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Twelve Years of Male Breast Cancer Experience at One Center

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Background: Male breast cancer is a sporadic disease and only 1 in every 100 new breast cancer patients is male. There are few satisfactory clinical studies on male breast cancers in the literature. We aim to share the clinicopathologic and demographic characteristics of male breast cancer patients admitted to our clinic in the past 12 years and our experience in the treatment of these patients.

Methods: The data of patients who were referred to our clinic with a diagnosis of breast cancer, suspicion of breast cancer, or who presented to our outpatient clinic with symptoms of breast discharge, palpable mass in the breast, and were diagnosed with breast malignancy or suspicion of malignancy between 2010 and 2022 were retrospectively evaluated from the data bank records of our hospital. A total of 28 patients were included in the study. Patients' clinical and pathologic data, treatment options, approach to the axilla, pathology results, and survival were evaluated.

Results: There were 28 patients in the research; 22 had mastectomies. No surgical intervention was carried out for the 5 patients who had metastases. One of these patients died during follow-up due to advanced comorbidities and metastatic disease. Another patient declined surgery following neoadjuvant chemotherapy and passed away during follow-up (deceased). The third patient died during neoadjuvant chemotherapy, and 2 patients are still undergoing neoadjuvant treatment.

Conclusions: Male breast cancers are rare diseases. Radiotherapy (RT) after mastectomy increases survival in male patients as well as in female patients. However, RT in male patients is not standardized today. In our study, 15 patients received adjuvant RT.

Key words: Male breast cancer – Segmental mastectomy – Sentinel lymph node biopsy – Breast conversing surgery – Radiotherapy30

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Male breast cancer (MBC) is a sporadic disease and only 1 in every 100 new breast cancer patients is male.[1] Moreover, only 0.2% of cancer-related deaths in men each year are due to breast cancer.[2] For these reasons, there are few satisfactory clinical studies on MBCs in the literature, and the diagnostic and therapeutic modalities and treatment algorithms are generally the same as in female breast cancer patients.[1–3]

Although it can be seen at any age, it is more common in the sixth and seventh decades. Patients in this age group usually have advanced-stage disease findings, such as large tumor diameter, lymph node involvement, and metastasis at the time of diagnosis. Genetic factors, BRCA mutation, family history, obesity, Kleinfelter syndrome, gynecomastia, liver disease, orchitis, undescended testis, alcohol use, exogenous estrogen and testosterone use, and radiation history are the most common causes in etiology.[1–7]

Patients usually present with a painless mass, ulcerated skin lesions, nipple discharge, or retraction.[8] The most common histologic type is invasive ductal carcinoma. The diagnosis is usually made by ultrasonography (USG) and magnetic resonance imaging followed by a thick-needle biopsy.[6,7]

This study aims to share the clinicopathologic and demographic characteristics of MBC patients admitted to our clinic in the past 12 years and our experience in the treatment of these patients.

Material and Methods

All procedures performed in this study involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local ethics committee.

The data of patients who were referred to our clinic with a diagnosis of breast cancer or suspicion of breast cancer or who presented to our outpatient clinic with symptoms of breast discharge, palpable mass in the breast, and were diagnosed with breast malignancy or suspicion of malignancy between 2010 and 2022 were retrospectively evaluated from the data bank records of our hospital. Forty-one patients whose data could be accessed were obtained.

Thirteen patients were removed from the trial because their data could not be obtained. Of these patients, the study included 26 with invasive carcinoma, 1 with mucinous carcinoma, and 1 with ductal carcinoma *in situ* (DCIS). Clinical and pathologic information, available treatments, the axilla approach, pathology findings, and survival were assessed in 28 cases.

All patients presented to the clinic with a breast mass. All patients were evaluated by physical examination. All patients underwent USG and trucut biopsy for pathological diagnosis. Metastatic cases were referred for neoadjuvant chemotherapy. Primary surgery was performed on patients without metastasis. The surgical method was applied as segmental mastectomy and mastectomy. Sentinel lymph node biopsy (SLNB) was performed on patients with clinically negative axillary lymph nodes, and axillary lymph node dissection (ALND) was performed in cases with clinically positive axillary lymph nodes. Isosulfan blue and gamma probe (marked with Tc-99m) were applied in combination for sentinel lymph node (SLN) sampling. The lymph nodes excised with this method were sent for intraoperative frozen examination.

