Epidemiological and clinicopathological profile of triple negative breast cancer at a tertiary cancer centre in Rajasthan: A three-year experience

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Abstract

Introduction: Triple negative breast cancer (TNBC) has attracted the attention of oncologists and pathologists because of its aggressive nature and lack of targeted therapy. Ample research has been reported in western literature on TNBC, all concluding poor prognostic features in comparison to other molecular subtypes. However extensive research from India is lacking.

Objectives: To study epidemiological and clinicopathological profile of TNBC.

Materials and Methods: This is a retrospective study of all cases of breast carcinoma enrolled in the department of surgical oncology and oncopathology at MGH,Jaipur between 2020 and 2023. Out of all the cases, 107 cases of TNBCs were included in the study and analysed.

Results: The median age at presentation was 54 years. Most of the patients were post-menopausal with no significant risk factors or family history. 5th and 6th decade were the commonest age at presentation. Most of the patients were multipara, only 10 patients (9.5%) were nullipara. Family history was positive in 8.4% cases. Infiltrating ductal carcinoma- NOS type was the most common histology (69.5%). Most of the tumors were of poorly differentiated variety (55.7%). 40.2% cases were in stage IIA. The patients showed good response to neoadjuvant chemotherapy with many of them showing complete pathological response (41%). Relapses were more common in non-responder group. Recurrences were mainly visceral relapses. Locally advanced stage and lymph node positivity showed poorer RFS and OS.

Conclusion: TNBC are very aggressive cancers that have marked epidemiological, pathological and prognostic characteristics. Around 18% of breast carcinoma reported at our institute were TNBCs. They are highly chemoresponsive and yet they have poorer outcomes. Still longer follow-up is necessary for more definite data on TNBCs.

Keywords: Triple negative breast cancer, epidemiology, clinicopathological profile, India, prognosis

Introduction

Invasive breast cancer is the most common malignancy in women worldwide. Greatest increase has been reported in Asian countries.[1] With rising incidence and awareness, breast cancer is the most common cancer in urban Indian women. It is the second leading cause of cancer India's rural areas, trailing only cervical cancer.[2] Breast cancer is a heterogeneous disease and not a single entity. Among different breast cancer types, great differences were seen in tumor behavior, clinical manifestation, treatment response and prognosis. Population based studies have proved that reproductive factors, like early menarche, late menopause, nulliparity, absence of breast feeding all these factors increases chances of carcinoma breast. Many lifestyle related factors also affect incidence of breast cancer. Molecular profiling of breast cancer is one of the main aspects in cancer management. The profile includes levels of expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2(HER2neu) in tumor cells. Four main subtypes of carcinoma breast have been identified according to molecular typing. Two of them involves ER positive tumors (luminal A and luminal B) and the other two involves ER negative tumors (basal like and Her-2 neu positive). The definition of basal like cancer breast is changing time to time. There is no universally agreed upon criteria for basal like breast cancer. The definition given by Nielsen *et al*. is accepted universally – basal like cancers are negative for Estrogen and progesterone receptor and Her2neu.[3] Triple negative breast cancer (TNBC) have been seen to be more common in young African-American women and are more aggressive tumors with shorter relapse free survival (RFS), a tendency to visceral rather than bony metastasis and high likelihood to breast cancer (BRCA) susceptibility type-1 mutation.[4] To date, studies on TNBC have been limited to western literature. In the usual setting, the basal-like tumor category is almost entirely comprised by triple negative breast cancers (TNBCs) (tumors those don't show ER, PR and HER2 expression), which can be easily diagnosed by immunohistochemistry (IHC). TNBCs involves 12-24% of all breast cancers and have grabbed eyes of many oncologists and pathologist. It has aggressive behavior and lack the benefit of specific systemic targeted therapy. Ample research has been reported in western literature on TNBC, all concluding poor prognostic features in comparison to other molecular subtypes. However extensive research from India is lacking. This present study is aimed to evaluate demographic profile, risk factors, clinical presentation, pathological features of triple negative breast cancer patients diagnosed and managed at our tertiary care cancer hospital.

