RESEARCH ARTICLE

FOLLOW-UP OF PATIENTS AND PROGNOSTIC IMPACT OF TUMOUR MARKER CA 15-3 ON PATIENTS OF BREAST CANCER: A RETROSPECTIVE COHORT STUDY

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Abstract

Introduction: Breast cancer is the most common cancer in women, with 5- and 10-year relative survival rates are 91% and 84%, respectively for women with invasive breast cancer. This study aimed to detect the role of serum breast cancer marker CA 15-3 for early detection of metastasis, relapse or recurrence for management of breast cancer patients.

Methods: It was a retrospective cohort study with a total of 132 breast cancer patients from the year 2010 to March 2020 were taken and followed up. For these patients demographic, biochemical parameters, radiological and clinico-pathological data were collected and analysed.

Result: The mean age at the time of presentation and mean duration of follow-up was 47 years and 31 months respectively. There was elevation in the serum level of CA 15-3 at the time of diagnosis of metastasis, recurrence or residual disease in 41 patients. This shows that sensitivity of elevated CA 15-3 (> 30 IU/ml) level in Ca Breast patients was 84%, 75% and 75% with respect to metastasis, recurrence and relapse. Log Rank test Chi-square value was 7.39 which was statistically significant (p=0.007). Cox proportional hazard model was created for effect of age at presentation, CA 15-3 at the time of diagnosis and MRM on distant metastasis and was statistically significant (p=0.037).

Conclusion: We recommend that for the management of breast cancer patients, Cancer antigen (CA 15-3) levels can be used as prognostic marker for early diagnosis of metastasis, recurrence or relapse.

Introduction:-
Breast cancer is the most common cancer in women, which can also appear in men. Along with cancer of oral cavity, breast cancer is collectively responsible for 25% cancer cases in India (1). As suggested by American cancer society, the 5- and 10-year relative survival rates are 91% and 84%, respectively for women with invasive breast cancer (2). With proper and regular screening, this mortality can be reduced. It has been possible only in developed countries while developing countries still lag behind. For measuring treatment response, predicting prognosis and early diagnosis of recurrence or relapse, serum tumour markers have been widely used. The serum tumour marker most widely used for breast cancer, are cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA) used for surveillance and treatment monitoring. CA15-3, is an epitope of MUC1 which is a large transmembrane
glycoprotein and derived from MUCI gene. The molecular weight of CA 15-3 is 300-450 kDa and is glycoprotein in nature. Apart from breast cancer, it can also be elevated in ovarian, lung, pancreatic and colorectal cancers (3). It can also be elevated in patients with vitamin B12 deficiency, menstruating women, pancreatitis, crohn’s disease, ulcerative colitis and benign gastrointestinal disease (4). However, the reference range for CA 15-3 for breast cancer is less than 30u/ml. In this study, we have focused on breast cancer marker CA 15-3 and its role in early detection of metastasis, relapse or recurrence; which can be used for management of breast cancer patients.

Material and Methods:-
This study was conducted at Delhi State Cancer Institute (New Delhi, India), a tertiary care hospital specially designated for the treatment of cancer patients. It was a retrospective cohort study where we have taken data of 132 breast cancer patients from the year 2010 and till march 2020 were registered and followed-up. Ethical clearance was sought. All these patients have histologically confirmed breast cancer whether previously treated and on follow up or ongoing treatment or treatment not yet started. We have collected demographical data, biochemical parameters, radiological and histological findings.

All patients were staged according to TNM staging followed by American Cancer Society (ACS). We have also noted type of surgery, tumour size, status of lymph node, hormonal marker status and also status of metastasis, recurrence or relapse. Blood samples from the cancer patients were collected in plain vial without additive and then serum separation was done after centrifugation at 2500rpm for 10 minutes. For detection of CA 15-3 commercially available fully automated Cobas e 411analyser (Roche Diagnostics Germany) based on Electro-Chemiluminescence (ECL) technology for immunoassay analysis was used.

