RESEARCH ARTICLE

Eight Year Survival Analysis of Patients with Triple Negative Breast Cancer in India

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Abstract

Background: Triple-negative breast cancer (TNBC) often presents as an interval cancer with short survival upon metastasis and thus represents an important clinical challenge. The present study investigated the clinicopathologic characteristics and long term survival outcome of early and locally advanced TNBC. Materials and Methods: Medical records were reviewed retrospectively for 148 consecutive confirmed cases of TNBC treated in a single unit at our centre. Demographic profile, tumor type, histopathology details, treatment and follow-up information was recorded and immunohistochemistry was performed. Results: Age group >50 years was associated with tumors of clinical stage 3 (53.8%), pathological stage 3 (46.2%), pathological grade 3 (45.7%), presence of extracapsular extension (ECE, 48.5%) and lymphovascular invasion (LVI, 64.9%). Locally advanced breast cancers (LABCs) were characterized by pathological stage 3 (96.2%), presence of ECE (100%) and absence of LVI (46.7%) as compared to early breast cancers (EBCs) which had higher incidence of lower stage tumors (100%), absence of ECE (82%) and presence of LVI (91.9%; p-value <0.001. Better relapse free survival was observed in patients with no axillary involvement (69%; p-value <0.001) and absence of ECE (64%; p-value <0.001). Improved overall survival was seen in patients with EBC (90%; p-value 0.008), clear axilla (86%; p-value <0.001), absence of ECE (87%; p-value <0.001) and negative lymph nodes (90%; p-value 0.006). Conclusions: TNBCs are aggressive tumors which show poor long term survival. Patients with TNBC benefit from chemotherapy, thus better and less toxic treatment options are needed. Identification of newer targets and development of targeted therapies are the need of the hour.

Keywords: Early breast cancer - locally advanced breast cancer - survival - triple negative breast cancer

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Introduction

Breast cancer is one of the most commonly diagnosed cancers and leading cause of cancer death among women around the world. It represented 23% (1.38 million) of the total new cancer cases and 14% (458,400) of the total cancer deaths in the year 2008. In the developing countries, about half the breast cancer cases and 60% of the deaths are estimated to occur (Jemal et al., 2011). Breast cancer is one of the most heterogeneous and complex disease in terms of tumor histology, cellular origin, molecular subtypes, gene mutations, metastasis, disease progression, therapeutic response, and clinical outcome (Cetin and Topcul, 2014; Foulkes et al., 2010). Increasing burden of breast cancer mainly due to lifestyle changes and urbanization has led to amendments in the treatment strategies due to discovery of specific prognostic and predictive biomarkers that enable the application of more individualized targeted therapies following hormone receptor testing which has been accepted in today's clinical practice as a standard established procedure in the patient management (Quiet et al., 1995).

Breast cancer can be classified into different subtypes based on the immunohistochemical protein overexpression of estrogen receptor (ER) progesterone receptor (PR) and human epidermal growth factor receptor type 2 (HER2). Triple-negative breast cancer (TNBC) is characterized by tumors that do not express ER, PR and HER2. These tumor subtypes represent approximately 12-17% of all diagnosed breast cancers (Foulkes et al., 2010). Studies from India have reported its prevalence from 11-18.5% (Krishnamurthy et al., 2012; Sharma et al., 2013). TNBCs are characterized by higher frequency in younger women (<50 years) and in African- American women, present as interval cancers, highly chemosensitive, weak association between tumour size and lymph node metastases, more aggressive, higher chance of brain metastases, increased chances of recurrence during first to third year with shorter survival upon metastasis (Fisher et al., 1990; Roche et al., 2006). This subtype represents an important clinical challenge because these cancers do not respond to endocrine therapy or other therapies targeting HER2.

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Epidemiology reports on TNBC are already available from our centre (Suresh et al., 2013). Long term survival data of this group of tumor from Indian population is limited. Therefore the study was taken up to investigate the clinicopathologic characteristics and long term survival outcome of early and locally advanced TNBC.

Materials and Methods

In the study period of 2005 to 2008, medical records were reviewed retrospectively of 148 consecutive confirmed cases of TNBC patients consisting only of early breast cancer (EBC) and locally advanced breast cancer (LABC) who underwent curative surgery and/or chemotherapy in a single unit at our Centre. Details of each patient such as the demographic profile, investigations, tumor type, histopathology details, treatment and follow up information was recorded. The study was granted waiver by the Institutional Review Board and has been performed in accordance with the Declaration of Helsinki.

