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Male Breast Cancer: A Single Institutional Clinicopathological Profiling

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Abstract

Background/Aim: Male breast cancer (MBC) is an infrequent occurrence accounting for <1% of overall breast cancers. With limited data, MBC remains a therapeutic challenge, warranting the need for meticulous recording of all cases encountered.
Patients and Methods: A retrospective observational study in an Indian tertiary public hospital where 29 MBC cases registered between August 2020 and July 2023 were recorded and their epidemiological data, clinical profile, treatment history and survival data were analyzed.
Results: MBC was 3% of all breast cancer cases reported in three years, and the most common age group affected was between 41 and 60 years. Most cases presented at Stage IIIB, with the majority showing axillary nodal involvement. Invasive ductal carcinoma was the most frequent histology with luminal B and triple-negative variants having the highest incidence. Most patients underwent upfront surgery followed by adjuvant chemotherapy. At the end of one year, 50% of patients were found to survive with no disease progression.
Conclusion: Our results corroborate with previously recorded experience with MBC in terms of age distribution, stage of presentation, histology and treatment offered. However, our results demonstrated a higher proportion of triple-negative breast cancer (TNBC) cases, as compared to previous literature. The increment of TNBC cases among males, therefore, reassures the need for breast cancer (*BRCA*) gene testing among all males afflicted with breast cancer.

Keywords: Male breast cancer, low middle-income country, triple-negative breast cancer, BRCA1/2 genetic testing, prognosis.

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Introduction

Male breast cancer (MBC) accounts for <1% of overall breast cancers and is known to occur in men with an increased lifelong exposure to estrogen (1). The biological nature, molecular profile, and prognosis of MBC differ significantly from female breast cancer (FBC). Due to its rare occurrence and limited data, MBC remains a challenge to oncologists, warranting the need for meticulous recording of all cases encountered.

According to an estimate published by the American Cancer Society, approximately 2,790 men are expected to present with newly diagnosed breast cancer, and 530 men are expected to die from it in 2024 (2). There is about a 1 in 726 average lifetime risk of developing breast cancer in men, although the individual risk depends on the presence of risk factors (3).

The important risk factors are increasing age, higher body mass index, tall height, exposure to exogenous estrogens, Klinefelter Syndrome (47, XXY), history of testicular disorders like cryptorchidism, mumps, orchitis, orchiectomy, cirrhosis of the liver, occupational exposure to electromagnetic rays and genetic mutations (4). There is a significant difference in incidence across different geographical regions and among various ethnic groups (5). Treatment of MBC is the same as FBC, entailing definitive surgery supplemented with neo-adjuvant/adjuvant chemotherapy, radiotherapy and endocrine therapy, as indicated.

Patients and Methods

Patients. All histopathologically proven cases of MBC that attended the Department of Radiation Oncology, Institute of Post Graduate Medical Education and Research (IPGME&R) and Seth Sukhlal Karnani Memorial (SSKM) Hospital, Kolkata, India between August 2020 and July 2023 were considered for the study, including all age group and stage of presentation. Patients with Eastern Co-operative Oncology Group (ECOG) performance status 3 or more were excluded from the study. The sample size came to be 29. The study was a retrospective observational single-institution study.

Ethical considerations. The study design was approved by the institutional ethics committee before the initiation of data collection (IEC SSKM REF No. 23/08/2020/NON-REG/BS/08). Informed consent was obtained from all subjects involved in the study.

Methodology. We collected the following epidemiological data: age, residence, addictions and comorbidities. Staging was done using the American Joint Committee on Cancer (AJCC) TNM Classification of Malignant Tumours, 8th Edition (6). A biopsy followed by histopathology was performed to prove malignancy. Hormone receptor assay and Human epidermal growth factor receptor 2 (HER2) neu immunohistochemistry (IHC) scoring were also performed. Estrogen receptor (ER), and progesterone receptor (PR) were scored using the Allred scoring system which summates proportion (0-5) and intensity (0-3) of ER-positive tumor cells into a score of 0 to 8 out of 8 (7). Scores 0 and 2 were interpreted as negative; scores 3 to 8 were interpreted as positive. HER2 IHC scoring was used where a score of 3+ was interpreted as positive, a score of 2+ was interpreted as equivocal and a score of 0/1+ is interpreted as negative. Ki67% IHC scoring was done, where a score of ≤5 was considered low, and a score of ≥30 was considered high. Treatment details were collected concerning the primary modality of therapy and adjuvant treatment. Overall Survival (OS) at 1 year was defined as the period from the time of diagnosis to death due to any cause.

