ORIGINAL RESEARCH PAPER

Clinicopathological profile of patients with up-front metastatic breast cancer: a study from North East India

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ABSTRACT

Introduction: Breast cancer is the most common cancer in Indian females and approximately 5-10% present with up-front metastasis and 20-30% patients develops metastasis during follow up, but still limited data is available regarding the same. ***Objectives****: To study the clinicopathological profile of breast cancer patients presenting with up-front metastasis.* ***Materials and methods****: This is a retrospective study of Metastatic Breast Cancer (MBC) patients who attended the Medical Oncology Department of State Cancer Institute, Guwahati. In the study, we reviewed the records regarding clinical and histological profile, receptor status and site of metastasis of breast cancer patients presented with up-front metastasis from January 2019 to December 2019.* ***Results****: Total of 65 cases of MBC were studied. The average age of presentation was 46 years (range 22-70 years) with an average duration of symptoms 8 months (range 3-18 months). Male and Female ratio was 2:63. MBC was common in post-menopausal (52.38%) and Para 2 (48.7%) women. 41.53% of patients were at performance status 1 at presentation. In the histopathological study, ductal carcinoma was the most common (93.85%) pathological type with Nottingham grade II (60%) was the most common. Baseline receptor status suggested that 56.92% were hormone receptor [HR] positive, 40% were human epidermal growth factor-2 [Her2] neu positive and 18.46% were triple-negative breast cancer [TNBC]. Various sites of metastasis were visceral only (20%), bone (40%), combined bone and visceral (36.92%), non-regional lymph nodes (15.38%) and brain (4.61%).* ***Conclusion****: MBC is common in younger patients with bony metastasis being the commonest site of metastasis.*

Keywords*: Histopathological profile; receptor status; sites of metastasis.*

INTRODUCTION

Breast cancer is one of the earliest known malignancies of mankind documented way back in 6th century as "Divine punishment".[1] Now in the 21st century breast cancer has become the most commonly occurring cancer in women both in developed and developing countries like India and the second most common cancer overall. According to GLOBOCAN 2018 statistics, there were over 2 million new cases of breast cancer in 2018 worldwide.[2] The incidence of breast cancer is increasing in the developing countries due to increased life expectancy, increased urbanization and adoption of western lifestyles. Indian Council for Medical Research [ICMR] reports 1.5 lakh new breast cancer cases in India per year. As reported in the Western literature,[3] approximately 5-10% of patients present with up-front metastasis and 20-30% of patients develop metastasis during follow up. The scenario is quite different in India with approximately 5-25% breast cancer patients still present in metastatic stage.[4] An average age of 50-53 years is reported for breast cancer patients in various population-based studies done in India.[5,6] Breast cancer is considered to be a systemic disease because it can metastasize to distant sites in early stages even before

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the primary tumour become clinically evident so the management approach and treatment strategy directed only to the primary tumour will not be sufficient. The management and prognosis of breast cancer are largely based on luminal classification i.e. molecular subtype, HR [ER and/or PR] and /or Her2neu status of the patient, visceral versus non-visceral metastasis, performance status [PS] and age of the patient. Hormonal therapy, targeted therapy and chemotherapy are the various modes of treatment apart from surgery, radiotherapy depending on patient profile. Targeted therapy will be more beneficial if we know the receptor targets and if the patients present at an early stage of the disease. State Cancer Institute, Guwahati is one of the tertiary care oncology centres of North Eastern region of India providing comprehensive oncology services to the patients from entire NE regions however data regarding the MBC patients is still limited from this part of the country. With the knowledge from the existing literature, we have aimed to evaluate the clinical and pathological characteristics of our breast cancer patients presenting with up-front metastasis so that it gives us an idea of the clinical spectrum of MBC patients from this part of the country and the pathological and molecular profile of these patients which would imply the treatments and outcomes.

MATERIALS AND METHODS

The present study is a hospital-based retrospective study carried out on 65 breast cancer patients attended Department Medical Oncology at State Cancer Institute, Guwahati presenting with features of up-front metastasis during one year period from January 2019 to December 2019.

During the study periods, 389 breast cancer patients were registered in the OPD services of State Cancer Institute, Guwahati. Out of these, 73 patients presented with up-front metastasis and 65 patients were considered for analysis and 8 patients were excluded because of incomplete medical records or lost to follow up after 1st visit.

We retrieved the data regarding patient's characteristics [age, sex, menopausal status, PS and duration of symptom], pathological features, receptor status [ER/PR/Her2neu], molecular subtype (**Table 1**) and metastatic profile by reviewing the patient's file from the medical records department.

Table 1 Luminal classification [Molecular subtypes] of breast cancer[7]

	Luminal A/B	Her2 enriched	Basal type	Luminal/ Her2
ER/PR expression	+	±	-	+
Her2 amplification	±	+	-	+

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; Her2, human epidermal growth factor receptor 2.

