

Clinicopathological Characteristics of Male Breast Cancer

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Purpose: To investigate clinicopathological characteristics and outcomes of male breast cancer (MBC). **Patients and Methods:** We retrospectively analyzed the data of 20 MBC patients in comparison with female ductal carcinoma treated at Yonsei University Severance Hospital from July 1985 to May 2007. Clinicopathological features, treatment patterns, and survival were investigated. **Results:** MBC consists of 0.38% of all breast cancers. The median age was 56 years. The median symptom duration was 10 months. The median tumor size was 1.7 cm, 27.8% showed node metastasis, and 71.4% were estrogen receptor positive. All 20 cancers were arisen from ductal cells. No lobular carcinoma was found. The incidence of stages 0, I, II, and III in patients were 2, 10, 4, and 3, respectively. All patients underwent mastectomy. One with invasive cancer did not receive axillary node dissection and stage was not exactly evaluated. Adjuvant treatments were determined by pathologic parameters and stage. Clinicopathological parameters and survival rates of MBC were comparable to those of female ductal carcinoma. **Conclusion:** The onset age of MBC was 10 years older and symptom duration was longer than in female patients. No difference in outcomes between MBC and female ductal carcinoma suggests that the biology of MBC is not different from that of females. Therefore, education, an appropriate system for early detection, and adequate treatment are necessary for improving outcomes.

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INTRODUCTION

Male breast cancer (MBC) is a rare disease and accounts for less than 1% of all cases of malignancy in men.¹ The incidence of MBC has significantly increased from 0.86 to 1.08 per 100,000 population over the past 26 years in the United States.² In Korea, MBC constitutes 0.4 - 0.6% of all breast cancers (BC).³⁻⁵ Because of its low incidence, MBC has not been studied as extensively as female breast cancer. Most studies related to MBC are retrospective analyses with a small number of patients. Appropriate management guidelines for MBC have not yet been clearly established, and limited information is available regarding the epidemiology, treatment, and prognosis of the disease.⁶ Therefore, the treatment guideline has been extrapolated from the data based on female breast cancer.

However, the incidence of MBC has been increasing significantly along with the increasing incidence of female breast cancer, although geographic variations in the incidence of MBC was reported.^{2,7,8} In Europe, approximately 1% of all BC occurs in males, but the incidence is much higher in other areas such as sub-Saharan Africa with 15%.^{9,10} Therefore, the study of MBC will become more important every day. In this study, we investigated clinicopathological characteristics, treatment patterns, and outcomes of MBC in Koreans.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of 20 MBC patients who had been treated at the

Department of Surgery, Yonsei University College of Medicine, in Seoul, Korea, between July 1985 and May 2007. This sample represents 0.38% (20/5,229) of all BC treated at our institution during the same period. Data regarding general characteristics of patients (age, presenting signs and symptoms, duration of symptoms, and site and location of tumor), histopathology of primary tumor, treatment modalities (surgery, chemotherapy, radiation and hormone therapy), disease-free survival, and overall survival were obtained by reviewing medical records. Tumor stage was based on the 6th American Joint Committee on Cancer (AJCC) criteria. Histological type and grading followed the World Health Organization (WHO) classification. Ten percent or more of positively stained cells was used as the cut-off for hormonal receptor positivity. Clinical follow-up included history taking, physical examination, laboratory tests and radiologic imaging tests every 6 - 12 months for detection of relapse. The differences between MBC and female ductal carcinoma were also investigated. Chi-square test was employed to confirm statistical significance. Disease-free survival and overall survival were estimated and plotted using Kaplan-Meier method. Group differences in survival time were tested by log-rank test. A *p* value < 0.05 was considered statistically significant. SPSS for Windows (ver. 13.0, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

