



Clinical features and prognostic factors of male breast cancer vs. female breast cancer

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Background: To investigate the clinicopathological features and prognostic factors of male breast cancer (MBC) and female breast cancer (FBC) patients.

Methods: A total of 90 MBC and 180 FBC patients were included in this retrospective study. The clinicopathological features, disease-free survival rate (DFS), and overall survival rate (OSR) were compared between the two groups. Cox proportional hazard model was used to analyze the factors affecting the survival rates.

Results: Most MBC were invasive ductal carcinoma (70/90, 77.8%) and luminal type (83/90, 92.2%), and were treated with modified radical mastectomy (78/90, 86.7%). Compared with women, there were more patients with one-set age of ≥ 70 years old, having family history of cancer, comorbid with underlying diseases in the male patients. They also had higher portion of patients at T3 and T4 stages. The rates of male patients receiving adjuvant radiotherapy, chemotherapy and endocrine therapy were lower ($P < 0.05$) than female patients. OSR and DFS were lower in the male patients than in the female patients ($P < 0.05$). T stage, TNM stage, the status of progesterone receptor and endocrine therapy were independent prognostic factors for survival of MBC ($P < 0.05$); TNM stage, chemotherapy or endocrine therapy were independent factors for survival of FBC ($P < 0.05$).

Conclusions: Compared with FBC, MBC occurs later with more underlying diseases and lower survival rates. MBC is less active in adjuvant therapy and endocrine therapy. Since MBC has more luminal type, increased endocrine therapy may improve the survival.

Keywords: Breast cancer; clinicopathological feature; prognosis; TNM stage

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Introduction

In the United States, 271,270 new breast cancers (BC) occur each year, accounting for about 15% all new malignant tumors, among them 42,260 patients died of BC (1). In China, over 42,000 cases of BC were diagnosed, among

them 70,700 patients died of BC (2,3). Compared with female breast cancer (FBC), male breast cancer (MBC) is relatively rare, accounting for less than 1% of all BC and 1% of all cancers in males (4), but the number of MBC has been rising gradually (1,5,6). Previously, most studies on BC were

conducted on FBC while MBC is less addressed. Because of the lack of guidelines and research data, the diagnosis and treatment of MBC have mainly relied on adopting clinical practices developed to treat female BC patients (7). However, it is generally agreed that there are considerable differences in survival rates and clinicopathological features between MBC and FBC (8-10). For example, MBC has its unique clinical features such as nipple ulcer and discharge with blood (11), advanced one-set age (12), high positive rate of estrogen receptor (ER) as compared with FBC (13). In addition, the prognosis with regard to the expression of ER is different between FBC and MBC (14). Therefore, it might be unreasonable to follow the treatment strategies for FBC to treat MBC. While extensive studies have been conducted with FBC regarding its clinical feature and risk factors (15-17) and many factors have been identified to be significant prognostic factors such as neutrophil to lymphocyte ratio (18), myeloperoxidase-positive neutrophil (19), expression of *FGD3* gene (20), in addition to histological grade (21,22), relatively less is known about MBC. According to a single-center study, ER, progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) were found to have predictive value for survival of MBC, and age, TNM stage and histological grade of tumor may affect the prognosis of MBC (23,24). However, these studies were conducted with relatively small samples, and the conclusions have not been validated in large and different populations. Recently, nomograms that predict BC-specific survival for MBC have been developed to assist the diagnosis and treatment of MBC. These nomograms are based on data from the Surveillance, Epidemiology, and End Results (SEER) database with large sample size, and indicate that the 3- and 5-year decision curve analysis curves could yield larger net benefits than the traditional American Joint Committee on Cancer (AJCC) stage (25). Clinically, MBC is different from FBC in a number of aspects, such as the biological characteristics, hormone levels, and risk factors (26,27) and is less characterized for optimal treatment and management.

