Original Article

Analysis of the distinct features of metastasis male breast cancer and its effect on overall survival based on the SEER database compared with female breast cancer

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Background: Male breast cancer (MBC) is a rare disease and differs from female breast cancer (FBC) in clinicopathological and immune tissue types. Given the limited research on MBC due to its rarity, an understanding of the shared and distinct features of MBC and FBC is vital for formulating efficacious treatment strategies.

Methods: Data of patients diagnosed with metastatic breast cancer in the Surveillance, Epidemiology, and End Results (SEER) database from 2012 to 2017 were analysed. Chi-square test was used to compare clinicopathological characteristics between male and female patients. Kaplan-Meier analysis was utilized to compare differences in overall survival (OS).

Results: A total of 2,858 patients with MBC were studied, 134 of whom had distant metastasis. Compared with 8,698 patients with metastatic FBC, a higher proportion of metastatic MBC patients had tumors located in the center of the breast, received surgical treatment, and had bone + lung metastasis. Survival analysis revealed no difference in OS between metastatic MBC and FBC patients (P=0.27), but there was a significant difference in OS between metastatic and nonmetastatic MBC (P=0.004). Compared with metastatic FBC, MBC patients with bone metastasis alone, lung metastasis alone, liver metastasis alone, and bone + lung metastasis also had worse prognosis (P=0.021, 0.019, 0.024, 0.011, respectively).

Conclusions: Metastatic MBC has unique clinicopathological disease features and patterns of metastasis. No significant difference between the survival of metastatic MBC and FBC patients was observed. Distant metastasis was an independent risk factor impacting the prognosis of MBC patients.

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

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Introduction

Male breast cancer (MBC) is a rare condition and distinct from female breast cancer (FBC) in clinicopathological features and immune cell infiltration (1-3). In 2018, about 2,550 MBC was diagnosed in the United States (US), and accounting for 480 deaths. In comparison, approximately 266,120 new cases of FBC were diagnosed and caused approximately 40,920 deaths (4). The MBCs were usually diagnosed at a later stage than FBCs, and exhibited more advanced disease features, such as larger tumor size, lymph node involvement, and distant metastases (5-7). MBCs usually expressed the estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR); were hormonally responsive (8-11). Researches try to reveal the germline mutations with increased prevalence in MBC, such as *BRCA2*, may help with the identification of novel treatment options such as poly(ADP-ribose) glycohydrolase (PARP) inhibitors (12,13), however, the distinct gene mutations have not been determined. Currently, no standard of care exists for MBC. The objective of this study is to compare MBC and FBC patients with distant metastasis to identify the clinical characteristics of MBC and the related factors affecting the prognosis of metastatic patients to provide a reference for the diagnosis and treatment of MBC patients. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1175/rc).

Highlight box

Key findings

- Distant metastasis is an independent risk factor affecting the prognosis of male breast cancer (MBC) patients.

What is known and what is new?

- The goal of treatment of metastatic breast cancer can be to extend life and improve quality of life. Treatment decisions are based on the metastatic breast cancer subtype. Metastatic MBC in general being treated similarly to female breast cancer (FBC).
- Compared with metastatic FBC, a higher proportion of metastatic MBC patients had tumors located in the center of the breast, received surgical treatment, and had bone + lung metastasis. MBC patients were more likely to develop bone and lung metastasis or bone, brain, and lung metastasis.

What is the implication, and what should change now?

- Distant metastasis was an independent risk factor that impacts the prognosis and survival of MBC patients. Early detection and treatment of male breast cancer is needed to reduce the rates of metastatic disease at diagnosis and improve survival.

Methods

Research objects

SEER*Stat software (version 8.3.6) was utilised to access Surveillance, Epidemiology, and End Results (SEER) 18 which is a is an authoritative source of information on cancer incidence and survival in the US [2000–2017], with the username 13054-Nov2020, obtaining the data of breast cancer patients from January 1, 2012 to December 31, 2017. A total of 368,765 patients were screened according to the inclusion and exclusion criteria, with detailed clinical pathology and follow-up data. Patients were included in the study if they fulfilled the inclusion criteria of a histological diagnosis of primary breast cancer and the availability of data on follow-up and outcome. Patients were excluded if there was no evidence of pathological diagnosis while the patient was alive, or if data regarding distant metastasis was unknown or unspecified.

