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Original Research Article

Histopathological Grade versus Hormone Receptor Status in Breast Carcinoma- Treasure The Past

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Abstract

Introduction: Breast carcinoma is the most common cancer among women.Prognosis and management of breast cancer are influenced by classic variables such as grade, stage, hormone receptor status of estrogen (ER), progesterone (PR) & Her2/neu overexpression.Though hormone receptor analysis is a prerequisite in this era, for management and prognosis, still histopathological grading can be taken up as an important variable for predicting prognosis.An attempt has been made in this study to correlate histopathological grade with hormone receptor status in breast carcinomas in our institution.

Objectives: To correlate the Histopathological grade with ER, PR and Her2/neu receptor status of breast carcinoma

Materials & Methods: A prospective study conducted from June 2011 to June 2014 in the department of Pathology, ESIC Medical College & PGIMSR, ESIC Model Hospital, Rajajinagar, Bangalore. Hundred Modified radical mastectomy specimens were subjected for routine histological examination and Immunohistochemical analysis. Clinical details were archived from the files. Statistical analysis was done and p value of <0.05 were taken as significant using chi-square test.

Results: The age of the patients ranged from 24 to 75 years.Majority of tumours were predominantly of histopathological grade two.By Immunohistochemistry 52% were ER+/PR+, 25% were Her2/neu positive and 20% of triple negatives.A significant association was seen between histologic grade and hormone receptor status.

Conclusion: Histologic gradingtogether with receptor status offers an excellent method of correlation of survival rate and response to hormonal therapy which lightens up a prospect of various treatment modalities.

Keywords: Breast carcinoma, histologic grading, hormone receptor status.

1.Introduction

Breast carcinoma is the most common cancer among women in the urban Indian population and second only to cervical cancer in the rural population based on cancer registry data [1-3]. Prognosis and management of breast cancer are influenced by classic variables such as grade, stage, hormone receptor status of estrogen (ER), progesterone (PR) & Her2/neu overexpression[4-8]. Few Studies have found consecutive decrements of ER, PR expression as a measure of differentiation of the tumour with grade I (well differentiated) having the highest and grade III (poorly differentiated) having the lowest ER/PR expression. Her 2/neu over expression is associated with poor histologic grade so also the triple negative breast carcinomas. [4-8]

Though hormone receptor analysis is a prerequisite in this era, for management and prognosis, still histopathological grading can be taken up as an important variable for predicting prognosis. [4-8] Carcinomas with ER/PR positivity have a good prognosis as compared to carcinomas with ER/PR negativity. Also the histological grade has a bearing on the prognosis, as high grade have poor prognosis and vice versa.[4-12] An attempt has been made in this study to correlate histopathological grade with hormone receptor status in breast carcinomas in our institution.

1.1 Objectives

To correlate the Histopathological grade with ER, PR and Her2/neu receptor status of breast carcinoma

2. Materials & Methods

A prospective study conducted from June 2011 to June 2014 in the department of Pathology, ESIC Medical College & PGIMSR, ESIC Model Hospital, Rajajinagar, Bangalore. Hundred Modified radical mastectomy specimens were subjected for routine histopathological examination and Immunohistochemical analysis.Clinical details were archived from the files. Specimens were routinely fixed 24-48 hours in 10% neutral buffer formalin. They were examined grossly and representative tissue bits were taken according to standard guidelines and then processed. Sections were stained with routine hematoxylin and eosin (H&E) stain. Histopathological features were determined.100 breast carcinomas diagnosed as infiltrating ductal carcinomas were histologically graded according to Modified Bloom–Richardson–Elston grading system. Representative sections with tumor and adjacent normal breast tissue (internal control) were further processed for IHC using Peroxidase-antiperoxidase (PAP) technique. Sections were taken on silane coated slides. Antigen retrieval was done by pressure cooker using EDTA buffer solution and slides stained with Monoclonal antibodies obtained from "Scytec" company. ER (mouse monoclonal clone 1D5), PR (mouse monoclonal clone PR88) Her 2/neu (rabbit monoclonal clone EP1045Y). 500 cells on tissue sections were counted for positivity. ER, PR positivity was denoted by nuclear staining using Allred scoring systemwhich takes into account both intensity of staining and proportion of positive tumour cells. ASCO (American Society of Clinical Oncology) guidelines 2007 denoting cytoplasmic membrane staining was used for Her2/neu grading.

2.1 Statistical analysis

The data was analyzed using SPSS software version 18.0. Obtained parameters were evaluated using descriptive statistical analysis and presented in terms of percentage.Association of patient's age, tumor grade, tumor stageand hormone receptor status were tested with chi-square test. A p value of <0.05 were taken as significant.

