


Original Research Article

Correlation of expression of ER, PR and HER2/neu receptor status with clinico-pathological parameters in breast carcinoma

Vanita Pandey*

Senior Consultant & Head of the Department, Meherbai Tata Memorial Hospital, Jamshedpur, Jharkhand, India

*Corresponding author email: doc.vanita@gmail.com

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Abstract

Background: Breast carcinoma is the most common malignant tumor and the leading cause of carcinoma death in women, worldwide. The immunohistochemical classification provides both therapeutic and prognostic information. The objective of present study was to know the association of molecular classification with clinicopathological parameters for prognostic significance in breast cancer.

Materials and methods: This was a retrospective cum prospective study was conducted in the Department of Pathology for a period of 2 years. Total 156 patients were included in this study, few patients presenting with palpable breast lump undergoing mastectomy whose clinical symptoms were suggestive of breast cancer, patients having recurrence undergoing further treatment and some of the slides were submitted to the department for second opinion were included.

Results: In the present study, 156 cases were included. Out of 156, infiltrating ductal carcinoma were 143 and other variants were 13. The age range of occurrence of carcinoma breast was between 26 years to 76 years. The mean age was 53.2 years. Out of 143 cases, 91 cases (63.63%) were seen in perimenopausal and menopausal age group with 52 of cases (36.37%) occurred below 45 years of age and the youngest being 26 years.

Conclusion: ER and PR positive expression was seen in grade 1 tumors and negative expression was seen with tumor size more than 2cm, positive lymph nodes and higher stage of disease. HER2/neu negative expression was seen in the post-menopausal age group, tumor size more than 2 cm, positive lymph nodes and higher stage of disease indicating bad prognosis. HER2/neu expression was

inversely related to ER and PR expression. HER2/neu expression was seen in 50% of medullary carcinoma which is rare. Triple negative cases were seen in 54.8% cases of infiltrating duct cell carcinoma indicating bad prognosis.

Key words

Estrogen Receptor, Progesterone Receptor, Breast Carcinoma, Malignancy, Triple Negative.

Introduction

Carcinoma breast is the most common malignant tumour worldwide and the leading cause of death in women [1]. In India, breast cancer is the most common cancer among women followed by cervical cancer [2]. The functional unit of the breast is the single gland, arranged into lobes and made-up of two major components: the Terminal Duct Lobular Unit (TDLU) and the large duct system [1]. The epithelium is bilayered, an inner epithelial layer and an outer myoepithelial layer. Myoepithelial cell layer is one of the main guide to the distinction between benign and malignant lesions [3]. Most of the breast malignancies are adenocarcinomas and based on the expression of Estrogen Receptor (ER), Progesterone Receptor (PR) and HER2 they can be divided into four major subgroups: luminal A, luminal B, HER2-overexpressing, and basal-like [4]. Immunohistochemical classification also provides both therapeutic and prognostic information. Anti-estrogen (tamoxifen) nowadays becomes treatment of choice in ER positive case [5]. The basal-like subtype, characterized by negativity for ER, PR and HER2, is associated with aggressive histology, poor prognosis, and unresponsiveness to the usual endocrine therapies [6]. Because the hormonal receptors are well-known predictive factors of the response to the hormonal therapy in mammary carcinoma, their evaluation through immunohistochemical methods is absolutely necessary. The assessment of prognostic factors, in order to provide a prediction of outcome, has become an essential part of the histopathologist's role in the handling and histological reporting of invasive breast carcinomas. HER2/neu is a member of the ErbB family that plays an important role in promoting estrogen transformation and tumour growth [7]. HER2

positivity is also useful for targeted therapy with monoclonal antibody (trastuzumab) against HER2 [8].

Aim of the study

The objective of present study was to know the association of molecular classification with clinicopathological parameters for prognostic significance in breast cancer.

Materials and methods

This was a retrospective cum prospective study was conducted in the Department of Pathology for a period of 2 years. Total 156 patients were included in this study. This study was based on cases or specimens received in the Department of Pathology at Meherbai Tata Memorial Hospital (MTMH) for duration of 2 years and this included trucut biopsy specimens, Imaging guided core biopsies, lumpectomy specimens, Modified Radical Mastectomy specimens (MRM), Revised MRM, Toilet mastectomy samples from various sources as MTMH being the tertiary referral oncocare centre. The specimens were collected and further studies were done in Department of Pathology. H&E staining was done to see the histological features and IHC staining was done for expression of ER, PR and HER2. The clinico-pathological features such as tumor size, histological type, Nottingham combined or modified Bloom-Richardson's histological grade, lymphovascular invasion, perineural invasion, status of margins, associated in situ component/Paget's disease and lymph nodal status were assessed. They were classified according to IHC staining into five molecular subtypes: Luminal A-like, luminal B-like HER2 (Negative), luminal B-like HER2 (Positive), HER2+ and triple negative/basal like. IHC study

was also done on recurrent masses following surgical removal.

