

Correlation of Hormonal Receptors Estrogen Receptor, Progesterone Receptor and Her-2/Neu with Tumor Characteristics in Breast Carcinoma: Study of 100 Consecutive Cases

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Abstract

Introduction-Breast cancer is the most common cancer and leading cause of death in women. In India, its incidence is rapidly rising over last few decades. Present study is aimed to study the pattern of expression of hormonal receptors and Her-2/neu in invasive breast carcinoma and to correlate estrogen receptor (ER), progesterone receptor (PR) and Her-2/neu expressions with various clinicopathological parameters. **Material and methods:** The present study was carried out in Department of Pathology, S.C.B. Medical College, Cuttack in the year 2013 taking consecutive 100 cases. Routine H&E staining for histological diagnosis and IHC analysis for ER, PR and Her 2/ neu was carried out in all 100 cases of breast malignancies. **Results:** 99% of cases are invasive breast carcinoma, not otherwise specify (IDC-NOS). The age ranges from 23 years to 72 years. Majority of tumors are of grade 2 (70%) followed by grade 3 (30%). ER PR and Her-2/neu expression are seen in 45%, 35% and 30% respectively. Triple negative cases comprise 35%. Higher number of grade 2 tumor shows ER, PR positivity as compared to grade 3 tumors. Her-2/neu expression does not show any significant correlation with age or lymph node status of the patient. **Conclusion:** ER and PR expression in breast cancers in the current study are found to be comparable to the findings of other authors, but the frequency of HER-2/neu expression is slightly higher. Significant correlation is observed between hormonal receptor status and the grade of the tumor. Inverse relationship is found between Her-2/neu expression and ER, PR receptor status. Her-2/neu expression is increased with size and high grade of tumor.

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Keywords

Breast Carcinoma, Estrogen Receptor (ER), Progesterone Receptor (PR), Her-2/Neu, Immunohistochemistry

1. Introduction

Breast cancer is the most common cancer of women in developed countries and 12% breast cancers occur between 20 - 34 years [1]. In India, breast cancer is second to cancer of the cervix among women, but is considered the leading cancer in certain metros such as Mumbai and Bangalore. It is estimated that approximately 80,000 cases occur annually. Breast cancer is strongly related to age, with only 5% of all breast cancers occurring in women under 40 years old [2]. Several pathological features have prognostic significance in breast carcinoma which includes histologic subtypes, grade, lymph node status, estrogen receptor (ER)/progesterone receptor (PR) status, growth factor and its receptors, proliferation activity and DNA content with tumor suppressor genes and oncogenes [3]. Prognosis of breast carcinoma is worse with higher grade, tumor subtypes like medullary and lobular carcinoma, lymph node metastasis, negativity for ER, PR and positivity for Her-e/neu, with excess of oncogenes and also presence of BRCA gene. Out of these, ER, PR and Her-2/neu immunostaining are a very useful tool for rapid diagnosis, treatment and prognosis of the patient. Determination of ER, PR status on biopsy specimens prior to therapeutic intervention is advocated as a standard practice [4]. Due to this, breast cancer is better represented by its combined receptor expression than by a single receptor status alone. Recent management protocol is focusing on separating triple negative and triple positive tumors for treatment and prognosis. With this background, the present study is undertaken to analyze the pattern of expression of hormone receptor ER, PR and Her-2/neu in invasive breast carcinoma and to correlate them with various clinicopathological parameters, especially in this part of country where studies are limited.

2. Materials and Methods

This study was carried out in the year 2013 taking 100 consecutive cases. The study was done as per standard ethics. All the cases histopathologically diagnosed as invasive carcinoma were included in the study. The clinical details like age, sex, duration of symptoms, laterality, size of the tumor, axillary lymph node status and imaging findings like MRI were recorded in each case. After carrying out the detailed gross examination, all tissues were fixed in 10% buffered formalin. Multiple sections were taken from the tumor and its margins and all the lymph nodes. Histopathological study of the specimen was done by Haematoxylin and Eosin staining and as per standard protocol. Grading of the tumor was done by modified Bloom Richardson grading system. Immunohistochemistry (IHC) for ER, PR and Her-2/neu was performed on representative blocks of paraffin embedded tissue in each case. 3 - 4 micron thick sections were submitted for IHC staining. Antigen retrieval was done by HIER method using citrate buffer at ph 2.5 for ER/PR and ph 6 for Her-2/neu. The normal epithelial component present in the tissue section served as internal control for ER/PR. IDC-NOS with known Her-2/neu over expression was used as external positive control for Her-2/neu with each lot of staining. The ER+ve cells showed nuclear staining (**Figure 1**) where the percentage of positive cells were counted and the intensity of staining was