Clinicopathological data and observation indicators

Demographic and clinical data obtained from the SEER database included age, race, lesion location, pathological diagnosis, treatment details including surgery, radiotherapy or chemotherapy, and presence or absence of distant metastasis. Distant metastasis in the SEER database is assessed at the time of cancer diagnosis. Involved organs with metastatic disease included lung, bone, brain and liver. Patients were divided into 15 groups depending on pattern of metastatic involvement-including single-organ metastasis groups (lung, bone, brain, or liver), two-organ metastasis groups (bone and liver, bone and brain, bone and lung, liver and brain, liver and lung, or brain and lung), three-organ metastasis groups (bone, liver, and brain; bone, liver, and lung; bone, brain, and lung; or liver, brain, and lung), and four-organ metastasis group (bone, liver, brain, and lung). The degree of pathological differentiation included highly differentiated (grade I), moderately differentiated (grade II), poorly differentiated (grade III), and undifferentiated (grade IV). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical methods

SPSS25.0 software (SPSS Inc., IBM Corporation, Chicago,

IL, USA) was used for statistical analysis of the data. Descriptive statistics were used to analyze the clinical variables. χ^2, Fisher's exact test or Mann-Whitney *U* test was used to compare clinicopathological characteristics between groups. Cox regression analysis were used to analyze overall survival (OS) of MBC and FBC. Two-sided tests were used, with a significance P value cut-off of 0.05.

Results

General clinical data of patients

A total of 368,765 patients with breast cancer were identified from 2012 to 2017 including 2,858 MBC patients, of which 134 cases were metastatic (4.70%) and 365,907 FBC patients of which 8,698 were metastatic (2.37%). Demographic and clinical data of included patients is summarised in *Table 1*, there was significant difference in age, location of primary tumor, degree of tumor differentiation, operation or not and molecular subtype between metastatic MBC and FBC. Patients were stratified by age into 2 groups: <60 or ≥60 years.

Compared with metastatic FBC, metastatic MBC patients were more likely to have tumors located in the center of the breast, received surgical treatment, and the presence of bone + lung metastasis.

General data of distant metastasis

Of the 134 cases of MBC with distant metastasis, the most common site of single metastasis was bone, accounting for 54 cases (40.3%), followed by lung metastasis in 18 cases (13.4%), liver metastasis in 13 cases (9.7%), and brain metastasis in 9 cases (6.7%). Twenty-eight MBC patients (20.9%) had two-organ metastasis, including 24 cases in which metastases occurred simultaneously in bone and lung. Three- or four-organ metastasis occurred in 10 (7.5%) and 2 (1.5%) patients, respectively (*Table 2*). A comparison of metastatic MBC and FBC (*Table 2*) revealed no significant difference in single-organ distant metastasis. For multiple-organ metastasis, MBC patients were more likely to have bone and lung metastasis (17.91% *vs.* 9.97%, P=0.002) or bone, brain, and lung metastasis (2.99% *vs.* 1.03%, P=0.079) than FBC patients.

Prognosis of patients with metastatic MBC

Cox regression analysis showed no statistically significant difference in OS between metastatic MBC and FBC patients (*Figure 1*). However, patients with metastatic MBC had worse OS than nonmetastatic MBC (*Figure 2*). Compared with metastatic FBC, MBC patients with bone metastasis alone, lung metastasis alone, liver metastasis alone, and bone + lung metastasis also had worse prognosis (*Figures 3-6*).

Discussion

The current study analysed the SEER database to review demographic, clinical and survival data of MBC patients with metastatic disease. We demonstrate a higher metastatic rate of MBC compared with FBC, as well as distinguishing clinical features between MBC and FBC.

In our study, the incidence of distant metastasis of MBC and FBC was 4.7% and 2.4%, respectively, which is similar to previous reports (14,15). A Croatian study found that only 29 of 100 MBC patients were diagnosed within 3 months of symptom onset, while 290 of 500 FBC patients were diagnosed within the same time frame (16). Lack of awareness of breast cancer in male patients compared to females is likely associated with a delay in seeking of medical attention. Hong *et al.* from South Korea theorized that the long gap between symptom onset and diagnosis was the main reason for the difference in the rate of occurrence of distant metastasis between MBC and FBC (17). Campos *et al.* reported that *BRCA1* and *BRCA2* gene mutations were closely related to the occurrence of MBC (18), while Abeni *et al.* demonstrated significant differences in DNA methylation between MBC and FBC in *GTPase Rho GAP/GEF*, *GTPase RAB*, *BRCAX*, *BRCA1* + *BRCAX*, and other genes (19). Therefore, it is speculated that genetic differences may also contribute to the differing rates of distant metastasis in MBC versus FBC. A difference in gene expression exists between different sexes and also for different ages. A Finnish study of MBC found that the *CHEK2c.1100delc* gene mutation was associated with increased risk of MBC, with a median age at diagnosis of 56 years in patients carrying the mutation, and with and an approximately half of patients less than 50 years old age (20). Treatment decisions are based on the metastatic breast cancer subtype. However, metastatic breast cancer in men is now being treated similarly to women. More clinical data of MBC needs to be provided to clarify the difference between FBC and MBC.