Axillary dissection was performed according to the rate of positive lymph nodes according to the frozen result. Classic immunohistochemistry markers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) were used to determine the tumor subtype. Patients were staged according to the Tumor Node Metastasis system (seventh or eighth TNM) valid at the time of diagnosis. BRCA 1 and BRCA 2 gene mutation analysis was performed on patients with a suspicious family history. Clinicopathological data including patient age, tumor size, tumor location, histological type of the tumor, receptor status of the tumor, grade of the tumor, stages, type of surgery, number of SLNs taken, and follow-up period were evaluated in detail.

Results

In this study, 28 male patients diagnosed with breast cancer pathologically were evaluated in detail. The average age of the patients was 63.6 (31–92). The tumor was located in the right breast in 15 (53.6%) patients and in the left breast in 13 (46.4%) patients. The tumor location was mostly retroareolar (78.5%). Seven patients (25%) had a family history of breast cancer and only 1 patient (3%) had a family history of MBC. For preoperative pathological diagnosis, trucut biopsy was performed on 20 (71.4%) patients, and fine needle aspiration was performed on 3 (10.7%) patients. Incisional biopsy was performed on 1 (6%) patient (simple mastectomy was performed on this patient to diagnose due to metastatic appearance and open wound in the breast

Table 1 Clinical and demographic data of patients

Patient	n = 28
Age, y	63.6 (31–92)
Symptom	n = 28 (%)
Palpable mass	24 (85.7)
Metastatic disease	1
Nipple discharge	1
Wound on nipple	1
Joint pain and hoarseness	1
Settlement	n = 28 (%)
Retroareolar	22 (78.5)
Upper outer quadrant	4
Lower outer quadrant	2
Risk factors	n = 28
Family history of breast cancer	7
Family history of male breast cancer	1
Imaging method	n = 28 (%)
Ultrasonography	28 (100)
Mammography	17 (60.6)
Magnetic resonance imaging	24 (81.8)
Other	9 (30.3)
Hormone receptor status	n = 28 (%)
Estrogen receptor (+)	28 (100)
Progesterone receptor (+)	19 (67.8)
KI67 (<14%)	7 (25)
HER2 +	2 (7.1)
BRCA1/BRCA2	n = 10
NEGATIVE	5
BRCA1	1
BRCA2	3
BRCA1 + BRCA2	1

preoperatively) and excisional biopsy was performed on 4 (14.2%) patients. All patients were estrogen positive and 19 patients (67.8%) were progesterone positive. One of the progesterone-negative patients was DCIS and 8 were invasive ductal carcinoma. HER2 was positive in 2 patients (7.1%) and negative in 25 patients (89.2%). One of these 2 patients had distant organ metastasis, and the other had axillary involvement. The Ki 67 index was low in 7 of the 28 patients, and high in the others (25%). When the genetic evaluation results of the patients included in the study were screened in our clinic, data of only 10 patients could be reached and no mutation was detected in 5 patients. A heterozygous pathogenic variant was found in the BRCA1 gene in 1 patient, a heterozygous pathogenic variant in the BRCA2 gene in 3 patients, and a mutation of unknown significance in the BRCA1 gene and a pathological variant in the BRCA2 gene was found in 1 patient (Table 1).

As a result of the biopsies performed in the preoperative evaluation, the most common diagnosis was invasive ductal carcinoma (22 patients), malignant lesion in 1 patient, invasive carcinoma in 2 patients, adenocarcinoma in 1 patient, mucinous carcinoma in 1 patient, and DCIS in 1 patient. After surgery, the most common histological type was invasive ductal carcinoma in 26 patients (92.8%), mucinous tumor in 1 patient (3.5%), and low-grade DCIS in 1 patient (3.5%) (Table 2). Pathological stages were I (n = 1), IIA (n = 9), IIB (n = 3), IIIA (n = 6), and IV (n = 9) (Fig. 1). Mastectomy was performed on 22 of the 28 patients, and breast-conserving surgery was performed on 1 patient. SLNB was performed on 8 patients, ALND on 9 patients, and ALND after SLNB on 3 patients (1 was operated after neoadjuvant chemotherapy) (Table 3). In 3 patients, only simple mastectomy was performed due to metastatic disease, and axillary sampling was not needed. Four patients received neoadjuvant chemotherapy; 2 patients died during treatment and 2 patients are still receiving treatment. One metastatic patient died during follow-up. There were 9 metastatic patients. Surgical intervention was not performed on 5 patients with metastasis. One patient died during follow-up due to advanced comorbidities and metastatic disease. One patient refused surgery after neoadjuvant chemotherapy and died during follow-up. One patient died during neoadjuvant chemotherapy and 2 patients are still receiving neoadjuvant treatment.

