IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 9 Ver. 12 (September. 2018), PP 31-36
www.iosrjournals.org

Study of Predictive and Prognostic Markers in Breast Cancer with Special Reference to Hormonal Receptors

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Abstract:
Aim: To study pattern of expression of Hormone receptors- ER, PR and HER2 in breast carcinoma and to correlate ER, PR status and HER2/neu expression with traditional prognostic factors.
Background: Breast cancer is one of the most common cancers in females. As breast carcinoma is a biologically heterogeneous disease, it is important to assess prognosis for each patient before a therapeutic plan is agreed upon .The use of established biomarkers such as estrogen, progesterone receptors and Her2 over expression play significant role in management of patients.
Material Methods: Total 54 histologically proved cases of breast carcinoma in Department of Pathology of the Institute were included in the study. All histopathological and hormonal receptor studies were done on specimens obtained in histopathology section. Detailed report of breast carcinoma that included evaluation of prognostic and predictive markers was given in each case. The correlation between Hormonal and Clinicopathological markers was analysed using Chi square test and Fisher exact test.
Results: *ER, PR positivity and Over-expression HER2 was seen in 48.15%, 55.56% and 38.89% respectively. Correlation between ER, PR and tumour grade was found to be statistically significant ($p<0.05$). No significant correlation was found between ER-PR status and Her2 positivity with other traditional prognostic factors.*
Conclusion: *Traditional gross and microscopic features of carcinoma of breast are important as independent prognostic markers. In addition ER, PR and HER2 should be assessed in every case of breast carcinoma as prognostic and predictive markers.*
Key Words: *Breast carcinoma, hormone receptors, prognostic factors, predictive markers*

Date of Submission: 14-09-2018 Date of acceptance: 30-09-2018

I. Introduction:

The number of tumor-related features available to predict the prognosis of patients with breast cancer has grown impressively in recent years. The cellular and molecular biological features have not only advanced the understanding of carcinogenesis, but have provided a host of new biologic measures potentially related to the clinical outcome[1]. Adjuvant hormonal therapy and polychemotherapy reduce the risk of both recurrence and death from breast cancer[2]. This study was undertaken to study ER, PR and HER2 status in breast carcinoma with the aim to evaluate correlation between the traditional and hormonal markers for breast carcinoma.

II. Material and Method:

This analytical study was conducted over a period of 2 years, in the Department of Pathology in a Tertiary Care Hospital and Medical Institute. Cases were selected from surgical specimens and biopsies which were sent for histopathological study during the study period. IHC was performed on total 54 histologically proved cases of carcinoma of breast. Patients with benign breast disease, inflammatory breast disease and patients who have taken hormone replacement therapy in the past were excluded from this study. Ethical clearance for the study was obtained from the Institutional Ethics Committee. Clinical details of the study cases were recorded in detail.

The breast specimen in the form of either Mastectomy which included Modified Radical Mastectomy and Simple Mastectomy, Lumpectomy and tissue specimens obtained by Core needle biopsy were fixed, grossed and processed with routine paraffin embedding. All the sections were stained with H and E stain, studied under light microscope at low power (100x) and high power (400x) and the relevant findings were noted. The tumour sections were evaluated for the traditional prognostic markers for breast carcinoma like histological type, tumour grade, accompanying ductal carcinoma in situ (DCIS), stromal reaction, necrosis, type of margins and lymphovascular invasion and axillary lymph node metastasis.

Histologic grading was done by Nottingham modification of Scarff Bloom Richardson system which involves semi quantitative evaluation of three morphological features[3]. The histopathological diagnosis and evaluation of breast cancer was confirmed independently by two pathologists in the Department. Representative paraffin blocks for each tumor showing the tumour and preferably the adjacent uninvolved breast tissue were selected and submitted for immunohistochemical staining. Three tumor sections were cut from the selected block in each case at 3 to 4 µm thickness.

Immunohistochemical study- Bio Genex Supersensitive TM One Step Polymer HRP Detection system (biotin free polymeric technology) was used for visualization of primary antibody. Positive and negative controls were included with every IHC assay batch to monitor assay performance over time and to detect loss of staining .Both external and internal controls were used. Immunohistochemically stained sections were observed under light microscope (both low and high power). ER/PR nuclear staining was scored according to Allred score method[4] and HER2 membrane staining was interpreted according to ASCO/CAP guidelines[5].

