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Original Research Paper

Pathology

# CORRELATION OF CLINICOPATHOLOGICAL PROFILE WITH RECEPTOR STATUS IN BREAST CARCINOMA: AN OBSERVATIONAL STUDY IN A TERTIARY CARE HOSPITAL

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| **Dr Pramod Soni** | PG Resident, Department of Pathology, Index Medical College Hospital & Research Centre, Indore (MP). |
| **Dr Sanjeev Narang** | Professor & HOD, Department of Pathology, Index Medical College Hospital & Research Centre, Indore (MP). |
| **Dr Vimal Kant Jain** | Professor, Department of Pathology, Index Medical College Hospital & Research Centre, Indore (MP). |
| **Dr Anjali Singh*** | Professor, Department of Pathology, Index Medical College Hospital & Research Centre, Indore (MP). *Corresponding Author |

**ABSTRACT**

**Introduction:** Breast cancer is the most prevalent cancer worldwide in females and a primary cause of mortality. It is a systemic disease with diverse biological subtypes, clinical presentation, pathological types, and molecular features that impact prognosis and outcome. The molecular organization of breast cancer is a better predictor for diagnosis and treatment. The study aimed to analyze the clinicopathological characterization and correlation of breast tumors with progesterone (PR), estrogen (ER), and human epidermal receptor protein-2/neu status (HER-2/neu). **Material and Methods:** After approval from the IEC, this prospective study was conducted on 100 patients diagnosed with breast carcinoma. The expression patterns of PR, ER and HER-2/NEU were studied. Clinical features, pathologic features such as age of the patient, tumour size, grade, and lymph node status and their correlation with receptors were compared. Relevant statistical analysis was done. **Results:** Of the 100 patients, ER positivity was seen in 42% cases, PR positivity in 32% and HER-2/neu (3+) in 30% cases. Majority of grade I tumors were ER and PR positive and majority of grade III tumors were triple negative. Triple negative profile was seen in secretory carcinoma. ER, PR and HER2 status was not significantly associated with age of the patients and tumour size. The immunohistochemical types ER/PR +ve Her2neu +ve and ER/PR -ve Her2neu -ve are significantly related to grading of tumours. **Conclusions:** From the results, it was concluded that ER, PR and HER-2 status correlates well with histopathological grading. These results highlight the fact that molecular subtypes correlate with diagnosis and aid in targeted therapy

**KEYWORDS :** Breast tumour, Estrogen receptor, Progesterone receptor, HER-2 neu

## INTRODUCTION

Breast cancer is the most common cancer in females worldwide, accounting for 11.7% of all cancers. In 2020, it surpassed lung cancer as the leading cause, with 2.3 million new cases [1]. Epidemiological studies predict a persistent rising trend with 3 million new cases by 2040 and 1 million deaths annually due to population growth and aging [2]. In India, it is the commonest cancer among females in urban areas, accounting for 30% of all cancers [3]. It is second to cancer of cervix in the rural population, based on national cancer registry data (2006) [4]. The incidence in India has been increasing significantly in the last 50 years, with an age-standardized incidence rate of 39.1% between 1990 and 2016. The Indian Council of Medical Research (ICMR) reports a crude rate of 4.5 to 39.0 and an age-adjusted risk of 7.0 to 48.0 per one lac population [3]. Breast cancer accounts for 13.5% of all cancers and 10.6% of all cancer deaths in India [5]. As per the ICMR-PBCR data, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Calcutta, and Trivandrum constituting more than 30 percent of all cancers in females. [4]

Various risk factors are associated with the development of carcinoma breast namely early menarche, late menopause, duration of breast feeding and hormone replacement therapy. It is more commonly seen in nulliparous women between 45-55 years of age. Self-breast examination and regular preventive check-ups have helped in early detection of cancer. Diagnostic modalities like mammography, fine needle aspiration and histopathology of breast tumours help in the diagnosis of breast carcinoma. Early detection of breast cancer and the use of aggressive multimodal treatment have successfully resulted in decreased mortality.[6]

The management and prognosis of breast cancer nowadays require the evaluation of estrogen receptor (ER), progesterone receptor (PR) and human epidermal receptor protein-2 (HER-2/neu) as they have a great influence on the clinical outcome. The hormone receptor status of breast carcinoma can predict the response to adjuvant hormone therapy.[7] ER positivity in particular, is thought to be of great importance, predicting an approximately 50% to 75% response rate to hormone therapy. Estrogen is the major steroid mitogen for the luminal epithelial cell population. It has a crucial role in the proliferation and progression of breast cancer. [8]

