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Original Research Article

Correlation of Histomorphological Prognostic Factors of Invasive Breast Carcinoma-NST with ER/PR and HER2

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ABSTRACT

Background: Breast carcinoma is one of the leading causes of mortality and morbidity in middle aged females. Numerous histomorphological prognostic factors including hormonal receptor status play vital role in further management of patient care. Objectives: This study was undertaken with the aims and objectives to study the correlation of tumor size, tumor grade and regional lymph node metastasis with hormone receptors(ER, PR and HER2).
Materials and methods: This is a retrospective study; all patients diagnosed with Invasive breast carcinoma-NST within June2013-Sep2015 were included. MRM specimen's gross and microscopic finding were collected and studied.
Results: Total 141 patients were studied. Maximum numbers of patients were from 5th decade, left sided tumor was found in 61%cases. Tumor size of 2.1-5cm was found in 58.9% cases. Axillary lymph node metastasis was found in 54.6% cases. Statistically significant association of ER/PR was found with Tumor size (P 0.041) and with Axillary lymph node status (P 0.012). Statistically significant association of HER2 was found with Axillary lymph node status (P 0.049).
Conclusion: Our study shows that ER/PR and HER2 are important indicators of breast carcinoma prognosis and are positively correlated with other important prognostic factors.

Key Words: Breast carcinoma, Estrogen Receptor, Progesterone Receptor, HER2, Breast

INTRODUCTION

Invasive breast carcinoma is the largest group of malignant mammary tumors, comprising approximately 75% of mammary carcinomas. [1,2] It is essentially a diagnosis by exclusion. [3] Fisher et al [4] (1984) have added the phrase 'without special features' or 'Not otherwise specified', (now changed to 'no special type' by WHO in 2012). The measured gross size represented by the largest dimension of a mammary carcinoma is one of the most significant prognostic variables. Numerous studies have shown that survival decreases with increasing tumor size and that there is a coincidental rise in the

frequency of axillary nodal metastases. [5,6] Histologic grading describes the microscopic growth pattern of invasive carcinoma- NST, as well as cytologic features of differentiation. The most widely used histologic grading systems are based on criteria established by Bloom, Bloom and Richardson, and Elston and Ellis. [7] The latter system is also known as the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system or the Nottingham combined histologic grade. [8]

Lymph node metastasis is one of the most important prognostic parameters. The most common site of lymph node involvement is axilla, followed by supraclavicular and internal mammary nodes. Not only is there a sharp difference in survival rates between patients with positive and negative nodes, but the survival rate also depends on the level of axillary node involved (low, medium, or high), the absolute number (fewer than four versus four or more) [9] the amount of metastatic tumor, the presence or absence of extranodal spread, [10] and the presence or absence of tumor cells in the efferent vessels. [11]

The determination of ER and PR status is a crucial element in the pathologic evaluation of breast carcinomas. Approximately 75% of all invasive breast carcinomas are positive for hormone receptors. Slightly more tumors are ER positive than are PR positive. Approximately 20% of all invasive breast carcinomas are positive for HER2. The 2013 ASCO-CAP HER2 testing guidelines recommend HER2 testing for all newly diagnosed primary or metastatic breast carcinomas and acceptance of the primary assessment of HER2 status using immunohistochemistry. [12]

MATERIALS AND METHODS

The present study on breast carcinoma was carried out in department of Pathology, at a tertiary care hospital during a period of 2 years 3 months (from June 2013 to September 2015). All the MRM specimens with axillary node dissection which were diagnosed to be invasive breast carcinoma-NST on microscopy according to WHO 2012 classification were included in the study. Breast cancer cases other than Invasive carcinoma-NST, male breast cancer cases were excluded. All the gross findings of specimen were studied and recorded from the description of the specimen in the files. Histologic sections of specimen and axillary lymph nodes were retrieved and reviewed to confirm the findings of histopathology which were in the report given by Pathology department. Histological grading was done according to modified Bloom Richardson by Elston and Ellis method. Tumor size was noted during grossing of tumor (largest dimension was taken as the size) and axillary lymph nodes were dissected and positive nodes for metastasis were noted. Tumor necrosis and tumor emboli were noted. Immunohistochemistry for ER, PR and HER2 hormone receptors were done and reported as positive and negative as per standard protocol.

