Correlation of Expression of Estrogen Receptor, Progesterone Receptor and Human Epidermal Growth Factor Receptor-2 with Histopathological Grade in Cases of Carcinoma Breast

Saurabh Juneja[1], Ruchi Agarwal[2], Deepti Agarwal[3], Parveen Rana[4], Kulwant Singh[5], Swaran Kaur[6]

ABSTRACT

Introduction: Breast carcinoma is the most common cancer among women in both developing and developed countries. It needs alarming attention because it causes high morbidity and mortality. There is a need to understand the initiation and progression of breast cancer on hormonal, cellular and molecular basis which forms the platform for designing of targeted therapy. This study was intended to find correlation between the expression of Estrogen receptor, Progesterone receptor and Human Epidermal Growth Factor Receptor-2 with histological grade in cases of carcinoma breast.

Material and methods: This study was conducted in the Department of Pathology at Bhagat Phool Singh Government Medical College for Women, Khanpur Kalan, Sonepat on 55 histologically confirmed breast cancer cases.

Results: The age of the patients ranged from 27 to 70 years and the mean age was 51.56 ± 11.39 years. Invasive ductal carcinoma - no special type was the most common histological type(92.72%). The most common histological grade observed was grade II i.e. 61.82%. Lymph nodes involvement was seen in 55.32% of the cases. ER, PR and HER-2/neu positivity was observed in 45.45%, 47.27% and 25.45% of the cases respectively. ER and PR were found to correlate with histological grade ($p<0.05$) while no correlation was observed between HER-2/neu and histological grade($p>0.05$).

Conclusion: Evaluation of ER, PR, and HER-2/neu status should be incorporated routinely as a part of histopathology reports in all cases of breast carcinoma as they not only help in assessment of prognosis, but also help in deciding management and improving overall survival.

Keywords: Carcinoma Breast, Estrogen Receptor, Histological Grade, Human Epidermal Growth Factor Receptor-2, Progesterone Receptor.

INTRODUCTION

Breast carcinoma is the most common cancer among women, affecting 2.1 million women each year, and also causes the highest number of cancer-related deaths among women. In 2018, 20,88,849 new cases were reported and 6,26,679 women died of carcinoma breast in the world.[1]

Breast cancer has been ranked as most common cancer among Indian females with age standardized incidence and mortality rates as high as 24.7 per 100,000 women and 13.4 per 100,000 women respectively in 2018 according to the global cancer observatory data.[1,2] According to GLOBOCAN data, 1,62,468 new cases and 87,090 deaths were reported for breast cancer in India in 2018. With an incidence of 14% cases, it has become most common cancer among females and even overall.[2]

Several histopathological features have prognostic significance in cases of carcinoma breast including histologic subtype, grade, lymph node status, estrogen receptor (ER) and progesterone receptor (PR) status, human epidermal growth factor and its receptors, proliferation activity and DNA content, oncogenes and tumor suppressor genes.[3] There is a need to understand the initiation and progression of breast cancer on hormonal, cellular and molecular basis to design the targeted therapy as early diagnosis and potential curability with proper treatment of early breast lesions can lead to improvement in mortality due to breast cancer.[4]

ER being a nuclear transcription factor, upon stimulation by estrogen stimulates cell proliferation in mammary cells which leads to increase in the rate of cell division and DNA replication, resulting in tumorigenesis and mutations. This results in cell cycle disruption, apoptosis and DNA repair therefore leading to tumor formation. PR is an intracellular steroid binding specifically to progesterone and expressed by a single gene (chr 11q22). PR is also a nuclear receptor, presence of which depicts a functional ER pathway, so positivity for both ER and PR is seen in various histological types of breast carcinoma. The presence of hormone receptors (ER and PR) in the tumor tissue has been found to correlate well with the response to hormone therapy and

[1]PG student 3rd year, Department of Pathology, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, [2]Associate Professor, Department of Pathology, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, [3]Associate Professor, Department of Pathology, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, [4]Associate Professor, Department of Pathology, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, [5]Associate Professor, Department of Pathology, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, [6]Professor, Department of Pathology, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, India

Corresponding author: Dr. Ruchi Agarwal, Associate Professor, Department of Pathology, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, India

