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Original Article

Triple-Negative Breast Cancer: Pattern of Recurrence and Survival Outcomes

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Abstract

Introduction: Triple-negative breast cancer (TNBC) is a subtype of breast cancer which is defined as the absence of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 overexpression by immunohistochemistry. As the survival data on TNBC in the Indian population are scant, this study was done to analyze the clinicopathological features and clinical outcomes of TNBC patients. **Materials and Methods:** Data from medical records of patients with breast cancer between 2009 and 2014 were retrieved, and patients with TNBC were identified and analyzed for demographic and clinicopathological features. Survival analyses were performed using the Kaplan–Meier method for disease-free survival (DFS) and overall survival (OS). **Results:** A total of 1024 breast cancer patients were registered at our institute during the study period, of which 198 were TNBCs accounting for 19.3% of all breast cancers. Median age at the diagnosis was 50 years (range, 22–78 years). Lymph nodal positivity in TNBC was associated with larger tumor size (P = 0.003) and higher tumor grade (P = 0.01). At a median follow-up of 48 months (range, 12–88), 36 (19.1%) patients had recurrence of the disease, whereas 28 (14%) patients were lost to follow-up. Lung (52.7%) was the most common site of recurrence followed by bone (25%) and brain (11.1%). Three-year DFS and OS were 63.2% and 65.6%, respectively. On univariate analysis, nodal status, size of tumor, and lymphovascular invasion were found to have a significant impact on OS and DFS. On multivariate analysis, only nodal status was significant for DFS and OS (P < 0.001 and P = 0.001, respectively). **Conclusions:** TNBCs have a rapid clinical course, and early recurrences are common inspite of timely medical intervention which reflects the aggressive tumor biology. This warrants further studies on intensification of chemotherapy and identification and development of targeted therapy aimed at decreasing recurrences and improving survival in this patient population.

Keywords: *Recurrences, survival, triple-negative breast cancer*

Introduction

Breast cancer is the most frequent cancer among women worldwide, with an estimated 1.67 million new cancer cases diagnosed in 2012 accounting for 25% of all cancers.[1] The age-adjusted incidence rate in India is as high as 25.8/100,000 women and mortality is 12.7 per 100,000 women.[2] Triple-negative breast cancer (TNBC) is a subtype of breast cancer which is defined as the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) overexpression by immunohistochemistry (IHC).[3] Although the terms TNBC and basal-like breast cancers are used interchangeably, they are not completely synonymous. The basal-like subtype is defined through the gene expression microarray analysis.[4,5] TNBCs have unique pathological, molecular, and clinical behavior.[3,6] TNBCs are considered to have a poor prognosis compared to other subtypes of breast cancer. Although TNBC is chemosensitive, its treatment continues to be a challenge, as recurrences are common, especially within the first 3–5 years of the diagnosis.[6-8] There are no approved targeted treatments available other than chemotherapy. As the survival data on TNBC in the Indian population are scant, this study was done to analyze the clinicopathological features and clinical outcomes of TNBC patients.

Materials and Methods

Data from medical records of patients with breast cancer between 2009 and 2014 were retrieved, and the patients with TNBC were identified. The study was approved by the

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Institutional Ethics Committee. Tumors were categorized based on ER, PR, and HER2 status. Tumors that have ≤1% expression of ER and PR as determined by IHC and that are HER2 negative, either 0–1+ by IHC or 2+ and fluorescence *in situ* hybridization negative, were identified as triple negative. IHC was done on formalin-fixed paraffin-embedded sections by polymer horseradish peroxidase technique on fully automated immunostainer.

The various IHC markers included are listed in Table 1.

TNBCs were classified histologically according to the WHO classification.[9] Histologic grade was determined based on the Nottingham histologic score which considers tubule formation, nuclear pleomorphism, and mitotic activity.[10] Staging of patients with TNBC was done according to the AJCC TNM staging seventh edition.[11] Patients with Stage I, IIA, or a subset of Stage IIB disease (T2N1) were categorized as having early breast cancer (EBC) and a subset of patients with Stage IIB disease (T3N0) and patients with Stage IIIA to IIIC disease were categorized as having locally advanced breast cancer (LABC).

