

Original Research Article

A study on correlation of histopathological grade with hormone receptor and HER2/neu status in invasive breast carcinoma at a tertiary care centre of Barak valley

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ABSTRACT

Background: Breast carcinoma is the most common malignancy occurring in females worldwide while in India it is the 2nd most common malignancy occurring after cervical cancer in females. The treatment modalities and prognosis of breast carcinoma depend largely on their hormone receptors (estrogen and progesterone receptors) and human epidermal growth factor receptor 2 (HER2/neu) status. The aim of this study was to correlate the receptor status in invasive breast carcinoma with histopathological grading of the tumor.

Methods: This is a retrospective study carried out in the department of pathology, Silchar medical college and hospital, Cachar from January 2019 to December 2020. A total of 69 cases were considered for the study, selected on the basis of inclusion and exclusion criteria. Histomorphology grading in invasive ductal breast carcinomas was done along with the status of estrogen receptor (ER), progesterone receptor (PR) and HER2/neu.

Results: The present study comprised of total of 69 infiltrating breast carcinoma cases. Out of all 51% cases were found to be in 4th decade of life. The most common type found in the study was invasive ductal carcinoma (not otherwise specified) seen in 86.96% cases. Maximum 41.67% of cases were histologically classified as grade III. A positive correlation was found between histological grading and immunohistochemistry of hormone receptors (ER, PR) and HER2/neu status.

Conclusions: From the present study, it can be concluded that there is a positive correlation between histopathological grade and hormone receptors status and HER2/neu. The estrogen receptor and progesterone receptor were found negative in high grade disease on histological evaluation. Triple negative breast carcinomas have poorer prognosis as they tend to be of high grade.

Keywords: Breast carcinoma, Invasive ductal carcinoma, Estrogen receptor, Progesterone receptor, HER2/neu

INTRODUCTION

Breast carcinoma is the most common malignancy worldwide and also a leading cause of the death among women.¹ It is the second most common cancer among females in India aged 40-44 years after carcinoma cervix.² Breast carcinoma constitutes 12% of all new

cases and 25% of all cancers in women.³ In India, with an annual incidence of an approximately 1,44,000 new cases of breast cancer, it is now the most common carcinoma in female in urban India and second commonest in rural Indian women. It is associated with poor prognosis and a high mortality in India as most of the cases present in the advanced stages.⁴ Numerous factors like the tumour size,

the lymph node metastasis, the histological grade and the hormone receptor status is used for the prognosis and the therapeutic management of breast carcinoma.⁵

The biomarker like the estrogen receptor (ER), the progesterone receptor (PR), the HER2/neu rare is the most commonly used for the assessment of breast carcinoma. The strong ER positive cases benefit from the endocrine therapy alone.^{6,7} PR status is independently associated with a disease free survival. HER2/neu (erbB-2) encodes an 185 kDa transmembrane phosphoglycoprotein with tyrosine kinase activity related to the epidermal growth factor and its overexpression indicates a low response to the tamoxifen and decreased the survival.^{8,9} Tumors with ER, PR, HER2/neu negative have a poorer prognosis as they tend to be of high grade.¹⁰ This study were done to determine the correlation of ER, PR and HER2/neu status in different histological grades of invasive breast carcinoma.

METHODS

This is a retrospective study carried out in department of pathology, Silchar medical college and hospital, Cachar. Samples of sixty-nine patients with histological proven diagnosis of breast carcinoma from January 2018 to December 2019 were selected for this study.

Inclusion criteria

Mastectomy specimen of all histologically confirmed invasive breast carcinoma were included in the study.

Exclusion criteria

Specimen of trucut biopsies, small biopsies and metastatic lesions were excluded.

Samples were collected using stratified random sampling technique. All the data were analyzed using Microsoft excel 2013 and figures were drawn using Microsoft word 2013.

Histopathological analysis was done on 10% formalin fixed, paraffin embedded tissue sections which were stained with hematoxylin and eosin (H and E) stain and examined under microscope. Sections were evaluated and histological typing was done based on WHO classification of breast tumors. All cases of invasive breast carcinoma were histologically graded according to Elliston-Ellis modification of the ScarffBloom-Richardson grading system.¹¹ This grade was obtained by adding up scored for tubule formation, nuclear pleomorphism, mitotic count, each of which was given 1,2 or 3 points. The total score was between 3 to 9 and the final grading was given as grade I (1.3-5), grade II (2.6-7) and grade III (3.8-9).

