



ORIGINAL RESEARCH PAPER

Pathology

EXPRESSION OF ER, PR AND HER – 2 / NEU IN BREAST CANCER

KEY WORDS: Breast carcinoma, Clinicopathological parameters, Hormonal status, Triple negative cases and ER, PR, HER2/NEU receptor study.

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ABSTRACT

Background: In English literature it is documented that the expression of ER and PR is low in Asian countries when compared to that of Western countries. HER2/NEU over expression is uniform throughout the world. Studies have shown that triple-negative breast carcinomas are aggressive, likely to spread beyond the breast and recur after treatment. The aim this study is to correlate the expression of ER, PR and HER 2/NEU with clinico-pathological parameters in infiltrating variants of breast carcinoma as well as to determine the clinicopathological parameters in triple negative cases.

Methods: This is a prospective study for a period of two years in the Department of pathology, Prathima Institute of Medical Sciences, Karimnagar, Tealangana, India as well as Department of Pathology, Asian Institute of Gastroenterology, Hyderabad, Telangana, India during June 2013 to May 2015. All cases clinicopathologically diagnosed as malignant and all age groups were included and were subjected for ER, PR, HER2/NEU receptor study.

Results: In the present study total cases analyzed were 52. Infiltrating ductal carcinoma was 29(96.67%) were females and only 1(3.33 %) was male. In our institute infiltrating duct cell carcinoma (NOS) type was the commonest type of carcinoma breast with significant group occurring in in-between 46 to 55 of age. In filtrating ductal carcinoma ER, PR positive expression has no association with age and size of tumor. Triple negative receptor expression was seen in 54.83% of infiltrating ductal carcinoma.

Conclusion: In the present study significant group occurred in between 46-55 years of age presenting in advanced stage of the disease. Triple negative cases were seen in 54.8% cases of infiltrating duct cell carcinoma indicating bad prognosis.

INTRODUCTION

Breast Cancer is the most common cancer of urban Indian women and the second most common in rural women.¹ In India cancer of breast has overtaken cervical cancer, which was the most frequent cancer a decade ago perhaps due to changes in lifestyle and western influences.² The breast is a modified sweat gland composed of both epithelial and connective tissue elements. Therefore, neoplasms arising from these elements have to be classified separately.³ The present study is based on the classification proposed by World Health Organization.⁴ Morphological classification of breast carcinomas divide these tumors into a number of subtypes. These tumors display marked heterogeneity in many of their biologic properties. One is the expression of steroid receptors in concert with the Human epidermal growth factor receptors 2.⁵ This has important clinical implications, such as selection of patients for endocrine therapy.⁶ Aims and objectives of the present study are: To study the histomorphological features of breast carcinoma as well as to study the expression of ER, PR & HER-2/NEU in carcinoma of breast.

MATERIALS AND METHODS

A prospective study on "Expression of ER, PR & HER2/NEU in Carcinoma of Breast was a two years prospective study" was conducted in June 2013 to May 2015, in the Department of pathology, Prathima Institute of Medical Sciences, Karimnagar, Tealangana, India as well as Department of Pathology, Asian Institute of Gastroenterology, Hyderabad, Telangana, India. All cases who are admitted in the general surgery department with clinicopathological diagnosis of breast carcinoma during the year 2013-15. All cases clinicopathologically diagnosed as malignant and all age groups were included.

The specimens were thoroughly examined and clinical details were analyzed. The specimen sent in formalin was sliced at 1 cm interval and fixed immediately in 10% NBF. One dedicated block from the tumor not fixed for more than 24 hours in formalin was used for IHC. Four micron thickness sections were cut and taken on poly-L-Lysine coated slides and stained for evaluating ER, PR receptors and HER-2/NEU expression. And also sections were routinely stained with H & E (Annexure III) and tumors were classified according to WHO classification.

Procedure followed for IHC staining is according to guidelines given in Dako Manual. Immunohistochemical staining sections

were observed under light microscopy and ER/PR nuclear staining was interpreted according to Allred score method and HER2 membrane staining was interpreted according to ASCO/CAP guidelines as following tables 1-2.

