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Metastasis pattern and prognosis of male breast cancer patients in US: a population-based study from SEER database

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Abstract

Background: The aims of this study were to analyze the metastasis pattern and prognosis of male breast cancer (MBC) and compare it with female breast cancer (FBC), and to determine the independent factors affecting the prognosis of MBC patients.

Methods: Metastatic MBC diagnosed in the Surveillance, Epidemiology and End results (SEER) database from 2010 to 2015 were selected. Chi-squared test was used to compare clinicopathological characteristics. Survival differences were compared by Kaplan–Meier analysis. Cox proportional hazard model was used to determine the prognostic factors affecting overall survival.

Results: A total of 2754 MBC patients were identified, of which 196 had distant metastasis. Compared with nonmetastatic MBC, metastatic MBC patients had a higher proportion of <60 years old and grade III–IV, and were more likely to receive chemotherapy and radiotherapy, while the proportion of surgery, central portion of the breast, and Her2–/HR+ was lower. Compared with metastatic FBC, metastatic MBC patients had a higher proportion of ⩾60 years old, central portion of the breast, surgery, simultaneous bone and lung metastasis, while the proportion of Her2+/HR–, triple negative, liver metastasis only, and simultaneous bone and liver metastasis was lower. MBC patients with lung alone, bone alone, and simultaneous lung and bone metastasis had a higher hazard ratio (2.41; 3.06; 2.52; $p < 0.0001$) compared with nonmetastatic patients.

Conclusions: Compared with nonmetastatic MBC patients, metastatic MBC patients had unique clinicopathological features, and were also different from metastatic FBC patients. However, there was no difference in prognosis between metastatic MBC and FBC patients. Distant metastasis was an independent risk factor for the prognosis of MBC patients.

Keywords: breast cancer, male, metastasis, prognosis, SEER

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Introduction

MBC is a rare disease, which has different clinicopathological and immunohistochemical features from FBC.[1–4] According to the latest data from the American Cancer Society, it accounts for about 0.98% and 1.18% of breast cancer morbidity and mortality, respectively.[5] The incidence of MBC has increased by 20–25% in the past few decades and continues to rise,[6,7] and even reached 15% in some specific populations.[8] The prognosis of MBC is worse than that of female patients due to older age and advanced stage at diagnosis.[9–11] Distant metastasis is an important factor influencing the prognosis of breast cancer. Nearly 20–30% of breast cancer patients with early age will finally develop metastatic lesions after diagnosis,[12,13] and 90% of breast cancer deaths are caused by metastasis leading to resistance to treatment.[14] Two previous studies based on the Surveillance, Epidemiology and End results (SEER) database have shown that stage IV accounts for about 7–9% of all MBC patients.[15–17]