To find correlation of histomorphological prognostic factors with hormone receptors, Bivariate analysis was carried out using chi-square test between tumor size, tumor grade, lymph node involvement, tumor emboli and tumor necrosis with ER/PR and HER2.

RESULTS

Total 141 cases were studied. Maximum number of patients were form 5th decade (36.2%) followed by 6th decade (25.5%). Left sided tumor was found in 61% cases.

Maximum cases had tumor size of 2.1-5cm (58.9%) followed by 5.1-10 cm (29.1%) cases. Majority of cases were of grade-III (48.2%) followed by grade-II (44%).

No axillary lymph node metastasis was found in 45.4% cases and 55.6% cases had metastasized to axillary lymph nodes. Tumor necrosis was found in 46.8% cases

and tumor emboli were present in 61% cases.

Table 1: Showing demography and characteristics of tumor

Parameter	Characteristic of parameter	Frequency	percentage
Age(top three decades)	31-40years	31	22%
	41-50years	51	36.2%
	51-60years	36	25.5%
Site	Left sided	86	61%
	Right sided	55	39%
Tumor size	Upto 2 cm	13	9.2%
	2.1-5cm	83	58.9%
	5.1-10	41	29.1%
Tumor grade	I	11	7.8%
	II	62	44%
	III	68	48.2%
Axillary lymph node	0	64	45.4%
	1-3	27	19.1%
	4-7	21	14.9%
	8-10	15	10.6%
	>10	14	9.9%
Tumor necrosis	Absent	75	53.2%
	Present	66	46.8%
Tumor emboli	Absent	55	39%
	Present	86	61%

Table 2: Showing distribution of cases according to ER/PR and HER2 status

Parameter	Characteristic of parameter	Frequency	Percent
ER/PR	P/P	61	43.3%
	N/N	73	51.8%
	P/N	5	3.5%
	N/P	2	1.4%
HER2	Positive	39	27.7%
	Negative	102	72.3%

Table 3: Showing association between ER/PR and prognostic factors, with P value

Parameter name	P-value	Inference
Tumor size	0.041	Significant
Axillary Lymph node involvement	0.012	Significant
Tumor grade	0.110	Not significant
Tumor emboli	0.137	Not significant
Timor necrosis	0.116	Not significant

Table 4: Showing association between HER2 and prognostic factors, with P value

Parameter name	P-value	Inference
Tumor size	0.609	Not Significant
Axillary Lymph node involvement	0.049	Significant
Tumor grade	0.699	Not significant
Tumor emboli	0.394	Not significant
Timor necrosis	0.149	Not significant

ER/PR: In tumor size category of up-to 2cm and from 2.1-5cm, 66.7% and 51.9% cases were both ER and PR negative. Tumor size more than 5 cm 71.1% cases showed double positivity for ER and PR.

With no axillary lymph node metastasis, ER/PR negative were seen in 50.8% cases. When lymph node metastasis was present 1-3, 4-7, 8-10 and >10 lymph nodes, double negativity for ER/PR increased gradually seen in 51.4%, 58.3%, 61% and 72.7% cases respectively.

Grade-I tumors showed more double positivity for ER/PR, but grade-II and III showed more double negativity of ER/PR. Tumor emboli whether present or absent showed more double negativity for ER/PR as compared to double positivity. When tumor necrosis was absent more ER/PR double positive was seen, but when tumor necrosis was present double negativity for ER/PR was seen more than double positivity.

HER2: In category of tumor size of up-to 2 cm, 2.1-5cm and >5 cm HER2 negativity was seen in 61.2%, 72.3%and 75.6% respectively. No axillary lymph node involvement showed 78.1%negativity, in category of 1-3, 4-7, 8-10 and >10 lymph nodes involvement showed 77%, 50%, 61% and 71.4% negativity respectively.

Grade-I, II and III showed 63.6%, 71% and 75% cases of HER2 negative. When tumor emboli were positive negative HER2 was seen in 71% and with absence of tumor emboli negative HER2 was seen in 74.5%. In presence of tumor necrosis HER2 was negative in 77.3% cases in comparison to 68% HER2 negative cases when tumor necrosis was absent.

