Male Breast Cancer: An 8-year experience in a single tertiary oncology centre in India

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Abstract

Background and Objectives: Male breast cancer is a rare disease with a paucity of published literature on this topic. The purpose of this study was to report our experience with male breast cancer, focusing on the need of pooling of multi-institutional data for these patients.

Methods: A retrospective review of 23 male patients with carcinoma breast from 2008 to 2015 was performed. All documented data on patient and tumour characteristics, treatment and clinical outcome information were analyzed.

Results: The median age at diagnosis was 54 years. Majority of our patients had Stage III disease (52.2%) with infiltrating ductal carcinoma (82.6%) being the commonest histology. Estrogen receptor and progesterone receptor positivity was seen in 91.3% and 78.26% patients respectively while Her-2 (human epidermal growth factor receptor-2) positivity was seen only in one patient. All patients underwent surgery and adjuvant radiation therapy was used in 10 (43.5%) patients. All patients except one received systemic chemotherapy. The 5-year disease-free survival was found to be 78%. Median follow-up was 40 months (6 - 68 months).

Conclusion: Unfortunately, in the face of the limitation of current scientific knowledge in determining the optimal treatment strategy for male patients with breast cancer we recommend that there is an urgent need for publishing multi-institutional experience with these tumours. Hence, allowing the physicians in forming guidelines with the goal of improving clinical outcomes for these patients.

Keywords: Ductal carcinoma, Estrogen receptors, Male breast neoplasms, Progesterone, Retrospective studies.

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Introduction

Male breast cancer (MBC) is rare, accounting for about 1% of all malignancies in men and 1% of all breast cancers[1]. The incidence of MBC is increasing as in women, approximately about 26% rise over the past 25 years[2]. MBC patients usually have advanced disease at presentation, longer time to presentation, more Her-2neu positivity and triple negativity[3]. Invasive ductal carcinoma is the most common type of breast malignancy observed in males[4].

In clinical practice, the scarcity of cases has reduced the focus of research in this area as compared with female breast cancer[5]. The treatment strategies for MBC aren't based on prospectively or retrospectively conducted randomized controlled trials. Majority of the information regarding the biology, natural history, and treatment strategies of MBC has been extrapolated from the vast knowledge of female breast cancer[6]. Treating these male patients in a manner similar to female breast cancer may not be entirely applicable since the gender differences may affect the patient preferences with regard to treatment options, side effects as a result of treatment, and survival outcome[7].

In Indian patients, considering the lack of awareness, associated stigma and the rarity of MBC, it's challenging for the oncologists to get enough participants from a single institution to arrive at a definitive conclusion on the best evidence-based practice in the treatment of MBC. There is limited availability of data on MBC from India. The purpose of present article is to analyze the clinico-pathological data, treatment received and survival outcome of MBC patients presenting at a cancer research institute in India. In addition, we emphasize on the need of pooling of multi-institutional data for these patients.

Methods

A prospective, observational study on male patients with histopathologically proven carcinoma of the breast was carried out at our institute from 2008 to 2015. A total of 26 patients were retrieved from the records. The case records of patients were reviewed to extract the information on age, presenting symptom, site of primary tumour, treatment details, recurrence, and follow-up. The inclusion criteria for the study were as follows: a diagnosis of histologically confirmed male breast cancer, stage I – IV, availability of complete information on clinico-pathological data, treatment employed and survival outcome.

Pre-Treatment Evaluation: The pre-treatment evaluation included a complete history and physical examination, chest radiograph, bilateral breast mammogram, liver function tests including alkaline phosphatase, complete blood counts and abdominal ultrasound. Bone scan was considered only for symptomatic patients or those with elevated alkaline phosphatase. All patients underwent trucut biopsy, followed by determination of histopathology and estrogen receptor (ER), progesterone (PgR) and Her-2 status. The patients were staged according to American Joint Committee on Cancer – Tumour, nodes and metastasis staging system for female breast cancer, depending on the time period. After the complete staging work-up, all patients were evaluated by a multidisciplinary team including surgical oncologist, medical oncologist, radiation oncologist and pathologist.

Treatment plan: Patients presenting with early stage breast cancer, underwent either lumpectomy or modified radical mastectomy, followed by adjuvant chemotherapy (CT) and external beam radiotherapy (RT), if indicated. Patients with locally advanced breast cancer, received neoadjuvant CT (3 to 4 cycles) followed by assessment for tumour response. These patients underwent mastectomy followed by systemic CT and adjuvant RT. Depending on the receptor status, hormonal therapy in the form of tamoxifen was offered to the patients.

