Male breast cancer-a 10-year review of 29 cases at Tanta University Hospital

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Abstract: Background /Aim: Male breast cancer (MBC) is a rare disease. To characterize male breast cancer in Tanta University Hospital, we systematically analyze available data on male breast cancer in our department. **Methods:** Twenty nine patients with non-metastatic MBC and a Karnofsky performance status (KPS) of ≥70, and adequate hematologic, renal and hepatic functions; were enrolled. All patients were symptomatic and diagnosed by preoperative fine needle aspiration cytology (FNAC) or biopsy. They were treated between January 2000 and January 2010 at Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital, Egypt and Surgery Department, Faculty of Medicine, Tanta University Hospital, Egypt. No Prior therapy was permitted. Characteristics of the patients, and tumors were analyzed. **Results:** The study included 29 males non-metastatic invasive breast carcinomas with their age ranging from 28 to 80 years at the time of diagnosis (mean 52.8 years). Their tumors ranged in size from 1.5 cm to 8 cm. The majority of cases were T3, node positive and grade II or greater. They showed ER positivity in 19 cases (65.5%) and HER-2 positivity in 6 cases (20.7%). Median follow-up was 53 (6–120) months. The 5 and 10 year overall survival rates were 70.6%, and 57.0% respectively. **Conclusion:** The tumor biology of MBC is not significantly different from that of females, however, limited public awareness and absence of adequate screening for MBC result in delayed diagnosis and poor outcomes. Therefore, education, an appropriate system for early detection, and adequate treatment are prerequisite for improving outcomes, and men presenting any breast symptoms should be examined in the same manner and degree of urgency as in women to detect cancer at an early stage and better treatment outcomes.

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1. Introduction

Male breast cancers in Africa are characterized as late onset and male-to-female breast cancer ratio is higher than populations in developed countries[(1)]. Estimated new cases and deaths from male breast cancer in the United States in 2012 were 2,190 and 410 respectively[(2)]. Less than 1% of all breast carcinomas occur in men[(3)]. In the United States, the ratio of female to male breast cancer is approximately 100:1 in whites, but lower (70:1) in blacks[(4)]. The median age of onset of MBC is 65 to 67, approximately 5 to 10 years older than in women [(4-10)].

Predisposing risk factors appear to include radiation exposure, estrogen administration, and diseases associated with hyperestrogenism, such as cirrhosis or Klinefelter syndrome[(5)]. The association of MBC with prolactinoma, a condition often associated with low plasma testosterone levels, is consistent with this hypothesis[(11,12)]. Inherited mutations in BRCA also increase the risk of MBC, although not to the same absolute level of risk as in women. The risk appears to be higher with inherited BRCA2 rather than BRCA1 mutations[(13)]. About 15 to 20 percent of men with breast cancer have a family history of the disease, compared to only 7 percent of the general male population[(7)]. This disparity implies that some families carry genetic mutations that increase their risk for both male and female breast cancer[(14)]. On the other hand, androgens may convey a protective effect on breast tissue by inhibiting cell proliferation. The pathology is similar to that of female breast cancer, and infiltrating ductal cancer is the most common tumor type[(15)].

Overall survival is similar to that of women with breast cancer. The impression that male breast cancer has a worse prognosis may stem from the tendency toward diagnosis at a later stage[(5,9,16)].
Therefore, we designed this trial to evaluate the clinicopathological features, treatment results and survival of male patients with non-metastatic breast cancer who were treated at Tanta University Hospital.

2. Patients and Methods

Patients

From January 2000 through January 2010, every male patient with non-metastatic breast cancer reported at Clinical Oncology Department, Tanta University Hospital and Surgical Department of Tanta University Hospital was considered eligible to

evaluate the clinical features and treatment results of this disease.

Patients were required to have a Karnofsky performance status ≥ 70, adequate bone marrow reserve (WBC count ≥3.5 x 10^9/L, platelets ≥100 x 10^9/L, and hemoglobin ≥10 gm/dL) and good renal (creatinine clearance ≥ 60 mL/min) and liver functions.

