Male Health

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ORIGINAL ARTICLE

The prognostic value of clinical and pathologic features in nonmetastatic operable male breast cancer

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Compared with female breast cancer, male breast cancer is a rare disease, and the relationship between clinical/pathologic features and prognosis is controversial, or even largely unknown. In this study, we performed a retrospective analysis using clinical and pathologic data from 109 nonmetastatic operable male breast cancer patients treated from January 1996 to December 2011 at Tianjin Medical University Cancer Institute and Hospital. Log-rank test showed that lower tumor stage, no lymph node involvement, and positive estrogen/progesterone receptor status were good predictors of both disease-free survival and overall survival on univariate analysis. However, hormonotherapy is only a good predictive factor of disease-free survival, and not of overall survival. In addition, based on a Cox proportional hazard regression model, only lymph node involvement, and estrogen/progesterone receptor status were statistically significant predictive factors on multivariate analysis. Our results demonstrated that although adjuvant systemic therapy is used extensively in male breast cancer patients and prognosis has improved over the last few decades, lymph node involvement, and estrogen/progesterone receptor status are still the most important prognostic factors. A prospective multi-center study with a larger sample size is urgently needed to further understand male breast cancer.
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Keywords: breast neoplasms; clinical/pathologic features; male; prognosis

INTRODUCTION

Compared with female breast cancer (FBC), male breast cancer (MBC) is an uncommon disease, accounting for only about 1.0% of all breast carcinomas, and <1.0% of malignant male diseases in the United States.[1,2]

Owing to its rarity, our understanding of MBC is not as profound as FBC.[3] Although several studies have included more than 1000 cases, their research is based on the Surveillance Epidemiology and End Results (SEER) database, which only consists of American clinical data.[1,4] However, some reports have shown unique tumor biological behavior among patients from different regions or of different races.[5–7] Therefore, more research regarding MBC patients in China, which accounts for more than 40.0% of the Asian population, is very important for gaining further insight into MBC patients.

Another consequence of MBC's rarity is that treatment is largely based on extrapolating results from FBC clinical trials. However, MBC management is challenging because the clinical/pathologic features of MBC are not completely consistent with FBC.[5,8] Therefore, it is necessary to deepen our understanding of MBC to improve patient management. In a previous study, Donegan *et al.*[9] found that older age at diagnosis and more advanced stage of disease at presentation are related to poorer prognosis of MBC patients in Wisconsin. According

to a study including 489 MBC cases in France, T stage and the presence of locoregional recurrence were metastatic risk factors, and axillary nodal involvement and high Scarff, Bloom, and Richardson histoprognostic grading (SBR) were important prognostic factors.[10] In a study undertaken in Turkey, the authors believed that only lymph node status and tumor size were independent prognostic factors for survival.[7] Therefore, there is much controversy regarding the clinical/pathologic predictive factors for MBC, especially in Chinese patients. In this study, we aimed to evaluate the relationship between clinical/pathologic features and prognosis in operable Chinese MBC patients.

MATERIALS AND METHODS

Patients

Data for the current study were retrospectively collected from Tianjin Medical University Cancer Institute and Hospital from January 1996 to December 2011. The 109 male breast cancer patients included in this study had to fulfill the following criteria: (1) the neoplasms were diagnosed as breast cancer by pathologists using incisional or excisional biopsies; (2) there were no indications that breast cancer cells had spread to other organs or patients had a second cancer at initial diagnosis; (3) all patients underwent curative

mastectomy surgery; and (4) clinical characteristic and follow-up were well-documented.

Biologic classification

Both the estrogen receptor (ER; ZSGB-BIO, Beijing, China) and progesterone receptor (PR; ZSGB-BIO, Beijing, China) were detected through semi-quantitative cell membrane scoring by immunochemistry (IHC). Human epidermal growth factor receptor 2 (HER-2; CerbB-2) status was recognized by IHC (Roche, Mannheim, Germany) and by fluorescent *in situ* hybridization (FISH; Abbott/ Vysis, Downers Grove, IL, USA). If HER-2 expression was ≥2+ by IHC, we further analyzed the specimen by FISH. Only FISH positivity was defined as HER-2 expression positive. For all other cases, HER-2 expression was considered negative.

