·Clinical Research·

Analysis of prognostic factors in male breast cancer: a report of 72 cases from a single institution

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[Abstract] Background and Objective: Male breast cancer (MBC) in China usually has been studied retrospectively with small sample size, and studies analyzing the prognostic factors are rare. This study was to investigate the prognostic factors of Chinese patients with MBC based on the data from a single institute with a relatively large sample. **Methods:** Clinical data of 72 patients with histopathologically confirmed MBC who received treatment at Sun Yat-sen University Cancer Center between January 1969 and March 2009, were collected. Kaplan-Meier, log-rank test and Cox regression model were used for statistical analysis. **Results:** The 5-year overall survival rate was 72.4%, and the survival rates for stage I, II, III, and IV were 100%, 74.2%, 57.2%, and 0%, respectively. Univariate analysis showed that the tumor size ($P < 0.001$), axillary lymph node status ($P = 0.001$), TNM stage ($P = 0.001$), operation model (with vs. without: $P < 0.001$; classic radical resection vs. modified radical resection, $P = 0.336$) and endocrine therapy ($P = 0.02$) significantly influenced the survival. Multivariate Cox regression showed that TNM stage ($P = 0.035$), operation model ($P = 0.021$) and endocrine therapy ($P = 0.019$) were independent prognostic factors for MBC. **Conclusions:** Early diagnosis and comprehensive treatment strategy consisting of surgery and endocrine treatment is essential to improve the survival of the patients with MBC, and TNM stage, operation and endocrine treatment are the significant prognostic factors for MBC.

Key words: Male breast cancer, survival rate, prognosis, univariate, multivariate

Male breast cancer (MBC) accounts for 1%–2% of all breast cancers and for less than 1% in all male malignant cancers[1,2]. Although the incidence of MBC is low, it shows an increasing trend[3]. The incidence varied widely in different races and regions. The Africa has the highest incidence, followed by North America and Europe, and the Asia has the lowest[1]. Because there are no randomized phase III clinical trials, the treatment guideline of MBC is followed with reference to the female breast cancer[1]. However, the male and female breast cancers are different. Reports of the male breast cancer in China are mostly the retrospective studies with small sample size[4,5]. The present study reviewed the clinical data of 72 patients with MBC who were treated in Sun Yat-sen University Cancer Center from January 1969 to March 2009. Our study enrolled relatively more patients, thus facilitating the elucidation of the factors influencing the outcome of the treatment.

Data and Methods

Clinical data

Inclusion criteria: patients with pathologically confirmed MBC who were treated in Sun Yat-sen University Cancer Center between January 1969 and March 2009, with complete follow-up data. Seventy-two patients with MBC aged between 27 and 90 years (median 61) were included. There were 36 (50%) cases of cancer in the left breast and 36 (50%) in the right breast.

Pathological classification

All diagnoses were confirmed pathologically. There were 59 cases of invasive ductal carcinoma (81.9%), four cases of intraductal carcinoma (5.6%), three cases of invasive lobular carcinoma (4.2%), two cases of each medullary carcinoma and papillary carcinoma (2.8%) and one case of each mucinous adenocarcinoma and adenoid cystic carcinoma (1.4%). Of the 62 patients undergoing radical axillary lymphectomy, 21 (33.9%) patients presented positive lymph node and 41 (66.1%) patients had negative lymph node.

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This paper was translated from Chinese into English by Guangzhou Liheng Medical Translation and edited by Jing-Yun Ma on 2009-12-21.

The Chinese version of this paper is avaiable at http://www.cjcsysu.cn/cn/article.asp?id=16543.

Received: 2009-09-04; Accepted: 2009-12-06

Seventeen of 62 patients had skin or nipple infiltrations (27.4%) according to the pathological reports.

A total of 33 patients underwent testing of hormone receptors. The positive rates of estrogen receptor (ER) and progesterone receptor (PR) were 90.9% (30) and 84.8% (28). Thirty patients were tested for HER-2. The immunohistochemical assay showed that there were 19 cases (63.3%) with '-', eight cases (26.7%) with '+', two cases (6.7%) with '++' and one case (3.3%) with '+++'. Three cases (6.6%) were negative for all these three receptors (ER, PR and HER-2).

Clinical staging

According to the sixth edition of AJCC: six cases had unknown TNM stage. Of the rest 66 patients, there were 16 cases (24.2%) of stage I, 22 (33.3%) of stage II, 26 (39.4%) of stage III and two (3.0%) of stage IV.