Patients with non-malignant systemic disease that precluded them from receiving CT/RCT (e.g. active infection, any clinically significant cardiac arrhythmia, or congestive heart failure) were not eligible. Patients with clinically significant pleural effusions or ascites were also not eligible.

We decided to perform a retrospective study for MBC, because of the scarcity of the disease would not allow the accrual of enough patients for a valid statistical analysis in a prospective study. Acceptance of this concept was quite satisfying, resulting in an analysis of 29 male patients with primary non-metastatic breast cancer as detailed in this report. Protocol radiotherapy and/or chemotherapy were obligatory and stratified according to stage of disease, histologic features, and nodal status.

Diagnostic and Staging Procedures

The diagnostic work-up included patients' history and physical examination, bilateral mammography, blood work such as liver enzymes, alkaline phosphatase, creatinine, urea and complete blood count, chest x-ray, bone scan, FNAC, if FNAC is not conclusive core or open biopsy of the tumor was performed, assay for hormone receptors, abdominal ultrasound, computed tomography of chest and abdomen if needed.

Biopsies were investigated immune-histochemically by staining for Her2neu. Some biopsies were investigated immune-histochemically by staining for Ki67 where available.

Treatment Protocol:

Surgery: Twenty one patients (72.4%) were eligible to modified radical mastectomy, while 8 patients (27.6%) underwent radical mastectomy due to presence of chest wall invasion that persists after the neoadjuvant chemotherapy. All patients had at least level II axillary lymph node dissection with an average of 15 lymph nodes removed.

Chemotherapy: A total of 16 patients had received neoadjuvant chemotherapy before surgery. All had residual tumor present in the subsequent mastectomy, with eight having a reduction in tumor size. Twenty patients had received adjuvant chemotherapy after surgery. Chemotherapy was applied in 18 (68.9%) patients in the form of FAC regimen which consisted of cyclophosphamide (600 mg/m^2, day 1), adriamycine (50 mg/m^2, day 1) and fluorouracil (600 mg/m^2 , days 1), intravenously and the cycle was repeated every 3 weeks. In 8 (27.6%) patients the FEC regimen was received in the form of cyclophosphamide (500 mg/m^2, day 1), epirubicine (100 mg/m^2, day 1) and fluorouracil (500 mg/m^2 , days 1), intravenously and the cycle was repeated every 3 weeks. Antiemetics were administered at the oncologist's discretion. Supportive care included blood transfusions, growth factors and the administration of analgesics, as appropriate. Prophylactic use of growth factors was not recommended.

Radiotherapy: Twenty six patients (89.7%) were treated with radiotherapy megavoltage equipment. Radiotherapy was initiated about 2 weeks after the sixth cycle of chemotherapy. Radiotherapy was delivered to the chest wall with individually shaped portals and daily fractions of 1.8 to 2.0 Gy on 5 consecutive days a week. A median total dose of 50 Gy given in 25 fractions over a period of 5 weeks (range 33 - 40 days) was applied. The chest wall and internal mammary lymph nodes (if indicated) were irradiated through two tangential fields. Supraclavicular and axillary nodes were treated with an anterior field to a total dose of 50 Gy prescribed at 3 cm to the supraclavicular area and to the midplane of the axilla. Immobilization techniques were used as required.

Hormonal therapy: Following surgery, only hormonal therapy in the form of anti-estrogen was restricted to 3 patients with strong positive hormonal receptors who aged ≥70 years, while 16 cases received adjuvant hormonal therapy in the form of anti-estrogens after chemotherapy and/or radiotherapy.

Follow-Up and Statistical Analysis

The date of this analysis was November 17, 2012. The median time of follow-up was 53 (6–120) months, from the first day of treatment.

Metastatic work up after completion of treatment included bilateral mammography, abdominal and pelvic computed tomography scan and/or ultrasound, chest x-ray, blood work as described above, and clinical examination as well as patient history.

Follow-up evaluation consisted of history, physical examinations, chest x-ray, and abdominal ultrasound. Additional tests were carried out if necessary. Patients were examined every 3 months at least for 2 years, and afterwards twice a year.

