Original Article

The effect of metastasis patterns on survival in male patients with different breast cancer subtypes: results from the Surveillance, Epidemiology, and End Results (SEER) database

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Background: Metastasis sites and breast cancer subtypes are important for breast cancer patients. This study aimed to assess possible relationships between them and their influence on prognosis in male breast cancer (MBC) patients.

Methods: We collected data on 2,983 patients with MBC from the Surveillance, Epidemiology, and End Results database, including 250 patients with M1 stage disease. Information on metastatic patterns was provided for bone, brain, liver, and lung metastases. MBC was classified into four subtypes: Her2–/HR+, Her2+/HR+, Her2+/HR–, and triple negative (TN). Univariate and multivariate logistic regression analysis were used to analyze the association, and Cox regression analyses were used to analyze prognosis.

Results: The bone was the most common metastatic site and the brain was the least common metastatic site. Patients with the Her2–/HR+ subtype had the highest proportion of metastatic disease, and Her2+/HR– patients had the lowest proportion. Univariate and multivariate logistic regression analyses showed that there were significant differences in distant metastasis patterns in patients with different subtypes. Men with the Her2+/HR+ or Her2–/HR+ subtypes with bone metastasis had better cancer specific survival (CSS), and those with the TN subtype had the worst CSS in all metastatic patterns.

Conclusions: MBC subtypes are associated with different metastasis patterns and can have different effects on prognosis. This study might provide insights into a better understanding of MBC.

Keywords: Male breast cancer (MBC); metastasis pattern; prognosis; breast cancer subtypes; Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death worldwide, with an estimated 2,088,849 new diagnoses and 626,679 mortalities in 2018 (1). However, male breast cancer (MBC) is uncommon. It accounts for less than 1% of all breast carcinomas worldwide (2). Although male patients account for only a small proportion of breast cancer patients, the incidence of MBC continues to increase by 1.1% annually,

and the reported mortality rates are comparable to those in women (3-5). Further, the overall breast cancer mortality rate has improved over time, but less improvement has occurred for men (6).

Many previous studies have reported the clinical characteristics, hormonal conditions, optimal treatment, and prognosis of female breast cancer (FBC). However, MBC mortality has been rising, possibly due to delayed diagnosis and lack of male-specific information. The diagnosis, treatment, and prevention of MBC have not been paid as much attention as those of FBC because of the low incidence of MBC. For a long time, our understanding of MBC was based on that of FBC. However, MBC differs from FBC in some important aspects (7). Relevant studies focusing on this particular population are rare due to its smaller proportion. To date, very few studies have evaluated the effect of molecular subtypes on specific metastatic sites in male patients. In particular, the distribution of molecular subtypes at different metastatic sites has been poorly understood. Therefore, further study of the prognostic factors affecting the survival of men with breast cancer is needed.

In the present study, we used the Surveillance, Epidemiology, and End Results (SEER) registered database to analyze the relationships between MBC subtypes and distant metastasis patterns. Importantly, we analyzed prognosis in patients with the same metastatic pattern according to different subtypes, as well as the prognosis of patients with the same subtype but different metastatic patterns.

Methods

Data collection

The population-based data for this study were extracted from the SEER database established by the National Cancer Institute. Since SEER is a publicly available database with anonymized data, no ethical review was required. We obtained data from SEER collected between 2010 and 2013, as Her2 status and the sites of distant metastases were collected by SEER starting in 2010. We put no restriction on age or race. The exclusion criteria were as follows: patients diagnosed with breast cancer at death or autopsy; primary malignant tumors in other organs; benign or borderline tumors; unknown age, cause of death, or survival time; unavailable or incomplete information on surgery or radiation therapy; and loss to follow-up. Finally, 2983 patients were included.

We extracted multiple variables from the selected object of study. Demographic characteristics consisted of age at diagnosis (20–29, 30–39, 40–49, 50–59, 60–69, 70–79, or ≥80 years) and race (white, black, or other). Pathological characteristics included T-stage (T1, T2, T3, or T4), N stage (N0, N1, N2, or N3), M stage (M0 or M1 stage), tumor grade, laterality (right, left, or bilateral), hormone receptor status, subtype, and distant metastatic sites. Treatment characteristics included surgery (yes or no). Breast tumors were classified into the following subtypes: Her2–/HR+, Her2+/HR+, Her2+/HR–, and triple negative (TN). The primary endpoints of this study were breast cancer-specific survival (BCSS) and overall survival (OS).

Statistical analysis

The univariate and multivariate logistic regression analysis were used to analyze the association between the BCS and the specific metastatic pattern. we used Cox proportional hazard regression analysis to estimate the hazard ratio (HR) and 95% confidence interval (CI). Kaplan-Meier analysis was used to generate survival curves, and the log-rank test was applied to analyze the differences among the curves. All statistical tests were two-sided, and a $P<0.05$ was considered statistically significant. The statistical software SPSS 22.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism version 6 (GraphPad Software Inc., La Jolla, CA, USA) were used for all data analysis.

Results

Patient demographics

There were 2,983 MBC patients reported in the SEER database from 2010 to 2013. The clinical characteristics and pathological features of all the patients are summarized in *Table 1*. Most patients were diagnosed at >50 years old (91.7%). Most patients were white (80.6%). Almost half (47.9%) of the patients were diagnosed with grade II disease, and 31.4% of patients were diagnosed with grade III disease. In addition, the proportions of patients with ER-positive, PR-positive, and HER2-negative tumors were 96.5%, 90.0%, and 87.4%, respectively. Interestingly, 85.4% of patients had the HER2–/HR+ subtype. The bone was the most common metastatic site (5.7%), and the brain was the least common metastatic site (0.7%).

