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ORIGINAL RESEARCH

Brain metastases in newly diagnosed colorectal cancer: a population-based study

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Background: Population-based incidence evaluations and prognosis assessments of brain metastasis (BM) at diagnosis of colorectal cancer (CRC) are lacking. Our study sought to determine the incidence of BM in CRC patients, median survival of patients with BM, and the risk factors of BM in CRC.

Patients and methods: Patients diagnosed with CRC were identified using the Surveillance, Epidemiology, and End Results database. Multivariable logistic and Cox regression analyses were performed to identify predictors of the presence of BM at CRC diagnosis and the factors associated with poor survival. Kaplan–Meier analysis was used to estimate the survival difference between subgroups.

Results: We identified 170,793 adult patients diagnosed with CRC between 2010 and 2013. From these patients, we identified 401 patients with BM at the time of CRC diagnosis, which represents 0.23% of the entire patient CRC cohort and 1.3% of the patients with metastatic disease to any site. Median survival of patients with BM was 7.0 months, and the survival could increase to 15.59 months if there was no metastasis to other organs. We found that extracranial metastases number, tumor site, and pathology type were associated with BM at CRC diagnosis.

Conclusion: The findings of this study indicate the incidence and prognosis for patients with BM at the time of CRC diagnosis. Our findings lend support for positive treatment for BM without metastasis to other organs.

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

Introduction

Approximately 20% of colorectal cancer (CRC) cases are found to have distant metastasis at the time of diagnosis, and the 5-year survival rate is <8%.[1] The most common metastasis sites of CRC are the liver, lung, and peritoneum, but other metastatic sites have been described, such as bone, spleen, brain, and distant lymph nodes.[2–4] A nationwide retrospective review from 3,827 autopsies generated insight into the metastatic patterns and demonstrated that primary cancers tend to metastasize differently with different frequencies to distinctive sites.[2,4,5] Patients with rectal cancer more often metastasize to extra-abdominal sites, whereas colon cancer patients show a higher frequency of abdominal metastasis according to the pathological records of CRC patients.[5]

It is well known that the most common metastatic site for CRC patients is the liver, followed by the lung.[2–4] However, the incidence of brain metastasis (BM) is very low (1.2%–3.2%)[6–9] and is of most concern because of neurological symptoms. Additionally,

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CRC with BM typically occurs at a later stage of disease progression. However, data regarding BM occurrence at the diagnosis of CRC are rare.

It has been reported that cases with uncommon metastases, including BM, are increasing.[7] However, the overall survival (OS) of advanced CRC has been improving due to treatment progression. Cytotoxic agents and targeted therapies have improved the prognosis of unresectable CRC patients up to 30 months.[10] Currently, the advancement of immunotherapy has markedly improved the prognosis of mismatch-repair deficient (microsatellite instability-deficient) cohort of CRC.[11] Multidisciplinary treatments could be applied for the treatment of metastatic lesions, including the BM.[12] Therefore, early diagnosis of BM is of vital importance. Unfortunately, the risk factors associated with the initial diagnosis of BM have not yet been fully investigated due to the limited number of patients.

It has been observed in clinical trial follow-ups that mucinous adenocarcinomas (MCs) have different distribution of metastatic disease compared with the more common adenocarcinoma (AC). Right-sided colon cancer (RCC) occurs in ~10%–15% of CRC cases. RCC has often been considered a distinct entity, consisting of characteristics similar to MC with a poor prognosis in metastatic disease.[13–15] However, whether these clinical factors contribute differently to BM in CRC remains unknown.

The purpose of the present study was to use the Surveillance, Epidemiology, and End Results (SEER) database to characterize the incidence of BM at the time of CRC diagnosis and examine if BM diagnosis is a risk factor for the prognosis of CRC. In addition, we sought to examine the clinical and sociodemographic predictors of poor survival among patients with BM at CRC diagnosis.

Patients and methods

Data regarding BM at the time of initial cancer diagnosis were retrieved from cases after 2010 in the SEER program of the National Cancer Institute SEER database. The data sets are available in the SEER data set repository https://seer.cancer.gov/ and could present information on 30% of the US population.