Chemotherapeutic regimens: CMF regimen was offered to 6 patients in view of Stage II disease as per the institutional protocol. Due to the higher stage (stage III and IV) at presentation, remaining patients received anthracycline- or taxane-based CT.

- CMF regimen

Cyclophosphamide 600 mg/m^2 i.v D1
Methotrexate 40 mg/m^2 i.v D1
5-Fluorouracil 600 mg/m^2 i.v D1
} Q3w x 6 cycles

- FAC regimen

5-Fluorouracil 500 mg/m^2 i.v D1
Adriamycin 50 mg/m^2 i.v D1
Cyclophosphamide 500 mg/m^2 i.v D1
} Q3w x 6 cycles

- FEC regimen

5-Fluorouracil 500 mg/m^2 i.v D1
Epirubicin 75 mg/m^2 i.v D1
Cyclophosphamide 500 mg/m^2 i.v D1
} Q3w x 6 cycles

- TAC regimen

Docetaxel 75 mg/m^2 i.v D1
Adriamycin 50 mg/m^2 i.v D1
Cyclophosphamide 500 mg/m^2 i.v D1
} Q3w x 6 cycles

Radiation therapy: Indications for post-mastectomy chest wall RT includes patients with four or more axillary lymph node metastasis, with a tumour size of 5 cm or more, and the presence of chest wall invasion[8,9]. These patients were planned on Acuity conventional simulator and treated with a linear accelerator of 6MV energy. Sites treated by RT included chest wall ± axilla, and supraclavicular regions, when indicated. Total RT dose consisted of 50 – 60 Gy at 2 Gy per fraction for 5 days in a week over 5–6 weeks with a two-field tangentially opposed photon beam arrangement for the chest wall. An additional direct anterior supraclavicular and axillary field were employed wherever indicated. Typically, the inferior border was located 1–2 cm below the inframammary fold, the superior border at the level of the suprasternal notch, the medial border at the mid-sternal line, and the lateral border at the mid-axillary line. In our setting, RT was recommended to patients with positive axillary nodes, large (≥ 5 cm) primary tumours and for those with chest wall invasion. Treatment was delivered daily, Monday through Friday.

Hormonal therapy: Hormonal manipulation in the form of tamoxifen 20 mg once a day for duration of 5 years was given to ER / PgR positive patients.

Follow-up: After completion of treatment, patients were called for follow-up 3 monthly for first 2 years, and then every 6 monthly for next 3 years and then annually. At each visit, evaluation included detailed history, physical examination and symptom directed investigations. Every 6 months, chest X-ray / abdominal ultrasound or computed tomography of chest and abdomen was done as a routine.

Statistical Analysis: The statistical analysis was performed using SPSS version 20.0. Disease-free survival (DFS) was defined as the time period from the date of initial diagnosis to the date of recurrence or last follow-up. DFS curve was calculated using Kaplan-Meier survival analysis. A p-value of 0.05 or less was considered as statistically significant. Univariate analysis was performed to assess if risk factors such as pathological T-stage and N-stage, lymphovascular invasion, grade of the tumour, close margin or extracapsular extension affect the occurrence of recurrence of disease.

Results

Twenty-six male patients were identified with a diagnosis of carcinoma of the breast. Among these, 23 patients were included in the study. Three patients were excluded as they did not complete the planned treatment because of personal reasons. The mean age (± standard deviation) of the overall study population was 56±9.65 years (range, 42 - 76 years). Metastatic sites were lung and bone. Twenty cases (86.9%) were classified as invasive ductal carcinoma of the breast (IDCA) while 2 (8.7%) patients had invasive lobular carcinoma of the breast. Only 1 (4.4%) patient had mucinous carcinoma of the breast (Table 1).

Table 1: The demographic and oncological characteristics

Patient characteristics	N = 23
Age (in years)	
Mean (range)	56±9.65 (42–76)
Habits	
Smoker	5 (21.7%)
Non-smoker	18 (78.3%)
Family history	
Negative	21 (91.3%)
Positive	2 (8.7%)
Symptoms	
Lump in the breast	23 (100%)
Axillary swelling	3 (13%)
Nipple retraction	3 (13%)
Side	
Right	9 (39.1%)
Left	14 (60.9%)
Site	
Central	17 (73.9%)
Upper Outer	5 (21.7%)
Upper Inner	1 (4.3%)
pT	
pT1	1 (4.3%)
pT2	7 (30.4%)
pT3	14 (60.9%)
pT4	1 (4.3%)
pN	
pN0	13 (56.5%)
pN1	7 (30.4%)
pN2	2 (8.7%)
pN3	1 (4.3%)
Stage	
Stage I	1 (4.3%)
Stage II	8 (34.8%)
Stage III	12 (52.2%)
Stage IV	2 (8.7%)
Receptor status	
ER positivity	21 (91.3%)
PgR positivity	18 (78.3%)
Her-2 positivity	1 (4.3%)

