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ORIGINAL ARTICLE

Patterns of bone metastases in newly diagnosed colorectal cancer: a real-world analysis in the SEER database

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Abstract

Purpose To investigate the incidence and the associated factors for bone metastases (BM) development and prognosis in initial colorectal cancer (CRC) with a large sample using Surveillance, Epidemiology, and End Results (SEER) cohort.

Methods Primary CRC patients, who were initially diagnosed between 2010 and 2015 in the SEER database, were included to analyze BM incidence and risk factors for BM occurrence. The patients with at least 1-year follow-up were involved to investigate the prognostic factors for BM. Multivariable logistic and proportional hazard regression models were used to investigate the risk factors for BM development and prognosis, respectively.

Results A total of 212,787 eligible CRC patients were included and 2557 of them were diagnosed with de novo BM (1.20%). Rectal cancer presented significantly higher BM incidence than right and left colon cancer ($\chi^2 = 107.64$, $P < 0.001$). T1 stage, poor differentiated grade, and brain metastases were homogeneously associated factors for BM development and BM patients' survival. Male gender, higher N stage, rectal site, elevated carcinoembryonic antigen, and lung and liver metastases were positively associated with BM occurrence. Older age, unmarried status, right colon site, and non-surgery were found to positively correlate with the death risk of CRC patients with BM.

Conclusions BM is rare in CRC patients. Homogeneous and heterogeneous factors were found for BM development and BM patients' survival. The risk factors and prognostic factors can be used for BM screening and patient's prognosis estimation.

Keywords Bone metastases · Colorectal cancer · Risk factor · Prognosis factor · SEER

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Introduction

Colorectal cancer (CRC) is the third most common malignancy in males and the second in females [1]. Annually, over 1.3 million new cases are estimated to be diagnosed worldwide and the incidence of cases of CRC increases every year [1]. Among CRC patients, metastases are the main cause for the high mortality [2]. It was reported that almost 50% of CRC patients presented with metastatic disease development, and approximately, 25% of patients presented with distant metastatic disease at initial diagnosis [3].

Bone metastases (BM), being one of the most common metastatic types, is rare in CRC patients, with a reported incidence of 0.96% to 11.1% in CRC patients [4, 5]. BM is accepted to result in a series of skeletal-related events (SREs), including severe bone pain, pathological fracture, spinal cord compression, and malignant hypercalcemia [6]. Accordingly, BM can radically decrease patients' functional status and quality of life [7, 8]. To identify BM among CRC patients with SREs occurrence, imaging examination, including bone scans, X-rays, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT) are routinely used. Undoubtedly, the extensive imagological examination will increase both the radiation exposure and the financial burden of patients. Thus, it is important to look into the risk factors for BM in CRC patients and conduct specific screening strategies to different risk patients.

The prognosis of CRC patients with BM is reported to be poor, with a 5-year survival rate of < 5% [2, 9]. However, the prognostic factors for BM in CRC patients were not fully studied. The latest study, analyzing 129 CRC patients with BM, reported that ≥ 2 other organ metastases, hypercalcemia, and pathologic fracture were significantly associated with prognosis; however, the sample size was small with potential selection bias for participants inclusion [10]. Thus, a real-world, multicenter study with a large sample size is warranted to precisely define the nature of prognosis factors for CRC patients with BM.

National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) is the largest publicly available cancer database in the world. SEER, being established in 1973, covers approximately 30% of the US population across various geographic regions. Identifying those that presented with BM at diagnosis of CRC through the SEER database, we aim to summarize the incidence, the risk factors, and the prognostic factors of BM, and estimate the overall survival of BM patients.

Methods

Study population

CRC patients were identified in the SEER database. Since the details of BM were not available before 2010, primary CRC patients initially diagnosed between 2010 and 2015 were collected (the latest data up to date is on December 31, 2015). The site recodes ICD-O-3 (International Classification of Diseases for Oncology-3)/WHO 2008 was restricted as "Colon and Rectum." The exclusion criteria were as follows: diagnosed with carcinoma in situ, benign or borderline tumors, diagnosed at autopsy or via death certificate, unknown information for BM, or follow-up.

Patients diagnosed with CRC from January 1, 2010, to December 31, 2015, were adopted to analyze BM incidence and risk factors. To conduct survival analysis and investigate the prognostic factors for BM, those CRC patients with BM diagnosed between 2010 and 2014 were retrieved. Those included to analyze prognosis required at least 1-year follow-up data.