Table 1 Estrogen and Progesterone Receptor scoring by Immunohistochemistry (allred score method)⁷

ER/PR	PROPORTION OF POSITIVE CELLS	SCORE	INTENSITY OF STAINING	SCORE
ER/PR	Nil	0	None	0
ER/PR	<1%	1	Weak	1
ER/PR	1%-10%	2	Intermediate	2
ER/PR	11%-33%	3	Strong	3
ER/PR	34%-66%	4	0	0
ER/PR	67%-100%	5	0	0

Sum of proportion score and intensity score: 0 to 8 and Allred score interpretation: 0,2 – Negative, 3 – Very poor positive, 4,5 – Poor, 6 – Intermediate positive and 7,8 – Rich positive.

The American society of clinical oncology (ASCO) and the college of American Pathologists (CAP). Guidelines for HER2/NEU Interpretation by IHC.

Table 2 HER2 Testing By Validated Immunohistochemistry Assay⁷

STATUS	SCORE	SIGNIFICANCE
Positive	3+	Uniform intense membrane staining of >30% of tumor cells
Equivocal	2+	Complete membrane staining, non uniform or weak in intensity, in at least 10% of the cells or intense complete membrane staining in 30% or less of tumor cells
Negative	1+	Weak or incomplete membrane staining in any proportion of tumor cells
Negative	0	No staining

OBSERVATIONS AND RESULTS

The study was undertaken at Prathima Institute of Medical Sciences, Karimnagar, Telangana, India from June 2013 - May 2015. Out of 30 invasive breast carcinoma cases, 29(96.67%) were females and only 1(3.33 %) was male. The mean patient age was 55 years and majority of cases were seen in 4th and 5th decades as shown in table 3.

Table3 Distribution of Cases According to Histological Type

HISTOLOGICAL TYPE	NUMBER OF PATIENTS	PERCENTAGE
IDC(NOS)	21	70
IDC + DCIS	2	6.67
MUCINOUS	1	3.33
CRIBRIFORM PAPILLARY	1	3.33
MEDULLARY	1	3.33
METAPLASTIC	1	3.33
ILC	2	6.67
Total	30	100

In this study of breast carcinomas the predominant histologic subtypes were IDC (NOS) accounting for 21 cases (70%), followed by 2 cases (6.67%) of IDC+DCIS, 2 cases (6.67%) of ILC and 1 case (3.33%) each of mucinous, cribriform, medullary, papillary and metaplastic carcinoma as shown in table 4 and majority of cases i.e. 12 (40%) are categorized as histologic grade-II followed by 11 cases (36.67%) of histologic grade I and 7 cases (23.33%) of histologic grade III, also Maximum cases were in the age range of 46 to 55 years. The mean age of the sample is 55 years, the maximum and minimum age being 75 years and 40 years respectively as shown in table 5.

Table 4 Histologic Grading of Tumors

HISTOLOGIC GRADE	NUMBER OF PATIENTS	PERCENTAGE
Grade I 11 36.67%	11	36.67%
Grade II 12 40%	12	40%
Grade III 7 23.33%	7	23.33%
Total	30	100%

Table 5 Ages and Sex Wise Distribution of Cases

AGE(yrs)	MALE	FEMALE	NUMBER OF CASES	PERCENT
< 45	-	6	6	20%
46-55	1	12	13	43.33%
56-65	-	6	6	20%
66-75	-	5	5	16.67%
Total	1	29	30	100%

Observations in this study Majority of malignant cases presented on left side 17 (56.67%), followed by 13 (43.33%) cases on right side as shown in table 6 and 22 cases (73.33%) measured 2 – 5cms, followed by 5 cases (16.67%) which measured < 2 cms and 3 cases (10 %) measured > 5 cm as shown in table 7 as well as 12 cases (40%) had nodal metastasis and 18 cases (60%) were negative for tumor deposits as shown in table 8.