Immunohistochemical demonstration of hormone receptors in breast cancer is cost effective, and can be done on paraffin processed tissue and the receptors are assessed within the actual tumour. The approach in managing breast cancers has undergone enormous changes over the last 20 years. The choice of breast conservative and reconstructive surgery today is more popular than mastectomy. There is increase in the use of systemic, hormonal and cytotoxic drugs following hormone receptor testing. ER, PR and HER-2/neu analysis have been accepted as established procedures in the routine management of patients with breast cancer. The combined expression of these three hormone receptors has thus become most informative in the molecular classification, clinical assessment, treatment and further outcome.[8]

The present study was conducted to find out clinico pathological characterization and correlation of breast tumor with receptor status ER, PR, Her-2 Neu. The results would aid the clinical prognostic assessment, better management and treatment of the patients.

## MATERIAL & METHODS

After approval from institutional ethical committee, this hospital-based prospective observational study was conducted on 100 consecutive patients of breast carcinoma

who reported to the OPD of Department of Gynaecology and Department of General Surgery and were referred to Department of Pathology of Index Medical College Hospital & Research Centre, Indore for further testing. Informed consent was obtained from all the patients. Patient with recurrence and lumpectomy specimens showing malignancy were excluded from the study.

### *Inclusion Criteria*

- Patients with histopathologically confirmed diagnosis of carcinoma breast, presented in surgical OPD and underwent modified radical mastectomy were included.
- Patients who consented for the study.

### *Exclusion Criteria*

- Patients who were with breast lump which made diagnosis obvious to be benign,
- Patient with no primary tumour found, diffuse disease, Paget's disease of the nipple, or in situ disease
- Patient not willing for the study were excluded from the study.

### *Methodology*

Detailed history, including the history related to the presence or absence of risk factors for breast cancers were collected. A detailed clinical examination was performed for every patient and recorded. Fine needle aspiration cytology (FNAC)/core needle biopsy (CNB) was done to obtain diagnosis in all patients. Patient of early carcinoma breast stage I and II were subjected to routine workup which included complete hemogram, renal function tests (RFT), liver function tests (LFT) and X-ray chest. Ultrasonography (USG) of abdomen and pelvis, CECT abdomen and bone scan was done only if the patient had abdominal and bony symptoms or if the ALP was raised. Patient was subjected to metastatic workup only if locally advanced carcinoma on clinical examination stage IIIA, IIIB, IIIC which was included bone scan, X-ray chest, CECT abdomen/USG abdomen and pelvis to rule out abdominal metastasis.

Early carcinoma breast, patient was subjected to upfront surgery. While patient of locally advanced carcinoma was either operated upfront or given neoadjuvant combined chemotherapy followed by surgery. Patient of metastatic carcinoma were to be given combined chemotherapy/ hormonal therapy followed by surgery. All patients had undergone modified radical mastectomy (MRM) with level II axillary nodal dissection.

Histopathologic data was obtained from the Pathology department. Specimen sent to pathology department for detailed histopathological examination including histopathological type, no. of lymph nodes retrieved and no. of positive axillary nodes, IHC staining for ER, PR and HER 2neu receptors and histological grade. Histological grading of the tumor was done by using Nottingham modification of Bloom-Richardson system of grading. [10] Other histopathologic features like lymphovascular invasion, perineural invasion, number of axillary lymph nodes were noted.

All the cases were subjected to immunohistochemical study for ER and PR. Immunohistochemistry (IHC) for ER, PR, and her-2/neu was performed on representative blocks of paraffin-embedded tumor tissue. Four micrometers thick sections were taken on poly-L-lysine-coated slides and submitted for IHC. Antigen retrieval was done using citrate buffer at pH 2.5 for hormone receptors and pH 6 for her-2/neu. They were then incubated for 30 min with primary monoclonal antibodies against her-2 (DAKO, clone 124, 1:100), ER (DAKO, clone 1D5, 1/25), and PR (DAKO, clone PgR636, 1/50), followed by incubation with biotin-labeled secondary antibodies. The streptavidin-peroxidase complex was visualized using diaminobenzidine as a chromogenic substrate. The normal breast ducts served as internal positive control for ER/PR. Breast carcinoma with known her-2 neu overexpression served as an external positive control for her-2/neu staining.