Immunohistochemistry (IHC) was performed on the FFPE tissue block with adequate tumor to study the expression of ER, PR and HER-2. HercepTest kit (Dako, Denmark) was used for the determination of HER-2 expression according to the manufacturer's instruction.

Final scores of the IHC were marked based on the percentage of positive cells for ER and PR. Breast cancer scoring was followed for the scoring of HER-2 staining (Wolff et al., 2007). HER-2 expression was interpreted as negative for protein expression 0 and 1, weakly positive for 2+ staining and strongly positive for 3+ staining. HER-2 gene amplification by fluorescent in situ hybridization was carried out to determine the positivity or negativity for 2+ score. Triple negative tumors were considered when ER, PR and HER-2 were negative.

SPSS version 16 for Windows (SPSS Inc, Chicago IL, USA) was used for all the statistical analysis. Pearson $\chi 2$ or Fisher's Exact Test, whichever was appropriate, was used for categorical variables. For the survival analysis, Kaplan–Meier method (Kaplan and Meier, 1958) was applied and Log Rank test was used to compare the difference in survival among the groups. A two sided p-value <0.05 was considered as significant.

Results

Median age of the patients was 49 years (range 22–75 years). Demographic profile of the patients is presented in Table 1. Comorbidities were reported in 27% patients. LABC constituted about 38.5% of all the cancers and the rest were early breast cancers. Majority of patients (69.9%) were postmenopausal, presented at stage II (68.2%) and clinical tumor size in a range of 2-5 cm (62.2%). Around 70% patients had the presence of lump in breast since more than 1 month. A total of 53.4% patients had right sided breast cancer. Modified radical mastectomy (79.2%) was the main surgical modality followed by breast conservation surgery (20.8%). Histological subtype of all the patients was Infiltrating Ductal Carcinoma. Extracapsular extension (ECE) and lymphovascular invasion (LVI) was seen in 22.9% and 25.7% patients, respectively in pathological examination. Regarding the type of adjuvant chemotherapy administered, non anthracyline and anthracycline based chemotherapy were given in 10 and 50 patients, respectively. Also, taxane based chemotherapy sequentially with anthracycline based chemotherapy was given in 39 patients where as taxane anthracycline continuous chemotherapy was administered in 41 patients. Median follow up time was 42 months (range 1 to 104 months). Thirty eight patients (25%) experienced recurrence and 18 (12%) deaths occurred. The recurrence free survival (RFS) and overall survival (OS) at 8 years for all the patients were 58% and 75%, respectively.

The comparative analysis of age group and breast cancer type with different clinicopathological parameters is given in Table 2. Higher age group (>50 years) was commonly associated with tumors of clinical stage 3 (53.8%), pathological stage 3 (46.2%), pathological grade 3 (45.7%), presence of ECE (48.5%) and LVI (64.9%). LABC were characterized by pathological stage 3 (96.2%), presence of ECE (100%) and absence of LVI (46.7%) as compared to EBC which had higher incidence of lower stage tumors (100%), absence of ECE (82%) and presence of LVI (91.9%); p-value <0.001.

The eight year survival analysis is mentioned in Table 3. Better RFS was observed in patients >50 years age (61%), premenopausal status (67%), early breast cancer (60%), no axillary involvement (69%; p-value <0.001),

Table 1. Demographic Profile of the Patients (N=148)

Characteristics	Number (percentage)
Median age	49 year
Range	22-75 years
Menopausal status	
Pre/ Post	45 (30.4)/ 103 (69.6)
Family history	
No/ Yes	140(94.5)/ 8(5.40)
Breast cancer type	
Early/ LABC	91 (61.4)/ 57 (38.5)
Surgery type*	
MRM/ BCS	114 (79.2)/ 30(20.8)
Pathological tumor size (cm)*	
<5/ >5	126 (87.5)/ 18 (12.5)
Grade#	
3-Feb	49 (34.3)/ 94 (65.7)
Pathological stage*	
0/ I/ II/ III	5 (34.5)/ 20 (13.8)/ 93 (64.6)/ 26 (18.0)
Lymphnodes*	
Positive/ Negative	53 (36.8)/ 91 (63.2)
ECE*	
Present/ Absent	33 (22.9)/ 111 (77.9)
LVI*	
Present/ Absent	37 (25.7)/ 107 (74.3)
Adjuvant Chemotherapy$	
Yes/ No	142 (95.9)/ 3 (20.0)
Status	
Recurrence/ Death	38 (25.7%)/ 18(12.2%)
Survival (8 year)	
OS/ RFS	75%/ 58%