The TNM stage was recorded as the SEER's "extent of disease" (for T and M stage) and the "number of positive nodes" (for N stage) coding schemes. Pathology was grouped as AC, MC, or other. Tumor grade was classified as well differentiated, moderately differentiated, poorly differentiated, or undifferentiated. Patients were stratified by CRC subtype, including 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. Data on the presence of bone, lung, and liver metastases at diagnosis were available in the SEER database and were categorized as the extent of extracranial metastasis among patients in our study.

Patients were observed after their first diagnosis of CRC until the last follow-up, death, or end of the study, whichever occurred first.

Therefore, we included patients from 2010 to 2013, and patients who were proven to have BM 6 months after the diagnosis of CRC or were proven dead by autopsy were excluded. Thus, there were 170,793 patients diagnosed with CRC who were included in our analysis. Of these CRC patients, 401 were diagnosed with BM.

Statistical analysis

Multivariable logistic regression was used to determine which characteristic was associated with the presence of BM at diagnosis among CRC patients or the M1 cohort. Multivariable Cox regression was performed to identify the covariates associated with poor survival. The Kaplan–Meier method was used to estimate the survival difference between the subgroups.

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

Ethics approval and consent to participate

As the data used were from SEER data set, which is publicly available; ethics approval and consent to participate are not applicable.

Results

Incidence of BM in patients diagnosed with CRC

Among the 170,793 patients diagnosed with CRC, we demonstrated that 40.5%, 26.1%, 30.9%, and 2.5% of patients had RCC, LCC, RSC, and appendix cancer, respectively. The number and incidence of patients with CRC and identified BM at CRC diagnosis are provided in Table 1, stratified by CRC cancer subtype.

Table 1 Incidence and median survival of patients diagnosed with CRC and identified brain metastases at diagnosis

Subtype	Patients (no.)			Incidence proportion of brain metastases, %		Survival among patients with brain metastases, median (IQR), months
	With CRC	With metastatic disease	With brain metastases	Among the entire cohort	Among the subset with metastatic disease	
Whole cohort	170,793	31,544	401	0.2%	1.3%	21.95 (21.87–22.03)
RCC	69,147 (40.5%)	12,451 (18.0)	167 (0.2%)	0.2%	1.3%	9.01 (7.0–11.15)
LCC	44,642 (26.1%)	8,797 (19.7%)	92 (0.2%)	0.2%	1.0%	10.26 (7.68–12.85)
Rectosigmoid cancer	52,784 (30.9%)	9,084 (17.2%)	139 (0.3%)	0.3%	1.5%	14.57 (11.89–17.26)
Appendix cancer	4,220 (2.5%)	1,212 (28.7%)	3 (0.1%)	0.1%	0.3%	5 (0.84–9.16)
Extracranial metastasis to bone, lung, and liver (no.)						
0 sites		145,175	110		0.1%	15.59 (11.60–19.59)
Bone		357	12		3.4%	10.53 (3.96–17.11)
Lung		1,999	55		2.8%	11.66 (8.35–14.97)
Liver		168,22	64		0.4%	10.52 (7.02–14.02)
Two sites		5,400	121		2.2%	8.85 (7.12–10.57)
All three sites		540	39		6.6%	7.34 (4.82–9.86)

Abbreviations: CRC, colorectal cancer; LCC, left-sided colon cancer; RCC, right-sided colon cancer; IQR, interquartile range.

Among the entire cohort, 401 patients presented with BM, reflecting 0.23% of the entire study population and 1.3% of the subset with metastatic disease at any site. Incidence proportions were highest among patients with RCC (0.2% of the entire cohort, 1.3% of the metastatic subset) and RSC (0.3% of the entire cohort, 1.5% of the metastatic subset) subtypes.

Also, 3.4% of the CRC patients with bone metastasis presented with BM at diagnosis, which was higher than that of liver or lung metastasis. Additionally, incidence proportions increased with extracranial metastatic sites (6.6% for ≥3, 2.2% for 2, 0.7% for 1, and 0.1% for 0). Interestingly, patients with liver metastasis demonstrated a low incidence rate (0.4%) of BM.

