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TRIPLE NEGATIVE BREAST CANCER- FIVE YEARS RETROSPECTIVE ANALYSIS FROM A TERTIARY CARE CANCER CENTRE IN SOUTH-INDIA

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ABSTRACT **Background:** Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer, which carries poor prognosis. In view of limited Indian data on TNBC, the present study was conducted to analyze the clinicopathology, and treatment outcome in TNBC patients. **Materials and Methods:** A retrospective review was conducted for TNBC patients treated between January 2014 and December 2018. Chi-square test, multivariate analysis, and Kaplan-Meier method were used for statistical analysis. P □ 0.05 was considered significant. **Results:** TNBC constituted 16.9% of total breast cancer, with median age of 48 years. Most patients were diagnosed at ≤50 years (64.8%), node positive (58.8%), and locally advanced stage (55.5%). Larger tumor size and higher tumor grade had greater propensity for nodal metastasis. De-novo metastasis was found in 8.2% patients, found commonly in older females, high grade, large tumor, and node positive patients. Recurrence occurred in 32.5% of TNBC patients (75% of which occurred at distant sites), with 1year, 2 years, 3 years recurrence rate of 9.3%, 25%, and 32% respectively. Overall survival was 77.3% at median follow up of 33 months. Factors associated with poor overall survival were advanced nodal stage, whereas with poor disease free survival were advanced tumor stage, nodal stage, and less than 10 lymph node dissections.**Conclusion:** TNBC has an aggressive clinical course compared to other biological subtypes of breast cancer. Recurrence occurs commonly at distant sites in the first three years. So, early identification, intensification of chemotherapy, and development of targeted therapy is required to improve its outcome.

KEYWORDS :

Introduction

Breast cancer is the commonest cancer and also the commonest cause of cancer related mortality among women, both in India as well as worldwide.[1] The age adjusted incidence rate of breast cancer is following an increasing trend across different parts of India.[2] Breast cancer is a heterogenous disease with variations in its tumor biology, treatment response and clinical outcomes.[3,4] Breast cancer is classified into different molecular subtypes, based on the overexpression of proteins, i.e the estrogen receptors (ER), the progesterone receptors (PR), the human epidermal growth factor receptors-2 neu (HER-2μ), as luminal A (ER positive, HER-2μ negative), luminal B (ER positive, HER-2μ positive), HER-2μ enriched (ER negative, HER-2μ positive), and triple negative or basal like (ER negative and HER-2μ negative).[5,6] The basal subtype can be differentiated from the triple negative breast cancer (TNBC) by gene expression microarray analysis.[7,8] Although TNBC is chemo sensitive, its recurrence and survival are poor compared to the other breast cancer subtypes, due to lack of approved targeted treatment. In view of paucity of information on TNBC from India, the present study was conducted to analyze the epidemiology, post treatment recurrence pattern, and the survival outcomes in TNBC patients treated in a tertiary cancer centre in South India.

Material and Methods

A retrospective analytical study was carried out in a tertiary cancer centre in south India. Information was retrieved from the record section for all confirmed cases of TNBC registered and treated between January 2014 and December 2018, after obtaining the permission from Institutional Ethical Committee, and the study was performed in accordance with the declaration of Helsinki. Information of each patient including demography, clinicopathology, treatments received, follow up information was noted in a pre designed proforma. The survival information was updated by phone calls using the contact numbers noted in the registry. All cases were diagnosed histopathologically, and molecular sub-typing was done using immunohistochemistry (IHC) study. Tumors with IHC negative (<1% expression) for ER, PR, and 1+ score for HER-2μ was considered TNBC. IHC result of 2+ score for HER-2μ was subsequently tested with fluorescence in-situ hybridization (FISH), and those negative for HER-2μ on FISH with ER and PR negative in IHC were considered as TNBC. The staging classification and prognostic stage grouping was done, based on the AJCC TNM staging (8th edition) into the early breast cancer (EBC), locally advanced breast cancer (LABC), and metastatic breast cancer (MBC). All cases of TNBC were considered for clinicopathological study, whereas ten out of total 182 patients, who had not undergone planned course of treatment, were excluded from consideration for the post treatment recurrence pattern and survival analysis. Disease free survival (DFS) was defined by the duration from start of primary treatment to the date of disease recurrence or death. The overall survival (OS) was defined as the time from the date of start of primary treatment to the date of death. The patients alive or lost to follow up were considered censored. The study was aimed to analyze the clinicopathological characteristics, recurrence pattern, factors affecting DFS and OS.