Immunostaining

- 1) ER/PR: All cases with at least 1% of positive cells were considered positive and quantification was done using Allred scoring system [9, 10].
- 2) HER2: Interpretation was done according to American Society of Clinical Oncology (ASCO)/College of American Pathologist (CAP) Guidelines [11].

Molecular subtypes were defined depending upon IHC expression of ER, PR, and HER2 and according to St. Gallen 2013 consensus conference in the following ways [12].

Results

In the present study, 156 cases were included. Out of 156, infiltrating ductal carcinoma were 143 and other variants were 13. The age range of occurrence of carcinoma breast was between 26 years to 76 years. The mean age was 53.2 years. Out of 143 cases, 91 cases (63.63%) were seen in perimenopausal and menopausal age group with 52 of cases (36.37%) occurred below 45 years of age and the youngest being 26 years. The size of tumor was more than 2 cm in 78 (54.54%) of cases. The grade of tumor was well differentiated (grade 1) in 68 cases (21.67%) and grade 2 in 49 cases (13.28%) and grade 3 in 39 (10.49%) of cases. Metastatic lymph nodes were seen in 84 cases with less than 4 lymph nodes involved in 27 cases. Out of 84 cases with positive lymph nodes 84.3% showed vascular invasion and necrosis was seen in 92.8 % of cases (**Table - 1**). In the present study 68.9% and 31.1% presented with stage I and stage II disease respectively.

Out of 143 cases of infiltrating ductal carcinoma positive expression of both ER and PR was seen in 63 cases (44.05%) of cases. In 39 (27.28%) showed negative expression of both ER and PR. Five cases showed ER positive and PR negative expression and three cases showed ER negative and PR positive expression. 33 cases (23.08%)

showed HER2/neu membrane positivity with score of 2+ meaning equivocal reaction, which has to be confirmed by FISH (**Table - 2**). HER2/neu membrane positivity with score 3 is shown in 15 cases (45.45%) and negative expression in 18 cases (54.55%) of cases. Triple Negative cases are tabulated in **Table - 3**.

Table - 1: Clinico-pathological parameters of Infiltrating Ductal Carcinoma.

Clinical pathological parameters	Number of cases	Percentage
Age		
≤45 years	64	44.76
>45 years	92	55.24
Parity		
≤2 children	89	57.05
>2 children	67	42.95
Tumor size		
≤2 cm	78	50
>2 cm	78	50
Histological grade		
Grade 1	68	43.59
Grade 2	49	31.41
Grade 3	39	25.00
Vascular invasion	67	46.85
Necrosis	76	53.15
Lymph node metastasis		
Negative	59	41.25
Positive	84	58.75
Number of lymph nodes involved		
≤4 lymph nodes	27	32.14
>4 lymph nodes	57	67.86

Medullary carcinoma, mucinous carcinoma tubular carcinoma is grade 1 tumors and more commonly seen beyond 49 years of age in this study. Out of 13 cases, 7 cases were negative for lymph nodes with 3 cases showing metastatic lymph nodes. Six cases presented with stage II disease. Triple negative receptor expression was seen in metaplastic carcinoma, invasive papillary carcinoma and invasive lobular carcinoma. In the English literature medullary carcinoma is negative for HER2/neu expression but in the

present study in 2 cases the expression for HER2/neu was positive.

Table - 2: Expression of ER, PR and HER2/Neu.

Number of cases		Percentage
ER expression/PR expression		
ER+/PR+	63	57.7
ER+/PR-	05	04.55
ER-/PR+	03	02.73
ER-/PR-	39	35.45
HER2/neu		
Positive	15	22.73
Negative	18	27.27
Equivocal	33	50.00

Table - 3: Clinico-pathological parameters in triple negative cases.

Age	
≤45 years	16
>45 years	41
Tumor size	
≤2 cm	19
>2 cm	38
Histological grade	
Grade 1	23
Grade 2	16
Grade 3	18
Lymph node metastasis	
Negative	21
Positive	36
Number of lymph nodes involved	
≤4 lymph nodes	24
>4 lymph nodes	33

Discussion

Breast cancer accounts for 21-39% of all cancer cases among women in India. As per the data from national and regional cancer registries, it is the commonest cancer and is listed as the second leading site among women. The age-standardized incidence rates vary from 9-28.6 per 100000 women, the lowest being from the rural area-based registry. The majority of the patients seek medical advice when the disease is fairly advanced. Early breast carcinoma constitutes

only 30% of the breast cancer cases seen at regional cancer centers in India, whereas it constitutes 60-70% of cases in the developed world. There is no prospective or retrospective published case series on early carcinoma of breast from India. There is a paucity of data regarding breast carcinoma in the developing world; hence individual institutes should have the knowledge of the various clinico-pathological parameters of carcinoma breast specific for their region.

