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Study of Correlation of ER, PR and Her2 neu Status in Breast Carcinomas with Histopathological Grading and other Clinicopathological Prognostic Factors.

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ABSTRACT

Background: Breast cancer is the most common cancer in women worldwide, in India too second only to cancer of cervix. Several histopathological features have prognostic significance in breast carcinoma which includes histologic subtype, grade, lymph node status, ER/PR and Her2/neu status, recent attention has been directed singularly at molecular classifications of breast cancer. The Immunohistochemistry (IHC) classification provides both therapeutic and prognostic information. **Methods:** This is a prospective study on patients attending Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar, with histopathologically proven diagnosis of breast carcinomas during the period of August 2017 to July 2019.immunohistochemistry for ER, PR and Her2 neu was performed on all the biopsies and correlations were done with histopathological grading and other clinicopathological prognostic factors. **Results:** An observational clinical correlation study of 75 patients with breast cancers is under taken to study the Immunohistochemistry for the detection of ER/PR and HER-2/neu status and correlation with Histopathological grading of breast cancers. In the present study, age ranged from 21-85 years and the mean age± SD was 54.04±12.3 years. Majority were of infiltrating duct cell carcinoma (92%), of size more than 5.0 cms (62.3%) and of grade 2 of Modified Bloom Richardson (MBR) score (36%). Immunohistochemistry showed 50% of cases are of ER/PR+ and Her2-,21.7% are of ER/PR+ and Her2+, 5% were of ER/PR- and Her2- (Tripple Negative), and 23% are of ER/PR – and Her2+. Clinicopathological correlation was done. Statistically significant values were noted for histologic grade, immunohistochemical subtypes, lymphovascular invasion and nuclear pleomorphism. **Conclusion:** ER, PR and HER-2 status correlates well with histopathological grading and other clinico-pathological parameters.

Keywords: Breast carcinoma, ER/PR and Her2 neu expression, Clinicopathological

INTRODUCTION

Breast cancer is the most common cancer in women in developed countries, and 12% of breast cancer occur in women between 20-34 years.[1] In India, breast cancer is second to cancer of cervix among women, but is considered the leading cancer in certain metros such as Mumbai and Bangalore. It is estimated that approximately 80,000 cases occur annually; the age adjusted incidence rates varying between 16 and 25/ 100,000 population.[2] Several histopathological features have prognostic significance in breast carcinoma which includes histologic subtype, grade, lymph node status, ER/PR status, Growth factors and its receptors, proliferation activity and DNA content, oncogenes and tumour suppressor genes.[3] Recent attention has been directed singularly at molecular classifications of breast cancer. While molecular and genetic testing is very elegant, prognostic and predictive, it is expensive and not yet widely available.[4] The Immunohistochemistry (IHC) classification provides both therapeutic and prognostic information which can be conducted relatively inexpensively on routinely processed tissue sections with no need for specialized equipment.

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Aims and Objectives

1. To assess the ER, PR and HER-2 status of breast carcinoma.
2. To study the relationship between clinic pathological parameters, IHC subtypes and histopathological grading.

MATERIALS AND METHODS

Study design

This is a prospective study on patients attending Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar, with histopathologically proven diagnosis of breast carcinomas during the period of August 2017 to July 2019.

Inclusion criteria:

All specimens of modified radical mastectomy were included in the study.

Exclusion criteria:

All tru-cut biopsies or lumpectomy specimens were excluded from the study.

Ethical committee approval has been taken from institutional ethical committee.

Relavent data such as patient's age, menstrual status, tumor size on gross examination, histologic subtype of breast cancer and axillary nodal status have been collected from surgical pathology records.

The haematoxylin and eosin (H&E) sections of the cases were retrieved from the records and screened for confirmation of diagnosis and selection of representative tumour paraffin blocks. The histologic grading of tumor was done on H&E stained sections according to Modified Bloom and Richardson grading.

