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### RESEARCH ARTICLE

#### CLINICAL BEHAVIOUR OF METASTATIC TRIPLE NEGATIVE BREAST CARCINOMA: AN INSTITUTIONAL REVIEW.

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Triple negative, younger, aggressive, worse prognosis, high recurrence

#### Abstract

**Introduction** - Triple Negative Breast Cancer (TNBC) is a type of breast cancer which is characterized by its unique molecular profile of ER, PR and HER2Neu Negativity. They are generally aggressive in nature, present with different metastatic patterns and there are no targeted therapies till date. It constitutes 15-20% of all breast carcinomas. To identify the clinical behaviour of TNBC, we evaluated the 62 patients of TNBC presenting in our department in last 3 years.

**Methods:-** Patients diagnosed with breast carcinoma (tissue diagnosis) presenting to our institution were evaluated for their ER, PR and HER2Neu status. Triple Negative (ER Negative, PR Negative, HER2Neu Negative) breast cancer subtype patients were given treatment according to the stage and patient preferences. Operable patients willing for mastectomy were operated followed by adjuvant treatment while inoperable patients were given Neo-adjuvant chemotherapy followed by surgery +/- radiotherapy.

**Results:-** Median age of patients was 45 years (range 28-81). Majority of patients were locally advanced (82.3%) and 79% had positive nodes at the time of presentation. Initial metastasis in the cohort was around 24.2% despite most tumours being locally advanced. Bone and Liver was the most common site of metastasis at diagnosis. Upfront surgery was done in 35.48% patients while 64.52% patients were started on chemotherapy out of which 62.5% patients were amenable to surgery. At a median follow up of 23 months local recurrence was seen in 9.7% and distant metastasis in 40.32% of cases. Most common site of distant metastasis was Brain (14.52%) followed by Liver (11.29%) and Lung (11.29%). The median disease free survival (DFS) and time to local failure in the study was 11 and 12.5 months respectively.

**Conclusion:-** TNBCs present in younger women show variable response to chemotherapy and carry the worse prognosis, having high recurrence rate.

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**Introduction:-**

Breast cancer is the most common cancer in women [1]. It has been divided into various subtypes depending upon oestrogen receptor (ER), progesterone receptor (PR) and HER2/neu status. ER-positive comprises about 70% of cases while ER-negative breast cancer constitutes approximately 40% [2,3,4]. HER2/neu oncogene is amplified in about 15-20% of breast cancer cases [2]. Triple negative breast cancer (TNBC) is a type of breast cancer that does not express any of the markers and accounts for about 10–15% of all cases.

TNBC in general are aggressive in nature as compared to other subtypes [5]. Histologically TNBC comprises of cells having high proliferation rate, are generally poorly differentiated, and, in most cases harbour mutations in the TP53 gene [6,7,8].

The aim of the present study is to evaluate the clinical characteristics and outcomes of patients with metastatic triple negative breast cancer treated at our institute in last three years.

**Materials and Methods:-****Patient selection:-**

Total 62 female patients diagnosed with breast carcinoma (tissue diagnosis) presenting to our institution between 2001-14 were evaluated for their ER, PR and HER2NEU status. Triple Negative (ER Negative, PR Negative, HER2neu Negative) breast cancer subtype patients (metastatic at presentation or having distant metastasis later on) were analyzed in this study.

**Pretreatment Evaluation:-**

Diagnosis of all cases was based on biopsy specimens. Staging was based on physical examination, USG whole abdomen, Chest radiograph and bone scan.

**Management:-**

All patients were managed by multimodality treatment, which includes chemotherapy, radiation therapy and surgery.

**Chemotherapy:-**

Chemotherapy consisted of 6 cycles of FAC chemotherapy, [F = 5-Fluorouracil 600mg/m<sup>2</sup> bolus injection (day 1) + A = doxorubicin 50 mg/m<sup>2</sup> in a 1-hour infusion (day 1) + C = cyclophosphamide 600 mg/m<sup>2</sup> as bolus injection (day 1)] either in the neo-adjuvant or adjuvant setting. Cycles were administered at 3-week intervals. Paclitaxel [175mg/m<sup>2</sup>] for 4 cycles was added after 4 cycles of FAC depending upon patients affordability. Evaluation of response to chemotherapy was performed either by physical examination or imaging, after the induction chemotherapy.

**Surgery:-**

Surgery in the form of Breast conserving surgery (BCS) or radical like total mastectomy (TMAC) depending upon the patient's preference or tumor status was planned as a primary treatment in some patients or after induction chemotherapy depending upon the response.

