RESEARCH ARTICLE

Outcomes of Triple-Negative Versus Non-Triple-Negative Breast Cancers Managed with Breast-Conserving Therapy

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Abstract

Background: Triple negative breast cancer is associated with aggressive behavior and high risk of local and regional failure. Aggressive surgical intervention is considered suitable. This makes role of breast conserving therapy (BCT) debatable in these patients. The objective of this study was to compare outcome of BCT for triple negative versus non-triple negative breast cancer. Materials and Methods: Medical records of patients who underwent breast conserving therapy from 1999 to 2009 at Shaukat Khanum Cancer Hospital and had complete receptor status information were extracted. Patients were divided into triple negative breast cancer (TNBC) and non-TNBC. Patient characteristics, medical treatment modalities and adverse events were compared. Expected five year locoregional recurrence free, disease free and overall survival was calculated. The Cox proportional hazard model was used to identify independent predictors of outcome. Results: A total of 194 patients with TNBC and 443 with non-TNBC were compared. Significant difference was present for age at presentation (p<0.0001), family history (p=0.005), grade (p<0.0001) and use of hormonal therapy (p<0.0001). The number of locoregional failures, distant failures and mortalities were not significantly different. No significant difference was present in 5 year locoregional recurrence free (96% *vs* 92%, p=0.3), disease free (75% *vs* 74%, p=0.7) and overall survival (78% *vs* 83%, p=0.2). On multivariate analysis, tumor size, nodal involvement and hormonal treatment were independent predictors of negative events. Conclusions: Breast conserving therapy has comparable outcomes for triple negative and non-triple negative breast cancers.

Keywords: Triple negative breast cancer - breast conservative therapy - outcome

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Introduction

Gene expression profiling has shown that breast cancer is not a single disease but a spectrum of biological diversity (Lowery et al., 2012). Expression and identification of 496-gene has classified breast cancers into various subtypes. These include luminal subtypes which express estrogen receptor (ER) and progesterone receptor (PR), Her2/neu subtype that over express Her2/neu but are negative for ER/PR and basal subtype that are predominantly ER/PR-ve and Her2/neu-ve (triple negative) (Perou et al., 2000; Sorlie et al., 2001). Triple negative receptor status serves as a proxy for basal like tumors in the clinical setting where whole genomic profiling is not possible and immunohisto chemical staining (IHC) serves the purpose with 80-97% positive predictive value (Nielsen et al., 2004; Rakha et al., 2008; Spitale, 2009; O'Brien, 2010). Triple negative breast cancer (TNBC) has been associated with worse prognosis, higher grade and poor differentiation (Mersin 2008; Dawood et al., 2009; Kwan et al., 2009; Ma et al., 2012; Lie et al., 2013). Although TNBC has been linked with an increased risk of local and distant recurrence and elevated rates of mortality within first five years of treatment; data regarding outcomes of BCT in TNBC remain conflicting (Haffty et al., 2006; Dent et al., 2007; Nguyen et al., 2008). A recent meta-analysis reported outcomes in 15,312 patients based on receptor status and treatment provided. In the cohort of TNBC, patients who received BCT were less likely to develop locoregional and distant mets when compared with mastectomy. In the cohort of BCT, the triple negative subtype increased the risk of both locoregional and distant relapse in comparison with Non-TNBC (RR 1.88, 95%CI 1.58-2.22; RR 2.12, 95%CI 1.72-2.62) (Wang et al., 2013).

The objective of this study was to compare locoregional recurrence free, disease free and overall survival between triple negative and non-triple negative breast cancer managed with breast conservative therapy in our center.

