Breast Cancer in Men: A Single Center Experience Over a Period of 22 years

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ABSTRACT: **Background:** Male breast cancer (MBC) is a rare disease that is poorly understood. Treatment protocols are widely extrapolated from breast cancer in women.

Objectives: To review the experience with MBC of a single center in Israel over a period of 22 years.

Methods: This single center retrospective study evaluated all patients diagnosed with MBC over a period of 22 years (1993–2015). Data were extracted from patient medical charts and included demographics, clinical, surgical, and oncological outcomes.

Results: The study comprised 49 patients. Mean age at diagnosis was 64.1 ± 13.5 years. The majority were diagnosed at early stages (1A–2A) (54.4%), 30.6% were stage 3B mostly due to direct skin and nipple involvement, and 59.2% of the patients had node negative disease. All of the patients were diagnosed with invasive ductal carcinoma and 30.6% had concomitant ductal carcinoma in situ. Estrogen receptor (ER) status was predominantly positive and luminal B (HER2-) was the most common subtype. Of the patients, 18.4% were BRCA carriers. The majority of patients underwent mastectomy. Radiotherapy was delivered to 46.9% and hormonal therapy to 89.8%. Chemotherapy was administered to 42.9%. Overall survival was 79.6% with a median survival of 60.1 (2–178) months; 5- and 10-year survival was 93.9% and 79.6%, respectively. Progesterone receptor (PR)-negative patients had a significantly improved overall survival.

Conclusions: MBC has increasing incidence. PR-negative status was associated with better overall survival and disease-free interval. Indications to radiotherapy and hormonal therapy need standardization and will benefit from prospective randomized control trials.

IMAJ 2020; 22: 160–163

KEY WORDS: BRCA, breast cancer, male gender, oncological outcome, surgical treatment

Breast cancer (BC) is the most common malignancy in women [1]. Research in breast cancer is vast and covers most of the clinical and oncological aspects of this common disease. Breast cancer in men (MBC) is uncommon and poorly understood. Most of the treatment plans are extrapolated from studies in women. Incidence of BC in women has been decreasing over the years, which has been attributed to a decline in use of hormone replacement therapy among post-menopausal females [1,2]. This change, of course, does not translate into the same incidence reduction in men and in fact the incidence of age-adjusted MBC is on the rise.

One percent of all cases of BC is the traditionally estimated incidence. Data from the Surveillance, Epidemiology, and End Results (SEER) program indicate that the age-adjusted incidence rate has increased from 0.85 cases per 100,000 men in the general population in 1975 to a high of 1.43 cases per 100,000 in 2011. The lifetime risk of breast cancer for a man is approximately 1:1000, as compared with 1:8 for a woman [2]. To improve this huge gap in data related to MBC, the European Society of Medical Oncology (ESMO) initiated the international MBC program. Partial results were published in 2017 in a population-based study of 1483 male patients with BC. The authors concluded that MBC is usually estrogen receptors (ER), progesterone receptor (PR), and androgen receptors (AR) positive, as well as Luminal B-like/HER2-negative. Most patients are T1 at diagnosis but only a few went through breast conserving surgery (BCS) with significant improvement of survival over time [3].

The purpose of the current study is to present an overview of the experience and outcome of male patients with breast cancer in a single center in Israel over a period of 22 years and to review the changes in clinical and oncological outcome over time.

PATIENTS AND METHODS

Charts of all male patients who underwent surgery for breast cancer at Sheba Medical Center in Tel Hashomer, Israel, from January 1993 through December 2015 were reviewed retrospectively. Data included demographics, clinical, surgical, pathological, and oncological outcomes.

The study was approved by the institutional review board. Informed consent was waived.

STATISTICAL ANALYSIS

Continuous parametric variables were analyzed using Student's *t*-test. The Mann-Whitney U test was used to analyze non-parametric variables. Chi-square test was applied to analyze the association between frequencies in a univariate fashion. Multivariate analysis was performed using a stepwise logistic regression model and a likelihood ratio test was applied to identify positive associations with the primary and secondary measure of outcome. JMP Pro for Mac (Version 14.0.0) was used to analyze the data. $P < 0.05$ (2-sided) was considered statistical significance.

