Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Bone Metastases in Newly Diagnosed Colorectal Cancer by Tumor Location: a Population-based Study

Lin Yang (yanglin1nfyy@smu.edu.cn)
Southern Medical University Nanfang Hospital https://orcid.org/0000-0003-4544-8071
Shousheng Liu
Sun Yat-sen University Cancer Center
Qiankun Xie
Southern Medical University Nanfang Hospital
Wenzhuo He
Sun Yat-sen University Cancer Center
Chang Jiang
Sun Yat-sen University Cancer Center
Bei Zhang
Sun Yat-sen University Cancer Center
Liangping Xia
Sun Yat-sen University cancer center

Primary research

Keywords: colorectal cancer, bone metastasis, tumor site, prognosis

Posted Date: February 12th, 2020

DOI: https://doi.org/10.21203/rs.2.23358/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Abstract

Purpose

Bone metastasis (BM) in colorectal cancer (CRC) is rare and data on population-based incidence is lacking. We aimed to evaluate the incidence of BM and the risk factors for BM in CRC.

Methods

The Surveillance, Epidemiology, and End Results (SEER) database was interrogated as part of the analysis. We used multivariable logistic and Cox regression analyses to determine predictors for the presence of BM at diagnosis, and the elements associated with poor survival. Kaplan–Meier analysis was used to estimate the survival difference among subgroups.

Results

A total of 166,388 adult patients were identified between 2010 and 2013 as being diagnosed with CRC. Of these, 1,659 patients developed BM representing 1% of the entire CRC cohort and 5.5% of patients had metastatic disease. The median survival period of patients with BM was merely 11.3 months. We found that extracranial metastases number and tumor site were associated with BM at CRC diagnosis and these parameters were also associated with poorer survival in the BM cohort. Unlike other solid tumors, patients with bone metastasis had poorer survival and the median survival time (MST) was significantly shortened for single metastasis disease or when lung and liver metastasis were present.

Conclusions

The findings of this study clearly reveal the incidence and prognosis for patients with BM at time of CRC diagnosis. Our findings lend support for positive treatment of BM without other organ metastasis.

Background

Colorectal cancer is the third most common type of cancer worldwide[1–3]. Approximately 20% of patients with colorectal cancer (CRC) have metastatic disease at the time of diagnosis[4]. The liver is the most common site of metastatic disease from CRC and between 15 to 20% of patients present with synchronous liver metastases[5, 6]. The incidence of lung metastasis in CRC is approximately 10%[7]. Compared with liver or lung metastasis in patients with CRC, bone metastasis is relatively rare and approximates between 10–15% [8].

Patients with bone metastasis are often diagnosed because of skeletal-related events (SREs), such as severe bone pain, spinal cord compression, pathologic fractures, and hypercalcemia[9]. Since SREs often represent the late events associated with bone metastasis, patients with bone metastasis often experience lower quality of life and poor physical condition. Therefore, the early diagnosis of bone metastasis is imperative. However, the characteristics associated with bone metastasis at diagnosis of CRC are not yet clear[10, 11].

The majority of patients with metastatic CRC (mCRC) have incurable disease. Studies have reported that the prognosis of patients with bone metastasis is very poor, with a 5-year survival rate less than 5%[12, 13]. However, survival in advanced CRC has improved because of concomitant advances in precision medicine, increased acceptance of metastasectomy, and the introduction of immunotherapy[14, 15]. There may be different survival benefits based on the site of disease metastasis and the different therapeutic options that are now available.

Our aim in this study was to evaluate characteristics of bone metastasis from CRC and to clarify the prognostic factors associated with survival in these patients.

Methods

The data were retrieved from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute SEER database, USA, after 2010. This included whether bone metastasis was confirmed at the diagnosis of CRC. The datasets are available https://seer.cancer.gov/ in the SEER dataset repository.

The “TNM” staging was determined by the “extent of cancer” at the initial diagnosis using the 7th AJCC edition. Pathology was stratified into adenocarcinoma (AC), or mucinous adenocarcinoma (MC), or other. Tumor grade was recorded as well differentiated, moderately differentiated, poorly differentiated, or undifferentiated. Only patients with a detailed tumor location were included in our analysis, including right-sided colonic cancer (RCC) (cecum, ascending colon, hepatic flexure, and transverse colon), left-sided colon cancer (LCC; splenic flexure, descending colon, and sigmoid colon), rectosigmoid cancer (RSC; rectosigmoid junction and rectum), and appendix cancer[16].

Race/ethnicity was categorized as previously described[17]. The SEER 9 dataset categorized ethnicity as white, African-American, Native American/Alaska Native, Asian/Pacific Islander, and unknown. The extent of disease was evaluated by the sites of metastasis and number of bone, lung, and liver metastases at diagnosis that were entered in the SEER database.

Patient survival was recorded by overall survival and CRC-cause specific death. The follow-up time was computed by the time of first diagnosis of CRC until the last follow-up, death, or end of the study, whichever occurred first. To assess CRC–specific mortality, we used Fine and Gray’s competing risk regression[18].

Patients that were found to have bone metastasis 6 months after the diagnosis of CRC or bone metastasis by autopsy were excluded. Thus, there were 166,388 patients diagnosed with CRC that were included in our analysis. Of these CRC patients, 1,659 were diagnosed with bone metastasis.

