Original Research Article

Is It Time to Bid Adieu to the Traditional Histological Prognostic Parameters in Breast Carcinoma? Not Yet

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Abstract

Introduction – With the coming of adjuvant hormonal therapy, evaluation of hormone receptors now plays a pivotal role in the therapeutic management in breast carcinoma. HER2/neu positive tumors are resistant to tamoxifen based therapies. With the advent of Trastuzumab, the prognosis of this subset of tumors has improved. In this bewildering array of prognostic factors, the conventional prognostic histological features seem to have lost their importance. **Material and methods**- Fifty cases of mastectomy performed for breast carcinoma were taken in the study. Immunohistochemistry was performed for ER, PR and HER2/neu. Correlation between them and the conventional histological prognostic features was studied. Chi square test was used for statistical analysis. **Results-** ER, PR showed a statistically significant positive correlation with each other. PR & HER2/neu showed no correlation with tumor size whereas ER showed a statistically negative correlation with size of the tumor. An inverse correlation was seen between tumor grades, mitotic count and ER, PR. HER2/neu showed no correlation with either grade or mitotic count though a significant positive correlation was seen with nuclear pleomorphism. Neither the hormone receptors not HER2/neu showed any correlation with lymph node status. **Conclusion-** Histological features are still valuable in judging the prognosis of breast carcinoma. Triple negative and ER+PR- tumors are unresponsive to systemic adjuvant hormone therapy. In addition cost and availability can be limiting factors in applicability of these tests especially in low socioeconomic conditions and resource limited centers.
Keywords: Breast carcinoma, ER, PR, HER2/neu, prognosis.

INTRODUCTION

Breast carcinoma is the most common cancer in women and is the leading cause of cancer related deaths in women worldwide. With advances in the treatment modalities, the management of these malignancy has changed in the past few decades by leaps and bounds. The task of choosing the therapeutic regimen for an individual patient is now a challenging task. Breast carcinoma is no more a simple disease entity. Understanding the disease is complex in terms of disease heterogeneity associated with diverse morphologies, molecular characteristics, clinical behavior and response to therapy.

In the present times, hormone and growth factor receptors have taken over the prognostic scenario completely as far as breast carcinoma is concerned. In this extremely competitive diagnostic and prognostic scenario, the traditional histological prognostic parameters seem to have taken a back seat.

In the late 1800s, Halsted [1] promoted radical mastectomy and Patey [2] modified radical mastectomy as the treatment for breast carcinoma based on the assumption that breast carcinoma spreads in an organized manner. Unfortunately with the Halstedian approach only 12% patients treated with mastectomy survived 10 years. It was later observed that 20-30% of node negative patients ultimately develop metastatic disease. These observations lead to the paradigm of micro metastatic disease that states many patients with early disease may harbor distant micro metastasis at the time of diagnosis putting them at a definite risk of overt metastatic disease later. The very purpose of administering adjuvant systemic therapy is to eradicate this distant micro metastasis [3]. Adjuvant systemic therapy comes with its own associated risks; therefore it would be prudent to optimally select patients who are likely to benefit from this therapy.

The Nottingham (Elston-Ellis) modification of the Scarff- Bloom- Richardson grading system also

known as the Nottingham Grading System (NGS) is the grading system recommended by various professional bodies internationally. NGS gives a view of the intrinsic biological characteristics and clinical behavior of the tumor. When used in Nottingham Prognostic Index (NPI), it adds important information to other at least partly time dependent prognostic factors such as tumor size and lymph node status.

In the present study we studied the expression of ER, PR and HER2/Neu expression in breast carcinoma and correlated them with the traditional prognostic factors.

MATERIAL AND METHODS

Fifty cases of radical mastectomy performed for Invasive Ductal Carcinoma were included in the study. Grossing was done as per standard protocol. H & E sections were examined and NSG grading was done and NPI was calculated. The same breast specimens were used for performing immunohistochemistry using DAKO kit. The Allred Scoring was done for ER, PR and intensity scoring (1+ to 3+) was done for HER2/neu. Chi square test was used for statistical correlation.

RESULTS

The highest numbers of cases were of Grade 2 (Fig-1).

