

ORIGINAL ARTICLE

Male breast cancer: a retrospective study of 15 years

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Summary

Purpose: To retrospectively evaluate the 15-year experience with breast cancer in males at a single institution.

Methods: The data from 25 male patients who had undergone surgery for breast cancer at a single center were retrospectively analysed. Their medical records were studied for clinical characteristics, therapeutic modalities used and factors associated with disease free (DFS) and overall survival (OS), like local recurrence/distant metastasis.

Results: The median patient age was 67 years (range 38-83). The most frequent presenting symptom was a palpable lump. Eighteen (72%) patients underwent modified radical mastectomy (MRM), while sentinel lymph node biopsy (SLNB) was performed in 14 (56%) cases. Of 25 patients, 21 (84%) underwent axillary lymph node dissection (ALND) and 15 (71.4%) of them had pathological axillary lymph node involvement. Two of 25 (8%) patients with bone and liver metastases underwent toilet mastectomy due to breast ulceration.

Estrogen receptor (ER) was positive in 15 (60%) patients, while progesterone receptor (PR) and C-erbB2 (HER-2) were positive in 10 (40%) and 2 (8%) patients, respectively. Ten patients (40%) had both ER(+) and PR(+). The median follow-up period was 19 months (range 3-102). Local recurrence developed in one (4%) patient and distant metastasis in 4 (16%). Five-year OS and DFS were 53 and 49%, respectively. In univariate and multivariate analysis, pathological tumor size (<2 vs. >2 cm), pathological lymph node involvement and preoperative skin involvement over the breast were not associated with breast recurrence. Only in univariate analysis local recurrence/distant metastasis were associated with poor OS.

Conclusion: Large cooperative studies are needed using strict clinical and laboratory criteria to advance the understanding of this disease and to identify the most effective treatment approaches.

Key words: male breast cancer, sentinel lymph node biopsy, tissue-sparing surgery

Introduction

Male breast cancer (MBC) accounts for less than 1% of all diagnosed breast cancers and less than 1% of all cancers in men [1]. Breast cancer in men and women contrasts in the age at diagnosis, the histological types and the expression of hormone receptors. The median age at diagnosis in men is 68 years, compared with 63 years in women [2-4]. Men with breast cancer have a higher occurrence of ductal histology. More than 85% of all cases are invasive ductal carcinomas (IDC), whereas its rate in women is 70-75% [5]. Male patients have also higher rate of hormone receptor positive disease [5,6].

Despite the biological differences, clinical outcomes for breast cancer in men are similar to those for

women when they are matched for age, treatment, and stage of cancer [5-7]. Currently, there is no standardized treatment guideline for MBC. However, management of MBC is mostly based on evidence derived from data analysis of female breast cancer (FBC) patients [3,8]. The usual treatment for male patients is to undergo MRM. Relatively recently, breast-conserving surgery (BCS) became more of an issue in women with breast cancer. With this trend, BCS has been demonstrated to be feasible in MBC cases, though there is little experience with BCS, the indication is limited and firm evidence about safety is lacking [8-14].

In this retrospective study we report a single center experience with MBC during the last 15 years, including clinicopathological features, recurrence and survival of patients treated with surgery (radical mas-

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tectomy/RM, MRM, SLNB and BCS), chemotherapy and/or hormonotherapy and radiotherapy (RT).

Methods

The data of 25 male patients who were operated on for breast cancer during the last 15 years (1994-2010) at the Breast Diseases Unit, Department of General Surgery, Istanbul School of Medicine, Istanbul University were retrospectively analysed. The medical records of these patients were analysed for patient and disease characteristics, including age, presenting symptom(s), tumor localization, histopathological type, diagnostic technique(s), surgical approach, SLNB results, hormone receptors and HER-2 status, stage, tumor size, lymph node involvement and adjuvant treatment. Factors associated with local recurrence and DFS and OS were registered and the TNM staging system was used for patient pathological stage classification.