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chemotherapy. Human epidermal growth factor receptor-2 (HER-2/neu) proto-oncogene (erb-2) present on chromosome 17, encodes a transmembrane phosphoglycoprotein having tyrosine kinase activity related to epidermal growth factor receptor on cell membrane. Its overexpression indicates low response to tamoxifen and decreased survival according to several studies.[5,6]

ER and PR status on invasive carcinoma biopsies prior to any therapeutic interventions has become a standard practice in the management of breast carcinoma. ER positive tumors respond more likely to hormonal therapy and thus have better prognosis. PR positivity in addition to ER increases the likelihood for response to hormonal therapy.HER-2/neu initially considered as a marker for poor prognosis, is now also valued in selection of patients for herceptin therapy.[5,7] Conventional histopathological grading along with hormone receptor status analysis has become a prerequisite for management and prognosis of breast carcinomas in this era.[8] Present study was intended to find correlation between the expression of ER, PR and HER-2/neu with histological grade in cases of carcinoma breast. It can be useful in finding diagnostic and therapeutic use of this procedure in management of breast lesions at our institute.

MATERIAL AND METHODS

This study was conducted in the Department of Pathology at Bhagat Phool Singh Government Medical College for Women, Khanpur Kalan, Sonepat. It was a cross sectional study in which 55 breast cancer cases was included. Ethical clearance was obtained from the institutional ethical committee. Written informed consent from all the cases included was taken. Mastectomy specimens of breast cancers other than carcinoma and cases who had received chemotherapy prior to mastectomy were excluded. Patient's confidentiality was ensured by deidentifying the data. Clinical information and relevant investigation findings were collected from the case sheet and requisition form sent by the treating clinician. Received specimen were grossed, processed and stained accordingly. Hematoxylinand eosin stained sections were studied to determine the histological type and grade of the tumor. Nottingham's modification of Bloom Richardson grading system was used to classify the cases into histological grades.[9] Immunohistochemistry slides were examined to determine the ER, PR and HER-2/neu status. Quick scoring system was used for ER and PR quantification.[10] The ASCO/CAP (American Society of Clinical Oncology and the College of American Pathologists) guidelines 2018 were used for interpretation of HER-2/neu and cases were classified into scores of 0,1+, 2+ and 3+.[11] Nottingham's prognostic index (NPI) was used to define the prognosis as good, moderate and poor.[12]

Statistical Methodology: Mean ± SD and percentage were used for statistical analysis of quantitative data. Correlation was found out using relevant coefficient. Chi-square test was used. The results then obtained were compared statistically for significance and p value < 0.05 was considered statistically significant.

RESULTS

All the 55 cases included in the study were females. The age of the patients ranged from 27 to 70 years. The maximum number of cases i.e. eighteen cases (32.72%) were found in the age group of 51-60 years followed by 30.9% cases in age group of 41-50 years. The mean age was 51.56 ± 11.39 years. The most common histological type of breast carcinoma diagnosed was invasive ductal carcinoma - no special type i.e. 51 cases (92.72%). Two cases of invasive lobular carcinoma (3.64%) and one case each of papillary carcinoma (1.82%) and medullary carcinoma (1.82%) were also reported. The most common histological grade observed was

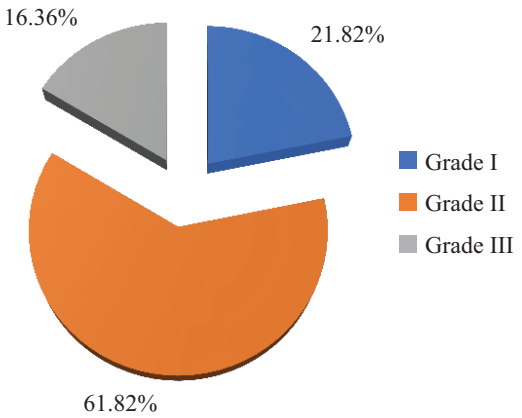

Figure-1: Distribution of cases according to histological grade of breast carcinoma using Nottingham's modification of Bloom Richardson grading system

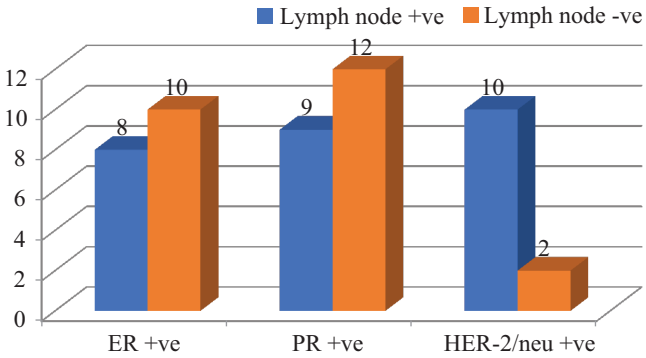

Figure-2: Distribution of ER, PR and HER-2/neu positive cases according to axillary lymph node status