Table S1 shows the clinicopathological data of the

Table 1 Demographic and clinicopathologic characteristics of 2,983 male patients with breast cancer

Characteristics	Number (%)
Age at diagnosis (year)	
Mean [range]	67.4 [22–105]
20–29 years	3 (0.1)
30–39 years	34 (1.1)
40–49 years	211 (7.1)
50–59 years	533 (17.9)
60–69 years	877 (29.4)
70–79 years	777 (26.0)
≥80 years	548 (18.4)
Race	
White	2,386 (80.6)
Black	430 (14.5)
Other	146 (4.9)
Laterality	
Right	1,364 (45.8)
Left	1,575 (52.9)
Bilateral	40 (1.3)
T stage	
T1	1,258 (45.4)
T2	1,172 (42.3)
T3	93 (3.3)
T4	248 (9.0)
N stage	
N0	1,644 (57.4)
N1	858 (30.0)
N2	228 (8.0)
N3	134 (4.7)
M stage	
M0	2,723 (91.6)
M1	250 (8.4)
AJCC stage	
I	968 (32.5)
II	1,156 (38.8)
III	453 (15.2)
IV	250 (8.4)
Unknown	156 (5.2)
Tumor grade	
I	338 (11.3)
II	1,429 (47.9)
III	938 (31.4)
IV	11 (0.4)
Unknown	267 (9.0)
ER status	
Positive	2,697 (96.5)
Negative	98 (3.5)
PR status	
Positive	2,500 (90.0)
Negative	279 (10.0)
Her2 status	
Positive	331 (12.6)
Negative	2,305 (87.4)
Breast cancer subtypes	
Her2–/HR+	2,243 (85.4)
Her2+/HR+	300 (11.4)
Her2+/HR–	28 (1.1)
Triple negative	54 (2.1)
Bone metastasis	
No	2,718 (91.1)
Yes	171 (5.7)
Unknown	94 (3.2)
Brain metastasis	
No	2,866 (96.1)
Yes	20 (0.7)
Unknown	97 (3.3)
Liver metastasis	
No	2,852 (95.6)
Yes	37 (1.2)
Unknown	94 (3.2)
Lung metastasis	
No	2,787 (93.4)
Yes	98 (3.3)
Unknown	98 (3.3)
Marital status	
Single	453 (15.2)
Married	2,333 (78.2)
Unknown	197 (6.6)
Surgery	
No	347 (11.6)
Yes	2,588 (86.8)
Unknown	48 (1.6)

patients with a single metastatic site. Patients ≥80 years accounted for 30.0% of the bone metastasis group, but only 18.3% of the control group (M0 group). Patients with brain or liver metastasis had a higher T stage and N

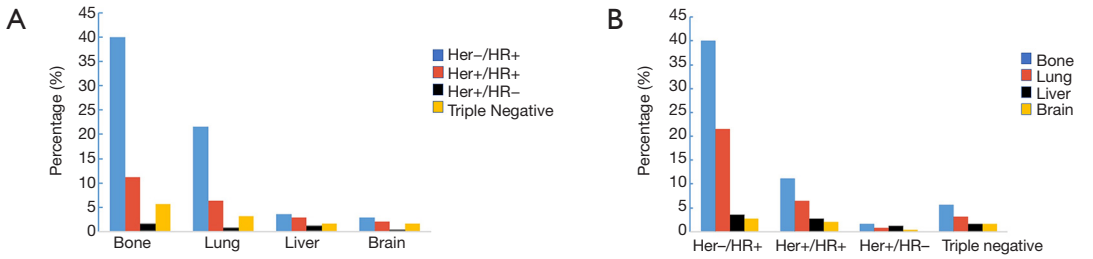

Figure 1 The percentage of distant metastasis sites. (A) The percentage of distant metastasis sites based on different BCS. (B) The percentage of BCS based on different distant metastasis sites.

stage than patients in the control group, with T3–4 stage accounting for 38.8% and 44.4% of patients with brain and liver metastasis, respectively, and N3 stage accounting for 10% and 18.5%, respectively (each P<0.001). Patients with M1 were more likely to be ER-negative and PR-negative, regardless of metastatic site (each P<0.05). As expected, patients with distant metastasis were less likely to undergo surgery than those in the control group and therefore had higher mortality rates (each P<0.05). *Table S2* shows the clinicopathological data of the patients with multiple metastatic sites. Patients <60 years accounted for 42.9% of patients with three metastatic sites, suggesting that younger patients were more likely to have multiple metastases. Further, ER-negative, PR-negative, and Her2-positive tumors were extremely common in the multiple metastases group (each P<0.05). Patients with multiple metastases were not significantly less likely to receive surgery or have a higher mortality rate than those with a single metastasis.

Patterns of metastasis based on subtype

The distant metastatic sites assessed were the bone, brain, liver, and lung. The bone was the most common metastatic site and the brain was the least common metastatic site, regardless of subtype (*Figure 1A*). Patients with the Her2−/HR+ subtype were most likely to have bone metastasis (40.0%), followed by lung metastasis (21.6%), liver metastasis (3.6%), and brain metastasis (2.8%). Patients with the Her2+/HR− had low percentages of brain metastasis (1.6%), lung metastasis (1.2%), liver metastasis (0.8%), and brain metastasis (0.4%). Patients with the Her2+/HR+ subtype experienced lung metastasis (6.4%), liver metastasis (2.8%), and brain metastasis (2.0%), as did patients with the TN subtype (3.2%, 1.6%, and 1.6%, respectively).

Patients with Her2−/HR+ tumors were most likely to develop metastasis, and patients with Her2+/HR− tumors were least likely to develop metastasis, regardless of metastatic pattern (*Figures 1B*). Patients with bone metastasis were most likely to have the Her2−/HR+ subtype, as were patients with lung metastasis.

Factors associated with distant metastasis in MBC

Of the 2983 MBC patients included in the analysis, 2723 (91.3%) were diagnosed with M0 stage, whereas 250 (8.4%) had M1 stage disease. Based on the results of the univariate analysis (*Table 2*), DM in MBC patients was associated with age, race, laterality, T stage, N stage, tumor grade, hormone receptor status, and subtype (all P<0.05). Compared with M0 stage patients, M1 stage patients had higher T status (T3 and T4 stage: 8.9% *vs.* 50.5%), higher N status (N1-3 stage: 39.0% *vs.* 71.1%), and more advanced disease (grade III and IV: 31.2% *vs.* 50.2%) (all P<0.001).

