

# Relationship of ER, PR, HER2 / neu with Other Prognostic Factors in Breast Cancer along with the Role of Androgen Receptor in Triple Negative Breast Cancer

Arshi Khan<sup>1</sup>, Reeni Malik<sup>2</sup>, Pramila Jain<sup>3</sup>, Deepshikha Verma<sup>4</sup>, Vedanti Newasker<sup>5</sup>

<sup>1,2,3,4,5</sup> Department of Pathology, Gandhi Medical College, Bhopal, Madhya Pradesh, India

## ABSTRACT

### BACKGROUND

Understanding various risk factors associated with breast cancer can help in early identification & prompt treatment of patients with breast cancer. Apart from clinical parameters like age, disease presentation and menopausal status, important prognostic indicators in histopathology are size and extent of tumour, histologic type, histologic grade and lymph node status. Also, there are other factors which are not only predictive of outcome, but also direct therapies against particular molecular targets. These factors are oestrogen receptor (ER) status, progesterone receptor (PR) status, HER2 / neu status, Ki-67 proliferation index & androgen receptor (AR) status. We wanted to analyse various hormone receptors & their correlation with prognostic factors. In addition, androgen receptor expression is also studied in triple negative breast cancer cases.

### METHODS

The study included 50 cases over a period of 18 months from January 2018 to June 2019 received in the Department of Pathology, Gandhi Medical College, Bhopal, India. These cases were subjected to histopathological & immunohistochemistry (IHC) evaluation.

### RESULTS

Among the 50 cases studied, the most common subtype was infiltrating ductal carcinoma (NOS - no special type, 84 %). Majority of patients were ER, PR, HER2 / neu negative (48 %) and among those triple negative cases, 25 % of cases were androgen receptor positive.

### CONCLUSIONS

Expression of the hormone receptor (ER and PR) and HER2 status may provide significant information in directing patient management. Since traditional pathological methods and IHC remain standard for guiding the use of treatment, clinicians may be challenged with equivocal results that directs towards additional testing for definitive diagnosis and, better patient outcome. The most used therapy for advanced breast cancers is based on the use of AR antagonists, such as bicalutamide and enzalutamide, first- and second-generation AR antagonists respectively. Gene signatures, bioinformatics, and other clinical trials are also beneficial for clinician in estimating the benefits expected from adjuvant chemotherapy.

### KEY WORDS

Breast Cancer, Oestrogen Receptor, Androgen Receptor, Triple Negative

*Corresponding Author:*

*Dr. Pramila Jain,  
Department of Pathology,  
Gandhi Medical College,  
Madhya Pradesh,  
Bhopal, India.  
E-mail: prmila8560@gmail.com*

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**BACKGROUND**

Breast carcinoma is the most common malignant tumour and second most common cancer overall. There were over more than 2.1 million cases occurring worldwide annually (according to WHO-World Health Organization 2019 statistics). It is the leading cause of carcinoma death in women.<sup>1</sup>

The spectrum of malignant breast lesion includes ductal carcinoma, lobular carcinoma, medullary carcinoma, metaplastic carcinoma, secretory carcinoma papillary carcinoma. Incidence for these malignant lesions increases after menopause. These histological variations influence the clinical presentation, biological behaviour & therapeutic response to a varying extent. Based on these morphological variations, several classifications have been developed over the years to guide for proper therapeutic management of these patients.<sup>2</sup>

A crucial development in treatment of breast carcinoma was recognition that the presence of hormone receptors (ER & PR) in tumour tissue, correlates well with response to hormone therapy (lowers the hormone levels or block hormone receptor) and chemotherapy. These are called as hormone receptor-positive breast cancer cells, which grows more slowly than hormone receptor-negative cancer cells & usually has good prognosis in the short-term.

Hormone receptor-negative breast cancers, also known as triple-negative breast cancer, as the name implies, they are negative for either of hormone receptors (ER, PR, HER2 / neu). So, treatment with hormone therapy is not useful. Also, they are more common in women who have not yet achieved menopause. For these, chemotherapy can still be useful.<sup>3</sup>

Triple-positive cancers are (ER, PR and HER2-positive) can be treated with hormone drugs as well as drugs which target HER2 protein.<sup>3</sup>

ER & PR are co-dependent variables. The presence of ER and PR hormone receptors are correlated with a better outcome, though PR being a weaker predictor of response to endocrine therapy than ER. ER positive tend to be better differentiated tumours conversely ER negative tend to have grade 3 histology

Identification of HER2 / neu tumours is critically important in selecting patients for HER2 / neu targeted therapies, such as trastuzumab (Herceptin). HER2 / neu overexpression is associated with poor prognosis.