All patients with the diagnosis of TNBC were analyzed for demographic and clinicopathological features. Chemotherapy regimens used were 5-fluorouracil 500 mg/m^2, adriamycin 50 mg/m^2, and cyclophosphamide 500 mg/m^2 (FAC) every 3 weeks for six cycles or doxorubicin 60 mg/m^2 on day 1 along with cyclophosphamide 600 mg/m^2 (AC) every 3 weeks for 4 cycles followed by paclitaxel (T) 175 mg/m^2 every 3 weeks for four cycles or 80 mg/m^2 weekly for 12 cycles or docetaxel 100 mg/m^2 every 3 weeks for four cycles. Patients were treated with capecitabine/gemcitabine at progression. Disease-free survival (DFS) was defined from the start of primary therapy to the date of disease recurrence, death, or last follow-up. Overall survival (OS) was defined as the time from the date of start of primary therapy to date of death or the last follow-up.

Statistical analysis

Clinical characteristics between the lymph node groups were compared using the Chi-square test. Univariate and multivariate analyses were done to assess the effect of age, menopausal status, nodal status, size, grade, and lymphovascular invasion on DFS and OS. GraphPad Prism software for Windows version 6 was used to plot the Kaplan–Meier curves for progression-free survival and OS (GraphPad Software, La Jolla, California, USA; http://www.graphpad.com). Univariate analysis for OS was done by plotting Kaplan–Meier curves, and the log-rank test was used to calculate *P* values. Logistic regression analysis for OS was carried out using MedCalc demo version statistical software 16.4.3 using the same independent variables after coding (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016). $P < 0.05$ was considered statistically significant.

Results

A total of 1024 breast cancer patients were registered at our institute between 2009 and 2014, of which 198 were TNBCs. This accounted for 19.3% of all breast cancers during this period. Median age at the diagnosis was 50 years (range, 22–78 years). Ninety-six patients (48.4%) had lump in the breast of <3 months. The classical risk factors for breast cancer, namely age >35 years at the first childbirth, nulliparity, and family history of breast cancer, were present in only 4%, 8%, and 3% of patients, respectively.

The tumor was right sided in 51%, left sided in 47%, and 2% had bilateral cancer at presentation. Clinically, T2 was the most common (58%) followed by T3 (18.2%), T4 (13.2%), and T1 (10.6%). Nodal involvement was seen in 115 patients (58%). N1, N2, and N3 disease was seen in 53 (26.7%), 32 (16.1%), and 30 (15.1%) patients, respectively. The patient and tumor characteristics are presented in Table 2.

EBC was seen in 107 (54%), 81 patients (41%) had LABC, and only 10 patients (5%) had metastatic disease.

Table 1: Immunohistochemistry markers

IHC marker	Clone	Supplier
ER	EP1	Biogenex
PR	EP2	Biogenex
HER2	EP1045Y	Biogenex

IHC – Immunohistochemistry; ER – Estrogen receptor; PR – Progesterone receptor; HER2 – Human epidermal growth factor receptor 2

Table 2: Patient and tumor characteristics

Characteristic	*n* (%)
Age (years)	
Median (range)	50 (22-78)
<60	146 (73.7)
≥60	52 (26.3)
Menopausal status	
Pre/perimenopausal	86 (43.4)
Postmenopausal	112 (56.6)
Tumor size (cm)	
≤2	22 (11.1)
>2	176 (88.8)
LVI	
No	175 (88.4)
Yes	23 (11.6)
Grade	
I	5 (2.5)
II	51 (25.8)
III	142 (71.7)
Nodal status	
Positive	115 (58)
Negative	83 (42)

LVI – Lymphovascular invasion

A modified radical mastectomy was done in 76.7%, and 18.2% underwent breast conservation surgery. Adjuvant chemotherapy was given to 157 patients (79.2%), while 31 (15.6%) patients received both neoadjuvant and adjuvant chemotherapy (NACT). Of the 31 patients who received NACT, pathological complete response (pCR) was seen in 8 (25.8%) patients. Postmastectomy radiation therapy, as part of adjuvant treatment, was given to 99 (52.6%) patients.

Lymphovascular invasion and margin positivity were present in 11.2% (21 patients) and 3.8% (7 patients) of the tumors, respectively. Grade 1, Grade 2, and Grade 3 were seen in 5 (2.5%), 51 (25.8%), and 142 (71.7%) of the tumors, respectively. At least one axillary lymph node was positive in 58% of patients. Correlation between lymph nodal status, tumor size, and grade is shown in Table 3. Lymph nodal positivity in TNBC was associated with larger tumor size ($P = 0.003$) and higher tumor grade ($P = 0.01$) when compared to their node-negative counterparts.