Statistical analysis

Patients' demographic and clinical characteristics were included as follows: age (< 65 and ≥ 65 years), race [White, Black, American Indian/Alaska Native (AI), and Asian or Pacific Islander (API)], marital status (married or unmarried), insurance status (insured or uninsured), primary tumor stage (T stage: T1, T2, T3, and T4), regional lymph node stage (N stage: N0, N1, and N2), primary site (right colon, left colon, and rectal), tumor grade (I = well differentiated, II = moderately differentiated, III = poorly differentiated, and IV = undifferentiated and anaplastic), carcinoembryonic antigen (CEA: normal or elevated), and the presence of lung metastases, liver metastases, or brain metastases. The differences in the BM incidence between the categorical variables were analyzed by Pearson's chi-square test or rank sum test. The risk factors for CRC patients with de novo BM were determined by univariable logistic regression. Those characteristics having a significance level of < 0.05 in the univariable logistic regression analysis were considered as candidates for the multivariable logistic analysis. The overall survival was analyzed using the Kaplan–Meier method with the log-rank test. Multivariable Cox regression model, including significant univariate factors ($P < 0.05$) and the surgical treatments of the primary site (none or yes), was conducted for analyzing the prognostic factors for BM. All statistical analyses were performed using SPSS 23.0 (IBM

Corporation, Armonk, NY) and all charts on survival were conducted by MedCalc 15.2.2. Two-sided $P < 0.05$ were considered as statistically significant.

Results

Demographic and clinical characteristics

A total of 212,787 eligible CRC patients met the inclusion criteria (Fig. 1). The patients' mean age was 66.46 ± 14.24 years, most of them were White (77.91%). Among these patients, 2106 CRC patients with BM were followed up for at least 1 year, and the mean age of them was 64.93 ± 14.01 years. The demographic and clinical characteristics of the included patients are shown in Table 1.

Incidence of bone metastases

Totally, 2557 CRC patients were diagnosed with de novo BM (1.20%) and the incidence of BM in the right colon, left colon, and rectal were 0.85%, 1.01%, and 1.40%, respectively with a