Statistical Analysis

Multivariable logistic regression was used to determine which characteristic was associated with the presence of bone metastasis at diagnosis among CRC patients or the M1 cohort (Patients with distant metastasis at the initial diagnosis). Multivariable Cox regression was performed to identify covariates associated with poor survival. The Kaplan-Meier method was used to estimate the survival difference between the subgroups.

Two-sided P values < 0.05 were considered statistically significant. Statistical analysis was performed using SAS, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Incidence

There were 166,388 patients diagnosed as having CRC in our analyses. This included 41.5% with RCC, 26.8% with LCC, and 31.7% with RSC, respectively. There were 30,203 patients with metastasis disease at any site and of these, there were 12,396 (41.0%), 8,758 (29.0%), and 9,049 (30.0%) patients with RCC, LCC, and RSC, respectively. The distribution of patients with CRC and identified bone metastases at diagnosis are provided in Table 1, as stratified by tumor location. Among the entire cohort, 1,659 patients presented with bone metastases at diagnosis, representing 1% of the entire study and 5.5% of the subset with metastatic disease at any site. Bone metastasis numbers were 563 (0.8%), 407 (0.9%) and 689 (1.3%) for RCC, LCC, and RSC, respectively. RSC had the highest incident percentage of bone metastasis (1.3% of the entire cohort; 7.6% of the metastatic subset).

Table 1
Incidence and median survival of patients diagnosed with CRC and bone metastases

Subtype	Patient numbers			Percentage Incidence of bone Metastases (%)		Survival Among Patients With Bone Metastases, Median (IQR), Mo	Survival Among Patients Without Bone Metastases, Median (IQR), Mo
	With CRC	Among Subset With Metastatic Disease	Bone Metastases	Among Entire cohort	Among Subset With Metastatic Disease		
Whole cohort	166,388	30,203	1,659	1%	5.5%	11.37 (10.54–12.19)	19.91 (19.65–20.17)
RCC	69,065	12,396	563	0.8%	4.5%	8.34 (7.38–9.40)	16.54(16.16–19.9)
LCC	44,548	8,758	407	0.9%	4.6%	12.43 (10.62–14.24)	22.29 (21.79–22.29)
RSC	52,739	9,049	689	1.3%	7.6%	12.98 (11.61–14.34)	22.23 (21.74–22.72)

Abbreviations: CRC, colorectal cancer; RCC, right-sided colon cancer; LCC, left-sided colon cancer; RSC, rectosigmoid cancer.

When multivariable logistic regression (Table 2) was performed on patients with metastatic cancer, being male (Female vs. male, OR = 0.854, 95%CI, 0.762–0.958, P < 0.001), advanced stage (N1 vs. N0, OR = 1.278, 95%CI, 1.102–1.483, P = 0.001; N2 vs. N0, OR = 1.548, 95%CI, 1.548–1.949, P < 0.001), mucinous carcinoma (mucinous vs. adenocarcinoma, OR = 1.447, 95%CI, 1.142–1.832, P = 0.002), poorly or undifferentiated (poorly vs. well, OR = 1.024, 95%CI, 1.186–2.309, P = 0.003; poorly differentiated vs. well-differentiated, OR = 1.913, 95%CI, 1.244–2.941, P = 0.003), and non-receipt of surgery (Yes, No, OR = 0.363, 95%CI, 0.309–0.426, P < 0.001) were all associated with significantly greater odds of having bone metastases at diagnosis. Notably, patients with brain metastasis were at highest risk of bone metastasis compared with other organ metastasis (brain metastasis (Yes vs. No, OR = 6.035, 95%CI, 2..848-12.787, P < 0.001), lung metastasis (Yes vs. No, OR = 3.881, 95%CI, 1.873–8.040, P < 0.001), and liver metastasis (Yes vs. No, OR = 2.168, 95%CI, 1.055–4.452, P = 0.035)). RAS cancer patients had higher risk of bone metastasis compared with RCC (HR = 1.600, 95%CI, 1.427–1.795, P < 0.001). Patients who had more organ metastatic lesions were at increased risk of bone metastasis (more extra-bone metastatic lesions (1 vs. 0, OR = 3.826, 95%CI, 1.662–8.808, P = 0.002; 2 vs. 0, OR = 6.557, 95%CI, 5.641–7.623, P < 0.001; 3 vs. 0, OR = 8.191, 95%CI, 6.381–10.514, P < 0.001)).

Table 2

Multivariable Logistic Regression for the Presence of Bone Metastases at Diagnosis of CRC.

Patient characteristic	Patients		Among Entire cohort		Among cohort with metastasis	
	Patients	Bone metastasis	OR (95%CI)	P value	OR (95%CI)	P value
Sex						
Male	87,092	830				
Female	79,296	559	0.801 (0.723–0.888)	0.001	0.854 (0.762–0.958)	< 0.001
Age group				< 0.001		0.002
<40	4,565	60	Reference		Reference	
40–49	13,330	155	0.922 (0.681–1.247)	0.596	0.995 (0.701–1.412)	0.978
50–59	33,968	362	0.953 (0.722–1.256)	0.731	1.126 (0.817–1.553)	0.469
60–69	41,326	385	0.913 (0.694–1.201)	0.516	1.039 (0.755–1.430)	0.814
>69	73,199	427	0.720 (0.549–0.945)	0.018	0.839 (0.611–1.152)	0.278
Surgery				< 0.001		< 0.001
No	25,682	988	Reference		Reference	
Yes	140,425	398	0.378 (0.294–0.486)	< 0.001	0.363 (0.309–0.426)	P < 0.001
Unknown	281	3	0.580 (0.210–1.601)	0.293	0.618 (0.190–2.004)	0.422
T stage				< 0.001		
Tis,T0,T1,T2 (0,1, 2、3)	54,934	226	Reference			

Abbreviations: CRC, colorectal cancer; RCC, right-sided colon cancer; LCC, left-sided colon cancer; RSC, Rectosigmoid cancer; ORs: odds ratios; CI: confidence interval.