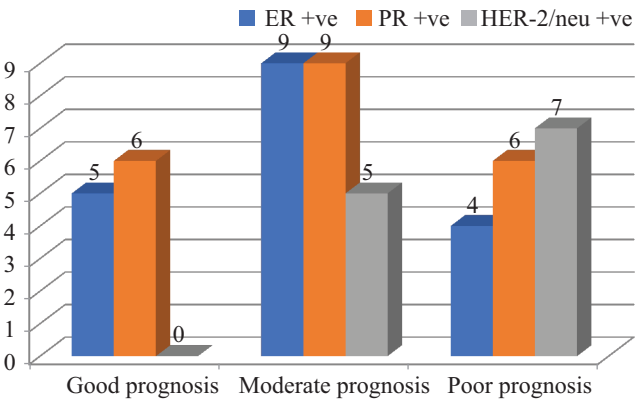

Figure-3: Distribution of ER, PR and HER-2/neu positive cases according to NPI

Histological grade	Grade I		Grade II		Grade III		Total	
	n	%	n	%	n	%	n	%
ER	9	75	15	44.11	1	11.11	25	45.45
PR	9	75	16	47.05	1	11.11	26	47.27
HER-2/neu	2	16.66	9	26.47	3	33.33	14	25.45
Total	12	21.82	34	61.82	9	16.36	55	100

Table-1: Cumulative grade-wise positivity of ER, PR and HER-2/neu in the study group

Histological Grade	Grade I		Grade II		Grade III		Total	
	N	%	N	%	N	%	N	%
ER +ve / PR +ve	6	50	10	29.41	1	11.11	17	30.9
ER +ve / PR -ve	3	25	5	14.7	0	0	8	14.54
ER -ve / PR +ve	3	25	6	17.64	0	0	9	16.36
ER -ve / PR -ve	0	0	13	38.23	8	88.89	21	38.18
Total	12	100	34	100	9	100	55	100

Table-2: Distribution of hormone receptors with histological grade

IHC Markers n(%)	ER +ve		ER -ve		PR +ve		PR -ve	
	n	%	n	%	n	%	n	%
HER-2/neu +ve 14 (25.45)	2	14.29	12	85.71	3	21.43	11	78.57
HER-2/neu -ve 41 (74.55)	23	56.1	18	43.9	23	56.1	18	43.9
Total = 55 (100)	25	45.45	30	54.55	26	47.27	29	52.72