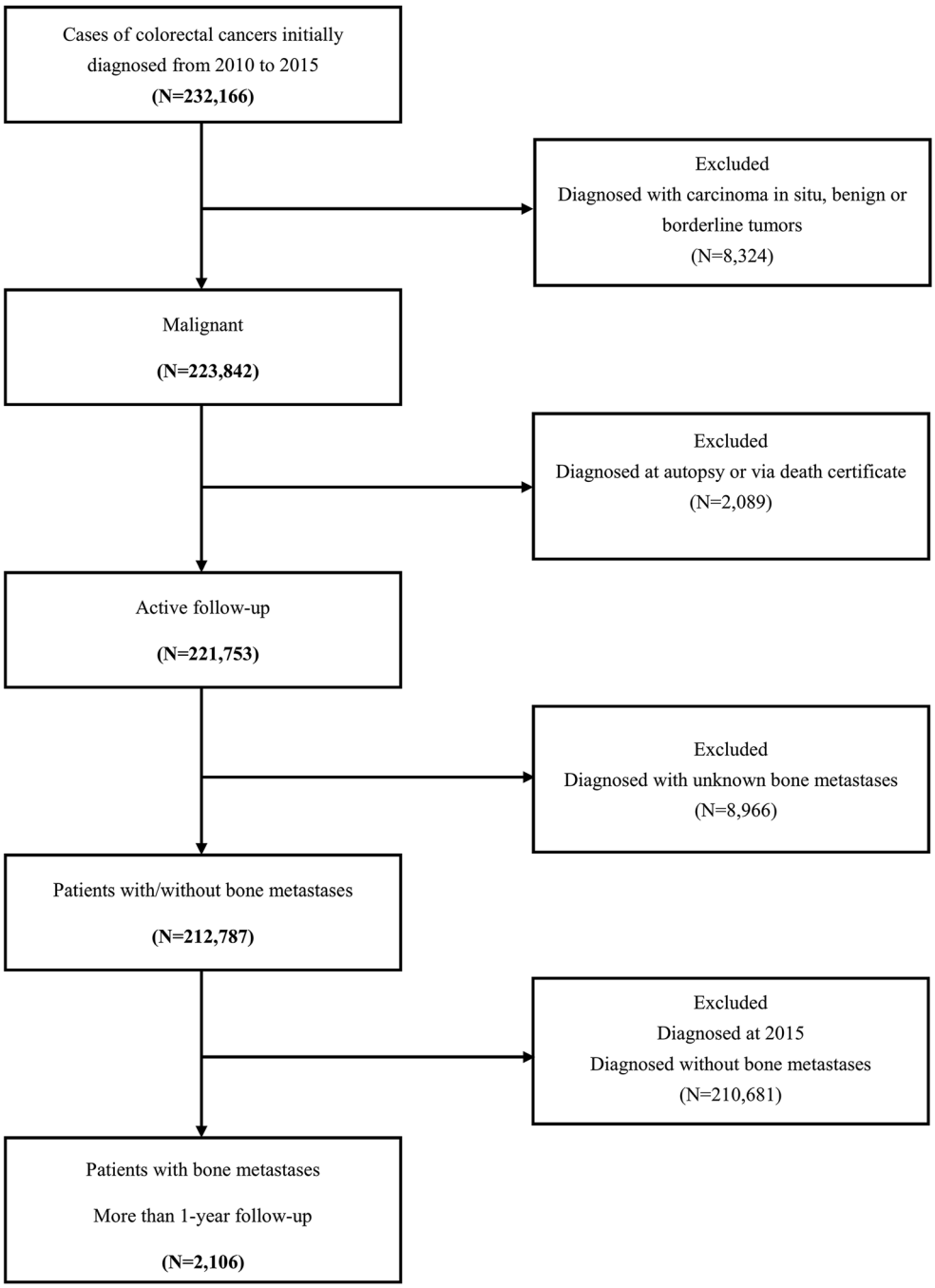

Fig. 1 The flowchart for the subjects' selection in the present study

Table 1 Baseline of the demographic and related clinical characteristics for patients diagnosed with colorectal cancer

Subject characteristics	No. of colorectal cancer patients (2010–2015)		No. of colorectal cancer patients (2010–2014)	
	With BM ($N = 2557$, 1.20%)	Without BM ($N = 210{,}230$, 98.80%)	With BM ($N = 2106$, 1.19%)	Without BM ($N = 174{,}728$, 98.81%)
Age, in years				
< 65	1259 (1.35)	92,330 (98.65)	1058 (1.37)	75,996 (98.63)
≥ 65	1298 (1.09)	117,900 (98.91)	1048 (1.05)	98,732 (98.95)
Sex				
Female	1010 (0.99)	100,630 (99.01)	827 (0.98)	83,824 (99.02)
Male	1547 (1.39)	109,600 (98.61)	1279 (1.39)	90,904 (98.61)
Race				
White	1939 (1.17)	163,846 (98.83)	1584 (1.15)	136,400 (98.85)
Black	390 (1.49)	25,797 (98.51)	333 (1.53)	21,410 (98.47)
AI	24 (1.45)	1636 (98.55)	17 (1.25)	1345 (98.75)
API	200 (1.15)	17,222 (98.85)	168 (1.16)	14,257 (98.84)
Unknown	4 (0.23)	1729 (99.77)	4 (0.30)	1316 (99.70)
Marital status				
Married	1255 (1.15)	107,684 (98.85)	1024 (1.13)	89,635(98.87)
Unmarried	1175 (1.31)	88,797 (98.69)	976 (1.31)	73,650 (98.69)
Unknown	127 (0.92)	13,749 (99.08)	106 (0.92)	11,443 (99.08)
Insurance				
Insured	2378 (1.19)	197,480 (98.81)	1948 (1.18)	163,797 (98.82)
Uninsured	121 (1.80)	6592 (98.20)	109 (1.84)	5815 (98.16)
Unknown	58 (0.93)	6158 (99.07)	49 (0.95)	433 (99.05)
T stage				
T1	312 (0.77)	40,073 (99.23)	261 (0.79)	32,980 (99.21)
T2	56 (0.23)	24,682 (99.77)	49 (0.24)	20,801 (99.76)
T3	446 (0.50)	88,037 (99.50)	376 (0.51)	73,757 (99.49)
T4	528 (1.68)	30,846 (98.32)	432 (1.67)	25,412 (98.33)
Unknown	1215 (4.37)	26,592 (95.63)	988 (4.34)	21,778 (95.66)
N stage				
N0	877 (0.68)	127,542 (99.32)	720 (0.67)	106,123 (99.33)
N1	771 (1.53)	49,502 (98.47)	613 (1.48)	40,921 (98.52)
N2	332 (1.32)	24,871 (98.68)	279 (1.33)	20,772 (98.67)
Unknown	577 (6.49)	8315 (93.51)	494 (6.67)	6912 (93.33)
Primary site				
Right colon	755 (0.85)	88,026 (99.15)	617 (0.84)	73,053 (99.16)
Left colon	544 (1.01)	53,262 (98.99)	440 (0.98)	44,403 (99.02)
Rectal	893 (1.40)	63,009 (98.60)	742 (1.40)	52,335 (98.60)
Unknown	365 (5.80)	5933 (94.20)	307 (5.85)	4937 (94.15)
Grade				
I	81 (0.39)	20,773 (99.61)	70 (0.41)	16,834 (99.59)
II	809 (0.65)	124,523 (99.35)	674 (0.65)	103,818 (99.35)
III	497 (1.72)	28,434 (98.28)	427 (1.76)	23,848 (98.24)
IV	89 (1.54)	5697 (98.46)	66 (1.39)	4692 (98.61)
Unknown	1081 (3.39)	30,803 (96.61)	869 (3.29)	4256 (96.71)
CEA				
Normal	217 (0.37)	58,788 (99.63)	178 (0.36)	48,697 (99.64)
Elevated	1424 (2.59)	53,632 (97.41)	1173 (2.57)	44,478 (97.43)
Unknown	916 (0.93)	97,810 (99.07)	755 (0.92)	81,553 (99.08)

Table 1 (continued)