Materials and Methodology

Study Duration: From 2020 to 2023

Study Site: Department of Surgical Oncology and department of Oncopathology, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India

Study Population: All the patient coming to MGH, Jaipur who underwent breast cancer surgery.

Study Design: Retrospective study, Sample Size – 107 cases of TNBCs were included in the study and analyzed.

Study Assessment: A detailed retrospective assessment was carried out according to planned Performa. Diagnosis of breast cancer was primarily based on clinical presentation, imaging (mammogram, ultrasonography or Magnetic resonance imaging of the breast when indicated) and cytopathological studies. Staging was done with X-ray chest, Ultrasound abdomen for localized disease with the addition of bone scan and computed tomography (CT) or positron emission tomography (PET) scan for locally advanced disease and metastatic disease. Patients were staged in accordance with American Joint Committee on Cancer (AJCC)-8th (TNM) staging system. These tests were carried out with standard Food and Drug Administration (FDA) approved kits by IHC.
Baseline epidemiological and tumor characteristics of triple negative cancers were analyzed for all 50 patients. Outcomes were analyzed for subgroups of early breast cancer (EBC) & locally advanced breast cancer (LABC). EBC was defined as a T-stage ≤ T2 and/or N-stage ≤ N1, LABC was defined as T-stage ≥ T3 and/or N stage ≥ N2 without any evidence of distant metastasis.

Inclusion criteria: All the breast carcinoma cases who underwent surgery and were found to be triple negative, Patient who gave consent

Exclusion criteria: All the breast carcinoma cases who were found to be ER positive/ PR positive/ Her2neu positive/equivocal, Patient who did not give consent Statistical Analysis was performed with help of Epi Info (TM) 7.2.2.2 EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC). Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations (S.D.). Test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference proportions. $p<0.05$ was taken to be statistically significant.

Results

Approximately 18.28% of breast cancers were found to be Triple negative breast cancer at out hospital during the period of 2020 to 2023. 107 patients satisfying the inclusion criteria were included in the study.
Minimum age at presentation was 21 years and maximum age was 87 years with median age being 54 years. 56 patients (52.3%) were <50 years of age and 51 patients (47.7%) were >50 years of age. Three patients had bilateral breast carcinoma and two cases of male breast carcinoma. 83(87.4%) patients were younger than 30 years during their first child birth and 12 (12.6%) patients were older than 30 years. Nulliparity was seen in 10 (9.5%) cases. Family history was positive in 9 (8.4%) cases.

Table 1: Demographic profile of the patients

Parameters	**Number**	**%**
Age (Years)		
<50	56	52.3%
≥50	51	47.7%

Age at first full term pregnancy* (Years)		
<30	83	87.4%
≥30	12	12.6%
Parity		
Multipara	95	90.5%
Nullipara	10	9.5%
Menopausal status		
Pre-/peri-menopausal	59	56.2%
Post-menopausal	46	43.8%
Family history		
Negative	98	91.6%
Positive	9	8.4%

*10(9.5%) was nullipara, The mean (±S.D.) age of the patients was 47.79±11.76 years with range 21 – 87 years and the median age was 48 years. The mean (±S.D.) age of 1st full term pregnancy the patients was 24.24±4.03 years with range 17 – 35 years and the median age was 24 years.

