

Original Research Article

Correlation of HER2/neu receptors and other prognostic factors in breast carcinoma

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Received: 10 November 2018

Revised: 15 December 2018

Accepted: 20 December 2018

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ABSTRACT

Background: Breast cancer is the most common malignancy and the leading cause of cancer related death among women all around the world. Evaluation of prognostic factors including biomarkers is highly recommended for the best management and therapeutic decision of breast cancer patients. Aim was to study the correlation of HER2/Neu receptors and other prognostic factors in breast carcinoma.

Methods: Patients who are clinically diagnosed as carcinoma breast a detailed history will be taken. Patients were assigned TNM staging according to AJCC classification and posted for surgery than to find out the receptor status from that specimen.

Results: In 60 cases, there is no significant correlation and association between the prognostic factors (age, menstrual status, tumour size, side of disease, nodal positivity, pathological subtypes, histological grading except ER receptor positivity PR receptor positivity) and HER2neu receptor positivity. Significant association noted between the HER2NEU receptor positivity and ER, PR receptor negativity. ER AND PR receptor status it shows that a significant proportion of PR receptor activation is independent on ER receptor activation. And also this independent PR receptor positive status give false positive results depends upon staining pattern ,transport method of tissue specimen.

Conclusions: Our study results indicate the importance of ER, PR and HER-2/neu expression as prognostic factors for therapeutic decision.

Keywords: Breast carcinoma, Breast prognostic factors, ER, HER-2/neu, PR

INTRODUCTION

Carcinoma breast affects all the communities worldwide. Breast carcinoma is one of the most common cancer among women and the leading cause of death in women. Worldwide 1.1 million women were diagnosed with this disease, each year and the incidence rate is still on increasing trend in several countries. It causes 3,76,000 deaths in a year worldwide. Among them, Indian women contribute 60% of the total cases along with carcinoma cervix in worldwide which accounts for 10.4% of total

carcinoma cases.¹ The approach to management of carcinoma breast has undergone enormous changes over the last two decades.² Such changes are accompanied by increasing range of systemic, hormonal and cytotoxic drugs used in both adjuvant and neoadjuvant therapy.³ Prognosis and management are influenced by variants such as histological type, grade, tumor size, lymph node status, estrogen, progesterone, and HER-2/neu receptor overexpression.⁴ Identification of biomarkers plays an important role in the management and prognosis of breast carcinoma. Tectin for estrogen, progesterone, HER-2/neu

receptor status is critical to plan optimal treatment for breast carcinoma.^{1,5} Therefore it is essential to find markers that have predictive and prognostic values as it predicts the chance of recurrence of cancer and identifies which patients do and which patients do not benefit from adjuvant treatment. HER-2/neu status detection is correlated clinically, that HER-2/neu receptor positive patients have the worst prognosis than the HER-2/neu receptor negative patient.⁵ So, it has been reported that HER-2/neu receptor positive status is noted as both a marker of aggressive and also a target for the treatment part and Immunohistochemistry detection has become essential in tumor diagnosis, treatment, and progressive assessment.

According to literature breast cancer occurring in younger women are of the more aggressive type. Recurrence of the tumor is more common in young women than compared to elderly women. Survival and response to treatment to hormone therapy are, most common and more favourable among women who are receptor positive, intermediate for a tumour discordant on receptor status and least favourable for negative receptor patients.

Aim of the research work was to study the correlation of HER2/Neu receptors and other prognostic factors in breast carcinoma.

METHODS

This cross-sectional study was conducted in Department of Surgery at KAPV Government Medical College Hospital from July 2016- July 2018 Patients who are clinically diagnosed as carcinoma breast a detailed history will be taken. Patients were assigned TNM staging according to AJCC classification and posted for surgery than to find out the receptor status from that specimen.

Inclusion criteria

- Age >30 years,
- Both sexes,
- All types of breast carcinoma,
- Patient willing to participate in the study.

Exclusion criteria

- Patient's refusal,
- Paediatric age group,
- Death or absconded from the study,
- Benign breast diseases.

Biopsy samples by either Trucut or from postoperative mastectomy specimens were sent to our pathology lab, where they were processed and analyzed for the histopathological subtype of a tumour, grading, and clearance of resected margins. Hormonal receptors assay was done by using immunohistochemistry technique in

our college Pathology Department, and results were interpreted.

RESULTS

Around 60 cases were included in the study, in that 58 cases were female which is 97%, and 2 cases were male which is 3%. The incidence of breast cancer is more common in females. Breast carcinoma is more common in 51-60years 38.3% and the second most common decade 41-50years,30%. Carcinoma breast is more common on the right side, 55% of cases (33) is on the right side, and 45% of the cases is on the left side. The distribution of carcinoma in the breast commonly occurs in upper outer quadrant (70%) and less commonly in upper inner (5%) and lower inner (5%). The distribution of carcinoma in the breast commonly occurs in upper outer quadrant (70%) and less commonly in upper inner (5%) and lower inner (5%).

