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ORIGINAL ARTICLE

Long-Term Follow-Up of Patients with Male Breast Cancer, Single-Center Experience

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OBJECTIVE

Male breast cancer (BC) represents <1% of all BC cases. Our study aimed to define immunohistochemistry (IHC) based surrogate subtype distribution of male BCs, and to define the recurrence pattern and survival among subgroups.

METHODS

We retrospectively reviewed the medical records of patients with male BC admitted to Ege University School of Medicine, Medical Oncology and Radiation Oncology Clinics between 1998 and 2017. Patient demographics, pathological feature of the primary tumor, adjuvant treatment options, and survival data were analyzed. We defined intrinsic BC subtypes according to estrogen receptor (ER), progesterone receptor (PR), HER-2, and ki-67 status.

RESULTS

We identified 58 patients with male BC. The median age at diagnosis was 59 years (IQR: 30–78), and median follow-up was 83.7 months. Invasive ductal carcinoma was the most common histology (79.3%). Of the patients, 8.6% presented with stage-4 disease. A total of 24 (41.4%) patients had luminal A-like, 28 (48.3%) had luminal B-like, 2 (3.4%) had HER-2 positive, and 4 (6.9%) had triple negative breast cancer (TNBC). Eighteen deaths were observed during follow-up. The overall survival (OS) and disease-free survival (DFS) rates among BC subgroups were not statistically significant. Median OS was 161 months (95% CI 94.7–228.4) in the patient group. DFS was statistically related to initial tumor stage.

CONCLUSION

The disease onset was found at younger age with more locally advanced setting compared to literature. Luminal predominance was demonstrated. Initial stage but not BC subtypes predict the risk of relapse in patients with male BC.

Keywords: Breast cancer subtypes; male breast cancer; prognosis; survival.

Introduction

Male breast cancer (BC) is a rare disease representing <1% of all BC cases.[1] Overall, 15%–20% of men with BC had a family history, and 10% carry a hereditary cancer.[2] BRCA-2 is the most clearly defined gene associated with male BC with a lifetime risk of 1%–6%. The risk is lower (1%) in BRCA-1 mutation.[2] The previous reports in literature demonstrated that male BC is almost exclusively hormone receptor positive

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and is diagnosed at later age than female counterparts.[3] Basal-like tumors were rare.[4] The data on HER-2 overexpression by IHC are inconsistent in studies. Two series reported 1.7% and 15% HER-2 positivity, respectively.[5,6]

As the incidence is low, the standard therapy approach is based on extrapolation of BC clinical trials most of which excluded male gender or had few numbers of patients. The Human Cancer Genome Atlas network sequenced breast tumor samples and identified four main subtypes caused by different subsets of genetic and epigenetic abnormalities.[7] These subtypes have diverse response to treatment procedures and have discrete prognoses.[8]

Luminal types are the most common subtypes of BC and make up the majority of ER positive BCs.[7,9] The human epidermal growth factor 2 (HER2)-enriched subtype constitute about 10%–15% of BCs and is characterized by high expression of HER2.[7] These tumors are often negative for ER and PR. The triple negative clinical phenotype mostly comprises the basal-like molecular subtype, although triple negative, and basal BCs are not synonymous, and there is substantial heterogeneity within TNBCs.[10]

The exact role of intrinsic BC subtypes in male BC is not clear. In Human Cancer Genome Atlas, only 6 of 507 tumors (1%) were sequenced from male tumors.[11]

As genomic profiling for every patient is not feasible in routine clinical practice, tumors are grouped into surrogate intrinsic subtypes, defined by routine immunohistochemistry (IHC), for the purpose of prognostication and treatment decision-making. In 2015, St. Gallen Consensus Conference defined surrogate definitions of intrinsic BC subtypes according to estrogen receptor (ER), progesterone receptor (PR), HER-2, and ki-67 to four BC subtypes: luminal A, luminal B, HER-2 overexpressed, and basal-like.[8] In most clinical studies and retrospective analyses including female patients, the impact of BC subtypes on disease prognoses had been demonstrated.[12]

To our knowledge, there is no data that specifically analyzed the patients with male BC in Turkey. In our study, we aimed to define the patient demographics and BC subtypes in single institution and to compare our findings with the literature.

Materials and Methods

We retrospectively analyzed medical data of patients with male BC admitted to Medical Oncology and Radiation Oncology Clinic of Ege University School of Medicine between 1998 and 2017. Patients with incomplete IHC data to define subtype were excluded. We collected patient demographics, clinical, and pathological characteristics of the primary tumor, adjuvant treatment types, and survival data.

