



Original Research Article

Study of Hormone Receptor Status of Breast Carcinoma and Its Correlation with the Established Prognostic Markers.

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ABSTRACT

Context: Breast cancer is a complex disease with heterogeneous prognosis. The selection of systemic adjuvant chemotherapy is based on prognostic and predictive factors. The hormone receptor levels are good predictive markers of response to hormone therapy; but their prognostic value is still debated.

Objective: The present study was undertaken to observe the trend and to analyze the status of hormone receptor expression in breast carcinoma at our institute, and to assess their value in terms of established prognostic markers, viz: tumor size, tumor grade, tumor necrosis, lymphovascular invasion, Cerb-B₂ overexpression and lymph node metastasis status.

Design: We analyzed 222 cases breast carcinomas reported at our institute from Jan 2002 to Dec 2010. Blocks of all cases were sent to Tata Memorial Hospital, Parel, Mumbai for Immunohistochemistry.

Results: Majority (57.65%) of our patients belonged to age group 31 to 50 years. Only 40% of the tumors were both ER and PR positive. The ER and PR receptor expression correlated well with tumor size, tumor grade, tumor necrosis and lymphovascular invasion, while it did not correlate with lymph node metastasis in our study.

Conclusion: Our study supported the findings by others that, breast cancer occurs a decade earlier, and hormone receptor expression is low in Asian women as compared to western world. We conclude that apart from being a predictive marker, hormone receptors have their role in selecting patients for targeted therapy and can be looked upon as a promising prognostic marker too.

Key words: Breast carcinoma, ER, PR, Prognostic marker.

INTRODUCTION

Only about one half of patients with early breast cancer are treated and cured by local surgical excision alone. Therefore, it is important to identify the set of patients in whom the disease is destined to recur and which patients are likely to benefit from systemic chemotherapy. ^[1] Systemic adjuvant chemotherapies that are designed to eradicate microscopic deposits of cancer cells that may have spread or metastasized from the primary breast cancer, have been demonstrated to increase a women's chance of long term survival. ^[2] The selection of systemic adjuvant therapy is based on prognostic and predictive factors. ^[2] A predictive marker gives information about a patient's response to treatment, while a prognostic marker tells about overall survival of the patient.

Although the value of hormone receptor levels in predicting response to hormone therapy in early breast cancer patients is undisputed; their prognostic value is still debated. ^[1] Moreover, studies have shown that in contrast to western literature, percentage of estrogen and progesterone receptor (ER and PR) positive tumors in Indian subcontinent is persistently low. ^[3, 4, 5]

The present study was undertaken to observe the trend and to analyze the status of

hormone receptor expression in breast carcinoma at our institute, and to assess their value in terms of established prognostic markers viz: size of tumor, grade of tumor, tumor necrosis, lymphovascular invasion, Cerb-B₂ status and lymph node metastasis status.

MATERIALS AND METHODS

We studied the breast carcinomas reported at our institute from Jan 2002 to Dec 2010 (9 years). During this period, a total of 233 cases were reported as breast carcinoma. Eleven cases were excluded from the study due to inadequate information available, thus we analyzed 222 cases. The types of specimens that were received included – MRM (modified radical mastectomy), wide excision, lumpectomy, palliative mastectomy and outside paraffin blocks for review. Axillary lymph nodes were received in 181 cases. Routine H&E slides were examined by the faculty members of our department. In 11 slides received from outside for review, comment about necrosis and lymphovascular emboli could not be made due to inadequacy of material. Blocks of all cases were sent to Tata Memorial Hospital, Parel, Mumbai for Immunohistochemistry. This study has been approved by the review board of our institute.

RESULTS

A total of 222 cases were included in this study. The age of the patients ranged from 26 to 80 years, with majority of them in the range of 31 to 50 years (57.65%). Females comprised of 99.1% (220/222) while rest 2 were males. Left side was slightly more commonly affected (51.8%). One patient had bilateral tumor and in two cases of blocks received from outside, the side was not mentioned.

Majority of the tumors were more than 2 cm in size (92.35%). Only 3.15% tumors were less than 2 cm in maximum diameter. Size of the tumor was not available in 10 cases of outside blocks for review. Majority of the tumors i.e. 70.7% were grade III tumors.

Hundred and one cases (47.85%) showed tumor necrosis, while lympho-vascular invasion was seen in 118 (55.90%) cases. Cerb-B₂ study was done in 209 cases, out of which only 34 (16.75%) cases were positive, 2 cases showed equivocal results.

Lymph nodes were received in 181 cases. Out of them, 108 cases showed metastatic breast carcinoma.