Table 6 Distribution of Tumors according to the side effected

LATERALITY	NUMBER OF CASES	PERCENTAGE
LEFT SIDE	17	56.67
RIGHT SIDE	13	43.33
TOTAL	30	100

Table 7 size of Tumor in various types of carcinoma breast

SIZE (CM)	NUMBER OF CASES	PERCENTAGE
< 2.0	5	16.67
2.0-5.0	22	73.33
>5.0	3	10
Total	30	100

Table 8 Lymphnode status in various types of carcinoma Breast

LYMPHNODE STATUS	NUMBER OF PATIENTS	PERCENTAGE
POSITIVE	12	40
NEGATIVE	18	60
TOTAL	30	100

In Immunohistochemical Profile study, 21 (70%) cases expressed ER, 21 (70%) cases expressed PR and 10 (33.33%) cases expressed HER-2/NEU as shown in table 9 and 30 cases, 17 (56.67%) were ER/PR+ HER2-, 6 (20%) were ER/PR- HER-2+, 3 (10%) were triple negative and 4 (13.33%) were triple positive as shown in table 10.

Table 9 ER, PR AND HER2/NEU positivity in various types of breast carcinoma

BREAST CARCINOMA	ER	PR	HER2/NEU
POSITIVE	21 (70%)	21 (70%)	10 (33.33%)
NEGATIVE	9(30%)	9 (30%)	20 (66.67%)
TOTAL	30	30	30

Table 10 Immunohistochemical subtypes

ER/PR AND HER2	NUMBER OF CASES	PERCENTAGE
ER/PR + HER2 -		56.67
ER/PR + HER2 +	4	13.33
ER/PR - HER2-	3	10
ER/PR - HER2+	6	20

The most common histologic subtype in which ER, PR and HER-2 positivity noted was IDC(NOS). 14 ER positive cases, 14 PR positive cases and 9 HER-2 positive cases were IDC(NOS). 2 cases of ILC, 1 case of IDC+DCIS, 1 case of mucinous, papillary and cribriform types are ER, PR + and HER-2 negative. 1 case of IDC with intraductal component and 3 cases of IDC(NOS) are triple positive. One each of IDC(NOS) medullary and metaplastic carcinoma were triple negatives shown in table 11 and Estrogen receptor (ER) and progesterone receptor (PR) positivity decreased with increase in tumor grade i.e. it is more in tumors with grade 1 and 2 compared to grade 3 as shown in table 12.

Table 11 relationship between histologic subtypes and ER, PR and HER-2/NEU positivity

Histologic Subtype	ER+ n (%)	PR+ n (%)	HER-2+ n (%)
IDC(NOS)	14 (66.67%)	14 (66.67%)	9 (42.86%)
IDC+DCIS	2 (100%)	2 (100%)	1 (50%)
ILC	2 (100%)	2 (100%)	0
MUCINOUS	1 (100%)	1 (100%)	0
CRIBRIFORM	1 (100%)	1 (100%)	0
PAPILLARY	1 (100%)	1 (100%)	0
MEDULLARY	0	0	0
METAPLASTIC	0	0	0

Table 12 ER, PR and HER-2/ NEU status Vs Histological grade

GRADE	ER +	ER-	PR+	PR-	HER-2 +	HER-2 -
1	11	0	11	0	0	11
2	10	2	10	2	6	6
3	0	7	0	7	4	3

Statistically significant correlation is seen between histological grade and ER expression. P value is calculated using fisher exact test calculator and statistically significant correlation is seen between histological grade and PR expression. P value is calculated using fisher exact test calculator, p- value was calculated using fisher exact test calculator and statistically significant (p < 0.05) correlation was observed between hormone receptor status and Her-2 NEU expression as shown in tables 13, 14 and 15.

Table 13 ER VS Histological grade

GRADE	ER STATUS		P VALUE
	POSITIVE	NEGATIVE	
GRADE 1	11	0	0.000016 (The result is significant as p < 0.05)
GRADE 2	10	2	
GRADE 3	0	7	

Table 14 PR Vs Histological grade

GRADE	PR STATUS		P VALUE
	POSITIVE	NEGATIVE	
GRADE 1	11	0	0.000016 (The result is significant as p < 0.05)
GRADE 2	10	2	
GRADE 3	0	7	

Table 15 ER /PR Receptor status Vs HER2 Expression

Type	Present study	Haque R et al ¹¹ (1980)	Lee et al ¹² (2006)
IDC (NOS)	70%	75%	76%
CRIBRIFORM	3.33%	-	-
MUCINOUS	3.33%	2.2%	1%
PAPILLARY	3.33%	-	-
MEDULLARY	3.33%	8.6%	0.4%
METAPLASTIC	3.33%	3.3%	0%
ILC	6.67%	1.1%	11%