3. Results

In the present study female patients with breast carcinoma were aged between 3rd and 7th decade of life. The youngest was 24 years and oldest 75 years. Majority (76%) were in 3rd and 4th decade of life. Left breast (50%) was marginally more affected than right side (49%) of breasts and in a single cases both breasts (1%) were affected. The commonest grade was grade 1accounting to 54% followed by grade 2 and 3 with 27% and 19 % respectively(Table 1)(Fig 1).

Table 1: Histopathological grading of breast carcinoma

Grade of The Tumor	Frequency	(%)
1	19	19.0
2	54	54.0
3	27	27.0
Total	100	100.0

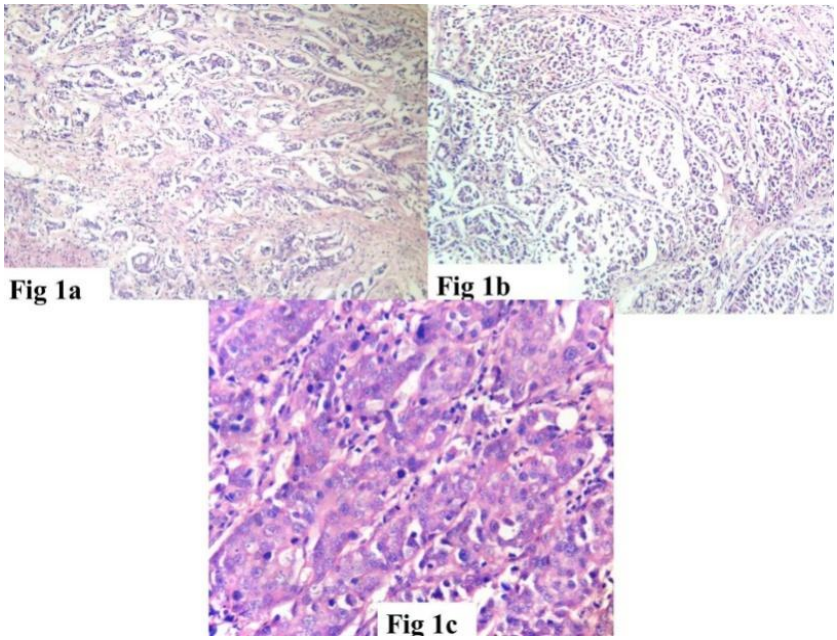

Fig 1: H&E showing (a) grade 1 (10x) (b) grade 2(10x) (c) grade 3(40x)

Table 2: IHC Hormone Receptor Status in breast carcinoma

Hormone Receptor Status	Frequency	%
ER+/PR+	52	52
ER+/PR-	2	2
ER-/PR+	0	0
HER2/neu+	25	25
Triple positive	1	1
Triple negative	20	20
Total	100	100

R+/PR+(52%) were the commonest hormone receptor expression followed by HER2/neu(25%) and triple negatives(20%).(Table 2)(Fig 2). Most of the breast carcinomas encountered was in stage 2(57%).The remaining were in stage 1(28%) and stage 3(15%).(Table 3)

Table 3: Pathological Staging of breast carcinoma

Stage	Frequency	%
1	28	28.0
2	57	57.0
3	15	15.0
4	0	0
Total	100	100.0

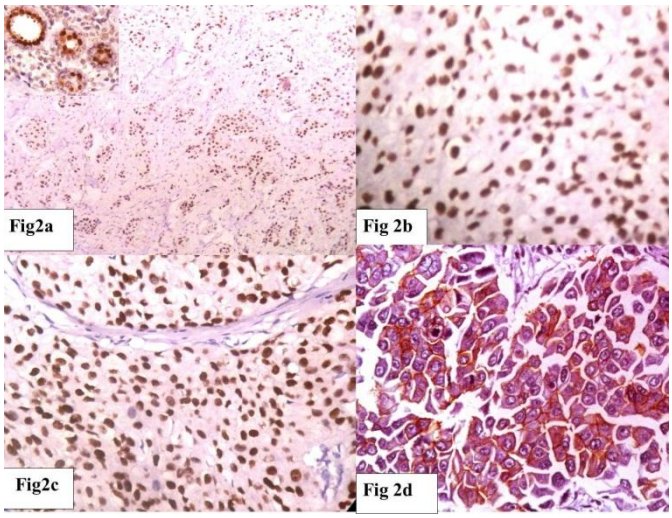

Fig 2: IHC photographs showing nuclear stain positivity for estrogen receptor (a) Allred score-8 (10x)Inset showing internal control, (b) Allred score-8 (40x) (c) Allred score-8 (40x) And (d) IHC cytoplasmic membrane stain positivity for Her2/neu receptor-score-3+ (40x)

