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Study of morphological features of breast carcinoma in relation to ER/PR status

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Abstract

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. Prognosis is related to a variety of clinical, pathologic and molecular features. Immunohistochemical evaluation of estrogen receptor (ER) and progesterone receptor (PR) status of breast carcinoma has become a routine investigation to predict the response to endocrine therapy.

Aims and Objectives: To study patient and tumor characteristics in relation to estrogen and progesterone receptor (ER & PR) status of the tumor.

Materials and Methods: This is a retrospective and prospective study of 100 cases of breast carcinoma diagnosed during January 2007 to September 2011 in the department of Pathology, NRI Medical College, and Chinakakani. Clinical details were archived from the files. Routine histological examination and Immunohistochemical analysis of all the cases were done.

Results: Tumors were separated into four categories: ER+PR+ (33%), ER+PR− (15%), ER−PR+ (7%) and ER−PR− (45%). ER and PR immunoreactivity increased with advancing age. 52% of cases were in the right breast. Invasive lobular carcinoma, and papillary carcinoma were more frequently ER+PR+. High-grade infiltrating ductal carcinomas, pure comedo ductal carcinoma in situ, mucinous carcinoma and medullary carcinoma were predominantly ER−PR−. ER & PR immunoreactivity decreased with increasing tumor grade, lymph nodal metastasis, presence of tumor necrosis, desmoplasia and lymphovascular emboli.

Conclusion: Histological grading together with receptor status offers an excellent method of predicting the prognosis and response to hormonal therapy which lightens up a prospect of various treatment modalities.

Keywords: Breast carcinoma, Morphological features, ER/PR status.

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)]

Breast cancer survival is linked to early detection, timely appropriate treatment and genetic predisposition. Prognosis is related to a variety of clinical, pathologic and molecular features which include classical prognostic factors viz. histologic type, grade, tumor size and lymph node metastases.[(2)]

The role of prognostic factors in optimizing treatment for breast cancer patients has clearly changed with the trend toward general use of adjuvant therapy. There are at least three situations in which prognostic factors could be helpful. The first is to identify patients whose prognosis is so good that adjuvant therapy after local surgery would not be cost-beneficial. The second is to identify patients whose prognosis is so poor that a more aggressive adjuvant approach would be warranted. The third is to identify patients likely to be responsive or resistant to particular forms of therapy.[(3)]

Immunohistochemical evaluation of estrogen receptor (ER) and progesterone receptor (PR) status of breast carcinoma has become a routine investigation to predict the response to endocrine therapy.[(4)] Survival and response to hormonal therapy are most favorable among women diagnosed with tumors positive for both the ER and PR, intermediate for tumors discordant on receptor status (ER+PR–, ER–PR+), and least favorable for tumors negative for both receptors.[(5)]

Objective

To study patient and tumor characteristics in relation to estrogen and progesterone receptor (ER & PR) status of the tumor.

Materials and Methods

100 Modified radical mastectomy specimens received during January 2007 to September 2011 were subjected for routine histopathological examination and Immunohistochemical analysis. Clinical details were archived from the files. Specimens were routinely fixed for 24-48 hours in 10% buffered formalin. They were examined grossly and representative tissue bits were taken according to instituitional guidelines and then processed. Sections were stained with routine hematoxylin and eosin (H&E) stain. Histopathological features were determined, 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 poly 'L' lysine coated slides. Antigen retrieval was done by microwave method using citrate buffer solution and slides stained with Monoclonal antibodies obtained from DAKO Company - ER (mouse monoclonal clone

clone ID5), PR (mouse monoclonal clone PgR 636). Staining pattern for both the receptors was looked for in the tumor nuclei and staining in even 1% of all the tumor nuclei was reported as positive.

Results

In this study of 100 breast carcinoma cases, estrogen positive (ER+) cases were 48 (48%), estrogen negative (ER–) cases were 52 (52%), progesterone positive (PR+) cases were 40 (40%) and progesterone negative (PR–) were 60 (60%).