DISCUSSION

Neoplasms of the breast are one of the common lesions of the breast which though virtually limited to females can occur in males as rare exceptions. Breast cancer is a heterogeneous disease composed of growing number of recognized biological subtypes. The current trend in analyzing the clinical outcome of a patient with breast cancer is to examine predictive and prognostic factors related to the patient and tumor. Prognostic factor is related to metastatic potential of the tumor.⁸

Prognostic indicators based on currently available clinical and histopathologic variables such as tumor size, tumor grade, lymph node status and hormone receptor status already exist and are used to predict a patient's clinical outcome in certain situations.⁹

It is well known that ER, PR and HER-2 represent the most acceptable factors for predicting prognosis, response or resistance to treatment and the potential use of newer drugs.⁶⁰ Assessment of ER/PR and HER2 in breast cancer is mandatory in clinical practice.¹⁰ and undertook the study of these important prognostic markers in various histological types as shown in table 16 and as shown in Figures 1-8.

Table 16 Similar to the present study

ER/PR STATUS	HER 2/NEU EXPRESSION		P value
	POSITIVE	NEGATIVE	
POSITIVE	4	17	0.011
NEGATIVE	6	3	(p< 0.05)

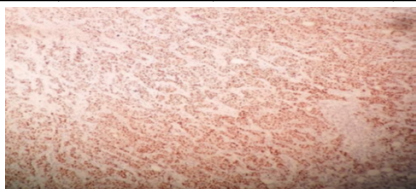


Figure 1 IDC (NOS) ER Positive (10x)

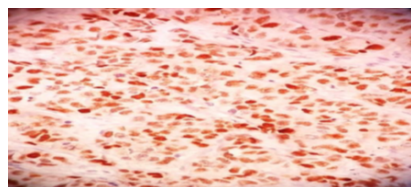


Figure 2 IDC (NOS) PR Positive (40x)

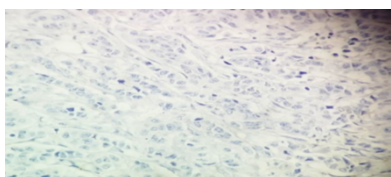


Figure 3 IDC (NOS) HER-2 Negative (40x)

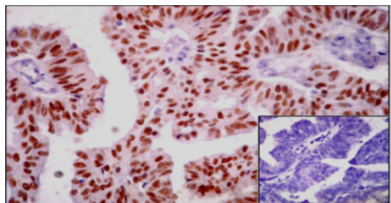


Figure 4 Papillary Carcinoma Showing PR Positivity (40x)

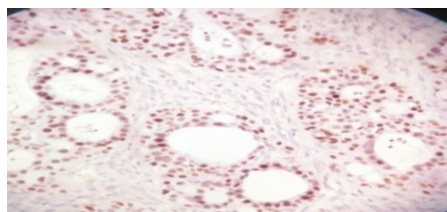


Figure 5 Cribriform Carcinoma Showing ER Positivity (10x)

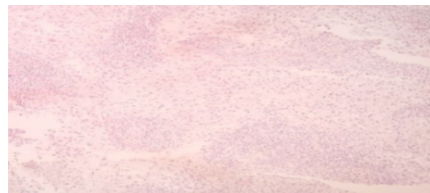


Figure 6 Medullary Carcinoma Showing ER Negativity (10x)

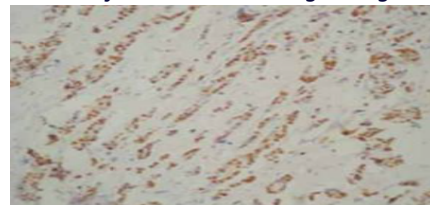


Figure 7 ILC Showing ER Positivity (10x)

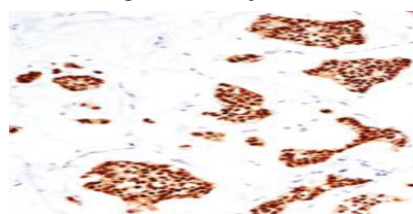


Figure 8 Mucinous Carcinoma Showing ER Positivity (10 X)

In this study of malignant tumors the predominant histologic subtype was Infiltrating ductal carcinoma (NOS) accounting for 21 cases (70%), followed by 2 (6.67%) cases each of IDC+DCIS, 2 cases ILC, 1 case (3.33%) each of mucinous, cribriform, medullary, papillary and metaplastic carcinoma. In the present study the incidence of IDC (NOS) was 70% correlates with that of Haque .R. et al and Lee et al. In the present study the incidence of medullary carcinoma (3.33%) correlates with that of Haque R et al as shown in table 17 and as shown in Figures 1-8.