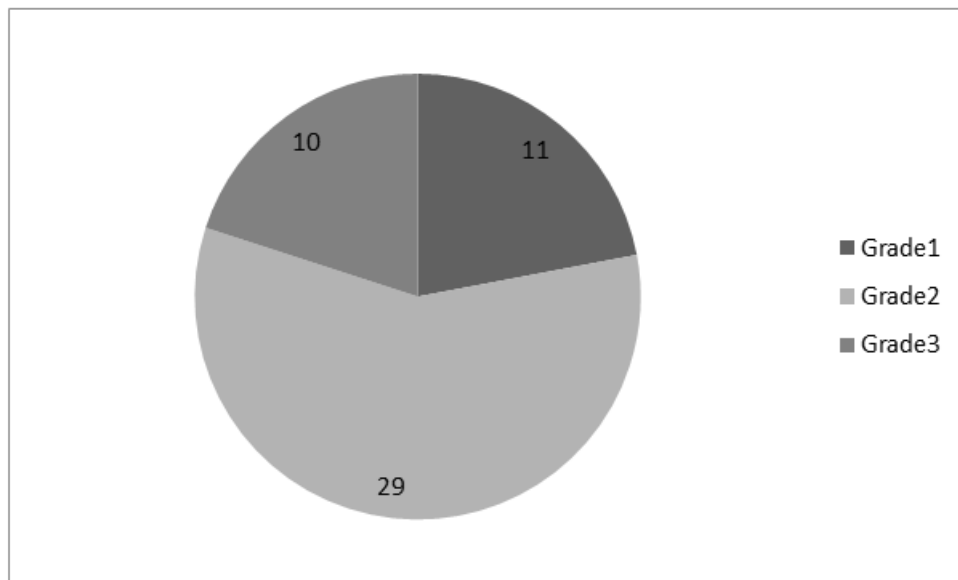On IHC, the following combinations of hormone expression were observed (Table-1).

Fig-1: Showing the distribution of cases according to the grade of tumor

Table-1: Showing the percentage of various combinations of hormone receptors and Her2/neu

BIOLOGICAL MARKER	PERCENTAGE
ER+/PR-/HER+	20%
ER+/PR+/HER-	6%
ER-/PR+/HER+	2%
Triple negative	22%
Triple positive	8%
ER-/PR-/HER+	42%

All cases of HER2/neu positive showed 3+ intensity score, no 1+ or 2+ were observed in our study.

The relationship of hormone receptors and HER2/neu expression with the mean size, age, number of lymph node and grade is shown in Table-2.

Table 2: Showing the relationship of hormone receptors and HER2/neu with prognostic factors (LN=Lymph node)

Parameters	HER3+	HER –ve	ER +ve	ER-ve	PR+ve	PR-ve
Mean age (yrs)	43.75	40.64	48.52	42.15	42.5	44.6
No. of cases ≤ 40 yrs	16	8	6	18	5	19
No. of cases ≥ 40 yrs	20	6	11	15	3	23
Mean size	4.4cms	4.7cms	5.6cms	4.0cms	5.8cms	4.3cms
No LN	6	3	4	5	3	6
1-3LN	11	2	3	10	1	12
≥4LN	4	0	4	0	0	4
Grade 1	9	2	5	6	2	9
Grade2	18	11	9	20	5	24
Grade3	9	1	3	7	1	9

Marked nuclear pleomorphism was seen in PR-ve & HER2/neu +ve tumors. In relation to mitotic count, maximum tumors (n=29) gave a low mitotic count (<5/10 HPF) in which an ER, PR score of 0-2 was seen & 19 cases gave HER2/neu +ve (3+). A high mitotic count (11-15/10HPF) was observed in only 6 tumors where a corresponding ER, PR score of 0-2 was seen in maximum tumors & 5 cases gave Her2/neu positivity (3+).

