Original Research Article

Estimation of Serum CA 15-3 Levels with Its Cytological and Histopathological Correlation in Breast Lesions

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Received: 17-04-2021 / Revised: 17-06-2021 / Accepted: 26-06-2021

Abstract

Background: Breast cancer makes the major burden of carcinomas in females. Timely diagnosis and treatment is the key. CA 15-3 is a tumour marker which is useful in diagnosis as well as prognosis of breast cancer. **Materials & Methods:** 100 cases of breast carcinoma were studied in a tertiary care hospital. Pre-operative CA 15-3 levels were done in all cases. Post-operative CA 15-3 levels were done in 60 patients and correlated with prognosis and metastasis. These findings were correlated with age, size, cytological, histopathological and IHC markers. **Results:** High pre-operative CA 15-3 result correlated with higher age of patient, bigger size of lesion, higher cytological grade, higher grade in histopathological examination, decrease ER and PR status and higher Her2neu grading. Hence high levels of pre-operative CA 15-3 correlate with bad prognosis. High post-operative CA 15-3 values correlated with re-occurrence or metastasis. **Conclusion:** In a developing country like India, CA 15-3 is a good tumour marker to screen for breast carcinoma. If the results of CA 15-3 are correlated with triple-test, it makes the diagnosis easier. Also the value of CA 15-3 provides an insight into the grading and staging of breast tumors. Moreover, CA 15-3 done for follow – up gives us an idea of re-occurrence or metastasis if any. This tumor marker should not be underestimated by surgeons and oncologists.

Key words: Breast Carcinoma, CA 15-3, Tumor marker, Ductal carcinoma

Introduction

Breast cancer is one of the most common malignancies causing mortality in women.[1] In 2020, there were 2.3 million women diagnosed with breast cancer and 6,85,000 deaths globally.[1] As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer.[1] In India, number of breast cancer cases is likely to increase from 13.9 lakh in 2020 to 15.7 lakh by 2025, an increase of nearly 20%.[2] A "triple test" approach, screening with clinical examination, mammography and fine needle aspiration cytology can easily divide almost all palpable breast lesions into benign and malignant categories; thus obviating the need of surgical biopsy in each and every palpable breast lesion and has also decreased the cost of screening and time required to reach definitive diagnosis.[3] Prognosis of Breast cancer depends on evaluation of various parameters like tumor histologic grading, cell proliferation index, estrogen receptor status and lymph node status are of growing interest.[4] Histological grade has been an important prognostic indicator that can predict overall and metastasis free survival for local and regionalized breast cancer.[5] Now a day, immunohistochemistry and serum tumor marker detection are 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).[6] Tumor marker, Cancer Antigen 15-3 (CA 15-3) also known as MUC1, is a product of the mucin one gene which is a transmembrane glycoprotein from the mucin family.[7] MUC1 is expressed on the surface of secretory epithelial cells including breast glands, gastrointestinal tract, respiratory, urinary and reproductive organ.[7] CA 15-3 determination is particularly useful in evaluating recurrence of disease and response to treatment. CA 15-3 is the most sensitive test in detecting metastatic breast cancer. CA15-3 may be useful marker for the diagnosis of secondary breast cancer

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Materials & Methods

Basic aims of present study are to study the role of tumor marker, CA15-3 test as a diagnostic and prognostic tool. It is a Prospective study of total 100 cases of female with breast lump which came to tertiary care centre of India during August 2019 to October 2020.Information concerning age, menopausal status, familiarity, tumor size (T), radiological investigation, serum investigations, type of surgery, microscopic diagnosis, therapy administered, estrogen (ER) or progesterone receptor (PR) status (if investigated), for each patient were collected. These patients were investigated for CA 15-3 levels in their serum with the use of ELISA (Enzyme Linked Immunosorbent Assay) test. Pre-operative CA 15-3 values were correlated with cytopathological and/or histopathological diagnosis of suspected mass. Post-operative CA 15-3 values were also measured after 7 days or after 3 cycles of radiotherapy/chemotherapy.

Samples Criteria:

The tests were performed on the patients' serum, after venous blood sampling on dry tube. For the pre-therapeutic assays, samples were taken before the first course of chemotherapy.