Table-3: Association of HER-2/neu status with ER and PR expression

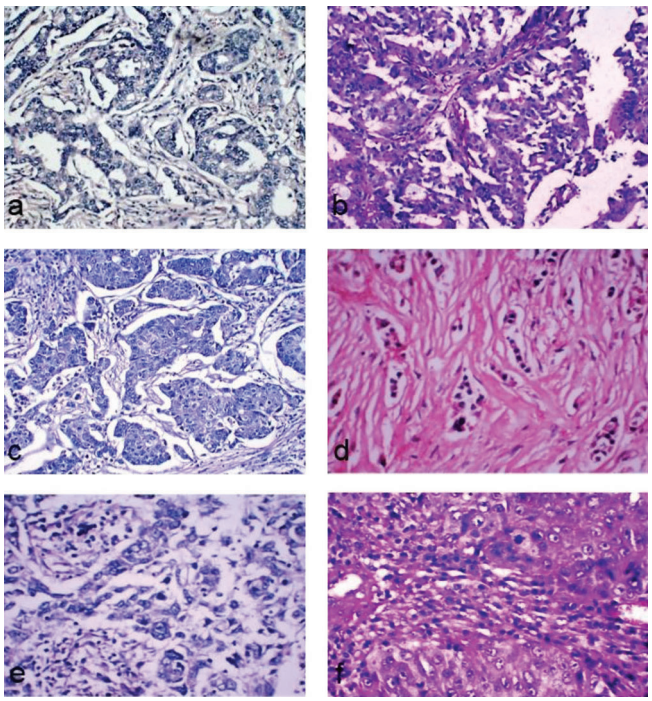

Figure-4: (a) Invasive ductal carcinoma-no special type, grade I showing tubule formation and mild nuclear pleomorphism [H&E, 200X], (b) Tissue section showing papillary carcinoma, grade I [H&E, 200X], (c) Invasive ductal carcinoma-no special type, grade II showing sheets of tumor cells with moderate nuclear pleomorphism. [H&E, 200X], (d) Invasive lobular carcinoma, grade II showing uniform small round cells [H&E, 400X], (e) Invasive ductal carcinoma-no special type, grade III showing sheets of tumor cells with moderate nuclear pleomorphism and mitosis. [H&E, 400X], (f) Medullary carcinoma, grade III showing poorly differentiated tumor cells with mitotic figures [H&E, 400X].

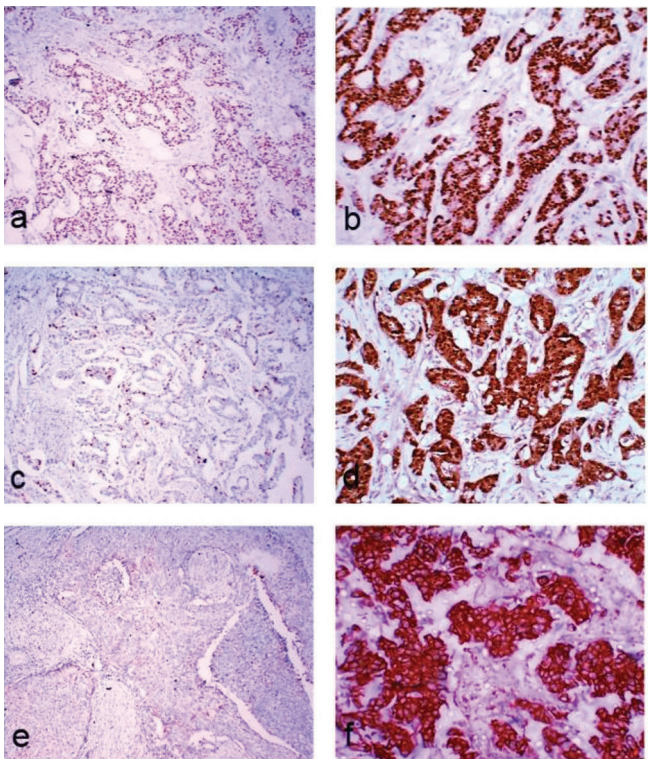

Figure-5: (a) Invasive ductal carcinoma showing immunostaining for ER, score 5 [ER, 100X], (b) Invasive ductal carcinoma showing immunostaining for ER, score 8 [ER, 400X], (c) Invasive ductal carcinoma showing immunostaining for PR, score 4 [PR, 100X], (d) Invasive ductal carcinoma showing immunostaining for PR, score 8 [PR, 400X], (e) Invasive ductal carcinoma showing immunostaining for HER-2/neu, score 1+ [HER-2/neu, 100X], (f) Invasive ductal carcinoma showing immunostaining for HER-2/neu, score 3+ [HER-2/neu, 400X].

IHC Marker	Nisa et al[18] 2008 (%)	Nikhra et al[25] 2014 (%)	Yadav et al[28] 2016 (%)	Verma et al[14] 2018 (%)	Singh et al[15] 2019 (%)	Present study (%)
ER	32.7	39.5	42.3	54.68	56	45.45
PR	25.3	41.8	37.6	42.18	38.0	47.27
Her-2/neu	24.7	32.5	56.2	29.68	30	25.45

Table-4: Comparative analysis of overall expression of ER, PR and HER-2/neu with previous studies.

grade II (61.82%) followed by grade I (21.82%) and grade III (16.36%) tumors [Figure 1].

Out of total 55 cases, lymph nodes were isolated in 47 cases (85.45%). Lymph nodes were positive for metastases in 26 cases (55.32%). On classification of cases according to NPI, most of the cases were in moderate prognostic group (46.8%) followed by poor prognostic group (38.3%). On comparison of axillary lymph node status according to histological grade, lymph node involvement was maximally observed in histological grade II (60.71%) followed by grade III (50%) and grade I (45.46%). On comparing histological types of breast carcinoma with lymph node status, 24 out of 43 cases (55.81%) of the cases of invasive ductal carcinoma showed positive lymph node involvement while both the cases of invasive lobular carcinoma showed lymph node involvement.

