TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2019
doi: 10.5505/tjo.2019.1957

ORIGINAL ARTICLE

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

Burcu ÇAKAR,[1] Fatma SERT,[2] Pınar GÜRSOY,[1] Barış EMEKDAŞ,[3] Zeynep ÖZSARAN,[2] Erhan GÖKMEN,[1] Ayfer HAYDAROĞLU[2]

[1]Department of Medical Oncology, Ege University Faculty of Medicine, Tulay Aktas Oncology Hospital, Bornova, İzmir-*Turkey*
[2]Department of Radiation Oncology, Ege University Faculty of Medicine, Bornova, İzmir-*Turkey*
[3]Department of Internal Medicine, Ege University Faculty of Medicine, Bornova, İzmir-*Turkey*

OBJECTIVE

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

METHODS

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

RESULTS

We identified 58 male breast cancer patients. 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%). 8.6% of the patients presented with stage 4 disease. 24 patients had (41.4%) luminal A-like, 28 (48.3%) had luminal B-like, 2(3.4%) had HER-2 positive, and 4 (6.9%) had triple negative (TNBC) breast cancer. 18 deaths were observed during follow-up. The overall survival (OS) and disease free survival(DFS) rates among breast cancer subgroups were not statistically significant. Median OS was 161 months (95% CI 94.7-228.4) in whole 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 breast cancer subtypes predict the risk of relapse in male breast cancer patients.

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

Introduction

Male breast cancer (BC) is a rare disease representing <1% of all breast cancer cases.[1] Overall, 15% to 20% of men with breast cancer 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%. In BRCA-1 mutation, the risk is lower (1%).[2] Proportionally, male breast cancers are more hormone receptor positive .The previous reports in literature demonstrated that male BC is almost exclusively hormone receptor positive and is diagnosed

Received: February 07, 2019
Accepted: March 07, 2019
Online: March 11, 2019

Accessible online at:
www.onkder.org

Dr. Burcu ÇAKAR,
Ege Üniversitesi Tıp Fakültesi,
Tülay Aktaş Onkoloji Hastanesi,
Bornova, İzmir-Turkey
E-mail: burcu.cakar@gmail.com

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

As the incidence is low, the standart therapy approach is based on extrapolation of breast cancer 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 breast cancer and make up the majority of ER-positive breast cancers.[7,9] The human epidermal growth factor 2 (HER-2)-enriched subtype constitute about 10 to 15 percent of breast cancers and is characterized by high expression of HER-2.[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 breast cancers are not synonymous and there is substantial heterogeneity within TNBCs.[10]

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

As genomic profilling for every patient is not feasible in routine clinical practice,for the purpose of prognostification and treatment decision making, tumours are grouped into surrogate intrinsic subtypes, defined by routine immunohistochemistry (IHC). In 2015, StGallen Consensus Conference has defined surrogate definitions of intrinsic breast cancer subtypes according to estrogen receptor (ER), progesterone receptor (PR), HER-2 and ki-67 to four breast cancer 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 prognose had been demonstrated.[12]

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

Materials and Methods

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

Surrogate definitions qualified by 2013 St Gallen International Consensus Conference and European Society of Medical Oncology guidelines were used to determine intrinsic breast cancer subtypes.[8] Patient population was divided into four subtypes based on estrogen receptor (ER), progesterone receptor (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 breast cancer 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; 25.9%, 17.2%, 19% of the patients had N1, N2, and N3 disease, respectively. 8.6% of the patients presented with stage 4 disease, 91.4% had nonmetastatic disease at initial diagnosis.

Clinical and pathological characteristics of the patient population according to surrogate subtypes are summarized in Table 1. Of the 58 male breast cancer

patients; 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 luminal A and B patients. Adjuvant chemotherapy and hormonotherapy was administered to 48 patients (82.8%), adjuvant radiotherapy was applied to 38 patients(65.5%). There were 5 patients ≤40 years old. Four of five had luminal B disease and 50% developed metastases on follow-up. 1 patient with TNBC has no evidence of disease and 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 at 13 patients (22.4%) on follow-up, 3 had local relapse, 10 had distant metastases. 25% of luminal B patients, 16% of luminal A patients, both HER-2 enriched patients had recurrence on follow-up. None of the TNBC patients did show relapse. All patients who developed metastatic disease had bone involvement, besides 2 patients had simultaneously lung and 3 patients had liver metastases.

DFS rates among breast cancer subgroups were not statistically significant (p=0.56); 5 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. 10 years DFS was found 100% in stage 1, 90% in stage 2, 47% in stage 3 patients (p=0.02).