General characteristics of patients

General characteristics of patients are summarized in Table 1. The median age at diagnosis was 56 years (range, 22 - 78 years). Fifteen patients (75%) were diagnosed after the age of 50 years and 6 were diagnosed during their 50s. Three patients had a history of alcohol drinking and 4 had a history of smoking. One patient diagnosed at 22 years of age had a family history of BC and his mother died of BC when he was 2 years old. Two patients had synchronous double primary tumors; 1 had poorly differentiated epidermoid carcinoma of the tonsil and the other had adenocarcinoma ex

Table 1. General Characteristics of Male Breast Cancer Patients

Characteristics	Patients (n = 20)	%
Age (yrs)		
20 - 29	2	10
30 - 39	1	5
40 - 49	2	10
50 - 59	6	30
60 - 69	4	20
≥ 70	5	25
Chief complaints		
Mass	18	90
Nipple discharge	2	10
Duration of symptom		
Sx ≤ 6 mo	8	40
6 mo < Sx ≤ 12 mo	6	30
12 mo < Sx ≤ 24 mo	3	15
Sx > 24 mo	3	15
Site of tumor		
Left	6	30
Right	14	70
Location of tumor		
Retroareolar	17	85
Other quadrant	3	15

Sx, symptom; mo, month.

pleomorphic adenoma of the submandibular gland. There was no history of bilateral BC. The most common symptom was a palpable mass (n = 18), and the median duration of symptoms was 10 months. One patient had nipple discharge for more than 10 years. Six of the 20 patients had cancer in the left breast and 14 in the right. Most tumors were located in the central subareolar area (n = 17). In 2 patients, the tumor was located in the upper outer quadrant and in the lower inner quadrant in 1 patient.

Histopathological characteristics of tumor

Histopathological characteristics of primary tumor are summarized in Table 2. All 20 cases were

Table 2. Histopathological Characteristics and Treatment Patterns of Male Breast Cancer Compared to Female Ductal Carcinoma

Characteristics	Male breast cancer (%)	Female ductal carcinoma (%)	<i>p</i> value
Age (yrs)			0.002
< 50	5 (25.0)	2,743 (59.0)	
≥ 50	15 (75.0)	1,905 (41.0)	
Tumor size			NS
≤ 2 cm	12 (60.0)	1,638 (53.5)	
> 2 cm	8 (40.0)	1,421 (46.5)	
Lymph node			NS
Negative	13 (72.2)	2,692 (58.5)	
Positive	5 (27.8)	1,908 (41.5)	
Stage*			NS
0	2 (10.5)	453 (9.8)	
I	10 (52.6)	1,334 (28.9)	
II	4 (21.1)	1,916 (41.5)	
III/IV	3 (15.8)	915 (19.8)	
Estrogen receptor [†]			NS
Negative	4 (28.6)	1,403 (36.4)	
Positive	10 (71.4)	2,452 (63.6)	
Progesterone receptor [†]			NS
Negative	6 (42.9)	1,602 (42.3)	
Positive	8 (57.1)	2,184 (57.7)	
Histologic grade [†]			NS
I	3 (25.0)	762 (23.2)	
II/III	9 (75.0)	2,520 (76.8)	
Operation method			0.014
BCS	0 (0)	1,087 (23.4)	
Mastectomy	20 (100)	3,561 (76.6)	
Chemotherapy			0.001
Not done	14 (70.0)	1,573 (34.6)	
Done	6 (30.0)	2,976 (65.4)	
Radiation therapy [‡]			NS
Not done	13 (72.2)	2,810 (63.2)	
Done	5 (27.8)	1,633 (36.8)	
Hormone therapy [‡]			NS
Not done	4 (25.0)	2,023 (45.3)	
Done	12 (75.0)	2,438 (54.7)	

NS, not significant; BCS, breast-conserving surgery.

*One male with invasive cancer did not receive axillary node dissection and stage was not exactly evaluated.

[†]Histopathologic reports of estrogen receptor/progesterone receptor and grade were not documented in 6 and 8 male patients, respectively.