For the Post-operative values were measured after 7 days post operatively or after 3 cycles of radiotherapy or chemotherapy.

Inclusion Criteria

- Patient presenting with clinical and radiological features of Carcinoma breast
- Female patient.

Exclusion Criteria

- Healthy volunteers
- Male patients

Result

Total-100 cases were studied. These included patients with suspected carcinoma of breast and presenting with lump in breast, pain, or discharge from nipple. Some cases presented directly with the metastatic disease and complaints of bone pains or hepatobiliary symptoms. All the cases were investigated either by FNAC or biopsy. On confirmation of malignancy by either cytology or histopathology of biopsy, modified radical mastectomy was done and the specimen was again sent for histopathology examination. Pretreatment serum levels of CA 15-3 were measured in every case diagnosed as carcinoma breast. Marker levels were correlated with the histopathological findings like size, grade, lymph node status and stage of tumor. Pre and post-operative values of CA 15-3 were measured for prognostic purpose, to monitor response to treatment as well as to detect recurrence or metastasis. (Post-operative values were measured after 7 days post operatively or after 3 cycles of radiotherapy or chemotherapy).

In present study, it was observed (Chart No-I) that, in 50 % of cases diagnosis of carcinoma breast was confirmed with FNAC following which MRM was done. In rest 50 % cases biopsy of breast lump, either excisional or incisional type was done out of which in only 24 % of cases biopsy was followed by MRM

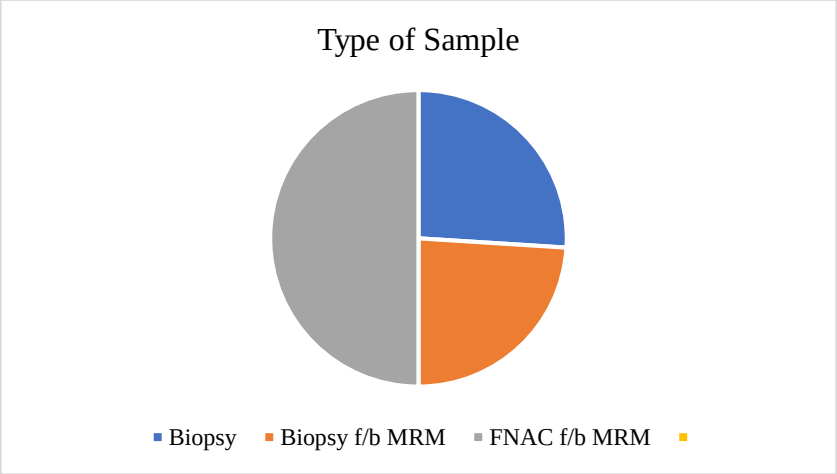

Chart I Type of Sample

In present study, it was observed (Chart No-II) that, in 91 % of cases diagnosis of carcinoma breast was Invasive Ductal Carcinoma of Breast NOS type.