At a median follow-up of 83.7 months, 18 deaths were observed. 2 of 5 patients with initial metastatic cancer, 10 of 13 patients with disease recurrence at fol-

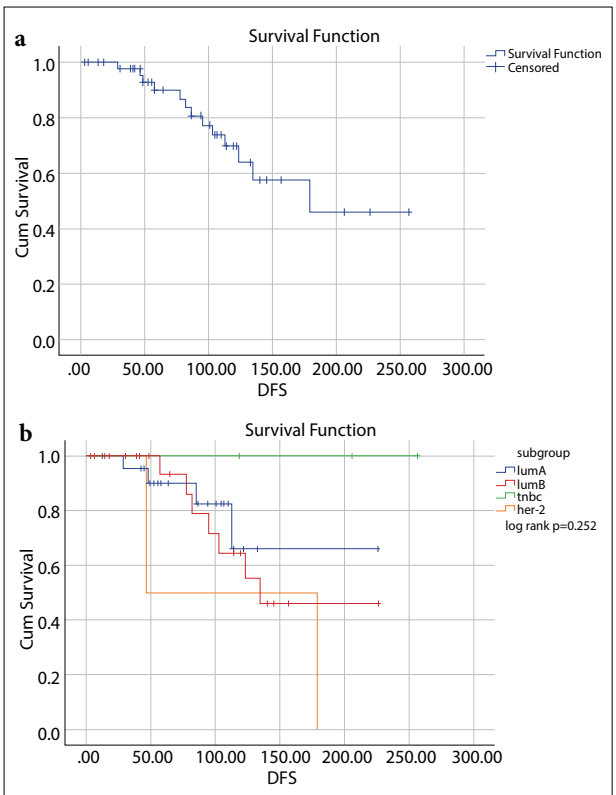

Fig. 1. (a) Disease free survival in patients with localised disease at presentation. (b) Disease free survival according to breast cancer subtypes.

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

low-up died due to breast cancer. 1 patient with TNBC developed secondary pancreas cancer and died due to hepatic metastases. Five patients death could not be attributed directly to BC as lack of data.

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 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

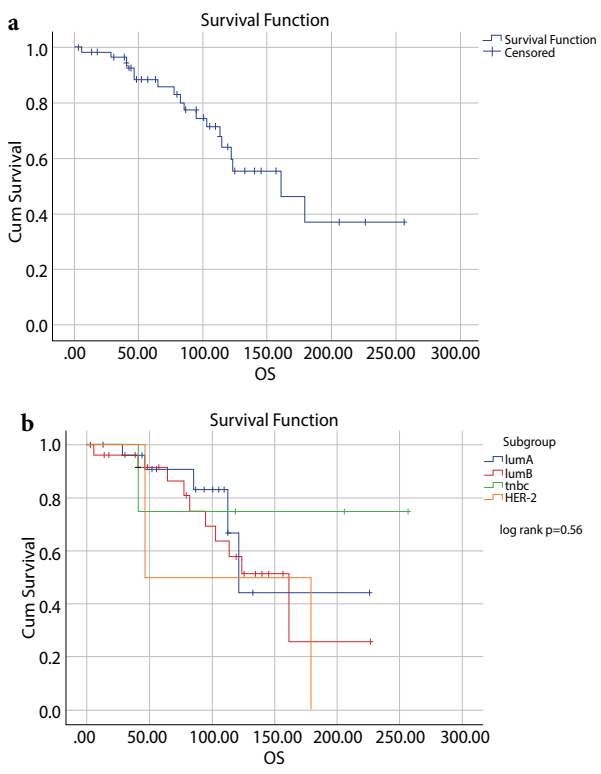

Fig. 2. (a) Overall survival in whole patient group. (b) Overall survival according to breast cancer subtypes.

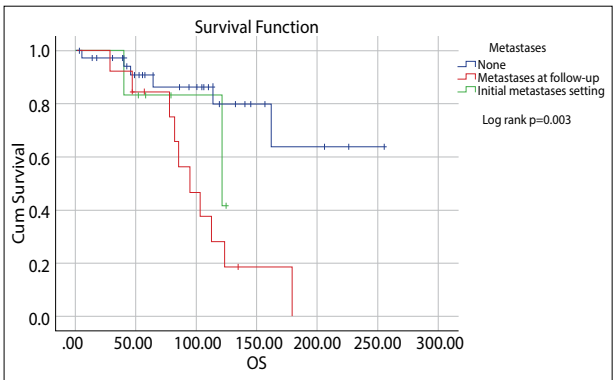

Fig. 3. Overall survival according to metastases.

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).