Among all the cases, Intraductal carcinoma (85%) were found to be commonly occurring while other types (ILC-8.3%, mucinous- 1.6%, medullary-1.6%) were the least occurring. Among all the cases, Intraductal carcinoma (85%) were found to be commonly occurring while other types (ILC-8.3%, mucinous-1.6%, medullary-1.6%) were the least occurring. Both low grade and high-grade tumors are commonly occurring with an only minor difference. 56% of patients presented with breast carcinoma had negative receptor status while 44% of the patients had positive receptor status. In this 44% of cases, 30% of patients had a more receptor intensity, and 11% had low intensity. The remaining 59% had a moderate receptor intensity. 50% of the patients had negative PR receptor status. 50% had positive status, in this 23% of patients with more receptor intensity while 13% had low receptor intensity, and the remaining 64% had moderate receptor intensity. Her2neu receptor status was negative for 71.6% of cases. Only 16% had more receptor intensity, 8% with moderate receptor intensity and 3% had low receptor intensity. Comparing HER-2/neu receptor positivity with the age groups, there is no association, there is no significant association between menstrual status and HER-2/neu, tumor size and HER-2/neu receptor positivity shows that there is no significant relation between the size of a tumour and HER-2/neu positivity.

It can be positive for any size of the tumour, and also no significant association is calculated between the side and her2 positivity, and P value of 0.488 and odds ratio is 1.823 on 95% confidence level in Table 2 signifies no association were found on nodal status and receptor positivity. HER2/neu receptor positivity can occur even in node-negative patients; there is only a chance but no significant relation. HER-2/neu receptor positivity in IDC is only 29.4% and ILC is 20%, even though some percentage of carcinoma relates with the HER2 receptor positivity indicates only a chance because the p-value is 0.991 which is not significant and also the odds ratio is

1.667 HER-2/neu receptor positivity in IDC is only 29.4% and ILC is 20%, even though some percentage of carcinoma relates with the her2 receptor positivity

indicates only a chance because the p-value is 0.991 which is not significant and also the odds ratio is 1.667 (Table 1).

Table 1: Pathological type and HER2neu receptor positivity.

Pathological grading	HER2/neu positive	HER2/neu negative	P value	Odd ratio
IDC	15	36	0.991	1.667
ILC	1	4		
Others	0	2		

Table 2: Pathological tumour grading and HER2neu.

Pathological grading	HER2/neu positive	HER2/neu negative	P value	Odd ratio
I	3	3	0.306	2.167
II	10	25		
III	3	14		

Table 3: Modified pathological grade and HER2 positivity.

Modified pathological grade	HER2/neu positive	HER2/neu negative	P value	Odd ratio
Low grade (I, II)	13	28	0.306	2.167
High grade (III)	3	14		

Table 4: ER, PR receptor and HER2neu receptor.

Receptor status	HER2/neu positive	HER2/neu negative	P value	Odd ratio
ER receptor	Positivity	2	0.003	0.106
	Negativity	15		
PR receptor	Positivity	4	0.02	0.201
	Negativity	13		

Table 5: ER and PR receptor association.

ER receptor status	PR positive	PR negative	P value	Odd ratio
Positivity	26	0	<0.0001	8.5
Negativity	4	30		

Grade is classified as I, II, III on the basis of tubule formation, nuclear pleomorphism and mitotic rate as per Bloom and Richardson classification in first table we correlates grades I, II, III with HER2 positive, odds ratio could not be calculated because this ratio is calculated only with the 2x2 tables only. So, we modified this in to low grade (I, II) and high grade tumours (III), in this we found the p value and odds ratio, but this shows that her2 receptor positivity may occur in any grade of the tumour and there is no significant association between these two variables (Table 2 and 3).

Most of the HER2 receptor positive occurs in ER receptor negative patients, and 13.3% of patients are positive for both PR and HER2 receptor and 86.7% of patients statistical analysis of ER and HER2 receptor positivity shows 7.7% of patients had both ER and HER2

receptor positive, 92.3% of patients had HER2 receptor positive but ER receptor negative, the p-value of these two variables is 0.003 and odds ratio is 0.106, this indicates the ER receptor negative and HER2 receptor positive is having a significant association (Table 4).

Most of the HER2 receptor positive occurs in ER receptor negative patients, and 13.3% of patients are positive for both PR and HER2 receptor and 86.7% of patients. Significant association between ER and PR receptor, because usually PR receptor is activated by activated ER receptor but in this study variables 11.8% of patients is PR receptor positive with ER receptor negative, and this variables p-value based on the chi-square test is <0.0001 and odds ratio is 8.5 this shows a significance (Table 5).