To better understand the clinicopathological feature and factors affecting the prognosis of MBC, we conducted this study retrospective analysis. The findings may help improve the diagnosis and treatment of MBC. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/tcr-21-1>).

Methods

Patients

This was a retrospective study. A total of 90 male patients diagnosed with BC between January 1, 2008 and December 31, 2014 at our centers were included in this study. Female patients were randomly drawn from a pool of 1,869 FBC patients. All patients were diagnosed by pathological analysis of biopsy or surgical samples. Patients were excluded if they did not have complete follow-up data and had other tumors. Demographic and clinical data were retrieved from the hospital databases, which include gender, age, menstrual status, clinical stage, type of surgery, tumour site, tumour type, grade, pathological stage, underlying diseases and family history of cancer. This study was approved by the Ethics Committee of Nanjing Medical University (approval No.: NMU 2719-3), conducted in accordance with the Declaration of Helsinki (as revised in 2013) and written informed consent was obtained from every participant.

Pathological diagnosis and staging

Pathological and immunohistochemical analyses were performed by two pathologists blinded to the patient information. Hematoxylin and eosin (HE) staining was used for histochemical analysis. The expressions of ER, PR and HER-2 were detected immunohistochemically by monoclonal antibodies against ER (1:500, cat. no. ss-121), PR (1:100, cat. no. as-221) and HER-2 (1:500, cat. no. es-321) using commercial kits from Mbiotech, Wuhan, China, according to the manufacturer's protocols. Cancer staging and molecular subtyping based on the expression of ER, PR, HER-2 and Ki-67 (cat. no. ks-212) were carried out according to the 8th edition of AJCC staging manual (28) and the United States National Comprehensive Cancer Network guidelines (29). Distant metastasis was diagnosed and confirmed by biopsy of the primary and metastatic lesions. Computed tomography (CT), B-ultrasound and whole-body bone scan (WBS) were performed to confirm the staging.

Treatments

For male patients, modified radical mastectomy was performed with axillary lymph node dissection or sentinel

node biopsy as described previously (30,31). Adjuvant radiotherapy was given with a dose of 50 Gy/25 F and classical CMF regimen [cyclophosphamide (C) days 1–14 with intravenous methotrexate (M) and fluorouracil (F) on days 1 and 8, repeated every 28 days] or ACT regimen (adriamycin, cyclophosphamide and taxol) was applied. Endocrine therapy was performed with tamoxifen, letrozole, or castration plus letrozole.

For female patients, both modified radical mastectomy and breast-conserving surgery were performed. In addition, the same adjuvant radiotherapy, CMF, ACT and endocrine therapy were used following surgery. For some patients, AC-TH regimen (adriamycin, cyclophosphamide, taxol and trastuzumab) were given.

Follow-ups

The follow-up time in this study was defined as the time between the date of diagnosis to December 31, 2018. Follow-up was made through inpatient visits, outpatient visits and phone interview if the patients did not make hospital visit. During the follow-up, data regarding patient's treatment, examinations and survival status were collected. Disease-free survival was defined as the time between the date of diagnosis to the recurrence of the disease, overall survival was defined as the time between the date of diagnosis to death or the last follow-up.

Statistical analysis

The data were analyzed using SPSS version 11.5 for Windows (SPSS Inc., Chicago, IL, USA). The normality of distribution of continuous variables was tested by one-sample Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean [standard deviation (SD)]; non-normal variables were reported as median [interquartile range (IQR)]. Means of 2 continuous normally distributed variables were compared by independent samples Student's *t*-test. The frequencies of categorical variables were compared using Pearson χ^2 or Fisher's exact test, when appropriate. Survival was estimated by the Kaplan-Meier method. The hazard ratio (HR) was estimated using a Cox proportional hazards regression model. A value of $P < 0.05$ was considered significant.

