



A CLINICOPATHOLOGICAL STUDY OF MALE BREAST CANCER WITH EMPHASIS ON ANDROGEN RECEPTOR POSITIVITY FROM SOUTHERN INDIA.

V Geethika	Post-doctoral Fellow, Department of Surgical Oncology, NIMS, Hyderabad
Monalisa Hui	Associate Professor, Department of Pathology, NIMS, Hyderabad.
Ranganath R*	Associate Professor, Department of Surgical Oncology, NIMS, Hyderabad. *Corresponding Author

ABSTRACT **Background-** Breast cancer in males is a rare malignancy worldwide. The present recommendations for diagnosis and management of breast cancer in males are based on our understanding of results from clinical trials of breast cancer in females. Therefore, clinical trials will help understand the tumor biology and management of this rare tumor and might play a role in decreasing mortality. **Aim:** To analyze the clinicopathological characteristics of breast cancer in males. **Methodology-** A retrospective analysis of case records of all the male patients diagnosed with breast cancer in our Institute between January 2017 and December 2021 was done. Demographic details, tumor profile, and histopathological parameters were collected and analyzed. **Results-** The median age at presentation was 60.5yrs. The most common site of primary breast cancer was the central quadrant (n=9). According to clinical T classification, 5 patients were T2 and 3 each in T3 and T4. Axillary nodes were found to be positive in 5 patients. All the patients were found to be Estrogen and Progesterone Receptor (ER, PR) positive. Her2neu receptor was found to be positive in only one patient. Androgen receptor was found to be positive in 91.67% of cases. **Conclusion-** In this series, almost all cases of male breast cancer were found to be hormone receptor positive, including the androgen receptor (AR). Routine testing of the androgen receptor in male breast cancer can provide an alternate treatment pathway, if necessary.

KEYWORDS : male breast cancer, immunohistochemistry, androgen receptor

INTRODUCTION

Breast cancer in males is a rare malignancy, with the cumulative risk of males developing breast cancer in India being 1 in 1022 [1]. Due to the uncommon nature of the disease in men, limited literature is available to understand the course of the disease. The present recommendations for diagnosis and management of breast cancer in males are based on our understanding of results from clinical trials of breast cancer in females.

Breast cancer in males is associated with high mortality rates, probably because half of the breast cancer diagnosed in men is at a more advanced stage compared to women. This is because of very little glandular tissue between the skin and the pectoralis major muscle and a low index of suspicion among the clinicians. In 2019, the American Cancer Society reported that more than three times as many males will be diagnosed with testicular cancer than with breast cancer [2].

However, paradoxically, over the last five years, more males have died from breast cancer than testicular cancer. Therefore, clinical trials will help understand the tumor biology and management of this rare tumor and might play a role in decreasing mortality. We performed this retrospective analysis to contribute to the scant literature on male breast cancer and contribute to the knowledge base required to formulate treatment algorithms.

MATERIALS AND METHODS

A retrospective analysis of the case records of all male breast cancer patients diagnosed and treated at our Institute over a five-year period between January 2017 and December 2021 was undertaken, after obtaining approval from the Institute Ethics Committee. A total of 12 male patients diagnosed with breast cancer were reviewed, and their demographic details, tumor profile and final histopathological findings were analyzed. During the same period, a total of 432 female patients were treated for cancer of the breast, which gave us a hospital incidence of 2.8% of male breast cancer, which agrees well with the literature.

All the patients were clinically assessed, radiologically imaged, and underwent core needle biopsy for histopathological confirmation. All operable patients underwent modified radical mastectomy (MRM). Post-operative therapy protocols were followed as that of post menopausal female breast cancer guidelines. Patients diagnosed with metastatic disease were offered palliative chemotherapy and hormonal therapy. Patients were followed up closely and clinical examination findings and imaging findings were recorded.

The hormone receptor (ER, PR), Her 2neu, Ki-67 positivity and the Androgen Receptor status were determined on the paraffin blocks

using immunohistochemical analysis. We were able to acquire all the information as the slides and blocks are archived for a period of fifteen years in our centre.

