

Study on Histopathological Correlation with ER, PR, and HER 2 Neu Receptor Status in Breast Carcinoma and its Prognostic Importance

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ABSTRACT

Background: Carcinoma breast 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 incidence is three times higher in urban areas than in rural setup. The disease pattern, clinical and histopathological presentation differs from that of the western world.

Methods: The present study was carried out in the Department of Pathology, G.S.V.M. Medical College Kanpur, India from July 2016 to August 2018. Total 54 female were considered for the study, selected on the basis of inclusion and exclusion criteria. Histomorphology and lymph node status in breast carcinomas, the status of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2/neu) in all these breast carcinomas and its prognostic importance in post operative patient.

Results: Present study comprised of total 54 female patients. Out of all 48.15% cases were found to be in 5th decade (premenopausal predilection) of life in our setup. Most common type found in study was Ductal carcinoma (not otherwise specified) seen in 92.6% cases. Lymph node metastasis was found in 66% positive cases. Maximum 54% cases were histologically classified as grade II. A positive correlation was found between histology and immunohistochemistry.

Conclusion: From the present study, it can be concluded that there is a positive correlation between histopathological grade and other prognostic factors including immunohistochemical markers. Immunohistochemical markers can be effectively used to predict prognosis and therapeutic management of patients with carcinoma breast.

Key-words: Breast Carcinoma, Histological Grading, Immunohistochemistry, Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2/neu)

INTRODUCTION

Breast carcinoma is the most common malignant tumor and the leading cause of carcinoma death in women. In our country, though the incidence of breast carcinomas is lower than the west yet it is the second most common

malignant tumor in females comprising 16 to 21%. The first being carcinoma cervix breast cancers are diagnosed at a relatively advanced stage ^[1]. Breast cancer is the most common female cancer in the world with an estimated 1.67 million new cancer cases diagnosed in 2012. This represents about 12% of all new cancer cases and 25% of all cancers in women ^[2]. Annual incidence of approximately 1, 44,000 new cases of breast cancers in India, it has now become the most common female cancer in urban India and the second commonest in the rural Indian women.

Currently, routine clinical management of breast cancer incorporates specific molecular markers; namely Estrogen Receptor (ER), Progesterone Receptor (PR),

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Human Epidermal Growth Factor Receptor 2 (HER2) gene that have been proven to provide therapeutic, predictive and prognostic value. The triple negative breast cancer (ER/PR/HER-2/neu) has the worst overall survival.

MATERIALS AND METHODS

The present study was carried out in the Department of Pathology, G.S.VM. Medical College Kanpur, India from July 2016 to august 2018. Total 54 female were considered for the study, selected on the basis of inclusion and exclusion criteria. We included in our study histomorphology and lymph node status in breast carcinomas, the status of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2/neu) in all these breast carcinomas and its prognostic importance in post-operative patient. Tumor mass was subjected to immunohistochemistry. The above study was approved by the institutional ethical committee and informed consent was obtained from the patients prior to the study. The Modified Scarf's Bloom-Richardson for Histopathological grading [3] and Allred scoring system used for estrogen receptors [4]. HER2/neu staining is graded from 0 - 3+; with no staining or membrane staining in more than 10% of tumor cells graded as 0 and strong complete membrane staining in more than 30% of tumor cells as 3+. 0-1 is negative; 2+, 3+ is positive according to ASCO/CAP (American Society of Clinical Oncology and the College of American Pathologist) [5].

Inclusion criteria

1. Mastectomy specimens of clinically/cytological diagnosed breast malignancy in the female of all age group.
2. Patients who gave written informed consent.

Exclusion criteria

1. Patients with metastatic malignancy of breast.
2. Patients already treated for contra lateral breast cancer.
3. Patients not willing to give written consent.

RESULTS

The above Table 1 shows that peak incidence of breast cancer is in the 5th decade i.e. 26 cases (48.15%). Closely followed by 6th decade in which 14 cases (25.93%) were reported.