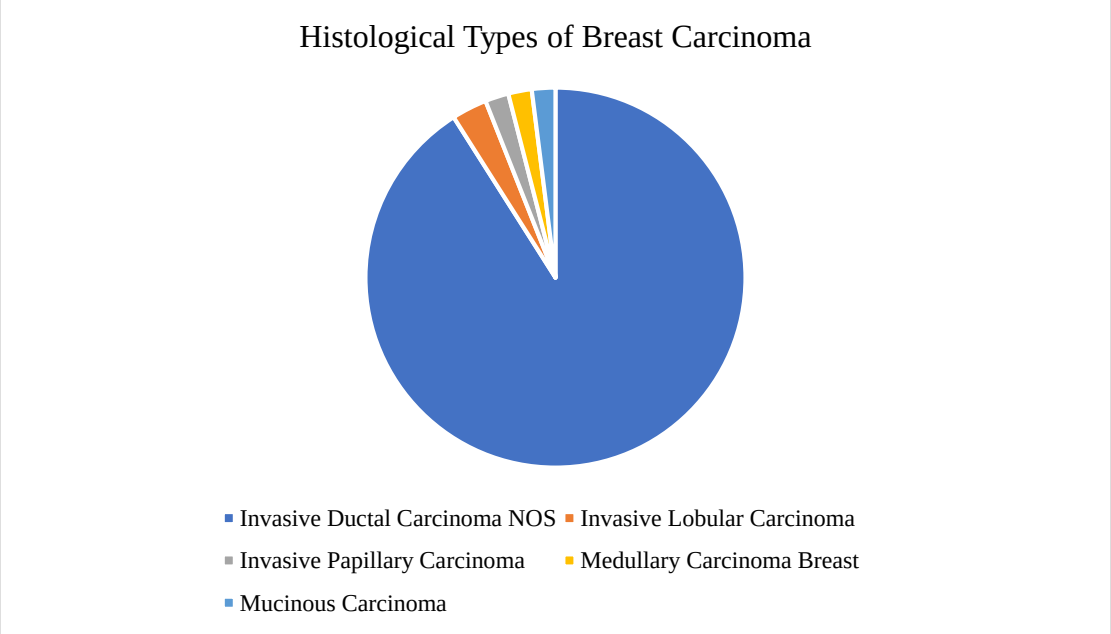

Chart II Histological Types of Breast Carcinoma

In present study, it was observed (Chart No-III) that, mean CA 15-3 level as well as positivity rates increased as age of the carcinoma breast patients increased.

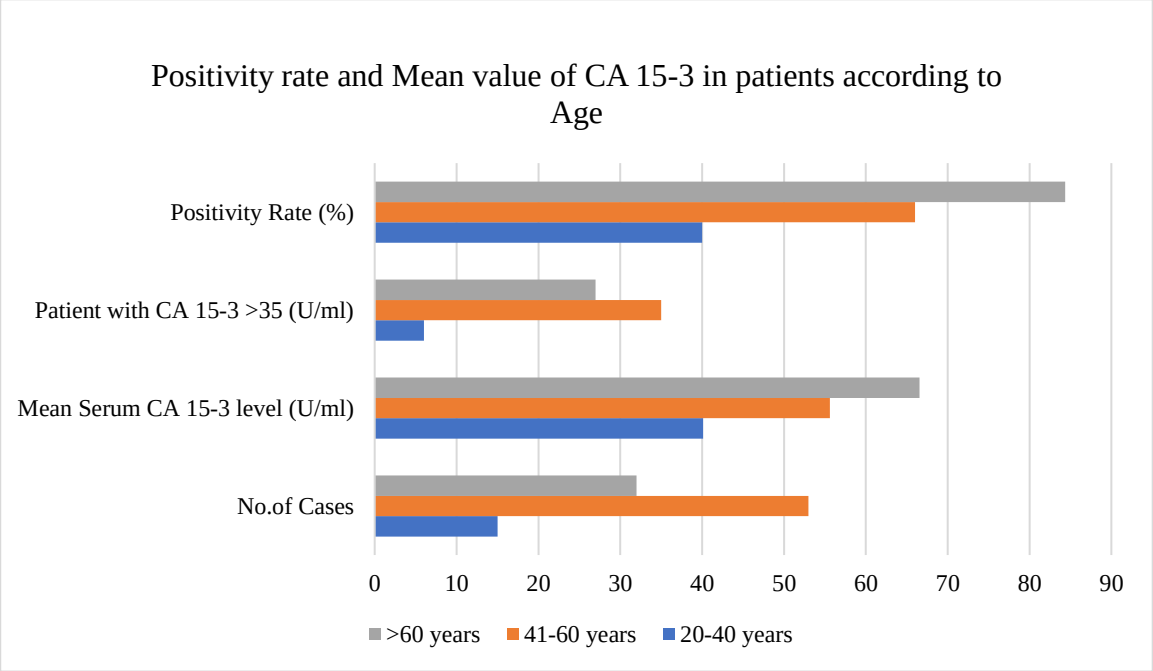

Chart III Positivity rate and Mean value of CA 15-3 in patients according to Age

In present study, it was observed (Chart No-IV) that, mean CA 15-3 level as well as positivity rates increased as size of the lesion increased in carcinoma breast patients.