Results

Patient clinical characteristics

The median age of male patients was significantly older than that of female patients [61 (33.0–86.0) *vs.* 46.6 (24.0–81.0) years, $P < 0.05$]. The median follow-up times were 58.3 (5.0–96.0) and 63.5 (8.0–96.0) months for male and female patients, respectively. While the most of the patients were Han nationality, there were 48 being ethnic minorities, including 8 Uyghur (3 male, 5 female), 9 Kazak (2 male and 7 female), 31 Mongolian (7 male, 24 female). For male patients, 27 (30%) had family history of cancer, among them 13 were BC, 32 had underlying diseases, including cardiovascular diseases, chronic renal insufficiency, and more than two of the three diseases (kidney disease, hypertension and coronary heart disease). For female patients, there were 16 cases with family history of cancer, among them 8 were BC; 6 case with underlying disease (coronary atherosclerotic heart disease). The percentages of male patients with family history of cancer and underlying diseases were significantly higher than female patients ($P < 0.05$). The marital status was similarly between the two groups with about 90% being married.

For MBC, based on T staging, there were 9 T1, 13 T2, 32 T3 and 36 T4 patients; based on TNM staging, there were 22 I, 34 II, 14 III and 20 IV patients. Among the IV BC, there were 13 lung metastases, 4 bone metastasis and 2 liver metastases. Molecular subtyping showed that 46 cases were positive for ER, 42 positive for PR and 4 positive for HER-2. Twelve percent of them were Ki-67 $\geq 14\%$. For female patients, there were 42 Tis, 40 T1, 22 T2, 38 T3 and 38 T4 BC and were 60 0, 42 I, 40 II, 20 III and 18 IV BC. Among the IV BC, there were 12 lung metastasis, 4 bone metastasis and 2 liver metastases. Molecular subtyping showed that 112 cases were ER⁺, 64 PR⁺ and 32 HER-2⁺. Fourteen percent of them were Ki-67 $\geq 14\%$. Patients with luminal cancer were more in MBC than in FBC (92.2% *vs.* 61.1%, $P < 0.001$), while there were more basal-like BC in female than in male (17.8% *vs.* 3.3%, $P < 0.001$, Table 1).

Compared with females, the percentages of male patients with onset time ≥ 70 years old, family history of cancer, underlying diseases, T3 and T4 stages, invasive ductal carcinoma and luminal type were significantly higher (all $P < 0.05$), while other clinical data were similar between

Table 1 Demographic and clinicopathological characteristics of breast cancer patients

Characteristics	Male (n=90)	Female (n=180)	χ^2	P
Ethnic group, n (%)			0.412	0.276
Han	78 (86.7)	144 (80.0)		
Minority	12 (13.3)	36 (20.0)		
Age (year), n (%)			18.762	<0.001
<70	32 (35.6)	124 (68.9)		
≥70	58 (64.4)	56 (31.1)		
Marital status, n (%)			0.712	0.196
Married	82 (91.1)	162 (90.0)		
Unmarried	5 (5.6)	6 (3.3)		
Unknown	3 (3.3)	12 (6.7)		
Family history of cancer, n (%)	28 (31.1)	16 (8.9)	21.283	<0.001
Underlying disease, n (%)	32 (35.6)	6 (3.3)	32.467	<0.001
Mass position, n (%)			1.443	0.215
Right	41 (45.6)	102 (56.7)		
Left	49 (54.4)	78 (43.3)		
Tumor type, n (%)				
Carcinoma in situ	3 (3.3)	44 (24.4)	5.016	0.025
Invasive ductal carcinoma	70 (77.8)	110 (61.1)	8.035	0.007
Invasive lobular carcinoma	7 (7.8)	14 (7.8)	1.581	0.358
Other*	10 (11.1)	12 (6.7)	0.048	0.294
T stage, n (%)			12.944	<0.001
Tis + T ₁ + T ₂	22 (24.4)	104 (57.8)		
T ₃ + T ₄	68 (75.6)	76 (42.2)		
N stage, n (%)			2.507	0.164
No	38 (42.2)	82 (45.6)		
Yes	52 (57.8)	98 (54.4)		
TNM stage, n (%)			3.271	0.072
0 + I + II	56 (62.2)	142 (78.9)		
III + IV	34 (37.8)	38 (21.1)		
Molecular type, n (%)				
Luminal (A + B)	83 (92.2)	110 (61.1)	14.286	<0.001
HER-2*	4 (4.4)	38 (21.1)	18.322	<0.001
Basal-like breast cancer	3 (3.3)	32 (17.8)	10.201	0.003
ER ⁺	46 (51.1)	112 (62.2)	1.322	0.281
PR ⁺	42 (46.7)	64 (35.6)	2.231	0.113