The representative neoplastic tissue blocks (paraffin embedded) were cut at 3.0µ on Poly-L-Lysine coated slides and subjected for immunohistochemistry. The peroxidase–antiperoxidase method of was followed by using Rabbit Monoclonal Antibodies. Biocare reagents were used for antigen retrieval and IHC staining process. The primary antibody used in the study were Biocare Anti-estrogen receptor(ER)(SP1) clone in 1:100 dilution, Anti-progesterone receptor (PR)(SP2) clone in 1:100 dilution and Anti c-erbB-2(HER-2/neu),(EP3) clone in 1:50-1:100 dilution. Biocare Tris–EDTA-based antigen retrival solution with a Ph of 9 and 6 was used for ER,PR staining and HER-2 neu staining respectively by using temperature controlled microwave. Then the slides were subjected through serial steps of procedure like wash with Tris buffer, peroxidise block, power block and application of primary antibody. After this again wash with Tris buffer, secondary antibody was applied and diaminobenzidine chromogen was applied. Then the slides were washed and counterstained with haematoxylin, dehydrated, cleared and mounted.

Scoring for ER, PR was done by Quick Score System which takes the proportion and intensity of nuclear staining into account. Scoring for HER2/neu was done by denoting membranous reactivity of the tumour cells.

Statistical Analysis: Collected data was entered into Microsoft excel 2016 and statistical analysis was done by using statistical software SPSS version 25. Descriptive and Inferential statistics get done. For qualitative data proportion and chi-square test were used to see the association and for quantitative data mean standard deviation were used. Statistical significance considered at 5% level of significance.

RESULTS

Study design: An observational clinical correlation study of 75 patients with breast cancers is undertaken to study the immunohistochemistry for the detection of ER/PR and HER-2/neu status and correlation with histopathological grading of breast cancers.

In the present study, age ranged from 21-85years and the mean age ±SD was 51.04 ±12.3 years. Majority, 44cases (58.6%) belonged to 41-60years.

On gross examination, 49cases (65.3%) measured> 5cms, followed by 21cases (28%) between 2.0-5.0 cms and 5 cases (6.7%) ≤2cms.[Figure 1A].

Histologic grading showed 27 (36.0%) of case stobe grade II, grade I and grade III included 24 (32%) cases each.

In our study the predominant histologic subtype was Infiltrating ductal carcinoma (NOS) 69 cases (92.0%), [Figure 1B], 2cases were lobular carcinomas and1case each of papillary, mucinous, medullary and apocrine carcinomas.

39cases (52%) had lymphnodal metastasis, 15(20%) were reactive and 1(1.3%) had epithelioid cell granulomas.

Graph 1: ER, PR and HER-2 status

57(76%) tumors expressed ER, 44(58.7%) tumors expressed PR and 33(44%) expressed HER-2/neu. [Graph 1]

Table 1: Immuno histochemical sub types

ER,PR and HER-2	Number of patients (n=75)	%	95% CI
ER/PR+ HER2-	30	50	37.74-62.28
ER/PR+ HER2+	13	21.7	13.12-33.62
ER/PR- HER2-	3	5	1.71-13.70
ER/PR- HER2+	14	23.3	14.44-35.44

Of 75cases, 30(50%) were ER/PR+ HER-2- [Figure 2A, 2B], 14(23.3%) were ER/PR- HER-2+,13 (21.7%) were ER/PR+ HER-2+and remaining 3(5%) were triple negative [Table 1].

Table 2: Relationship of ER to the following clinicopathological features

Clinicopathological features	ER		
	Positive (n=57)	Negative (n=18)	p value
Menstrual Status			
Premenopausal	16 (28.1%)	1 (5.6%)	0.1
Perimenopausal	14 (24.6%)	4 (22.2%)	
Postmenopausal	27 (47.4%)	13 (72.2%)	
Tubule Formation			
Score 1	13 (22.8%)	0 (0%)	0.001**
Score 2	28 (49.1%)	4 (22.2%)	
Score 3	16 (28.1%)	14 (77.8%)	
Nuclear pleomorphism			
Score 1	13 (22.8%)	0 (0%)	0.014*
Score 2	33 (57.9%)	10 (55.6%)	
Score 3	11 (19.3%)	8 (44.4%)	
Mitosis Grading			
Score 1	15 (26.3%)	1 (5.6%)	<0.001**
Score 2	28 (49.1%)	4 (22.2%)	
Score 3	14 (24.6%)	13 (72.2%)	
Histological Grading			
Grade 1	23 (40.4%)	1 (5.6%)	<0.001**
Grade 2	24 (42.1%)	3 (16.7%)	
Grade 3	10 (17.5%)	14 (77.8%)	