The androgen receptor (AR) is a proven clinical target in carcinoma prostate. Recent research says that it is an emerging hormonal target in breast cancer as well, with clinical benefit in both oestrogen receptor (ER) positive and negative tumours.<sup>4</sup> The presence of AR receptors is associated with poorer survival in stage III triple negative breast cancer (TNBC) in comparison with those at earlier stages.<sup>3</sup>

The most useful therapy for advanced breast cancers (tamoxifen resistant breast cancers and TNBCs) is based on the use of molecular target androgen receptors and so AR antagonists, such as bicalutamide and enzalutamide. Both the antagonists have been used in clinical trials with positive results.<sup>5</sup>

We wanted to evaluate histopathological spectrum and its correlation with hormone receptors of breast cancer patients attending the pathology department at GMC Bhopal, India.

**METHODS**

The study included prospective as well as retrospective cases over a period of 18 months from January 2018 to June 2019 in Department of Pathology, Gandhi Medical College, Bhopal, India. This study has been done as per standard ethics & by maintaining confidentiality of patient information. The study was approved by ethics committee.

Total 50 cases were studied which included lumpectomy, simple mastectomy, modified radical mastectomy as well as biopsy specimens. These specimens were fixed in 10 % formalin solution for 24 hrs. Detailed gross examination of all received specimens was carried out for tumour size, location & nodal metastases. Then tissue was submitted for processing and paraffin embedded tissue were cut and stained routinely by haematoxylin & eosin stain and reported.

All cases were histologically graded according to Modified Bloom Richardson Elston grading system.<sup>6</sup> (Table 1) After that, breast cancer tissue blocks were selected for IHC evaluation. Representative sections of tumour were processed for ER, PR, HER-2 / neu and AR immunohistochemical staining. Normal breast tissue was taken as internal positive control. Sections were taken on poly L lysine coated slides. Antigen retrieval was done by citrate buffer and slides were stained with monoclonal antibodies against ER, PR, HER-2 / neu and AR receptors. The results were screened and interpreted according to published guidelines by The American Society of Clinical Oncology & The College of American Pathologist (ASCO / CAP).<sup>7,8</sup>

Interpretation of HER2 / neu staining is done by membranous staining (Table 2).

	Features	Score
Tubule and gland formation	Majority of tumour > 75 %	1
	Moderate degree 10 - 75 %	2
	Little or none < 10 %	3
Nuclear pleomorphism	Small, regular uniform cells	1
	Moderate increase in size and variability	2
	Marked variation	3
Mitotic counts	Dependent of microscopic field area	1 - 3
Mitotic count / 10 high power fields	1 point	0 - 9
	2 points	10 - 19
	3 points	> 20

**Table 1. Semi-Quantitative Method for Assessing Histological Grade in Breast from Elston and Ellis Modified Scarff-Bloom-Richardson Scoring System\*\***

HER2 IHC Score	Staining Pattern	HER2 Protein Expression
0	No reactivity seen	Negative
1	Weak incomplete membrane staining in any proportion of tumour cells	Negative
2	Non uniform or weak to moderate complete membranous reactivity in > 10 % of tumour cells or intense complete staining of < 30 % of the invasive tumour cells	Equivocal
3	Uniform, intense, complete membranous reactivity in > 30 % of the invasive tumour cells.	Positive

**Table 2. Interpretation of HER2 / neu Staining**

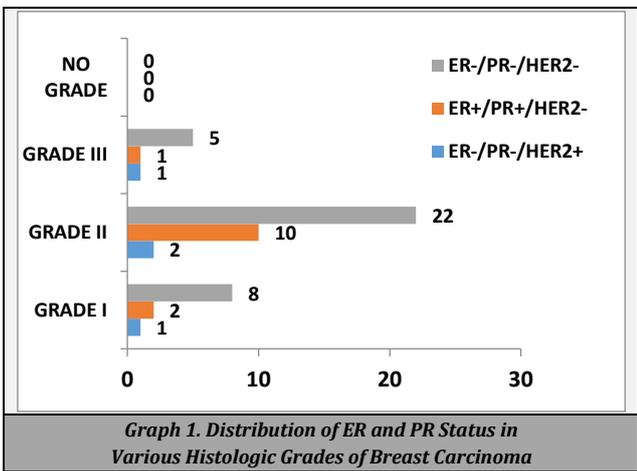
**Statistical Analysis**

Statistical analysis was done using IBM SPSS software version 24. Simple percentages were graphed against various parameters and report analysed.

