RESEARCH ARTICLE

Male Breast Cancer: 20 Years Experience of a Tertiary Hospital from the Middle Black Sea Region of Turkey

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Abstract

Background: Male breast cancer is a rare neoplasm, and its treatments are based on those of female breast cancer. This study aimed to analyze 20 years of male breast cancer clinical characteristics and treatment results from the Middle Black Sea Region of Turkey. Materials and Methods: A retrospective analysis of 16 male breast cancer patients treated in our tertiary hospital between 1994 and 2014 was performed. Epidemiologic data, tumor characteristics, and treatments were recorded and compared with 466 female breast cancer ((premenopausal; n = 230) + (postmenopausal n = 236)) patients. The 5-year disease-free and overall survival rates were calculated. Results: Male breast cancer constituted 0.1% of all malignant neoplasms in both sexes, 0.2% of all malignant neoplasms in males, and 0.7% of all breast cancers. The mean patient age in this study was 59.8 ± 9.5 (39-74) years. The mean time between first symptom and diagnosis was 32.4 ± 5.3 (3-60) months. Histology revealed infiltrative ductal carcinoma in 81.3% of patients. The most common detected molecular subtype was luminal A, in 12 (75%) patients. Estrogen receptor rate (93.8%) in male breast cancer patients was significantly higher than that in female breast cancer (70.8% in all females, p = 0.003; 68.2% in postmenopausal females, p = 0.002) patients. Most of the tumors (56.3%) were grade 2. Tumor stage was T4 in 50% of males. The majority (56.3%) of the patients were stage III at diagnosis. Surgery, chemotherapy, radiotherapy and endocrine-therapy were applied to 62.5%, 62.5%, 81.2% and 73.3%, respectively. Loco-regional failure did not occur in any of the cases. All recurrences were metastastic. The 5-year disease-free and overall survival rates in male breast cancer patients were 58% and 68%, respectively. Conclusions: Tumors found in male breast cancer patients were similar in size to tumors found in females, but they advanced to T4 stage more rapidly because of the lack of breast parenchymal tissues. The rate of estrogen receptor expression tended to be higher in male breast cancer patients than in female breast cancer patients. Metastasis is the most important problem in initially non-metastatic male breast cancer patients.

Keywords: Epidemiology - male breast cancer - pathology - treatment outcome - Turkey

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Introduction

Male breast cancer (MBC) is a rare neoplasm (Zygogianni et al., 2012), but the incidence of MBC is increasing and shows geographical variations. The rate of MBC is less than 0.5/100,000 in Japan, and is approximately 1/100,000 in Europe and North America, but is more frequent in Egypt and Zambia (Giordano et al., 2004; Fentiman, 2009). According to United States (US) statistics, MBC accounts for 0.1% of all malignant neoplasms in both sexes, 0.2% of all malign neoplasms in males and 0.9% of all breast cancers (Siegel et al., 2012).

In Turkey, 1-1.7% of all breast cancer cases are MBC (Haydaroglu et al., 2005; Ozmen, 2014), and surgery is the major treatment. Adjuvant chemotherapy (ChT), endocrine-therapy (End-T) and radiotherapy (RT) are applied based on treatment experience in female breast cancer (FBC) cases due to the rarity of MBC. However, MBC shows some biological differences from FBC (Giordano et al., 2004). Due to the rarity of MBC, prospective randomized trials cannot be performed, and our knowledge of MBC is derived from case reports and small retrospective trials.

The aim of this study was to evaluate MBC patient features and treatment results from a tertiary hospital in the Middle Black Sea Region of Turkey.

Materials and Methods

In this retrospective study, the files of 15,143 cancer patients were examined, all of whom had been treated in our radiation oncology department between January 1994 and April 2014. During this time period, 8080 male cancer patients, 2342 breast cancer patients, and 16 MBC patients

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were identified. The 16 MBC patients were enrolled in this study along with 466 FBC (n=230 premenopausal; n=236 postmenopausal) patients for which we had complete data. All patients were from the Middle Black Sea Region in Turkey.

