ORIGINAL ARTICLE

Correlation of Estrogen Receptor(ER), Progesterone Receptor(PR) and Her2/neu expression with Clinicopathological Parameters in Primary Breast Carcinoma -A Study of 175 cases

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ABSTRACT

Introduction: Breast carcinoma is the most common malignant tumor worldwide and leading cause ofdeath in women .Present study was aimed to study patterns of expression of Hormone receptor (ER PR) andHer-2/neu in invasive breast carcinoma and to correlate ER PR status and Her-2/neu expression with various clinicopathological parameters.

Materials and Method: 175 cases of Invasive primary Breast carcinoma were studied from May 2014 to September 2017.Routine H and E staining for histopathological diagnosis and IHC analysis for ER,PR receptor with Her2/neu were carried out in all cases.

Results: Mean age at diagnosis was 51.3 years. The predominant histology was Invasive ductal carcinoma 90.9% cases. Most lesions 65.1% were >2 to5 cm in size. Majority of cases were grade II (47.2%) and grade III (47.8%).. Immunohistochemistry revealed 29.8% cases to be ER positive, 32.0% cases PR positive and 29.1% cases Her2/neu positive. 55.7% cases were triple negative. .

Conclusion: In our study ER,PR receptor and Her2neu expression revealed significant association with clinicopathological parameters. As the grade of the tumor increased ER and PR positivity gradually decreased. No significant correlation was seen between Her2/neu and tumor grade . ER, PR and Her2/neu expression did not show any significant correlation with age.

Key Words: ER-Estrogen receptor, PR-Progesterone receptor, Her2/Neu, Primary Breast carcinoma

INTRODUCTION

Breast cancer is the most common cancer in women worldwide. The breast cancer burden is increasing in developing countries. An estimated 70% of new cancer cases will occur in developing countries by the year 2020.[1] In India, breast cancer is most common malignancy followed by cervical cancer. Breast cancer has ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per lakh women.[2]

Breast cancer is biologically heterogeneous in nature. So survival depends on early diagnosis, timely appropriate treatment and genetic predisposition.[3,4]So prognosis and management of breast cancer are influenced by age, clinical presentation ,size of tumor, histopathological type, grade of tumor, lymph node metastasis, Estrogen receptor(ER) status, Progesterone receptor(PR) status ,Her2/neu (HER-2) status of tumor.[5,6,7,8]

Current therapeutics strategies for management of primary breast carcinoma rely on accurate immune histochemical (IHC) determination of hormone receptors - ER,PR status .Patient with ER ,PR positive tumors have a better prognosis than patient with negative expression of ER and PR tumors.[5,6] In addition to hormone receptors Her2/neu emerged as an important independent predictive marker in breast carcinoma. Approximately 15-20 % of breast cancer have amplification of the Her2 gene or over expression of its protein. Her2/neu also called Erb2,is a member of human epidermal growth factor family and encodes a transmembrane tyrosine kinase receptor.Her2/neu status as determined by fluorescence in situ hybridization (FISH) or IHC, has become important for prognostic implication and to assess potential response of patients to treatment with the monoclonal antibody transtuzumab (herceptine).[7].

The objectives of this study were to study status of hormone receptor ER,PR and Her2/neu in primary breast carcinoma and to correlate the hormone receptors and Her2/neu expression with various clinicopathological parameters like age, size of tumor ,grade of tumor, lymphnode metastasis, lymphovascular invasion and histological diagnosis.

MATERIALS AND METHOD

175 cases of Invasive primary Breast carcinoma were studied from May 2014 to September 2017. Modified radical mastectomy and lumpectomy specimens were included while post chemotherapy specimens were excluded from study. Relevant clinical history was archived from case files. All tissues were fixed in 10% buffered formalin solution for 24 hours.

