DETERMINATION OF CANCER ANTIGEN CA 15-3, IN BREAST CARCINOMA

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ABSTRACT

In breast carcinoma, carbohydrate antigen 15-3 (CA 15-3), a mucin component, is the most important and commonly used tumor marker. It is a transmembrane glycoprotein containing a large extracellular domain of 69 amino acids. Several studies suggested that its evaluation could provide valuable clinical information. Assessment of CA 15-3 can also be useful during treatment of Breast cancer as well as to detect recurrence following primary treatment. CA 15-3 is a breast-cancer-associated antigen defined by reactivity with two monoclonal antibodies, DF3 (raised against a membrane-enriched fraction of human breast cancer) and 115D8 (raised against antigens of human milk fat globule membrane). The main clinical application of CA 15-3 suggested being in monitoring the response to the treatment and gives reliable information on the recurrence of the disease. The aim of present study is to assess CA 15-3 in patients with breast carcinoma and its usefulness in monitoring and therapy. Serum samples of female patients (n = 56) suspected of or diagnosed with breast carcinoma were analyzed for CA 15-3. Significantly elevated levels were noted in most of the patients and correlated with their malignant tumor status and clinical conditions. It is concluded that CA 15-3 is currently the most widely used circulating cancer marker for breast carcinoma. CA 15-3 can provide useful information regarding successfulness when comparing pre-operative and post-operative values. In our study, breast carcinoma patients showed decrease in CA 15-3 levels post-operatively (although most of them still above normal reference range), depicting successfully of treatment and intervention, in addition to suggesting that CA 15-3 concentrations can also provide prognostic information . Furthermore, serial concentrations analyses have the potential both to detect recurrences pre-clinically and to monitor the treatment of metastases breast carcinoma.

Key words : CA 15-3, mucin, Tumor Markers, Breast Carcinomas.

INTRODUCTION :

In many countries all around the world, breast cancer is the most common malignancy affecting the women. It is documented to be the major cause of deaths in women between the ages of 35-54 years. By the year 2000, an estimated i million new breast cancer cases had been identified Worldwide. There are several common and clinically useful tests assays, which have been designed and identified which helps in the diagnosis, assessing, prognosis, predicting likely response to therapy and monitoring patients in breast carcinoma[1-4]. Examples are, Estrogen and Progesterone Receptors assays, CEA, CA 15-3, CA 27.29 circulating cancer antigen and c-erb-B2 oncogene assays[3-6].

CA 15-3 cancer antigen:

CA 15-3 is a breast-associated antigen, glycoprotein in nature, defined by reactivity with two monoclonal antibodies namely, DF3 and 115D8. The 115D8 is antibody which was prepared against human mil-fat globulin membrane while DF3 antibody was raised against a membrane - enriched fraction of a human breast carcinoma[6-9]. It is reported that Ca 15-3 is a mucin being product of a *MUCI* gene, other names for this mucin is "PEM" (polymorphic epithelial mucin) and "EMA" (epithelial membrane antigen)[3-7].

CA 15-3 Concentration in blood: Normal and pathological ranges:

A: Healthy Subjects:

Using immuno- radiometric assay, it was found that the mean concentration of CA 15-3 in 1050 apparently healthy controls in 13.3 (+ & - 6) U/ml. Another study measured CA 15-3 concentration in 938 healthy women 18 U/ml as the mean results.

B: Patients with benign disease:

Mean Serum CA 15-3 concentration in 25 patients with benign breast disease was reported to be 16.5 U/ml.

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C: Patients with breast cancer:

Although different cut - off are used (between 20 to 40 U/ml), most of the studies showed that pre-operative CA 15-3 concentrations are elevated depending upon the stage or size of the primary tumor.

Clinical Utility:

A: Screening and diagnosis of early breast cancer.

From the data available, it is reported that pre-operative measurement of CA 15-3 in some of the early stages of breast cancer is of little value. However, pre-operative values of CA 15-3 are strongly dependent on size of tumor and stage of metastases[10.11].

