



The Management and Outcomes of Male Breast Cancer

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ABSTRACT

Objective: Due to a lack of sufficient data, the treatment protocols for male breast cancer are usually the same as those used for female breast cancer. The aim of the current study was to present our clinical experience with male breast cancer.

Materials and Methods: The records of 37 patients who were treated for male breast cancer in our hospital between 2004 and 2014 were reviewed retrospectively. The data of patients were recorded and analyzed.

Results: The mean age of the patients was 63.03 ± 12.36 years. Thirty-three patients (89.2%) had invasive ductal carcinoma, two (5.4%) had ductal carcinoma in situ, and two had invasive lobular carcinoma (5.4%). The most common molecular subtype was luminal A (17 cases, 45.9%). Twenty-nine patients with male breast cancer underwent mastectomy and two underwent breast conserving surgery. Axillary lymph node dissection was performed in 25 patients. The most common surgical procedure was modified radical mastectomy. Distant metastases were present in 17 (45.9%) patients. Overall, the 5-year survival was 60%. The 5-year survival was 100% for those with stage 0-I disease, 87% for stage II, and 42% for stage III. The 3-year survival was 14% for stage IV.

Conclusion: Patients with male breast cancer presented at an older age, a later stage, and with earlier metastasis. Early metastasis and death increases with increasing stage. Poor prognosis correlates with late admission. Data from different centers should be compiled and reviewed in order to determine a specific treatment protocol for male breast cancer; each paper published reveals new data.

Keywords: Breast cancer, male, diagnosis, disease management

Introduction

In contrast to female breast cancer (FBC), male breast cancer (MBC) is a rare disease that is not well characterized. MBC accounts for <1% of breast cancer incidence and less than 1% of all male cancer cases (1-4).

MBC can arise from anywhere in breast tissue and can include rare forms, such as invasive papillomas and medullary lesions. Invasive ductal carcinoma accounts for 90% of all MBC cases, and 80% of all FBC cases. Invasive lobular carcinoma (ILC) accounts for 1% of MBC cases; it occurs predominantly in men with Klinefelter syndrome (5, 6). Ductal carcinoma in situ (DCIS) constitutes about 10% of MBC cases (7).

It has been reported that there are significant differences between MBC and FBC with respect to the expression of a variety of biologic factors, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) (8). MBC tumors tend to express estrogen receptor (ER) and progesterone receptor (PR) at higher levels than do FBC tumors. In addition, MBC tumors have different cellular origins and are affected differently by various environmental risk factors. Further, patients with MBC have a lower overall-survival rate (9, 10).

Due to the lack of sufficient data in males, treatment regimens for MBC are based on the assumption that MBC is very similar to FBC; therefore, the prognostic features and therapeutic aims of FBC are extrapolated to MBC. Although there are similarities between MBC and FBC, there is also mounting evidence that they are quite different biologically. There is little proof that the prognostic features found in FBC are also valid for MBC (11-13).

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In the current study, we aimed to present our clinical experience with MBC in order to expand the data pool such that specific management protocols can be developed for MBC; therefore, we will no longer have to depend on management protocols intended for patients with FBC.

Materials and Methods

A total of 41 patients with MBC were admitted to the Oncology Department of our Hospital between 2004 and 2014. Thirty-seven patients were included in the study; 4 were excluded because their data were missing. All procedures adhered to the ethical principles of the Helsinki Declaration. The demographic characteristics, symptoms, treatment methods, stage, tumor histopathologic features, tumor size, and lymph node status for each patient were retrospectively recorded from the hospital database. Tumor size was recorded as the greatest dimension of the tumor. Immunohistochemical staining was used to classify the breast cancer cases into four different subtypes as follows: luminal A, luminal B, HER2-overexpressing, and triple-negative.

Statistical analysis

Survival rates were estimated using life-table method in SPSS version 18 (SPSS Inc.; Chicago, IL, USA).

Results

We retrospectively reviewed the medical records of 37 patients with MBC between 2004 and 2014. Of the 37 patients, 21 (57%) had left breast cancer and 16 (43%) had right breast cancer. The mean age of the patients was 63.03±12.36 years (range, 32-79 years). All patients presented with a palpable mass. Associated findings included axillary lymphadenopathy (1 patient) and skin involvement (7 patients, 3 of which had ulcerated skin lesion). Thirty-three (89.2%) patients had invasive ductal carcinoma, of which three were mucinous subtype. Two patients (5.4%) had DCIS and 2 (5.4%) had invasive lobular carcinoma. The general characteristics of the patients are summarized in Table 1.