MRM, modified radical mastectomy; BCS, breast conservation surgery; LABC, locally advance breast cancer; ECE, extracapsular extension; LVI, lymphovascular invasion; RFS, recurrence free survival; OS, overall survival. * n=144; # n=143; $ n=145

Table 2. Comparative Analysis with Different Clinicopathological Parameters (N=148)

Characteristics	Age group <50 n (%)	Age group >50 n (%)	p-value	Breast cancer type EBC n (%)	Breast cancer type LABC n (%)	p-value
Tumor size (cm)						
<2	13 (56.5)	10 (43.5)	0.875	17 (73.9)	6 (26.1)	0.408
2.1-5	54 (58.7)	38 (41.3)		56 (60.9)	36 (39.1)	
>5	12 (66.7)	6 (33.3)		11 (61.1)	7 (38.9)	
Peau du orange	8 (53.3)	7 (46.7)		7 (46.7)	8 (53.3)	
Clinical stage						
I	13 (61.9)	8 (38.1)	0.354	17 (81)	4 (19)	0.024
II	62 (61.4)	39 (38.6)		63 (62.4)	38 (37.6)	
III	12 (46.2)	14 (53.8)		11 (42.3)	15 (57.7)	
Pathological tumor size (cm)*						
<5	72 (57.1)	54 (42.9)	0.224	78 (61.9)	40 (38.1)	0.396
>5	13 (72.2)	5 (27.8)		13 (72.2)	5 (27.8)	
Pathological Grade#						
2	33 (67.3)	16 (32.7)	0.131	31 (63.3)	18 (36.7)	0.855
3	51 (54.3)	43 (45.7)		58 (61.7)	36 (38.3)	
Pathological stage*						
0	3 (60)	2 (40)	0.465	5 (100)	0 (0)	<0.001
1	15 (75)	5 (25)		20 (100)	0 (0)	
2	53 (57)	40 (43)		65 (69.9)	28 (30.1)	
3	14 (53.8)	12 (46.2)		1 (3.8)	25 (96.2)	
ECE*						
Absent	68 (61.3)	43 (38.7)	0.318	91 (82)	20 (18)	<0.001
Present	17 (51.5)	16 (48.5)		0 (0)	33 (100)	
LVI*						
Absent	61 (57.0)	46 (43.0)	0.402	57 (53.3)	50 (46.7)	<0.001
Present	24 (64.9)	13 (35.1)		34 (91.9)	3 (8.1)	
Recurrence						
No	62 (56.4)	48 (43.6)	0.309	73 (66.4)	37 (33.6)	0.038
Yes	25 (65.8)	13 (34.2)		18 (47.4)	20 (52.6)	

EBC, early breast cancer; LABC, locally advanced breast cancer; ECE, extracapsular extension; LVI, lymphovascular invasion. *n=144; #n=143

Table 3. Eight Year Survival Analysis (N=148)

Characteristics	Relapse free survival %	Relapse free survival p-value	Overall survival %	Overall survival p-value
Age (years)				
<50	55	0.194	79	0.736
>50	61		70	
Menopausal status				
Premenopausal	67	0.621	91	0.097
Post menopausal	52		66	
Breast cancer type				
Early	60	0.086	90	0.008
LABC	56		51	
Surgical procedure*				
MRM	56	0.986	74	0.409
BCS	58		80	
Axillary involvement				
Clear	69	<0.001	86	<0.001
Involved	35		53	
Pathological tumor size (cm)*				
<5	58	0.106	74	0.741
>5	47		80	
Grade#				
2	45	0.418	73	0.973
3	66		75	
LVI*				
Absent	44	0.297	72	0.118
Present	59		73	
ECE*				
Absent	64	<0.001	87	<0.001
Present	41		41	
Lymphnode*				
Positive	56	0.1	50	0.006
Negative	60		90	

MRM, modified radical mastectomy; BCS, breast conservation surgery; EBC, early breast cancer; LABC, locally advance breast cancer; ECE, extracapsular extension; LVI, lymphovascular invasion. *n=144; #n=143

higher tumor grade (66%), presence of LVI (59%), absence of ECE (64%; p-value <0.001) and negative lymph nodes (60%). Improved OS was seen in patients with <50 years age (79%), premenopausal status (91%), EBC (90%; p-value 0.008), no axillary involvement (86%; p-value <0.001), higher tumor grade (75%), presence of LVI (73%), absence of ECE (87%; p-value <0.001) and negative lymph nodes (90%; p-value 0.006).

