SIGNIFICANCE OF ESTROGEN AND PROGESTERONE RECEPTOR STATUS IN PROGNOSIS OF BREAST CANCER

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ABSTRACT: OBJECTIVE: (1) To assess the ER and PR status in breast malignancies. (2) Correlate them with modified Bloom and Richardson grading. **MATERIAL AND METHODS:** This study comprised of 39 cases of breast lesions reported during a last two year period from September 2009 to August 2011 in the department of Pathology, M.L.B. Medical College, Jhansi. Out of these 39 cases six cases were of fibroadenoma, used as positive control. 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:** As evident from study out of 33 cases, 87.88% were IDC (NOS) and two cases (6.06 %) of invasive lobular and mucinous each. Grade was II in 48.49% cases followed by grade III in 30.30 % in remaining 21.21% cases grade was I. Out of 33 cases, 42.42% were ER positive and 33.33% were positive for PR. Correlating with histological grade out of 7 cases of grade I, 85.71 % were positive for both ER and PR. Out of 16 cases of grade II, 25% were ER positive and 31.25% were PR positive and in remaining 10 cases of grade III, 20% were found ER positive and not even a single case was PR positive. **CONCLUSION:** Histological grading was significantly associated with ER and PR. Hormone receptor immunoreactivity was found inversely correlated with histological grade.

KEYWORDS: Breast carcinoma, Immunohistochemistry, Estrogen Receptor, Progesterone Receptor.

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

Common denominator for most of these factors is strong and prolonged estrogen stimulation, operating on a genetically susceptible background. Genetic predisposition with 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 for early stage in breast cancer. 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)² method first by Bloom & Richardson (1957)³ and more recently by Elston and Ellis (1991).⁴

Hormones appear to hold the key to the understanding of breast cancer and ER & PR status is 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 & in elderly patients' age groups.^{5,6}

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AIMS & OBJECTIVES

- To establish histological type of breast malignancy.
- To carry out histological grading of malignant breast lesions.
- To assess the hormone receptor status: Quantization of hormone receptor in malignant breast lesions as a predictor of prognosis.
- To correlate histological grading with hormone receptor status in malignant breast lesions.

MATERIAL AND METHODS: The present study entitled “Significance of Estrogen and Progesterone Receptor status in Prognosis of Breast Cancers” was conducted in the department of Pathology, MLB Medical College, Jhansi.

This case study was prospective and retrospective. Prospective cases were selected from the patients admitted for mastectomy in the surgery ward of the Medical College Hospital. As regards retrospective cases, they were obtained from the histopathological records obtained from the Pathology department of college:

- Routine Haematoxylin and Eosin staining has been done for histological typing and grading of all cases.
- Immunohistochemistry has been done using labelled antibodies for hormone receptor status (Estrogen receptor and progesterone receptor).

All H&E stained tissue sections were classified according to WHO and then histological grading were done.

Histological Grading of Invasive Carcinoma: Invasive ductal carcinomas and all other invasive tumors are graded based on an assessment of tubule/gland formations nuclear pleomorphism and mitotic counts. Assessment of histological grade has become more objective with modifications of the Patey and Scarff (1928)² method first by Bloom and Richardson (1957)³ and more recently by Elston and Ellis (1991).⁴

Quick Scoring of Hormone Receptor Status: In all cases of breast malignancy, nuclear staining is assessed for ER & 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).⁷

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

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Total Score = Proportion Score + Intensity Score

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

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

RESULTS:

Age group (in years)	No. of cases	Percentage
0-10	-	-
11-20	-	-
21-30	-	-
31-40	02	06.06
41-50	17	51.52
51-60	09	27.27
>60	05	15.15

TABLE I: Age wise distribution of cases

Histological type	Total cases	Grade I (3-5)		Grade II(6-7)		Grade III(8-9)	
		frequency	%	frequency	%	frequency	%
Infiltrating ductal CA (NOS)	29	05	17.24	15	51.72	09	31.04
Infiltrating lobular CA	02	02	100.00				
Mucinous	02			01	50.00	01	50.00

TABLE II: Correlation of histological grades with histological types

Histological type	Total cases	ER Positive		PR Positive	
		Frequency	%	Frequency	%
Infiltrating ductal carcinoma (NOS)	29	10	30.30	08	27.59
Infiltrating lobular	02	02	100	02	100
Mucinous	02	01	50.0	01	50.0

TABLE III: Distribution of Estrogen and Progesterone Receptor in different histological types of Breast carcinoma

Histological Grade	Total cases	ER Positive		PR Positive	
		Frequency	%	Frequency	%
Grade I	07	06	85.71	06	85.71
Grade II	16	04	25.00	05	31.25
Grade III	10	02	20.00	00	00.00

TABLE IV: Correlation of ER and PR Immunoreactivity with Histological Grade

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DISCUSSION: 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).⁸

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).⁹

Out of the 33 cases studied, maximum patients were in age group 41-50 years .(table -1) This is in accordance with study of Hussain et al 1994,¹⁰ who found peak incidence between age of 41-50 years.

