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Correlation of Histological Tumour Grade and Hormonal Receptor Status In Infiltrating Ductal Carcinoma Breast- A Referral Centre Study

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Introduction

Breast cancer is the one of the most common malignancy in females worldwide apart from cervical cancer and more than 1 million women are diagnosed with breast cancer each year [1]. Most cases of invasive carcinoma breast are ductal in origin (over 90%) with invasive ductal carcinoma of no special type not otherwise specified (NOS) accounting for nearly 70% of all cases [2]. Although, incidence of breast cancer is low in India as compared to western countries, it is associated with poor prognosis and high mortality, may be due to late presentation when it is in advanced stages [3].

Breast carcinoma shows heterogeneity in its clinical behavior with several features having prognostic significance; including histologic subtype, grade, lymph node status, estrogen receptor (ER)/progesterone receptor (PR) status, human epidermal growth factor receptor-2/neu (her-2/neu) status, proliferative activity and DNA content, growth factors and its receptors, oncogenes, and tumor suppressor genes [4]. At present, ER status is regarded as the most powerful predictive marker in the treatment of breast cancer and it is well known fact that strong ER-positive cases benefit from endocrine therapy alone [5,6] ; even though ER and PR are codependent variables.[2]. Her-2 neu overexpression is a useful parameter to predict response to herceptin, but it is not a good predictor of response to chemotherapy or overall survival [2,3].

With introduction of adjuvant hormonal or chemotherapeutic regimens, determination of the hormonal receptor status in breast cancer has become practice as positive status confers survival advantage in these patients [5,7].

Hormone receptors study is not routinely measured as it is expensive and is still considered a research tool in many parts of our country [4,7]. This could adversely impact decision making regarding treatment protocol and sometimes patients are treated empirically with tamoxifen which is not always required. The present study was planned keeping in mind predictive importance of receptor

status for the prognosis of illness and application of appropriate therapy. The objective was to determine receptor status and it′s correlation with histopathological grade of the invasive ductal carcinoma (NOS) type in an Indian population.

Material And Methods

This was a retrospective study carried out in a tertiary care centre in Central India. Samples of Sixty patients with histological proven diagnosis of infiltrating ductal breast carcinoma from January 2015 to June 2018 were selected for this study. Clinical details were archived from the files. Modified radical mastectomy specimens were subjected to Immunohistochemical (IHC) analysis where required and hematoxylin and eosin stained sections were reviewed.. Samples were histologically graded according to Modified Bloom-Richardson-Elston (MRB) grading system. MRB grade was obtained by adding up the scores for tubule formation, nuclear pleomorphism and mitotic count [6] . Each of which was given 1, 2 or 3 points. 3 to 5 points were grade I, 6 to 7 points were grade II and 8 to 9 points were grade III.

ER / PR and Her-2Neu status was evaluated by IHC technique with monoclonal antibodies (DAKO) using conventional antigen-antibody Streptavidin immunoperoxidase method [8]. Positive and negative controls were run simultaneously with each batch of IHC staining to ascertain validity of the test run. Tumors that showed strong complete membranous staining in > 10% cells were taken as positive for Her-2neu. Nuclear staining was taken as positive for estrogen and progesterone receptors [4,9]. ER/PR expressions were assessed by Quick scoring which is based on assessment of proportion score and intensity score [9]. The 2 scores are added together for a final score with 8 possible values. Score of 0-2 were taken as negative and 3-8 were taken as positive.

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The level of significance “p” value was considered statistically significant if <0.05.

This study was conducted after obtaining the ethical approval from the Ethical Review Committee of our institution and our institution took care of the entire financial burden for the completion of this retrospective research study.

Results

This was a retrospective study where sixty cases of infiltrating ductal carcinoma (NOS) were reviewed. Histomorphology was reascertained and hormone receptor status was analyzed. In old cases hormone receptor analysis was done where required. In this study, age ranged from 29-74 years with youngest being 29 years and oldest 74 years, the mean age being 49.3 years. In this study we found 6 cases (10%) of grade I, 32 cases of grade II (53.33%) and 22 cases (36.66%) of grade III.

Of all the cases, only 12 were found to be ER positive, 14 PR positive and 24 were Her 2 Neu positive. Hormone receptor status is as per table 1

Table 1. Hormone receptor status

Hormone receptor	ER	PR	Her 2 Neu
Negative	48 (80 %)	46 (76.7%)	8 (13.3%)
Positive	12 (20 %)	14 (23.3%)	24 (40 %)
Equivocal			28 (46.7%)
p value	0.0019	0.0062	0.06

Amongst all ER positive cases, 2 were of grade 1, 8 of grade 2 and 2 of grade 3. Their relative distribution and % amongst ER and % within grade and total are summarized in table 2.