Statistical analysis

Statistical analysis of the data was performed using SPSS (SPSS 18.0 software TM, SPSS Inc., Chicago, IL, USA). The Kaplan-Meier method was used to estimate DFS and OS. The impact of tumor size, lymph node involvement and skin involvement on DFS and OS were evaluated by univariate analysis using log-rank test. Factors identified in univariate analysis were further evaluated by Cox stepwise regression multivariate analysis to determine independent predictors of DFS and OS. Statistical significance was set at a p-value <0.05.

Results

The median patient age was 67 years (range 38-83). The most frequent presenting symptom was a palpable lump in the breast (12 patients; 48%). Eight (32%) patients had both a lump and breast ulceration. Other presenting symptoms in decreasing order were pain (8%), nipple discharge (4%), gynecomastia (4%) and change of the color of the skin over the breast (4%).

Two (8%) patients had family history of breast cancer. The father of one patient had a history of breast cancer, while one second-degree male relative of the other one had also breast cancer. One patient had an operated and then metastatic prostate cancer. The tumor was localized in the left breast in 19 (76%) patients and in the right breast in 6 (24%). Table 1 shows the basic patient and disease characteristics, as well as the preoperative diagnostic methods.

Eighteen (72%) patients underwent MRM, while SLNB was performed in 14 (56%) cases. Of them, 10 (71.4%) had positive SLNB and underwent ALND. In total, 21 (84%) patients underwent ALND, along with 2 (14.2%) patients who had negative SLNB, while by that time SLNB was a newly introduced method. Of them, 15 (71.4%) had axillary lymph node metastases, where-

Table 1. Patient and histological tumor characteristics

Characteristics	N	%
Age (years)		
38-49	4	16
50-59	4	16
60-69	7	28
≥ 70	10	40
Breast involved		
Right	6	24
Left	19	76
Tumor localization		
Retroaxillary	16	64
Upper outer quadrant	7	28
Upper inner quadrant	1	4
Lower outer quadrant	1	4
Diagnostic techniques		
Tru - Cut	8	32
Excisional biopsy	7	28
Frozen section	4	16
FNAC	3	12
Other	3	12
Histopathological type		
Invasive ductal carcinoma	22	88
Ductal carcinoma <i>in situ</i>	1	4
Malignant epithelial tumor	1	4
Malignant fibrous histiocytoma	1	4
SLNB		
Done	14	56
Not done	11	44
Positive	10	40
Negative	4	16
Receptor status		
ER (+)	15	60
PR (+)	10	40
C-erbB2 (+)	2	8
TNM stage (after surgery)		
0	1	4
I	2	8
II A	2	8
II B	4	16
III A	2	8
III B	11	44
III C	1	4
IV	2	8
T stage (after surgery)		
pT1	5	20
pT2	19	76
pT4	1	4
N stage (after surgery)		
pNx	1	4
pN0	7	28
pN1	14	56
pN2	2	8
pN3	1	4
M stage (after surgery)		
M1*	2	8

*These patients underwent toilet mastectomy

FNAC: fine-needle aspiration cytology, SLNB: sentinel lymph node biopsy, ER: estrogen receptor, PR: progesterone receptor

as no such metastases were found in 6 (28.6%) cases. ALND was not performed in 2 patients with advanced disease stage (T4N1M1, T2NxM1) and 2 cases with negative SLNB. No axillary lymph node involvement was found in 2 SLNB negative patients who underwent ALND (Table 2).

Receptor analysis was performed in 20 (80%) patients and receptor status was defined in 15; it could not be defined in 5 cases. ER was positive in 15 (60%) patients, while PR and HER-2 were positive in 10 (40%) and 2 (8%) patients, respectively. Ten (40%) patients had both ER(+) and PR(+), while 3 (12%) were triple negative (Table 1). These patients received adjuvant chemotherapy (5-fluorouracil, doxorubicin, cyclophosphamide/FAC), and/or hormonotherapy (tamoxifen), and/or trastuzumab and/or RT after multidisciplinary breast council decision (Table 2).