Hormone receptor status was divided into four groups, viz: (ER+PR+), (ER+PR-), (ER-PR+) and (ER-PR-). Positivity for both the receptors was seen in 40.1% of cases, while 48.2% were negative for both of them. Thirteen cases each belonged to the groups (ER+PR-) and (ER-PR+). (Table1)

Table 1: HORMONE RECEPTOR EXPRESSION

CATEGORY	NUMBER	PERCENTAGE
ER+PR+	89	40
ER+PR-	13	5.9
ER-PR+	13	5.9
ER-PR-	107	48.20
TOTAL	222	100

Table 2: AGE DISTRIBUTION OF PATIENTS

AGE GROUP	NUMBER	PERCENTAGE
<21	0	0
21-30	5	2.27
31-40	53	23.87
41-50	75	33.78
51-60	50	22.52
61-70	32	14.41
>70	7	3.15
TOTAL	222	100

Table 3: Correlation of Hormone receptors with the prognostic markers

PARAMETER		ER+PR+	ER+PR-	ER-PR+	ER-PR-	TOTAL
TUMOR SIZE	2-5 cm	5 (71%)	0	0	2(29%)	7
	<2 cm	59(49%)	9(7%)	7(6%)	46(38%)	121
	>5cm	23(27%)	4(5%)	6(7%)	51(61%)	84
	NA*	02(20%)	0	0	08(80%)	10
GRADE	I	5(100%)	0	0	0	5
	II	33(56%)	2(3.5%)	5(8.5%)	18(32%)	58
	III	51(33%)	11(7%)	8(5%)	87(55%)	157
TUMOR NECROSIS	POSITIVE	28(27.7%)	5(4.9%)	7(6.9%)	61(60.5%)	101
	NEGATIVE	58(52.9%)	8(7.2%)	6(5.4%)	38(34.5%)	110
	NA*	3(37.5%)	0	0	8(62.5%)	11
LYMPHOVASCULAR INVASION	POSITIVE	44(37.29%)	8(6.78%)	4(3.39%)	62(52.54%)	118
	NEGATIVE	42(45.5%)	5(5.4%)	9(9.6%)	37(39.5%)	93
	NA*	3(37.5%)	0	0	8(62.5%)	11
Cerb-B₂	POSITIVE	10(29%)	0	0	24(71%)	34
	NEGATIVE	69(40%)	13(7.5%)	13(7.5%)	78(45%)	173
	EQUIVOCAL	2(100%)	0	0	0	2
	NA*	8(61.5%)	0	0	5(38.5%)	13
LYMPH NODE METASTASIS	PRESENT	48(44.4%)	7(6.5%)	5(4.7%)	48(44.4%)	108
	ABSENT	27(37%)	2(2.7%)	5(6.8%)	39(53.5%)	73
	NA*	14(34.14%)	4(9.75%)	3(7.33%)	20(48.78%)	41
TOTAL		89(40%)	13(5.9%)	13(5.9%)	107(48.2%)	222

*NOT AVAILABLE.

Size of the tumor, grade of the tumor, tumor necrosis and lymphovascular invasion correlated well with the receptor positivity, while lymph node positivity showed no correlation.

DISCUSSION

Sistrunk and MacCarthy had said almost 90 years back that, “It is impossible to foretell the duration of life of all patients with carcinoma of the breast, because the degree of malignancy varies widely, and persons react differently to the disease.”^[6] National Institutes of Health Consensus Development Panel in their special article^[2] provided an assessment of currently

available data regarding the use of adjuvant therapy for breast cancer. They recommended adjuvant hormonal therapy to women whose breast tumors contain hormone receptor protein, regardless of age, menopausal status, involvement of axillary lymph nodes, or tumor size. At the same time, they mentioned that hormonal adjuvant therapy should not be recommended to women whose breast cancers do not express hormone receptor protein. This makes

hormone receptor study of every breast carcinoma an essential prerequisite in patient management. The prevalence of hormone receptor- positive breast cancer in Asian countries has been found to be lower than western world where more than 50% tumors express hormone receptors. However, the number of studies performed on this topic is much less in the Asian communities compared to the western world. In the present study, 45.95% cases were ER+ and an equal number of cases were PR+(Table 1). Vaidyanathan et al [7] reported 59.4% ER+ and 58.3% PR+, while Desai et al³ reported 32.6% ER+ and 46.1% PR+. Teguh et al [8] reported 51.7% ER+ and 48.2% PR+. Majority of the patients (57.65%) were in age group 31 -50 years of age, which was similar to the findings documented by Shet et al [4] (60%) and by Dutta et al [9] (50%). Valerie Jeanne et al found in a study conducted over a 28 yr. period in Texas, U.S.A. that a majority of the patients (88.42%) diagnosed with breast cancer were more than 50 yrs. of age. [1] This corroborated the observation that breast carcinomas occur at a younger age in Indian subcontinent than in the western world.(Table 2)

Majority of the patients included in this study (70.7%) were grade III tumors, which explains the low prevalence of hormone receptor expression. It is common to find high grade tumors showing low hormone receptor positivity. Similar findings were noted by Shet et al [4] (70% of grade III tumors), Muddawa [11] (49% of grade III tumors). Dutta et al [9] and Azizun – Nisa et al [5] recorded Grade II being the commonest. Grade of the tumor correlated inversely with the hormone receptor positivity. While 100% of grade I tumors showed (ER+PR+), 55.41% of grade III tumors were (ER-PR-). Shet et al [4] reported 100% receptor positivity in grade I tumors,

93% in grade II and only 39.5% of grade III tumors were (ER+PR+). (Table 3)

IDC-NOS formed the predominant histologic type in our study, comprising of 93.24% of all the tumors. Azizun-Nisa [5] et al recorded 85.3%, Vaidyanathan et al [7] 90.3%, while Sandhu DS et al [10] reported 97.3% tumors of IDC-NOS histologic type. Amelia K Hausauer et al [11] studied breast carcinoma in Asian pacific, Hispanic, African-American and non-Hispanic whites and found respectively 73.9%, 66.5%, 67.1% and 66.3% tumors of IDC-NOS type.