Cases were divided into following 4 groups based on expression of ER and PR:

Group 1. ER+/PR+: 33 cases (33%) (Fig. 1), Group 2. ER+/PR–: 15 cases (15%), Group 3. ER–/PR+: 7 cases (7%), Group 4. ER–/PR–: 45 cases (45%).

Age range for breast carcinoma was from 22 to 85 years with a mean of 50 years and highest incidence in the age group of 40 – 49 years (37%). The least incidence of breast carcinoma was in the age group of < 30 years (4%). Of the total 37 cases in 40-49 age group, 8 (21.62%) were ER+/PR+**,** 5 (13.51%) were ER+/PR–, 3 (8%) were ER–/PR+, and 21 cases (56.75%) were ER–/PR–.

In the present study out of 100 cases, a total of 70 cases (70%) were postmenopausal cases and 30 cases (30%) were premenopausal cases. 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–. Of the 30 premenopausal cases, 10 cases (33.33%) were ER+/PR+, four cases (13.33%) were ER+/PR–, two cases (6.66%) were ER–/PR+ and 14 cases (46.66%) were ER–/PR–.

Out of 100 cases of breast carcinomas, 52 cases (52%) were from right breast, 47 cases (47%) were from left breast and one case (1%) was bilateral. 56% of all the tumors showed involvement of upper outer quadrant of the breast.

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

Among the 82 cases of breast carcinoma with size between 2 cm 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–.

In the present study out of 100 cases, 86 cases (86%) were Invasive duct cell carcinoma NOS and the other minor group of histologic types were 2 cases (2%) of Paget's disease, 3 cases (3%) of Lobular carcinoma, 3 cases (3%) of Mixed ductal and lobular carcoinoma, 1 case (1%) of Intraductal comedo carcinoma, 1 case (1%) of Cribriform carcinoma, 1 case (1%) of Mucinous carcinoma (Fig. 2), and 1 case (1%) of Medullary carcinoma.

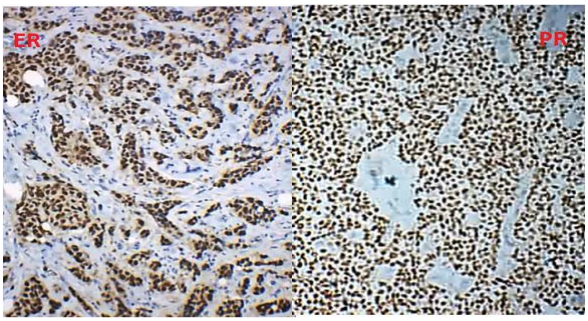

Fig. 1: Positive (nuclear) Estrogen and Progesterone receptor status (IHC x400)

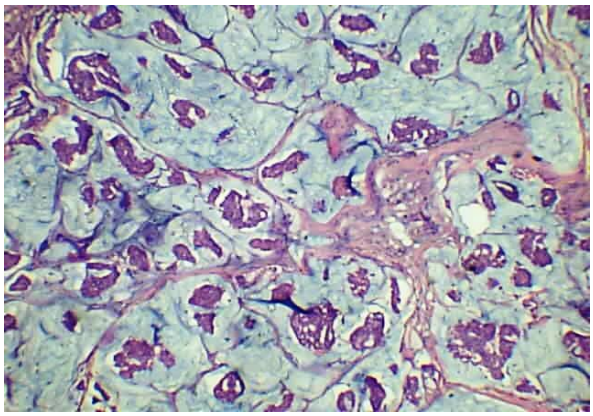

Fig. 2: Mucinous carcinoma. Lakes of mucus separated by thin fibrous septae and a few isolated or clusters of tumor cells are seen floating in the mucus lakes (H & E, x100)