Grading of ER and PR was done by using Allred score based on the proportion of stained cells and the intensity of staining. Immunohistochemical estimation of the HER2/neu was done and categorized into one positive-negative, two positive-weakly positive, three positive-positive.[11]

### *Statistical analysis*

The responses of frequencies were calculated and analyzed by using the raw data of 100 subjects. The raw data was entered into the computer database. Statistical software, SPSS version 22.0 was used for statistical analysis. Prevalence of an outcome variable along with 95% confidence limits was calculated. Correlation of age, tumor size, histologic type, histologic grade, and the expression of ER, PR, HER2/neu, were studied. The statistical analysis for correlation among these parameters was determined using the Pearson Chi-square test. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

*Demographic and clinical pathological characteristics of the patients:* All the patients involved in the study were females. Age of patients ranged from 28-77 years. Mean age of presentation was 52.1 years. Majority of the patients were in the age group of 40-50 years (40%). Presence of lump in the breast was the common clinical feature noticed in 94% cases. The major risk factor observed in the study participants was age more than 50 years. In our study 96 patients out of 100 had breast fed their babies.

In our study it was found that carcinoma breast was more common in the right breast (60%). 62 patients had lump in the upper outer quadrant and only two had lump in the central quadrant. There was no multicentric or multifocal lump. On FNAC/CNB 90 out of 100 patients had duct cell carcinoma i.e., 90%. In our study, 68 (68%) patients were found to have early breast carcinoma. Locally advanced carcinoma was found in 32 (32%) cases. Most of the cases in the study were reported as infiltrating duct carcinoma, NOS type (98%) and (2%) cases belonging to secretory type. Table 1

**Table 1: Clinicopathologic characteristics of the patients.**

| Variables | No of Patients [N (%)] |
|---|---|
| Age Group in Years | |
| <30 | 2 (2%) |
| >31-40 | 14 (14%) |
| >41-50 | 40 (40%) |
| >51-60 | 26 (26%) |
| >61-70 | 10 (10%) |
| >71 | 8 (8%) |
| Clinical Features | |
| Lump | 94 (94%) |
| Nipple discharge | 24 (24%) |
| Pain breast | 14 (14%) |
| Nipple retraction | 18 (18%) |
| Lump in axilla | 4 (4%) |
| Ulcer | 4 (4%) |
| Peau de orange | 2 (2%) |
| Fungating mass | 2 (2%) |
| Risk factors | |
| Family history | 6 (6%) |
| Early menarche | 2 (2%) |
| Late Menopause | 4 (4%) |
| Nulliparity | 2 (2%) |
| First child after 30 years | 4 (4%) |
| Alcohol consumption | 16 (16%) |

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|---|---|
| Ongoing oral contraceptive use | 2 (2%) |
| No breast feeding | 4 (4%) |
| Previous benign breast disease | 8 (8%) |
| Mammographic breast density | Not evaluated |
| Affected side | |
| Right | 60 (60%) |
| Left | 40 (40%) |
| Quadrant affected | |
| Upper outer | 62 (62%) |
| Upper inner | 8 (8%) |
| Lower outer | 16 (16%) |
| Lower inner | 2 (2%) |
| Both upper | 6 (6%) |
| Both inner | 4 (4%) |
| Central | 2 (2%) |
| FNAC/CNB | |
| Duct cell carcinoma | 92 (92%) |
| Metaplastic | 2 (2%) |
| Infiltrating duct carcinoma with medullary feature | 2 (2%) |
| Ductal carcinoma in situ cell | 2 (2%) |
| Suspicious for malignancy (intra-ductal carcinoma) | 2 (2%) |
| Clinical classification | |
| Early breast carcinoma | 68 (68%) |
| Locally advanced breast carcinoma | 32 (32%) |
| Treatment | |
| Neoadjuvant chemotherapy and MRM | 18 (18%) |
| Modified radical mastectomy and adjuvant chemotherapy | 82 (82%) |
| Histopathological type | |
| IDC (NOS) | 98 (98%) |
| Secretory | 02 (2%) |
| Histological grade (modified Bloom-Richardson grading) | |
| I | 44 (44%) |
| II | 48 (48%) |
| III | 30 (30%) |
| ER | |
| Positive | 42 (42%) |
| Negative | 58 (58%) |
| HER2/neu | |
| Positive | 32 (32%) |
| Negative | 68 (68%) |
| Immunohistochemical subjects | |
| ER/PR + HER2- | 16 (16%) |
| ER/PR + HER2+ | 16 (16%) |
| ER/PR - HER2- | 48 (48%) |
| ER/PR - HER2+ | 10 (10%) |
| ER+PR - HER2- | 10 (10%) |

