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ROLE OF HORMONE RECEPTORS AND HER2 IMMUNOHISTOCHEMISTRY IN PREDICTING RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER

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ABSTRACT

Introduction:
In locally advanced breast cancers neoadjuvant chemotherapy is used to downstage the tumor before surgery. Ability to predict those who would respond to neo-adjuvant chemotherapy would be of great clinical use to maximize the treatment and minimize unnecessary toxicity and cost. The objective of this study is to find out the relationship between the immunohistochemical markers (ER, PR and Her2) in pretreatment trucut biopsy of breast cancer and the response to neoadjuvant chemotherapy.

Methods:
Expression of ER, PR and Her2 were studied in the pretreatment trucut biopsies of 47 cases. Trucut biopsies were graded according to Bloom Richardson grading and degree of fibrosis and necrosis also assessed. These were correlated with the pathological response to neoadjuvant chemotherapy in subsequent mastectomy specimens.

Results:
22 out of 47 cases demonstrated pathological complete response. The highest rate of pathological response was found in grade 3 tumors (81.8% with a significant p value of 0.0127) and triple negative tumors (65% with a significant p value of 0.0314). No statistically significant correlation was found between presence of fibrosis and necrosis in the original tumor and pathological response.

Conclusion:
Tumor grade and triple negativity in the trucut biopsies of breast cancer can predict the response to neoadjuvant chemotherapy in breast cancer. Tumor grading and immunohistochemistry status should be assessed in pretreatment trucut biopsy before selecting patients for neoadjuvant chemotherapy.

Key Words: immunohistochemistry, locally advanced breast cancer, neoadjuvant chemotherapy, pathological complete response.

INTRODUCTION

Breast cancer is a biologically heterogenous disease and patients with the same diagnostic and clinical prognostic profiles can have markedly different clinical outcomes. Analysis of gene

expression data suggest that breast cancer can be divided into molecular subtypes which have distinct clinical features, with markedly differing prognosis and clinical outcomes. Immunohistochemistry surrogate panels of estrogen receptor (ER), progesterone receptor (PR), Human Epidermal Growth Factor Receptor 2(HER2) and Ki67 have been proposed to potentially discriminate the subtype as a substitution of gene expression profiling.(1).

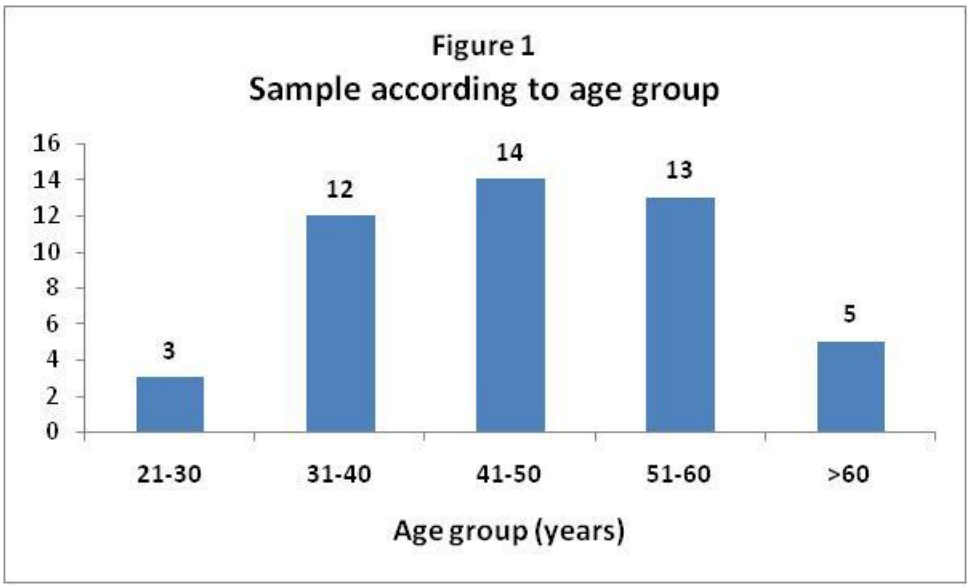
The treatment of newly diagnosed breast cancer is primarily determined by the extent of disease and generally includes surgery—either breast-conserving surgery, usually combined with postoperative radiation therapy, or total mastectomy. In locally advanced breast cancer, neoadjuvant chemotherapy (NCT) is used to downstage the tumor. The prediction of possibility of pathological complete response before starting NCT can be used to maximize the treatment and minimize unnecessary toxicity and cost.(2) The aim of this study is to determine the role of immunohistochemical markers in predicting the response to neoadjuvant chemotherapy in breast cancer in patients from North Kerala.

