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ORIGINAL ARTICLE

Male Breast Cancer: 37-Year Data Study at a Single Experience Center in Turkey

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Purpose: The aim of this study is to evaluate the effects of prognostic factors on the overall survival (OS) and locoregional control (LC) among male breast cancer (MBC) patients treated at Cerrahpasa Medical School Hospital, along with a review of the related literature. **Methods:** The data of 86 patients treated for MBC from 1973 to 2010 are retrospectively reviewed. Patient demographics and clinical information, including the date of diagnosis, treatment, clinical course, and the date and causes of death are routinely recorded. **Results:** Median follow-up was 66 months. Isolated local-regional recurrence and distant metastases were observed in 15 (17.4%) and 24 (34.1%) of the cases, respectively. The 5-year OS rate was 65.8%; the disease-free survival rate was 72.4%, and the LC rate was 89.7%. The prognostic factors influencing local relapse were the T stage ($p=0.002$) and the chest wall muscular invasion ($p=0.027$) in the univariate analysis. The prognostic factors influencing OS were the presence of a positive axillary lymph node ($p=0.001$) and the T stage ($p=0.001$) in the univariate analysis. The T stage ($p=0.008$) and node (N) stage ($p=0.038$) were significant prognostic factors for OS in the multivariate analyses. Also, the T stage ($p=0.034$) was found to be significant for LC. **Conclusion:** We found that only the tumor size and lymph node status were independent prognostic factors for survival. In addition, only the tumor size was an independent prognostic factor for locoregional relapse. Modified radical mastectomy and conservative surgical procedures had similar outcomes for LC.

Key Words: *Breast neoplasms, Male, Outcome, Prognosis, Therapeutics*

INTRODUCTION

Male breast cancer (MBC) is rare, accounting for less than 1% of all breast cancer and less than 1% of all cancer cases, with less than 0.5% of all cancer deaths in men, annually [1].

MBC usually presents as a firm, painless mass along with palpable axillary nodes, nipple retraction, and ulceration of the skin at presentation. MBC is usually located in the subareolar region, but can also be seen in the upper outer quadrant [2]. As is the case with women, the left breast is involved more predominantly than the right breast, and approximately 1% all of cases are bilateral [2]. Approximately 90% of MBC are invasive ductal carcinomas. Lobular histology is rare, accounting for only 1.5% of MBC [2]. MBC has high rates of hormone-receptor expression; approximately 90% express oestrogen receptor (ER), and 81% express progesterone receptor (PR) [2]. Tumor size and lymph node involvement are important prognostic factors in MBC, as is for female breast cancer [2]. There are no prospective randomized trials comparing the efficacy of different treatment options for MBC. The standard surgical approach for localized MBC is a modified radical mastectomy (MRM), but as with women, retrospective studies suggest that equal effectiveness can be achieved with a radical mastectomy, MRM, or simple mastectomy in terms of local recurrence and survival [3,4]. There is limited data regarding the indications for postmastectomy radiation therapy (RT) in men treated for breast cancer; the recommendation is to follow the same guidelines as for women. Postmastectomy RT appears to reduce locoregional recurrence in MBC; however, the influence on survival is unknown [5,6]. Many retrospective studies have evaluated the role of adjuvant hormonal therapy, and these studies have revealed that most male patients can benefit from adjuvant tamoxifen in terms of recurrence and death [7,8].

Adjuvant chemotherapy has been used to treat male and female patients with substantial risks of recurrence and death from breast cancer. Whereas the data supporting adjuvant

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chemotherapy in women is strong, there is little information on the effectiveness of adjuvant chemotherapy for MBC [7].

The aim of this study is to evaluate the effects of prognostic factors on overall survival (OS) and locoregional control (LC) among MBC patients treated at our institution over a 37-year period as weel as to review the related literature.