Distribution of distant metastasis sites

The distributions of distant metastasis sites are shown in *Table 3*. The most common metastatic site was the bone, followed by the lung, liver, and brain. Interestingly, many breast cancer patients developed metastasis at more than one site. A total of 115 (46.0%), 59 (23.6%), 21 (8.4%), and 3 (1.2%) patients had one, two, three, and four metastatic sites, respectively.

Combination metastasis analysis based on different subtypes

The different metastasis patterns are summarized in *Table 4*. 21.2% of patients with the Her2−/HR+ subtype, 4.0% of patients with the Her2+/HR+ subtype, 0.4% of patients with the Her2+/HR− subtype, and 2.4% of patients with the TN subtype had only bone metastasis. Sole liver

Table 2 The relationship between clinicopathological factors and distant metastasis in male breast cancer

Characteristics	M0 (n=2,723), n (%)	M1 (n=250), n (%)	P value
Age at diagnosis (year)	67.66±12.352	64.39±12.709	<0.001*
<55 years	445 (16.3)	52 (20.8)	
≥55 years	2,278 (83.7)	198 (79.2)	
Race			0.008*
White	2,219 (81.5)	180 (72.0)	
Black	373 (13.7)	56 (22.4)	
Other	131 (4.8)	14 (5.6)	
Laterality			0.019*
Right	1,257 (46.2)	105 (42.0)	
Left	1,441 (52.9)	130 (52.0)	
Bilateral	25 (0.9)	15 (6.0)	
T stage			<0.001*
T1	1,386 (50.9)	21 (10.7)	
T2	1,096 (40.2)	76 (38.8)	
T3	68 (2.5)	24 (12.2)	
T4	173 (6.4)	75 (38.3)	
N stage			<0.001*
N0	1,663 (61.1)	65 (28.9)	
N1	756 (27.8)	102 (45.3)	
N2	199 (7.3)	29 (12.9)	
N3	105 (3.9)	29 (12.9)	
Grade			<0.001*
I	526 (19.3)	10 (5.3)	
II	1,345 (49.4)	83 (44.4)	
III	848 (31.1)	90 (48.1)	
IV	4 (0.1)	4 (2.1)	
ER status			<0.001*
Positive	2,656 (97.5)	190 (86.0)	
Negative	67 (2.5)	31 (14.0)	
PR status			<0.001*
Positive	2,497 (91.7)	169 (76.1)	
Negative	226 (8.3)	53 (23.9)	
Her2 status			0.005*
Positive	585 (21.5)	42 (20.1)	
Negative	2,138 (78.5)	167 (79.9)	
Subtypes			<0.001*
Her2–/HR+	2,403 (88.2)	145 (70.0)	
Her2+/HR+	265 (9.7)	35 (16.9)	
Her2+/HR–	21 (0.8)	7 (3.4)	
Triple negative	34 (1.2)	20 (9.7)	

*, represent the P value <0.05.

Table 3 The distribution of distant metastases sites

Specific site of distant metastasis	n
Bone alone	80
Brain alone	2
Liver alone	6
Lung alone	27
Bone + brain	4
Bone + liver	9
Bone + lung	44
Brain + liver	1
Brain + lung	0
Liver + lung	1
Bone + brain + liver	1
Bone + brain + lung	8
Bone + liver + lung	11
Brain + liver + lung	1
Bone + brain + liver + lung	3

metastasis or brain metastasis were seldom seen, regardless of subtype. In patients with two sites of metastasis, the two sites were different among the subtypes. In patients with the Her2−/HR+, Her2+/HR+, and TN subtypes, the most common combination was the bone and lung (11.2%, 2.8%, and 0.8%, respectively). In patients with the Her2+/HR− subtype, the most common combination was the bone and liver (0.8%). In patients with three sites of metastasis, the most common combination was the bone, liver, and lung in all subtypes (Her2−/HR+, 1.6%; Her2+/HR+, 1.2%; and TN, 0.4%). Metastasis to four sites was rare, accounting for only 0.4% of patients across all subtypes.

Association between subtype and site of distant metastasis

In order to further evaluate the relationship between site of metastasis and breast cancer subtype, univariate and multivariate logistic regression analyses were performed. Patients with the Her2−/HR+ subtype had a significantly higher probability of developing bone metastasis than those with other subtypes (Her2+/HR+ *vs.* Her2−/HR+: OR 0.958, 95% CI: 0.426–4.143; Her2+/HR− *vs.* Her2−/HR+: OR 0.296, 95% CI: 0.021–4.248; TN *vs.* Her2−/HR+: OR 0.727, 95% CI: 0.155–3.419) (*Table 5*). Patients with the Her2−/HR+ and TN subtypes had a significantly higher probability of lung metastasis than patients with the Her2+/HR− subtype (Her2+/HR− *vs.* Her2−/HR+: OR 0.860, 95% CI: 0.067–10.977; Her2+/HR− *vs.* TN: OR 0.415, 95% CI: 0.027–6.299). Patients with the Her2−/HR+ subtype had a significantly lower probability of liver metastasis than patients with the other three subtypes (Her2+/HR+ *vs.* Her2−/HR+: OR 4.035, 95% CI: 0.968–16.827; Her2+/HR− *vs.* Her2−/HR+: OR 7.100, 95% CI: 0.416–121.149; TN *vs.* Her2−/HR+: OR 5.396, 95% CI: 0.889–32.755) (*Table 5*). Patients with the Her2−/HR+ subtype had a significantly lower probability of brain metastasis than patients with the Her2+/HR+ and TN subtypes (Her2+/HR+ *vs.* Her2−/HR+: OR 9.991, 95% CI: 1.274–78.340; TN *vs.* Her2−/HR+: OR 12.437, 95% CI: 0.967–159.880) (*Table 5*).

