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A Study of Hormone Receptor Status & Its Correlation With Age, Tumor Size, Histological Grade, Lymph Node Metastasis In Carcinoma Breast

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Abstract

Background: Breast cancer is an extremely heterogenous disease caused by interaction of both inherited and environmental risk factors. It is the most common cancer in women worldwide.

Methods: The present study was conducted on patients with carcinoma breast, admitted in various surgical wards of Govt. Medical College & associated group of Hospitals, kota. All patients with Cytologically or histopathologically proven operable breast carcinoma undergoing Modified radical mastectomy or Breast conserving surgery in department of surgery were included.

Results: Maximum number of cases in our study were seen in Luminal A (n=32, 45.07%) followed by Basal subtype (n=22, 30.9%) followed by Luminal B(n=10, 14.08%) and HER2 neu (n=7, 9.85%). Maximum percentage of metastatic pathology of lymph nodes was seen in HER-2 molecular subtype. HER-2 tumors were having maximum percentage of metastatic pathology in lymphovascular invasion (85.71%) followed by luminal B(80%) basal like (63.63%)and luminal A (59.37%).

Conclusion: The current study recommends IHC classification as an important clinical tool, at a reasonable cost, aiding in therapeutic decisions and prognosticating cancer breast.

Keywords: Breast, Carcinoma, IHC classification.

Introduction

Breast cancer is an extremely heterogenous disease caused by interaction of both inherited and environmental risk factors. It is the most common

cancer in women worldwide. The life time risk of a woman developing invasive breast cancer is 12.6%.[1]

It has been documented that factors such as age, age at menarche, marital status, age at menopause, place of residence (rural/urban), diet, hormonal exposure and family history of breast cancer can all play roles as risk factor.[2]

Prognosis is related to a variety of clinical, pathological and molecular features which include classical prognostic factors viz. histologic type, histologic grade, lymphovascular invasion, lymph node metastases and status of hormonal receptors-estrogen receptor (ER) and progesterone receptor(PR) and HER2 status of the tumor.[3]

Hormonal status of tumor is the most important predictive and prognostic marker. Current breast cancer treatment strategies rely on the characterization of estrogen and progesterone hormone receptor [estrogen receptor (ER)/progesterone receptor (PR)] protein expression status and human epidermal growth factor (HER2) protein expression or gene amplification.[3]

Prolonged exposure to estrogen could lead to increased proliferation of mammary epithelial cells and mutation events. Progesterone receptor (PR) expression is driven by ER transcriptional activation of the PR gene. Only 5% of Breast cancers are PR Positive and ER negative. In contrast 30% of ER Positive Breast cancer fails to express PR. The role of PR in breast cancer etiology and progression is not well understood.[3]

Materials & Methods

Source of data: The present study was conducted on patients with carcinoma breast, admitted in various surgical wards of Govt. Medical College & associated group of Hospitals, kota. All patients with Cytologically or histopathologically proven operable breast carcinoma undergoing Modified radical mastectomy or Breast conserving surgery in department of surgery were included.

Duration of Study: July 2018 to December 2019.

Method of Collection of Data: Patients with invasive breast cancer were included in the study. After explaining about the study to the patients an informed valid consent was obtained, followed by a detailed history with clinical examination with more emphasis on the parameters given below in variable outcome.

Outcome Variable: The tumors were classified into four groups (luminal A, luminal B, HER2, and triple negative) by their ER/PR/HER2 profile: (1) ER+ve and/or PR+ve but HER2-ve; (2) ER+ve and/or PR+ve and HER2+ve; (3) ER-ve and/or PR-ve but HER2+ve; and (4) ER-ve, PR-ve and HER2-ve (triple-negative).

1.ER/PR+ve, HER 2-ve Receptor relation to age, histological grade, size of lesion and lymph node metastasis.

2.ER/PR+ve, HER 2+ve Receptor relation to age, histological grade, size of lesion and lymph node metastasis.

3.ER/PR-ve, HER 2+ve Receptor relation to age, histological grade, size of lesion and lymph node metastasis.

4.ER/PR-ve, HER 2-ve Receptor relation to age, histological grade, size of lesion and lymph node metastasis.

Sample Size: Patients admitted with carcinoma breast at Department of Surgery at Govt. Medical College & associated Group of Hospitals, Kota, 71 cases of carcinoma breast from July 2018 to dec. 2019 were included in the study.

