

Study of Morphological Features of Carcinoma of Breast in Relation to ER/PR and Her2/neu Status

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ABSTRACT

Introduction: A steep rise in breast cancer cases is anticipated over the coming years in India. Breast cancer in India, is the most common cancer among women in the urban areas and ranks second in the rural population. **Aims:** To study the morphological features of breast carcinoma, to identify hormone receptor status and to study the relation between morphological features and hormone receptor status. **Materials and Methods:** This was a retrospective and prospective study carried out over a period of two years. A total of 100 cases of carcinoma breast were studied for morphological features and their relation to hormone receptor status. **Results:** The mean age at presentation was 50 years and was more common in postmenopausal women, (70 %) cases. Right breast, especially the upper outer quadrant was most frequently involved. (52% cases). Most common size of tumor ranged between 2 to 5cm. Most common histological type of breast carcinoma was invasive ductal carcinoma NOS (not otherwise specified) (83.2%). Both premenopausal and postmenopausal cases showed triple negative as the most common pattern. Among the invasive ductal carcinoma cases, triple negative was the most common pattern. Most common tumor grade in the present study group was grade II and triple negative was the most common pattern in this group. Well defined lymphovascular emboli were present in 16 %, tumor necrosis in 53% of cases and desmoplasia in 60% of cases. Only 16% of cases showed infiltration of basal cut margin. **Conclusion:** Breast cancer cases diagnosed at an earlier stage have more favorable prognosis. Increasing the awareness in the public and good programs for early detection of the disease will go a long way in reducing breast cancer.

Key words: Breast carcinoma, Immunohistochemistry, Morphology and Triple markers.

Introduction

A steep rise in breast cancer cases is anticipated over the coming years in India. A 2005 study conducted by the international Association of Cancer Research, France, projected that India would have 250 000 cases of breast cancer by 2015. India reports around 100000 new cases per year.[1] Breast cancer, in India, is the most common cancer among women in the urban areas and ranks second in the rural population.[2]At present,

the routine histopathology report of breast carcinomas is followed by Immunohistochemistry for estrogens and progesterone receptor status (ER & PR) and Her2/neu markers study. [3]Based on the result of these markers, further treatment is planned and the response to treatment also depends on the expression of these markers. **Our aim is to** study the morphological features of breast carcinoma, identify hormone receptor status and to study the relation between morphological features and hormone receptor status.

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Materials and Methods

This was a retrospective and prospective study carried out in the department of Pathology, MNJ Institute of Oncology & Regional Cancer Center, and Osmania

Medical College, Hyderabad, over a period of two years, from September 2010 to September 2012.

Detailed clinical history was recorded which included patient demography, clinical presentation and examination findings plus staging investigations. Lab investigations, mammography and fine needle aspiration cytology reports were also noted when available.

For the prospective cases, specimens were fixed in 10% buffered formalin for 18-24 hours. The tumor size was assessed macroscopically and representative tissue bits were processed in automatic processor and paraffin blocks were made. For the retrospective cases, formalin fixed, paraffin embedded tissue blocks were recovered from archives. Routine hematoxylin and Eosin (H & E) staining was done for each case and examined for the following features:

- Histological type of tumors based on 2003 WHO classification [4] and grade based on Nottingham modification of Scarf-Bloom Richardson histological grading system.
- Vascular involvement
- Lymph node involvement: Number of lymph nodes with tumor deposits was noted.
- Area of necrosis
- Desmoplasia
- Status of basal cut margin: Infiltrated or free
- Adjacent area changes: in situ component, sclerosing adenosis, fibrocystic disease, lymphocytic infiltration

Estrogen and Progesterone receptor and Her2/neu staining technique by IHC:

DAKO monoclonal mouse antihuman estrogen receptor of clone ID5 and PgR 636 were used for estrogen and progesterone receptor respectively. BIOGENICS monoclonal mouse anti human antibody for Her2/neu receptor was used.