We used the surrogate definitions qualified by 2013 St. Gallen International Consensus Conference and European Society of Medical Oncology guidelines to determine intrinsic BC subtypes [8]. Patient population was divided into four subtypes based on ER, PR, HER-2, and ki-67 expression: luminal A-like (ER positive, HER-2 negative, ki-67 low, and PR high), luminal B like (ER positive, HER-2 negative, and either ki-67 high or PR low OR ER positive, HER-2 positive with any ki-67, and PR value), HER-2 positive (HER-2 positive, ER, and PR negative), triple negative (ER, PR, and HER-2 negative). Suggested threshold value for PR and high ki-67 were 20%. For ER positivity, 1% threshold was selected.

Categorical data were summarized as count and percent, and continuous data were summarized as median and interquartile range (IQR). Chi-square and Kruskal–Wallis tests were used to compare categorical and continuous data among patient subgroups. Survival durations were estimated with Kaplan–Meier method, and log rank test was used to compare survival durations of patient subgroups. Disease-free survival (DFS) was defined as the interval between diagnosis of inflammatory BC and date of recurrence or death from any cause. Overall survival (OS) was measured from diagnosis to death from any cause. All p-values reported were two-sided, and a p-value of less than 0.05 was considered significant. Statistical analyses were performed using the Stata software (version 14, TX, StataCorp LP).

Results

Fifty-eight patients were included in the final analysis. The median age at diagnosis was 59 years (IQR: 30–78), and median follow-up was 83.7 months. Invasive ductal carcinoma was the most common histology (79.3%); 5.1% of the patients had inflammatory carcinoma and 3.4% had lobular carcinoma. Axillary lymph nodes were negative in 27% of patients; and 25.9%, 17.2%, and 19% of the patients had N1, N2, and N3 disease, respectively. Of the patients, 8.6% presented with stage 4 disease, and 91.4% had nonmetastatic disease at initial diagnosis.

Clinical and pathological characteristics of the patient population according to surrogate subtypes are

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summarized in Table 1. Of the 58 patients with male BC; 24 (41.4%) were luminal A-like, 28 (48.3%) were luminal B-like, 2 (3.4%) were HER-2 positive, and 4 (6.9%) were triple negative (TNBC). ER was positive in 81%, PR was positive in 63.7%, hormone positivity was in 87.9%, and HER-2 was positive in 18.9% patients. The tumor stage and nodal stage was not found different between patients with luminal A and B. Adjuvant chemotherapy and hormonotherapy was administered to 48 patients (82.8%), and adjuvant radiotherapy was applied to 38 patients (65.5%). There were five patients aged ≤40 years. Four of them had luminal B disease, and 50% developed metastases on follow-up. One patient with TNBC has no evidence of disease and is still alive.

In initial setting, 4.1% of luminal A and 14.2% of luminal B subgroup presented with metastatic disease. The HER-2 and TNBC subgroup had few patients; however, these patients presented with localized disease at first presentation. Local recurrence/metastatic disease occurred in 13 patients (22.4%) on follow-up: 3 had local relapse, 10 had distant metastases. On follow-up, 25% of luminal B patients, 16% of luminal A patients, and both HER-2-enriched patients had recurrence. None of the patients with TNBC showed relapse. All patients who developed metastatic disease had bone involvement, besides two patients had simultaneously lung and three patients had liver metastases.

The DFS rates among BC subgroups were not statistically significant (p=0.56); five-year DFS was 90% in luminal A, 93% in luminal B, 100% in HER-2 positive, and 50% in TNBC (Fig. 1a, 1b). DFS was statistically related to initial tumor stage. Ten-year DFS was found 100% in stage 1, 90% in stage 2, and 47% in stage 3 patients (p=0.02).