Survival analysis based on metastatic pattern

The results for the univariate and multivariate analysis of BCSS are shown in *Table 6*. Univariate analysis showed that bone, lung, liver, and brain metastases were prognostic factors affecting BCSS in patients with the Her2−/HR+ subtype (all P<0.001). Liver metastasis was not a prognostic factor affecting BCSS in patients with the Her2+/HR+ subtype (χ^2=2.380, P=0.123). Bone and lung metastases were significant factors affecting BCSS in patients with the TN subtype (χ^2=17.007, P<0.001; χ_2=7.426, P=0.006, respectively). However, we found no factors affecting BCSS in patients with the Her2+/HR− subtype. Further multivariate analysis showed that bone metastasis was an independent prognostic factor for BCSS (all P<0.05) (*Table 6*). Interestingly, lung metastasis was not an independent prognostic factor affecting BCSS in patients with the Her2+/HR+ subtype (HR 0.398, 95% CI: 0.101–1.571, P=0.188). However, it was an affecting factor in patients with the Her2+/HR− subtype (HR 0.015, 95% CI: 0.001–0.359, P=0.010).

The results for the univariate and multivariate analyses of OS are shown in *Table 7*. Univariate analysis showed that bone, lung, liver and brain metastases were prognostic factors for OSS except for Her2+/HR−subtype patients (all P<0.05). Further multivariate analysis showed that bone metastasis was an independent prognostic factor for BCSS with Her2−/HR+, Her2+/HR− and TN (all P<0.05) (*Table 7*). Interestingly, lung metastasis was an affecting prognostic factor affecting BCSS in patients with the Her2+/HR−

Table 4 Frequencies of combination metastasis sites in male breast cancer with M1

Metastatic site	Her2-/HR +, n (%)	Her2 +/HR +, n (%)	Her2 +/HR-, n (%)	Triple negative, n (%)	P value
Only one site					0.853
Bone	53 (21.2)	10 (4)	1 (0.4)	6 (2.4)	
Brain	1 (0.4)	0	0	1 (0.4)	
Liver	3 (1.2)	0	0	0	
Lung	16 (6.4)	3 (1.2)	1 (0.4)	2 (0.8)	
Two sites					0.094
Bone + brain	3 (1.2)	1 (0.4)	0	0	
Bone + liver	2 (0.8)	2 (0.8)	2 (0.8)	1 (0.4)	
Bone + lung	28 (11.2)	7 (2.8)	0	2 (0.8)	
Brain + liver	0	0	0	0	
Brain + lung	0	0	0	0	
Liver + lung	0	0	0	0	
Three sites					0.793
Bone + brain + liver	0	1 (0.4)	0	0	
Bone + brain + lung	3 (1.2)	2 (0.8)	0	2 (0.8)	
Bone + liver + lung	4 (1.6)	3 (1.2)	0	1 (0.4)	
Brain + liver + lung	0	0	0	0	
Four sites					1.0
Bone + brain + liver + lung	0	1 (0.4)	1 (0.4)	1 (0.4)	

subtype (HR 0.015, 95% CI: 0.001–0.359, P=0.010).

Kaplan-Meier analyses were also used to analyze prognosis. The results showed that patients with the TN subtype with bone or lung metastases had the worst BCSS (bone: χ^2=30.54, P<0.001; lung: χ^2=10.48, P=0.0149) (*Figure 2A,B,C,D*).

Conclusions

In this study, we investigated the characteristics of MBC patients and the effect of distant metastatic patterns of different subtypes on survival. The subtype not only affects the survival of breast cancer patients (8), but different subtypes may also be associated with different organ-specific metastases (9). Our study suggests that patients with different subtypes have different metastatic patterns; patients with all subtypes were most prone to bone metastases, and patients with the Her2–/HR+ subtype had a significantly higher probability of bone metastasis. Patients with the Her2–/HR+ subtype had a lower probability of brain or liver metastasis. Further, patients with the TN subtype primarily developed bone or lung metastasis.

The bone, liver, lung, and brain are the most common sites of distant metastasis in breast cancer (10). Some studies have shown that differences in survival in FBC may be linked to different metastatic patterns (11). However, studies on the association between different subtypes and the exact patterns of distant metastasis have been limited and inconsistent, especially for male patients.

The bone is the most common distant metastatic organ in breast cancer patients, with up to 75% of stage IV BC patients developing skeletal metastases (12-14). Bone metastasis is also the main cause of pathologic fractures and spinal cord compression, which seriously affect the quality of life of breast cancer patients (15). Our results also showed that the bone was the most common metastatic site in MBC patients. It has been reported that patients with ER-positive and PR-positive tumors have a higher

Table 5 Univariate and multivariate logistic regression analysis were used to evaluate the relationship between the distant metastatic pattern and BCS

Metastasis site/subtype	Univariate analysis		Multivariate analysis	
	Wald χ^2	P	OR (95% CI)	P
Bone	19.788	<0.001*		
Her2+/HR+ *vs.* Her2−/HR+			0.958 (0.426–4.143)	0.036*
Her2+/HR− *vs.* Her2−/HR+			0.296 (0.021–4.248)	0.027*
TN *vs.* Her2−/HR+			0.727 (0.155–3.419)	0.048*
Her2+/HR+ *vs.* Her2+/HR−			4.273 (0.259–70.386)	0.310
Her2+/HR+ *vs.* TN			1.826 (0.306–10.901)	0.509
Her2+/HR− *vs.* TN			0.407 (0.023–7.131)	0.538
Lung	9.230	0.002*		
Her2+/HR+ *vs.* Her2−/HR+			1.626 (0.650–4.063)	0.299
Her2+/HR− *vs.* Her2−/HR+			0.860 (0.067–10.977)	0.008*
TN *vs.* Her2−/HR+			2.075 (0.524–8.212)	0.298
Her2+/HR+ *vs.* Her2+/HR−			2.114 (0.153–29.213)	0.576
Her2+/HR+ *vs.* TN			0.784 (0.170–3.616)	0.755
Her2+/HR− *vs.* TN			0.415 (0.027–6.299)	0.026*
Liver	62.243	<0.001*		
Her2+/HR+ *vs.* Her2−/HR+			4.035 (0.968–16.827)	0.036*
Her2+/HR− *vs.* Her2−/HR+			7.100 (0.416–121.14)	0.046*
TN *vs.* Her2−/HR+			5.396 (0.889–32.755)	0.027*
Her2+/HR+ *vs.* Her2+/HR−			0.259 (0.017–3.895)	0.858
Her2+/HR+ *vs.* TN			0.748 (0.108–5.192)	0.769
Her2+/HR− *vs.* TN			1.316 (0.074–23.431)	0.852
Brain	59.215	<0.001*		
Her2+/HR+ *vs.* Her2−/HR+			9.991 (1.274–78.340)	0.028*
Her2+/HR− *vs.* Her2−/HR+			NI	NI
TN *vs.* Her2−/HR+			12.437 (0.967–159.880)	0.043*
Her2+/HR+ *vs.* Her2+/HR−			NI	NI
Her2+/HR+ *vs.* TN			0.803 (0.063–10.267)	0.866
Her2+/HR− *vs.* TN			NI	NI

