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Triple negative breast cancer: A therapeutic challenge

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Abstract
Triple negative breast cancer (TNBC) is special subgroup of breast cancer accounting for 15-25%, with clinico-pathological heterogenesity, aggressive course and limited treatment options making clinical management challenging as they lack benefit of specific targeted therapy. The aim was to study the incidence, clinico-pathological characteristics and treatment outcomes of TNBC's at our institute. We have reviewed 65 cases of TNBC operated between 2005-2010. Their clinical presentations, pathological and immunohistochemistry features were studied and their correlations with recurrences were reviewed. Most of the patients had grade 3 histology (53.8%) particularly patients under 50 years (65.7%). There were 14 recurrences (21.5%); Most of the recurrent cases were grade 3(9/14) and lymphnode positive (11/14). 13 patients had undergone chemotherapy and 8 had radiotherapy also as part of initial treatment. 12 patients had distant metastasis (85.7%) and 2 had local recurrences (14.2%). Triple negative breast cancers have aggressive course with susceptibility for visceral metastasis, with poor prognosis inspite of chemotherapy.

Keywords: TNBC, visceral metastasis, chemotherapy, estrogen receptor

Introduction
Breast cancer is the most common malignancy worldwide constituting 21% of all cancers in females [1]. It is also the most common malignancy in urban India. It is also the leading cause of cancer death in females [2]. Breast cancer is a heterogeneous disease in terms of biological behaviour, prognosis and response to treatment [3]. Molecular pathology and genetics have revealed number of subtypes of breast cancers. Triple negative breast cancer (TNBC) is a subgroup of breast cancer which lacks estrogen, progesterone and Her2neu receptor expression. Various western study literature have reported poor prognosis for this group as they lack benefit of any specific targeted therapy. TNBC is characterised by aggressive course requiring special consideration in management. TNBC patients usually undergo adjuvant or neoadjuvant chemotherapy, but TNBC tends to develop visceral metastases and aggressive clinical behaviour despite the clinical response. It has no subtype-specific treatment and chemotherapy remains the only possible therapeutic option in the adjuvant or metastatic setting**.** The aim of our study was to study the incidence, the clinico-pathological characteristics and treatment outcomes of TNBC's at our tertiary care institute.

Materials and methods
We have reviewed a total of 287 breast cancer patients who have undergone surgery (modified radical mastectomy or wide local excision and axillary clearance) and adjuvant treatments in our institute. Patient's clinical data, investigations, pathology reports, type of surgery, adjuvant treatment, final histopathology report including tumor size, tumor grade, presence of lympho-vascular, axillary lymphnode status and the pathological tumor stage were noted down. Patient's follow-up data was collected from the records and also by telephonic information on status of patients, who are not regular for follow up. Those who had recurrences have been studied further in the form of local, regional recurrence, and distant recurrences. Also reviewed the disease free time, histological confirmation and type of treatment for the recurrence were noted down along with the duration of follow up.

Patients were divided into two age groups for analysis: including 50 years or less and older than 50 years of age. Patients were also divided into three groups as per the size of the primary tumor, according to the TNM system: tumours less than 2 cm, 2-5 cm and larger than 5 cm in diameter. Axillary lymph node status was divided into three groups according to the number of positive nodes: negative, one to three positive nodes, and four or more positive nodes. The Modified Bloom Richardson grading system was used for determination of tumor grade.

Immunohistochemical staining for receptor status was performed automatically on the DAKO TechMate HORIZON immunostainer. The immunostaining results were interpreted using a light microscope. Immunoreactivity for estrogen receptor (ER) and progesterone receptor (PR) was graded as negative and positive according to the H-score and patient age. For HER-2/neu, membrane staining was considered positive with a staining intensity of 3+, as recommended by the manufacturer. If the HER 2/neu was reported as grade 2

positive (equivocal), we have done FISH to confirm or exclude.

