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ORIGINAL ARTICLE

Clinical and histopathological characteristics of male breast cancer: A single center experience

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Summary

Purpose: *To evaluate male breast cancer patients in terms of clinicopathological, treatment parameters, and determine progression-free survival, and the parameters that affect it.*

Methods: *We retrospectively investigated the treatment files of 32 male breast cancer patients diagnosed histopathologically between June 2006 and June 2021. We evaluated clinicopathologic features of the patients and treatment characteristics. The study's primary endpoint was to determine progression-free survival (PFS) and the statistically significant influencing parameters. PFS analysis was evaluated by the Kaplan-Meier method, while comparing the effects of parameters, log-rank analysis was used.*

Results: *The median age of the patients was 56 years (33-88). The median tumor size was 2.6 cm (0.6-7). The tumor was HR (hormone receptor) positive HER2 (Human epidermal growth factor receptor) negative in 25 patients (78.1%), HER 2 positive in 6 patients (1.8%). Only one patient (3.1%) was triple negative.The median follow-up time was 26 months (3-121). The median PFS was 22 months, and 2-year PFS was 72%. A statistically significant correlation was found between PFS and tumor size (p 0.042). The 2-year PFS was calculated as 100% in patients with tumor size less than 3 cm and in 55% in patients with tumor size 3 cm and above.*

Conclusion: *In this study the patients were younger compared to Western series. Apart from this, the patients were compatible with the literature in terms of clinicopathological and treatment features. Tumor size (≥3cm) was a prognostic factor affecting PFS.*

Key words: *male breast cancer, diagnosis, treatment, progression-free survival*

Introduction

Male breast cancer is a rare tumor, accounting for less than 0.5% of male cancers and 1% of all breast cancers. However, its frequency has increased by 26% in the last 25 years [1]. Due to lack of prospective randomized studies, the treatment algorithm was tailored according to the treatment of postmenopausal breast cancer patients. Although there are similarities with female breast cancer, there are also differences in many aspects.There are differences in terms of histologic subtype and receptor expressions. Male breast cancer is diagnosed at an older age, a more advanced stage, with more frequent lymph node involvement. In developed countries, approximately two-thirds of female breast cancers are localized at the time of diagnosis, while half of the male breast cancers are localized [2]. Male patients were found to be inferior in terms of quality of care [3].

In recent years, there has been a decrease in female breast cancer mortality, but this is not the case for male breast cancer. The 5-year survival rate is lower in male breast cancer patients than in female breast cancer patients [4-6]. As a result of SEER data, the risk of death was 43% higher in male patients at follow-up [2].

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There are studies investigating overall survival and affecting parameters in male breast cancer patients. However, there are very few studies that comment on PFS. In our study, male breast cancer patients were evaluated retrospectively in terms of demographic, histological, and treatment characteristics. Parameters affecting PFS were investigated.

Methods

We retrospectively investigated the treatment files of 32 male breast cancer patients diagnosed histopathologically between June 2006 and June 2021. We evaluated patient characteristics (age, body mass index/BMI, blood group,comorbidity, family history), tumor characteristics (size, location,histology, hormonal receptors, location, stage), and treatment characteristics (type of surgery,

Table 1. Patient and tumor characteristics

	N 32 (%)
Median age (range)	56 (33-88)
Median BMI (range)	27 (21-34)
Blood group, n (%)	
0	6(18.8)
A	8(25)
B	7(21.9)
AB	5(15.6)
Unknown	6(18.8)
Handedness, n (%)	
Right handed	28(87.5)
Left handed	1(3.1)
Ambidextrous	1(3.1)
Unknown	2 (6.3)
Comorbidity, n (%)	
Yes	10(31.2)
No	22(68.8)
History of previous radiotherapy, n (%)	
Yes	2(6.3)
No	30(94)
Family history of cancer, n (%)	
Yes	2(6.3)
No	30(93.7)
Family history of breast cancer, n (%)	
Yes	5(15.6)
No	27(84.4)
Breast cancer laterality, n (%)	
Right	11(34.4)
Left	20(62.5)
Bilateral	1(3.1)
Region, n (%)	
Upper inner quadrant	1(3.1)
Upper outer quadrant	2(6.3)
Lower outer quadrant	7(21.9)
Lower inner quadrant	1(3.1)
Retroareolar	21(65.6)
Histology, n (%)	
IDC	25(78.1)
ILC	1(3.1)
IDC+ILC	1(3.1)
Papillary	4(12.5)
Mucinous	1(3.1)
Grade, n (%)	
1	1(3.1)
2	16(50)
3	13(40.6)
Unknown	2(6.3)
Receptor status, n (%)	
Estrogen receptor	
Negative	1(3.1)
Positive	31(96.9)
Progesterone receptor	
Negative	3(9.4)
Positive	29(90.6)
HER2 receptor, n (%)	
Negative	26(81.2)
Positive	6(18.8)
Triple –	1(3.1)
Androgen receptor, n (%)	1(3.1)
Median tumor size (range)	2.6 cm (0,6-7)
T, n (%)	
1	11(34.4)
2	16(50)
3	1(3.1)
4	4(12.5)
N, n (%)	
0	13(40.6)
1	10(31.3)
2	6(18.8)
3	3(9.4)
M, n (%)	
0	23(71.9)
1	9(28.1)
Metastatic sites, n (%)	
Bone	3(9.4)
Lung	4(12.5)
Bone +lung	2(6.3)
Stage	
1	7(21.9)
2	7(21.9)
3	9(28.1)
4	9(28.1)