Table 2. Correlation of MRB grade with ER

	Grade 1	Grade 2	Grade 3	Total
Negative	4	24	20	48 (80.0%)
% within ER	8.30%	50.00%	41.70%	
% within Grade	66.70%	75.00%	90.90%	
% of Total	6.70%	40.00%	33.30%	
Positive	2	8	2	12 (20.0%)
% within ER	16.70%	66.70%	16.70%	
% within Grade	33.30%	25.00%	9.10%	
% of Total	3.30%	13.30%	3.30%	
Total	6	32	22	60
	10.00%	53.30%	36.70%	

p value : 0.4962

Amongst all PR positive cases, 2 were of grade 1, 12 of grade 2 and none of grade 3. Their relative distribution and % amongst PR and % within grade and total are summarized in table 3.

Table 3. Correlation of MRB Grade and PR

	Grade 1	Grade 2	Grade 3	Total
Negative	4	20	22	46 (76.7%)
% within PR	8.70%	43.50%	47.80%	
% within Grade	66.70%	62.50%	100.00%	
% of Total	6.70%	33.30%	36.70%	
Positive	2	12	0	14 (23.3%)
% within PR	14.30%	85.70%	0.00%	
% within Grade	33.30%	37.50%	0.00%	
% of Total	3.30%	20.00%	0.00%	
Total	6	32	22	60
	-10.00%	-53.30%	-36.70%	

p value : 0.0703

Amongst all Her 2 Neu positive cases, 4 were of grade 1, 14 of grade 2 and 10 of grade 3. Their relative distribution and % amongst ER and % within grade and total are summarized in table 4.

Table 4. Correlation of MRB Grade with Her 2neu

	Grade 1	Grade 2	Grade 3	Total
Equivocal	0	4	4	8 (13.3%)
% within Her2Neu	0.00%	50.00%	50.00%	8 (13.3%)
% within Grade	0.00%	12.50%	18.20%	
% of Total	0.00%	6.70%	6.70%	
Negative	2	14	8	24 (40.0%)
% within Her2Neu	8.30%	58.30%	33.30%	24 (40.0%)
% within Grade	33.30%	43.70%	36.40%	
% of Total	3.30%	23.30%	13.30%	
Positive	4	14	10	28 (46.7%)
% within Her2Neu	14.30%	50.00%	35.70%	28 (46.7%)
% within Grade	66.70%	43.70%	45.50%	
% of Total	6.70%	23.30%	16.70%	60
Total	6	32	22	60
	-10.00%	-53.30%	-36.70%	

p value : 0.9071

Discussion

Improved breast cancer treatment requires integration of cancer biology and clinical pathology as this could affect patient outcome. The relevance of ER and PR status as a predictive marker in breast cancer patients has been established beyond doubt for the last few decades [10]. In our study, we found expression of ER to be only 20 % and PR only 23.33%. Data from the US suggest that around 44%–59% patients were both ER and PR positive, and only 20%–35% were negative for both ER and PR [11]. The Indian data on the other hand, suggest a larger number of patients negative for both ER and PR status (42%–48%) [12,13]. In European, 60-80 % patients were found with positive receptor expression [14]. This may be due to lower average age at diagnosis or racial difference.

A Jordanian study revealed 50.8% ER-positive tumors and 57.5% of PR-positive tumors in their study sample [15]. A prevalence of 32.6% for ER-positive and 46.1% for PR-positive breast cancers has been documented in a study carried out in India [13,17]. This could be partially explained by the age at diagnosis of breast cancer. In our study, 70.6% of the ER-negative cases were below the age of 50 years. Biological and lifestyle factors are also likely to contribute to these findings.

Tumor grade is one of the important predictors of tumor behavior in breast cancer. In contrast to other studies, tumor grade II was the commonest in our study followed by grade III and I [3,6,7,12]. Increased histological grade and late presentation possibly reflects lack of health awareness and miscellaneous social taboos in this part of the country. In our study, we found that hormonal receptors like ER and PR correlated well with tumour (p=0.0019 and p=0.0062 respectively). As the tumour grade advances the hormonal receptor positivity decreases [10,16] . Our results confirmed that non-reactivity of

hormonal receptors increases with increase in tumor grade.

Triple-negative breast cancer (TNBC) is defined as that group of breast carcinomas that are negative for ER, PR and HER2/neu. In our study, of 60 cases, we found 8 such tumors. All of them were of grade II or III. 75% had lymph node metastasis and lymphatic vessel invasion and 62.5% had tumor necrosis. Our results showed that TNBC had poor prognostic characteristics as compared with other subtypes of breast cancers. Other authors have also found similar results [17,18]. Although patients with TNBC tend to have a poor prognosis, only chemotherapy is expected to be effective because no therapeutic targets have yet been established.

Conclusion

Immunohistochemical analysis of ER and PR receptors is widely available at a reasonable cost and is prognostic as well as somewhat predictive. This study confirms that receptor expression of ER and PR is inversely associated with tumor grade. High percentage of grade II and III tumours in our centre highlights the need to increase health awareness in this area in order to decrease the morbidity and mortality. Further functional analysis of ER, PR and Her 2Neu receptors are needed to investigate the effects of compounds in inhibiting cancer in humans. These findings can have profound impact in breast cancer treatment.

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