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Correlation of estrogen receptor and Her-/2neu receptor with age, lymph node status, apoptotic index and mitotic index

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Abstract

Introduction: Tumor markers are done to screen, help diagnosis, staging, determine prognosis, guide treatment, monitor treatment and determine recurrence. They define a particular disease entity and are targets for therapeutic intervention in clinical trials. Thus, the current study of IHC of Her-2/neu and estrogen receptor along with mitotic index and apoptotic index in human breast cancer is carried to determine the prognosis of the patients. Furthermore, no such comparative study has been carried out in this region to know the incidence of these markers along with their statistical importance and interrelationship with various parameters.

Material and Methods: The present study was conducted on 160 cases of carcinoma breast which were received as lumpectomy (15) or mastectomy (145) specimens in the Department of Pathology. Histopathological grading of the breast carcinoma was done on the H&E sections. Mitotic index and apoptotic index was calculated on the H&E stained slides. The sections were further stained immune histochemically for the Estrogen Receptor and Her-2/neu marker.SPSS programme was used for calculating statistical values.

Results: ER positivity was seen in 17.5 % of the cases with percentage of positive cells varying from 10 – 92 %. It was found that ER positivity has no direct relationship with age, tumor size and lymph node status but is inversely proportional to the grade. Her-2/neu receptor positivity was observed in 18.1% of the cases which were ER negative. Percentage positive cells varied from 12 – 92%.While comparing the two markers statistical difference was seen in age (p=0.0106) and lymph node metastasis (p=0.046). But no difference was seen in tumor size, AI and MI. ER positivity was more in lower grades as compared to Her-2/neu which was seen more in higher grades.

Conclusion: All the cases should be screened for ER. All the cases which are ER negative especially in higher grades should be evaluated for Her-2/neu (incidence is 18.1% in the present study) as these cases respond very well to adjuvant chemotherapy and cytotoxic therapy thus prolonging the survival time and resulting in better prognosis.

Keywords: Estrogen receptor; Her-/2neu receptor;Tumor markers

Introduction

Many tumor markers are detected by IHC particularly of breast carcinoma. Tumor markers are the biochemical indicators of the presence of tumor. They include cell surface antigens, cytoplasmic proteins, enzymes and hormones. Tumor markers can be produced directly by the tumor or by non-tumor cells as a response to the presence of a tumor. They are done to screen, help diagnosis, staging, determine prognosis, guide treatment, monitor treatment and determine recurrence. They define a particular disease entity and are targets for therapeutic intervention in clinical trials.[1]

According to guidelines by American Society of Clinical Oncology Estrogen Receptor, Progesterone receptor and Her-2/neu are recommended to measure on every breast cancer and on metastatic lesions if the results influence treatment planning. DNA flow cytometry for S phase content along with CEA is not recommended.[2]

Her-2 neu is a protooncogene that is amplified in some of the human breast cancers.[3]It is associated with a more aggressive phenotype. Her-2/neu over expressing tumors are known to be refractory to various types of chemotherapy and endocrine therapy to be associated with shortened overall survival, especially in node positive patients.[4,5]

Breast cancer was the first tumor type in which abnormalities of Her-2/neu gene copy number or expression were associated with reduced disease free and overall survival. It is accepted universally as the new prognostic marker and predictor of therapeutic response in carcinoma breast.[6]There is increasing clinical demand for Her-2/neu analysis in breast cancer, especially since the release of transtuzumab.[7]

Estrogen receptor assays predict clinical response correctly in about 2/3rd of patients with estrogen receptor positive tumors i.e., two third of ER positive tumors respond to hormonal manipulators whereas virtually all (96%) of the ER negative tumors fail to respond to endocrinal therapy. Similarly, Estrogen Receptor positive tumors have a longer disease free survival as compared to estrogen receptor negative tumors.[8]In Indian studies Estrogen Receptor positivity in breast tumors was reported as varying from, 24 %, 31.6% to 32.6%.[9-11]

Apoptosis and mitosis are two important indices of the cell growth and death respectively.[12]High apoptotic index is associated with tumour necrosis, lack of tubule formation, dense stromal lymphocytic infiltration, high

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grade of tumor, DNA aneuploidy, high S phase fraction, high mitotic rate, lack of sexual steroid receptors and expression of tumor suppressor genes.[13]Mitotic index, which is increased in malignant tumors indicates the rate of cellular proliferation and grade of the tumor. It is the oldest way of measuring proliferation activity and gives very useful information.[12]

Thus, the current study of IHC of Her-2/neu and estrogen receptor along with mitotic index and apoptotic index in human breast cancer plays an important role in determining the prognosis of the patients. Furthermore, no such comparative study has been carried out in this region to know the incidence of these markers along with their statistical importance and interrelationship with various parameters.