Of the 86 Invasive ductal carcinoma NOS cases, 26 cases (30.23%) were ER+/PR+, 13 cases (15.11%) were ER+/PR–, 7 cases (8%) were ER–/PR+ and 40 cases (46.51%) were ER–/PR–. Both the Paget's disease cases were ER–/PR–. Among 3 Lobular carcinomas, 2 (66.66%) were ER+/PR+, and 1 (33.33%) was ER–/PR–. All the 3 cases of Papillary carcinoma were ER+/PR+. Both the cases of Mixed ductal and lobular carcinoma were ER+/PR–. Intraductal comedo carcinoma was ER+/PR+. Cribriform carcinoma was ER+/PR+. Mucinous carcinoma was ER–/PR–. Medullary carcinoma was ER–/PR–.

Out of 100 cases, 38 cases (38%) were grade I tumors, 47 cases (47%) were grade II tumors and 14 cases (14%) were grade III tumors according to Nottingham modification of Bloom–Richardson's histopathological grading. 1 case was Ductal in situ carcinoma with intermediate grade morphology.

Of the 38 grade I tumors, 18 cases (47.36%) were ER+/PR+, 7 cases (18.42%) were ER+/PR–, 3 cases (7.8%) were ER–/PR+ and 10 cases (26.31%) were ER–/PR–.

Of the 47 grade II tumors, 12 cases (25.53%) were ER+/PR+, 6 cases (12.76%) were ER+/PR–, 3 cases (6%) were ER–/PR+ and 26 cases (55.31%) were ER–/PR–.

Of the 14 grade III tumors, 2 cases (14.28%) were ER+/PR+, 2 cases (14.28%) were ER+/PR–, 1 case (7%) was ER–/PR+ and 9 cases (64.28%) were ER–/PR–.

Out of the 100 breast carcinoma cases, 91 cases were modified radical mastectomy (MRM) specimens with identifiable lymph nodes, a majority of 48 cases (53%) showed tumor deposits in the lymph nodes and 43 cases (47%) did not show any deposits. In 9 cases, no lymph nodes were identified during grossing and are labeled as nil.

Out of the 48 breast carcinomas with lymph nodal deposits, a majority of 20 cases (41.66%) were ER–/PR–, other patterns in the order of occurrence were 17 cases (35.41%) with ER+/PR+, 9 cases (18.75%) with ER+/PR– and 2 cases (4.16%) with ER–/PR+ expression. Of the 43 breast carcinoma cases with no lymph nodal deposits, a majority of 21 cases (48.88%) were ER–/PR–, 13 cases (30.23%) were ER+/PR+, six cases (13.95%) were ER+/PR– and three cases (6.9%) were ER–/PR+.

Out of 100 cases of breast carcinoma, 56 cases (56%) showed tumor necrosis and 44 cases (44%) did not show any necrosis in the slides studied. Out of 56 cases with tumor necrosis, 10 cases (17.85%) were ER+/PR+, 10 (17.85%) cases were ER+/PR–, four cases (7%) were ER–/PR+ and 32 cases (57.14%) were ER–/PR–.

Out of 100 cases of breast carcinomas, 60 cases (60%) showed desmoplasia. Among the 60 breast carcinoma cases with desmoplasia, 19 cases (31.66%) were ER+/PR+, 11 cases (18.33%) were ER+/PR–, five cases (8.33%) were ER–/PR+ and 25 cases (41.66%) were ER–/PR–.

The neoplastic and non–neoplastic lesions of breast noted 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 5 cases (15%), Atypical ductal hyperplasia (ADH) in six cases (6%), and Atypical lobular hyperpasia in three cases (3%).

Note: Surrounding tissue in some cases showed multiple lesions in the same case in different combinations and lesions would have been missed due to limited tissue sampling.

