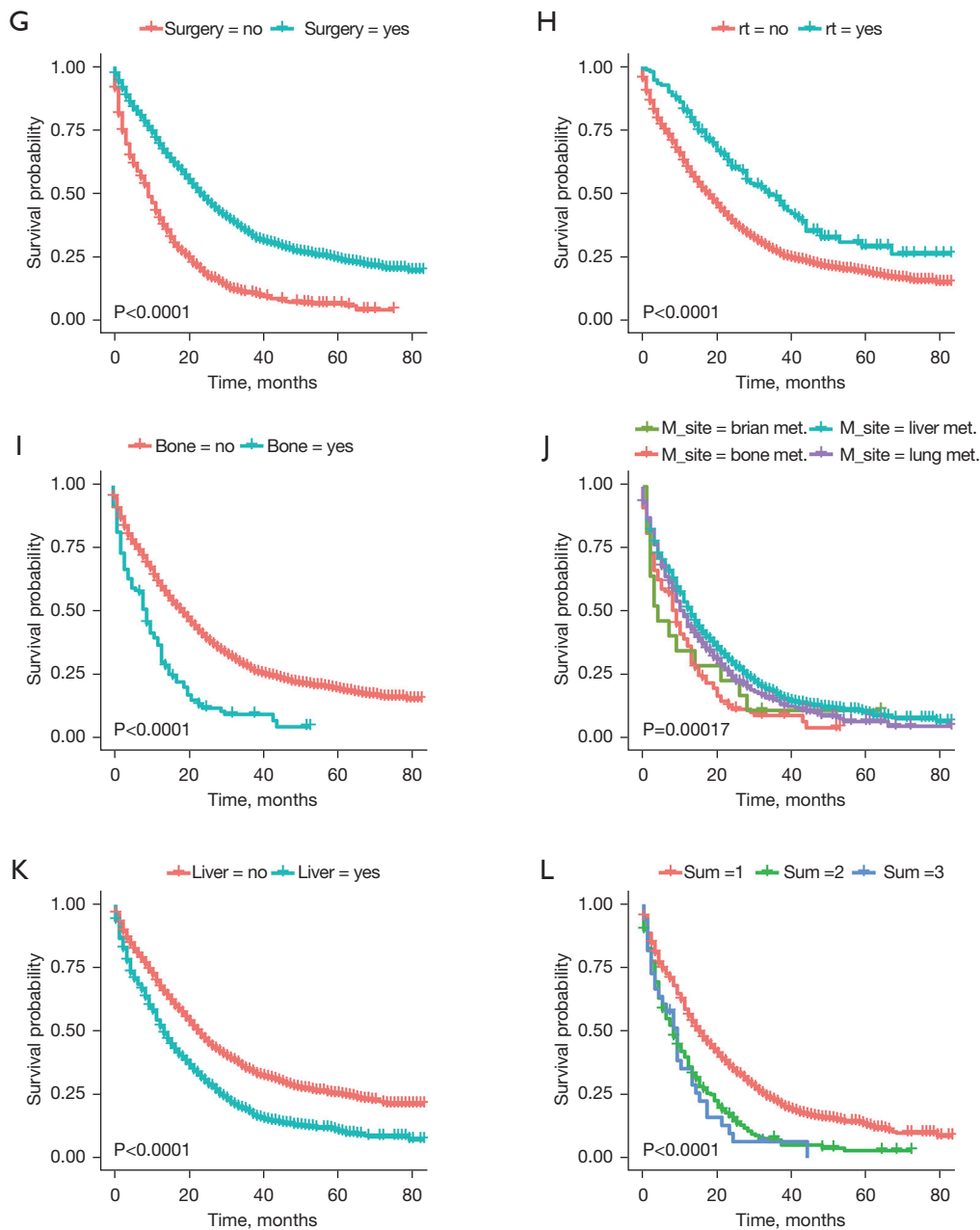
In-depth subgroup analysis of factors affecting therapy found that OS was significantly improved in patients who were recommended for chemotherapy, radiotherapy, and surgery. Multiple organ resection improves OS without increasing short-term mortality (18). Thus, appropriate

surgery is critical to improving OS in mMC patients. Similarly, we found that radiotherapy, which is often used in patients with left colon cancer and rectal cancer, confers survival benefits. Our findings showed that chemotherapy, radiotherapy, and surgery are protective factors in MC.