Among the T stages, T2 (63 patients;60%) was the most frequent stage, followed by T3 (28 patients;26.7%) and T1 (14 patients;13.3%) was the least common stage. Regarding the nodal staging, 66 patients (62.3%) were node negative.
71 patients (66.4%) were in early breast carcinoma category and 36 patients (33.6%) were in locally advanced breast carcinoma group. 95 patients (88.8%) underwent modified radical mastectomy and 12 patients (11.2%) had breast conservative surgery. Seventy three patients' (69.5%) histology showed invasive ductal carcinoma- NOS (not otherwise specified) type, making it the most common histopathology. 11 patients (12.5%) were of well differentiated grade, 28 patients (31.8%) had moderately differentiated and 49 patients (55.7%) were having poorly differentiated grade of tumor. Pathologically stage IIA was most common with 43 patients (40.2%).
Total 29 patients took neoadjuvant chemotherapy. Total 96 patients were alive on last follow up and 11 patients were dead. Twenty one patients showed relapse. Many of the patients had visceral metastasis on relapse.

Table 2: Clinico-epidemiological profile of the patients

Clinico-epidemiological parameters	Number	%
Laterality of tumors		
Billateral	3	2.8%
Left	62	57.9%
Right	42	39.3%
Size of tumor (mm)		
1.0 – 2.0	14	13.3%
2.1 - 5.0	63	60.0%
>5.1	28	26.7%
Histopatholical findings		
IDC NOS	73	69.5%
IDC medullary	14	13.3%
Metaplastic carcinoma	7	6.7%
IDC mucinous	5	4.8%
IDC papillary	3	2.9%
IDC squamous	2	1.9%
IDC poorly differentiated	1	1.0%

Histopatholical Grade		
Well differentiated	11	12.5%
Moderately differentiated	28	31.8%
Poorly differentiated	49	55.7%
Status of lymph node		
Positive	40	37.7%
Negative	66	62.3%
Number of positive lymph node		
0	66	62.3%
1 - 3	18	17.0%
4 - 8	12	11.3%
>9	10	9.4%
Stage		
IA	23	21.5%
IIA	43	40.2%
IIB	13	12.1%
IIIA	13	12.1%
IIIB	6	5.6%
IIIC	9	8.4%
Type of breast cancer		
EBC	71	66.4%
LABC	36	33.6%

Table 3: Type of surgery underwent

Surgery	Number	%
MRM	95	88.8%
BCS	12	11.2%

Table 4: Post-treatment health status

Outcome	Number	%
Alive	96	89.7%
Dead	11	10.3%
Recurrence with distant metastasis		
Yes	21	31.8%
No	45	68.2%
Site of distant metastasis		
Bone	3	14.3%
Brain	1	4.8%
Liver	5	23.8%
Liver + Brain	1	4.8%
Lung	6	28.6%
Lung + Bone	3	14.3%
Opposite breast	2	9.5%

The mean (±S.D.) overall survival of the patients was 456.08±204.64 days with range 37 – 987 days and the median were 454 days.

Eight (20%), seventeen (42.5%), fifteen (37.5%) patients with T1, T2, T3 stage respectively had positive lymph nodes with p value 0.010, so there was significant association with T stage and lymph node positivity. (Table-5)

Table 5: Association between Pathological Tumor size and Lymph Node status

Variables		Lymph Node status		P value
		Negative	Positive	
Pathological Tumor size	(0-2.0) T1	6 (9.2)	8 (20.0)	0.010
	(2.1-5.0) T2	47 (72.3)	17 (42.5)	
	5.1 and above (T3)	12 (18.5)	15 (37.5)	

A total of 29 patients underwent neoadjuvant treatment, of which 12 (41.4%) patients showed complete response, 12 (41.4%) patients showed partial response and 5 (17.2%) patients were non responders, of the five non responders 3 patients and out of twelve partial responders 1 patient showed relapse. None of the complete responder patient to chemotherapy showed recurrence (p = 0.01). (Table-6)

Most of the patient underwent modified radical mastectomy. Out of 95 patients who underwent modified radical mastectomy, 17 patients had relapse and out of 12 patients who had breast conservative surgery, 4 patients had relapse. There was no statistically significant association with type of surgery and relapse (p=0.246). (Table-7)

The predominant stage was early breast carcinoma, out of 71 EBC patients 3 patients were dead on follow up and out of 36 LABC patients 8 were dead on follow up (p=0.006), indicating there was significant association with stage and survival of patient. (Table-8)