METHODS

Study design and population

The data of patients treated for MBC at the Istanbul University Cerrahpasa Medical Faculty and Hospital from 1973 to 2010 are retrospectively reviewed. Patient demographic and clinical information including the date of diagnosis, treatment, clinical course, and the date and causes of death are routinely recorded. The staging was made according to the American Joint Committee on Cancer (7th edition). Immunohistochemical method was used in the examination of estrogen and progesterone receptors. Antigen retrieval was made using high-pressure heat. Monoclonal mice antiestrogen protein antibody (Neomarks, Clone SP1, in 1/400 dilution) and monoclonal mice antiprogesterone protein antibody (Novo Castra, 1A6, in 1/100 dilution) were administered. Intranuclear staining in the cells was expressed as the percentage of stained cells; ≥1% staining was defined as positive. The evaluation of c-erbB-2 positivity was based on the guidelines of American Society of Clinical Oncology (College of American Pathologists) [9].

Approval from the local ethics committee (IRB approval number is B.30.2.İST.0.30.11.00/9175) was obtained prior to the study, along with the informed consent of the patients or their next of kin.

Study procedures

The following information was retrieved from patient charts: medical history, physical examination, patients' age at diagnosis, laterality, tumor grade (low, intermediate, or high), tumor histology, and tumor size. In addition, chest wall muscular involvement, nipple, breast, or skin invasion, stage, axillary lymph node status, and hormone receptor expression were noted. The surgical procedures, adjuvant chemotherapy, radiotherapy, and hormonal therapy applied to patients were also documented.

Study endpoints

The OS rate, disease-free survival (DFS) rate, and local LC rate were the primary endpoints in this study. These rates were calculated from the date of the diagnosis. The LC was defined as the time until locoregional relapse. DFS was defined as the time until disease recurrence or progression, whichever occurred first. OS was defined as the time of death from any cause.

Statistical analysis

Categorical and continuous variables were summarized using descriptive statistics (e.g., median, range, frequency, and percentage), and were compared using the chi-square or Fisher's exact test and Mann-Whitney U tests, respectively. The LC, DFS, and OS rates were estimated by the Kaplan-Meier method. The effects of clinical variables on the LC and OS were assessed by the univariate analysis. The log-rank test was used to compare the curves for the univariate analysis. All variables that were significant in the univariate analysis were entered into a multivariate analysis. In backward, stepwise fashion, the significant univariate variable with the least significance was eliminated from the multivariate model. This process was continued until only the significant variables remained. We performed a multivariate analyses using a Cox proportional hazard model in order to calculate the hazard ratio as well as the 95% confidence intervals. The statistical level of significance was defined as $p<0.05$. All analyses were performed using the SPSS version 15.0 (SPSS Inc., Chicago, USA) software.

RESULTS

Treatment modalities and response

All but two patients underwent surgery. The most common type of surgical treatment procedure was MRM (71%). Two patients (2%) underwent simple mastectomy. Eleven patients (13%) underwent lumpectomy axillary dissection (breast conservative surgery). Of all patients, 64 (74.4%) received adjuvant radiotherapy for the whole breast as well as for peripheral lymphatics, due to the high risk factors. The median total dose was 50 Gy with a daily fraction dose of 2 Gy. Adjuvant chemotherapy and hormonal therapy were used in 45 (51%) and 28 (32%) patients, respectively. The most common chemotherapy regimen was AC (doxorubicin, cyclophosphamide). The treatment modalities applied to patients with MBC along with stages of the disease are shown in Table 1.

Clinical and pathological characteristics

Data from 86 patients were retrieved. The median follow-up period was 66 months (range, 6-192 months). For the censored patients, the follow-up period was 98 months (range, 24-201 months). The majority of tumors occurred in the central (50%) and upper outer quadrant (20%). A hard, nontender mass was the main symptom of presentation in 88% of the patients, followed by nipple retraction in 10% of the cases. The median

age at presentation was 62 years (range, 35-90 years). The clinical characteristics of the patients are presented in Table 2.