Patient characteristic	Patients		Among Entire cohort		Among cohort with metastasis	
	Patients	Bone metastasis	OR (95%CI)	P value	OR (95%CI)	P value
T3-T4 (4,5)	94,713	627	1.230 (1.050–1.442)	0.001		
Unknown	16,741	536	1.337 (1.145–1.562)	0.01		
N stage				< 0.001		< 0.001
N0	96,044	464	Reference		Reference	
N1	38,670	420	1.305 (1.135-1.500)	< 0.001	1.278 (1.102–1.483)	0.001
N2	21,119	250	1.756 (1.421–2.169)	< 0.001	1.548 (1.229–1.949)	< 0.001
Unknown	10.555	255	1.202 (1.031–1.401)	< 0.001	1.289 (1.095–1.517)	0.002
Pathology type				< 0.001		0.004
Adenomas	148,848	1,146	Reference		Reference	
Mucinous	12,430	110	1.602 (1.322–1.942)	< 0.001	1.447 (1.142–1.832)	0.002
Other type	3,897	93	1.322 (1.083–1.615)	0.006	1.260 (1.003–1.582)	0.047
Unspecified	1,213	40	1.124 (0.833–1.518)	0.445	0.907 (0.643–1.280)	0.580
Pathology grade				< 0.001		< 0.001
Well differentiated	15,215	48	Reference		Reference	

Abbreviations: CRC, colorectal cancer; RCC, right-sided colon cancer; LCC, left-sided colon cancer; RSC, Rectosigmoid cancer; ORs: odds ratios; CI: confidence interval.

Patient characteristic	Patients		Among Entire cohort		Among cohort with metastasis	
	Patients	Bone metastasis	OR (95%CI)	P value	OR (95%CI)	P value
Moderately differentiated	101,357	526	1.196 (0.907–1.575)	0.204	1.024 (0.744–1.410)	0.884
Poorly differentiated	23.044	310	2.216 (1.663–2.953)	< 0.001	1.655 (1.186–2.309)	0.003
Undifferentiated	4,488	48	2.305 (1.580–3.362)	< 0.001	1.913 (1.244–2.941)	0.003
Unknown	22,284	457	1.483 (1.119–1.964)	< 0.001	1.326 (0.958–1.835)	0.089
Number of Lymph node				< 0.001		0.012
0	74,454	74	Reference		Reference	
<12	44,662	202	1.559 (1.172–2.072)	0.002	0.899 (0.638–1.267)	0.543
>=12	3,621	76	3.129 (2.163–4.525)	< 0.001	1.391 (0.897–2.158)	0.140
Unknown	43,651	1,037	1.786 (1.173–2.721)	0.007	1.459 (0.922–2.309)	0.107
Tumor site				0.001		< 0.001
RCC			Reference		Reference	
LCC			1.126 (0.991–1.279)	0.068	0.979 (0.859–1.116)	0.753
RSC			1.633 (1.461–1.825	< 0.001	1.600 (1.427–1.795)	< 0.001
Brain metastasis						
No	166,004	1,322				

Abbreviations: CRC, colorectal cancer; RCC, right-sided colon cancer; LCC, left-sided colon cancer; RSC, Rectosigmoid cancer; ORs: odds ratios; CI: confidence interval.

Patient characteristic	Patients		Among Entire cohort		Among cohort with metastasis	
	Patients	Bone metastasis	OR (95%CI)	P value	OR (95%CI)	P value
Yes	384	67	2.860 (2.012–4.067)	< 0.001	6.035 (2.848–12.787)	< 0.001
Lung metastasis				< 0.001		0.001
No	158,660	782	Reference		Reference	
Yes	7,206	580	1.838 (1.519–2.225)	< 0.001	3.881 (1.873–8.040)	< 0.001
Unknown	522	27	2.343 (0.952–5.764)	0.064	3.734 (0.941–14.821)	0.061
Liver metastasis						0.107
No	143,768	378			Reference	
Yes	22,336	1006			2.168 (1.055–4.452)	0.035
Unknown	284	5			2.032 (0.585–7.058)	0.264
Extrabone metastasis sites to brain, lung and liver				< 0.001		< 0.001
0	141,400	243	Reference		Reference	
1	19,016	631	3.811 (1.655–8.773)	0.002	3.826 (1.662–8.808)	0.002
2	5,116	458	6.600 (5.676–7.674)	< 0.001	6.557 (5.641–7.623)	< 0.001
3	112	28	8.278 (6.448–10.628)	< 0.001	8.191 (6.381–10.514)	< 0.001
Other organ metastasis	744	29	9.061 (4.860-16.895)	< 0.001	8.959 (4.805–16.703)	< 0.001

Abbreviations: CRC, colorectal cancer; RCC, right-sided colon cancer; LCC, left-sided colon cancer; RSC, Rectosigmoid cancer; ORs: odds ratios; CI: confidence interval.