Table3: Relationship of PR to the following clinicopathological features

Clinicopathological features	PR		
	Positive (n=44)	Negative (n=31)	p value
Menstrual Status			
Premenopausal	12 (27.3%)	5 (16.1%)	0.577
Perimenopausal	10 (22.7%)	8 (25.8%)	
Postmenopausal	22 (50%)	18 (58.1%)	
Tubule Formation			
Score 1	12 (27.3%)	1 (3.2%)	<0.001**
Score 2	22 (50%)	10 (32.3%)	
Score 3	10 (22.7%)	20 (64.5%)	
Nuclear pleomorphism			
Score 1	11 (25%)	2 (6.5%)	0.002**
Score 2	28 (63.6%)	15 (48.4%)	
Score 3	5 (11.4%)	14 (45.2%)	
Mitosis Grading			
Score 1	13 (29.5%)	3 (9.7%)	0.003**
Score 2	22 (50%)	10 (32.3%)	
Score 3	9 (20.5%)	18 (58.1%)	
Histological Grading			
Grade 1	22 (50%)	2 (6.5%)	<0.001**
Grade 2	18 (40.9%)	9 (29%)	
Grade 3	4 (9.1%)	20 (64.5%)	

Table 4: Relationship of HER-2 to the following clinicopathological features

Clinicopathological features	HER-2		
	Positive (n=44)	Negative (n=31)	p value
Menstrual Status			
Premenopausal	6 (18.2%)	11 (26.2%)	0.581
Perimenopausal	7 (21.2%)	11 (26.2%)	
Postmenopausal	20 (60.6%)	20 (47.6%)	
Tubule Formation			
Score 1	1 (3%)	12 (28.6%)	0.002

Score 2	13 (39.4%)	19 (45.2%)	
Score 3	19 (57.6%)	11 (26.2%)	
Nuclear pleomorphism			
Score 1	2 (6.1%)	11 (26.2%)	0.052
Score 2	20 (60.6%)	23 (54.8%)	
Score 3	11 (33.3%)	8 (19%)	
Mitosis Grading			
Score 1	3 (9.1%)	13 (31%)	0.0164*
Score 2	13 (39.4%)	19 (45.2%)	
Score 3	17 (51.5%)	10 (23.8%)	
Histological Grading			
Grade 1	3 (9.1%)	21 (50%)	<0.001**
Grade 2	14 (42.4%)	13 (31%)	
Grade 3	16 (48.5%)	8 (19%)	

Table 5: Clinicopathological correlation with immune histochemical subtypes

Clinical Variables	ER/PR+ & HER2neu- (n=30)	ER/PR+ & HER2neu+ (n=13)	ER/PR-HER2neu- (n=3)	ER/PR-& HER2neu+ (n=14)	p-value
Age (Min-Max) in Yrs	28-70	35-84	52-65	35-75	
Age in years	49.97±12.5	49.46±15.13	58.33±6.51	54.14±11.39	0.534
Duration in months	9.10±6.42	10.23±4.97	5.67±1.16	7.93±5.48	0.568
Tumor stage					
Stage I	2(6.7%)	0	0	0	0.044
Stage II	14(46.7%)	3(23.1%)	0	2(14.3%)	
Stage III	6(20.0%)	4(30.8%)	1(33.3%)	9(64.3%)	
Tumor Size					
<2 cms	3(10.0%)	1(7.7%)	0 (0%)	1 (7.1%)	0.422
2-5 cms	11(36.7%)	1(7.7%)	0 (0%)	4 (28.6%)	
>5 cms	16(53.3%)	11(84.6%)	3 (100%)	9 (64.3%)	
Lymphovascular Invasion					
Present	10(33.3%)	6(46.2%)	1 (33.3%)	12 (85.7%)	0.008**
Absent	20(66.7%)	7(53.8%)	2 (66.7%)	2 (14.3%)	
Cancer Type					
IDC (NOS)	28(93.3%)	13(100.0%)	3 (100%)	13 (92.9%)	
Lobular Carcinoma	1(3.3%)	0 (0%)	0 (0%)	0 (0%)	
Papillary Carcinoma	1(3.3%	0 (0%)	0 (0%)	0 (0%)	
Mucinous Carcinoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Medullary Carcinoma	0 (0%)	0 (0%)	0 (0%)	1 (7.1%)	
Apocrine carcinoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Tumor grade					
Grade I	19(63.3%)	3(23.1%)	1(33.3%)	0	<0.001**
GradeII	9(30.0%)	8(61.5%)	0	2(14.3%)	
Grade III	2(6.7%)	2(15.4%)	2(66.7%)	12(85.7%)	