Majority of the tumors in our study ranged in size between 2 to 5 cm i.e. 54.5%. Similar findings were recorded by Muddawa [12] (74%) and Teguh et al [8] (59.8%). Azizun-Nisa et al [5] reported tumor size less than 2 cm being the most common presentation. Amelia K Hausauer et al [11] found tumor size less than 2 cm the commonest in all the four races studied by them. Tumor size correlated inversely with the hormone receptor expression. 71.4% of tumors less than 2 cm showed (ER+PR+), while 60.7% of tumors greater than 5 cm in size were (ER-PR-).

Out of 181 cases where axillary lymph nodes were received, 48.64% cases showed metastasis. The findings by others were – Muddawa [12] (57.6%), Vaidyanathan et al [7] (59%), Azizun-Nisa et al [5] (71.3%), Dutta et al [9] (70%) and Teguh et al [8] (62.5%). Out of 108 cases showing metastasis in our study, both (ER+PR+) and (ER-PR-) comprised of 44.4% each.

Tumor necrosis and lymphovascular invasion was seen in 47.85% and 55.9% of cases respectively. Sixty point four percent of cases showing tumor necrosis were (ER-PR-), while 52.7% of cases without tumor necrosis were (ER+PR+) (Table 3). Fifty two point five percent of cases with lymphovascular invasion were (ER-PR-), while 45.1% of cases without it were (ER+PR+). Desai et al [3] and Dutta et al [9] reported

inverse relationship of tumor necrosis and lympho-vascular invasion with hormone receptor protein expression. Extensive tumor necrosis is a prognostically unfavorable feature in invasive mammary carcinoma, possibly reflecting a growth rate so rapid that it exceeds tumor sustaining angiogenesis to a substantial degree. [6]

Several studies have shown that peritumoral lymphatic emboli were prognostically unfavorable in node negative patients treated by mastectomy. [6] Moreover, metastases that developed in node negative patients with peritumoral emboli tended to occur more than 5 years after diagnosis, and they were almost always systemic. Lymphatic tumor emboli were associated with an increased risk of local recurrence in patients treated by breast conserving surgery. [6]

Cerb-B₂ gene is a proto-oncogene expressed in 10 – 34% of breast carcinomas and is associated with poor clinical outcome. It is a trans-membrane growth factor receptor belonging to type I receptor tyrosine kinase family of proteins. Cerb-B₂ over expression was seen only in 16.35% cases (Table 3). Similar findings were noted by Azizun-Nisa et al [5] (24.1%), Nidal M Almasri et al [13] (24%), and Mudduwa [12] (19.1%), while Dutta et al [9] and Teguh et al [8] reported a high prevalence of Cerb-B₂ over expression, in 64.16% of cases each. Cerb-B₂ over expression is associated with poor response to hormone receptor modulators. These patients are resistant to conventional therapy. They can opt for herceptin therapy which is highly efficient for these patients. These are more aggressive tumors than those which do not express this receptor. It is an indicator of reduced disease free survival in lymph node positive cases. [9] Some researchers presumed that tumors with positive ER and Cerb-B₂ did not respond to Tamoxifen treatment due to cross talk or interaction of Cerb-B₂ tyrosine kinase

pathway with hormonal pathway or tumors with positive Cerb-B₂ grew very fast. [8]

The National Institute of Health Consensus Development Panel [2] recommended that the decisions regarding adjuvant hormonal therapy should be based on the presence of hormone receptor protein in tumor tissues. Adjuvant hormonal therapy should be offered only to women whose tumors express hormone receptor protein, regardless of age, menopausal status, involvement of axillary lymph nodes or tumor size. [6] Thus, determining hormone receptor status becomes a key factor in deciding the patient management. Available data suggests that chemotherapy and Tamoxifen are additive in their impact on survival when employed as adjuvant treatment of breast cancer.

CONCLUSION

Breast cancer occurs about a decade earlier in Asian women than in the West. The hormone receptor expression is low in Asian women. Moreover, the ER and PR receptor expression correlated well with the established prognostic markers. We suggest that low hormone receptor positivity in Asian countries may be explained by the fact that, majority of the tumors are larger in size, of higher grade, and many of them have lymph node metastasis at the time of diagnosis. The late presentation of the patients is because of lack of awareness, poverty, illiteracy and many other social reasons. Thus we propose that health education may bring more and more patients to seek treatment earlier. Also, increased screening programs for breast cancer may cause its detection at earlier stages, thus increasing hormone receptor expression, better response to treatment, and hence, better prognosis.

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