Discussion

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

Luminal subtypes (89.7%) constitute the majority of the patients similar to previous studies.[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 a previous study.[13]

The most largest dataset analysed on male cancer was achieved from EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Programme. [13] 1483 tumors underwent central pathology review: Tumor 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. 4% had denovo metastatic disease. Although in our study, metastatic disease rates are similar; in nonmetastatic setting our patients seems to be presented at locally advanced stage than early stage breast cancer. 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 can not fully reproduce a direct statement.

The OS and DFS did not show any significant difference among breast cancer subtypes. For HER-2 positive group, we had only 2 patients. Among them, one had adjuvan trastuzumab and presented with visseral crisis. The second patient did not receive adjuvan 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 male BC patients, however they defined a proportion of patients with HER-2 negative by IHC but HER-2 enriched by PAM50 analyses.[4]

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

One of the limitations in our study that as patient data could be extracted from 19 years period retrospectivelly ; the surgical treatments, the adjuvan chemotherapy options and even histologic grade classifications vary between patients, so it would not be possible to compare these data properly between IHC subtypes. As the survival data retrospectivelly evaluated, the relation of death and cancer in 5 patients could not be confirmed as 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 breast cancer subtypes predict the risk of relapse in male breast cancer patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Ethics Committee Approval: Approval from the research ethics board was obtained from Ege University Ethic Committee.

Financial Support: None declared.

Authorship contributions: Concept – B.Ç., F.S., P.G., B.E., Z.Ö., E.G., A.H.; Design – B.Ç., F.S., P.G., B.E., Z.Ö., E.G., A.H..; Supervision – B.Ç., F.S., P.G., B.E., Z.Ö., E.G., A.H.; Materials – B.Ç., F.S., P.G., B.Ö.; Data collection &/or processing – B.Ç., P.G., B.E.; Analysis and/or interpretation – B.Ç., F.S.; Literature search – P.G., F.S., B.E.; Writing – B.Ç.; Critical review – B.Ç., F.S., P.G., B.E., Z.Ö., E.G., A.H.

References

1. Korde LA, Zujewski JA, Kamin L, Giordano S, Domchek S, Anderson WF et al. Multidisciplinary meeting on male breast cancer: summary and research recommendations. J Clin Oncol 2010;28(12):2114-22.
2. Leon-Ferre RA, Giridhar KV, Hieken TJ, Mutter RW, Couch FJ, Jimenez RE et al. A contemporary review of male breast cancer: current evidence and unanswered questions. Cancer Metastasis Rev 2018;37(4):599-614.
3. Gucalp A, Traina TA, Eisner JR, Parker JS, Selitsky SR, Park BH et al. Male breast cancer: a disease distinct from female breast cancer. Breast Cancer Res Treat 2019;173(1):37-48.
4. Sánchez-Muñoz A, Vicioso L, Santonja A, Álvarez M, Plata-Fernández Y, Miramón J et al. Male breast cancer: correlation between immunohistochemical subtyping and PAM50 intrinsic subtypes, and the subsequent clinical outcomes. Mod Pathol 2018;31(2):299-306.
5. Bloom KJ, Govil H, Gattuso P, Reddy V, Francescatti D. Status of HER-2 in male and female breast carcinoma. Am J Surg 2001;182(4):389-92.
6. Curigliano G, Colleoni M, Renne G, Mazzarol G, Gennari R, Peruzzotti G et al. Recognizing features that are dissimilar in male and female breast cancer: expression of p21Waf1 and p27Kip1 using an immunohistochemical assay. Ann Oncol 2002;13(6):895-902.
7. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012;490(7418):61-70.
8. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v8-30.
9. Ma CX, Ellis MJ. The Cancer Genome Atlas: clinical applications for breast cancer. Oncology (Williston Park) 2013;27(12):1263-9, 1274-9.

10. Burstein MD, Tsimelzon A, Poage GM, Covington KR, Contreras A, Fuqua SA et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. Clin Cancer Res 2015;21(7):1688-98.
11. Piscuoglio S, Ng CK, Murray MP, Guerini-Rocco E, Martelotto LG, Geyer FC et al. The Genomic Landscape of Male Breast Cancers. Clin Cancer Res 2016;22(16):4045-56.
12. Mazouni C, Rimareix F, Mathieu MC, Uzan C, Bourgier C, André F et al. Outcome in breast molecular subtypes according to nodal status and surgical procedures. Am J Surg 2013;205(6):662-7.
13. Vermeulen MA, Slaets L, Cardoso F, Giordano SH, Tryfonidis K, van Diest PJ et al. Pathological characterisation of male breast cancer: Results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Eur J Cancer 2017;82:219-227.