Material and Methods

The present study was conducted on 160 cases of carcinoma breast which were received as lumpectomy (15) or mastectomy (145) specimens in the Department of Pathology, Government Medical College, Amritsar. The history and clinical findings regarding age, site, duration etc were recorded according to the proforma attached. The Histopathological grading of the breast carcinoma was done on the H&E sections according to the Nottingham modification of the Bloom Richardson grading system.[14,15] Tumor areas with nuclei having maximum atypia in size and shape were observed. Mitotic figures were counted only at the periphery of the tumor. 10 high power fields were counted in the same area (but not necessarily contiguous) in the fields which were filled with as much tumor as possible. Poorly preserved areas were not observed. Cells in the prophase were ignored.

Mitotic index was calculated by counting mitotic activity among 1000 tumor cells using 40x objective and then calculating in 100 cells.Apoptotic cells and bodies were counted among 1000 cells using 40x objective and apoptotic index was calculated in 100 cells.Areas of necrosis and inflammation were excluded from the count.Mitotic index and Apoptotic index were also calculated on the H&E stained slides. The sections were further stained immunohistochemically for the Estrogen Receptor and Her-2/neu marker.

Immunohistochemistry of the tumors was done for Her-2/ neu and Estrogen Receptor.Antigen retrieval was done by using the pressure cooker..The primary antibody for Her-2/neu was put on the sections and sections were kept overnight in the moist chamber.The biotinylated secondary antibody was applied for 30 minutes at room temperature.Haematoxylin counterstaining was done for 2-5 minutes and sections were washed under running tap water. For IHC procedure of Estrogen Receptor all the steps were same as given above except that Primary antibody for Estrogen Receptor was used instead of Her-2 neu primary antibody.

For interpretation of results, brown colour of the cell membrane was taken as positive for Her-2/neu and brown nuclei were taken as positive for Estrogen Receptor. Cytoplasmic brownish colouration was ignored in both the receptors.

Positive and negative controls were run with every batch of the IHC.

Endometrium was taken as positive control for Estrogen Receptor and Positive control cell line was provided by the company for Her-2/neu and afterward the tissue of the case showing positivity was taken as positive control for Her-2/neu receptor.Table 1 shows criteria for scoring of immunoreactivity for HER-2/NEU.

Table 1: Scoring of immunoreactivity for HER-2/NEU

%age positivity	Score	Staining Intensity	Score
<10	0	Negative	0
10- 25	1	Low	1
25-50	2	Moderate	2
>50	3	Strong	3

The percentage positive tumor cells and staining intensity were multiplied to get the final score which ranged from 0-9.All the cases with more than 10 % positive tumor cells were taken into consideration and the score 0-1 were taken as negative and 2& more than 2 were reported to be positive.

Another scoring system used for the scoring of Her-2/neu was by taking into account staining intensity only as shown below:

Score 0: No evident staining or membrane staining in less than 10% tumor cells.

Score 1: Partial staining in more than 10% tumor cells.

Score 2: Complete weak to moderate staining of more than 10% tumor cells.

Score 3: Strong complete staining of more than 10% tumor cells.

Only membrane staining of tumour cells was considered as positive.

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Table 2: Scoring of estrogen receptor

Percentage positivity	Score	Staining intensity	Score
<25 %	1	Low	1
25–50 %	2	Moderate	2
50–75 %	3	Strong	3
>75 %	4		

Table 2 shows scoring method of estrogen receptor. The percentage positive tumor cells and staining intensity were added to get the final score which ranged from 2- 7.All the cases with more than 10% tumor cells were taken into scoring system.SPSS programme was used for calculating statistical values.

Results

Estrogen Receptor was positive in 28 cases while Her-2/neu Receptor was positive in 29 cases (figure 1). One case showed positivity for both the receptors. The mean age of the patients with ER positivity was 50.1 and for Her-2/neu positive was 44% (figure 2). So, ER positive patients were older than the Her-2/neu positive patients ($p = 0.0106$, student's t test).Skin involvement was observed more in ER positive cases (12.3%) as compared to 5.3 % in Her-2/neu positive cases (figure 3).