Molecular subtype classification was determined as follows: Luminal A, ER positive and/or PR positive and HER2 negative; Luminal B, ER positive and/or PR positive and HER2 positive; HER2 over-expression, ER and PR negative and HER2 positive; and Basal-like (triple negative), ER, PR and HER2 negative.[11,12]

Statistics

Data were analyzed using SPSS (17.0; IBM Corp., Armonk, NY, USA). Disease-free survival (DFS) and overall survival (OS) were determined by Kaplan–Meier survival curve (Log-rank). Univariate analysis for DFS and OS were performed with age, histologic type, tumor stage, lymph node involvement, ER/PR status, HER2 status, surgery method, chemotherapy, radiotherapy, and hormonotherapy. Multivariate analysis was performed using a Cox proportional hazard regression model, including interactions between age, tumor stage, lymph node involvement, ER/PR status, HER2 status, chemotherapy, and hormonotherapy. A $P < 0.05$ was considered as statistically significant. OS was defined as the time from surgery to death by any cause. DFS was defined as the time from surgery to events such as relapse, appearance of a second primary cancer (including contralateral breast recurrence), or death, whichever occurs first.

RESULTS

Patients characteristics

Based on the inclusion criteria, we identified a total 109 patients who had well-documented patient data for survival analysis. The number of patients excluded and the reasons for exclusion are shown in **Figure 1**. **Table 1** summarizes the general characteristics of the MBC patients. The mean and median ages at diagnosis were 59.4 and 59 years (range: 26–83 years), respectively. The mean follow-up time was 70.0 months with a range from 10 to 178 months. Left breast carcinomas accounted for the same approximate proportion of MBC as right breast carcinomas (53.2% *vs* 46.8%). Because of the small breast size, <40.0% of MBC took place in the center of the breast.

With respect to MBC clinical and pathologic characteristics, 30.3%, 52.3%, 8.3%, and 10.1% of cases were diagnosed as T_1, T_2, T_3, and T_4, respectively (**Table 2**). Besides, lymph node involvement was present in 36.7% of MBC patients. In addition, the most common clinical stage was stage II (58.7%) while stages I and III accounted for 19.3% and 22.0%, respectively. In total, 84 (77.1%) patients had invasive ductal carcinoma. Based on the IHC results, ER and PR were positive in 85 (78.0%) and 72 (66.1%) patients, respectively, and HER2 was positive on the basis of FISH results in 20 (18.3%) patients. According to the 2004 St. Gallen consensus, 58, 18, 2 and 8 patients with well-documented HER2 status were classified into Luminal A, Luminal B, HER2 overexpression, and triple negative, respectively.

Detailed information of treatment modalities is shown in **Table 3**. Of the 109 MBC patients, 99 (90.8%) underwent radical

Table 1: General characteristics of male breast cancer patients

Characteristics	n (%)
Age at diagnosis (year)	
21–30	1 (0.9)
31–40	2 (1.8)
41–50	15 (13.8)
51–60	43 (39.4)
61–70	33 (30.3)
>70	15 (13.8)
Mean±s.d.	59.4±9.5
Median (range)	59 (26–83)
Laterality	
Left	58 (53.2)
Right	51 (46.8)
Tumor location	
Central	42 (38.5)
Peripheral quadrant	67 (61.5)
Follow-up time (month)	
Mean±s.d.	70.0±34.6
Median (range)	62 (10–178)

s.d.: standard deviation

Table 2: Clinical and pathologic characteristics of male breast cancer patients

Characteristics	n (%)
Tumor stage	
T_1	33 (30.3)
T_2	57 (52.3)
T_3	9 (8.3)
T_4	11 (10.1)
Lymph node involvement	
No	69 (63.3)
Yes	40 (36.7)
AJCC stage	
I	21 (19.3)
II	64 (58.7)
III	24 (22.0)
Histologic type	
Invasive ductal carcinoma	84 (77.1)
Other types	25 (22.9)
ER status	
Positive	85 (78.0)
Negative	19 (17.4)
Unknown	5 (4.6)
PR status	
Positive	72 (66.1)
Negative	32 (29.4)
Unknown	5 (4.6)
HER2 status	
Positive	20 (18.3)
Negative	66 (60.6)
Unknown	23 (21.1)
Molecular subtype	
Luminal A	58 (53.2)
Luminal B	18 (16.5)
HER2 overexpression	2 (1.8)
Triple negative	8 (7.3)
Unknown	23 (21.1)