Menopausal status is assessed from clinical history as the permanent cessation of menstrual periods, i.e. when a woman has not had any menstrual bleeding for a year without any other obvious pathological or physiological cause.

Performance status is assessed using Eastern Cooperative Oncology Group performance status [ECOG PS] grading as shown in **Table 2**.

Table 2 ECOG PS[8]

Grade 0	Fully active, able to carry on all pre-disease performance without restriction
Grade 1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of light and sedentary nature
Grade 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of working hours
Grade 3	Capable of only limited self-care, confined to bed or chair more than 50% of working hours
Grade 4	Completely disabled. Cannot carry on any self-care. Confined to a bed or chair
Grade 5	Dead

HR and Her2neu status was tested by standard immunohistochemistry [IHC] methods. IHC testing was performed in the paraffin-embedded breast tissue blocks [true cut or excisional biopsy specimen] stained with monoclonal antibodies. Allred scoring system was used for reporting the HR status. Allred or H score of 3 or more was considered as positive.[9] Her2neu status was tested as per the American Society of Clinical Oncology [ASCO]guidelines.[10] A score of 3+ was considered positive and 2 + was considered equivocal and 1+ as negative. All 2+ results of her2neu were confirmed by fluorescence in situ hybridization [FISH] amplification. Histologic type and grade were assessed according to the World Health Organization [WHO] standard and Nottingham grading respectively.[11] A metastatic workup was done using ^{18}F-NaF bone scan, CT scan of thorax and abdomen, magnetic resonance imaging [MRI] of brain or FDG positron emission tomography [PET] CT scan. Bone only, visceral [lung, liver, adrenal], brain and non-regional lymph nodes [LN] were recorded for the site of metastasis. Patient with 5 or fewer metastases involving 1 or 2 organs is considered to have the oligometastatic disease.

RESULTS

The median age of presentation was 46 years [range, 22 to 70 years] and the median duration of symptoms was 8 months [range, 3-18 months]. The male-female ratio was 2:63. MBC was common among postmenopausal women [N=33, 52.38%]. 7 patients [11.11%] were nulliparous and 20 patients [31.74%] had a history of use of some form of hormonal contraceptive medication at some part of their reproductive life. 11 patients [16.92%] had a family history of malignancy and 5 of them were specific for breast cancer (**Table 3**).

Table 3 Clinical characteristics of MBC patients

Parameters	Number [%]
Total number of patients Included	65
Median age at presentation (years)	46 years [range, 22-70]
Average duration of symptoms in months	8 months [range, 3-18]
Sex: (n=65)	
Male	2
Female	63
Menopausal status: (n=63)	
Premenopausal	30 [47.62%]
Postmenopausal	33 [52.38%]
ECOG PS: (n=65)	
PS 0	8 [12.3%]
PS 1	27 [41.53%]
PS 2	21 [32.30%]
PS 3	7 [10.76%]
PS 4	2 [3.76%]

Ductal carcinoma was the most common [93.85%] histologic type and Nottingham grade II being the most common grade in MBC patients (**Table 4**).

Table 4 Pathological profile

Parameter	Number [%]
Histologic type	
Ductal Carcinoma	61 [93.85%]
Lobular Carcinoma	3 [4.61%]
Others	1 [1.52%]
Histologic Grade [Nottingham Grade]	
Grade I	3 [4.61%]
Grade II	39 [60%]
Grade III	23 [35.85%]

HR status [ER and/or PR] were positive in 37 patients. Her2neu was positive in 21 patients and 12 patients were found to have TNBC (**Figure 1**).
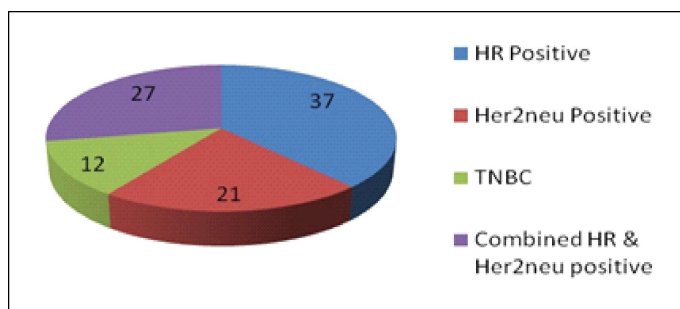

Figure 1 Baseline receptor status

Abbreviations: HR, Hormone receptor; Her2 neu, Human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

The most common site of metastasis was bone [40%], followed by combined bone and visceral metastasis in 36.92%, only visceral metastasis in 20%, non-regional LNs in 15.38% and brain in 3 patients (**Figure 2**). In visceral metastasis, the liver was most frequently involved [60.87%] followed by lung and adrenal.