Multivariable logistic regression

On multivariable logistic regression (Table 2) among patients with metastatic cancer, T3–T4 stage patients vs Tis, T0, T1, and T2 (OR=1.456, 95% CI, 1.048–2.022, P=0.025), MC vs AC (OR=2.874, 95% CI, 1.385–5.967, P=0.005), tumor site (LCC vs RCC: OR=0.756, 95% CI, 0.581–0.983, P=0.037; appendix vs RCC: OR=0.151, 95% CI, 0.04–0.488, P=0.002), and metastatic disease to extracranial sites (bone vs none: OR=7.761, 95% CI, 5.372–11.214, P<0.001; two sites vs none: OR=8.832, 95% CI, 3.484–22.386, P<0.001; three vs none: OR=14.353, 95% CI, 9.311–22.125, P<0.001) were associated with significantly greater odds of presenting with BM at diagnosis. Age, gender, pathology grade, N stage, tumor size, pathology grade, race, or marital status was not associated with a higher risk of BM at CRC diagnosis using the multivariable model (Table 2).

Survival

The median survival among patients with BM (with metastasis to other organs) at diagnosis was 7.0 months (Figure 1A). As shown in Figure 1B, the median survival was 15.59 months (range 11.60–19.59 months) for patients with BM merely without metastasis to other organs (Figure 1B), which showed that patient prognosis could be improved if BM was diagnosed early. Then we compared survival difference of patients without metastasis, patients with BM only, patients with metastasis but without BM, and patients with metastasis including BM. Additionally, patients with multi-metastasis having shorter survival, and the reason maybe the BM as shown in Figure 1B (patients with metastasis without BM vs patients with metastasis including BM, P<0.001).

The median survival was 9.01, 10.26, 14.57, and 5 for RCC, LCC, RSC, and appendix cancer, respectively (Table 1). In the entire cohort of patients, RCC had the poorest survival and appendix cancer had the best survival (P<0.001; Figure 2A). However, in patients diagnosed with BM, RCC had the best survival (P=0.002; Figure 2B).

The multivariable Cox regression analysis of all patients is presented in Table 3. Age, T stage, N stage, pathology grade, pathology type, tumor sites, tumor size, race, marital status, extracranial metastatic number, and BM were all independent factors for poorer survival (all P<0.001). Multivariable Cox

Table 2 Multivariable logistic regression for the presence of brain metastases at diagnosis of colorectal cancer