Table 1: Age distribution of patients with Breast cancer

| Age group (Yrs) | No. of cases (n=54) | Percentage (%) |
|-----------------|---------------------|----------------|
| <30 | 1 | 1.85 |
| 31-40 | 6 | 11.11 |
| 41-50 | 26 | 48.15 |
| 51-60 | 14 | 25.93 |
| 61-70 | 5 | 9.26 |
| >70 | 2 | 3.70 |
| Total | 54 | 100 |

Table 2: Histomorphological distribution of malignant breast lesions

| Type | No. of cases | Percentage |
|---------------------------|--------------|------------|
| Ductal carcinoma (NOS) | 50 | 92.60 |
| Malignant phyllodes tumor | 1 | 1.85 |
| Lobular carcinoma | 1 | 1.85 |
| Mucinous carcinoma | 1 | 1.85 |
| Medullary carcinoma | 1 | 1.85 |
| Total | 54 | 100 |

The most common type found in the study was Ductal carcinoma (not otherwise specified) seen in 92.6% cases. Only 50 cases classified as Ductal carcinoma (NOS) were included in this analysis.

Table 3: Distribution of cases according to tumor size

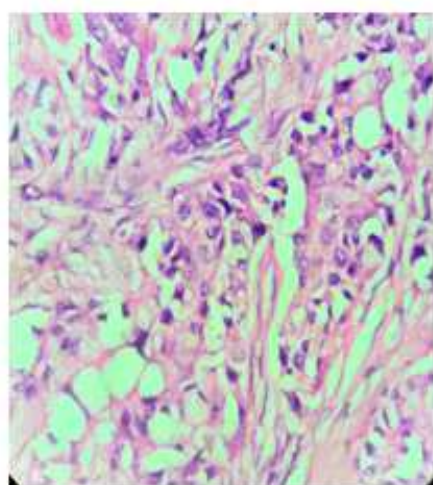
| Tumor size (cm) | No. of cases (n=50) | Percentage (%) |
|-----------------|---------------------|----------------|
| < 2 | 08 | 16% |
| 2-5 | 30 | 60% |
| >5 | 12 | 24% |

12 cases had tumor more than 5 cm i.e. 24% (T3), 60% had tumor size 2 to 5 cm (T2) and 16% cases had tumor size between 1 to 2 cm (T1).

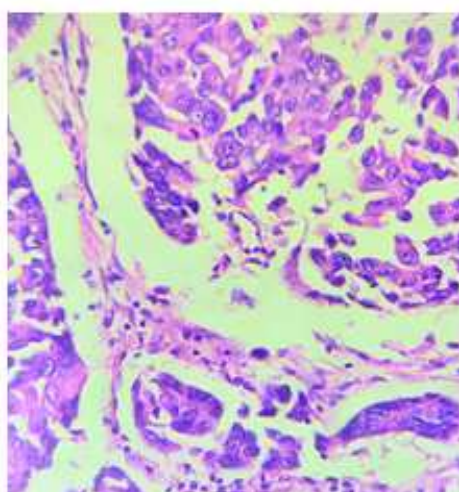
Table 4: Distribution of cases according to lymph node status

| Lymph node status | No. of cases (n=50) | Percentage |
|-----------------------|---------------------|------------|
| Not identified | 10 | 20 |
| Negative (0) | 07 | 14 |
| Positive (1-3) | 18 | 36 |
| Positive (4 or more) | 15 | 30 |

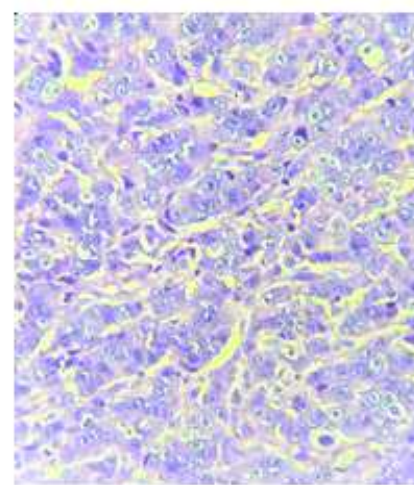
Lymph node metastasis was found in 66% positive cases.



IDC Grade I (H & E 400x)



IDC Grade II (H & E 400x)



IDC Grade III (H & E 400x)

Fig. 1: Histological grades of Breast carcinoma**Table 5: Distribution of cases according to modified Bloom Richardson's Grade**

| Histological grade | No. of cases (n=50) | Percentage |
|--------------------|---------------------|------------|
| I | 10 | 20 |
| II | 27 | 54 |
| III | 13 | 26 |

Maximum 54% cases were histologically classified as grade II.