Table 17 in contrast to the present study

Type	Present study	Rao et al ¹³ (2013)	Mudholkar et al ¹⁴ (2012)
IDC (NOS)	70%	59%	88%
CRIBRIFORM	3.33%	-	-
MUCINOUS	3.33%	3.8%	1.5%
PAPILLARY	3.33%	2.4%	0.75%
MEDULLARY	3.33%	5.6%	0.75%
METAPLASTIC	3.33%	0%	1.5%
LOBULAR	6.67%	15.1%	0.75%

Incidence of various histological types of breast carcinoma in the present study did not correlate with studies conducted by Rao et al¹³ and Mudholkar et al¹⁴.

Age of the cancer patient is an important factor both for occurrence and management of the case. In India, breast cancer incidence peaks among women of 45-50 years of age. In the present study the average age of the breast cancer case at presentation was found to be 55 years with peak in 46 - 55 age range According to American Cancer Society (Breast Cancer Facts and Figures 2013-2014. Atlanta: American Cancer Society, Inc. 2013) 79% of new cases and 88% of breast cancer deaths occurred in women 50 years of age and older and during 2006-2010, the median age at the time of breast cancer diagnosis was 61.14.13. The average age of occurrence of the breast cancer in India reveals that the disease occurs a decade earlier, as compared to western countries as shown in table 18.

Table 18 Similar to the present study

Authors	Present study	Peiro G et al ¹⁵ (2007)	Ambrose et al ¹⁶ (2011)
Mean Age (years)	55	55.9	53.8
Age range (years)	40 - 75 yrs	23-86	24-99

In this study mean age was 55 yrs which is in concordance with the study conducted by Peiro G et al⁷⁵ and Ambroise et al.¹⁵ In the study conducted by Piero G et al¹⁶ and Ambroise et al¹⁵ mean age was 55.9 yrs and 53.8 yrs respectively as shown in table 19.

Table 19 in contrast to the present study

Authors	Present study	Pathak TB et al ¹⁷ (2011)	Munjal.K et al ¹⁸ (2009)
Mean Age (years)	55	48	49.4
Age range (years)	40 – 75 yrs	21-800	30-95

In the present study mean age were 55 and did not correlate with the studies conducted by Munja k et al and Pathak TB et al. In the study conducted by Munja k et al and Pathak TB et al mean age was 49.4 and 48 yrs respectively and it was less compared to the present study. The study conducted by Fakeha Rehman et al¹⁹ mean age was 60 years and it was more compared to the present study and The study conducted by Ambroise M et al²⁰ and Azizun Nisa et al²¹ the left breast was more commonly involved accounting for 59.2% and 57% respectively. In the present study left breast (56.6%) was more commonly involved and is correlating with the studies conducted by Ambroise M et al²² and Azizun Nisa et al²³ as shown in table 20.

Table 20 Comparison of tumor size on gross examination with other studies

Size (cms)	Authors		
	Present study (n=30)	Muddawa LKB et al ²⁴ (2009)	Ayadi L et al ²⁵ (2008)
< 2 cms	16.67	14.5%	12.9%
2-5 cms	73.33	74%	63.2%
5 cms	10	11.5%	23.8%

Various studies have shown that the gross size of tumor is one of the most significant prognostic factors in breast carcinoma and there is increased incidence of axillary lymph node metastasis and decreased survival with increasing size of the tumor. American Cancer Society. Breast Cancer Facts & Figures 2013-2014:13: Incidence rates of breast cancer by tumor size differ between white and African American women. African American women are less likely to be diagnosed with smaller tumors (≤ 2.0 cm) and more likely to be diagnosed with larger tumors (> 5.0 cm) than white women. In the present study, 73.3% cases had the tumor size between 2-5 cms, 16.67 cases had tumor size < 5 cm and 10% of cases had tumor size > 5 cm. In the study conducted by Muddawa LKB et al, 74% cases had the tumor size between 2-5 cms, 14.5 cases had tumor size < 5 cm and 11.5% of cases had tumor size > 5 cm. In the study conducted by Ayyadi L et al, 63.2% cases had the tumor size between 2-5 cms, 12.9% cases had tumor size < 5 cm and 23.8% of cases had tumor size > 5 cm. The present study correlated with observations made by Muddawa LKB et al and did not correlate Ayyadi et al as shown in table 21.