Overall bony metastasis was the most common site of metastasis irrespective of receptor status. The vertebrae were the most common bone involved by metastasis. 25 patients [38.46%] had the oligometastatic disease. Patients with TNBC presented at an earlier age [37 years, range 22-55 years] and most are premenopausal [66.67%] with poor PS [ECOG PS 2-3] and had multiple sites metastasis at presentation.
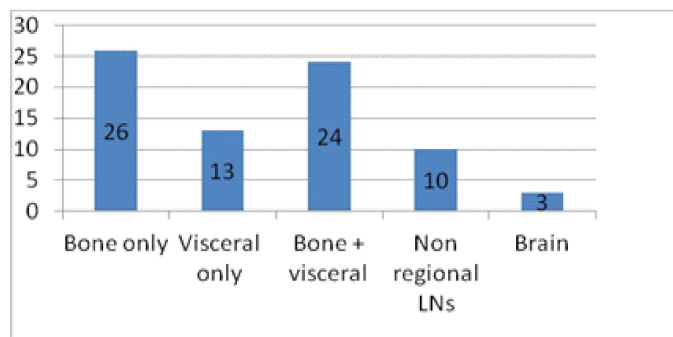

Figure 2 Sites of metastasis

DISCUSSION

Breast cancer is the most common cancer in women worldwide, with the widely variable incidence among countries and regions. As per the ICMR Population-based Cancer Registry data, breast cancer is the most common cancer among women in urban registries and second most common cancer in women after cancer of the uterine cervix in rural registries in India.[5,6]

In general, breast cancer has been reported to occur a decade earlier in Indian patients compared with their Western counterparts. Although the majority of patients with breast cancer in Western countries are postmenopausal and in their 60s and 70s, the picture is quite different in India, with premenopausal patients constituting approximately 50% of all patients.[4] More than 80% of Indian patients are younger than 60 years of age. The average age of patients with breast cancer has been reported to be 50 to 53 years in various population-based studies done in different parts of the country.[5,6] In the present study we have documented a median age of 46 years [range, 22 to 70 years]. In studies from Western countries, the median age of presentation was 55 to 60 years.[12,13] In our study we found the average age of presentation was 46 years which is almost similar to the study by Gogia A et al.[14] The present study documented that approximately 47.62% of patients were premenopausal and 52.38% were postmenopausal, whereas studies from the

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Western world have documented 70% to 80% patients are postmenopausal at presentation.[12,13]

In this study, HR was positive in 56.92% of patients; previous studies documented approximately 49% to 68% (**Table 5**). The incidence of TNBC in the present study is 18.46% which is almost similar to the study by Kunikullaya SU et al.[15]

Table 5 Comparison of the present study with previous studies

Parameters	Dafni et al[12]	Giordano et al[13]	Gogia A et al[14]	Present study
Total no of patients	364	105	375	65
Duration of study	2003-2006	1995-2000	2012-2018	1 year
Age at presentation [years]	60 [27-84]	49 [26-73]	49 [22-80]	46 [22-70]
Menopausal status:				
Premenopausal	19.5%	48%	39.8%	47.69%
Postmenopausal	80%	52%	60%	52.69%
Receptor Status:				
HR positive	68%	49%	61.4%	56.92
Her2neu positive	-	-	38.6%	40%
TNBC	-	-	-	18.46%
Site of metastasis:				
Bone only	50%	28%	26.7	40%
Visceral Only	72.5%	37%	58.4%	20%
Non regional LN	25%	30%	5.6%	15.38%
Brain	-	-	2.7%	4.61%
Combined bone and visceral	-	-	-	36.92%

In patients who had metastasis in this study, 16.71% presented with up-front metastasis. Common sites of metastasis were bone, lung, liver, lymph nodes and brain. Kennecke et al.[16] and Smid et al.[17] in their studies concluded that HR-positive tumours commonly spread to the bone and HR-negative and/or Her2 positive tumours are likely to spread to the viscera; however, in the present study, we have found that bone is a most common site of metastasis irrespective of the receptor status. The liver is the most common site of visceral metastasis [60.7%]. Park et al.[18] in his study found out the correlation between the molecular subtype and pattern of distant metastasis and concluded that Her2 over-expression provide aggressiveness to the tumour and commonly associated with brain metastasis. In the present study, we also found that Patients with visceral and brain metastasis commonly have Her2 enriched MBC.

CONCLUSION

In the study, we have found that the majority of the patients were younger and premenopausal at presentation and in the productive years of their life. Overall receptor status [ER/PR/Her2neu] is positive in 81.54% patients i.e. quite a large number of patients can be treated with curative intent if they present in early stage and can be prevented from developing metastatic disease. Patients with visceral and brain metastasis is commonly associated with Her2 overexpression so the patients who have her2 enriched tumour at baseline receptors status assessment need special attention during follow up so that early detection of metastasis is possible and targeted therapy can be considered for them. A quite large number of patients in our study presented in a later stage of disease when the performance status was deteriorating indicating that there is a lack of awareness of the disease in the general population.

Limitation of the study: A limitation in our study is that it was a retrospective study and the duration and study population was less so we advocate for further studies with a large number of patients over a larger duration of the period.

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