Table 1: ER/PR status in relation to age, menstrual status and histopathological features

Parameter	ER+/PR+ (%)	ER+/PR– (%)	ER–/PR+ (%)	ER–/PR– (%)
Age Distribution				
20–29	50	–	–	50
30–39	36.36	18.18	18.18	45
40–49	21.62	13.51	13.51	56.75
50–59	36.36	13.63	13.63	31.81
60–69	45	25	25	30
70–79	50			50
> 80	–	–	–	100
Menstrual Status				
Premenopausal	33.33	13.33	6.66	46.66
Postmenopausal	32.85	15.71	7	44.28
Tumor Size				
< 2cm	37.5	12.5	–	50
2–5cm	35.36	15.85	6	42.79
> 5cm	10	10	20	60
Tumor Type				
Ductal	30.23	15.11	8	46.66
Lobular	66.67	–	–	33.33
Mixed	–	100	–	–
Tumor Grade				
I	47.36	18.42	7.8	26.31
II	25.53	12.76	6	55.31
III	14.28	14.28	7	64.28
Lymphnode Deposit				
Present	35.41	18.75	4	41.66
Absent	30.23	13.95	6.9	48.88
Tumor necrosis				
Present	17.85	17.85	7	57.14
Absent	52.27	11.36	6.81	29.54

Desmoplasia				
Present	31.66	18.33	8.33	41.66
Absent	35	10	5	50

Discussion

Breast cancer incidence rates are increasing worldwide. In India, it is the most common cancer among women in many regions and has overtaken cervix cancer, which was the most common cancer a decade ago.[6]

The current trend in analyzing the clinical outcome of a patient with breast cancer is to examine predictive and prognostic factors related to the patient and the tumor. The former is related to the degree to which the patient could respond to a specific therapy, while the latter is related to the metastatic potential of the tumor. Several studies have examined predictive and prognostic factors, such as the age of the patient, tumor size, grade, proliferation, histological type of the tumor, lymph node involvement and hormone status, to mention a few.[7]

For more than two decades, hormone receptor status has played a key role in treatment decisions for patients with newly diagnosed breast carcinoma and for patients with recurrent disease.[8]

The ER and PR are dimeric, gene–regulatory proteins. These two hormones work together through their nuclear receptors to modulate transcription of target genes to direct mammary epithelial growth, differentiation, and survival. To improve the value of ER determinations for tumor prognosis, tests for the presence of the estrogen–regulated PR protein are routinely performed.[9] It has been suggested that joint ER/PR expression identifies breast cancer variants better than either independent ER or PR expression. There may be general agreement concerning concordant joint profiles (ER+/PR+ and ER–/PR–), but the discordant pair (ER+/PR– and ER–/PR +) has been problematic.[10]

In the present study based on hormone receptor status, cases were divided into four groups ER+/PR+, ER+/PR–, ER–/PR+ and ER– /PR–.

Table 2: Comparison of ER/PR patterns

	ER+/PR+ n (%)	**ER+/PR– n (%)**	**ER– /PR+ n (%)**	**ER– /PR– n (%)**
S.B. Desai et al[11]	199 (25)	59 (7.4)	167 (21.1)	373 (46.5)
Vaidyanathan K et al[12]	152 (42.45)	28 (7.8)	16 (4.4)	162 (45.25)
Col V Dutta et al[13]	10 (13)	13 (18.33)	22 (27.33)	50 (66.66)
Mehrdad Nadji et al[14]	3,016 (55)	1,084 (20)	0 (0)	1,397 (25)
Grazia Arpino et al[15]	31,415 (57)	13,404 (25)	1,621 (3)	8,425 (15)
Present study	33 (33)	15 (15)	7 (7)	45 (45)

In the present study, the most common pattern of hormone receptor expression was ER– /PR– similar to Indian studies conducted by S B Desai et al,[11] Vaidyanathan K Kumar et al[12] and Col V Dutta et al.[13]

Tumors with ER– /PR– pattern of expression tend to have higher proliferation rates, more cells in S–phase, and less likelihood of response to hormone therapy than other tumors.[8] Li et al[8] suggested that both biologic and environmental factors may contribute to these associations. In contrast, studies done by Mehrdad Nadji et al[14] and Grazia Arpino et al[15] showed predominance of ER+/PR+ pattern.