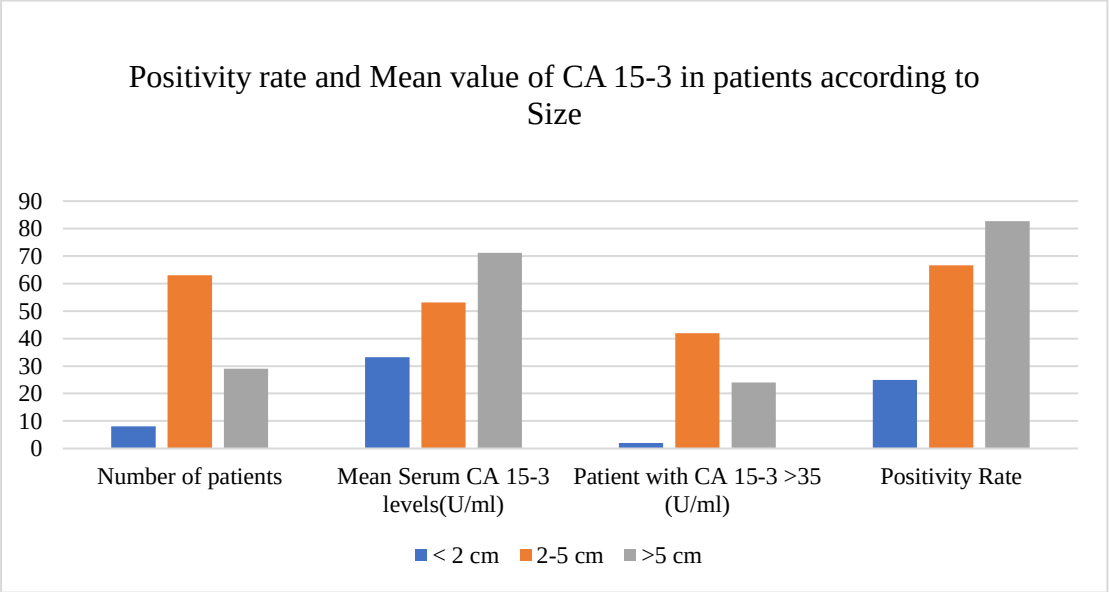

Chart IV Positivity rate and Mean value of CA 15-3 in patients according to Size

In present study, it was observed (Chart No-V) that, mean serum CA 15-3 value as well as positivity rates increased with increase in grade

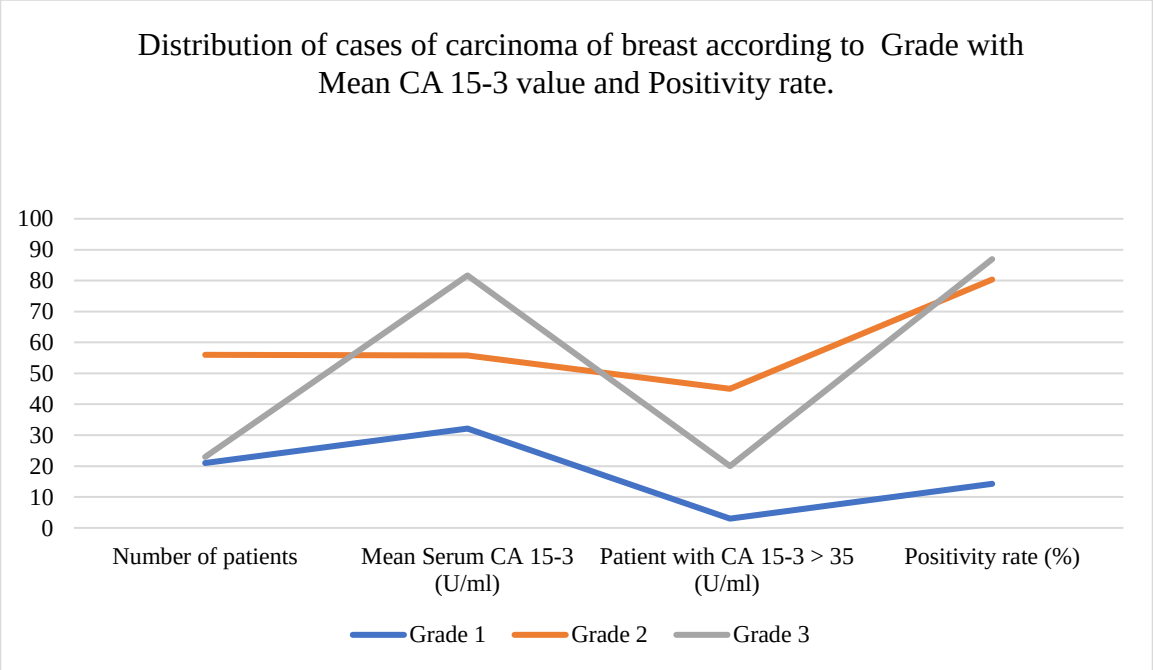

Chart V Distribution of cases of carcinoma of breast according to Grade with Mean CA 15-3 value and Positivity rate.

