

# Effects of Nodal Status and Extent of Surgery on Survival in Triple Negative Breast Cancer

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**Abstract:** *Background:* Triple Negative Breast Cancer (TNBC) is one of the most aggressive but least understood subtypes of breast cancer. The roles of nodal status and type of surgery while essential in determining the outcomes of patients with TNBC remain controversial and require more examination.

*Materials and Methods:* Clinical and pathological data were retrieved from 1990 until 2001 by retrospective chart review for patients with breast cancer at the American University of Beirut Medical Center. Out of 1455 patients, 524 had complete histological data, of which 138 (26.3%) were diagnosed with TNBC. Median follow up time of patients with TNBC was 3.34 years (Range 0.55 - 10 years). We used the Kaplan-Meier and Cox proportional hazard models to evaluate prognostic effects and estimate hazard ratios (HR).

*Results:* For the 138 patients with TNBC, median age at presentation was 50.91 years (Range 26 - 81). One-year, 5 and 10-year survivals for node-negative patients (N0) were respectively 98.3 %, 91.1% and 74.5 %, compared to 98.5%, 70.3 % and 42.2% for node-positive patients (N1-N3). Numerical nodal staging did not significantly correlate with survival. On multivariate analysis, higher stage (H.R 3.01) and Breast-Conserving Therapy (BCT) had a significant effect on the survival of TNBC patients (H.R 0.195)

*Conclusion:* Lymph node-positivity predicted poorer survival in patients with TNBC. However, within the group of patients with positive LN, the number of positive lymph nodes did not alter survival nor did the tumor size. BCT including radiation therapy had a better effect on survival when compared to mastectomy.

**Keywords:** Triple negative breast cancer, nodal status, breast conservative therapy, modified radical mastectomy, survival.

## INTRODUCTION

Breast cancer is the most common non-skin cancer in women; accounting for 23% of newly diagnosed cancer cases worldwide and also for 14% of total cancer related death [1]. Based on immunohistochemistry, breast cancer is classified into various categories according to the expression of estrogen receptor (ER) and progesterone receptor (PR) and human epidermal growth factor receptor 2 (Her2): Luminal A, Luminal B, HER2-overexpressive and Triple Negative Breast Cancer (TNBC). Microarray-based expression defined the "basal-like breast cancer" subtype which shows substantial but incomplete overlap with TNBC [2-8]. The different biological, hormonal and molecular behaviours between the breast cancer subtypes reflect clearly on the anatomical and clinical manifestations. TNBC accounts for 7-20% of all breast cancer cases [9-10]. Patients with TNBC present at a younger age. Typically, these

tumors usually have a higher grade and a larger size when compared to other subtypes [11-13]. Clinically TNBC is characterized by an earlier locoregional recurrence rate and a worse overall survival rate [14-19]. Interestingly, the linear correlation between tumor size and the number of lymph nodes classically found in breast cancer is absent in TNBC [5, 13, 20]. There is also a higher predilection for seeding into lungs and brain than to bone in contrast to other subtypes [21-23].

Traditionally, prognosis in solid tumors is correlated with gross anatomical features as depicted by the TNM staging system [24]. In breast cancer, a larger tumor size and a higher number of positive lymph nodes imply a worse impact on survival [25-26]. But recently, the prognostic role of lymph node status in TNBC patients has been subject of a rising debate [27-28]. Also effect of surgery in patients with early TNBC is controversial [29].

Our aim was to evaluate the impact of classical prognostic factors on survival of patients with Triple Negative Breast Cancer (TNBC), and to evaluate specifically the prognostic role of nodal status and the type of primary surgical approach on survival.

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## MATERIAL AND METHODS

From 1991 to 2001, 1450 breast cancer patients were seen at the American University of Beirut Medical Center. After approval by the Institutional Review Board (IRB), medical charts were reviewed and clinical and pathological data were retrieved. ER and PR positivity were defined as nuclear staining of any intensity in at least 1% of tumor cells. HER2-positivity was defined either immunohistochemically, where tumors showed strong and complete circumferential membranous staining in at least 30% of cells, or by gene amplification, as measured by Fluorescent In Situ Hybridization FISH, where the currently used test does not include centromeric staining for chromosome 17, and the cut off for HER-2 positivity was an average of 6-fold amplification of the HER-2 gene in the assessed (at least 20) tumor cells. After checking for the full immunohistochemical profile, including the HER2 overexpression not common at that time, only 524 patients satisfied the full criteria to be assigned into any

of the four immunohistochemical classes. Out of these patients, 138 (26.3%) had TNBC. The tumor, node and metastasis (TNM) system of the American Joint Committee on Cancer (AJCC) 6th edition was used for staging [24].