Patient's medical records were reviewed for this study. The elapsed time between symptoms and diagnosis, age at diagnosis, family history, physical examination, laterality, tumor localization, tumor size, lymph node status, histopathologic type, hormone receptor (HR) status, Scarff-Bloom-Richardson (SBR) tumor grade, primary breast cancer diagnosis date, surgery type, adjuvant RT technique and applied doses, adjuvant ChT regimens, relapse date, metastasis date, metastasis localization, and date of death or last follow-up date were documented. Human epidermal growth factor 2 (HER-2) receptor status was re-analyzed for all patients. Of these, age, grade, tumor size, tumor stage, HR status, HER-2 receptor status and molecular subtypes were compared between MBC, FBC, and post-menopausal FBC patients. All patients were re-staged according to the 7th edition (2010) of the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) staging system for breast cancer. Survival was categorized into two types: disease-free survival (DFS) and overall survival (OS). DFS was defined as the time from the date of surgery to the date of the first confirmed loco-regional (LRF) or distant failure (DF), and OS as the time to death or the last patient follow-up. The Kaplan-Meier method was used to estimate DFS and OS. The long-rank test was used to compare data from males and females. Chi-squared and independent t-tests were used to compare categorical variables and continuous variables between groups, respectively. p-Values <0.05 were considered to indicate significance. All calculations were performed using SPSS, version 16.0 (SPSS, Inc., Chicago, IL, USA).

Results

In the present study, 0.1% of total malignant neoplasms in both sexes, 0.2% of all malignant neoplasms in males, and 0.7% of all breast cancers were MBC. Mean follow-up time was 53±10.8 (11-133) months. The mean age was 59.8±9.5 (39-74) years. The most common presenting symptoms of MBC were a subareolar lump in eight patients (50%), an upper outer quadrant lump in three patients (18.7%), a nipple wound in two patients (12.5%), bloody nipple discharge in one patient (6.3%), both a subareolar lump and bloody nipple discharge in one patient (6.3%) and axillary lymphadenopathy in one patient (6.3%). The mean elapsed time between first symptom and diagnosis was 32.4±5.3 (3-60) months. The tumor was left-sided in 10 (62.5%) patients. There was no bilaterality. The tumor was localized in the subareolar region in 13 (81.3%) patients, and in the upper outer quadrant in the remaining three (18.7%) patients. After physical examination and axillary ultrasonography (USG), 11 (68.8%) patients were found to have positive axillary lymph nodes. None of the patients had a family history of MBC. Table 1 shows the clinical characteristics of MBC patients. Pathological analysis of the specimens with tru-

Table 1. Patients' Clinical Characteristics

	n (%)
Histology	
Invasive ductal carcinoma	13 (81.3)
Intraductal papillary carcinoma	3 (18.7)
Grade	
I	3 (18.7)
II	9 (56.3)
III	4 (25)
Estrogen receptor	
Positive	15 (93.7)
Negative	1 (6.3)
Progesterone receptor	
Positive	11 (68.8)
Negative	5 (31.2)
HER-2	
Positive	4 (25)
Negative	12 (75)
Moleculer subtypes	
Luminal A	12 (75)
Luminal B	3 (18.7)
HER2 overexpressing	1 (6.3)
Basal like (Triple negative)	0 (0)
Tumor size	
≤ 2 cm	6 (37.5)
2 – 5 cm	7 (43.8)
≥ 5 cm	3 (18.7)
Tumor stage	
T1	4 (25)
T2	3 (18.7)
T3	1 (6.3)
T4	8 (50)
Lymph node disease*	
Negative	5 (31.2)
Positive	11 (68.8)
N1	6 (37.5)
N2	4 (25)
N3	1 (6.3)
Metastasis (preoperative)	
M0	13 (81.3)
M1	3 (18.7)
Surgery (n = 16)	
Yes	10 (62.5)
Modified radical mastectomy	6 (60)
Tumorectomy	3 (30)
Simple mastectomy	1 (10)
No	6 (37.5)
Axillary dissection (n =16)	
Yes	7 (43.7)
No	8 (50)
Biopsy only	1 (6.3)
AJCC stage (n = 16)	
I	3 (18.7)
II	3 (18.7)
III	9 (56.3)
IV	1 (6.3)
Curative/adjuvant RT (n = 16)	
Yes	10 (62.5)
No	6 (37.5)
Chemotherapy (n = 16)	
Yes	13 (81.3)
No	3 (18.7)
Tamoksifen (n = 15, ER positive)	
Yes	11 (73.3)
No	4 (26.7)