Seventeen patients had adequate follow-up data. The median follow-up period was 19 months (range 3-102). Local recurrence developed at the 7th month in one patient (stage IIA) who had received adjuvant RT and chemotherapy after MRM. He is alive 24 months following FAC chemotherapy and trastuzumab administration (he was HER-2 positive). Distant metastasis developed in 4 patients after a median of 26.7 months (range 18-34). Two patients developed bone metastasis, while 2 had both bone and liver metastasis. The patients with bone metastasis received palliative RT, tamoxifen and bisphosphonate, whereas FAC chemotherapy was administered to those with liver metastasis. Of those with

distant metastasis, 2 died after 20 months, one after 33 months and the last one after 34 months. Four (23.5%) patients are still alive and disease-free for more than 5 years; one of them had stage I on presentation and the remaining stage II.

The 5-year OS and DFS were 53 and 49%, respectively (Figure 1). Statistically significant lower OS was registered in cases with local recurrence/distant metastasis (log-rank; $p=0.004$; Figure 2).

Univariate and multivariate analyses for DFS and OS included skin involvement by the tumor before pathological tumor size and pathological lymph node involvement; none of these factors impacted significantly DFS and OS (Table 3).

In univariate analysis ($p=0.004$) but not in multivariate analysis ($p=0.216$) local recurrence/distant metastasis was associated with significantly poorer OS survival (Table 4).

Discussion

In this study we reported our experience with 25 MBC cases. We found that our patients had similar diagnostic and clinical findings, histopathologic types and therapeutic characteristics (treatment approaches) with the relevant literature on MBC. Also, several factors, including pathological tumor size, pathological lymph node involvement, and skin involvement were not associated with development of local recurrence.

Published studies report a median age of 68 years at MBC diagnosis [2-4]. In our series, it was 67 years; however it was higher than that of other series from our

Table 2. Therapeutic modalities applied

Therapeutic modalities	N	%
Radical mastectomy +ALND	1	4
Modified radical mastectomy	8	32
Mastectomy + SLNB(+)+ALND	8	32
Mastectomy + SLNB(-)+ALND	2	8
BCS+ SLNB(+)+ALND		
BCS+ SLNB(-)	1	4
Simple mastectomy+SLNB(-)	1	4
Salvage mastectomy	2	8
Non-surgical interventions		
Neoadjuvant CT	4	16
Adjuvant therapy		
CT	5	20
HT	3	12
RT	1	4
CT + RT	4	16
HT + RT	3	12
HT + CT + RT	7	28
Trastuzumab + CT + RT	2	8

MRM: modified radical mastectomy, SLNB: sentinel lymph node biopsy, BCS: breast conserving surgery, ALNB: axillary lymph node biopsy, RT: radiotherapy, CT: chemotherapy, HT: hormonotherapy

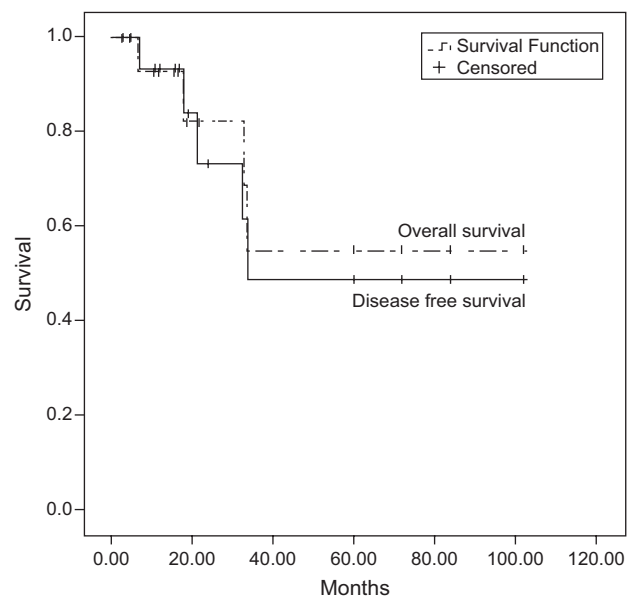


Figure 1. Disease-free and overall survival for all patients.