Variable	Patients (no.)		Among entire cohort		Among the subset with metastatic disease	
	Number of patients	With brain metastases	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age at diagnosis (years)				*P*<0.001		<0.001
<40	5,239	11 (0.2%)	1 (reference)		1 (reference)	
40–49	13,938	30 (0.2%)	1.045 (0.519–2.103)	0.902	1.027 (0.511–2.066)	0.939
50–59	35,039	112 (0.3%)	1.634 (0.871–3.064)	0.126	1.754 (0.936–3.285)	0.079
60–69	42,210	121 (0.3%)	1.402 (0.748–2.629)	0.292	1.473 (0.787–2.755)	0.226
>70	74,078	127 (0.2%)	0.853 (0.454–1.603)	0.621	0.963 (0.514–1.805)	0.907
Sex				NA		NA
Male	88,925	206 (0.2%)	1 (reference)	NA	1 (reference)	NA
Female	81,467	195 (0.2%)	NA	NA	NA	NA
T stage				**0.005**		**0.007**
Tis, T0, T1, T2 (0, 1, 2, 3)	55,514	65 (0.1%)	1 (reference)		1 (reference)	
T3–T4 (4, 5)	96,802	186 (0.2%)	1.240 (0.899–1.710	0.189	1.456 (1.048–2.022)	0.025
Tx	18,076	150 (0.8%)	1.695 (1.224–2.347)	0.001	1.085 (0.803–1.467)	0.594
N stage				0.030		NA
N0	98,168	134 (0.1%)	1 (reference)		1 (reference)	NA
N1	39,027	118 (0.3%)	1.408 (1.053–1.882)	0.021	NA	NA
N2	21,348	76 (0.4%)	1.838 (1.202–2.811)	0.005	NA	NA
Nx	11,849	73 (0.6%)	1.273 (0.923–1.756)	0.141	NA	NA
Pathology grade				NA		0.050
Well differentiated	16,648	8 (0.0%)	1 (reference)	NA	1 (reference)	
Moderately differentiated	102,478	160 (0.2%)	NA	NA	0.581 (0.384–0.880)	0.010
Poorly differentiated	23,548	100 (0.4%)	NA	NA	1.006 (0.635–1.596)	0.978
Undifferentiated	4,588	16 (0.3%)	NA	NA	1.355 (0.745–2.463)	0.320
Unknown	23,130	117 (0.5%)	3.134 (1.516–6.480)	0.002	5.149 (2.475–10.713)	<0.001
Pathology type				<0.001		**0.005**
Adenocarcinoma	151,257	339 (0.2%)	1 (reference)		1 (reference)	
Mucinous carcinoma	13,983	27 (0.2%)	2.738 (1.336–5.613)	0.006	2.874 (1.385–5.967)	0.005
Other type[a]	3,932	22 (0.6%)	2.011 (0.968–4.176)	0.061	1.898 (0.927–3.888)	0.089
Unknown	1,220	13 (1.1%)	4.813 (2.023–11.452)	<0.001	2.660 (1.119–6.323)	0.027
Tumor site				**0.004**		**0.003**
RCC	68,980	167 (0.2%)	1 (reference)			
LCC	44,550	92 (0.2%)	0.766 (0.588–0.996)	0.047	0.756 (0.581–0.983)	0.037
Rectosigmoid	52,645	139 (0.3%)	0.657 (0.513–0.842)	0.001	0.808 (0.633–1.033)	0.089
Appendix	4,217	3 (0.1%)	0.377 (0.119–1.199)	0.098	0.151 (0.04–0.488)	0.002
Tumor size (mm)				NA		NA
≤40	69,456	81 (0.1%)	1 (reference)	NA	1 (reference)	NA
40–70	48,304	114 (0.2%)	NA	NA	NA	NA
≥70	18,304	47 (0.3%)	NA	NA	NA	NA
Unknown	34,328	159 (0.5%)	NA	NA	NA	NA
Race				0.088		NA
Hispanic	20,436	46 (0.2%)	1 (reference)		1 (reference)	NA
Black	115,273	280 (0.2%)	0.702 (0.511–0.966)	0.030	NA	NA
White	13,841	22 (0.2%)	1.005 (0.735–1.375)	0.973	NA	NA
Asian/Pacific Islander	1,222	0	0.620 (0.399–0.962)	0.033	NA	NA
Native American/Alaska Native	1,217	5 (0.4%)	1.439 (0.583–3.547)	0.990	NA	NA
Unknown	1,144	0	0.000 (0.000-)	0.990	NA	NA
Marital status				NA		NA
Unmarried	71,525	184 (0.3%)	1 (reference)	NA	1 (reference)	NA
Married	87,779	199 (0.2%)	NA	NA	NA	NA
Unknown	11,088	18 (0.2%)	NA	NA	NA	NA
Extracranial metastasis to bone, lung, and liver (no.)				<0.001		<0.001
0 sites	145,065	110 (0.1%)	1 (reference)		1 (reference)	
Bone	19,047	131 (0.7%)	19.212 (10.264–35.964)	<0.001	7.761 (5.372–11.214)	<0.001

(*Continued*)

Table 2 (*Continued*)

Variable	Patients (no.)		Among entire cohort		Among the subset with metastatic disease	
	Number of patients	With brain metastases	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Lung			21.320 (15.045–30.212)	<0.001	1.306 (0.690–2.470)	0.413
Liver			2.572 (1.846–3.583)	<0.001	1.327 (0.944–1.866)	0.171
Two sites	5,279	121 (2.2%)	12.780 (9.469–17.249)	<0.001	8.832 (3.484–22.386)	<0.001
All three sites	506	34 (6.3%)	34.847 (22.767–3.336)	<0.001	14.353 (9.311–22.125)	<0.001
Unknown	495	5 (1.0%)	6.922 (2.780–17.236)	<0.001	1.510 (0.604–3.774)	0.377

Note: [a]The pathology type other than adenocarcinoma or mucinous carcinoma. Bold values indicate the *P* value is significant when two-sided *P*<0.05 was considered statistically significant.
Abbreviations: LCC, left-sided colon cancer; NA, not available; RCC, right-sided colon cancer.