*Clinical or surgical

cut biopsy revealed infiltrating ductal carcinoma in 13 (81.3%) patients. According to SBR classification, most of the tumors (56.3%) were grade two. The estrogen receptor (ER) was positive in 15 (93.7%) patients, and HER-2 was positive in 4 (25%) patients. The most common detected molecular subtype was luminal-A in 12 (75%) patients. Metastasis was detected in three (18.7%) patients at diagnosis.

Table 2 compares MBC and FBC ((premenopausal; n=230) + (postmenopausal; n=236)) patients. There was statistically significant difference between age (59.8 *vs* 50.8; p=0.003), ER positivity (93.8% *vs* 70.8%; p=0.03), and tumor stage (p<0.0001) between MBC and FBC. Additionally, ER positivity rate (93.8% *vs* 68.2%; p=0.02) and tumor stage (p<0.0001) were significantly different when compared to post-menopausal FBC.

Table 3 presents the treatment summary of all MBC patients. Surgery was performed in 10 (62.5%) patients. The remaining six (37.5%) patients only underwent biopsy due to metastasis in two patients (12.5%), and chest wall fixation in four (25%) patients. Modified radical mastectomy (MRM) was the most common (60%) preferred surgery type. The mean tumor size was 33.5±17.4 (8-70) mm. Fifty percent of tumors were in the T4-stage; however, 62.5% of T4 tumors were smaller than 5 cm. Axillary dissection (AD) was performed in seven (43.7%) patients. Treatment decision was based on clinical examination and USG results from the axillary region in eight (50%) patients. The mean number of dissected lymph nodes was 18.1±3.8 (8-35). In seven cases of axillary dissection, lymph node metastasis (pN(+)) was detected in five patients. After all axillary evaluations, node status was positive in 11 (68.8%) patients, and extranodal extension was positive in 1 of 5 pN(+) patients. The majority (56.3%) of patients were stage III.

End-T was administered to 11 (73.3%) of 15 ER (+) patients, and all received tamoxifen (TMX). Of these, one (6.7%) patient was given End-T as a neo-adjuvant therapy to shrink the tumor. In this patient (AJCC stage=T4N2M0), the lymph nodes regressed completely, but the primary tumor did not respond. The remaining four ER (+) patients did not receive TMX due to adverse effects. TMX was used for a mean time of 34.9±7.8 (9-84) months. ChT was administered to 13 (81.3%) patients. ChT was the primary treatment in six (37.5%) patients, was used as a neo-adjuvant therapy in four (25%), and was used due to metastasis in two (12.5%) patients. The ChT regimens administered to the patients were: adriamycin + cyclophosphamide (AC) in four patients (30.7%), cyclophosphamide + methotrexate + fluorouracil (CMF) in two patients (15.4%), fluorouracil + adriamycin + cyclophosphamide (FAC) in two patients (15.4%), fluorouracil + epirubicine + cyclophosphamide (FEC) in two patients (15.4%), adriamycin + docetaxel (AT) in one patient (7.7%), epirubicine + docetaxel (ET) in one patient (7.7%), and epirubicine + cyclophosphamide (EC) in one patient (7.7%).