Few more sections were obtained on poly-L-lysine coated slides and processed for immunohistochemistry (IHC)

using DAKO monoclonal antibody and antigen-antibody streptavidin-biotin immunoperoxidase method. Positive and negative control was run with each batch of IHC simultaneously. Tumors showing strong complete membranous staining in >10% cases was taken positive for HER2/neu. Nuclear staining was taken positive for ER and PR.¹² Allred/Quick scoring system were used for ER and PR interpretation whereas ASCO/CAP were used for HER2/neu scoring.^{13,14}

RESULTS

In the present study of sixty nine cases of female breast carcinoma, the age ranged from 25 years to 62 years, with youngest being 25 years and oldest 62 years. Majority were in the age group of 40 to 55 years. The age distribution is shown in (Figure 1).

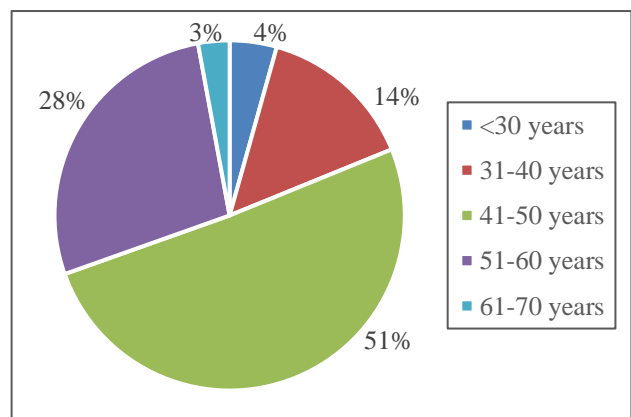


Figure 1: Distribution of cases according to age.

The most common type found in the study was invasive ductal carcinoma (not otherwise specified) seen in 86.96% cases. Other types were lobular (10.14%), mucinous (1.45%) and medullary (1.45%). Only 60 cases classified as ductal carcinoma (NOS) were included in the analysis. Histomorphological distribution is shown in Figure 2.

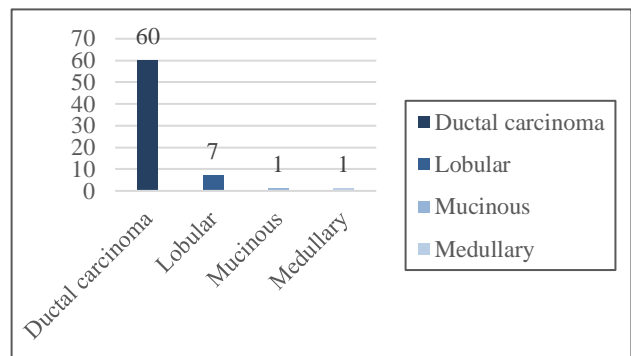


Figure 2: Bar diagram showing histomorphological distribution of malignant breast carcinoma.

In the study among the 60 invasive ductal carcinoma cases modified Bloom Richardson grading was done and

25% (15 cases) were classified as grade I, 33.33% (20 cases) as grade II and 41.67% (25 cases) as grade III. Therefore maximum 41.67% cases were grade III (Figure 3).

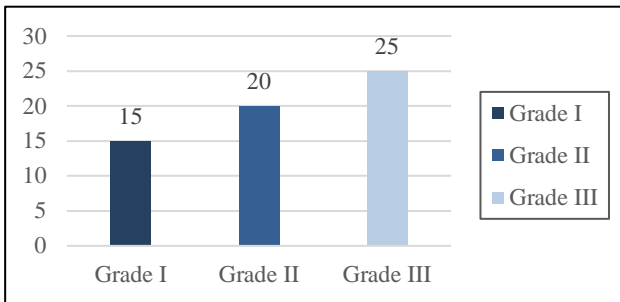


Figure 3: Distribution of cases according to modified Bloom Richardson's grade.

In our study, we found 75% cases were ER positive, while 25% cases were ER negative 35% cases were PR-positive and 65% cases were PR negative 66.67% cases were HER2/neu positive and 33.33% were negative.

Most of the tumors of grades I and II were ER positive, while most of the grade III tumors were ER negative. Most PR positive cases were from grade I and II, while most cases of grade III tumor were PR negative and HER2/neu positive.