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; AJCC: american joint committee on cancer

mastectomy (RM) or modified radical mastectomy (MRM). Owing to different surgical procedures and high-risk factors, only 42 (38.5%) patients received radiotherapy for the chest wall or the whole breast as well as for peripheral lymphatics. Typically, the total radiotherapy dose was 50 Gy with a daily fractional dose of 2 Gy. In addition, 92 (84.4%) patients received chemotherapy (details for chemotherapy are shown in **Table 4**), while 49 patients received hormonotherapy.
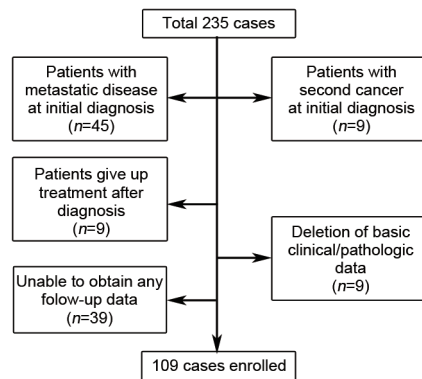

Figure 1: Flowchart showing the number of patients excluded and the reasons for exclusion.

Table 3: Treatment modalities of male breast cancer patients

Treatment	n (%)
Surgery	
RM or MRM	99 (90.8)
Others	10 (9.2)
Adjuvant chemotherapy	
No	17 (15.6)
Yes	92 (84.4)
TA/TE	28 (25.7)
TAC/TEC	13 (11.9)
CAF/CEF	21 (19.3)
CMF	19 (17.4)
Other	11 (10.1)
Adjuvant radiotherapy	
No	67 (61.5)
Yes	42 (38.5)
Adjuvant hormonotherapy	
Unknown	5 (4.6)
No	55 (50.5)
Yes	49 (45.0)
Tamoxifen	38 (34.9)
Aromatase inhibitor	11 (10.1)

RM: radical mastectomy; MRM: modified radical mastectomy

Survival analysis

Kaplan–Meier survival curves (Log-rank) were used to calculate DFS and OS; estimated 5-year and 10-year survival rate were 58.7% and 27.7% for DFS, 72.7% and 29.7% for OS, respectively (**Figure 2a** and **2b**).

Univariate analysis was performed to reveal the relationship between tumor and treatment-related factors on MBC patient survival; patients with smaller tumor stage (T_1–T_2 *vs* T_3–T_4) had better prognosis (DFS and OS, $P < 0.05$, **Figure 3a** and **3b**). In addition, statistical analysis supported the notion that positive ER/PR status and negative lymph node involvement were associated with a better prognosis (DFS and OS, $P < 0.001$, **Figure 3c–3f**). Interestingly, adjuvant hormonotherapy was related to good DFS ($P < 0.05$), but not OS. However, there is only a slight trend toward decreasing DFS for patients with positive HER2 status ($P = 0.09$). **Table 5** shows further information regarding 5- and 10-year survival rates for DFS and OS by univariate analysis.

To further investigate the potential relevance of these factors and patient survival, clinical related factors, including age, tumor stage, lymph node involvement, ER/PR status, HER2 status, chemotherapy, and hormonotherapy, were entered into a Cox proportional hazard regression model (**Table 6**). The results indicated that only ER/PR status and lymph node involvement were independent factors related to prognosis (ER/PR status: $P = 0.048$ and $P = 0.035$ for DFS and OS; lymph node involvement: $P = 0.006$ and $P = 0.010$ for DFS and OS).

DISCUSSION

Several reports have suggested an alarming increase in MBC incidence over the past few decades.[1,13,14] However, the incidence of MBC in China is still largely unknown. In addition, MBC diagnosis and treatment are still mainly based on the criterion for treating FBC due to MBC exiguity.[1,5] Thus, a better understanding of MBC is urgently needed.