RT was given to 10 (62.5%) patients. RT was used in MBC patients as an adjuvant therapy in five patients (50%), as a curative treatment in four patients (40%), and as a palliative treatment (breast irradiation due to pain and bleeding) in one patient (10%). The mean radiation

Table 2. Comparison of Male and Female Breast Cancer Patients

	All Females (n=466)	p	Male (n=16)	p	Postmenopausal Females (n=236)
Age		0.003		0.855	
Mean ± SD	50.8 ± 11.7		59.8 ± 9.5		54.4 ± 8.8
Tumor size (cm)		0.493		0.493	
Mean ± SD	3.7 ± 2.0		3.3 ± 1.7		3.6 ± 1.7
Tumor stage (%)		0.0001		0.0001	
T1	15		25		12.7
T2	63.7		18.7		66.1
T3	19.5		6.3		19.1
T4	1.8		50		2.1
Grade (%)		0.721		0.817	
G1	12		18.8		13.1
G2	60.5		56.2		60.2
G3	27.5		25		26.7
ER (%)		0.033		0.022	
Negative	29.2		6.2		31.8
Positive	70.8		93.8		68.2
PR (%)		0.259		0.136	
Negative	42.7		31.2		48.7
Positive	57.3		68.8		51.3
HER2 (%)		0.395		0.853	
Negative	68.2		75		72.9
Positive	31.8		25		27.1
Moleculer subtypes (%)		0.219		0.193	
Luminal A	52.6		75		54.7
Luminal B	19.5		18.8		14.4
HER2	15.7		6.3		18.2
Triple negative	12.2		0		12.7

Table 3. Stage, Treatment, Recurrence and Survival Details of 16 Patients

Stage [Treatment]	Recurrence/metastasis [time]	Survival [cause of death]
1-[T1N1M0] [MRM+AD] + [4×AC] + [Adjuvant RT] + [TMX]	No	36 months [alive]
2-[T2N1M1] [6×AT] + [TMX] + [Palliative capecitabine]	Lung + bone metastasis [at diagnosis]	23 months [dead /breast cancer]
3-[T1N0M0] [Tumorectomy] + [Adjuvant RT] + [TMX]	No	121 months [alive]
4-[T4N0M0] [4×ET] + [Curative RT] + [TMX]	Bone metastasis [12 months]	133 months [alive]
5-[T4N2M0] [MRM+AD] + [4×AC] + [Adjuvant RT] + [TMX]	Lung + bone [93 months]	101 months [dead/breast cancer]
6-[T4N2M0] [TMX] + [Curative RT] + [TMX]	No	17 months [follow-up loss]
7-[T1N0M0] [MRM+AD] + [6×CMF]	No	121 months [alive]
8-[T4N2M0] [3×FAC] + [MRM+AD]	Lung + bone [31 months]	50 months [dead/breast cancer]
9-[T4N3M1] [4×FEC] + [palliative breast RT]	Bone + skin [at diagnosis]	12 months [dead/breast cancer]
10-[T4N1M0] [3×FAC] + [Curative RT] + [TMX]	Bone [11 months]	29 months [dead/breast cancer]
11-[T3N1M0] [MRM+AD]	Liver [22 months]	30 months [dead/breast cancer]
12-[T2N1M1] [Tumorectomy] + [4×EC] + [TMX]	Bone [at diagnonsis]	30 months [dead/breast cancer]
13-[T4N2M0] [3×FEC] + [Curative RT] +[3×FEC]	No	12 months [follow-up loss]
14-[T4N0M0] [SM] + [4×AC] + [Adjuvant RT] + [TMX]	No	84 months [dead/heart failure]
15-[T1N0M0] [MRM+AD] + [6×CMF] + [TMX]	Bone [17 months]	54 months [alive]
16-[T2N1M0] [Tumorectomy+AD] + [4×AC] + [Adjuvant RT] + [TMX]	No	11 months [alive]

dose was 54.8±8.1 (50-70) Gy. Four patients that received radiation as a curative treatment were HR (+). Curative RT with sequential TMX achieved complete response in three of four patients. Two of these three patients had received 68 and 70 Gy radiotherapy. In addition, one of these patients had received chemotherapy alone due to patient's refusal of End-T, and a complete response was not achieved. The patient treated with palliative radiation showed no response. This patient was HR (-) and HER-2 (+). No loco-regional recurrence developed in patients treated with curative and adjuvant RT.