Selection of patients:

1. Patients of all age groups
2. Patients with diagnosis of carcinoma breast admitted for operation.

All the breast cancer patients were divided into two age groups, <40 years younger age group and >40 years old age group.

Inclusion Criteria

Cytologically or Histopathologically proven operable breast carcinoma undergoing MRM or BCS.

Locally advanced breast carcinoma

Those patients who have given consent for the study.

Exclusion criteria

Metastatic breast Carcinoma.

Patient not willing for surgery

Patient who had received neoadjuvant chemothepy

Patient examination

1. A detailed history was noted with regards to presenting symptoms, onset of the disease, and duration in chronological order. A detailed interrogation regarding the personal, obstetric, lactational & family history was also taken.
2. Detailed local examination including axillary lymph node, size of tumor was done .
3. The examination includes a thorough systemic examination to find the metastasis of the disease. Diagnosis was established by FNAC or Tru-cut biopsy .The patient were subjected to various investigations – routine and specific to find out any metastasis which included x-ray chest, x-ray pelvis and spine LFT,USG Abdomen & pelvis. All these findings were used to interpret the staging pattern of the disease.

Management

The fit patients were operated and axillary dissection was done thoroughly. The specimen obtained after surgery were studied in detail on the basis of histopathology and status of the ER/PR & HER 2 was established.

The Hematoxylin and Eosin stained slides were studied by pathologist. Slides were studied under low power and high power and observations were recorded.

The following parameters were specifically examined:

1. Type of specimen
2. Histologic type
3. Histologic grade- The modified Bloom-Richardson-Elston histological system was used for grading the invasive carcinoma[13,32]
4. Positive lymph nodes for duct carcinoma
5. Lymphovascular invasion

Representative sections with tumor and the adjacent normal breast tissue (internal control) were processed for ER, PR and HER2 immunohistochemical staining.

The observations were received according to the heading in the proforma, the master chart was prepared. On the basis of observations obtained correlation was studied between hormone receptor and age, tumor size, histological grade & lymph node metastasis in carcinoma breast.

Statistical Analysis

Statistical analysis was performed with the SPSS, version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA). The Categorical data were presented as numbers (percent) and were compared amongst groups using Chi square test. Probability was considered to be significant if less than 0.05

Results

This study was conducted on 71 women who fulfilled the inclusion criteria of the study. Hormonal (ER and PR) and HER2 receptor status of all women were studied using immunohistochemistry and following observations were seen.

Table 1: Age Wise Distribution of Patients

Serial no.	Age in years	No. of patients	Percentage (%)
1.	21-30	5	7.04
2.	31- 40	16	22.53
3.	41 -50	18	25.35
4.	51 -60	17	23.94
5.	>61	15	21.12
	Total	71	100

Majority of patients in the present study belonged to 5th (25.35%) and 6th decades (23.94%) accounting for a total of cases. Patients were in the age group between 26 and 75 years, with mean age 50.5 years.

Table 2: Relation of Hormonal Receptor Status to Age in Breast Cancer

Age	No of case	Luminal A	Luminal B	Her 2 neu	Basal like
< 40	21	13(61.90%)	4(19.04%)	0	4(19.04%)
>40	50	19(38%)	6(12%)	7(14%)	18(36%)
Total	71	32	10	7	22

p = 0.043 (S)

In younger age groups Luminal A (61.90%) was most common subtype followed by Luminal B (19.04%), basal like (19.04%).

In old age groups Luminal A (38%) was most common subtype followed by basal like (36%), Her 2 (14%) and Luminal B(12%).

Table 3: Distribution of Patients According to Molecular Subtypes

	Luminal A	Luminal B	HER 2	Basal
Total Cases	32	10	7	22
Percentage	45.07	14.08	9.85	30.9

Maximum number of cases in our study were seen in Luminal A (n=32, 45.07%) followed by Basal subtype (n=22, 30.9%) followed by Luminal B(n=10, 14.08%) and HER2 neu (n=7, 9.85%)

Table 4: Relation of Hormonal Receptor Status to Size of Tumor in Breast Cancer

Size of tumors	No. of cases	Luminal A	Luminal B	Her2 neu	Basal like
<19mm	23(32.39%)	16(69.56%)	2(8.69%)	2(8.69%)	3(13.04%)
20-50mm	28(39.43%)	10(35.71%)	4(14.28%)	5(17.85%)	9(32.14%)
>50 mm	20(28.16%)	6(30%)	4(20%)	0(0)	10(50%)
Total	71	32	10	7	22

P value = 0.028 (S)

In our study the size of the tumor, we saw that out of 71cases; 28 cases (39.43%) were between 2 to 5cms , 23 cases (32.39%) were less than 2cms in size and 20 cases (28.16%) were more than 5 cms in size .Tumor size less 2 cm luminal A (69.56%) was most common followed by basal like (13.04%) and more than 5 cm in tumor size basal like triple negative (50%) was most common followed by luminal A (30%).