This current study compared the distant metastases of MBC and FBC patients and found that the rates of bone,

Table 1 General clinicopathological characteristics of patients

Factor	Nonmetastatic MBC (N=2,724), n (%)	Metastatic MBC (N=134), n (%)	Metastatic FBC (N=8,698), n (%)	χ^2	P
Age, years				42.073	<0.001
<60	720 (26.4)	2 (1.5)	6 (0.1)		
≥60	2,004 (73.6)	132 (98.5)	8,692 (99.9)		
Location of primary tumor					
Areolar or nipple	142 (5.2)	8 (6.0)	42 (0.5)	36.141	<0.001
Central region	1,128 (41.4)	38 (28.4)	545 (6.3)		
Inner upper quadrant	106 (3.9)	1 (0.7)	510 (5.9)		
Inner lower quadrant	48 (1.8)	4 (3.0)	285 (3.3)		
Outer upper quadrant	320 (11.7)	8 (6.0)	1,798 (20.7)		
Outer lower quadrant	95 (3.5)	1 (0.7)	405 (4.7)		
Other	885 (32.5)	74 (55.2)	5,113 (58.8)		
Degree of tumor differentiation				137.663	<0.001
Grade I	325 (11.9)	5 (3.7)	650 (7.5)		
Grade II	1,359 (49.9)	43 (32.1)	2,814 (32.4)		
Grade III	879 (32.3)	43 (32.1)	2,695 (31.0)		
Grade IV	7 (0.3)	1 (0.7)	48 (0.6)		
Other	156 (5.7)	42 (31.3)	2,491 (28.6)		
Bilateral				69.826	<0.001
Left	1,444 (53.0)	72 (53.7)	4,120 (47.4)		
Right	1,268 (46.5)	53 (39.6)	3,877 (44.6)		
Other	12 (0.4)	9 (6.7)	701 (8.1)		
Operation				539.869	<0.001
Yes	2,506 (92.0)	37 (27.6)	2,089 (24.0)		
No	218 (8.0)	97 (72.4)	6,609 (76.0)		
Radiotherapy				0.20	0.887
Yes	838 (30.8)	42 (31.3)	2,440 (28.1)		
No	1,886 (69.2)	92 (68.7)	6,258 (71.9)		
Chemotherapy				4.310	0.038
Yes	979 (35.9)	60 (44.8)	2,984 (34.3)		
No	1,745 (64.1)	74 (55.2)	5,714 (65.7)		
Molecular subtype				61.347	<0.001
HR+/*HER2*–	2,122 (77.9)	82 (61.2)	4,844 (55.7)		
HR+/*HER2*+	283 (10.4)	13 (9.7)	927 (10.7)		
HR–/*HER2*+	20 (0.7)	6 (4.5)	457 (5.3)		
HR–/*HER2*–	42 (1.5)	11 (8.2)	940 (10.8)		
Other	257 (9.4)	22 (16.4)	1,530 (17.6)		

MBC, male breast cancer; FBC, female breast cancer; HR, hormone receptor; *HER2*, human epidermal growth factor receptor 2.

Table 2 General data of distant metastasis of breast cancer

Transfer site	MBC (N=134), n (%)	FBC (N=8,698), n (%)	χ^2	P
Bone	54 (40.30)	3,636 (41.80)	0.123[a]	0.726
Brain	9 (6.72)	350 (4.02)	2.453	0.117
Liver	13 (9.70)	973 (11.19)	0.293[a]	0.588
Lung	18 (13.43)	1,361 (15.65)	0.491[a]	0.483
Bone and brain	0 (0)	121 (1.39)		0.267[c]
Bone and liver	4 (2.99)	532 (6.12)	1.754[b]	0.185
Bone and lung	24 (17.91)	867 (9.97)	9.178[a]	0.002
Brain and liver	0 (0)	23 (0.26)		1.000[c]
Brain and lung	0 (0)	63 (0.82)		1.000[c]
Liver and lung	0 (0)	218 (2.51)		0.082[c]
Bone, brain, liver	1 (0.75)	38 (0.44)	0.000[b]	1.000
Bone, brain, lung	4 (2.99)	90 (1.03)	3.095[b]	0.079
Bone, liver, lung	5 (3.73)	344 (3.95)	0.000[b]	1.000
Brain, liver, lung	0 (0)	19 (0.22)		1.000[c]
Bone, brain, liver, lung	2 (1.49)	63 (0.72)	0.274[b]	0.601