All failures were metastases. Metastasis occurred in 6 (46%) of 13 initially non-metastatic MBCs, but in only 72 (15.5%) FBC patients. The most common site of metastasis was bone, which occurred in five (83%) of six MBC patients with metastases. None of the MBC patients developed a carcinoma in the contra-lateral breast. No late toxicity occurred. Five-year DFS and OS rates in MBC patients were 58% and 68%, respectively.

Discussion

A medical papyrus written by Imhotep in ancient Egypt between 3500-2500 BC was found by American Egyptologist Edwin Smith, and this is thought to be the first ever record of breast cancer. Nine patients were described in the papyrus, and all of them were male (Erkin and Ardahan, 2014). In addition, Franciscus Arcaeus (1493-1573) published the first MBC case report in the medical literature (Somerville, 1952).

The reported risk factors for MBC are family history, BRCA-2 mutation, androgen receptor gene mutation, CYP 17 polymorphism, CHECK2 mutation (Li-Fraumeni Syndrome), PTEN mutation (Cowden Syndrome), hereditary non-polyposis colorectal cancer (Lynch syndrome), Kleinfelter's syndrome, low frequency magnetic field exposure, high temperature, exhaust emissions, alcohol, obesity, gynecomastia, higher economic status, chest wall RT, estrogen intake, anti-androgen therapy, prolactine drugs (pituitary prolactinomas), bilateral orchiectomy, undescended testis, mumps over the age of 20 years, and liver damage (Fentiman, 2009; Zygogianni et al., 2012). No risk factors were found in the patients in the present study. As mentioned previously, the rates of MBC in the Middle Black Sea Region of Turkey are similar to US rates. The rate of MBC in all breast cancers was 0.7% in this Turkish region, but previous reports have reported values of 1-1.7% (Haydaroglu et al., 2005; Ozmen, 2014). The reported mean age of MBC patients in Turkey is between 54 and 68.7 years (Gunhan-Bilgen et al., 2002; Atahan et al., 2006). The mean age was 59.8±9.5 years in this study. Young age is a favorable prognostic factor for OS. Median OS in MBC patients under and over the age of

60 was reported to be 50.8 and 22.6 months, respectively (Engin and Unsal, 1993).

The most frequent reported symptoms are a painless subareolar lump, nipple retraction, nipple discharge, ulceration, axillary adenopathy, and pain. (Yildirim and Berberoglu, 1998; Atahan et al., 2006; Reis et al., 2011; Selcukbiricik et al., 2013). A subareolar lump was the first symptom in 50% of the MBC patients in this study. The mean symptom duration was 29 months in the 1940s, but is only 6-10 months today (Fentiman and Fourquet, 2006). The symptomatic period was 32.4±5.3 months in the MBC patients in this study. The late diagnosis of MBC is likely due to the rarity of breast cancer in males; therefore, symptoms are ignored by both patients and physicians (Fentiman and Fourquet, 2006). Gynecomastia, lipoma, epidermal inclusion cysts, intraductal papilloma, abscesses, metastases and sarcoma should be considered during diagnosis (Gunhan-Bilgen et al., 2002; Adibelli et al., 2010). In most cases, the diagnosis is made by triple assessment which in most cases include clinical (physical examination), radiologic (mammography (MMX) and/or USG) and histopathologic (fine needle aspiration (FNA) or core biopsy) evaluations (Fentiman and Fourquet, 2006).

Reported laterality rates are 51.2-64.3% on the left side, 33.3-48.8% on the right side, and 2.3-2.4% bilateral (Engin and Unsal, 1993; Yildirim and Berberoglu, 1998; Atahan et al., 2006; Selcukbiricik et al., 2013). In the patients in this study, tumors were localized on the left side in 10 (62.5%) patients. The majority of breast tissue in males is located in the subareolar region. For this reason, tumors are usually located at this site. Tumor rates in the subareolar region are reported to be 46-88%. The second most common region is the upper-outer quadrant. (Gunhan-Bilgen et al., 2002; Atahan et al., 2006; Selcukbiricik et al., 2013). In the present study, 13 (81.3%) patients had tumors in the subareolar region and the remaining three (18.7%) had tumors located in the upper outer quadrant.