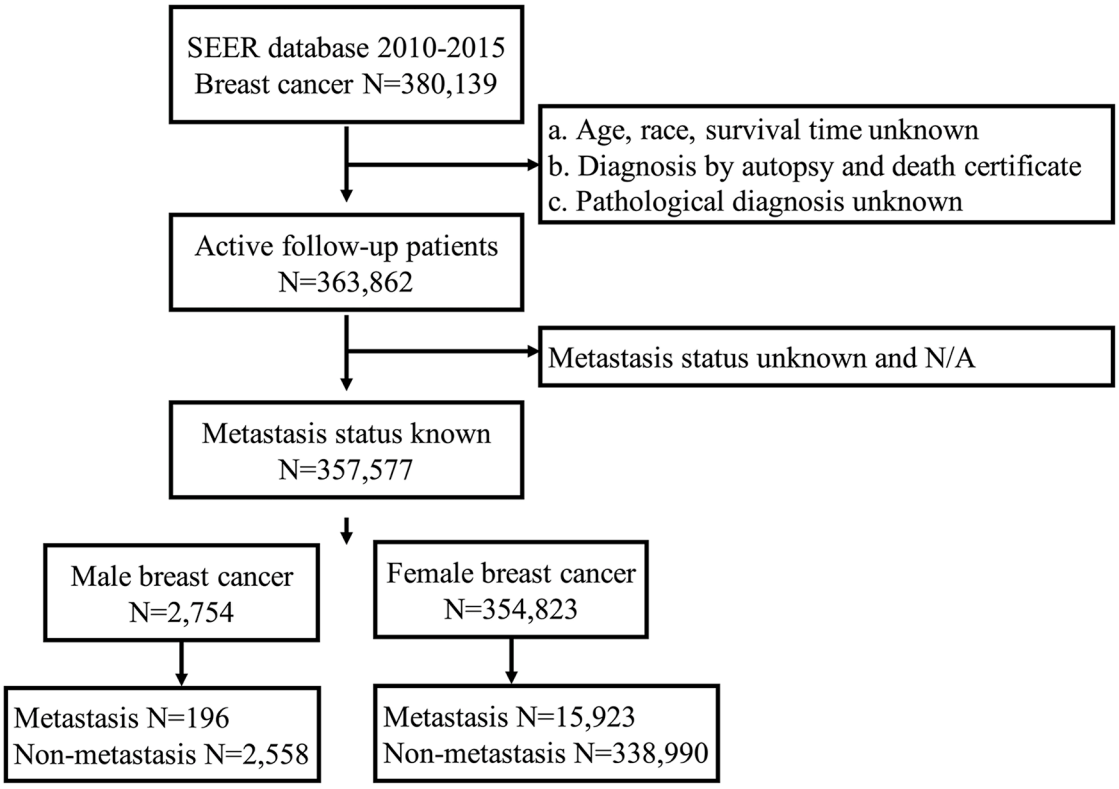

Figure 1. Flowchart of patient selection.
Detailed selection of MBC and FBC patients diagnosis at 2010–2015 from SEER database.
FBC, female breast cancer; MBC, male breast cancer; SEER, surveillance, epidemiology and end results database.

Because distant solid organ metastasis data in the SEER database was collected from 2010, previous studies were unable to study the specific metastasis sites of stage IV MBC patients.

Therefore, we identified MBC data recorded from 2010 to 2015 in the SEER database for this study. We studied metastatic MBC patients horizontally and longitudinally to determine their clinicopathological features and differences from metastatic FBC patients, and, at the same time, to determine independent factors affecting the prognosis of MBC patients.

Methods

Patient selection

For this study, we signed the SEER research data agreement to access SEER information with the username10067-Nov2018. Data were obtained following approved guidelines. The ethics committees considered this research to be on nonhuman subjects because the subjects were patients who had been researched by the United States Department of Health and Human Services and were publicly accessible and deidentified. Thus, this study was exempted by the ethics committee of the Third Affiliated Hospital of Soochow University.

The SEER database is one of the world's largest open cancer databases, established by the National Cancer Institute of the United States, and accounts for about 28% of the U.S. population. The data we selected came from Incidence-SEER 18 Registries Custom Data (with additional treatment fields), released April 2019, based on the November 2018 submission. MBC patients with definite metastasis from 1 January 2010 to 31 December 2015 were included in this study. The specific screening process is shown in Figure 1. In short, we excluded patients whose age, race, survival time, pathological diagnosis, and metastasis were unknown, and whose pathological results were from autopsy or death certificate.

Variable classification

Age at diagnosis, race, primary site, laterality, grade, breast subtype, chemotherapy, radiation,

surgery, and metastasis were obtained from the database. Age was divided into <60 years old and ⩾60 years old. Metastasis of distant organs is defined in SEER as the state of metastasis of distant organs at the time of the first diagnosis of cancer. Distant metastatic sites included bone, brain, liver, and lung, according to the different metastatic sites, the distant metastasis was divided into 15 groups, which were single organ metastasis (bone, liver, brain, lung), two kinds of organ metastasis (bone and liver, bone and brain, bone and lung, liver and brain, liver and lung, brain and lung), three kinds of organ metastasis (bone, liver and brain; bone, liver and lung; bone, brain and lung; liver, brain and lung), and four organs metastasis (bone, liver, brain and lung). The degree of differentiation of tumors was divided into three groups: grade I (well differentiated) and grade II (moderately differentiated), grade III (poorly differentiated) and grade IV (undifferentiated), and unknown.