Outer quadrant was more involved in all positive cases as compared to inner quadrant. Right side was more frequently involved in all positive cases than left side (Figure 4). Mean tumor size in ER positive patients was 11.1 as opposed to mean value of 14.7 in Her-2/neu patients. Tumors with Her-2/neu positivity were larger in size as compared to ER positive tumors (figure 5).

Lymph node metastases was seen in 17 cases out of 28 positive cases in ER with the mean of 0.75 whereas in Her-2/neu lymph node metastases was seen in 19 cases out of 29 positive cases with the mean of 1.2 showing a statistically significant difference ($p=0.046$, student's t test) (figure 6).

Most of the cases positive for both the markers belonged to IDC with one case of DCIS positive for Her-2/neu and ER each (figure 7).

Her-2/neu positivity was observed more in Grade III among Her-2/neu positive cases and also when compared with Her-2/neu negative cases. ER positivity was more in grade I and II as compared to grade III when compared with ER negative cases. So, more ER positivity was seen in low Grade while Her-2/neu tumors were more positive in higher grades (figure 8).

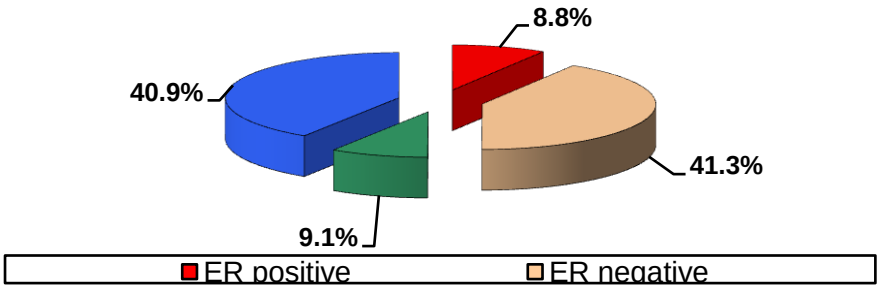

Figure 1: Positivity of receptors

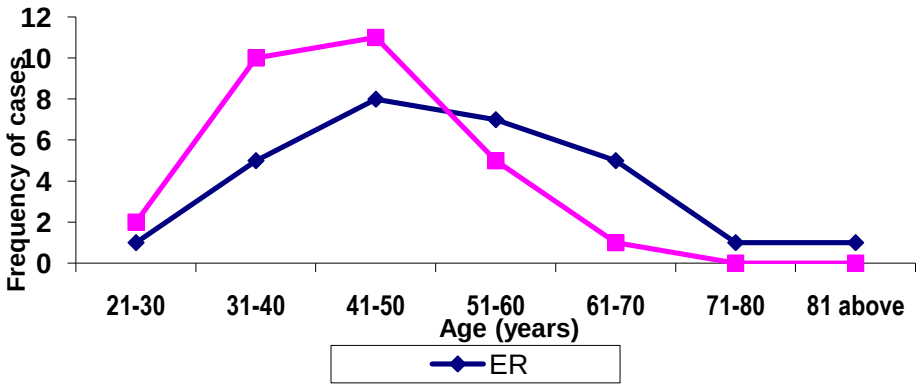

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Figure 2:Variation of positive cases with age