Table 5: Relation of Hormonal Receptor Status to Grade of Tumor in Breast Cancer

Grade Of Tumor	No. of cases	Luminal A	Luminal B	Her2 neu	Basal like
I	14(19.71%)	12(85.71%)	1(7.14%)	0(0)	1(7.14%)
II	33(46.47%)	14(42.42%)	5(15.15%)	3(9.09%)	11(33.3%)
III	24(33.80%)	6(25%)	4(16.66%)	4(16.66%)	10(41.66%)
	71	32	10	7	22

P value = 0.030 (S)

In our study, majority of tumors were in Grade II (n=33, 46.47%) followed by Grade III (n=24, 33.8%) and then Grade I (n=14, 19.71%).

Table 6; Relation of Hormonal Receptor status to No. of Positive Lymph Node in Breast cancer

No. of lymph node	No. of cases	Luminal A	Luminal B	Her2 neu	Basal like
0	25(35.21%)	13(52%)	2(8%)	2(8%)	8(32%)
1-3	17(23.94%)	8(47.05%)	4(23.5)	2(11.7)	3(17.6)
4-9	17(23.94%)	7(41.17%)	2(11.7%)	2(11.7%)	6(35.29%)
>9	12(16.9%)	4(33.3%)	2(16.6%)	1(8.33%)	5(41.66%)
	71	32	10	7	22

P value = 0.966 (NS)

Out of 71 cases 46 (64.78%) came out to be positive for metastatic pathology in lymph nodes and 35.21% cases were negative axillary lymph node tumor. They found no association between lymph node status and molecular subtypes.

Table 7: Histopathological Subtype Distribution in All Age Groups

S. No.	Histological Subtype	No.	Percentage (%)
1.	Infiltrating duct carcinoma NOS	66	92.95
2.	Lobular carcinoma	2	2.81
3.	Medullary carcinoma	1	1.40
4.	Colloid carcinoma	2	2.81

Most common histopathological subtype was infiltrating duct carcinoma which comprised 92.95% of all tumor subtype.

Table 8: Relation of Hormonal Receptor status lymphovascular invasion [LVI] in Breast cancer

Molecular subtypes	No. of case	Number	Percentage (%)
Luminal A	32	19	59.37
Luminal B	10	8	80
HER2	7	6	85.71
Basal	22	14	63.63
Total	71	47	66.19

In our study out of 71 cases, 47 cases (66.19%) lymphovascular invasion, HER2 tumors were having maximum percentage of metastatic pathology in lymphovascular invasion (85.71%) followed by luminal B (80%) basal like (63.63%) and luminal A (59.37%).

Table 9. Relation of Hormonal Receptor status to Menopausal status in Breast cancer

Menopausal Status	No. of cases	Luminal A	Luminal B	Her2	Basal
Pre	29(40.84%)	14(48.27%)	6(20.68%)	2(6.80%)	7(24.13%)
Post	42(59.15%)	18(42.85%)	4(9.52%)	5(11.90%)	15(35.71%)
Total	71	32	10	7	22

In our study the mean age at presentation of carcinoma breast was 50.5 years. 59.15 % of cases occurred in the post-menopausal age group with 40.84 % of cases occurred in the pre-menopausal age group

Table 10: Relation of Hormonal Receptor status to Side of Tumor in Breast cancer

Side	No. of cases	Luminal A	Luminal B	Her2	Basal
Right	29(40.84%)	14(48.27)	2(6.89%)	3(10.3%)	10(34.4%)
Left	41(57.74%)	17(41.46%)	8(19.04%)	4(9.52%)	12(28.57%)
Bilateral	1(1.40)	1(100)	0	0	0
	71	32	10	7	22

P value = 0.746 (NS)

In our study, we also saw that 41tumors involved the left side breast (57.74%) while 29 tumors arise from the right side breast (40.84%) and 1 case involve in both side of breast (1.40%) most occurring in the outer upper quadrants. No significant association between side of tumor and molecular study.