Statistical analysis

We use descriptive statistics to summarize demographic and clinical variables. Chi-squared test or Fisher's exact test was used to compare the clinicopathological characteristics between different cohorts. Kaplan–Meier curves and log-rank test were conducted to analyze the overall survival (OS) of different metastasis organs in MBC and FBC patients. In addition, we use univariate and multivariate Cox proportional hazard models to find other variables that may affect prognosis. Statistical significance was considered at two-sided p value <0.05. All data were obtained using SEER*Stat Software version 8.3.5. All statistical analyses were performed using SPSS Statistics 25 (IBM, New York, NY, USA).

Results

Population characteristics

From the SEER database, we finally identified 2754 MBC patients from 2010 to 2015. Among these MBC patients, 196 cases (7%) had distant metastasis, while 2558 cases (93%) did not. Compared with nonmetastatic MBC patients, MBC patients with distant metastasis had a higher proportion of <60 years old (35% *versus* 25%), grade III–IV (40% *versus* 32%), and were more likely to receive chemotherapy (49% *versus* 36%) and radiotherapy (35% *versus* 26%), while the proportion of surgery (36% *versus* 94%), central portion of the breast (27% *versus* 42%), and Her2–/HR+ (58% *versus* 79%) was lower. Detailed patient clinical characteristics is summarized in Table 1.

In addition, we compared the clinicopathological features of patients with metastatic breast cancer between different genders (Table 1). A total of 354,823 FBC patients were enrolled in the study, of which 15,923 were patients with distant metastasis, accounting for 4% of the total. Compared with metastatic FBC patients, MBC patients with distant metastasis had a higher proportion of ⩾60 years old (65% *versus* 56%), surgery (36% *versus* 28%), and central portion of the breast (27% *versus* 6%), while the proportion of Her2+/HR– (3% *versus* 8%), triple negative (8% *versus* 12%), and was lower. There was no difference in race, laterality, grade, chemotherapy, and radiation.

Metastasis pattern

In the cohort of MBC with distant metastasis, the most common single site of metastases was bone with 81 cases, which takes up 41% of patients with distant metastasis, followed by lung metastasis with 26 (13%) cases, only 5 (3%) and 2 (1%) patients were with liver and brain metastasis, respectively. Most patients had distant metastasis of a single organ, accounting for 58%. There were 58 (30%) MBC patients who had distant metastasis of two organs, 43 of whom had bone and lung metastasis; 21 (12%) and 3 (2%) patients were diagnosed with three and four organ metastases, respectively. Detailed results are presented in Table 2.

Additionally, we compared differences in metastasis patterns between males and females (Table 2). The results showed that, in terms of single organ metastasis, the incidence of liver metastasis in MBC patients was significantly lower than that in FBC patients (3% *versus* 8%; $p=0.005$). In terms of multiple organ metastasis, the incidence of both bone and liver metastasis in MBC patients was also lower than that in FBC patients (5% *versus* 9%; $p=0.023$), while the proportion of both bone and lung in MBC patients was higher than that in FBC patients (22% *versus* 11%; $p<0.0001$), as well as in patients with bone, brain, and lung metastases (5% *versus* 1%; $p<0.0001$).

Survival and prognosis of MBC patients with metastasis

In metastatic MBC patients, there were mainly bone metastasis alone, lung metastasis alone, and

Table 1. Clinical characteristics of male and female breast cancer.

