A study of Estrogen Receptor, Progesterone Receptor and hER2/NEU expressions in cases of breast cancer in a tertiary care hospital

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**ABSTRACT**

The study of Estrogen receptor, Progesterone receptor and HER-2/neu expressions in cases of ca breast was carried out over a period of 2 years at tertiary care hospital karad which included 101 breast cancer cases. Maximum numbers of patients (34.65%) were in the 41 – 50 years group. All patients were female. Family history was seen in 10 (9.90%) cases. Out of 101 cases equal cases were in the category of invasive breast carcinoma grade -II (46.42%) and grade- III (46.42%). While grade- I tumors comprised of 7.41% cases. Invasive breast carcinoma - no special type accounted for maximum cases (77.22%). Other histological types were medullary carcinoma (7.92%), mucinous carcinoma (2.97%). Out of 101 cases, 56.43% of breast cancer cases were positive for estrogen and progesterone receptors. Maximum number of HER-2/neu over expression 5/10 (50%) was seen in 41-50 years of age group. A positive correlation was found between ER and PR expression. Maximum number of triple negative cases were seen in medullary carcinoma (100%), metaplastic carcinoma (100%) followed by invasive breast carcinoma. Out of 101 cases of breast cancer, 42 cases (41.58%) showed axillary lymph node metastasis. Axillary metastasis was divided as 0 lymph node (no metastasis) - 58.41% cases, 1-3 lymph node metastasis – 21.78% and >3 lymph node metastasis – 19.80%. Tumor emboli were noted in 31.68% of cases. Estrogen and Progesterone receptor expression correlate well with the established prognostic markers like- age, type of tumor, histological grade, axillary lymph node metastasis and tumor emboli.

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**INTRODUCTION**

Breast cancer is well-known malignancy in ladies in created nations. In India, Breast Cancer is underdog to malignancy of the cervix among women. (Bhagat et al., 2012) It is assessed that around 80,000 cases happen every year; the age balanced occurrence rates shifting between 16 to 25/100,000 population (Harrison et al., 2010). In Asian nations the pinnacle age for bosom malignant growth is somewhere in the range of 40 and 50 years, though the pinnacle age in western nations is somewhere in the range of 60 and 70 years. In India, a huge extent of patients have high evaluation tumors and hormone receptors negative tumors (Leong et al., 2010). Assurance of
ER, PR status on biopsy example before restorative mediation is pushed as a standard practice. Only around one portion of patients with early bosom disease are dealt with and relieved by nearby careful extraction alone. Along these lines, it is critical to recognize the arrangement of patients with whom the ailment is bound to repeat and which patients are probably going to profit by fundamental chemotherapy (Shrigondekar et al., 2011). The selection of systemic adjuvant therapy is based on prognostic and predictive markers. A predictive marker gives information about a patient’s response to treatment, while prognostic marker tells about overall survival of the patient. Apart from being a prescient marker, hormone receptors have their job in choosing patients for focused treatment and can be viewed as a promising prognostic marker as well.

**Aim**

To study the status of Estrogen Receptor, Progesterone Receptor and HER2/neu hormone receptor expressions in breast cancer cases in a tertiary care hospital.

**Objectives**

1) To correlate ER, PR and HER2/neu expressions with established prognostic factors viz. type of tumour, tumour size, tumour grade, tumour necrosis, lymphovascular invasion (tumor emboli), and axillary metastasis status.

2) To correlate immunohistochemical marker status (ER, PR and HER2/neu) with clinical details (age and sex) of patients.

**MATERIALS AND METHODS**

The present study is a two year cross sectional study which includes Estrogen receptor, Progesterone receptor and HER-2/neu status of breast cancer cases and their correlation with established prognostic factors. Current study had been carried out in Molecular and Genetics laboratory, which includes 101 cases. Inclusion Criteria All the breast cancer cases who underwent lumpectomy or mastectomy with informed consent. Exclusion Criteria 1) Cases where only a trucut biopsy had been done were excluded. 2) Cases with tumor necrosis without sufficient viable tumor cells were excluded because they were not helpful for accurate evaluation of the immune histochemical result.