Of these treatments, surgery may be the most important. A previous retrospective study suggested that surgical resection of primary tumors and synchronous liver metastasis was always unnecessary (19). Nevertheless, where





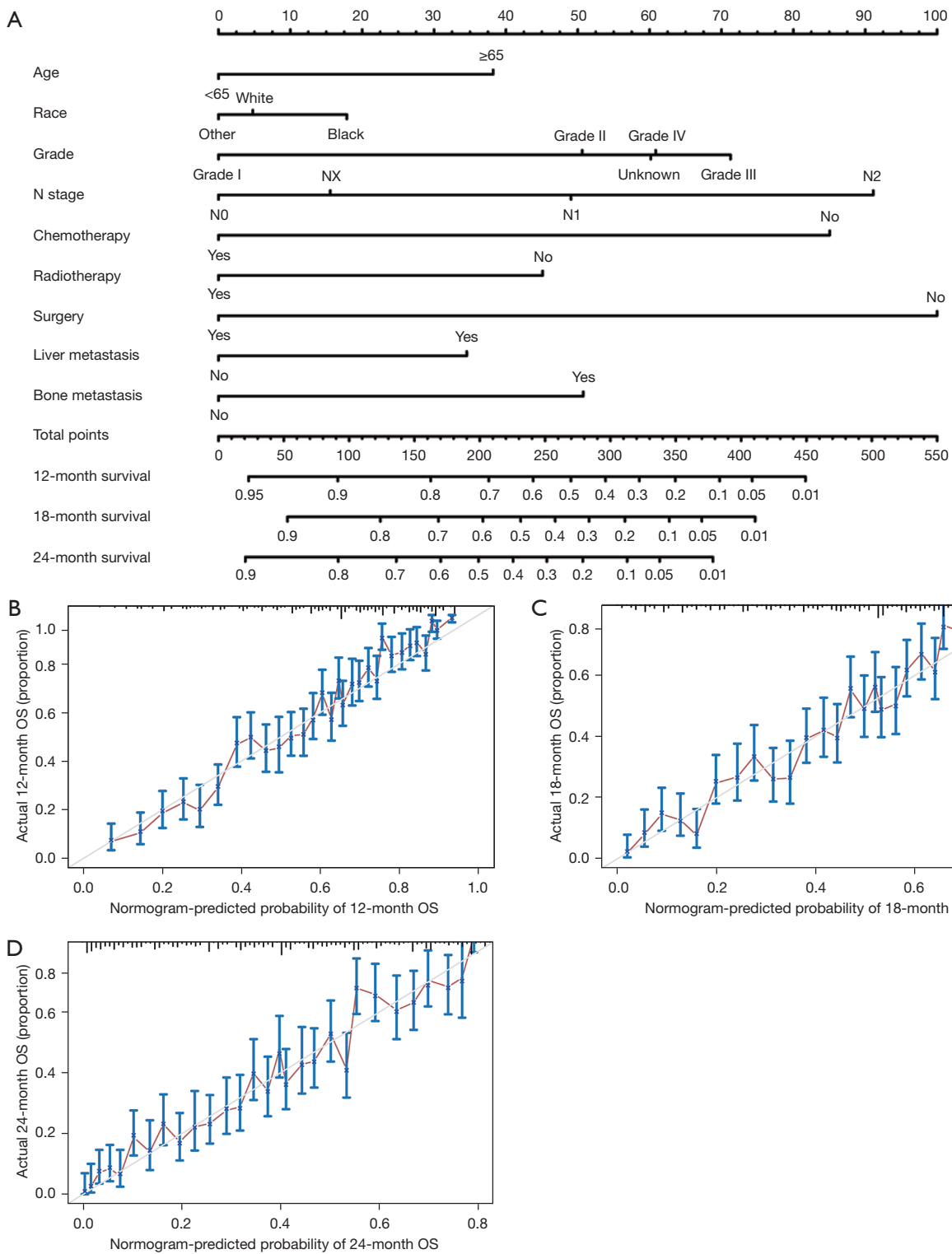


**Figure 2** Kaplan-Meier curve of overall survival: (A) all patients with mMC; (B) in patients aged  $\geq 65$  and  $< 65$  years; (C) in patients with different tumor grades; (D) in patients of different races; (E) in patients with different N staging; (F-H) in patients with and without chemotherapy, surgery, and radiotherapy, respectively; (I) in patients with and without bone metastasis; (J) in patients with different metastatic organs; (K) in patients with and without liver metastasis; (L) in patients with the number of metastatic organs. mMC, metastatic mucinous adenocarcinoma; met., metastasis.

possible, current guidelines recommend resection of both primary CRC and distant disease with curative intent in patients with liver and/or lung metastases. Radical resection of primary and distant metastases may improve long-term

survival and cure rates (20).