Survival

The median survival time (MST) for patients with bone metastasis was 11.3 months (Fig. 1A). For RCC, LCC, and RSC, the MST was 19.9 months, 22.3 months and 22.2 months when bone metastasis was absent, respectively. However, when bone metastasis was present, the MST decreased significantly and was 11.4 months, 12.4 months and 13.0 months for RCC, LCC, and RSC, respectively (Fig. 1B and Table 1). Additionally, patients with bone metastasis were able to benefit from surgery as shown in Fig. 1C.

Multivariable Cox regression (Table 3) for OS among patients with bone metastases at diagnosis revealed that older age (60–69 vs. <40, HR = 1.739, 95%CI, 1.226–2.468, P = 0.002; >69 vs. <40, HR = 2.171, 95%CI = 1.53–3.072, P < 0.001), poorly and undifferentiated (poorly vs. well, HR = 1.451, 95%CI, 1.058–1.990, P = 0.021; undifferentiated vs. well, HR = 1.845, 95%CI, 1.231–2.766, P = 0.003), RCC (LCC vs. RCC, HR = 0.844, 95%CI, 0.728–0.978, P = 0.024; RSC vs. RCC, HR = 0.709, 95% CI, 0.622–0.809, P < 0.001), and more extra-bone metastasis lesions (2 vs. 0, HR = 1.236, 95%CI, 1.050–2.429, P = 0.011; 3 vs. 0, HR = 1.612, 95%CI, 1.070–2.429, P = 0.023) were all significantly associated with poorer OS. CRC–cause mortality among patients with bone metastases at diagnosis is also presented in Table 3.

Table 3

Multivariable Cox Regression for All-Cause Mortality and CRC Cancer–Specific Mortality

Patient characteristic	All-cause Mortality		CRC-Specific Mortality	
	HR (95%CI)	P value	HR (95%CI)	P value
Age group		< 0.001		< 0.001
<40	Reference		Reference	
40–49	1.157 (0.791–1.695)	0.452	1.211 (0.805–1.823)	0.358
50–59	1.354 (0.951–1.927)	0.093	1.340 (0.913–1.966)	0.135
60–69	1.739 (1.226–2.468)	0.002	1.799 (1.229–2.634)	0.003
>69	2.171 (1.534–3.072)	< 0.001	2.183 (1.493–3.194)	< 0.001
Surgery		< 0.001		< 0.001
No	Reference		Reference	
Yes	0.598 (0.512–0.698)	< 0.001	0.551 (0.461–0.660)	< 0.001
Unknown	1.393 (0.517–3.757)	0.214	1.712 (0.541–5.417)	0.360
N stage		< 0.001		< 0.001
N0	Reference		Reference	
N1	0.923 (0.802–1.063)	0.267	0.856 (0.728–1.008)	0.062
N2	1.180 (0.984–1.414)	0.074	1.255 (1.023–1.539)	0.030
Unknown	1.076 (0.920–1.259)	0.362	1.075 (0.897–1.288)	0.431
Diagnosed methods				
Other method vs. Biopsy		< 0.001		< 0.001

Abbreviations: CRC, colorectal cancer; RCC, right-sided colon cancer; LCC, left-sided colon cancer; RSC, Rectosigmoid cancer; HRs: hazard ratios; CI: confidence interval.

Patient characteristic	All-cause Mortality		CRC-Specific Mortality	
	HR (95%CI)	P value	HR (95%CI)	P value
Pathology type		< 0.001		< 0.001
Adenomas	Reference		Reference	
Mucinous	1.165 (0.954–1.423)	0.135	1.301 (1.039–1.630)	0.022
Other type	1.435 (1.168–1.763)	0.001	1.536 (1.204–1.958)	0.001
Unspecified	2.465 (1.822–3.334)	< 0.001	2.033 (1.399–2.955)	< 0.001
Pathology grade		< 0.001		< 0.001
Well differentiated	Reference		Reference	
Moderately differentiated	0.960 (0.705–1.308)	0.797	0.951 (0.672–1.345)	0.777
Poorly differentiated	1.451 (1.058–1.990)	0.021	1.477 (1.036–2.106)	0.031
Undifferentiated	1.845 (1.231–2.766)	0.003	2.199 (1.385–3.493)	0.001
Unknown	1.107 (0.809–1.515)	0.524	1.136 (0.800-1.614)	0.475
Tumor site		< 0.001		< 0.001
RCC	Reference		Reference	
LCC	0.844 (0.728–0.978)	0.024	0.857 (0.724–1.016)	0.075
RSC	0.709 (0.622–0.809)	< 0.001	0.733 (0.631–0.850)	< 0.001
Liver metastasis				0.001
Yes			Reference	
No			1.227 (1.060–1.421)	0.006
Unknown			4.792 (1.748–13.134)	0.002

Abbreviations: CRC, colorectal cancer; RCC, right-sided colon cancer; LCC, left-sided colon cancer; RSC, Rectosigmoid cancer; HRs: hazard ratios; CI: confidence interval.