Statistical analysis

IBM SPSS statistics for windows, version 21.0 (Armonk, NY: IBM Corp) was used for statistical analysis. The association between different qualitative variables was analyzed using Chi-square test. Survival analysis was performed using Kaplan-Meier method, and was compared between different factors using Log-Rank (Mantle-Cox) testing. $P < 0.05$ was considered significant. The factors affecting OS and DFS were evaluated by multivariate analysis (with $P < 0.05$ and 95% confidence interval).

Results

TNBC constituted 16.9% (182 out of 1077) of the total breast cancer patients treated in the center between January 2014 and December 2018. The clinicopathological characteristic of TNBC in the present study is depicted in the table 1. The median age of diagnosis was 48 years with majority of patients (64.8%) were diagnosed at ≤50 years of age. Most of the TNBC patients (55.5%) were diagnosed at locally advanced stage, with high prevalence (58.8%) of node positive disease. The larger size and higher grade tumors were found to have greater prospensity for nodal metastasis (depicted in figure 1, and 2). Out of the total 182 confirmed patients of TNBC, 15 (8.2%) were diagnosed with de-novo metastasis. De-novo metastatic TNBC was found frequently among older age females (66.7% vs. 33.3% in >50 years and ≤ 50 years of age respectively, *P* 0.028), positive family history (33.3% vs. 7.8% in positive and negative family history respectively, *P* 0.03). high grade tumor (0% vs. 1.1% vs. 19.2% in low grade, intermediate grade, and high grade tumor respectively, *P* 0.000), advanced tumor stage (0% vs. 3.2% vs. 7.0% vs. 29.4% in T1, T2, T3, and T4 respectively, *P* 0.000), advanced nodal stage (0% vs15% in node negative and node positive disease respectively, *P* 0.001), whereas it had no predilection in relation to menopausal status, histopathological subtypes. The treatment characteristic in the present study is depicted in the table 2. Most of the cases underwent modified radical mastectomy (MRM), due to younger age patients, large tumor size and locally advanced stage at presentation. Approximately one

third (32.5%) of the TNBC cases had recurrence at median follow up of 33 months, of which three fourth had distant recurrence and one fourth had locoregional recurrences (depicted in the table 3). The 1year, 2 years, 3 years recurrence rates were 9.3%, 25%, and 32% respectively. Fifty-five of total fifty six recurrences (98.4%) occurred in the first three years of primary treatment. The multivariate analysis showed the factors associated with poor DFS were advanced tumor stage, advanced nodal stage, and less than 10 lymph nodes dissections. Whereas, only advanced nodal stage was associated with poor OS (depicted in table 4). Comparison of OS and DFS between the stage groups, tumor stages, nodal stages, and the number of lymph nodes dissected are depicted in figure3 to 10.

Table 1: Clinicopathological characteristics of TNBC

Clinicopathological parameters	Number (%)
Age (in years)	
Median	48
Range	24-85
≤50 years	118 (64.8)
>50 years	64 (35.2)
Menopausal status	
Premenopausal	79 (43.4)
Postmenopausal	103 (56.6)
Family history	
Positive	6 (3.3)
Negative	176 (96.7)
Side	
Right	84 (46.2)
Left	96 (52.7)
Bilateral	2 (1.1)
Histopathology	
Invasive ductal	173 (95.0)
Metaplastic	5 (2.7)
Medullary	4 (2.2)
Grade	
I	9 (4.9)
II	94 (51.6)
III	79 (43.4)
LVI	
Present	17 (9.4)
Absent	154 (84.6)
Unknown	11 (6.0)
Tumor stage	
T1	16 (8.8)
T2	94 (51.6)
T3	43 (23.6)
T4	29 (15.9)
Nodal stage	
N0	75 (41.2)
N1	56 (30.8)
N2	33 (18.1)
N3	18 (9.9)
De-novo metastasis	
Metastatic	15 (8.2)
Non metastatic	167 (91.8)
Stage Group	
Early stage	66 (36.3)
Locally advanced	101 (55.5)
Metastatic	15 (8.2)