Details about relevant clinical information were recorded. Gross examination of all specimens was carried out for tumor size, evaluation of involvement of margins, base and lymph node metastasis. Representative tumor tissues were submitted in 4 to 5 sections (according to tumor size) ,sections from base, margins ,lymph node ,nipple and areola were also submitted for tissue processing. The sections were stained with H&E stain, diagnosis and grading was done according to Nottingham modification of the Bloom–Richardson system. Tubule formation- 1 point: Tubular formations in >75% of the tumor, 2 points: Tubular formations in 10–75% of the tumor,3 points: Tubular formations in <10% of the tumor, Nuclear pleomorphism-1 point: Nuclei with minimal variation in size and shape, 2 points: Nuclei with moderate variation in size and shape , 3 points: Nuclei with marked variation in size and shape . Mitotic count (40X)-1 point 0–5, 2 point 6–10, 3 point->11. Final grading score- Sum of points 3–5-grade I, 6–7 grade II, 8–9-grade III.

4 μm thick sections were taken from representative paraffin embedded block. IHC for ER,PR and Her2neu were performed -on poly L lysine coated slide. The antigen retrieval was done by HIER method using laboratory microwave for 20 minutes at 95° C. Citrate buffer solution was used at pH 9 for antigen retrieval. Primary antibodies used were clone ID5 for ER assay ,PR assay clone PR88 and EP3 clone for Her2neu . External positive controls were kept with each batch of ER, PR,Her2neu staining.

For detection of hormone receptor Allred score between 0 to 8 was applied, proportional score(PS) range from 0 to 5 and intensity score (IS) from 0 to 3. Proportion score (PS) -0 -- No staining,1--staining of <1% of tumor cells,2 –staining of 1-10% tumor cells,3--staining of 11-33% tumor cells,4--staining of 34-66% tumor cells,5-- staining of 67-100% tumor cells. Intensity score- Intensity of positivity 0- None, 1 -Weak, 2 -Intermediate,3 -Strong. The proportion score and intensity score are added together for a total score.

For Her2/neu reporting following method was used. Score 0: No staining is observed or membrane staining that is incomplete observed in <10% of the tumor cells. Score 1+: A Faint/barely perceptible membrane staining is detected in >10% of tumor cells. The cells exhibit incomplete membrane staining. Score 2+: Equivocal, circumferential membrane staining that is incomplete and/or weak/moderate and within >10% of tumor cells or complete and circumferential membrane staining that is intense and within ≤ 10% of tumor cells. Score 3+: Strongly Positive, circumferential membrane staining that is complete, intense, and within >10%of tumor cells.

All statistical tests were performed and analyzed by the software MedCalc . Statistical significance was determined at $p<0.05$.

RESULTS

We studied 175 cases of invasive breast carcinoma. Table 1 shows age distribution of patient according to grade. Majority of cases 63 (36%) were between 41 to 50 years of age .Mean age of presentation was 51.3 years. Out of 175 cases 174 cases were female only one case was male (M:F ratio0.006:1).

Table 1: Distribution of age and number of cases in relation to grade

Age	Cases	Grade 1	Grade 2	Grade 3
21-30	5(2.9%)	1	1	1
31-40	27 (15.4%)	0	10	15
41-50	63 (36.0%)	2	29	29
51-60	46 (28.3%)	3	20	20
61-70	27 (15.4%)	1	13	8
71-80	5 (2.9%)	1	2	2
81-90	2 (1.1%)	0	0	1
Total	175 (100)	8(5.03%)	75(47.2%)	76(47.8%)

Table 2: Clinicopathological profile of breast carcinoma cases

Clinicopathological profile	No of cases (%)
\Gender	
Female	174(99.4%)
Male	01(0.57%)
Age Group	
≤40 years	32(18.3%)
>40 years	143(81.7%)
Side	
Left Breast	86(49.1%)
Right Breast	89(50.9%)
Grade	
I	8 (5.03%)
II	75 (47.2%)
III	76 (47.8%)
Size Of Tumor	
<2 cm	7(4.0%)
2-5 cm	114(65.1%)
>5 cm	54(30.9%)
Lymph node Status	
Positive for Metastasis	107(66.0%)
Negative for Metastasis	55(34.0%)
Not received	13
Lymphovascular Invasion	
Present	86(49.1%)
Absent	89(50.9%)