B:Prognostic Value:

Recent evidences showed that patients with either high pre- or post-operative CA 15-3 concentrations have worse outcome than those with low concentrations[12-14]. It is also concluded that post-operative values are strong indicator of prognosis than pre-operative concentrations[14,15].

C: Monitoring therapy:

As CA 15-3 concentrations are found elevated in most of the breast cancer patients with distant metastases, it is suggested that CA 15-3 assessment be used to monitor response to therapy and treatment[16-19]. It is concluded that patients with chemotherapy- induced disease regression exhibited a decrease in CA 15-3 concentrations 20-22 a large number with stable disease condition showed no change and 80% with progressive disease displayed increasing concentrations23-27.

Objectives of The Study

Role of assessment of CA 15-3 cancer antigen with breast carcinoma and its usefulness in monitoring and therapy.

Salient features:

- Patients with breast carcinoma: Pre-operative
- Patients with breast carcinoma: Post-operative
- Patients with benign diseases

  Ovarian cysts

  Breast lesions

  GIT ulcers

  Liver cirrhosis

Note: For our main objective of the study, which is assessment of CA 15-3 in Breast cancer, we included only those patients with primarily breast carcinoma. We excluded those patients, which have major primary or secondary metastases other than that of breast.

Methods and Research Design:

Selection Criteria:

- A total of 192 female patients were targeted in the study, of which clinical history of 56 patients (age 25-60yrs), who qualifies the inclusion criteria, was taken with clinical symptoms and signs and initial diagnosis. Study period was July 2002 to Dec 2004.
- Patients admitted in wards or visiting OPDs with primary diagnosis (or suspicions) of breast cancer and related diseases were selected and classified according to subgroups.
- Their carcinoma status was evaluated and classified according to clinical condition.

Sample Collection:

- Blood (5 ml) was collected in clot activated tubes
- Serum was separated and stored at-10^{o}C until analyzed.

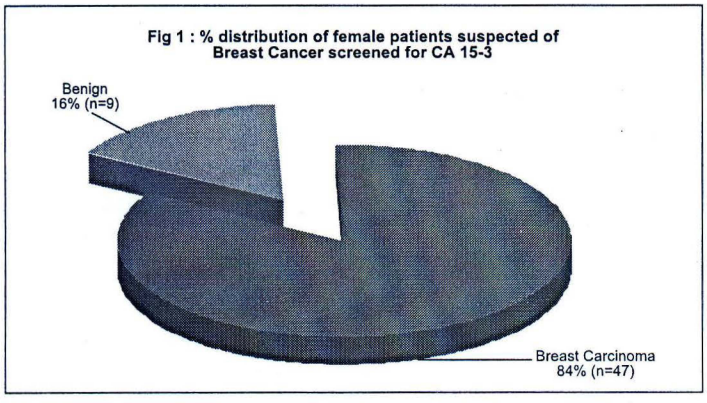
Analysis and Calculation:

- All CA 15-3 analysis was performed in duplicates by Automated ELISA and Chemi-luminscence techniques (Cobas Core, Eleesys 1010, Roche) with two-point calibration and controls with definite cut-off values.
- CA 15-3 reference value is less than 22 U/ml in healthy subjects.
- Patients with breast carcinoma: Pre-operative
- Data is presented in the form of percentage occurrence. Statistical analysis was performed using Microsoft SSP version 10 statistics program with level of significance at P

value less than 0.05.

Results

CA 15-3 analysis Pre and Post-operative was carried out in 56 female patients (Fig 1-5). The highest Pre-Operative value determined was 275 U/ml. The Pre-op elevated values are in the range of 36 U/ml to 275 U/ml. Normal cut-off value for adults is less than 22.00 U/ml and all patients are in age range of 25-60 years with varying degree of benign condition and breast carcinoma. For clarity the results are presented in chronological form.

