Clinicopathological Evaluation of Various Prognostic Factors in Breast Cancer Along with Hormonal Receptor Status and HER2/neu Expression

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Abstract

Introduction: The prevalence of hormone receptor positive breast cancer in Asian countries is found to be lower than the western world where more than 50% of the tumors express hormone receptors. Studies have found consecutive decrease of ER, PR expression as a measure of differentiation of the tumour with low grade having the highest and high grade having the lowest ER/PR expression. Detection of vascular invasion in the primary tumor is a marker of metastatic potential and has prognostic significance, particularly in the lymph node negative group and helps to predict both recurrence and long-term survival. *Aims and Objectives*: To study the expression of ER, PR and HER2/neu status by immunohistochemistry and correlation of clinico-pathological parameters with hormone receptor status and HER2/neu expression. *Results*: In the present study the age range of the patients was between 35-80 years. Out of 53 cases, majority (72%) of them were invasive ductal carcinoma. Other tumors included medullary carcinoma, lobular carcinoma, metastatic carcinoma and poorly differentiated carcinoma. Nineteen out of 53 tumors (36% of the cases) showed triple negativity and only one tumor showed triple positivity. Of the total cases 32% of the tumors were ER+/PR+, 17 % ER+/PR- and 4% showed ER-/PR+. *Conclusion*: This study highlights the importance of various prognostic factors and hormone receptor status evaluation that will aid in therapeutic intervention.

Keywords: Breast Cancer; ER; PR; HER2/neu; Lymphovascular.

Introduction

Breast carcinoma is the most common cancer among urban Indian female population and the second most common in the rural areas, where the most frequent is carcinoma cervix, according to the Cancer registry data [1,2,3,4] Carcinoma breast comprises of more than 30% of all cancers in females . It is a multifaceted disease with a diverse natural history.

It presents with a varied spectrum of clinical, pathological and molecular features thereby having different prognostic and therapeutic implications .

An important prognostic factor of carcinoma breast

is the hormone receptor status which helps to determine whether a patient is suitable for hormonal therapy, thereby serving as an excellent tool for quick diagnosis and treatment [5,6]. It has been found that there is an association between Estrogen (ER)/ Progesterone (PR) status, HER2/neu over expression and different clinical features like age, gender, menopausal status etc and pathological features like tumor size, grade, stage, histological subtype, axillary lymph node status. In Asian countries the prevalence of hormone receptor positive breast cancer is found to be low compared to the western world where more than 50% of the tumors express hormone receptor positivity. Patients with ER / PR positive status have a lower mortality rate in contrast to the hormone receptor negative carcinoma breast cases [4]. Young patients have low expression of steroid receptors due to the higher levels of circulating estrogen, which is reflected in their tumours. At present, where breast conservative and reconstructive surgery is the more

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popular modality of treatment of breast carcinoma , it is now standard practice to determine the ER /PR status on biopsy specimen prior to therapeutic intervention [7].

Another important prognostic indicator is the detection of lymphovascular invasion in the primary tumor, which is also a marker of the metastatic potential.

Aims

• To study the expression of ER, PR & HER2/neu.

• To correlate the clinico-pathological parameters with the hormone receptor status.

Materials and Methods

This is a retrospective study conducted over a period of two years from February 2015 to February 2017 in the Department of Pathology, Yenepoya medical college, Mangalore. A total of 53 cases were included in the study. All post mastectomy female patients irrespective of age who were histologically diagnosed as malignant were included in the study. Patients who had already received treatment in the form of radiotherapy or chemotherapy before Modified radical mastectomy were excluded from the study. Clinical details were archived from the case files.