At a median follow-up of 48 months (range, 12–88), 36 (19.1%) patients had a recurrence of the disease, while 28 (14%) patients were lost to follow-up. Lung (52.7%) was the most common site of recurrence followed by bone (25%) and brain (11.1%). Recurrence rates were high in the first 2–3 years after the diagnosis after which there is almost a plateau. Three-year DFS and OS were 63.2% and 65.6%, respectively. The Kaplan–Meier estimate for DFS and OS is shown in Figures 1 and 2, respectively.

The 3-year DFS for patients with EBC and LABC was 77.5% and 44.4%, respectively ($P < 0.001$) [Figure 3]. The 3-year OS for patients with EBC and LABC was 84.1% and 48.1%, respectively ($P < 0.001$) [Figure 4]. Median OS in patients with metastatic disease was 19.5 months.

Univariate and multivariate survival analyses

In the univariate analysis, nodal status, size of the tumor, and lymphovascular invasion were found to have a significant impact on OS and DFS, whereas menopausal status and grade of the tumor did not impact survival. Univariate analysis of treatment variables is shown in Table 4. On multivariate analysis, only nodal status was significant for DFS and OS ($P < 0.001$ and $P = 0.001$ for DFS and OS, respectively).

Discussion

TNBC is a heterogeneous disease. Although it is generally considered to be more chemosensitive than other subtypes of breast cancer, it has more aggressive behavior with early recurrence. Conventional chemotherapy has been the mainstay of treatment for this subtype of breast cancer for decades.

In the present study, TNBCs accounted for 19.3% of all the breast cancers. It is similar to the incidence reported by other studies from the West and other authors from India ranging from 12.5% to 26%.[12-14] The median age of 50 years in the present study was almost similar to that described in the Western literature (median age of 53 years).[15] In two studies from India by Suresh *et al*.[12] and Das *et al*.,[13] the median age of the patients was 49 and 44 years, respectively. The usual risk factors for breast cancer, which were found only in a minority of patients in the present study, are similar to that reported by Suresh *et al*.[12]

Table 3: Correlation between lymph nodal status, tumor size, and grade

Characteristics	N0 (*n*=83), *n* (%)	N1 (*n*=53), *n* (%)	N2 (*n*=32), *n* (%)	N3 (*n*=30), *n* (%)	*P*
Tumor size					
T1	13 (15.7)	4 (7.5)	2 (6.2)	2 (6.7)	0.003
T2	56 (67.5)	37 (69.8)	12 (37.5)	10 (33.3)	
T3	10 (12.0)	8 (15.1)	9 (30.0)	8 (26.7)	
T4	4 (4.8)	4 (7.6)	9 (30.0)	10 (33.3)	
Grade					
I/II	29 (35)	10 (18.8)	13 (40.6)	4 (13.3)	0.01
III	54 (65)	43 (81.2)	19 (59.4)	26 (86.7)	

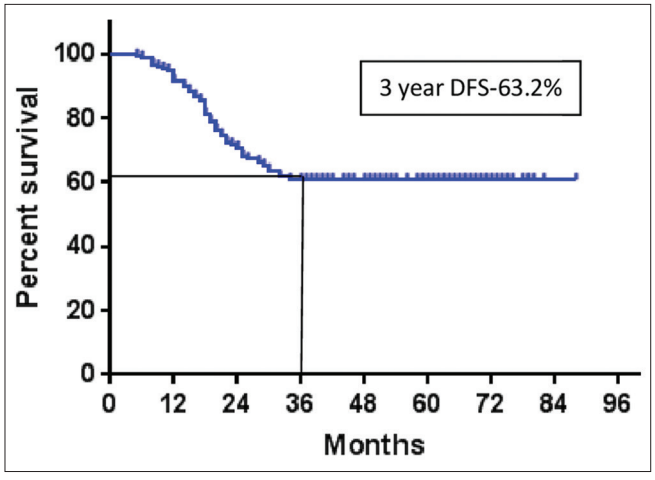

Figure 1: Kaplan–Meier estimates of disease-free survival for EBC and LABC. EBC – Early breast cancer; LABC – Locally advanced breast cancer

