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Male breast cancer in a single-center experience: Diagnosis, clinicopathological features, and treatment strategies

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ABSTRACT

OBJECTIVE: Although breast cancer is the most common cancer type in women worldwide, it is a rare tumor in men, accounting for less than 1% of all male cancers. Therefore, the characteristics of the tumor, the management of the disease, and our overall survival data are quite limited.

METHODS: We retrospectively analyzed the data of 51 male patients diagnosed and treated for breast cancer, whose follow-up processes continue, at our hospital. We examined in detail the patients' age, comorbid diseases, history of concomitant malignancies, family history, stage of the disease, tumor size, lymph node status, estrogen receptor (ER)/progesterone receptor (PR) along with Human Epidermal Growth Factor Receptor-2 (HER-2) status. Additionally, we analyzed the type of surgery, history of radiotherapy, and chemotherapy and hormonal treatments in the adjuvant and metastatic periods.

RESULTS: In our study, where we determined a median survival time of 122 months (29–214), we found that the stage at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, and discontinuation of adjuvant endocrine therapy significantly affected survival. While the median survival was not reached in stage 1 patients at diagnosis, the median survival times for stage 2, 3, and 4 patients were 118, 83, and 39 months, respectively. The differences between the groups were statistically significant (p=0.005). Similarly, the median survival was not reached for patients with an ECOG performance status of 0, but it was 84 months for those with a status of 1 and 98 months for those with a status of 2. The differences among these three groups were also statistically significant (p=0.001). The median survival was not reached for patients who completed adjuvant endocrine therapy, whereas it was 83 months for those who discontinued the therapy, with the difference being statistically significant (p=0.021). Besides these data, the presence of perineural invasion was found to be a factor close to statistical significance in terms of survival (p=0.066). Histological subgroups, grade, lymphovascular invasion, adjuvant chemotherapy, and Ki-67 were not significant parameters for survival.

CONCLUSION: Despite the differences in the stage at diagnosis, response to treatments, lower awareness of the disease, older age at diagnosis, and consequently, the increase in accompanying comorbid diseases, male breast cancer is managed according to studies and guideline recommendations for female breast cancer due to the lack of sufficient randomized studies. By presenting our clinical experience, we have emphasized the necessity for further studies in this field.

Keywords: Breast cancer survival; male breast cancer; rare; treatment.

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Breast cancer is the most common type of cancer among women worldwide but is exceptionally rare in men, representing less than 1% of all male cancers [1]. Due to its rarity, our understanding of tumor characteristics, disease management, progression-free survival, and overall survival is limited. These data are derived from studies involving a small number of patients, and there are no specific guidelines for male breast cancer (MBC).

Although one in eight women is at risk of developing breast cancer over their lifetime, the risk for men is one in 1000, with a female-to-male incidence ratio of 125:1 globally [2]. Age is a significant risk factor for male breast cancer, with the risk increasing as men get older. Unlike women, the average age of diagnosis in men is approximately five years later, with a mean age of 67 compared to 62 in women [3]. Factors such as smoking, alcohol consumption, obesity-induced hyperestrogenism, liver cirrhosis, testicular damage, and Klinefelter syndrome also contribute to the increased incidence of male breast cancer [4, 5]. Men with Klinefelter syndrome (XXY) have a 50-fold increased risk of developing breast cancer, accounting for 3% of all male breast cancer cases [6]. A family history of breast cancer similarly increases the risk for men. Additionally, childhood chest wall radiation is a known risk factor.

Beyond these factors, hereditary genetic mutations are also significant risk factors for MBC; literature suggests that 15–20% of patients exhibit hereditary breast or ovarian cancer, highlighting the crucial role of genetic factors in MBC susceptibility [7, 8]. Approximately 10% of male breast cancer patients have genetic predispositions, compared to 5–7% of hereditary tumors among women [9, 10]. Mutations in genes such as BRCA2 (Breast Cancer Gene 2), BRCA1 (Breast Cancer Gene 1), CHECK2 (Checkpoint Kinase 2), MLH1 (MutL Homolog 1), MSH2 (MutS Homolog 2), MSH6 (MutS Homolog 6), and PALB2 (Partner and Localizer of BRCA2) are associated with male breast cancer [9–11].

