Original Article

A study of estrogen and progesterone receptor status in breast carcinoma and its correlation with tumor grading

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Abstract

Introduction: Rise in the incidence of breast cancers in India. **Objective:** 1. To determine the ER and PR status in unselected breast malignancy cases. 2. Correlate them with modified Bloom and Richardson grading. **Material and Methods:** This study comprised of 70 cases of breast carcinoma reported in a period of 4 years in the department of Pathology, Gandhi Medical College, Secunderabad. Tissue sections were stained with H and E and histological examination was done. Sections for IHC were taken onto poly-l-lysine coated slides and stained by immunoperoxidase method using ER and PR monoclonal antibodies**. Results:** Out of 70 cases, 87.88% were IDC (NOS) and two cases (6.06 %) of invasive lobular and mucinous each. Grade was II in 58.49% cases followed by grade III in 20.30 %in remaining 21.21% cases grade was I. Out of 70 cases, 43.42% were ER positive and 39.33% were positive for PR. Correlating with histological grade out of 15 cases of grade I, 86.67 % were positive for both ER and PR. Out of 34 cases of grade II, 44.1% were ER positive and 47.05% were PR positive and in remaining 21cases of grade III, 19.04% were found ER positive and 14.29% PR positive. **Conclusion**: Histological grading was significantly associated with ER and PR. Hormone receptor immunoreactivity was found to be inversely correlating with histological grade.
Keywords: Breast carcinoma, Immuno-histochemistry, Estrogen Receptor, Progesterone Receptor.

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Received Date: 12/08/2016 Revised Date: 30/09/2016 Accepted Date: 30/09/2016

Access this article online

Quick Response Code:

Website: www.statperson.com

DOI: 30 September 2016

INTRODUCTION

Carcinoma of the breast is the most common malignant tumor and the leading cause of death from carcinoma in females all over the world.[1] According to Oncology experts India faces a potential breast cancer epidemic over the next decade as women are adopting Western lifestyles by marrying and bearing children later in life. Oncologist Umberto Veronesi, scientific director of the European Institute of Oncology and a pioneer in breast conservation surgery, stated that Indian women are at higher risk of contracting breast cancer as they are adopting to western life style, nursing fewer children and weaning them earlier, altering hormone flows and urged Indian government to aggressively adopt early detection strategies, including the purchase of mammography machines for hospitals and health care facilities.[2] In India 144,937 women were newly detected with breast cancer and 70,218 women died of breast cancer in the year 2012[3]. For the year 2015 WHO predicted an estimation of 1,55,000 new cases of breast cancer and about 76000 deaths. The gap only seems to be widening, which means, we need to work aggressively on early detection. Common denominator for most of these factors is strong and prolonged estrogen stimulation, operating on a genetically susceptible background. Genetic predisposition of familial breast carcinoma:
BRCA-1 gene located on chromosome 17q
BRCA-2 gene located on chromosome 13q
In recent years, interest in prognostic factors has been stimulated by the success of systemic adjuvant therapy

How to site this article: K Vijaya Lakshmi, K Rama Devi. A study of estrogen and progesterone receptor status in breast carcinoma and its correlation with tumor grading. *International Journal of Recent Trends in Science and Technology*. September 2016; 20(2): 273-277 http://www.statperson.com (accessed 30 September 2016).

for early stage in breast cancer. Management of breast carcinoma involves assessment of various tumour related and patient related prognostic factors such as age, performance status, size of tumour, lymph node involvement, estrogen and progesterone receptor (ER/PR), grade of tumour, histological type and HER-2 status to decide on various treatment options. It is well established that ER/PR and HER-2/neu are the most powerful prognostic factors in deciding on treatment.[4] Histological grading is now recognized as a powerful prognostic factor and should be included as a component of the minimum data set for histological reporting of breast cancer. Assessment of histological grade has become more objective with modifications of Patey and Scarff (1928)[5] method first by Bloom and Richardson (1957)[6] and more recently by Elaston and Ellis (1991).[7] Hormones appear to hold the key to the understanding the biology of breast cancer and ER and PR status is an important biomarker that helps physicians to individualize therapy. Fisher *et al* (1980) found that presence of estrogen receptor to be significantly associated with high nuclear and low histological grade, absence of tumor necrosis, presence of marked tumor elastosis and in elderly patients' age groups.[8,9.] Breast cancer in Asia has certain features different from the Western countries, the objective of this study was to determine association between the pattern of expression of estrogen and progesterone receptors in relation to grade of tumour in India.

MATERIAL AND METHODS

The present study was conducted in the department of Pathology, Gandhi Hospital, Secunderabad. This study is both prospective and retrospective consisting of 70 cases during a 3 year period. The specimens included were MRM (modified radical mastectomy), wide excision, lumpectomy, palliative mastectomy and outside paraffin blocks for review. Routine Haematoxylin and Eosin staining was done for histological typing and grading of all cases. Immunohistochemistry was done using labelled antibodies for hormone receptor status (Estrogen receptor and progesterone receptor). All HandE stained tissue sections were classified according to WHO and then graded histologically.