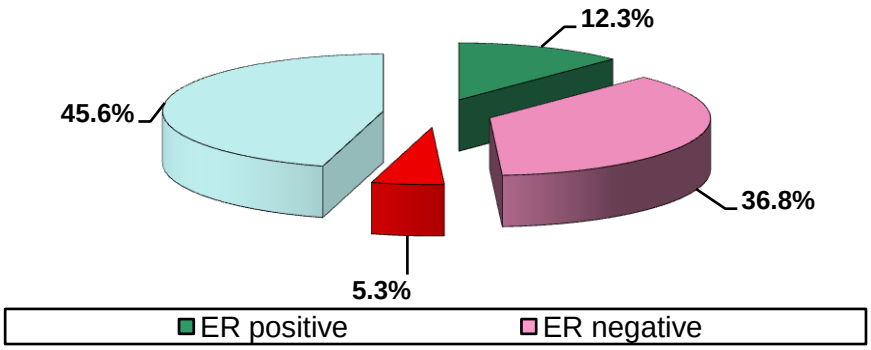

Figure 3:Skin involvement in positive cases

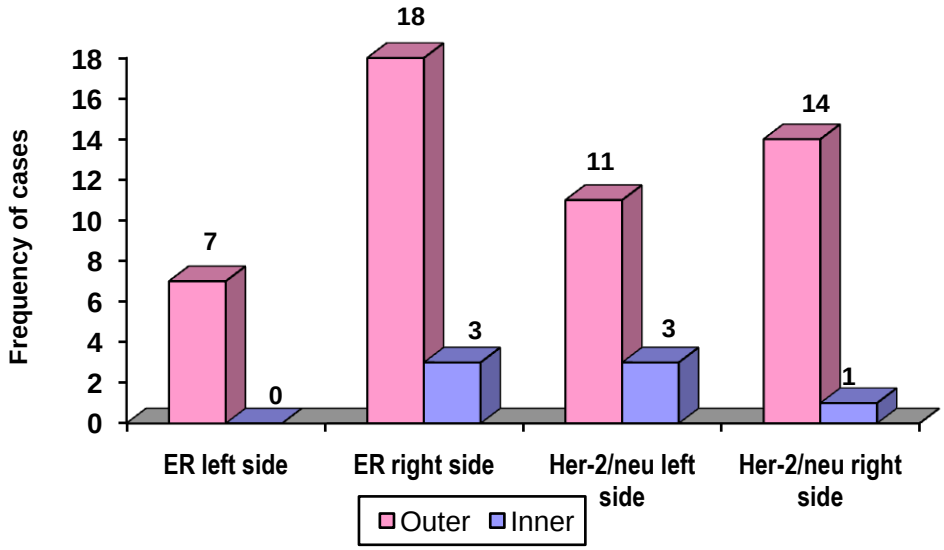

Figure 4: **Side and Site Variation in Positive Cases**

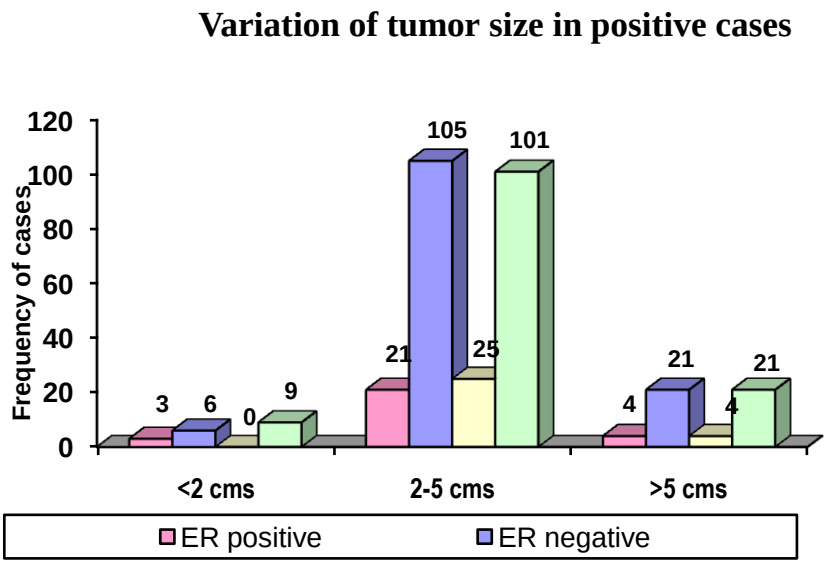

Figure 5: Variation of tumor size in positive cases

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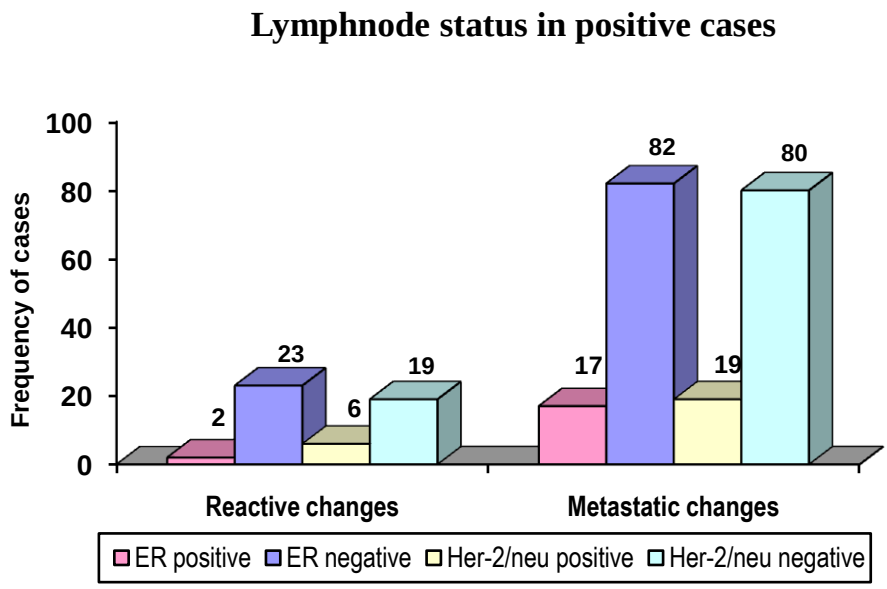