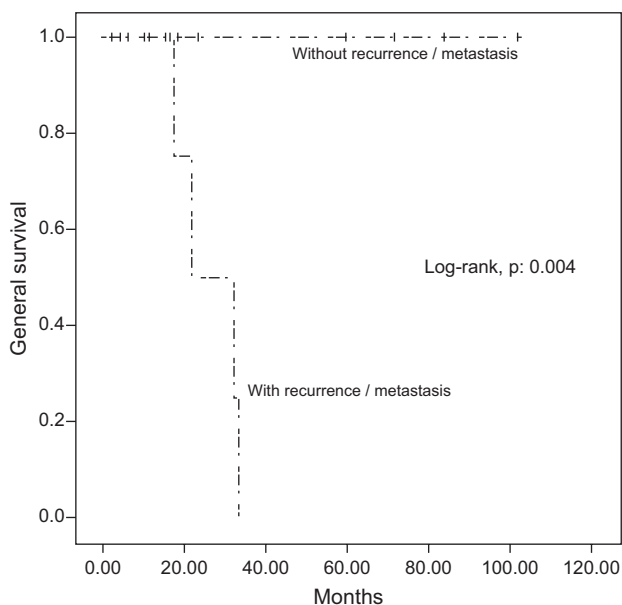


Figure 2. Overall survival in relation with recurrence / metastasis.

country which reported 60 [15] and 58.8 years [16] of age at diagnosis, probably because the patients in those series were younger compared to those in the published literature.

MBC is typically seen as a firm, sometimes ulcerated, painful lump, leading to nipple retraction; yet, patients can rarely present with an axillary mass [9,11,17-19]. The vast majority of patients in our series also presented with a lump with or without skin ulceration.

As male breast does not have lobular elements, the most frequently encountered MBC type is IDC (85-90%) [5]. Although pure ductal carcinoma *in situ* (DCIS) has been reported in 17-26% of the cases in some series, it made up 5% of MBCs [20-22]. The results in our study were similar to those of the literature, with a ratio of 88 and 4% for IDC and DCIS, respectively.

Breast cancer in men is managed in a very similar fashion to that of breast cancer in females. Radical mastectomy was a traditional approach for MBC patients in the past, since the rationale for this approach was the localization of the lesion near the pectoralis major muscle and the tumor being in a more advanced stage compared to women at the time of diagnosis [8,10,12,23]. However, there seems to be no prominent difference in survival and local control rates between RM and MRM. Furthermore, some studies are in favor of MRM or simple mastectomy combined with RT to control the disease. This approach also causes fewer arm and shoulder dysfunction. Therefore, MRM has increasingly replaced RM for the treatment of MBC, like in women [14,24,25].

In our series 18 (72%) patients underwent MRM. Radical surgery was performed in a patient with infiltra-

Table 3. Univariate and multivariate analysis of predictors for disease free survival

Predictors	Univariate analysis p-value	Multivariate analysis p-value
Skin involvement (pos. vs. neg.)	0.058	0.062
Tumor size (<2 vs. ≥2 cm)	0.531	0.194
Lymph node involvement (pos vs. neg)	0.515	0.544

Table 4. Univariate and multivariate analysis of predictors for overall survival

Predictors	Univariate analysis p-value	Multivariate analysis p-value
Recurrence (yes vs. no)	0.0040	0.216
Skin involvement (pos vs. neg)	141	172
Tumor size (<2 vs. ≥2 cm)	0.984	0.553
Lymph node involvement (pos vs. neg)	0.166	62

tive ductal cancer involving the chest wall. One patient with DCIS underwent simple mastectomy. BCS+SLNB and ALND were performed in 2 cases and BCS+SLNB in one patient. Salvage mastectomy was performed in 2 patients with stage IV disease (liver and bone metastases), and the patients died after 20 and 33 months, respectively, from the appearance of disease dissemination.

Although it has been demonstrated that SLNB could be successfully performed in men with breast cancer [23] it is not routinely performed and is limited to selected patients. In our study, SLNB was carried out successfully in 14 patients and nodal involvement was found in 10 (71.4%) of them. Frequently, breast cancer is diagnosed in men at an advanced stage, making SLNB inappropriate, but still a considerable proportion of patients present with clinically negative axilla, therefore making them candidates for a less invasive method of axillary staging. Gentilini et al. reported that 32 of 75 patients (42%), underwent SLNB, and 26 (34%) had negative SLNB and were spared an unnecessary axillary dissection [26].