Male breast cancer management relies on female breast cancer studies due to insufficient male-specific trials. Differences in disease mechanisms, hormonal variations, and chemotherapeutic responses indicate treatment gaps. More research is needed to optimize surgery, radiotherapy, and chemotherapy for male patients. Additionally, prognosis reports for male breast cancer are inconsistent. Some publications state that the overall prognosis is like that of female breast cancer [12]. Conversely, other studies report a poorer overall prognosis for male breast cancer cases [13, 14].

Highlight key points

- Male breast cancer is managed according to studies and guideline recommendations for female breast cancer due to the lack of sufficient randomized studies.
- It is a rare tumor in men. The characteristics of the tumor, the management of the disease, and our overall survival data are quite limited.
- The stage at diagnosis, ECOG performance status, and discontinuation of adjuvant endocrine therapy significantly affected survival.

In this study, we aim to present the clinicopathological features, treatments administered, and real-world outcomes of male patients diagnosed with breast cancer.

MATERIALS AND METHODS

Study Design and Patient Selection

This retrospective study analyzed the data of 51 male patients diagnosed with breast cancer and treated in our clinic, with ongoing follow-ups. Patient data included age, comorbidities, history of accompanying malignancies, family history, disease stage, tumor size, lymph node involvement, estrogen receptor (ER)/progesterone receptor (PR) status, and Human Epidermal Growth Factor Receptor-2 (HER-2) status. Additionally, surgical treatments, radiotherapy history, adjuvant and metastatic chemotherapy and hormonal therapies were analyzed.

Pathological examination and reporting of specimens, as well as decisions regarding adjuvant and metastatic treatments, were made in accordance with international guidelines for female breast cancer. Follow-ups were conducted every three months for the first two years, every six months up to the fifth year, and annually after that.

Statistical Analysis

The primary endpoints were disease-free survival (DFS) and overall survival (OS). Kaplan-Meier curves and log-rank tests were used to compare survival between groups. Univariate and multivariate Cox regression analyses were performed for survival endpoints, and hazard ratios (HR) with 95% confidence intervals were reported. P-values <0.05 were considered statistically significant. Data analysis was performed using SPSS software, version 25.0 (IBM Corp., Armonk, NY, USA).

Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. The Kartal Dr. Lutfi Kirdar City Hospital Scientific Research Ethics Committee granted approval for this study (date: 27.05.2024, number: 2024/010.99/4/18).

RESULTS

Study Population

In our study, we analyzed the retrospective data of fifty-one patients. Patient characteristics are displayed in Table 1. The average age at diagnosis was 58.6 years (range 19–85). The number of patients diagnosed with right and left breast cancer was equal (25 each), with one patient diagnosed with bilateral breast cancer. The ECOG performance status was 0 or 1 in 48 patients, with only three patients having an ECOG score of 2. Twenty-three patients had comorbidities, predominantly hypertension. Three patients had additional malignancies (lung, prostate, and bladder cancer). Only one patient had a family history of breast cancer.

Table 1. Patient characteristics of the male breast cancer patients

Variables	n=51 (%)
Median age (range)	58.6 (19–85) years
Laterality	
Right	48
Left	48
Bilateral	2
Comorbidities	
Hypertension	39
Diabetes mellitus	17
CAD	15
None	55
Family history	
Family history of breast cancer	2
Family history of other malignancies	5
Additional malignancies	5
Smoking	59
ECOG performance score	
0	53
1	41
2	6

CAD: Coronary artery disease; ECOG: Eastern cooperative oncology group; 0: Fully active, able to carry on all pre-disease performance without restriction; 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work; 2: Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.