Table 2: Treatment characteristics

Treatment characteristics	N = 23
Surgery	
MRM	22 (95.7%)
Lumpectomy	1 (4.3%)
Chemotherapy	
Neo-adjuvant	7 (30.4%)
Adjuvant	20 (86.9%)
No chemotherapy	1 (4.3%)
Palliative	2 (8.7%)
Type of chemotherapy	
CMF	6 (26.1%)
FAC / FEC	14 (60.9%)
TAC	3 (13%)
Radiation therapy	
Adjuvant	10 (43.5%)
Not given	13 (56.5%)
Hormonal therapy	
Adjuvant	21 (91.3%)
Not given	2 (8.7%)

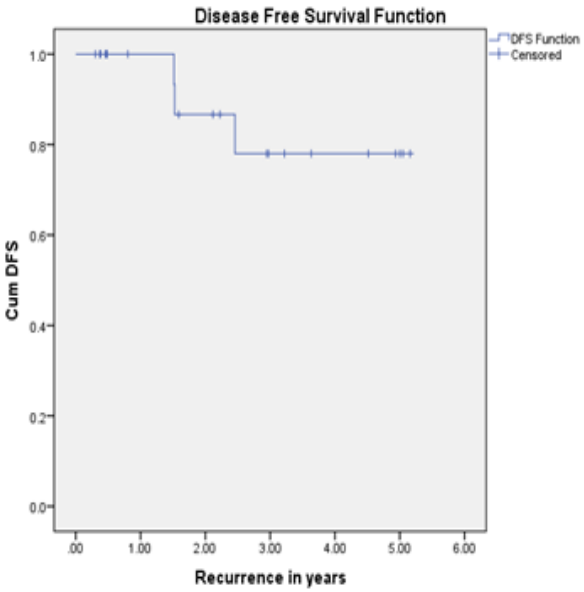

Fig. 1: Kaplan Meier survival analysis curve for DFS

Table 3: Kaplan Meier Survival analysis curve for DFS

Total N	N of Events	Censored		DFS at the end of 5 years
		N	Percent	
22	3	19	86.4%	78%

Univariate analysis of risk factors such as pathological T-stage (p = 0.24) and N-stage (p = 0.55), lymphovascular invasion (p = 0.91), grade of the tumour (p = 0.85), or extracapsular extension (p = 0.63) did not significantly affect the occurrence of recurrence of the disease (Table 4).

Table 4: Univariate cox regression analysis model

		No recurrence	Recurrence	p- value	Odds ratio	95.0% CI for Odds ratio	
Age		56.32±9.32	59.25±12.37	0.437	1.044	.937	1.162
HPE: T stage	1	1 (100.00%)	0 (0.00%)	.239	Variable		
	2	4 (57.14%)	3 (42.86%)				
	3	13 (92.86%)	1 (7.14%)				
	4	1 (100.00%)	0 (0.00%)				
HPE: N stage	0	12 (92.31%)	1 (7.69%)	.554	Variable		
	1	5 (71.43%)	2 (28.57%)				
	2	2 (100.00%)	0 (0.00%)				
	3	0 (0.00%)	1 (100.00%)				
Staging	1	1 (100.00%)	0 (0.00%)	.594	Variable		
	2	6 (75.00%)	2 (25.00%)				
	3	11 (91.67%)	1 (8.33%)				
	4	1 (50.00%)	1 (50.00%)				
LVI	No	13 (86.67%)	2 (13.33%)	0.913	1		
	Yes	6 (75.00%)	2 (25.00%)		0.875	.079	9.688
Grade	0	1 (100.00%)	0 (0.00%)	.853	Variable		
	1	2 (66.67%)	1 (33.33%)				
	2	11 (100.00%)	0 (0.00%)				
	3	5 (62.50%)	3 (37.50%)				
ECE	No	17 (80.95%)	4 (19.05%)	0.633	1		
	Yes	2 (100.00%)	0 (0.00%)		0.038	.000	26436.749

Discussion

MBC accounts for 0.5% of all diagnosed cases of breast cancer and less than 0.2% of all male cancers[10]. Due to the low Incidence of MBC, it has not been investigated thoroughly throughout the world[11,12]. Keeping this in mind, we reviewed our 8-year data of male patients with carcinoma of the breast focusing on clinical and pathological characteristics, treatment options, and disease outcome parameters.