*, represent the P value <0.05. NI, not included in the multivariate logistic regression analysis.

risk of bone metastasis (16,17). However, a study in Korea showed that there was no significant difference in the incidence of bone metastasis among patients with different subtypes (18). In our study, patients with the Her2−/HR+ subtype had a significantly higher probability of developing bone metastases than patients with other subtypes. The study by Piggott *et al.* (19) suggested that breast cancer subtype could influence OS, but bone metastasis was not a factor influencing survival. Patients with bone metastasis from breast cancer often have a notably increased survival

Table 6 Univariate and multivariate Cox regression analysis were used to evaluate the influence of distant metastasis sites on CSS based on different BCS

Subtype/Metastasis site	Univariate analysis		Multivariate analysis	
	Log rank	P	HR (95% CI)	P
Her2–/HR+				
Bone metastasis (no *vs.* yes)	214.182	<0.001*	0.105 (0.062–0.178)	<0.001*
Brain metastasis (no *vs.* yes)	16.007	<0.001*	0.153 (0.052–0.452)	0.001*
Liver metastasis (no *vs.* yes)	26.440	<0.001*	0.235 (0.093–0.596)	0.002*
Lung metastasis (no *vs.* yes)	70.037	<0.001*	0.731 (0.368–1.451)	0.370
Her2+/HR+				
Bone metastasis (no *vs.* yes)	18.241	<0.001*	0.272 (0.078–0.947)	0.041*
Brain metastasis (no *vs.* yes)	5.322	0.021*	0.645 (0.106–3.937)	0.635
Liver metastasis (no *vs.* yes)	2.380	0.123	2.676 (0.419–17.082)	0.298
Lung metastasis (no *vs.* yes)	15.952	<0.001*	0.398 (0.101–1.571)	0.188
Her2+/HR–				
Bone metastasis (no *vs.* yes)	3.342	0.068	0.030 (0.002–0.548)	0.018*
Brain metastasis (no *vs.* yes)	0.170	0.680	NI	
Liver metastasis (no *vs.* yes)	0.465	0.496	5.625 (0.234–135.439)	0.287
Lung metastasis (no *vs.* yes)	2.768	0.096	0.015 (0.001–0.359)	0.010*
Triple negative				
Bone metastasis (no *vs.* yes)	17.007	<0.001*	0.196 (0.067–0.572)	0.003*
Brain metastasis (no *vs.* yes)	2.701	0.100	1.185 (0.211–6.652)	0.847
Liver metastasis (no *vs.* yes)	3.340	0.068	1.158 (0.216–6.223)	0.864
Lung metastasis (no *vs.* yes)	7.426	0.006*	0.833 (0.196–3.530)	0.804

*, represent the P value <0.05. NI, not included in the multivariate Cox regression analysis.

over patients with visceral or brain metastases (17,20). In agreement with these prior studies, we found that patients with bone metastasis had better BCSS only if the patients had the Her2+/HR+ or Her2–/HR+ subtypes. This can be mainly explained by the fact that patients with bone metastasis are more likely to have endocrine-responsive disease, which would lead to more lines of effective therapy, as these patients benefit from endocrine therapy. Interestingly, patients with Her2+/HR+ breast cancer have better BCSS and OS (17); this survival advantage was not affected by the receipt of Her2-targeted therapy (21). As expected, our research showed that patients with the TN subtype had the worst BCSS in all metastatic patterns. This can be mainly explained by the fact that these patients do not benefit from endocrine therapy or the targeted drug trastuzumab.

Approximately 60% of metastatic breast cancer patients develop lung or bone metastases in their lifetimes (22). Despite a variety of available treatments for lung metastasis, such as chemotherapy, radiotherapy, and targeted therapy, the survival rate of these patients remains very low. The incidence of lung metastasis can reach up to 50% in TNBC cases, compared to only 17.98% in non-TNBC cases (23), which is in accordance with our conclusion. Xiao *et al.* analyzed the survival of patients with lung metastasis and found that Her2+/HR– and Her2–/HR+ breast cancers had the best clinical outcome, whereas TNBCs had the worst prognosis (24). Similarly, we found that TN patients in our study had the worst prognosis, especially compared to Her2+/HR+ and Her2–/HR+ patients. Endocrine therapy

Table 7 Univariate and multivariate Cox regression analysis were used to evaluate the influence of distant metastasis sites on OS based on different BCS