Treatment strategies

A summary of the treatment strategies is shown in Table 1. Of the 72 patients, 60 received comprehensive treatment (83.6%), 11 received operations alone (15%) and one received chemotherapy alone (1.4%). Sixty-eight patients underwent operations, 36 received postoperative adjuvant chemotherapy and 11 received neo-adjuvant chemotherapy. The chemotherapy strategies included CEF, CMF, and TA. Chemotherapy was performed using thiotepa or tegafur for 2–8 courses (mean 6) before 1990. Fourteen patients underwent postoperative radiotherapy, covering the primary lesion on the chest wall and regional lymph nodes (supraclavicular, subaxillary and internal mammary lymph node). The radiotherapy dose was 20–64 Gy (lymphatic fistula was reported in one case with 8 Gy radiotherapy). A total of 32 patients received endocrine therapy with drugs of tamoxifen and Fareston, or diethylstilbestrol before 1990. Two patients underwent testicular resection in the 1970s.

Table 1 Treatment modalities of 72 patients with MBC

Treatment modality	Patient No.	Percentage (%)
Operation	68	
Classic radical resection	46	67.6
Modified radical resection	15	22.1
Mastectomy+lymph nodes dissection	3	4.4
Lumpectomy	2	2.9
Mastectomy	1	1.5
Unknown	1	1.5
Chemotherapy	41	
Adjuvant chemotherapy	36	50.0
Induction chemotherapy	11	15.3
Postoperative radiotherapy	14	19.4
Endocrine treatment	32	44.4

Follow-up

Follow-up was initiated from the first day after treatment. Local or regional recurrence referred to those with recurrence in ipsilateral breast or regional lymph node identified clinically or histologically. Distal metastasis referred to distal metastatic lesions demonstrated by clinical evaluation or image studies. The total survival period was calculated from the first day of therapy to death or end point of follow-up.

Statistical analysis

Data were analyzed using SPSS13.0 software. Univariate analysis of survival and clinical outcomes was performed using Kaplan-Meier. The comparison of survival rates was made using log-rank. Multivariate analysis was performed with Cox regression analysis. Significance was defined when $P < 0.05$.

Results

Local recurrence and distal metastasis

The follow-up duration was three months to 32.6 years (mean 5.2 years). Nine patients reported local recurrence at one month to 29 years after treatment (mean 12 months). Nine patients reported distal metastasis at two months to ten years after treatment (mean 14 months). The most commonly involved sites of distal metastasis were bone (six cases), liver (two cases), lung (two cases), brain (one case) and mediastinal lymph node (one case).

Survival rate

The total five-year survival rate in our study was 72.4%. Stratified by TNM staging system, the five-year survival rates were 100% for stage I, 74.2% for stage II, 57.2% for stage III and 50% for stage IV (Figure 1).

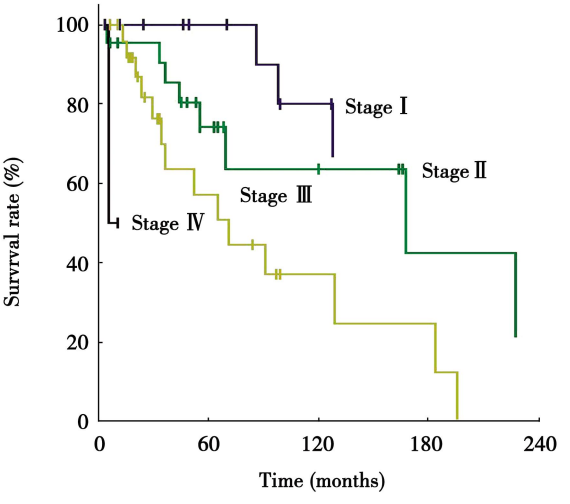

Figure 1 Five-year survival curve of patients with MBC in different TNM stages

Univariate and multivariate analyses of the prognostic factors

Univariate analyses were performed with regard to the following factors: ages (divided by the median age of 61 years into the group younger than 61 and the group older than 61), location of the mass (left and right), size of the mass (< 5 cm

group and ⩾ 5 cm group), axillary lymph node (metastatic group and non-metastatic group), skin and/or nipple infiltration (infiltrative and non-infiltrative groups), TNM stage (I + II, III + IV), the expressions of ER/PR (negative for both and positive for both), treatment strategies (comprehensive treatment and operation alone), operation procedures (radical mastectomy, modified radical mastectomy, other procedures and those without operations), postoperative radiotherapy (groups with or without postoperative radiotherapy), endocrine therapy (groups with or without endocrine therapy), and pathological types (invasive ductal carcinoma and other types). The results are shown in Table 2. Five factors including the size of the mass, axillary lymph node, TNM stage, surgical procedure and endocrine treatment were found to be significantly associated with the survival rate.