In 10% of cases, slides for IHC from the same tissue block were sent for ER, PR, and HER2 assay to the Cancer Research Centre of the region for crosscheck and confirmation. Statistical analysis was done using SPSS for Windows software version 20.0. The correlation between various immunohistochemical parameters (ER , PR and HER2) with clinicopathological parameters was analysed using Chi-square test and Fisher exact test. P value was calculated. Any correlation between the two variables was considered to be statistically significant if p value was less than 0.05.

III. Results:

In the present study, age group of the patients ranged from 28-80 years with a mean age of 50.16 years and a median age of 50 years. 53 cases (98%) were female patients and one was a 72 year old male patient.

26(49.06%) patients were premenopausal and 27(50.94%) patients were postmenopausal.

51(94%) patients included in the present study had undergone modified radical mastectomy. Core needle biopsy, wide local excision and lumpectomy were performed in one patient each. In our study, 27 (50%) patients had tumor size between 2 to 5cm and 24 (44.44%) had tumour size greater than 5 cm. Only in 3 (5.565) patients the tumor size was less than 2cm.

The predominant histologic subtype was Invasive ductal carcinoma(IDC) of no special type accounting for 48 cases (88.88%). One case each was of medullary carcinoma, IDC with mucinous and IDC with medullary features.

Out of 54 cases, 32 cases (59.26%) had axillary lymph node metastasis, 19 cases (35.19%) were negative for tumour deposits and in 3 cases nodes were not available for the examination.

According to Nottingham modification of Scarff Bloom Richardson system of histologic grading, 36 (66.67%) patients in the present study had Grade II breast carcinoma,followed by 13 patients (24.07%) with grade III tumours.Only 5 (9.265) had Grade I tumor.

Table – 1: ER,PR and HER2/neu status in cases of breast carcinoma

Receptor status	No of cases	Percentage
ER Positive	**26**	48.15
ER Negative	**28**	51.85
PR Positive	**30**	55.56
PR Negative	**24**	44.44
Her/2eu Positive	**21**	38.89
Her2/neu Negative	**33**	61.11

In the present study, ER was positive in 26 (48.15%) cases, PR was positive in 30 (55.56%) cases and HER2/neu was positive in 21(38.89%) cases as depicted in (Table-1).

Table 2: Correlation between ER and PR status (P=0.000)

		PR		Total	p value
		Positive n(%)	Negative n(%)		
ER	**Positive**	**22(84.62%)**	**4(15.38%)**	**26**	**0.000**
	Negative	**8(28.57%)**	**20(71.43%)**	**28**	
Total		**30**	**24**	**54**	

Correlation of ER and PR- (Table 2).The association between ER and PR was found to be highly significant (p=0.000).

Table 3: Correlation between Her2 over expression and receptor status

Receptor status	HER+ n (%)	HER - n (%)	P value
ER+	8 (38.10)	18 (54.55)	o.238
ER-	13 (61.90)	15 (45.45)	
PR+	10 (47.62)	20 (60.61)	o.349
PR-	11 (52.38)	13 (39.39)	

As seen in Table3,the correlation between expression of ER and PR with Her2/neu over expression was not statistically significant.

Table 4 : Correlation of ER, PR and HER2 positivity with histologic grade of tumour of breast carcinoma cases.

Grade of tumour	ER + n(%)	ER- n(%)	p value
I and II	23(56.1%)	18(43.9%)	0.03
III	3(23.08%)	10(76.92%)	
Grade of tumour	**PR + n(%)**	**PR- n(%)**	**p value**
I and II	27 (65.85%)	14(34.15%)	0.06
III	3(23.08%)	10(76.92%)	
Grade of tumour	**HER2 + n(%)**	**HER2- n(%)**	**p value**
I and II	16(39.02%)	25(60.98%)	0.97
III	5(38.46%)	8(61.54%)	

Our study demonstrated higher ER and PR positivity in grade I and II tumors compared to that in grade III tumors indicating an inverse correlation between ER-PR positivity and grade of the tumor (Table 4).The correlation between estrogen and progesterone receptor expression and the grade of the tumor was statistically significant because p value was less than 0.05. Correlation between HER2 positivity and tumor grade was not statistically significant p= 0.97.

No statistically significant correlation was found between expression of ER ,PR and HER2 with the age of the patients , menstrual status of the patients, tumour size, tumor necrosis, lymphovascular invasion , DCIS component or axillary lymph node metastasis .

