

Male Breast Cancer: A Retrospective Study

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ABSTRACT

Background: The male breast cancer (MBC) is a rare disease and represents less than 1% of all malignancies in men and less than 1% of all breast cancers incident.

Aim of study: In this descriptive retrospective study we aimed to provide clinico-epidemiological characteristics of MBC. To present the treatment given with respect to DFS , TTP & OS, to identify possible prognostic factors of the disease and the toxicities encountered by the treatment given.

Patients and Method: Out of 11313 cancer patients 3046 were breast cancer; 28 of them were MBC. All patients presented to clinical oncology department in Ain Shams University in the period from January 2008 to December 2014 and follow up till December 2016

Results: The median age of patients was 59 years. Around 90% had hormone receptor positive (estrogen and/or progesterone receptors).Two third of the patients had advanced T-stage (T3 and T4). Infiltrating ductal carcinoma the most common type of histology was encountered. Modified radical mastectomy was the most common (75%) type of surgery done followed by chemotherapy for 21 patients and loco-regional radiotherapy for 20 patients. Tamoxifen was administered in 19 patients. Relapse occurred in 14 patients (50%). The 5-year disease-free survival (DFS) was 21.4%, the 5-year time to progression (TTP) rate was 21.4% and the 5-year old overall survival (OS) rate was 35.7%.

Conclusion: There is always a delay in the male patients since the first complaint until they seek medical advice, which results in an advanced disease at presentation.

Keywords: Male breast cancer, Female breast cancer, BRCA gene, Tamoxifen, Aromatase inhibitor

INTRODUCTION

Male breast cancer (MBC) is a rare disease, accounting for less than 1% of all malignancies in men and for less than 1% of all incidents of breast carcinoma (BC) ⁽¹⁾.

Establishing the precise risk factors for MBC has proved challenging due to the rarity of the disease. However the etiology of MBC is unclear, but hormonal levels may play a role in the development of this disease ⁽²⁾.

Factors which have been associated with an increased risk are: testicular abnormalities, obesity, physical inactivity, bone fractures after the age of 45, liver cirrhosis, radiation exposure and alcoholic beverages intake. Many of these risk factors are associated with an altered ratio of estrogen/androgen, resulting in a relative excess of estrogen ⁽³⁾.

The most well-known single condition predisposing for MBC is Klinefelter's syndrome (carrier type XXY) with a 30-50 relative risk of developing breast cancer ^(3,4).

Similar to female breast cancer (FBC), a positive family history (FH) of breast cancer is

associated with increased risk of MBC; approximately 15% to 20% of men with breast cancer report a family history of breast or ovarian cancer ⁽⁵⁾.

A personal history of a second primary tumor is reported in more than 11% of MBC patients. Men diagnosed with a first primary breast cancer have a 16% increased risk of developing a second primary cancer in comparison with the general male population. The risk of a second site-specific cancer is elevated for gastrointestinal cancer, cancer pancreas, cancer prostate, melanoma and non-melanoma skin tumors ⁽⁶⁾.

BRCA2 mutations have been identified in 4-40% of MBC patients, whereas BRCA1 mutations are infrequent. The estimated risk for male carriers of BRCA 2 of developing breast cancer is 5-10%, whereas the risk for BRCA1 carriers is 1-5% ⁽³⁾.

About 90% of all male breast tumors prove to be invasive ductal carcinomas, followed by ductal carcinoma in situ .Since the male breast lacks terminal lobules, unless it is exposed to high doses of endogenous and/or exogenous estrogens, the

lobular histotype accounts for only 1.5% of invasive cancers ⁽⁶⁾.

The vast majority of MBCs are low grade (68–78% G1–2). In large studies MBC has been found to express high levels of hormone receptors (HR). The estrogen receptors are more likely to be positive in MBC (80–90%) and the progesterone receptors (73–81%), and HER2 expression has been found in about 15% of MBCs ⁽⁶⁾. The most common clinical symptom of MBC is a painless lump in the breast. The tumors are most often located in the retro-areolar area and nipple involvement is a relatively early event, typical changes are ulceration, retraction, & discharge ^(4, 7).

