

Original Research Article

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Clinicopathological characterization and correlation of breast tumour with receptor status

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ABSTRACT

Background: Malignancy of breast is the leading cause of cancer deaths in women. Molecular organisation of breast cancer is considered as better predictive factor for diagnosis and treatment. The present study was done with the aim to find out clinicopathological characterization and correlation of breast tumor with receptor status progesterone (PR), estrogen (ER) and human epidermal receptor protein-2/neu status (HER-2/neu).

Methods: This was a prospective study done on 50 patients with breast carcinoma. The expression patterns of PR, ER and HER-2/NEU were studied. Clinical features, pathologic features such as age of the patient, tumour size, grade, and lymph node status and their correlation with receptors were compared.

Results: Of the 50 patients, ER positivity was seen in 42% cases, PR positivity in 32% and HER-2/neu (3+) in 30% cases. Majority of grade I tumors were ER and PR positive and majority of grade III tumors were triple negative. Triple negative profile was seen in secretory carcinoma. ER, PR and HER2 status was not significantly associated with age of the patients and tumour size. The immunohistochemical types ER/PR +ve Her2neu +ve and ER/PR -ve Her2neu -ve are significantly related to grading of tumours.

Conclusions: From the results, it was concluded that ER, PR and HER-2 status correlates well with histopathological grading. These results highlight the fact that molecular subtypes correlate with diagnosis and aid in targeted therapy.

Keywords: Breast tumour, Estrogen receptor, Progesterone receptor, HER-2 neu

INTRODUCTION

Breast cancer is the most common malignancy in women and is the leading cause of cancer mortality worldwide. It is responsible for more than 500,000 deaths annually.¹ In urban Indian population breast carcinoma is the most common cancer among women. It is second to cancer of cervix in the rural population, based on national cancer registry data (2006).² The incidence of breast cancer is steadily rising in India. As per the ICMR-PBCR data, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Calcutta,

and Trivandrum constituting more than 30 percent of all cancers in females.²

Various risk factors are associated with the development of carcinoma breast namely early menarche, late menopause, duration of breast feeding and hormone replacement therapy. It is more commonly seen in nulliparous women between 45-55 years of age. Self-breast examination and regular preventive check-ups have helped in early detection of cancer. Diagnostic modalities like mammography, fine needle aspiration and histopathology of breast tumours help in the diagnosis of

breast carcinoma. Early detection of breast cancer and the use of aggressive multimodal treatment have successfully resulted in decreased mortality.³

The management and prognosis of breast cancer nowadays require the evaluation of estrogen receptor (ER), progesterone receptor (PR) and human epidermal receptor protein-2 (HER-2/neu) as they have a great influence on the clinical outcome. The hormone receptor status of breast carcinoma can predict the response to adjuvant hormone therapy.⁴ ER positivity in particular, is thought to be of great importance, predicting an approximately 50% to 75% response rate to hormone therapy. Estrogen is the major steroid mitogen for the luminal epithelial cell population. It has a crucial role in the proliferation and progression of breast cancer.⁵

Immunohistochemical demonstration of hormone receptors in breast cancer is cost effective, and can be done on paraffin processed tissue and the receptors are assessed within the actual tumour. The approach in managing breast cancers has undergone enormous changes over the last 20 years. The choice of breast conservative and reconstructive surgery today is more popular than mastectomy. There is increase in the use of systemic, hormonal and cytotoxic drugs following hormone receptor testing. ER, PR and HER-2/neu analysis have been accepted as established procedures in the routine management of patients with breast cancer. The combined expression of these three hormone receptors has thus become most informative in the molecular classification, clinical assessment, treatment and further outcome.⁶

The present study was conducted to find out clinicopathological characterization and correlation of breast tumor with receptor status ER, PR, Her-2 Neu. The results would aid the clinical prognostic assessment, better management and treatment of the patients.

METHODS

This was a hospital-based study to be conducted between July 2015 to June 2016 and included 50 consecutive patients of carcinoma breast reporting to the Department of General Surgery, Indira Gandhi Medical College, Shimla (exact study place, hospital name should be given). Informed consent was obtained from all the patients. Patient with recurrence and lumpectomy specimens showing malignancy were excluded from the study.

