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ORIGINAL ARTICLE

Colorectal Cancer Metastases to Brain or Bone and the Relationship to Primary Tumor Location: a Population-Based Study

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Abstract

Background The association of primary tumor location with incidence and prognosis of brain or bone metastasis in metastatic colorectal cancer (mCRC) patients remains unclear. We dissect this association across a large population.

Methods A total of 202,401 CRC patients from the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2015 were included. For brain metastasis, 9478 cases without brain metastasis information were excluded, leaving 192,923 CRC for incidence analysis and multivariable logistic/Cox regression analyses. Similarly, 193,013 CRC were eligible for bone metastasis analyses.

Results The incidence of brain or bone metastasis at initial diagnosis was 1.38% and 6.12% in mCRC cohort, respectively. Median survival of CRC patients with brain or bone metastasis was 4 and 5 months, respectively. Primary tumor location is not associated with the incidence of brain metastasis but with bone metastasis. For bone metastasis, right-sided colon cancer (RCC) patients exhibited the lowest incidence, whereas rectal cancer (RC) patients had the highest. For both brain and bone metastases, RCC patients always had the shortest median survival, whereas RC patients had the longest. The common risk factors for brain or bone metastasis were grade III and multi-extracerebral or ectosteal metastases. The favorable prognostic factors for brain or bone metastasis were being female, married, insured, and RC. RCC is an unfavorable prognostic factor.

Conclusions Primary tumor location impacts incidence proportions of bone metastasis and survival of both brain and bone mCRC patients. Primary tumor location should be taken into consideration in clinical practice and prognostic assessment.

Keywords Colorectal cancer · Primary tumor location · Metastasis · Incidence · Prognosis

Shijun Lei and Yizhi Ge contributed equally to this work.

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Introduction

Colorectal cancer (CRC) has the third highest incidence and mortality rate among all cancers in the USA.[1] Distant metastases, accounting for 20% of CRC patients at diagnosis,[2] are a major cause of treatment failure and death. Early detection of metastasis in CRC patients and subsequent timely treatment might improve prognosis.[3]

Though the rather dismal prognosis of CRC patients with brain or bone metastasis, it has been much less investigated. This is in part due to low occurrence rate and a lack of a sufficiently large CRC patient cohort for analysis. Consequently, the estimates on the incidences of brain or bone metastasis in literature are scarce and inconsistent.[4–7] The reported incidence of brain metastasis varied widely from 0.1% to 10%, a 100-fold difference,[8–11] and the median survival ranged from 4 to 8 months in CRC patients.[4, 12, 13] Similarly, the incidence of bone metastasis was reportedly from 3.7% up to 11%,[14] and its median survival was 5 to 7 months.[13, 15] The cohorts used in previous investigations were often derived from single-center registries with limited numbers of patients and relatively outdated,[16–19] which would not faithfully reflect current metastasis incidence and survival of CRC patients receiving modern therapy.[20] Therefore, it is highly desired to reassess these rare metastatic events in CRC patients using an up-to-date large cohort.

CRC is not a single illness but rather a heterogeneous genetic disease.[21] Primary tumors at different locations are thought to differ in their epidemiology, pathology, and molecular features. These differences have guided researchers to explore the predictive and prognostic value of primary tumor location (PTL) in CRC. A recent meta-analysis revealed that PTL is an independent prognostic factor for CRC patients,[22] suggesting the necessity of taking PTL as a stratification factor in CRC studies. However, whether PTL of CRC patients is associated with brain or bone metastasis or both remains unclear.

Herein, utilizing the Surveillance, Epidemiology, and End Results (SEER) database,[23] we stratified CRC patients by PTL to elucidate the incidence of brain and bone metastases in CRC patients at initial diagnosis. The median survival of these patients was also determined. Meanwhile, we analyzed influence factors and prognostic factors underlying brain or bone metastasis.

Materials and Methods

SEER database, founded by the National Cancer Institute (NCI) in 1973, is one of the most representative tumor registration databases covering approximately 28% of the US population. It involves information about various types of cancers and their metastatic sites in the brain, bone, liver, and lung.[1] From SEER, we identified 202,401 primary CRC patients between 2010 and 2015. After excluding those with unknown status of metastases at diagnosis, 192,923 CRC cases were for brain analysis, of which 532 were diagnosed with brain metastasis. Of the cases, 193,013 were for bone analysis, of which 2375 were diagnosed with bone metastasis. For survival analysis, 11 cases were further excluded because their diagnosis of CRC was from postmortem and death certificate.

