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ORIGINAL ARTICLE

Breast Cancer Subtypes Based on ER, PR and HER2/neu Expression and Its Clinico-pathological Correlation

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Abstract

Background: Carcinoma of the breast is one of the most common cancer in women and it is the second cause of cancer deaths only to lung cancer**.** Recent attention has been directed singularly at molecular classifications of breast cancer. Molecular subtypes have different prognostic and therapeutic implications. **Objective:** The aim of this study was to assess the ER, PR, and HER-2/neu reactivity pattern in breast carcinomas and to correlate this reactivity pattern with stage tumor size and lymph node metastasis. **Methodology:** This is a prospective analytical observational study was conducted in the North East Cancer Hospital and Department of Pathology of North East Medical College, Sylhet, Bangladesh during a 42 months period from July 2015 to December 2018. **Result:** Among 67 Cases of primary invasive breast carcinoma only one case was male and 66 were female. In aspect of tumor size most of the patient presented with 2 to 5cm tumor, 47(70.2%) cases and (80.6%) presented with more than 2cm tumor size. In our study 38(56.7%) cases of breast cancer found ER positive, 38.8%(26 cases) PR positive and 22.4% (15 cases) HER2/neu positive, most common presentation of the disease was at stage llB(29 cases,45%), lymph node positivity 46(68.7%) cases and lymph node negative 21(31.3%) cases, 5(7.5%)cases. In aspect of molecular subtyping we found luminl A 29 (43.3%) cases Luminal B 11.9% (8 cases) basal like 22(32.8%) cases and HER-2/neu over expressed 8(11.9%) cases. **Conclusion:** Cancer screening and early detection program can improve our scenario**.** [*Journal of Current and Advance Medical Research, January 2020;7(1):30-35*]

Keyword: breast carcinoma; HER-2/neu; ER/PR; Immunohistochemistry

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Introduction

Carcinoma of the breast is the most common non-skin malignancy in women and it was the second cause of cancer deaths only to lung cancer[1]. Over the last few decades there have been outstanding advance in breast cancer management leading to earlier detection of disease and the development of more effective treatments resulting in significant decline in breast cancer deaths and improved outcomes for women living with the disease[2,3]. Recent attention has been directed singularly at molecular classifications of breast cancer[4].

Molecular subtypes have different prognostic and therapeutic implications[5]. Screening for ER, PR and HER-2/neu status in breast tumor has become a standard method in determining the appropriate therapy for Breast cancer patient management throughout the world[6]. Estrogen is an important mitogen exerting its activity by binding to its receptor (ER). Therapeutic hormones like Tamoxifen competitively block ER thus antagonizing transcriptional activation of gene required for tumor growth.

The presence of hormone receptors (ER and PR) in the tumor tissue correlates well with the response to hormone therapy and chemotherapy. HER-2/neu also known as C-erb B2 (HER-2), is a proto-oncogen located on chromosome 17. It is amplified and the protein (HER-2) overexpressed in 15-25% of invasive breast carcinoma with associated poor prognosis. HER-2/neu is also an independent negative predictor of overall survival and time to relapse in patients with lymph-node positive breast cancer[7-12]. The objectives of this study was to assess the ER, PR, and HER-2/neu reactivity pattern in breast carcinomas and to correlate this reactivity pattern with stage tumor size and lymph node metastasis.

Methodology

This prospective analytical observational study was conducted in the North East Cancer Hospital and Department of Pathology of North East Medical College, Sylhet, Bangladesh during a 42 months period from July 2015 to December 2018. Patients of different age group and both sex were selected for this study according to inclusion and exclusion criteria. All histologically diagnosed invasive primary breast cancer patients who had completed the chemo and/or radio therapy were included in this study. IHC analysis for ER, PR, Her-2/neu status was carried out in all cases. The exclusion criteria were, recurrence or secondary breast cancer, incomplete or palliative therapy, unable to IHC analysis for ER, PR, Her-2/neu status. The present study included sixty seven cases of primary invasive breast carcinoma patients having mastectomy. Detailed gross examination of all received specimen was carried out for tumor size and nodal metastasis. All tissues were fixed in 10.0% buffered formalin not more than 24 hours. Representative tumour tissue was submitted for processing and H&E stain for histopathological diagnosis. IHC for ER, PR, Her-2/neu were performed on representative blocks of paraffin embedded tissue by outsourcing from various hospital of Dhaka city. All patients were admitted in North East Cancer Hospital and completed their chemo and/or radio therapy. The length of survival was calculated from the date on completed the therapy. Molecular sub typing was done based on ER, PR, Her-2/neu expression in four groups designated as Luminal A who were ER- positive, Her-2/neu negative and Luminal B, sometimes referred as triple-positive cancer, ER positive, Her-2/neu positive and Basal like also named as Triple-negative cancer who were ER negative, Her-2/neu negative. Her-2/neu over expressed were ER-negative, Her-2/neu positive. Quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. Statistical analysis was performed by using SPSS for windows version 20.0. 95% confidence limit was taken. Probability value <0.05 was considered as level of significance.