The factors with *P* value less than 0.2 were included into the multivariate analysis (Table 3). Of these factors, the clinical stage, surgical procedures and endocrine therapy were correlated with the clinical outcome. Of note, the five-year survival rate was > 50% in the patients undergoing surgical operations, while those without operations had the survival rate of 0% ($P < 0.001$). Furthermore, the five-year survival rat es of those with classic radical mastectomy and those with modified radical mastectomy were insignificantly different ($P < 0.325$).

Table 2 Univariate analysis of prognostic factors on MBC

Characteristic	Patient No. (%)	5-year overall survival rate(%)	*P*	Median survival time (months)	95% CI	
					lower	upper
Age (years)						
< 61	34(45.2)	76.5	0.499	129	62.9	195.0
⩾ 61	38(52.8)	67.9		98	6.3	189.7
Tumor location						
Left	36(50.0)	76.3	0.924	168	0.0	360.7
Right	36(50.0)	68.4		128	81.2	174.8
Tumor size (cm)						
< 5	44(80.0)	82.5	< 0.001	129	24.5	233.5
⩾ 5	11(20.0)	22.7		23	14.4	31.6
Nodal status						
Negative	41(66.1)	87.8	0.001	228	151.0	304.9
Positive	21(33.9)	53.2		71	29.5	112.5
Skin/nipple involvement						
No	45(72.6)	79.2	0.165	168	70.0	266.0
Yes	17(27.4)	70.7		184	60.7	307.3
TNM						
I + II	38(57.6)	84.5	0.001	228	83.1	372.9
III + IV	28(42.4)	55.2		65	29.1	100.9
ER/PR						
Negative	2 (6.1)	0	0.659	–	–	–
Positive	31(93.9)	73.1		–	–	–
Treatment modality						
Comprehensive	60(83.8)	76.1	0.881	128	76.4	179.7
Operation only	11(15.2)	63.6		228	–	–
Operation model[a]			< 0.001			
Halsted	46(63.8)	79.0		184	104.6	263.4
Modified	15 (0.8)	66.7		91	29.0	115.0
Others	7 (9.7)	51.4		61	18.6	103.4
Not operation	4 (5.5)	0		13	1.0	25.0
Chemotherapy			0.484			
Yes	36(50.0)	79.8		168	65.0	271.0
No	36(50.0)	65.2		91	50.5	131.5
Adjuvant radiotherapy(Stages II + III)						
Yes	10(20.8)	61.7	0.197	71	33.6	108.4
No	38(79.2)	67.0		184	19.5	348.5
Endocrine therapy						
Yes	32(44.4)	100	0.02	184	151.4	216.5
No	40(55.5)	56.0		69	27.4	110.6
Pathologic type						
Infiltrating ductal carcinoma	59(81.9)	71.5	0.916	128	78.4	177.5
Non-infiltrating ductal carcinoma	13(18.1)	76.9		184	44.6	323.4

Modified vs. Halsted, $P = 0.336$.

Table 3 Multivariate analysis of prognostic factors on MBC

Variable	*P*	HR	95% CI	
			Lower	Upper
Skin/nipple involvement	0.878	0.895	0.216	3.702
Axillary nodal status	0.689	1.343	0.317	5.681
Radiotherapy	0.866	0.878	0.196	3.939
Tumor size	0.308	1.878	0.560	6.298
TNM stage	0.035	3.144	1.084	9.117
Endocrine treatment	0.019	0.178	0.042	0.754
Surgery	0.021	2.324	1.138	4.744

Discussion

Investigations into the prognosis of MBC is rare in China and the sample size is only 30 cases[4], which is due to that papers on MBC from Chinese mainland are primarily the summaries of clinical experience with small sample size from single institute, and the analysis of prognostic factors cannot be conducted. The number of cases is mostly less than 60 (mean 21.18 ± 1.10). The present study aimed to analyze the prognostic factors of MBC by reviewing the clinical data of 72 patients who had been treated in Sun Yat-sen University Cancer Center from its establishment, thereby providing more evidences for the diagnosis, treatment and prevention of MBC.

TNM stage is an important prognostic factor influencing the outcomes of patients with malignant tumors, without exception of MBC. One study demonstrates that the prognostic factors of MBC are similar to the female breast cancer, except for the size of mass and axillary lymph node metastasis[6]. The present study also showed that the size of the mass, axillary lymph node status and TNM stage were significantly correlated with the clinical outcome in univariate analysis. However, the multivariate analysis showed that only TNM stage was associated with the outcome, which was likely due to that the TNM stage had included the size of mass and the axillary lymph node status.