DISCUSSION

Rosen et al, attempted to correlate estrogen, progesterone receptors status along with various histological types of breast carcinoma.⁶ Wilbur D et al, studied about hormone receptor status in 30 patients by IHC method on paraffin-embedded blocks.⁷ He documents estrogen receptor positivity in 73% (22/30), progesterone receptors positivity in 63% (19/30), and HER-2/neu expression in 37% (11/30). Lici et al, found the incidence of invasive carcinoma by hormone receptor status from 1992 to 1998 in a population-based study.⁸ He found that hormone receptor positivity increased from 75.4% to 77.5% in the United States with a rise in prevalence over the years. Desai et al, studied the estrogen, progesterone receptors status of carcinoma breast in India.⁹ The procedure was done by immunohistochemical method. Out of 798 tumors, 32.6% of estrogen receptor positive and 46.1% of progesterone receptor were found positive. He obtained a high incidence of steroid receptors non-reactivity in breast carcinoma patients in India. Dutta CV et al, conducted a study in the Armed Forces Medical College, Pune, he analyzed Hormone receptors and HER-2/neu expression in breast carcinoma.¹⁰ This study reveals that receptor negativity is higher when compared with western communities. Mudduwa LKB, studied the hormone receptor status of carcinoma breast by using the Quick score method.¹¹ She has reviewed 151 cases and documented the prevalence of estrogen receptor positivity in 45.7%, progesterone receptor positivity in 48.3% and both receptors negativity in 54.3%. According to this study, HER-2/neu over expression was seen only in 19.1% (26/136) cases. Shet T et al, studied hormone receptors expression in the last 8 years from 1999 to 2006 in a cancer referral center in India.¹² A total of 11,780 cases were reviewed. The percentage of hormone receptor expression were varied from 52% to 57%. Kumar V et al, studied HER-2/neu oncogene overexpression which was much higher among Indian breast cancer patients 46.3% in comparison to 25-30% in Western countries.¹³ Reiner et al, found that papillary carcinomas are 100% estrogen receptor positive, 80% progesterone receptor positive and they have HER-2/neu negativity.¹⁴ Rosen et al, studied HER-2/neu expression in negative nodal patients.¹⁵ He had found the low incidence of oncogene expression in Papillary carcinomas. In 1991 Soomro S et al, studied about oncogene expression in different histological types of invasive breast carcinomas and quoted low expression in Neuroendocrine carcinomas.¹⁶ Horsfall et al, conducted the study on the relationship between ploidy and steroid receptors. Soomro S et al, showed a low incidence of HER-2/neu receptor overexpression in medullary and metaplastic carcinoma of the breast.⁵⁶ Kuenen-Boumeester V et al, studied immunohistochemistry of androgen receptor about estrogen and progesterone receptors.¹⁷ He found that a small set of lobular carcinomas tend to express both ER, PR receptors negativity and androgen receptor positivity. A study by Rosen PP et al, showed estrogen receptor positivity in

87.55% and, progesterone receptor positivity in 75% of the tumors in Invasive lobular carcinomas of the breast.¹⁸ Riva et al, studied immunohistochemical analysis of androgen receptor in breast carcinoma shows frequent expression in lobular carcinomas of the breast along with estrogen, progesterone receptors negativity.¹⁹ In contrast with Goyle S et al, conduct study showed estrogen, progesterone receptor positivity of 100% in grade I, 60.8% in grade II, none in grade III tumors.²⁰ HER-2 /neu overexpression showed 100% in grade III, 56.5% in grade II, none in grade I tumors. It explains the overexpression of oncoprotein with high histological grade tumors. Hence, it reflected a direct relationship with higher nuclear grade, which was compared with Rosen PP et al.¹⁵ Bhargava R et al, had reviewed 205 cases and concluded that 15% (32/205) were triple negative, 4% (8/205) were found positive for estrogen receptor and HER-2/neu hybrid overexpression.²¹

CONCLUSION

There is no association or correlation between HER-2/neu receptor positivity and prognostic factors except ER and PR receptor status. There is a strong association found between HER-2/neu receptor positivity and ER, PR receptor negativity, among them, 44.1% of patients had ER receptor negative with HER2 receptor positive and 43.3% of patients had PR receptor negative but HER2 receptor positive, hence in this study HER2 receptor is significantly independent, even though ER and PR receptors are negative HER-2/neu receptor positivity occurs and it is beneficial to the patients to start on hormonal therapy. According to molecular classification, my study support with the HER2 enriched breast cancer. HER2-enriched cancers tend to grow faster than luminal cancers and can have a worse prognosis, but they are often successfully treated with targeted therapies aimed at the HER2 protein, such as Herceptin (chemical name: trastuzumab), Perjeta (chemical name: pertuzumab), Tykerb (chemical name: lapatinib), and Kadcyla (chemical name: T-DM1 or ado-trastuzumab emtansine).

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Srihari S, Amalan AJ, Sivakumar D, Gobinath M. Correlation of HER2/neu receptors and other prognostic factors in breast carcinoma. *Int Surg J* 2019;6:130-4.