Estrogen receptors are a group of proteins that are found in breast tissue. These receptors are activated by the hormone estrogen and its exposure is a risk factor for breast carcinoma [13]. It is a predictive marker and has significant therapeutic effects [14]. It consists of two subtypes such as ERalpha and ER-beta [15]. ER-alpha is expressed in majority of the breast carcinoma cases. However, its predictive value is not ideal, as around one-third of ER+ breast carcinoma patients show no response to the hormonal therapy [16].

Progesterone receptors are also an estrogen-regulated protein found in the cells of breast tissue. Therefore its expression is believed to function as in ER pathway [17]. Assessment of both ER and PR is helpful in predicting response to hormonal therapy more accurately. There are few proposals which indicate that PR positive tumors are more likely to respond to tamoxifen [18]. The predictive value of PR positivity in the absence of ER is controversial [19]. Breast tumors which are ER+ and /or PR+ show low mortality risk in comparison with ER- and /or PR- tumors.

Human epidermal growth factor receptor 2 (HER-2): The human epidermal growth factor receptor 2 is a member o epidermal growth factor receptor (EGFR) family of tyrosine kinases. It is located on chromosome 17q21. It is a protein found in humans which is encoded by ERBB2 gene and called as HER2-neu. Amplification or over-expression of HER2-neu has been seen in 18–20% of breast cancers. It plays an important

role in the development and progression of certain aggressive types of breast carcinoma. HER2-neu positivity is associated with high grade tumors, lymph node involvement, mortality and poor prognosis [20]. HER2-neu expression is a predictive factor in response to trastuzumab [Herceptin] therapies [21]. HER-2 positivity may also predict for resistance to hormonal therapy.

Molecular breast carcinoma classification is into four groups:[22]

1. ER/PR+,HER2-neu+ = ER+/PR+,HER2-neu+;ER-/PR+,HER2-neu+; ER+/PR,HER2-neu+ ;
2. ER/PR+,HER2-neu- =ER+/PR+,HER2-neu-;ER-/PR+,HER2-neu-; ER+/PR,HER2-neu-;
3. ER/PR-,HER2-neu+ = ER-/PR-, HER2-neu+
4. ER/PR-,HER2-neu- = ER-/PR-, HER2-neu-

The classification of Molecular subtypes of breast carcinoma in correlation with IHC expression:

- Luminal A ER/PR+, HER2-neu- ;
- Luminal B ER/PR+, HER2-neu+ ;
- HER2 enriched ER/PR-, HER2-neu+;
- Triple negative ER/PR-,HER2-neu-.

In the present study, 156 cases were included. Out of 156, infiltrating ductal carcinoma were 143 and other variants were 13. The age range of occurrence of carcinoma breast was between 26 years to 76 years. The mean age was 53.2 years. Out of 143 cases, 91 cases (63.63%) were seen in perimenopausal and menopausal age group with 52 of cases (36.37%) occurred below 45 years of age and the youngest being 26 years. The size of tumor was more than 2 cm in 78 (54.54 %) of cases. The grade of tumor was well differentiated (grade 1) in 68 cases (21.67 %) and grade 2 in 49 cases (13.28 %) and grade 3 in 39 (10.49 %) of cases. Metastatic lymph nodes were seen in 84 cases with less than 4 lymph nodes involved in 27 cases. Out of 84 cases with positive lymph nodes 84.3 % showed vascular invasion and necrosis was seen in 92.8 % of cases. In the

present study 68.9% and 31.1% presented with stage I and stage II disease respectively.

Out of 143 cases of infiltrating ductal carcinoma (NST) positive expression of both ER and PR was seen in 63 cases (44.05%) of cases. In 39 (27.28%) showed negative expression of both ER and PR. Five cases showed ER positive and PR negative expression and three cases showed ER negative and PR positive expression. 33 cases (23.08%) showed HER2/neu membrane positivity with score of 2+ meaning equivocal reaction, which has to be confirmed by FISH . HER2/neu membrane positivity with score 3 is shown in 15 cases (45.45%) and negative expression in 18 cases (54.55%) of cases. Triple Negative cases are tabulated in **Table - 3**.

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Conclusion

ER and PR positive expression was seen in grade 1 tumors and negative expression was seen with tumor size more than 2cm, positive lymph nodes and higher stage of disease. HER2/neu negative expression was seen in the post-menopausal age group, tumor size more than 2 cm, positive

lymph nodes and higher stage of disease indicating bad prognosis. HER2/neu expression was inversely related to ER and PR expression. HER2/neu expression was seen in 50% of medullary carcinoma which is rare. Triple negative cases were seen in 54.8% cases of infiltrating duct cell carcinoma (NST) indicating bad prognosis.

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