Statistical analysis. The hospital medical records were accessed and demographic profile, clinicopathological characteristics and survival was analyzed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and Statistical Package for the Social Sciences (SPSS) version 27.0 (IBM Corporation, Chicago, IL, USA). We did not use any statistical test of significance, only mean±standard deviation (SD) was used.

Results

Epidemiology. Among a total of 970 cases of BC, MBC accounted for 3%, while 0.7% of male patients who presented between 2020 and 2023 were suffering from MBC. All patients were from West Bengal, among which 22% were from the Kolkata district, followed by North 24 Parganas, Hooghly, and Howrah districts, each accounting for 16% of the total population. The most common age group affected was 41-60 years (15 patients) with a median of 60 years, while 21-40 years, 61-80 years, and 81-100 years were found to be 3, 10, and 1 in count, respectively (Figure 1).

A total of 33.3% of patients were tobacco addicts, while only 1 patient was an alcoholic. Two patients had a history of pulmonary tuberculosis, currently in remission, and 2 patients were known hypertensives on anti-hypertensive drugs. In 66.7% of cases, the left breast was affected. The most common presenting symptom was a breast lump.

Staging. As far as nodal involvement was concerned, 44.4% of patients showed axillary node involvement, out of which 25% of patients had N1 disease and 75% of patients had N2 disease. Stage IIIB was the most frequent stage at presentation, observed in 33.3%, followed by stage IIA in 27.7%, stage IV (metastatic) in 16.7%, stage IIIA in 16.7%, and stage IIB in 5.6% of all cases (Figure 2).

Histology and molecular biology. Invasive ductal carcinoma (not otherwise specified) was the most frequent histologic subtype detected in 77.7% of patients. Two patients were diagnosed with adenocarcinoma of the breast, one with squamous cell carcinoma of the breast, and one with invasive papillary carcinoma of the breast. Luminal A type was 16.7%, luminal B was 33.3%, HER2 enriched was 16.7%, and triple-negative breast cancer (TNBC) was 33.3% (Figure 3).

Treatment. A total of 65.5% of patients underwent upfront surgery, among which 75% were selected for modified radical mastectomy and the remaining 25% for breast conserving surgery. 20.7% of patients received neo-adjuvant chemotherapy followed by definitive surgery, while 13.8% of cases were started on chemotherapy with palliative intent. All patients were offered adjuvant therapy following the National Comprehensive Cancer Network (NCCN) guidelines. Adjuvant endocrine therapy was started for all patients with positive estrogen and/or progesterone receptor status, while anti-Her2neu therapy with Trastuzumab was given to all patients with positive HER2 status.

Survival. At the end of one year, 50% of patients were found to survive with no disease progression, 27.8% passed away during follow-up and 22.2% of patients were lost to follow-up (Figure 4).

Discussion

Owing to the rarity of the entity, conducting clinical trials has been challenging for MBC due to poor recruitment. Knowledge of MBC is primarily derived from retrospective single-institute studies and mostly extrapolated from evidence on FBC. However, some distinguishing features have been noted between the disease in males and females. In comparison with FBC, MBC is diagnosed at a more advanced stage, with larger tumor size and axillary nodal involvement. Lack of awareness and stigma associated with the disease among men is the most important contributing factor to late diagnosis, with early involvement of skin and nodes due to lack of breast tissue, resulting in poorer prognosis (8). The 5-year survival rate for MBC in India is estimated to be around 56% compared to 66.4% for FBC (9, 10).