RESULTS

During the time frame of the study 49 male patients were diagnosed with breast cancer and were treated surgically. Mean age of the patients was 64.1 ± 13.5 years. The most common ethnicity was Ashkenazi Jewish in 66% [n=29] of the cases. Mean age at diagnosis of the Ashkenazi Jews was not different from the Sephardic Jews [63.9 ± 13.8 vs. 68.4 ± 10.1, $P = 0.56$). Family history of breast cancer in a first degree relative was observed in 24.5% (n=12) of the patients. Genetic testing was performed in 46.9% of the patients and 18.4% (n=9) were BRCA carriers. Five patients tested positive for the BRCA1 and the remaining for BRCA2 [Table 1]. Mean age of the BRCA carriers at diagnosis was lower but this did not reach statistical significance (58.4 ± 14.8 vs. 65.8 ± 12.8, $P = 0.13$).

Mean tumor size was 2.2 ± 1 cm and most of the patients were node negative at diagnosis (59.2%). Accordingly, the majority of patients were diagnosed at early stages (IA and 2A in 29.2% and 25%, respectively). Stage 3B at diagnosis was as common (31.3%) not due to the size of the tumor or nodal disease but because of direct involvement of the skin and the nipple.

Co-morbidities included hyperlipidemia, diabetes mellitus, and benign prostatic hypertrophy. One patient had Klinefelter syndrome, which is known to have an increased incidence of breast cancer [4] [Table 1]. Six patients (12.2 %) had a previous or later diagnosis of prostate cancer and seven patients (14.3%) had other types of cancer (esophagus, stomach, urothelial transient cell carcinoma, colon cancer, and squamous cell carcinoma).

Table 1. Demographic and clinical data

	N=49
Age, years	64.1 ± 13.5
Ethnicity	
Ashkenazi Jews	66% (n=29)
Sephardic Jews	22.7% (n=10)
Non-Jews	12.2% (n=6)
Unknown	9% (n=4)
Family history of breast cancer (first degree)	24.5% (n=12)
Family history of breast cancer (non-first degree)	6.1% (n=3)
BRCA status	
Carrier	18.4% (n=9)
BRCA1	55.6% (n=5)
BRCA2	44.4% (n=4)
Non-carrier	34.7% (n=17)
Unknown	46.9% (n=23)
Side (left)	63.3% (n=31)
Co-morbidities	
Diabetes mellitus	25% (n=12)
Chronic renal failure	10.4% (n=5)
Benign prostatic hypertrophy	27.1% (n=13)
Hypertension	43.8% (n=21)
Ischemic heart disease	20.8% (n=10)
Hyperlipidemia	16.7% (n=8)

TREATMENT

The vast majority of patients underwent mastectomy as their initial surgical intervention. Six patients had excisional biopsy resulting with positive margins and followed by mastectomy. Two patients had lumpectomy as the curative procedure of choice, both resulting as well with positive margins requiring completion mastectomy. Sentinel lymph node biopsy (SLNB) was attempted in 33 patients (67.3%). In nine cases the sentinel node was not detected and a level 1 axillary lymph node dissection (ALND) was performed. Level 2 ALND was performed in 15 patients (30.6%). A significant change over time was observed in the treatment plan with more axilla conserving surgery in 2015 than in the year 2000 ($P = 0.02$) [Table 2].

ALND level 1 and 2 yielded 13.3 ± 5.3 lymph nodes while level 1 alone 9.3 ± 7.8. Post-mastectomy radiation therapy was delivered to 23 patient, 16.3% (n=8) of them were node-negative and to 83.3% (n=15) of the node-positive ones. Adjuvant chemotherapy was delivered to 21 patients of them 20.7% (n=6) were node negative patients and 78.9% (n=15) were node-positive. Five patients received neoadjuvant hormonal therapy and one patient neoadjuvant chemotherapy. Hormonal therapy was administered to 87.8% (n=43) and frequency of this therapy did not change over time [Table 2].