Detailed history, including the history related to the presence or absence of risk factors for breast cancers were collected. A detailed clinical examination was performed for every patient and recorded. Fine needle aspiration cytology (FNAC)/core needle biopsy (CNB) was done to obtain diagnosis in all patients. Patient of early carcinoma breast stage I and II were subjected to routine workup which will include complete hemogram,

renal function tests (RFT), liver function tests (LFT) and X-ray chest. Ultrasonography (USG) of abdomen and pelvis, CECT abdomen and bone scan was done only if the patient had abdominal and bony symptoms or if the ALP was raised. Patient was subjected to metastatic workup only if locally advanced carcinoma on clinical examination stage IIIA, IIIB, IIIC which was included bone scan, X-ray chest, CECT abdomen/USG abdomen and pelvis to rule out abdominal metastasis.

Early carcinoma breast, patient was subjected to upfront surgery. While patient of locally advanced carcinoma was either operated upfront or given neoadjuvant combined chemotherapy followed by surgery. Patient of metastatic carcinoma were to be given combined chemotherapy/hormonal therapy followed by surgery.

Histopathologic data was obtained from the Pathology department. Histological grading of the tumor was done by using Nottingham modification of Bloom-Richardson system of grading.⁷ Other histopathologic features like lymphovascular invasion, perineural invasion, number of axillary lymph nodes were noted. All the cases were subjected to immunohistochemical study for ER and PR. Grading of ER and PR was done by using Allred score based on the proportion of stained cells and the intensity of staining. Immunohistochemical estimation of the HER2/neu was done and categorized into one positive-negative, two positive-weakly positive, three positive-positive.⁸

Correlation of age, tumor size, histologic type, histologic grade, and the expression of ER, PR, HER2/neu, were studied. The statistical analysis for correlation among these parameters was determined using the Pearson Chi-square test. Significance was done at $p < 0.05$.

RESULTS

Demographic and clinical pathological characteristics of the patients was given in Table 1. All the patients involved in the study were females. Age of patients ranged from 29-75 years. Mean age of presentation was 51.2 years. Majority of the patients were in the age group of 40-50 years (36%). Presence of lump in the breast is the common clinical feature noticed in 96% cases. The major risk factor observed in the study participants was age more than 50 years. In our study 48 patients out of 50 had breast fed their babies. In our study it was found that carcinoma breast was more common in the right breast (58%). 31 patients had lump in the upper outer quadrant and only one had lump in the central quadrant. There was no multicentric or multifocal lump. On FNAC/CNB 46 out of 50 patients had duct cell carcinoma which turned out to be equal to 92%. In our study, 34 (68%) patients were found to have early breast carcinoma. Locally advanced carcinoma was found in 16 (32%) cases. Most of the cases in the study were reported as infiltrating duct carcinoma, NOS type (98%) and 1 (2%) cases belonging to secretory type.

Table 1: Clinicopathologic characteristics of the patients.

Variables	Number of patients	
	N (%)	
Age group in years		
<30	1 (2)	
>31-40	8 (16)	
>41-50	18 (36)	
>51-60	14 (28)	
>61-70	5 (10)	
>71	4 (8)	
Clinical feature		
Lump	48 (96)	
Nipple discharge	6 (12)	
Pain breast	7 (10)	
Nipple retraction	9 (18)	
Lump in axilla	2 (4)	
Ulcer	2 (4)	
Peau de orange	1 (2)	
Fungating mass	1 (2)	
Risk factors		
Family history	3 (6)	
Early menarche	1(2)	
Late Menopause	2 (4)	
Nulliparity	1 (2)	
First child birth after 30 years	2 (4)	
Alcohol consumption	8 (16)	
Ongoing oral contraceptive use	1 (2)	
No breast feeding	2 (4)	
Previous benign breast disease	4 (8)	
Mammographic breast density	Not evaluated in most	
Affected side		
Right	(58)	
Left	(42)	
Quadrant affected		
Upper outer	31 (62)	
Upper inner	4 (8)	
Lower outer	8 (16)	
Lower inner	1 (2)	
Both upper	3 (6)	
Both inner	2 (4)	
Central	1 (2)	
FNAC/CNB		
Duct cell carcinoma	46 (92)	
Metaplastic	1 (2)	
Infiltrating duct carcinoma with medullary feature	1 (2)	
Ductal carcinoma in situ cell	1 (2)	
Suspicious for malignancy (intra-ductal carcinoma)	1 (2)	
Clinical classification		
Early breast carcinoma	34 (68)	
Locally advanced breast carcinoma	16 (32)	
Treatment		
Neoadjuvant chemotherapy and MRM	9 (18)	
Modified radical mastectomy and adjuvant chemotherapy	41 (82)	

Continued.