[‡]We are not able to verify whether 2 and 4 male patients received radiotherapy and hormone therapy, respectively, or not.

ductal cell in origin. The most frequent histologic type was infiltrating ductal carcinoma (n = 14). Four patients (20%) had special type ductal carcinoma; 2 had tubular carcinoma, 1 had mucinous carcinoma, and 1 had papillary carcinoma. Two patients (10%) had non-invasive carcinoma. The median size of the tumor was 1.7 cm (range, 0.5-4 cm) and 12 cases (60%) were categorized as T1 lesions. Five of the 18 patients who underwent axillary node dissection (27.8%) showed lymph node metastasis in the axillary area. The median number of axillary lymph nodes removed was 19.5 (range, 8 - 34). The median number of axillary lymph nodes involved was 4 (range, 1 - 16) among patients with axillary lymph node metastasis. One patient had 16 axillary lymph nodes involved. According to the TNM staging system, there were 2, 10, 4, and 3 patients in stages 0, I, II, and III, respectively. One with invasive cancer did not receive axillary node dissection and stage was not exactly evaluated. In terms of histologic grade, 3 patients had a well-differentiated tumor and 9 had a moderately to poorly differentiated tumor. Among 14 patients available for hormone receptors assays, the estrogen receptor was positive in 10 patients (71.4%) and the progesterone receptor was positive in 8 (57.1%). The status of c-erbB-2 was available in 12 patients, 3 (25%) of whom were positive.

Treatment patterns

Treatment patterns are summarized in Table 2. Of the 20 patients, 18 underwent modified radical mastectomy, 1 simple mastectomy, and 1 subcutaneous mastectomy. No patients received neoadjuvant chemotherapy. After completion of surgery, adjuvant therapies were administered: 6 received chemotherapy, 4 CMF (cyclophosphamide, methotrexate, fluorouracil) regimen, and 2 anthracycline based chemotherapy. Radiation therapy was done in 5 patients with a mean dose of 50 grays (Gy). Twelve patients daily received hormone therapy with 20 mg of tamoxifen.

Survival

The median period of follow-up was 53 months (range, 6 - 209 months). There were no local or

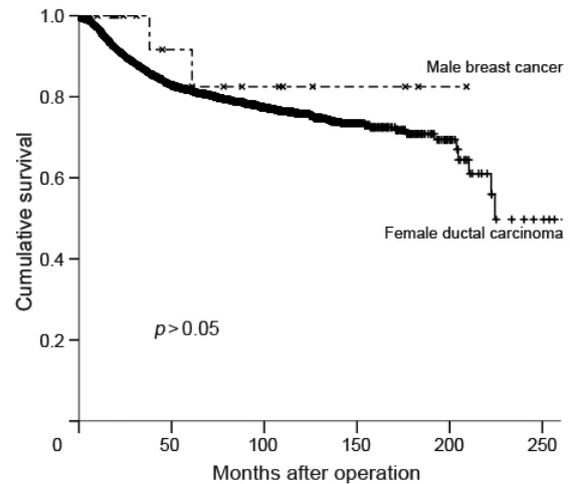


Fig. 1. Disease-free survival curve. The dotted line represents male breast cancer and the bold line represents female ductal carcinoma.

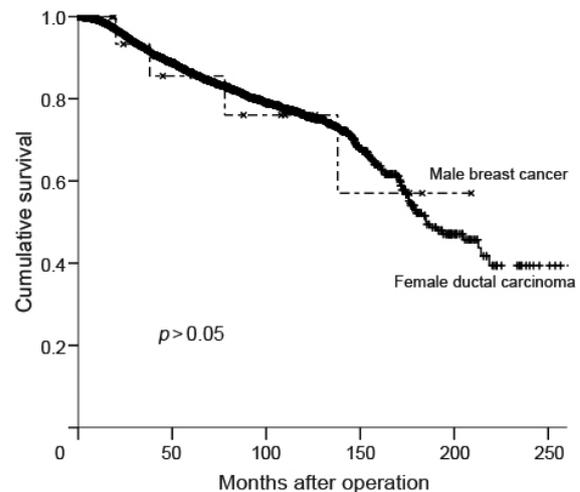


Fig. 2. Overall survival curve. The dotted line represents male breast cancer and the bold line represents female ductal carcinoma.