Overall survival (OS) was defined as the time extending from the date of diagnosis of breast cancer till the last date of follow up or date of death. Patients were divided as dead or alive, with the appropriate date of each variable after completion of a follow up by chart review.

## ANALYSIS

Data from the medical records of 138 patients were retrieved, coded and entered into the SpSS software (v.18). Frequency and percentage were used to describe our sample with the exception of age where the median and range were calculated. Kaplan Meier and Log Rank test were applied in order to compute

**Table 1: Patients Demographics**

Parameter	N	(%)
<b>Age</b>		
<45	47	(34)
46 – 65	74	(53)
>65	16	(11)
<b>Family History of Breast Cancer</b>		
Yes	21	(15)
No	119	(85)
<b>Previous malignancies</b>		
Present	3	(2)
Absent	136	(98)
<b>Type of surgery</b>		
None	8	(5)
Mastectomy	82	(59)
Conservative surgery	42	(30)
<b>Radiotherapy</b>		
Yes	83	(60)
No	46	(33)
<b>Number of LN dissected</b>		
Less than 10	11	(7.9)
10 and more	112	(80.6)
<b>Number of LN dissected</b>		
Median	17	
Range	2 – 49	
<b>Age at menarche</b>		
≤ 11 years	10	(13)
12 – 13 years	46	(61)
≥14 years	19	(25)

cumulative survival rates at 1, 5 and 10 years and to calculate the p-values among the different variables. A Cox-proportionate Hazard Technique was implemented in order to create a multivariate analysis. Alpha was set at 5% significance level.

## RESULTS

138 patients with negative ER, PR, and HER2 overexpression were identified as having TNBC. Median age at presentation was 50.91 (Range 26 - 81). Table 1 summarizes the clinical and pathological

characteristics of all patients. On univariate analysis 1, 5 and 10 year survival for node-negative patients (N0) was 98.3 %, 91.1% and 74.5 % respectively, compared to 98.5%, 70.3 % and 42.2% for patients who had any positive lymph node (N1-N3) ( $p = 0.044$ ). When comparing groups N1, N2 and N3, a higher number of positive lymph nodes affected overall survival but without statistical significance ( $p = 0.773$ ). Other significant factors on survival were stage ( $p < 0.001$ ), breast conservative therapy ( $p = 0.03$ ), tumor size ( $p = 0.047$ ), and lymph vascular invasion ( $p = 0.028$ ) (Table 2). On multivariate analysis, and after computing for all

**Table 2: Univariate Analysis of Survival**

Parameter	N	Survival probability			p-value
		1 year	5 year	10 year	
<b>Age</b>					
< 45	47	95.7 ± 5.7	78.5 ± 14.9	78.5 ± 14.9	0.319
46 – 65	74	100	83.2 ± 10.2	63.3 ± 18.4	
≥ 66	16	93.3 ± 12.5	76.6 ± 23.7	28.7	
<b>Stage</b>					
I	20	100	100	66.7 ± 53.3	< 0.001
II	69	98.6 ± 2.7	88.2 ± 9	68.1 ± 16.3	
III	31	96.8 ± 6.3	59.1 ± 21.6	29.5	
IV	8	100	0	0	
<b>Grade</b>					
I	8	100	100	66.7 ± 53.3	0.206
II	51	96.1 ± 5.3	84.4 ± 11.9	64 ± 22.9	
III	71	100	76.8 ± 12.2	49.5 ± 19.2	
<b>Type of Surgery</b>					
Modified Radical Mastectomy	82	97.6 ± 3.3	74.9 ± 11.2	48.5 ± 17.1	0.003
Breast Conservative Therapy	42	100	92.7 ± 9.9	84.9 ± 17.1	
<b>Tumor size</b>					
Less than or equal 2 cm	29	100	91.7 ± 15.7	68.8 ± 40.6	0.047
Between 2 and 5 cm	83	98.8 ± 2.4	77.4 ± 10.6	58.7 ± 14.9	
More than 5 cm	15	93.3 ± 12.5	51 ± 37.2	25.5	
<b>Lympho-vascular invasion</b>					
Negative	70	98.6 ± 2.7	90.7 ± 7.8	74.8 ± 14.7	0.028
Positive	53	98.1 ± 3.7	67.2 ± 16.5	43.2 ± 21.9	
<b>Number of positive LN</b>					
0	57	98.2 ± 3.3	91.1 ± 8.4	74.5 ± 15.1	0.213
1 - 3	35	100	66.9 ± 21.2	38.2 ± 34.9	
4 – 10	18	92.9 ± 13.5	82.5 ± 22.5	41.3	
> 10	17	94.1 ± 11.2	70.6 ± 24.5	47.1 ± 40.9	
<b>Number of positive LN</b>					
1 – 3	35	100	66.9 ± 21.2	38.2 ± 34.9	0.773
4 – 10	18	92.9 ± 13.5	82.5 ± 22.5	41.3	
> 10	17	94.1 ± 11.2	70.6 ± 24.5	47.1 ± 40.9	
<b>Positive LN</b>					
Present	68	98.5 ± 2.9	70.3 ± 14.3	42.2 ± 24.5	0.044
Absent	58	98.3 ± 3.3	91.1 ± 8.4	74.5 ± 15.1	