CRC patients were stratified into three location subsets by PTL: left-sided colon cancer (LCC), right-sided colon cancer (RCC), and rectal cancer (RC). LCC includes splenic flexure, descending colon, sigmoid colon, and rectosigmoid junction. RCC includes cecum, ascending colon, hepatic flexure, and transverse colon. We identified the numbers of CRC patients with brain or bone metastasis at initial diagnosis and calculated the corresponding incidences, which are referred to as initial incidences throughout our study. Incidences of brain or bone metastasis at initial diagnosis were compared across these three location subsets using Pearson's chi-squared test. Bonferroni correction was applied to assess the differences in the incidences of brain or bone metastasis between any two of three location subsets. Kaplan-Meier method was used to analyze survival outcomes. Multivariable logistic regression model was employed to explore risk factors of brain or bone metastasis. Multivariable Cox regression was applied to survival analysis for examining prognostic factors related to all-cause mortality. For the analysis of colorectal cancer-specific mortality, we performed Fine and Gray's competing risk regression to exclude the effects of death from other diseases on the prognosis.[24] Since the hazard function for unknown subtype patients was not proportional over time, the interaction of this covariant with time was included in regression analysis. Statistical analyses were performed using SPSS (V22, IBM) and R (version 3.4.0; R Foundation). For competing risk analysis, the cmprsk package (version 2.2-72014) in R software was used.

Results

Incidence of Brain or Bone Metastasis and the Corresponding Influence Factors

As shown in Supplementary Table 1, the overall incidence of brain metastasis at initial diagnosis was 0.28% (532/192,923) among entire CRC cohort and 1.38% (532/38,659) among mCRC patients. Stratification of the data by different PTL revealed that the incidence of brain metastasis showed no difference in mCRC patients. For bone metastasis at initial diagnosis, the overall incidence was 1.23% for CRC cohort (2375/193,013) and 6.12% (2375/38,783) for mCRC patients (Table 1). Among CRC cohort, the incidence of bone metastasis at initial diagnosis was 1.10% for LCC, 0.85% for RCC,

Table 1 Incidence proportions and median survival of colorectal cancer patients with bone metastasis stratified by primary tumor location at initial diagnosis

Subset	Patients, no.			Incidence proportion of bone metastasis, %[b]		Survival of patients with bone metastasis, median (IQR), months
	Subset patients	With metastatic disease	With bone metastasis	Within subset cohort[c]	Within mCRC corhort of subset[d]	
LCC	65,762	13,586	726	1.10	5.34	5 (2–16)
RCC	79,968	14,546	682	0.85	4.69	4 (1–12)
RC	41,283	7264	622	1.51	8.56	8 (2–19)
Unknown[a]	6000	3387	345	5.75	10.19	2 (1–6)
All subsets	193,013	38,783	2375	1.23	6.12	5 (1–14)

LCC left-sided colon cancer, *RCC* right-sided colon cancer, *RC* rectal cancer, *IQR* interquartile range

[a] Unknown: the subset without detailed information regarding primary tumor location

[b] Pearson's chi-squared test was applied to detect the difference in the incidences across LCC, RCC, and RC patients

[c] Among three different primary tumor location subsets, $\chi^2 = 140.752$, $P < 0.001$. Comparison: any two of these three location subsets: LCC vs. RCC, $\chi^2 = 6.342$, $P = 0.01$; LCC vs. RC, $\chi^2 = 81.107$, $P < 0.001$; RCC vs. RC, $\chi^2 = 129.354$, $P < 0.001$

[d] Among three different location subsets, $\chi^2 = 108.728$, $P < 0.001$. Comparison: any two of these three location subsets: LCC vs. RCC, $\chi^2 = 23.787$, $P < 0.001$; LCC vs. RC, $\chi^2 = 33.076$, $P < 0.001$; RCC vs. RC, $\chi^2 = 109.405$, $P < 0.001$

and 1.51% for RC; among mCRC patients, the incidence was 5.34% for LCC, 4.69% for RCC, and 8.56% for RC. Thus, for any given PTL, the initial incidence of brain metastasis was 3.5–6-fold lower than that of bone metastasis. Intriguingly, the incidences of brain metastasis were not statistically different across LCC, RCC, and RC patients ($P = 0.80$ in entire CRC cohort and $P = 0.20$ in mCRC patients). In contrast, the incidences of bone metastasis were significantly different across LCC, RCC, and RC patients ($P < 0.001$), the lowest in RCC patients and the highest in RC patients (Table 1). Thus, PTL was differentially associated with the incidences of bone and brain metastases.