Table 3 Histological Diagnosis

Histological Diagnosis	Cases(%)
IDC NOS type	159(90.9%)
ILC	3 (1.7%)
Mucinous carcinoma	5 (2.9%)
Secretary carcinoma	1 (0.6%)
Metaplastic carcinoma	3 (1.7%)
Medullary carcinoma	2 (1.1%)
Cribriform carcinoma	1 (0.6%)
Micropapilary carcinoma	1 (0.6%)

IDC NOS type-Invasive Ductal Carcinoma Not other-wised - specified, ILC –Invasive Lobular carcinoma

Table 4 Distribution of receptor status

Receptor Status	Cases(%)
ER status	
Positive	52(29.8%)
Negative	123(70.3%)
PR status	
Positive	56(32.0%)
Negative	119(68.0%)
Her2/neu expression	
Positive	51(29.1%)
Negative	115(65.7%)
Equivocal	9(5.1%)

In our study 8(5.03%) cases were grade I, 75 (47.2 %) grade II and 76 (47.8%) grade III on histology. (Table 2)

In our study, invasive ductal carcinoma not otherwise specified(IDC NOS) was most commonly observed histological type of breast cancer with 159 cases followed by 5 cases of mucinous carcinoma, 3 cases of Invasive lobular and metaplaststic carcinoma, 2 of medullary carcinoma and 1 case each of cribriform, micropapillary carcinoma (Table 3).

Histopathology reporting and ER, PR and Her2/neu scoring was done by at least three independent observers and results were recorded.

ER positive cases were 52(29.8%),ER negative cases were 123 (70.3%), PR positive cases were 56 (32.0%), PR negative cases were 119 (68.0%). Whereas Her2Neu positive cases were 51 (29.1%) , negative cases were 115 (65.7%) and Her2/neu equivocal cases were 9(5.1%).(Table 4)

ER, PR and Her2 Neu status were correlated with age, grade of tumor, tumor size, lymph node status, lymphovascular invasion and histological diagnosis.(Table 5,6). On correlating age with ≤40 years ER positive cases were 5(15.6%), PR positive cases 10(31.3%),Her2/neu cases12(37.5%) whereas >40 years ER positive cases 47(32.9%),PR positive cases 46(32.2%) and Her2/neu positive cases 40(28.0%) . No statistically significant correlation was obtained between the age of patient and ER, PR andHer2/neu status.

ER positive cases in grade I tumor were 62.5%, grade II tumor 37.3% and grade III tumor 13.2%.PR positive cases in grade I tumor were 37.5%, grade II tumor 40.0%, grade III tumor 21.1%.ER, PR positivity were more in grade I and grade II tumor. As seen in table 5. Only 2 (25.0%) cases of grade I tumor were Her 2 Neu positive, whereas 23 (30.6%) and 25 (32.9%) grade II and grade III tumor respectively were positive for Her 2 Neu. (Table 5). As the grade of the tumor increased ER and PR positivity gradually decreased. This was statistically significant for both ER and PR (P value 0.0003 for ER and 0.0381 for PR).Her2/neu expression was increased as grade of tumor increased. This was not significant statistically. (P value0.7978)

Table 5 Correlation of clinicopathological parameters and immunohistochemical profile