Both observational studies and randomized trials have found that women with breast carcinoma who have tumors that test positive for ER and/or PR live longer than women who have tumors that test negative for both hormone receptors.[8]

The least common pattern in the present study was ER– /PR+ pattern similar to Vaidyanathan K Kumar et al,[12] Mehrdad Nadji et al[14] and Grazia Arpino et al.[15] Although < 5% of tumors are ER–/PR+, these tumors respond to hormone therapy, and PR status is predictive of response to hormone manipulation. It has been suggested that PR may be a better indicator of endocrine responsiveness than ER alone.[8]

Studies done by S B Desai et al[11] and Col V Dutta et al[13] showed ER+/PR– and ER+/PR+ as the least common pattern respectively.

Patients with ER+/PR– tumors respond nearly as well to anastrozole (aromatase inhibitor) as those with ER+/PR+ tumors suggests that the ER signaling pathway is functional in many ER+/PR– tumors, consistent with the well–known fact that the PR gene is regulated by the estrogen pathway.[15]

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– expression in contrast to study by Victor R Grann and co–workers[8] which showed 60.5% of ER+/PR+ as the predominant hormone receptor expression pattern.

The ER–/PR– tumors have been associated with younger patient ages as well as poorer tumor stage and grade.[16]

With increase in age, the ER/PR expression pattern showed increase in ER+/PR+ cases similar to studies done by Victor R. Grann et al,[8] Julie A. Britton et al,[17] Yoo KY et al[18] and Yasui Y et al.[19]

In the present study, 70% of breast carcinoma cases were detected in postmenopausal women similar to studies done by William F. Anderson et al[10] (77%), H J Huang et al[20] (68%).

In the present study, both premenopausal and postmenopausal women with breast carcinoma showed predominance of ER–/PR– pattern similar to study by Col V Dutta et al,[13] but in contrast to study by William F. Anderson et al,[10] which showed ER+/PR+ as the predominant pattern.

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 William F. Anderson et al study respectively.[10]

Present study showed predominant involvement of the right breast (52%) which is similar to study done by Farid Saleh and Suad Abdeen.[7]

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[21] and Farid Saleh et al[7] and ER–/PR– pattern as the predominant pattern in all the tumor size groups.

In the present study, the most common histologic type of breast carcinoma was invasive ductal carcinoma similar to studies done by Farid Saleh and Suad Abdeen.[7]

Table 3: Comparison of histologic type and ER/PR status

Tumor type		Ductal	Lobular	Mixed
ER+/PR+ (%)	A	62.70	73.56	76.74
	B	62.77	73.19	76.06
	C	65	73	77
	D	30.23	66.67	–
ER+/PR– (%)	A	12.31	17.69	13.58
	B	12.20	17.70	13.66
	C	14	19	15
	D	15.11	–	100
ER–/PR+ (%)	A	3.22	2.3	2.3
	B	3.37	2.46	2.61
	C	2	2	2
	D	8	–	–
ER–/PR– (%)	A	21.77	6.45	7.38
	B	21.66	6.65	7.67
	C	19	6	6
	D	46.66	33.33	–

A – Lisa K Dunnwald et al[23] B – Victor R. Grann et al[8] C – CI Li et al[22] D – Present study

Patients with histology of Invasive ductal carcinoma (NST) have a poor survival compared to other types.[6]

Women with lobular, mucinous, comedo, tubular, medullary, and papillary carcinomas have lower risks of mortality compared to women with ductal carcinomas.[22]

In the present study, among the invasive ductal carcinoma cases, ER–/PR– was the most common pattern, similar to Indian study done by Rashmi Kaul et al,[24] but is in contrast to studies done by Lisa K Dunnwald et al[23] Victor R. Grann et al[8] and Ci Li et al[22] which showed ER+/PR+ as the most common pattern.

In the present study, all the three papillary carcinoma cases showed ER+/PR+ expression which is similar to the study by Ci Li et al,[22] who showed 80% cases with ER+/PR+ expression.