regional recurrences, however, there were 2 systemic metastasis and 4 deaths during follow-up. The 5- and 10-year disease-free survival rate was 91.7% and 82.5%, respectively (Fig. 1), whereas the 5- and 10-year overall survival rate was 85.6% and 76.0%, respectively (Fig. 2). Although survival was not significantly different, older age, larger size, axillary lymph node metastasis, advanced tumor stage, hormone receptor negativity, and higher grade showed a trend for poor overall survival in

Table 3. 10-year Disease-free Survival and 10-year Overall Survival According to Clinicopathological Characteristics in Male Breast Cancer

Characteristics	10-yr disease-free survival	10-yr overall survival	<i>p</i> value
Age (yrs)			NS
< 50 (n = 5)	80.0	80.0	
≥ 50 (n = 15)	83.3	72.0	
Tumor size			NS
≤ 2 cm (n = 12)	80.0	88.9	
> 2 cm (n = 8)	83.3	62.5	
Lymph node			NS
Negative (n = 13)	83.3	90.0	
Positive (n = 5)	67.7	66.7	
Stage*			NS
0/I (n = 12)	83.3	90.0	
II/III (n = 7)	75.0	75.0	
Estrogen receptor [†]			NS
Negative (n = 4)	75.0	75.0	
Positive (n = 10)	66.7	100	
Progesterone receptor [†]			NS
Negative (n = 6)	75.0	75.0	
Positive (n = 8)	66.7	100	
Histologic grade ^{†‡}			NS
I (n = 3)	100	100	
II/III (n = 9)	66.7	66.7	
Chemotherapy			NS
Not done (n = 14)	87.5	79.5	
Done (n = 6)	66.7	66.7	
Radiation therapy [§]			NS
Not done (n = 13)	83.3	90.0	
Done (n = 5)	66.7	33.3	
Hormone therapy [§]			NS
Not done (n = 4)	100	75.0	
Done (n = 12)	75.0	75.0	

NS, not significant.

*One male with invasive cancer did not receive axillary node dissection and stage was not exactly evaluated.

†Histopathologic reports of estrogen receptor/progesterone receptor and grade were not documented in 6 and 8 male patients, respectively.

‡5-yr disease-free survival rate was compared.

§We are not able to verify whether 2 and 4 male patients received radiotherapy and hormone therapy, respectively, or not.

our study (Table 3).

As mentioned above, there were 4 deaths during follow-up. The first patient was 22 years old at diagnosis. He had a history of familial BC and had a stage IIa tumor. He received adjuvant chemotherapy with CMF regimen and radiotherapy. However, he developed systemic metastasis and died of BC after a follow-up period of 38 months. The second patient was 51 years old at diagnosis. He had stage I BC and also stage IV tonsillar cancer. He received radiation therapy to the head and neck area. After 20 months, he died probably of recurrent tonsillar cancer. The third patient was 53 years old at diagnosis and had stage I tumor. He received adjuvant hormonal therapy. However, systemic metastases in the bones and lung were found at 61 and 71 months after surgery, respectively. He finally died of BC at 138 months after surgery. The last patient was 63 years old at diagnosis. He did not receive axillary lymph node dissection. The tumor size was 2.5 cm. He received radiation and hormonal therapy. He died at 78 months after surgery without evidence of recurrence.

Comparison with female ductal carcinoma

To evaluate outcomes of MBC, we compared MBC to female ductal carcinoma, which is the most frequent type of female breast cancer. We retrospectively analyzed 4,648 female ductal carcinoma patients whose last follow-up data were available during the same period. The results are summarized in Table 2.