Table 2: Treatment characteristics in the present study

Treatment parameters	Number (%)
Surgery	
MRM	154 (89.5)
BCS	3 (1.7)
No surgery	15 (8.7)
Nodal dissection	
≥10 LND	114 (66.3)
<10 LND	43 (25.0)
No LND	15 (8.7)
Chemotherapy	
NACT	29 (16.9)
ACT	152 (88.4)
Palliative	15 (8.7)
Radiotherapy	
Adjuvant	95 (55.2)
Palliative	23 (13.3)

Table 3: Pattern of recurrences in TNBC

Relapse parameters	Number (%)
Pattern of first relapse	
Locoregional	14 (8.1)
Distant	42 (24.4)
Total relapse	56 (32.4)
Site of distant relapse	
Lung	33 (19.2)
Bone	18 (10.5)
Distant node	17 (9.9)
Brain	17 (9.9)
Liver	12 (7.0)
C/L Breast	5 (2.9)

Table 4: Factors affecting overall survival and disease free survival

Factors	Number (%)	OS		DFS	
		%	*P*	%	*P*
Age					
≤50 years	103 (59.9)	81.6	0.398	66	0.725
>50 years	69 (40.1)	71		52.2	
Menopausal status					
Pre-menopausal	74 (43)	79.7	0.727	64.9	0.647
Post-menopausal	98 (57)	75.5		57.1	
Family history					
Positive	6 (3.5)	66.7	0.698	50	0.722
Negative	166 (96.5)	77.7		60.8	
Histopathology					
IDC	163 (94.8)	76.7	0.450	58.9	0.114
Metaplastic	5 (2.9)	80		80	
Medullary	4 (2.3)	100		100	
Grade					
I	9 (5.2)	66.7	0.592	66.7	0.555
II	90 (52.3)	82.2		70	
III	73 (42.4)	72.6		47.9	
Tumor stage					
T1	14 (8.1)	78.6	0.069	78.6	0.034
T2	91 (52.9)	87.9		70.3	
T3	39 (22.7)	66.7		56.4	
T4	28 (16.3)	57.1		25	
Nodal stage					
N0	72 (41.9)	94.4	0.000	83.3	0.000
N1	51 (29.7)	76.5		54.9	
N2	32 (18.6)	62.5		37.5	
N3	17 (9.9)	35.3		23.5	
Stage group					
EBC	65 (37.8)	93.8	0.002	81.5	0.011
LABC	92 (53.5)	72.8		55.4	
MBC	15 (8.7)	33.3		0	
Margin status					
Positive/Close	7 (4.5)	57.1	0.074	57.1	0.587
Negative	150 (95.5)	82.6		64.5	
LVI					
Present	12 (7)	75	0.837	41.7	0.07
Absent	150 (87.2)	80		66	
Unknown	10 (5.8)	30		0	
LND					
≥10	115 (66.9)	84.3	0.072	81.7	0.000
<10	57 (33.1)	63.2		33.3	
Surgery					
MRM	154 (98.1)	82.1	0.513	66.2	0.317
BCS	3 (1.9)	100		66.7	
PMRT					
Yes	96 (61.1)	78.9	0.121	63.2	0.224
No	61 (38.9)	85.2		68.9	
Chemotherapy					
Anthra	137 (81.5)	80.3	0.815	62.8	0.634
Anthra + Tax	23 (13.7)	73.9		60.9	
Plat + Tax	8 (4.8)	50		50	

Abbreviations: OS; Overall survival, DFS; Disease free survival, IDC; Invasive ductal carcinoma, EBC; Early breast cancer, LABC; Locally advanced breast cancer, MBC; Metastatic breast cancer, LVI;

Lymphovascular invasion, LND; Lymph node dissection, MRM: Modified radical mastectomy, BCS; Breast conservation surgery, PMRT; Post mastectomy radiotherapy, Anthra; Anthracycline, Tax; Taxane, Plat; Platinum compound