Assessing MBC via radiology is performed in a similar manner to FBC assessment. MMX is the first radiologic imaging technique performed for a suspicious breast mass in males due to the high sensitivity (92%) and specificity (90%) of the technique (Fentiman and Fourquet, 2006; Gradishar et al., 2015). However, Adıbelli et al. (2009) reported that USG was more sensitive (100% *vs* 85%) and specific (97% *vs* 84%) than MMX. In addition, they suggested that USG should be the first imaging technique performed in male patients since it is effective, simple, and inexpensive. After local imaging, all suspicious masses should be verified with a biopsy, and this can be performed by means of FNA or core biopsy. However, HR and HER-2 status should be evaluated in all patients, and therefore core biopsy is preferred due to the amount of sample obtained (Giordano et al., 2004; Fentiman and Fourquet, 2006; Fentiman, 2009; Gomez-Raposo et al., 2010).

The most common histopathologic diagnosis in MBC patients is invasive ductal carcinoma, and the rate of this subtype has been reported at 88-92%. (Engin and Unsal, 1993; Yildirim and Berberoglu, 1998; Atahan et al., 2006; Arslan et al., 2012; Selcukbiricik et al., 2013). In the patients in this study, 81.3% had invasive ductal carcinomas. Other possible subtypes include papillary carcinoma, medullary carcinoma, mucinous carcinoma, tubular carcinoma and invasive lobular carcinoma (Engin and Unsal, 1993; Yildirim and Berberoglu, 1998; Atahan et al., 2006; Fentiman, 2009; Arslan et al., 2012; Selcukbiricik et al., 2013). According to the SBR grading system, the reported tumor grade distribution is as follows: 10.7-14.8% are grade 1, 55.5-59.5% are grade 2 and 29.6-29.8% are grade 3 (Arslan et al., 2012; Selcukbiricik et al., 2013). The most frequently observed SBR grade in this study was grade 2. SBR grade is an independent prognostic factor for OS. The 5-year OS rates for grade 1, 2 and 3 MBC are 76-94%, 66-75% and 25-43%, respectively (Cutuli, 2007; Cutuli et al., 2010; Dabakuyo et al., 2012). The rate of HR expression is higher in MBCs compared to FBCs, and increases with age. ER and progesterone receptor (PR) positivity rates are 90-92% and 81-96%, respectively (Giordano et al., 2004; Fentiman, 2009; Cutuli et al., 2010) in countries other than Turkey. From Turkey, rates have been reported at 69.8-82.9% and 64.8-75.8%, respectively (Arslan et al., 2012; Selcukbiricik et al., 2013), and were 93.7% and 68.8% in our study. HR positivity is a favorable prognostic factor, and 5-year OS rates decrease from 78% in ER(+) to 25% in ER(-) patients (Cutuli, 2007; Fentiman, 2009). In contrast to HR status, the rate of HER-2 overexpression is lower in MBCs compared to FBCs, and occurs in 2-15% of patients around the world (Gomez-Raposo et al., 2010). In Turkey specifically, the rate of HER-2 overexpression was reported to be 8-23.4% (Arslan et al., 2012; Selcukbiricik et al., 2013), but was 25% in this study. MBC molecular subtype rates were as follows: 67.5% luminal A, 20.8% luminal B, 9.1% basal-like, and 2.6% HER-2 over-expressing type (Arslan et al, 2012). The most frequent molecular subtype was luminal A (75%) in the present study.

After MBC diagnosis, the first task is disease staging, which is similar to FBC. According to large case studies from Europe, the percentage of MBC patients in each stage was: stage I, 37%; stage II, 21%; stage III, 33% and stage IV, 9%. (Fentiman and Fourquet, 2006). The rates in Turkey were 2.5-17.9%, 28.9-43.5%, 33.3-55.4% and 5.1-13.2%, respectively. (Engin and Unsal, 1993; Yildirim and Berberoglu, 1998; Selcukbiricik et al., 2013). More than 50% of the patients in this study were stage III. AJCC stage is an independent prognostic factor (Sipetic-Grujicic et al., 2014), and 5-year OS rates are as follows: stage I, 91.7-100%; stage II, 73.7-87%; stage III, 38-41.1% and stage IV, 0% (Selcukbiricik et al., 2013; Sipetic-Grujicic et al., 2014).