MBC patients were older at diagnosis than female ductal carcinoma patients. The median age of female ductal carcinoma patients was 47 years. No breast-conserving surgery was performed in males. Other factors such as tumor size, lymph node, stage, steroid receptors, histologic grade, radiotherapy, and hormone therapy were not different between the 2 groups. The median tumor size of female ductal carcinoma was 2 cm and was not significantly different from that of MBC. Fewer male patients had axillary lymph node metastasis and more had estrogen receptor positivity. Chemotherapy was more frequently employed in female ductal carcinoma, and hormone therapy was more frequently applied in MBC. The incidence rate of

stage 0 in-situ carcinoma of males was comparable to that of females.

The 5- and 10-year disease-free survival rate of female ductal carcinoma was 81.7% and 75.8%, respectively (Fig. 1), whereas the 5- and 10-year overall survival rate of female ductal carcinoma was 86.3% and 76.2%, respectively (Fig. 2). Survival rates were not statistically different between MBC and female ductal carcinoma. There was no different pattern in subgroup analysis dividing female ductal carcinoma into premenopausal and postmenopausal when compared with MBC. The 10-year disease-free and overall survival rates of premenopausal ductal carcinoma patients were 74.3% and 77.1%, respectively, while the 10-year disease-free and overall survival rates of postmenopausal ductal carcinoma patients were 78.3% and 74.7%, respectively.

DISCUSSION

The incidence of MBC varies widely between countries. MBC accounts for 1.2% of newly diagnosed BC in the United States and approximately 1% of all BC in Europe.^{9,11} However, the incidence is much higher in sub-Saharan Africa with 15% of all BC, and the relatively high incidence is attributed to possible hyperestrogenism as a result of liver damage from endemic infectious disease.¹⁰ In our study, the incidence of MBC was 0.38%, and it has been reported as 0.4 - 0.6% of all BC in Korea.^{3,5} It is quite low and comparable to that in Western countries despite the high prevalence of viral hepatitis B infection in men (5.1%), according to the 1998 National Health and Nutrition Survey in Korea.¹² MBC accounts for 0.49% of all cases during 1975 - 1997 in Osaka, Japan.¹³ The incidence of MBC may be lower in Asia than in the West due to biological and/or environmental factors, since the incidence of female breast cancer is much higher in Western countries.¹⁴

MBC in Western countries was presented mostly in their 60s (range, 63 - 68 years), which is 10 years later than in females.^{9,13,15} However, as in female breast cancer, the onset of MBC in Korea is 10 years earlier than in Western countries and appears to peak in their 50s.^{3,4,9} The median duration of symptoms before diagnosis was 10

months, which was a little longer than that in Western countries,¹⁶ but it was significantly shorter than what was reported 18 years ago in Korea.¹⁷ The shortened symptom duration may be associated with general improvements in quality of life and awareness, which can affect the outcome of disease.

Ductal carcinoma in situ accounts for 5 - 10% of all breast tumors in men, and the most common growth pattern is papillary subtype.^{2,15,18} Infiltrating ductal carcinoma is the most frequent invasive carcinoma in men, accounting for 70 - 95% of MBC, and lobular carcinoma is rare (around 1% of all cases) due to lack of terminal lobules in the male breast.^{1,2,15,18,19} Our study showed that 2 out of 20 patients (10%) had non-invasive cancers and the others (90%) were invasive cancers of ductal cell origin including special type histology, but there was no case of lobular type. These results are compatible with previous studies.^{1,2,15,18,19}

The expressions of estrogen and progesterone receptor in MBC are higher than in female breast cancer, and they have been reported to be 81 - 90.6% and 74 - 81.2%, respectively.^{16,20} In our study, the expressions of estrogen and progesterone receptor in MBC were little higher than in female breast cancer, but it was 10 - 20% lower than that in Western populations.