The mean tumor size was 35.5±16.2 mm, the mean metastatic lymph node was 3.5 (range, 0-22), the mean number of totally removed lymph nodes (TLN) was 16.4 (range, 3-31), and the mean follow-up period was 40.6 months (range, 9-123 months).

While ER was positive in 31 (83.8%) cases, PR was positive in 30 (81.1%) cases. HER2 analysis results were available in 33 (89.2%) cases; 20 of these were negative (54.1%), 13 were positive (35.1%), and 4 were unknown (10.8%). There were 17 (45.9%) cases with luminal A molecular subtype, 12 (32.4%) with luminal B, 3 (8.1%) with triple-negative, 1 (2.7%) with HER-2—overexpressing subtypes, and there were 4 (10.8%) cases where the molecular subtypes were not defined. Seven patients underwent sentinel lymph node biopsy (SLNB). Four of these patients were node negative at histopathologic assessment and 3 were positive. The 3 patients who were node positive underwent axillary dissection. Twenty-five patients underwent axillary lymph node dissection (ALND), six of which had no metastatic lymph node. Eight patients did not undergo any axillary procedure; 5 were inoperable, 1 underwent salvage mastectomy, 1 underwent BCS for DCIS, and 1 refused surgery. The most common surgical procedure was MRM (24 patients, 64.9%). The treatment options are summarized in Table 2.

Distant metastases were present in 17 (45.9%) of the 37 patients with MBC. The most frequent involvements were bone (n=12; 70.6%),

Table 1. Histopathologic characteristics of the patients with MBC

	n	%
Histopathologic type		
Invasive ductal carcinoma	33	89.2
Invasive lobular carcinoma	2	5.4
DCIS	2	5.4
ER status		
Positive	31	83.8
Negative	6	16.2
PR status		
Positive	30	81.1
Negative	7	18.9
Her-2 status		
Positive	13	35.1
Negative	20	54.1
Unknown	4	10.8
Molecular type		
Luminal A	17	45.9
Luminal B	12	32.4
Triple-negative	3	8.1
Her-2 overexpressing	1	2.7
Unknown	4	10.8

ER: estrogen receptor; PR: progesterone receptor; DCIS: ductal carcinoma in situ; MBC: male breast cancer

lung (n=6; 35.3%), cranial field (n=3; 17.6%), brain (n=2; 11.8%), liver (n=2; 11.8%), pleura (n=1; 5.9%), and mesenteric (n=1; 5.9%).

The 5-year survival was 100% for stage 0-I disease, 87% for stage II, and 42% for stage III. Three-year survival was 14% for stage IV. Early metastasis and death increases as the stage of MBC increases.

Discussion and Conclusion

Male breast cancer has been reported between the ages of 5 and 93 years, with a median age of 68 years (14-16). In our current study, the ages of the patients with MBC ranged between 32 and 79 years (mean age: 63 years).

MBC usually presents as a painless subareolar lump that is usually identified by palpation (17-20). Pain is associated with the lump in only 5% of cases (21). Nipple involvement is quite an early event; 9% of cases are reported to have nipple retraction, 6% have discharge, and 6% have ulceration, though ulceration was separate from the nipple in half of these cases (3). In the current study, all of the patients presented with a palpable mass, and the mean tumor size (36 mm) was much larger than that reported in the literature (24 mm) (22). Associated findings included axillary lymphadenopathy in one patient, and skin involvement in seven patients (3 of whom had ulcerated skin lesions). MBC are generally identified in physical examination and usually have associated sonographic and/or mammographic findings. At mammography, microcalcification is more rarely seen in males than in females, and there are typically high-density irregular masses with well-defined

Table 2. General characteristics of the patients with MBC

	n	%
Site of cancer		
Left	21	56.8
Right	16	43.2
Stage		
In situ	2	5.4
I	4	10.8
II	12	32.4
III	12	32.4
IV	7	18.9
Treatment		
MRM*	24	64.9
Inoperable	5	13.5
Mastectomy+SLNB	4	10.8
BCS**	1	2.7
BCS+ALND	1	2.7
Salvage mastectomy	1	2.7
Refused surgery	1	2.7
Metastasis		
Absent	20	54.1
Present	17	45.9
Bone	12	70.6
Lung	6	35.3
Cranial Field	3	17.6
Brain	2	11.8
Liver	2	11.8
Pleura	1	5.9
Mesentery	1	5.9
Survey		
Survivor	26	70.3
Dead	11	29.7

SLNB: sentinel lymph node biopsy; MRM: modified radical mastectomy; BCS: breast-conserving surgery; ALND: axillary lymph node dissection; MBC: male breast cancer.