Patient characteristic	All-cause Mortality		CRC-Specific Mortality	
	HR (95%CI)	P value	HR (95%CI)	P value
Extrabone metastasis sites to brain, lung and liver		0.008		0.012
0	Reference		Reference	
1	1.029 (0.882–1.201)	0.713	1.167 (0.887–1.535)	0.271
2	1.236 (1.050–1.457)	0.011	1.309 (1.129–1.517)	< 0.001
3	1.612 (1.070–2.429)	0.023	1.855 (1.509–2.281)	< 0.001
Other organ metastasis 4	1.141 (0.780–1.670)	0.495	1.044 (0.776–1.405)	0.775

Abbreviations: CRC, colorectal cancer; RCC, right-sided colon cancer; LCC, left-sided colon cancer; RSC, Rectosigmoid cancer; HRs: hazard ratios; CI: confidence interval.

We then compared the MST by extent of metastasis sites (Fig. 1D). In general, patients with more metastasis sites had poorer survival. However, there was no survival difference for those with two or three extra-bone metastasis sites (P = 0.336). Then, we further compared the MST by subtype as stratified by tumor location and ascertained the extent of systemic disease (Table 4). We also found that the presence of bone metastases at initial diagnosis was associated with shorter survival time compared with patients presenting with 1 metastatic site without baseline bone involvement, except in RCC with brain metastasis (Table 4). There was no survival difference for single brain metastasis (MST = 8.9) and both brain and bone metastasis (MST = 9.0). Notably, for RSC with single brain metastasis, the MST was 14.0 months and then suddenly decreased to 1 month.

Table 4

The median survival of metastasis CRC with single metastatic site and multiple-sites

Subtype	Survival, Median (IOQ), month	
	Extra bone metastasis Disease Only	Extra bone metastasis and Bone Metastases
All cohort		
Subsite of metastasis		
0	45.8 (45.67–45.93)	13.98 (11.74–16.21)
Brain	12.62 (9.25-16)	6.5 (1.19–11.81)
Lung	24.04 (22.92–25.15)	14.31 (11.26–17.35)
Liver	21.30 (20.94–21.66)	11.28 (9.97–12.58)
Two sites		
Lung and liver	14.78 (14.22–15.31)	9.53 (8.43–10.64)
Lung and brain	7.75 (5.25–10.25)	5.82 (1.96–9.66)
Liver and brain	7.79 (4.98–10.60)	8.02 (2.75–13.29)
Three sites		
Lung, liver, and brain	6.10 (3.74–8.26)	6.98 (4.27–9.69)
Other sites	16.63 (18.21–18.21)	9.54 (4.75–14.32)
RCC		
Subsite of metastasis		
0	43.96 (43.76–44.16)	10.37 (7.33–13.41)
Brain	8.94 (4.43–13.44)	9 (0-18.02)
Lung	19.81 (17.86–21.78)	12.13 (8.27–15.99)
Liver	17.06 (16.55–17.57)	7.85 (6.54–9.15)
Two sites		
Lung and liver	11.41 (10.65–12.17)	6.79 (5.50–8.09)
Lung and brain	9.15 (2.48–15.83)	6.43 (1.34–11.50)
Liver and brain	6.65 (3.52–9.78)	7.14 (0.62–13.66)

Abbreviations: CRC, colorectal cancer; RCC, right-sided colon cancer; LCC, left-sided colon cancer; RSC, Rectosigmoid cancer.

Subtype	Survival, Median (IOQ), month	
	Extra bone metastasis Disease Only	Extra bone metastasis and Bone Metastases
Three sites		
Lung, liver, and brain	6.93 (4.93–8.83)	6.5 (2.72–10.28)
Other sites	14.04 (11.84–16.25)	7.46 (2.59–12.33)
LCC		
Subsite of metastasis		
0	47.00 (46.77–47.24)	12.78 (8.69–16.87)
Brain	13.99 (8.11–19.88)	1 (0–1)
Lung	25.01 (22.71–27.31)	14.11 (7.14–21.08)
Liver	24.29 (23.61–24.96)	13.02 (10.10-15.93)
Two sites		
Lung and liver	15.47 (14.44–16.49)	11.33 (8.78–13.87)
Lung and brain	8.04 (3.83–12.25)	9 (0-20.76)
Liver and brain	13.03 (6.89–19.16)	2.5 (0.39–4.61)
Three sites		
Lung, liver, and brain	2.56 (1.67–3.45)	1.67 (1.01–2.33)
Other sites	18.76 (15.66–21.87)	9.88 (0-22.41)
RSC		
Subsite of metastasis		
0	47.24 (47.03–47.46)	15.16 (12.02–18.30)
Brain	15.39 (10.16–20.61)	3.8 (0-7.89)
Lung	26.06 (24.44–27.68)	15.56 (10.98–20.15)
Liver	24.49 (23.77–25.21)	13.72 (11.21–16.22)
Two sites		
Lung and liver	17.31 (16.32–18.31)	10.15 (8.53–11.78)

Abbreviations: CRC, colorectal cancer; RCC, right-sided colon cancer; LCC, left-sided colon cancer; RSC, Rectosigmoid cancer.

