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"CA15-3 IN PREDICTING AXILLARY LYMPH NODE METASTASIS IN BREAST CANCER"

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ABSTRACT

Introduction: Breast cancer is one of the most common cancers worldwide. A number of marker available among them CA15-3 levels provide useful information for diagnosis, treatment, assessing prognosis, the early detection of disease progression in breast cancer. Some author described rise of Ca 15-3 also associated with axillary lymph node metastasis. This was not established in our country. **Objectives:** Utility of CA15-3 in predicting metastasis of breast cancer to axillary lymph node. **Methods:** A cross sectional study was performed among 60 patients who underwent mastectomy with axillary dissection. Association seen between preoperative elevated CA 15-3 with histologically proven axillary lymph node metastasis postoperatively. **Results-** Majority (88.3%) patients are within normal CA15-3 level but only 11.7% patients showed raised CA15-3 level preoperatively among breast cancer patient. Mean ± SD (Min-Max) were 20.92 ± 20.38 (0.19-150.8) Those who have axillary lymph node positive, only 7 (13.2%) patients showed raised CA15-3 level but remaining 53 (86.8 %) patients showed normal CA15-3 level (statistically insignificant, p<0.584). Validity test of CA15-3 shows sensitivity, specificity, PPV, NPV and accuracy were 24.5%, 100%, 100%, 14.9% and 33.3% respectively. **Conclusion**: in our study, we found that raised CA15-3 level did not show significant association with lymph node metastasis in breast cancer.

KEYWORD: Breast cancer, CA 15-3, Axillary lymph node metastasis.

INTRODUCTION

Breast cancer is one of the most common cancers related death worldwide in women and the second most common cause of death among female after lung cancer.[1] Several tumor markers have been evaluated in breast cancer. Most of the markers are of prognostic value. The diagnostic values of each marker separately or in combinations were evaluated. Further, the diagnostic values can be improved at 85th percentiles.[2] Serum carbohydrate antigen 15-3 (CA15-3) are established prognostic marker in breast cancer patients.[3]

The carbohydrate antigen 15-3 (CA 15-3) is a tumor marker, a glycoprotein that is secreted by breast cancer cells.[4] CA15-3 can be measured by reactivity with two monoclonal antibodies[5], DF3 (raised against a membrane-enriched fraction of human breast carcinoma) and 115D8 (raised against antigens of human milk fat globule membrane) its main clinical application lies in the monitoring of them in order to detect early recurrences and/or distant metastasis, as well as to know the effectiveness of a therapy. Likewise, this marker can be useful with PET/CT to show tumor recurrence[6], especially when undetected by other imaging techniques. The European Group on Tumor Markers has recommended the CA15-3 levels can be used for assessing prognosis, the early detection of disease progression, and treatment monitoring in breast cancer.[7] Study has shown that preoperative CEA levels combined with CA15-3[8] levels may provide further useful information for diagnosis and treatment of breast cancer.

Not every breast tumor caused a rise in CA15-3 particularly those tumors that do not produce CA15-3 or with early-stage breast cancer.[9] Only 30% of patients with localized breast cancer have increased levels of

CA15-3.[10] In patients with metastatic breast cancer, CA15-3 can be found increased in 50–90% cases. In the absence of measurable lesion, CA15-3 often predict axillary lymph node status of breast carcinoma patients with early stage or localized cancer.[11]

Axillary lymph node dissection (ALND) is considered important in breast cancer surgery to clear metastatic nodes, predict patient prognosis and guide adjuvant therapy.[12] So, preoperative axillary lymph node status assessment is an important basis for selection of the most appropriate surgical procedure. Ultrasonogram often show enlarged lymph node but failed to show whether metastatic or not.[13] Moreover, Biopsy or FNAC are invasive procedure and often become false negative.[14] Therefore, a reliable and simple method were attempted by many authors to predict the axillary lymph node status of patients with breast cancer. 2 common markers of breast cancer, carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3), can predict patient prognosis.[15] High serum levels them seem to be associated with a poorer survival.[16]

Despite the rising incidence of breast cancer, the survival rates have improved in recent years due to earlier detection and an increasing use of more effective systemic treatments based on prognostic factors.[17] Therefore, identifying prognostic and predictive factors is important to assist in decision making about treatment and to improve survival.[18] So, this study was conducted to see any association of preoperative elevated CA 15-5 with lymph node metastasis.

MATERIALS AND METHODS

Cross sectional analytical study was carried out in the department of surgery, BSMMU, Shahbag, Dhaka over a period of one year from august 2017 to july 2018. All female Patients irrespective of age with histopathologically proven breast cancer with or without axillary lymph node involvement and who underwent mastectomy / breast conservative surgery (BCS) with axillary dissection were included in this study. Patients received neoadjuvant therapy/ recurrent disease or in whom axillary dissection was not done excluded from this study. Preoperative CA 15-3 was recorded and axillary metastasis confirmed by histopathology.