Breast Cancer patients were treated according to American Society of Cancer Oncology (ASCO) which further depends on hormone receptor status, grade of cancer, tumour type and metastasis status. Depending upon all these factors treatment regimen includes combination of chemotherapy, radiotherapy and surgery (Breast conservative surgery (BCS) or Modified radical mastectomy (MRM). Each chemotherapy cycle was of 21 days duration. Radiotherapy was given to most patient, dose depending upon the body surface area of the patient. All patients were regularly assessed for response both radiologically and clinically.

Statistical Analysis: Survival analysis was done, Kaplan-Meiers curve was constructed for survival function. Log Rank test was performed to differentiate between levels of variable. Cox proportional hazard model was created for metastasis as dependent variable and age, CA 15-3 at the time of diagnosis and MRM as independent variable. Statistical analysis was performed using SPSS version 23. A P-value of less than 0.05 was considered significant.

Result:-
In this study we had included a total of 132 patients of breast cancer, of which one was male and rest other were females. The mean age at the time of presentation was 47 years with the range from 20 years to 82 years. Out of total 132 breast cancer patients, 68 had left breast carcinoma, 62 had right sided breast carcinoma and rest 2 had bilateral breast Ca (table no. 1). The mean duration of follow-up is 31 months with the range being 1 month to 124 months (during study period), which shows that approximately maximum number of patients were followed for 1-23 months.

We had tried to collect serum levels of CA 15-3 of each 132 study patients at 6 monthly interval from the time of diagnosis. Although, out of 132 persons, 25 study patients had newly detected Ca Breast and in 20 study patients we could not record 6 monthly CA 15-3 values. In 39 Ca breast patients, there was metastasis, recurrence or residual disease after chemotherapy or even after surgery. Out of these 39 patients, 33 had metastasis, 4 had recurrence and rest 4 had residual disease in which 2 patients had metastasis along with recurrence and/or relapse. There was elevation in the serum level of CA 15-3 at the time of diagnosis of metastasis, recurrence or residual disease in 41 patients as shown in table no.2. This shows that sensitivity of elevated CA 15-3 (> 30 IU/ml) level in Ca Breast patients was 84%, 75 % and 75 % with respect to metastasis, recurrence and relapse.

Overall median time for metastasis for the patients after MRM was 15 months. Median time for metastasis for patients with MRM was 24 months in comparison to patients without MRM was 4 months. Log Rank test Chi-square value was 7.39 which was statistically significant (p=0.007) as shown in figure no. 1. Cox proportional hazard model was created for effect of age at presentation, CA 15-3 at the time of diagnosis and MRM on distant
metastasis. Model was statistically significant with Chi-square value of 74.49 (p=0.037). Clinico-pathological response was analysed taking tumour size, tumour grade, tumour stage, histopathological type of tumour, hormonal receptor status (ER, PR and Her 2 neu status). But we could not find definitive association between metastasis and hormone receptor status with the P value being 0.189, 0.140 and 0.279 for ER, PR and Her 2 neu status respectively.