Most MBCs are unilateral at diagnosis, presenting after the age of 50 years. The median age at diagnosis was calculated to be 65 years in a large retrospective cohort study of 19,795 MBC patients, with 15% of patients diagnosed at age <50 years (11). This was in line with the age distribution of our sample. The usual presentation of MBC is a painless lump in the retro-areolar area with early nipple involvement resulting in retraction or ulceration

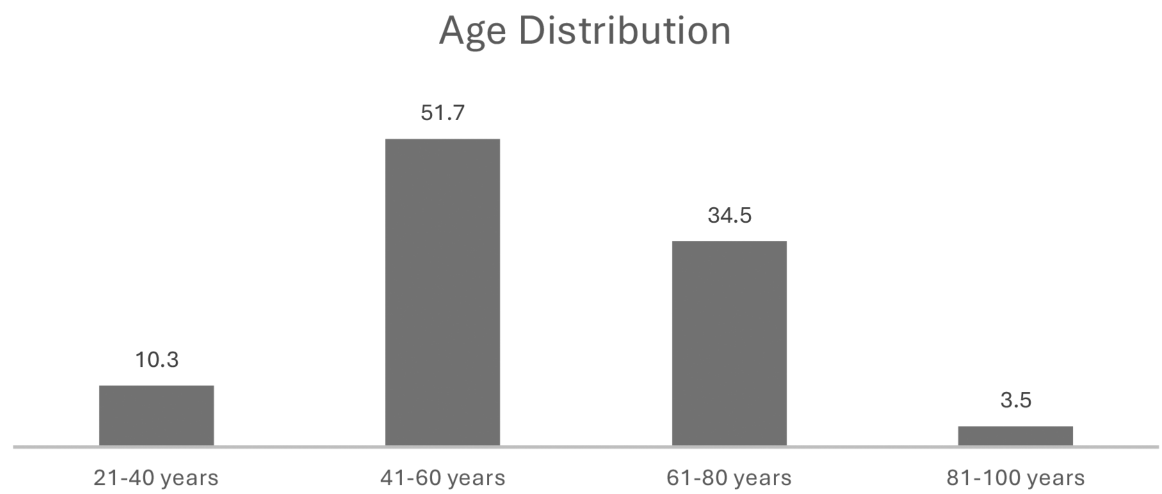

Figure 1. *Bar chart representation of age distribution of 29 patients of male breast cancer (in percentage) divided into the age groups of 21-40, 41-60, 61-80, and 81-100 years.*

