CORRELATION OF EXPRESSION OF HORMONE RECEPTORS AND HER2 WITH HISTOLOGICAL GRADING IN 60 CASES OF BREAST CARCINOMAS

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Abstract:
Objective To analyse the expression of estrogen receptor, progesterone receptor and HER2 status using immuno histochemistry in 60 cases of breast carcinomas. To correlate the expression of hormone receptors and HER2 status with histological grading of tumor.

Study design In this study, 60 cases of carcinoma breast were selected from department of pathology, Coimbatore medical college, Coimbatore for the period of September 2009 to July 2011. Immuno histochemistry for ER, PR and HER2 were performed. The results were analysed and the correlation of ER, PR and HER2 with histological grading was done.

Results Out of 60 cases of carcinoma breast, hormone receptor expression was seen in 100 cases of grade 1, 54.35 of grade 2 and 57.14 of grade 3. HER2 expression was seen in 0 cases of grade 1, 46.81 cases of grade 2 and 42.86 cases of grade 3.

Correlation of hormone receptor expression with HER2 was also done. In grade 1 carcinoma hormone receptor expression was 100 and HER2 expression was 0. In grade 2 hormone receptor expression was 54.35 and HER2 expression was 46.81. In grade 3 hormone receptor expression was 57.14 and HER2 expression was 42.86.

Conclusion Hormone receptor status and HER2 testing are the two available modalities for effective management of patients with carcinoma of breast NOS type. Histological grading of breast carcinoma is also of paramount importance which should be included in the surgical pathology report. Therefore hormone testing and HER2 status are important ancillary investigations which should be performed in all cases of breast carcinomas.

Keyword: Breast carcinoma, Hormone receptor, ER and PR, HER2, Histological tumour grading

Introduction:
Breast carcinoma is the second most common malignancy in Indian women. Carcinoma of breast is a heterogenous disease with variable array of histological appearance.
Since carcinoma of breast arises in an exposed organ which is readily accessible to self examination and clinical diagnosis, early diagnosis and appropriate treatment are of paramount importance.

They are many prognostic and predictive markers for breast carcinomas\(^2\). Pathological features of breast carcinomas that have prognostic significance include tumor size, lymph node status, histological typing of tumor, nuclear grade, mitotic activity, hormone receptor status (ER and PR) and HER2 status.

Histological grading is based on Bloom Richardson system\(^3\) which include the assessment of tubule formation, nuclear pleomorphism and mitotic activity. Estrogen and progesterone receptor expression\(^4\) are weak prognostic factors, but powerful predictive factors in assessing the likelihood of response to hormonal therapy.

HER2/Neu is a 185KD glycoprotein with tyrosine kinase activity. In the absence of adjuvant therapy, HER2 expression is associated with worst prognosis. Even more important is the role of HER2 in predicting the response to taxane based therapy\(^5\).

Materials and Methods:

This is a prospective study design. 60 cases of breast carcinoma diagnosed histopathologically using paraffin embedded sections from modified radical mastectomy specimens received at department of pathology, Coimbatore medical college, Coimbatore during the period from September 2009 to July 2011. Paraffin embedded blocks were retrieved and immuno histochemistry was performed using monoclonal antibodies to ER, PR and HER2 using indirect peroxidise- anti peroxidise method. Stains for ER and PR were scored as positive and negative based on the presence or absence of unequivocal staining. HER2 receptor expression was scored using 0-3+ scoring system as currently recommended by the ASCO study group\(^6\).

The results were analysed. ER and PR expression were correlated with HER2 expression. Hormone receptor expression and HER2 were correlated with the histological grade of tumor.

In this study 60 cases of carcinoma of breast were included. Out of 60 cases, 54 cases were Invasive Ductal Carcinoma NOS (No Special Type). Other six cases include 3 cases of colloid carcinoma, 1 case of invasive ductal carcinoma with neuro endocrine differentiation, 1 case of atypical medullary carcinoma and 1 case of metaplastic carcinoma. The age of the patients in this study range from 30 to 74 years (mean age= 51 years).