HISTOLOGY AND RECEPTORS STATUS

All patients presented with invasive ductal carcinoma (IDC), 30.6% (n=15) had concomitant ductal carcinoma in situ (DCIS) within the specimen. Most of the patients presented as grade 2 (42.9%) and 3 (42.9%); and 93.9% (n=46) were ER positive as depicted in Table 3. HER2 and Ki67 were not reported routinely 15 years ago and its status is unknown in 16.3% (n=8) and 51%

Table 2. Treatment offered for patients and differences

	N=49	2000–2005	2005–2010	2010–2015	*P* value
Mastectomy + SLNB + level 1	67.3% (n=33)	18.2 (n=2)	56.3 (n=9)	73.7 (n=14)	0.02
Mastectomy + ALND	30.6% (n=15)	72.7 (n=8)	41.8 (n=7)	26.3 (n=5)	
Radical mastectomy	2% (n=1)	9 (n=1)	0	0	
Radiotherapy (yes)	52.3% (n=23)	14.3 (n=6)	21.4 (n=9)	16.7 (n=7)	0.43
Hormonal therapy (yes)	87.8% (n=43)	19.6 (n=9)	34.8 (n=16)	39.1 (n=18)	0.87

ALND = axillary lymph node dissection, SLNB = sentinal lymph node dissection

(n=25), respectively. We were able to calculate the breast cancer subtype for 67.3% (n=33) of the patients. The most common type was luminal B (HER2 negative) (52.4%) followed by luminal A (31%).

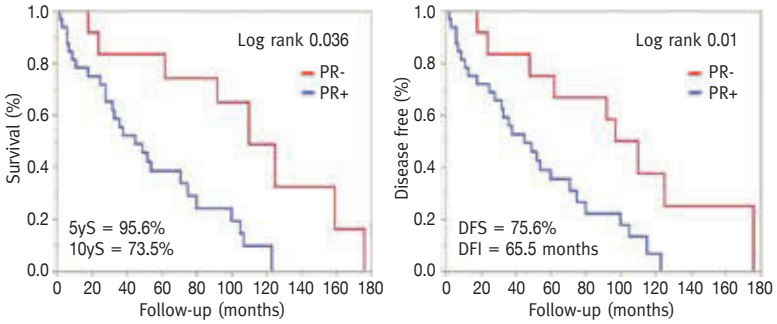
PR negative patients had a better overall survival than those who were positive (99 vs. 49 months, $P = 0.008$). The role of ER could not be ascertained because of the low number of ER-negative patients. These results were also consistent with overall survival and disease-free survival (DFS) that were significantly improved for the PR-negative patients (0.036 and 0.01, respectively) [Figure 1].

Table 3. Oncological outcome, staging, related overall survival, and disease-free interval

	N=49	Overall survival (months)	Disease-free survival (months)
Stage IA	31.3% (n=15)	67.2	59
Stage 2A	25% (n=12)	61	44
Stage 2B	2.1% (n=1)	28.3	19.8
Stage 3A	8.3% (n=4)	61.7	N/A
Stage 3B	31.3% (n=15)	48.4	71.9
Stage 3C	4.2% (n=2)	117.1	107
Stage 4	0% (n=0)	N/A	N/A

Progression (yes)	28.6 (n=14)
Site of progression Bone Lung Brain Axilla	 45.5 (n=5) 36.4 (n=4) 18.2 (n=2) 27.3 (n=3)
Overall survival	79.6%
Median overall survival (months)	60.1 (2–178)
Disease-free survival	75.6%
Disease-free interval (median)	65.5 (11.3–178.4)
5-year survival	93.9%
7-year survival	85.7%
10-year survival	79.6%

Figure 1. Kaplan-Meier curve showing significant increase in overall survival ($P = 0.036$) and disease-free survival ($P = 0.01$) of patients grouped by PR status



5yS = 5 year survival, 10yS = 10 year survival, DFI= DFI = disease-free interval, DFS = disease-free survival, PR = progesterone receptor

ONCOLOGICAL OUTCOME

The most common stage was 3B (31.3%) followed by stage 1A (29.2%), as depicted in Table 3. Single recurrence in the axilla was observed in 27.3% of the patients. Disease progression was observed in 28.6% of the cases. The most common site of progression was bone metastases in 45.5% of the cases followed by lung in 36.4% and brain in 18.2%. Overall survival was 79.6% with a median survival of 60.1 (2–178) months. Overall survival of the grade 2 patients was 61.4 (6–178) months and the grade 3, 51.2 (6.1–129) months with no significant difference between the two. Ten-year survival rate was 73.5%, and only 6.1% of the patients were lost to follow-up. Median follow-up time was 53 (2–176) months. Survival of the luminal B (HER2-) group was 38 months and the luminal A 80 months with no significant difference between the groups as depicted by Table 3. This finding should be interpreted cautiously due to a low number of patients in the luminal A group. On multivariate analysis BC subtype was the only independent predictor of survival ($P = 0.03$) when adjusted to grade ($P = 0.12$) and stage ($P = 0.23$).

