

Original Research Article

Correlation between Tumour Marker CA 15-3 Level and TNM Staging in Breast Cancer

Harsh P. Trivedi¹, Khan Mohd Aizaz², Shailesh Parmar²

¹Additional Professor, ² Resident,
Dept of Surgery, Shri M.P. Shah Govt Medical College, Jamnagar, Gujarat.

Corresponding Author: Harsh P. Trivedi

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ABSTRACT

Background: Carbohydrate antigen 15-3 is an epitope of a large membrane glycoprotein encoded by MUC1 gene that tumour cells shed in to the blood stream. CA 15-3 level is directly related to tumour burden and independent prognostic factor for breast cancer .The normal level of CA 15-3 is 30-35 units/ml. A frequently used staging system is the TNM (tumor, nodes, and metastasis) system given by American Joint Committee on Cancer (AJCC).

Aims: To analyse the correlation between CA15-3 level and TNM staging of carcinoma breast.

Method: 30 female patients diagnosed with carcinoma breast were staged according to TNM classification and Serum CA 15-3 level were assayed by ELISA method.

Result: In this study out of 30 patients, 3 patients (10%) with stage I disease had a mean CA 15-3 level of 37.8u/ml, 17 patients (56.67%) with stage II disease had a CA 15-3 level of 43.56u/ml and 10 patients (33.33%) with stage III disease had CA 15-3 level of 99.92u/ml.

Conclusion: There is a positive correlation between CA 15-3 level and TNM staging of carcinoma breast, as the stage of disease increases, CA 15-3 level also increases.

Keywords: Breast cancer, CA 15-3, TNM, Metastasis.

INTRODUCTION

Breast cancer is the most commonly occurring female cancer in the world. Breast cancer accounts for 23% of all newly occurring cancers in women worldwide and represents 13.7% of all cancer death. Breast cancer in urban areas of India is three times higher than in rural parts of the country. ⁽¹⁾

In India , breast cancer is the second most common cause (after cervical cancer) with an estimated 115,251 new diagnosed and the second most common cause of cancer related deaths with 53,592 breast cancer death in 2008. In 2008, 115251 new cases of breast cancer were diagnosed in India which accounts for 12.14 percent of all malignant cases (an incidence rate of 22.9 per lac population). ⁽²⁾ Prognosis of

Breast cancer depends on evaluation of various parameters like tumour histological grading, cell proliferation index, oestrogen receptor status and lymph node status is of growing interest. ⁽³⁾ The diagnosis of breast cancer at an earlier stage allows a woman more choice in the selection of treatment option. While physical examination and mammography are useful screening procedures for the early detection of breast cancer, they are also labor intensive and require health professionals who are highly trained and experienced. Nowadays, immunohistochemistry and serum tumour marker detection is widely used in evaluation in case of breast carcinoma. Tumor markers may be used in diagnosis (early detection and differential diagnosis),

prognostic evaluation and follow up (therapeutic monitoring and diagnosis of recurrence).⁽⁴⁾ A frequently used staging system is the TNM (tumor, nodes, and metastasis) system given by American Joint Committee on Cancer (AJCC).⁽⁵⁾

CA 15-3 is a mucin belonging to a large family of glycoprotein's encoded by the MUC1 gene. Elevated pre-operative CA 15-3 level is directly related to tumour burden and independent prognostic factors for breast cancer. It could be considered for clinical use such as predicting patient outcome and determining adjuvant treatment for better outcome.⁽⁶⁾ The 2007 ASCO guidelines state that the routine use of CA 15-3 for screening, diagnosis, staging, or surveillance of breast cancer is not recommended because available data are insufficient. For monitoring patients during active therapy, CA 15-3 can be used in conjunction with diagnostic imaging and history and physical examination CA 15-3 determination is particularly useful in evaluating recurrence of disease and response to treatment.⁽⁷⁾ In this study, the correlation of CA 15-3 level in breast cancer patients i.e. clinicopathological staging and preoperative CA 15-3 level is evaluated.

Aims: To analyse the correlation between CA 15-3 level and TNM staging of carcinoma breast.