*, including medullary carcinoma and apocrine gland carcinoma.

Table 2 Treatment of patients

Group	N	Surgery			Adjuvant radiotherapy	Chemotherapy	Endocrine therapy
		Modified radical mastectomy	Conserving	No			
Male	90	78 (86.7)	0	12 (13.3)	18 (20.0)	55 (61.1)	17 (18.9)
Female	180	96 (53.3)	68 (37.8)	16 (8.9)	74 (41.1)	164 (91.1)	77 (42.8)
χ^2		4.715	26.482	4.415	7.451	6.540	3.542
P		0.051	<0.001	0.020	0.011	0.025	0.029

the two groups, such as mass positions, ethnic group and invasive lobular carcinoma.

Treatment of MBC vs. FBC

For male patients, 78 received modified radical mastectomy and 12 did not receive surgical treatment. Eighteen patients were treated with adjuvant radiotherapy and 55 with chemotherapy including CMF for patients underlying disease. Endocrine therapy was performed on 17 patients including three using letrozole and one with castration plus letrozole. For female patients, 96 received modified radical mastectomy and 68 had conserving surgery. Sixteen did not receive surgical treatment. Chemotherapy was performed on 82 patients including one patient with CMF due to heart disease, 20 with AC-TH and the rest with ACT. Endocrine therapy was used in 62 patients, among them, 46 used tamoxifen, 38 used letrozole and 2 used anastrozole. Analysis of treatments showed that about 87% of male patients were treated by modified radical mastectomy and the remaining was not treated surgically, while for female patients, both modified radical mastectomy (53.3%) and conserving surgery (37.8%) were used and only less than 10% of patients were not surgically treated (Table 2). In addition, less male patients received adjuvant radiotherapy, chemotherapy and endocrine therapy as compared with female patients ($P < 0.05$, Table 2).

Overall survival rate (OSR) and disease-free survival rate (DFSR)

The OSR and DFSR of patients with BC were 85.4% and 72.2%, respectively. Among them, the OSR and DFSR of MBC were 68.5% and 47.9%, respectively, which were significantly lower than those of FBC (91.7% and 87.1%,

$\chi^2 = 12.335$, $P < 0.001$; $\chi^2 = 23.453$, $P < 0.001$, respectively, Figure 1).

Univariate analysis of factors affecting survival

Univariate analysis of factors influencing the survival of MBC patients showed that T stage, TNM stage, PR status, chemotherapy and endocrine therapy had significant impact on 5-year survival rate in the male patients. Patients at T3 and T4 T stages, III and IV TNM stages, with PR⁺ status, and without chemotherapy and endocrine therapy had significantly lower 5-year OSR, as compared with patients at Tis, T1 and T2 T stages, 0, I and II TNM stages, with PR⁻ status, and with chemotherapy and endocrine therapy. For female patients, the same risk factors were identified except PR status, which did not impact the survival rate in the female patients (Table 3).

