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Research Article

AXILLARY LYMPH NODE METASTASIS IN SONOLOGICALLY NODE-NEGATIVE BREAST CARCINOMA

ADARSA S BABU*, SUNIL S, JOMINE JOSE

Department of General Surgery, Government Medical College, Kottayam, Kerala, India.
Corresponding author: Jomine Jose; Email: jomine9@gmail.com

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ABSTRACT

Objectives: This study describes the risk factors for axillary metastasis in patients with sonologically node-negative breast carcinoma and also develops a predictive model to evaluate the risk of axillary metastasis in these patients.

Methods: Patients admitted to the Department of General Surgery with carcinoma breast qualifying the inclusion and exclusion criteria were included in the study for a period of 1 year. Study was conducted to determine the risk factors of Carcinoma breast by evaluating some clinical and pathological parameters of carcinoma breast patients.

Results: Out of 102 patients, 41 had axillary metastasis, factors found significant with $p<0.05$ were T stage, grade of tumor, estrogen receptor (ER), progesterone receptor (PR) < human epidermal growth factor receptor 2 (HER 2) neu status, histology, and lymphovascular invasion. Mathematical model was developed by binary logistic regression analysis and the probability of axillary metastasis is obtained.

Conclusion: The present study demonstrated that T stage, grade of tumor, ER, PR, HER 2 neu status, histology, and lymphovascular invasion are associated with a high risk of axillary metastasis and the newly generated tool shows a sensitivity of 87.8% and specificity of 93.44% for an optimum cut off of >0.2708.

Keywords: Sentinel lymph node biopsy, Ultrasound, Axillary lymph node metastasis, Breast cancer.

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INTRODUCTION

Breast cancer is the most common form of malignancy and the second leading cause of mortality in women. In 2022 cancer incidence in India was 105.4/1 lakh people. The status of axillary lymph nodes is a powerful prognostic tool for deciding the mode of adjuvant treatment in breast cancer. The number of metastatic lymph nodes, the ratio of metastatic to dissected lymph nodes, and the level of metastases in the axilla predict survival in breast cancer. Thus, obtaining information about the axillary lymph node status in breast cancer patients is the main purpose of axillary surgery. For this reason, sentinel lymph node biopsy (SLNB) has recently replaced axillary dissection in patients with clinically negative axillary lymph nodes [1]. Axillary lymph node dissection (ALND) was the gold standard in diagnosis and treatment of axillary node metastasis in breast cancer for decades. Because of the significant morbidity associated with the procedure, several randomized controlled trials were conducted and as a result, SLNB was adopted. SLNB is the gold standard in axillary staging in clinically node negative breast cancer [2]. Even SLNB may lead to complications such as seroma, sensory nerve damage, development of lymphedema and restriction of shoulder movement in some cases [3]. Hence, axillary treatment is undergoing a paradigm shift and efforts are being made to determine whether SLNB can be omitted in low risk patients [2]. Here is the importance of preoperatively predicting axillary metastasis using a non-invasive tool.

METHODS

This cross-sectional study was conducted from May 2022 to May 2023 at the Department of General Surgery. The study was conducted after obtaining ethical clearance from the Institutional Ethics Committee and written informed consent was taken using case record form, ultrasound scan report, and histopathology. A report from the study population of patients with carcinoma breast with ultrasound showing no axillary metastasis data were collected. People included in the study were the ones with biopsy-proven breast cancer patients who are sonologically/clinically negative for axillary metastasis. Patients who had undergone neoadjuvant chemotherapy and patients presenting with recurrent breast cancer were excluded from the study. The following information is gathered from the study subjects.

- Detailed history
- Complete clinical examination of breast and axilla
- Axillary and breast ultrasound report
- Histopathology and immunohistochemistry report.

From the above data, the following factors are obtained.

- Histopathological size of primary tumor
- T- stage
- Body mass index
- Lymphovascular invasion
- Multifocality
- Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2) status
- Histological grade.

Collected data were recorded on a case record form and analyzed. Univariate analysis comparing patients with axillary lymph node metastasis to those without axillary metastasis was carried out. Confirmation of axillary involvement is done by ALND or SLNB.

Sentinel lymph node (SLN)

The SLN is the first node to receive the drainage directly from a tumor [4].