Consent- Informed and written consent for the procedure and research was taken before undertaking the procedure.

**Data collection**

The following clinical details were obtained from the case file of the patients: i. Name ii. Age iii. Sex iv. Family history / recurrence v. Clinical presentation – Lump in the breast, duration of lump, nipple discharge, ulceration, palpable axillary lymph node vi. Investigations – Mammogram

**Equipment**

1. Fixative – Specimens were fixed 10% neutral buffered formalin. 2. Slides – Clean, grease free slides. 3. Other materials – Haematoxylin and Eosin (H&E) stain, Paraffin wax, Xylene, 100% Isopropanol, Antigen retrieval buffer, Alcohol, DPX etc. for routine tissue processing and preparation of slides. 4. For IHC : Horseradish peroxidase, substrate buffer, peroxidase blocking agent, antigen retrieval buffer, wash buffer; distilled water. 5. ER: Ready-to-use monoclonal rabbit Anti-Human Estrogen Receptor alfa clone EP1 antibody provided in liquid in a buffer contained stabilizing protein & 0.015 mol/Liter sodium azide. (DAKO autostainer) 6. PR: Ready-to-use Monoclonal mouse anti-human Progesterone receptor clone PgR636 Liquid situation in a buffer contained stabilizing protein and 0.015 mol/Liter sodium azide. (DAKO autostainer) 7. Her-2/neu: Mouse monoclonal anti-HER-2/neu (c-erbB-2) antibody from tissue cultures supernatant diluted in PBS, pH 7.6, containing 1% BSA carrier protein and 0.09% sodium azide. (BioGenex)

**Method**

1. Collection of specimens and grossing techniques -Specimens of breast cancer (lumpectomy or mastectomy) were collected after surgery 10% neutral formalin and were fixed for a period of 12 hours. Care was taken to prevent over fixation of tissue, as it would interfere with receptor interpretation. Careful grossing of axillary tail was done. Size of largest lymph node was noted and all the lymph nodes were given for processing.

2. Staining protocol

i. Routine Hematoxylin & Eosin staining as per standard guidelines was done to make the histopathological diagnosis.

ii. The marker study – ER, PR and HER-2/neu were performed by Immunohistochemistry.

Slide preparation for Poly-L-Lysine use: Slides washed with soap & water and then with distilled water three times. Then, they rinsed with methanol & dried in room temperature.

**OBSERVATIONS AND RESULTS**

The Estrogen & Progesterone receptor and HER-2/neu expressions with cases of breast carcinoma done within our institute with attached tertiary care
Total 101 cases were obtained within a period of 2 years, which was a hospital based cross sectional study. ER, PR and HER-2/neu receptors were correlated individually with each of the prognostic factors those are age, tumor shape & size, histological type and grade, axillary metastasis, lymphovascular invasion (tumor emboli) and tumor necrosis.

Distribution of ER, PR & HER-2/neu status in breast cancer cases

Correlation of ER status with PR facts in breast cancer cases-When ER and PR status were analysed, both were positive in 57 cases (56.43%) and negative in 44 cases (43.56%). A positive correlation existed between ER and PR expression.

Age distribution of breast cancer cases

The patient was 32 years old and oldest was 80 years of age. Maximum numbers of cases had been with age group of 41-50 yrs. followed by 51-60 yrs. of age group. Out of 101 cases studied 42% were below 50 years while the remaining 58% were above the age50 years.

Family history & recurrence in breast cancer cases

Out of total 101 breast cancer cases; positive family history was reported in 10 (9.90%) cases. History of recurrence was not seen in any cases.

Mammogram reporting in breast cancer cases

Mammography was done in all 101 cases of breast cancer. 57.42% cases were in BIRADS- V and 42.57% cases were in BIRADS VI category.