**Table 3: Multivariate Cox Regression**

Parameter	HR	95% CI	P-value
<b>Tumor size</b>			
Less than 2 cm	1		
Between 2 – 5 cm	2.4	0.3 – 19.5	
More than 5 cm	4.9	0.5 – 45.9	0.260
<b>Stage</b>			
I and II	1		
III and IV	3.1	1.1 – 8.4	0.027
Nb. of positive LN	1.00	0.9 – 1.0	0.396
<b>Type of surgery</b>			
Modified Radical Mastectomy	1	1	
Breast Conserving Therapy	0.2	0.04 – 0.9	0.03

the significant variables found in the univariate analysis, only advanced stages (III & IV) H.R= 3.01, 95% C.I (1.13 – 8.4) and BCT (breast conserving therapy including radiation therapy) (H.R= 0.195, 95% C.I (0.04- 0.85) had a significant effect on the survival of TNBC patients (Table 3). Chi-square analysis to evaluate the association between tumor size and Positive Lymph node, did not show any proportional relationship between the two variables (p=0.045) (Table 4).

## DISCUSSION

We evaluate the different prognostic factors that can affect the overall outcome of the patients with TNBC in

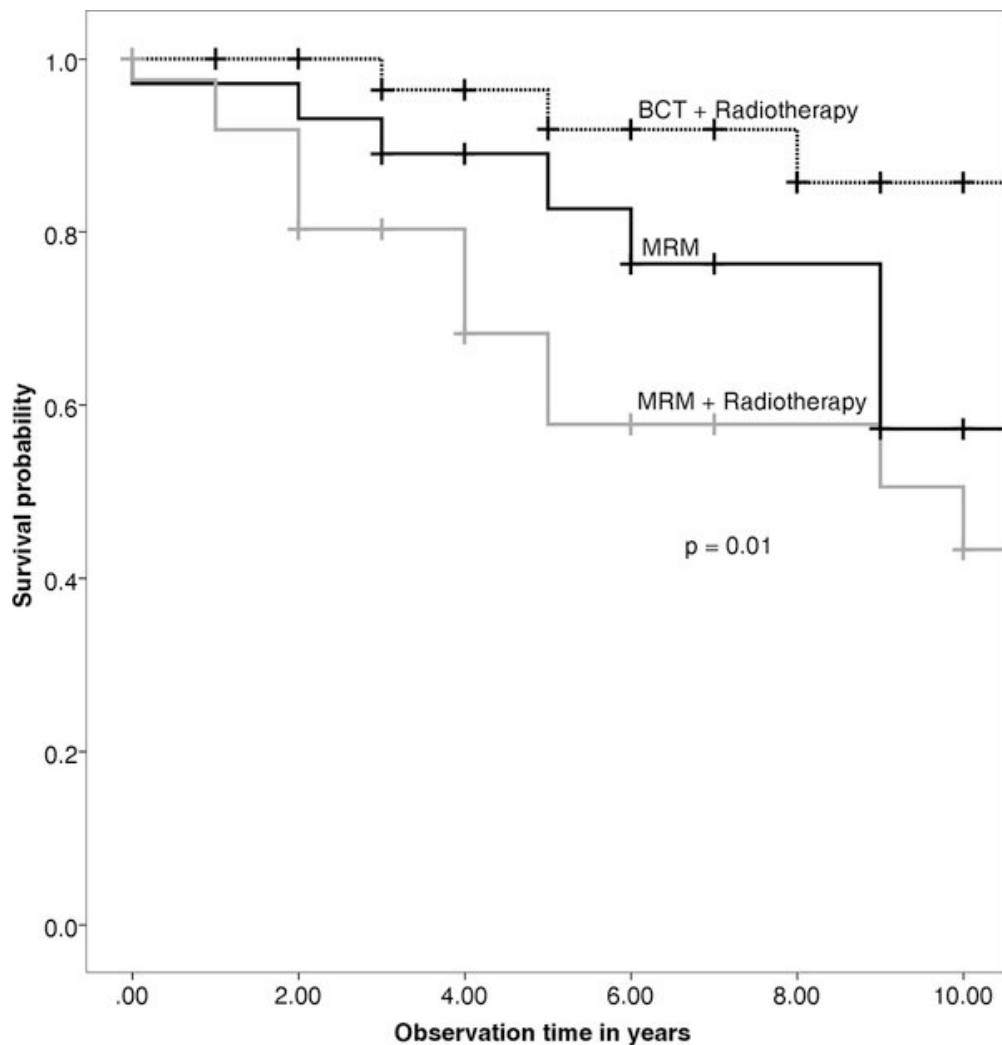
a study of 138 patients with TNBC. We report a lack of direct correlation between nodal status and survival. Advanced nodal status does not contribute to a worse survival with a statistical significance when considered outside the TNM staging. Our findings concur with the results of a recently published cohort on 1711 patients with TNBC where, after stratifying patients into different subcategories based on tumor size, authors found that the prognosis is not affected by the added number of positive lymph nodes, however having a negative nodal status led to a more favourable prognosis than having any positive nodal status [27]. The observed dissociation between tumor size and nodal status is also consistent with recent literature analysis [5, 11, 20, 25].