Result

This present study comprised of 67 Cases of primary invasive breast carcinoma of which only one case was male and 66 were female.

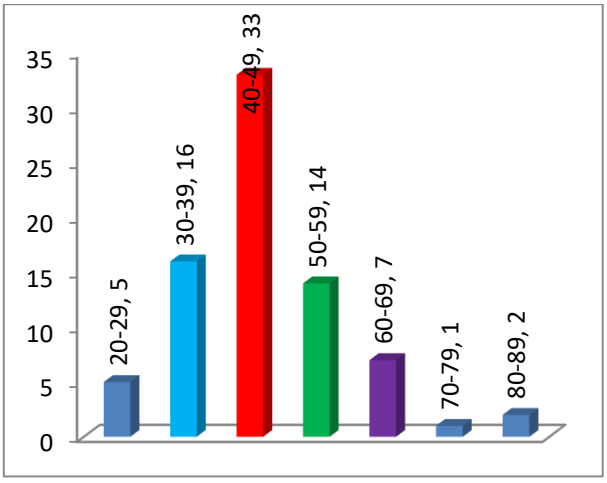

Figure I: **Age group distribution (n=67)**

Age of our study population ranges from minimum 26 years to maximum 85 years with the mean age 45.25 years. In the present study high incidence of invasive breast carcinoma was observed in fourth decades accounting for 32.84% of overall case distribution (Figure I).

Table 1: **Different Sizes of the Tumour (n=67)**

Tumour size	Frequency	Percent
2cm/>2cm	11	16.4
2 to 5 cm	47	70.2
More than 5 cm	9	13.4
Total	**67**	100

In aspect of tumor size most of the patient presented with 2-5cm tumor, 47 cases (70.2%) and (80.6%) presented with more than 2cm tumor size (Table 1).

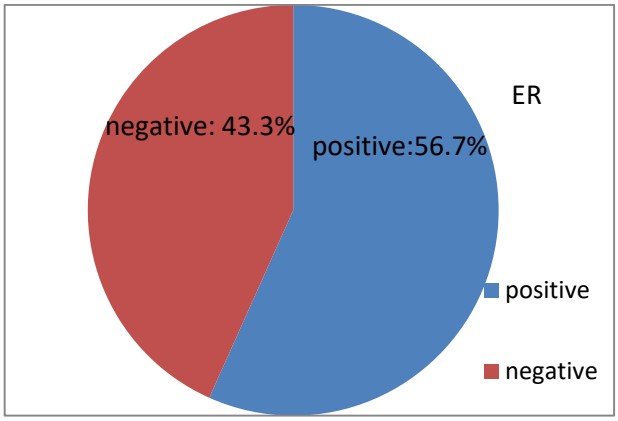

Figure II: **ER Status distribution (n=67)**

Out of 67 cases in this study 38 (56.7%) cases of breast cancer found ER positive (Figure II), 26(38.8%) cases PR positive (Figure III) and 15(22.4%) cases HER2/neu positive (Figure IV).