The overall positivity for estrogen receptor was found to be positive in 45.45% of cases. On comparing receptor positivity with histological grade, the positivity for ER decreased with increasing grade with maximum positivity in grade I (75%) followed by grade II (44.11%) and grade III (11.11%). The correlation between estrogen receptor positivity and histological grade was found to be statistically significant (p= 0.014). Progesterone receptor status was found to be positive in 47.27% of cases. With increasing histological grade, the positivity for progesterone receptor was reported to decrease. Maximum percentage of PR positivity was observed in grade I (75%) which declined subsequently in grade II (47.05%) and grade III (11.11%). The correlation between progesterone receptor positivity and histological grade was also found to be statistically significant (p= 0.015). A total of 25.45% of the cases showed HER-2/neu overexpression in the present study. HER-2/neu positivity was found to increase along with the histological grade with maximum positivity in grade III (33.33%) followed by grade II (26.47%) and grade I (16.66%). However no significant statistical correlation was found between HER-2/neu status and histological grade. (p>0.05) [Table 1].

Association of hormone receptors with histological grade was calculated which showed maximum cases 21 (38.18%) to be ER -ve / PR -ve followed by ER +ve / PR +ve: 17 cases (30.9%), ER -ve / PR +ve: 9 cases (16.36%) and ER +ve / PR -ve: 8 cases (14.54%) [Table 2].

On comparing HER-2/neu overexpression with ER and PR status, it was observed that in HER-2/neu negative cases, ER positivity was seen in 56.1% cases and also PR positivity was seen in 56.1% of the cases. A statistically significant inverse relationship was obtained between HER-2/neu and ER (p<0.05) and also HER-2/neu and PR (p<0.05) [Table 3]. The overexpression of HER-2/neu was more frequently observed in lymph node positive cases while ER and PR positivity was more frequently observed in lymph node negative cases [Figure 2].Most of the ER positive and PR positive cases were found to be in moderate prognostic group while HER-2/neu positivity was seen more frequently in poor prognostic group [Figure 3].

Triple positivity of both hormone receptors and HER-2/neu overexpression were observed in 3.6% of the cases while 18.18% of the cases were found to be triple negatives. All the triple positive cases were of histological grade I. Triple negativity was seen in 55.55% of the cases of grade III and 14.7% of the cases of grade II. No triple negative case was seen in grade I.

DISCUSSION

Prognosis and management of breast cancer are very much influenced by prognostic factors such as histological type and grade, lymph node involvement, hormone receptor status and HER-2/neu overexpression. In our study, the maximum number of 18 cases (32.72%) was found in the age group of 51-60 years. Seventeen cases (30.9%) were found in age group of 41-50 years. Our study correlated well with the study of Nabi et al.[13] having maximum number of cases found in the age group of 51-60 years (33.81%). Bhagat et al.[3], Verma et al.[14] and Singh et al.[15] reported maximum number of cases as 41.37%, 43.75% and 48.15% respectively in the age group of 41-50 years. The most common histological type of breast carcinoma diagnosed in the present study was invasive ductal carcinoma (no special type) in 51 cases (92.72%). It was also reported as the predominant histological type in the studies by Bhagat et al.[3], Thiygarajan et al.[16], Tiwari et al.[17] and Verma et al.[14] as 94.82%, 84.3%, 81.17% and 87.5% respectively.

In our study, majority of the cases presented with grade II tumors (61.82%), followed by grade I (21.82%) while least number of the patients belonged to grade III (16.36%). Grade II had also been observed as the most common grade by the studies of Nisa et al.[18] (55.33%), Ahmed et al.[19] (55.2%), Bhagat et al.[3] (43.1%), Geethmala et al.[20] (54.0%) and Tiwari et al.[17] (68.7%).