Next, multivariable logistic regression analysis was employed to dissect the factors that might affect the incidences of brain and bone metastases in mCRC patients. For brain metastasis (Supplementary Table 2), grade III, two extracerebral metastatic sites and three extracerebral metastatic sites were the risk factors.

For bone metastasis (Table 2), grade III (vs grade I; OR, 1.640; 95% CI, 1.254–2.145; $P < 0.001$), grade IV (vs grade I; OR, 1.633; 95% CI, 1.146–2.326; $P = 0.007$), two ectosteal metastatic sites (vs 0 or 1 ectosteal metastatic site; OR, 2.209; 95% CI, 2.006–2.433; $P < 0.001$), three ectosteal metastatic sites (vs 0 or 1 ectosteal metastatic site; OR, 7.298; 95% CI, 5.106–10.431; $P < 0.001$), CEA-positive (vs CEA-negative; OR, 1.221; 95% CI, 1.046–1.425; $P = 0.01$), and RC (vs LCC; OR, 1.437; 95% CI, 1.282–1.612; $P < 0.001$) were found to be the risk factors. The protective factors were being female (vs male; OR, 0.789; 95% CI, 0.722–0.862; $P < 0.001$) and perineural invasion positive (vs perineural invasion negative; OR, 0.755; 95% CI, 0.626–0.909; $P = 0.003$). Of note, the common risk factors for both brain and bone metastases are grade III and multiple extracerebral or ectosteal metastatic sites (two or three sites).

Survival and Influence Factors

We next identified the prognostic factors using multivariable Cox regression analysis and took time effect into consideration when dealing with this large-scale epidemiological statistics, which would reduce bias and enhance reliability.

The median survival of all CRC patients with brain or bone metastasis was 4 and 5 months, respectively (Table 1, Supplementary Table 1, Fig. 1a, and Supplementary Fig. 1A). RCC patients with brain or bone metastasis had the shortest median survival (3 months for brain metastasis and 4 months for bone metastasis) (Fig. 1b and Supplementary Fig. 1B), while RC patients with brain or bone metastasis had the longest median survival (7 and 8 months, respectively). We also assessed the median survival of mCRC patients stratified by PTL and the extent of systemic metastatic disease. For LCC, the patients with only brain metastasis showed longer survival than those with only bone metastasis (9 vs 5 months) (Table 3 and Supplementary Table 3). Conversely, for RCC or RC, the patients with only brain metastasis had shorter survival than those with only bone metastasis (3 vs 4 months for RCC, 7 vs 10 months for RC) (Table 3 and Supplementary Table 3). Nevertheless, overall, mCRC patients with more systemic metastasis exhibited shorter median survival (Table 3, Supplementary Table 3, Fig. 1c, and Supplementary Fig. 1C). mCRC patients who had brain and concurrent extracerebral metastases exhibited drastically reduced median survival compared to those who had the

Table 2 Multivariable logistic regression for the presence of bone metastasis at diagnosis of colorectal cancer