NPI was possible in only 26 cases where LN were isolated &/or sent and maximum cases belonged to intermediate risk group. In this group Her2/neu positivity was seen in maximum tumors (Fig-2).
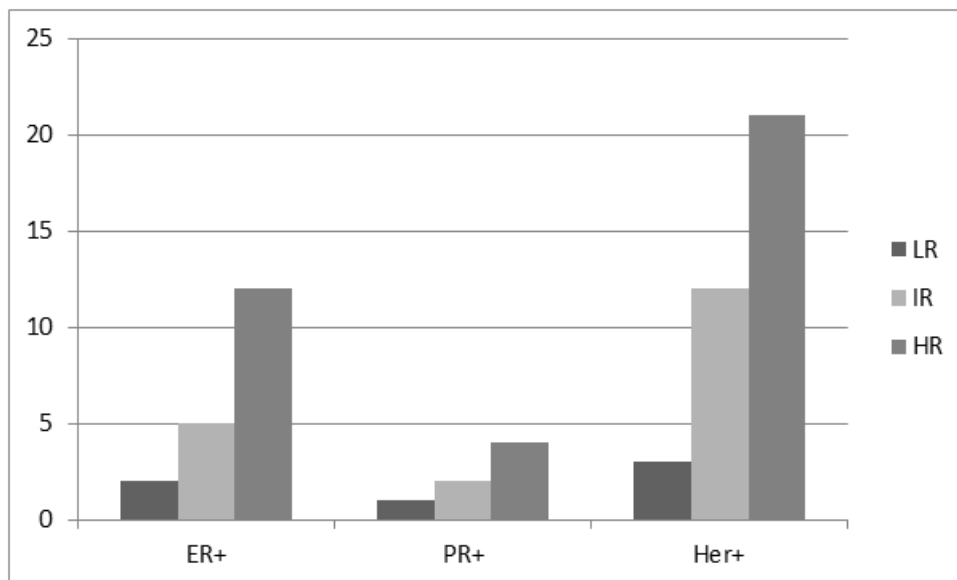

Fig 2: Showing the distribution of cases with ER, PR and HER2/neu expression in relation to NPI (LR=low risk, IR=intermediate risk, HR=high risk).

On statistical analysis, ER showed a positive correlation with PR expression (p=0.001) & though PR did show a positive correlation with HER2/neu it was not statistically significant. ER & PR positivity correlated with LN involvement with marginal significance (p=0.074) whereas HER2/neu showed no correlation with LN involvement. PR & HER2/neu showed no correlation with tumor size whereas ER showed a statistically negative correlation with size of the tumor. An inverse correlation was seen between tumor grade & mitotic count with ER, PR expression. HER2/neu showed no correlation with either grade or mitotic count.HER2/neu showed a statistically significant positive correlation, ER showed no correlation whereas PR showed an inverse negative correlation with nuclear pleomorphism. None of the biological markers showed any correlation with age.

DISCUSSION

Breast cancer is the most common cancer in women in urban Indian population. It is second only to cervical cancer in rural areas according to cancer registry data [4]. The knowledge of outcome of the disease forms an integral part of the decision making process which is important for the fulfillment of the potential expectations of the patient & for addressing the outcomes that are against expectations. Some form of either hormone therapy or chemotherapy or targeted therapy in various combinations &/or in sequence can now be offered to these patients making the treatment

more individualized. Given the enormous benefits of hormone therapy that have been documented by various studies worldwide, it has now become a practice to assess the hormone receptor status in breast cancer patients. Similarly HER2/neu serves as an important marker for benefit from therapies such as trastuzumab which targets the receptor tyrosine kinase. The use of biomarkers can be prognostic, predictive or both. The over-expression of HER2/neu is associated with poor prognosis i.e. high risk of recurrence (ROR); however there is benefit from anthracyclins and taxane based chemotherapies and therapies that target HER2/neu receptor (trastuzumab) but not to hormone therapy.

In our study we observed that majority of tumors (both ≥40 yr and ≤40 yrs age) were grade 2, similar results have been reported by various studies [5-13]. Women diagnosed in grade 2 reflect delay in seeking medical consultation allowing the tumor to progress to histological grade 2. This could be either due to lack of awareness as well as unavailability of medical facilities. This fact highlights the importance of educating women about breast cancer and the significance of regular breast self examination.

