

Correlation between Human Epidermal Growth Factor Receptor and Hormonal Receptor Status with Grade and Nodal Status in Carcinoma Breast: A Prospective Observational Study

Manjunath K^a, Rohit Krishnappa^a, Raksha Ravikumar^b, S. Rajagopalan^c

^aAssistant Professor ^bJunior Resident ^cProfessor and Head, Department of General Surgery, Rajarajeswari Medical College and Hospital, Kambipura, Mysore Road, Bangalore, Karnataka 560074, India.

Abstract

Breast carcinoma is the most common malignant tumor and the leading cause of carcinoma death in women. Tissue evaluation gives information about various receptors which are yield prognostic information for further treatment. Identification of clinically predictive and prognostic factors is considered as an important issue in treatment of breast cancer. There are a number of tumor related features available to predict the prognosis of breast cancer. The involvement of axillary lymph nodes (ALNs) is the most important prognostic factor in operable primary breast cancer.

In our study we try to find out the correlation between human epidermal growth factor receptor (HER-2/neu) and hormonal receptor status (Estrogen/Progesterone ER,PR) with grade and nodal status in carcinoma breast.

Keywords: Carcinoma Breast; Human Epidermal Growth Factor; Estrogen/Progesterone Receptors; Axillary Lymph Node; Sentinel Node Biopsy.

Introduction

Breast carcinoma is the most common malignant tumor and the leading cause of carcinoma death in women, with more than 1,000,000 cases occurring

worldwide annually [1]. Prognostic information is important in counseling patients about the likely outcome of their disease and planning management. Identification of clinically predictive and prognostic factors is considered as an important issue in treatment of breast cancer. There are a number of tumor related features available to predict the prognosis of breast cancer. The involvement of axillary lymph nodes (ALNs) is the most important prognostic factor in operable primary breast cancer and is strongly associated with both disease-free and overall survival [2]. Lymph node status is critical for the treatment of breast cancer.

The three immunological predictive markers, oestrogenreceptor, progesterone receptor (ER, PR) and HER-2/neu have an independent prognostic value. ER expression was demonstrated in 80-90% of breast-cancer cases, while PR expression was demonstrated in 70-80% of cases and their expression is associated with better prognosis [3,4]. HER-2/neu is over-expressed in about 15-20% of breast cancer cases and is associated with poor prognosis [5]. Breast cancer is therefore, better represented by its combined receptor expression than by a single receptor status alone [6,7].

Axillary Lymph Node Dissection (ALND) is based on the concept of sequential metastasis in lymphatic vessels and has not been proven a success by the Halsted radical mastectomy compared with local excision. The use of Sentinel Node Biopsy (SNB) has shown good predictability, thus avoiding unnecessary ALND and its associated morbidity. But it is at the expense of increasing the risk of missed nodal metastasis [8]. So we here assess the ER, PR and HER-2/neu reactivity pattern in breast carcinomas and correlate this reactivity pattern with axillary lymph node metastasis.

Corresponding Author: Rohit Krishnappa, Assistant Professor, Department of General Surgery, Rajarajeswari Medical College and Hospital, Kambipura, Mysore Road, Bangalore, Karnataka, India 560074.

Email: rohitkrishnappa@yahoo.co.in

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Materials and Methods

Method of Collection of Data

- *Study Design:* Prospective observational study.
- *Study Period:* January 2016 to January 2017
- *Place of Study:* Rajarajeshwari Medical College and Hospital, Kambipura, Bangalore.
- *Sample Size:* 30 cases
- *Inclusion Criteria:*
 - All diagnosed cases of carcinoma breast, both male and female irrespective of histological type, nodal status and stage.
- *Exclusion Criteria*
 - All diagnosed benign breast diseases
 - Recurrent breast carcinoma
 - Patient who underwent neoadjuvant therapy
 - Non-epithelial malignant tumours

Methodology

All patients underwent surgical removal of tumors by modified radical mastectomy. The tissue was sent for receptor study (ER and PR) as per protocol. It was assessed by quantitative analysis (frozen-70°). If value is more than 10 units (f/mols) per gram of tissue then it is called the receptor positive status. Measurement of HER-2/neu is done from a resection specimen by

the immunohistochemistry method. The following clinical and pathological risk factors were studied in these 30 patients.

- A) Tumor size
- B) Grade
- C) Nodal status
- D) Statistical Analysis:

SPSS version 20.0 was used for data analysis. The frequency of a categorical observation among lymph node status was compared by Chi-Square Test (χ^2). The correlation between lymph node status and other continuous variables was evaluated by Spearman's rho Test. Multivariate binary logistic regression was used to define the most important variable influencing axillary node metastasis.

Results

The study was conducted on 30 female patients with breast cancer. The mean age (SD) of the study group was 49.0 (9.04) with a median of 49.0 years and range of 31-75 years. Tumour size ranged from 1 to 8cm with mean and median being 4cms and 4 cms respectively.