ER positivity was noted in 27cases (47.4%) of post-menopausal women. ER positivity was most common with tubule formation, nuclear pleomorphism, and mitotic grade of score-2. Histologic grading in correlation with ER positivity was found to be statistically significant (p <0.001). 23(40.4%) of grade I, 24(42.1%) of grade II and 10 (17.5%) of grade III tumors were positive for ER. [Table 2]

PR positivity was noted in 22 cases (50%) of postmenopausal women. PR positivity was most common with tubule formation, nuclear pleomorphism and mitotic grade of score-2. Histologic grading in correlation with PR positivity was found to be statistically significant (p<0.001), 22 (50%) of grade I, 18(40.9%) of grade II and 4 (9.1%) of grade III tumors were positive for PR. [Table 3]

Out of 33 positive cases of HER-2/neu, 20cases (60.6%) were in postmenopausal women, followed by 7cases (21.2%) of perimenopausal and 6cases (18.2%) of premenopausal women.HER-2 positivity was most common with tubule formation and mitotic rate of score-3 and nuclear pleomorphism of score-2. Histologic grading in correlation with HER-2 positivity was found to be statistically significant ($p<0.001$). 16(48.5%) of grade III, 14(42.4%) of grade II and 3(9.1%) of grade I tumors were positive for HER-2 [Table 4].

As we have considered score -2+&3+ both as HER-2 positive cases, the number of cases in the post-menopausal age group appears more in our study.

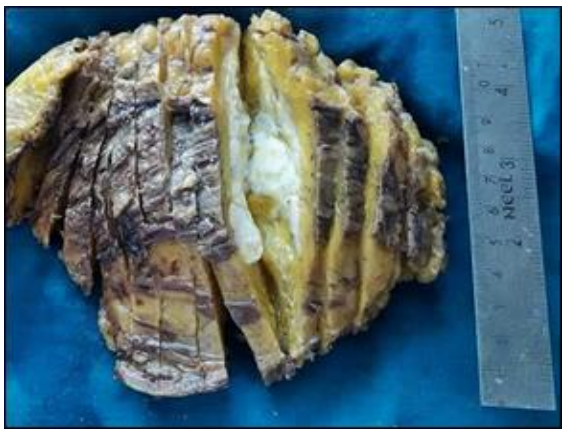

Figure 1(A): IDC(NOS): Gross specimen.

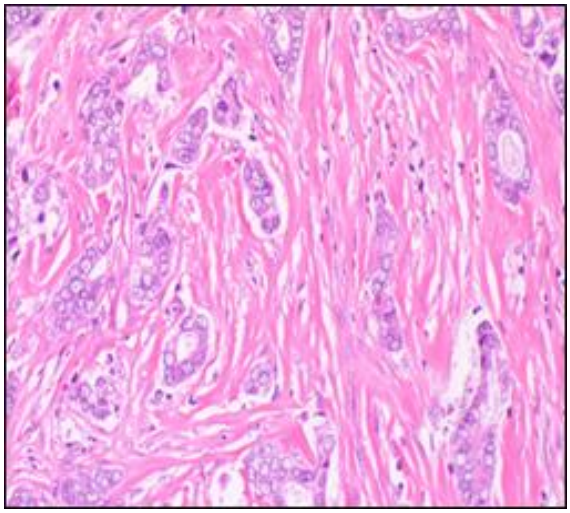

Figure 1(B): Grade I IDC(NOS) with predominant tubular pattern (x400H&E)

Subjects with ER/PR+ HER-2- were 30 in number, younger compared to the other subtypes, with more number of stage II cancer. Histologic grades were well correlated with the immune histochemical subtypes ($p<0.001$). 19 (63.3%) of grade I, 9 (30.0%)of grade II and 2(6.7%) of grade III tumors were ER/PR+, HER-2-, 3(23.1%) of gradeI, 8(61.5%) of grade II& 2 (15.4%) of grade III tumors were triple positive, 1 (33.3%) of grade I, 2 (66.7%) of grade III tumours were triple negative, and 2(14.3%) of grade II and 12 (85.7%) of grade III tumours were ER/PR-, HER-2+. Most of them were larger than 5cms, 10 (33.3%) showed LVI. Majority 93.3%were IDC (NOS).There were13 triple positive cases, most were larger than 5cms, and all of them were IDC (NOS).The triple negative cases were only 3 and all were larger than 5cms with IDC (NOS) type. There were 14ER/PR-, HER-2+cases, the patients were older in this subtype, 9 (64.3%) were larger than 5cms and in stage- III,12 (85.7%) showed LVI and majority 13 (92.9%) were IDC (NOS) [Table 5]