Characteristics	MBC without metastasis		MBC with metastasis		FBC with metastasis		*p* value*	*p* value**
	n **2558**	**%** **93**	***n*** **196**	**%** **7**	***n*** **15,923**	**%** **4**		
Age							0.001	0.013
<60	631	25	69	35	7016	44		
⩾60	1927	75	127	65	8907	56		
Race							0.060	0.403
White	2078	81	146	74	12,033	76		
Black	360	14	39	20	2710	17		
Others	120	5	11	6	1180	7		
Primary Site							<0.0001	<0.0001
Upper-outer	301	12	15	8	3663	23		
Lower-outer	95	4	2	1	832	5		
Upper-inner	101	4	4	2	975	6		
Lower-inner	46	2	6	3	546	3		
Central portion	1082	42	53	27	937	6		
Other	933	36	116	59	8970	56		
Laterality							<0.0001	0.601
Left	1351	53	103	53	7798	49		
Right	1198	47	84	43	7380	46		
Other	9	0	9	5	745	5		
Grade							<0.0001	0.752
I-II	1599	63	77	39	6469	41		
III-IV	829	32	79	40	6005	38		
Unknown	130	5	40	20	3449	22		
Breast Subtype							<0.0001	0.019
Her2–/HR+	2019	79	114	58	8655	54		
Her2+/HR–	21	1	5	3	1205	8		
Her2+/HR+	260	10	30	15	2333	15		
Triple negative	36	1	16	8	1853	12		
Other	222	9	31	16	1877	12		
Chemotherapy							<0.0001	0.326
No/Unknown	1641	64	100	51	7563	47		

(Continued)

Characteristics	MBC without metastasis		MBC with metastasis		FBC with metastasis		*p* value*	*p* value**
	n 2558	% 93	*n* 196	% 7	*n* 15,923	% 4		
Yes	917	36	96	49	8360	53		
Radiation							0.012	0.406
No/Unknown	1883	74	128	65	10,842	68		
Yes	675	26	68	35	5081	32		
Surgery							<0.0001	0.042
No	160	6	126	64	11,340	71		
Yes	2398	94	70	36	4489	28		
Unknown	0	0	0	0	94	1		

*Comparison between MBC without metastasis and MBC with metastasis.
**Comparison between MBC with metastasis and FBC with metastasis.
FBC, female breast cancer; MBC, male breast cancer.

Table 2. Comparison of organ metastasis patterns between male and female patients with breast cancer.

Parameter	Male		Female		*p* value
	N = 196		*N* = 15,923		
	n	%	*n*	%	
Bone metastasis only	81	41	6948	44	0.517*
Brain metastasis only	2	1	250	2	0.744**
Liver metastasis only	5	3	1274	8	0.005*
Lung metastasis only	26	13	1848	12	0.471*
Bone and brain	4	2	298	2	1**
Bone and liver	9	5	1483	9	0.023*
Bone and lung	43	22	1716	11	<0.0001*
Brain and liver	1	1	47	0	1**
Brain and lung	0	0	133	1	0.415***
Liver and lung	1	1	433	3	0.094**
Bone, brain, and liver	1	1	118	1	1**
Bone, brain, and lung	9	5	205	1	<0.0001*
Bone, liver, and lung	10	5	895	6	0.754*
Brain, liver, and lung	1	1	55	0	1**
Bone, brain, liver, and lung	3	2	220	1	1**

*Pearson chi-squared test.
**Chi-squared test of continuity correction.
***Fisher's exact test.

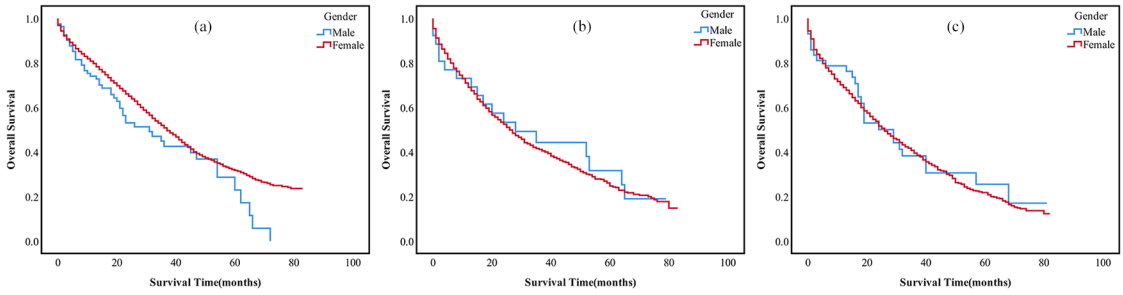

Figure 2. OS rate of MBC and FBC patients at different metastasis sites.
(a) OS of bone alone metastasis between MBC and FBC patients, $p = 0.05$; (b) OS of lung alone metastasis between MBC and FBC patients, $p = 0.772$; (c) OS of both bone and lung metastasis between MBC and FBC patients, $p = 0.766$.
FBC, female breast cancer; MBC, male breast cancer; OS, overall survival.