In this study, we found the estimated 5-year OS rate at 72.7%, which is higher than previously published data. For instance, according to Foerster *et al.*[15] study, the 5-year OS is about 68.0% in patients diagnosed with MBC from 1995 to 2007. Similarly, Willsher *et al.* and Marchal *et al.* showed 5-year OS rates of 55.0% and 58.9%, respectively.[16,17] The fact that our patient OS is above previously reported averages may be attributed to the inclusion of nonmetastatic operable MBC patients involved in this study. In addition, the average age at diagnosis was 59.4 years in our study, which is younger than the average age in other studies, and thus may have contributed to the improved 5-year OS.[15–17] However, owing to the small sample size in our study, there was no significant difference in OS between <60 and ≥60 groups by univariate analysis ($P = 0.120$).

Tumor stage is a controversial prognosis factor. Some researchers support the opinion that advanced tumor stage is associated with a higher risk of death, while others believe that it is not a pivotal factor.[15,18] In this paper, tumor stage is a prognostic factor for DFS and OS on univariate analysis, but not an independent factor on multivariate analysis. Similarly, lymph node involvement is another focus of debate;

Table 4: Chemotherapy details

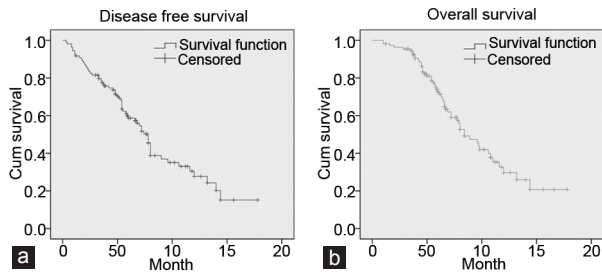|	Taxotere	Adriamycin	Epirubicin	Cytoxan	Methotrexate	5'-FU	Days per cycle	Cycles
TA	75 mg m^{-2} (day 1)	50 mg m^{-2} (day 1)	-	-	-	-	21	6
TE	75 mg m^{-2} (day 1)	-	50 mg m^{-2} (day 1)	-	-	-	21	6
TAC	75 mg m^{-2} (day 1)	50 mg m^{-2} (day 1)	-	500 mg m^{-2} (day 1)	-	-	21	6
TEC	75 mg m^{-2} (day 1)	-	50 mg m^{-2} (day 1)	500 mg m^{-2} (day 1)	-	-	21	6
CAF	-	50 mg m^{-2} (day 1)	-	500 mg m^{-2} (day 1)	-	500 mg m^{-2} (day 1, 8)	21	6
CEF	-	-	50 mg m^{-2} (day 1, 8)	500 mg m^{-2} (day 1, 8)	-	400 mg m^{-2} (day 1, 8)	28	6
CMF	-	-	-	500 mg m^{-2} (day 1, 8)	40 mg m^{-2} (day 1, 8)	600 mg m^{-2} (day 1, 8)	28	6

Figure 2: Kaplan–Meier curve illustrates prognosis of male breast cancer cases. (**a**) Disease-free survival of male breast cancer patients. (**b**) Overall survival of male breast cancer patients.

Table 5: Univariate analysis of prognostic factors that may affect the DFS and OS

Characteristics	n	DFS			OS		
		5-year	10-year	P	5-year	10-year	P
Age							
<60	55	58.7	36.0	0.276	75.9	40.8	0.120
≥60	54	59.1	18.5		69.6	17.5	
Histologic type							
IDC	84	55.6	29.0	0.557	71.4	28.1	0.263
Other types	25	69.7	23.2		77.6	33.9	
Tumor stage							
T_1–T_2	89	63.7	31.4	0.013*	78.0	32.3	0.044*
T_3–T_4	20	38.2	10.2		51.1	14.6	
Lymph node involvement							
Yes	40	39.7	5.2	0.001**	68.3	7.2	0.002**
No	69	70.1	39.7		75.2	42.1	
ER/PR status							
Yes	91	63.1	31.6	0.003**	77.0	35.2	0.004**
No	13	30.8	15.4		44.9	11.2	
HER2 status							
Yes	20	50.0	11.1	0.090	67.1	15.3	0.332
No	66	61.2	35.2		74.3	38.3	
Surgery							
RM and MRM	99	58.6	28.2	0.414	72.0	29.7	0.884
Others	10	58.3	23.3		77.8	33.3	
Adjuvant chemotherapy							
Yes	92	58.6	29.9	0.504	72.5	31.2	0.373
No	17	58.8	17.2		73.2	25.6	
Adjuvant radiotherapy							
Yes	38	69.5	24.3	0.227	82.0	23.9	0.319
No	71	52.8	29.9		67.8	34.9	
Adjuvant hormonotherapy							
Yes	49	66.9	33.8	0.014*	78.8	36.9	0.142
No	55	51.4	24.2		67.4	27.3	