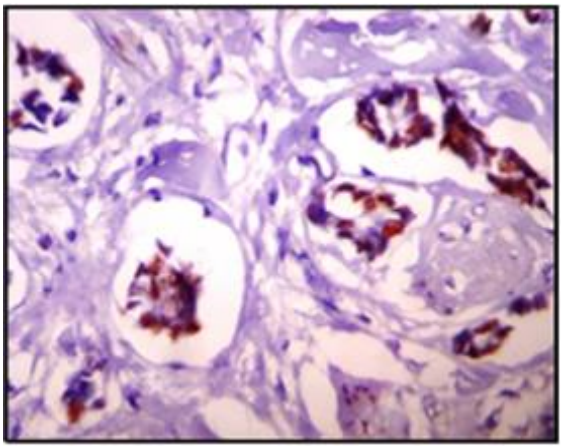

Figure 2A:Grade1 IDC showing ER of score positivity (x400)

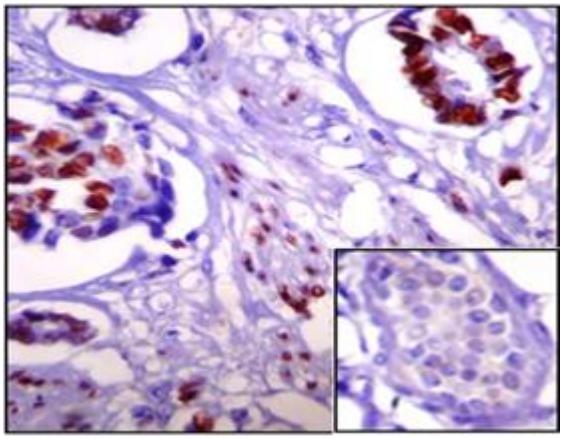

Figure 2B:Grade 1 IDC showing PR -8 nuclear positivity of score-8, inset shows HERR-2 negativity (x400).

DISCUSSION

As breast cancer being the most common cancer among women in India and in many regions of the world, constant research on prognostic and predictive markers of breast carcinoma are going on. Classic variables such as histologic type and grade, tumor size, lymph node status, status of hormone receptors–Estrogen receptor (ER) and Progesterone receptor (PR) of the tumor, and more recently HER-2/neu status influence the prognosis and management.5 So, we took to study these important

prognostic markers and correlate with the histological grading of breast cancers. Our study is a prospective study which included 75 cases of breast cancers which were proven histopathologically during the period of August 2017 to July 2019

In the present study, age at presentation ranged from 21-85 years with a mean age of 51.04 years which is similar to the observations made by Pathak TB et al6 where the age range was between 21-80 years with the mean age being 48 years.

In the present study 49(65.3%) tumors were more than 5cms, which was higher when compared to other studies, Raina V et al (l6%) and Pawan Nikhra et al (13.9%).[7,8]

In the present study 69 (92.0%) were Invasive ductal carcinoma (NOS). Similar observation was made by Peiro G et al 9(94.3%) Zafrani B et al (77%).[9,10] Other types of carcinomas had varied incidence in different studies.

In the present study, histological grading was done using Modified Bloom Richardson grading, majority 36% were grade II. Similar observations were made by Zafrani B et al (40)%, Le Doussal et al (55%) and Piero G et al (37.1%).[9-11]

In our study majority of tumors were larger measuring >5cm and therefore, lymphnode metastasis was noted in more number of cases (52%), when compared to other studies Zafrani B et al (37%) and Huang JH et al (35.4%).[10,12]

Lymphovascular invasion was noted in more number of cases (48%) in the present study when compared to Zafrani B et al (36%), Peiro G et al (31.4%)and Chandrika Rao et al (19.1%).[9,10,13]

Huang JH et al,[12] have shown that subjects with ER/PR+, HER-2- subtypes were more likely to be older and postmenopausal when compared to premenopausal ones. Our study also shows similar results.