MBC has often been reported to be diagnosed at a more advanced stage, older age and a higher incidence of lymph node metastases than FBC ⁽⁸⁾.

The recommended diagnostic work-up is a combination of clinical examination, mammography and/or ultrasonography and histopathological verification with fine-needle aspiration or core biopsy ⁽⁷⁾.

Because robust clinical evidence is lacking, treatment standards for men have generally been extrapolated from the enormous literature and clinical experience in women. However, these data may not be entirely applicable to men. The male hormonal milieu may be a unique and powerful determinant of risk, prognosis, and treatment outcome. Moreover, gender differences may affect patient preferences, toxic effects from therapies, and survivorship priorities ⁽⁹⁾.

Surgery is the cornerstone of treatment of MBC pts. In MBC, modified radical mastectomy is considered most feasible in the majority of cases because of the paucity of breast tissue together with the predominantly central location of tumors ^(6, 10).

Lymph node involvement is a strong predictor of both local recurrence and metastatic risk. Sentinel node biopsy (SLNB), which uses the techniques of blue dye and radioisotope localization to identify the sentinel node, is recommended as the initial procedure for determining the lymph node status, while lymph node dissection is clearly an important component of therapy, because men who have nodal dissection omitted tend to have poorer outcomes ^(1, 2).

As MBC frequently presents at an advanced stage with early nodal involvement, loco-regional relapse

rates after surgery alone are quite high, so radiotherapy (RTH) does appear to be effective in preventing local recurrences in male patients ^(2, 6).

A majority of MBC tumors express estrogen receptors (ER) and/or progesterone receptors (PR), and endocrine treatment is considered an important part of the treatment ⁽¹¹⁾.

Although chemotherapy (CTH) benefits in general are more apparent in endocrine non-responsive breast cancer, in high-risk groups, and in younger patients, it is likely more difficult to detect a chemotherapy benefit in male breast cancer, where the majority of tumors are ER positive and where patients are older and have multiple comorbidities ⁽⁵⁾.

Given the established benefit of chemotherapy in women and the suggestive evidence in men, most clinicians use similar guidelines for adjuvant chemotherapy in male and female patients ⁽²⁾.

Targeted therapies make use of drugs that target specific molecules involved in tumor growth and progression, with the aim of blocking the growth and spread of the tumor. Examples of drugs used in targeted therapy that are currently being investigated and used in FBC the monoclonal antibody trastuzumab, which is directed against HER2. The tyrosine kinase inhibitor lapatinib, mammalian target of rapamycin (mTOR) inhibitor everolimus and Poly (ADP-ribose) polymerase (PARP) inhibitors are another examples of drugs being investigated for targeted therapy in connection with FBC, and it has shown that they selectively kill cells with defective double-stranded DNA break repair mechanisms, and are thus interesting for the treatment of breast cancer tumors with a BRCA1 or BRCA2 mutation ⁽¹¹⁾.

MBC has traditionally been considered to have a less favorable prognosis than FBC, but the reason for this discrepancy has been a matter of controversy. Some authors have shown a similar prognosis when compared stage for stage, suggesting that the poorer outcome is related to a more advanced stage at presentation related to the small size of the male breast and earlier access of tumor cells to dermal lymphatics and fascia, together with the higher age of male patients often leading to the coexistence of serious co-morbidities, others have shown a different prognosis, indicating that male breast cancer is a different disease than female breast cancer with a different biologic

behavior^(6,12).

Staging is particularly important, with 5-year survival for stage I disease at 78%, falling to 19% for stage IV. Men have a lower survival rate at each stage than women with equivalent disease. However, when the figures were adjusted to account for population variation in age, sex, and race, the survival rates become comparable, in terms of DFS or OS. The overall 5- and 10-year survival rates for MBC are 63% and 41%, respectively⁽⁷⁾.

AIM OF STUDY

In this descriptive retrospective study we aimed to provide clinico-epidemiological characteristics of MBC.

To present the treatment given with respect to DFS, TTP & OS, to identify possible prognostic factors of the disease and the toxicities encountered by the treatment given.