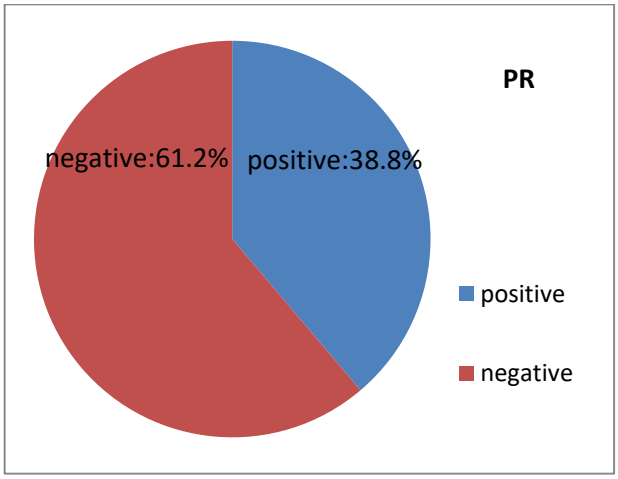

Figure III: **PR status distribution (n=67)**

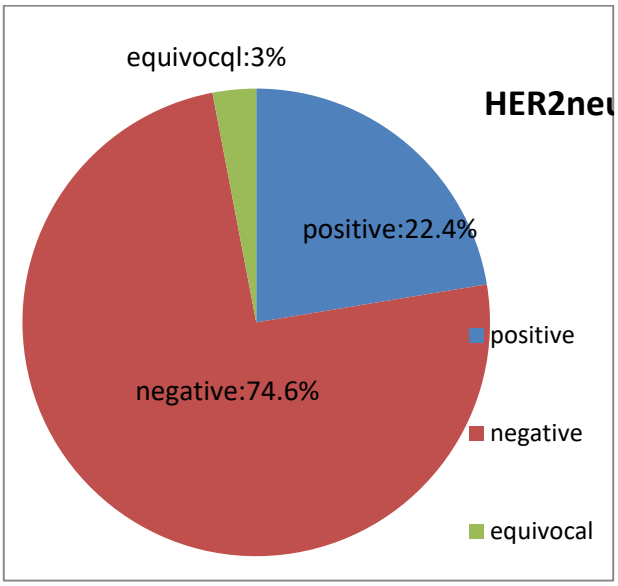

Figure IV: **HER2/neu Expression (n=67)**

In present study most common presentation of the disease was at stage IIB (29 cases, 45%) followed by IIA (23 cases 34%) stage IIIA (7 cases, 10%) stage IA (4cases 6%) stage IIIB and stage VI (2 cases 3%, both) (Figure V).

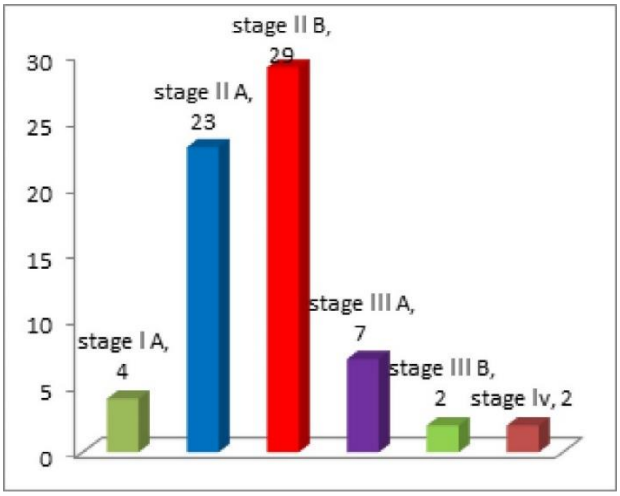

Figure V: Stages of Tumor (n=67)

Table 2: Lymph Node Status of Breast Cancer Patient (n=67)

Lymph Node Involvement	Frequency	Percent
No lymph involvement (n0)	21	31.3
1 to 3 node involvement (n1)	41	61.2
More than 3 node involvement (n2)	5	7.5
Total	**67**	100.0

This study showed lymph node positivity 46(68.7%) cases and lymph node negative 21(31.3%) cases, 5(7.5%) cases showed more than 3 lymph nodes positive (Table 2).

In aspect of molecular subtyping we found luminal A in 29(43.3%) cases, Luminal B in 8(11.9%) cases basal like 22(32.8%) cases and HER-2/neu over expressed 8(11.9%) cases (Table 3).

Table 3: Molecular Subtype (n=67)

Lymph Node Involvement	Frequency	Percent
Luminal A	29	43.3
Luminal B	8	11.9
Basel like	22	32.8
HER2 over express	8	11.9
Total	**67**	100.0

Luminal A=ER positive, HER2 Negative; Luminal B=ER-positive, Her-2/neu positive; Basel like=triple negative

In relation to sex, only one male case was Her2 over express. On the other hand Her2 over express patients were present at more early than Her2 negative (Table 4).

Table 4: Association of Molecular Subtype with Gender (n=67)

Molecular Subtype	Female	Male	P value
Luminal A	29	0	0.12
Luminal B	8	0	
Basal like	22	0	
Her2 over express	7	1	
Total	**66**	**1**	

Luminal A=ER positive, HER2 Negative; Luminal B=ER-positive, Her-2/neu positive; Basal like=Triple negative

In relation to size of the tumour, Luminal A (24.13%) and Basal like (9.09%) were present with more than 5 cm size whereas Luminal B was present 25% up to 2 cm size. Though most cases were present between 2cm to 5cm in all type. (Table 5).