Histological Grading of Invasive Carcinoma

Invasive ductal carcinomas and all other invasive tumors were graded based on an assessment of tubule /gland formations, nuclear pleomorphism and mitotic counts in accordance to Modified Bloom Richardson Grading by Elaston and Ellis (1991).[6, 7]

Quick Scoring of Hormone Receptor Status

In all cases of breast malignancy, nuclear staining is assessed for ER and PR. The two parameters evaluated in immunohistochemical preparations of hormone receptors are the proportion/number of tumor nuclei stained and the intensity of staining. The two parameters are combined into a scoring system, 'Quick score (Barnes *et al*1998).[10]

Proportion Score

0 - No nuclear staining
1 - <1 % nuclear staining
2- 1-10% nuclear staining
3 - 11-33% nuclear staining
4- 34-66% nuclear staining
5 - 67-100% nuclear staining

Intensity Score

0- No staining
1- Weak staining
2- Moderate staining
3- Strong staining

Total Score = Proportion Score + Intensity Score

Note - Best preserved and best stained areas of the sections were assessed.

The hormone receptor status for each group of lesions is correlated with the histological grade.

RESULTS

The age of the patients ranged from 28 to 80 years, with majority of them in the range of 31 to 50 years (58.57%). Females comprised of 100% (70/70). Left side was slightly more commonly affected (53.8%). One patient had bilateral tumor and in one case of blocks received from outside, the side was not mentioned. Majority of the tumors were more than 2 cm in size (57/70, 81.42%). Only 13/70, 18.58% tumors were less than 2 cm in maximum diameter. Lymph nodes were received in 60% - 42/70 cases. Out of them, 38/42 cases showed metastatic breast carcinoma. Hormone receptor status was divided into four groups, viz: (ER+PR+), (ER+PR-), (ER-PR+) and (ER-PR-). Positivity for both the receptors was seen in 40% of cases, while 48.6% were negative for both of them.

Table 1: Age distribution of patients

Age Group <21	Number 0	Percentage 0
21-30	2	2.85
31-40	17	24.28
41-50	24	34.28
51-60	14	20
61-70	11	15.74
>70	2	2.85
Total	**70**	**100**

Table 2: Hormone receptor expression

Category	Number	Percentage
ER+ PR +	28	40
ER + PR -	4	5.7
ER – PR +	4	5.7
ER – PR-	34	48.6
Total	**70**	**100**

Table 3

Histological type	Total cases	Grade I(3-5)	Grade II(6-7)	Grade III()
Infiltrating duct cell carcinoma	63	17.46%	50.79%	31.75%
Infiltrating lobular	04	100%		
Mucinous	03		66.67%	33.33%

Table 4

Histological Grade	Total cases	ER Positive	PR Positive
Grade I	15	86.67 (13/15)%	86.67%
Grade II	34	44.1 (15/34)%	47.05%
Grade III	21	19.04 (4/21)%	14.29%