PATIENTS AND METHOD

Study population

- Out of 11313 cancer patients 3046 were breast cancer; 28 of them were pathologically proved and documented as male breast cancer.
- Clinical data was collected from Jan 2008 to December 2014 and the follow up was till December 2016 at the department of Clinical Oncology and Nuclear Medicine, Ain Shams University.

Outcome measures

- Patients were monitored retrospectively and analyzed statistically for:
 1. Response to therapy (disease free survival, time to progression and overall survival).
 2. Toxicity of treatment given

Response evaluation

- The response evaluation was based on Recist Criteria 1.1⁽¹³⁾.
- Survival endpoints was calculated as⁽¹⁴⁾:
 - Overall survival (OS) was calculated from the start of treatment to the date of last follow-up or death from any cause

- Disease-Free Survival (DFS) was calculated from the start of treatment to date of recurrence or death or the last follow up.
- Time To Progression (TTP) was calculated from the start of treatment until objective tumor progression or death.

Toxicity evaluation

- Toxicity evaluation was based on Common Terminology Criteria for Adverse Events (CTCAE) version 4⁽¹⁵⁾.
- Assessed by severity and denoted as grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life-threatening; and grade 5, death.

The study was done after approval of ethical board of Ain Shams university.

Data collection and Analysis:

The collected data were revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (IBM SPSS Statistics v. 24.0 for windows, 2016). Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

Patients with follow-up data less than one month (range: 2 – 7 days) were excluded from survival analyses.

- **p-value:** level of significance
 - p>0.05: Non significant (NS).
 - p< 0.05: Significant (S).
 - p<0.01: Highly significant (HS).

RESULTS

The median age of patients was 59 years old which is similar to MENA region (Middle East and North Africa) but much lower than Europe and USA. Only 3 (7.7%) patients had positive family history of cancer. All patients presented by breast swellings that were associated with axillary mass in about one third of them with no evidence to affect survival.

Around 90% had hormone receptor positive (estrogen and/or progesterone receptors). Two third of patients had advanced T-stage (T3 and T4). Left sided breast cancer occurred in 57.1%.

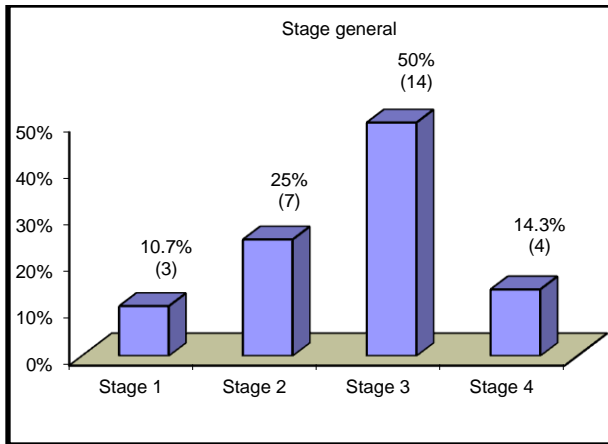


Figure 1: Staging

Infiltrating ductal carcinoma was the most common type of histology encountered and grade 2 was the predominant grade of tumor.

Modified radical mastectomy was the most common (75%) type of surgery done with increasing interest to BCS although its difficulties were followed by chemotherapy for 21 patients mostly Anthracycline based protocols (FAC, FEC). Only seventeen patients developed toxicities and only one case discontinued treatment due to grade 4 hepatotoxicity. Loco-regional radiotherapy delivered to 20 patients.