We reported lymph node positivity as 55.32%. Our findings correlated well with the studies of Bhagat et al.[3] and Thiyagarajan et al.[16] with lymph node involvement seen in 53.44% and 53.3% of the cases respectively. However, Ahmed et al.[19], Nisa et al.[18] and Siadati et al.[8] had a higher incidence of lymph node involvement i.e. 75.3%, 71.3 and 85.67% respectively. On calculating NPI, we reported most of the cases in moderate prognostic group (46.8%) followed by poor prognostic group (38.3%) and good prognostic group (14.9%). Similar findings were observed in studies

by Vedashree et al.[21], Agarwal et al.[22], Thangjam et al.[23] and Shukla et al.[24]

We observed that positivity for estrogen receptor decreased as the grades increased. Maximum percentage of ER positivity was observed in cases with grade I (75%) which declined in grade II (44.11%) followed by grade III (11.11%). The findings show close resemblance with various studies conducted by Nisa et al.[18], Nikhra et al.[25], Gore et al.[26], Verma et al.[14] and Singh et al.[15] Positivity for PR also decreased as the grades increased in our study. Maximum percentage of PR positivity was observed in grade I (75.0%) which declined subsequently in grade II (47.05%) and grade III (11.11%). Similar findings were observed in studies conducted by Nisa et al.[18], Verma et al.[14], Gore et al.[26], Nikhra et al.[25] and Singh et al.[15] On comparing HER-2/neu positivity with histological grade, we found that the positivity for HER-2/neu increased with increasng histological grade. Overexpression of HER-2/neu was found to be maximum in grade III (33.33%) followed by 26.47% of cases in grade II and 16.66% of cases in grade I. However no statistical significance was observed ($p > 0.05$) on comparing grade and HER-2/neu overexpression. Similar findings were reported by Nisa et al.[18], Bhagat et al.[3], Vedashree et al.[21] and Gore et al.[26]

Overall, ER positivity was observed in 45.45% cases while PR positivity was seen in 47.27%. HER-2/neu overexpression was seen in 25.45% cases in present study. Similar findings were obtained in studies of Nisa et al.[18], Verma et al.[14], Nikhra et al.[25] and Singh et al.[15] In a study by Desai et al.[27] in 2000 at Mumbai, ER positivity was reported in 33% cases while PR positivity in 46% cases. However Yadav et al.[28] in 2016 reported a high positivity of HER-2/neu in 56.2% cases. The disparity can be explained by regional variations and variation in sample size [Table 4].

On comparison of HER-2/neu with ER and PR positivity, it was observed that in HER-2/neu positive cases, ER was positive in 2 cases (14.29%) and PR was positive in 3 cases (21.43%). In HER-2/neu negative cases, ER was positive in 23 cases (56.1%) and PR was positive in 23 cases (56.1%) of the cases. A statistically significant inverse relationship was obtained between HER-2/neu and ER ($p=0.007$) and also HER-2/neu and PR ($p=0.025$). Similar strong inverse relationship was demonstrated by study conducted by Almsari et al.[29], Huang et al.[30], Puvitha etal.[31] and Yadav et al.[28] also reported inverse relationship between ER and PR positivity with HER-2/neu overexpression.

We observed 18.18% triple negative cases in our study. The association between triple negative receptor status of tumors and histological grading was found to be statistically significant ($p= 0.003$). These findings are in agreement to those observed in studies of Geethmala et al.[20], Verma et al.[14] and Singh et al.[15] where triple negative cases were found to be 20.0%, 28.12% and 30.0% respectively and the pattern of grade-wise percentage of triple negative cases increased with histological grade. In our study, two cases (3.6%) were found to be triple positives andboth the cases belonged to histological grade I. This indicates that HER-2/neu positivity does not always translate to worst survival. In a study coonducted by Bauer et al.[32], excellent survival of patients with ER +ve breast carcinoma irrespective of HER-2/neu status was reported. Therefore, ER negativity appears to be a stronger predictor of poor survival than HER-2/neu positivity. Geethmala et al.[20] found 1% triple positive cases while Gupta et al.[7] in 2015 found 6.0% triple positive cases in their study.

CONCLUSION

Carcinoma breast is the most common cancer among Indian females and rising at an alarming pace in our population. Prognosis and management of breast cancer are very much influenced by various prognostic factors. A statistically significant correlation with histological grade was observed for ER and PR. However HER-2/neu expression did not show any statistically significant correlation with histological grade. On comparing HER-2/neu overexpression with ER and PR status, a statistically significant inverse correlation was observed. These findings reflected the importance of these biomarkers as they provide valuable information for the best therapeutic intervention of the breast carcinoma patients. Immunohistochemical assessment of these biomarkers improves the prognostic accuracy of histopathological assessment along with grading of breast carcinoma.

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