Table 6: Association of ER, PR expression with HER-2 status

Immunohistochemical subtypes	Onitilo AA et al (%)[14]	Huang JH et al (%)[12]	Present study %
ER/PR+, HER2-	68.9	66.4	50
ER/PR+, HER2+	10.2	30.9	21.7
ER/PR-, HER2-	13.4	13.8	5
ER/PR-, HER2+	7.5	45.6	23.3

Present study data are consistent with those of other published studies like those of Huang JH et al,[12] Onitilo AA et al,[14] in that ER and or PR expression is generally correlated inversely with HER-2 overexpression. However, a substantial number of HER-2+ tumors still expressed ER and or PR. In our study they constitute 21.7% [Table 6].

- Lal P et al,[5] Ayadi L et al,[15] and other studies in literature demonstrated high ER, PR positivity with IDC (NOS) invasive lobular carcinomas and mucinous carcinomas. But medullary carcinomas evoked controversial results. When HER-2 status was analysed according to histologic features, HER-2 positivity was limited to IDC (NOS). In our study 1 each of medullary and apocrine carcinomas were positive for HER-2.1 papillary carcinoma was positive for both ER& PR and negative for HER-2.

Table 7: Comparison of Immunohistochemical subtypes with Histologic grading

Immunohistochemical Subtypes (%)	Histologic Grades						
	Onitilo AA et al			Present study			p-Value
	Grade I	Grade II	Grade III	Grade -I	Grade II	Grade III	
ER/PR+, HER2-	28.9	44.9	21.5	63.3	30	6.1	<0.001
ER/PR+, HER2+	6	41.4	49.1	23.1	61.5	15.4	
ER/PR-, HER2-	4	12.5	76.3	33.3	0	66.7	
ER/PR-, HER2+	1.2	20	77.7	0	14.3	85.7	

Onitilo AA et al,[14] Ayadi L et al,[15] Huang JH et al,[12] Perio G et al,[9] and Lal P et al,[5] have shown that well differentiated tumours express hormone receptors with decreased expression of HER-2. In our study 63.3% of Grade-I tumours expressed both ER, PR with negative HER-2 expression while only 6.1% of grade III were this subtype. None of the grade I ER/PR- tumors expressed HER-2.85.7%of Grade-III tumors expressed HER-2 with negative ER/PR expression, indicating that poorly differentiated tumors have less hormone receptors with increased HER-2expression. Therefore overexpression of HER-2 is inversely related to ER/PR status. [Table 7] Stierer Metal16correlated individual characteristics like tubule formation, nuclear plemorphism and mitotic rate with steroid receptor status. They concluded that there was no correlation between tubule formation and ER content while nuclear pleomorphism and rate of mitosis showed significant correlation. ER and PR expression in nuclear grade 2 tumors was significantly higher than that in nuclear grade III tumors (ER&PR, p<0.01).However, HER-2, positivity was also noted in nuclear grade-II tumors. Our findings were similar to other studies as in Lal P et al & Peiro G et al.[5,9]

Large tumors of >5cms with ER/PR positivity & HER-2 negativity had less lymphovascular invasion (33.3%) when compared to the ER/PR-,HER-2+ subgroup (85.7%). These findings were comparable with the findings of Onitilo AA et al,[14] & Peiro et al,[9] 64.3% tumors of ER/PR-,HER2+ subgroups were in stage III and 20% of tumours of ER/PR+,HER-2+ subgroup were in stage III. This

reflects the higher incidence of metastasis and aggressive biologic behaviour with HER-2 overexpression. [Table 5]

CONCLUSION

Over the last few decades these have been outstanding advances in breast cancer diagnosis and management. Recently anti-HER-2 antibodies (Herceptin) have been shown to be effective against HER-2 overexpressing breast carcinomas.

In this study an attempt was made to understand the correlation of ER, PR&HER-2 status with histopathological grading and clinicopathological parameters. In conclusion, ER, PR and HER-2 status correlates well with histopathological grading and other clinico-pathological parameters. Higher grade is associated with HER-2 positivity and ER/PR negativity, tumor size, lymphovascular invasion, lymphnode metastasis, and higher clinical stage.

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