Discussion

TNBC are distinct subtype of breast cancer that are clinically characterized as aggressive and less responsive to treatment and associated with poorer prognosis. Management of the disease also requires stringent approaches. The median age at the time of diagnosis was 49 years in our study which may be considered as younger age. Previous reports have also suggested a younger age at diagnosis in TNBCs (Hudis and Gianni, 2011; Sen et al., 2012). Majority of patients in the present data were postmenopausal. Studies suggest that the hormonal status of the patient in postmenopausal state may have an implication in the tumor growth. It was also earlier suggested that some conditions related to patient's menopausal status may select tumor cells in relation to angiogenesis (Demicheli et al., 2004). Locally advanced tumor was seen in 57 (38.5%) patients and had distinct clinical features of large tumor size and/ or lymph nodes involvement. Majority of the patients were pathological stage II (64.4%), and grade 3 tumors (65.7%). Comparison of EBC and LABC offered statistical significance in terms

of clinical stage. Higher disease stages are associated with LABC (Table 1). The above features suggest an aggressive nature of this disease which also correlates with other published studies (Malorni et al., 2012).

MRM was the main surgical procedure followed by breast conserving surgery. The selection of surgical procedure depends on the extent of disease as well as patients choice, social and cultural differences in the Indian population. Age group wise comparison showed that the pathological tumor size > 5 cm was observed more commonly in the patients age group less the 50 years while patients > 50 years of age had higher preponderance of tumor size < 5 cm. The results confirm that majority of the patients are diagnosed in the early stages of the disease (Hudis and Gianni, 2011; Sen et al., 2012).

Survival analysis revealed that better RFS and OS are significantly associated with EBC. The patients with EBC in the present study were offered adjuvant systemic chemotherapy and/or radiotherapy to minimize the risk of relapse. In LABC group, majority of the patients were offered with neo-adjuvant chemotherapy followed by surgery and adjuvant chemotherapy. TNBC usually respond well to the systemic radiotherapy and chemotherapy although there are increasing risks of relapse. This is also true in the present study as well as published literature (Rhee et al., 2008). Axillary lymphnode involvement results in poor RFS as well as OS which is also statistically significant. It is well known that nodal disease involvement is one of the prognostic factors in breast cancer that can predict relapse of the disease. Our result is in accordance with other published studies (Ovcaricek et al., 2011; Tian et al., 2008). Pathological characteristics such as presence of LVI did not significantly affect the RFS and OS, however, ECE presence was found to be associated with decreased RFS and OS significantly. The result is in line with a study by Kong et al (Kong and Hong, 2013).

Eight year RFS and OS was 58% and 75%, respectively. The data from one of the Chinese studies had revealed disease free survival and overall survival as 77.78% and 79.92% (Li et al., 2013). Another study from USA has showed a 3 year survival as 63% for RFS and 71 % for OS (Dawood et al., 2009). Study from one of the European countries has observed 5 year RFS to be 68.2% and OS as 74.5% (Ovcaricek et al., 2011). These data revealed variability in the survival outcomes across different regions of the world. It may be due to the differences in the stage of disease at presentation, possible omission of stage 4 disease from survival analysis, different chemotherapy regimens, etc. Literature has pointed out that TNBC has increased chances of early recurrences and poor overall survival outcomes followed by treatment. Our results also represent this phenomenon, though the overall survival is better keeping in view of the number of recurrences 38 (25%). Liedke et al (2008) have also showed that relapses as well as deaths are higher in the first 3 years after the diagnosis of breast cancer. Even with the risk of relapses, patients who are disease free in long term are less likely to die with the disease. Patients with TNBC do not get benefited from hormonal therapy and/or trastuzumab. However, these tumors are chemosensitive in nature, they respond well to the standard systemic chemotherapy regimens of anthracyclins and taxanes which provide a good treatment response, though may result in early relapse (Liedke et al., 2008; Keam et al., 2007). Research is underway in the area of targeted treatment for this group of cancer. Some TNBCs may have a dysfunctional BRCA1 pathway and thus may be sensitive to the inhibitors of the PARP enzyme that selectively target cell's deficient DNA repair (Foulkes et al., 2010).

The present study has limitation of selection bias which may be due to the retrospective nature. Overall, TNBCs are aggressive tumors which show poor long term RFS and OS. TNBCs who had locally advanced disease had higher recurrence rate and more aggressive clinicopathological characteristics than EBC. Early TNBC patient had a better OS than LABC patients. Patients with TNBC benefit from chemotherapy, thus better and less toxic treatment options are needed. Identification of newer targets and development of targeted therapies are the need of the hour.

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