Table1: Anthracycline frequency and toxicities

Anthracycline based	Total	Grade I&II	Grade III&IV
Total no.	27 (100.0%)		
Toxicities	23 (85.2%)		
<i>Leucopenia</i>	13 (48.1%)	7 (25.9%)	6 (22.2%)
<i>Anemia</i>	9 (33.3%)	8 (29.6%)	1 (3.7%)
<i>Thrombocytopenia</i>	3 (11.1%)	3 (11.1%)	0 (0.0%)
<i>Nausea & vomiting</i>	22 (81.5%)	12 (44.4%)	10 (37.0%)
<i>Diarrhea</i>	9(33.3%)	9 (33.3%)	0 (0.0%)
<i>Mucositis</i>	4 (14.8%)	4 (14.8%)	0 (0.0%)
<i>Alopecia</i>	17 (63.0%)	5 (18.5%)	12 (44.4%)
<i>Fatigue</i>	16 (59.3%)	15 (55.6%)	1 (3.7%)
<i>Hepatotoxicity</i>	1 (3.7%)	0 (0.0%)	1 (3.7%)
<i>Cardiotoxicity</i>	1 (3.7%)	1 (3.7%)	0 (0.0%)

Tamoxifen was administered in 19 patients; 10 only developed toxicities while only one case discontinued treatment due to severe nausea & vomiting, while letrozol was used

in 2 patients and it is another point of interest in our study that needs in the future a prospective study to address the benefits of aromatase inhibitors in treating hormonal positive male breast cancer patients.

Table 2: Tamoxifen frequency and toxicities

Tamoxifen	Total	
Patients	19	(100.0%)
Toxicities	10	(52.6%)
<i>Emotional liability</i>	3	(15.8%)
<i>Hot flahes</i>	4	(21.1%)
<i>Decreased libido</i>	3	(15.8%)
<i>Weight gain</i>	5	(26.3%)
<i>Skin rash</i>	1	(5.3%)
<i>Musculoskeletal pain</i>	5	(26.3%)
<i>Nausea&vomiting</i>	1	(5.3%)

Relapse occurred in 14 patients (50%) and that considered a high rate that makes impact on survival later. The 5-year disease-free survival (DFS) was 21.4%, the 5-year time to progression (TTP) rate was 21.4% and the 5-year overall survival (OS) rate was 35.7%.

Table 3: 1, 2, 3, 4 & 5 years (TTP,DFS,OS)

	DFS	OS	TTP
1 year	22 (78.6%)	27 (96.4%)	22 (78.6%)
2 years	18 (64.3%)	24 (85.7%)	19 (67.9%)
3 years	15 (53.6%)	19 (67.9%)	15 (53.6%)
4 years	14 (50.0%)	15 (53.6%)	11 (39.3%)
5 years	6 (21.4%)	10 (35.7%)	6 (21.4%)

MRM (p =0.034), stage 1 (p=0.049), bleeding per nipple (p=0.029), ER &PR positivity (p=0.022, 0.048 respectively) and Her2 negativity (p=0.013) were significantly associated with favorable OS.

Regarding DFS; ER positivity (p = <0.001) and PR positivity were significantly better than negative receptors (p= 0.025), while negative Her2 were highly significant than positive Her2 (p=0.004).

MRM (p=<0.001), ER positivity (p=0.025), and stage 1 (p=<0.001) were significantly associated with favorable TTP.

DISCUSSION

Male breast cancer is a rare malignancy accounting for approximately 1% of all breast

cancers and < 1% of all malignancies diagnosed in men. However, MBC incidence is much higher in sub-Saharan Africa, approximately up to 9%. This high incidence is attributed to increased endogenous estrogen levels as a result of liver damage from endemic infectious disease in these areas as bilharziasis and viral hepatitis⁽¹⁶⁾.

The incidence of MBC in our study was 0.9 % (28/3046) of all breast cancers, which is consistent with that reported in other studies from Egypt^(16, 17).

While lower than that reported in Sudanese study which was 2.3% (34/1,505) and more than that reported in Canadian study 0.5% (158/32,657)^(18, 19).

The most striking finding in this study is the age at presentation which was revealed to be 59 years old (median) and range (22-85 years) which is much lower than that reported in studies from USA, France, Canada that were (65years, 66.5years, 69.5years) respectively^(19, 20, 21).

Similar to that reported from other studies in Egypt & Sudan, while it is more in that reported from study in West Africa with median age 52.8 years^(17, 18, 22, 23).