In present study, in all cases undergone MRM the number of lymph nodes were divided according into - cases with less than 4 lymph nodes involved and cases with more than 4 lymph nodes involved.

It was found around 56.7 % of cases showed more than 4 lymph nodes involved. Mean serum CA 15-3 level of patients with more than 4 lymph node involvement was 72.48 U/ml and 90.47 % of cases with more than 4 lymph nodes involved showed CA 15-3 levels more than 35U/ml. 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.

In present study, it was observed (Table VI, Table VII) that, good prognostic factors of receptor positivity (ER/PR Receptor) correlate with low serum CA 15-3 levels and poor prognostic factors like Her2neu correlates with high CA 15-3 values

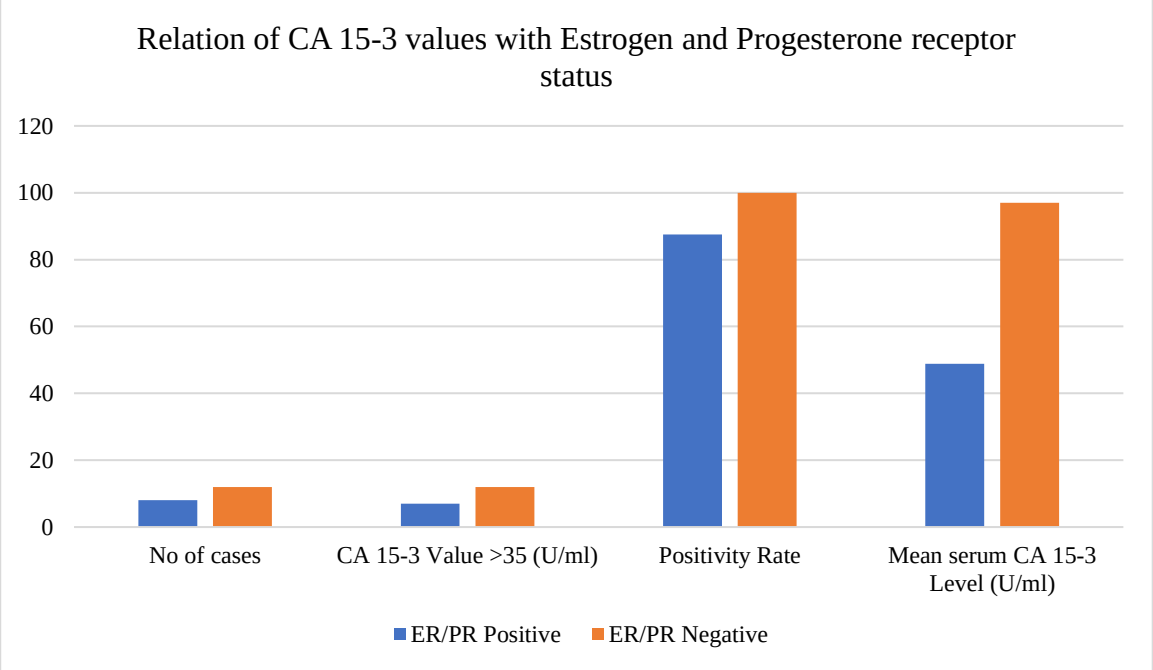

Chart VI Relation of CA 15-3 values with Estrogen and Progesterone receptor status.