Laterality in breast cancer cases

Out of 101 breast cancer cases in 58 cases (57.43%) the tumor was found on left side of breast whereas in remaining 43 cases (42.57%) it was on the right side. Bilaterality was not observed in any one of these cases.

Invasive breast carcinoma

no special type accounted for maximum cases (77.22%). Other histological types were medullary carcinoma (7.92%), mucinous carcinoma (2.97%). IBC with medullary features, IBC with mucinous change, metaplastic carcinoma, neuroendocrine carcinoma (1.98% each) and 0.99% each of encapsulated papillary carcinoma, IBC with focal neuroendocrine differentiation, invasive lobular carcinoma and mixed invasive (ductal & lobular) carcinoma.

Out of 101 cases, 56.43% of breast cancer cases were positive for estrogen and progesterone receptors.Only 9.90% cases revealed HER-2/neu receptor overexpression. Present study revealed decreased ER & PR expression as compared to western population. In the present study very few cases (9.90%) of HER-2/neu overexpression were noted hence significant correlation among HER-2/neu expressions with various parameters could not be derived. Maximum number of HER-2/neu overexpression 5/10 (50%) was seen in 41-50 years of age group. HER-2/neu receptor status alone didn’t show any significant histopathological correlation. A positive correlation was found between ER and PR expression. An inverse relationship was seen between hormone receptors positivity and HER-2/neu overexpression. Increasing pattern of ER & PR positivity was seen with increasing age of the breast cancer patients. Majority of triple negative cases were below age 50 years. Maximum triple negative cases were seen in medullary carcinoma (100%), metaplastic carcinoma (100%) followed by invasive breast carcinoma no special type grade III (85.71%). Size of tumor categorized as < 2cm, 2- 5 cm, > 5cm. Maximum cases (74.25%) were having tumor size between 2- 5cm, which is in contrast to the findings observed by western population. No significant association was found between the presence of ER, PR expression and size of the tumor. ER, PR positivity and HER-2/neu receptor negativity was associated with lower grade of tumor (grade I – 100%, grade II – 82.05%). Out of 101 cases of breast cancer, 42 cases (41.58%) showed axillary metastasis. Axillary metastasis was divided as 0 lymph node (no metastasis) - 58.41% cases, 1-3 lymph node metastasis – 21.78% and >3 lymph node metastasis – 19.80%. ER and PR negativity was associated with breast carcinoma cases having axillary metastasis. Out of 101 breast cancer cases tumor necrosis was present in 38.61%. ER, PR expression was not significantly associated with presence or absence of tumor necrosis. Tumor emboli were noted in 31.68% of cases. Decreased ER & PR expression had been seen with breast cancer patients with tumor emboli.

DISCUSSION

Distribution of ER, PR & HER-2/neu fact in breast cancer cases

Out of 101 cases, 56.43% of breast cancer cases were positive for estrogen & progesterone receptors. Only 9.90% cases revealed HER-2/neu receptor overexpression. A study done on Indian population by (Ambroise et al., 2011) found 59% positive estrogen receptor, 51% positive progesterone receptor 27.1% positive HER-2/neu receptor. Similar findings were observed by (Shet et al., 2009; Munjal et al., 2011).
Correlation of ER status with PR fact in breast cancer cases

A positive correlation existed between ER and PR expression. Similar findings were observed by (Alexieva-Figusch et al., 1988; Al-Nuaimy et al., 2015).

In current study, there had been an inverse relationship among hormone receptors and HER-2/neu overexpression which was statistically significant (p = 0.0018 (S), X² = 9.73). We found that ER & PR expression increased in HER-2/neu negative tumors compared to HER-2/neu overexpressing tumors. This was in concordance with study done by (Bhagat et al., 2012; Puvitha and Shifa, 2016; Rashed et al., 2007; Ahmed et al., 2011; Siadati et al., 2015).