Allred scoring was used for ER and PR expression. Her2/neu [5] was scored on a 0 to 3 scale

0 - Negative – no staining, 1+ (negative) = faint/ barely perceptible partial membrane staining in any proportion of tumor cells

2+ (weak positive)= A weak to moderate complete membrane staining of > 10% of tumor cells or strong complete membrane staining of < 30% of tumor cells.(since FISH technique was not available, 2+ was considered as negative.)

3+ (Strong positive) = A strong complete membrane staining in >30% of tumor cells.

Results

A total of 100 cases of breast carcinoma were studied with patient age ranging from 22 to 79 years, the mean being 50 years. The highest incidence of breast carcinoma was found in the age group of 40-49 years (37%) and the least incidence was in the age group of < 30 years (4%). Right breast was involved in 52 cases (52%), 47 cases (47%) were from left breast and one case (1%) was bilateral. The upper outer quadrant of the breast was involved in 56% of all the tumors.

In 100 cases, ER+ cases were 48 (48%), ER- cases were 52 (52%), PR+ cases were 40 (40%) and PR- were 60 (60%). Her2 /neu +ve 48 cases (48%) Her 2/neu-ve 52 cases (52%)

In the present study, cases were divided into following 6 groups based on expression of ER, PR and Her 2/ neu expression

Group 1 ER+/PR+: 33 cases (33%)

Group 2 ER+/PR-: 15 cases (15%)

Group 3 ER-/PR+: seven cases (7%).

Group 4 ER-/PR-: 45 cases (45%)

Group 5 Her2 neu+: 48 cases (67%)

Group 6 Her2 neu- : 33 cases (33%)

Table 1: Age wise- ER, PR, Her2/neu positivity

Age (years)	No. of cases (%)	ER+/PR-	ER+/PR-	ER-/PR+	ER-/PR-	HER2/neu+	HER2/neu-
20-29	4	50	-	-	50	50%	50%
30-39	11	36.36	18.18	-	45	63.63%	36.36%
40-49	37	21.62	13.51	8	56.75	37.83%	62.16%
50-59	22	36.36	13.63	18.18	31.81	40.9%	59.09%
60-69	20	45	25	-	30	60%	40%
70-79	6	50	-	-	50	66.66%	33.33%

In the present study, 70 cases (70%) were postmenopausal and 30 (30%) were premenopausal. Of the 70 postmenopausal cases, 23 cases(32.85%) were ER+/PR+, 11 cases (15.71%) were ER+/PR-, five cases (7%) were ER-/PR+ and 31 cases (44.28%) were

ER-/PR-. Her 2 neu -ve were 45 (64.28%); Her2 neu +ve were 25 (35.71%)Of the 30 premenopausal cases, 10 cases(33.33%) were ER+/PR+, 11 cases (15.71%) were ER+/PR-, five cases (7%) were ER-/PR+ and 31 cases (44.28%) were ER-/PR-,two cases (6.66%) were

ER-/PR+ and 14 cases (46.66%) were ER-/PR-. 16 cases Her 2 neu -ve (53.30%) ; 14 cases Her2 neu +ve (46.6%)

Tumor size and its relation to ER and PR expression:

Out of 100 cases, eight cases (8%) had tumor size of <2 cm in maximum diameter, 82 cases (82%) were 2 cm to 5 cm and 10 cases (10%) were >5 cm.

Among the eight cases of breast carcinoma with size <2 cm, three cases (37.5%) were ER+/PR+, one case (12.5%) was ER+/PR- and four cases (50%) were ER-/PR-. 4 cases Her2/ neu + (50%), 4 cases Her2/ neu - (50%).

Among the 82 cases with size between 2cm and 5 cm, 29 cases (35.36%) were ER+/PR+, 13 cases (15.85%) were ER+/PR-, five cases (6%) were ER-/PR+ and 35 cases (42.68%) were ER-/PR-. 32 cases Her2 /neu + (39%), 50 cases Her2 /neu - (60.9%)

Of the 10 breast carcinoma cases with size > 5 cm, one case (10%) was ER+/PR+, one case (10%) was ER+/PR-, two cases (20%) were ER-/PR+ and six cases (60%) were ER-/PR-. 3 cases Her2/ neu + (30%), 7 cases Her2 /neu - (70%).