Variable	Patients, no.		Among entire cohort		Among subset with metastatic disease	
	Patients ($n = 193,013$)	With bone metastasis ($n = 2375$)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age at diagnosis, years[a]						
< 40	5892	95	1 [reference]	NA	1 [reference]	NA
41–60	56,778	800	0.899 (0.718–1.126)	0.36	1.017 (0.812–1.273)	0.89
61–80	92,565	1115	0.806 (0.645–1.007)	0.06	0.998 (0.799–1.246)	0.98
> 80	37,772	365	0.578 (0.454–0.736)	< 0.001	0.799 (0.627–1.018)	0.07
Sex						
Male	101,224	1428	1 [reference]	NA	1 [reference]	NA
Female	91,789	947	0.750 (0.687–0.819)	< 0.001	0.789 (0.722–0.862)	< 0.001
Race[a]						
White	151,657	1804	1 [reference]	NA	1 [reference]	NA
Black	22,947	362	1.084 (0.960–1.223)	0.20	1.045 (0.925–1.179)	0.48
Other	17,506	207	0.926 (0.797–1.077)	0.30	1.010 (0.867–1.176)	0.90
Marital status						
Unmarried	82,488	1104	1 [reference]	NA	1 [reference]	NA
Married	98,614	1151	1.003 (0.917–1.096)	0.96	1.028 (0.940–1.125)	0.54
Unknown	11,911	120	0.823 (0.674–1.005)	0.06	0.919 (0.751–1.124)	0.41
Grade						
I	14,767	68	1 [reference]	NA	1 [reference]	NA
II	119,421	774	1.336 (1.037–1.722)	0.03	0.973 (0.751–1.262)	0.84
III	27,015	447	3.102 (2.386–4.034)	< 0.001	1.640 (1.254–2.145)	< 0.001
IV	5306	70	3.356 (2.379–4.735)	< 0.001	1.633 (1.146–2.326)	0.007
Unknown	26,504	1016	2.836 (2.196–3.663)	< 0.001	1.488 (1.146–1.931)	0.003
Insurance status						
Uninsured	6095	117	1 [reference]	NA	1 [reference]	NA
Insured	181,883	2206	1.006 (0.823–1.230)	0.95	1.076 (0.881–1.314)	0.47
Unknown	5035	52	0.770 (0.543–1.091)	0.14	0.966 (0.681–1.370)	0.85
No. of ectosteal metastatic sites (brain, liver, or lung)						
0 or 1	184,855	1412	1 [reference]	NA	1 [reference]	NA
2	6715	734	5.888 (5.318–6.520)	< 0.001	2.209 (2.006–2.433)	< 0.001
All 3	155	46	18.975 (13.049–27.591)	< 0.001	7.298 (5.106–10.431)	< 0.001
Unknown	1288	183	9.147 (7.669–10.909)	< 0.001	4.272 (3.588–5.086)	< 0.001
CEA						
Negative	56,641	207	1 [reference]	NA	1 [reference]	NA
Positive	52,546	1385	3.310 (2.840–3.858)	< 0.001	1.221 (1.046–1.425)	0.01
Unknown	83,826	783	1.689 (1.443–1.978)	< 0.001	1.156 (0.982–1.361)	0.08
Perineural invasion						
Negative	132,494	595	1 [reference]	NA	1 [reference]	NA
Positive	16,170	146	1.394 (1.158–1.679)	< 0.001	0.755 (0.626–0.909)	0.003
Unknown	44,349	1634	3.796 (3.410–4.225)	< 0.001	1.837 (1.651–2.044)	< 0.001
Subset						
LCC	65,762	726	1 [reference]	NA	1 [reference]	NA
RCC	79,968	682	0.893 (0.799–0.998)	0.046	0.902 (0.807–1.008)	0.07
RC	41,283	622	1.178 (1.053–1.318)	0.004	1.437 (1.282–1.612)	< 0.001
Unknown[b]	6000	345	1.739 (1.500-2.016)	< 0.001	1.331 (1.150–1.540)	< 0.001

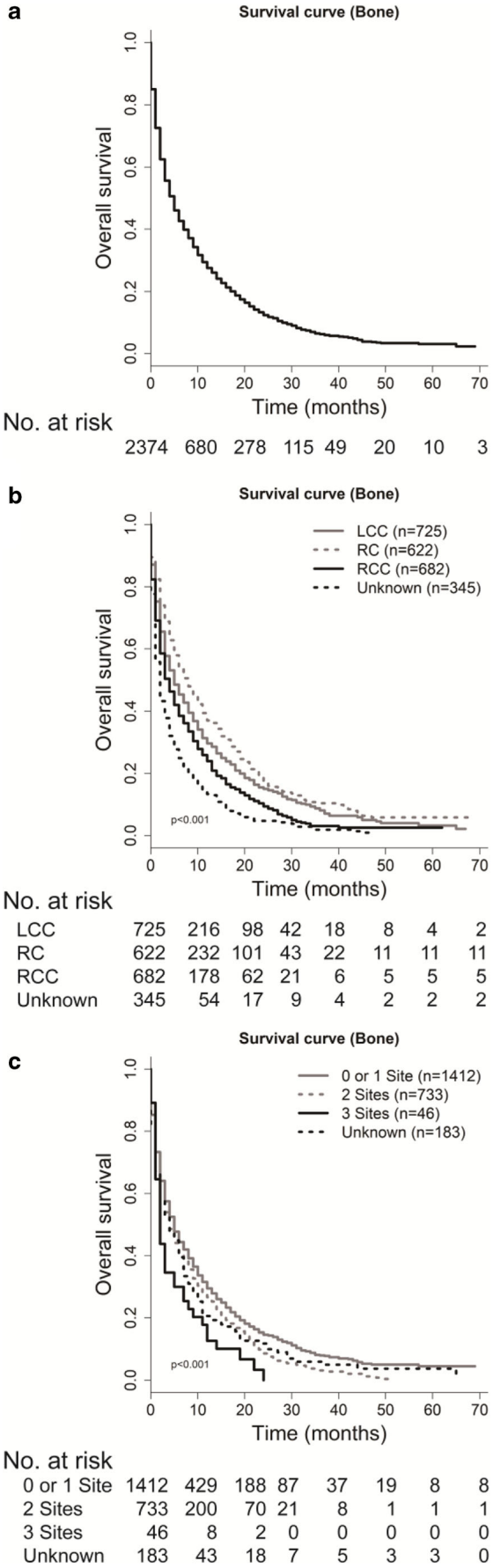
LCC left-sided colon cancer, *RCC* right-sided colon cancer, *RC* rectal cancer, *CEA* carcinoembryonic antigen, *OR* odds ratio, *NA* not available