Simple mastectomy was performed on 3 of the metastatic patients, mastectomy and SLNB were performed on 1 patient following neoadjuvant chemotherapy, and ALND was performed following SLNB. In patients who underwent isolated SLNB, the average number of lymph nodes (LNs) removed was 3.87 (3–5 LNs), and the positivity rates are included in Table 4. One patient, who was proven to have metastatic LNs in the axilla by trucut biopsy before surgery, was evaluated as having a good response after neoadjuvant chemotherapy, and after SLNB was reported as 1 of 3 metastatic and 19 of 19 reactive LN (final result 1 of 22 positive), ALND was performed (Table 5). In metastatic patients, the most common site of metastasis was bone (7 patients),

Table 2 Pathological pre-postoperative diagnosis

Pathological diagnosis (preoperative)	n = 28	Pathological diagnosis (postoperative)
Invasive ductal carcinoma	22 (78.5)	Invasive ductal carcinoma
Mucinous tm	1	Mucinous tumor
Ductal carcinoma *in situ*	1	Ductal carcinoma *in situ*
Invasive carcinoma	2	Invasive ductal carcinoma
Adenocarcinoma	1	Invasive ductal carcinoma
Malignant lesion	1	Invasive ductal carcinoma

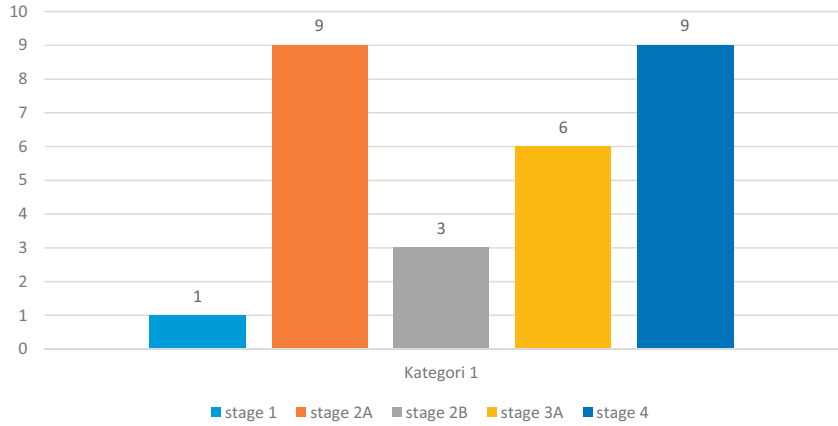

Fig. 1 Stage of patients at the time of admission.

followed by lung (4 patients), brain (3 patients), and contralateral axilla (2 patients) (some patients had multiple metastases). Six (21.4%) of the patients who were initially metastatic or later developed metastases implemented chemotherapy as first-line systemic treatment, and 3 (3%) hormone therapy. In response to first-line treatment, partial response was achieved in 5 (17.9%) patients and stable disease response was achieved in 4 (10.7%) patients. The median invasive disease-free survival was 90 months in 19 patients who were not initially metastatic. The median overall survival in the entire group was 93 months. Ten (35.7%) patients received adjuvant radiotherapy (RT) at our clinic, and 5 patients received RT at an outside center. A total dose of 50 Gy to the chest wall and 60 Gy to the breast was given using the simultaneous integrated boost technique with a boost to the tumor bed. In 3 (10.7%) of the patients who are still being treated at our clinic, RT was applied only to the chest wall without LN irradiation, whereas in 6 (21.4%) patients, the LNs were included in the RT treatment area. One (3.5%) patient received RT to the breast and LNs. Intensity-modulated RT technique was used in 7 (25%) patients; three-dimensional RT was preferred in 1 (3.5%) patient, and two-dimensional RT technique was preferred in 1 (3.5%) patient. Two (7.1%) patients underwent 30-Gy RT for bone and brain due to bone metastasis.