Subtype/metastasis site	Univariate analysis		Multivariate analysis	
	Log rank	P	HR (95% CI)	P
Her2–/HR+				
Bone metastasis (no *vs.* yes)	123.631	<0.001*	0.205 (0.137–0.305)	<0.001*
Brain metastasis (no *vs.* yes)	15.545	<0.001*	2.061 (0.606–7.005)	0.247
Liver metastasis (no *vs.* yes)	20.044	<0.001*	0.788 (0.242–2.570)	0.693
Lung metastasis (no *vs.* yes)	46.210	<0.001*	0.921 (0.533–1.592)	0.768
Her2+/HR+				
Bone metastasis (no *vs.* yes)	11.596	<0.001*	0.753 (0.258–2.203)	0.605
Brain metastasis (no *vs.* yes)	26.166	<0.001*	0.203 (0.054–0.770)	0.019*
Liver metastasis (no *vs.* yes)	6.834	0.009*	2.184 (0.517–9.228)	0.288
Lung metastasis (no *vs.* yes)	14.258	<0.001*	0.432 (0.142–1.315)	0.140
Her2+/HR–				
Bone metastasis (no *vs.* yes)	3.342	0.068	0.030 (0.002–0.548)	0.018*
Brain metastasis (no *vs.* yes)	0.170	0.680	NI	
Liver metastasis (no *vs.* yes)	0.465	0.496	5.625 (0.234–135.439)	0.287
Lung metastasis (no *vs.* yes)	2.768	0.096	0.015 (0.001–0.359)	0.010*
Triple negative				
Bone metastasis (no *vs.* yes)	19.196	<0.001*	0.247 (0.088–0.692)	0.008*
Brain metastasis (no *vs.* yes)	4.606	0.032*	1.411 (0.319–6.250)	0.650
Liver metastasis (no *vs.* yes)	10.339	0.001*	0.668 (0.160–2.778)	0.579
Lung metastasis (no *vs.* yes)	12.095	0.001*	0.744 (0.195–2.842)	0.665

*, represent the P value <0.05. NI, not included in the multivariate survival analysis.

may prolong the survival of HR+ patients compared to TN patients, who are not sensitive to endocrine therapy.

The survival of patients with liver metastasis is lower than that of patients with bone or lung metastasis (25). They not only bear a great burden of tumor cells but also have a progressive deterioration of liver function, which made the overall survival rates very low and most patients died within the first year after diagnosis of liver lesions (26). Breast cancer with liver metastasis has a poor outcome if left untreated, with a survival period ranging from 4 to 8 months (27). A previous study revealed that, compared with the TN subtype, the Her2+ subtype was significantly associated with liver metastasis (9). Our results showed that patients with the Her2–/HR+ subtype had a significantly lower probability of developing liver metastasis than patients with the other three subtypes. Further, Her2+ patients had a better prognosis than TN patients after 10 months. There are several treatment options for patients with liver metastasis, including surgical resection, systematic chemotherapy, and transarterial chemoembolization. The choice of different therapies may have an impact on patient survival, and our results may have incorporated some clinical confounding factors.

Brain metastasis from breast cancer is usually a catastrophic event. The incidence of brain metastasis has been continuously rising because of technological advances in earlier detection and more advanced therapy (12). It has been previously demonstrated that high-grade tumors constitute a much higher proportion of breast cancers that subsequently develop brain metastases (28). We did not

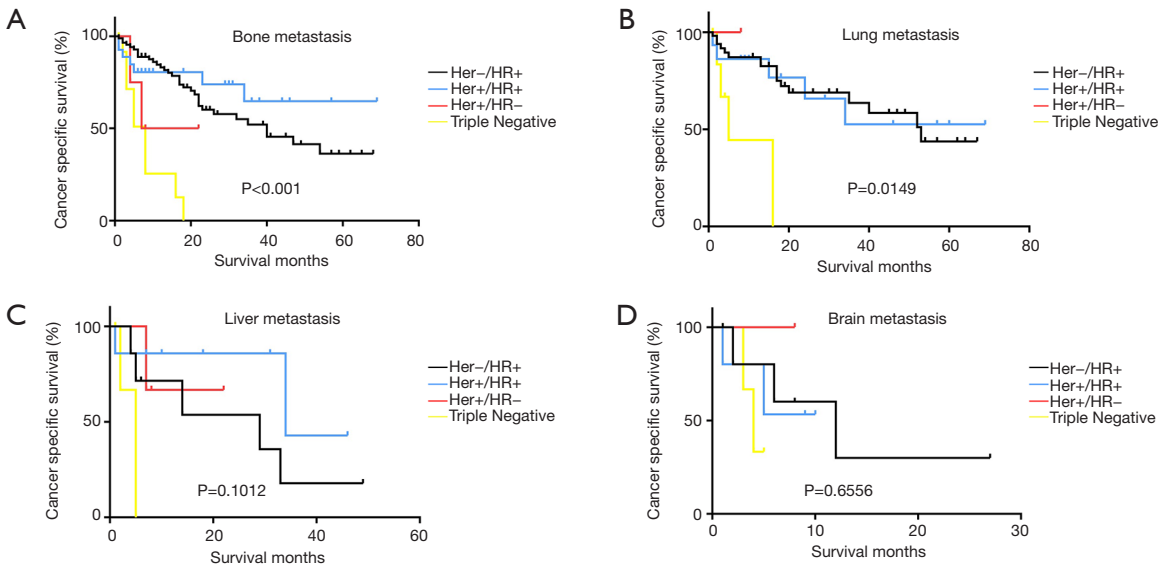

Figure 2 The CSS curves in male breast cancer patients with different distant metastasis sites. (A) The CSS curves in MBC patients with different BCS according to bone metastasis pattern (bone: χ^2=30.54, P<0.001). (B) The CSS curves in MBC patients with different BCS according to lung metastasis pattern (lung: χ^2=10.48 P=0.0149). (C) The CSS curves in MBC patients with different BCS according to liver metastasis pattern (liver: χ^2=6.224, P=0.1012). (D) The CSS curves in MBC patients with different BCS according to brain metastasis pattern (brain: χ^2=1.517, P=0.6556).

see this in our data, probably because of the limited sample size. Our results are consistent with previous studies that found that the risk of brain metastasis in Her2+ patients is significantly higher than that in Her2− patients (29). Further, there have also been controversies regarding the prognostic significance of breast cancer subtypes in patients with brain metastasis in the very few previously published studies. In our study, we found that, among patients with brain metastasis, only patients with the Her2+/HR− subtype have a decent prognosis. It further proves that trastuzumab can prolong survival in breast cancer patients with brain metastases.