	ER Status			PR Status			Her2/neu Status			
	ER+ (%)	ER- (%)	P value	P R+ (%)	PR- (%)	P value	Her2 + (%)	Her2- (%)	Equivocal (Not taken in P value	P value
Age										
≤40 years	5 (15.6)	27 (84.4)	0.0607	10 (31.3)	22 (68.8)	0.9199	12 (37.5)	20 (62.5)	0	0.4032
>40 years	47 (32.9)	96 (67.1)		46 (32.2)	97 (67.8)		40 (28.0)	94 (65.7)	9 (6.3)	
Grade										
I	5 (62.5)	3 (37.5)	0.0003	3 (37.5)	5 (62.5)	0.0381	2 (25.0)	6 (75.0)	0	0.7978
II	28 (37.3)	47 (62.6)		30 (40.0)	45 (60.0)		23 (30.6)	48 (64.0)	4 (5.3)	
III	10 (13.2)	66 (86.8)		16 (21.1)	60 (78.9)		25 (32.9)	48 (63.2)	3 (3.9)	
Tumor Size										
<2 cm	6 (85.7)	1 (14.3)	0.0016	4 (57.1)	3 (42.9)	0.3358	1 (14.3)	6 (85.7)	0	0.2169
2-5 cm	35 (30.7)	79 (69.3)		36 (31.6)	78 (68.4)		30 (26.3)	78 (68.4)	6 (5.3)	
>5cm	11 (20.4)	43 (79.6)		16 (29.6)	38 (70.4)		20 (37.0)	31 (57.4)	3 (5.6)	
Lymph node status										
Positive	33 (30.8)	74 (69.2)	< 0.0001	41 (38.3)	66 (61.7)	< 0.0001	33 (30.8)	68 (63.6)	6 (5.6)	< 0.0001
Negative	16 (20.1)	39 (36.4)		13 (23.6)	42 (76.4)		13 (23.6)	39 (70.9)	3 (5.5)	
Lymphovascular Invasion										
Positive	20 (23.3)	66 (76.7)	0.0009	29 (33.7)	57 (66.3)	0.0016	28 (32.6)	53 (61.6)	5 (5.8)	0.0009
Negative	32 (36.0)	57 (64.0)		27 (30.3)	62 (69.7)		23 (25.8)	62 (69.6)	4 (4.5)	

Table 6 Correlation of ER,PR ,Her2/neu status with histopathological type

Histological Diagnosis	ER Status			PR Status			Her2/neu Status			
	ER+ (%)	ER- (%)	P value	PR+ (%)	PR- (%)	P value	Her2 + (%)	Her2- (%)	Equivocal (%)	P value
IDC NOS	43 (27.0)	116 (73.0)	0.0203	49 (30.8)	110 (69.2)	0.2819	50 (31.4)	102 (64.1)	7 (4.4)	0.2622
ILC	2 (66.6)	1 (33.3)		1 (33.3)	2 (66.6)		0	3 (100)	0	
Mucinous carcinoma	4 (80.0)	1 (20.0)		3 (60.0)	2 (40.0)		0	4 (80.0)	1 (20.0)	
Secretary carcinoma	1 (100.0)	0		0	1 (100.0)		0	0	1 (100.0)	
Metaplastic carcinoma	0	3 (100.0)		0	3 (100.0)		0	3 (100.0)	0	
Medullary carcinoma	0	2 (100.0)		0	2 (100.0)		0	2 (100.0)	0	
Cribriform carcinoma	1 (100.0)	0		1 (100.0)	0		0	1 (100.0)		
Micropapilary carcinoma	1 (100.0)	0		1 (100.0)	0		1 (100.0)	0	0	

IDC NOS type-Invasive Ductal Carcinoma Not other-wised -specified, ILC –Invasive Lobular carcinoma

Table 7 Correlation of hormone receptor with Her2/neu expression

Her2/neu	ER+ PR + (%)	ER+ PR- (%)	ER-,PR+ (%)	ER –PR- (%)
Positive	6(11.8%)	3(5.9%)	5(9.8%)	37(72.5%)
Negative	30(26.1%)	9(7.8%)	12(10.4%)	64(55.7%)
Equivocal	2(22.2%)	2(22.2%)	1(11.1%)	4(44.4%)
Total 175	38 (21.7%)	14(8.0%)	18(10.3%)	105(60.0%)

The size of tumor ranged from 0.5 cm to 15 cm. The mean size of tumor was 4.9 cm. 114(65.1%) cases had tumor size of 2 to 5cm, 54(30.9%) cases had tumor size >5 cm. Only 7(4.0%) cases had tumor size of <2 cm. (Table2). ER positive cases in <2 cm size of tumor were 85.7% and in 2 to 5 cm size tumor 30.7% and in >5 cm size 20.4%. Tumor <2 cm and 2 to 5 cm were found to have more positivity for ER, PR receptors. As seen in table 3. Maximum no. of cases of Her 2Neu positivity 20(37.0%) were seen in tumor size >5cm. (Table 5). There was significant association between tumor size and ER status (P value0.0016). PR and Her2/neu status were not statistically significant association with size of tumor.