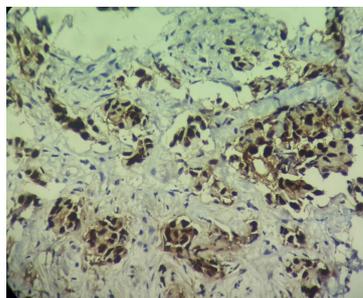


Figure 1. Photomicrograph showing ER positivity of malignant tumor cells of IDC-NOS of breast. IHC \times 400.

recorded. For PR also nuclear staining was observed (Figure 2) and accordingly scored. Her-2/neu is a membrane stain and Her-2/neu positive cells showed intense membrane staining (Figure 3) without cytoplasmic staining.

Following scoring system was used for noting down the results of immunohistochemistry in each case.

Interpretation of IHC in Carcinoma Breast

All red score for ER and PR Evaluation in Ca Breast.

Proportional score (PS)	Percentage of positive cells	Intensity score	Intensity of positivity
0	0	0	None
1	<1	1	Weak
2	1 - 10	2	Intermediate
3	11 - 33	3	Strong
4	34 - 66		

Total score (PS + IS)	Interpretation
0 - 2	Negative
3 - 8	Positive

Interpretation of Her-2/Neu by IHC.

IHC score	Criteria
0 (Negative)	No reactivity/Reactivity in $\leq 10\%$ tumour cells
1+ (Negative)	Faint weak reactivity in $>10\%$ of tumour cells but only a portion of the membrane is positive
2+ (Equivocal)	Weak to moderate complete membrane reactivity in $>10\%$ of tumour cells or circumferential intense membrane staining in $\leq 30\%$ of cells
3+ (Positive)	$>30\%$ of tumour cell must show circumferential intense and uniform membrane staining. A homogenous (Chicken wire) pattern should be present

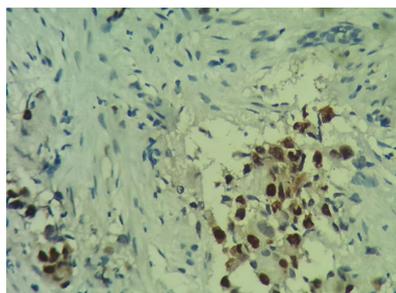


Figure 2. Photomicrograph showing PR positivity of nuclei malignant tumor cells of IDC-NOS of breast. IHC $\times 200$.

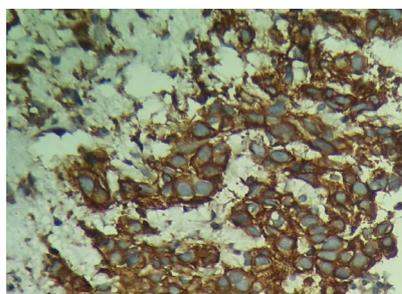


Figure 3. Photomicrograph showing Her-2/neu positivity of cytoplasmic membrane of malignant tumor cells of IDC-NOS of breast. IHC $\times 400$.

3. Results

In our study, a total of 100 consecutive cases of invasive carcinoma of breast were taken. Age of the patients ranged from 23 - 73 years. Most common age group was 41 - 50 (37% cases) as shown in **Table 1**. Majority of the patients were above 40 years of age.

All cases except one were IDC-NOS and only one case was diagnosed as medullary carcinoma. Majority (70 cases –70%) belonged to grade 2 according to B-R Grading system. However, lymph nodes were negative in maximum cases *i.e.* 73 negative in comparison to 27 positive cases (**Table 2**). ER and PR were positive in 45% and 35% cases respectively. Her-2/neu was found to be negative in 70 cases (70%).

Correlation of ER, PR and Her-2/neu with grade of tumor has been shown in **Table 3**. Grade 2 tumors showed maximum ER positivity (40 cases or 40%) and minimum Her-2/neu positivity.

Table 1. Age distribution of patients of invasive ductal carcinoma-NOS of breast.