**Radiation:-**

For patient who underwent TMAC radiation dose of 35Gy/40Gy in 15 fractions was given to chest wall and supraclavicular area respectively. The dose to patients undergoing BCS was 40Gy/40Gy in 16 fractions to whole breast and supraclavicular area respectively followed by boost to tumor bed of 10Gy in 5 fractions.

For patients with metastatic disease at presentation, 6 cycles of palliative chemotherapy with either FAC alone or 4 cycles of FAC followed by 4 cycles of paclitaxel were planned. Local radiotherapy was given with radical or palliative intent depending upon response to chemotherapy.

After treatment, patients were followed by physical check-ups. Additional studies, including if necessary biopsy, were performed when indicated. Outpatients were followed every 3 months for 2 years and then twice a year.

**Statistical Analysis:-**

In this retrospective study, frequency tables with counts and percentages were used to describe pre-treatment and treatment characteristics of the patients. Disease free survival (DFS) and Local control rates (LC) were calculated by the Kaplan–Meier method using statistical software SPSS for windows (version 19.0).

**Results:-****Patient Profile And Treatment Details:-**

Table 1 shows the patient profile and treatment given. The median age of presentation is 45 years(range 28-81 years).37.1% of the patients were <40 years of age while 62.9% were >40 years of age.51.6% of the tumors were right sided with most common involved quadrant being the upper outer(41.9%)

82.3% of the patients had T3-4 tumors.79% of the patients had nodal positivity.15 patients(24.2%) had metastatic disease at presentation with most common site of metastasis being bone(40%) followed by liver(20%).

Upfront surgery was possible in 22(35.48%) patients while 40 patients required upfront chemotherapy after which surgery was possible in 25 patients (62.5%).Among the 47 patients who underwent surgery TMAC was done in 45 cases while BCS was done in only 2 patients.

**Response to Treatment:-**

Out of 25 patients who underwent neoadjuvant chemotherapy followed by surgery 3 patients had complete pathological response (12%).

**Pattern of failure (Table 2):-**

At median follow up period of 23 months, out of 62 patients, 34 (54.8%) patients failed the treatment. Majority of the failures (25 out of 34), were distant (40.32%). 3 patients (4.8%) had both local and distant failure, and 6(9.7%) failed locally. The most common site of distant failure was Brain (14.52%), followed by liver(11.29%) and lung (11.29%).

**Local Control rates (Figure 1):-**

The 1 year, 2 year and 5 year local control rates were 91.3%, 73% and 37 % respectively. The median time to local failure was 12.5 months.

**Disease free survival (Figure 2):-**

The 1 year, 2 year and 5 year disease free survival were 84.9%, 72.3% and 13.5% respectively. The median time to any failure was 11 months.

**Discussion:-**

The term “TRIPLE NEGATIVE” specifies histologically proven ER/PR/Her2neu negativity [10,11,12].TNBC are more commonly present in younger, premenopausal as compared to old age (24% versus 15%)[13,14].In this study, the median age of presentation is 45 years(range 28-81 years).37.1% of the patients were <40 years of age while 62.9% were >40 years of age.

TNBC comprising of 13-25% of breast cancers have a highly aggressive nature than other breast cancer subtypes accounting for a large number of metastatic disease. In our study 82.3% of the patients had T3-4 tumors.79% of the patients had nodal positivity.24.2% had metastatic disease at presentation with most common site of metastasis being bone (40%) followed by liver (20%).

Chemotherapy is the standard treatment for TNBC. It is very sensitive to cytotoxic therapy despite its aggressive nature. After treatment with chemotherapy approximately 30-45% of patients achieve complete pathological response [15, 16]. In this study 12% patients who underwent neoadjuvant chemotherapy followed by surgery had complete pathological response.

As reported in two studies done on TN breast cancer 6% of patients with early stage breast cancer had brain metastasis [17, 18, 19]. TNBC and HER2-positive breast cancers were associated with high rates of local recurrence in comparison to other groups as shown in a meta-analysis of studies comparing breast cancer subtype and loco

regional recurrence [20]. Patients with TNBC have a poor prognosis as compared to luminal subtypes and this difference was most common in the first 2 years after diagnosis[21]. This is in comparison with the present study which shows at median follow up period of 23 months, out of 62 patients, 34 (54.8%) patients failed the treatment. Majority of the failures (25 out of 34), were distant (40.32%). 3 patients (4.8%) had both local and distant failure, and 6(9.7%) failed locally. The most common site of distant failure was Brain (14.52%), followed by liver(11.29%) and lung (11.29%).