Table 11: Expression of estrogen receptors, progesterone receptor and human epidermal growth factor receptor compared

	ER+ve	ER-ve	PR+ve	PR-ve	Her2+ve	Her2-ve
No. of case	42	29	39	32	17	54
Percentage	59.15	40.84	54.92	45.07	23.94	76.05

(p=0.007)

In the present study, positive expression of ER, PR and Her2/neu was found to be 59.15 %, 54.92%, and 23.94% respectively which correlate well with other studies.

Discussion

In our study the size of the tumor, we saw that out of 71cases; 28 cases (39.43%) were between 2 to 5cms , 23 cases (32.39%) were less than 2cms in size and 20 cases (28.16%) were more than 5 cms in size .Tumor size less 2 cm luminal A (69.56%) was most common followed by basal like (13.04%) and more than 5 cm in tumor size basal like triple negative (50%) was most common followed by luminal A (30%).

In India, due to lack of awareness and absence of breast cancer screening program, the majority of breast carcinomas are diagnosed at an advanced stage.

Lobna Ayadi et al.[4] documented in their study that in 12.9% the size of tumor was less than 2cm and in 87% greater than 2 cm.

Study by Nikhra et al.[5] have found a significant association between increasing tumor size and HER2neu expression. In our study Tumors size more than 2cms had high rate of HER2neu expression than those of tumors less than 2cms in size.

In our study, according to Nottingham Modified Bloom–Richardson System score, majority tumors were in Grade II (n=33, 46.47%) followed by Grade III (n=24, 33.8%) and then Grade I (n=14, 19.71%).

This study is similar to grade I, grade II and grade III tumors in the study by Lobna Ayadi et al.[4]was 10.9%, 63.2% and 25.8% and also comparable to study by Dr. Sumita A Jain et al[6] (2014), grade I (11.8%), grade II (53.7%), grade III (31%).

Grade I tumors showed 85.71% positivity in IHC groups Luminal A and 7.14% in Luminal B and Basal like while 42.42% of Grade II tumors showed Luminal A and 41.66% Grade III tumors shows Basal like. In our study Luminal A subtype was maximum no. in Grade I (85.71%) and Grade II (42.42%) tumor and basal like (triple negative) was maximum no. in Grade III tumor (41.66%).

When ER/PR positivity was compared with tumor grades we found that patient with lower tumor grade were more likely to be ER/PR positive as compared to patients with high grade tumor.

It was concluded that ER/PR expression compared to tumor grade was statistically significant and HER/neu was not significant.

In our study out of 71 cases 46 (64.78%) came out to be positive for metastatic pathology in lymph nodes and 25 cases (35.21%) were negative axillary lymph node tumor, 23.94 % in 1-3 lymph node positive, 23.94% in 4-9 lymph node positive and 16.9% in more than 9 lymph node positive tumor. When we compared ER/PR positivity with positive axillary lymph node we found that patient with less numbers of positive nodes more likely to be ER/PR negative as compared to patient with more number of positive lymph nodes.

In our study, 52% cases were ER/PR positive in negative axillary lymph node tumor compared to 47.05% in 1-3 lymph node positive, 41.1% in 4-9 lymph node positive and 33.3% in more than 9 lymph node positive tumor. 32% cases were ER/PR negative in negative axillary lymph node tumor compared to 17.6% in 1-3 lymph node positive, 35.29% in 4-9 lymph node positive and 41.6 % in more than 9 lymph node positive tumor.

These results are according to the result of the studies conducted by Amrut V.et al 2011.[6]

Hormonal receptor positivity inversely proportional to number of positive lymph nodes which is statistically significant.

Out of 71 cases 46 (64.78%) came out to be positive for metastatic pathology in lymph nodes. This is comparable with study done by R R Turner et al.[7] (1997).

In our study comprised of 71 cases of breast carcinoma out of which; 66 cases were of Infiltrating Ductal Carcinoma (IDC) (92.95%), 2 cases of Lobular carcinoma (2.81%), 2 case of Mucinous carcinoma (2.81%) and 1 case of Medullary carcinoma (1.41%).

Our findings were similar to other studies done by Gupta P, Rai N N, Agarwal L, et al[8].(2018) by Invasive carcinoma of no special type (NST) was the most

common histological subtype (n=54, 90.0%). Other subtypes documented were lobular carcinoma, colloid carcinoma, tubular carcinoma, medullary carcinoma, and infiltrating ductal carcinoma (IDC) with neuroendocrine differentiation.