Subtype	Survival, Median (IOQ), month	
	Extra bone metastasis Disease Only	Extra bone metastasis and Bone Metastases
Lung and brain	7.39 (3.94–10.84)	7.01 (5.06–8.94)
Liver and brain	15 (3.80–26.20)	11.98 (4.98–18.99)
Three sites		
Lung, liver, and brain	9.77 (5.98–13.56)	9.82 (5.33–14.29)
Other sites	18.61 (15.56–21.65)	11.15 (4.91–17.39)
Abbreviations: CRC, colorectal cancer; RCC, right-sided colon cancer; LCC, left-sided colon cancer; RSC, Rectosigmoid cancer.		

When patients had metastasis at two sites, such as liver and lung metastasis, other bone metastasis was associated with poorer survival except in those with LCC. Patients with liver, brain, and bone metastasis in the LCC, had a MST of 2.5 months but the MST increased to 13.0 months when bone metastasis was not present.

For patients with three organs affected by metastasis, survival difference was independent of bone metastasis.

Discussion

Similar to previous reports, our study showed that the rate of bone metastasis from CRC was extremely low[19, 20]. In this study, we summarized the clinicopathological features associated with bone metastasis and prognostic factors for bone metastasis. Especially noteworthy was our finding that RCC is a more significant risk factor for bone metastasis. Bone metastases were also associated with the presence of lung metastases.

Bone is a common site of metastasis from malignant solid tumors such as prostate, breast, kidney, lung, and thyroid cancers[21]. In contrast, metastases to bone in CRC patients account for less than 10%[22]. This suggests that bone metastasis in CRC behaves differently compared with other cancers. Reports have demonstrated that the environment of a specific organ can influence tumor cell adhesion contributing to the efficacy of tumor spread[23, 24]. Liver and lungs are the most frequently affected organs in CRC. As reported in the literature, the first sites of metastases in CRC tend to be the liver or lungs, which both contain dense capillary beds that can trap tumor cells and seed into these organs[24].

Several interesting observations emerge from our analysis of the relationship between lung metastases and RSC with bone metastases. Previous reports have supported a high frequency of lung metastases with brain metastases[25, 26]. However, the relationship has not been as clearly defined with bone metastases even though metachronous pulmonary metastases have been shown be an independent risk factor of bone metastases[27]. These observations may relate to a longer survival associated with lung metastases. Our series confirms previous observations of an increased incidence of bone metastases in patients with RSC[25,

28]. A previous study reported that a higher incidence of lung metastases was observed in RSC compared with other colon cancers[29]. Thus, we speculated that RSC patients with lung metastases are at particularly high risk of developing bone metastasis.

Our research highlights the differences in OS based on metastatic sites and the number of disease sites at the time of initial diagnosis. We found that the OS of patients with mCRC varied by location of the metastatic disease and the metastatic number at the time of initial diagnosis. Potential reasons for the survival difference among the various groups may be due to treatment differences associated with various groups and the metastasis effects on critical organ function (e.g., brain metastasis). The median survival for patients with bone metastasis was 11.3 months, which is consistent with Santini et al[30]. These patients showed poorer prognoses than patients with metastasis to other organs. One of the reasons for the very poor prognosis may be that 80 to 90% of patients with bone metastasis from CRC also have extra-bone metastasis; often in the lung and/or liver[12]. It is thus important to be alert for bone metastasis during surveillance of patients with lung or liver metastases.

Treatment options for bone metastasis are limited; the most used methods include radiotherapy and bisphosphonate, which appear to be only effective in cases diagnosed early. Consequently, early diagnosis is very important in mitigating against high-risk of bone metastasis.

There are several weaknesses in our study. First, the study was retrospective in design and we did not collect detailed information on treatment methods, which could influence prognosis. This may be a confounding factor in our results. Another confounding factor is the bone metastasis number and the location of bone metastasis, which needs further study.

Conclusions

We reported the incidence of bone metastasis from CRC[19, 20]. Especially noteworthy is our finding that RSC and the presence of more metastasis sites is a significant risk factor for bone metastasis. Unlike other solid tumors, patients with bone metastasis had poorer survival and the MST was significantly shortened for single metastasis disease or when lung and liver metastasis were present.

Abbreviations

CRC: Colorectal cancer; SREs: Skeletal-related events; mCRC: metastasis colorectal cancer; SEER: Surveillance, Epidemiology, and End Results; RCC: Right-sided location cancer; LCC: Left-sided colon cancer; RSC: rectosigmoid cancer; MC: mucinous adenocarcinoma; AC: adenocarcinoma; OS: Overall Survival; MST: Median Survival Time.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the institution through the respective institutional review boards, which belong to the Ethics Committee of Sun Yat-sen University Cancer Center. All patients provided written informed

consent to participate in this study.

Consent for publication

Not applicable

Availability of data and material

Raw data was deposited in the Research Data Deposit system (http://www.researchdata.org.cn) of Sun Yat-sen University Cancer and can be obtained from the corresponding authors on reasonable request.

Funding

This work was supported by the National Natural Science Foundation of China (Grants no. 81272641). We would like to thank the native English speaking scientists of Elixigen Company (Huntington Beach, California) for editing our manuscript.

Competing Interests

The authors have declared that no competing interest exists.

Authors' contributions

Conceptualization, YL, ZB, and LSS; Methodology, YL, WDH; Software and data curation, YL HWZ ; Formal Analysis, LSS, JC, XQK; XLP revised it critically for important intellectual content; Writing-Original Draft Preparation, YL; Project Administration and Funding Acquisition, XLP. All authors (YL, LSH, XQK, HWZ, JC, ZB, WDH, XLP) have read and approved the final manuscript.