Age group	Cases	Percentage (%)
21 - 30	05	05
31 - 40	23	23
41 - 50	37	37
51 - 60	24	24
61 - 70	09	09
71 - 80	02	02
Total	100	

Table 2. Comparative analysis of clinicopathological features and receptor status of breast carcinoma.

Histopathological features		Number	Percentage
Type	IDC NOS	99	99
	Medullary carcinoma	01	01
Grade	1	Nil	
	2	70	70
	3	30	30
Tumour size	Less than 2 cm	14	14
	More than 2 cm	86	86
Lymph node status	Positive	27	27
	Negative	73	73
ER	Positive	45	45
	Negative	55	55
PR	Positive	35	35
	Negative	65	65
Her2/neu	Positive	30	30
	Negative	70	70

Table 3. Comparison of ER, PR, Her2/neu IHC positivity with grade of breast carcinoma.

Grade	Cases	ER positivity	PR positivity	Her2/neu positivity
2	70	40	28	06
3	30	05	07	24

Triple positive—Grade 2 - 18 cases (18%), Grade 3 - 12 cases (12%); Triple negative—Grade 2 - 20 cases (20%), Grade 3 - 15 cases (15%).

4. Discussion

Present study comprised of 100 cases of primary breast carcinoma. Majority of cases were seen in between 4th to 6th decades, mostly perimenopausal and postmenopausal females. 86% of the cases (**Table 2**) showed more than 2 cm tumor size. This was compatible to the results observed in Eastern countries like Aziun Nisa *et al.*, A Moses *et al.* and Mona M Rashed *et al.* [5]-[7]. Studies from Western country, Adendaya *et al.* showed 71% cases with less than 2 cm size which could be due to early cancer detection programme [8]. Present study showed 45% of cases with positive ER status while 35% PR positive status. Simultaneous triple negative breast cancer was found in 35% (35 cases) and simultaneous triple positive breast cancer occurred in 30% (30 cases). The study by Mona A Rashed *et al.* showed 41.41% positivity for ER and PR. The original work done by Sheet T *et al.* also revealed similar result [9]. Azizun Nisa *et al.* showed 32.7% & 25.3% ER and PR positivity respectively. But the incidence of both triple negative and triple positive cases were more in present study. Significant inverse association was found between hormonal receptor and histology grade (**Table 2**). Greater percentage of grade 2 tumors had ER, PR positivity as compared to grade 3 tumors (**Table 3**). Findings observed by Azizun Nisa *et al.*, showed similar results. Her-2/neu positivity in our study was 30%. Earlier studies detected 17.7% to 27.58% positivity by different authors.

In our study, Her-2/neu receptor revealed a significant inverse association with hormonal receptor status. We found that ER, PR expression was increased in Her-2/neu negative tumors as compared to Her-2/neu positive tumors. Similar results were found by Mona M Rashed *et al.* Triple negative breast carcinoma is characterized by lack of ER, PR and Her-2/neu expression. Our study showed 35% cases as triple negative. Study by Bhagat Vasudha M *et al.* showed 25.86% cases and Patil *et al.* showed 19.9% cases as triple negative respectively.

Triple negativity was again found in 20% of breast carcinomas with a histopathologic grade 2 cases where as it was slightly reduced *i.e.* 15% in grade 3 breast carcinomas. Similarly triple positivity was seen in 18% of grade 2 tumours and about 12% in grade 3 tumours.

In our institutions IDC-NOS was diagnosed in almost all cases of breast carcinomas (99%). Only 1 case of medullary carcinoma of breast was encountered among the total cases studied. Comparing the statistics of western countries, our studies show that we had infiltrating ductal carcinoma NOS as the most common breast cancer [8]. Most of the patients were detected in stage 2 or stage 3 as compared to western studies where the patients are detected in stage 1 also. So early detection programmes need to be more strengthened in developing countries like India.

5. Conclusion

In present study, ER, PR and Her-2/neu expression in breast carcinoma by IHC method indicate higher rate of positive expression correlated with various clinicopathological aspects. Higher number of grade 2 tumor shows ER, PR positivity as compared to grade 3 tumors. Inverse relationship is observed between Her-2/neu expression and ER, PR receptor status. Her-2/neu expression is increased with increased grade of the tumor. ER, PR and Her-2/neu do not show any significant correlation with lymph node status and age.

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