*Three patients with positive SLNB underwent modified radical mastectomy.

**This patient's histopathologic examination revealed DCIS, and therefore, this patient did not undergo axillary intervention.

contours (Figure 1a, b). MBC has similar ultrasound (US) features as in FBC. The margins are angulated, microlobulated, or speculated (Figure 2) (23).

Hormone receptor-positive expression has been reported more commonly among men than women (22). In large studies of MBC, more than 90% of tumors were reported to be positive for estrogen receptor, and 92-96% were positive for progesterone-receptor (24, 25). However, the positivity rates were similar in men when

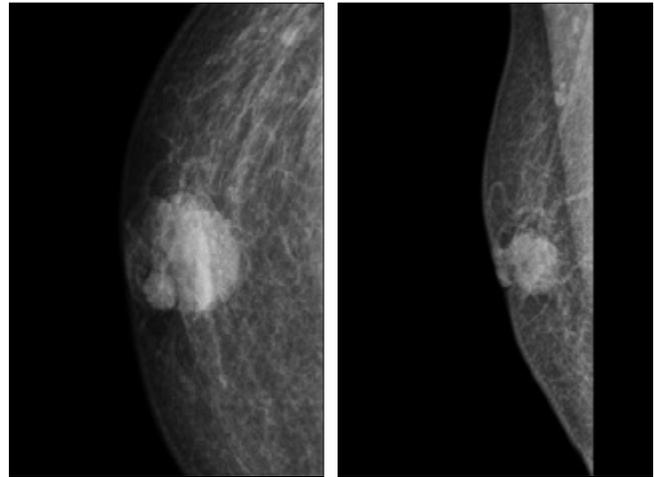


Figure 1. a, b. Invasive ductal carcinoma in a man with a palpable mass of the right breast (a, b). Craniocaudal and mediolateral oblique mammograms of the right breast show high density mass with well-defined in the retroareolar region

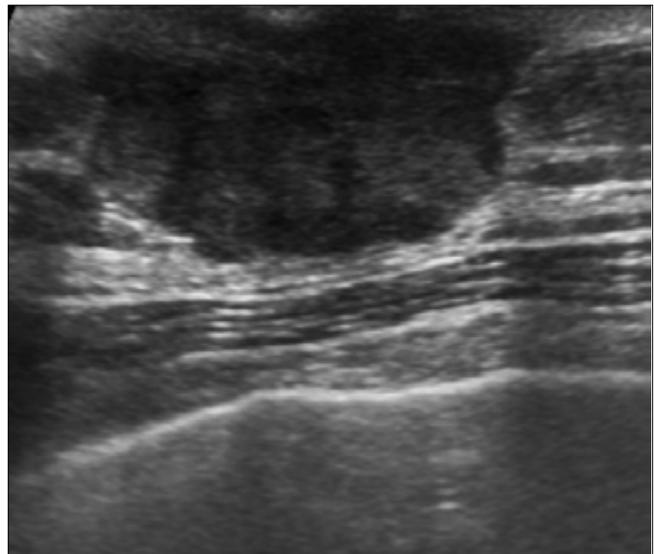


Figure 2. US image shows the hypoechoic mass with irregular margins in the retroareolar region

compared with postmenopausal women (25, 26). Many studies have reported different rates of HER2 overexpression in MBC (27-30). In our study, ER results were positive in 31 (83.8%) cases, PR results were positive in 30 (81.1%) cases, and HER2 results were positive in 13 (35.1%) cases. The literature reveals that luminal A is the most common MBC subtype (1). In the current study, the molecular subtype was luminal A in 17 (46%) cases, luminal B in 12 (32%) cases, triple-negative in 3 cases, and HER-2 overexpressing in 1 case; there were no data regarding molecular subtypes in four cases. The antiestrogen drug, tamoxifen, is usually accepted as the standard of care for hormonal therapy in MBC because it is hormone-receptor positive in about 90% of cases (3). In our study, hormonal therapy was performed in 18 (48.7%) patients. The treatment protocols of chemotherapy and radiotherapy were performed based on the management protocols for FBC.