Predominantly 66 patients had negative lymph nodes on final histopathology, of which 5 patients relapsed and 3 patients were dead. 16 out of 41 patients from lymph node positive group had relapse and 8 patients were dead (p=0.001, p=0.020). There was significant association between lymph node positivity and relapse as well as survival of the patients. (Table-8)

Table 6: Association between Treatment effect and Relapse

Variables		Relapse		P value
		No	Yes	
Treatment effect	Non responder	2 (8.0)	3 (75.0)	0.010
	Partial Responder	11 (44.0)	1 (25.0)	
	Complete Responder	12 (48.0)	0 (0.0)	

Table 7: Association between Type of Surgery and Relapse

Variables		Relapse		P value
		No	Yes	
Type of Surgery	MRM	78 (90.7)	17 81.0)	0.246
	BCS	8 (9.3)	4 (19.0)	

Table 8: Association between Clinical stage and Relapse

Variables		Survival		P value
		Dead	Alive	
Clinical stage	EBC	3 (4.2)	68 (95.8)	0.006
	LABC	8 (22.2)	28 (77.8)	

Variables		Survival		P value
		Dead	Alive	
Lymph Node status	Negative	3 (27.3)	63 (65.6)	0.020
	Positive	8 (72.7)	33 (34.4)	

Variables		Relapse		P value
		No	Yes	
Lymph Node status	Negative	61 (70.9)	5 (23.8)	<0.001
	Positive	25 (29.1)	16 (76.2)	

Discussion

In our study we focused on clinical and pathological profile of triple negative breast cancer (TNBC) and their correlation as well as response to neoadjuvant treatment and its impact on recurrence and survival at our institute. The incidence of TNBC in our population was seen 18.28% which stands within the range of 15-20%, generally reported in the literature. The incidence was comparable to that of study showing the incidence of TNBC as 19.9% in Indian population. [Patil]. [5] Our population data was similar (median age 54 years) as the ones described in western data [4] (median age 53 years). As compared to our study, other studies showed different incidence of TNBC as 25% (Ambroise *et al*, 2011) [6] and 11.8% (Sharma *et al*, 2013) [7] in Indian population. The peak incidence was observed in 5th and 6th decade (52%) in our study. None of the standard risk factor had any significant association as noted in other studies. [8] Clinical and pathological stage IIA was the most common stage (40.2%) followed by stage IA (21.5%) and stage IIB & IIIA (both 12.1%). This shows that early breast cancer cases (66.4%) were found to have higher incidence as compared to locally advanced breast cancer (33.6%) in our study.

The bias towards MRM (95/107) was highly significant in our study. This reflects social and cultural differences in Indian population. Irrespective of the type of surgery, the relapse was predominantly systemic in our study and no cases of local relapse seen in our study.

In our study we found association with T stage and N stage, where lymph node positivity rate was low in T1 stage (20%) as compared to T2 and T3 stage e.g., 42.5% and 37.5% respectively. It is highlighted in the study by Atika Dogra *et al* [14] in which the increasing tumor size was related to lymph node positivity. The most of the TNBCs were found to be of high grade invasive ductal carcinoma of NOS type (69.5% %) and few were medullary carcinoma (13.3%) and metaplastic carcinoma (6.7%). This suggests that TNBC can occur in all histological subtypes of breast malignancies with probable association with pathogenesis, progression and prognosis. (Reis-Filho *et al*, 2008; Thike *et al*, 2010; Kutomi *et al*, 2012). [9, 10, 11]

TNBC is known to be highly chemoresponsive with high pCR rates, then HR positive tumors. In our study, pCR rate after NACT of 41.4% was found to be similar to the study done by Liedtke *et al*. [12] 21/107 patients (in upfront/after NACT) showed relapse.

All the 16 patients showed systemic relapse, in which only 5 patients had bony metastasis.