[a], Pearson Chi-square test; [b], Chi-square test of continuity correction; [c], Fisher exact probability test. MBC, male breast cancer; FBC, female breast cancer.

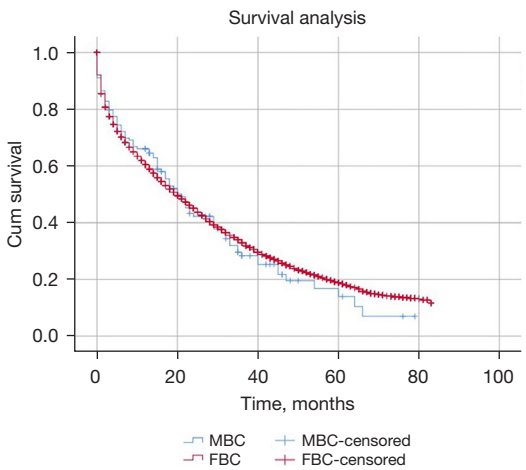

Figure 1 Cumulative OS in MBC and FBC patients. MBC, male breast cancer; FBC, female breast cancer; OS, overall survival.

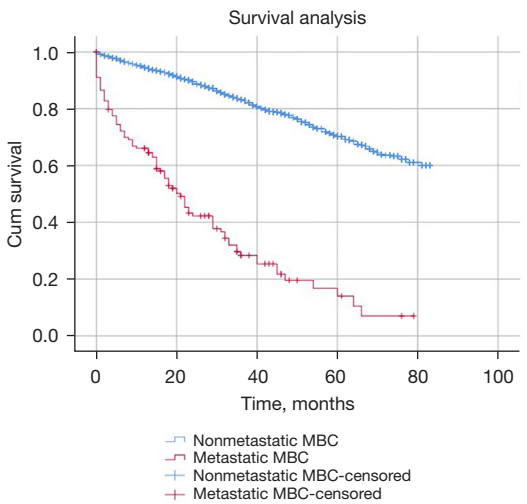

Figure 2 Cumulative of OS in patients with metastatic and nonmetastatic MBC. MBC, male breast cancer; OS, overall survival.

lung, liver, and brain metastases in patients with metastatic MBC were 40.3%, 6.7%, 9.7%, and 13.4% respectively, while for FBC, they were 41.8%, 4.0%, 11.2%, and 15.7%, respectively (P>0.05). In MBC, bone was the most common site of metastasis, and the brain the least common; both findings are consistent with previous studies (21,22). In MBC, although the incidence of isolated brain metastasis was only 6.7%, brain combined with other sites of organ metastases accounted for 11.9%. Similarly, in FBC, the

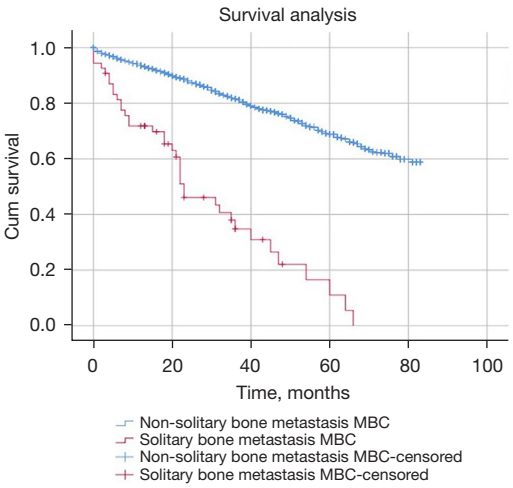

Figure 3 Cumulative OS in MBC patients with solitary bone metastasis and non-solitary bone metastasis. MBC, male breast cancer; OS, overall survival.