Axillary lymph node metastasis has been reported with a frequency of 55% in several series with MBC. This ratio was 60% in our study and was consistent with the MBC literature. With the administration of systemic therapy or RT in patients with axillary lymph node involvement, better survival results have been obtained compared with patients who did not receive these treatments [9-11]. In our series, of the 25 patients with adjuvant treatment, chemotherapy was administered to 21 (84%) of them and adjuvant RT plus chemotherapy to 4 (16%) patients. HER-2 positivity was diagnosed in 2

out of the 17 tested patients (12%), which is similar with previous reports [26,27]. Both of these 2 patients with HER-2 positive tumor were given adjuvant trastuzumab (Table 2).

ER positivity is more frequent in MBC compared with FBC [28]. In different studies, ER and PR positivity in MBC was reported as 75-93% [9,28-30]. In our study, receptor analysis yielded a meaningful result in 20 patients. Of them, 75% were ER(+), while 50% were PR(+). As MBC is hormone-receptor positive in a high number of patients, there are several studies advocating that hormonotherapy should be prescribed as adjuvant therapy and the other adjuvant therapies should be reserved for larger tumors and cases with axillary lymph node involvement [31]. The response of MBC to hormonotherapy and ablative treatment is better than that of FBC [9,32]. Tamoxifen has been shown to improve survival in men with stage II and operable stage III disease [1,11]. In our cohort, all patients with ER(+) and PR(+) received adjuvant hormonotherapy (Table 2).

The developmental pattern of recurrence and metastasis in MBC is similar to those of FBC. In decreasing order, MBC most frequently metastasizes to bone, lung and brain. Isolated metastases are best treated with excision or RT. Systemic treatment options include ablative or additive hormonal therapies and chemotherapy [10,11,13,33,34]. In our series, local recurrence and distant metastasis developed in 1 and 4 patients, respectively. The patient with local recurrence was treated with MRM, chemotherapy, hormonotherapy and RT before the appearance of recurrence, and he received chemotherapy and hormonotherapy (he was receptor-positive) following local excision. Distant metastases occurred in a median of 26.7 months after initial diagnosis. The patients with bone metastasis were treated with palliative RT, hormonotherapy and bisphosphonate, whereas chemotherapy and hormonotherapy were administered to patients with liver metastasis.

Guinee et al. have shown that clinical axillary lymph node involvement as well as clinical tumor size had a role on prognosis in their study comprising 335 cases [35]. In men, skin and chest wall involvement and ulceration have been reported more frequently than in women with breast cancer; however, they had no impact on prognosis in multivariate analysis [9]. No statistically significant difference was found in DFS and OS in cases with skin involvement.

Men with breast cancer have a poorer survival than women with breast cancer. While some investigators attribute this to a more aggressive biologic behavior of MBC, a more sound explanation is the rarity of MBC and its diagnosis at more advanced stages [19,36]. In our series, 5-year OS was 52.5% and 5-year DFS 49%.

Stage III or IV were confirmed in 64% of our patients. Our results were better compared with other studies [20,22], and were similar with a very recent Chinese retrospective study [14].

Our study has several shortcomings. First, it is retrospective in nature. Second, it has small sample size and moreover, only two-thirds of our cohort had an adequate follow-up time. Third, it is not homogeneous in terms of therapeutic approaches. The rarity of MBC and the lack of standardized treatment guidelines mainly cause these limitations in most of the studies on MBC, as in our study. However, the increasing number of reports from large single-institution series describing the natural history and outcomes of MBC suggests that prospective clinical trials and collaborative laboratory research are potentially feasible.

In conclusion, MBC is a rare but important oncological problem. We reported 15-year experience with our 25 patients with MBC. In the present study, SLNB rate was higher (56%) compared to published studies [26,37] and lymph node involvement was found in 71.4% of these patients. Nowadays MBC is treated in many respects like postmenopausal FBC. OS has improved. Large cooperative studies are needed using strict clinical and laboratory criteria to advance the understanding of this disease, as well as to identify the most effective treatment approaches.

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