In the present study no significant correlation was obtained between the age of the patients with breast carcinoma and Hormone receptor status by IHC.(Table 4) ($p>0.05$). However significant association was seen among histologic grading and hormone receptor status wherein,78.9% of grade 1 were ER+/PR+, 64.9% of grade 2 were also ER+/PR+ and 62.9% grade 3 were triple negative breast carcinoma.(Table 5)($p< 0.001$). No significant correlation was obtained between stage of breast carcinoma and IHC hormone receptor status (Table 6) ($p>0.05$)

Table 4: Association of IHC hormone receptor status with AGE of the patients with breast carcinoma

IHC hormone receptor status	<50 YEARS (%)	>50 YEARS (%)
ER+/PR+	41(51.3)	11(55)
ER+/PR-	2(2.5)	0
ER-/PR+	0	0
HER2/neu+	20(25)	5(25)
Triple Positive	1(1.2)	0
Triple Negative	16(20)	4(20)
TOTAL	80	20

Table 5: Association of IHC hormone receptor status with Grade of the tumor

IHC hormone receptor status	GRADE 1(%)	GRADE 2(%)	GRADE 3(%)
ER+/PR+	15(78.9)	35(64.9)	2(7.4)
ER+/PR-	1(5.3)	1(1.8)	0
ER-/PR+	0	0	0
HER2/Neu+	3(15.8)	15(27.8)	7(26.4)
TP	0	0	1(3.3)
TN	0	3(5.5)	17(62.9)
Total	19(100)	54(100)	27(100)

Table 6: Association of IHC hormone receptor status with stage of the patients with breast carcinoma

IHC Hormone receptor status	Stage 1(%)	Stage 2(%)	Stage 3(%)	Stage 4(%)
ER+/PR+	12(42.9)	31(54.4)	9(60)	0
ER+/PR-	2(7.1)	0	0	0
ER-/PR+	0	0	0	0
HER2/Neu	7(25)	14(24.6)	4(26.8)	0
Triple Positive	0	0	1(6.6)	0
Triple Negative	7(25)	12(21)	1(6.6)	0
TOTAL	28	57	15	0

4. Discussion

The conventional prognostic factors for breast carcinoma include age, tumor grade, histological type, stage and hormone receptor status for estrogen, progesterone receptors and Her2/neu overexpression [4-13].

Age range among Indian breast cancer patients is found to be lower when compared to the Western countries with an average difference of one decade. This is likely to be due to the different age distribution of the Indian population, where only 7% of the population is above the age of 60 years [2-9]. In the present study 49% of women were in the age group of 41-50 years, in contrast a study by Pakseresht *et al*[9] had lower age range from 31-40 years (34.5%), whereas Ambroise *et al*[6](46.4%) Suvarchala *et al*[8] (45.31%), and Rhodes *et al*[10] (36.42%) had higher age range between 51-60years.

Literature search reveals breast carcinomas are more common in the left breast than the right. The possible explanations are that, the left breast being more bulky and having larger volume of breast tissue comparatively. However side of breast involved has no clinical significance [7,11]. In the present study also left breast were marginally more affected than right and a single case of bilateral breast carcinoma noted.

In the present study majority of breast tumors were grade 2 (54%) followed by grade 3(27%) and grade 1(19%) which is in concordance with other studies except for one study by Ghosh *et al* having more of grade 3 (75.4%)[5-8,12,](Table 7)

Table 7:- Comparative Incidence of Frequency of Grade of the tumor

Grade of The Tumor	Azizun-Nisa *et al*, 2008[7]	Adedayo *et al* 2009 [12]	Suvarchala *et al* 2011[8]	Ambroise *et al*2011[6]	Ghosh *et al* 2011[5]	Present study 2014
1	6.7	21.2	28.12	9.4	0.3	19
2	55.3	38.4	42.18	57.3	15.9	54
3	38.0	35.9	29.69	33.3	75.4	27

Immunohistochemistry revealed 52% ER+/PR+, 25% Her2/neu positivity and 20% of triple negatives. These results were in concordance with other Indian studies having lowered positive receptors and higher Her2/neu expression and triple negatives [4-6,8]. However western literature showed higher positive receptor status and lower triple negatives and Her2/neu [7,10,12,14],.(Table 8)

Table 8:- Comparative Incidence of Frequency of Hormone Receptor status.