Table 3 Surgical approach to the breast and axilla

	No intervention	SLNB	ALND	SLNB+ ALND	Total
Mastectomy	3	8	8	3	22
BCS	0	0	1	0	1
Total	3	8	9	3	23 (5 patients without surgery)

ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

Discussion

MBC, unlike breast cancer in women, is a rare and understudied disease. The American Cancer Society records for 2020 show the diagnosis of breast cancer in 2620 men and 526 of them died.[9] The 5-year age-adjusted incidence of breast cancer in men varies from 0.67 to more than 2.4 per 100,000 people.[10] The mean age at diagnosis is 62 years in women and 67 years in men. The mean age at diagnosis in our patients was 63.6 ± 0.12 (31–92), which is close to this value. A group of risk factors for MBC identified the general risk factors and genetic factors.

General risk factors include age, a positive family history, exposure to high estrogen levels, a history of orchitis/epididymitis, gynecomastia, Klinefelter syndrome, radiation exposure, obesity, and use of external estrogen or testosterone preparations. In a very large prospective cohort study, Brinton *et al*[11]

Table 4 Patients who underwent sentinel LN biopsy and positivity rates

Patient no.	Sentinel LN	Nonsentinel LN	Positive LN	Total
1	2	1	0	3
2	4	1	1 (nSLN)	5
3	3	1	0	4
4	3	2	0	5
5	1	2	0	3
6	2	1	0	3
7	3	2	0	5
8	3	0	0	3

LN, lymph node; nSLN, non-sentinel lymph node.

Table 5 Patients with isolated axillary lymph node dissection and positivity rates

Patient no.	Metastatic LN	Reactive LN	Total
1	15	1	16
2	1	6	7
3	8	9	17
4	0	9	9
5	4	23	27
6	5	9	14
7	5	3	8
8	4	8	12
9	0	10	10

LN, lymph node.

reported MBC at nearly twice normal for people reporting a history of breast cancer in first-degree relatives. The relative risk was 1.92 and the 95% confidence interval was 1.19 to 3.09.

In our series of 28 patients, 7 or 25% of the probands had a first-degree relative with breast cancer, and 1 or 3% had a family member with MBC. Therefore, a family history of breast cancer was found in 8 of 28 persons. Our study confirmed high-stage, ER-positive male cases. A study by the ample Veterans Affairs Database system likewise indicated that gynecomastia, obesity, and orchitis/epididymitis are connected to MBCs.[12] Klinefelter syndrome, a chromosomally connected embryologic defect with a high estrogen/androgen ratio, is also a significant positive factor.[13]

Several high-penetrance genes have been found to increase a man's risk of developing breast cancer. The most extensively researched are mutations in the BRCA1 and BRCA2 genes. BRCA1 and BRCA2, tumor suppressor genes involved in DNA repair, were discovered in 1994[14] and 1995,[15] respectively. Mutations in either gene have been linked to an increased risk of numerous cancers, the most prevalent of which are ovarian and breast cancers. As noted by Thorlacius *et al*[16] in 1995 and later discovered in numerous other investigations, individuals with a harmful germline BRCA2 mutation have a markedly elevated risk of MBC.

A total of 1939 households were examined in a sizable research using data from the National Cancer Institute Database.[17] Of the 97 individuals with MBC, 2.6% and 7.0%, respectively, had detectable BRCA2 and BRCA1 mutations. BRCA1 and BRCA2 mutation carriers had a greater cumulative risk of breast cancer than did noncarriers at all ages. Men with BRCA1 mutations had an age-adjusted cumulative breast cancer risk of 1.2% (95% confidence interval [CI], 0.22%–2.8%) at age 70, whereas those with BRCA2 mutations had an age-adjusted cumulative risk of 6.8% (95% CI, 3.2%–12.0%). Because our investigation was retrospective, a BRCA panel was completed on 10 of the 28 individuals, and 5 of them had negative results. One patient had positive BRCA 1 results and 3 patients had positive BRCA 2 results.

Although there are various ways that MBC might manifest, palpable breast mass is the most typical observation.[18] Other less frequent symptoms include ulceration, skin retraction, and nipple discharge or bleeding. In more severe situations, some patients may even present with axillary lymphadenopathy. Comparably, in our series, 85.7% of patients had a palpable lump in their breast as their initial complaint. Ninety percent of individuals receive an early-stage diagnosis. According to one study, the patients' diagnoses for stages 1, 2, 3, and 4 of the disease were 37%, 21%, 33%, 33%, and 9%, respectively.[19] These rates were discovered to be, in our investigation, 4%, 42%, 22%, and 32%, respectively (Fig. 1).