Presentation of MBC almost by lump in 61 - 95% of patients with similar results our study revealed that presentation of patients were lump (57.1%), nipple retraction (21.5%), ulcer (14.3%) and bleeding per nipple (7.1%) & with respect to OS bleeding per nipple was significantly better than other presentations (p=0.029), while it was highly significant regarding TTP (p= <0.001).

The most frequently encountered histological type of MBC is IDC, representing about 61%-97% in several series, 92.8% in current study.

The other varieties are less common than in FBC, particularly the lobular type, as the male breast gland is devoid of lobules. Ductal carcinoma in situ (DCIS) is relatively rare in breast tumors in men (1- 10% of cases) compared to women⁽²⁴⁾.

The current study revealed that most cases 20 (71.4%) were grade 1 and 2, which is similar in incidence to the study by El-Beshbeshi & Abo-Elnaga that found 73% of patients were grade 1 and 2, also similar finding by Abreu *et al.*; 74.5% but Soliman & Hetnał in Alexandria experience

found in their study that grade 1 and 2 represents 79.5% of their patients^(16, 22, 25).

MBC is more hormone dependent than in women. When comparing hormonal receptors in breast cancer between two sexes, breast cancer in men expresses estrogen receptors (ER) in 67-96% of cases and progesterone receptors (PR) in 73-92% of cases; while breast cancer in women expresses ER in 77% and PR in 69%⁽²⁴⁾.

In present study, 92.9% of patients were positive for ER and 89.3% for PR, while her2 were positive in 3.6 %. Regarding OS; ER & PR positivity were significantly better than negative receptors (p=0.022, 0.048 respectively), while negative Her2 were significantly better than positive Her2 (p=0.013) and regarding DFS; ER positivity were highly significant than negative receptors (p = <0.001) and PR positivity were significantly better than negative receptors (p= 0.025), while negative Her2 were highly significant than positive Her2 (p=0.004).while for TTP; ER positivity were significantly better than negative receptors(p=0.025).

Axillary lymph node involvement is a very important prognostic factor of survival and relapse and is decisive for adjuvant treatment modalities, however we found no significant correlation between axillary lymph node involvement and OS, DFS, TTP (p = 0.775, 0.736, 0.849 respectively).

The positive node metastasis was 66.7% (16 patients) among our patients who underwent axillary clearance (24 patients), which was consistent with the literature, whereas rate varies from 34% to 84%.

TNM staging found a high distribution of T3 and T4 (71.4%) in our patients, indicating a locally advanced stage of cancer. In Africa the rate varies from 54% to 100%, but it was about 40% in Western countries. Several reasons can account for this delayed diagnosis in Africa including ignorance of the patients, low economic levels of the population, and error in initial diagnosis⁽¹⁶⁾, and also more frequently found in male than in female breast cancers. This is due to the small volume of male breast, so that the tumor quickly expands to the chest wall or the breast upper skin with, in some cases, inflammatory signs⁽²⁴⁾.

Our results revealed that Stage III and IV were

encountered in 71.4% of patients, which is considered to be higher than other studies regarding stage at presentation in the USA , Canada & Sudan (25%, 31%, 58.3%, 61.8%) respectively^(18, 19, 20) .

The current study confirms that stage 1 have significant impact on OS ($p=0.049$), while it was highly significant than other stages ($p<0.001$) regarding TTP.

Surgery is the cornerstone of treatment of MBC, the preservative methods applied for FBC should not be used for MBC because of small breast, central tumors, invasion of the skin, and the pectoral muscle⁽²³⁾ .

However BCS was performed to 20.8% in our study whereas modified radical mastectomy (MRM) was carried out in the majority of the cases (75%) and with respect to OS & TTP; MRM was a significant factor ($p=0.049$, <0.001 respectively) while there was no significance of any type of surgery to DFS.

A Study carried out by Elshafiey et al. revealed that MRM was performed for 40.6% of patients, curative surgery was significant as regards overall 5 years survival ($p = 0.011$) & surgery type with better survival with MRM ($p=0.185$) was borderline significant. Regarding disease free survival, surgery type was the only variable significantly affecting survival ($p = 0.002$)⁽¹⁷⁾ .