Subject characteristics	No. of colorectal cancer patients (2010–2015)		No. of colorectal cancer patients (2010–2014)	
	With BM (*N* = 2557, 1.20%)	Without BM (*N* = 210,230, 98.80%)	With BM (*N* = 2106, 1.19%)	Without BM (*N* = 174,728, 98.81%)
Lung Met				
None	1405 (0.70)	200,564 (99.30)	1152 (0.69)	166,823 (99.31)
Yes	1052 (10.51)	8957 (89.49)	866 (10.61)	7294 (89.39)
Unknown	100 (12.36)	709 (87.64)	88 (12.59)	611 (87.41)
Liver Met				
None	728 (0.40)	181,589 (99.60)	601 (0.40)	150,946 (99.60)
Yes	1775 (5.91)	28,243 (94.09)	1461 (5.87)	23,431 (94.13)
Unknown	54 (11.95)	398 (88.05)	44 (11.14)	351 (88.86)
Brain Met				
None	2308 (1.09)	209,572 (98.91)	1895 (1.08)	174,173 (98.92)
Yes	123 (22.57)	422 (77.43)	97 (21.32)	358 (78.68)
Unknown	126 (34.81)	236 (65.19)	114 (36.66)	197 (63.34)
Surg(pri)				
None	1946 (5.42)	33,988 (94.58)	1578 (5.42)	27,529 (94.58)
Yes	603 (0.34)	175,867 (99.66)	521 (0.35)	146,899 (99.65)
Unknown	8 (2.09)	375 (97.91)	7 (2.28)	300 (97.72)

BM, bone metastases; *CEA*, carcinoembryonic antigen; *Met*, metastases; *Surg* (*pri*), surgical treatments of primary site

significant difference among each other ($\chi^2 = 107.64$, $P < 0.001$) (Table 1). For the CRC patients diagnosed with BM, rectal cancer is presented at a significantly lower age ($\chi^2 = 31.90$, $P < 0.001$), in a lower percentage of females ($\chi^2 = 19.79$, $P < 0.001$), lower percentage of Black patients ($\chi^2 = 29.18$, $P < 0.001$), and relative lower N2 stage ($\chi^2 = 37.94$, $P < 0.001$), lower differentiated grade IV ($\chi^2 = 25.04$, $P < 0.001$) and lower liver metastases patients ($\chi^2 = 15.22$, $P < 0.001$) than left and right colon cancer patients. No significant differences were found among other factors (Table 2).

Subgroup analysis also showed male patients presented with a significantly higher incidence (1.39%) of BM than females ($\chi^2 = 70.89$, $P < 0.001$). Moreover, patients with younger age ($\chi^2 = 29.01$, $P < 0.001$), black race ($\chi^2 = 20.69$, $P < 0.001$), unmarried status ($\chi^2 = 9.68$, $P = 0.002$), uninsured ($\chi^2 = 20.40$, $P < 0.001$), higher T stage ($\chi^2 = 546.37$, $P < 0.001$), N stage ($\chi^2 = 307.74$, $P < 0.001$), poor differentiated grade ($\chi^2 = 420.23$, $P < 0.001$), elevated CEA ($\chi^2 = 988.72$, $P < 0.001$), and with lung ($\chi^2 = 8018.71$, $P < 0.001$), liver ($\chi^2 = 6726.71$, $P < 0.001$), and brain metastases ($\chi^2 = 2216.92$, $P < 0.001$) presented higher BM incidence than the counterparts (Table 1).

Risk factors for developing bone metastases

Univariable logistic analysis showed the factors of younger age at presentation and T2/T1 and T3/T1 stage were negatively associated with BM occurrence. However, male gender, unmarried status, uninsured, higher N stage, left colon and rectal primary site, poor differentiated grade, elevated CEA, and the presence of lung metastases, liver metastases, and brain metastases were all positively associated with BM risk, individually (Table 3).

Multivariable logistic regression indicated males, higher N stage, rectal sites, T2/T1 and T3/T1 stage, poorly differentiated grade, elevated CEA, and the presence of lung, liver, and brain metastases were all significantly associated with de novo BM development (Table 3, Fig. 2).

Survival analysis and prognostic factors for BM

Once patients developed BM, CRC patients' survival rates dramatically decreased. The overall 1-year and 3-year overall survival rates of the cohort were 81% and 64%, respectively, while they decreased to 30% and 7% respectively after BM diagnosis. For the 2106 CRC patients with de novo BM (diagnosed between 2010 and 2014), the median overall survival time was 5.00 months (95% CI, 4.50–5.50 months, Fig. 3A). Kaplan–Meier analysis showed the overall survival in subjects with older age (Fig. 3B, $P < 0.001$), unmarried status (Fig. 3C, $P < 0.001$), T1 stage (Fig. 3D, $P < 0.001$), right colon (Fig. 3E, $P < 0.001$), poor differentiated grade (Fig. 3F, $P < 0.001$), and with liver metastases (Fig. 3 G, $P < 0.001$) and brain metastases (Fig. 3H, $P = 0.03$) were shorter than their counterparts. Besides, patients with surgical treatment of the primary site