To cure MBC, surgery should be the primary treatment modality (Fentiman, 2009), and the standard surgical treatment technique is mastectomy. Radical mastectomy (RM) was initially preferred, but over time this technique has been replaced by less-aggressive surgeries such as MRM and simple mastectomy (SM), and there are no reported differences in survival or recurrence between surgeries (Patten et al., 2013). Breast-conserving surgery (BCS) in MBC patients is controversial compared to FBC due to the lack of breast tissue, advanced stage at

diagnosis, and the subareolar localization of most tumors (Gomez-Raposo et al., 2010). In addition, the survival and recurrence rates in MBC patients are reported to be worse after BCS compared to mastectomy (Reis et al., 2011; Patten et al., 2013). Surgical evaluation of axillary nodes should be performed in all MBC patients by sentinel lymph node biopsy (SLNB) or AD (Fentiman, 2009). The first approach should be SLNB in patients with tumors measuring less than 2.5 cm in size and/or clinically negative lymph nodes (Gennari et al., 2004; Fentiman, 2009). Reported lymph node positivity rates were between 48.5-74.4% (Engin and Unsal, 1993; Yildirim and Berberoglu, 1998; Atahan et al., 2006; Arslan et al., 2012; Selcukbiricik et al., 2013), and the rate was 68.6% in the present study. Nodal status is the most important independent prognostic factor. The 5-year OS rate of lymph node negative patients was reported to be more than twofold that of positive patients (70% *vs* 30%) (Yildirim and Berberoglu, 1998).

RT guidelines are similar for MBC and FBC patients. According to the US guidelines, postmastectomy RT (PMRT) is recommended in patients with axillary lymph node metastasis (> 1), positive surgical margin (R1), close surgical margin (< 1 mm), or for tumors greater than 5 cm (≥ T3) (Gradishar et al., 2015). However, the European Institute of Oncology recommends PMRT for MBC patients with tumors less than 1 cm, or with more than one metastatic axillary lymph node due to the small size of the male breast (Gennari et al., 2004). In addition, PMRT is recommended by some for patients with skin and/or pectoral muscle involvement, and poor prognostic factors such as high SBR grade and vascular invasion (Fentiman, 2009; Zygogianni et al., 2012). RT should also be delivered after BCS (Gennari et al., 2004; Gradishar et al., 2015). In a retrospective study from the Johns Hopkins Oncology Center, PMRT had similar indications to those recommended for FBC (Chakravarthy and Kim, 2002). RT is known to increase local control of MBC, and local control rates with or without RT are 75-92.7% and 68-87%, respectively. However, no survival benefit has been shown, likely due to the small patient numbers in MBC studies (Patten et al., 2013). Despite this, an Early Breast Cancer Trialists' Collaborative Group meta-analysis reported that RT positively impacted survival, and that a 20% absolute reduction in 5-year local recurrence leads to 5.2% reduction in 15-year mortality (Clarke et al., 2005). Recommended RT targets and doses are similar to FBC. Unlike FBC, the majority of tumors in males are centrally located and the internal mammary lymph nodes should be irradiated (Fentiman and Fourquet, 2006; Patten et al., 2013).