Figure 6: Lymph node status in positive cases

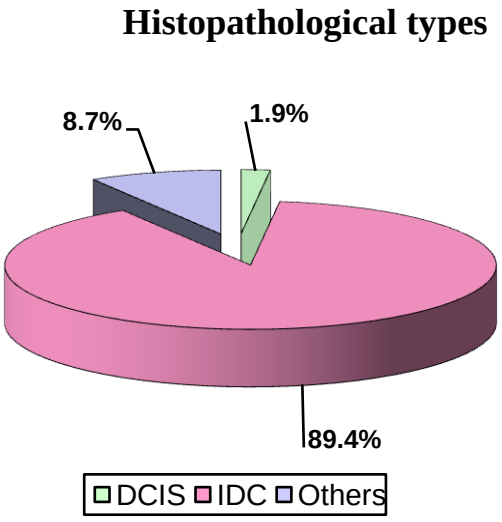

Figure 7: Histopathological types

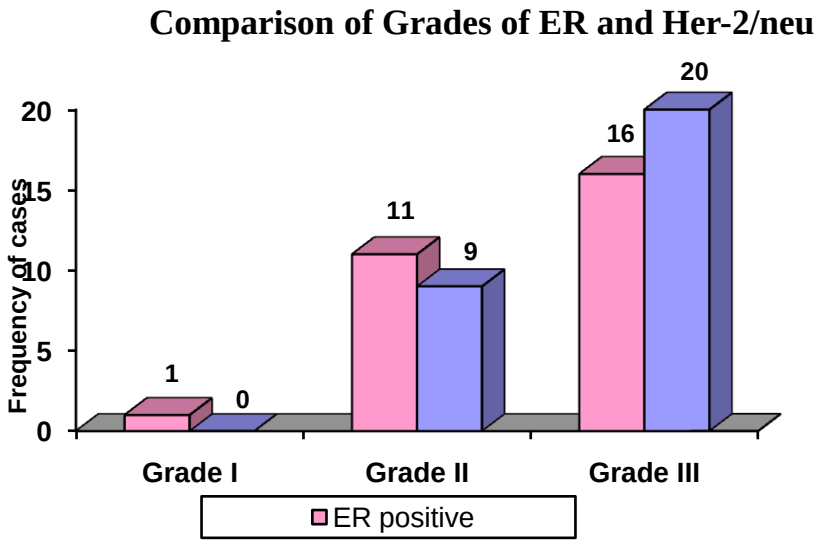

Figure 8:Comparison of Grades of ER and Her-2/neu

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Therefore, patients with ER positive tumors were older than Her-2/neu positive cases. More lymph node metastasis was seen in Her-2/neu positive cases as compared to ER positive cases. Her-2/neu tumors belonged to higher grades as compared to ER positive tumors. No significant correlation was observed in tumor size, type of tumor histopathology and side, site involved.