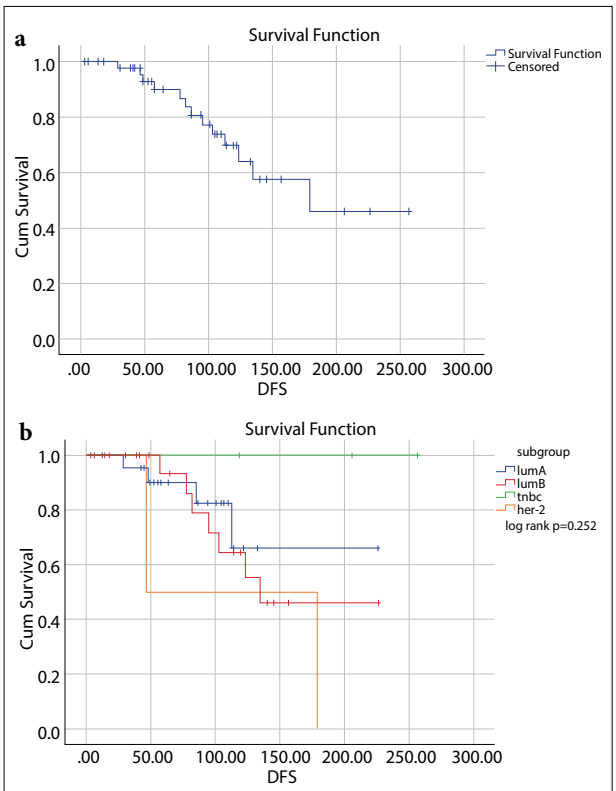

Fig. 1. (a) Disease-free survival in patients with localized disease at presentation. (b) Disease-free survival according to breast cancer subtypes.

Table 1 Patient characteristics and tumor features

	Number (%)		Number (%)		Number (%)
Age at diagnosis				**Adjuvan treatment**	
Median	59	**Node**		Chemotherapy	48 (82.8)
Range	30-78	N0	16 (27)	Hormonotherapy	48 (82.8)
		N1	15 (25.9)	Trastuzumab	9 (15.5)
Tumor histology		N2	10 (17.2)	Radiotherapy	38 (65.5)
Invasive ductal	46 (79.3)	N3	11 (19.0)	Primary surgery	55 (94.8)
Inflammatory	3 (5.1)	Unknown	6 (10.3)		
Lobular	2 (3.4)				
Others	7 (12)				
				IHC subgroups	
Tumor stage		**Stage**		Luminal A	24 (41.4)
T1	18 (31)	Stage 1	9 (15.5)	Luminal B	28 (48.3)
T2	29 (50)	Stage 2	21 (36.2)	Triple negative	4 (6.9)
T3	6 (10.3)	Stage 3	23 (39.7)	Her-2 enriched	2 (3.4)
T4	2 (3.4)	Stage 4	5 (8.6)		
Unknown	3 (5.1)				

Table 2 Overall survival in male breast cancer subgroups

	Luminal A (n=24)	Luminal B (n=28)	HER2 positive (n=2)	Triple-negative (n=4)	All (n=129)
Overall survival					
No. of events	5 (20.8%)	10 (35.7%)	2 (100%)	1 (25%)	61 (47.3%)
Median OS, months	121.770	161.600	46.7	NE	161.6
(95% CI)	(105.1-138.3)	(106.4-216.7)			(94.7-228.4)

Abbreviations: NE: Not estimable; OS: Overall survival

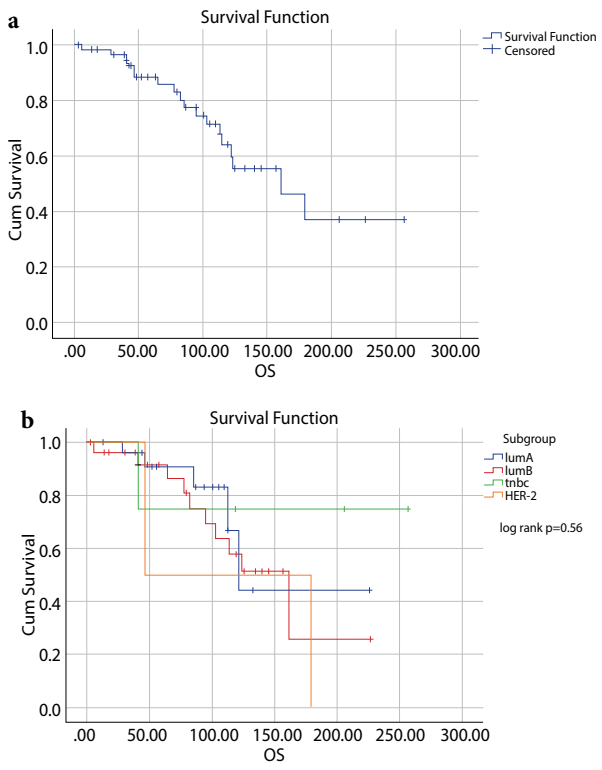

Fig. 2. (a) Overall survival in whole patient group. (b) Overall survival according to breast cancer subtypes.