End-T aims to reduce the effects of estrogen. This can be achieved by preventing the production of estrogen, or by blocking the estrogen receptor (Nordman and Dalley, 2008). The production of estrogen is the most important difference between males and postmenopausal females. In males, 75-80% of estrogen is produced from androgens by peripheral aromatization. The remainder is produced in the testes, independently of aromatase enzymes (Nordman and Dalley, 2008; Hayes, 2009). Therefore, estrogen production cannot be prevented without interrupting production in the testes. Currently, estrogen production can be prevented by surgical (hipophysectomy, adrenelectomy, orchiechtomy) and pharmacological (aromatase inhibitors, gonadotropin-releasing hormone analogs) methods (Nordman and Dalley, 2008), but it is not possible to inhibit estrogen production using a single method without serious side effects. Therefore, blocking estrogen receptors with TMX is more reasonable and simple. TMX is a standard End-T treatment, and effectiveness rates are more than 90% in MBC patients (Cutuli, 2007; Gomez-Raposo et al., 2010). There are no prospective randomized trials on the use of TMX in males. In retrospective studies, DFS and OS were reported to increase with TMX treatment, despite a treatment time of less than 5 years (Ribeiro et al., 1996; Goss et al., 1999). In the study by Ribeiro et al. (1996), in the surgery group alone, 5-year DFS and OS rates were reported to be 28% and 44%, respectively; however, the rates were 56% and 61% in patients who had received both surgery and TMX treatment. Despite the positive results, TMX is discontinued in 20% of MBC patients due to negative side effects such as decreased libido, deep-vein thrombosis, mood alterations, hot flashes and depression (Gomez-Raposo et al., 2010; Patten et al., 2013).

The 5-year DFS and OS rates in HR-positive patients are 50% and 92% with surgery + RT, 90% and 81% with surgery + TMX and both 100% with surgery + RT + TMX (Fogh et al., 2011), respectively. Another study from France reported the 5-year survival as 89% in MBC patients treated with surgery + RT + End-T (Dabakuyo et al., 2012).

ChT studies in male breast cancer patients are quite limited (Cutuli, 2007). Only one prospective randomized study is available, in which 24 males with stage II breast cancer were treated with adjuvant cyclophosphamide, methotrexate and fluorouracil (CMF) regimen, and the 5-year survival rate was over 80% (Bagley et al., 1987). This survival rate was significantly higher than the historical controls. The University of Texas M.D. Anderson Cancer Center recommends chemotherapy in MBC patients with tumors larger than 1 cm and lymph node involvement, regardless of HR status (Giordano, 2005).

HER-2 overexpression in MBC was reported in 9% to 29% of patients (Cutuli, 2007), and the rate in the present study was 25%. Trastuzumab is a monoclonal antibody against to HER-2 receptor, but the role of trastuzumab in MBC is unknown. Few case reports in the literature discuss the use of trastuzumab in MBC patients (Hayes, 2009). In one of these studies, paclitaxel plus trastuzumab therapy achieved a good response in both the primary and metastatic sites (Hayashi et al., 2009). Although no randomized study exists, trastuzumab therapy is recommended in HER2-positive MBC patients by most researchers (Cutuli, 2007; Hayes, 2009; Patten et al., 2013).

LRF and DF rates in non-metastatic patients are reported to be 3.0-17.4% and 28.9-34.1%, respectively (Engin and Unsal, 1993; Arslan et al., 2012; Selcukbiricik et al., 2013). The most common reported LRF sites are the chest wall (47%), the supraclavicular area (40%), the and axillary area (27%) (Selcukbiricik et al., 2013). The

most common reported DF sites are the bones and lungs (Engin and Unsal, 1993; Arslan et al., 2012). In our study, recurrence occurred in 46% of non-metastatic patients, and all of them were DF. The 5 year DFS and OS rates with multidisciplinary approaches are reported at 42.1-72.4% and 65.8-82%, respectively (Atahan et al., 2006; Fentiman, 2009; Arslan et al., 2012; Selcukbiricik et al., 2013) and were 58% and 68%, respectively, in the present study.

The limitations of this study include its retrospective nature, single institution data set, small number of patients, and non-homogeneity of ChT.

In conclusion, the results in MBC patients from the Middle Black Sea Region of Turkey show that MBC patients' tumors were similar in size to those found in females, but they advanced to T4 stage more rapidly due to the lack of breast parenchymal tissues. MBC should be treated in the same way as post-menopausal FBC due to the pathologic and molecular similarities, but the difference in estrogen production should be taken into account. Metastasis is the most important problem in initially non-metastatic MBC patients. There is a clear need for studies involving a greater number of MBC patients.

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