*As per modified Bloom-Richardson grading*: Out of 98 cases, 44 (44%) cases were reported as grade I, 48 (48%) cases as grade II and 30 (30%) as grade III tumors. Among 100 patients, 37%, 33% and 30% expressed ER, PR and HER2/neu status in receptors respectively. The proportion of patients expressing ER/PR -ve HER2 subtype was 50%. Table 1

**Table 2. Correlation of age, tumour size, and grade with receptor types**

| Receptors | Age in years | | P value | Tumour size | | P value | Tumour grade | | | P value |
|---|---|---|---|---|---|---|---|---|---|---|
| | <50 (n=54) | >50 (n=46) | | <5 cm (n=46) | >5 cm (n=54) | | I (n=22) | II (n=46) | III (n=30) | |
| | N (%) | N (%) | | N (%) | N (%) | | N (%) | N (%) | N (%) | |
| ER +ve (%) | 16 (29.6) | 26 (56.52) | 0.052 | 20 (43.47) | 22 (40.7) | | 14 (54.5) | 28 (52.2) | 0 | |
| ER -ve (%) | 38 (70.4) | 20 (43.48) | | 26 (56.53) | 32 (59.3) | 0.85 | 8 (45.5) | 20 (47.8) | 30 (100) | 0.0003 |
| PR +ve (%) | 16 (29.6) | 16 (34.8) | | 16 (34.8) | 16 (29.6) | | 10 (45.5) | 20 (43.5) | 2 (6.7) | |
| PR -ve (%) | 38 (70.4) | 30 (65.2) | 0.68 | 30 (65.2) | 38 (70.4) | 0.70 | 12 (54.5) | 26 (56.5) | 28 (93.3) | 0.035 |
| HER2Neu +ve | 18 (33.3) | 12 (26.1) | | 12 (26.1) | 18 (33.3) | | 4 (18.2) | 22 (47.8) | 4 (13.3) | |
| HER2Neu -ve | 36 (66.7) | 34 (73.9) | 0.57 | 34 (73.9) | 36 (66.7) | 0.58 | 18 (81.8) | 24 (52.2) | 26 (86.7) | 0.044 |

*Correlation of age, tumour size, and grade* was presented ER, PR and HER2 status was not significantly associated with age of the patients and tumour size. However, all the receptor status was significantly related to tumour grade ($p<0.05$). [Table 2]

## DISCUSSION

The incidence of breast cancer in India is rising and it is the most common cancer among women in the urban Indian population. The outcome of the disease varies widely and is partially dependent on the interaction between hormones and growth factors with tumour cells. Hence immunohistochemical evaluation of hormone receptors have become a routine investigation to predict response to hormone therapy.

Understanding the underlying mechanisms of ER, PR and HER-2/neu showed a great influence on the clinical outcome. ER positivity in particular, is thought to be of great importance, predicting an approximately 50% to 75% response rate to hormone therapy such as anti-estrogen drugs (tamoxifen). [12] PR is an intracellular steroid receptor. It has two main isoforms A and B. Estrogen is necessary to induce progesterone receptors.

Analysis of PR expression is generally reported along with ER expression. It has been conclusively demonstrated that PR status is independently associated with disease-free and overall survival of patients. ER, PR positive tumors have a better prognosis than patients with ER positive PR negative tumors.[13]

The human epidermal receptor protein-2 (HER-2/neu) oncogene is a trans-membrane glycoprotein belonging to epidermal growth factor receptor family. It is expressed at low levels in a variety of normal epithelia, including breast duct epithelium. Amplification of the HER-2/neu gene and concomitant protein over expression is present in 10–20% of primary breast cancers.[12] HER-2/neu is an independent prognostic marker of aggressive disease with propensity for recurrence and a target for treatment using humanized monoclonal anti HER-2/neu antibody transtuzumab (Herceptin). It gives substantial clinical benefit in patients with metastatic breast cancer so the determination of HER-2/neu status in breast cancer is of great interest.[14]

Triple negative breast cancer (TNBC) refers to the tumors with ER, PR and HER-2/neu negative status. They are also known as Basal-like breast cancers. TNBC are more frequently seen in younger patients. They have aggressive histology, poor clinical outcome, short survival and are unresponsive to usual hormonal therapies.[12] TNBCs are associated with BRCA1 mutation.[15]

In the present study, the peak age incidence of malignant breast cancer was 41-50 years. This was similar to the findings of Puvitha et al. [16] In another study by Ejam et al, the peak age incidence was 30-50 years.[17]] The mean age incidence was 49 years in a study done by Ghosh et al. [18] This was in accordance with our study observations in which the mean age was 51.2 years.