Most of the histopathologic variations of breast cancer observed in women are also present in men, albeit at varying rates. Men are seldom diagnosed with DCIS, and more than 85% of breast cancer cases are invasive.[20] As Table 2 illustrates, DCIS was found in just 1 patient in our investigation. One possible explanation for this could be the low rate of screening mammography among men.

Most MBCs were negative for HER-2 and positive for ER and PR (ER+ and PR+). Cardoso *et al*[21] conducted a retrospective evaluation of 1483 patients in a very large international MBC program collaboration between 1990 and 2010. Eighty-two percent of the patients were PR+, 887% were ER-2 negative, and just 3% were triple negative.[21] These rates were 100% ER+, 67.8% PR+, and 7.1% HER-2 positive in our investigation.

It is evident that, albeit surgeon-dependent, our clinic's approach to the axilla has shifted toward conservatism since the start of this study in 2010 (9 ALND, 3 SLNB+ALND, 8 SLNB). Mastectomies are still the preferred method of treating breasts (1 breast-conserving surgery (BCS); 22 mastectomies). Both male and female patients' survival rates are increased by RT following mastectomy.[22] However, RT is not currently standardized for male patients. Adjuvant RT was administered to 15 individuals in our research. In this study, no patient's treatment decision was made using genomic testing.

Early-stage MBC is managed in the same way as it is for women. Depending on the results of the operation, the presence or absence of hormone receptors, and other prognostic markers, most

patients with early-stage breast cancer have surgery followed by adjuvant endocrine therapy, chemotherapy, or radiation therapy.[23] In contrast to women, males prefer not to have BCS, and most men have mastectomy. However, research suggests that survival rates of MBC patients treated by BCS and RT are nearly the same if not better. Only when all mastectomy patients had stage I cancer and had RT following surgery was the 5-year case-specific survival rate found to be equivalent between treatment groups in a study of 1777 cases of MBC, in which 17% of male patients underwent BCS and 40% underwent radical or simple mastectomy. With only 46% of patients undergoing RT, the necessity for RT did not, however, substantially impact the survival of patients receiving BCS.[24] Of the 22 patients in our series, only 1 had axillary dissection and BCS. In MBC-eligible instances, BCS may now be recommended because of its comparable long-term oncologic outcomes to mastectomy. There are no prospective data on the function of adjuvant RT in MBC, and most of the time, breast cancer patient guidelines are adhered to.

MBCs are high-stage, estrogen-positive instances, as our investigation has shown. Similar to the study by Spreafico *et al*,[25] we also discovered that the number of metastatic cases at the time of diagnosis was high in our investigation. Endocrine therapy should be the first-line treatment for male patients with advanced or metastatic hormone receptor–positive breast cancer, according to the most recent American Society of Clinical Oncology guidelines.[26] Chemotherapy should be used only in cases of visceral crisis or fast-progressing disease. Endocrine therapy was not the first choice for our metastatic patients. With the latest methods, we should now treat metastatic patients with hormone therapy.

Conclusion

Just like in women, MBC patients undergo breast-conserving surgery, but more importantly, axilla-conserving surgery.[27] In addition to this approach, which is important to prevent possible morbidities, studies with larger samples are needed in terms of genetic counseling and prophylactic procedures.

Because of the low prevalence, there have not been many male patients included in prospective studies on the treatment of breast cancer, which has led to a lack of information on MBC. Increasing the viability of including male patients in organized clinical trials will undoubtedly aid in the creation of evidence-based guidelines for the treatment of MBC. To understand tumor genesis, risk factors, and prognostic variables in MBC, further molecular research is required.

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The authors have no conflicts of interest to declare. The datasets generated and/or analyzed in this study are available from the corresponding author upon reasonable request. S.C., B.O., and M.G. wrote the paper. M.K., D.A., E.M., and I.S. collected the data and the literature for the article. S.C., B.O., M.G., and M.K. analyzed and interpreted the data. E.S., S.C., A.A., and D.A. revised the manuscript for important intellectual content. All the authors read and approved the final manuscript. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Erciyes University Faculty of Medicine (2024/278).

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