SLNB

SLNB is based on an ordered dissemination of tumor cells from peritumoral lymphatics to the SLN, and then to more distant lymph nodes. Clinical identification of these nodes is performed through injection of numerous types of tracers, dyes, and radioisotopes into

Table 1: Patient and tumor characteristics versus axillary lymph node status

Factors	Axillary metastasis				Total		p	OR	95% confidence interval for OR
	Absent		Present						
	N	%	n	%	n	%			
Body mass index									
<23	37	62.7	22	37.3	59	100	0.483	1.3	0.6–3
>23	24	55.8	19	44.2	43	100			
Tumor stage									
T1	54	78.3	15	21.7	69	100	<0.001	13.4	4.9–36.8
T2 or higher	7	21.2	26	78.8	33	100			
Multifocality									
Absent	59	65.6	31	34.4	90	100	0.001	9.5	2–46.2
Present	2	16.7	10	83.3	12	100			
Estrogen receptor +									
Negative	18	39.1	28	60.9	46	100	<0.001	0.2	0.1–0.5
Positive	43	76.8	13	23.2	56	100			
Progesterone receptor +									
Negative	18	39.1	28	60.9	46	100	<0.001	0.2	0.1–0.5
Positive	43	76.8	13	23.2	56	100			
Human epidermal growth factor receptor 2+									
Negative	53	64.6	29	35.4	82	100	0.044	2.7	1–7.5
Positive	8	40.0	12	60.0	20	100			
Lymphovascular invasion									
Absent	58	81.7	13	18.3	71	100	<0.001	41.6	11–158.1
Present	3	9.7	28	90.3	31	100			
Histology									
Ductal carcinoma	59	63.4	34	36.6	93	100	0.016	6.1	1.2–30.9
Lobular carcinoma	2	22.2	7	77.8	9	100			
Grade									
Grade I	47	73.4	17	26.6	64	100	<0.001	4.7	2–11.2
Grade II or III	14	36.8	24	63.2	38	100			

Table 2: Binary logistic regression initial model for axillary metastasis

Factors	B	S.E.	Wald	df	p	Adj. OR	95% confidence interval for adj. OR
Tumor stage (R-T1)	4.53	1.30	12.12	1	<0.001	92.7	7.2–1186.4
Grade (R-Grade1)	1.67	0.91	3.34	1	0.068	5.3	0.9–31.7
Multifocality (R-Absent)	0.97	2.12	0.21	1	0.647	2.6	0–168.7
Estrogen receptor +(R-Negative)	−3.13	1.38	5.18	1	0.023	0	0–0.6
Human epidermal growth factor recepto+(R-Negative)	0.25	1.21	0.04	1	0.834	1.3	0.1–13.7
Lymphovascular invasion (R-Absent)	4.85	1.28	14.43	1	<0.001	127.4	10.4–1553.6
Histology (R- ductalcarcinoma)	0.32	1.48	0.05	1	0.831	1.4	0.1–25
Constant	−2.84	1.05	7.33	1	0.007	0.1	

Table 3: Binary logistic regression final model for axillary metastasis using backward step-wise likelihood ratio method

Factors	B	S.E.	Wald	df	p	Adj. OR	95% confidence interval for adj. OR
Tumor stage (R-T1)	4.70	1.28	13.50	1	<0.001	110.435	8.98–1358.36
Grade (R-Grade1)	1.69	0.83	4.13	1	0.042	5.434	1.06–27.79
Estrogen receptor+(R-Negative)	−3.41	1.20	8.11	1	0.004	0.033	0.003–0.345
Lymphovascular invasion (R-Absent)	5.07	1.26	16.24	1	<0.001	158.99	13.5–1871.1
Constant	−2.68	0.84	10.22	1	0.001	0.068	

R = β coefficient

the peritumoral site depending on the type and location of the tumor. Labeled lymph nodes are surgically excised and histologically examined for the presence of disease. Identification and biopsy of the SLN can correctly indicate the status of the draining lymph node [4].

Limitations expected

The inaccuracies associated with ultrasound imaging and the variability in the clinical assessment of axilla are potential limitations of the study.