Acknowledgements

Not applicable

References

References:

1. van der Stok EP, Spaander M, Grunhagen DJ, Verhoef C, Kuipers EJ. Surveillance after curative treatment for colorectal cancer. NAT REV CLIN ONCOL. 2017; 14**:** 297-315.
2. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B, et al. Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival. J Natl Cancer Inst. 2017; 109.
3. Ando K, Oki E, Saeki H, Kasagi Y, Tsuda Y, Zaitsu Y, et al. Number of Lymph Node Metastases May Indicate the Regimen for Adjuvant Chemotherapy in Patients with Stage III Colorectal Cancer. ANTICANCER RES. 2015; 35**:** 6207-6211.
4. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. ONCOLOGIST. 2007; 12**:** 20-37.

5. Galizia G, Lieto E, Orditura M, Castellano P, Imperatore V, Pinto M, et al. First-line chemotherapy vs bowel tumor resection plus chemotherapy for patients with unresectable synchronous colorectal hepatic metastases. Arch Surg. 2008; 143: 352-358, 358.
6. de Mestier L, Manceau G, Neuzillet C, Bachet JB, Spano JP, Kianmanesh R, et al. Primary tumor resection in colorectal cancer with unresectable synchronous metastases: A review. World J Gastrointest Oncol. 2014; 6: 156-169.
7. Rotolo N, De Monte L, Imperatori A, Dominioni L. Pulmonary resections of single metastases from colorectal cancer. SURG ONCOL. 2007; 16 Suppl 1: S141-S144.
8. Edge SB, Sobin LH, Page DL, Gospodarowicz MK, Greene FL, Winchester DP. Re: Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst. 2005; 97: 463-464, 464-465.
9. Coleman RE. Skeletal complications of malignancy. CANCER-AM CANCER SOC. 1997; 80: 1588-1594.
10. Nozue M, Oshiro Y, Kurata M, Seino K, Koike N, Kawamoto T, et al. Treatment and prognosis in colorectal cancer patients with bone metastasis. ONCOL REP. 2002; 9: 109-112.
11. Heras P, Karagiannis S, Kritikos K, Hatzopoulos A, Mitsibounas D. Ibandronate is effective in preventing skeletal events in patients with bone metastases from colorectal cancer. Eur J Cancer Care (Engl). 2007; 16: 539-542.
12. Roth ES, Fetzer DT, Barron BJ, Joseph UA, Gayed IW, Wan DQ. Does colon cancer ever metastasize to bone first? a temporal analysis of colorectal cancer progression. BMC CANCER. 2009; 9: 274.
13. Khattak MA, Martin HL, Beeke C, Price T, Carruthers S, Kim S, et al. Survival differences in patients with metastatic colorectal cancer and with single site metastatic disease at initial presentation: results from South Australian clinical registry for advanced colorectal cancer. Clin Colorectal Cancer. 2012; 11: 247-254.
14. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J CLIN ONCOL. 2004; 22: 1209-1214.
15. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J CLIN ONCOL. 2004; 22: 229-237.
16. Rabeneck L, Davila JA, El-Serag HB. Is there a true "shift" to the right colon in the incidence of colorectal cancer? AM J GASTROENTEROL. 2003; 98: 1400-1409.
17. Liang PS, Mayer JD, Wakefield J, Ko CW. Temporal Trends in Geographic and Sociodemographic Disparities in Colorectal Cancer Among Medicare Patients, 1973-2010. J RURAL HEALTH. 2017; 33: 361-370.
18. Zhang X, Zhang MJ, Fine J. A proportional hazards regression model for the subdistribution with right-censored and left-truncated competing risks data. STAT MED. 2011; 30: 1933-1951.
19. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst. 2004; 96: 1420-1425.

20. Sundermeyer ML, Meropol NJ, Rogatko A, Wang H, Cohen SJ. Changing patterns of bone and brain metastases in patients with colorectal cancer. Clin Colorectal Cancer. 2005; 5**:** 108-113.
21. Buckwalter JA, Brandser EA. Metastatic disease of the skeleton. AM FAM PHYSICIAN. 1997; 55**:** 1761-1768.
22. Katoh M, Unakami M, Hara M, Fukuchi S. Bone metastasis from colorectal cancer in autopsy cases. J GASTROENTEROL. 1995; 30**:** 615-618.
23. Schluter K, Gassmann P, Enns A, Korb T, Hemping-Bovenkerk A, Holzen J, et al. Organ-specific metastatic tumor cell adhesion and extravasation of colon carcinoma cells with different metastatic potential. AM J PATHOL. 2006; 169**:** 1064-1073.
24. Chambers AF, Groom AC, MacDonald IC. Dissemination and growth of cancer cells in metastatic sites. NAT REV CANCER. 2002; 2**:** 563-572.
25. Lee KC. Brain metastases from colorectal carcinoma: the long term survivors. CANCER-AM CANCER SOC. 1997; 79**:** 1842.
26. Ko FC, Liu JM, Chen WS, Chiang JK, Lin TC, Lin JK. Risk and patterns of brain metastases in colorectal cancer: 27-year experience. DIS COLON RECTUM. 1999; 42**:** 1467-1471.
27. Li A, Tan Z, Fu C, Wang H, Yuan J. [Analysis of risk factors for bone metastasis after radical resection of colorectal cancer within 5 years]. Zhonghua Wei Chang Wai Ke Za Zhi. 2017; 20**:** 58-61.
28. Besbeas S, Stearns MJ. Osseous metastases from carcinomas of the colon and rectum. DIS COLON RECTUM. 1978; 21**:** 266-268.
29. Pihl E, Hughes ES, McDermott FT, Johnson WR, Katrivessis H. Lung recurrence after curative surgery for colorectal cancer. DIS COLON RECTUM. 1987; 30**:** 417-419.
30. Santini D, Tampellini M, Vincenzi B, Ibrahim T, Ortega C, Virzi V, et al. Natural history of bone metastasis in colorectal cancer: final results of a large Italian bone metastases study. ANN ONCOL. 2012; 23**:** 2072-2077.