ER/PR/HER2: Triple positive cases for ER/PR/HER2 were 13 (9.2%) and triple negative for ER/PR/HER2 were 34 (24.1%).

DISCUSSION

In our study maximum number of patients were form 5th decade (36.2%), left sided tumor were more common than right sided, more than half of cases had tumor size between 2.1-5cm(58.9%), Axillary lymph node metastasis was found in 54.6% cases, tumor necrosis was found in 46.8% cases and tumor emboli was found in 61% cases. These findings are concordant with other studies who found similar results. [13,14,15,4]

In our study we found ER/PR positive in 43.3% ER/PR negative in 51.8%, these results were comparable with the study done by Bharti et al, [16] they also reported maximum number of patients with ER/PR negative, but present study is not in concordance with Fritz et al [17] who reported more number of ER/PR positive patients. Several studies have shown that ER- and/or PR- status is associated with poor treatment response, as negative ER/PR cases can't be given tamoxifin and increased mortality risk in patients with metastatic breast cancer. [18] Takeuchi et al. studied recurrence in Japanese women and showed that ER- and PR- statuses were poor predictive factors for mortality. [18] Similarly, Jun et al. reported that both ER- and PR- status is associated with mortality in the multivariate analyses. [19] Vamesu studied angiogenesis and ER/PR status in primary breast cancer patients and observed that the highest mean vascular density was seen in ER-/ PR- individuals followed by ER+ / PR+. [20] Similarly Bharti et al [16] found highest mean vascular density in ER-/ PR- followed by ER-/ PR+ and ER+ / PR-. The more the vascular density the more chances of metastasis and survival of tumor cells.

In our study about 3/4th of cases were HER2 negative (72.3%) and rest were positive, this study was comparable with study done by Santos et al [21] who also reported similar results for HER2 status. One study found that node-positive patients who were HER2+ had a lower 10-year overall survival proportion, 50% versus 65% for those who were HER2-. [22] After 10 years the difference in survival persisted, although it became somewhat smaller. As for patients with node- negative tumors, HER2 did not seem to affect long-term survival significantly. [22] Tumors that over express HER2 are more likely to contain p53 abnormalities, tend to be hormone receptor negative and bcl-2 negative and a high mitotic index, all known to be markers of poor prognosis. [22]

In present study we observed triple negative for ER/PR/HER2 in 24.1% cases and triple positive in 9.2% cases. Kakarala et al [23] in their study concluded that triple negative breast cancer is biologically aggressive, resistant to conventional cytotoxic chemotherapy treatment and associated with reduced survival compared to other subtypes of breast cancer.

In present study positive association ($P<0.05$) of ER/PR was found with tumor size and axillary lymph node status while of HER2 was found positively associated only with axillary lymph node status. Study done by Siadati et al [24] and Tokatil et al [25] also reported HER2 association with lymph node status. Lymph node status is important in determining cancer staging and treatment options. It is worth noting that it is the most important factor in the prognosis of patients with breast cancer. As the number of positive axillary lymph nodes increases, survival rate decreases and relapse rate increase. [24] One more study conducted by Azizun-Nisa et al [26] did not find any correlation of ER with lymph node status. ER/PR are hormonal receptors, if positive the patient can be given hormonal therapy tamoxifen therefore positivity of ER/PR is better for the patient outcome. But on the contrary HER2 is an epidermal growth factor on the surface of a cell that transmits growth signals to the cell nucleus. Over-expression of the receptor is associated with poor prognosis. Approximately 20% of all

invasive breast carcinomas are positive for HER2. HER2 gene amplification is a prognostic marker of poor outcome in the absence of adjuvant therapy, independent of nodal status, tumor size, grade, and hormone receptor status. [27,28] It is associated with an increased rate of metastasis, decreased time to recurrence, and decreased overall survival.

CONCLUSION

Present study showed that biologically adverse prognostic factors of tumor are present in more than 50% patients like high tumor grade, ER/PR negativity, tumor necrosis etc. which make the job of treating clinician very difficult. ER/PR and HER2 are independent prognostic factors in breast carcinoma. ER/PR was found significantly associated with axillary lymph node status and tumor size whereas HER2 was found significantly associated with axillary lymph node status only. Therefore analyses of these prognostic factors are helpful in better treatment plan of patient.

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