**Table 4A: Cross-Tabulation of Tumor Size with the Presence of Positive Lymph Nodes**

Parameter	Presence of positive LN		Total	p-value
	No	Yes		
<b>Tumor size</b>				
< 2cm	17 (65.4)	9 (34.6)	26	
2 – 5 cm	35 (44.9)	43 (55.1)	78	
> 5cm	3 (21.4)	11 (78.6)	14	
Total	55 (46.6)	63 (53.4)	118	0.025

**Table 4B: Cross-Tabulation of Tumor Size with Number of Positive Lymph Nodes**

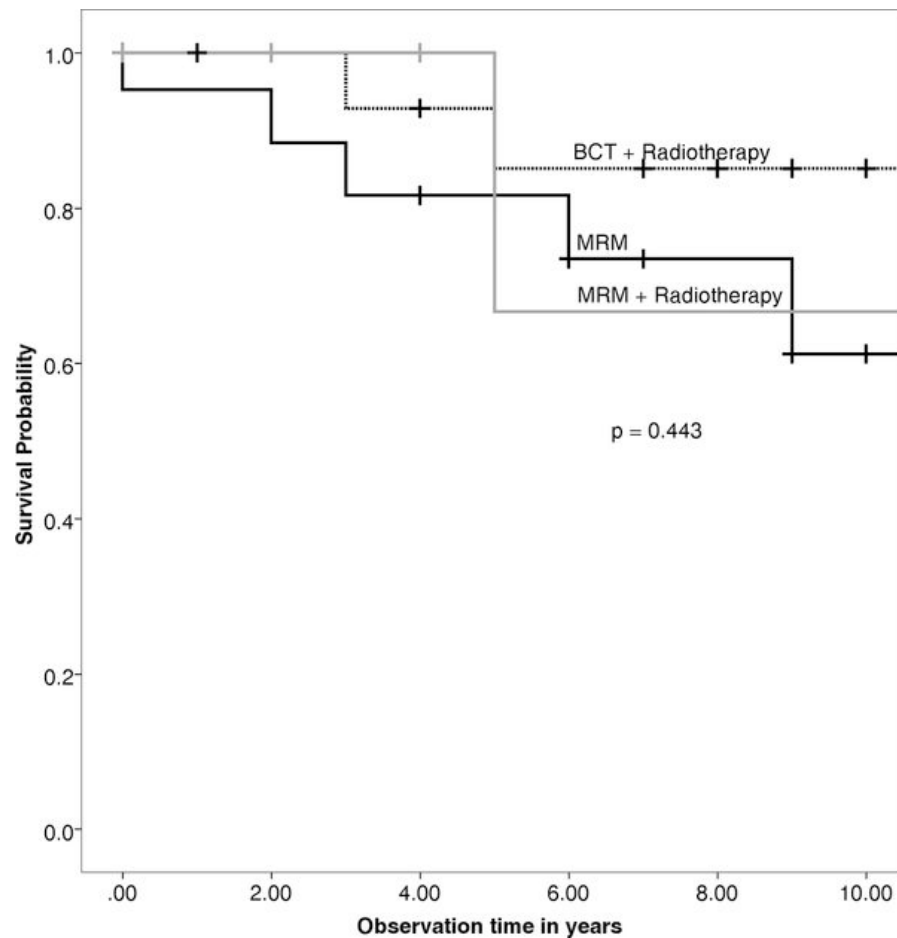
Parameter	Range of nb. of positive lymph node N (%)			Total	p-value
	1 – 3	4 – 10	>10		
<b>Tumor size</b>					
< 2 cm	7 (77.8)	2 (22.2)	0 (0)	9	
2 – 5 cm	22 (51.2)	9 (20.9)	12 (27.9)	43	
> 5 cm	5 (45.5)	1 (9.1)	5 (45.5)	11	
Total	34	12	17	63	0.227