SPSS (Statistical package [version 15.0]) was used for data analysis. Mean and standard deviation were estimates of quantitative data. Chi-square/ Fischer exact were tests of proportion independence. Kaplan-Meier[17] method was used for estimating survival and log rank to compare curves. *P* value is significant at 0.05 level.

3. Results

Patient characteristics: The study included 29 male patients with non-metastatic invasive breast carcinoma, with their age ranging from 28 to 80 years at the time of diagnosis (mean 52.8 years). Their tumors ranged in size from 1.5 cm to 8 cm. The majority of cases were T3, node positive and grade II or greater. They showed ER positivity in 19 cases (65.5%) and HER-2 positivity in 6 cases (20.7%). The tumor was found on the left breast in 19 cases (65.5%) and on the right breast in 10 cases (34.5%).

Patients' and tumor characteristics were summarized in table (1).

Table (1): Patients' and tumor characteristics of the 29 patients with male invasive breast carcinomas.

Characteristic	No. patients (%)
Age (years)	
Mean	52.8 years
Range	(28 – 80)
Family history	
+ve	1 (3.4%)
-ve	28 (96.6)
Tumor Status	
T1	1 (3.4%)
T2	10 (34.5%)
T3	15 (51.8%)
T4	3 (10.3%)
ER	
-ve	10 (34.5%)
+ve	19 (65.5%)
PR	
+ve	18 (62.1)
-ve	11 (37.9%)
Her-2-neu	
+ve	6 (20.7%)
-ve	23 (79.3%)
Tumor side	
Left	19 (65.5%)
Right	10 (34.5%)
Bilateral	0 (0%)
Tumor Grade	
G1	2 (6.9%)
G2	18 (62.1%)
G3	9 (31%)
Histology	
Invasive ductal	22 (75.9%)
Others	7 (24.1%)
Cutaneous invasion	
Yes	3 (10.3%)
No	26 (89.7%)
Lymph nodes dissected (median, range)	15 (10-25)
Involved lymph node (median, range)	7 (0-24)
nodal status	
Positive	20 (69%)
N1	9 (31%)
N2	8 (27.6%)
N3	3 (10.3%)
Negative	9 (31%)

The risk factors found are represented by the gynaecomastia in 4 cases (13.8%), breast trauma in 3 cases (10.3%), alcohol consumption in 2 cases (6.9%), jaundice in 2 cases (6.9%); physical inactivity in 3 cases (10.3%), use of exogenous androgens in 1 case (3.4%), obesity in 5 cases (17.2%) and sterility in 1 case (3.4%). The majority of patients came from rural areas in 21 cases (72.4%).

Clinical features

The most common clinical presentation is a painless, firm, subareolar mass. The duration of the evolution of these signs (time passed between the discovery of the tumor and the first consultation) varied from 1 to 47 months. Table 2 summarizes symptoms at presentation in all patients.

Table 2. Symptoms at presentation

Symptom	Number of patients (total n. = 29)	%
Breast mass	29	100
Skin ulceration	3	10.3
Skin redness	2	6.9
Skin edema	3	10.3
Nipple discharge	1	3.4

Treatment patterns and survival

Twenty one patients (72.4%) were eligible to modified radical mastectomy, while 8 patients (27.6%) underwent radical mastectomy due to presence of chest wall invasion that persists after the neoadjuvant chemotherapy. All patients had at least level II axillary lymph node dissection with an average of 15 lymph nodes removed.

A total of 16 (55.2%) patients had received neoadjuvant chemotherapy before surgery. All had residual tumor present in the subsequent mastectomy,

with eight having a reduction in tumor size. Twenty patients had received adjuvant chemotherapy after surgery. Twenty six patients (89.7%) were treated with radiotherapy with a mean dose of 50 grays (Gy). Nineteen patients received daily hormone therapy with 20 mg of tamoxifen (Table 3).

Table 3. Treatment patterns in the 29 patients with male invasive breast carcinomas.