Most of the recurrence were found to occur within 1.5-2 years. The higher predilection for visceral metastasis was evident in our study. It was similar to the data obtained from western studies.[4]

Survival:

In our study maximum follow up that could be achieved was 35 months. However, the mean follow up was 16 months. There were 11 deaths (all related to disease progression) and 21 relapses in this period. The 2 years OS and RFS in our study was 86% and 82 % respectively. This was comparable to the survival curve of TNBC

group in studies by dent *et al.* [4], where OS/BCSS and RFS were 74% and 67% and by Rakha *et al.* [13], where BCSS and RFS were 83% and 73% of TNBC at 5 years. Log Rank (Mantel-Cox) showed that the pattern of survival of node negative cases was better than node positive cases but it was not significant (p=0.065) and the pattern of survival of EBC patients was significantly better than LABC patients (p=0.004).

Survival analysis

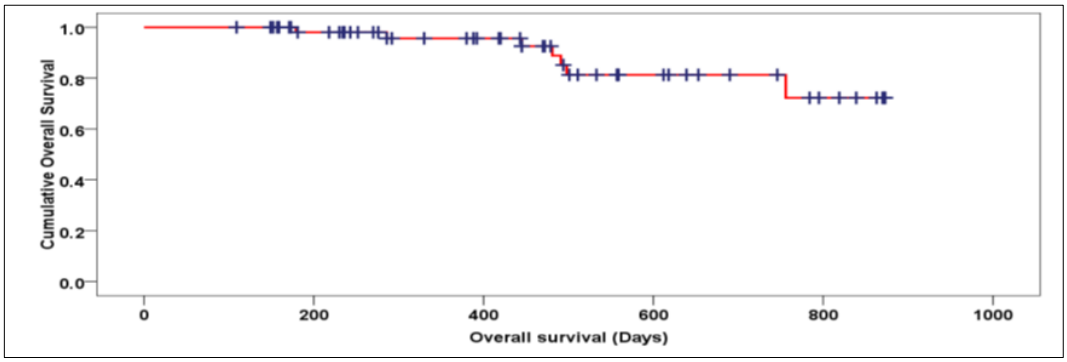

Fig 1: Overall Survival (Days)

The mean (±S.D.) disease free survival of the patients was 491.28±206.20 days with range 109 – 1012 days and the median were 473 days.

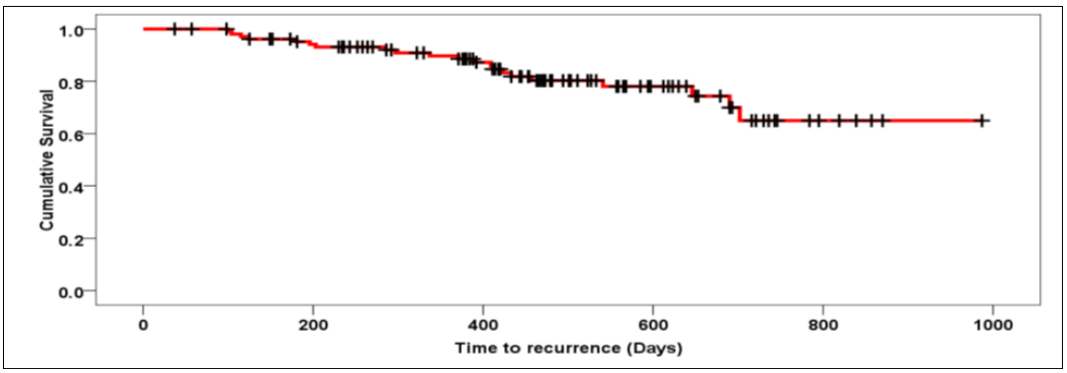

Fig 2: Recurrence Free Survival (Days)