RESULTS

During the study period, a total of 444 patients were diagnosed with breast cancer, of which 432(97.29%) were females and 12(2.78%) were males. The median age at presentation in our study was 60.5 years, ranging between 45 and 70 years. The tumor was in the right breast in 5(41.67) patients and left-sided in 7(58.33). The most common site of primary breast cancer was the central quadrant (n=9). 5 male patients presented to us in clinical T2 and 3 patients each in T3 and T4. The clinical tumor size of one patient was unavailable as the patient had undergone an excision biopsy at a local hospital. Clinically nodes were positive in 8(66.67%) patients [Table 1]

All 12 patients received treatment. 10 (75%) cases were surgically managed, out of which 9 underwent MRM and 1 patient underwent wide local excision. The pathological T classification data were available for 9 patients, and most of them were pT2(50%), with only 25% being pT3. On pathological examination, nodes were found to be positive in 5 patients. In our study, invasive ductal carcinoma, the NST subtype was diagnosed in all patients and most tumors showed moderate to poor differentiation (G2 - 50%, G3 - 33.3%). All the patients were found to be ER and PR positive. Her2 neu was positive in only one patient. Androgen receptor (AR) was found to be positive in 91.67% of cases. Ki 67, a marker of mitotic activity of the tumor, was measured taking a threshold value of 14%, and was found to be uniformly elevated in all the patients [Table 3]. Postoperatively all the patients received adjuvant chemotherapy and radiotherapy and were started on hormone therapy (Tamoxifen 20mg for 5 years).

One of the patients, diagnosed with metastatic disease was offered palliative chemotherapy and hormonal therapy. Another patient presented in locally advanced stage i.e. stage IIIB and received neoadjuvant chemotherapy (NACT). After receiving NACT, there was partial regression of the tumor, following which the patient defaulted for a year. Presently, the patient has metastatic disease and is on palliative chemotherapy and hormonal therapy.

The median duration of follow-up was 23 months (range 50 - 12 months). 9 patients are alive with no regional or systemic failure. One patient expired, probably because of natural causes.

DISCUSSION

Breast cancer in males is a rare entity, representing approximately 1% of malignancies that occur in males [3,4]. In our study the incidence of breast cancer 2.7%, which is slightly higher than the reported

worldwide incidence. Few Indian studies have variably reported the incidence, ranging between 0.4% to 4.1% [5-7]. Breast cancer in males is usually seen in the elderly population. The median age is 60.5 years in our study. Breast cancer in females is diagnosed at a younger age, which is nearly a decade earlier than that of men diagnosed with breast cancer.

The most common presenting symptom was a painless lump in the breast and nipple involvement was noticed in 3 patients. Early involvement of the nipple and spread to the lymph nodes is due to scanty glandular tissue between the skin and the underlying pectoralis major muscle.

According to WHO classification, invasive carcinoma of no special type is the most common microscopic subtype of male breast cancer. Our study has shown similar results. Half of our patients presented to us in the locally advanced stage and one patient presented with metastatic disease. This may be attributed to the increasing awareness among the population. Breast cancer in males is more likely to be node positive with more frequent lymphovascular invasion as seen in various studies.

Studies have shown that breast cancer in males is ER and PR positive with a positivity rate of 90% [8]. Our results are consistent with the findings in the literature. Androgen receptor was found to be positive in 91.67% of cases. Various studies have shown the expression of AR in male breast cancer with positivity ranging from 40.1% to 90% [9-11]. These results suggest the possibility of utilizing additional therapeutic modalities in the treatment of breast cancer in males, especially in cases who are not responding to conventional chemotherapy or hormonal therapy. Ongoing clinical trials are using AR antagonists in breast cancer.

The choice of surgery in males for breast cancer is mastectomy. This is because of early involvement of the skin and the underlying pectoralis major muscle and considerably less breast volume in males. In a few cases, part of the muscle underlying the tumor may also have to be excised as a deep margin due to the involvement by the tumor. The efficacy of adjuvant chemotherapy and radiotherapy in male breast cancer has not been evaluated because of the rarity of the disease. As per the data extrapolated from the female breast cancer studies, all the patients were offered adjuvant chemotherapy.

According to a study by Yadav BS et al, chemotherapy had no impact on disease-free survival (DFS) and overall survival (OS) [12]. 9 patients received adjuvant radiotherapy due to axillary involvement and/or T4 disease. A retrospective Indian study of 81 men, showed significant improvement in DFS and OS with adjuvant radiotherapy and hormonal therapy [11].

All the cases were hormone receptor positive, hence, all the patients were started on oral tamoxifen for 5 years. There are no prospective trials to evaluate the efficacy of aromatase inhibitors in male breast cancer. Ribeiro and Swindell compared patients who received mastectomy and tamoxifen with mastectomy alone. Patients who were on Tamoxifen, DFS, and OS were 56% and 28% compared to that 61% and 41% respectively in patients who underwent mastectomy alone [13].