In the present study, mucinous carcinoma showed ER–/PR– in contrast to the most common pattern of ER+/PR+ in CI Li et al study.[22]

In the present study, the most common tumor grade was grade II (47%) similar to studies by Hiroko Yamashita et al[25] (57%), Col V Dutta et al[13] (76%) and Judith Hugh et al[26] (45.10 %), and negative ER and PR expression was predominant pattern similar to studies done by Farid Saleh et al,[7] Rashmi Kaul et al[24] and Azizun–Nisa et al.[21]

In the present study, a majority of 53% cases showed axillary lymph nodal involvement similar to Azizun–Nisa et al[21] and Zubair Ahmad et al[27] studies.

In contrast, the study done by Lisa K et al[23] showed only 37% of lymph nodal involvement.

In the present study, predominance of ER–/PR– pattern was seen in both types of breast carcinoma cases with or without lymph nodal involvement in contrast to Lisa K Dunnwald et al[23] study which showed ER+/PR+ pattern predominance.

Table 4: Comparison of lymph nodal deposits and ER/PR status

Lymph node deposit		Absent	Present
ER+/PR+ (%)	A	64.83	60.86
	B	30.23	35.41
ER+/PR– (%)	A	12.3	12.72
	B	13.95	18.75
ER–/PR+ (%)	A	3.1	3.4
	B	6.9	4
ER–/PR– (%)	A	19.76	22.93
	B	48.88	41.66

A – Lisa K Dunnwald et al[23]
B – Present study

The positivity of axillary lymph nodes for metastases is one of the most important prognostic parameters in breast carcinoma with sharp differences in survival rates between those with negative and positive nodes.[28]

In the present study, 56% of cases showed tumor necrosis in contrast to only 37% of cases in Gloria Peiró et al[29] study. But similar to our study a higher proportion of tumor necrosis was noted in Azizun–Nisa et al[21] study (70%).

In the present study, among the breast carcinoma cases with tumor necrosis, ER– /PR– pattern was the predominant pattern similar to Gloria Peiró et al[29] study.

Extensive tumor necrosis appears to be associated with an aggressive clinical course and decreased survival rates.[27]

In the present study, only 60% of cases showed desmoplasia in contrast to 94% in Azizun–Nisa et al[21] study.

In the present study, breast carcinoma cases with desmoplasia showed a predominant ER– and PR– expression similar to Flávia Silva Ferrini et al[30] study.

Multiple studies has shown survival advantages among women with hormone receptor–positive tumors relative to women with hormone receptor–negative tumors. A study by Grann et al[8] that also used data collected from the SEER program reported that joint ER/PR status was an independent predictor of outcome in a large cohort of women with breast carcinoma. A further expansion on this study by Lisa K Dunnwald et al,[31] revealed higher risks of mortality associated with ER+/PR–, ER–/PR+, or ER–/PR– tumors relative to ER+/PR+ tumors, consistently across almost all tumor characteristics.

In ER+ breast cancers, PR– tumors are more aggressive than PR+ cancers.[32]

It has been documented that ER–/PR+ patients have a higher frequency of soft tissue and central nervous system metastases, a lower frequency of bony metastasis and partial responsiveness to tamoxifen treatment as compared to 80% response rate for double positive tumors.[13]

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. Young patients have high levels of circulating estrogens and a correspondingly low expression of steroid receptors which is reflected in their tumors. Due to differences in genetics, environment, lifestyle, socio–demographic structure and ethnicity, the presentation and behaviour of breast cancer in India may be different.[24]

It is well known that breast cancer cases diagnosed at an earlier stage have more favorable prognosis compared to those detected at late stage. However, because of lack of awareness, fear of disease and psychological reasons, most of the patients in our country try to ignore or hide the disease and by the time they come to the hospital, the disease is already in the late stages. This reflects a need for awareness and to initiate programs for early diagnosis of the cancer.

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