Tumor Characteristics

Table 2 presents the tumor characteristics. The average tumor size was 2.74 cm (range 0.6–7.4). Forty-six patients had invasive ductal carcinoma. Twenty-eight patients were diagnosed at stage T2, 15 at T1, seven at T4, and one at T3. Thirty-five patients had positive lymph nodes, while 16 did not. Stage 2 disease was most common at diagnosis, with five patients presenting with metastatic disease. Tumor grade at diagnosis was predominantly grade 2 (34 patients), and the average Ki-67 index was 32.2 (range 5–90). Forty-six patients were hormone receptor-positive, with 36 having hormone-positive HER-2 negative subtypes, and three patients had triple-negative breast cancer.

Treatment and Survival

Neoadjuvant therapy was administered to seven patients, and adjuvant chemotherapy to 31 patients. Adjuvant endocrine therapy was administered to 43 patients, with tamoxifen being the treatment for all except one patient who received an aromatase inhibitor plus Luteinizing Hormone-Releasing Hormone (LHRH). Thirty-four patients received radiotherapy. The median survival was 122 months (range 29–214). Diagnosis stage, ECOG performance status, and discontinuation of adjuvant endocrine therapy significantly impacted survival. Median survival was not reached for stage 1 patients at diagnosis, while it was 118, 83, and 39 months for stages 2, 3, and 4, respectively, with statistically significant differences (p=0.005).

Similarly, median survival was not reached for patients with ECOG 0. Median survival was 84 months for ECOG 1 and 98 months for ECOG 2, showing statistically significant differences (p=0.001). The median survival was not reached for patients who completed adjuvant endocrine therapy, but it was 83 months for those who did not, with significant differences (p=0.021). Patients with perineural invasion in surgical specimens had near-significant shorter survival than those without (p=0.066). Tumor subtypes, grade, biopsy pathology, lymphovascular invasion, adjuvant chemotherapy, and Ki-67 differences did not significantly impact survival.

TABLE 2. Tumour characteristics of the male breast cancer patients

Characteristic	n=51 (%)
Tumor size	2.4 (0.6–7.4) cm
Histology	
Inv ductal carcinoma	90
Inv lobular carcinoma	4
DCIS (ductal carcinoma in situ)	6
T stage	
T1	29
T2	55
T3	2
T4	14
N stage	
N0	33
N1	39
N2	10
N3	8
Stage at diagnosis	
Stage 1	27
Stage 2	45
Stage 3	18
Stage 4	10
Meme ca subtype	
Hormone-positive cerbb2-negative	71
Hormone-positive cerbb2-positive	19
Hormone-negative cerbb2-positive	4
Triple-negative	6
Ki-67	32.2 (5–90)
Patients receiving neoadjuvant chemotherapy	14
Patients receiving adjuvant chemotherapy	61
Patients receiving adjuvant endocrine therapy	85
Patients receiving adjuvant radiotherapy	67

T stage: This category describes the size and extent of the main tumor. The numbers following the T indicate the size of the tumor and/or the extent to which it has spread into nearby tissue; T1: Tumor is 2 cm or smaller; T2: Tumor is larger than 2 cm but not larger than 5 cm; T3: Tumor is larger than 5 cm. T4: Tumor of any size with direct extension to the chest wall and/or to the skin. N stage: This category describes whether the cancer has spread to nearby lymph nodes. N0: No regional lymph node metastasis; N1: Metastasis in 1–3 axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node biopsy but not clinically apparent; N2: Metastasis in 4–9 axillary lymph nodes, or in clinically apparent internal mammary nodes in the absence of axillary lymph node metastasis; N3: Metastasis in 10 or more axillary lymph nodes, or in infraclavicular (level III axillary) lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes, or in more than 3 axillary lymph nodes with clinically negative internal mammary nodes, or in ipsilateral supraclavicular lymph nodes.

DISCUSSION

Despite increasing incidence in recent years, male breast cancer remains a rare tumor. Treatment algorithms are based on guidelines for female breast cancer, yet the two diseases exhibit distinct characteristics. Male breast cancer tends to show more locoregional spread or distant metastasis at diagnosis [15]. Additionally, hormone positivity rates are higher, and HER-2 positivity rates are lower in male breast cancer compared to female breast cancer [16]. Due to the higher genetic predisposition, male breast cancer treatment differs from female breast cancer and requires distinct diagnostic, treatment, and follow-up plans.