[a] Cases without information regarding age or race were removed

[b] Unknown: the subset without detailed information regarding primary tumor location

extracerebral metastases only (Supplementary Table 3). This was similarly observed for bone metastasis (Table 3).

The multivariable Cox regression analysis on CRC patients with brain or bone metastasis revealed the risk and protective factors related to all-cause and colorectal cancer-specific mortality. In patients with brain metastasis (Supplementary Table 4), the risk factors of all-cause mortality were 61 to 80 years old (vs < 40 years old; hazard ratio [HR], 1.585; 95% CI, 1.501–1.674; $P < 0.001$) and over 80 (vs < 40 years old; HR, 3.277; 95% CI, 3.100–3.464; $P < 0.001$), black race (vs white race; HR, 1.146; 95% CI, 1.119–1.173; $P < 0.001$), grade II (vs grade I; HR, 1.227; 95% CI, 1.184–1.272; $P < 0.001$), grade III (vs grade I; HR, 1.973; 95% CI, 1.898–2.051; $P < 0.001$), and grade IV (vs grade I; HR, 2.168; 95% CI, 2.055–2.287; $P < 0.001$), two extracerebral metastatic sites (vs 0 or 1 extracerebral metastatic site; HR, 2.781; 95% CI, 2.699–2.865; $P < 0.001$) and three extracerebral metastatic sites (vs 0 or 1 extracerebral metastatic site; HR, 3.458; 95% CI, 3.193–3.744; $P < 0.001$), CEA-positive (vs CEA-negative; HR, 2.210; 95% CI, 2.160–2.260; $P < 0.001$),



◀ **Fig. 1** Survival analysis of bone metastatic colorectal cancer patients identified at initial diagnosis. **a** Overall survival of CRC patients with bone metastasis. **b** Survival of CRC patients with bone metastasis stratified by primary tumor location. **c** Survival of CRC patients with bone metastasis stratified by the extent of extracerebral metastatic disease. Extent of extracerebral metastatic disease is classified by the number of metastatic sites (brain, liver, or lung)

perineural invasion positive (vs perineural invasion negative; HR, 1.723; 95% CI, 1.678–1.770; $P < 0.001$), and RCC (vs LCC; HR, 1.068; 95% CI, 1.048–1.088; $P < 0.001$). The protective factors of all-cause mortality were being female (vs male; HR, 0.820; 95% CI, 0.807–0.834; $P < 0.001$), married (vs unmarried; HR, 0.744; 95% CI, 0.732–0.757; $P < 0.001$), insured (vs uninsured; HR, 0.796; 95% CI, 0.762–0.831; $P < 0.001$), and RC (vs LCC; HR, 0.905; 95% CI, 0.885–0.926; $P < 0.001$).

In patients with bone metastasis (Table 4), the risk factors of all-cause mortality were 61 to 80 years old (vs < 40 years old; HR, 1.574; 95% CI, 1.491–1.663; $P < 0.001$) and over 80 (vs < 40 years old; HR, 3.242; 95% CI, 3.067–3.427; $P < 0.001$), black race (vs white race; HR, 1.145; 95% CI, 1.118–1.172; $P < 0.001$), grade II (vs grade I; HR, 1.228; 95% CI, 1.185–1.273; $P < 0.001$), grade III (vs grade I; HR, 1.978; 95% CI, 1.903–2.057; $P < 0.001$), and grade IV (vs grade I; HR, 2.173; 95% CI, 2.059–2.292; $P < 0.001$), two ectosteal metastatic sites (vs 0 or 1 ectosteal metastatic site; HR, 2.721; 95% CI, 2.640–2.805; $P < 0.001$) and three ectosteal metastatic sites (vs 0 or 1 ectosteal metastatic site; HR, 3.950; 95% CI, 3.342–4.668; $P < 0.001$), CEA-positive (vs CEA-negative; HR, 2.232; 95% CI, 2.183–2.283; $P < 0.001$), perineural invasion positive (vs perineural invasion negative; HR, 1.725; 95% CI, 1.680–1.772; $P < 0.001$), and RCC (vs LCC; HR, 1.067; 95% CI, 1.047–1.088; $P < 0.001$). The protective factors of all-cause mortality were being female (vs male; HR, 0.819; 95% CI, 0.805–0.832; $P < 0.001$), married (vs unmarried; HR, 0.745; 95% CI, 0.733–0.758; $P < 0.001$), insured (vs uninsured; HR, 0.797; 95% CI, 0.764–0.833; $P < 0.001$), and RC (vs LCC; HR, 0.904; 95% CI, 0.884–0.925; $P < 0.001$).