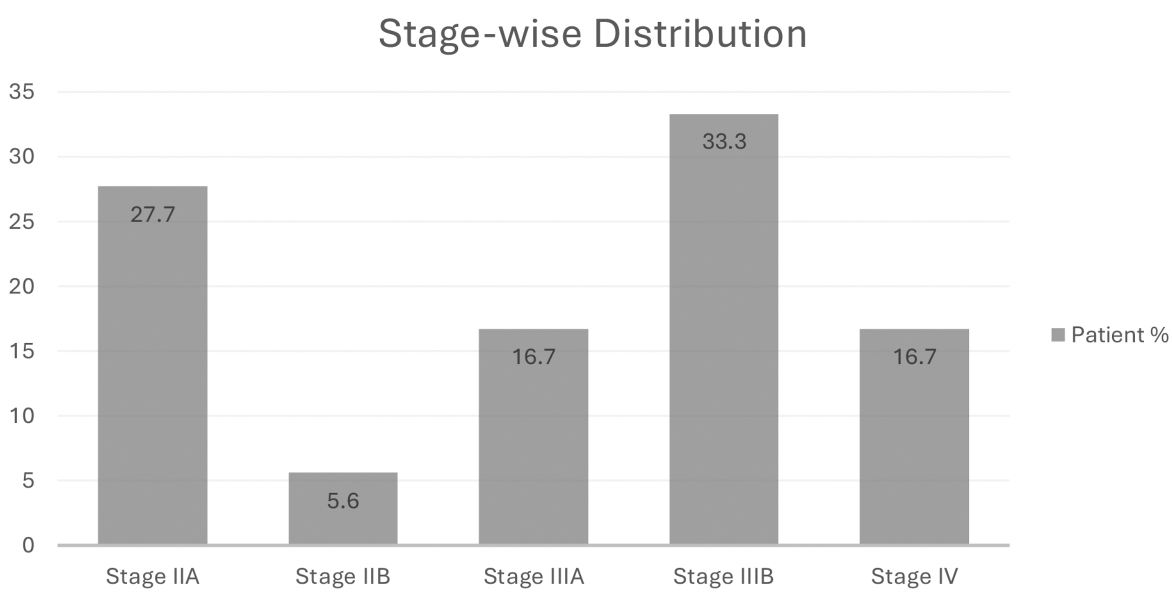

Figure 2. *Bar chart representation of stage-wise distribution of male breast cancer patients at presentation divided into stages IIA, IIB, IIIA, IIIB and IV.*

due to spread to rudimentary breast ducts, subcutaneous to the nipple. Early nodal involvement is also a typical characteristic of MBC with approximately 46.7% of cases having at least one positive lymph node at diagnosis, as reported in the International MBC Program (12).

Diagnostic and staging workup is the same as FBC, including radiological studies like USG of the breasts, mammography, and contrast-enhanced computed tomography (CT) scan of the thorax, abdomen and pelvis, followed by histopathological examination and immunohistochemistry by means of core needle biopsy. Invasive ductal carcinoma is the most prevalent histopathological variant of MBCs, accounting for 80%, with ductal carcinoma *in situ* being the second most common. Papillary histology

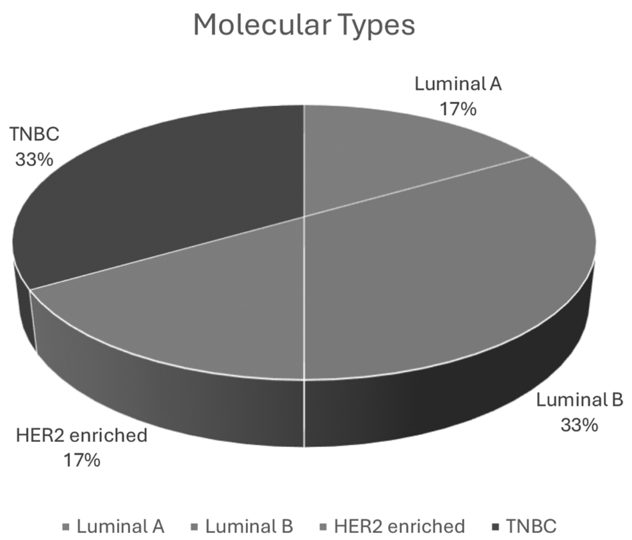

Figure 3. *Pie chart representation of the percentage distribution of male breast cancer patients according to the molecular subtype of their disease, i.e. Luminal A, Luminal B, HER2 enriched and TNBC.*

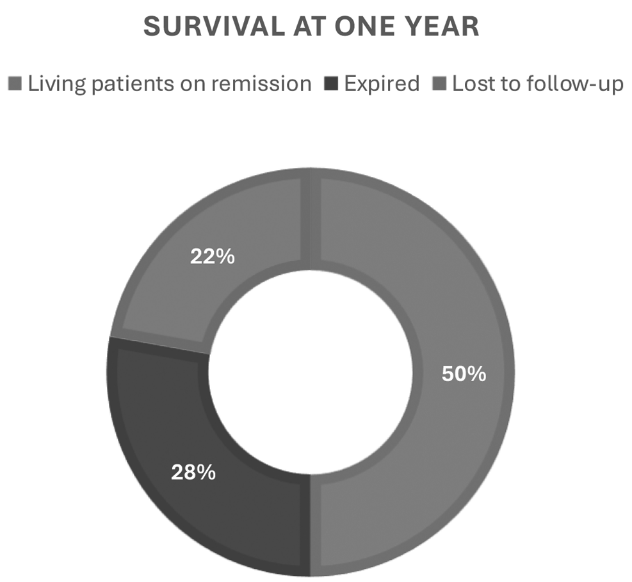

Figure 4. *Pie chart representation of the survival outcome of our study at the end of a one-year follow-up period for each patient.*