The etiology of MBC is unclear, however, many risk factors, including hormonal imbalance, and genetic, environmental and epidemiologic factors, have been associated with MBC. Abnormalities in estrogen and androgen balance may play an important role in the development of disease.^{1,18,19} Although there is high prevalence of liver injury from viral hepatitis B infection in Korea, the incidence of MBC was low. Increasing age, Ashkenazi Jewish ancestry, African-American ethnicity, previous chest wall irradiations, alcohol drinking, and benign breast conditions such as nipple discharge, breast cysts, and breast trauma have been suggested as risk factors.²¹⁻²⁵ It is unclear whether gynecomastia is a risk factor for MBC.^{18,19,26}

The most common surgical treatment for MBC is modified radical mastectomy, which has displaced radical mastectomy with no significant difference in survival.^{15,16,19} Unlike in female breast cancer, however, lumpectomy probably does not play an important role in the treatment of MBC,

because of small volume of male breast tissue.^{1,16} For invasive breast cancer, axillary lymph node assessment is usually performed either via sentinel node biopsy or axillary sampling/clearance.^{16,19} As the validation, sentinel lymph node biopsy is established as an accurate and low morbid procedure in female breast cancer, and sentinel node biopsy plays an important role in MBC and is being currently advocated as the standard surgical procedure.⁸ Recently, one patient underwent sentinel node biopsy. In our study, 2 patients did not receive axillary node dissection: One patient had intraductal papillary carcinoma, and is still alive and disease-free at more than 108 months after surgery. The other had invasive papillary carcinoma of 2.5 cm in diameter and received radiation and hormone therapy, however, he died of unknown causes at 78 months after surgery.

Although adjuvant chemotherapy and hormonal therapy have proven benefits for a subgroup of female breast cancer patients, the role of adjuvant chemotherapy in MBC is less clear.¹ Adjuvant chemotherapy in MBC can usually be decided by assessing the risks and benefits in the same manner as in female breast cancer.^{1,15,16,27} Because of high expression rates of hormone receptor positivity in MBC, adjuvant hormone therapy with tamoxifen is theoretically the rational therapeutic strategy and should be considered in men with BC.^{1,15,16,27} In several retrospective studies, tamoxifen increased disease-free survival and overall survival in MBC patients.^{28,29} Although aromatase inhibitors recently showed improved survival for postmenopausal women with BC,³⁰ aromatase inhibitors alone may be problematic because 20% of circulating estrogens are produced by testes in men independent of aromatase.^{15,16}

In general, men with BC had a longer duration of symptoms than women, and subsequent delay in diagnosis contributes to advanced stage.^{1,27} Tumor size and axillary lymph node involvement are the most important prognostic factors for male and female breast cancer.^{20,31} When matched for age and stage, men and women have similar prognoses.^{2,20} In Korea, it has been reported that the 5- and 10-year observed overall survival rate of female patients with breast cancer was 84.1 - 89.4% and 70.1 - 82.9%, respectively.^{4,32,33} In our study, although the sample size was too small to have

an exact comparison, there was no difference in disease-free survival and overall survival between MBC and female ductal carcinoma. Although it was not statistically significant, older age, larger size, axillary lymph node metastasis, advanced stage, higher grade, and hormone receptor negativity were related to poor overall survival in MBC. It is known that men with BC have poorer overall survival rates than women, but this is probably due to older age at diagnosis, more advanced stage at presentation, and higher rates of death from comorbid disease, but not due to the biology of the disease itself.^{1,2,18,20}

The 5- and 10-year survival rates of MBC have been reported at 57% and 28%, respectively, in 1990,¹⁷ however, those in this study were improved at 85.6% and 76.0%, respectively. The main reason for such an improvement in 20 years could be early detection and adequate treatment, resulting in shortened symptom duration, smaller tumor size, much lower incidence of axillary node involvement, and increased use of tamoxifen. These results suggest that early detection, adequate treatment, and close follow-up would be the mainstay for improving survival of MBC.

In conclusion, the tumor biology of MBC is not significantly different from that of females, however, limited public awareness and absence of adequate screening for MBC result in delayed diagnosis and poor outcomes. Therefore, education, an appropriate system for early detection, and adequate treatment are prerequisite for improving outcomes, and men presenting any breast symptoms should be examined in the same manner and degree of urgency as in women to detect cancer at an early stage and better treatment outcomes.

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