IDC: infiltrative ductal carcinoma; ILC: infiltrative lobular carcinoma; HER2: Human epidermal growth factor receptor 2

radiotherapy (RT), chemotherapy, and endocrine treatment). The American joint committee on cancer (AJCC, 8th, edition) TNM classification was used for staging.

Adjuvant curative radiotherapy was applied in patients with tumors larger than 5 cm and/or positive lymph nodes after mastectomy. RT was applied with tangential fields to the whole chestwall. The median dose to the chestwall was 50 Gy. Also, a median total dose of 50 Gy was applied to regional lymphatics when indicated. Palliative radiotherapy of 30 Gy was given to patients with bone metastasis.

The primary endpoint of the study was to determine the progression-free survival (PFS) and the statistically significant influencing parameters. PFS was defined as the time between the date of diagnosis and the date of any failure. PFS analysis was evaluated by the Kaplan-Meier method. The results were evaluated at a 95% confidence interval and $p < 0.05$ significance level.While comparing the effects of parameters such as age, BMI, blood group, tumor size, histology, grade, hormonal receptors, log-rank analysis was used. SPSS 22 software was used for statistical analysis and graphics.

Results

The median age of the patients was 56 years (33-88). Median BMI was 27 (21-34). The blood group of 8 patients was A, 7 patients had B, 6 patients had 0, and 5 patients had AB. Twenty-eight patients were right-handed, one patient was left-handed, one patient was amphidextrous.Ten patients had a comorbid disease. One patient had a history of gynecomastia. One of the patients had previous radiotherapy for Hodgkin's disease, and the other had a history of radiotherapy for thymoma. Twenty patients had a family history of cancer. Five of them had a family history of breast cancer. While the tumor was in the right breast in 11 patients (34.4%), it was in the left breast in 20 patients (62.5%), one patient (3.1%), had bilateral breast cancer. The tumor was located retro areolar in 21 patients (65.6%). Patient and tumor characteristics are given in Table 1.

The histopathological diagnosis was made with fine-needle aspiration biopsy/FNAB in 3 patients (9.4%), trucut biopsy in 16 patients (50%), incisional biopsy in 6 patients (18.8%), and excisional biopsy in 3 patients (9.4%). The pathology of the tumor was infiltrative ductal carcinoma in 25 patients (78.1%), papillary carcinoma in 4 patients (12.5%), infiltrative lobular carcinoma/ILC in one patient (3.1%), mixed (infiltrative ductal carcinoma + infiltrative lobular carcinoma) in one patient (3.1%), and mucinous carcinoma in one patient (3.1%). The tumor was histopathologically grade 2 in 16 patients (50%), grade 3 in 13 (40.6%), and grade 1 in one patient (3.1%).

The median tumor size was 2.6 cm (0.6-7). The tumor was estrogen receptor/ER positive in 31 patients (96.9%) and ER negative in one patient (3.1%).Twenty-nine patients (90.6%) were progesterone receptor/PR positive, and 3 patients (9.4%) were PR negative. Six patients (18.8%) had human epidermal growth factor receptor/HER2 positive, and 26 (78.8%) had HER 2 negative. Only one patient (3.1%) was triple-negative.

Modified radical mastectomy/MRM and axillary dissection/AD were performed in 20 patients (62.5%), MRM and sentinel lymph node dissection/SLND in 2 patients (6.3%), Radical mastectomy/RM was performed in 3 patients (9.4%) and simple mastectomy/SM in 3 patients (9.4%). Lymph node metastases were present in 19 patients (59.4%). Nine patients (28.1%) had distant metastases at the time of diagnosis. Three patients had bone metastases, 4 patients had lung metastases, 2 patients had bone and lung metastases. The stages of the patients according to AJCC, 8th edition are given in Table 1.