Thus, brain and bone metastatic CRC patients shared several favorable prognostic factors: being female, married, insured, and RC and a common unfavorable prognostic factor RCC. Of note, the factors mentioned above were consistently identified for both all-cause mortality and cancer-specific mortality (Table 4 and Supplementary Table 4).

Discussion

Based on the SEER data, we stratified CRC patients by PTL and reported the incidence proportions, influence factors, and the prognosis of CRC patients with brain or bone metastasis at initial diagnosis. We for the first time reported the relationship

Table 3 Median survival of colorectal cancer patients by extent of metastasis (bone)

Subset	Sites of metastasis	Survival, median (IQR), months	
		No concurrent bone metastasis	With concurrent bone metastasis
LCC	Brain	9 (4–27)	NA
	Liver	19 (5–40)	7 (1–19)
	Lung	20 (6–45)	7 (2–17)
	Any 2 of 3	11 (2–23)	5 (2–14)
	All 3	7 (2–18)	2 (1–8)
RCC	Brain	3 (1–7)	NA
	Liver	11 (2–25)	3 (1–10)
	Lung	13 (3–31)	5 (2–16)
	Any 2 of 3	6 (1–18)	3 (1–11)
	All 3	3 (2–12)	2 (1–9)
RC	Brain	7 (4–21)	NA
	Liver	20 (7–38)	7 (3–18)
	Lung	22 (8–43)	7 (3–19)
	Any 2 of 3	12 (4–25)	8 (2–20)
	All 3	7 (2–13)	3 (2–14)
Unknown[a]	Brain	2 (1–4)	NA
	Liver	3 (0–11)	1 (0–4)
	Lung	7 (1–21)	3 (1–16)
	Any 2 of 3	2 (0–10)	2 (1–7)
	All 3	NA	1 (0–2)
All subsets	Brain	5 (2–13)	1 (1–9)
	Liver	14 (3–32)	4 (1–14)
	Lung	18 (5–38)	6 (2–17)
	Any 2 of 3	9 (2–21)	4 (1–14)
	All 3	3 (1–12)	2 (1–8)

LCC left-sided colon cancer, *RCC* right-sided colon cancer, *RC* rectal cancer, *IQR* interquartile range, *NA* not applicable, the data cannot be statistically analyzed due to lack of sufficient number of cases

[a] Unknown: the subset without detailed information regarding primary tumor location

between PTL and the incidence of brain or bone metastasis. Given that SEER is the largest database covering approximately 28% of population in the USA, performing stringent quality control, and updating data per annum to ensure accuracy of statistics,[23] our results should be reliable and generalizable.

Back in 1990, the concept was proposed that distal colon (left-sided colon) and proximal colon (right-sided colon) were two different organs with respect to epidemiology, pathology, and molecular features.[25] It has been clear that primary tumors from different locations follow distinct molecular pathways during carcinogenesis.[26] For instance, KRAS gene mutations preferentially occur in LCC, whereas BRAF mutations is more often detected in RCC.[27] Further, LCC patients or RCC patients exhibited differential therapeutic responses to target therapy (i.e., the CALGB/SWOG 80405 study).[28] Moreover, it was reported that LCC had an increased risk of liver metastasis, whereas RC had a preference for pulmonary metastasis, indicating that CRC patients with different PTL display differential metastatic tendency for distant sites.[29] Although PTL was somewhat taken into consideration in previous CRC studies, these studies either simply analyzed colon cancer (excluding RC) by comparing LCC with RCC or took colon cancer as a whole (without distinguishing LCC from RCC) and compared it with RC.[15, 30] Furthermore, some studies even classified RC into LCC,[26, 31] which might lead to biased results. Therefore, systemic stratification of CRC patients based on PTL would provide a more precise perspective for analyzing clinical data and guiding clinical practice.