Table 2 Difference in the demographic and related clinical characteristics for patients diagnosed with bone metastasis among right colon, left colon, and colorectal cancer

Subject characteristics	Right colon *N* (%)	Left colon *N* (%)	Rectal *N* (%)	χ^2	*p* value
Age, in years				31.90	< 0.001
< 65	321 (42.5)	297 (54.6)	496 (55.5)		
≥ 65	434 (57.5)	247 (45.4)	397 (44.5)		
Sex				19.79	< 0.001
Female	343 (45.4)	211 (38.8)	310 (34.7)		
Male	412 (54.6)	333 (61.2)	583 (65.3)		
Race				29.18	< 0.001
White	588 (77.9)	390 (72.2)	696 (77.9)		
Black	128 (17.0)	84 (15.6)	111 (12.4)		
AI	2 (0.3)	6 (1.1)	12 (1.3)		
API	37 (4.9)	60 (11.1)	74 (8.3)		
Marital status				5.99	0.05
Married	378 (52.2)	292 (56.7)	424 (49.9)		
Unmarried	346 (47.8)	223 (43.3)	426 (50.1)		
Insurance				1.65	0.44
Insured	713 (96.0)	508 (95.0)	826 (94.6)		
Uninsured	30 (4.0)	27 (5.0)	47 (5.4)		
T stage				12.14	0.059
T1	105 (23.6)	72 (23.9)	118 (21.8)		
T2	13 (2.9)	9 (3.0)	33 (6.1)		
T3	148 (33.3)	93 (30.9)	197 (36.4)		
T4	179 (40.2)	127 (42.2)	193 (35.7)		
N stage				37.94	< 0.001
N0	239 (38.2)	180 (41.7)	309 (42.9)		
N1	228 (36.5)	173 (40.0)	322 (44.7)		
N2	158 (25.3)	79 (18.3)	89 (12.4)		
Differentiated grade				25.04	< 0.001
I	30 (6.2)	18 (5.2)	31 (5.2)		
II	224 (46.6)	215 (62.1)	346 (57.8)		
III	194 (40.3)	90 (26.0)	189 (31.6)		
IV	33 (6.9)	23 (6.6)	33 (5.5)		
CEA				5.43	0.066
Normal	421 (83.9)	341 (89.3)	498 (86.6)		
Elevated	81 (16.1)	41 (10.7)	77 (13.4)		
Lung Met				4.80	0.09
None	440 (60.5)	305 (58.1)	480 (55.1)		
Yes	287 (39.5)	220 (41.9)	391 (44.9)		
Liver Met				15.22	<0.001
None	205 (27.5)	124 (23.2)	287 (32.7)		
Yes	541 (72.5)	410 (76.8)	591 (67.3)		
Brain Met				1.08	0.58
None	693 (94.7)	490 (95.1)	817 (95.8)		
Yes	39 (5.3)	25 (4.9)	36 (4.2)		

CEA, carcinoembryonic antigen; *Met*, metastases

presented significantly longer overall survival than those without surgery (Fig. 3I, $P < 0.001$).

Multivariable Cox regression results showed older age, unmarried status, poor or undifferentiated grade, and the presence of brain metastases were all associated with poor prognosis. However, left colon site, rectal site, and T2/T1 and T3/T1 stage were associated with better survival of CRC patients with BM. Additionally, surgery of the primary

Table 3 Univariable and multivariable logistic regression for analyzing the associated factors for developing bone metastases in patients diagnosed with colorectal cancer. (Diagnosed between 2010 and 2015)