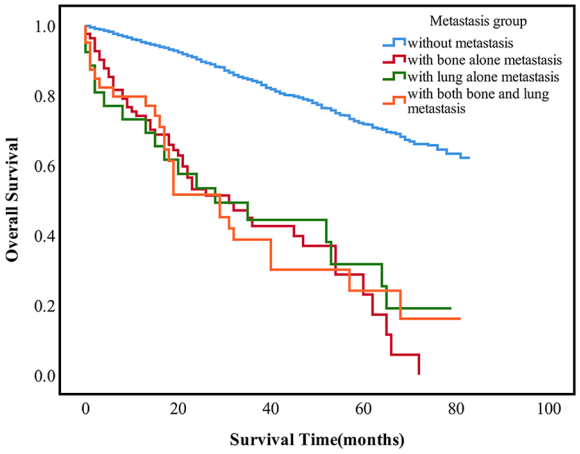

Figure 3. The survival difference among the different metastasis sites in MCB patients, $p < 0.0001$.
MBC, male breast cancer.

simultaneous bone and lung metastasis, which accounted for more than three-quarters of the total metastasis population. Therefore, we included these three groups of people in the survival and prognostic analysis to explore the impact of distant metastasis on prognosis.

Kaplan–Meier analysis showed that there was no statistical difference in OS between MBC and FBC patients with distant metastasis (Figure 2). However, there was significant difference between metastatic MBC and nonmetastatic MBC patients (Figure 3). Moreover, there was no difference in survival among the three groups mentioned earlier.

We then performed multivariate analysis on variables that were meaningful in univariate analysis. As shown in Table 3, multivariate analysis showed that age, grade, breast subtype, chemotherapy, surgery, and metastasis were independent factors for OS ($p < 0.0001$). In details, patients ⩾60 years old had a worse OS than patients <60 years old (HR:1.90, 95%CI:1.53–2.37, $p < 0.0001$), and a worse prognosis was found in grade III–IV (HR:1.62, 95%CI:1.36–1.93, $p < 0.0001$), breast subtype of triple negative (HR:3.32, 95%CI:2.10–5.26, $p < 0.0001$) and patients with distant metastasis (HR:2.40, 95%CI:1.47–3.91, $p < 0.0001$; HR:3.08, 95%CI:2.22–4.27, $p < 0.0001$; HR:2.51, 95%CI:1.65–3.80, $p < 0.0001$). Patients receiving chemotherapy and surgery had a better prognosis (HR:0.64, 95%CI:0.53–0.77, $p < 0.0001$; HR:0.32, 95%CI:0.25–0.41, $p < 0.0001$).

Discussion

In this study, we systematically analyzed the distant metastasis of MBC patients through the SEER database. The results showed that MBC patients not only had a higher distant metastasis rate than FBC patients, but also had different metastasis patterns. They had unique clinicopathological features. In addition, a multivariate analysis was conducted to determine independent factors affecting the prognosis of MBC patients.

The distant metastasis rate of MBC was 7% in our study, which was consistent with previous studies,[15,16] while the distant metastasis rate in FBC was 4%. The distant metastasis rate of MBC was 1.75 times higher than that of female patients. At present, it is believed that it is mainly lack of awareness of breast cancer in male patients or delays in diagnosis that might be the cause of this phenomenon.[7,18,19] A study found that only 29% of 100 Croatian MBC patients were diagnosed

Table 3. Univariate and multivariate survival analysis of male breast cancer patients with lung alone, bone alone and simultaneous lung and bone metastasis.