The androgen receptor, a steroid hormone nuclear receptor, is responsible for the development and progression of prostate cancers. The role of androgen deprivation therapy and anti-androgens as the standard treatment for advanced prostate cancers is well established.

Androgen receptor (AR) is prevalent in 90% of all breast cancers [14]. But the controversy remains as to if AR is a good or poor prognostic factor in breast cancer. There are ongoing trials to determine the efficacy of AR antagonists in the management of breast cancer. The determination of AR status at the time of diagnosis might help the selected group of patients, especially those not responding to chemotherapy or hormonal therapy.

Ki 67 was already in use as a prognostic marker, and there are now studies attempting to determine its role as a predictive parameter in the response of breast cancer to chemotherapy.

CONCLUSION

Male breast carcinoma is a rare disease, but its frequency has been increasing recently. Breast carcinoma in males differs from its female

counterpart in morphological characteristics and biology of the tumor. The age of presentation in male breast cancer is nearly a decade later compared to that in females. Male breast cancer is almost exclusively hormone receptor positive, and expresses the Androgen receptor (AR). Androgen receptor positivity will add another therapeutic modality for selected patients. Though the sample size of the study is small, it adds valuable information to the literature about male breast cancer.

List of abbreviations used in the manuscript

1. “T” classification – Tumor stage as per the AJCC TNM classification
2. ER, PR, Her 2neu – Estrogen receptor, Progesterone receptor, Human epidermal growth factor receptor
3. AR – Androgen receptor
4. MRM – Modified radical mastectomy
5. NST – no specific type
6. NACT – neoadjuvant chemotherapy
7. WHO – World Health Organisation
8. DFS – disease free survival
9. OS – overall survival

Table 1. Clinical characteristics of the patient cohort (N=12)

Parameter	Number of Patients	Percentage %
Location		
Central quad rant	9	75%
Upper outer quadrant	3	25%
Laterality		
Right	5	41.6%
Left	7	58.3%
cT		
T2	5	41.6%
T3	3	25%
T4	3	25%
Tx	1	8.3%
cN		
Positive	8	66.6%
Negative	4	33.3%

Table 2. Treatment received

Treatment	Number of Patients	Percentage %
Surgery (n=10) MRM	9	90%
Wide local excision	1	10%
Chemotherapy (n=12)	1	8.3%
Neoadjuvant Adjuvant	9	75%
Palliative	2	16.6%
Radiotherapy (n=9)		
Adjuvant	9	100%
Hormonal therapy (n=12)		
Adjuvant	9	75%
Palliative	2	16.6%

Table 3. Histopathological parameters of the patient cohort

Histopathological Characteristics	Number of Patients	Percentage %
Histologic type IDC	11	91.67
Mucinous Differentiation	1	8.33
Grade		
I	0	0
II	6	50%
III	4	33.3%
pN		
N0	4	44.4%
N1	1	11.1%
N2	4	44.4%
LVI		
Positive	5	62.5
Negative	3	47.5
DCIS		
Positive	3	37.5
Negative	5	62.5
Ki67		
< 14%	0	0
>14%	12	100



Fig 1. Clinical presentation of carcinoma breast in males

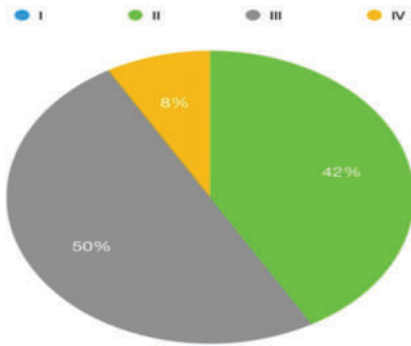


Fig 2. Stage distribution of the patient cohort (N=12)

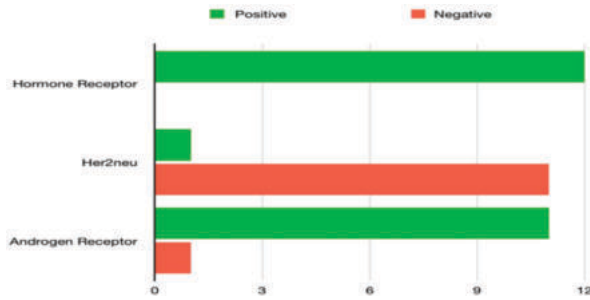


Fig 3: Pathologic receptor positivity (ER, PR, AR, Her 2neu)

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