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CLINICAL AND ONCOLOGICAL OUTCOME OF PATIENTS TREATED FOR BREAST CARCINOMA OVER 8 YEARS: A COMPARISON BETWEEN TRIPPLE NEGATIVE(ER/PR/Her2neu) AND NON – TRIPPLE NEGATIVE CASES OPERATED AT A TERTIARY CARE CENTRE IN NORTH INDIA – A RETROSPECTIVE CASE STUDY.

Dr. Dheer S. Kalwaniya[1], Dr. Akshay Narayan[2], Dr. Satya.V. Arya[3], Dr. Jaspreet S. Bajwa[1], Dr. Gautam K. Chowdegowda[2], Dr. Raj.K Chejara[4], Dr. Ashok K. Sharma[4]

[1]Assistant Professor, Department of General Surgery, Safdarjung Hospital, New Delhi
[2]Junior Resident, Department of General Surgery, Safdarjung Hospital, New Delhi
[3]Professor & Head, Department of General Surgery, Safdarjung Hospital, New Delhi
[4]Associate Professor, Department of General Surgery, Safdarjung Hospital, New Delhi

Conflicts of Interest: Nil

Corresponding author: Dr Satya.V. Arya

Abstract:

Carcinoma Breast is the most common cancer to be diagnosed amongst women in India and worldwide. Research shows that breast cancer is not a single entity but a heterogeneous disease with various subtypes. One such subtype called the Triple Negative Breast Cancer (TNBC) has certain peculiar characteristics; however the data regarding this subtype is scarce in our country. A retrospective observational study conducted at Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi wherein data was collected from Breast Cancer patients attending the surgical OPD between May 2011 to May 2016. The patients with metastatic disease were excluded from the study. The patients were followed up for a period of 3 years i.e. till may, 2019.A total of 583 patients were registered. 61 patients had metastatic disease and hence were excluded from the study. Of the remaining 482 patients, 110 were diagnosed to have TNBC and 372 had non-TNBC disease. The TNBC patients presented at a younger age (Average age 44.02 +/- 9.348 years) with larger tumor size (Average size 5.82 +/- 1.66 cm) with involvement of axillary lymph nodes (61.8%). A positive family history of breast cancer was noted in 1.8% of patients with TNBC and more patients with TNBC had locally advanced disease at presentation (57.2%). Upfront surgery could be performed in 38.1% of TNBC patients and 61.8% patients were offered Neo-Adjuvant Chemotherapy. There was no significant difference in the 3-year survival and recurrence rates between the two groups. In conclusion we can say that in comparison to the non-TNBC patients, TNBC patients present at a younger age with larger and more advanced tumors with early involvement of Axillary Lymph nodes requiring Neo-Adjuvant Chemotherapy.

Keywords: *TNBC, Non – TNBC, estrogen receptor, progesterone receptor, Her 2/ neu, LABC (Locally advanced breast carcinoma).*

Introduction:

Carcinoma of the breast is the most common cancer amongst women with approximately 1.67 million new cases every year (25% of all cancers). It is also the 2nd most common cancer worldwide.[1]Breast cancer is the most common diagnosed malignancy is India, accounting for 27% of all cancers, with an age standardised rate of 25.8/100,000 women.[1]In the past, the incidence of breast cancer was higher in the developed countries, however recent data suggests an increase in the incidence in developing countries with the incidence now comparable to developed countries. Breast cancer has long been recognised as a heterogenous disease rather than a single entity and the increasing burden of this disease has led to a change treatment protocols and discovery of several predictive and prognostic biomarkers. Gene expression studies with DNA microarray has led to the identification of the following subtypes of breast cancer:-[2]

- Estrogen Receptor (ER) positive: Luminal A & Luminal B.
- ER negative (Basal-like &Human Epidermal growth factor Receptor -2 (HER-2) positive)
- Unclassified basal like phenotype.

Of these the basal-like and unclassified are of major concern as they account for approximately 10-20% of carcinoma breast cases and majority (approximately 70%) are ER, Progesterone Receptor (PR) and HER-2 neu negative, the so called Triple Negative Breast Cancer (TNBC), in addition to being

positive for cytokeratin (CK) 5/6 or Epidermal Growth Factor Receptor (EGFR).

This subset of patients is of special importance as they have certain characteristics, for e.g. an early age at presentation, a more aggressive tumour, poor clinical outcome, significant likelihood of BRCA-1 mutation, absence of hormonal and targeted therapy.

Even though the incidence of breast cancer is on the rise in our country, the disease is somewhat inadequately studied. It is reported that the prevalence of TNBC is higher in India as compared to the western population, however reliable data on TNBC in Indian setting is scarce and hence the need for this study.