Materials and Methods

Retrospective chart review of patients who underwent BCT at our institute from 1997 to May 2009 was performed. A total of 637 patients with identifiable

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estrogen, progesterone and Her2/neu receptor status were included in the study. All patients received breast conservation surgery with adjuvant radiation. The standard dose of adjuvant radiation was 50Gy to whole breast and 10Gy boost to surgical cavity. Neoadjuvant chemotherapy was used in patients with locally advanced and node positive tumors. Adjuvant chemotherapy was used in patients with pathologically staged T2 tumors or above, positive nodes and poor differentiation. Hormonal therapy was used in estrogen and progesterone receptor positive tumors. Receptor status was confirmed using Immunohistochemical staining (IHC) and equivocal Her2/neu (2+) results were subjected to Florescent in Situ Hybridization (FISH). Staining of 1% or above on IHC was considered positive for estrogen and progesterone receptors. Patients were followed 3 monthly for 1 year, 6 monthly for 2 years and yearly thereafter with regular bilateral mammograms.

Patients in the current study were divided into 2 groups. Tumors that were Estrogen receptor (ER), Progesterone receptor (PR) and Her2neu negative were grouped as Triple negative breast cancer (TNBC). If any one, two or three receptors were positive; patients were considered as Non-TNBC. Patient characteristics including age at presentation, family history and clinicopathological variables were assessed. Actual number of observed adverse events was compared between two groups. Adverse events included locoregional failures, distant failures and death. Local failure was defined as a recurrence in operated breast. Regional failure was defined as recurrence in ipsilateral axillary, supraclavicular or internal mammary lymph nodes. Any other site of recurrence was defined as distant metastasis. Locoregional Recurrence Free Survival (LRRFS) was calculated by subtracting date of locoregional failure from date of surgery while Disease Free Survival (DFS) was calculated by subtracting date of local, regional or distant failure from date of surgery. Overall Survival (OS) was calculated by determining time duration between death of patient irrespective of cause or date of last follow up from date of surgery.

For statistical analysis of patient characteristics, medical treatments and adverse events, chi square test or Fishers exact test was used. Tumor size was grouped as early (T1/T2) and advanced (T3/T4) for statistical analysis. Kaplan Meier curves were used to calculate expected 5 year LRRFS, DFS and OS and Log rank test was used to determine significant differences between TNBC and Non-TNBC groups. Cox proportional hazard regression model was used for univariate and multivariate analysis. Variables that were found significant on univariate analysis were included in multivariate analysis and 95% confidence intervals and hazard ratios were calculated. A P value <0.05 was considered significant for all analysis. SPSS version 20 was used for statistical analysis. This study was granted exemption from formal review by local ethics committee.

Results

A total of 194 patients with TNBC and 443 patients with Non-TNBC were included in the study. Median age was 39.4(19-71) years and 43.2(17-82) years for two groups respectively. Median follow up was 48 (9-142) months for TNBC and 49 (1-169) months for Non-TNBC. Table 1 represents distribution of various patient characteristics in two groups. A statistically significant difference was present for age at presentation, family history of breast cancer, grade of tumor and use of hormonal therapy between two groups. TNBC had 56% patients aged <40 years as opposed to 39% patients in Non-TNBC group (p<0.0001). A positive family history was present in 22% patients with triple-ve breast cancers and 13% patients with Non-TNBC (p=0.005). A significantly high percentage of TNBC had poorly differentiated tumors when compared with their counterparts i.e. 78% versus 46% (p<0.0001). Use of hormonal therapy was significantly high in Non-TNBC group where 352 (80%) patients received hormonal therapy versus 1(0.5%) patients in TNBC group (p<0.0001).

Despite statistically significant difference in certain patient characteristics, distribution of adverse events was not significantly different between two groups. As shown in Table 2, the number of observed locoregional failures (4.6% versus 6.3%), distant failures (17.5 % versus 15.6%) and deaths (19.6% versus 15.3%) were not significantly different in two groups.