Discussion:
Breast cancer is one of the most common cancer globally after lung and colon cancer, and being most common cancer in women. In the year 2012, almost 1.7 million cases of breast cancer were diagnosed and almost half million persons died from disease (5). Hence early detection of breast cancer or breast cancer metastasis, recurrence or relapse is crucial for survival of these patients. In order to detect tumour early, a tumour marker detectable in serum which is sensitive and specific would definitely prove helpful. CA 15-3 is one such marker, which is serum based and product for the MUC1 gene. Earlier CA 15-3 levels have already been demonstrated to predict outcome in locally advanced breast cancer (6). However, its definitive role with respect to clinical and pathological response and disease prognosis needs further study. In the year 2006, Duffy et al suggested that most important implication of tumour marker CA 15-3 is in monitoring therapy in patients with locally advanced breast cancer (7). However, due to its non-specific nature, as it is also elevated in a number of benign and malignant conditions, as routine use of CA 15-3 in locally advanced breast cancer is recommended only as adjunctive by the American society of clinical oncology (8). Our study also support this, that level of serum tumour marker CA 15-3 should be used as adjunctive marker of tumour metastasis, recurrence or relapse. Our study had demonstrated sensitivity of elevated CA 15-3 (>30 IU/ml) level in Ca Breast patients was 84%, 75 % and 75 % with respect to metastasis, recurrence and relapse which eventually decreased following treatment. Similar results were also shown by Duffy et al., which showed significantly higher concentration of CA 15-3 in patients with histological confirmed breast cancer patients (9). Pedersen et al., showed higher sensitivity of CA 15-3, CEA and serum HER2 for early detection of recurrence of breast cancer (10). Thriveni et al., had also shown significant correlation (24.8%) with large tumour size and advanced stage (11). Further studies are required to evaluate the role of CA 15-3 values for early diagnosis of metastasis, recurrence or relapse in Ca breast patients.

Table:
Table no. 1:- Clinico-pathological characteristics of Ca Breast patients.

| Characteristic                  | Total number | Percentage |
|--------------------------------|--------------|------------|
| Age                            |              |            |
| ≤ 50 years                     | 82           | 62         |
| >50 years                      | 50           | 38         |
| Histology                      |              |            |
| Invasive ductal carcinoma      | 102          | 77         |
| Invasive medullary carcinoma   | 1            | 1          |
| Ductal carcinoma in situ       | 10           | 7          |
| Others                         | 13           | 10         |
| Unknown                        | 6            | 5          |
| Surgery                        |              |            |
| Modified Radical Mastectomy    | 96           | 73         |
| Breast Conservative Surgery    | 22           | 17         |
| Unknown                        | 14           | 10         |
| Site Of Cancer                 |              |            |
| Left                           | 68           | 52         |
| Right                          | 62           | 47         |
| Bilateral                      | 2            | 1          |
| Tumour Size (cm)               |              |            |
| ≤2cm                           | 16           | 12         |
| >2cm                           | 77           | 58         |
| Unknown                        | 39           | 30         |
Table no. 2: Showing relation of CA 15-3 level at the time of diagnosis of Metastasis/ Recurrence/ Relapse:

| Total no. of patients with | Total number of patients with CA 15-3 value >30 iu/ml | Total number of patients with CA 15-3 value <30 iu/ml |
|----------------------------|-----------------------------------------------|-----------------------------------------------|
| Metastasis                 | 33                                            | 28                                            | 5                                            |
| Recurrence                 | 4                                             | 3                                             | 1                                            |
| Relapse                    | 4                                             | 3                                             | 1                                            |

Table no. 3: Showing Cox proportional hazard model with metastasis as dependent variable and age, CA 15-3 at the time of diagnosis and MRM as independent variable.

| Variables in the Equation | B    | SE    | Wald  | df | Sig.  | Exp(B) |
|---------------------------|------|-------|-------|----|-------|--------|
| Age at Presentation      | .027 | .017  | 2.395 | 1  | .122  | 1.027  |
| CA 15-3 at the time of diagnosis | .008 | .003  | 8.102 | 1  | .004  | 1.008  |
| MRM                      | -.958| .436  | 4.832 | 1  | .028  | .384   |

Figure no. 1: Kaplan-Meiers survival curve showing association of metastasis with duration of surgery.

Conclusion:
Our study shows that the serum tumour marker CA 15-3 concentration was found to be highly sensitive and elevated in breast cancer patients during metastasis, recurrence and relapse. Hence, we recommend that for the management of breast cancer patients, Cancer antigen (CA 15-3) levels can be used as prognostic marker for early diagnosis of metastasis, recurrence or relapse.

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