In our study, the average age of diagnosis was 58.6 years, consistent with the literature [17]. Modified radical mastectomy (MRM) was the surgical procedure for all suitable patients. Due to the small amount of breast tissue and the larger tumor-to-breast ratio, breast-conserving surgery, commonly performed in female breast cancer, was not applicable in our male patients. Although the literature indicates larger primary tumors and more locoregional spread at diagnosis in male breast cancer, our study found early-stage diagnosis in terms of primary tumor size, locoregional involvement, and stage, likely due to increased awareness and advancements in imaging techniques over the years, leading to earlier diagnosis. The most common histological subtype was invasive ductal carcinoma (58%), with invasive lobular carcinoma accounting for 5%. Hormone positivity was 92%, and HER-2 positivity was 24%. Our findings align with historical literature [7, 18].

Fourteen percent of our patients received neoadjuvant chemotherapy, while 62% received adjuvant chemotherapy. No significant survival difference was found between patients who received chemotherapy and those who did not. This could be due to earlier-stage diagnosis in non-chemotherapy patients, resulting in a lower recurrence risk compared to those requiring chemotherapy or with more aggressive histology. The literature does not specify a distinction in chemotherapy application between male and female breast cancer, with Giordano et al. [18] reporting a 43% reduction in mortality with chemotherapy.

Tamoxifen is the most used agent in adjuvant hormonal therapy, although LHRH combined with aromatase inhibitors is also used. In our study, 28% of patients discontinued adjuvant hormone therapy due to side effects or patient preference, resulting in significantly shorter survival for these patients. While the same hormonal agents are used in female breast cancer, ongoing studies aim to target androgen receptors with new treatments, with results pending [19].

We found a 5-year survival rate of 77%. Larger tumor size, nodal involvement, advanced stage at diagnosis, and high-grade tumors were associated with higher recurrence rates and lower overall survival. Literature indicates a 5-year survival rate of 36–66% for male breast cancer, significantly lower than the 80–86% for female breast cancer [20, 21]. The poorer prognosis in male breast cancer may be attributed to a later stage at diagnosis, higher prevalence of comorbidities, and older age at diagnosis. Additionally, the small sample sizes in studies on male breast cancer necessitate further research to provide more definitive conclusions regarding prognosis.

Our study is one of the few providing detailed real-world data on male breast cancer from a single center. However, there are several limitations, including the small sample size and retrospective design, which may introduce various biases in treatment and follow-up. Additionally, we could not perform detailed genetic analyses on our patients, preventing us from determining their BRCA status. For some older cases, hormone and HER-2 status could not be determined. Another limitation of our study is the presence of patients with second primary malignancies, which may affect survival endpoints. This variability could influence the robustness of our findings and should be taken into account when interpreting the results. Future studies with larger cohorts, comprehensive genetic analyses, and detailed hormone and HER-2 assessments are needed to establish standardized treatment guidelines specific to male breast cancer.

Conclusion

Despite the more advanced stage of diagnosis, there is no dedicated treatment approach for male breast cancer. Factors such as inadequate awareness, embarrassment in seeking medical attention for breast lumps, and rapid local invasion due to the small size of male breast tissue contribute to later diagnoses. Treatment options, including surgery, adjuvant chemotherapy, radiotherapy, and hormone therapy, are based on guidelines for female breast cancer. However, male breast cancer differs genetically and clinicopathologically from female breast cancer. Male patients are diagnosed at an older age and have more comorbid conditions. Hormone status and HER-2 expression also differ from those in female breast cancer cases. Completing hormonal therapy is associated with lower relapse rates, and chemotherapy and radiotherapy have shown clear benefits for survival. Consequently, more extensive studies are required to develop disease-specific guidelines for male breast cancer.

Ethics Committee Approval: The Kartal Dr. Lutfi Kirdar City Hospital Scientific Research Ethics Committee granted approval for this study (date: 27.05.2024, number: 2024/010.99/4/18).

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