There are several reasons that account for the survival benefits of surgical intervention for both primary and metastases sites. Firstly, resection of primary and metastases



**Figure 3** Nomogram construction and validation based on the distant metastases patterns for predicting the OS in MC CRC. (A) The nomogram was developed using the observed cohort to predict the 12-, 18-, and 24-month OS. (B-D) Plot depicting the nomogram calibration in terms of agreement between the predicted and observed outcomes. The plot shows the performance of the nomogram compared to a perfect prediction (indicated by the dotted line). OS, overall survival; MC, mucinous adenocarcinoma; CRC, colorectal cancer.

sites could reduce the tumor burden, thereby improving the response to chemotherapy. Secondly, surgical resection of primary and metastatic tumors may restore the patient's immune function. Thirdly, surgical excision may reduce obstruction, perforation, and other complications associated with master surgery mortality and morbidity (21,22). However, careful consideration is needed before surgery in patients with multiple organ metastases. Thus, multidisciplinary team meetings may guide appropriate clinical decisions in MC patient management.

MC patients have been reported to have lower progression-free survival (PFS) and shorter mOS (15,18). However, other studies found that poor prognosis mainly existed in stage III and IV, and rectal cancer, but not colon cancer (4,23). The poor prognosis of stage IV MC may be due to its metastasis pattern. MC patients are more likely to have multiple-site metastases, and the distribution and composition of metastases differs from that of non-MC patients. In addition to liver metastasis, distant lymph node or peritoneal surface metastases are also common MC metastases (23-25). The presence of these metastases, especially in the peritoneum, is associated with very poor prognosis (26).

Our study found that patients with fewer metastatic sites had better mOS relative to those with higher numbers of organ involvement. This result is consistent with the principle of AJCC staging. On the contrary, no survival benefit was observed between patients with fewer versus additional metastatic sites in pancreatic cancer, indicating that this phenomenon is not found in all metastatic diseases (27).

Considering that MC patients have a unique metastasis pattern, independent prognostic factors were estimated and compared in detail between the subgroups. Univariate Cox regression analysis found that the factors associated with poor survival are as follows: diagnosis at  $\geq 65$  years, higher tumor grade, higher lymph node staging, as well as liver and bone metastasis. Patients with liver metastasis had the best survival, while those with bone and brain metastasis had the worst. These results are similar to SEER data on CRC (28).

In recent years, a series of studies have used the SEER database for nomogram construction and studied its prognostic value in patients with metastatic CRC (29,30). In this study, age, race, grade, N stage, chemotherapy, radiation, surgery, liver metastasis and bone metastasis were used for nomogram construction. Our prognostic nomogram exhibited good prediction for OS using the SEER database (c-index: 0.745). Recent years, a series

of clinical studies have provided new evidences for the treatment and management of MC patients. However, the exact molecular mechanisms of promoting MC metastasis are still unclear, and it will possibly enable further tailoring of treatment.

Although SEER datasets have high integrity and validity, our research had some limitations. Firstly, the SEER data did not provide the specific numbers of metastases. Secondly, the sequence of chemotherapy, radiotherapy, and surgery, as well as detailed information on the drug regimen and whether the patients received adjuvant or neoadjuvant therapy were not clear. Thirdly, the gene expression characteristics of the patients were not available. Thus, studies with larger sample sizes, especially randomized controlled trials, are needed to verify our findings.

## Conclusions

In summary, we observed that patients with mMC had a characteristic distant metastasis pattern. We constructed a new and accurate mMC prognostic model based on population-based data. These findings can be utilized to predict prognosis and guide mCRC MC patient management.

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## Footnote

*Reporting Checklist:* The authors have completed the TRIPOD reporting checklist. Available at <https://dx.doi.org/10.21037/jgo-21-824>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/jgo-21-824>). The 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. This study is a retrospective cohort study based on data from the SEER database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The SEER Program collects data from population-based cancer registries with anonymous information. The SEER is a publicly available database; thus, no ethical approval was required.

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