Table -5 : Immunohistochemical subtypes in cases of carcinoma breast

Groups	Subtype	Number of Patients	Percentage
I	ER + PR +,HER2 +	7	12.96%
II	ER + PR +, HER2-	15	27.77%
III	ER + PR -, HER2+	1	1.85%
IV	ER + PR -, HER2-	3	5.55%
V	ER - PR +, HER2+	3	5.55%
VI	ER - PR +, HER2-	5	9.25%
VII	ER - PR -, HER2+	10	18.51%
VIII	ER - PR -, HER2-	10	18.51%
Total		54	100%

As seen from table 5,10 cases (18.51%) were of triple negative type in our study . Out of these 10 cases 50% were associated with high grade (grade III) (p=0.03) .Significant correlation was found between grade of the tumour and triple negative cases. 60% of them showed necrosis , 30% showed lymph node metastasis and 30% were associated with large tumour size (size greater than 5 cm) and 80% triple positive tumours showed lymphovascular invasion.

IV. Discussion:

As breast cancer is recognised being a heterogeneous disease, patients with the same diagnostic and clinical prognostic profiles can have markedly different clinical outcomes[6]. It is important to assess prognosis for each of the patient before a therapeutic plan is agreed upon[7]. Breast cancer management and its prognostication parameters have undergone vast changes.

Prognostic markers are factors which allow a clinician to judge the natural course of cancer. Patient's age, tumour size, Histological type and grade, lymph node status, lymphovascular invasion, presence of necrosis and in situ component are important traditional prognostic markers[8].

Predictive markers are factors that provide upfront information as to whether or not a patient will benefit from a specific therapy and are direct targets of drugs. ER/PR and HER2/neu are both prognostic and predictive markers for carcinoma breast. The presence of estrogen receptor and progesterone receptor in a breast malignancy play significant role in selection and management of patients for endocrine therapy andHER2 is a strong predictor of response to trastuzumab[9].

Careful evaluation of these biomarkers is required to determine whether their measurement or monitoring offer significant clinical benefits. Given the importance of these biological markers in patient management, it is essential that their assays are robust and quality controlled, and the interpretation of results is standardized. It is important to be aware of the limitations of their predictive power[10].

Immunohistochemistry (IHC) assays are carried out at selected laboratories that are overburdened with referrals from centers lacking the facility. With ER, PR and HER2 becoming almost mandatory for treatment of breast cancer, we tried to establish the setup at our centre.

Mean age of 50.16 years of the patients in this study was in concordance with the studies done by other workers in India [6,11,12] and other countries[13,14,15]. Age of Indian breast cancer patients is found to be lower when compared to the western countries with an average age difference of one decade[16,17].

In the present study, 50 % of cases had the tumor size between 2-5 cms and lymph node metastasis was noted in 59.26% cases. Similar observations had been made by Desai et al (2000)[18] and Ambroise et al (2011)[19].36 (66.67%) patients in the present study had Grade II breast carcinoma,followed by 13 patients (24.07%) with grade III tumours. According to Cianfrocca et al (2004)[2] tumor grade has prognostic significance and is primarily used to make decisions for lymph node-negative patients with borderline tumor sizes. Lymph node positivity at first clinical presentation is a bad prognostic factor. There is a sharp difference in the survival rates between the patients with positive nodes and negative nodes.

Table 6 depicts the variable results of ER and PR positivity and Her2/neu overexpression amongst studies carried out in India [20,21,22,6,23,12,24] and other countries[13,14,15]. Higher Positivity of 70-75% for ER and PR in Western countries is quoted by various studies.[25,12]

Explanation of lower ER,PR positivity in Indian patients given by the authors includes younger age and higher tumourr grade at diagnosis as well as at parameters like difference in techniques of evaluation, high tumour grade and postmenopausal females[20,18]. While others correlated the cause for lower receptor expression with racial and geographic difference, lower average age of patients and higher grade of breast cancers[26].However the option of hormone therapy is nowadays offered to every patient of breast cancer irrespective of age, based on tumour receptor status [27].

Correlation between ER and PR status: We found a significant positive correlation between estrogen and progesterone receptor positivity (p=0.00)Table 2 . P value less than 0.05 indicates significant correlation. The correlation between ER and PR found in present study was similar to the study done by Ayadi L et al (2008)[13].PR is an oestrogen-regulated gene. Its expression is therefore thought to indicate a functioning ER pathway. Recent studies have redefined PR as a predictive marker of ER activity of growth factors and also as a fundamental marker for indicating hormone therapy in breast cancer patients [28] . We have done PR assessment in all the cases and found it to correlate with ER positivity.

Over-expression of HER2 in our study was found to be 38.89%. Since its initial discovery, HER2 was used as a therapeutic target because of the efficacy of trastuzumab ,a recombinant humanized monoclonal antibody that binds with high affinity to HER2, in advanced breast cancer [29]. Overexpression of HER 2 occurs through either amplification of the gene or mRNA overexpression[24].