Multivariate analysis of factors affecting survival

For multivariate analysis, T stage was assigned to 0 (Tis + T1 + T2) or 1 (T3 + T4), TNM stage to 0 (0 + I + II) or 1 (III + IV), ER and PR expressions to 0 (positive) or 1 (negative), endocrine and chemotherapy to 0 (with) or 1 (without), and were used as independent variables to analyze their relationship with survival (1 for death, 0 for survival). The results showed that T stage, TNM stage, PR status and endocrine therapy were significant independent factors of the survival in the MBC patients ($P < 0.05$). For women, these factors were TNM stage, chemotherapy and endocrine therapy ($P < 0.05$, Tables 4, 5).

Therapeutic difference between MBC and FBC

To further assess the different response of MBC and FBC to

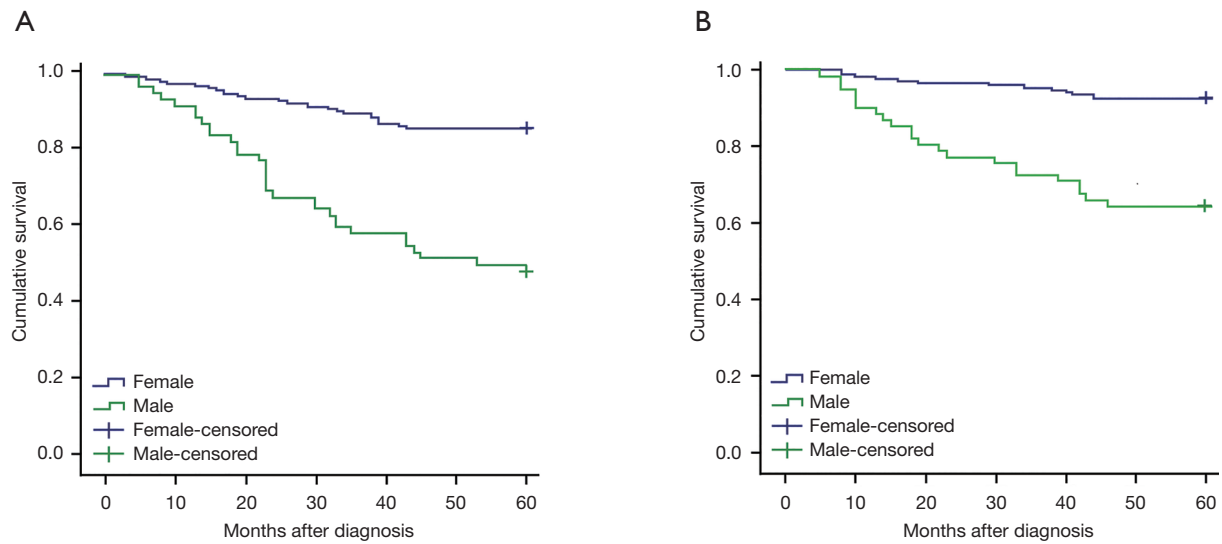


Figure 1 Five-year overall survival rate (A) and disease-free survival rate (B) in male and female breast cancer patients.

Table 3 Univariate analysis of factors affecting 5-year survival rate in male and female breast cancer patients

Variables	Male			Female		
	5-year survival rate (%)	χ^2	P	5-year survival rate (%)	χ^2	P
T stage		19.241	<0.001		18.044	<0.001
Tis + T ₁ + T ₂	74.7			92.1		
T ₃ + T ₄	23.9			70.4		
TNM stage		22.335	<0.001		17.358	<0.001
0 + I + II	83.2			98.7		
III + IV	22.7			78.6		
ER status		2.456	0.115		3.441	0.051
+	64.6			93.4		
-	86.6			85.7		
PR status		10.447	<0.001		1.968	0.265
+	71.9			95.4		
-	35.7			87.2		
Chemotherapy		6.419	0.006		11.952	<0.001
Yes	79.7			97.1		
No	36.3			70.9		
Endocrine therapy		10.234	<0.001		8.563	0.004
Yes	97.4			91.5		
No	38.5			82.4		