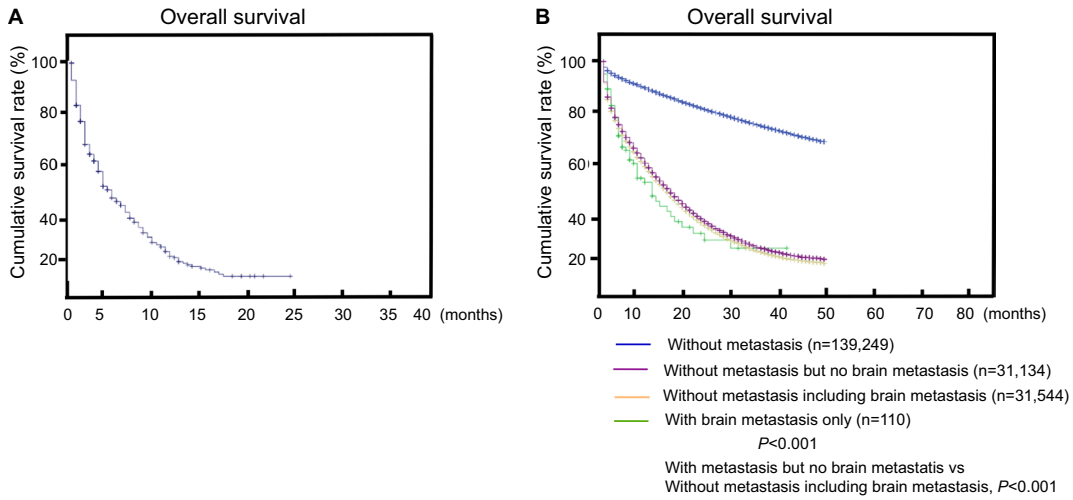

Figure 1 (**A**) Overall survival among patients with BM. (**B**) Survival stratified by subtype (nonmetastatic patients, patients with only BM, patients with metastasis to other sites but no BM, and patients with metastasis to multiple sites including BM).
Abbreviation: BM, brain metastasis.

regression analysis also showed that among patients with BM at CRC diagnosis, age, pathology type (MC vs AC, HR=1.146, 95% CI, 1.062–1.237, *P*<0.001), tumor site (RSC vs RCC, HR=0.661, 95% CI, 0.491–0.890, *P*<0.001), and extracranial metastatic number (2 vs 0/1, HR=1.471, 95% CI, 1.127–1.920, *P*<0.001; all 3 vs 0/1, HR=1.686, 95% CI, 1.102–2.579, *P*=0.016) were significantly associated with poorer survival (Table 3).

OS estimates by the extent of extracranial metastatic disease is shown is Figure 2C, D. In general, survival was poorer among patients who displayed more extensive systemic disease at CRC diagnosis. However, this trend was merely significant in the cohort of extracranial systemic disease only (3 sites vs 2 sites, *P*<0.001; 2 sites vs 1 site, *P*<0.001; Figure 2E) and was not found in the BM cohort (2 sites vs 1 site, *P*=0.559; 3 sites vs 2 sites, *P*=0.322; Figure 2F).

Table 4 displays the median survival by subtype as stratified by the extent of systemic disease in the cohort of extracranial systemic disease only and the cohort of extracranial systemic disease and BM. In addition, we found that the presence of BM at initial diagnosis was associated with a shorter survival time compared with patients who presented with de novo metastatic disease without baseline brain involvement (Table 4).

Discussion

In the present study, the median OS for patients with BM (with metastasis to other organs) was 7 months, which was shorter than reported previously (14.5 months).[17] The median survival was 15.59 months (range 11.60–19.59 months) for patients with BM merely without metastasis to other organs. Recent studies have proved that the OS in CRC patients has