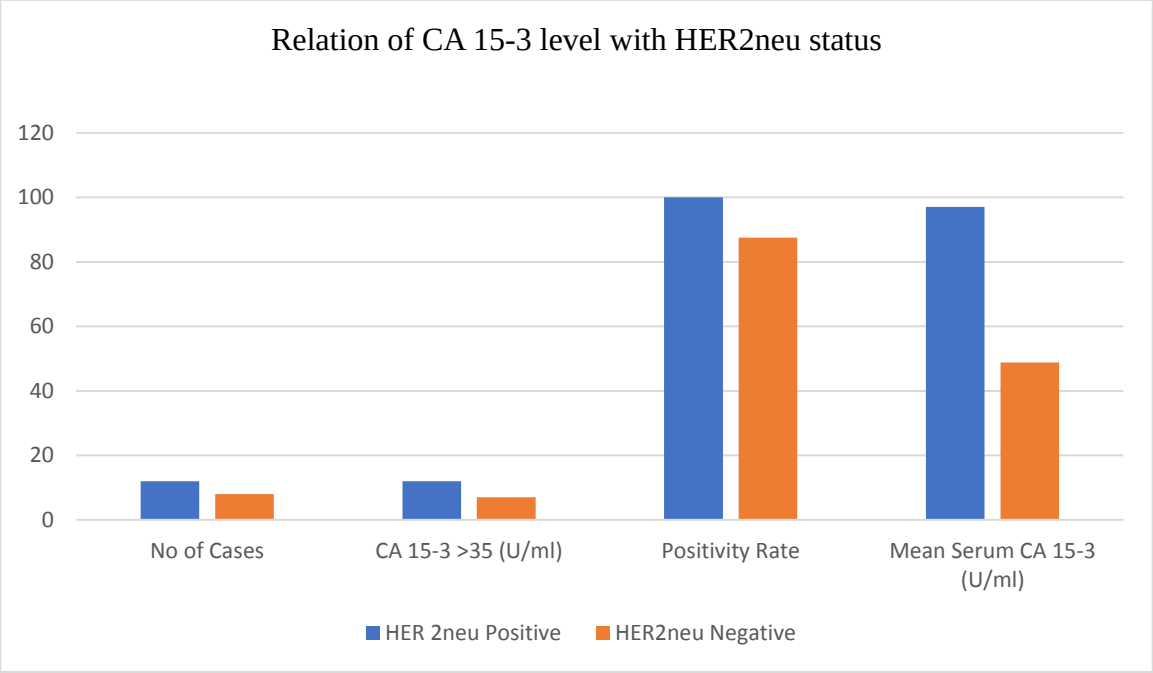

Chart VII Relation of CA 15-3 level with HER2neu status

In all the 100 cases in present study preoperative CA 15-3 levels were measured. Post treatment values were measured in 60 cases following MRM or chemotherapy. In rest of cases postoperative value detection could not be done due to loss of follow up. It was found that 54 cases (90%) showed decreased value of CA 15-3 post operatively. 6 out of 60 cases showed no change in CA 15-3 levels. These cases were further followed up regularly with CA 15-3 level detection and clinical and radiological investigations. It was found that 5 out of these 6 cases developed recurrence (2 cases) or metastatic disease (Opposite Breast Mets -1 case, Bone Mets -2) cases in further course of time. These patients were clinically normal and metastatic disease was detected by radiological investigations like CT scan, MRI and various serum biochemistry investigations as they had high CA 15-3 values. Thus, serum CA 15-3 evaluation helped early detection of metastatic disease as compared to their clinical presentation in 5 out of 6 cases. The response to treatment either the surgery or the chemotherapy was seen in the form of decreased value of mean CA 15-3 levels. This decrease in CA 15-3 value directly correlated with complete tumor removal.

In present study the post treatment value of CA 15-3 in detection of metastatic disease or recurrent disease was evaluated, which has 83.3% sensitivity and 98.1 % specificity. Similarly positive predictive value of CA 15-3 was and negative predictive value was found to be 83.5% and 98.1% respectively.

(Pre-operative and Post-operative CA 15-3 values were compared using "paired t test" and for detecting significance of this study p value was measured using SPSS software.)

Table I Statistical Study

CA 15-3 LEVEL	MEAN	N	STD. DEVIATION	T TEST	P VALUE
Pre op.	69.8	60	20.74	8.095	<0.0001
Post op	36.85	60	23.86		

(Here p value is highly significant. As p value < 0.0001, With above value t value found was = 8.0950)

These findings suggest that CA 15-3 has definitive prognostic role (p value<0.0001) in breast carcinoma. Even with normal preoperative CA 15-3 values, post-operative CA 15-3 values are important to detect any recurrence or metastasis. And pre-operative value is important for post-operative follow up of patients.