The patient was 32 years old and oldest was 80 years of age. Maximum cases were in age group 41-50 yrs followed by 51-60 yrs. of age group. Out of 101 cases studied 42% were below 50 years while the remaining 58% were 50 or above years of age. In contrast to current study, study done by (Taucher et al., 2003) on western population found maximum breast cancer patients were above age of 50 years (72.5%). Only a small number of patients were younger than 35 years of age (2.8%). Present study showed increased ER and PR receptor positivity with increasing age and it was statistically significant. (p = 0.02 (S), χ² = 11.56) The present study was in concordance with other studies which also found that the frequency of positivity and the level of ER & PR increases with age, reaching their highest levels within postmenopausal women. (AlZaman et al., 2016) The difference was statistically significant (p= 0.045) and this difference was related to the menopausal fact of the patient. A study done by (Dowsett et al., 2014) found a significant relationship between age and menopausal status. The mean age of ER positive tumors was 58.9 years which was higher than ER negative tumors having mean age of 53.7 years. A study by (Al-Nuaimy et al., 2015) mean age of subjects with ER & PR expression had been 57.4% as against to 45.7 years with in subjects deprived hormonal expression (p= 0.002). Similarly, 53.1% of subjects 50 years above were ER & PR positive as opposed to 31.9% of subjects < 50 years old: this difference was statistically significant (p = 0.008).

Hormone receptors and tumor size

In current study, cases having tumor size < 2cms were only 2 (1.98%) followed by tumor size > 5cms – 24 cases (23.76%). Maximum cases were found in tumor size in between 2-5 cms – 75 cases (74.25%) which is in contrast to findings observed by Western studies. A study done by (Taucher et al., 2003) 80 on western population found most tumors had been smaller than 2 cm (59.9%).

Most of the studies in the literature had been failed to show significant relationship among presence of ER, PR and size of the tumor. (McCarty et al., 1980) In present study no statistical significance was found between tumor size and hormone receptor positivity. (p = 0.45 (NS), χ² = 1.60) The receptor status did not depend upon the tumor size.

Similar to present study, few other studies by (McCarty et al., 1980; Millis, 1980; Bhagat et al., 2012) have observed no correlation between the hormone receptor status and size of the tumor in their studies. However various authors (Almasri and Hamad, 2005) have found a significant association between hormone receptor status and tumor size. A study by (Dutta et al., 2008) showed, 38.4% of tumors with size > 5cms were ER/PR positive as compared to 28.4% of tumors with size < 2cms i.e more number of hormone receptor positivity was observed with large tumors. In present study, number of cases with size < 2cm were less (2%), compared to tumors with size more than 5 cms (24%). Significant association between PR positivity and small tumor size was observed by (Mohsin et al., 2004).

Hormone receptors and histological type

In present study IBC-NST constituted the largest group i.e 78 cases (77%), which is similar to the trend found by (McCarty et al., 1980; Ahmed et al., 2011; Chua et al., 1986; Reiner et al., 1988; AlZaman et al., 2016). Out of 78 cases of IBC-NST, 49 (63%) were ER and PR positive while 29 (37%) were negative for both the receptors and it was statistically significant. Similar findings were observed by (Reiner et al., 1988) 177/265 (67%), (Chua et al., 1986) 22/35(63%), (Al-Nuaimy et al., 2015) 67/101(66.3% ) , (Millis, 1980) 116/156 (74%) in cases of IBC- NST. Usually approximately 70-80% of invasive ductal ca are Estrogen receptor (ER) positive.