DISCUSSION

Clinical trials have shown that survival advantage for women with hormone receptor positive tumors is enhanced by the treatment with adjuvant hormonal and/or chemotherapeutic regimens. (Goldhrisch *et al* 2000).[11] The large number and variety of papers published on carcinoma of the breast, the treatment, prognosis and associated factors, are an index of the complexity of the problem and indeed of the study of any tumor (Chevallier *et al* 1990, Du-Toir *et al* 1990).[12] Breast cancer in Asian countries tend to have certain common features such as high tumour size at presentation because of poor screening strategies and high positivity for ER. The prevalence of hormone receptor- positive breast cancer in Asian countries has been found to be lower than western world where more than 50% tumors express hormone receptors. However, the number of studies performed on this topic is much less in the Asian communities compared to the western world. In the present study, 45.7% cases were ER+ and an equal number of cases were PR+ (Table 1). Vaidyanathan *et al* [13] reported 59.4% ER+ and 58.3% PR+, while Desai *et al* [14] reported 32.6% ER+ and 46.1% PR+. Teguh *et al* [15] reported 51.7% ER+ and 48.2% PR+. Majority of the patients (58.5%) in this study were in the age group of 31 -50 years of age, which was similar to the findings documented by Shet *et al*[16] (60%) Dutta *et al* [17][9] (50%) and Hussain *et al* 1994[18]. Valerie Jeanne *et al*[19] found in a study conducted over a 28 yr. period in Texas, U.S.A. that a majority of the patients (88.42%) diagnosed with breast cancer were more than 50 yrs. of age. This corroborated the observation that breast carcinomas occur at a younger age in Indian subcontinent than in the western world. (Table 2) In our study, tumor size varied from 2-5 cm in 39 cases (55.7%) followed by 21 cases (30%) with size > 5cm and in only 10/70 cases (14.28%) size was < 2cm. This is in accordance with the study of Patel *et al* (2002)[20] studied 100 cases and distributed cases in 3 groups according to tumor size with less than 2cm approximately in 8 cases, 2-5cm in 64 cases and more than 5cm in 28 cases. According to our study 45 (64.28%) out of 70 cases, had undergone radical mastectomy and had palpable lymph nodes. 35 (50%) / 70 cases were positive for metastasis and 10 were negative. The findings by others were – Muddawa[21] (57.6%), Vaidyanathan *et al* [13] (59%), Azizun-Nisa *et al*[22] (71.3%), Dutta *et al* [17] (70%) and Teguh *et al*[23] (62.5%). Pallavi Shrigondekar *et al*[24] (() reported 48.64% metastasis. According to Wartgotz and Norris (1994)[25] about one third of the reported cases had lymph node metastasis. Out of these 70 cases, all (100%) were invasive carcinomas of epithelial origin. These findings were in accordance with the study of Hussain *et al* (1994)[10] who noticed in his study that there was 97.6% of epithelial and 2.4% of stromal tumors. Amongst the 70 invasive carcinomas (epithelial), 63(90%) were of invasive ductal type (NOS), four cases were (5.7%) of Invasive lobular and three cases were (4.28%) mucinous carcinoma. Similar findings were noted by Berg and Hutter (1995).[26] In this study, all invasive epithelial tumors were graded according to the Modified Bloom Richardson Grading by Elaston and Ellis (1991). 34 out of the 70 cases of invasive ductal carcinomas that is 48.57% were Grade II, 30%were Grade III and remaining 21.43% were Grade I. Our results closely matched with the study of Doussal *et al*,[27] 1989. In his study of 1262 patients 11 to 14% were grade I, 55 to 57% were grade II and 29 to 34% were grade III. Similar findings were observed in the study of Zubair Ahmad *et al*,[28] 2009 who studied 120 cases of invasive breast carcinoma to acquire the information about the extent and spread of breast carcinoma by grading the tumors (based on modified Bloom and Richardson grading system), determining the tumor size and axillary lymph node status, tumor staging and Nottingham prognostic index (NPI) scoring. Out of 120 cases, 5(4.17%) were grade I, 91(75.83%) were grade II, and 24(20%) were grade III, concluding that the large majority of the cases were grade II tumors. For all invasive carcinomas, hormone receptor status was also studied using immunoperoxidase method and Quick scoring was done. The Quick score for ER was 0 in 51.42% (36/70) cases and for PR was 0 in 57.17% (40/70) cases, indicating no hormone expression in the majority. This was in accordance with the study of Lakmini and Mudduwa,[21] 2009 in which out of 151 breast cancer patients studied, the Quick score for ER was 0 in 54.3%(82/151) cases and for PR was 0 in 51.7% (75/145) cases. Desai *et al*[14] 2000 in their study documented the ER and PR status of breast cancer in Indian population. Only 32.6% of tumors were ER positive and 46.1% were PR positive in Indian population as compared to high rates in Western world. Among the 70 cases studied, 45.7% cases were positive for ER and 45.7% cases were positive for PR (table -3). Both ER and PR positive immunostaining was observed in 86.71% cases of grade I,

44.1% cases of grade II were found ER positive and 47.05% were found PR positive and 19% cases of grade III were found ER positive and 14% were PR positive. The ER and PR positivity was highest in grade I lesions followed by grade II lesions and grade III lesions. On statistical analysis there was an inverse high correlation ($P<0.05$) between hormone receptor immuno-reactivity and histological grading. These findings were in accordance with the study of Buon (2004)[29] who studied 80 cases and reported positive immune reactivity for ER and PR in 71.25% and 60.00% cases; ER and PR positive immune staining in 100% well-differentiated (grade I) breast carcinomas, 76.36% positivity in grade II tumors and 61.2% in grade III tumors. Kenneth, *et al*.[30] studied 500 consecutive primary mammary carcinomas at Duke University Medical Centre and cooperating community hospitals in North Carolina. Using a modification of the histologic grading system of the NSABP, they observed a trend towards higher levels of estrogen (ER) and progesterone receptor (PR) content in well (grade-I) and moderately (grade-II) differentiated mammary carcinomas. Considering the fact that grade-I tumours are less commonly seen in India, these results point towards an important fact of conducting a larger sample review and a definitive need for more screening / awareness programs.

CONCLUSION

The results of this study indicate inverse correlation between hormone receptor immunoreactivity and tumor histological grade. In this study, most tumours were ER/PR negative and a trend towards grade-II tumours expressing ER/PR was observed, however, a larger sample size study is needed to corroborate this finding. Breast cancer occurs about a decade earlier in Asian women than in the West. The hormone receptor expression is low in Asian women. The low hormone receptor positivity in Asian countries may be explained by the fact that, majority of the tumors are larger in size, of higher grade, and many of them have lymph node metastasis at the time of diagnosis. The late presentation of the patients is because of lack of awareness, poverty, illiteracy and many other social reasons. There is urgent need for health education, to bring more and more patients seeking early treatment and increase in screening programs for breast cancer early detection, thus increasing hormone receptor expression, better response to treatment, and hence, better prognosis.

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Source of Support: None Declared
Conflict of Interest: None Declared