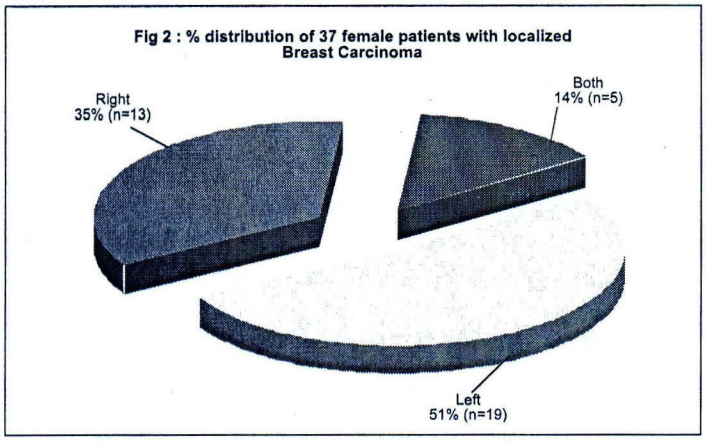


Out of 56 breast cancer patients

- 84.00% [n=47] showed Pre-Op elevated levels of CA 15-3.
- 16.07% [n=9] showed normal levels of CA 15-3.

All those showing Pre-Operative elevated values (n=47) are confirmed cases of Breast carcinoma, further classified as

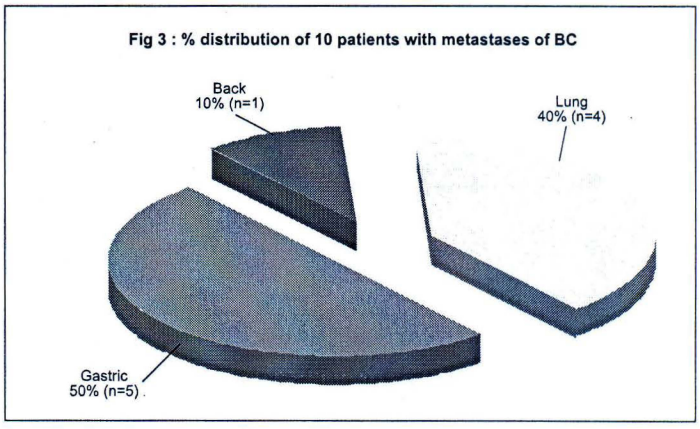
- Localized to Breast only: n=37 (out of 47: 78.70%) (Fig 2)



- Both: n = 5 (13.51%)
- left: n = 19 (51.35%)
- Right: n = 13 (35.13%)

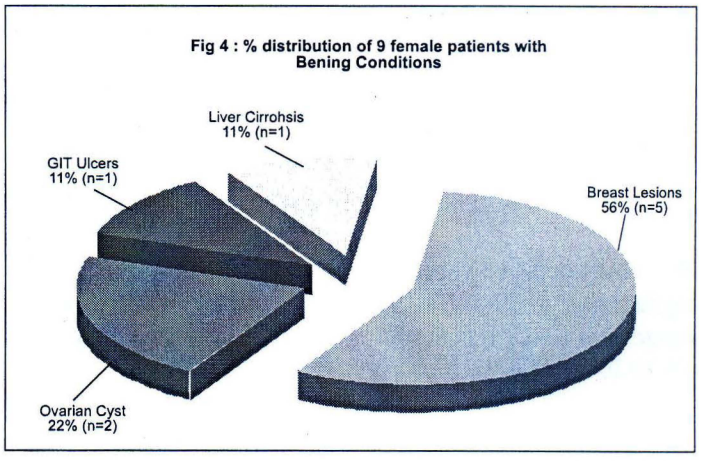
❖ Metastases to other parts of the body: n = 10 (out of 47: 2127%)

(Fig 3)



- Lung: n = 4 (40.00%)
- Gastric: n = 5 (50.00%)
- Back: n = 1 (10.00%)

❖ All of those (n = 9: out of 56: 16.07%) showing normal values are identified as benign cases, further classified as (Fig 4):



- 55.5% (n = 5) with breast lesions

- 22.22% (n = 2) with ovarian cyst
- 11.11% (n = 1) with GIT ulcers
- 11.11% (n = 1) with liver cirrhosis

❖ As stated earlier, Pre-operative Elevated values of CA 15-3 was in the range 36.275 IU/ml in patients (n = 56) with Breast carcinoma.