Data were collected in a predesigned data collection sheet attached here with. After compilation, analyzed by SPSS-21.0 (Statistical Package for Social Sciences). The statistical terms were included in this study- mean, percentage, standard deviation etc. Statistical analysis was done by students' t-test for quantitative variables. Chi-square (χ^2) test or Fisher's exact test for qualitative variables. Probability value <0.05 was considered as level of statistical significance and 95% confidence interval was taken.

RESULTS

Demographic data

Maximum (40%) patients were in age group 30-40 yrs and 41-50 yrs. followed by 11.7% and 8.3% were in group 51-60 yrs and 61-70 yrs, respectively. Mean age was 44.72 ± 9.47 (30-70). 53.3% patients of breast cancer located on left side & UOQ site (71.7%), 81.7% patients tumor size on 2-5 cm, but 12 (20%) patients had fixed lump & Nipple retraction 9 (15%) patients. 29 patients had palpable axillary lymph node and only 2 (3.3%) had clinically distal metastasis (Table I)

Tumor marker

Majority (88.3%) patients are within normal CA15-3 level but only 11.7% patients showed raised CA15-3 level preoperatively. Mean ± SD (Min-Max) was 20.92 ± 20.38 (0.19-150.8) (Table II)

Axillary Lymph node

93.3% patients had axillary lymph node positive on USG but only 6.7% patients had no lymph node positive on USG preoperatively (Table III)**.** Here, 57 patients showed positive histopathological lymph node. Among them, Majority of the patients (23) presented maximum number of lymph node (3-5) (Table IV)

CORRELATION

Only 7 (13.2%) patients showed raised CA15-3 level of metastasis of breast cancer but remaining (53) patients showed normal level of CA15-3 level. There was no significant difference of CA15-3 level between these two groups (p = 0.584) (Table V)**.** Validity test showed sensitivity, specificity, PPV, NPV and accuracy were 24.5%, 100%, 100%, 14.9% and 33.3% respectively (Table VI). Receiver Operating Characteristics (ROC) Curve of CA15-3 for the prediction of lymph node metastasis of carcinoma breast cancer by diagnosis of post-operative histopathology also support the data.

Table I: Distribution of the patients according to clinical features.

Clinical features	Frequency	Percent
Side		
○ Right	28	46.7
○ Left	32	53.3
Site		
○ UOQ	43	71.7
○ UIQ	7	11.7
○ LOQ	7	11.7
○ LIQ	3	5.0

Size		
○ ≤2cm	7	11.7
○ 2-5 cm	49	81.7
○ >5cm	4	6.7
Lump fixity TO muscles, chest wall and skin		
○ Yes	12	20.0
○ No	48	80.0
Skin change		
○ Yes	13	21.7
○ No	47	78.3
Nipple retraction		
○ Normal	51	85.0
○ Abnormal	9	15.0
Clinical lymph node		
○ Palpable	29	48.3
○ Not palpable	31	51.7
Number of lymph node		
○ 1-3	26	89.7
○ 3-5	3	10.3
Clinically distal metastasis		
○ Present	2	3.3
○ Absent	58	96.7

Table II: Distribution of the patients according to CA15-3 level.

CA15-3 level	Frequency	Percent
Normal	53	88.3
Raised	7	11.7
Total	**60**	**100.0**
Mean ± SD (Min-Max)	20.92 ± 20.38 (0.19-150.8)	

Table III: Distribution of the patients according to USG.

USG	Frequency	Percent
Node positive	56	93.3
Node negative	4	6.7
Total	**60**	**100.0**

Table IV: Distribution of the patients according to post-operative histopathological lymph node.

Metastatic LN	Frequency	Percent
Positive	53	88.3
If positive number of LN		
○ 1-3	17	32.1
○ 3-5	23	43.4
○ 6-10	9	17.0
○ >10	4	7.5
Negative	7	11.7
Total	**60**	**100.0**

Table V: Distribution of the patients according to CA15-3 by post-operative histopathological lymph node.

CA15-3 level	Post-operative histopathology lymph node		p value*
	Positive (n=53)	Negative (n=7)	
Raised	7 (13.2)	0 (0.0)	0.584
Norm	46 (86.8)	7 (100.0)	

*Fisher's Exact test was done to measure the level of significance.
Figure within parentheses indicates in percentage.

Table VII: Validity test of CA15-3 by post-operative histopathology lymph node.

Validity tests	Percentage	95% CI
Sensitivity	24.5%	19.2-24.5
Specificity	100.0%	59.8-100.0
PPV	100.0%	78.3-100.0
NPV	14.9%	8.9-14.9
Accuracy	33.3%	23.9-33.3

CI = Confidence Interval
PPV = Positive Predictive Value
NPV = Negative Predictive Value