Treatment pattern	Number of patients (total n. = 29)	%
Surgery + Hormonal therapy	3	10.3
Chemotherapy+ Surgery+ Radiotherapy+ Hormonal therapy	16	34.5
Surgery+ Chemotherapy+ Radiotherapy	10	55.2

Survival

The median period of follow-up was 53 months (range, 6 - 120 months). There were no local or regional recurrences. The 5-year and 10-year disease free survival rate for all stages of breast cancer in men have been reported to be 70% and 36%, respectively. The 5-year overall survival rate was 70.6%, and the 10-year overall survival rate was 57.0%. Although survival was not significantly different, older age, larger size, axillary lymph node metastasis, advanced tumor stage, hormone receptor negativity, and higher grade showed a trend for poor overall survival in our study.

4.Discussion

Male breast cancer is rare. In Europe, approximately 1% of all BC occurs in males, but the incidence is much higher in other areas such as sub-Saharan Africa with 5 to 15%[18-20]. According to Simon *et al*.[21] these differences do not have any racial basis.

Male compared with female breast cancers occurred later in life with higher stage, lower grade, and more estrogen receptor-positive tumors[1]. Male breast cancer in Western countries was presented mostly in men in their 60s (range: 63–68 years), which is 10 years later than in females. Male breast cancer is rare before the age of 40 years[5,18-20,22,23]. In our study, 56% of the patients were between 50 & 60 years old. This is compatible with the results reported by Atahan *et al.* who evaluated 42 male patients with breast cancer & they found that the median age is 55years (range 33-77 years)[2].

The study of the risk factors of MBC is unclear; however many risk factors have been suggested. Among these factors, some are common in men and women: chest wall irradiation, breast trauma and endogenous hyperoestrogenism secondary to a hepatic dysfunction due to a parasitic disease (bilharzias) or the viral infection (hepatitis B) what would explain the high frequency in Africa and Asia and gynaecomastia[18,19,23,24]. Other risk factors include Klinefelter syndrome, and use of exogenous androgens[25,26] or estrogens[27,28], physical inactivity [29,30], obesity[29-33], alcohol consumption [34,35] and gene deteriorations[5,8,18,20,23]. In our study the risk factors found were gynaecomastia (13.8%), breast trauma (10.3%), alcohol consumption (6.9%), use of exogenous androgens (3.4%), jaundice (6.9%), physical inactivity (10.3%) and obesity (17.2%).

TNM staging finds a high distribution of T3 and T4 (62.1%) in this study, which means an advanced stage of cancer. More than 40% of patients with MBC present with stage III or IV disease in Western countries, while in Africa the rate varies from 54–100%[5,19, 23,36-39]. Several reasons can account for the high distribution in our patients including ignorance of the patients, error in initial diagnosis in rural health centers. Because of these factors, MBC is often confused with benign pathologies of the skin. The duration of the evolution of MBC in our country is usually longer, which explains the advanced clinical presentation: it varies from 1 to 47 months in our study. According to El Hajjam *et al.* [23] this duration varies from 4 to 36 months.

In our study, infiltrating ductal carcinoma is the most frequent invasive carcinoma in men accounting for 75.9%. This was comparable with other studies which reported that infiltrating ductal carcinoma is the most frequent invasive carcinoma in men accounting for 70–95% of MBC, while lobular carcinoma is rare (around 1% of all cases) due to lack of terminal lobules in the male breast. The rarer subtypes, such as carcinomas (medullary, tubular, mucinous, and squamous) and sarcoma, have all been reported in men, although they may be slightly more uncommon than in women[5,18-20,22,23,38].

The hormone-dependence of MBC is established, the hormonal receptors are positive in 65 to 90% of cases according to the series, those with estrogens in 65 to 86% and those with progesterone in 67 to 80%[18,40]. In our study these receptors were tested in all patients and 65.5% were positive for estrogen receptors and 62.1% were positive for progesterone receptors.