Breast cancer is seen at a relatively early age in Indian males[5]. The mean age of 56 years in our study is in concordance with another study from India[13]. As per the literature, the most common location of the lump in female breast cancer is upper outer quadrant. Majority (73.9%) of our patients had lump involving the central portion. This difference in the location of the lump is likely to be due to paucity of breast tissue in males as compared to females[2].

We found ductal carcinoma (86.9%) as the commonest histology in MBC patients followed by 8.7% patients with lobular and only 4.4% had mucinous carcinoma. Similar findings of entire spectrum of histological variants of breast cancer seen in clinical practice have been reported[14]. Men with breast cancer tend to present at advanced stages of disease[15]. Consistent with this, approximately 60% of our patients had stage III or IV disease on diagnosis[16,17]. This tendency for advanced disease at presentation is attributed to ignorance about breast cancer in males, patients presenting with symptoms other than a lump, and often the patient presents for an unrelated condition[18].

There is a paucity of sufficient information in guiding the clinicians in choosing the optimal combination of surgery, RT, systemic therapy and/ or hormonal therapy. In most of the oncology centers, treatment of MBC is largely similar to established National Comprehensive Cancer Network guidelines for female breast cancer treatment. Hence, the standard therapy for MBC starts with mastectomy as majority of these patients present with locally advanced breast cancer[15,19]. Among our MBC patients, 95.7% underwent mastectomy while only one patient underwent lumpectomy.

After thoroughly searching the literature we found that the data regarding indications for adjuvant RT in male patients is limited. Men do tend to be treated with RT more often after mastectomy than women, perhaps because they are more likely to have nipple or skin involvement[20]. We have considered RT as a component of multimodality therapy for 43.5% patients undergoing mastectomy with these advanced features. We had 6 patients with axillary lymph node metastases, 3 patients with T3 tumour and only one patient with chest wall invasion.

Likewise, the information on the role of CT in MBC patients is limited by the number of cases. In a prospective study of 24 patients with node-positive stage II breast cancer, adjuvant CMF regimen was reported to be highly encouraging treatment option with 5-year survival rate of > 80% when compared to that of historical controls of similar stage in which 5-year DFS rates were < 30%[21]. Several retrospective series have provided supporting evidence that adjuvant CT lowers

the risk for recurrence in male patients[22,23]. In the largest case-control study comparing men and women treated for stage 0 - IIIB breast cancer, the results showed that male patients received systemic therapy comparable to that received by their female counterparts, and they had similar OS and DFS[24]. We have administered chemotherapy (neoadjuvant, adjuvant or palliative) to all patients except one with stage I disease.

Tamoxifen, a selective estrogen receptor modulator has been used to treat female breast cancer for more than 30 years[25], with the World Health Organization citing tamoxifen as an essential drug in breast cancer treatment[26]. Tamoxifen is generally accepted as the "Standard of care" for adjuvant hormonal therapy for MBC patients since 90% of these tumours express ER and 81–96% express PgR[13,27]. However, overall survival is not affected significantly if there is remarkably low hormone receptor expression for these patients[28]. In view of receptor positivity, twenty-one (91.3%) patients received hormonal therapy in the form of tamoxifen.

On comparing the survival rates for MBC with female breast cancer, the relative survival rates were found to be lower for men. This overall worse prognosis for patients with MBC could be attributed to older age as well as advanced stage disease at presentation[2], despite the fact that similar treatment options were considered for both MBC and female breast cancer patients. However, this difference in survival rate became less apparent when the cohorts were stratified according to various prognostic factors[2,29,30]. Estimated overall 5- and 10-year survival rates for MBC are 63% and 41%, respectively, ranging from 5-year survival rate of 78% for stage I disease to 19% for stage IV disease[2]. We found 5-year DFS of 78%. This could be because of small sample size. In addition, the limitations of our work include retrospective data, and single institutional experience.

Conclusions

MBC is an area of fertile research because of the limited knowledge available to guide its treatment. Majority of the information regarding this disease has been gathered from case reports and retrospective, single-institutional cohort studies. This evidence is low on the hierarchial levels of evidence, and a major pitfall in formulating guidelines for the optimal management of these patients. Therefore, MBC should be brought to the forefront of breast cancer research. We also emphasize on obtaining more information in order to provide complete landscape of this disease. However, rarity of the disease might be a serious problem. It is thus important to direct future efforts towards publishing multi-institutional experience with these tumours supporting the treatment decisions.

Conflict of interest

There are no conflicts of interest.

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