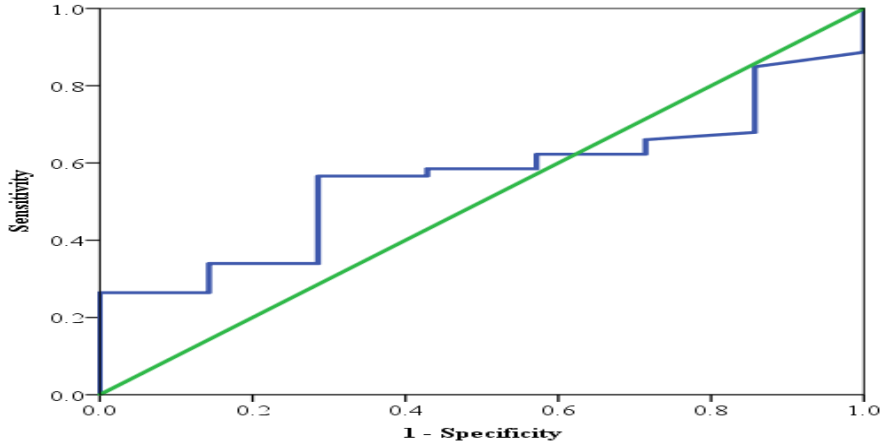

Figure: ROC (Receiver Operative Characteristics) Curve of CA15-3 for the prediction of lymph node metastasis of carcinoma breast cancer by diagnosis of post-operative histopathology showed sensitivity and specificity was 24.5 % and 100% respectively but result was not significant.

Under the Curve (AUC) of Receiver Operating Characteristics (ROC) Curve of CA15-3 for the prediction of lymph node metastasis of carcinoma breast cancer by diagnosis of post-operative histopathology.

Variable	Area	p value	95% Confidence Interval	
			Lower Bound	Upper Bound
CA15-3	0.559	0.612	0.385	0.734

Null hypothesis: true area = 0.5

DISCUSSIONS

This single centered cross sectional analytic study was conducted to evaluate the value of preoperative CA15-3 in predicting ALNM in patients with breast cancer. Demographic data including age, family history of breast cancer and use of OCP and other variables of primary diseases of breast cancers with its features includes location of tumor (site), Size of tumor, Fixity, Skin involvement, Nipple retraction, Lymph node status & histopathological reports were also recorded.

In our study, maximum (40%) patients were in age group of 30-40 years, The mean age was found (44.72 ± 9.47) year within the range of 30 -70 yrs. Similar data seen in San-Gang Wu et al.,[11] that the median age was 47 years (range: 21-90 years). Only 12(20%) patients showed fixed lump in chest wall, muscles and skin. Only 9 (15%) patients showed nipple retraction. 29 (48.3 %) patients showed clinically palpable lymph node. we also found that tumor location, tumor stage, tumor grade, LVI, and BCS were independent factors predicting ALNM. Gangi *et al*.,[12] reported a close relationship between tumour size and axillary lymph node involvement.

In our study, only 11.7% patients showed raised CA15-3 level preoperatively. M.T. Agyei Frempong et al.,[19] showed 11(31.4%) had normal serum CA 15-3 levels and the other 24(68.6%) had higher than normal serum CA 15-3 levels. This results did not not match with our study.

On USG, node positivity was found in 93.3% patients. Jayant S. V et al.,[20] showed USG had higher specificity and higher positive predictive value than clinical examinations (CE). Together, CE + USG had higher sensitivity and higher negative predictive value than CE alone. In our study, 53 patients (88.3%) showed positive lymph node on histopathology postoperatively for malignancy with 3-5 lymph nodes involved in 43.4% patients & 1-3 lymph nodes involved in 32.1% patients.

Mahindocht et al.,[21] showed there was an abnormal elevation in CA15-3 values, when ≥ 4 lymph nodes were involved. The correlation between the elevated CA15-3 values and the number of involved lymph nodes, as compared with the total number of lymph nodes, was significant ($P < 0.001$). in our study, 13.2% involved lymph node patients showed raised CA15-3 level but

86.8% histopathological lymph node positive patients showed normal CA15-3 level. This results was statistically not significant, ($p < 0$ .584).

The diagnostic accuracy was 33.3%, sensitivity was 24.5%, and specificity was 100%. The positive predictive value was 100%, and negative predictive value was 14.9 %. When CA15-3 cut off value is fixed to 25 U /L. Wojtacki J et al.,[22] reported that The overall diagnostic sensitivity and specificity of the CA 15-3 test was 19.3% and 94.8%, respectively. The positive and negative predictive values were 80.0% and 52.1%.

K Kandylis et al.,[23] showed that Sensitivity *and* specificity for *CA 15-3* were 65.7% and 76.6%, our study showed lower but within the range values of diagnostic accuracy, sensitivity and. The positive predictive value was 20% higher than the upper margin, but the negative predictive value was lower than the mean. Probable cause will be different access and different cut off value of CA15-3. ROC curve also showed result is not significant. P value of CA15-3 is 0. 612 and area is only 0.559. To get positive result area should be as close as 1.

Study had some limitation as smaller sample size, short duration of study time, different system CA15-3 assay and different cut off value in different journal.

This study was conducted with the purpose to the use of preoperative serum levels of CA15-3 in patients of carcinoma breast in predicting axillary lymph metastasis. Though the result of the study is influenced by its smaller sample size and significant statistical differences were not achieved but it was showed that raised CA 15-3 level was raised in axillary lymph node metastasis.

CONCLUSION

Raised CA15-3 level did not show significant association with metastatic lymph node in our study. But clinicians should consider the use of preoperative CA15-3 for guiding locoregional management decisions.

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Conflicts of interest

None.

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