❖ Further distribution of Pre- operative values according to sub groups are as follows;

❖ Localized to Breast Only; 36-275 IU/ml

- Both; 220-275 IU/ml (257 ± 10)
- Left; 42-170 IU/ml (116 ± 8.80)
- Right; 36-188 IU/ml (128 ± 13.94)

❖ Metastases to other parts of the body;70-201 IU/ml

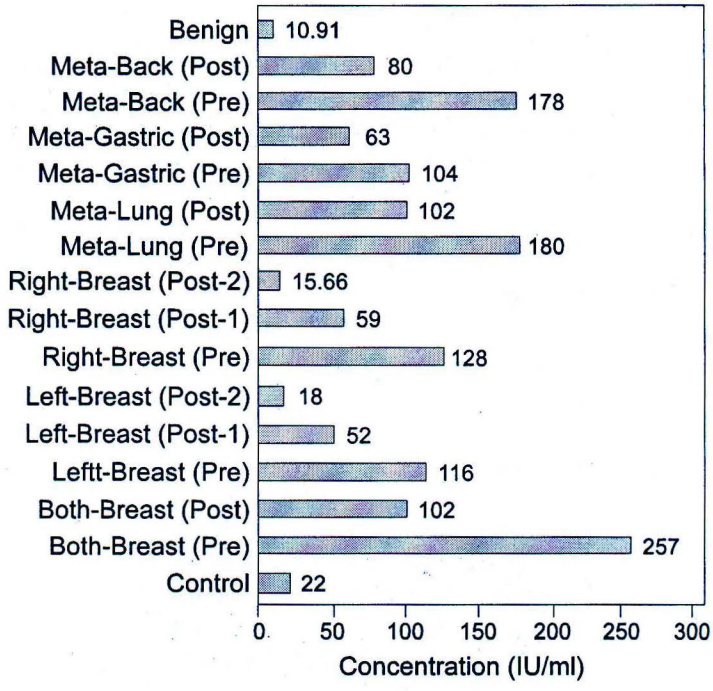
- Lung; 160-189 IU/ml (180 ± 9.22)
- Gastric; 70-150 IU/ml (104 ± 13.36)
- Back; 201 IU/ml

❖ CA 15-3 levels in Benign groups (n = 9; out of 56; 16.07%) showed normal values, in the range 7.0 to 17 IU/ml and presented as follows

- 8.2-17 IU/ml (13.45 ± 4.56) with breast lesions
- 7.5-8.0 IU/ml (7.89 + 1.20) with overian cyst
- 7.5 IU/ml with GIT ulcers
- 7.0 IU/ml with liver cirrhosis

❖ Post-operative values of CA 15-3 was also found in the higher range of 30-120 IU/ml in all group of right BC, where range was 12-18 IU/ml and 5 in left BC, where range was 18-20 IU/ml (fig-5).

Fig 5: Pre and Post Operative CA 15-3 levels in patients with Breast Carcinoma



❖ Further distribution of Post-operative values according to sub groups are as follows;

❖ Localized to Breast Only; 30-120 IU/ml

- Both; 80-120 IU/ml (102 + 7.40)
- Left; 30-71 IU/ml (52.07+3.23)n=14
- Left; 16.20 IU/ml (18.0 + 0.71) n= 5
- Right; 40-70 IU/ml (59.0 + 3.24)n= 10
- Right;12-18 IU/ml (15-6 + 1.84)n=3

❖ Metastases to other parts of the body; 40-120 IU/ml

- Lung; 91-114 IU/ml (102 + 4.8)
- Gastric; 40 - 86 IU/ml (63.2 + 5.06)
- Back; 120 IU/ml

Discussion:

Present study describes the estimation of tumor marker CA 15-3 cancer antigen in pre- and post-operative status of breast carcinoma patients. A wide range of CA 15-3 level was noted in pre-operative status of patients from as low as 36 U/ml to as high as 275 U/ml, depicting a certain degree of dependence on tumor burden and specificity, as reported in several studies[1,2,18,28,29]. It is recommended by several in depth trails that the highest sensitivity for active breast cancer detection was obtained by combined use of a panel of tumor marker14,30. However, conclusion had been drawn from a large number of studies that CA 15-3 is suitable tumor maker for assessment and monitoring of breast carcinoma[12, 21-24, 31, 32]. When CA 15-3 assessment was compared with other tumor makers such as tissue- polypeptide specific protein (TPS), no relationship was noted either with prognostic factor or patients' survival[23], concluding that TPS is not a good serum marker for breast cancer, whereas another study suggests that TPS monitoring may provide additional value when used in combination with CA 15-3[14]. Moreover, evaluation of cancer antigens CA 27.29 and Ca 15-3 in 145 breast cancer patients revealed that CA 27.29 is similar in sensitivity and specificity to CA 15-3 for metastatic breast cancer detection and monitoring, suggesting a specific reference value of CA 15-3 in evaluating diagnostic utility of new tumor markers[24]. In present study, metastatics, other han within the breast was also noted in few patients, reaching o lungs, stomach and back. CA 15-3 level was also found o be significantly high ($P < 0.01$) in these patients as compared to those with cancer localized to either breast only. Existence of correlation between elevated level of CA 15-3 and distant metastasis in breast cancer has been noted with sensitivity of 70% and specificity of 96%[15]. Facilitation in evaluating the disease course is another area for CA 15-3 detection in breast cancer, which had been investigated during last one decade[25,26,32,33]. Furthermore, CA 15-3 showed best predictive positive value, when retrospectively evaluated in 2483 cases of breast cancer, all under went surgery, mastectomy in 1979 cases and conservative surgery in 503 cases[34]. Similarly, CA 15-3 was noted to be the only marker associated with stage of breast cancer, when compared with CEA, AFP and TPS[27]. CA 15-3 was observed to be having significantly higher level than CEA in metastatic breast cancer when assessed in 121 patients with histologically proven breast cancer, suggesting CA 15-3 to be more sensitive and more specific[35].

It was investigated thoroughly that low diagnostic sensitivity for early disease detection might restrict the usefulness of circulating tumor marker in the management of the breast carcinoma[1, 28, 36]. Reported studies have shown that serum concentration and the positivity rate of tumor markers increases with the extent of disease, specifically those for CEA and mucins including CA 15-3[37-43]. Mucin family of tumor markers, to which CA 15-3 belongs, has been investigated extensively to improve their diagnostic effectiveness. Several variables can effect the *in vivo* detection and quantification of MUCI-related markers. The *in vivo* detection of MUCI products may be further hindered by the presence of circulating anti-mucin autoantibodies, occasionally found in cancer patients as a result of a host response to altered mucin biochemistry[1]. The variables result obtained in our study, such that significantly much higher CA 15-3 levels ($P < 0.001$) in localized breast cancer, than in metastatic status ($P<0.01$), suggesting alteration in recognition sites for CA 15-3 antibody and existence of heterogeneity which may occur in patients at time of course of the disease[1]. However, pre-operative serum concentration of CA 15-3 appears to have a significant relation to outcome of patients with early breast cancer and may have a role in the rational selection of patients for appropriate adjuvant treatments[14a, 33]. Assessment of CA 15-3 during post-surgical follow-up or therapy in 307 patients with breast cancer, revealed sensitivity of 70% and found elevated in those patients presenting metastasis to lung and bones, with a decline in level, post treatment reflecting response to therapy[44].

In conclusion, CA 15-3 is currently the most widely used circulating cancer marker for breast carcinoma. CA 15-3 can provide useful information regarding successfulness when comparing Pre-operative and Post- operative values. In our study, breast carcinoma patients showed decrease in CA 15-3 levels post- operatively (although most of them still above normal reference range), depicting successfulness of treatment and intervention, in addition to suggesting that CA 15-3 concentrations can also provide prognostic information. Only 3 patients showed post- operative normal Ca 15-3 levels. It was also concluded that serial cocentrations analyses have the potential both to detect recurrences pre- clinically and to monitor the treatment of metastases breast carcinoma.

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