Figures

Figure 1

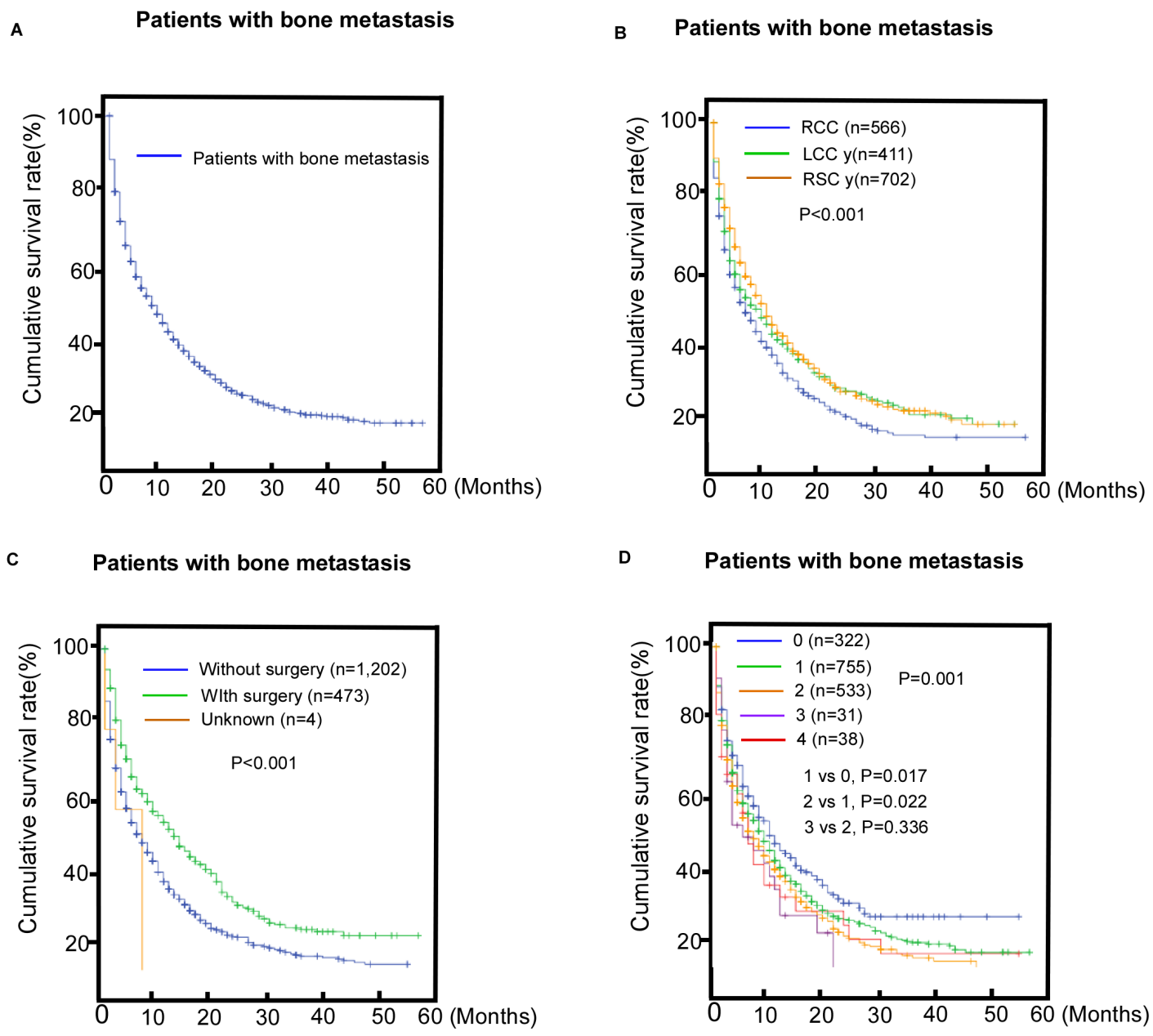

Figure 1

A, Overall survival among patients with bone metastasis; B, Survival difference stratified by subtype in cohort with bone metastasis (RCC, right-sided colon cancer; LCC, Left-sided colon cancer; RSC, Rectosigmoid Cancer); C, The cohort benefit associated with bone metastasis from surgery; D, Survival difference stratified by metastasis number of extra-bone metastases (0, Patients with only BM; 1, Patients with 1 extra-bone metastasis site; 2, Patients with 2 extra-bone metastasis sites; 3, Patients with 3 extra-bone metastasis sites and 4, Patients with 4 extra-bone metastasis sites).