We received 162 cases with axillary lymph node dissection. Out of 162 cases 107 (66.0%) cases had axillary lymph node metastasis which was detected on H&E stain (Table2). ER, PR Her2/neu expression also show statistically significant (p value<0.0001) association with lymph node metastasis (Table 5).

Lymphovascular Invasion was seen in 86(49.1%) cases this was statistically significant in association with ER, PR, Her2/neu status. (P value <0.0009) (Table 5)

Out of 159 cases of IDC NOS type 43(27.0%) cases were ER positive, 49(30.8%) cases PR positive and 50(31.4%) cases were Her2/neu positive. One case of IDC basal type, three cases of Metaplastic carcinoma and two cases of Medullary carcinoma were triple negative (ER, PR, Her2/neu negative). Out of three cases of lobular carcinoma, two were ER positive and one case was PR positive. All three cases of lobular carcinoma were Her/neu negative. (Table 6)

Correlations of hormone receptor with Her 2 status are illustrated in table 7. Immunohistochemistry revealed ER+PR+38(21.7%) cases, ER+PR- 14(8.0 %) cases, ER-PR+18(10.3%) cases and ER-PR-105(60.0%) cases whereas 64(55.7%) cases were triple negative(ER,PR,Her2/neu negative .

DISCUSSION

The present study comprised of 175 cases of primary breast carcinoma diagnosed on modified radical mastectomy and lumpectomy specimens. Majority of cases 63(36 %) were in the age group of 41 to 50 years which is similar to study by Geethamala K et al[8] 49% and Bhagat Vasudha et al[9] 41.37%.

In the present study 75(47.2%) breast tumors were grade II, 76(47.8%) grade III and 8(5.03%) grade I which is similar to other study as showed in Table 8.

There were 52(29.8%) cases ER positive and 56(32.0%) cases PR positive. The study by Seshie et al[12]showed 32% ER positive,25.6% PR positive and Chandrika Rao et al[13] showed 36.5% ER positivity,31.7% PR positivity. Hormonal receptor positivity was lower in Indian female compared to western countries where 60-80% patients were found with positive hormonal receptor expression.

Overall ER,PR negative expression were 70.3% and 68..0% respectively which was higher than positive expression similar to other studies [13,14].

In our study 29.1% cases were Her2Neu positive. Similar results were seen by Nabi et al [5] who reported 36.3% cases, Gore et al[15] reported 28.0% cases, Bansal et al[11] reported 40.7% cases and Sharif et al[16] reported 31.0% cases positive for Her2 Neu.

ER positive cases with ≤40 years were 15.6%, PR positive cases 31.3% ,Her2/neu cases 37.5% whereas ER positive cases>40 years 32.9% ,PR positive cases 32.2% and Her2/neu positive cases 28.0%.

Table 8 Comparative Incidence of Grade of Tumor

Grade	Geethamala Ket al 2015[8]	Bhagat Vasudha et al 2012[9]	Adedayo et al 2009[10]	Bansal et al 2017[11]	Present Study
Grade I	19	27.58	21.2	3.9	5.03
Grade II	54	43.10	38.4	64.0	47.2
Grade III	27	29.31	35.9	28.7	47.8

Table 9 Comparative Incidence of frequency of Hormone Receptor expression

	Geethamala K al 2015[8]	Bhagat V et al[9] 2012	Suvarchala et al 20111[7]	Desai et al[23]	Present Study
ER+PR+	52.0%	36.20%	32.81%	25.0%	21.7%
ER+PR-	2.0%	12.06%	14.06%	7.4%	8.0%
ER-PR+	0	1.72%	10.94%	21.1%	10.3%
ER-PR-	--	48.27%	42.19%	46.5%	60.0%

Literature reveals ER, PR positivity increases with age and elderly age patients express more hormone receptors whereas Her2/neu expression declines with age.[5,10,13,17].In present study no statistically significant correlation was obtained between the age of patient and ER,PR andHer2/neu status. Similar results were observed by Geetamala et al[8], Vaidyanathan et al[18] ,Azizun-nisa et al.[19]