The frequency of HER2 positivity varies among Indian studies from 2.4% to 57.2% (Table 6).HER2 has a significant prognostic value as a marker since it can predict resistance to hormonal treatment .HER2 receptor overexpression is found to be a poor prognostic marker independent of tumour grade, tumour size and lymph node status by[30]. HER2 amplified breast cancers have unique biological and clinical characterisatics. (1)They have increased sensitivity to therapeautic and certain cytotoxic agents such as doxorubin, (2) They have relative resistance to hormonal agents and, (3) They have propensity to metastasize to the brain and viscera.These tumours have higher proliferation rates and are associated with poorer patient prognosis. The poor outcome is dramatically improved with appropriate chemotherapy combined with the HER2 targeting drug trastuzumab[31].

Herceptin is anti HER-2/neu antibody that is effective in cases with HER-2/neu over expression and improves survival of patients. Its efficacy has been proven in western set up.Due to cost factor it is still not affordable by majority of Indian patients.[32] However results of the HER 2 testing can be utilised for prescribing Herceptin in patients who can afford the treatment and for prognostication.

Correlation of ER- PR with HER2 overexpression: In our study HER2 positivityof 38.89% did not demonstrate any significant direct or inverse correlation with ER (p=0.23) and PR (p=0.34) as p value was greater than 0.05. While Vaidyanathan K et al (2010)[33] did not find a statistically significant correlation between ER , PR status and HER2 ,Dodiya et al (2013)[21] and Krishnamurthy et al (2016)[8]demonstrated an inverse relationship between HER2 and ER -PR expression.

The mechanism of negative correlation of ER and PR with HER 2 /neu over expression is dependent upon down regulation of HER2 and involves a complex molecular interaction as reported by Vaidyanathan et al(2010)[34] Konecny et al(2003).[35]

Correlation of ER and PR with various clinicopathological parameters: Our study demonstrated higher ER and PR positivity in grade I and II tumours compared to that in grade III tumours indicating an inverse correlation between ER-PR positivity and grade of the tumour. Correlation between ER, PR and tumour grade was found to be statistically significant ($p<0.05$). This important finding of lower grade tumours showing high ER and PR positivity is evident from other studies Satti M B et al (2011),Kaul et al(2011), Shahi et al(2011), Rao C et al (2013), Dodiya H et al (2013). Krishnamurthy J et al (2016) also noted that ER PR positivity decreased with increase in tumour grade.

No significant correlation was found between expression of ER ,PR and HER2 with the age of the patients , menstrual status of the patients, tumour size, necrosis , lymphovascular invasion and DCIS component. All traditional gross and microscopic factors for carcinoma of breast remain important as independent prognostic markers. Small number of study cases and unavailability of post-treatment follow-up data is the limitation of this study.

Table6:ER,PRpositivityandHER2overexpressioninbreastcarcinomainvariousstudies

Study - Year	ER + %	PR + %	HER2 overexpression %
Ayadi et al - 2008	59.4	52.3	18.1
Dutta et al - 2008	24	30	57.2
Nisa et al - 2008	32.7	25.3	37.3
Ambroise et al -2011	59.19	51.09	27.1
Dodiya et al - 2013	64.2	54.9	46.7
Rao et al - 2013	36.5	31.7	2.4

As seen from Tables 6, there is variability between number of breast carcinoma patients showing expression of ER, PR and HER2 among studies carried out by different workers .Correlation of expression of these markers with previously known prognostic markers is also variable according to various studies carried out in India.

Differences in the (1) timing of fixation of tissue,(2) use of reagent kits from different manufacturers, (3) method used,(4) variation in duration of steps i.e., interlaboratory variations,(5) lack of standardization of technique are some of the reasons responsible for variability of IHC results. Variation of results of ER, PR and HER2 expression among Indian and regional studies can be attributed partially to the heterogeneity of breast carcinoma.

IV. Conclusion:

Presently in addition to all the traditional morphological prognostic factors ER, PR and HER2 should be assessed in every case of carcinoma of breast as prognostic and predictive markers.

Uniform and standardized technique of IHC with long term survival studies from different regions will be helpful to confirm the present status and importance attributed to prognostic and predictive markers of breast carcinoma.

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Dr Sandhya V Poflee." Study of Predictive and Prognostic Markers in Breast Cancer with Special Reference to Hormonal Receptors ."IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 9, 2018, pp 31-36.