The majority of the investigated cases were grade II 20 (66.7%) tumours, while grade I and III occurred in 6 (20%) and 4 (13.3%), respectively. Metastatic deposit of the tumour tissue in the ipsilateral ALN was reported in 13 patients (43.3%).

Table 1:

Patient Statistics	
Females	30(100%)
Mean age(SD)	49 years(9.04)
Median	49 years
Range	31-75years

Table 2:

Grade of Tumour [n=30]	
Gr I	6(20%)
Gr II	20(66.7%)
Gr III	4(13.3%)

Table 3:

Receptor Status	
ER+	11(36.7%)
PR+	13(43.3%)
HER2neu over expression	14(46.7%)

ER and PR were positive in 11 (36.7%) and 13 (43.3%) cases respectively and HER2 neu over-expression was seen in 14 cases (46.7%). A strong association was noted between ER and PR expression ($\chi^2=22.7$, $p<0.0001$). But there was no significant association between HER2 with either ER or PR ($p=0.389$, 0.431).

Analysis of different clinical and pathological parameters of the group revealed a strong correlation between tumour size with lymph node involvement (Spearman's rho = 0.478, $p<0.001$). The largest tumours showed positive metastatic deposits of ALN when compared to smaller tumours.

Similarly high tumour grade was significantly associated with ALN metastasis, $\chi^2=4.3$, $p<0.05$ only 33.3% of grade I tumours had metastatic deposits compared to 40% of grade II tumours and 75% of grade III tumours.

Only 4 of the 11 ER-positive breast cancers (36.6%) had positive ALN deposits compared to 9 of the 19 ER-negative tumours (62%). Similarly, only 5 of the 13 PR-positive tumours (47.3%) had metastatic deposits in the ALN compared to 7 of the 17 PR-negative tumours (41.1%)

Over-expression of HER2 neu was significantly associated with presence of ALN deposits, $\chi^2(2)=32.4$, $p<0.000$.

For different combinations of ER/PR/HER2 expression status; ER-/PR-/HER2+ (NNP) is more likely to have ALN metastasis ($\chi^2=16.7$, $p<0.001$) and the ER-/PR-/HER2- (NNN-triple negative) is, $\chi^2=20.30$, $p<0.001$ least likely to metastasize.

HER2 over expression is the most important defining factor for ALN metastasis among these three molecules. A multivariate binary logistic regression analysis revealed that HER2 expression had the strongest predictive value for ALN metastasis (Wald Chi square = 22.7, $p<0.0001$), whereas PR expression and ER expression were insignificant.

While comparing the risk of ALN metastasis among different ER/PR/HER2 combination subgroups in comparison to NNN subgroup, which was the least likely metastasizing breast cancer subgroup. NNP and triple positive breast cancer have 255 and 45 times increase in the risk of ALN metastasis compared to NNN subgroups respectively. None of the PPN, NPN or NPP showed significant increased risk of ALN metastasis compared to NNN breast cancer cases.

Discussion

ALN involvement represents an acceptable factor for predicting prognosis [9]. 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.

Our study infers that higher tumour grade and increasing tumour size are significantly associated with ALN metastasis. Several studies (Elsayed M Ali et al [9], Patani, et al [10], Xie, et al [11], Yoshihara et al [12], Chengshuai Si et al [13], Abhjith et al [14], Sepideh et al [15]) conclude the same, thus driving the fact that tumour grade and size are important factors which influence nodal metastasis in breast carcinoma.

Overexpression of Her-2/neu is associated with poor prognosis, while ER and PR expression are indicators of response to hormone therapy and better prognosis.

In our study, HER-2/neu expression significantly correlated with lymph node involvement. This is in line with a study by Tokatli et al [16]. Many other authors [9,14,15] also demonstrated HER-2/neu expression is associated with lymph node metastasis and found that number of positive lymph nodes and HER-2/neu expression were related to poor prognosis.

HER2/neu over expression is the most important defining factor for ALN metastasis among these three biomarkers. Though 62% of ER negative patients had ALN metastasis, they were statistically not significant.

Our study suggests that while considering combinations of ER, PR, Her2/neu biomarker as indicators for ALN metastasis, NNP and triple positive breast cancer had 255 and 45 times increased risk for ALN metastasis when compared to NNN. This again reiterates the fact that HER-2 over expression is the most important factor for ALN metastasis among these three molecules. This fact is echoed in various studies where PPP is associated with ALN metastasis and PPN being protected against metastasis [9,13]. And also the presence or absence of ER and PR did not significantly influence the presence of ALN metastasis.

Conclusion

Tumour size, grade and Her2Neu receptor are significantly associated with ALN metastasis whereas PR and ER status does not significantly influence ALN metastasis.

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