MATERIAL & METHODS:

This study is a retrospective observational study conducted at Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi a tertiary care teaching institute in India. In this study, the data of breast cancer patients attending the surgical OPD from May 2011 to May 2016 have been collected for analysis. Data regarding demographic details, risk factors, clinical and pathological profile, treatment and response were recorded. Confirmation of diagnosis was by fine needle aspiration cytology (FNAC) and core needle biopsy. Patients with complete information on all the receptors (ER, PR, HER-2) only have been included in the study. Patients with distant metastases were excluded from the study. TNBCs were defined as tumours that did not stain for ER, PR and Her2 on Immunohistochemistry (IHC). Follow-up details of patients were updated during scheduled visits. Patients managed operatively underwent modified radical mastectomy and axillary lymph nodes were removed till level II using Auchincloss method of retraction of pectoralis minor to expose level II lymph nodes (figure 1 and 2). The patients were followed up for a period of 3 years from the onset of treatment. Patients with incomplete data or lost to follow-up patients were excluded from the study. Overall survival (OS) was defined as the time period from diagnosis to death due to any cause. Disease-free survival (DFS) was defined as the time period from diagnosis to the first loco-regional or distant recurrence. The data is calculated using SPSS 17.0 software and various significant values were noted.

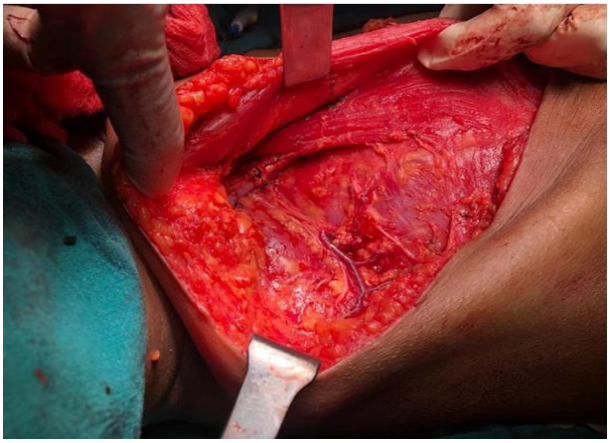

Figure 1: showing modified radical radical mastectomy post specimen removal with visible pectoralis major, dorsolumbar neurovascular bundle.

Figure 2: showing specimen of breast along with tail containing axillary lymph nodes.

RESULTS:

543 breast cancer patients were registered in our OPD from May 2011 to May 2016. Of these, 61 patients had metastatic disease at presentation and hence were excluded from our study. Out of the remaining non-metastatic 482 patients, 110 (22.8%) patients were characterised as TNBCs. This study compares these 110 TNBC patients with the remaining 372 non-TNBC patients.

In our study it was noted that the mean age at which the patients presented was relatively younger amongst the TNBC patients (44.01 years) as compared to the non-TNBC patients (49.78 years) (table 1)

Table 1:- showing average age difference between two categories.

Age (years)	TNBC	Non-TNBC	P value
Mean ± SD	44.02 ± 9.348	49.79 ± 7.894	<0.0001

P value is highly significant showing that age has a significant effect on prognosis of patient. Earlier the onset (as seen in TNBC), poorer is the prognosis.

The average tumour size at presentation was also slightly higher in the TNBC patients (5.82cm) as compared to non-TNBC patients (5.0cm) (table 2).

Table 2:- Comparison between sizes of the two categories.

Tumour size (cm)	TNBC	Non-TNBC	P value
Mean ± SD	5.82 ± 1.660	5.00 ± 1.209	<0.0001

P value is significant (<0.05).

Axillary lymph nodes were clinically palpable in 61.8% 0f TNBC patients as compared to 42.2% non-TNBC patients (table 3).

Table 3:- axillary lymph nodes status clinically palpable at presentation.

Axillary Lymph Nodes	TNBC	Non-TNBC	P value
Positive	68	157	<0.000
Negative	42	215	
Total	110	372	

P value is highly significant which shows that triple negative patients have more advanced stage than non – TNBC patients. Here also at presentation, 61.8% of TNBC and 42.2% of patients had palpable axillary lymph nodes and hence, advanced disease.
The duration of symptoms i.e. from the onset to the first hospital visit, however was similar in both the groups (5.8 months vs 5.5 months) [P=0.0917] as shown in table 4.

Table 4:- average duration of symptoms and the difference between the two categories.

Duration of lump (months)	TNBC	Non-TNBC	P value
Mean ± SD	5.86 ± 1.600	5.55 ± 1.716	0.0917

A positive family history of breast cancer was seen in 1.8% patients in the TNBC group and 4.3% patients in the non-TNBC group [P=0.192] as shown in table 5.

Table 5:- family history and frequency of each disease category.

Family History	TNBC	Non-TNBC	P value
Positive	2	17	0.192
Negative	108	355	
Total	110	372	

P value is non significant (0.192) and hence it can be said that there is no role of family history in determining which type of tumor will develop in a patient.