As observe in our study that in 16 cases (48.48%) tumor size varied between 2-5 cm followed by 13 cases (39.40%) with size more than 5cm and in only 4 cases (12.12%) size was less than 2cm. This is in accordance with the study of Patel et al (2002)¹¹ 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.

As evident from our study that out of 33 cases, 22(66.66%) had undergone radical mastectomy or having lymph nodes and out of these 22 cases 17(77.28%) were positive for metastasis and 5(22.72%) were negative. According to Wartgotz and Norris (1994)¹² about one third of the reported cases had lymph node metastasis.

Out of these 33 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.

Out of these 33 of invasive carcinomas (epithelial), 29(87.88%) were of invasive ductal CA (NOS), two cases were (6.06%) of Invasive lobular CA and two cases were (6.06%) of mucinous carcinoma. Similar findings were noted by Berg and Hutter (1995).¹³

In this study, all invasive epithelial tumors were graded according to the Modified Bloom Richardson Grading by Elaston and Ellis (1991).⁴ Out of the 33 cases of invasive ductal carcinomas, 48.49% were Grade II, 30.30% were Grade III and remaining 21.21% were Grade I. Our results closely matched with the study of Doussal et al, 1989.¹⁴ 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, 2009¹⁵ 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 & 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 57.58% (19/33) cases and for PR was 0 in 66.67% (22/33) cases, indicating no hormone expression in the majority. This was in accordance with the study of Lakmini & Mudduwa, 2009¹⁶ in which out of 151 breast cancer patients studied, the Quick score for ER was 0 in 54.3%(82/151) cases & for PR was 0 in 51.7% (75/145) cases.

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Desai et al 2000¹⁷ in their study document the ER & 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 compare to high rates in Western world.

Among the 33 cases studied, 39.40% cases were positive for ER and 33.33% cases were positive for PR. (table -3)

Both ER & PR positive immunostaining was observed in 85.71% cases of grade I, 25% cases of grade II were found ER positive and 31.25% were found PR positive and 20% cases of grade III were found ER positive and not even a single case was found PR positive.

The ER & PR positivity was highest in grade I lesions followed by grade II lesions & grade III lesions. On statistical analysis there was an inverse high correlation ($P < 0.05$) between hormone receptor immunoreactivity and histological grading. These findings were in accordance with the study of Buon (2004)¹⁸ who performed a study on 80 invasive breast carcinomas to evaluate the immune histochemical analysis of estrogen receptor (ER) and progesterone receptor (PR) in invasive breast carcinomas of various histological subtypes and grades.

Positive immune reactivity for ER and PR were seen in 71.25% and 60.00% cases, respectively. Both ER and PR positive immune staining was observed in all (100%) well-differentiated (grade I) breast carcinomas, while in grade II tumors ER and PR-positive cancer cells were 76.36% and 61.62%, respectively. The corresponding figures for grade III carcinomas were 41.18% and 35.29%. A significant association ($P < 0.05$) between different histological grades of breast carcinomas and ER and PR immune reactivity was found.

However the number of cases in present study is small and long follows up is required to reach any definitive conclusion. Ultimate goal of each study is how it can be beneficial to the society.

Any research by itself on breast carcinoma is useful because of the sheer numbers of women worldwide who suffer morbidity & mortality due to this disease.

CONCLUSION: Thus it was concluded from present study, that hormone receptor immunoreactivity correlate inversely with histological grade.

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Fig. 1(a) & (b): Photomicrograph of breast –Infiltrating ductal adenocarcinoma (NOS)-Grade I showing brown nuclear immunostaining for ER and PR (IHC 40X 10)

Figure 1(a) (ER)

Figure 1(b) (PR)

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Fig. 2(a) & (b): Photomicrograph of breast –Mucinous adenocarcinoma showing brown nuclear immunostaining for ER and PR (IHC 40X 10).

Figure 2(a) (ER)

Figure 2(b) (PR)

Fig. 3(a) & (b): Photomicrograph of breast –Infiltrating lobular carcinoma showing brown nuclear immunostaining for ER and PR (IHC 40X 10).

Figure 3(a) (ER)

Figure 3(b) (PR)

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