P value was determined by Log-rank test. **P*<0.05; ***P*<0.01. DFS: disease-free survival; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; OS: overall survival; IDC: invasive ductal carcinoma; RM: radical mastectomy; MRM: modified radical mastectomy; PR: progesterone receptor

Soliman *et al*. reports that it has a negative effect on OS in a cohort of 69 MBC patients, whereas other authors are in denial.[19,20] In our cohort, lymph node involvement is one of the most important prognosis factors for DFS and OS both on univariate and multivariate analyses.
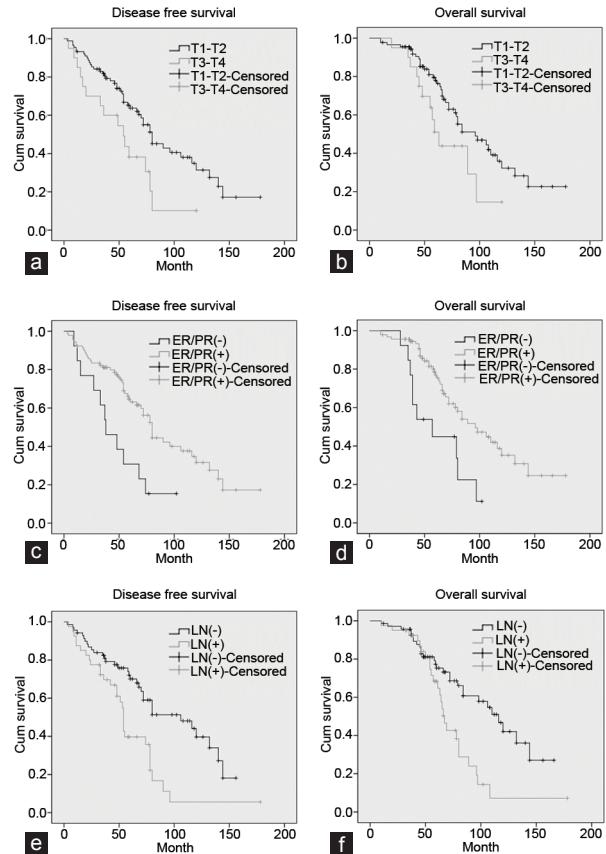

Figure 3: Monofactorial analysis of clinical and pathologic factors related to DFS and OS. Comparison of DFS (**a**) and DFS (**b**) between T1–T2 and T3–T4 patients. Comparison of DFS (**c**) and OS (**d**) between ER/PR negative and positive patients. Comparison of DFS (**e**) and OS (**f**) between lymph node negative and positive patients. *P* value was determined by Log-rank test. DFS: disease-free survival; OS: overall survival; ER: estrogen receptor; PR: progesterone receptor; LN: lymph node.