Variables	Number of patients	
	N	(%)
Histopathological type		
IDC (NOS)	49	(98)
Secretory	01	(02)
Histological grade (modified Bloom-Richardson grading)		
I	11	(22)
II	24	(48)
III	15	(30)
ER		
Positive	21	(42)
Negative	29	(58)
PR		
Positive	16	(32)
Negative	34	(68)
HER2/neu		
Positive	15	(30)
Negative	35	(70)
Immunohistochemical subtypes		
ER/PR + HER2-	08	(16)
ER/PR + HER2+	8	(16)
ER/PR - HER2-	24	(48)
ER/PR - HER2+	05	(10)
ER+PR - HER2-	05	(10)

Table 2: Correlation of age, tumour size, and grade with receptor types.

Receptors	Age in years		P value	Tumour size		P value	Tumour grade			P value
	<50 (n=27)	>50 (n=23)		<5 cm (n=23)	>5 cm (n=27)		I (n=11)	II (n=23)	III (n=15)	
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	N (%)	
ER +ve (%)	8 (29.6)	13 (56.52)	0.054	10 (43.47)	11 (40.7)	0.85	7 (54.5)	14 (52.2)	0	0.0004
ER -ve (%)	19 (70.4)	10 (43.48)		13 (56.53)	16 (59.3)		4 (45.5)	10 (47.8)	15 (100)	
PR +ve (%)	8 (29.6)	8 (34.8)	0.69	8 (34.8)	8 (29.6)	0.70	5 (45.5)	10 (43.5)	1 (6.7)	0.036
PR -ve (%)	19 (70.4)	15 (65.2)		15 (65.2)	19 (70.4)		6 (54.5)	13 (56.5)	14 (93.3)	
HER2Neu +ve	9 (33.3)	6 (26.1)	0.58	6 (26.1)	9 (33.3)	0.58	2 (18.2)	11 (47.8)	2 (13.3)	0.046
HER2Neu -ve	18 (66.7)	17 (73.9)		17 (73.9)	18 (66.7)		9 (81.8)	12 (52.2)	13 (86.7)	

As per modified Bloom-Richardson grading out of 49 cases, 11 (22%) cases were reported as grade I, 24 (48%) cases as grade II and 15 (30%) as grade III tumors. Among 50 patients, 36%, 32% and 30% expressed ER, PR and HER2/neu status in receptors respectively. The proportion of patients expressing ER/PR -ve HER2 subtype was 48%.

Table 2 Correlation of age, tumour size, and grade was presented ER, PR and HER2 status was not significantly associated with age of the patients and tumour size.

However, all the receptor status was significantly related to tumour grade ($p<0.05$).

DISCUSSION

The incidence of breast cancer in India is rising and it is the most common cancer among women in the urban Indian population. The outcome of the disease varies widely and is partially dependent on the interaction between hormones and growth factors with tumour cells. Hence immunohistochemical evaluation of hormone

receptors have become a routine investigation to predict response to hormone therapy.

Understanding the underlying mechanisms of ER, PR and HER-2/neu showed a great influence on the clinical outcome. ER positivity in particular, is thought to be of great importance, predicting an approximately 50% to 75% response rate to hormone therapy such as anti-estrogen drugs (tamoxifen).⁹ PR is an intracellular steroid receptor. It has two main isoforms A and B. Estrogen is necessary to induce progesterone receptors. Analysis of PR expression is generally reported along with ER expression. It has been conclusively demonstrated that PR status is independently associated with disease-free and overall survival of patients. ER, PR positive tumors have a better prognosis than patients with ER positive PR negative tumors.¹⁰

The human epidermal receptor protein-2 (HER-2/neu) oncogene is a trans-membrane glycoprotein belonging to epidermal growth factor receptor family. It is expressed at low levels in a variety of normal epithelia, including breast duct epithelium. Amplification of the HER-2/neu gene and concomitant protein over expression is present in 10–20% of primary breast cancers.¹⁰ HER-2/neu is an independent prognostic marker of aggressive disease with propensity for recurrence and a target for treatment using humanized monoclonal anti HER-2/neu antibody trastuzumab (Herceptin). It gives substantial clinical benefit in patients with metastatic breast cancer so the determination of HER-2/neu status in breast cancer is of great interest.¹¹

Triple negative breast cancer (TNBC) refers to the tumors with ER, PR and HER-2/neu negative status. They are also known as Basal-like breast cancers. TNBC are more frequently seen in younger patients. They have aggressive histology, poor clinical outcome, short survival and are unresponsive to usual hormonal therapies.⁹ TNBCs are associated with BRCA1 mutation.¹²

In the present study, the peak age incidence of malignant breast cancer was 41-50 years. This was similar to the findings of Puvitha et al.¹³ In another study by Ejam et al, the peak age incidence was 30-50 years.¹⁴ The mean age incidence was 49 years in a study done by Ghosh et al.¹⁵ This was in accordance with our study observations in which the mean age was 51.2 years.