Survival and univariate analysis

All 86 patients were enrolled in our survival analysis study, with a median follow-up duration of 66 months (range, 6-192 months). Isolated local-regional recurrence and distant metastases were observed in 15 (17.4%) and 24 (34.1%) cases, respectively. The 5-year OS rate was 65.8%, while the DFS rate was 72.4%. The 5-year survival rates were as follows: 91.7% for patients with stage I; 73.7% with stage II; and 41.1% with stage III. Regarding time until diagnosis, four patients had metastasis presentation, and all stage IV patients died by the second year (Figure 1). The LC rate was 89.7%. The most common locoregional relapses were in the chest wall (47%), supraclavicular area (40%), and axillar area (27%). The prognostic factors influencing local relapse were the T stage ($p=0.002$) and chest wall muscular invasion ($p=0.04$) in the univariate anal-

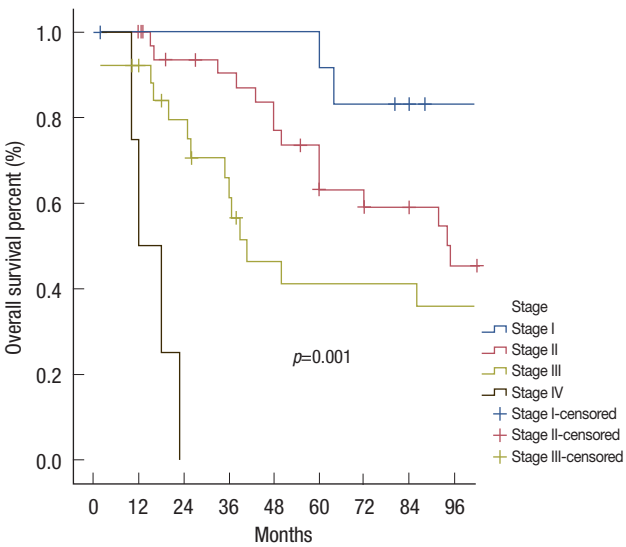

Figure 1. Overall survival in 86 patients with male breast cancer based on each stage.

Table 1. The treatment modalities applied to patients with MBC along with stage of disease

	Stage I No. (%)	Stage II No. (%)	Stage III No. (%)
Surgical procedure			
Modified radical mastectomy	10 (72)	25 (74)	26 (100)
Simple mastectomy	2 (14)		
Lumpectomy axillary dissection	2 (14)	9 (26)	
Adjuvant treatment			
Radiotherapy	9 (64)	32 (94)	24 (92)
Chemotherapy	5 (35)	19 (55)	21 (80)
Hormonal therapy	8 (57)	11 (32)	9 (35)

MBC = male breast cancer.

Table 2. The clinical characteristics of the patients and univariate analysis for locoregional control rate and overall survival

	No. (%)	5-yr LC (%)	*p*-value	5-yr OS (%)	*p*-value
Age at diagnosis (yr)*	62 (35-90)		NS		NS
50<	12 (14)	90.1		66.2	
50-60	22 (25.5)	90.2		66.4	
61-70	32 (37.2)	89.8		65.3	
>70	20 (23.3)	89.2		65.5	
Histology			NS		NS
Ductal	75 (86.8)	89.9		65.9	
Lobular	2 (2.4)	89.2		65.5	
Ductal and lobular	1 (1.2)	89.8		65.7	
Mucinous	1 (1.2)	89.1		65.1	
Papillary	2 (2.4)	89.2		65	
Medullary	2 (2.4)	89.3		65.8	
Unknown	3 (3.6)	89.2		66	
Grade			NS		NS
I	8 (9.3)	91.2		67	
II	30 (34.9)	90.1		66.2	
III	16 (18.6)	89.2		65.1	
Unknown	32 (37.2)	89.6		65.6	
Stage†			0.002		0.001
I	14 (16.3)	100		91.7	
II	34 (39.5)	95		73.7	
III	26 (30.2)	76		41.1	
IV	4 (4.7)	-		0	
Unknown	8 (9.3)	72.2		52.4	
Tumor size (cm)			0.002		0.001
≤1	4 (4.5)	100		94	
>1-2≤	34 (38.6)	95		74	
>2-5≤	39 (44.3)	84		68	
>5	9 (10.2)	68		48	
Unknown	2 (2.2)	68.6		54.3	
Lymph node status			NS		0.001
Negative	36 (41.9)	91.1		87.5	
Positive	34 (38.5)	88.3		44	
Unknown	16 (18.6)	87.8		48.2	
Oestrogen receptor			NS		NS
Negative	16 (18.6)	88.2		63.1	
Positive	37 (43)	91.2		67.8	
Unknown	33 (38.4)	88.4		66.1	
Progesterone receptor			NS		NS
Negative	19 (22.1)	87.3		64.1	
Positive	35 (40.7)	91.2		67.2	
Unknown	32 (37.2)	89.4		65.2	
c-erbB-2 receptor			NS		NS
Negative	21 (24.4)	91.4		66.4	
Positive	2 (2.6)	88		64.1	
Unknown	62 (72)	89		64.8	
Laterality			NS		NS
Left	44 (51.2)	90		66	
Right	42 (48.8)	89		65.2	
Bilateral	2 (2.3)	89.4		65	
Chest wall muscular involvement			0.041		NS
Present	9 (10.4)	81		63.8	
Absent	75 (87.2)	93		66.8	
Unknown	2 (2.4)	84		65.1	