MATERIALS AND METHODS

This retrospective study was done on patients in Department Of Surgery, at tertiary care hospital, affiliated to Medical College, from April 2012 to March 2014. Total 30 patients diagnosed with Carcinoma Breast were included in this study. Detailed history and clinical examination was done of all the patients. Routine and Specific investigation (ultrasonography, mammography and FNAC) was sent. Many patients in this study also underwent incisional or excisional biopsy before any treatment for confirmation. Sera samples of all these cases were collected on the day of surgery and sent for preoperative CA 15-3 estimation. In this study no controls were

used, but based on other studies of CA 15-3⁽⁸⁻¹³⁾ which used controls, normal serum CA 15-3 level was taken as 35u/ml. Hence in this study also we have taken the normal CA 15-level as 35u/ml. CA 15-3 level were determined by CA 15-3 Enzyme Immunoassay Kit based on the principle of a solid phase enzyme-linked immunosorbent assay (ELISA), and was done department of pathology. Blood samples were collected and processed generally within an hour. The samples were centrifuged and stored in multiple tubes at -20°C. The CA 15-3 conjugates reagents prepared by the entire 1ml of conjugate concentrate to 21ml of the enzyme conjugate diluents. Washing buffer was prepared by adding 50ml of the buffer to 950ml of distilled water.

All the results of clinical examination, mammography, and FNAC and CA 15-3 level before and after surgery were combined and then compared with histopathology examination.

The study was approved by the Ethical Committee of the medical college and informed written and verbal consent was obtained from the cases.

Serum CA15-3 concentration was determined by CA15-3 Enzyme Immunoassay Kit based on the principle of a solid phase enzyme-linked immunosorbent assay (ELISA), purchased from Diametra.

Statistical analysis was performed by SPSS 17. One-way analysis of variance (ANOVA) test was used for the determination of relation between different breast cancer stages. Pre operative and post operative CA-15 3 values were compared using "paired t test". P<0.05 was considered statistically significant.

Inclusion Criteria:

- Patient presenting with clinical features of Carcinoma breast
- Female patient
- Age greater than 20 years

Exclusion Criteria:

- Age less than 20 years
- Healthy volunteers
- Male patients

RESULTS

I) Tumour Size in Carcinoma Breast with Mean Ca 15-3 Value

Table 1: Size distribution of cases of carcinoma breast with Mean CA 15-3 value.

Size	Number of patients	Mean Serum CA 15-3 Levels(U/ml)
Less than 2	3	37.8
2 to 5	18	46.5
more than 5	9	99.92
Total	30	100

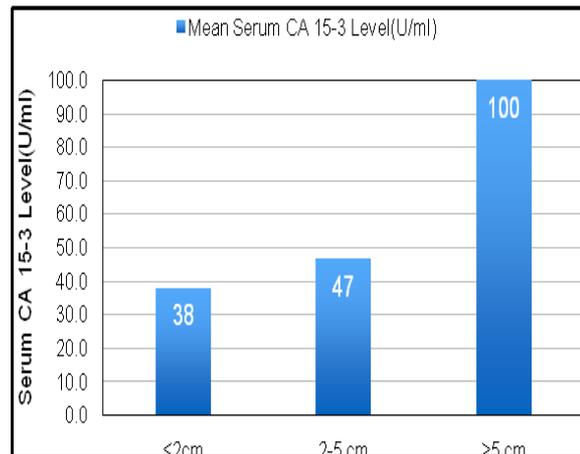


Chart 1: Tumour size with Mean CA 15-3 value

Table 2: Positivity rate of CA 15-3 in patients according to size

Size (cm)	Number of patients (n=30)	Number of patients whose CA 15-3 value is more than 35 u/ml	Positivity rate (%)
Less than 2	3	2	66.7
2 to 5	18	15	83.3
more than 5	9	8	88.9

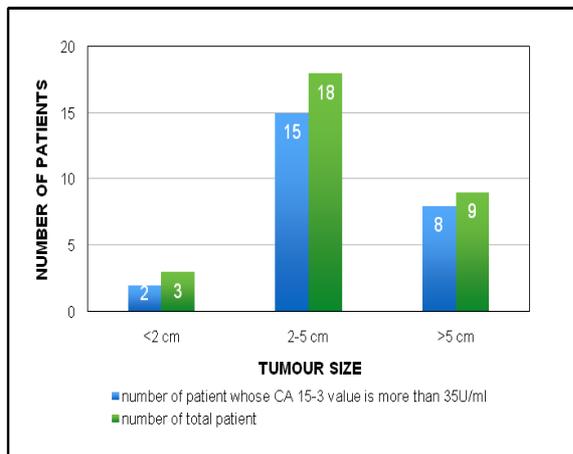


Chart 2: Case and positivity rates of CA 15-3 according to tumour size of patient.