Table 21 similar to the present study

LYMPH NODE STATUS	Present study %	Zafrani B et al ²⁶ (2000)	Huang JH et al ²⁷ (2005)	Onitilo AA et al ²⁸ (2009)
POSITIVE	40	37	35.4	31.0
NEGATIVE	60	63	64.6	69.0

Lymph node involvement is an important prognostic factor. Positive lymph nodes is associated with worst outcome. In the present study, majority of the tumour size was between 2-5 cms and lymph node metastasis was noted in 40 % of cases ie. Lymph node positive cases were less compared to negative cases. Zafrani B et al observed 37% of node positive cases and 63% node negative cases. In the study conducted by Huang HJ et al 34.5 percent were node positive and 64.6 cases were negative. Onitilo et al observed lymph node metastasis in 31 % cases. Present study is similar to the studies conducted by Zafrani B et al, Huang JH et al and Onitilo et al who also observed less number of lymph node positive cases compared to positive cases as shown in table 22.

Table 22 In contrast to the present study

LYMPH NODE STATUS	Present study %	Dinesh Chandra et al ²⁹ (2015)	Ayyadi et al ³⁰ (2008)
POSITIVE	40	52.9	58.1
NEGATIVE	60	47.1	41.9

In this study, majority of the tumour size was between 2-5 cms and lymph node metastasis was noted in 40 % of cases ie. lymph node positive cases were less compared to negative cases. Inesh Chandra et al observed 52.9% of node positive cases and 47.1% of node negative cases. In the study conducted by Ayyadi et al metastasis was seen in 58.1 cases. Observations made in the present study regarding lymph node status did not correlate with studies conducted by Dinesh Chandra et al and Ayyadi et al who observed more number of lymph node positive cases compared to negative cases as shown in table 23.

Table 23 comparison of histological types of carcinoma breast with other studies

AUTHORS	HISTOLOGY IDC (NOS)	ILC
Present study	70	6.67
Zafrani B et al ⁶⁰ (2000)	77	18
Dinshaw et al ⁶¹ (2005)	92	2
Bhurgri et al ⁶² (2007)	92	1
Satti MB et al ⁶³ (2011)	90.6	6.1

In this study, 21 cases (70%) were IDC (NOS) and is close to the study done by Zafrani B et al (77%) and 2 cases (3.03%) were invasive lobular carcinoma which correlated with study done by Satti MB et al (6%). Other types of carcinomas had varied incidence in different studies. In contrast to the present study Dinshaw et al observed 92% of IDC-NOS cases and 2% of ILC cases. Observations made by Bhurgri et al ie. 92% of IDC-NOS cases and 1% of ILC cases, also did not correlate with the present study as shown in table 24.

Histologic grade has also been found to be useful predictor of prognosis in patients with different stages of disease especially among those with negative axillary lymph nodes. It has been found to be significantly related not only to increased recurrence and death in breast carcinoma patients, but also to disease free interval and overall length of survival after mastectomy regardless of clinical stage with early treatment failures occurring more commonly in high grade tumors. In the present study, majority of the patients are categorized as grade 2 i.e., 40% of cases. and next is grade I tumors i.e. 36.7% cases. Rakha et al⁸⁴ conducted a study on a series of 2,608 cases out of which 2,219 cases had complete data on grade, LN stage, size, VI, and outcome data and these cases, 412 cases (18.6%) were grade 1, 790 were grade 2 (35.6%), and 1,017 cases (45.6%) were grade 3. Suci C. et al⁸⁵ observed that majority of the tumors were ductal invasive carcinomas (n = 19), of which 47.36% (n = 9) had G2 differentiation grade, 42.11% (n = 8) were poorly differentiated (G3), and only two of the cases had G1 histopathological grade as shown in table 25.