Specimens received in the Department of Pathology were fixed in 10% neutral buffered formalin for 24-48 hours. Gross examination was carried out and representative tissue sections from the tumor and lymph nodes were given and then processed according to standard protocol. The sections were stained with routine hematoxylin and eosin (H and E) stain and studied under the microscope to arrive at a histological diagnosis. Immunohistochemistry was performed on the suitable blocks. HER2/neu scoring was done as per Table 1. Immunohistochemistry methodology used was: Poly Excel HRP/DAB Detection System from PathnSitu. For interpretation and scoring of HER2/ neu staining the following method was used (Table 1).

Results

Of the total 53 mastectomy cases diagnosed as malignant, the most common type of malignant breast carcinoma was invasive ductal carcinoma (72%, 38 cases). The frequency of occurrence of the malignant lesions are shown in Table 2.

Of the total cases, 51% (27 cases) were ER positive and 38% (20 cases) were PR positive. Only four cases (8%) showed Her 2 neu positivity (Score 3) (Table 3). Majority of the ER positive and PR positive cases were in the fourth to sixth decade of life. In the present study

Table 1: HER2/neu Scoring

Interpretation	Observation
Negative	No membrane staining is observed
1+ Negative	Faint, partial staining of the membrane in any proportion of the cancer cells
2+ Equivocal	Weak to moderate complete staining of the membrane, greater than 10% of cancer cells
3+ Positive	Strong, complete staining of the membrane greater than 10% of cancer cells

Table 2: Types of tumor

Types	Frequency	Percentage (%)
Invasive Ductal Carcinoma	38	72
Lobular Carcinoma	1	2
Medullary Carcinoma	2	4
Mucinous Carcinoma	1	2
Metastatic Carcinoma	1	2
Poorly Differentiated Carcinoma	1	2
Miscellaneous	9	17
Total	53	100

Table 3: Distribution of ER, PR and HER2/neu

ER		PR		HER 2 NEU			
Positive	Negative	Positive	Negative	0	1	2	3
27(51%)	26(49%)	20(38%)	33(62%)	24	10	15	4(8%)

Table 4: Hormonal receptor status in different age groups

Age Range (In Years)	ER		PR	
	Positive	Negative	Positive	Negative
20-30	1	0	1	0
31-40	4	5	2	8
41-50	8	7	5	10
51-60	10	6	9	7
61-70	1	5	0	6
71-80	3	3	3	2

Table 5: Hormone Receptor Status in breast carcinoma

Hormone Receptor Status	Frequency	Percentage (%)
ER+/ PR+	17	32
ER+/PR-	9	17
ER-/PR+	2	4
Triple Positive	1	2
Triple Negative	19	36
HER 2 Neu Positive	4	8

no significant correlation was obtained between the age of the patients with breast carcinoma and hormone receptor status by immunohistochemistry (Table 4).

Triple negative cases were the commonest hormone receptor expression which accounted for 36% of the total cases (19 cases) followed by ER/PR positive cases which comprised of 32% of the cases (17 cases) (Table 5).

Discussion

Our study showed 53 cases of primary malignant breast carcinoma. Majority of the cases were between a wide age range of 31-60 years which was in concordance with the study by Mudduwa [8]. This may be due to the different age distribution of the Indian population, where only 7% of the population is above the sixth decade of life [4]. Asian countries show an early onset of breast carcinoma compared to the Western countries, which present a decade later as shown in the study by Rhodes [9] wherein majority of the cases were above fifty years of age.

In a study conducted by PritiLal et al [10] ER was positive in 71.6%, PR in 47.4% & Her2/neu in 26.89%. Sughayer et al [11]found that ER was positive in 50.8%, PR was positive in 57.5%, & Her2/ neu was positive in 17.5% of the cases. These are some of the studies conducted in the western population. According to a study by Mudduwa [8] the prevalence of hormone