Table 4 Multivariate Cox regression analysis for male breast cancer survival

Variable	B	SE	Wald χ^2	P	HR (95% CI)
T stage	-1.279	0.290	4.211	0.015	0.218 (0.072–0.724)
TNM stage	-2.338	0.439	7.345	0.016	0.102 (0.011–0.420)
ER status	-0.120	0.915	0.224	0.764	0.823 (0.191–3.123)
PR status	1.885	0.763	9.347	0.001	6.558 (2.953–11.800)
Chemotherapy	-0.224	0.437	0.408	0.523	0.721 (0.328–1.954)
Endocrine therapy	2.658	1.215	4.382	0.040	9.960 (1.557–14.260)

ER, estrogen receptor; PR, progesterone receptor; HR, hazard ratio; CI, confidence interval.

Table 5 Multivariate Cox regression analysis for female breast cancer survival

Variable	B	SE	Wald χ^2	P	HR (95% CI)
T stage	1.209	0.449	0.018	0.667	1.015 (0.323–3.277)
TNM stage	-2.150	0.731	9.477	0.002	0.105 (0.045–0.411)
ER status	1.337	3.252	0.132	0.773	2.208 (0.112–7.868)
PR status	-2.633	3.666	0.436	0.455	0.179 (0.110–2.799)
Chemotherapy	1.871	0.585	9.226	0.001	6.496 (2.223–18.450)
Endocrine therapy	2.600	0.707	8.113	0.004	11.433 (2.277–29.458)

ER, estrogen receptor; PR, progesterone receptor; HR, hazard ratio; CI, confidence interval.

Table 6 Five-year survival rate of MBC and FBC following chemotherapy and endocrine therapy

Cancer classification	MBC survival (%)	FBC survival (%)	P
TNM stage			
<III	60.8	92.2	0.0012
>III	41.4	80.8	0.0022
ER/PR status			
Positive	73.2	93.2	0.0211
Negative	63.2	73.2	0.0115

ER, estrogen receptor; PR, progesterone receptor; MBC, male breast cancer; FBC, female breast cancer.

therapeutic treatments, we analyzed the survival of patients after endocrine therapy and chemotherapy. The results showed that MBC with >3 TNM stage and negative ER/PR status had poor prognosis as compared with those with <3 TNM stage and positive ER/PR status. Meanwhile, with similar TNM stage and ER/PR status, MBC appeared to

have poor response to endocrine therapy and chemotherapy with low 5-year survival rate (*Table 6*).

Discussion

Our study showed that the median age of male patients was 61, which is over 10 years older than that of female patients. Compared with female patients, there were more patients aged ≥ 70 years and having underlying diseases. OSR and DFSR were significantly lower in patients with MBC than with FBC; T stage, TNM stage, PR status and endocrine therapy are found to be independent factors affecting the survival of MBC.

BC is the most common malignant tumor in women, but it is relatively rare in male (1). Because of this, the cohort of MBC in this study includes near 90% of all MBC diagnosed at our centers during the study period, while FBC is only a small portion of FBC patients treated at the same period. Previous studies show that the incidence of MBC is usually 5 to 10 years later than FBC and peaks around 68–71 years old, and MBC patients often have more underlying diseases

(32,33) and family history of BC (34). These are consistent with our results. Partially due to older age, the male patients were less proactive and more reluctant to treatments, leading to less patients to receive adjuvant radiotherapy, chemotherapy and endocrine therapy as compared with female patients. In addition, drugs for endocrine therapy such as tamoxifen for MBC have side effects such as hot flashes, changes in vision, cognitive changes, and a lower sex drive (35), which might also result in low treatment rates in the male patients.