Discussion

Breast cancer, like many other types of cancer, is controlled by a multitude of genetic and epigenetic alterations. It is now well recognized fact that conventional predictive and prognostic markers fail to capture this heterogenicity. So, a novel eight tumor markers IHC based prognostic test for patients with advanced lymph node positive tumors more than 4 lymph nodes disease is described. The eight markers included in the analysis were estrogen receptor (ER), progesterone receptor (PR), Ki-67, Her-2/neu, epidermal growth factor receptor (EGFR), cytokeratin 5/6, p53 and carbonic anhydrase IX (CA IX).[16]

Estrogen receptor positivity was seen in 28 cases comprising 17.5% of the total cases. Percentage positive cells varied from 10–92% with weak, moderate and strong staining intensity. This percentage is less than the number of ER positive cases reported in the western literature (50–70%) however in Indian literature the positivity is 30-40%. Dutta et al reported the incidence as 24% of the cases.[9]Tiwari et al[17]reported it as 42.6% and Kuraparthy et al[18] reported it as 31.6% in south.whereas Coppola Det al[19] reported it as 56 & 57.6%. This shows that there is a marked difference between the incidence of India and other countries which may be due to racial difference, low prevalence of oral contraceptives and hormone replacement therapy. Our figure is much less to the ones reported but no such study has been done in this part of the country and it may be that majority of the population is based in villages and oral contraceptives and hormone replacement therapy is still not prevalent in this part of the country.

In our study there is strong correlation between age and ER expression. ER positive cases showed mean age of 53.0$\pm$2.65 while ER negative cases showed mean age of 47.6$\pm$0.99. So, the mean age for ER expressing carcinomas was six years older than those lacking ER expressionwhich is found to be statistically significant.

24.3% of the patients who were 50 years or above were ER positive as opposed to 10.9% patients less than 50 years of age; this difference was statistically significant (p value = 0.02, Chi square test). These findings are in agreement with other reports in the literature, which show an association between ER expression in breast carcinoma patients and age at the time of the diagnosis.[20]

In our study ER expressing breast carcinomas were, on average, 2.8 cms smaller than carcinomas lacking ER expression. Similarly 75% of the tumors (2-5 cms) in size were ER positive as opposed to only 14.3% tumors (>5 cms) in size. This is in accordance with the data reported in the literature. Almasri NM et al[20]also reported the size of ER expressing breast carcinomas on an average 1.6 cms smaller than carcinoma lacking ER expression.These findings are also supported by AndersonWF et al.[21]

Lymph nodes were recovered in 19 cases out of 28 ER positive cases, 89.5% of which showed metastatic deposits and 10.5% showed reactive changes. There was no statistically significant difference in lymph node status with positivity of ER. The tumor size, and nodal status showed no correlations with the positivity of the ER positivity. Kansei K et al[22]and Chariyalertsak S et al[23] also showed no significant difference.

Maximum number of cases were seen in Grade I (33.3%) as compared to other Grades (Grade II-19.2% and Grade III-16%).So, as the grade increased ER positivity decreased. Kansei K et al[22]and Anderson WF et al[21] also found as statistical significant relation between the grade of malignancy and ER positivity.

Comparison among ER, with p53, bcl2 and PR was done on the parallel studies going on at the same time in the Dept of Pathology, Govt. Medical College, Amritsar on 38 cases and it was observed that amongst them 36.8% were positive for ER receptor, 60.5% for bcl2 receptor, 34.2% for p53 and 31.5% for PR receptor.26.3% cases were positive for both ER and bcl2 receptor, 23.6% for ER and PR receptor, 15.7% for ER,PR and bcl2 receptor and only 5.2% cases were positive for all the 4 markers. So maximum correlation was seen in ER and bcl2 which was also shown in many related studies and presence of these markers predicts better prognosis and survival rate.

In the present study, Her-2/neu receptor positivity was observed in 18.1% of the cases. Percentage positive cells varied form 12–92% with weak, moderate and strong staining intensity.Western studiesgive a range of 10–34% [24,25] for Her-2/neu amplification in carcinoma breast whereas Indian studies repot it varying from 46.3%[26] and 57.1%.[9]No study has been done in this part of the country.

Age of the patients varied from 28 to 70 years in Her-2/neu positive cases with the mean age of 44.7 as compared to 49.5 in Her-2/neu negative cases. This difference is statistically significant (p- 0.049, student's t test). Similarly, Her-2/neu expression was seen in 19 patients less than 50 years of age (65.5%) while 10 patients were of age 50 or older (34.5%). There was statistically significant difference between the two age groups (p-0.0001, student's t test). Thus, Her-2/neu positivity shows a negative correlation with the age of the patients as mean age of Her-2/neu positive patients is 5 years less than mean age of the Her-2/neu negative patients. Similarly, Her-2/neu expression was more in patients with 50 years of age or below than 50 or older group.

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Higher rates of Her-2/neu overexpression had been shown by Almasri NM et al,[20]which documented that mean age of Her-/neu positive patients was 11 years less than those patients lacking Her-2/neu expression. Other authors have also observed the same.