This study also has several limitations. First, due to the absence of information on chemotherapy, targeted therapy, and Ki-67 status in the SEER database, their effects on survival could not be evaluated. Second, this study is a non-randomized study and the sample size is relatively small, so intrinsic defects exist. Although there were some instances in our study where the P value was >0.05 and the survival curves crossed, this may be due to the limited sample size or clinical confounding factors of MBC and the different recurrence peaks in different patterns. We can still draw some conclusions from the trends of these data. Third, in the present study, only metastases to the bone, lung, liver, and brain were included. Although these are the common sites of distant metastasis in breast cancer, metastases to other sites may influence the prognosis of breast cancer patients.

In conclusion, our study further clarified the relationship between distant metastatic patterns and subtypes in MBC. These results suggest that different patterns of metastasis in male patients with different breast cancer subtypes have different impacts on clinical outcomes. Importantly, we performed a prognostic analysis for patients with different distant metastatic patterns based on subtypes, which may assist physicians in evaluating the survival potential of male patients with breast cancer.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.03.43). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Clinical features and single metastasis sites

Variables	Control, N=2,723 (%)	Bone, N=80 (%)	Brain, N=2 (%)	Liver, N=6 (%)	Lung, N=27 (%)
Survival (months)	29.94±20.344	18.31±17.647	5.00±1.414	12.00±14.913	25.19±22.412
Age at diagnosis, y		0.028*	0.598	0.590	0.786
<40	32 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)
40–59	684 (25.1)	18 (22.5)	0 (0)	1 (16.7)	5 (18.5)
60–79	1,509 (55.4)	38 (47.5)	1 (50.0)	5 (83.3)	18 (66.6)
≥80	498 (18.3)	24 (30.0)	1 (50.0)	0 (0)	4 (14.8)
Race		0.706	0.528	0.274	0.184
White	2,199 (80.8)	64 (80.0)	2 (100.0)	6 (100.0)	18 (66.7)
Black	373 (13.7)	15 (18.8)	0 (0)	0 (0)	8 (29.6)
Other	131 (4.8)	1 (1.3)	0 (0))	0 (0)	1 (3.7)
Unknown	20 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Grade		0.008*	0.666	0.159	0.623
I	325 (11.9)	3 (3.8)	0 (0)	0 (0)	1 (3.7)
II	1,345 (49.4)	36 (45.0)	1 (50.0)	2 (33.3)	8 (29.6)
III	848 (31.1)	31 (38.8)	1 (50.0))	0 (0)	10 (37.0)
IV	4 (0.1)	0 (0)	0 (0)	1 (16.7)	1 (3.7)
Unknown	201 (7.4)	10 (12.5)	0 (0)	3 (50.0)	7 (25.9)
T stage		<0.001*	0.756	0.649	<0.001*
T1	1,237 (45.4)	11 (13.8)	1 (50.0)	1 (16.7)	2 (7.4)
T2	1,096 (40.2)	29 (36.3)	1 (50.0)	2 (33.3)	8 (29.6)
T3	68 (2.5)	10 (12.5)	0 (0)	0 (0)	3 (11.1)
T4	173 (6.4)	21 (26.3)	0 (0)	1 (16.7)	9 (33.3)
Unknown	149 (5.5)	9 (11.3)	0 (0)	2 (33.3)	5 (18.5)
N stage		<0.001*	–	0.736	<0.001*
N0	1,579 (58.0)	24 (30.0)	0 (0)	2 (33.3)	6 (22.2)
N1	756 (27.8)	37 (46.3)	0 (0)	1 (16.7)	8 (29.6)
N2	199 (7.3)	10 (12.5)	0 (0)	0 (0)	6 (22.2)
N3	105 (3.9)	8 (10.0)	0 (0)	1 (16.7)	5 (18.5)
Unknown	84 (3.1)	1 (1.3)	2 (100.0)	2 (33.3)	2 (7.4)
ER		0.001*	<0.001*	0,032*	<0.001*
Positive	2,507 (92.1)	70 (87.5)	1 (50.0))	3 (50.0)	18 (66.7)
Negative	67 (2.5)	7 (8.8)	1 (50.0))	1 (16.7)	4 (14.8)
Unknown	149 (5.5)	3 (3.8)	0 (0)	2 (33.3)	5 (18.5)
PR		0.015*	0.041*	0.035*	0.002*
Positive	2,331 (85.6)	64 (80.0)	1 (50.0))	2 (33.3)	16 (59.3)
Negative	226 (8.3)	13 (16.3)	1 (50.0))	2 (33.3)	7 (25.9)
Unknown	166 (6.1)	3 (3.8)	0 (0)	2 (33.3)	4 (14.8)
HER2		0.334	0.603	0.004*	0.001*
Positive	289 (10.6)	11 (13.8)	0 (0)	0 (0)	4 (14.8)
Negative	2,138 (78.5)	59 (73.8)	2 (100.0)	3 (50.0)	18 (66.7)
Unknown	296 (10.9)	10 (12.5)	0 (0)	3 (50.0)	5 (18.5)
Subtype		<0.001*	<0.001*	0.400	0.014*
HR–/HER+	2,908 (77.0)	53 (66.3)	1 (50.0))	3 (50.0)	16 (59.3)
HR+/HER+	265 (9.7)	10 (12.5)	0 (0)	0 (0)	3 (11.1)
HR+/HER-	21 (0.8)	1 (1.3)	0 (0)	0 (0)	1 (3.7)
TN	34 (1.2)	6 (7.5)	1 (50.0))	0 (0)	2 (7.4)
Unknown	305 (11.2)	10 (12.5)	0 (0)	3 (50.0)	5 (18.5)
Laterality		0.978	0.216	0.032*	0.054
Right	1,253 (46.0)	38 (47.5)	0 (0)	1 (16.7)	7 (25.9)
Left	1,441 (52.9)	40 (50.0)	2 (100.0)	4 (66.7)	20 (74.1)
Bilateral	25 (0.9)	2 (2.5)	0 (0)	1 (16.7)	0 (0)
Unknown	4 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)
Surgery		<0.001*	0.016*	<0.001*	<0.001*
No	185 (6.8)	41 (51.2)	1 (50.0)	5 (83.3)	15 (55.6)
Yes	2,498 (91.7)	38 (47.5)	1 (50.0)	1 (16.7)	12 (44.4)
Unknown	40 (1.7)	1 (1.3)	0 (0)	0 (0)	0 (0)
Status		<0.001*	0.001*	0.010*	<0.001*
Alive	2,283 (83.8)	41 (51.2)	0 (0)	1 (16.7)	12 (44.4)
Dead	440 (16.2)	39 (48.8)	2 (100.0)	5 (83.3)	15 (55.6)