The treatment guideline has been extrapolated from the data based on female breast cancer: surgery, radiotherapy chemotherapy, and hormone therapy. The traditional surgical approach

for localized breast cancer in men is modified radical mastectomy (MRM). Although randomized studies have not been conducted in men, retrospective data suggest the equivalence of radical mastectomy and MRM in terms of local recurrence and survival[41]. Moreover, randomized studies in women also support the therapeutic equivalence of these two surgical procedures, however, the preservative methods in application in women should not be used in men (central tumors, invasion of the skin, and the pectoral muscle). The only exception is that men who have extensive chest wall muscle involvement may benefit from a radical mastectomy[41]. In our study 8 patients (27.6%) underwent radical mastectomy due to presence of chest wall invasion that persists after the neoadjuvant chemotherapy.

The node metastasis is of 69% among all patients who underwent axillary clearance; in the literature the rate varies from 35 to 84%[18,19,23,36].

RT techniques vary substantially between series and over time, complicating the clinical assessment of benefit. For women with node-positive breast cancer, a survival advantage for post-mastectomy chest wall irradiation has been shown in randomized trials. Whether these results can be extrapolated to men is unclear, but at least one review from Johns Hopkins suggests that similar indications for post-mastectomy RT should be applied to both men and women with breast cancer[42]. The radiotherapy was carried out in 26 cases (89.7%) in this study, it is indicated in the presence of risk factors of local recurrence (four or more metastatic lymph node [N2/N3], large tumors [T3/T4], lymphovascular invasion, cutaneous invasion, reduced safety margins). Several studies have found that radiation reduces the risk for local recurrence but does not change the overall survival[5,18,43]. In fact, at least some data suggest that men are more likely to be offered post-mastectomy RT than women, possibly because they have a higher incidence of nipple or skin involvement. However, few studies showed that male breast cancer patients with extensive nodal involvement appeared not to have had a significant benefit from postmastectomy irradiation[44].

In our study, a total of 16 (55.2%) patients had received neoadjuvant chemotherapy before surgery. All had residual tumor present in the subsequent mastectomy, with eight having a reduction in tumor size. Other studies found that neo-adjuvant chemotherapy of induction allows for early treatment of the systemic disease and for the reduction of tumoral volume with sometimes complete response, and indicated it in advanced T2, T3, and T4[8,19].

In this study, 20 patients had received adjuvant chemotherapy after surgery. The low incidence of MBC precludes the development and completion of clinical trials to assess the efficacy of adjuvant systemic therapy, and few prospective data are available to guide treatment. Nevertheless, the data supporting benefit from adjuvant systemic therapy in women with early breast cancer are strong, and the limited data that have been published support a similar benefit for adjuvant systemic therapy in men as has been observed in women[45]. In addition, several investigators considered chemotherapy a standard treatment using several protocols comparable with those of women[8,19].

In our study, the majority of MBCs are hormone receptor-positive, and five years of adjuvant tamoxifen is recommended for 19 men (65.5%) with hormone receptor-positive tumors following mastectomy. This recommendation is based largely upon the benefits that have been observed in clinical trials performed in women. Prospective trials to confirm the validity of this approach in men are not available. However, retrospective comparisons support a survival benefit from adjuvant tamoxifen in MBC[5,8,19,46,47].

Male breast cancer patients seem to have a less positive prognosis than female breast cancer patients due to a later discovery and a more advanced stage in men. A comparison between men and women with same stage indicate any difference in their prognosis[8,18-20]. The 5-year overall survival rates for all stages of breast cancer in men have been reported to range from 36% to 66%, and 10-year overall survival rates range from 17% to 52%[5,22,40]. However, those in this study were improved at 70.6% and 57.0%, respectively. The main reason for such an improvement could be adequate treatment, and increased use of suitable chemotherapy, optimum radiotherapy and use of tamoxifen. These results suggest that adequate treatment, and close follow-up would aid in improving survival of MBC.

The 5-year and 10-year disease free survival rate in this study, was 68% and 36%, respectively, which was comparable with that reported by Höller *et al.* [48] who found in his study that the disease-specific 5-year and 10-year survival rate was 69% and 35%, respectively.

5. Conclusion

Male breast cancer is a rare affection, and still ignored in our developing countries. Male breast cancer has the same clinical and histopathological characteristics as female breast cancer. The advanced clinical forms are most frequent in our environment. Therefore, education, an appropriate system for early

detection, and adequate treatment are necessary for improving outcomes.

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