METHODS

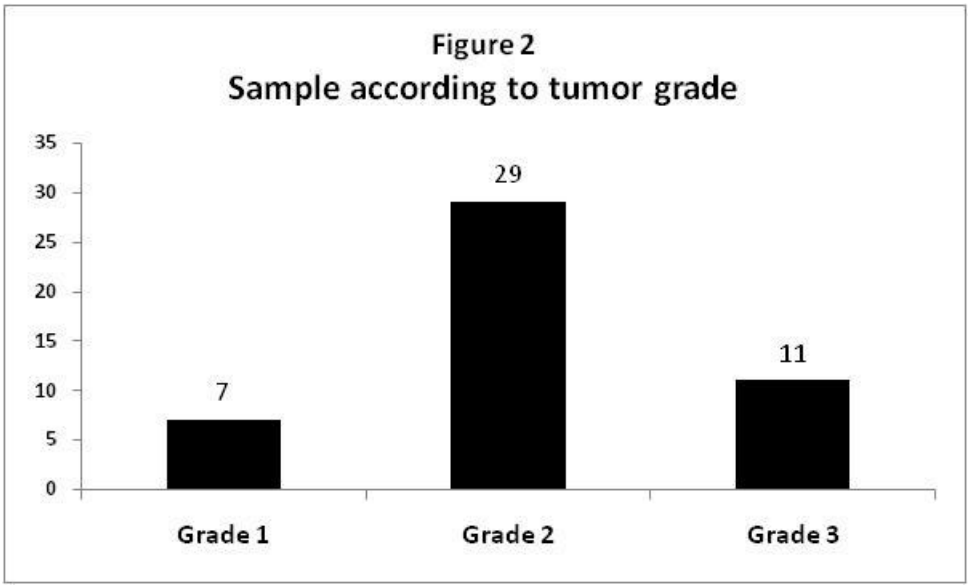
This is a prospective study done in breast cancer patients who underwent neoadjuvant chemotherapy followed by mastectomy in a major tertiary hospital in North Kerala, India, during the period from January 2012 to October 2013 which was given clearance by the Institutional Ethics Committee. These cases had tru cut / incisional biopsy done prior to neoadjuvant chemotherapy for diagnosis and immunohistochemistry. Those cases for which tru cut/ incisional biopsy were not representative of the tumor and paraffin -blocks of biopsy were not available were excluded from the study. Paraffin embedded blocks of tru cut/incisional biopsy of the cases were retrieved. One section was stained for Haematoxylin & Eosin (H&E) and three sections stained by a panel of immunohistochemical markers ER, PR and Her2/neu. Immunohistochemistry was performed using polymer HPR method. The primary antibodies used were for ER -mouse recombinant ER protein Ig G1class from Biogenex, for PR-Novocastra ready to use mouse monoclonal antibody and for Her2 -rabbit immunogen clone EP 1045Y from Biogenex. The secondary antibody used was Poly HRP reagent(HK 519) of Biogenex. The H&E stained sections were examined and tumor graded according to Bloom Richardson grading and presence of necrosis was noted. Fibrosis was graded as 1 - <25%, 2 – 25-50%, 3 - 50-75%, 4 - >75%.The corresponding IHC slides were analysed. For ER and PR >1% nuclear immunostaining was taken as positive. For HER2, a strong complete membrane staining observed in >30% of tumor cells was taken as positive. Sections from post neoadjuvant chemotherapy mastectomy specimens of the corresponding cases were studied to assess pathological response. The pathological complete response was taken as no residual invasive or in situ cancer in the excised tumor or lymph nodes after completion of neoadjuvant chemotherapy. The parameters ER, PR and Her2 status, grade of the tumor, presence of fibrosis and necrosis were correlated with pathological response. Statistical analysis was done using the software EPIINFO. Chi square test was done and a p-value of <0.05% was considered significant.

RESULTS

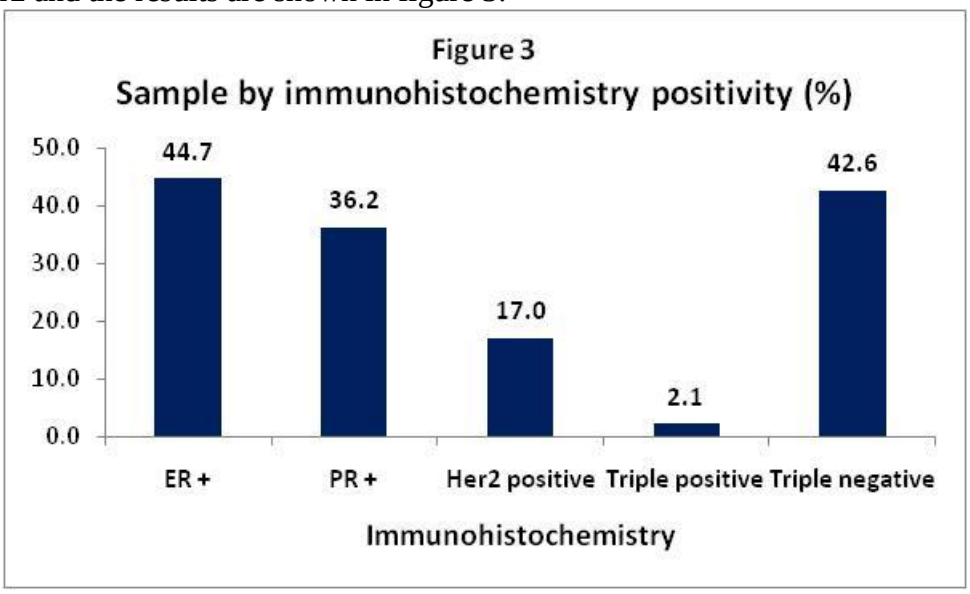
The total number of samples studied was 47 and all were females. The maximum numbers of cases were of the age group 41-50 yrs and the median age was 47 yrs (figure 1).