Table 5: Relationship of Molecular Subtype with Size (n=67)

Size	Luminal A	Luminal B	Basal like	Her2 over express	Total	P value
2cm/,2cm	4(13.8%)	2(25%)	4(18.18%)	1(12.5%)	11(16.4%)	0.402
2-5 cm	18(62.6%)	6(75%)	16(72.73%)	7(87.5%)	47(70.2%)	
>5 cm	7(24.13%)	0(0.0%)	2(09.09%)	0(0.0%)	9(13.4%)	
Total	**29(100.0%)**	**8(100.0%)**	**22(100.0%)**	**8(100.0%)**	**67(100.0%)**	

In relation to stage of the tumour, Luminal A had wide range of presentation from stage 1A to stage IV. Other types were present mostly in stage II (Table 6).

Table 6: Correlation of Molecular Subtype and Stages (n=67)

Stages	Luminal A	Luminal B	Basal like	Her2 over express	Total	P value
Stage IA	4	0	0	0	4	0.754
Stage IIA	9	2	8	4	23	
Stage IIB	12	4	10	3	29	
Stage IIIA	2	1	3	1	7	
Stage IIIB	1	0	1	0	2	
Stage IV	1	1	0	0	2	
Total	29	8	22	8	67	

Discussion

This present study has comprised of 67 cases of primary invasive breast carcinoma of which only one case is male and 66 cases are female which is similar to Lester[1] (male-1 %). Age of this study population ranges from minimum 26 years to maximum 85 years with the mean age 45.25 years. In this present study high incidence of invasive breast carcinoma has been observed in fourth

decades accounting for 32.84% of overall case distribution. Vasudha et al[8] have also found highest incident of invasive breast carcinoma in fourth decade (41.37%).

In aspect of tumor size most of the patient presented with 2 to 5 cm tumor, 47(70.2%) cases and (80.6%) presented with more than 2cm tumor size which is similar Vasudha et al[8] study while study from western country Onitilo et al[5] have showed 71.4% cases with less than 2cm size, this could be to early cancer detection programs.

The expression ratio of ER and HER-2/neu receptors in breast tumor is population specific. Out of 67 cases in this study 56.7% (38 cases) of breast cancer found ER positive, 26 (38.8%) cases PR positive and 22.4% (15 cases) HER2/neu positive. Vasudha et al[8] have found 48.2% PR positive 37.9% HER-2/neu 27.58% positive which is similar to our study but Onitilo et al[5] in USA fond ER 77.9% positive, PR 59.1% positive, HER-2/neu 17.7% positive. Pandey and Pandey[9] found 57% cases ER positive, 51.4% cases PR positive and 51.4% cases HER2/neu positive; Kinsella et al[10] have found 45.0% cases ER positive 37.0% cases PR positive and 32% HER-2/neu positive.

In present study most common presentation of the disease is at stage IIB (29 cases, 45%) followed by IIA (23 cases 34%), stage IIIA (7 cases, 10%), stage IA (4 cases 6%), stage IIIB and stage IV (2 cases 3%, both). Onitilo et al[5] have found stage I in 56.4% cases, stage II 36% cases, stage-III 7.6% cases. They have found most of the patient presented at early stage this also could be to early cancer detection programs.

In respect of lymph node involvement this study has shown lymph node positivity 46 cases (68.7%) and lymph node negative 21 (31.3%) cases, 5(7.5%) cases showed more than 3 lymph node positive. Vasudha et al[8] found lymph node positive 53.44% cases and negative 46.56% cases which is all most similar to our study whereas Onitilo et al[5] have found 31.0% cases positive, 61.2% cases negative and 7.8% cases not examined case.

In aspect of molecular subtyping we found luminal A (ER-Positive, HER-2/neu-negative) 43.3% (29 cases) Luminal B (ER- Positive, HER-2/neu-Positive) 11.9% (8 cases) basal like (triple negative/ER- negative HER-2/neu - negative) 32.8% (22 cases) and HER-2/neu over expressed (ER-negative , HER-2/neu-Positive) 11.9% (8 cases). Onitilo et al[5] found luminal A (ER-Positive, HER-2/neu-negative) 68.9% luminal B (ER-Positive, HER-2/neu-Positive) 11.2% basal like (triple negative/ER- negative HER-2/neu-negative) 13.4% HER-2/neu over expressed (ER - negative , HER-2/neu-Positive) 7.5% which is almost similar to our study except basal like (triple negative/ER-negative HER-2/neu- negative) found increased in number in our population[5].

Her-2/neu positivity is 22.4% cases in this study which is comparable with Vasudha et al[8] and Lal et al[11] and have shown 27.58% cases and 26.89% cases positivity in their study respectively.

Conclusion

The patients were presented in our study in later stage compare to western country. Cancer screening and early detection program can improve our scenario. In case of survival, multicenter and long tram study can valided the result of our study.

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