Subject characteristics	Univariable		Multivariable	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Age, in years				
< 65	1 (reference)	1.00	1 (reference)	1.00
≥ 65	0.81 (0.75–0.87)	< 0.001	0.87 (0.73–1.04)	0.13
Sex				
Female	1 (reference)	1.00	1 (reference)	1.00
Male	1.41 (1.30–1.52)	< 0.001	1.24 (1.05–1.48)	0.01
Marital status				
Married	1 (reference)	1.00	1 (reference)	1.00
Unmarried	1.14 (1.05–1.23)	0.002	0.88 (0.74–105)	0.15
Unknown	NA	NA	NA	NA
Insurance				
Insured	1 (reference)	1.00	1 (reference)	1.00
Uninsured	1.52 (1.27–1.83)	< 0.001	1.10 (0.76–1.60)	0.60
Unknown	NA	NA	NA	NA
T stage				
T1	1 (reference)	1.00	1 (reference)	1.00
T2	0.29 (0.22–0.39)	< 0.001	0.41 (0.26–0.66)	< 0.001
T3	0.65 (0.56–0.75)	< 0.001	0.44 (0.34–0.57)	< 0.001
T4	2.20 (1.91–2.53)	< 0.001	0.82 (0.63–1.06)	0.13
Unknown	NA	NA	NA	NA
N stage				
N0	1 (reference)	1.00	1 (reference)	1.00
N1	2.27 (2.06–2.50)	< 0.001	1.41 (1.13–1.75)	0.002
N2	1.94 (1.71–2.20)	< 0.001	1.45 (1.13–1.85)	0.003
Unknown	NA	NA	NA	NA
Primary site				
Right colon	1 (reference)	1.00	1 (reference)	1.00
Left colon	1.19 (1.07–1.33)	0.002	0.88 (0.70–1.11)	0.28
Rectal	1.65 (1.50–1.82)	< 0.001	1.77 (1.45–2.16)	< 0.001
Unknown	NA	NA	NA	NA
Differentiated Grade				
I	1 (reference)	1.00	1 (reference)	1.00
II	1.67 (1.33–2.10)	< 0.001	1.14 (0.74–1.74)	0.56
III	4.48 (3.54–5.67)	< 0.001	2.60 (1.68–4.04)	< 0.001
IV	4.01 (2.96–5.42)	< 0.001	2.25 (1.29–3.92)	0.004
Unknown	NA	NA	NA	NA
CEA				
Normal	1 (reference)	1.00	1 (reference)	1.00
Elevated	7.19 (6.23–8.30)	< 0.001	2.27 (1.79–2.88)	< 0.001
Unknown	NA	NA	NA	NA
Lung Met				
None	1 (reference)	1.00	1 (reference)	1.00
Yes	16.77 (15.44–18.21)	< 0.001	5.29 (4.37–6.40)	< 0.001
Unknown	NA	NA	NA	NA
Liver Met				
None	1 (reference)	1.00	1 (reference)	1.00

Table 3 (continued)

Subject characteristics	Univariable		Multivariable	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Yes	15.68 (14.37–17.10)	< 0.001	6.11 (4.97–7.52)	< 0.001
Unknown	NA	NA	NA	NA
Brain Met				
None	1 (reference)	1.00	1 (reference)	1.00
Yes	26.47 (21.56–32.49)	< 0.001	8.66 (5.30–14.14)	< 0.001
Unknown	NA	NA	NA	NA

CEA, carcinoembryonic antigen; *Met*, metastases; *NA*, not available. All factors with unknown data were removed from logistic regression model

site was shown to be negatively associated with overall death risk and the median survival time could be prolonged from 4 months to 9 months after surgery of the primary site (Table 4, Fig. 2i).

Discussion

To our knowledge, the present study included the largest population to look into the clinical characteristics, risk factors, and