Hormone receptor status	Adedayo *et al* 2009[12]	Sharif *et al* 2010[14]	Suvarchala *et al* 2011[8]	Ambroise *et al* 2011[6]	Ghosh *et al* 2011[5]	Present study 2014
ER+/PR+	68.9	62.8	32.8	47	51.2	52
ER+/PR-	-	11.8	14.0	1		2
ER-/PR+	-	4.1	10.94	0		0
HER2/neu+	7.5	28.1	-	27	24.8	25
Triple positive	10.2	-	-	-		1
Triple negative	13.4	-	42.19 (ER-/PR-)	25	29.8	20

Staging of breast carcinomas showed higher in stage 2 accounting to 57% followed by stage 1(28%) and stage 3(15%) in concordance with other Indian studies [15,16]. In western countries stage 1(56.4%) are the majority followed by stage 2 and 3 possibly due to increased awareness and rampant breast cancer screening programs.[12,17]

In the present study correlation between hormone receptor status with patients age, grade of the tumor and stage of breast carcinoma were carried out. No statistical significance was found between patient's age and stage. Literature reveals ER positivity increases with age, that is elderly aged patients express more estrogen receptors [5,7,8,12]. PR positivity does not show any correlation with age[6,7]. Whereas younger patients have breast carcinomas with triple negative phenotype compared to the elderly [5,18]. Studies reveal no correlation between patients age and Her2/neu expression similar to our study except for one study by Ambroies *et al* showed that Her-2/neu expression decreased with age [6,7,19]. (Table 9)

Table 9: Comparison of Hormone receptor status with Age of the patients with Breast carcinoma

Study	AGE	Hormone receptor status
Azizun-nisa *et al* 2008 [7]	>50 years No correlation No correlation	ER+ PR+ HER2/neu
Adedayo *et al* 2009 [12]	>60 years	ER+/PR+
Vaidyanathan*et al* 2010 [19]	No correlation	HER2/neu
Ambroise *et al* 2011 [6]	>65 years No correlation <50 years	ER+ PR+ HER2/neu
Ghosh *et al* 2011 [5]	>70 years <35 years	ER+/PR+ Triple negatives
Patil*et al* 2001[18]	<35 years	Triple negatives
Present study 2014	No correlation	ER,PR,HER2/neu

In the present study significant correlation was established between ER/PR hormone receptor status and grade of the tumor. 78.9% of grade 1 and 64.9% of grade 2 were ER+/PR+ and 62.9 % grade 3 tumors were triple negatives. This was in concordance with other Indian and western literatures [6,7,8,12,19-25]. In the present study no significant correlation was seen between Her2/neu and tumor grade similar to other studies except for a study by Ambroise*et al* wherein he concluded Her2/neu overexpressed tumors are grade 3 [6,7,19,26](Table 10)

Table 10:- Comparison of Hormone receptor status with Grade of the tumor

Study	Grade Of Tumor	Hormone Receptor Positive
Azizun-nisa*et al* 2008 [7]	Grade1 No correlation	70% ER+/PR+ Her2/neu
Adedayo *et al* 2009 [12]	Grade 1&2 Grade 3	28.9% & 44.9% ER+/PR+ 76.3% triple negatives
Vaidyanathan *et al* 2010 [19]	No correlation	Her2/neu
Ambroise *et al* 2011 [6]	Grade 1 Grade 3	ER+/PR+ Her2/neu Triple negatives
Suvarchala *et al* 2011[8]	Grade 2	51.85% ER+/PR+
Present study 2014	Grade 1 Grade 3	78.9% ER+/PR+ 62.9% Triple negatives

Very few studies have compared hormone receptor expression and stage of the breast carcinoma and revealed that patients with ER, PR positive present with early stage breast carcinoma [12,17]. Her2/neu receptor showed no correlation with the staging [27]. However in the present study no significant correlation was established between all three receptors and the stage of breast carcinoma. (Table 11)

Table 11: Comparison of Hormone receptor status with Staging of Breast carcinoma

Study	Stage	Hormone Receptor Status
Adedayo*et al* 2009 [12]	Stage 1	ER+/PR+
Vaidyanathan*et al* 2010 [19]	No correlation	Her2/neu
Rai *et al* 2010 [17]	Stage 1	ER+
Present study 2014	No correlation	ER,PR,HER2/neu

5. Conclusion

Majority of tumours of grade 1 were ER, PR positive and majority of grade 3 tumours were triple negatives which exemplifies the fact that higher the grade, lower is the hormone receptor expression. This study highlights the importance of grading and hormone receptor status evaluation. Grading highly correlates with the survival rate and receptor status predicts the response to hormonal therapy. Histopathological grading put together with receptor status offers an excellent method of correlation of survival rate and response to hormonal therapy. This lightens up a prospect of various treatment modalities for the needful.

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