Original Article

Clinical outcome and pattern of recurrence in patients with triple negative breast cancer as compared with non-triple negative breast cancer group

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ABSTRACT

Aim: To compare the clinical characteristics and outcomes in terms of survival, propensity and time of local and distant recurrence for women with triple-negative breast cancer (TNBC) to women with non-triple negative breast cancer (NON TNBC). **Materials and Methods**: A retrospective cohort study was done with 1,026 breast cancer patients with known receptors and Her2neu status diagnosed between January 2005 and January 2011. **Statistical Analysis:** Comparison of clinical outcomes between the two groups was done using *t*-tests for mean and chi square tests for frequencies. For overall and recurrence-free survival Kaplan-Meier survival analyses were done. **Results:** The mean follow-up time for TNBC was 2.9 years and NON TNBC was 4.1 Years. Among the total 1026 patients, 312 patients (30.4%) had TNBC. Compared with non TNBC, those with TNBC had an increased likelihood of death [27.8% vs. 17.8%, $P < 0.0008$, > 95% confidence interval (CI)], and distant recurrence (41.48% vs. 33.17%; $P = 0.02$, C I >95%). Visceral metastasis was high in TNBC which showed Brain metastasis (21.11% vs. 6.18%, $P < 0.0002$), liver metastasis (15.56% vs. 5.02%, $P < 0.0002$), lung metastasis (25.19% vs. 10.03%, $P < 0.0002$); while bone metastasis was higher in NON TNBC group (5.2% vs. 20.55%, $P < 0.0002$). **Conclusions:** TNBC have a more aggressive clinical course and adverse outcomes as compared to NON-TNBC, but local tumor size and propensity of local recurrence do not vary significantly with receptor status. Though, chance of visceral metastasis is higher in TNBC, bone metastasis is high in NON-TNBC.

Key words: Distal metastasis, survival, triple negative breast cancer

INTRODUCTION

Breast cancers are represented by a heterogeneous group of tumors, characterized by a wide spectrum of clinical, pathological and molecular features.[1,2] The wide spectrum of facts account for variations in response to therapy and outcomes among women diagnosed with breast cancer.[3,4] Routine clinical variables have more recently been complemented by molecular profiling in an attempt to refine prognosis and response to therapy in breast cancer patients.[5,6] Recent attention has been devoted toa classification system that uses three common molecular markers, estrogen receptor (ER), progesterone receptor(PR) and HER2 neu and classifies patients into subtypes.[2,4,7] Four Molecular subtypes approximated by receptor status include (i) Luminal A (ER/PR+, Her2neu-); (ii) Luminal B(ER/PR+, Her2neu+); (iii) Basal like (ER/PR-, Her2neu-); and (iv) Her2neu+(ER/PR-, Her2neu+). Luminal subtypes make up the hormone receptor expressing tumors and generally carry a favorable prognosis. HER2 subtypes refer to pre-dominantly hormone receptor negative tumors with a specific gene expression pattern positive for HER2 neu.[2,4] The basal like subgroup consistently segregates as a distinct cluster characterized by cytokeratins 5/6 and 17, laminin, fatty acid binding protein and by lack of expression of hormone receptor and also HER-2.[8] Triple negative breast cancers are characterized by lack of expression of

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estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER 2).[9,10] These cancers occur in approximately 20% to 25% of all patients with breast cancers, and are associated with an unfavorable prognosis.[10,11] Previous reports have indicated that patients with early-stage basal-like or triple-negative breast cancers experience reduced disease-free and overall survival compared with other breast cancer subtypes.[1,11] In a retrospective study led by Haffty *et al.*,[11] the triple-negative subtype was found to be an independent predictor of distant recurrence and shortened cause-specific survival in patients with early-stage breast cancer. Perou *et al.*[1] reported that women with basal-like breast cancers had shorter relapse-free survival times than women with other types of breast cancer. Basal-like breast cancers also have a tendency toward visceral (versus bone) metastasis.[12,13]

We performed a retrospective study from January 2005 to January 2011 on a large series. Breast cancer patients attended in our department having both triple negative and non-triple negative breast cancer patients with long term follow up and compare their outcomes in terms of survival, propensity of locoregional relapse, recurrence free survival and distant metastasis.