With regards to invasive carcinomas, female and male tumors are morphologically indistinguishable. A number of studies on MBC frequently reported that the major histologic subtypes were nonlobular

breast carcinomas such as ductal carcinoma (92%) (4, 31-33). Despite the absence of mammography screening, the incidence of in situ carcinoma is rising in men (34). DCIS constitutes approximately 5-10% of all male breast carcinomas (22, 34, 35). An especially rare type of MBC is ILC, which constitutes about 1% of all MBC cases. ILC is unusual in men because male breast tissue lacks lobules (36). In the current study, primary mucinous carcinoma was seen in 2 (5.4%) patients, DCIS was seen in 2 (5.4%), and ILC was seen in 2 (5.4%) patients.

Twenty-nine (78.4%) of the patients with MBC in the present study underwent mastectomy, and 2 (5.4%) underwent BCS. Studies published in the 1990s reported that 87% to 100% of males with breast cancer underwent mastectomy, and that only a small subset were treated with a breast-conserving approach (37-39).

Axillary lymph node involvement is the strongest predictor of both metastatic and local recurrence risk; it is present in about 50% MBCs (4, 14, 40). It has been reported that there are more than three nodes involved in approximately 40% of patients with nodal involvement (4, 41). In our study, the mean metastatic lymph node was 3.5 (range, 0-22), and 10 of the patients who underwent ALND did not have lymph node metastasis. Recently, SLNB was used in MBC cases with similarly encouraging results (42). The Memorial Sloan-Kettering Cancer Center recently reviewed their experience, and indicated that 49% of patients with MBC had a positive sentinel lymph node compared with 31% of patients with FBC (43). In the current study, 7 patients underwent SLNB; ALND was performed in 3 of these because they had positive SLNB.

General public awareness regarding MBC is minimal, and this leads to possible delays in diagnosis; therefore, men with breast cancer have a worse prognosis than women with breast cancer because of the extent of the disease at the time of diagnosis. In the literature, more than 40% of patients with MBC present with stage III or IV disease (44, 45). In our study, the overall 5-year survival was 60%. The 5-year survival was 100% for stage 0-I disease, 87% for stage II, and 42% for stage III. Three-year survival was 14% for stage IV. Seven patients initially presented with metastatic disease, and 10 (7 patients who were stage III and 3 patients who were stage II) developed metastatic disease during follow-up.

Databases show that up to 93% of MBC cases are of advanced disease, and that distant metastases are observed in approximately 30% of these patients at the time of diagnosis (19, 46). In the current study, the most frequent involvements were bone (n=12, 70.6%), lung (n=6, 35.3%), cranial field (n=3, 17.6%), brain (n=2, 11.8%), liver (n=2, 11.8%), pleura (n=1, 5.9%), and mesentery (n=1, 5.9%). There are other case series that reported different metastatic sites, among which were bones (48.78%), lungs (29.26%), liver (17.07%), spine (up to 30%), skin, and pleura (19, 46).

One recently published study suggested that they were the first to report brain metastasis in a patient with MBC; to the best of their knowledge, there are no other cases in the literature that prove the existence of brain metastasis from MBC (19). We also found no other reports of brain metastasis due to MBC in the literature. In our study, we reported two brain metastases due to MBC.

Overall prognosis is poor in MBC, but two studies proposed that the prognoses of MBC and FBC appeared similar when adjusted for stage and age (4, 47). Other studies reported that when matched by stage and

age, men with breast cancer appeared to have a comparable or better prognosis than women (48). However, perhaps due to poor awareness of the disease and diagnostic delays, several studies argued that MBC with higher stage tumors and had a poorer overall prognosis (49).

Estimates for overall 5-year survival range between 40-65% (37, 50). The 5-year survival for patients with MBC grouped by stage at presentation are as follows: 75-100% for stage I disease, 50-80% for stage II disease, and 30-60% for stage III disease (50). In the current study, the overall 5-year survival was 60%. The 5-year survival was 100% for stage 0-I disease, 87% for stage II, and 42% for stage III. Three-year survival was 14% for stage IV. Early metastasis and death increases as the stage of MBC increases.

Although it is a rare disease, MBC is accompanied by significant morbidity and mortality. Men generally present with higher stage and older age than females with breast cancer. Early metastasis and mortality rates increase with advanced stages of MBC. Therefore, in order to obtain earlier detection, education of both patients and health care providers is needed to increase awareness of MBC. In our study, we saw patients with MBC who had rare histopathologic types, including ILC and mucinous cancer. In addition, 2 patients had brain metastases. The most widely used surgical procedure was MRM. SLNB can be performed successfully in MBC. More studies from different centers are essential in order to define a specific treatment regimen because the rarity of MBC precludes large clinical trials. Collection of data from different centers will also address essential questions in the treatment of MBC.

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