Patients with LABC at the time of presentation was significantly different in both the groups with 57.2% patients in TNBC group and 41.3% patients in the non-TNBC group [P=0.003]. The locally advanced disease is defined in case of carcinoma breast as a disease which has spread to local muscles, skin and lymph nodes but not to distal organs(stage II & stage III).

Table 6:- showing patients with both TNBC and non – TNBC which presented as locally advanced breast carcinoma (LABC).

LABC	TNBC	Non-TNBC	P value
Yes	63	154	0.003
No	47	218	
Total	110	372	

The p value is highly significant (0.03) which concludes that patient with TNBC have higher stage of getting advanced staged than Non – TNBC. Out of total TNBC patients 57.7% had LABC as compared to 41.39%.

Surgery at the outset was performed in 38.1% patients in the TNBC group and 57.7% patients in the non-TNBC group [P<0.003] as shown in table 7.

Table 7:- comparison between total TNBC and non – TNBC patients which went for surgery upfront.

Upfront Surgery	TNBC	Non-TNBC	P value
Yes	42	215	<0.003
No	68	157	
Total	110	372	

P value came out to be highly significant (0.003) which concludes that TNBC patients, due to advanced disease underwent chemoradiotherapy before undergoing surgery.

Neo-Adjuvant chemotherapy (NACT) was offered to 61.8% TNBC patients as compared to 42.2% non-TNBC patients [P=0.0002] as shown in table 8.

Table 8:- comparison between two groups on basis of prior receiving of chemotherapy.

NACT	TNBC	Non-TNBC	P value
Yes	68	157	0.0002
No	42	215	
Total	110	372	

Since p value is highly significant, it is concluded that the TNBC patients at presentation have advanced disease and hence, more patients undergo neoadjuvant chemotherapy in TNBC as compared to non – TNBC.

Median follow-up duration in both the groups was 3 years. The 3-year Overall Survival (OS) was 92.7% for TNBC patients and 91.39% in non-TNBC patients. The 3-year Disease Free Survival (DFS) was 66.36% in TNBC patients and 66.39% in non-TNBC patients respectively, which is statistically insignificant [P=0.873].

Table 9:- mortality & morbidity comparison between two groups after duration of 3 years in the follow up

Outcome at 3 years	TNBC	Non-TNBC	P value
Alive	73	247	0.873
Dead	5	24	
Recurrence	29	93	
Recurrence + Dead	3	8	
Total	110	372	

A total of 134 recurrences were recorded out of the 482 patients included in the study. In the TNBC group 29.09% (32) patients had recurrence as compared to 27.15% (101) in the non-TNBC group [P=0.73] and the findings are given in table 10.

Table 10:- post operative recurrences

Recurrence	TNBC	Non-TNBC	P value
Yes	32	102	0.73
No	78	270	
Total	110	372	

DISCUSSION:

Breast cancer has been a concern for healthcare providers worldwide and in India due to its rising burden and hence forms an interesting area of research. Of these the subset of TNBC patients pose a special challenge to the clinician in terms of its early presentation, aggressive nature and absence of targeted therapy.

In our study 110 out of the 482 patients with breast cancer were found to have TNBC (22.8%). Bauer et al[4] reported a prevalence of 12.5%. The National Comprehensive Cancer Network (NCCN) reported a prevalence of 17% from January 2000 to January 2006.[5] Ghosh et al [6]and Agarwal et al [7] reported a prevalence of 30% and 35.3% respectively.

The mean age at presentation was younger amongst the TNBC patients (44.01 years) as compared to the non-TNBC patients (49.78 years) [P<0.0001] which is similar to the results observed by Eralp et al [8]and Bauer et al.[4]

In our study, we observed that the average tumour size was larger in the TNBC patients (5.81cm) as compared to non-TNBC patients (5.0cm) [P<0.001]. The number of patients with LABC at the time of presentation was significantly different in both the groups with 57.2% patients having LABC at presentation in the TNBC group as compared to 41.3% patients in the non-TNBC group [P=0.003]. The higher incidence of LABC at presentation in the TNBC group is consistent with other studies, with Nabi et al. [9]reporting 45% stage 3 tumours in TNBC group as compared to 35.5% in non-TNBC group.

Axillary lymph nodes were clinically palpable in 61.8% 0f TNBC patients as compared to 42.2% non-TNBC patients [P<0.000]. Similar findings were observed in other studies namely Agarwal et al [7]and Dent et al.[10]

The 3-year OS and DFS were found to be similar in both TNBC and non-TNBC groups and had no statistical significance, which is in contrast to the findings of Lin et al. and Agarwal et al. which found that the OS and DFS of TNBC patients was inferior to those of non-TNBC patients. [5,7] This difference could arise because of the shorter follow up period in our study.

CONCLUSION:

To conclude our study suggests that patients with TNBC present at a younger age with larger and more locally advanced tumours with early involvement of the Axillary Lymph nodes. However, no significant difference was noted in the 3-year OS and DFS amongst the TNBC and non-TNBC groups.

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