AIMS AND OBJECTIVES

To compare the clinical characteristics and outcomes in terms of survival, propensity and time of local and distant recurrence for women with triple-negative breast cancer (TNBC) and women with non-triple negative breast cancer (NON TNBC). In several other studies,[11,14] outcomes of Triple negative breast cancers were analyzed in terms of survival, metastasis and pattern of recurrence. In our study, in addition to those, we have analyzed viscera wise propensity of metastasis in both TNBC and NON-TNBC group and compared them and also compared the pattern of local recurrence.

MATERIALS AND METHODS

From January 2005 to January 2011, the no. of Breast Cancer patients were registered in our institute was 1860. Review of the outcomes of these patients was approved by the institutional ethical committee. Only those patients in whom estrogen receptor (ER), progesterone receptor (PR), HER2 neu status was available were included in the current analysis. So the actual accrual for this study was 1026 patients.

The data on ER, PR, HER2 neu were obtained through standard clinical testing, and we recorded the immunohistochemistry reports. For ER and PR positivity was based on more than 10% of the cells test positive, in accordance with standard guidelines. HER2 scores of 0 and 1 were considered to be negative, score of 3 as positive and score 2 were asked for confirmation by FISH study as per our institutional protocol. Patients were classified as triple negative if they were negative for all three receptors and as non-triple negative if they were positive for any one of the three markers. In our study, 312 patients were triple negative and 714 patients were non-triple negative breast cancer.

All the modalities of treatment were taken into account. Local or regional relapses were defined as clinically and histological documented relapse in the ipsilateral breast or chest wall and/or regional nodes. Distant metastasis was defined as clinical evidence of distant disease based on clinical and/or imaging findings.

All events were calculated from the time of diagnosis. Overall and recurrence free survival, distant metastasis, and local recurrence free times were calculated using standard statistical methods.

Strict follow up was maintained as per our institutional protocol, initially 3 monthly for 1st year after the completion of treatment, then 4 monthly for the next 2 years, then 6 monthly and patients were advised to attend whenever symptom arises and necessary investigations were done. Loco regional relapse or recurrence after complete response was taken as considerable events. For deceased patients, dates and causes of death, if possible were obtained from medical records.

Outcomes

Overall survival was defined as from the time of diagnosis to last follow up/time of death. Relapse free survival was defined as the time of diagnosis to development of first evidence of clinical/radiographic metastatic disease.

Analysis

Baseline demographic, tumor characteristics and outcomes were compared between the triple-negative and other group using a *t* -test for means and Chi - square statistic for frequencies. Kaplan-Meier survival analyses were carried out for overall survival and recurrence-free survival.

RESULTS

Among 1026 patients under study, 312 (30.60%) were triple negative breast cancer patients. The features of TNBC and NON-TNBC s are compared in Table 1 and outcome in Table 2.

- Mean age of diagnosis of triple negative breast cancers was 48.8 years, as compared with non-TNBC group, which was 53.6 years; $P < 0.002$, showed TNBC occurred at significantly younger age.

Table 1: Characteristics and distributions in both the triple-negative breast cancer and non-triple negative breast cancer groups are tabulated below

Variables	Non TNBC (*n* = 714)	TNBC (*n* = 312)	*P* Value
Mean age (years)	53.6	48.8	<0.0002
Mean follow-up (years)	4.1	2.9	<0.003
Lymph node status			
Positive	296 (46.85%)	153 (56.45%)	0.02
Negative	338 (53.15%)	118 (43.15%)	
Unknown	78	41	
Tumorsize			
T1	112 (17.33)	51 (18.41%)	
T2	323 (50%)	143 (51.62%)	
T3	211 (33.66%)	83 (29.96%)	0.67
Unknown	68	35	
ER status			Not applicable
Positive	594 (83.19%)	0 (0 %)	
Negative	120 (16.81%)	312 (100%)	
PR status			Not applicable
Positive	482 (67.50%)	0 (0 %)	
Negative	232 (32.50%)	312 (100%)	
Her 2 neu status			Not applicable
Positive	190 (26.61%)	0 (0%)	
Negative	524 (73.39%)	312 (100%)	