ER, PR positivity was significantly high with grade I and grade II tumor compared to grade III tumor. Her2/neu positivity was high in Grade III tumor compared to ER, PR positivity. As the grade of the tumor increased ER and PR positivity gradually decreased. Similar results was observed by Geetamala et al,[8] Vasudha et al, [9] Adedayo et al,[10] Yadav et al,[14]Azizun-nisa et al.[19] In present study no significance correlation was seen between Her2/neu and tumor grade which is similar to other studies. [8,13.18.19]

The tumor cases <2 cm in size were 4.0%, 2 to5 cm size 65.1% and >5 cm in size 30.9 % .Majority of our cases were 2 to5 cm in size.[5,9,20] ER positive cases in <2 cm size of tumor were 85.7% and in 2 to 5 cm size tumor 30.7% and in >5 cm size 20.4%. Her2Neu positivity was increased as size of tumor increased. 37.0% cases of Her2/neu positive were >5cm in size. Tumor size correlated inversely with ER positivity. We found significant association between tumor size and ER status (P value0.0016). Similar results was obtained by Rao at al[13] and Dutta at el.[21] No statistically significant correlation was observed between tumor size and PR, Her2/neu status .Study by Geethamala et al[8] Bansal et al[11] and Rao et al[13] also showed similar result in their study.

Lymph node involvement is an important prognostic factor. Positive (Metastatic) lymph node was associated with worst outcome. In present study axillary lymph node metastasis was seen in 107(66.0%) cases .There was statistically significant correlation between receptor expression and lymph node involvement (P value<0.0001).The findings were correlated with study by Nabi et al[5] who reported 66.9% cases, Lakhsmi K Madduva et al[20] reported 57.6% and Pallavi Shrigondkar et al [22] reported 48.64% cases of axillary lymph node metastasis. Lymphovascular Invasion was seen in 49.1% cases.[22] ER positive 23.3% cases ,PR positive 33.7% cases and Her2/neu positive 32.6 cases were present with lymphovascular invasion which was statistically significant. (P value <0.05).

Infiltrating ductal carcinoma was predominant histology seen in 90.9% of cases[5,9,15,17,22]. IDC NOS type 27.0% cases were ER positive, 30.8% cases PR positive and 31.4% cases were Her2/neu positive. Immunohistochemistry revealed ER+PR+ in 21.7% cases, ER+PR- in 8.0 % cases, ER-PR+ in10.3% cases and ER-PR- in 60.0% cases. These results were similar to other studies shown in Table 9.

There were 6 (11.8%) cases ER, PR, Her2neu positive where as 37(72.5%) cases were ER-PR-Her2/neu positive.Her2/neu overexpression is good predictor of response to herceptine, but it is not a useful predictor of response to chemotherapy or overall survival.[11]

30 (26.1%) cases were ER+PR+ Her2/neu negative. 64 (55.7%) cases were triple negative, which is higher than normally reported in literature. Seshie et al[12] reported 49.4%, Rao et al[13] reported 50% triple negative breast cancer. Triple negative breast carcinoma is aggressive phenotype affecting younger age group and has poor prognosis. By adding CK 5/6 and EGFR as positive marker to triple negative phenotype, a significantly worst outcome group can be identified among triple negative cases-basal like subtype. The basal like subtype have more aggressive pathological behavior.[5,7,13]

CONCLUSION

Immunohistochemical analysis of ER,PR receptor, Her2neu expression is widely used for prognostic and therapeutic purpose .In our study ER,PR receptor and Her2neu expression revealed significant association with tumor grade , size, lymph node status and lymphovascular invasion. Higher no of grade I tumors showed ER,PR positivity compared to grade III tumors . As the grade of the tumor increased ER

and PR positivity gradually decreased. This was statistically significant for both ER and PR (P value <0.05). No statistically significant correlation was seen between Her2/neu and tumor grade .ER positivity decreased as size of tumor increased (P value 0.0016).No statistically significant correlation was established with size of tumor and PR,Her2 neu expression. Lymph node metastasis and lymphovascular invasion show statistically significant correlation with ER,PR and Her2/neu expression.(P value<0.05). ER, PR and Her2/neu expression did not show any significant correlation with age. 64 (55.7%) cases were triple negative.

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