Characteristics	Univariate analysis	Multivariate analysis		
	p value	Hazard ratio	95%CI	*p* value
Age	<0.0001			<0.0001
<60		Reference		
⩾60		1.90	1.53–2.37	<0.0001
Race	0.028			0.057
White		Reference		
Black		1.24	1.00–1.53	0.047
Others		0.78	0.51–1.20	0.256
Primary Site	0.001			0.103
Upper-outer		Reference		
Lower-outer		0.64	0.35–1.18	0.152
Upper-inner		1.24	0.74–2.07	0.418
Lower-inner		0.95	0.47–1.94	0.893
Central portion		1.24	0.92–1.67	0.153
Other		1.30	0.97–1.75	0.078
Laterality	0.170	NA		
Left				
Right				
Other				
Grade	<0.0001			<0.0001
I–II		Reference		
III–IV		1.62	1.36–1.93	<0.0001
Unknown		1.58	1.18–2.13	0.002
Breast Subtype	<0.0001			<0.0001
Her2–/HR+		Reference		
Her2+/HR–		0.90	0.40–2.07	0.807
Her2+/HR+		1.24	0.95–1.62	0.121
Triple negative		3.32	2.10–5.26	<0.0001
Other		1.25	0.96–1.61	0.094

(Continued)

Table 3. (Continued)

Characteristics	Univariate analysis	Multivariate analysis		
	p value	Hazard ratio	95%CI	*p* value
Chemotherapy	<0.0001			<0.0001
No/Unknown		Reference		
Yes		0.64	0.53–0.77	<0.0001
Radiation	0.518	NA		
No/Unknown				
Yes				
Surgery	<0.0001			<0.0001
No		Reference		
Yes		0.32	0.25–0.41	<0.0001
Metastasis	<0.0001			<0.0001
None		Reference		
Lung Only		2.40	1.47–3.91	<0.0001
Bone Only		3.08	2.22–4.27	<0.0001
Lung and Bone		2.51	1.65–3.80	<0.0001

within 3 months of symptoms, compared with 58% of 500 Croatian FBC patients at the same time.[20] In addition, Hong and colleagues suggested that the prolonged period of symptom duration of MBC was also the reason for the difference in the rate of distant metastasis between MBC and FBC patients,[17] and NI and colleagues' study of 64 cases of male breasts without breast cancer showed columnar cell changes in 39 cases (61%), which was considered to be a transitional stage in the development of some low-grade ductal carcinoma *in situ* and invasive breast cancer.[21] In our opinion, in addition to the above reasons, differences in gene mutation may also cause this phenomenon. There are differences in genomics between MBC and FBC.[22,23] It was found that the mutation rate of CHEK2 c.1100delC in MBC was higher than that in FBC, and the mutation rate of CHEK2 c.1100delC was positively correlated with the rate of metastasis.[24,25]

There were differences in age of diagnosis, primary site, grade, subtypes, and treatment methods (including chemotherapy, radiotherapy, and surgery) between metastatic MBC and nonmetastatic MBC. The difference in gene expression exists not only between different genders, but also at different ages of the same sex. Hallamies and colleagues found that median age of the *CHEK2*c.1100delC carriers was 56 years, and half of the patients were <50 years old in MBC patients.[24] Poorly differentiated tumors seem to be more prone to distant metastasis, which seems to be associated with a higher frequency of local invasion of poorly differentiated tumors.[26] Previous studies have found that breast cancer subtypes were independent factors affecting the occurrence of metastasis. Compared with the other three subtypes, patients with luminal A (Her2–/HR+) had the lowest incidence of distant metastasis.[27,28] In our study, metastatic MBC patients had a lower proportion of luminal A compared with nonmetastatic patients; in contrast, the proportions of other three subtypes were higher. As expected, patients with metastatic MBC tend to lose the opportunity for surgery, and were more likely to choose radiotherapy and chemotherapy.