Data management and statistical analysis

Data were entered in a Microsoft Excel sheet and univariate analysis was conducted to assess risk factors for axillary metastasis using the χ^2 test. All statistical tests are two-sided and factors with p<0.1 in the univariate analysis are included in a binary logistic regression analysis using a backward step-wise likelihood ratio method. The logistic regression analysis is used as a basis for a predictive model, which includes all variables with p<0.05. A mathematical model was generated from the logistic regression analysis to predict the risk of axillary metastases, with p denoting the probability of axillary metastases:

OBSERVATION AND RESULTS

Axillary lymph node status is the most important prognostic indicator in Carcinoma breast ALND aims mainly at determining the nodal

status of the patient hence SLNB has replaced ALND now. This study aims at finding the risk factors for axillary metastasis in patients with sonologically node negative breast carcinoma and to develop a predictive model to evaluate the risk of axillary metastasis in these patients.

Out of 102 patients with sonologically node negative carcinoma breast, 41 patients are found to have axillary metastasis among the factors studied T stage with p<0.001, multifocality with p<0.001 ER, PR status with p<0.001, HER2 neu status with p<0.001and lymphovascular invasion with p<0.001, histology with p<0.016 and grade with p<0.001 are found to be significant (Table 1). Variables with p<0.05 in the univariate analysis were included in a binary logistic regression analysis using a backward step-wise likelihood ratio method (Table 2). The logistic regression analysis was used as a basis for a predictive model, which included all variables with p<0.05 (Table 3). Area under the receiver operating characteristic curve (AUC) was used to evaluate the discrimination of the model and Hosmer–Leme show goodness- of-fittest was used to assess the calibration of the model (Table 4). Sensitivity and specificity of the model were calculated for various cut off values.

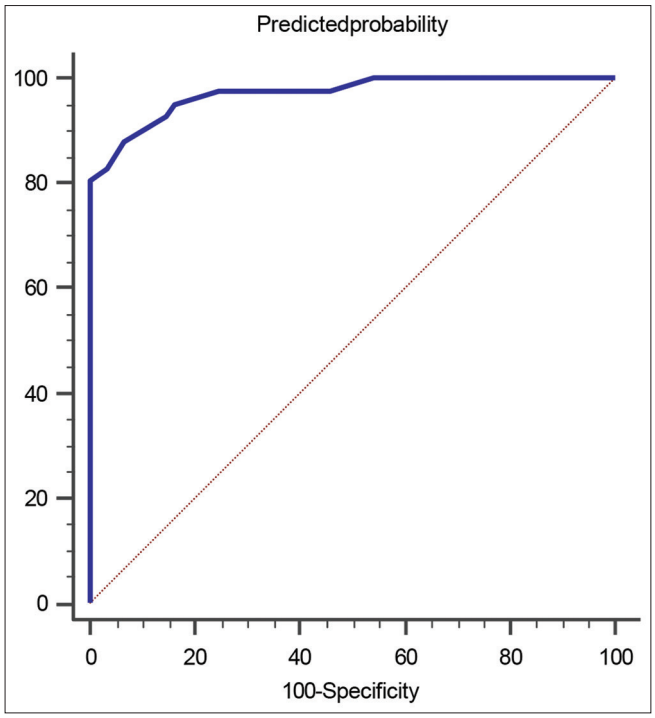

Fig. 1: Receiver-operating characteristic curve curve of predicted probability to discriminate axillary lymph node metastasis

Table 4: Predicted probability

Variable	Predicted probability
Classification variable	Axillary metastasis
Sample size	102
Positive group (axillary metastasis present)	41
Negative group (axillary metastasis absent)	61
Area under the receiver-operating characteristic curve	0.971
Standard error	0.0149
95% confidence interval	0.917–0.994
Z statistic	31.546
P	<0.0001
Youden index J	0.8125
Optimum cut off	>0.2708
Sensitivity	87.8
Specificity	93.44