Photomicrograph in the Figure 4 showing invasive ductal carcinoma of grade I show cells of small monomorphic nuclei consisting of tubules, invasive ductal carcinoma of grade II showing more solid nests of cells and pleomorphic nuclei with less tubule formation, invasive ductal carcinoma of grade III showing infiltration with sheets of pleomorphic cells along with numerous mitotic figures and central tumor necrosis.

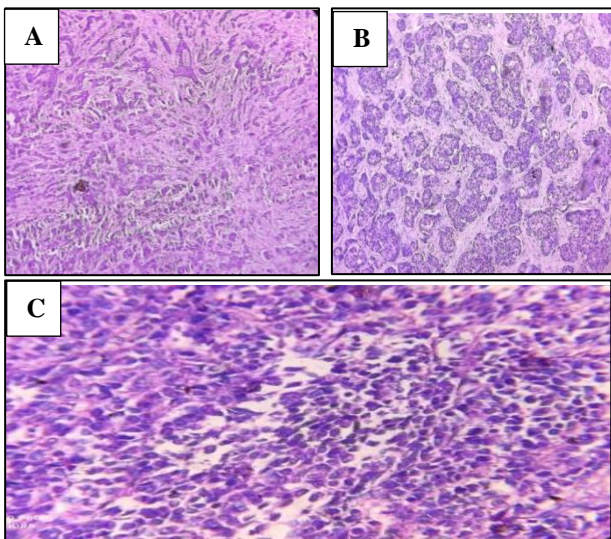


Figure 4: Histological grades of breast carcinoma; (A) IDC grade I (H and E 100X); (B) IDC grade II (H and E 100X); (C) IDC grade III (H and E 100X).

Photomicrograph in the Figure 5 showing estrogen receptors taking nuclear stain which is visualized as brown chromogen in invasive ductal carcinoma in grade I and grade II tumors.

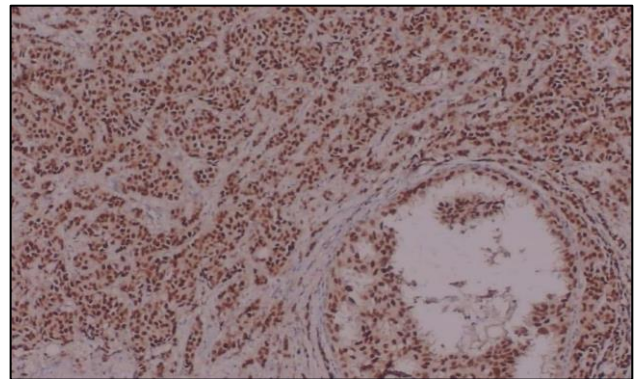


Figure 5: ER positivity in invasive ductal carcinoma.

Photomicrograph in the Figure 6 showing progesterone receptors taking nuclear stain indicated by the brown chromogen in invasive ductal carcinoma in grade I and grade II.

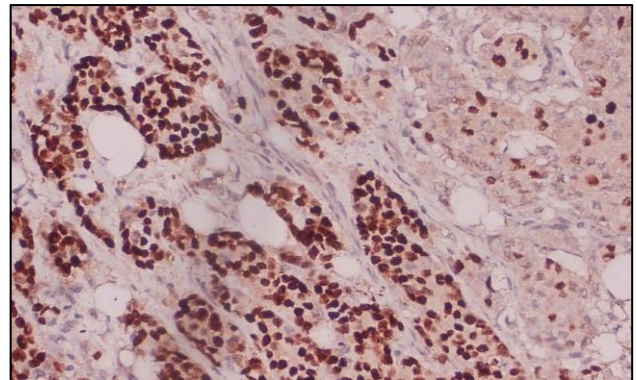


Figure 6: PR positivity in invasive ductal carcinoma.

Photomicrograph in the Figure 7 showing complete intense circumferential cytoplasmic membranous staining of tumor cells by HER2/neu in grade III tumors.