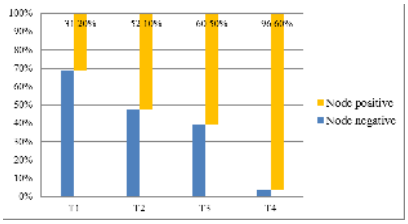

Figure 1: Association between tumor size and nodal metastasis

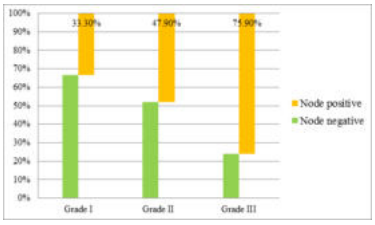

Figure 2: Association between tumor grade and nodal metastasis

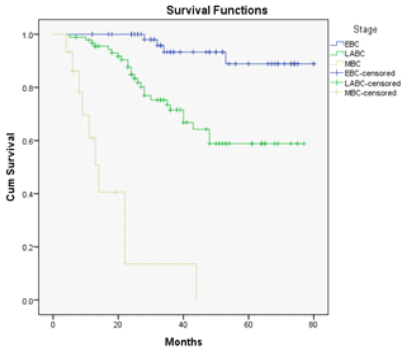

Figure 3: Comparison of overall survival by Kaplan-Meier method (Log rank testing) between different stages (P 0.000)

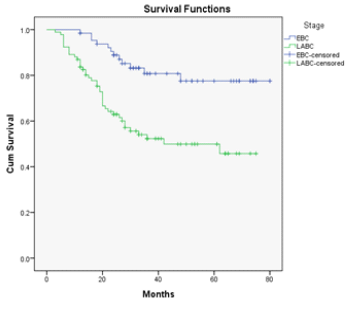

Figure 4: Comparison of disease free survival by Kaplan-Meier method (Log rank testing) between different stages (P 0.000)

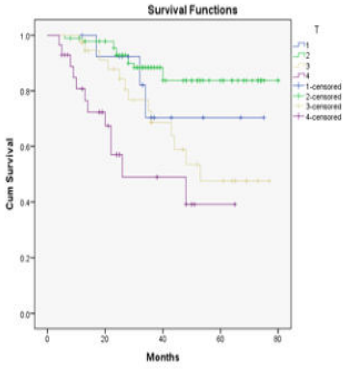

Figure 5: Comparison of overall survival by Kaplan-Meier method (Log rank testing) between different tumors sizes (P 0.000)

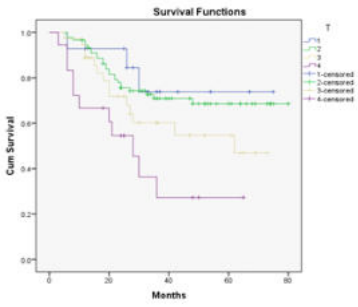

Figure 6: Comparison of disease free survival by Kaplan-Meier method (Log rank testing) between different tumors sizes (P 0.005)

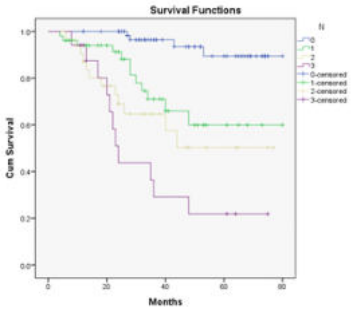

Figure 7: Comparison of overall survival by Kaplan-Meier method (Log rank testing) between different nodal stages (P 0.000)

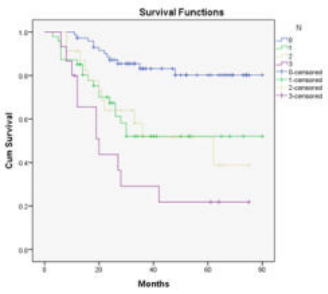

Figure 8: Comparison of disease free survival by Kaplan-Meier method (Log rank testing) between different nodal stages (P 0.000)

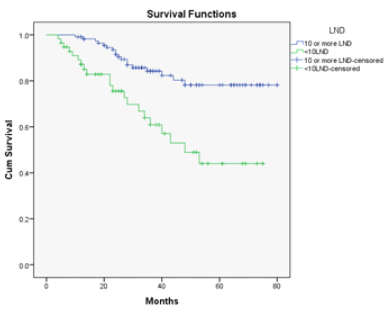

Figure 9: Comparison of overall survival by Kaplan-Meier method (Log rank testing) between numbers of lymph node dissected (P 0.000)