Incidence of Brain or Bone Metastasis

Metastases to the brain or bone in CRC patients are relatively rare. Precise estimation of incidence requires

Table 4 Multivariable Cox regression for all-cause mortality and colorectal cancer-specific mortality among patients with bone metastasis

Variable	Patients, no.		All-cause mortality		Colorectal cancer-specific mortality	
	Patients ($n = 193,013$)	With bone metastasis ($n = 2375$)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age at diagnosis, years[a]						
< 40	5892	95	1 [reference]	NA	1 [reference]	NA
41–60	56,778	800	1.010 (0.956–1.068)	0.71	0.934 (0.882–0.990)	0.02
61–80	92,565	1115	1.574 (1.491–1.663)	< 0.001	1.111 (1.049–1.175)	< 0.001
> 80	37,772	365	3.242 (3.067–3.427)	< 0.001	1.810 (1.705–1.921)	< 0.001
Sex						
Male	101,224	1428	1 [reference]	NA	1 [reference]	NA
Female	91,789	947	0.819 (0.805–0.832)	< 0.001	0.899 (0.880–0.919)	< 0.001
Race[a]						
White	151,657	1804	1 [reference]	NA	1 [reference]	NA
Black	22,947	362	1.145 (1.118–1.172)	< 0.001	1.137 (1.102–1.173)	< 0.001
Other	17,506	207	0.871 (0.846–0.898)	< 0.001	0.947 (0.913–0.983)	0.004
Marital status						
Unmarried	82,488	1104	1 [reference]	NA	1 [reference]	NA
Married	98,614	1151	0.745 (0.733–0.758)	< 0.001	0.774 (0.757–0.792)	< 0.001
Unknown	11,911	120	0.745 (0.719–0.773)	< 0.001	0.706 (0.671–0.742)	< 0.001
Grade						
I	14,767	68	1 [reference]	NA	1 [reference]	NA
II	119,421	774	1.228 (1.185–1.273)	< 0.001	1.397 (1.328–1.470)	< 0.001
III	27,015	447	1.978 (1.903–2.057)	< 0.001	2.571 (2.434–2.716)	< 0.001
IV	5306	70	2.173 (2.059–2.292)	< 0.001	2.804 (2.604–3.019)	< 0.001
Unknown	26,504	1016	2.016 (1.938–2.096)	< 0.001	2.344 (2.218–2.476)	<0.001
Insurance status						
Uninsured	6095	117	1 [reference]	NA	1 [reference]	NA
Insured	181,883	2206	0.797 (0.764–0.833)	< 0.001	0.742 (0.706–0.781)	< 0.001
Unknown	5035	52	0.829 (0.776–0.885)	< 0.001	0.813 (0.747–0.886)	< 0.001
No. of ectosteal metastatic sites (brain, liver, or lung)						
0 or 1	184,855	1412	1 [reference]	NA	1 [reference]	NA
2	6715	734	2.721 (2.640–2.805)	< 0.001	3.191 (3.073–3.313)	< 0.01
All 3	155	46	3.950 (3.342–4.668)	< 0.001	4.831 (4.051–5.761)	< 0.001
Unknown	1288	183	2.489 (2.337–2.651)	< 0.001	2.693 (2.454–2.955)	< 0.001
CEA						
Negative	56,641	207	1 [reference]	NA	1 [reference]	NA
Positive	52,546	1385	2.232 (2.183–2.283)	< 0.001	2.725 (2.643–2.809)	< 0.001
Unknown	83,826	783	1.436 (1.405–1.468)	< 0.001	1.471 (1.427–1.517)	< 0.001
Perineural invasion						
Not present	132,494	595	1 [reference]	NA	1 [reference]	NA
Present	16,170	146	1.725 (1.680–1.772)	< 0.001	2.107 (2.038–2.178)	< 0.001
Unknown	44,349	1634	2.142 (2.102–2.182)	< 0.001	2.537 (2.475–2.600)	< 0.001
Subset						
LCC	65,762	726	1 [reference]	NA	1 [reference]	NA
RCC	79,968	682	1.067 (1.047–1.088)	< 0.001	1.049 (1.023–1.076)	< 0.001
RC	41,283	622	0.904 (0.884–0.925)	< 0.001	0.898 (0.872–0.924)	< 0.001
Unknown[b]	6000	345	1.709 (1.648–1.771)	< 0.001	1.735 (1.649–1.826)	< 0.001

LCC left-sided colon cancer, *RCC* right-sided colon cancer, *RC* rectal cancer, *CEA* carcinoembryonic antigen, *HR* hazard ratio, *NA* not available