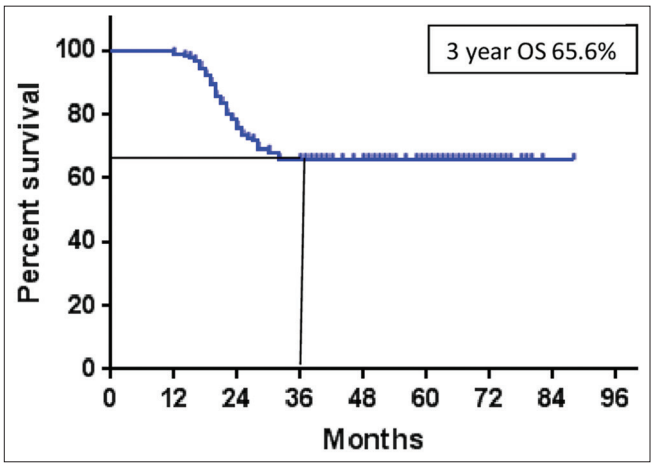

Figure 2: Kaplan–Meier estimates of overall survival for all patients

Table 4: Univariate analysis

Variable	*n* (%)	DFS	OS	HR (95%CI)	
				P for DFS	*P* for OS
Age (years)					
<60	146 (73.7)	58.9	64.4	0.3930	0.889
≥60	52 (26.3)	65.3	67.3	1.178 (0.711-1.953)	1.072 (0.6258-1.836)
Menopausal status					
Pre/perimenopausal	86 (43.4)	58.1	61.6	0.4868	0.410
Postmenopausal	112 (56.6)	62.5	67.8	1.145 (0.731-1.793)	1.216 (0.755-1.959)
Nodal status					
Positive	115 (58)	44.3	53	<0.0001	<0.0001
Negative	83 (42)	82.9	83.1	3.946 (2.462-6.326)	3.521 (2.188-5.667)
Size (cm)					
>2	176 (88.8)	57.9	83	0.0499	0.0335
≤2	22 (11.1)	81.8	86.3	2.618 (1.323-5.181)	3.229 (1.591-6.55)
Grade					
III	142 (71.7)	56.3	61.9	0.0430	0.0819
I + II	56 (28.3)	70.9	74.5	1.741 (1.077-2.813)	1.665 (0.9919-2.795)
LVI					
No	175 (88.4)	22.7	40.9	0.0005	0.0024
Yes	23 (11.6)	65.7	69.1	2.868 (1.126-7.302)	3.732 (1.596-8.727)

DFS – Disease-free survival; OS – Overall survival; HR – Hazard ratio; CI – Confidence interval; LVI – Lymphovascular invasion

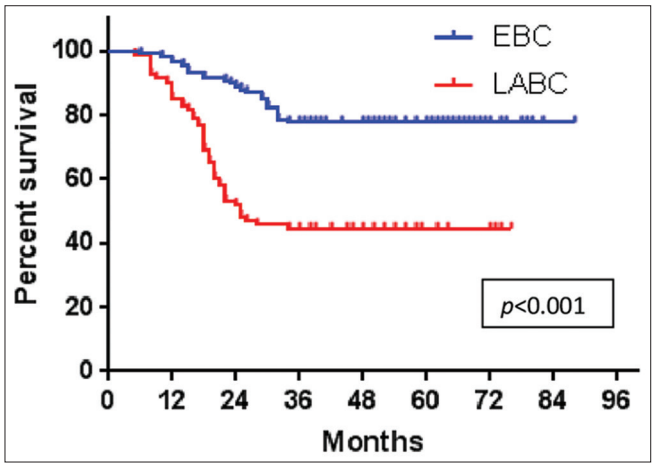

Figure 3: Kaplan–Meier estimates of comparison of disease-free survival for EBC and LABC. EBC – Early breast cancer; LABC – Locally advanced breast cancer

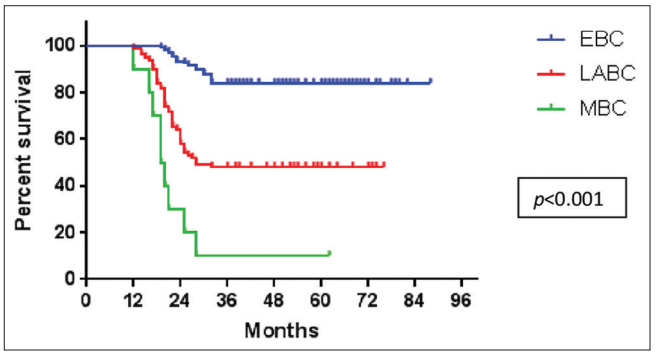

Figure 4: Kaplan–Meier estimates of comparison of overall survival for EBC, LABC, and MBC. EBC – Early breast cancer; LABC – Locally advanced breast cancer; MBC – Metastatic breast cancer