is seen more commonly in men (4.4% male *vs.* 0.7% female) whereas lobular invasive carcinoma is uncommon (1.2% male *vs.* 8.2% female). MBCs are mostly known to be hormone receptor-positive (80%). HER2-positive and TNBC are approximately 10-15% and 3-5% of the cases, respectively (8). Contrary to existing literature, we found a higher proportion of triple-negative cases in our study population (3-5% *vs.* 33.3%). An Italian study carried out from 2013 to 2021 evaluated 136 women with TNBC, revealing deleterious mutations of breast cancer genes 1 and 2 (*BRCA1/2*) in 28.7% of cases (13). A systematic review analyzing 35 research studies on the relationship between female TNBC and BRCA1/2 carrier status revealed *BRCA1* mutations ranging from 9-100% (mean 35%) and *BRCA2* mutations ranging from 2-12% (mean 8%) among TNBC cases (14). Such data establish a significant correlation between TNBC and germline *BRCA* mutations, implying that our study population may have a high likelihood of harboring *BRCA* mutations.

Genetic predisposition in MBC is significant, with 10% of all cases being hereditary in nature due to germline mutations in *BRCA2*, *p53*, *ATM*, *CHEK2*, and *PALB2* genes (7). *BRCA1* and *BRCA2* mutations are the top contributors in the development of MBCs, with *BRCA2* mutations associated with a lifetime risk of 6.8%. The genomic landscape of MBC shows significant heterogeneity, with recurrent mutations in *PIK3CA*, *TP53*, and *GATA3* being the most common. Luminal B-like tumors show more DNA repair variants than Luminal A-like. Epigenetic alterations, most importantly promoter hypermethylation in DNA repair and cell adhesion genes (*e.g.*, *MSH6*, *CDH13*) are detected, contributing to poorer prognosis. Genetic counseling and testing are strongly recommended for all men diagnosed with MBC, although uptake remains limited due to barriers like psychosocial factors, economic constraints, and healthcare provider unfamiliarity (6). Using MALDI-TOF mass spectrometric technology on protein-expression alterations in male breast tumors, Chahed *et al.* revealed overexpression of structural proteins, glycolytic enzymes, stress related proteins, enzymes involved in the synthesis of AMP and heat-shock proteins (15). Zografos *et al.* confirmed this and detected more proteins that were unregulated in MBC, involved in chaperonin-mediated protein folding, protein biosynthesis and transport, cytoskeleton organization, DNA synthesis, cell division and ATP synthesis, proteasome assembly, mRNA processing, cell adhesion, and endocytosis (16).

Due to a lack of prospective clinical data, the treatment of MBC is extrapolated from that of FBC. In early cases, surgery is the preferred treatment in the form of modified radical mastectomy (MRM) and, less commonly, breast conserving surgery (BCS). MRM is performed in the majority of cases, as most tumors are centrally located, making BCS unsuitable. BCS, when performed, is supplemented with axillary lymph node dissection, while sentinel lymph node dissection is underutilized compared to FBC. Adjuvant radiotherapy in FBC is recommended in cases of T3/T4 tumors, positive tumor margins, gross extracapsular extension, four or more nodal involvements, metastasis to supraclavicular or internal mammary nodes, and in all cases of BCS. It may be considered in cases of close margin, less than 35 years of age, lympho-vascular infiltration and grade 3 tumors (17). Adjuvant radiotherapy is indicated in MBC to reduce the chance of recurrence and disease-specific mortality, in line with FBC. In our study, we delivered adjuvant radiotherapy to 25 out of 29 patients with a tele-cobalt machine at a dose of 40 Gy in 25 fractions over 5 weeks, followed by tumor bed boost radiotherapy, in cases of BCS at a dose of 14 Gy in 7 fractions.