Out of 60 cases ER expression was seen in 50% of cases, PR expression was seen in 53.33% of cases and HER2 expression was seen in 45% of cases. Correlation of hormone receptor expression with tumor grade

In this study ER and PR expression is seen in 100% cases of grade 1 carcinoma (1/1), 54.35% cases of grade 2 carcinomas (25/46), 57.14% cases of grade 3 carcinomas (4/7) and in 66.67% cases of carcinomas of other types (4/6).

Correlation of HER2 expression with tumor grade

In this study correlation of HER2 expression was done with tumor grade and the results were summarised as follows: 0% HER2 expression was found in grade 1, 46.81% expression in grade 2, 42.86% expression was found in grade 3 and 40% expression in carcinomas of other types.
The decrease in hormone receptor expression and HER2 expression in grade 3 compared with grade 2 is only minimal and it is not statistically significant.

**Discussion**

ER and PR are hormone receptors expressed in cases of carcinoma of breast. Estrogen and progesterone receptors bind hormones that exert their effects in nucleus. Nuclear immune staining for receptor proteins can be demonstrated in normal breast acini which serves as internal control. One effect of estrogen is to induce progesterone. Hence in carcinoma of breast, most PR positive tumors are also ER positive. Hence even if one receptor is positive, it is considered as hormone receptor positive. In our study ER positivity is seen in 50% of cases and PR positivity is seen in 53.33%.

Hormone receptor expression is of little prognostic significance only. It is mainly used for predicting the response to hormonal therapy. In our study, 100% of grade 1 were positive for hormone receptor which implies that these patients respond well to hormonal therapy. Similarly in grade 2 and grade 3 also 54.35% and 57.14% cases showed positivity which clearly implies that hormone receptor expression is essential in further management of patients. The association between high level of HER2 expression and adverse clinical outcome has been proven in several large trials. Our study also revealed that in grade 1 cases of invasive ductal carcinoma of NOS type HER2 expression was not seen whereas in grade 2 and grade 3 cases HER2 expression was associated with 46.81% and 42.86% cases respectively. This observation clearly shows that HER2 expression increases with increasing grade of tumor in carcinomas of NOS type. Also it has been proven in a recent study by Michael et al., that HER2 expression is associated with poor clinical outcome in cases not treated with taxane based therapy. Hence it is of vital to analyse the HER2 expression in all cases of carcinoma of breast.

In this study an attempt has been made to correlate hormone receptor expression with HER2 grading. It has been shown that hormone receptor expression correlated inversely with HER2 expression in invasive ductal carcinoma of NOS type. In grade 1 tumor, 100% positivity for hormone receptors where as no positivity for HER2. In grade 2 hormone receptor expression is seen in 54.35% compared with 46.81% for HER2. In grade 3 hormone receptor expression is seen in 57.14% as compared with 42.86% of HER2. This clearly shows that the association is stronger in grade 1 and to some extent in grade 2 and grade 3 carcinomas. This observation also shows that hormone positive cases have more indolent course and responds well to treatment.
Though there are many clinical trials available regarding the prognostic significance of hormone receptors and HER2, in this study an attempt has been made to correlate hormone receptor expression and HER2 with histological grading of tumor. The correlation between the hormone receptor expression and HER2 with grading system is established in this study for invasive ductal carcinoma NOS type. However for carcinomas of special type, more number of cases should be included in the study to achieve correct results. In the era of genetic analysis, carcinoma of breast is now classified based on molecular classification using gene expression profiling. But these procedures are costly and cannot be performed in small laboratories. Hence currently histological grading, hormone receptor expression and HER2 testing are the available modalities which has to be utilised effectively in breast carcinomas and treatment has to be given.

**Conclusion:**
Histological grading of breast carcinoma must be essentially included in all surgical pathology report forms. Hormone receptor expression predicts the response to treatment. HER2 testing is of predictive and prognostic significance which can help in the postoperative follow up of patients. Further hormone receptor testing and HER2 can be performed on paraffin embedded sections itself. If immuno histochemical techniques are standardised, these ancillary investigations are cost effective and are valuable prognostic and therapeutic indicators.

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