Table 6: Distribution of cases based on Estrogen, Progesterone & HER 2 neu receptor

| Receptor | No. of cases (n=50) | % |
|---------------------|---------------------|-----|
| Estrogen | | |
| Positive | 28 | 56% |
| Negative | 22 | 44% |
| Progesterone | | |
| Positive | 19 | 38% |
| Negative | 31 | 62% |

| | HER 2 neu | |
|----------|-----------|-----|
| Positive | 15 | 30% |
| Negative | 35 | 70% |

- 56% cases were ER-positive, while 44% cases are ER negative.
- 38% cases were PR-positive and 62% cases were PR negative
- 30% cases were Her 2 neu positive and 70% were negative.

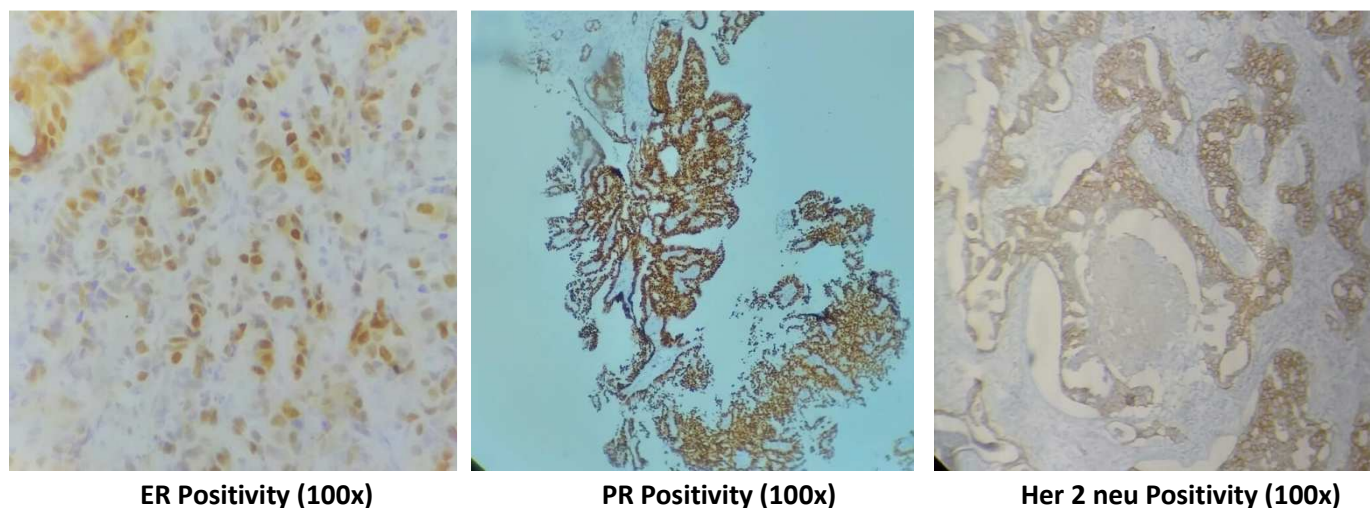


Fig. 2: Immunohistological Status

Table 7: Distribution of Cases Based on ER, PR, HER 2 neu positive and triple negative cases according to Grade of tumor

| Grade of tumor | No. of cases (n=50) | ER positive cases | PR positive Cases | HER 2 neu positive cases | Triple negative cases |
|----------------|---------------------|-------------------|-------------------|--------------------------|-----------------------|
| I | 10 | 8 | 7 | 3 | 0 |
| II | 27 | 19 | 11 | 9 | 6 |
| III | 13 | 1 | 1 | 3 | 9 |

Most of the tumors of grade I & II were ER positive, while most of the grade III tumors were ER negative. Most PR positive cases were from grade I & II, while most cases of

grade III tumor were PR negative. Overall Few cases were shown HER 2 neu positive.

Table 8: Relation between histological and molecular classes (N=50)

| Histological grade | Luminal A | Luminal B | HER 2 neu over expression | Triple negative |
|--------------------|-----------|-----------|---------------------------|-----------------|
| Grade 1 | 7 | 2 | 1 | 0 |
| Grade 2 | 7 | 8 | 6 | 6 |
| Grade3 | 1 | 0 | 3 | 9 |

15 cases were classified as luminal a, 10 cases as luminal b. 10 cases show HER 2 neu over expression and 15 cases were classified as triple negative. After applying chi

square test, no significant association between age and molecular subtypes was seen.

Table 9: Relation between patient's age and molecular classes (N=50)

| Age of patient | Luminal A | Luminal B | HER 2 neu over expression | Triple negative |
|----------------|-----------|-----------|---------------------------|-----------------|
| <45 yrs | 7 | 5 | 6 | 8 |
| >45 yrs | 8 | 5 | 4 | 7 |

DISCUSSION

Age group- This study shows that peak incidence of breast cancer is in the 5th decade i.e. 40 cases (48.15%). Closely followed by 6th decade in which 20 cases (25.93%) were reported which is comparable to other studies done previously^[6-9].