Understand the pathological type of cancer is important for therapeutic planning. Korde *et al.* showed that the main pathological type of both MBC and FBC is nonspecific invasive ductal carcinoma (36), and Ottini *et al.* found the invasive ductal carcinoma accounts for 87% of MBC (37). In this cohort, most of MBC also had invasive ductal carcinoma with a small proportion of ductal carcinoma *in situ* (DCIS). Although modified radical mastectomy was used for both MBC and FBC (38), more women have adapted breast-conserving surgery due to aesthetic and health considerations and advances in radiotherapy technology, particularly for women with early BC (39). However, over 10% MBC patients declined surgical treatment in our study. In man, there is no enough gland tissue to delay the infiltration of the tumor to the surrounding area, leading to invasion of the pectoralis major muscle and skin (40). In addition, MBC is often located in the areola area, making it inappropriate to treat using conserving surgery. Due to less glandular tissue, the nipple or local skin are often invaded by MBC, leading to more radiotherapy after surgery (41). However, in this study, most patients who treated with modified radical mastectomy were treated with adjuvant radiotherapy, likely due to their older age and comorbidities.

BC ranks the first in the major malignant tumors in our hospitals. The 5-year OSR is 84.23%, which is higher than what are reported for other regions such as Shanghai and Zhejiang (42). In this study, the 5-year OSR was 85.4%, which is similar to the results of previous studies (42), and the OSR and DFSR of MBC are lower than those of FBC in the same period ($P < 0.05$), which is similar to the conclusion of earlier studies (4,43). However, the OSR and DFSR of MBC are lower than those reported outside China (23) and higher than those reported inside China (44), suggesting that the survival rate is likely linked to the medical levels in addition to the biological features of the disease.

The results of this study showed that T stage, TNM stage, endocrine therapy are significant prognostic factors

for MBC and FBC. This is consistent with most previous studies (45). In this study, male patients had more luminal type as compared with female patients, which is consistent with previous findings (4). Based on SEER database, it was found that the death rate had reduced by 42% in female but only 28% in male between 1996 and 2005, due to wide-spread use of endocrine therapy. However, endocrine therapy is less adapted in male patients. It is likely due to severe adverse reactions and poor compliance to endocrine therapy in male patients (46).

Since BC is highly heterogeneous (47), molecular typing has been widely used to characterize its biological features and augment traditional methods to improve our understanding of BC and their clinical management (48,49). During the last 20 years, five intrinsic molecular subtypes (luminal A, luminal B, HER-2-enriched, basal-like and claudin-low) have been identified for BC and have been linked to therapeutic outcomes for female patients as well as for MBC (50). For example, ER⁺/PR⁺ MBC patients were found to have lower survival rate than ER⁺/PR⁻ patients (51) and patients with HER-2⁺/HER-2-enriched disease is likely to benefit the most from neoadjuvant trastuzumab (50). In this study, we also found that PR status is an independent risk factors for survival, and PR⁻ patients have high death risk (HR 6.5) for MBC, ER status is significantly related to the survival in FBC but not in MBC. This is different from the previous study based on SEER Database (25). In addition, although chemotherapy is a prognostic factor for FBC, it does not significantly impact the OSR of MBC patients in this study. This is likely because chemotherapy has greater side reactions in male patients, who are older and have more underlying diseases, leading to poor tolerant and subsequently poor outcomes.

There are limitations of this study, including small sample size, partially due to low incidence rate of MBC and single-center study. Female patients were randomly drawn from a large patient pool, which may have bias for characterizing the clinical features of patients. The following up time was short, particularly for lately enrolled patients. In addition, BRCA2 germline mutations and DNA-repair genes such as *CHEK2* and *PALB2* have been shown to be a major risk factor for MBC (4) but were not available for analysis in this study.

Conclusions

Although MBC seems globally similar to FBC, it has distinct features, such as older on-set age, high portion of

luminal cells and more comorbidities. MBC is more related to family history of cancer and has low OSR and DFSR as compared with FBC. T stage, TNM stage, PR status and endocrine therapy were independent prognostic factors for survival of MBC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/tcr-21-1>

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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. This study was approved by the Ethics Committee of Nanjing Medical University (approval No.: NMU 2719-3), conducted in accordance with the Declaration of Helsinki (as revised in 2013) and written informed consent was obtained from every participant.

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