The 1 year, 2 year and 5 year local control rates were 91.3%, 73% and 37 % respectively. The median time to local failure was 12.5 months. The 1 year, 2 year and 5 year disease free survival were 84.9%, 72.3% and 13.5% respectively. The median time to any failure was 11 months. This is consistent with findings from the previous studies which shows that the chances of developing metastases is more common in the first 2 years after diagnosis with a decline after the fifth year [22,23,24,25].

### Conclusion:-

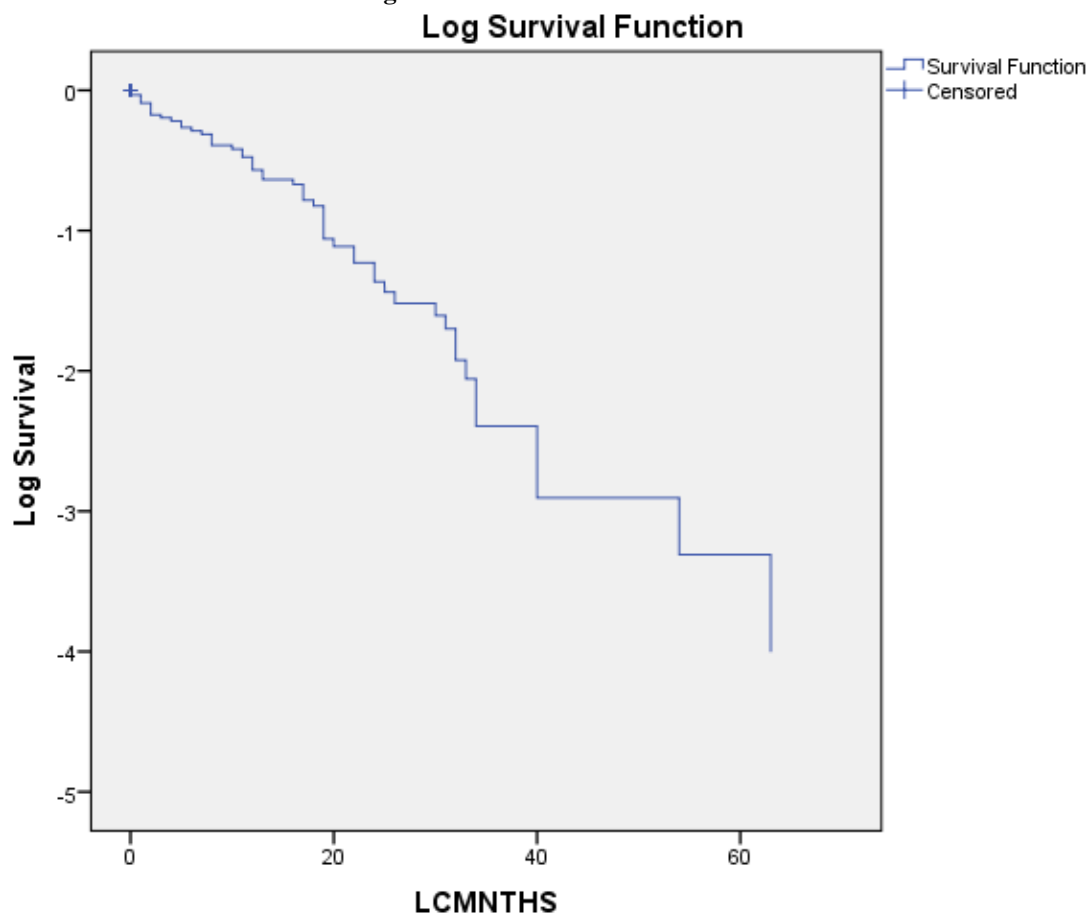
Molecular subtyping of breast cancer is commonly done now a day as it helps in predicting the tumor behaviour and guiding further treatment. TNBCs present in younger women show variable response to chemotherapy and carry the worse prognosis. There are high chances of developing CNS metastases, especially in the first 5 years of diagnosis.