TNBC: Triple-negative breast cancer, NON TNBC: Non-triple negative breast cancer

Table 2: Treatment outcome

Outcomes	Non-TNBC (*N* = 618)	TNBC (*N* = 270)	*P* Value
Death due to breast cancer and related causes	110 (17.8%)	75 (27.8%)	<0.0008
Median time of death in months	37	21	<0.0001
Local recurrence	98 (15.86%)	47 (17.4%)	0.67
Mean time of local recurrence in months	31	23	
Distant metastasis (total)	205 (33.17%)	112(41.48%)	0.02
Brain mets	41 (6.18%)	57(21.11%)	<0.0002
Liver mets	31 (5.02%)	42(15.56%)	<0.0002
Lung mets	62 (10.03%)	68 (25.19%)	<0.0002
Bone mets	127 (20.55%)	14 (5.2%)	<0.0002

TNBC: Triple-negative breast cancer, NON TNBC: Non-triple negative breast cancer

- In TNBC group 56.45% patients were node positive, but in other group node positivity was 46.85% ($P < 0.02$), which is, showing TNBC patients had higher propensity of lymph node positivity.
- 29.96% patients of triple negative breast cancer group were presented with initial tumor size T3, while 33.66% patients of Non TNBC group presented with tumor size T3 at diagnosis, $P = 0.67$,which was statistically insignificant; showing that large tumor size was not related to receptor status.
- Comparing the outcomes in both the groups, mortality rate due to breast cancer and related causes, was high in TNBC group, which was 27.8% as compared with other group, where breast specific death rate was 17.8%, $P < 0.0008$, which was significant. So breast cancer specific death rate was greater in TNBC group.
- The median time of death was calculated in those patients, who died in the both the groups, and we found that the median time of death of TNBC were 21 months which is significantly earlier as compared with non TNBC group, which were 37 months, $P < 0.001$.
- A higher proportions of TNBC patients had distance metastasis than non TNBC group (41.48% vs. 33.17%); $P = 0.02$.
- Mean time of distant recurrence in TNBC group was 14 months; while in the other group was 36 months, which was significantly less with $P < 0.002$.
- We also compared the rate of local recurrence in both the groups, which was 17.4% in TNBC group, while 15.86% in Non TNBC group $P = 0.67$, showing that local recurrence did not vary much with receptor status. But the mean time of local recurrence was earlier in TNBC group, 23 months, as compared with the other group which is 31 months.
- The rate of visceral metastases in different organs was also compared. 21.11% patients in the TNBC group presented with brain metastasis, while the rate was 6.18% in non TNBC group, $P < 0.0002$, so propensity of brain metastasis was higher in TNBC group. Rate of hepatic metastasis was significantly higher (15.56%) in TNBC group and 5.02% in non TNBC group; $P < 0.002$, so also lung metastasis (25.19% vs. 10.03%, $P < 0.002$). But the rate of bone metastasis was significantly higher in non TNBC group 20.55% as compared with TNBC 5.2% ($P < 0.002$).
- Kaplan-Meier survival analyses were carried out to compare overall survival and distant Recurrence-free survival rates [Figures 1 and 2]. The analysis showed that there was increased likelihood of death from triple negative breast cancer group ($P < 0.0008$, confidence interval > 95%) than non TNBC group.
- A similar effect was seen for distant recurrence means compared with the non TNBC group, women with triple-negative breast cancer had shown an increased likelihood of distant recurrence with P value < 0.0001, confidence interval >95%.

DISCUSSION

This study addresses the short-term and long-term outcomes of patients with triple-negative breast cancers within the context of other known prognostic factors. Classification of breast cancers into basal like type (triple negative), luminal A, luminal B, and HER2 neu has recently been proposed as a classification scheme based on gene expression profiles.[1,2] Basal like breast cancer subtype is defined via gene expression microarray analysis. Triple negative breast cancer and basal like breast cancer are not completely synonymous, although they are used interchangeably.