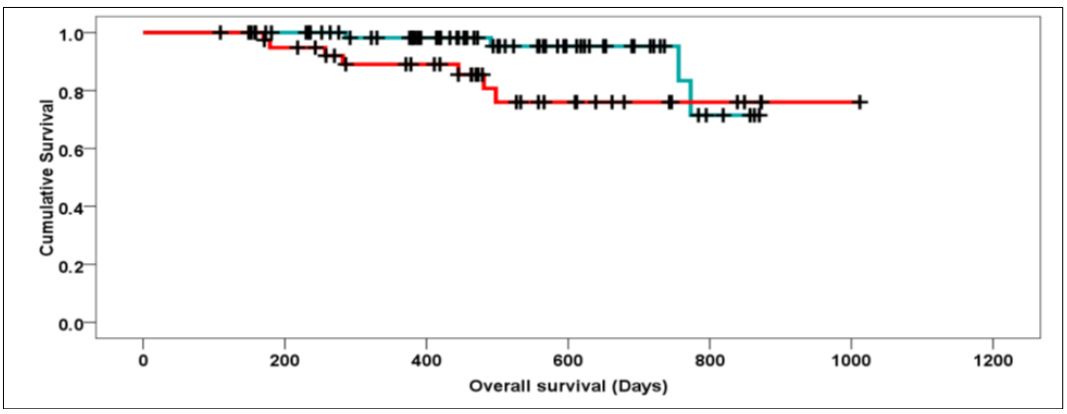

Fig 3: Overall Survival in Node Positive and Node Negative Group (Days)

_ Node Negative
_ Node Positive

Log Rank (Mantel-Cox) showed that the pattern of survival of node negative cases was better than node positive cases but it was not significant (p=0.065)

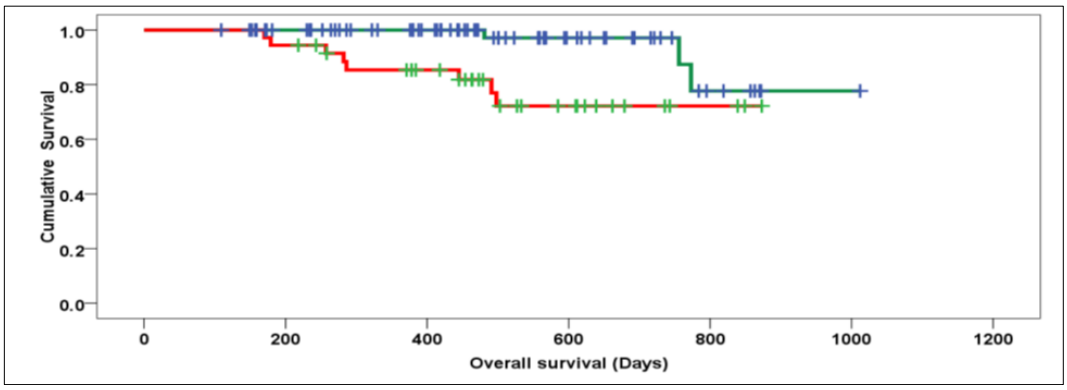

Fig 4: Overall Survival in EBC and LABC Group (Days)

_ EBC
_ LABC
Log Rank (Mantel-Cox) showed that the pattern of survival of EBC patients was significantly better than LABC patients (p=0.004)

Conclusion

TNBC has been always challenging for the clinician and to the patient due to fewer treatment options and poorer prognosis and a lack of targeted therapies which projects to higher mortality compared to other breast cancer subtypes. TNBC are very aggressive cancers that have marked epidemiological, pathological and prognostic characteristics. Around 18% of breast carcinoma reported at our institute were TNBCs.

Disease staging at presentation is an important prognostic factor influencing the treatment failure and survival among TNBC. As evident in our study where we found higher tumor grade, higher stage and lymph node positivity to be associated with a significant number of early relapse and those relapses were mainly visceral and not bony metastasis. Still longer follow-up is necessary for more definite data on TNBCs. Ample research has been reported in western literature on TNBC, all concluding poor prognostic features in comparison to other molecular subtypes. However extensive research from India is lacking.

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