In current study, mucinous carcinoma was present in 3 cases (3%). Two out of three cases (67%) were positive for ER and PR expression. This observation was in concordance with study done by (Reiner et al., 1988). In contrast to this study, (Al-Nuaimy et al., 2015) found 0% ER &PR positivity in their study group. In current study, 2 cases (2%) were of metaplastic carcinoma. Metaplastic carcinomas...
tend to be ER and PR negative. In our study, both the cases were negative for ER and PR expression. Similar results were observed by (Al-Nuaimy et al., 2015). There were 2 cases of neuroendocrine carcinoma in present study. Only 1 case (50%) showed positivity for ER & PR. Usually ER and PR positivity is seen in neuroendocrine carcinoma. However, we could not make a confident statement about ER & PR fact in neuroendocrine carcinoma as only 2 cases were showing neuroendocrine carcinoma. There was only 1 case (1%) of invasive lobular carcinoma, which was positive for both the hormone receptors. In the present study, only 1 case of mixed (ductal and lobular) carcinoma was seen which was positive for both ER & PR expression. Carcinoma with angaged ductal & lobular epithelial morphology are more likely positive for ER and PR expression (Arps et al., 2013). Similar observation was noted in our cases. There was 1 case encapsulated papillary ca in present study, which was positive (100%) for both ER and PR expression.

Hormone receptors and grade of the tumor

In present study, statistically significant association among various parameters of IBC - NST grade and ER & PR status was seen. This finding was in concordance with those of many previous studies (Gupta et al., 2015). In the present study, ER & PR positivity decreased as the grade of the tumor increased. There was a highly significant negative correlation between receptor positivity and grade of the tumor.

Hormone receptors and axillary lymph node metastasis

In present study, decreasing ER & PR positivity is noted with increasing number of axillary metastases. It was statistically significant (p = 0.0002 (S), \( \chi^2 = 22.16 \)). Similarly, 35% of lymph node positive patients were PR negative compared with 10% of lymph node negative patients (p = 0.01). However, (Almasri and Hamad, 2005) could not find any significant relationship between ER and PR level and the presence and absence of axillary lymph node metastasis.

Hormone receptor and tumor necrosis

In most of the studies the presence of necrosis has been associated with the lack of ER & PR expression (Dutta et al., 2008). 38.61% of cases showed necrosis in present study. These cases revealed lower percentage of ER & PR positive status than the cases without tumor necrosis. However, there was no statistical significance between ER & PR positivity and presence or absence of necrosis.

Hormone receptor status and tumor emboli

In present study, ER & PR positivity is found to be inversely related to tumor emboli. It was statistically significant.

In a similar study by (Dutta et al., 2008) on 75 breast cancer cases observed an inverse relationship of lymphovascular invasion (LVI) with ER and PR immunoreactivity.

HER-2/neu over-expression and age

In present study, out of total 101 cases only 10 cases (9.90%) were positive for HER-2/neu overexpression which was a limitation. No significant statistical correlation (p = 0.62 (NS), \( \chi^2 = 2.64 \)). However, more number of cases 5/10 (50%) with HER-2/neu overexpression are seen in the age group of 41-50 years of age group.

HER-2/neu overexpression and tumor size

In present study HER-2/neu receptor negativity was seen in most of the tumors irrespective of the size of tumor and there was no statistical significance between the two (p = 0.15 (NS), \( \chi^2 = 3.85 \)) which is similar to study done by (Almasri and Hamad, 2005).

HER-2/ neu overexpression and histological type

In present study, out of 101 HER-2/neu overexpression was seen only in 10 (9.90%) cases which was a limitation and it was not statistically significant. Among lobular carcinomas, HER-2/neu positivity was observed only in the pleomorphic type and not in classic-type tumors. None of the special-type carcinomas showed HER-2/neu overexpression.

Triple positive breast cancer case

In present study, one case of triple positive breast cancer case was observed. Patient was 65 years female with a 4x3x3 cm breast lump. She underwent modified radical mastectomy. Histopathological diagnosis of Invasive breast carcinoma (No special type) grade-II was made.

CONCLUSIONS

Estrogen & Progesterone receptor expression correlate well with the established prognostic markers like- age of the patient, type of tumor, histological grade, lymph node metastasis and tumor emboli.

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Conflict of Interest

None.
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