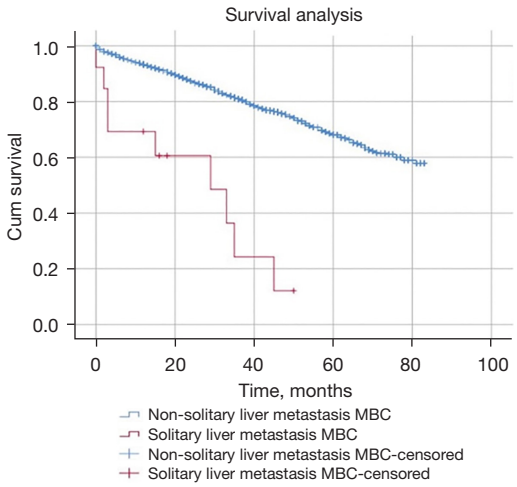

Figure 5 Cumulative OS in MBC patients with solitary liver metastasis and non-solitary liver metastasis. MBC, male breast cancer; OS, overall survival.

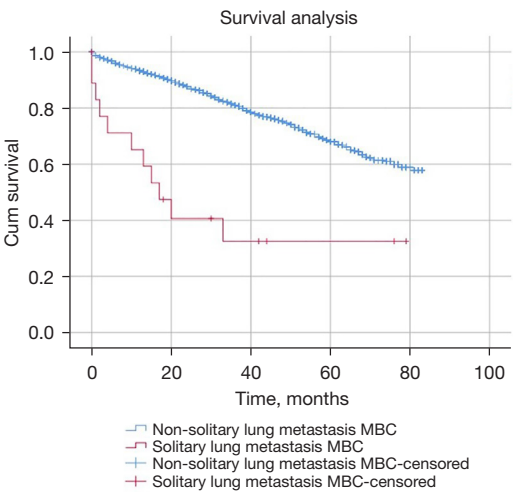

Figure 4 Cumulative OS in MBC patients with solitary lung metastasis and non-solitary lung metastasis. MBC, male breast cancer; OS, overall survival.

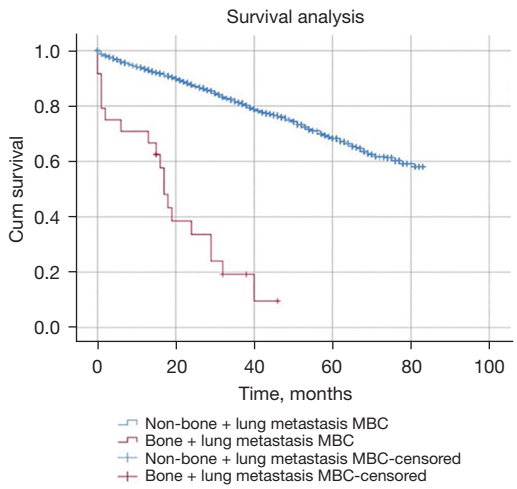

Figure 6 Cumulative OS in MBC patients with bone + lung metastasis and non-bone + lung metastasis. MBC, male breast cancer; OS, overall survival.

incidence of brain metastasis alone was 4.0%, while brain combined with other organ metastases accounted for 8.8%. Therefore, we speculate that once metastasis occurs, it may promote metastasis to other organs. This study also revealed that although there was no significant difference in the rates of isolated bone or lung metastasis between MBC and FBC, the incidence of two-organ metastasis in MBC patients was approximately 1.8 times higher than FBC. This finding may be linked to a higher smoking prevalence in males, with smoking identified as a risk factor for distant metastasis (23,24).

This study has several limitations. Most importantly, data on patients was retrospectively obtained from SEER. And the credibility was limited by small number of MBC patients enrolled. More clinical studies were expected to launch, and we will update new data of SEER in the next research.

Conclusions

In conclusion, metastatic MBC was shown to have unique clinicopathological characteristics and metastasis patterns, although no significant difference was seen between the prognosis and OS of metastatic MBC and FBC patients. Distant metastasis was an independent risk factor affecting the prognosis of MBC patients. A number of factors including delayed diagnosis, higher smoking prevalence and adverse gene mutations may account for the higher rates of metastatic disease at diagnosis in MBC patients compared with females. More studies are needed to have a better understanding of metastatic MBC, as well as its treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1175/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1175/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1175/coif). FPC receives consulting fees from Astrazeneca; serves as the Advisory Board of Pfizer, Roche, MSD; receives payment or honoraria for lectures from Roche, Pfizer, Libbs, MSD, Astrazeneca. The other 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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