Most common presentation of tumour in the present study was painless lump (96%). The present study was comparable with study by Ayoade et al. [19] In the present study, majority had tumour in the right breast (58%). Similar was observed in the study of Giuliano et al. [20] Most of patients (40%) were presented with lump of size in between 2-5 cms (T2). Similar findings have also been reported by Verma et al. [21]

The important epidemiological risk factors for the development of breast cancer are age, family history, parity, age at menarche and menopause, prior history of breast biopsy, diet, socioeconomic status, and history of exposure to radiation and use of oral contraceptive pills.[22] In our study 3 (6%) patient had a positive family history of breast cancer. Similar finding was reported by Sandhu et al. [23] Carcinoma breast is more common in postmenopausal because of their relative advanced age.[24] In the present study it was shown that that breast cancer affected females more commonly in their postmenopausal period.

Histopathological type is a well-documented prognostic factor. In the present study the majority of the cases (98%) were of infiltrating duct carcinoma. This was in accordance with the findings of Pathak et al. [25]

In our study, the grading was done on the excised specimen. It was not done on trucut biopsy specimen as accurate grading only possible on excised specimens. So out of 50 cases graded by modified Bloom Richardson grading system. In our study grade I was reported in 22% of the cases, grade II in 48% and grade III in 30% of the cases. These observations were comparable with findings of Pathak et al and Rajesh et al.[25,26]

In our study estrogen receptor positivity was seen in 21 (42%) patients. Ghosh et al in their study conducted at a tertiary cancer care hospital at Mumbai reported 51.2% of the cases to be positive for ER.[18] The incidence was higher than our present study, this could be due to larger study size. progesterone positivity was seen in 16 (32%) patients. Similarly, Bhagat et al and Jain et al reported PR positivity in 37.93% and 34% cases respectively.[27,28]

In our study maximum number of cases were of combined ER and PR negative tumors constituting 58% cases, followed by ER and PR positive tumors constituting 32%, followed by ER positive and PR negative tumors (10%). Desai et al in their study also observed that tumors with combined ER and PR negativity were most common and were present in 46.5% cases, followed by both ER and PR positivity in 25% cases.[29] In our study HER-2/neu positivity was seen in 15 cases which comprised 30% of the total cases. In the studies conducted by Rajesh et al and Ambroise et al, HER-2/neu positivity was seen in 27.9% and 27.10% cases respectively. [26,30] These results were slightly lower than the present study, this could be due to the larger study population in the two studies. In the present study, HER-2/neu over expression was found to be inversely related to ER and PR expression. Majority of the tumors expressing ER/PR positivity were seen to be HER-2/neu negative and vice-versa. The inverse association between steroid hormone receptors and HER-2/neu has also been described in various clinical studies.[31]

In our study majority of the cases belonged to basal subtype group (48% cases). This was similar to the findings of Ratnatunga et al. [32] In our study, ER and tumors were more in the age group of >50 years. This was also found in the study done by Ayadi et al. [33]

A positive correlation (p=0.001) between ER and PR expression and histological grade was noted in the present study. No association was found between ER and PR expression and tumor size which were similar to the observation made by Ayadi et al. [33] In our study close correlation was observed between tumor grade and immunohistochemical subtypes which was similar to the study done by Onitilo et al. [34]

## CONCLUSION

It was concluded that the frequency of ER, PR, and HER-2/neu receptors is crucial for cancer treatment optimization. These receptors correlate well with histopathological grading, with higher tumor grades indicating higher likelihood of Her2+ and ER/PR negative or triple negative ductal carcinoma. This supports the use of immunohistochemistry (IHC) as a clinical tool for breast cancer, as it is widely available, therapeutically informative, and prognostic. Further follow-up studies are needed to assess prognostic significance.

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