Most of the cases which were Her-2/neu positive belonged to Infiltrating Ductal Carcinoma Breast, NOS type (93.1%) with one case of Ductal Carcinoma in situ and one case of IDC, mucinous type.

Maximum cases were of Grade III (69%) with 31% being of Grade II. No case of Her-2/neu receptor was positive in Grade I. This is in accordance with the study of ReshmaAriga[215] which showed that the amplification of Her-2/neu receptor in breast carcinoma was maximum in grade III tumors 54 (27%) but Almasri NM et al[20] did not find any such association.

Her-2/neu positive cases were maximum in 2-5 cms tumor size.Tumors with Her-2/neu expression tended be larger than those lacking expression, with mean size of 14.7 and 13.0, respectively. Among tumor size 2 and upto 5 cms, 86.2% cases were positive as compared to 13.7% with tumors more than 5 cms. (p=0.31, chi square test). Thus there is no statistically significant correlation between the size and Her-2/neu expression.

Lymph nodes were recovered in 86.2% of the cases out of which 24% showed reactive changes while 76% showed secondary deposits. So, Her-2/neu positive tumors showed more secondary deposits than reactive pathology. If compared with Her-2/neu negative cases no definite correlation was seen (p>0.59, chi square test). Other authors also did not find any correlation between the tumor size and lymph node status.[20]

No significant difference was observed in apoptotic index in Her-2/neu positive cases while mitotic index was more in Her-2/neu positive cases.

Most of the cases positive for Her-2/neu receptor were negative for ER receptor except one case which showed positivity for both the markers. Therefore, two distinct subgroups were noted in the study: group 1 includes those with negative Her-2/neu and positive ER; and group 2 includes those with positive Her-2/neu and negative ER status. The mean age of the patients with ER positivity was 50.1 and for Her-2/neu positive was 44%. Thus, ER positive patients were older than the Her-2/neu positive patients. ($p = 0.0106$, student's t test).Mean tumor size in ER positive patients was 11.1 as opposed to mean value of 14.7 in Her-2/neu patients. Tumors with Her-2/neu positivity were larger in size as compared to ER positive tumors.

Lymph node metastases was seen in 17 cases out of 28 positive cases in ER with the mean of 0.75 whereas in Her-2/neu lymph node metastases was seen in 19 cases out of 29 positive cases with the mean of 1.2 showing a statistically significant difference ($p = 0.046$, student's t test).

Most of the cases positive for both the markers belonged to IDC with one case each of DCIS positive for Her-2/neu and ER.

Therefore, it shows an inverse relationship of the two markers. Priti L[27] also observed that ER and PR expression were decreased significantly in Her-2/neu tumors compared with Her-2/neu negative tumors (ER, 49.1% vs 78.17%; PR, 24.3% vs 53.13%).Even among Her-2/neu tumors, the rate of ER or PR expression in high-grade tumors was significantly decreased compared with intermediate-grade tumors. Her-2/neu was positive in 10.87% of grade II and 27.84% of grade III ductal carcinomas and negative in all grade I ductal carcinomas.

Studies have shown that **e**xpression of ER is associated with a better outcome. Survival and response to hormone therapy are most favorable among women with tumors positive for ER, intermediate for tumors discordant on receptor status, and least favorable for tumors negative for both.[28]The interrelationship of ER and Her-2/neu has come to have an important role in the management of breast cancer. It has been shown that patients with breast carcinoma overexpressing Her-2/neu receptor do not respond to tamoxifen therapy.

Conclusion

It is concluded that ER and Her-2/neu are the independent markers in carcinoma breast.Her-2/neu is associated with some known bad pathological and clinical prognostic factors, such as young age, large tumor size and lack of ER receptors. In contrast ER expression was seen more in older patients with small tumor size as compared to Her-2/neu. It is for the first time that Her-2/neu and ER positivity was studied in this area and percentage of the positive cases along with other parameters was defined. Thus, the subgroup with Her-2/neu positivity represents an aggressive form of breast cancer which needs treatment with adjuvant therapy and are resistant to the hormonal therapy. If Her-2/neu overexpressingprimary tumors, are treated in combinationwith cytotoxic chemotherapy this can increase the time to recurrence and overallresponse rates in metastatic breast cancer while patients with positive ER can benefit from the hormonal therapy.

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