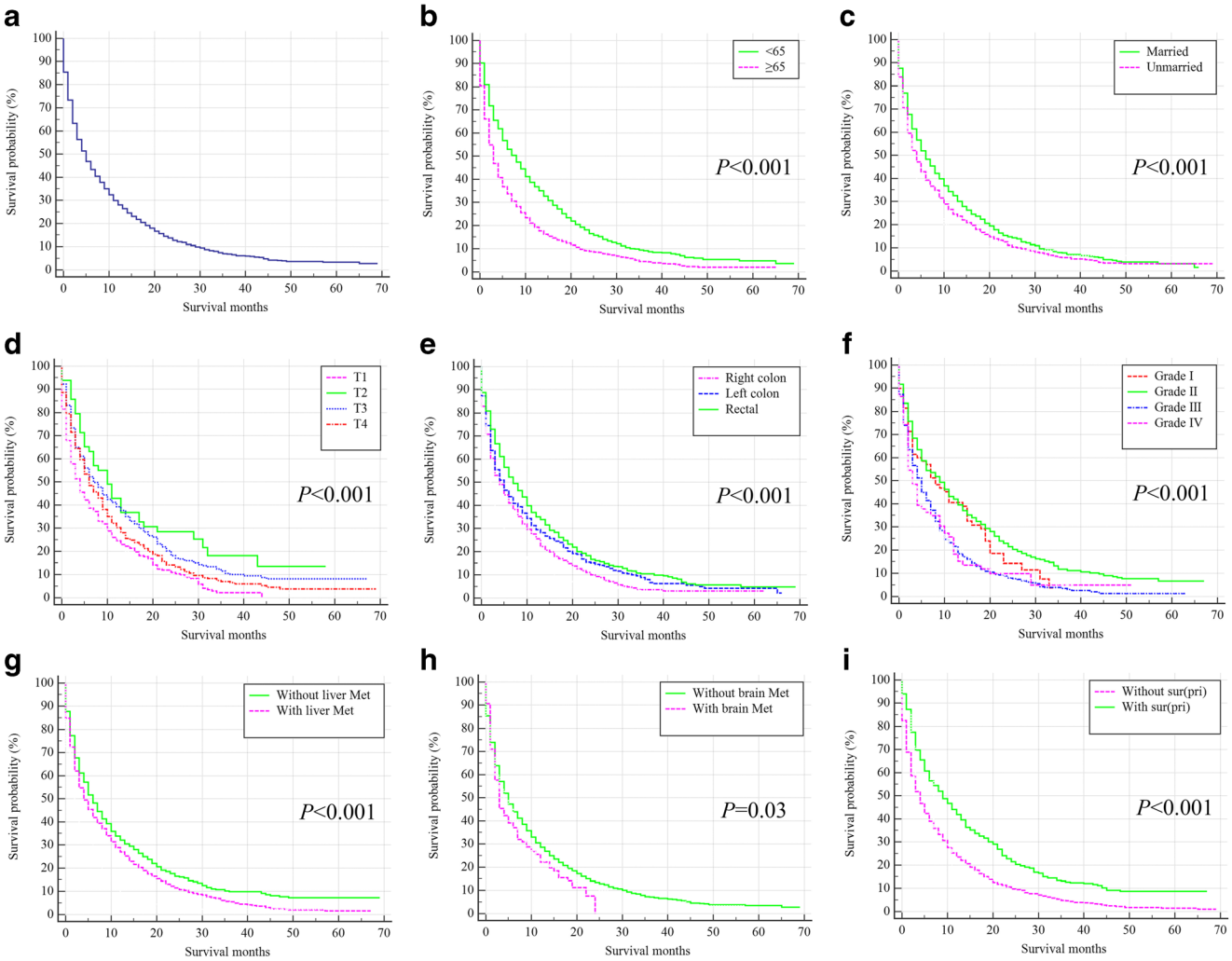

Fig. 2 Kaplan–Meier analysis of overall survival among CRC patients who were diagnosed with bone metastases for **a** total population and **b** stratified by age, **c** marital status, **d** T stage, **e** primary site, **f** histological grade, **g** the presence of liver metastases, **h** brain metastases, and **i** surgical treatments of primary site. CRC, colorectal cancer; liver Met, liver metastases; brain Met, brain metastases; sur(pri), surgical treatments of primary site

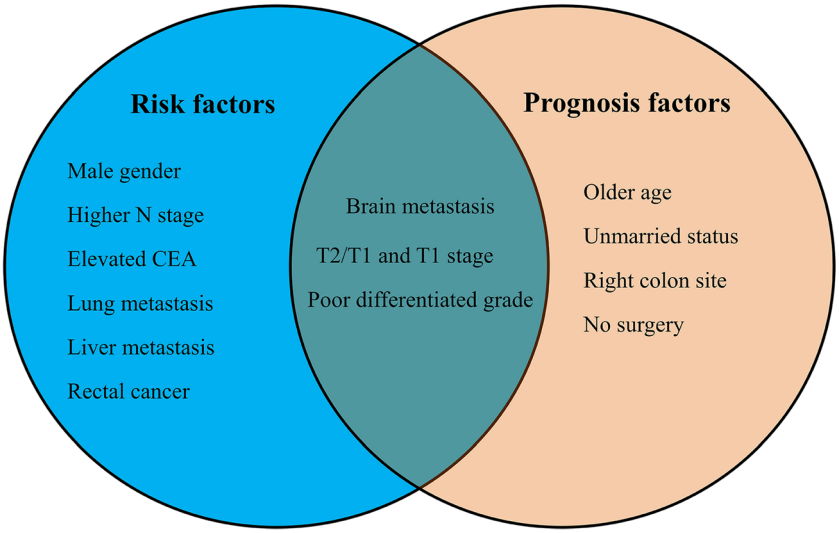

Fig. 3 The homogeneous and heterogeneities for the risk factors and prognosis factors of bone metastases in patients with colorectal cancer. All the factors included in the left circle represented the risk factors for developing bone metastases and the ones in the right circle exhibited the prognosis factors for colorectal cancer patients with bone metastases, the factors in the overlapping area represents the homogeneous factors for bone metastases development and prognosis

prognostic factors of BM from CRC. A series of BM incidence in CRC were reported previously and the incidence ranged from 0.96 to 11.1% [4, 11]. Roth et al., after a retrospective analysis with 252 American CRC patients, reported the incidence of BM at diagnosis to be 5.5% [2]. Another retrospective study for CRC in France suggested the incidence of BM was 4.5% and the latest study conducted in China showed BM occurred in approximately 4.9% CRC patients during the course of the disease [5, 12]. Our results showed the incidence of BM in initial CRC patients is 1.2% and rectal cancer showed higher BM incidence than colon cancer, which is in agreement with previously reported literatures [13].

It is important to investigate the associated environmental factors for BM development and screening performance among high-risk CRC patients. The present study identified male gender, higher N stage, rectal site, poor differentiated grade, elevated CEA, and the presence of lung, liver, and brain metastases was significantly associated with de novo BM development, which was partly consistent with the previous studies [5, 14, 15]. Thus, it is important to be alert for CRC patients with the aforementioned factors at diagnosis. Moreover, further examinations for BM screening such as skeletal radiographic scanning should be recommended in high-risk patients. For those high-risk CRC patients with atypical symptoms, the prophylactic treatment can be considered to prevent SREs [16]. Few data suggested the correlation between T stage and BM in CRC patients [14]. One single-center study conducted in China showed T stage was not associated with BM risk in CRC patients. The present study showed that T2/T1 and T3/T1 stages of CRC was negatively associated with BM development, however, no association was found for T4/T1. The results were partly consistent with the studies in prostate cancer [8] and ovarian cancer [17], but not for breast cancer [18]. More studies are warranted to further verify the results.