Table 25 various other studies with incidence of grades of tumor

STUDIES	NUMBER OF PATIENTS	GRADE -I	GRADE -II	GRADE -III
Elston (1984) ³¹	625	17%	37%	46%
Davis et al (1986) ³²	1537	22%	49%	29%
Hoptonet al (1989) ³³	874	29%	46%	25%
Le Doussal et al (1989) ³⁴	1262	11%	45%	46%
Balslev et al (1994) ³⁵	9149	32%	49%	19%
Samurai et al (1999) ³⁶	741	19%	37%	44%
Reed et al (2000) ³⁵	613	25%	41%	35%
Simpson et al (2000) ³⁸	368	22%	45%	33%
Lundin et al (2001) ³⁹	1554	26%	47%	27%
Frkovic-Grazio and Bracko (2002) ⁴⁰	270	38%	38%	24%
Warwick et al (2004) ⁴¹	1988	23%	37%	40%
Williams et al (2006) ⁴²	1058	20%	34%	34%
Thomas et al (2009) ⁴³	1650	26%	45%	29%
Blamey et al (2009) ⁴⁴	16944	29%	41%	30%

In this study it was found that grade II the most common grade of tumors. From the above tables discussion it is clear that in most of the Indian and western studies grade II is the most common grade

which is followed by grade I. From this it is clear that Present study is in concordance with most of the Indian and western studies as shown in table 26.

Table 26 Comparison of ER, PR and HER2/NEU status in breast carcinoma with other studies

ER, PR and HER2 status	Present Study (n=30)%	Authors			
		Dinesh Chandra et al ⁶⁸ (2015)	Ayadi L et al ⁵⁹ (2008)	Huang JH et al ⁵⁴ (2005)	Rao et al ⁶⁵ (2013)
ER	-	-	-	-	-
Positive	70	62.2	59.4	81.1	36.5
Negative	30	37.8	40.6	18.9	63.4
PR	-	-	-	-	-
Positive	70	53.2	52.3	64.2	31.7
Negative	30	46.8	47.1	35.8	68.2
HER 2	-	-	-	-	-
Positive	33.33	23	18.1	10.9	2.4
Negative	66.67	77	81.9	89.1	97.6

In this study, ER+ were more than ER- cases which was consistent with observation made by Hung HJ et al, Ayyadi et al and Dinesh Chandra et al. In the study conducted by Rao et al the observations made were in contrast to the present study. Rao et al observed more number of ER-ve compared to positive cases. PR + cases were more in number than PR- cases which was consistent with observation made by Hung JH et al, Ayyadi et al and Dinesh Chandra et al. In the

study conducted by Rao et al the observations made were in contrast to the Rao et al observed more number of PR-ve compared to positive cases. Her-2 negative cases are more compared to positive cases which is consistent with the observation made by Huang JH et al, Ayyadi et al, Rao et al and Dinesh Chandra et al as shown in table.

Table 27 Comparison of immunohistochemical subtypes with other studies

Immunohistochemical Subtypes	Present Study (%)	Satti MB et al ⁸³ (2011)	Onitilo AA et al ⁶⁰ (2009)	Rao et al ⁶⁵ (2013)
ER/PR+, HER 2-	56.67	53	68.9	21.4
ER/PR +, HER 2+	13.33	11	10.2	-
ER/PR -, HER 2-	10	24	13.4	50
ER/PR -, HER 2+	20	12	7.5	2.4

In the present study there are 56.67% of ER/PR+HER2-, 20% of ER/PR -, HER 2+, 10% of triple negative and 13.33% of triple positive cases. The observations made in present study close to the study conducted by Satti MB et al who observed 53% ER/PR+HER2-, 12% ER/PR -HER 2+, 24% of triple negative and 11% triple positive cases.

The observations made in present study did not correlate with studies conducted by Onitilo AA et al and Rao et al. Onitilo AA et al observed 68.9% ER/PR+HER2-, 7.5% ER/PR-HER 2+, 13.4% triple negative and 10.2% triple positive cases. Rao et al observed 21.4% ER/PR+HER2-, 2.4% ER/PR -HER 2+, 50% of triple negative and 10% triple positive cases as shown in table 28.