Expected 5 year LRRFS for the TNBC and Non-TNBC groups was 96% and 92% respectively. Although a small difference in LRRFS were present, it was not significantly different on Log rank test (p=0.33). Similarly, 5 year DFS for two groups was 75% and 74% and was not statistically significant (p=0.73). The expected 5 year OS for these groups was 78% and 83% and not significantly different (p=0.28). Figure 1 represents Kaplan Meier curves with

Table 1. Patient Characteristics and Treatment Modalities

		Total	TNBC		Non-TNBC		p value
			No.	%	No.	%	
		637	194	30.5	443	69.5	
Age	<40	283	109	56.2	174	39.3	<0.0001
	>40	354	85	43.8	269	60.7	
Family History	Positive	101	43	22.2	58	13.1	0.005
	Negative	485	132	68	353	79.7	
	Unknown	51	19	9.8	32	7.2	
Histology	Ductal	616	188	96.9	428	96.6	NS
	Lobular	12	3	1.5	9	2	
	others	9	3	1.5	6	1.4	
Grade	Well	36	7	3.6	29	6.5	<0.0001
	Moderate	248	36	18.6	212	47.9	
	Poor	353	151	77.8	202	45.6	
Tumor size	T1	119	39	20.1	80	18.1	NS
	T2	437	128	66	309	69.8	
	T3	66	24	12.4	42	9.5	
	T4	15	3	1.5	12	2.7	
Nodal involvement	N0	317	107	55.2	210	47.4	NS
	N+	320	87	44.8	233	52.6	
Stage	I	72	21	10.8	51	11.5	NS
	II	428	139	71.6	289	65.2	
	III	137	34	17.5	103	23.3	
Neoadjuvant	Received	163	50	25.8	113	25.5	NS
	Not received	474	144	74.2	330	74.5	
Hormonal	Received	353	1	0.5	352	79.5	<0.0001
	Not received	284	193	99.5	91	20.5	
Adjuvant chemo	Received	415	136	70.1	279	63	NS
	Not received	222	58	29.9	164	37	

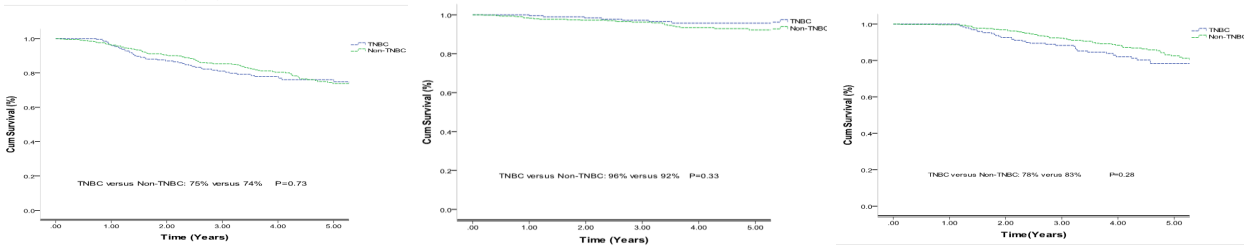

Figure 1. Expected 5 Year Locoregional Recurrence Free Survival, Disease Free Survival and Overall Survival for Patients with Triple Negative Versus Non Triple Negative Breast Cancers

Table 2. Adverse Events Observed in TNBC Versus Non-TNBC Groups

	Total	TNBC		Non TNBC		p value
		No.	%	No.	%	
Locoregional Failures	37	9	4.6	28	6.3	NS
Distant Failures	103	34	17.5	69	15.6	NS
Deaths	106	38	19.6	68	15.3	NS

Table 3. Multivariate Analysis of Risk Factors Found Significant on Univariate Analysis for Locoregional Recurrence Free, Disease Free and Overall Survival