Our results, based on a real-world large population analysis, clarified the prognosis of CRC patients with BM is poor. We identified that the median overall survival for CRC patients with BM is 5 months, which is similar to the study conducted in the Japan CRC cohort [10]. Compared with the previously reported median overall survival (from 7 to 18 months), the survival in the present study was lower [4, 15, 19]. One of the possible reasons for the poor prognosis was thought to be led by multi metastatic diseases. It was reported that metastases only to the bone in CRC patients is rare, 25% BM cases combined with lung metastases while 30% BM cases have liver metastases [2].

A series of prognostic factors for BM in CRC patients were found in the present study, including older age, unmarried status, right colon, T2/T1 and T3/T1 stage, poor or undifferentiated grade, surgery on the primary site, and the presence of brain metastases, which was not consistent with the previous study [11]. The heterogeneities in the prognosis factors may partly be due to the different sample size and more studies are needed to further confirm these results.

Limitations of this study include: (1) detailed information on the diagnosis method for BM is not available in public SEER database; (2) the SEER database merely recorded the initial diagnosis of BM, thus real initial BM rate in CRC patients might be underestimated for unrecording asymptomatic cases; (3) the treatment information for the included patients were not recorded in the SEER cohort, we could not investigate the specific surgical options on the survival of CRC patients with BM.

Conclusion

The occurrence of bone metastases in colorectal cancer is rare (1.2%), and the prognosis of bone metastases cases in

Table 4 Multivariable Cox Regression for analyzing the prognosis factors for colorectal cancer with bone metastases (diagnosed between 2010 and 2014)

Subject characteristics	Survival, median (IQR), mo	HR (95% CI)	*p* value
Age, years			
< 65	8.00 (7.02–8.98)	1 (reference)	1.00
≥ 65	3.00 (2.64–3.36)	1.42 (1.21–1.67)	< 0.001
Marital status			
Married	6.00 (5.16–6.84)	1 (reference)	1.00
Unmarried	4.00 (3.43–4.57)	1.23 (1.05–1.44)	0.01
Unknown	NA	NA	NA
T stage			
T1	4.00 (2.85–5.15)	1 (reference)	1.00
T2	10.00 (6.57–13.43)	0.55 (0.36–0.84)	0.01
T3	7.00 (5.25–8.75)	0.67 (0.52–0.85)	0.001
T4	6.00 (4.86–7.14)	0.88 (0.69–1.11)	0.28
Unknown	NA	NA	NA
Primary site			
Right colon	4.00 (3.26–4.74)	1 (reference)	1.00
Left colon	5.00 (3.80–6.21)	0.80 (0.65–0.99)	0.04
Rectal	7.00 (5.88–8.12)	0.74 (0.61–0.90)	0.003
Unknown	NA	NA	NA
Differentiated grade			
I	8.00 (4.46–11.54)	1 (reference)	1.00
II	9.00 (7.52–10.48)	0.92 (0.62–1.36)	0.67
III	5.00 (4.19–5.81)	1.65 (1.11–2.46)	0.01
IV	3.00 (1.96–4.04)	2.14 (1.31–3.49)	0.002
Unknown	NA	NA	NA
Liver Met			
None	6.00 (5.06–6.94)	1 (reference)	1.00
Yes	4.00 (3.49–4.51)	1.14 (0.96–1.35)	0.13
Unknown	NA	NA	NA
Brain Met			
None	5.00 (4.49–5.51)	1 (reference)	1.00
Yes	3.00 (1.72–4.28)	1.59 (1.11–2.26)	0.01
Unknown	NA	NA	NA
Sur(pri)			
None	4.00 (3.55–4.45)	1 (reference)	1.00
Yes	9.00 (7.25–10.75)	0.62 (0.52–0.75)	< 0.001
Unknown	NA	NA	NA

Met, metastases; *NA*, not available; all factors with unknown data were removed from Cox and Kaplan–Meier model

colorectal cancer patients is poor (median overall survival time, 5 months). Results showed homogeneous and heterogeneous associated factors for BM development and prognosis. The risk factors we reported can be involved in future BM predictive score system, and the prognostic factors we reported can be clinically used for estimating the prognosis of the patients.

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Compliance with ethical standards

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

Ethical approval The present study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and the study was approved by the Research Ethics Board of the Tianjin Medical University Cancer Institute and Hospital.

Informed consent The SEER database is an open public database, and the release of data from the SEER database does not require informed patient consent because cancer is a reportable disease in every state of the USA.

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