Table 6: Comparative study of the ER, PR & HER2/neu positivity

Study	No of Cases	ER+(% of cases)	PR+(% of cases)	HER2 NEU+ (% of cases)
PritiLal et al[10]at New York	3655	71.6	47.4	26.89
Sughayer et al[11] at Jordan	267	50.8	57.5	17.5
AzizunNisa et al[12] at Karachi	150	32.7	25.3	24.7
Dutta V et al[13] New Delhi	75	24	30	57.2
Vedashree M K et al[14]	55	30.9	25.5	30.9
PRESENT STUDY	53	51	38	8

receptor positive breast carcinoma in Asian countries is found to be low compared to the western population where more than 50% tumors show hormone receptor positivity. However the number of studies performed on this topic in Asian countries is less in comparison to the western countries. Azizun Nisa et al [12] found ER positivity in 32.7%, PR positivity in 25.3% and HER2/neu positivity in 24.7% of the cases. The results of the studies conducted in Asian countries are not concordant with the studies done in the western world.

The results of our study are comparable to the studies conducted in Asian countries [13,14] (Table 6). The low ER and PR positivity may be due tothe difference in techniques of evaluation [15] and a majority ofpost menopausal women in our study. A higher percentage of HER2/neu immunoreactivity may be present inherently in breast carcinoma in Indian women. However , HER2/neu positivity in our study was 8%. A study by Adedayo et al [16] showed 7.5% positivity which was comparable to our study. An increased

risk of developing an ER positive tumour is associated with nulliparity, late primigravida, early menarche, higher body mass index and use of hormone replacement therapy.

Table 7: Comparative Incidence of Frequency of Hormone Receptor status

Hormone Receptor Status	Present study	Suvarchala et al[17] (2011)	Geethamala k et al[4] (2015)	Ambroise et al [18](2011)	Sharif et al[19] (2010)
ER+/PR+	17 (32%)	32.8%	52%	47%	62.8%
ER+/PR-	9 (16%)	14%	2%	1%	11.8%
ER-/PR+	3 (6%)	10.94%	0	0	4.1%
HER 2 NEU	4 (8%)	-	25%	27%	28.1%
triple positive	1 (2%)	-	1%	-	-
triple negative	19 (36%)	42%	20%	25%	-

Hormone receptors in this study were found as follows: ER+/PR+(32%), ER+/PR- (17%), and ER- / PR+(4%). This was comparable to the study by Bhagat et al [7] which showed ER+/PR+(36.20%), ER+/PR- (12.06%) and ER- /PR+(1.72%) Study by Hussain et al and Arafah also showed similar results [20,21].

Our study showed 32% ER+/PR+ and 36% triple negatives. A study by Geethamala K et al [4] showed 52% ER+/PR+ and 20% of triple negatives (Table 7). These results were in concordance with other Indian studies having low positivereceptors and higher triple negatives [16,17,22,23]. However western literature showed higher positive receptor status and lower triple negatives [9].

In our study , there is inverse relationship between HER 2/neu and ER/ PR receptor. According to Kriti Chauhan [6] , estrogen and its receptor are required to suppress HER2/neu. This is probably why women who express HER2/neu may be resistant to Tamoxifen.

In our study majority of the ER positive and PR positive cases were in the fourth to sixth decade which is in concordance with the study by Adedayo [16], Ghosh J [23], Azizun- Nisa [12] and Suvarchala [17]. According to literature ER positivity increases with age that is elderly patients express more estrogen receptors. However in the present study PR positivity does not show any correlation with age.

In our study out of 53 cases, 52 cases were node positive and 33 cases showed lymphvascular invasion. Adequate precautions should be taken to avoid overdiagnosis in case of Ductal carcinoma in situ (DCIS) and in carcinoma associated with shrinkage artifact.

Problems can be greatly reduced by obtaining good fixation and by following simple but strict criteria such as tumor emboli must be seen within spaces having a clear lining of endothelial cells, should be assessed in peritumoral area and the configuration of the tumor cells should not conform to the shape of the space.

Conclusion

In the present study there is inverse relationship between HER2/neu and ER/ PR receptor and receptor positivity is lower compared to the western countries. Majority of the parameters are in concordance with the other studies in India .

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