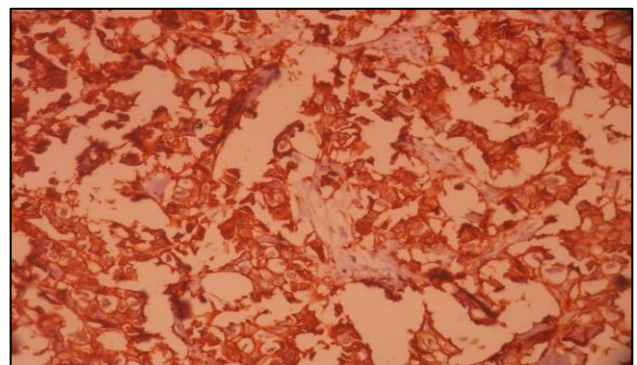


Figure 7: HER2/neu positivity in invasive ductal carcinoma.

Table 1: Distribution of cases based on estrogen, progesterone and HER2/neu receptor.

Receptors		Number of cases (n=60)	Percentage (%)
Estrogen	Positive	45	75
	Negative	15	25
Progesterone	Positive	21	35
	Negative	39	65
HER2/neu	Positive	40	66.67
	Negative	20	33.33

Table 2: Distribution of cases based on ER, PR, HER2/neu positive and triple negative cases according to grade of tumor.

Grade of tumor	Number of cases	ER positive	PR positive	HER2/neu positive	Triple negative
Grade I	15	15	8	5	2
Grade II	20	18	11	15	6
Grade III	25	12	2	20	7

DISCUSSION

In Indian, breast carcinoma and cervical carcinoma account for about 60% of malignancies in women. It has been proposed that the common denominator of risk factors such as nulliparity, menarche, age at first birth of child and late menopause that lead on to the breast carcinoma is a strong and prolonged estrogen stimulation operating in a genetically susceptible background.^{15,16} The hormonal receptor status has shown that overall positivity rate for ER and PR is lower in India as compared to western literature.^{3,17} In our study, maximum cases were from rural area and were of high grade nature indicating a dearth in awareness and lack of screening facilities needed for early diagnosis of breast carcinoma. In European and American population, 60-80% patients were found with positive receptor expression.¹⁸

The peak age incidence of malignant breast carcinoma in our study was between 41-50 years. Ejam and Farhood in his study had observed the peak age incidence as 30-50 years.¹⁹ Onitilo et al in their study had mentioned the peak incidence as 62.7 years.²⁰ The mean age incidence in Ghosh et al study was 49 years, which coincides with our study.²¹

In our study the most common was invasive ductal carcinoma variant which was also found in other studies like Dixon et al and Hameed.^{22,23} In Nikhra et al study also, 95.34% of the tumor was invasive ductal carcinoma.²⁴

Tumor grade is one of the important predictors of tumor behavior in breast cancer. Among 60 cases of invasive ductal carcinoma, 25% cases belonged to grade I of Bloom Richardson grading, while 33.33% and 41.67% cases belonged to grade II and grade III respectively, which was comparable to other studies.²⁵

Both ER/PR and HER2/neu biomarkers were done in our study. ERs and PRs are nuclear transcription factors that are involved in breast development growth, differentiation and tumorigenesis.^{26,27} ER and PR positive tumors tend to have a significantly longer disease-free survival than with receptor negative tumors.²⁸ HER2/neu [c-erbB-2] is an epidermal growth factor receptor oncogene that encodes a transmembrane glycoprotein with tyrosine kinase activity located in 17q11.2-q12.13. HER2/neu overexpression in breast carcinoma leads to recurrence and worst prognosis.²⁹ Our results confirmed that non-reactivity of hormonal receptors increases with increase in tumor grade.

In our study, ER and PR were positive maximum in grade I and grade II cases while maximum PR negative in grade III. HER2/neu positivity increased with increase in tumor grading, having maximum positivity in grade III cases (33.33%). Triple negative breast cancers constituted overall 25% (15 cases), with increasing trend from grade I through grade III invasive carcinomas. Rosen et al and Jovicic Milentijevic et al studies correlated with ours in this aspect.^{24,25}

This study highlighted the importance of grading and hormone receptor status evaluation. The grading of the tumors highly correlates with the survival rate and receptor status predicts the response to hormonal therapy. Histopathological grading put together with receptor status offers an excellent method of correlation of survival rate and response to hormonal therapy.

Study limitations include the fact that we did the biomarkers status only in invasive ductal carcinoma and not in other types of invasive breast carcinoma.

CONCLUSION

In our study we found significant correlation between ER and PR positive status and low grade tumor. On the other

hand, there were significant correlation between HER2/neu and high grade tumors. Therefore the study showed importance of the biomarkers as they provide valuable prognostic information for best therapeutic decision.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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