LC = locoregional control; OS = overall survival; NS = not significant.
*Median (range); †American Joint Committee on Cancer (7th edition).

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Table 3. Multivariate analysis for LC rate and OS

	LC		OS	
	p-value	HR (95% CI)	*p*-value	HR (95% CI)
Tumor size (cm)				
1<	0.034	1	0.008	1
1-1.9	0.005	1.6 (1.27-2.27)	0.048	1.2 (1.12-1.33)
2-5	0.023	4.3 (1.2-6.71)	0.04	1.32 (1.09-1.52)
>5	0.011	5.5 (2.28-6.61)	0.3	1.5 (0.67-3.97)
Lymph node status				
Negative			0.038	1
Positive				1.8 (1.23-4.81)

LC = locoregional control; OS = overall survival; HR = hazard ratio; CI = confidence interval.

ysis (Table 2). In the current study, the LC rate was 90.8% and 87.6% for patients who underwent MRM and lumpectomy axillary dissection, respectively. There was no statistical significance between the two groups. Patients who underwent an MRM due to a local relapse showed no improvement when compared with those who underwent conservative surgery (lumpectomy axillary dissection). The median time of distant recurrence was 48 months (range, 2-192 months). The most common distant recurrences were 60% bone and 29% lung, respectively. During the 37-year follow-up, contralateral second primary breast cancer was found in 2 (2.3%) of the 86 patients in the 4th and 7th year of follow-up, respectively.

The prognostic factors influencing OS were the presence of a positive axillary lymph node ($p=0.001$) and the T stage ($p=0.001$) in the univariate analysis. We did not determine the effects of age, tumor laterality, tumor histology, surgical procedure, tumor grade, estrogen receptor expression, progesterone receptor expression, and analyses on survival in the univariate analysis. The effects of clinical variables on the 5-year OS rate are given in Table 2.

Multivariate analysis for locoregional control and overall survival

Based on the results from the univariate analyses, we performed multivariate analyses using a Cox proportional hazard model (Table 3). The T stage ($p=0.008$) and node (N) stage ($p=0.038$) were significant prognostic factors for OS in the multivariate analyses. Also, the T stage ($p=0.034$) was found to be significant for LC.

DISCUSSION

In our cohort, the median age for males with MBC was younger than those in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute [2]. Previously, some studies had shown an older median age for MBC compared to female breast cancer [1]. The median age in the current study was 62, whereas it was 67 years in a prior study [1]. Several studies from Sweden and Denmark suggested that men tended to be older than women at the time of diagnosis [10,11]. In the current study, a hard, non-tender mass was the main symptom of presentation. An earlier study revealed that the clinical presentation rate for the same type of mass for MBC was 75% to 95%. MBC has different biological features than female breast cancer. Previous studies have reported that 64.0% to 93.4% of men with breast carcinoma had an invasive ductal histology [2,12], and only 1.5% were histologically lobular in nature [2]. However, in female breast cancer, 12% are lobular [2]. Most cases of MBC (86.8%) are invasive ductal carcinomas, with only 2.4% being lobular in our series. In some studies, most of the MBC tumors were of high grade [13], whereas other series have predominantly demonstrated grade 1 and grade 2 [14,15]. In the present series, the majority of tumors in MBC had low and intermediate grades. In the previously reported series, the ER positivity rate was approximately 64% to 90% and PR positivity rate was between 70% and 81% in MBC [2,16,17]. In the present study, 70% of all patients had ER-positive and 65% had PR-positive disease. The c-erbB-2 status with immunochemistry has been determined in only 24 patients. Among these patients, two (8%) had the c-erbB-2 positive disease. A prior study of 75 patients found that only 5.3% of MBC patients overexpressed c-erbB-2. Similarly, Muir et al. [18] and Bloom et al. [19] discovered that only 1.7% overexpressed c-erbB-2, whereas 15% of MBC were c-erbB-2-positive in the European Institute of Oncology series [20].