Table 28 Comparison of ER, PR and HER-2/NEU status in various types of carcinoma breast with other studies

HISTOLOGIC SUBTYPES	Satti MB et al ⁸³ (2011)					Present study (%)
	ER	PR	HER2	ER	PR	
-						
IDC (NOS)	63	63	25	66.67	66.67	42.86
MEDULLARY CARCINOMA	0	0	0	0	0	0
INVASIVE LOBULAR CARCINOMA	100	100	100	0	100	0

PAPILLARY CARCINOMA	-	-	-	100	100	0
MUCINOUS TYPE	-	-	-	100	100	0
METAPLASTIC CARCINOMA	0	0	0	0	0	0

The present study demonstrated ER, PR positivity with IDC (NOS), invasive lobular carcinomas and IDC mucinous carcinomas which correlates with Satti MB et al. In the present study one case each of papillary and mucinous carcinoma were positive for ER/PR and negative for HER2.

In the present study 1 case of medullary and metaplastic carcinoma were triple negative and the findings were in consistent the study done by Satti MB et al as shown in table 29.

Table 29 Comparison of idc (nos) grading and er/pr receptors and HER2/NEU status with other studies

Grades	Satti MB et al ⁸³ (2011)			Present Study
Grade I	HER2+%	ER/PR+%	HER2+%	ER/PR+%
Grade II	0	86.6	0	100(8)
Grade III	33	53	80(4)	0

In this study, 100% of grade I, 75% of grade II and none of grade III IDC (NOS) were ER/PR +ve. ER/PR positivity decreased with increase in the grade of tumor which is similar to the study conducted by Satti MB et al and 0%, 62.5% and 80% of HER 2 + were observed in grade 1, 2 and 3 respectively. HER 2 positivity increase with increase in tumor grade which is similar to the study conducted by Satti MB et al as shown in table 30.

Table 30 Proportion of estrogen receptor, HER2/NEU status and triple negative breast cancers among different studies

STUDY	ER +VE	HER-2/NEU +VE	TRIPLE NEGATIVE
Present Study	70	33.33	10
Onitilo et al ⁶⁰ (2009)	68.9	7.5	13.4
Indrojit Roy et al ¹⁰⁰ (2009)	60	11	36
Ghosh et al ¹⁰¹ (2011)	51.2	16.7	29.8
Rao et al ⁶⁵ (2013)	36.5	2.4	50
Dinesh Chandra et al ⁶⁹ (2015)	62.2	23	23.8

In this study statistically significant correlation is seen between histological grade and ER expression. The present study correlated with the study conducted by Ayyadi et al and Rao et al in which there was statistically significant correlation between ER status and histological grade as shown in table 31.

Table 31 ER status vs histological grade in comparison with other studies

HISTOLOGICAL GRADE	Present study		Rao et al ⁶⁵ (2013)			
	ER STATUS		PVALUE	ER STATUS		
	POSITIVE	NEGATIVE		POSITIVE	NEGATIVE	
			0.000016 (p < 0.05)		< 0.05	
GRADE 1	11	0		23		33
GRADE 2	10	2		11		39
GRADE 3	0	7		0	17	

CONCLUSION

The present study is an attempt to assess the histomorphological characteristics of carcinoma breast and analyse ER, PR and HER-2/NEU status in breast carcinoma. The interrelationship between ER, PR and Her-2/neu provide valuable prognostic, predictive and therapeutic information and has an important role in the management of breast cancer. Endocrine therapy (tamoxifen) is recommended for tumors expressing ER/PR. Patients with breast carcinoma overexpressing HER-2/NEU do not respond to tamoxifen therapy. Recently anti-HER-2 antibodies (Herceptin) have been shown to be effective against HER-2/NEU overexpressing breast carcinomas. The present study not only

highlights the importance of histopathological examination in breast lumps but also emphasizes the prediction of prognosis by typing and grading malignant neoplasms of the breast. In conclusion ER, PR and HER-2/NEU status correlates well with histopathological grading. Higher the tumor grade, the more likely that ductal carcinoma will be HER2 + and ER/PR negative or triple negative. Hence, present study support IHC classification as a clinically-used, therapeutically informative classification of breast cancer based on immunophenotype / biologic phenotypes, and is prognostic as well as predictive. Follow up study of these patients is needed to assess the prognostic significance.

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