**RESULTS**

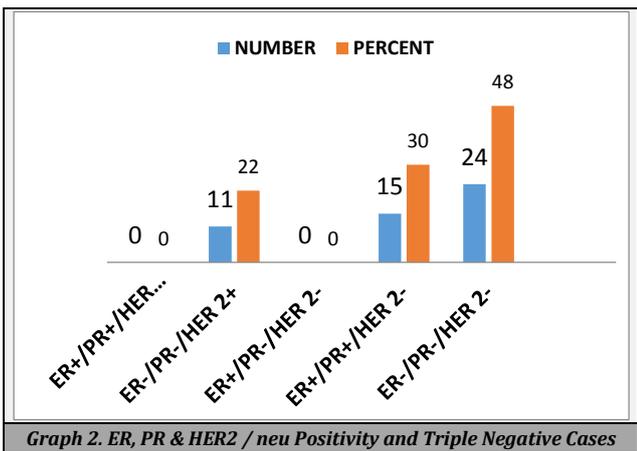
The age of the patients ranged from 20 to 88 years. 13 out of 50 patients (26.0 %) had tumour size less than or equal to 4 cms. The most common histologic type of breast carcinoma was invasive ductal carcinoma (NOS). 45 patients out of total 50 (75 %) had invasive ductal carcinoma (IDC) (NOS) type. Majority of tumours were predominantly of histopathological grade 2 (72 %). 74 % (37 patients out of 50) presented with lymph node metastasis.

In present study it was observed that grade I tumours are 72.7 % triple negative, 18 % are ER / PR positive and 9 % are HER2+. In grade 2 tumours, 64.7 % are triple negative, 5.8 % HER2+ and 29.4 % ER / PR positive. In grade 3 tumours 71.4 % are triple negative and 14.2 % are ER and PR positive as well HER2 positive. No cases were found to be of grade 0. (Graph 1)



Graph 1. Distribution of ER and PR Status in Various Histologic Grades of Breast Carcinoma

In our present study, no patient showed ER, PR and HER2 positivity, 11 patients out of 50 (22 %) showed ER, PR negative and HER2 positive, whereas 15 out of 50 (30 %) showed ER, PR positive but HER2 negative. Remaining 24 out of 50 (48 %) patients showed ER, PR, HER2 negative. Based on these triple negative cases, we further proceeded with applying androgen receptor on same. (Graph 2).

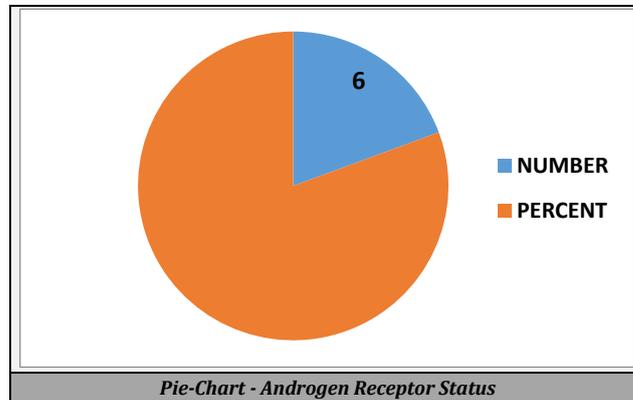


Graph 2. ER, PR & HER2 / neu Positivity and Triple Negative Cases

Majority of cases with lymph node metastasis were triple negative (68.4 %). Majority of grade 2 tumours were in the age group of 40 - 49 yrs. followed by the age group of 50 - 59 yrs. Majority of tumours in the present study were triple negative (70.0 %). Both cases less than 30 yrs. were triple negative. 52.3

% of cases in the age group of 40 - 49 yrs. were triple negative. Also 34.6 % of cases in the age group of 40 - 49 yrs. were triple negative. As the age increase majority of tumours were ER and PR positive and HER2 / neu (luminal A) followed by luminal B patients (triple positive).

- 6 cases out of 24 cases (25 %) are androgen receptor positive whereas 18 cases out of 24 were androgen receptor negative which constitutes 75 %. (Pie-Chart).



Pie-Chart - Androgen Receptor Status

**DISCUSSION**

The current study was done to assess if histopathological methods can be aided by immunohistochemical markers like ER, PR and HER2 / neu, AR in predicting the response to hormone therapy and neoadjuvant chemotherapy. Total 50 cases of modified radical mastectomy specimens over a period of 18 months from January 2018 to June 2019 received in Department of Pathology, Gandhi Medical College, Bhopal, India, for breast cancer were evaluated by light microscopy to determine the histological type and immunohistochemistry was done to find out the ER, PR, HER2 / neu & AR status of the tumour.