Morphology

Based on morphology , 86 cases (86%) were Infiltrative duct cell carcinoma NST (No specific type)

and the other histological types were two cases (2%) of Paget's disease, three cases (3%) each of Lobular carcinoma, and Mixed ductal and lobular carcinoma, and one case (1%) each of Intraductal Comedo-carcinoma, Cribriform carcinoma, Mucinous carcinoma, and Medullary carcinoma.

Of the 86 Invasive ductal carcinoma NST cases, 26 cases (30.23%) were ER+/PR+, 13 cases (15.11%) were ER+/PR-, seven cases (8%) were ER-/PR+ and 40 cases (46.51%) were ER-/PR-. Her2/ neu +ve 30 cases (34.8%), Her 2/ neu -ve 56 cases (65.11%)

Both the Paget's disease cases were triple negative.

Out of three Lobular carcinomas, two cases (66.66%) were ER+/PR+, and one case (33.33%) was ER-/PR-. 3 cases Her2 /neu +ve (100%)

All the three cases of papillary carcinoma and one case of Intraductal Comedo carcinoma were triple positive.

Both the cases of mixed ductal and lobular carcinoma were ER+/PR-.

Cribriform carcinoma was ER+/PR+. Her2 /neu -ve

Mucinous and Medullary carcinoma were triple negative.

According to Scarf Bloom Richardson grading, 38 % were of grade I, 47 % were grade II and 14 % were grade III.

Table 2: Grade wise distributions and Immunohistochemistry Triple Marker Results (99 cases)

Histologic Grade	No of Cases	%	ER/PR +	ER+/PR-	ER-/PR+	ER/PR-	Her2/neu+	Her2/neu-
Grade I	38	38	47.3%	18.42%	7.8%	26.3%	55.2%	44.7%
Grade II	47	47	25.5%	12.7%	6.0%	55.3%	36.1%	63.8%
Grade III	14	14	14.2%	14.2%	7.0%	64.2%	14.2%	85.7%

Vascular /Perineural involvement

Out of 100 cases, only 15 cases (15%) showed well defined vascular emboli, four cases (4%) showed Perineural invasion and a majority of 79 cases (79%) did not show well defined vascular involvement in the slides studied. Two cases (2%) showed both vascular emboli and Perineural involvement.

Lymph nodal involvement

Out of the 100 cases, 91 cases were modified radical mastectomy (MRM) specimens with identifiable lymph nodes, a total of 48 cases (53%) showed tumor deposits in the lymph nodes and 43 cases (47%) did not show any deposits.

In nine cases, no lymph nodes were identified. Among these, one case was simple mastectomy and eight were lumpectomy specimens.

Tumor necrosis

Out of the 100 cases, 56 cases (56%) were positive and 44 cases (44%) were negative for tumor necrosis.

Desmoplasia

Out of the 100 cases, 60 cases (60%) showed desmoplasia.

Margin status

Out of the 100 cases, only 6 cases (6%) showed infiltration of the basal cut margin.

Surrounding breast tissue lesions

The lesions surrounding the tumor were, Ductal carcinoma in situ (DCIS) in 24 cases (24%), Fibroadenoma in two cases (2%), Sclerosing adenosis in 41 cases (41%), Lymphocytic infiltration in 19 cases (19%), Fibrocystic disease (FCD) in 15 cases (15%), Lobulitis in five cases (5%), Atypical ductal hyperplasia (ADH) in six cases (6%), and Atypical lobular hyperplasia in three cases (3%).

Note: surrounding tissue in some cases showed multiple lesions in the same case in different combinations. No abnormality was seen in surrounding tissue in 12 cases.

Discussion

Breast cancer incidence rates are increasing worldwide. In India, it is the most common cancer among women in many regions and has overtaken cervical cancer, which was the most common cancer a decade ago.[2] At present, lot of weightage is given to the predictive and prognostic factors in breast carcinoma. The former is related to the patient response to a specific therapy,

while the latter is related to the metastatic potential of the tumor. It is important to know the hormone receptor status for treatment planning. Especially, the status of Her2/neu as its amplification is present in approximately 30% of breast cancers and is associated with increased disease recurrence. Patients with positive Her 2/ neu are amenable to treatment with Trastuzumab.[6]Joint ER/PR expression is better in identifying breast cancer variants than individual ER or PR expression. There may be general agreement concerning concordant joint profiles (ER-/PR+ and ER-/PR-), but the discordant pair (ER+/PR- & ER-/PR+) is controversial.