Adjuvant chemotherapy was administered to 13 patients (40.6%), while chemotherapy was administered to 6 patients (18.8%) due to metastatic disease.Tamoxifen was administered to 31 patients (96.9%). Sixteen patients (50%) received curative radiotherapy, and 2 patients (6.3%) received pal-

Table 2. Treatment characteristics

	n (%)
Biopsy type	
FNAB	3 (9.4)
Trucut	16 (50)
İncisional	6 (18.8)
Excisional	3 (9.4)
None	4 (12.5)
Surgery type	
MRM+AD	20 (62.5)
MRM+SLND	2 (6.3)
RM	3 (9.4)
SM	3 (9.4)
None	4 (12.5)
Chemotherapy	
None	13 (40.6)
Adjuvant	13 (40.6)
Metastatic	6 (18.8)
Endocrine treatment	
Tamoxifen	31 (96.9)
None	1 (3.1)
Radiotherapy	
Curative	16 (50)
Palliative	2 (6.3)
None	14 (43.8)

FNAB: fine needle aspiration biopsy; MRM: modified radical mastectomy; AD: axillary dissection; SLND: sentinel lymph node dissection; RM: radical mastectomy; SM: simple mastectomy

liative radiotherapy. Treatment characteristics are shown in Table 2.

The median follow-up time was 26 months (3-121).During this period, local-regional recurrence developed in 3 patients and visceral recurrence in 5 patients. During follow-up, secondary neoplasm (lung cancer) developed in 2 patients.

The median PFS was 22 months and 2-year PFS was 72%. A statistically significant correlation was found between PFS and tumor size (p 0.042). The 2-year PFS was calculated as 100% in patients with tumor size less than 3 cm, and 55% in patients with tumor size 3 cm and above (Figure 1).

Discussion

In our study, the median patient age was 56 years, which is approximately 10 years younger than stated in the literature. In the literature, the median age is 67 in male breast cancer patients and 62 in female breast cancer patients [7, 8]. In our country, female breast cancers are also seen at a younger age compared to western countries [9].

Family history, estrogen, and androgen imbalance lie in the etiology. Their frequency increases in conditions such as Klinefelter syndrome, obesity, gynecomastia, cirrhosis, and a previous history of radiotherapy to the chestwall [10]. In our study, 5 patients had a family history of breast cancer, one patient had gynecomastia, and 2 patients had a history of radiotherapy to the chestwall. It may be beneficial for patients in the risk group to be included in the routine breast cancer screening programs in women.

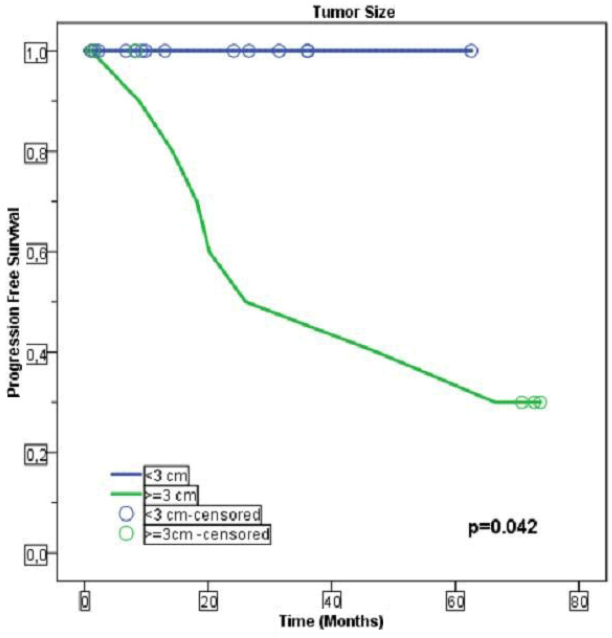

Figure 1. Kaplan-Meier curve for PFS by size (≥3 cm vs <3 cm).

ABO blood type has been associated with several malignancies such as gastric and pancreatic cancer; however, the relationship between the ABO blood group and breast cancer risk or survival is inconsistent [11]. The type, grade, stage, and hormonal status of breast cancer showed no significant associations with the ABO blood group [12]. There is no study in the literature on the relationship between blood group and breast cancer in male patients only, and it is not possible to comment because the number of patients is small. There was no difference between blood groups in our study either.

In the literature, the rate of carcinoma *in situ* was approximately 10%, and the rate of infiltrating ductal carcinoma approximately 85%. Infiltrative lobular carcinoma, which is the second most common in women, is rare in men due to lack of breast tissue. Unlike women, papillary carcinoma is the second most common in men [13,14]. In our study, IDC was observed in 78.1%, papillary carcinoma in 12.5% of the patients, and ILC was seen in one patient (3.1%).