Diagnosing grade 2 breast tumors has other implications for the patient as well. Assigning grade 1 to grade 3 and visa versa are rarely reported but grade 2 tumors are the ones which are notorious for showing the lowest degree of concordance. In meeting of Saint Gallen International Expert Consensus on Primary Therapy of early breast cancer it was recommended that grade 1 and grade 3 be considered for assessment of indications of adjuvant chemotherapy. Grade 2 was regarded as having similar risk to other parameters of intermediate risk such as tumor size between 2-5 cms

and low number (1-3) of lymph nodes involved. Therefore it was inferred that they do not provide a definitive indication of risk with respect to taking the decision whether to give or withhold chemotherapy [14]. The various combinations of hormone receptors and HER2/neu expression in grade 2 tumors in our study portray the heterogeneity of breast carcinoma with respect to their biological behavior despite being in the same histological grade.

The mean tumor size in our study was 4.56 cms, which is similar to the size reported by Gupta *et al.,* [10], and Prasad *et al.,* [15]. However Ambriose *et al.,* [13] and Taucher *et al.,* [16] Yamashita *et al* have reported a smaller mean tumor size. The tumor size reported in most Indian studies is greater than that of studies on western population. The disparity in tumor size may be due to early detection programs (breast screening program) which are prevalent in western countries which our country unfortunately lacks till date.

The mean age in our study was 44.3 years with the eldest patient being 80 years and youngest 22 years. This is similar to other studies conducted in the country [6, 10, 15, 17]. The mean age reported is almost a decade earlier than western women. This difference can be explained by the prevalence of risk factors. The younger age at menarche, older age at first child birth and/or menopause and higher prevalence of obesity could be the attributing factors. Cultural differences in the physical parameter, diet, alcohol consumption & exogenous estrogen use could also contribute to the differences in age related incidence between the Western and Asian population [18].

Table-3: Showing results of our study in comparison with other studies

Study	Mean age(yrs)	Mean size (cm)	Grade	ER+ PR+	ER+	PR+	HER2/ neu +ve	Triple +ve	Triple -ve
Yamashita H *et al.,* 2004 [5]	-	<2	2	-	-	-	20%		-
Nisha A *et al.,* 2008 [8]	48.3	2-5	2	4%	32.7%	25.3%	24.7%	-	-
Wandy V *et al.,* 2009	-	-	-	-	66%	12%	3%	-	-
Ambriose M *et al.,* 2011 [13]	53.	2.5	2	-	59.19%	51.1%	27.10%	-	25%
Sofi GN *et al.,* 2012 [6]	48.2	3.6	2	60.4%	66.3%	63.4%	-	-	-
Prasad K *et al.,* 2013 [15]	41-5-	<5	1	-	36.5%	31.7%	2.4%	-	50%
Sepideh S *et al.,* 2015	40.2%	3.15	2	-	-	-	-	-	-
Geethmala K *et al.,* 2015 [17]	35	-	1	52%	2%	-	25%	1%	20%
Our study	44.3	4.56	2	4%	34%	16%	72%	8%	22%

An interesting observation in our study was that 72% patients showed HER2/neu positivity and all

these cases showed an intensity score of 3+. No cases showed 1+ or 2+ intensity. Similar results have been shown by Ayadi *et al*., in his study [19].

Another important revelation in our study was that a substantial percentage (22%) of cases was triple negative which is more than Arafah *et al*., [11] & Manraj *et al*., [20]. However it is lesser than the figure reported by Suvarchala *et al*., [21], Ghosh *et al*., [22], Geethmala *et al*., [17] and Ambriose *et al*., [13] Triple negative Breast Cancer (TNBC) has been reported from 6.7 % to 27.9% in different countries. Unfortunately India has reported the highest percentage followed by Indonesia & Algeria. Prevalence of TNBC in north, south, east & west of the country was 28%, 34%, 30% & 31% respectively. After reviewing and meta-analysis of 17 cross sectional studies the overall prevalence of TNBC in India ranged from 27-35% across studies with the summary estimate of 31% [23]. This is comparable to the prevalence seen in African women but twice the rate seen in white women [24-26]. Multiple factors may account for the higher prevalence of TNBC reported among Indian patients with breast cancer which includes early age of onset, lifestyle factors & socioeconomic status [23]. Another important factor could be potential genetic susceptibility of Indians to TNBC. More focused research into these factors will help to clarify underlying factors of TNBC in India as they may have implications for decreasing the burden of breast cancer mortality in India. The first step in this direction would be to institute a prospectively managed population based database of breast cancer patient with reliable histopathology testing. This subset of patient will not benefit from hormone therapy or from trastuzumab. Although these patients do responds fairly well to chemotherapy, they have a tendency to recur. So far, no perfect therapy has been devised for this subset of patients.