Neoadjuvant chemotherapy may be used in stage II/III disease to improve resectability, chances of attaining a negative margin, and reduce the likelihood of developing micro-metastasis and recurrence. In our study cohort, 6/29 patients received neoadjuvant chemotherapy. Six cycles of docetaxel, carboplatin, and trastuzumab (TCH) chemotherapy were used every 21 days for HER2-positive disease, and in HER2-negative cases, four cycles of dose-dense doxorubicin and cyclophosphamide (AC), followed by four cycles of dose-dense taxane chemotherapy, were used every 14 days. Improvement of OS has been associated with the use of adjuvant chemotherapy (anthracycline-based or anthracycline-taxane-based) in stage II/III disease. Zheng *et al.* recommends patients with large tumors, lymph node involvement, hormone receptor-negative disease, and young age at diagnosis to receive adjuvant chemotherapy (12). Likewise, we administered adjuvant chemotherapy with the same regimens used in the neoadjuvant setting in 19 out of 29 chemo-naïve patients who underwent upfront surgery.

In hormone receptor-positive breast cancer (in both genders), Oncotype Dx, a 21 gene recurrence score (RS), has been used to prognosticate and predict benefits from adjuvant chemotherapy. As compared to FBC, MBC is more likely to have scores ≥31 (12.4% male *vs.* 7.4% female) and <11 (33.8% male*.* 22.1% female) (18). As per Surveillance, Epidemiology, and End Results (SEER) and National Cancer Data Base (NCDB) data analysis, men with node-negative, hormone receptor-positive breast cancer with RS <11 have excellent outcomes even without adjuvant chemotherapy while those with RS ranging between 11-25 also showed no additional survival benefit with chemotherapy. However, for N1 disease with RS <25, omitting chemotherapy may be considered, based primarily on prospective clinical data from females. In all cases of Oncotype Dx RS ≥26, adjuvant chemotherapy and endocrine therapy are recommended, regardless of nodal status (19, 20). More than 90% of MBC patients being hormone receptor-positive makes endocrine therapy crucial in its management. Tamoxifen, a selective ER modulator, has shown improved OS in several retrospective studies on early-stage MBC, especially with nodal involvement (21, 22).

In our sample, 4 out of 29 patients (13.8%) had metastatic disease at presentation, two with extensive lung involvement, one with spread to T10-T11 vertebrae, and the other with deposits in the bilateral cerebral cortices of the brain. All 4 cases were treated with systemic chemotherapy and endocrine therapy depending on hormone receptor and HER2 status, alongside palliative radiation to bone and brain, where indicated.

Conclusion

Our study cohort yielded similar results to previously reported data on MBC, except for a few parameters. The increased incidence of MBC, particularly the triple negative variant, reported at our institute highlights the importance of checking for mutations in the *BRCA1/2* genes of such patients. However, genomic testing is rarely available free of cost in the Indian public health sector, except in clinical trial settings. In the private health sector, the cost of such tests is prohibitively high and must be borne by the patient. As a result, we were unable to offer BRCA testing at our institute, and our patients could not afford it through private services. Detecting a mutant *BRCA* gene helps clinicians identify the root cause of the disease, which in turn aids in prognostication and prediction of outcomes. It not only assists in genetic counselling of the patient and their family about the possibility of a familial BRCA syndrome but also enables the use of a poly-ADP ribose polymerase inhibitor in recurrent/refractory cases. Hence, the necessity of BRCA testing in all MBC patients, a category 2A recommendation by NCCN, must be acted upon by stakeholders to make it an accessible tool in the management of the disease (23). Public awareness of disease incidence, the benefit of early detection on prognosis, and the significance of genetic counselling must be promoted. Furthermore, it is vital to record and report data on all cases of MBC worldwide to estimate changing trends in epidemiology, characterize the disease further, and lay out recommendations for its management.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contributions

Conceptualization, S.DeS. and S.Ba.; methodology, S.Ba.; software, A.I.; validation, S.DeS. S.Ba., and S.Bo.; formal analysis, S.DeS. and S.Ba.; investigation, A.M. and A.G.; resources, S.C.; data curation, A.I. and A.G.; writing – original draft preparation, S.DeS.; writing – review and editing, S.Ba., and S.Bo.; visualisation, A.M. and S.C.; supervision, S.Bo.; project administration, S.Bo.; funding acquisition, S.Bo. All Authors have read and agreed to the published version of the manuscript.

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