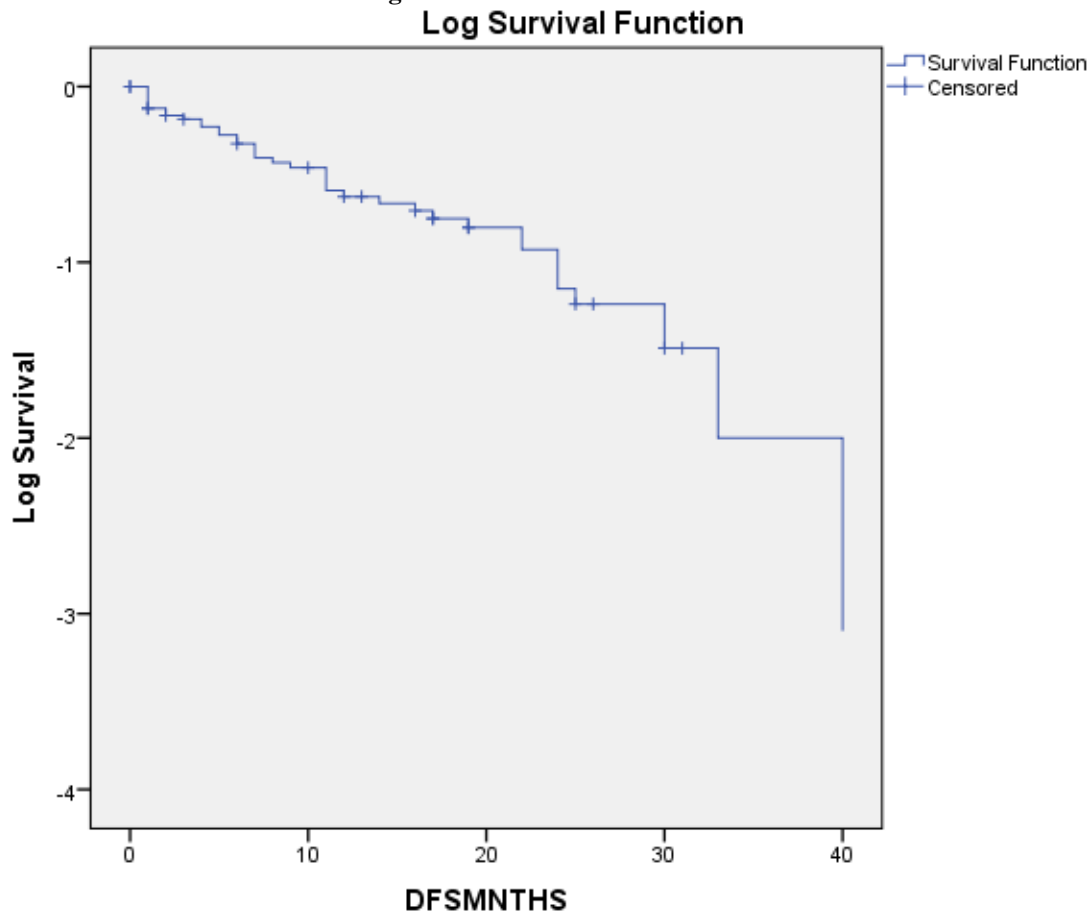
**Table 1:-** Patient profile and treatment characteristics.

Characteristics	Number of patients (percentage)
Gender	
Male	0(0%)
Female	62(100%)
Age(years)	
Median	45
Range	28– 81
<40	23(37.1%)
>40	39(62.9%)
Tumor Site	
LEFT	29(46.8%)
RIGHT	32(51.6%)
B/L	1(1.6%)
Tumor Quadrant	
UPPER OUTER	26 (41.9%)
UPPER INNER	5(8.1%)
CENTRAL	17(27.4%)
LOWER OUTER	12(19.4%)
LOWER INNER	2(3.2%)
T SIZE	
T1-2	11(17.7%)
T3-4	51(82.3%)
NODE	
N0	13(21%)
N1	27(43.5%)
N2	16(25.8%)
N3	6(9.7%)
Metastasis	
M0	47(75.8%)
M1	15 (24.2%)
Treatment	
Sx ---> ADJUVANT	22 (35.48%)
NEO ADJ-->Sx	25 (40.32%)
CCT	15 (24.19%)
Sx type	
TMAC	45 (95.75%)
BCS	2 (4.25%)

**Table 2:-** Pattern of failure.

Failure type	Number of failures (percentage)
Total	34 (54.8%)
Local	6 (9.7%)
Distant	25 (40.3%)
Both	3(4.8%)
Distant Failure-	
Bone	3(4.84%)
Brain	9(14.52%)
Liver	7(11.29%)
Lung	7(11.29%)
Cervical node	2(3.23%)

**Figure 1:-** Pattern of local control.

**Figure 2:- Pattern of distal failure.****References:-**

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