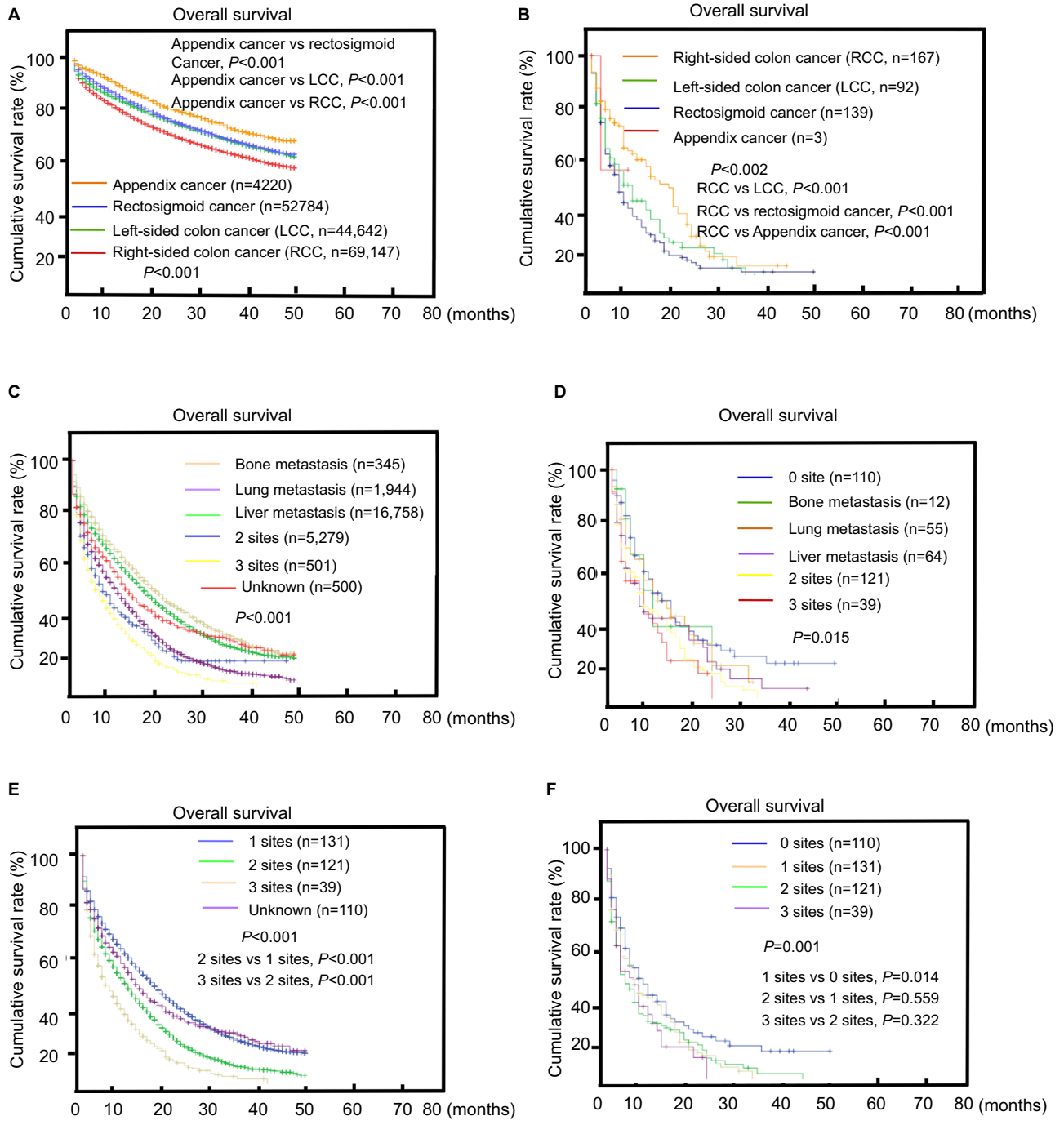

Figure 2 Overall survival among patients with colorectal cancer and brain metastases at diagnosis.

Notes: Survival stratified by tumor site (RCC, LCC, rectosigmoid cancer, appendix cancer) (**A**) in the whole cohort or (**B**) in patients with BM. Survival stratified by the metastasis organ and the extent of extracranial metastatic disease in the (**C**) cohort of extracranial systemic disease only and the (**D**) brain metastasis cohort. Extent of extracranial metastatic disease is classified by the number of metastatic sites to the bone, lung, or liver in the (**E**) cohort of extracranial systemic disease only and (**F**) the brain metastasis cohort.

Abbreviations: LCC, left-sided colon cancer; RCC, right-sided colon cancer.

improved since the late 1990s;[18,19] therefore, new analyses are needed to focus on treatment for BM in patients diagnosed with CRC, especially for the patients with BM merely without metastasis to other organs.