Tumor size- 12 (24%) cases have tumor size >5 cms. 30(60%) cases were having 2-5 cms, and 8 (16%) cases were having less than 2 cms in size^[10]. Study shows that mean size of the lesion was 3.3cm. Majority of our cases (60%) had tumor size of >2 to 5cm. Other studies also recorded the majority of patients presenting with tumor size of 2 to 5 cm. (24%) cases had tumor size of greater than 5 cm at presentation^[11,12].

Lymph node status- About 66% cases have metastatic lymph node half of them are having >4 metastatic lymph node. In developed countries, in majority of patients lymph node was not involved, but studies carried out in India documented a greater percentage of breast carcinoma with lymph nodal metastasis compared to western figures. In the study cases with lymph node involvement was 74.3%. same were observed previous studies^[13-15]. Most common histological type is invasive ductal carcinoma (NOS) comprises 90% of total cases, which is similar to other Indian studies.

Histological types and grades- Most common histological type is invasive ductal carcinoma (NOS) comprise 92.6% of total cases, which is similar to other Indian studies. 54% cases belongs to grade II of Bloom Richardson grading, while 26% and 20% cases belonged to grade III and grade I respectively, which is comparable to other studies^[12,16-19].

Hormonal receptor status- 56% cases shows ER positive and 44% cases shows ER negative, however 38% cases

shows PR positive and 62% cases are PR negative. 30% cases are HER 2 neu positive and 70% cases are HER 2 neu negative 30% cases are triple negative. Most of the grade 1 and 2 tumors were ER positive and most of the cases of grade 3 were ER negative. Most of the studies noted the relatively higher percentage of estrogen and progesterone positivity^[14-23]. Among molecular Luminal A type constitutes 30%, Luminal B 20%, HER 2 neu enriched 20% and Triple negative cases 30%.^[15]. Our study also shows an inverse relationship between expression of HER 2 neu and estrogen/progesterone, still a substantial amount (20%) cases were triple positive^[20]. Most of the grade 1 and 2 tumors are PR positive and most of the cases of grade 3 are PR negative. It was observed in this study that Grade III tumors, in 90% of cases have unfavorable hormone receptor status, in contrast to Grade I and Grade II tumors, which shown association with favorable hormone receptor status. In this study, most common molecular subtype was luminal A representing 30%. We were observed a proportion of Her-2/neu subtype (20%) than previously reported in the literature^[14]. There was no correlation found between molecular type of breast cancer and age of the patients^[14]. Majority of cases of luminal A, luminal B, and normal-like subtypes had less number of lymph node (1-3) involvement while in Her-2/neu and basal-like phenotype majority of cases had more number of lymph node (4-9) involvement^[14]. Luminal A had lower tumor grade while Her-2/neu positive and basal-type phenotype are associated with higher grade tumors. This association was found to be statistically significant^[14]. Luminal B, Her-2/neu and basal-like are associated with higher stage than luminal A, which are associated with earlier stage. Majority of tumors of grade 1 were ER, PR positive and majority of grade 3 tumors were triple negatives, which exemplifies the fact that higher the grade, lower is the hormone receptor expression. This

study highlights the importance of grading and hormone receptor status evaluation. Grading 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.

CONCLUSIONS

Carcinoma of the breast is a common clinical problem in our society. The present study shown invasive ductal carcinoma is most common histological type prevalent in Indian population but at an early age compared to western countries. The patients presenting at an early age were associated with higher grades of a tumor along with over expression of HER 2 neu and triple negative cases. It was also found that large tumor size, high Nottingham modification of Bloom-Richardson grade were usually associated with Luminal B, HER 2/neu positive and triple negative phenotype than luminal A. As the traditional histological classification were not able to evaluate the biological behavior of the different breast tumors, molecular classification of breast cancer is useful for clinical management and superior to the histological classification in short term prognostic value. Different immunophenotypes respond differently to different therapies. Luminal groups respond to hormonal treatment, while HER 2/neu group responds well to biological therapies using transtuzumab. On the other hand, basal like phenotype, usually respond well to chemotherapy.

In the light of the above findings and the availability of newer drugs, hormonal therapy and biological therapies, this type of classification must be investigated and taken into account when assessing response to these treatments.

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