	Variable	Hazard Ratio	95% CI	p value
Locoregional recurrence free survival				
Tumor size	T1/T2	1	1.38-5.98	0.005
	T3/T4	2.87		
Nodal involvement	N0	1	1.12-4.69	0.023
	N+	2.29		
Disease free survival				
Tumor size	T1/T2	1	1.16-2.65	0.007
	T3/T4	1.75		
Nodal involvement	N0	1	1.34-2.7	<0.0001
	N+	1.89		
Hormonal treatment	Not received	1	0.36-0.83	0.005
	Received	0.56		
Overall survival				
Tumor size	T1/T2	1	1.23-3.14	0.005
	T3/T4	1.96		
Nodal involvement	N0	1	1.47-3.34	<0.0001
	N+	2.21		
Hormonal treatment	Not received	1	0.27-0.71	0.001
	Received	0.44		

Log rank test values for LRRFS, DFS and OS. Univariate analysis was done for all patient characteristics and medical treatment modalities. Tumor size, nodal involvement and use of hormonal therapy were statistically significant for LRRFS, DFS and OS. In addition use of neoadjuvant chemotherapy was found to be significant for DFS and OS while adjuvant chemotherapy was significant for OS alone. Table 3 represents multivariate analysis of variables found significant on univariate analysis for LRRFS, DFS and OS. Advance tumor size (HR=2.87, CI=1.38-5.98, p=0.005) and nodal involvement (HR=2.29, CI=1.12-4.69, p=0.02) were independent predictors of LRRFS. Advanced tumor size, nodal involvement and use of hormonal therapy were independent predictors of DFS and OS. Use of hormonal therapy was associated with nearly 50% reduction in risk of local/regional/distant disease recurrence (HR=0.56, CI=0.36-0.83, p=0.005) or death (HR=0.44, CI=0.27-0.71, p=0.001) of patient.

Discussion

The current study supports a favorable role of BCT in TNBC. Despite a significantly young age at presentation, poor differentiation and strong family history of breast cancer, no significant difference in locoregional or distant failures and mortalities was observed. Expected 5 year locoregional recurrence free, disease free and overall survival was also comparable between TNBC versus Non-TNBC patients. With a median follow up of more than four years, locoregional recurrence rate was comparable with randomized trials of BCT versus mastectomy (Van et al., 2000; Fischer et al., 2002).

A case for aggressive surgical management of TNBC is made due to an alleged elevated rate of locoregional and distant adverse events when compared with Non-TNBC. Zaky et al. (2011) in their study on outcome of BCT for triple negative tumors showed a high local (12% versus 4%) and distant (15% versus 4%) recurrence rate for TNBC versus Non-TNBC. Triple negative status and African American race were independent predictors of inferior overall survival. The study however had a relatively small sample size with 33 TNBC and 160 Non-TNBC patients. Nguyen et al. (2008) also showed a higher local recurrence rate of 7% in triple negative group when compared with recurrence rates for luminal type A (0.8%) and type B (1.5%) subgroups. Variable results were reported in other studies on TNBC managed with BCT (Nguyen et al., 2008; Freedman et al., 2009; Miller et al., 2009; Voduc et al., 2010). In a recent meta-analysis, Lowery et al. (2012) included 12, 592 patients from 15 studies who either received BCT (n=7176) or mastectomy (n=5416). Around 15% (n=1865) patients had TNBC. Patients with TNBC or her2/neu over expression had high rate of locoregional recurrence when compared with luminal tumors irrespective of whether they received BCT or mastectomy. They concluded that breast cancer subtypes may help guide which patients need more aggressive local intervention. Contrary to this, it was shown that T1-2, N0 TNBC patients managed with BCT had low locoregional recurrence rate in comparison with patients in same stage managed with modified radical mastectomy (Abdulkarim et al., 2011; Adkins et al., 2011) in their study on outcomes of BCT versus mastectomy in 1325 patients with TNBC showed no benefit of mastectomy over BCT. There was improved 5 year LRRFS (76% *vs* 71%), distant metastasis free survival (68 *vs* 54) and overall survival (74 *vs* 63) for patients who received BCT. The type of operation (BCT *vs* mastectomy) was not an independent predictor

on multivariate analysis. Another study showed minimal difference in local failure between patients with TNBC and Non-TNBC who received BCT (Solin et al., 2009). At median follow up of 3.9 years, local failure was high in TNBC group (8% *vs* 4%, p=0.04), but on multivariate analysis triple negative status did not emerge as an independent predictor of local failure.