Oestrogen receptor determinations have significantly improved the predictability of response to endocrine therapy in advanced breast cancer. Patients with ER+ have a 50 % and 60 % probability of response to endocrine manipulation.

Premenopausal women were treated with a selective oestrogen receptor modulator, like tamoxifen. Postmenopausal women were treated with an aromatase inhibitor like Arimidex. Both treatments starve the cancer cells of oestrogen so they can't grow.

**Histologic Subtype of Breast Carcinoma**

Among subtypes, in invasive ductal carcinoma ER, PR, HER2 neu is positive in 30 % (N = 50) cases, while ER, PR, HER2 neu is negative in 70 % (N = 50) cases. In lobular carcinoma ER, PR, HER2 neu is positive in 33 % (N = 50) cases, while ER, PR, HER2 neu is negative in 66 % (N = 50) cases. In mucinous ER, PR, HER2 neu is positive in 65 % (N = 50) cases, while ER, PR, HER2 neu is negative in 35 % (N = 50) cases. In medullary carcinoma ER, PR, HER2 neu is positive in 44 % (N = 50) cases, while ER, PR, HER2 neu is negative in 56 % (N = 50) cases. These studies were consistent with study by Rao c, Shetty J et al.,<sup>9</sup> while the studies done by Cherry Bansal, Aarti Sharma et al.,<sup>10</sup> showed lesser number of triple negative cases (23 %).

### Lymph Node Status

In the present study axillary lymph node metastasis were present in 68 % (34 patients out of 50) cases. Majority of the cases with lymph node metastasis, 46 % (N = 50) were triple negative, while 16 % (N = 50) are ER, PR positive and HER2 negative, whereas 18 % (N = 50) are ER, PR negative and HER2 positive. This finding was in concordance with other studies also while inverse relationship was found in studies done by Chakarborty A, Bose CK et al.<sup>11</sup>

Cases without lymph node metastasis are mainly 90 % (N = 50) triple negative, while 04 % (N = 50) are ER, PR positive and HER2 negative whereas 6 % (N = 50) are ER, PR negative and HER2 positive.

The survival rate depends on level of axillary node involved (low, medium, high), the absolute number, the amount of metastatic tumour & presence or absence of extranodal extension.

### Grade of Tumour

In the present study grade 2 was most common 40 % (N = 50) followed by grade 1 and grade 3. In present study it is observed that grade I tumours are mostly 72 % (N = 50) triple negative, 18 % (N = 50) are ER, PR positive and HER2 negative whereas 9 % (N = 50) are ER, PR negative and HER2 positive. In grade II tumours 64 % (N = 50) are triple negative, 5.8 % (N = 50) are ER, PR positive and HER2 negative whereas 29 % (N = 50) are ER, PR negative and HER2 positive. In grade III tumours 71.4 % (N = 50) are triple negative, 14.5 % (N = 50) are ER, PR positive and HER2 negative whereas 14.5 % (N = 50) is ER, PR negative and HER2 positive.

In present study, IHC was used to measure protein expression levels of biomarkers like ER, PR and HER2 / neu in 50 cases of breast cancer which were divided into two groups triple negative (TNBC) and non-triple negative (non-TNBC). In this study non triple negative tumours are the most commonly occurring subtype. Lack of significant association between these subtypes and their clinical and pathological behaviour could be due to the small sample size. In the present study among triple negative cases, androgen receptor was positive in 25 % (N = 50) of cases. Bianchini G, Balko JM found 33 % (N = 70), Mayer IA found 26 % (N = 100) of triple negative cases were androgen receptor positive.<sup>12</sup> While Green AR et al. found 75 % (N = 100), Tan W et al. found 63 % (N = 214) higher androgen receptor positivity,<sup>13,14</sup> as compared to the present study.

### CONCLUSIONS

Expression of the hormone receptor (ER and PR) and HER2 status may provide significant information in directing patient management and response to hormonal and biological agents. Oestrogen receptor expression is the main indicator of potential responses to endocrine therapy. The use of hormonal therapy in breast cancer has seriously improved the overall outcome for patients with early stage hormone receptor positive breast cancer.

The androgen receptor is an emerging and promising target in breast cancer especially in TNBC subtype, both because of the lack of a well-established targetable feature (ER

& PR) and the presence of a solid molecular subtype with different prognosis.

Gene signatures from gene expression analysis, bioinformatics, and other clinical trials can now help the clinician in estimating the benefits expected from systemic adjuvant chemotherapy.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.

Financial or other competing interests: None.

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