We demonstrated that tumor site, bone metastases, and more number of extracranial metastasis were associated with BM at CRC diagnosis. Sundermeyer et al reported that lung metastasis is a risk factor for BM; the incidence is higher in

Table 3 Multivariable Cox regression for overall survival among patients with brain metastases or among metastatic disease subsets

Variable	Among the subset with metastatic disease		Among the brain metastasis cohort	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Age at diagnosis (years)		<0.001		<0.001
<40	1 (reference)		1 (reference)	
40–49	1.004 (0.915–1.102)	0.928	0.681 (0.264–1.753)	0.425
50–59	1.175 (1.078–1.280)	<0.001	1.161 (0.525–2.564)	0.712
60–69	1.411 (1.297–1.535)	<0.001	1.832 (0.836–4.014)	0.131
>70	2.171 (1.997–2.359)	<0.001	2.660 (1.212–5.840)	0.015
Sex		NA		NA
Male	1 (reference)		1 (reference)	
Female	NA	NA	NA	NA
T stage		<0.001		NA
Tis, T0, T1, T2 (0, 1, 2, 3)	1 (reference)		1 (reference)	
T3–T4 (4, 5)	1.018 (0.970–1.069)	0.469	NA	NA
Tx	1.099 (1.048–1.153)	<0.001	NA	NA
N stage		<0.001		NA
N0	1 (reference)		1 (reference)	
N1	0.926 (0.887–0.967)	0.001	NA	NA
N2	1.090 (1.028–1.155)	0.004	NA	NA
Nx	1.082 (1.032–1.134)	0.001	NA	NA
Pathology grade		<0.001		NA
Well differentiated	1 (reference)		1 (reference)	
Moderately differentiated	1.723 (1.591–1.865)	<0.001	NA	NA
Poorly differentiated	1.845 (1.668–2.041)	<0.001	NA	NA
Undifferentiated	2.577 (0.858–7.740)	0.092	NA	NA
Unknown	1.584 (0.605–4.146)	0.349	NA	NA
Pathology type		<0.001		<0.001
Adenocarcinoma	1 (reference)		1 (reference)	
Mucinous carcinoma	1.102 (1.048–1.159)	<0.001	1.146 (1.062–1.237)	<0.001
Other type[a]	1.613 (1.512–1.721)	<0.001	0.883 (0.337–2.315)	0.800
Unknown	2.269 (2.083–2.471)	<0.001	1.185 (0.450–3.123)	0.731
Tumor site		<0.001		0.029
RCC	1 (reference)		1 (reference)	
LCC	0.813 (0.786–0.842)	<0.001	0.984 (0.722–1.342)	0.919
Rectosigmoid	0.654 (0.631–0.679)	<0.001	0.661 (0.491–0.890)	0.006
Appendix	0.423 (0.381–0.470)	<0.001	0.372 (0.047–2.970)	0.351
Tumor size		<0.001		NA
≤40	1 (reference)		1 (reference)	
40–70	1.122 (1.077–1.168)	<0.001	NA	NA
≥70	1.278 (1.218–1.342)	<0.001	NA	NA
Unknown	1.182 (1.131–1.235)	<0.001	NA	NA
Race		<0.001		NA
Hispanic	1 (reference)		1 (reference)	
Black	1.117 (1.073–1.163)	<0.001	NA	NA
White	1.013 (0.966–1.061)	0.599	NA	NA
Asian/Pacific Islander	0.946 (0.896–1.000)	0.050	NA	NA
Native American/Alaska Native	1.273 (1.086–1.491)	0.003	NA	NA
Unknown	0.712 (0.459–1.105)	0.130	NA	NA
Marital status		<0.001	NA	NA
Unmarried	1 (reference)		NA	NA
Married	0.802 (0.779–0.826)	<0.001	NA	NA
Unknown	0.849 (0.796–0.907)	<0.001	NA	NA
Extracranial metastasis to bone, lung, and liver (no.)		<0.001		0.004
0/1	1 (reference)			
2	1.109 (1.066–1.153)	<0.001	1.471 (1.127–1.920)	0.004

(*Continued*)

Table 3 (*Continued*)

Variable	Among the subset with metastatic disease		Among the brain metastasis cohort	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All three	1.423 (1.356–1.494)	<0.001	1.686 (1.102–2.579)	0.016
Unknown	1.854 (1.673–2.054)	<0.001		
Brain metastasis (yes vs no)	1.360 (1.203–1.536)	<0.001		

Note: [a]The pathology type other than adenocarcinoma or mucinous carcinoma.
Abbreviations: LCC, left-sided colon cancer; NA, not available; RCC, right-sided colon cancer.