Table 3: Comparison of ER/PR patterns

	ER+/PR+ (%)	ER+/PR- (%)	ER-/PR+ (%)	ER-/PR-(%)
Nadji et al[7]	3016 (55)	1084 (20)	0 (0)	1397 (25)
Desai et al[8]	199 (25)	59 (7.4)	167 (21.1)	373 (46.5)
Vaidyanathan et al[9]	152 (42.4)	28 (7.8)	16 (4.4)	162 (45.2)
Dutta et al[10]	10 (13)	13 (18.3)	22 (27.3)	50 (66.6)
Arpino et al[11]	31415 (57)	13404 (25)	1621 (3)	8425 (15)
Present study	33 (33)	15 (15)	7 (7)	45 (45)

Table 4: Comparison of Her 2 Neu expression

	Her 2 Neu +	Her 2 Neu -
AzizunNisa et al [12]	56 (37.4%)	94 (62.7%)
Bhagat et al [13]	16 (27.5%)	42 (27.5%)
Ambroise et al[14]	87 (27.1%)	234 (72.9%)
Present study	48 (48%)	52 (52%)

In the present study, the most common pattern of hormone receptor expression was ER- /PR- similar to Indian studies conducted by Desai et al[8], Vaidyanathan et al [9] Dutta et al.[10]and to the study of Arpino et al [11]In the present study Her2/neu positivity was 48% & negativity was higher, at 52%. Different studies [12, 13, 14] were reviewed and compared with the present study. All the reference studies have shown a definite increase in Her 2/neu negativity in the tumors. These negative tumors cannot be considered for treatment with Trastuzumab. Studies done by Bhagat et al [13] and Ambroise et al. [14] showed percentage of 27.5% and 72.9% Her2/neu negativity compared to other studies. Women with breast carcinoma who have triple positive tumors live longer than women who have triple negative tumors because of lesser therapeutic options in the latter group. The least common pattern in the present study was ER+/ PR- pattern similar to Vaidyanathan et al [9], and

Arpino et al [11].Although <5% of tumors are ER-/PR+, these tumors respond to hormone therapy, and PR status is predictive of response to hormone manipulation. It is felt that PR may be a better indicator of endocrine responsiveness than ER alone.[15] Studies done by Desai et al[8]and Dutta et al [10] showed ER+/PR- and ER+/PR+ as the least common pattern respectively. Patients with ER+/PR negative tumors respond nearly as well to anastrozole (aromatase inhibitor) as those with ER+/PR+ tumors suggests that the ER signaling pathway is functional in may ER+/PR- tumors, which is due to the PR gene regulation via the estrogen pathway.[11]

Age distribution and its relation to ER, PR and Her 2/neu expression

In the present study, the average age of the cases at presentation was 50 years similar to findings of the