In recent years, mastectomy rates have decreased and breast-conserving surgery rates have increased in female breast cancer patients. Conversely, there was an increase in mastectomy rates in male breast cancer patients [15]. This is due to reasons such as lack of breast tissue in male patients, the tumor being around the nipple-areola, and the inability to obtain a safe surgical margin [16]. In our study 66% of the patients complained of retro areolar mass, and all patients underwent mastectomy. Since axillary lymph node metastases are common in male breast cancer patients, the most frequently applied surgical method was MRM. In the studies, no difference was found between mastectomy and breast-conserving surgery in terms of disease-free survival and overall survival in male patients. Thus, it is recommended that lumpectomy be performed more frequently [17]. However, more prolonged survival with mastectomy has been demonstrated in the T4 or N+,M0 patient group [18].

Compared to female patients, the rate of ER and PR positivity is higher in male patients. In male breast cancer, the tumor is usually ER and PR +, and triple negative ratio is unilateral [2]. In our study, the tumor was 97% ER+, 91% PR +, and it was triple negative in only one patient. The tumor was unilateral in 97% of the patients and bilateral in only one patient. Our findings are compatible with the literature.

In our study, adjuvant radiotherapy was delivered to 16 patients (50%). Adjuvant curative radiotherapy was applied in tumors larger than 5 cm and/or positive lymph nodes after mastectomy. In the

literature, adjuvant radiotherapy is recommended in tumors larger than 5 cm and/or positive lymph nodes in the presence of other risk factors such as early age, high tumor grade, LVI, extranodal extension, and positive surgical margins [19, 20]. There was an increased survival in male breast cancer patients with T4 or N+,M0 with radiotherapy in the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database [21]. There are also studies showing that disease-free survival is increased with adjuvant radiotherapy [22]. Some of the studies are showing that there is no increase in survival with additional radiotherapy in older women with early-stage ER+ tumors undergoing breast-conserving surgery and endocrine treatment [23]. However, due to lack of compliance with endocrine therapy and differences in tumor biology in male breast cancer patients, this situation is uncertain, and radiotherapy is more effective in elderly male patients than elderly females [15].

The role of neoadjuvant chemotherapy in male breast cancer patients is unclear. Neoadjuvant chemotherapy was not applied to any patient in our study. Adjuvant chemotherapy was administered to 13 patients (40.6%), while chemotherapy was given to 6 patients (18.8%) due to metastatic disease. Yadav et al found increased survival with chemotherapy in stage 2 and 3 patients. No increase in survival was found in stage 1 patients. Adjuvant chemotherapy schemes were also created based on studies on female patients [15].

Since most male breast cancers are ER+, adjuvant endocrine therapy is usually applied. Men with hormone receptor-positive breast cancer candidates for adjuvant endocrine therapy should be offered tamoxifen [24]. In our study, tamoxifen was applied to 31 patients (97%). Studies are showing increased survival with tamoxifen use in ER+ male breast cancer patients [25,26]. However, approximately 20% of male patients interrupt the treatment due to side effects that reduce the quality of life, such as decreased libido [27].

In our study, the median follow-up time was 26 months (3-121). During this period, local-regional recurrence developed in 3 patients and visceral recurrence in 5 patients. During follow-up, secondary neoplasm (lung cancer) developed in 2 patients. The median PFS was 22 months, 2-year PFS was 72%. A statistically significant correlation was found between PFS and tumor size (p 0.042). The 2-year PFS was calculated as 100% in patients with tumor size less than 3 cm, and 55% in patients with tumor size 3 cm and above. There are studies in the literature exploring the effect of age , tumor size, molecular subtype, axillary lymph node involvement, and tumor grade on overall survival [10,15,28,29]. However, there are very few studies on prognostic predictors for PFS. Many studies have shown that male patients have lower survival than female patients [6].This is due to the fact that screening programs that are routine for women are not applied to men. However, most male breast cancer patients have a history of other comorbid diseases and/or secondary cancer, and these patients die from other diseases more frequently than women. In our study, lung cancer developed in 2 patients during follow-up, and therefore, they died.

The limitations of our study are that it is a single-center, retrospective study with a small number of patients. Our median follow-up period is also 26 months, which is shorter when compared to similar studies in the literature [28-31]. Since our follow-up period was short, we could not evaluate overall survival and disease-specific overall survival.

In conclusion, patients in this study were younger compared to Western series. Apart from this, the patients were compatible with the literature in terms of clinicopathological and treatment features. Tumor size (≥3cm) was found to be a prognostic factor affecting progression-free survival. The application of routine screening programs in female breast cancers to risky groups in male patients has prognostic importance.

Conflict of interests

The authors declare no conflict of interests.

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