Table 4 Median survival of colorectal cancer patients by the extent of systemic metastatic disease

Subtype	Survival, median, months	
	Extracranial systemic disease only	Extracranial systemic disease and brain metastases
Extracranial metastasis to bone, lung, and liver or number of metastasis sites		
Bone	23.91 (22.81–25.01)	10.53 (3.96–17.11)
Lung	14.36 (13.86–14.86)	10.52 (7.02–14.02)
Liver	21.21 (20.86–21.57)	11.66 (8.35–14.97)
Two sites	13.93 (11.76–16.10)	8.85 (7.13–10.97)
All three sites	9.51 (8.41–10.62)	7.34 (4.82–9.86)

lung metastasis than with liver and peritoneal metastases.[7] Many studies have found that metastasis progresses sequentially in many patients, and that BM is one of the late sites of involvement.[20,21] RCC showed more frequency of BM than any other tumor site among all the BM patients. Furthermore, we found that RCC was an independent risk factor of BM. Previous studies have shown that RCC may be a different entity from LCC, including differences in epidemiological, clinical, and molecular biological, and prognostic findings between RCC and LCC.[22–24] Additionally, we found that RCC had the poorest survival. However, when patients were diagnosed with BM, RCC patients had better survival than LCC patients and appendix cancer had the poorest survival. We are unsure of the mechanism of this phenomenon.

In addition, age and pathology type were independent factors in patients with BM at the diagnosis of CRC (in the whole cohort and the M1 cohort). Additionally, patients presenting with appendix tumors with BM, of age >70 years, and with MC showed the poorest survival. Age at the time of initial diagnosis was the variable that constantly revealed a significant effect on survival, suggesting a better performance status in younger patients.[25–28] Major immune defects occur at an older age, including the lack of naïve T-cells, impaired activation pathways of T-cells, antigen-presenting cells, and age-related changes in the tumor microenvironment. Patients with MC showed poorer survival than patients with AC in CRC diagnosed with BM. The presence of metastatic disease in more than one location was more frequent in MC compared with AC.[5] In MC patients, we found a high rate of peritoneal metastases. Several clinical studies have suggested differences in metastatic patterns between histological subtypes.[13,29,30] Since curative surgery is an option that is mainly limited to liver metastases, this may be an explanation for the poor performance of MC patients in trials for metastatic disease.[13,29]

In the current study, the unadjusted probability of BM was calculated as 3.4% for CRC metastases. The incidence of BM has increased as much as 3% since recent extended treatment options have been made available, which have caused an improvement in advanced CRC prognosis.[7] Therefore, the potential of BM should be made aware to the clinicians, especially when patients present with RCC, have bone metastases, or more than three extracranial metastases. For such high-risk patients, brain scans may have to be considered.

Limitations of this study include its retrospective design, selection bias, and heterogeneous population. Furthermore, in the CRC patients, brain imaging was not routinely performed, except at the occurrence of symptoms, which may potentially underestimate the true positive rate of BM. In addition, our patients were not analyzed for the effects of gene mutation in BM tumors at the initial diagnosis, although a recent study demonstrated that RAS- or PIK3CA-mutant CRC patients were more likely to develop BM.[31]

In this study we found that RCC, MC, bone metastases, and more than three extracranial metastases were independent predictors of BM in CRC patients. People with BM without metastasis to other organs had relatively better survival than BM patients with metastasis to other organs. So, it is important to improve available therapeutic options to enhance quality of life, especially for the people with BM without metastasis to other organs.

Data sharing statement

All data were retrieved from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute between 2010 and 2012. The data sets are available in the SEER data set repository https://seer.cancer.gov/.

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Author contributions

Conceptualization: YL, ZB, and XLP; methodology: YL and HWZ; software and data curation: YL, HWZ, and XQK; formal analysis, LSS, KPF, and JC; revising the article critically for important intellectual content: XLP; writing-original draft preparation: YL; project administration and funding acquisition: XLP. All authors (YL, HWZ, XQK, LSS, KPF, JC, ZB, and XLP) have read and approved the final manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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