[a] Cases without age or race information were removed

[b] Unknown: the subset without detailed information regarding primary tumor location

a sufficiently large CRC patient cohort. Although some studies investigated incidence of brain or bone metastasis, the cohorts they employed were limited, ranging from 627 to 49,096 cases,[3, 12, 14, 17, 18] which likely accounted for inconsistent, widely spanning incidences found in literature (0.1% to 4% for brain metastasis; 3.7% to 11% for bone metastasis). In addition, previous studies did not fully assess the association of PTL with the incidence of brain or bone metastasis. Taking PTL into consideration, our analyses revealed that (1) for any given PTL, initial incidence of brain metastasis was always lower than that of bone metastasis; (2) RCC patients had the lowest initial incidence of bone metastasis, while RC patients had the highest; (3) and, intriguingly, the initial incidences of brain metastasis across three location subsets were not statistically different, suggesting that primary tumors in RCC, LCC, and RC might have similar tendency of metastasizing to the brain. Consistently, PTL was not found to be a factor affecting the occurrence of brain metastasis.

Survival

Although sporadic studies reported the median survival of CRC patients with brain or bone metastasis, they were based on the limited number of cases and did not consider the potential impact of PTL.[15, 19, 32–34] Our large cohort analyses however reveal that PTL is a prognostic factor for the survival of brain or bone mCRC patients. RCC patients had the shortest median survival, while RC had the longest. Given poor prognosis of RCC patients with brain or bone metastasis (despite its lowest incidence), our study suggests that timely and effective interventions may be particularly critical for RCC patients towards improving prognosis. Imaging surveillance, such as magnetic resonance imaging (MRI) and positron emission tomography combined with computed tomography (PET-CT), is not recommended to CRC patients for routine screening of brain or bone metastasis, likely because of their low incidence and no significant benefits identified towards improved prognosis of CRC patients with liver metastasis.[35] Nevertheless, such imaging examination may be important and can be suggested to some selected cases, for instance, RCC patients with high risk factors, in the hope of detecting possible brain or bone metastasis at early stages.

Influence Factor Analysis

The factor of "age over 80" lowered risk of brain and bone metastases at initial diagnosis in CRC cohort but affected survival. Lowered metastatic risk might be partly due to the high proportion of well-differentiated adenocarcinomas and their slow progression in elderly patients,[36, 37] while the dismal prognosis might be attributed to their poor responses to chemotherapy.[38] Although tumor grade was reported to be an independent risk factor of survival, the relationship between tumor grade and the incidence of brain or bone metastasis in CRC patients was not previously reported. Our work identified that grade III is a risk factor for both brain and bone metastases, while grade IV affected bone metastasis but not brain metastasis.

Of note, we identified RCC as an unfavorable prognostic factor in CRC patients with brain or bone metastasis. Our work also found that being female, married, or insured had a favorable influence on survival in CRC patients, consistent with previous studies,[15, 39, 40] and that RC was a favorable prognostic factor for CRC patients with brain or bone metastasis. These results together reinforce the notion that clinical features of CRC are heterogeneous and underscore the necessity of stratifying CRC patients by PTL for clinical practice and data analyses.

Limitations

First, CRC patients included in our analysis were limited to those with CRC identified at initial diagnosis. Those without clinical evidence of metastasis upon diagnosis but later developing detectable metastases might be missed. Thus, the incidence of brain or bone metastasis might be underestimated. Second, many other factors, such as treatments that likely impact metastasis rates and prognosis, were not provided by the database we employed. This made us unable to investigate the influence of these factors on incidence proportions and patient survival.

Conclusion

By employing a large SEER cohort, we stratified CRC patients by PTL and reported the incidence proportions of brain or bone metastasis in mCRC patients at the time of initial diagnosis and their corresponding median survival. We also identified the risk factors of metastasis and prognostic factors for brain or bone mCRC patients. Primary tumor location was not associated with brain metastasis incidence but did impact the incidence of bone metastasis and the survival of CRC patients with either brain or bone metastasis. Our findings support the importance of incorporating PTL into clinical decision-making for CRC patients and also provide useful and reliable information for oncologists and future studies aiming to improve detection rates of brain or bone metastasis in CRC patients.

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Authors' Contributions Shijun Lei and Yizhi Ge: Research design, data collection, interpretation and analysis, manuscript drafting. They contribute equally to this work. Shaobo Tian, Bo Cai, Xiang Gao, and Ning Wang: Work design and manuscript's critical revision for main intellectual content. Guobin Wang, Lin Wang, and Zheng Wang: Research design, data analysis, results interpretation, paper writing, and critical revision of the manuscript. All authors approved the final version and agreed to be accountable for all aspects of the work.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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