Patients who had lump size less than 2 cm, 66.7% showed higher level while, 83.3% of patients with lump size between 2-5 cm had higher level and 88.9% of patients who had lump size more than 5 cm had higher level. In present study, it was observed that in majority of patients, size of the lesions was between 2 to 5 cm. Mean value of CA 15-3 level was highest i.e. 88.9U/ml in patients with lesion larger than 5 cm. Maximum number of patients among lesion larger than 5 cm showed serum CA 15-3 levels more than 35 u/ml. Thus, Mean CA 15-3 level as well as positivity rates increased as size of the lesion increased in carcinoma breast patients.

II) Lymph node involvement in carcinoma breast with mean ca 15-3 value

Table 3: Distribution of cases according to no. of lymph nodes involved.

Number of Lymph nodes	Number of patients	Number of patients whose CA 15-3 value is more than 35 U/ml	Positivity rates (%)
less than 4	18	5	27.78
more than 4	12	10	83.33

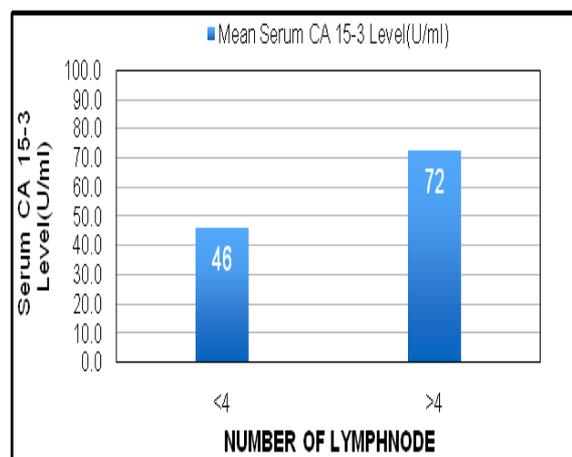


Chart 3: Number of Lymph node involved with Mean CA 15-3 value.

Table 4: Positivity rate of CA 15-3 in patients according to number of lymph nodes involved.

Number of Lymph nodes	Number of patients	Mean Serum CA 15-3 Levels (U/ml)	Percentage
less than 4	18	46.12	60
more than 4	12	72.48	40
Total	30		

In present study it was found around 60% of cases showed less than 4 lymph nodes involved and 40 % showed more than

4 lymph nodes involved. Mean serum CA 15-3 level of patients with less than 4 lymph node is 46.12U/ml and with more than 4 lymph node involvement was 72.48 u/ml .27.78% of cases with less than 4 lymph node and 83.33 % of cases with more than 4 lymph node involved showed CA 15-3 levels more than 35U/ml.

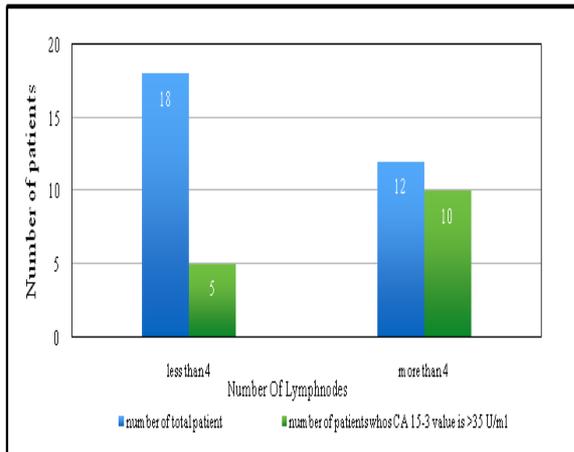


Chart 4: Distribution of Cases and Positivity rates of CA 15-3 according to number of lymph nodes involved.

Thus, Mean serum CA 15-3 levels and positivity rate of CA 15-3 increased as number of lymph node involvement increased in carcinoma breast patients.