The fact that ER/PR expression in MBC is higher than FBC is less controversial.[4,8] However, how ER/PR status affects MBC prognosis is still unclear owing to possible differences in ER/PR function between males and females. In the present research, 91 patients were ER/PR positive, which accounted for 86.6% of ER/PR status known cases. In addition, ER/PR status was also a predictive factor for DFS and OS both on univariate and multivariate analyses. HER2 overexpression rate is variable in MBC, and ranges from 11.1% to 35.3%.[20,21] In this study, HER2 overexpression accounted for 23.3% of HER2 status known cases, which is consistent with the findings reported by Arslan *et al*.[18] However, our results demonstrated that HER2 was not a prognosis factor on either univariate or multivariate analyses, which is inconsistent with opinions in FBC.[22] On the basis of ER/PR and HER2 status mentioned above, the proportions of each molecular subtype were distributed as follows: Luminal A, 67.4%; Luminal B, 20.9%; HER2 overexpression, 2.3%; and triple negative, 9.3%. Although Luminal A was the predominate subtype in this cohort, this is not consistent with previous reports, and this phenomenon may be associated with geographical factors.[23]

With respect to MBC treatment, people in the north of China preferred RM and MRM over other surgical methods owing to their conservative culture, which is in contrast to patients in other countries.[17,18] Although it has been proven that treatment of FBC

Table 6: Multivariate analysis of prognostic factors that may affect the DFS and OS

Characteristics	DFS			OS		
	P	Exp(B)	95% CI for Exp(B)	P	Exp(B)	95% CI for Exp(B)
Age						
<60 versus ≥60	0.573	1.215	0.618–2.388	0.926	1.037	0.482–2.230
Tumor stage						
T_1–T_2 versus T_3–T_4	0.687	0.836	0.349–1.999	0.836	1.113	0.402–3.081
Lymph node involvement						
Yes versus no	0.006**	0.369	0.182–0.747	0.010*	0.355	0.162–0.778
ER/PR status						
Positive versus negative	0.048*	2.558	1.010–6.479	0.035*	3.194	1.088–9.378
HER2 status						
Positive versus negative	0.147	0.595	0.294–1.201	0.305	0.656	0.293–1.469
Chemotherapy						
Yes versus no	0.611	1.224	0.562–2.668	0.534	1.315	0.555–3.116
Hormonotherapy						
Yes versus no	0.380	1.371	0.677–2.777	0.918	1.041	0.485–2.233

P value was determined by a Cox proportional hazard regression model. *$P<0.05$; **$P<0.01$. DFS: disease-free survival; OS: overall survival; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; CI: confidence interval

can benefit from chemotherapy, radiotherapy, and hormonotherapy, the role of these therapies is less clear in MBC patients.[9,24–26] Our results indicate that chemotherapy and radiotherapy do not affect the prognosis. However, hormonotherapy is a predictor of DFS on monofactorial analysis, but not by Cox regression analysis. However, these outcomes may be a result of the limited sample size or unadjusted clinical/pathologic data. In addition, Trastuzumab is rarely used for Chinese MBC patients because of the low HER2 overexpression rate and exorbitant price.

MBC management is based on extrapolation from breast cancer trials in women, yet the issue of different clinical/pathologic prognostic factors and treatments between MBC and FBC is a constant debate.[5,10,13,27] Owing to the relative rarity of MBC, our understanding of this disease is limited on a global level, let alone in China. However, recently, several groups have begun studying MBC patients in China.[20,28]

In the present study, limitations such as bias and systemic error were inevitable owing to the small sample size and retrospective study design. Nevertheless, to our knowledge, this is one of few research articles investigating MBC prognosis, including univariate and multivariate analysis with more than 100 cases, in the north of China. Our study corroborates the fact that the ER/PR positivity in MBC is higher than in FBC and supports the notion that ER/PR is a good predictive factor.[5,29] Radiotherapy and hormonotherapy are always a key point of contention in MBC treatment.[29] Our data provide evidence that radiotherapy and hormonotherapy do not have a positive impact on the survival of MBC patients. In addition, through multivariate analysis, this study provides new information that disproves the notion that tumor stage is related to poor survival and confirms that lymph node involvement is a vital predictive factor for prognosis.

As a result of low MBC incidence, nearly all data are obtained from retrospective studies to date, and there is only scant research based on prospective studies for evaluating local and systemic treatment modalities. Thus, to better understand MBC, prospective studies with larger sample sizes are necessary.

AUTHOR CONTRIBUTIONS
LG conceived the idea of the study and participated in its design. BS performed statistical analysis and drafted the manuscript. LNZ and JZ collected the clinical and pathologic data. NZ and LG revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS
The authors declare no competing interests.

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