As MBC frequently presents with tumor extension to skin and/or the chest wall, radiotherapy is an important component of local treatment in breast cancer⁽²⁶⁾ .

Regarding local control of the disease RTH was carried out in 20 cases (71%) in this study. Several studies have found that radiotherapy reduces the risk of local recurrence but does not change the OS. The effect of radiotherapy on local recurrence was not detected in our study as only 4 patients did not receive post operative radiotherapy.

MBC is sensitive to chemotherapy and indications are again guided by female breast cancer guidelines and recommendations⁽²⁴⁾ .

In many other retrospective studies, adjuvant chemotherapy was associated with a reduced risk of relapse and death related to disease. Giordano et al. found that adjuvant chemotherapy was correlated to 43% decreased risk of death. In

metastatic and neo-adjuvant settings and in the absence of response to hormone therapy, a 13% objective response rate can be achieved with fluorouracil mono chemotherapy, whereas 67% objective response can be reached with an anthracycline-based chemotherapy (FAC and FEC protocols)⁽²⁷⁾ .

Results of this Ain Shams experience revealed that 2 cases received neo-adjuvant chemotherapy (7.2%) and 21 cases (75%) received adjuvant chemotherapy and palliative chemotherapy in 4 cases (14.3%) patients depending on the extent of tumor (T- & N-stage), hormone receptor status, age, performance status of the patients, and associated co-morbidities, These results are similar to other studies that revealed that adjuvant chemotherapy delivered to (23-92%) and palliative chemotherapy delivered to (8-20%) of patients^(16, 17, 19, 29) .

Side effects of chemotherapy given ranged from mild to severe grade with good compliance as only one case reported severe toxicity (grade 4 hepato-toxicity) that lead to discontinuation of the treatment (with anthracycline based protocol), while Bagley et al., 1987 (28) in the National Cancer Institute showed that 3 out of 24 patients developed severe mucositis two of them stopped treatment while one died from treatment related gastro-intestinal hemorrhage.

As MBC is often HR positive, there is clear evidence that men may benefit from the use of hormone therapy⁽²⁴⁾ . Treatment by tamoxifen consistent with other studies which range from 56%-86% whereas in this Ain Shams experience 19 patients (79.2%) were treated by tamoxifen in adjuvant setting and 2 by letrozole, 2 patients metastatic at presentation received letrozole one of them was treated later by exemestane. At relapse 9 received letrozole and one of them was treated later by exemestane.

Relapse occurred in 14 patients (58.3%) of those who underwent curative surgery⁽²⁴⁾ , which considered high rate comparing to other studies from Egypt and other countries while lower than that reported by Sudanese study. This high rate of relapse unfortunately had a great impact on survival rates whereas the state of our patients at the last follow up revealed that 8 patients died and 20 were still alive; 10 of them were free from metastasis and 10 with metastasis.

In literature 5years OS range from (44%-84%) and our results are in consistent with the survival results by Hochlef *et al.*, whereas much lower than the study by Soliman & Hetnal which they relied their improved survival rates compared to other worldwide trials. These may be a reflection of the proper adjuvant treatment received in most of their patients and we believe that this may be because of the large number of LN negative patients (46.2 %) which had significant impact on survival ($p = 0.001$)^(22, 24).

Median TTP was 40 months similar to results obtained by Foerster *et al.*, Whereas 5years DFS was 21.4%, which is in consistent with literature that range from (21%-89%)^(20, 23, 30).

These lower survival rates as mentioned before considered sequel of high relapse rate which in turn may be as a result of delayed presentation with high tumor stage.

To our best knowledge this is the first study of MBC in Ain Shams University and one of the fewer studies in Egypt. The strength of this study is actually the accurate data registry, collection and analysis which give reliable scope on incidence, management and outcome of MBC Egyptian patients which complete the picture of disease with other Egyptian universities studies.

CONCLUSION AND RECOMMENDATIONS

The prognosis of the MBC is undoubtedly worse of breast cancer in women. Some researchers justify this by assuming a different and greater biological aggressiveness.

We believe, besides retrospective series; efforts to develop randomized, prospective studies in cooperative groups and other consortia clinical trials are essential.

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