At a median follow-up of 83.7 months, 18 deaths were observed. Two of five patients with initial metastatic cancer and ten of thirteen patients with disease recurrence at follow-up died due to BC. One patient with TNBC developed secondary pancreas cancer and died due to hepatic metastases. Five patients' death could not be directly attributed to BC because of lack of data.

The median OS was 161 months (95% CI 94.7–228.4) in whole patient group (Fig. 2a). We found no significant differences between luminal A and B in OS (Table 2, Fig. 2b). When all patients' survival was evaluated according to absence or presence of metastatic disease, patients with initial metastatic disease [121.7 (95% CI 5.4–238)] or disease recurrence at follow-up [median OS 95.0 (95% CI 67.2–122.8)] period had demonstrated inferior survival than nonmetastatic disease (median OS not reached, log rank p=0.003) (Fig. 3).

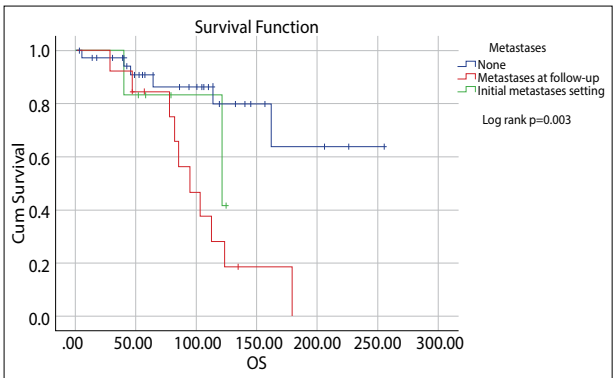

Fig. 3. Overall survival according to metastases.

Discussion

In our study, we found that median age of patients with male BCs in Turkey is younger than the global studies with similar hormone receptor positivity rates and prominent histology ductal carcinoma.[1,11]

Similar to previous studies, luminal subtypes (89.7%) constitute the majority of the patients.[2] The HER-2-enriched and TNBC subtypes were few to evaluate in statistical analyses. We did not find significant differences in tumor characteristics and relapse rates between luminal A and B. Although our HER-2-enriched subtype is few, in luminal B subtype 32.1% of the patients had HER-2 positivity. HER-2 was positive in 18.9% of total patient group, which is far more common than in a previous study.[13]

The largest dataset analyzed on male cancer was achieved from EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program.[13] A total of 1483 tumors underwent central pathology review: tu-

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mor stage was T1 in 49%, T2 in 38%, T3 in 2%, and T4 in 11%. Pathological nodal stage was NO in 59%, N1 in 32%, N2 in 5%, and N3 in 3%. Four percent had denovo metastatic disease. Although in our study, metastatic disease rates are similar, in nonmetastatic setting our patients seem to be presented at locally advanced stage than early-stage BC. We demonstrated N2 and N3 disease frequency as 17.2% and 19%, respectively. In contrast, T1 (31%) and T2 (50%) tumors were more common in our analyses. Despite smaller tumor size, larger nodal involvement may indicate an unfavorable genetic profile in our dataset. However, as no further genomic analyses could be performed, the present knowledge cannot fully reproduce a direct statement.

The OS and DFS did not show any significant difference among BC subtypes. For HER-2 positive group, we had only two patients. Among them, one had adjuvant trastuzumab and presented with visceral crisis. The second patient did not receive adjuvant trastuzumab and could achieve a stable disease with chemotherapy and trastuzumab combination in metastatic setting. Sanchez-Munoz et al. confirmed the correlation between IHC and PAM50 intrinsic subtypes in patients with male BC; however, they defined a proportion of patients with HER-2 negative by IHC but HER-2 enriched by PAM50 analyses.[4]

Although in female patients with BC, luminal A had a favorable prognosis than luminal B; in our male BC dataset, patients with luminal A and B had similar recurrence pattern and metastatic involvement. EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program also did not reveal any recurrence-free survival and OS in their dataset among BC subtypes.[13]

One of the limitations in our study is that as patient data was retrospectively extracted from 19-year period, the surgical treatments, the adjuvant chemotherapy options, and even histologic grade classifications vary between patients; so it would not be possible to properly compare these data between IHC subtypes. As the survival data were retrospectively evaluated, the relation of death and cancer in five patients could not be confirmed because of lack of information.

Conclusion

In conclusion, our results are valuable as we do not have a real-life data of male BC in our region. The disease onset was found at younger age with more locally advanced setting when compared to literature. Luminal predominance was demonstrated. Initial stage but not BC subtypes predict the risk of relapse in patients with male BC.

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