DISCUSSION

This study is a single center retrospective cohort study of male patients with breast cancer who underwent surgery as part of their treatment. We presented the clinical, surgical, and pathological data as well as their oncological outcome. We found that the vast majority of MBC patients presented with IDC and 30.6% of our patients also had features of DCIS within the specimen with cribriform being the most common DCIS histological subtype. Rates of DCIS features are quite high compared to other large reports that reported incidence of roughly 10% [3,5-7]. Lobular carcinoma in men is very rare and although there are some case reports [8-10], we did not report any in our cohort of patients. Genetic testing was not routine during the whole time frame of the study and was performed in 46.9% of the patients. Median overall survival of the BRCA carriers was lower than the non-BRCA carriers but this did not reach statistical significance (51.2 vs. 61.4, $P = 0.92$).

During the time frame of the study a significant change in the surgical treatment plan offered to the patients with a shift towards conservative surgery performing mastectomy and SLNB instead of upfront ALND ($P = 0.02$) in patients with clinical negative axilla. Analysis of data from the SEER database showed that only 18% of node-negative, T1 patients, underwent breast-conserving surgery and there was no overall survival differences between the two procedures [11]. It seems that the lack of data and disease misconceptions persuade the surgeon to offer radical procedures to patients with tumors as small as 5 mm that might benefit from BCS. These results combined with the current study

might suggest that BCS is an appropriate approach in MBC but in only highly and carefully selected patients.

Grade 2 and 3 (42.9% for both) were equally presented in our cohort as reported in other studies [12-14], but more importantly grade was not associated with survival in any of the analyses. These results were similar to those of Cardoso and colleagues [3] but were contradicted by a population-based study published by Humphries MP and co-authors [15].

The negative association of grade with survival needs to be confirmed in further studies. The results might have an impact on the chemotherapy regimens of patients, in particular the high-grade, node-negative patients where the NCCN guidelines recommend to consider adjuvant chemotherapy. This recommendation should be reconsidered in men [16].

As confirmed by other studies the vast majority of MBC are ER and PR positive and luminal B (HER2-) subtype. The increased survival of the luminal A (80 months) compared to the luminal B (HER2-) group (38 months) did not reach statistical significance. This result should be interpreted cautiously due to a low number of patients in the luminal A group.

Our study shows direct association of PR and survival. Patients who were PR negative had a better overall survival and DFS compared to the positive ones [Figure 1]. This result is not supported by other studies [3,13] and needs further evaluation by prospective data and meta-analyses. Androgen receptor (AR) positivity was reported in various studies [3]. Our study is limited by its retrospective nature and AR expression was not analyzed routinely in our center, and thus is not reported.

Multivariate survival analysis showed that BC subtype is the only variable independently associated with survival ($P = 0.03$). The fact that the stage was not correlated with overall survival is probably attributed to the low number of patients in each group. Of interest, grade on univariate and multivariate analysis was not associated with overall survival.

Radiotherapy is an integral part of the treatment of breast cancer. In our study, post-mastectomy radiation therapy was delivered to 46.9% of the patients. Several of the node-positive patients with skin or nipple involvement did not receive radiation therapy (RT) while other, node-negative patients without skin or nipple involvement did receive RT. We attribute this discrepancy to the evolution of RT along the years of the study. Prospective data is needed to further evaluate the choices regarding RT in MBC. Hormonal therapy was delivered to 89.8% of the patients. This finding is explained by high rate of ER positivity as reported in other studies. Patients in our study received aromatase inhibitors, tamoxifen, and a combination of both in some. The rate of hormonal therapy administration is relatively high to that reported in other studies and did not change over time [3].

LIMITATIONS

The current study is limited by the retrospective pathologic evaluation and prolonged time span. To evaluate the BC subtype, HER2 status and Ki67 are needed and these were not reported for all patients. In those present, luminal B (HER2-) was the most common BC subtype. We found that BC subtype is not independently associated with overall survival, although PR status alone was associated with survival.

CONCLUSIONS

MBC is a rare disease although its incidence is on the rise. Despite the fact that median tumor size at diagnosis is relatively small, BCS is uncommon. The most common BC subtype is luminal B (HER2-). PR negative status is associated with better overall survival and disease-free interval. Indications to RT and hormonal therapy need standardization and will benefit from prospective randomized control trials.

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