Most predictors have been reported to affect the prognosis in MBC patients, with the tumor stage and axillary nodal status shown to be the most important independent predictors of OS [21]. Giordano et al. [2] found the 5-year OS rates of 78% for MBC patients with stage 1, 67% with stage II, 40% with stage III, and 19% with stage IV.

The 5-year OS rate was 76% for patients with a node negative disease and 54% for those with a node positive disease [2]. The tumor grade has been shown to affect the prognosis significantly in the univariate analysis; however, the significance of this association is not noted in the multivariate analysis [2,22]. In the current study, the 5-year OS for patients with a node negative disease was 87.5% and 43.8% for those with a node positive disease; however, the tumor grade was not shown to affect the prognosis in the univariate analysis. Several studies have noted that ER and PR positivity predicted better OS in the univariate analysis; yet, this difference was not significant after the adjustments for the tumour stage and axillary lymph node status, in the multivariate analysis [2,23]. The overex-

pression of c-erbB-2 has been associated with shortened survival in some studies [24]; however, others have failed to demonstrate a similar correlation [25,26]. In our study, neither ER nor PR was shown to affect the prognosis in the univariate analysis. The principles of management for MBC have been extrapolated from the treatment of female breast cancer. Surgery is the basis of disease control. In our study, most of the patients were applied MRM (76%) and only 11% of the remaining underwent breast conservative surgery (lumpectomy axillary dissection). In the current study, as has been reported in previous studies, there was no significant difference in patients who underwent MRM compared with a conservative surgical procedure [3,4]. In this study, 64 (74.4%) patients received adjuvant radiotherapy. The 5-year local relapse rate was 11.3%, and the most common local relapse sites were the chest wall and supraclavicular areas. Only the T stage was an independent prognostic factor for locoregional relapse. Perkins et al. [27] determined that for 142 patients who received RT, 18% had a locoregional relapse, with the most common site also being the chest wall and supraclavicular areas. They revealed that the margin status, the tumor size, and number of involved axillary lymph nodes were the predictors for locoregional relapse. There are a few small, retrospective studies which describe the use of postmastectomy radiation in MBC. In these studies, between 3% and 100% of the patients received RT, and the local recurrence rates ranged from 3% to 29% [28,29]. Adjuvant chemotherapy and hormonal therapy were used in 45 (51%) and 28 (32%) patients, respectively. We did not evaluate the effects of hormonal treatment and chemotherapy for survival, because for the patients who received these adjuvant treatments, there was no homogeneity between the different stages, and there further, were not enough patients who received these treatments. In a SEER database review, which included 4,873 MBC cases diagnosed between 1973 and 2003, there was a 1.9% incidence of the second primary MBC [30]. We also determined a 2.3% risk for contralateral breast cancer in this 37-year follow-up study.

The main limitations of this study are its retrospective design and the limited number of cases. Also, there was no homogeneity based on adjuvant chemotherapy and hormonal therapy. Therefore, we did not evaluate their effects on survival.

In conclusion, we found that only tumor size and lymph node status were independent prognostic factors for survival. This agrees with the previous findings of the SEER database study [3]. However, ER and PR positivity along with the tumor grade had no effect on survival in the univariate analysis. Only the tumour size was an independent prognostic factor for locoregional relapse; MRM and conservative surgical procedures had similar outcomes for LC.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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