Our findings were similar to other studies done by, Bhagat et al [9], and Ghosh et al[10] and it was concluded that Invasive Ductal Carcinoma is the most common histological subtype.

Our findings were almost similar to an another study done by Nikhra et al[4]. Who found that out of 43 cases of breast carcinoma, 41 cases were of Infiltrating ductal carcinoma (95.34%), 1 case of medullary carcinoma (2.32%) and 1 case of Invasive lobular carcinoma (2.32%).

In our study, there were two cases of Mucinous carcinoma showing ER/PR positive and HER2-neu negative and one case of Medullary carcinoma with triple negative status which matches with the findings of Nikhra et al.[4] showing Medullary carcinoma with basal-like gene expression pattern with triple negativity for (ER/PR/HER2-neu), so Medullary carcinomas has poor prognosis and no response to hormonal therapy and Herceptin.

In our study, there were 2 cases of Invasive Lobular carcinoma showing ER/PR positive and HER2neu negative status which matches with the study done by Nikhra et al.[48] Invasive Lobular carcinoma with luminal-A gene expression pattern with positivity for ER/PR and negativity for HER2-neu, so Lobular carcinomas has good prognosis and better response to hormonal therapy.

In our study out of 71 cases, 47 cases (66.19%) lymphovascular invasion, HER2 tumors were having maximum percentage of metastatic pathology in lymphovascular invasion (85.71%) followed by luminal B (80%) basal like (63.63%) and luminal A (59.37%).

In the our study the mean age at presentation of carcinoma breast was 50.5 years. 59.16 % of cases occurred in the post-menopausal age group with 40.84 % of cases occurred in the pre-menopausal age group.

In the study by LobnaAyadi et al[11.] 51.6% of cases occurred in more than 45 years of age with median age of 51 years and 46% of cases occurred in less than 45 years.

In our study, we also saw that 41tumors involved the left side breast (57.74%) while 29 tumors arise from the right side breast (40.84%) and 1 case involve in bilateral breast (1.40%) most occurring in the outer upper quadrants. No significant association between side of tumor and molecular study.

Whereas in a study conducted by Nikhra et al.[4] left breast was found to be more commonly involved, comprising of 23 cases (53.4%) than right breast comprising of 20 cases (46.51%).

In the present study, positive expression of ER, PR and Her2/neu was found to be 59.15 %, 54.92%, and 23.94% respectively which correlates well with other studies. Hormonal receptor status has shown that overall positivity rate for ER and PR was lower in India than that reported in Western literature. In European and American population, 60–80 % patients were found with positive receptor expression[12]. This may be due to lower average age at diagnosis or racial difference. Our study described inverse correlation of Her2/neu expression with ER and PR expression which is well correlated with other studies.[13] These results might reflect women who overexpress Her2/neu may be resistant to Tamoxifen.

Molecular classification of breast should be adopted as a part of routine work up as Hormonal (ER, PR) and

HER2 receptor status is the most important prognostic and predictive factor which helps in guiding chemotherapy. Tamoxifen, estrogen antagonist is the mainstay of treatment for Hormonal receptor positive tumors. Apart from this, receptor status also helps in determining etiology. It is postulated that risk factors are closely associated with breast tumors ER+ and PR+ and may involve mechanisms related to exposure to estrogen and progesterone, while etiology of breast cancer ER- and PR- should be independent of hormone exposure[14].

Currently, the humanized monoclonal antibody Trastuzumab, directed against the extracellular domains of HER2, is indicated for the treatment of HER2 positive breast cancer cases.

Young women have unique biology of breast cancer due to hormonal exposure due to various factors like marriage, child birth, oral contraception.

Further evidence for unique biology in breast cancer in young women comes from molecular studies.

Conclusion

Molecular classification of Carcinoma breast is definitely a useful predictive and prognostic tool being the mainstay of deciding therapy in all age groups.

The current study verifies Infiltrating Ductal carcinoma (NOS) to be the most common histopathological subtype of breast carcinoma. Most cases of Grade II showed ER/PR positivity expression implying a better prognosis. As the tumor grade increases, ER/PR expression decreases and HER2-neu expression increases and Grade 3 had maximum number of triple negative cases indicating for poor prognosis. Breast carcinoma with HER2-neu positivity or with triple negativity shows more aggressive nature. IHC improves the more prognostic accuracy into the histopathological assessment along with staging and grading of breast carcinoma.

The current study recommends IHC classification as an important clinical tool, at a reasonable cost, aiding in therapeutic decisions and prognosticating cancer breast.

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