In the current study, 194 patients with TNBC received BCT. Median follow up was >4 years which is significant as it has been shown that TNBC have a high risk of an adverse event in the first five years post treatment (Haffty et al., 2006; Dent et al, 2007; Nguyen et al., 2008). No significant difference was observed in actual numbers of observed adverse events between TNBC and Non-TNBC patients. Also, LRRFS, DFS and OS were similar for both groups. It is believed that factors like young age and poor differentiation of triple negative cancers contribute to their aggressive nature (Mersin et al., 2008; Kwan et al., 2009; Dawood et al., 2010). These factors have been shown to be independent predictors of outcome in breast cancer patients (Adami et al., 1986; Chung et al., 1996; Sidoni et al., 2003; Sharif et al., 2010). Lack of effectiveness of hormonal therapy limits the medical options available for management of TNBC. In the present study, a high number of Non-TNBC patients also had poorly differentiated tumors (46%) and presented at a younger age (40%). In addition, very few patients with Her2 neu expressing tumors received trastuzumab in the present study. Trastuzumab significantly reduces the risk of locoregional recurrence in this patient subgroup. This might partly explain why similar outcomes were seen for these two groups of cancers in the current study. The 5 year OS for all breast cancers is estimated to be around 89% and drops to less than 80% for TNBC patients (Haffty et al, 2006; Bauer et al., 2007). No statistically significant difference in overall survival between TNBC and Non-TNBC was observed in the present study (78% *vs* 83%, p=0.2).

Nearly 25% patients in both groups received neo adjuvant chemotherapy. This group represents patients who presented with advance tumor size and/or nodal involvement. Adkins, et al. (2011) excluded patients who received neoadjuvant chemotherapy in their study on outcomes of BCT *vs* mastectomy in TNBC in order to have accurate pathological variables. They accepted that this might exclude patients with high risk tumors and introduce bias in the study. Since a significant number of patients in the present study had locally advanced disease at presentation and neoadjuvant chemotherapy was frequently used, we included these patients to avoid selection bias. TNBC are not sensitive to hormonal therapy and it remains unclear whether aggressiveness of TNBC is due to lack of medical treatment options or an inherent aggressive nature (Chu et al., 2012). A significantly high use of hormonal therapy in Non-TNBC versus TNBC patients was understandably guided by the receptor status of patients. On multivariate analysis, hormonal therapy was an independent predictor of disease free and overall survival alongside tumor size and nodal involvement. Use of hormonal therapy reduced the inferior disease free and overall survival by nearly 50%. Despite the fact that hormonal therapy was an independent predictor of outcome and was used selectively in Non-TNBC; adverse events and survival was not different between the two groups.

A limitation of the study was its retrospective design. The study included patients over a period of thirteen years and changes in diagnostic methods, treatment modalities and follow up in this time period and their effects on outcome could not be measured due to retrospective nature of the study. Also, it can be argued that outcomes between TNBC and Non-TNBC could have been different if patients had a longer follow up.

In summary, no difference in outcomes between TNBC and Non-TNBC in the current study was observed. Considering that facilities for IHC staining, stereotactics, sentinel lymph node biopsy, tumor boards, multi-modality treatment and long term follow up are seldom available in developing countries like Pakistan; the study reports outcomes of TNBC managed with BCT in a significantly high number of patients. In the background of late presentation due to absence of screening, younger age, nodal involvement and poor differentiation; this characteristic population demonstrates comparable results after BCT in TNBC and Non-TNBC patients. Studies with longer follow up and significant sample size are required to better identify the differences, if any present, between outcomes of TNBC and TNBC after BCT.

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