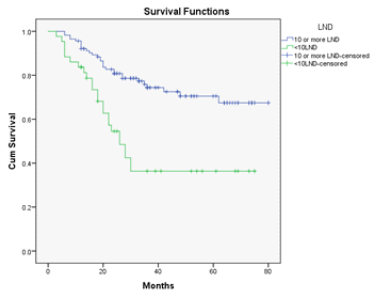

Figure 10: Comparison of disease free survival by Kaplan-Meier method (Log rank testing) between different lymph node dissections (P 0.000)

Discussion

TNBC exhibit substantial heterogeneity in its occurrence based on the ethnicity. Higher prevalence of TNBC is seen among Hispanics, Africans, African-Americans (25 to 60%), as compared to the Caucasians (12 to 16%).[9,10] Similarly in India, the prevalence of TNBC shows a high degree of variability (ranging from 11.8% to 31.9%).[11-14] Whereas, its prevalence in the present study was 16.9%, which was similar to another study report of 19.3% prevalence of TNBC from south India by Reddy et al.,[15] whereas another south Indian study by Kumar et al.,[16] have reported higher prevalence (37%) of TNBC with a decreasing trend of its prevalence over time, probably due to under reporting of HER 2 positive tumor by FISH, in case of equivocal finding (2+ score) of HER-2neu by IHC.[16]The median age at diagnosis of TNBC cases was 48 years in the present study, which similar to the findings of Suresh et al.,[17] and Doval et al.,[18] where the median age of TNBC cases was 49 years in both of the studies. Majority (56.6%) patients in the present study were postmenopausal, which was exactly the same (56.6%) as reported by Reddy et al.[15] Positive family history of breast cancer was found in 3.3% of TNBC in the present study, which was found in 5.4% of patients of TNBC in a study done by Doval et al. [18] Women of age ≤50 years constituted majority (64.8%) of the TNBC cases. Most cases (91.2%) in the study had tumor size of >2cm. Node positive tumor constituted 58.8% of the total TNBC cases, which was supporting the reported node positivity rate of 58% in TNBC by Reddy et al.[15] In the present study most of the TNBC cases (55.5%) were diagnosed in locally advanced stage, and 43.4% cases had high grade tumor. Above all findings of the present study support the meta analysis findings of Kulkarni et al.,[14] and Sandhu et al.,[19] which have reported the TNBC cases to be commonly diagnosed in younger women, with aggressive clinical behavior, and advanced stage at diagnosis. The present study found larger tumor size and higher grade tumor to have higher rate of nodal metastasis as well as higher rate of distant metastasis, which was in concordance with the study finding of Reddy et al.,[15] and Wang et al.,[20] whereas it is contrary to the study findings of Dent et al.,[21] and Suresh et al.,[17] who have found even smaller tumor can have a high chance of lymph node positivity. Most of the cases (89.5%) in the present study underwent MRM, probably because of locally advanced stage at presentation. Similarly the greater majority of TNBC (79.2%) cases underwent MRM in another Indian study by Doval et al.[18] De novo metastasis was found in 8.2% of TNBC cases in the present study, which was seen in 5% of TNBC cases in the previous study by Reddy et al.[15] The disease recurrence was seen in 32.4% of TNBC cases at a median follow up of 33months. The recurrence most commonly occurred at distant sites (in 75% of total recurrence), and the recurrence was high in the first 3 years after primary treatment, following which there was almost a plateau, which was in concordance with previous study finding of Reddy et al.,[15] where they also have found most of the recurrence to occur at distant sites and within three years of primary treatment. In the present study, the multivariate analysis revealed the factors having negative impact on DFS were advanced tumor stage, advanced nodal status, less than ten axillary lymph node dissections, whereas the factor associated with poor OS was advanced nodal status. Previous studies by Ovcaricek et al.,[22] and Reddy et al.,[15] have reported the nodal status as an important prognostic factor having significant impact on DFS and OS.

Conclusion

TNBC constituted 16.9% of total breast cancer. Most patients are diagnosed at younger (≤50 years) age, node positive and locally advanced stage. Larger tumor size and high grade tumors are associated with increased nodal and distant metastasis. Recurrences in TNBC occur mostly at distant sites and in the first three years of treatment. Advanced tumor stage, nodal positivity, and lesser than 10 lymph nodes dissection have higher risk of recurrence. Advanced nodal stage is an independent risk factor for poor overall survival in TNBC patients. TNBC has aggressive clinical course, which needs early detection, multimodal treatment including intensification of chemotherapy, development of targeted therapy to improve the outcome.

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