Observations and results

There were total 65 (23.3%) cases identified as triple negative, out of 279 cases with known receptor status. Most of these were less than 50 year old (67.7%) with mean age of 46 years and most patients were premenopausal (50.8%). Most of the patients in TNBC were grade 3 tumors (53.8%) particularly in patients under the age of 50 years (65.7%). Most of the patients of TNBC had tumor size between 2.1cm to 5cm at presentation. Triple negative breast cancers have metastases in lymphnodes (LN) (39/169), more than estrogen receptor (ER) and progesterone receptor (PR) positive cases (26/170). However, there was no correlation between tumor size and nodal status. Lymphovascular invasion (LVI) was positive in 11 cases (78.6%).

Table 1: Clinicopatological factors of present study

		TNBC
Total no of cases		65/279
Age(years)	21-30	2
	31-40	23
	41-50	19
	51-60	15
	61-70	3
	71-80	3
Menopausal status	Premenopausal	33(50.8%)
	Postmenopausal	26(40%)
Size of tumour (T)	T1	4
	T2	36
	T3	15
	T4	5
	Tx	5
Grade	I	7
	II	23
	III	35 (53.8%)
LN	N0	26
	N+(N1/N2/N3)	39(18/11/10)
LVI	Positive	78.6%
	Recurrences	14 (21.5%)

There were 14 recurrences (21.5%), with 13 patients having undergone chemotherapy and 8 patient's radiotherapy. Most of them were within 2 years of treatment inspite of adjuvant chemotherapy and radiotherapy. 12 patients had distant metastasis (85.7%) and 2 had local recurrences (14.2%) which occurred inspite of chemotherapy and radiotherapy. Most of the cases were grade 3 (9/14) and were LN positive (11/14).There were 2 deaths within 2 years of treatment due to distant metastasis to lung and brain with patients being less than 40 year old. Another patient with h/o familial breast cancer died after 6 years due to liver metastasis. 5 patients had visceral metastasis and 4 patients had bone only metastasis.

Table 2: Recurrences in TNBC

Age	**Stage**	**Grade**	**CT**	**RT**	**Site**	**TTR**	**Foll.up**	
28	T3N1	III	-	-	lung	2	2.1	
40	T3N1	III	Y	-	lung	1	1	dead/'11
58	T2N1	II	Y	-	lung/liver	1	1	
33	T3N1	III	Y	Y	brain	1.5	1.5	dead/'07
63	T3N0	III	Y	-	Dissemi.	2	2	
54	T2N2	III	Y	-	liver	6	6	dead/'11
59	T2N2	II	Y	Y	bone	1	6	
54	TXN0	III	Y	Y	bone	7	8	
40	TXN1	III	Y	Y	bone	3	6	
55	T2N1	II	Y	-	bone/local	2	2	
53	T2N2	II	Y	Y	SCLN	6m	1	
37	T3N2	II	Y	Y	opposite	2	2	
58	T4N0	III	Y	Y	local	1.6	2.2	
64	T3N3	III	Y	Y	local	5m	5m	

(CT-chemotherapy, RT- radiotherapy, TTR-time to recurrence)

Discussion

Triple-negative breast cancer (TNBC) is characterized by the lack of estrogen receptor (ER), progesterone receptor (PgR), and HER2neu expression. Clinicopathologic features TNBC include young age at onset, large mean tumor size, high grade and higher incidence of node positivity at presentation. TNBC status remains an independent risk factor for distant relapse and survival, with a rapid rise in distant relapse in the first

three years after diagnosis [4, 5]. Additionally, patients with TNBC have an increased propensity for lung and brain metastases, making these tumors especially challenging to treat.

TNBC has no subtype-specific treatment and chemotherapy remains the only possible therapeutic option in the adjuvant or metastatic setting. Therefore, TNBC patients usually undergo adjuvant or neoadjuvant chemotherapy, but TNBC tends to develop visceral metastases and aggressive clinical behaviour despite the clinical response which could be correlated with our study.