*, represent the P value <0.05.

Table S2 Clinical features and multiple metastasis sites

Variables	Control, N=2,723 (%)	Double, N=59 (%)	Three, N=21 (%)	Four, N=3 (%)
Survival (months)	29.94±20.344	17.29±17.048	12.05±16.209	6.33±4.726
Age at diagnosis, y		0.075	0.039*	0.573
<40	32 (1.2)	2 (3.4)	1 (4.8)	0 (0)
40–59	684 (25.1)	15 (25.5)	8 (38.1)	1 (33.3)
60–79	1,509 (55.4)	36 (61.0)	9 (42.9)	1 (33.3)
≥80	498 (18.3)	6 (10.2)	3 (14.3)	1 (33.3)
Race		0.001*	0.206	0.439
White	2,199 (80.8)	39 (66.1)	15 (71.4)	3 (100.0)
Black	373 (13.7)	13 (22.0)	4 (19.0)	0 (0)
Other	131 (4.8)	7 (11.9)	2 (9.5))	0 (0)
Unknown	20 (0.7)	0 (0)	0 (0)	0 (0)
Grade		0.038*	0.257	0.020*
I	325 (11.9)	4 (6.8)	1 (4.8)	0 (0)
II	1,345 (49.4)	14 (23.7)	6 (28.6)	1 (33.3)
III	848 (31.1)	25 (42.4)	8 (38.1))	0 (0)
IV	4 (0.1)	1 (1.7)	0 (0)	0 (0)
Unknown	201 (7.4)	15 (25.4)	6 (28.6)	2 (66.7)
T stage		<0.001*	<0.001*	0.501
T1	1,237 (45.4)	2 (3.4)	2 (9.5)	1 (33.3)
T2	1,096 (40.2)	14 (23.7)	7 (33.3)	0 (0)
T3	68 (2.5)	3 (5.1)	4 (19.0)	0 (0)
T4	173 (6.4)	25 (42.4)	5 (23.8)	1 (33.3)
Unknown	149 (5.5)	15 (25.4)	3 (14.3)	1 (33.3)
N stage		<0.001*	0.242	0.811
N0	1,579 (58.0)	15 (25.4)	8 (38.1)	1 (33.3)
N1	756 (27.8)	28 (47.5)	7 (33.3)	2 (66.7)
N2	199 (7.3)	6 (10.2)	0 (0)	0 (0)
N3	105 (3.9)	6 (10.2)	3 (14.3)	0 (0)
Unknown	84 (3.1)	4 (6.8)	3 (14.3)	0 (0)
ER		<0.001*	0.001*	<0.001*
Positive	2,507 (92.1)	46 (78.0)	16 (76.2)	1 (33.3)
Negative	67 (2.5)	6 (10.2)	3 (14.3)	2 (66.7)
Unknown	149 (5.5)	7 (11.9)	2 (9.5)	0 (0)
PR		0.002*	<0.001*	<0.001*
Positive	2,331 (85.6)	40 (67.8)	12 (57.1)	0 (0)
Negative	226 (8.3)	12 (20.3)	7 (33.3)	3 (100.0)
Unknown	166 (6.1)	7 (11.9)	2 (9.5)	0 (0)
HER2		<0.001*	<0.001*	0.003*
Positive	289 (10.6)	12 (20.3)	6 (28.6)	2 (66.7)
Negative	2,138 (78.5)	38 (64.4)	10 (47.6)	1 (33.3)
Unknown	296 (10.9)	9 (15.3)	5 (23.8)	0 (0)
Subtype		0.001*	<0.001*	<0.001*
HR–/HER+	2,908 (77.0)	35 (59.3)	7 (33.3)	0 (0)
HR+/HER+	265 (9.7)	10 (16.9)	6 (28.6)	1 (33.3)
HR+/HER–	21 (0.8)	2 (3.4)	0 (0)	1 (33.3)
TN	34 (1.2)	3 (5.1)	3 (14.3)	1 (33.3)
Unknown	305 (11.2)	9 (15.3)	5 (23.8)	0 (0)
Laterality		0.736	0.296	0.130
Right	1,253 (46.0)	31 (52.5)	9 (42.9)	1 (33.3)
Left	1,441 (52.9)	25 (42.4)	10 (47.6)	1 (33.3)
Bilateral	25 (0.9)	3 (5.1)	2 (9.5)	1 (33.3)
Unknown	4 (0.1)	0 (0)	0 (0)	0 (0)
Surgery		<0.001*	<0.001*	<0.001*
No	185 (6.8)	43 (72.9)	16 (76.2)	3 (100.0)
Yes	2,498 (91.7)	15 (25.4)	3 (14.3)	0 (0)
Unknown	40 (1.7)	1 (1.7)	2 (9.5)	0 (0)
Status		<0.001*	<0.001*	0.018*
Alive	2,283 (83.8)	31 (52.5)	9 (42.9)	1 (33.3)
Dead	440 (16.2)	28 (47.5)	12 (57.1)	2 (66.7)

*, represent the P value <0.05.