The median age of diagnosis of MBC was 5–10 years older than that of FBC patients in many studies.[29–31] This may be that the proportion of MBC patients with distant metastasis ⩾60 years old is higher than that of FBC patients. The rate of metastasis in the central portion of the breast in metastatic MBC was significantly higher than that in female patients, but on the contrary in the upper outer of the breast, which may be related to anatomical difference between male and female breasts. As with the findings reported by Li and colleagues,[32] there were differences in molecular subtypes in patients with metastatic breast cancer of different genders.

As far as we know, this is the first time that the distant metastasis patterns of MBC and FBC patients have been compared in detail through a large cancer database. Our study found that the metastasis rates of bone, lung, liver, and brain metastasis in metastatic MBC patients were 82%, 47%, 16%, and 11%, respectively. Under the same conditions, the metastasis rates of various organs in women were 75%, 35%, 28%, and 8%, respectively. Bone metastasis rates were higher than in previous studies, with bone metastasis rates of 50% in metastatic MBC patients in a previous German study,[33] and 75% in another study based on the SEER database.[34] However, the highest incidence of bone metastasis and the lowest incidence of brain metastasis were consistent with previous studies. Although the rate of single liver metastasis was only 3%, it seems that the rate of liver metastasis combined with other metastases was not low, accounting for 13% of the total metastases, and also in brain metastases (1% *versus* 10%). We believed that once a tumor had distant metastasis of one organ, it may accelerate metastasis in other parts, although single liver or brain metastasis was not common, but when the tumor had metastasis in other parts, it accelerated liver and brain metastases. This requires the attention of clinicians. We also found that, although there was no difference in the rate of single lung and bone metastasis between MBC and FBC patients, the risk of simultaneous bone and lung metastasis in male patients was twice as high as that in female patients. Male patients have a higher smoking rate, at about 1.5 times that of women.[35] Smoking is a risk factor for cancer metastasis, including bone and lung metastasis.[36,37] Studies have found that the liver microenvironment is an important factor affecting liver metastasis of breast cancer. For example, lysyl oxidase inhibits liver metastasis,[38] while osteopontin and vascular endothelial growth factor promote liver metastasis.[39,40] This may be one of the reasons for the difference in liver metastasis rate between male and female patients with breast cancer.

Although metastatic MBC patients had unique clinicopathological features and metastatic pattern, we found that there was no difference in OS compared with metastatic FBC patients. Our results were consistent with those of other similar studies, such as stage IV breast cancer patients,[34] gastric cancer patients with liver metastasis,[41] and colorectal signet ring cell carcinoma patients with distant metastasis.[42] Multivariate analysis showed that distant metastasis was an independent risk factor affecting the prognosis of MBC. Metastatic MBC patients had a worse OS rate compared with nonmetastatic MBC patients ($p < 0.0001$). There was no survival difference between patients with single lung or bone metastasis and patients with both bone and lung metastasis. We also found that the prognosis of HER–/HR+ was similar to that of HER+/HR–, and that triple-negative breast cancer patients had the highest risk of death, which was consistent with previous studies, possibly because HER+ patients benefited from the use of trastuzumab.[43,44] In addition, age, chemotherapy, surgery, and histological grade were also important factors affecting the prognosis of MBC. Because there are fewer MBC patients, for a long time, the treatment of MBC refers to FBC.[2] Although radiotherapy seem to have no effect on prognosis in our cohort, we do not know what organs have received radiotherapy, and studies have shown that radiotherapy can improve the prognosis of MBC patients,[45–47] so this conclusion needs to be further verified.

Our research still has some limitations. Firstly, there are only liver, brain, lung, and bone metastasis in distant parenchymal organ metastasis in SEER database; however, it has been reported that MBC can also metastasize to other sites, such as oral mucosa,[48] or choroidal sites.[49] Secondly, reasons for the difference in breast cancer metastasis between men and women still need further exploration. Finally, our conclusions may apply only to patients from the United States.

To sum up, through this study, we found that metastatic MBC patients have unique clinicopathological features and metastatic patterns, and that these differed from metastatic FBC patients. However, there was no difference in prognosis

between MBC and FBC patients with metastasis. Distant metastasis was an independent risk factor for the prognosis of MBC patients.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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