Trucut biopsy from all the samples were graded according to Bloom Richardson grading. The majority of tumors belonged to grade 2 (figure 2)



The immunohistochemical analyses of all the samples were done on the trucut biopsy using ER, PR and Her2 and the results are shown in figure 3.



The mastectomy specimens of all these samples received after neoadjuvant chemotherapy were studied for the presence or absence of residual neoplasm and was then correlated with various parameters like age group, initial grade of tumor, fibrosis and necrosis in trucut biopsy, ER,PR and Her2 status in trucut biopsy. The results are shown in table 1.

Table 1

Initial parameter	**% Residual tumor**		**P**
Age group			
21-30	33.3	3.3	0.5031
31-40	41.7		
41-50	71.4		
51-60	46.2		
>60	60		
Tumor grade			
1	85.7	8.7	0.0127
2	58.6		
3	18.2		
Fibrosis grade in initial biopsy			
1	41.7	1.7	0.6289
2	64.3		
3	44.4		
4	58.3		
Necrosis in Initial biopsy			
Yes	85.7	3.5	0.0616
No	47.5		
Estrogen receptor			
Positive	61.9	1.2	0.2819
Negative	46.2		
Progesterone receptor			

Positive	58.8	0.3	0.5602
Negative	50		
Her 2			
Positive	62.5	0.3	0.5624
Negative	51.3		
Triple negativity		4.6	0.0314
Triple negative	35		
Non-Triple negative	66.5		

DISCUSSION

In the current study 47 patients were selected and all were females. Of the 47 cases studied 22 cases (46.8%) demonstrated pathological complete response. The highest rate of pathological complete response was seen in grade 3 tumors (81.8%) and triple negative tumors (65%), which is in concordance with similar studies (1,3,4,5,6) . The presence of fibrosis and necrosis in trucut biopsy didn't show any statistically significant correlation with pathological response. It is well known that tumor grade shows good correlation with response to chemotherapy. This study shows that apart from tumor grade, triple negativity also correlates with pathological response to chemotherapy. But individual immunohistochemical markers (ER, PR, Her 2) showed no correlation. Thus this study proposes the use of grading and immunohistochemistry in trucut biopsy as a method to assess the response to neoadjuvant chemotherapy.

The following were the limitation of our study.The study was done in a small sample of 47 cases. Bloom Richardson grading of carcinoma breast was done in very small trucut biopsy which may not be representative of the original tumor. Her2 immunohistochemistry showed 9 equivocal cases and as fluorescent insitu hybridization could not be done due to financial constraints, they were taken as negative.

CONFLICTS OF INTEREST: none.

REFERENCES

1. Minhao LV, Li B, Li Y et al. Predictive Role of Molecular Subtypes in response to Neoadjuvant Chemotherapy in Breast Cancer Patients in North East China. Asian Pacific J Cancer Prev. 2007; 12: 2411-2417.
2. Avril N, Sassen S, Roylance R. Response to therapy in breast cancer. J Nucl Med.2009; 50:55-63.
3. Bhargava R, Beriwal S, Dabbs DJ, Ozbek U, Soran A, Johnson RR et al. Immunohistochemical surrogate markers of breast cancer molecular classes predicts response to neoadjuvant chemotherapy. Cancer 2010; 116:1431-1439.
4. Colleoni M, Viale G, Zahrieh D, Bottiglieri L, Gelber RD, Veronesi P et al. Expression of ER,PgR, HER1, HER2, and response: a study of reoperative chemotherapy. Annals of Oncology 2008;19:465-472.
5. Lips EH, Mulder L, de Ronde JJ, Mandjes IA, Koolen BB, Wessels LF et al. Breast cancer subtyping by immunohistochemistry and histological grade outperforms breast cancer intrinsic subtypes in predicting neoadjuvant chemotherapy response. Breast Cancer Res Treat. 2013; 140:63-71.
6. Lv M, Li B, Li Y, Mao X, Yao F, Jin F. Predictive role of molecular subtypes in response to neoadjuvant chemotherapy in breast cancer patients in Northeast China. Asian Pac J Cancer Prev. 2011;12:2411-7