National Cancer Registry Project (NCRP) network during the period of 1994 -98 which reported age range from 44.2 years in Dibrugarh to 49.6 years in Bangalore and Chennai registries. [16]In contrast, the average age of occurrence of breast cancer among US white females has been reported to be 61years.[16]In Indian population, the incidence begins to rise in the early thirties and peaks at 50-64 years. The reasons are not clear, but it could be due to under-diagnosis and under-reporting amongst the elderly population in India.[17] Pillers (1992) combined data on histological grading from two centers and found that there was a higher frequency of poorly differentiated carcinomas in patients aged 34 years and below.[18]In the present study, majority of patients were in the age group of 40-49 years with predominance of 56.75% cases with ER-/PR negative expression in contrast to study by Grann and co-workers [19] which showed 60.5% of ER+/PR+ as the predominant hormone receptor expression pattern. The triple negative tumors have been associated with younger patient ages as well as poorer tumor stage and grade.[17]In the present study, cases with age below 30 years showed equal incidence of ER+/PR+ and ER-/PR- pattern of expression and in age group between 30 to 50 years ER-/PR- pattern was more common. In our study, highest positivity for Her2/neu was noted in the age group of 70-79 with 66-66% which is indeed a good prognostic factor as these patients can be offered Trastuzumab. With increase in age, the ER/PR expression pattern showed increase in ER+/PR+ cases similar to studies done by Grann et al [19]. The age frequency distributions are greatly affected by ER/PR statuses as well as by racial/ ethnic groups. The ER+PR+ tumors tend to have 2 age peaks, one at younger ages (age peaks of 37-52 years) and one at older ages (age peaks of > 65 years).[17]In the present study when the ER/PR expression pattern was studied in the age group above 60 years, it was noted that the incidence of ER-/PR- again increased gradually, but sample is too small for generalizing the expression pattern.In the present study, incidence of ER-/PR+ tumors were seen comparatively in younger

patients that ER+/PR- cases similar to reports of Anderson et al [7]Which is consistent with the association of increased ER concentration with ageing and increased PR concentration with premenopausal status.

Menstrual status and its relation with ER, PR and Her2/neu expression

In the present study, 70% of breast carcinoma cases were detected in postmenopausal women similar to studies done by Anderson et al where it was reported as 77%. [15]In our study, both premenopausal and postmenopausal women showed predominance of ER-/PR- pattern in contrast to study by Anderson et al [15]which showed ER+/PR+ as the predominant pattern. Concordant with the present study, persistence of ER-/PR- pattern was also found in the menopausal age group in study by Dutta et al.[10]Among the postmenopausal women, the incidence of ER+/PR-cases and among the premenopausal women, the incidence of ER-/PR+ cases were higher, similar to Anderson et al study respectively.[15]In the present study Her 2 neu negativity is observed in both premenopausal and post menopausal women with a percent of 53.3% % 64.28% respectively. The findings are similar to the reference study by Zheng W et al[20]which also showed Her2 Neu negativity in premenopausal and post- menopausal women as27.4% and 24.8% respectively. In the reference study Her 2/ neu positivity pattern is close relatively in both premenopausal and post menopausal women. Present study showed predominant involvement of the right breast (52%) which is similar to the study done by Saleh. [21]where it was reported as 53. 6 %.

Tumor size and its relation to ER, PR and Her 2 /neu expression

In the present study, in majority of cases the tumor size ranged between 2 and 5 cm similar to studies by Azizun-Nisa et al [12] and Saleh et al [21].

Table 5: Comparison of tumor size distribution

Tumor size (cm)	Farid Salah et al [21] (%)	Azizun-Nisa et al[12] (%)	Present study n(%)100cases
< 2	25 (15.1)	18 (12)	8 (8)
2-5	89 (53.6)	79 (52.7)	82 (82)
> 5	52 (31.3)	53 (35.3)	10 (10)

In the present study, the least common tumor size was <2 cm similar to studies done by Saleh et al.[21] and

Azizun-Nisa et al [12], but the incidence of tumors with size >5 cm was comparatively higher in their

studies than the present study. Breast cancer patients of Indian origin tend to be younger, with high grade, larger tumors as compared to western series.[22]

Comparison of tumor size and Her2 /neu status

In the present study there is predominant Her2 /neu negativity in all the size groups in concordance with the reference study by Azizun-Nisa et al.[12]

Tumor type and its relation to ER, PR and Her 2/neu expression

In our study, the most common histological type was invasive ductal carcinoma similar to studies done by Saleh et al [21]. Histology as a prognostic factor has been well documented. Invasive ductal carcinoma (NST) has a poor survival compared to other types.[16] In the present study, among the invasive ductal carcinoma cases, ER-/PR- was the most common pattern, similar to Indian study done by Kaul et al[22], but is in contrast to studies done by Dunnwald et al [23].. Grann et al [19] which showed ER+PR+ as the most common pattern. The high frequency of positive ER in invasive lobular carcinoma may reflect a special selective sensitivity of this distal segment of the duct to estrogens and other hormones. In the present study, ductal carcinoma showed a predominant Her2 /neu negative pattern in about 65.11% which is similar to the study by Hoff et al [24] which showed negativity in 60 %. In contrast to the ductal carcinoma, the lobular and mixed variants showed a predominant Her2 /neu positivity with about 100% and 100% respectively in the present study. This is similar to the study by Hoff et al[24] which showed 97% & 96% positivity respectively.