Most common presentation of tumour in the present study was painless lump (96%). The present study was comparable with study by Ayoade et al.¹⁶ In the present study, majority had tumour in the right breast (58%). Similar was observed in the study of Giuliano et al.¹⁷ Most of patients (40%) were presented with lump of size in between 2-5 cms (T2). Similar findings have also been reported by Verma et al.¹⁸

The important epidemiological risk factors for the development of breast cancer are age, family history,

parity, age at menarche and menopause, prior history of breast biopsy, diet, socioeconomic status, and history of exposure to radiation and use of oral contraceptive pills.¹⁹ In our study 3 (6%) patient had a positive family history of breast cancer. Similar finding was reported by Sandhu et al.²⁰ Carcinoma breast is more common in postmenopausal because of their relative advanced age.²¹ In the present study it was shown that that breast cancer affected females more commonly in their postmenopausal period.

Histopathological type is a well-documented prognostic factor. In the present study the majority of the cases (98%) were of infiltrating duct carcinoma. This was in accordance with the findings of Pathak et al.²²

In our study, the grading was done on the excised specimen. It was not done on trucut biopsy specimen as accurate grading only possible on excised specimens. So out of 50 cases graded by modified Bloom Richardson grading system. In our study grade I was reported in 22% of the cases, grade II in 48% and grade III in 30% of the cases. These observations were comparable with findings of Pathak et al and Rajesh et al.^{22,23}

In our study estrogen receptor positivity was seen in 21 (42%) patients. Ghosh et al in their study conducted at a tertiary cancer care hospital at Mumbai reported 51.2% of the cases to be positive for ER.¹⁵ The incidence was higher than our present study, this could be due to larger study size. Progesterone positivity was seen in 16 (32%) patients. Similarly, Bhagat et al and Jain et al reported PR positivity in 37.93% and 34% cases respectively.^{24,25}

In our study maximum number of cases were of combined ER and PR negative tumors constituting 58% cases, followed by ER and PR positive tumors constituting 32%, followed by ER positive and PR negative tumors (10%). Desai et al in their study also observed that tumors with combined ER and PR negativity were most common and were present in 46.5% cases, followed by both ER and PR positivity in 25% cases.²⁶

In our study HER-2/neu positivity was seen in 15 cases which comprised 30% of the total cases. In the studies conducted by Rajesh et al and Ambroise et al, HER-2/neu positivity was seen in 27.9% and 27.10% cases respectively.^{23,27} These results were slightly lower than the present study, this could be due to the larger study population in the two studies. In the present study, HER-2/neu over expression was found to be inversely related to ER and PR expression. Majority of the tumors expressing ER/PR positivity were seen to be HER-2/neu negative and vice-versa. The inverse association between steroid hormone receptors and HER-2/neu has also been described in various clinical studies.²⁸

In our study majority of the cases belonged to basal subtype group (48% cases). This was similar to the

findings of Ratnatunga et al.²⁹ In our study, ER and tumors were more in the age group of >50 years. This was also found in the study done by Ayadi et al.³⁰

A positive correlation ($p=0.001$) between ER and PR expression and histological grade was noted in the present study. No association was found between ER and PR expression and tumor size which were similar to the observation made by Ayadi et al.³⁰ In our study close correlation was observed between tumor grade and immuno-histochemical subtypes which was similar to the study done by Onitilo et al.³¹

CONCLUSION

The findings of the current study help in determining the frequency of ER, PR and HER-2/neu receptors in order to optimize the treatment of cancer. In our study, ER, PR and HER-2 status correlates well with histopathological grading. Higher the tumor grade, the more likely that ductal carcinoma will be Her2+ and ER/PR negative or triple negative. Hence, our study support IHC classification as a clinical tool as ER/PR and HER2 testing is widely available, is a clinically-used, therapeutically informative classification of breast cancer based on immunophenotype/biologic phenotypes, and is prognostic as well as predictive. Follow up study of these patients is needed to assess the prognostic significance.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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