Discussion

About 40 years before the writing of this study began, the first author was given the opportunity to begin a series of experiments that would lead to the discovery of CA 15-3 as a human tumor marker, and to the myriad avenues of CA 15-3 research that are being actively pursued at the present moment.

In case of malignant tumors, one of the tests to diagnose carcinoma is use of tumor markers. In carcinoma of breast, ELISA test to measure CA 15-3 is reliable, sensitive, rapid and cost-effective test. CA 15-3 is the preferred tumor marker of choice for detection of tumor recurrence after surgery or radiotherapy in cases of carcinoma breast with pretreatment elevated CA 15-3. It is also a good serum marker for monitoring response to treatment for carcinoma breast patients.

In present study range of patients age was from 32 years to 84 years. Maximum number of patients were seen in post-menopausal age group i.e., 76%. In study of Rudy Budijono', Carcinoma of breast seen in age group of 26 years to 72 years, with an average age of 49.2 years.[7] In study of Meliha Melin Uygur', the percentage of premenopausal and postmenopausal patients was 53.5%; and 46.5%, respectively.[8]

Various studies conducted like Alsaeed'[10], Daniele'[11] showed that majority of cases of carcinoma breast were Invasive ductal carcinoma-NOS type i.e. 84.8%, i.e. 84.8%, 86.3%, 83.5%, and 88.3% respectively. Present study conducted at our institute also correlated with the other studies and it was found that 91% of cases were of Invasive Ductal Carcinoma –NOS type and only 9% belonged to other types, like medullary carcinoma, mucinous carcinoma and papillary type of breast carcinoma.

In present study it was observed that a greater number of cases i.e., 63% belonged to lesion size between 2 to 5 cm, while least belonged

to less than 2 cm size i.e., 8 %. Alsaeeed'[10] showed a greater number of cases with lesion size more than 5 cm size, Daniele'[11] showed a greater number of lesions with size between 2 to 5 cm.

In present study, it was observed that, mean serum CA 15-3 value as well as positivity rates increased with histopathological grade. In study of Rudy Budijono', there was a significant correlation between increasing the tumour histopathology grading from low grade – high grade to the increase of marker CA 15-3 ($p = 0.032$).[7]

According to present study, good prognostic factors of receptor positivity (ER/PR Receptor) correlate with low serum CA 15-3 levels and poor prognostic factors like Her2neu correlates with high CA 15-3 values. In study of Meliha Melin Uygur'HER2 negative patients had significantly higher levels of CA 15–3 ($p =0.011$).[8]

In present study the role of pre and post treatment value of CA 15-3 in detection of metastatic disease or recurrent disease was evaluated, which has statistically significance. In study of Khan MA' on comparing preoperative serum CA 15-3 level to the postoperative level, it was found that Ca 15-3 level falls following breast surgery. The elevated preoperative serum levels of CA 15-3 were significantly correlated with the presence of metastatic disease.[12] In study of Ali HQ , preoperative CA15-3 values were significantly higher in patients as compared to the values after three cycles of chemotherapy ($p<0.05$).[13]

Conclusion

As the most common malignancy in women, breast cancer is a great threat for women's health worldwide. Its treatment by chemotherapy requires relevant clinical, radiological and biological evidence to assess the response to treatment. Our study allowed an assessment of tumour marker CA 15-3. The main limitations of the study are the size of the population and the fact that tumour markers were measured in a limited number of patients after chemotherapy. Our results suggest that the levels of CA 15-3 may be useful in predicting the prognosis of breast cancer in patients. Higher the pre-operative value of CA 15-3, worse is the prognosis and more chance of metastasis or reoccurrence. Post-operative values of CA 15-3 helped in stratification of patients in low and high risk group. High post-operative levels of CA 15-3 point towards a reoccurrence or metastasis. As the examination of these markers is still not widely used in daily clinical practice, the data obtained provided important information for identifying patients with a poor response to chemotherapy. Hence value of CA 15-3 as a diagnostic and prognostic marker should be valued and it should be used religiously in breast carcinoma patients.

Conflict of Interest: Nil Source of support: Nil

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