Tumor grade and its relation with ER, PR and Her2/ neu expression

In the present study, the most common tumor grade was grade II (47%) similar to studies by Yamashita et al(57%), [25] Dutta et al(76%).[10] The least common was grade III in contrast to grade I in both Yamashita et al[25] and Dutta et al. [10] In the present study the Her2/neu negativity increased from Grade I to III which compares well with the study of Azizun- Nisa et al [12]In the present study, grade I tumors showed predominance of positive ER and PR expression similar to studies done by Saleh et al [21] and Azizun-nisa et al [12]. Similar association of ER positivity with low grade tumors was shown by Rosen et al.[26]In the present study among the grade II tumors, negative ER and PR expression was predominant

similar to studies done by Saleh et al [21], Kaul et al[22] and Azizun- Nisa et al. [12]Among the grade III tumors, negative ER expression was predominant type and correlated well with studies done by Saleh et al [21], Peiro et al [27] and Azizun- Nisa et al [12], but negative PR expression showed predominance in the present study in contrast to Saleh et al [21] and Azizun –Nisa et al [12] studies. High grade tumors are likely to have more lymph nodal metastases, recurrences and metastasis related deaths.[28]

Lymphovascular/Perineural involvement

In our study, only 16% cases showed vascular emboli in contrast to 31.4 % reported by Peiro et al [27]where 210 cases were studied. The incidence of blood vessel invasion ranges from under 5% to almost 50%. This is due to variety of factors including patient population, the criteria and methodology used and difficulty in identifying blood vessels.Vascular invasion correlates with grade of the tumor, tumor size and lymph nodal status.[28]

Lymph nodal involvement

In the present study, a majority of 53% cases showed axillary lymph nodal involvement similar to studies by Azizun-Nisa et al [12] and Ahmad et al [28]. In contrast, the study done by Lisa et al [23] showed only 37% of lymph nodal involvement.

The survival rate also depends upon the level of the axillary node involved (low, medium or high), the absolute number (fewer than4, versus 4 or more) the amount of metastatic tumor and the presence or absence of extra nodal spread.[29]

Tumor necrosis

In the present study, 56% of cases showed tumor necrosis in contrast to only 37% of cases in Peiro et al [27] study. But similar to our study a higher proportion of tumor necrosis was noted in Azizun-nisa et al study (70%).[12] Extensive tumor necrosis is associated with an aggressive clinical course and decreased survival rates. [28]

Desmoplasia

Desmoplasia, is a poorly understood phenomenon often associated with invasive carcinoma.It is regarded as a host reaction to the invasive tumor. In the present study, only 60% of cases showed desmoplasia in contrast to 94% in Azizun-Nsa et al [12] study.

Margin status

In the present study, 16% of cases showed microscopic involvement of basal resected margin. Tumor margins often represent a reliable source of positive or negative disease outcome.[21]

In the present study, the most common associated lesions in the surrounding breast tissue were sclerosing adenosis and fibrocystic disease (FCD). The intensity of the lymphoid and plasmacytic reaction in or around a primary mammary carcinoma represents an immunological reaction to tumor antigens.

Conclusion

The high proportion of receptor negative cases can be partially explained by the younger age of our patients or due to real racial differences. Due to differences in genotype, phenotype, lifestyle, socio-demographic structure and ethnicity, the presentation and behavior of breast cancer in India may be different [22]. It is well known that breast cancer cases diagnosed at an earlier stage have more favorable prognosis. Increasing the awareness in the public and good programs for early detection of the disease will go a long way in reducing breast cancer.

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Source of Support: Nil

Conflict of Interest: None