The incidence of TNBC in our study was 23.3% which is comparable to other studies. Literature from India and the rest of the world showed TNBC was observed in a younger population. TNBC has been consistently associated with younger age group and high-grade tumor in many studies. The present study also shows that TNBC is significantly associated with younger age and high-grade tumours**.** Our population was slightly younger than the one described in western data. This finding of younger median age most likely reflects the general trend of breast cancers occurring a decade earlier in India.

Table 3: Comparison of various Indian and Western studies of triple negative breast cancer

	Dent[4]	**Lakshmaiah *et al* (KMIO) [6]**	**Ullas *et al* [7]**	**M.Sharma. *et al* [8]**	**Gogia *et al* [9]**	**Present study**
Incidence	11.2%	26%	12.5%	31.9%	21.9%	23.3%
Median age (years)	53	44.5	49	40	46.2	46
<50 yrs	-	72.6%	60%			67.7%
Premenopausal	-		52%			50.8%
T1	-	1.1%		20%	12	
T2		35.7%	60.5%	43.2%	72	
T3		33%		31.6%	25	
T4		25%	10.5%		8	
					6	
N0	-	36.9%	65%	39%	61	
N1		30.9%	28%		29	
N2		28.6%	4%	55.8%	28	
N3		3.6%	3%		12	
Grade III	61%	88%	61%		43%	53.8%
LVI			76%			78.6%

The association with menopausal status, tumour size, nodal status and grade and LVI were comparable to other studies (table-3). Some studies have shown that TNBC patients present with larger tumor size and advanced nodal stage [4, 10]. The correlation between tumor size and nodal status was not seen in Ullas *etal* [7], A. Gogia *etal* [9] and M. Arkthar studies [11]. Triple negative breast cancer patients have an increased likelihood of distant recurrence and death compared to other women with other types of cancers. Unlike ER+/PR+ tumors, which often metastasize first to the bone, triple negative tumors have a tendency to metastasize first to the lung, liver and brain. However, metastatic disease is found in multiple organs when it is first detected in about one-third of cases. We had 14 recurrences (21.5%) which correlated with other studies, including the sites of relapse (distant as well as local). In our study also visceral metastasis were more than the bone metastasis and were comparable to other studies. Factors significantly associated with recurrence included increasing tumor size, positive nodal status and the grade of the tumour which were also comparable to the other studies. Traditionally as the tumour size increases the rate of nodal positivity increases and this relation was not seen among triple negative group and same was reported by and suggested that the mode of spread these cancers is hematogenous.

Table 4: Comparison of recurrences of TNBC

Studies	**Total**	**Bone**	**Lung**	**Liver**	**brain**	**local**	**Opposite breast**	**disseminated**
Ullas *etal*(*n=34*) [7]	22.2%	8.8	20.6	-	17.6	17.6	11.8	23.5
Katarzyna Pogoda(*n=79*) [12]	35%	11%	14%	8%	15%	14%	-	-
Lauren Steward MD(*n=91*) [13]	26.6%	34.1%	41.7%	-	35.2%	-	-	-
Present study(*n=21*)	21.5%	21.4%	14.2%	7.1%	7.1%	14.2%	14.2%	14.2%

Emerging evidence is indicating that patients with TNBC are sensitive to chemotherapy, and that some therapies directed at molecular targets frequently associated with TNBC may be effective. The main limitation of our study was the lack of testing for basal CK5/CK6. Further, large scale prospective trials incorporating basal CK markers and gene expression profiling are required for complete characterization of these tumors and to identify a positive marker that can facilitate targeted therapy.

Conclusions

Triple negative breast cancers are highly aggressive subtype, with high-grade with limited treatment options and very poor prognosis following progression after standard chemotherapy regimens. TNBCs are more common in our country than the western literature. Even in our country also the incidence is varies in different regions. TNBCs are significantly associated with young aged patients. There was a lack of association between tumor size and lymph node positivity. Triple negative breast cancers have high likely hood of visceral metastasis making prognosis very poor for this subgroup of breast cancer patients. Further molecular level studies help in dealing with these subgroups with targeted approach to improve the prognosis.

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