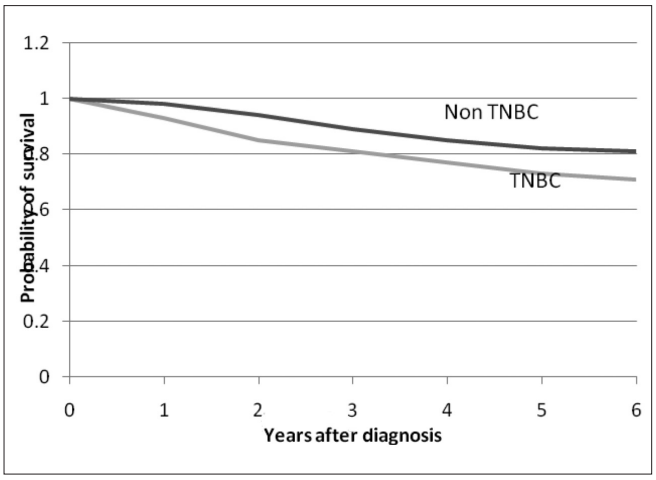

Figure 1: Kaplan-Meier survival curves showing overall survival in triple negative breast cancer and non triple negative breast cancer group

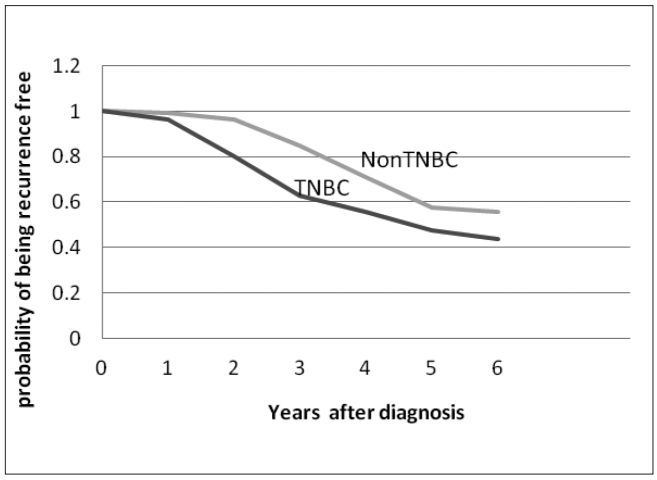

Figure 2: Comparing the rates of recurrence free survival in triple-negative breast cancer and non-triple negative breast cancer group

To date the basal like classification is available only in the research settings, thus for convenience, triple negative phenotype serves as reliable surrogate in the clinical area.

It has been demonstrated in various studies that this classification scheme has prognostic significance and implications with respect to response to therapy.[1-3] In the current study, we evaluated 1026 breast cancer patients treated with various available modalities of treatment, in whom all three markers were available to validate the prognostic utility of this classification scheme and to determine whether triple negative breast cancers have a more aggressive loco regional relapse rate. But one potential weakness of the study is, unavoidable selection biases in a retrospective series such as this. For the current study, only patients who had available ER, PR, and HER2 neu data were included.

In our retrospective, single-institution study, we found that the poor outcome of patients with triple-negative breast cancer persists in the metastatic setting. In our study, we have shown that patients with triple-negative breast cancer have an increased likelihood of distant recurrence and of death compared with women with other types of cancer, and the difference persists after controlling for established prognostic factors. Patients in the triple-negative category had relatively high rate of node positivity (56.4%), but tumor size did not vary significantly as compared to non triple negative breast cancer group. We also observed a strikingly high rate of visceral metastasis as compared to bone metastasis in triple negative breast cancer patients.

Despite differences in taxonomy, there is a consistent trend across all studies confirming the relatively poor prognosis of the triple-negative breast cancer subgroup.[15-17] The lack of association between tumor size and lymph node positivity, the high rates of distal recurrence, and the relative rarity of local recurrence all suggest that these patients have a tendency to develop visceral metastases early in the course of their disease. In conclusion, by using three standard pathologic markers, we are able to show that the triple-negative category of breast cancers exhibits a distinct pattern of recurrence as increased propensity and relatively earlier tendency of distant visceral metastasis. Several studies have also supported a significantly increased rate of visceral versus bone metastasis among patients with TNBC compared with NON- TNBC.[15]

CONCLUSION

Triple negative breast cancers have a more aggressive clinical course and adverse outcomes in terms of survival and distal recurrence as compared to Non TNBC group. TNBC patients suffered from visceral metastasis more than Non TNBC group, among which lung metastasis was highest. But propensity of bone metastasis was higher in Non TNBC group. Local tumor size and propensity of local recurrence do not vary significantly with receptor status. TNBC patients suffer earlier recurrence than non TNBC patients.

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