Another unfavorable subset of breast cancer(ER+/PR-) contributed 20 % of cases in our study. The outcome of this subtype is either as bad as or worse than TNBC. These tumors have certain characteristics that set them apart from other tumors. ER+/PR-tumor is a more aggressive phenotype & is resistant to tamoxifen. At the cellular level, they have a higher S- phase fraction, resulting in a higher proliferation rate & are more likely to be aneuploid. These tumors show a greater genomic instability compared to ER+/PR+ and ER-/PR- tumors. They also have a much higher levels of growth factors signaling i.e. HER2/neu and EGFR than ER+/PR+ tumors. HER2/neu over-expression is associated with significant shorter disease free survival (DFS) interval in patient with ER+/PR- as compared to ER+/PR+ tumors in which HER2/neu over-expression is not associated with DFS [27]. The response of ER+/PR- breast carcinoma to SERM (selective ER modulators) is lesser as compared to ER+/PR+ tumors. This resistance to hormone therapy may be explained by the dependence of ER activity on PR expression, the absence of PR therefore reflects a non functional ER [28]. A short course of estrogen to restore PR levels could be an option for developing a treatment strategy for this aggressive phenotype and improve the prognosis. However the most challenging part would be selection of patients and the timing & regulation of estrogen administration. This area still needs to be explored cautiously before any further substantial improvement in treatment is expected in future for these tumors.

Conventionally age, tumor size, grade and Nottingham prognostic index are used for evaluating the prognosis of breast cancer. In our study we correlated ER, PR & HER2/neu expressions with these prognostic factors & with each other as well. ER showed statistically positive correlation (p=0.001371) with PR. Neither ER nor PR showed any correlation with HER2/neu. Statistically significant positive correlation between ER & PR has been shown in various studies [9-11]. The positive correlation between ER & PR is explained by the theory of ER dependent PR synthesis.

With regards to NPI, majority cases (n=16) were in the intermediate risk group. With all the risk groups, HER2/neu showed the highest expression.

In our study we observed that the hormone receptor expression did not show statistical correlation with the conventional histological parameters. Axillary lymph node involvement is the most important prognostic factor for recurrence in early stage in breast cancer according literature. Patients with positive lymph node have reported to have 4 to 8 time higher mortality rate in comparison to patients with negative lymph nodes. There is also a direct correlation of positive lymph node status with the risk of distant recurrence [29]. In our study ER/PR positivity was associated with lymph node involvement with marginal significance only (p=0.074) where as HER2/neu show no correlation.

PR & HER2/neu showed no correlation with tumor size whereas ER showed a statistically negative correlation with tumor size. An inverse correlation was seen between tumor grade and ER, PR expression. HER2/neu showed no correlation with grade in our study.

Though our study suffered the limitation of a small sample size, some very important aspects of breast carcinoma in our region were revealed. A significant proportion of cases in our study showed a biologically aggressive phenotype where hormone therapy would be of no use (20% of ER+/PR- & 22% of TNBC). Further 42 % cases were ER-/PR-/ HER2/neu +. This subset is reported to have unfavorable prognosis with regard to age as well as grade of the

tumor [21]. It has also been reported that HER2/neu positive and ER negative breast cancer is resistant to trastuzumab. This is supported by the existence of potential "cross talk" between HER2/neu and ER pathways [30]. Therefore effectively in 84% of patients in our study; prognosis would be disappointing as the treatment options would be limited. This further emphasizes the need for early detection programs for breast cancer in our country.

CONCLUSION

Taking into the consideration our results, it would only be unfair to overemphasize the prognostic and/ or predictive benefit of evaluating the expression of ER, PR & HER2/neu over the conventional histological prognostic parameters especially in resource limited medical institutions in our country. With bulk of our patients coming from middle or lower socioeconomic background even if they were to derive any benefit from endocrine and targeted therapies, the cost of such treatment would be a limiting factor for them. Therefore it would not prudent to totally disregard the prognostic histological features for breast carcinoma yet. ER, PR & HER 2/neu expression can be used to complement rather than compete with histological features. Early detection is the key to reduce the breast cancer mortality in our country.

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