Majority of the patients in this study had a tumor size of >2 cm at presentation (88.8%), and more than half of the patients had lymph nodal involvement (58%). Other studies have also reported that TNBCs are relatively large tumors with a high incidence of involvement of the lymph nodes.[10,14] Majority of the patients in this study underwent modified radical mastectomy (MRM) (76.7%). Various reasons for this are the extent of disease at presentation, concern about recurrence, patient and/or surgeon's choice.

The fact that majority of patients in this study presented with a history of breast lump of <3 months, duration shows that TNBCs have a rapid growth pattern, and they are more likely to be diagnosed clinically than mammographically.

The finding that lymph nodal positivity in our patients was associated with larger tumor size when compared to their node-negative counterparts is contrary to the observations made in the studies by Dent *et al*.[15] and Suresh *et al*.[12] who have reported that, in TNBCs, even small tumors can have a high chance of lymph node positivity. However, in a study from China, Wang *et al*.[16] reported that lymph node-positive patients had a larger tumor size than lymph node-negative patients, similar to the present study.

pCR rate of 25.8% observed in this study is similar to that reported in studies by Suresh *et al*.[12] (25%) and Liedtke *et al*.[17] (22%). The results from several studies show that patients with TNBC have an increased likelihood of recurrences and death compared to other types of breast cancer. In this study, 36 patients had recurrence of disease, mostly distant recurrences (lung, brain, and bone), suggesting the hematogeneous spread of these cancers. We

have also found that the pattern of recurrence is different. Recurrence rates were high in the first 2–3 years after the diagnosis, after which there is almost a plateau in the present study. In the study by Dent *et al*.,[15] there was an increased likelihood of distant recurrence and death within 5 years of the diagnosis in the TNBC subgroup, whereas the recurrences were mostly constant during follow-up in other subgroups of breast cancer. This suggests that, though TNBCs are aggressive malignancies with early recurrences, women who do not develop recurrence within the first 3–5 years after the diagnosis are less likely to die of their disease.

The 3-year DFS in this study was 63.2%, and the 3-year OS was 65.6%. In their study, from the USA, Dawood *et al*.[18] reported 3-year relapse-free survival as 63% and OS as 71%. In their study on TNBC patients, Ovcaricek *et al*.[19] from Europe observed a 5-year recurrence-free survival to be 68.2% and OS as 74.5%. The 3-year OS in the study by Suresh *et al*.[12] from India was 80%. The differences in survivals among various studies might be probably due to differences in the stage of disease at presentation, omission/inclusion of patients lost to follow-up in the survival analysis, and the use of different chemotherapy regimens.

In the univariate analysis for prognostic factors such as age, menopausal status, grade, size of the tumor, nodal status, and LVI, nodal status, size of the tumor, and LVI had a significant impact on DFS and OS. On multivariate analysis, only nodal status retained its independent prognostic value for DFS and OS. These results are similar to that of Ovcaricek *et al*.[19] who found that age and nodal status were independent prognostic factors for DFS and nodal status was a prognostic factor for OS. However, in the study done by Suresh *et al*.,[12] no statistically significant differences were observed for breast cancer-specific survival or OS for prognostic factors such as age, tumor size, and nodal status. This might be probably due to a small number of events and short follow-up of 30 months in their study.

Survival analysis in the present study revealed better survival for patients with EBC when compared with LABC and metastatic breast cancer. This is in accordance with the previous studies on TNBC from India by Suresh *et al*.[12] and Chandra *et al*.[20] who have also reported that patients with EBC have better survival than patients with LABC.

Conclusions

TNBCs are a distinct subtype of breast cancers with unique pathological and clinical behavior. They have a rapid clinical course and early recurrences inspite of timely medical intervention, which reflects the aggressive tumor biology. This warrants further studies on the intensification of chemotherapy and identification and development of targeted therapy aimed at decreasing recurrences and improving survival in this patient population.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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