Management of MBC should be the operation-centered comprehensive treatment, and the operation is the most important prognostic factor. The radical mastectomy requires extensive resection and carries high risks of postoperative complications. Since 1970, the modified radical mastectomy has began to replace the radical mastectomy[7]. Thus, the modified radical mastectomy is the standard treatment for MBC at present[1]. A total of 68 patients underwent operations in our study, 67.6% of them received radical mastectomy and 22.1% received modified radical mastectomy. However, of the 13 patients treated after 2004, 11 underwent modified radical mastectomy, one underwent radical mastectomy and another one patient underwent simple mastectomy. Univariate analysis of our study showed that surgical operation, irrespective of its procedure, was associated with the clinical outcome, which is another evidence of the rationale of current surgical procedure. Postoperative adjuvant chemotherapy plays an important role in the comprehensive management of MBC and 40% patients underwent this adjuvant chemotherapy[8]. The principles of this strategy can be referenced to the management of female breast cancer[9]. Several studies have demonstrated the benefits of adjuvant chemotherapy. The adjuvant chemotherapy can reduce the mortality of those with positive axillary lymph nodes (HR 0.78)[10,11]. And prospective studies also proved that adjuvant chemotherapy could improve the survival rate of patients with MBC[12]. Eleven and 37 patients in our study received neo-adjuvant chemotherapy and postoperative chemotherapy, respectively, with a median number of six treatment courses. The regimens included CEF, CMF and TA. Of the 21 patients with positive lymph nodes, 16 (76.2%) received adjuvant chemotherapy. However, the result was statistically insignificant due to the small sample size. Similarly, postoperative radiotherapy is another important part of the comprehensive management of MBC, and nearly 80% patients received this radiotherapy[8]. However, there is no evidence showing that the postoperative radiotherapy can improve the overall survival (OS) or the disease free survival (DFS), though it can improve the local control rate of MBC[13-15]. Fourteen patients of stage II or III had undergone radiotherapy. Their survival rates were compared, which, however, was not significant (P = 0.197). Nevertheless, the 5- or 10-year local contrcl rates of the 14 patients with adjuvant radiotherapy were 90.9% , indicating the adjuvant radiotherapy can improve the local control rate, which was consistent with other reports[13-15].

Breast cancer carries specific hormone receptors and its management includes the endocrine therapy, this is another prognostic factor. Consistently with other studies, the positive rates of ER and PR were 90.9% and 84.8% , which were significantly higher than female breast cancer (80% –90% and 73%-81% vs. 75% and 65.9%)[16]. The expressions of ER and/or PR are the indices of optimal outcomes. Thus, the endocrine therapy of MBC is more effective in male breast cancer than that in female breast cancer[17]. Other investigators contend that the high expression of hormone receptors in MBC is due to the low level estrogen in male patients[17-18]. The expression of ER is a prognostic factor of patients with negative lymph node. Those with positive ER carry a better survival rate[19]. However, the expressions of ER/PR were not correlated with the outcome, possibly due to the small number of cases with negative expression. Another reason of the better outcome of those expressing hormone receptors is that they can benefit from the endocrine treatment. Those who received endocrine therapy had significantly increased DFS and OS[7]. Iredale *et al.*[20] analyzed 163 patients with MBC retrospectively and found that 126 (78%) of them received tamoxifen. However, the efficacy of aromatase inhibitor in the treatment of MBC has not been defined. Mauras *et al.*[21] enrolled healthy male volunteers and found that, as opposed to results of female patients, the oral intake of anastrozole was not able to completely inhibit the male hormones. However, a small sized trial demonstrated that aromatase inhibitor was able to prolong the stable period of the disease and improve the remission rate[22].

In conclusion, while the efficacy of tamoxifen has been established in the treatment of MBC, the aromatase inhibitor requires further investigations. Of the 33 patients (45.2%) who received endocrine therapy in our study, 28 (84.8%) took

tamoxifen and only one (3.3%) took aromatase inhibitor. The univariate analysis showed that the five-year survival rates of those with endocrine therapy and those without were significantly different (100% vs. 56%). And the endocrine therapy remained to be the prognostic factor in the multivariate analysis. Thus, endocrine therapy is an important part of the management of the patients with MBC, which can improve the overall survival rate. Particularly, for those with positive expressions of hormone receptors, tamoxifen is the first-line drug of the endocrine therapy.

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