Of the 102 patients, 41 (40.2%) had axillary lymph node metastases. Factors associated with axillary metastases in the univariate analysis were tumor stage (p<0.001), Multifocality (p=0.001), ER + (p<0.001), PR+ (p<0.001), HER2+ (p=0.044), lymphovascular invasion (p<0.001), histology (p=0.016) and Grade (p<0.001). Tumor stage (p<0.001), ER+(p=0.004), lymphovascular invasion (p<0.001), and grade (p=0.042) remained statistically significant in the multivariate logistic regression analysis and were included in the predictive model. The model produced a p=0.058 for the Hosmer–Lemeshow goodness-of-fittest indicating good fit and calibration of the model. The AUC for the predicted probability was 0.971 (95% confidence interval [CI] 0.917–0.994, which suggests good discrimination (Fig 1). A mathematical model was generated from the logistic regression analysis to predict the risk of axillary metastases, with p denoting the probability of axillary metastases.

$$\text{Logit}(p) = -2.683 + 4.704*a + 1.693*b - 3.414*c + 5.069*d \quad (1)$$

The letters in the equation denote the variables: a=Tumor stage (1 if Tumor stage is T2 or higher, 0 if Stage T1); b=Grade (1 if grade 2 or higher, 0 if grade 1 or less); c=ER+(1 if ER+ is positive, 0 if not); d=Lymphovascular invasion (1 if Lymphovascular inVasion is present, 0 if not).

- For patient SLNo1: Logit(p)=−2.68+4.7*a+1.69*b3.41*c+5.07*d=0.3

p=1/(1 + exp[-logit(p)])

Pluggingin0.3for logit(p), p=1/(1 + exp (−0.3))

p=1/(1 + 0.731058578)

Solving for p, we get p=0.5743

Therefore, if logit (p)=0.3, the n p=0.5743

- For patient SLNo:2, Logit (p)=−2.68+4.7*a+1.69*b−3.41*c+5.07*d=−0.990

p=1/(1 + exp (-logit(p)))

Plugging in 0.990 for logit (p), p=1/(1 + exp (0.990))

p=1/(1 + 2.691)

Solving for p, we get p=0.2708

Therefore, if log it (p)=−0.990, then p=0.2708 (Table 5).

DISCUSSION

The study conducted by Meretoja *et al.* [2] shows significance for histological size, multifocality, palpability of tumor, and lymphovascular invasion with a sensitivity of 84.4 and specificity of

Table 5: Sample data calculation

S. No.	T stage	Grade 2	Estrogen receptor	Lymphovascular invasion	PRE_1	Logit (p)
1	1	1	1	0	0.5743	0.300
2	0	1	0	0	0.2708	−0.990

62.1 for a cut-off value of <30% risk. In the proposed study T stage, grade of tumor, ER and PR negative, HER 2 neu positive status, ductal carcinoma histology and lymphovascular invasion are associated with high risk of axillary metastasis and the newly generated tool shows a sensitivity of 87.8 and specificity of 93.44 for an optimum cut off <27.08%. In similar studies on literature regarding factors predicting the axillary lymph node metastasis in breast cancer by Ashturkar *et al*. [5], no correlation was observed between tumor size, patient's age, histological type of tumor, and axillary metastasis. There was a strong association between histological grade and the presence of axillary metastasis. ER and PR-negative status were significantly associated with a low risk of axillary node metastasis. while in present study T stage, grade of tumor, ER and PR negative, HER 2 neu positive status, Ductal carcinoma histology, and lymphovascular invasion are associated with a high risk of axillary metastasis. In another study by Karahallı *et al*. [6], the mean lymphovascular invasion was detected to have a statistically significant effect on the SLNB positivity. Lee *et al*. [7] found in their study that lymphovascular invasion, a triple negative profile and a palpable mass were the independent predictive factors for axillary node metastasis and tumor size was the strongest predictor.

CONCLUSION

Factors associated with a high risk of axillary metastasis as per this study are higher T stage, higher grade of tumor, ER and PR negative status, HER 2 neu positive status, Ductal carcinoma histology, and presence of lymphovascular invasion. The mathematical model and the newly generated tool show a sensitivity of 87.8% and specificity of 93.44 for an optimum cut-off of <27.08%.

AUTHORS' CONTRIBUTIONS

Conceptualization and Final Review: Dr. Sunil S, Dr Jomine; Methodology: Dr Sunil S, Dr Jomine Jose; Formal Analysis: Data collection; Writing–Original Draft Preparation: Dr. Adarsa S Babu

CONFLICTS OF INTEREST

The authors declare no conflicts of interest associated with this research.

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