III) Preoperative Ca 15-3 Levels Correlated According To Tnm Staging

In this study at time of presentation i.e preoperatively, 2 out of 3 patients having stage I had CA 15-3 level >35u/ml and 1 patient had CA 15-3 level <35u/ml. Out of 17 patients with stage II, 14 patients showed CA 15-3 level >35u/ml ranging from 35.9 to 59.7u/ml and the remaining 3 showed CA level <35u/ml. In stage III all the 10 patients

showed CA 15-3 level >35u/ml ranging from 66.7 to 118 U/ml.

TABLE 5: Relation of preoperative Ca 15-3 level according to stage of disease

Clinical stage	Number of cases	Mean ca 15-3 level (u/ml)	P value
I	3	37.8	P < 0.0001
II	17	43.56	
III	10	99.41	

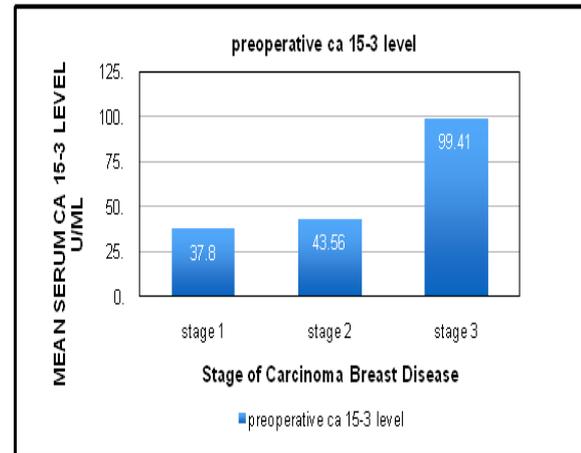


Chart 5: Relation of preoperative Ca 15-3 level according to stage of disease.

One-way analysis of variance (ANOVA) test was used for the determination of relation between different breast cancer stages. P<0.05 was considered statistically significant. A statistically significant (p<0.0001) increase was noticed in CA15-3 values across breast cancer stages; from stage I to stage III.

Table 6: Comparison of the size of the lesion of carcinoma breast patients

Studies	Size		
	< 2 cm	2 -5 cm	> 5cm
Alsaeed ⁽⁸⁾ 2013	25.0%	34.0%	41%
Daniele ⁽⁹⁾ 2013	36.2%	46.7%	18.7%
Gion ⁽¹⁰⁾ 1991	48.0%	48.9%	3.1%
Present study ²⁰¹⁴	10%	60%	30%

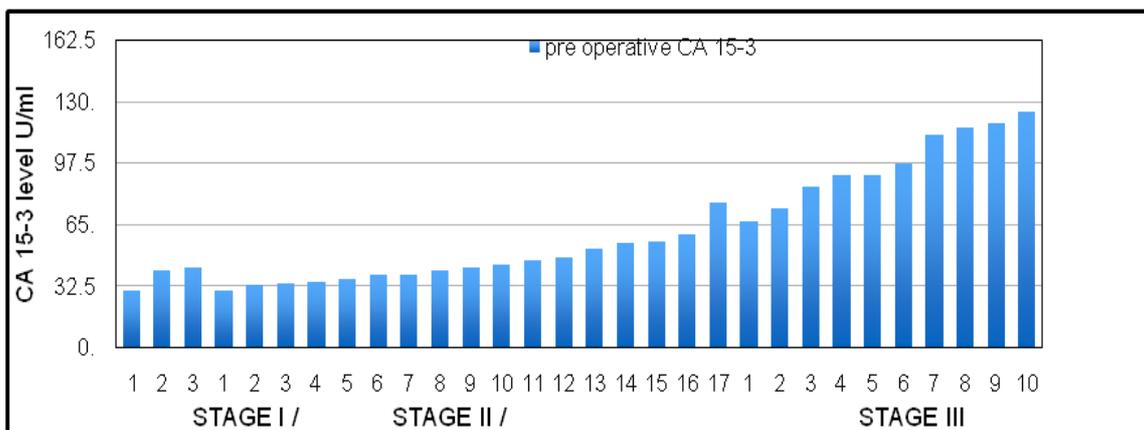


Chart 6: Preoperative Serum Ca 15-3 according to TNM stage of all patients.

DISCUSSION

In various studies conducted on carcinoma breast, cases were divided according to size of the lesion as cases with lesion size less than 2 cm, cases with lesion size between 2 to 5 cm and those with lesion size more than 5 cm.

Observations varied in these studies. Alsaeed2013 showed more number of cases with lesion size more than 5 cm size, Daniele2013 showed more number of lesions with size between 2 to 5 cm and Gion1991 showed almost equal number of cases of both less than 2 cm lesions and those with size between 2 to 5 cm. ⁽⁸⁻¹⁰⁾

Table 7: Comparison of the lymph node status of carcinoma breast patient

Studies	Distribution	%	% of cases with CA 15-3 values > 35u/ml
Alsaeed ⁽⁸⁾ 2013	N ₀	5.4	0
	N ₁	17.0	72.4
	N ₂	35.6	85
	N ₃	42.0	100
Gion ⁽¹⁰⁾ 1991	0	55.9	10.3
	1-3	23.4	11.5
	>3	20.7	31.3
Present study 2014	< 4	60	27.7
	>4	40	83.3

In present study it was observed that more number of cases i.e. 60% had lesion

size between 2 to 5cm while 10% were of less than 2 cm size.

Various studies conducted divided the lymph node examination into different patterns. Alsaeed2013 divided the cases according to clinical examination of lymph nodes into N₀, N₁, N₂, N₃ with number of cases being 5.4%, 17.0%, 35.6% and 42.0% respectively. It was observed that as level of lymph node involvement increased the number of cases showing mean serum CA 15-3 value more than 35 u/ml also increased with 0 % in N₀ and 100% in N₃ lymph node involvement. ⁽⁸⁾

Gion 1991 observed the distribution according to number of lymph nodes involved into 0, 1 to 3 and more than 3 lymph nodes involvement. It was observed that number of patients showing CA 15-3 values more than 35u/ml increased as more number of lymph nodes were involved. ⁽¹⁰⁾

In present study, also it was observed that i.e. 83.33% of patients among those with more than 4 lymph nodes involved showed serum value CA 15-3 more than 35u/ml as compared to 27.78 % of those with less than 4 lymph nodes involved.

Table 8: Comparison of the stage of the lesion of carcinoma breast patients

Studies	Alsaeed ⁽⁸⁾ 2013		S Velaiutham ⁽¹¹⁾ 2008		Dhafir Al-Azawi ⁽¹²⁾ 2013		Gion ⁽¹⁰⁾ 1991		Hiba ⁽¹³⁾ 2013		Present study 2014	
	% of cases	CA 15-3 >35u/ml	% of cases	CA 15-3 >35u/ml	% of cases	CA 15-3 >35u/ml	% of cases	CA 15-3 >35u/ml	% of cases	CA 15-3 >35u/ml	% of cases	CA 15-3 >35u/ml
I	18.75	32.4	08	0	-	-	48.0	12.7	16.67	44.06	10	37.8
II	41.96	82.4	43.2	7.9	15	8.3	48.1	16.2	66.67	83.22	56.67	43.56
III	39.2	85.2	36.8	36.7	82.1	83.3	3.9	31.2	16.67	97.54	33.33	99.41

In study conducted by Alsaeed in 2013, it was observed that maximum number of cases had stage II tumours i.e. 41.96%. It was also observed that in tumours with higher stage, more number of patients showed serum CA 15-3 values more than 35u/ml than those of lower grade tumours. It was seen that 8%, 43.2% and 36.8 % of cases had higher marker values in among those stage I, II and III tumour patients respectively. ⁽⁸⁾

Similar observations were made in studies conducted by S Velaiutham in 2008, Dhafir Al-Azawi in 2013 and Gion in 1991 that as stage of the tumour

increases more number of patients showed higher tumour marker values. ⁽¹⁰⁻¹²⁾

In present study out of 30 patients, 3 patients (10%) with stage I disease had a mean CA 15-3 level of 37.8u/ml, 17 patients (56.67%) with stage II disease had a CA 15-3 level of 43.56u/ml and 10 patients (33.33%) with stage III disease had CA 15-3 level of 99.41u/ml. As the stage of disease increases mean CA 15-3 level also increases.

CONCLUSION

There is a positive correlation between CA 15-3 level and TNM staging

of carcinoma breast, as the stage of disease increases, CA 15-3 level also increases. Elevated serum CA 15-3 was found in breast cancer and directly related to advanced stages within breast cancer females.

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