**Figure 1:** Kaplan-Meier survival analysis for all patients.

Another major clinical finding is the controversial role of surgery in TNBC. A longer survival is observed with BCT compared with modified radical mastectomy (MRM) after controlling for tumor size, nodal status and stage on multivariate analysis. In fact, a significant superiority of a breast conservative approach was observed at 5 years with H.R= 4.11 C.I (1.29-4.27) and 10 years with H.R= 0.195 C.I (0.04- 0.85). The same idea was entertained in a large cohort published recently showing that patients who had conservative surgery with radiotherapy had a lower locoregional recurrence compared to TNBC patients who had MRM [29]. A large meta-analysis by the EBCTCG found a significant association between survival and locoregional recurrence [30]. The improved outcomes with breast conservative therapy challenge the historical wisdom whereby a more extensive surgery achieves better outcomes. With MRM, the tumor bulk is removed but circulating tumor cells are still there and can later on repopulate the original tumor site and/or

implant at distant metastatic sites [31]. The advantage of BCT in our data invites further discussion of potential additive benefits of radiation therapy in the management of TNBC. Radiation therapy has been shown to reduce the risk of locoregional recurrence by one third, so in absolute terms this reduction is more pronounced in high risk tumors as in the case of triple negative breast cancer [30]. Additionally, triple negative tumors have a high preponderance of p53 and BRCA mutations, their DNA is labile and sensitive to radiation induced damage [32]. The second potential explanation is that more surgery implies a worse outcome. Exposure of patients to surgical stress was shown to induce the release of plethora of inflammatory cytokines and growth stimulating factors promoting metaplasia, angiogenesis and metastasis [33-36]. When combining surgery and radiation into a new set of variables, we found that BCT is superior to MRM or MRM with radiotherapy (RT) (HR=3.1 and 5.55 for MRM and MRM+RT respectively with a p-value of



**Figure 2:** Kaplan-Meier survival analysis for patients with tumour size less than 5 cm and negative nodal status.

0.009). One potential confounder is the fact that larger tumors with more advanced nodal status subjected to MRM+RT inherently have a worse prognosis. After controlling for tumor size and nodal status, in patients with a tumor size less than 5 cm and negative nodal status, BCT was still superior to MRM but without statistical significance (HR=2.75 and 1.56 for MRM and MRM + RT respectively and p-value of 0.433). It is also of interest to note that 26% of our patients with breast cancer had triple negative disease. This represents a rather high percentage of TNBC when compared to other series [11-13].

## CONCLUSION

We addressed the prognostic factor of TNBC in this paper and concluded that the nodal status has an important role in predicting the survival of the patients; this role loses its importance once we take into consideration the effect of added number of positive lymph nodes. We also highlighted the potential benefit of a conservative approach combining limited surgery and radiation therapy in improving overall survival in this particular patient population. Our findings in triple

negative breast cancer provide additional insight to rethink current notions of nodal numerical staging and surgical management in early stage TNBC.

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## ETHICAL APPROVAL

Charts review was approved by the Institutional Review Board.

## CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

## DISCLAIMERS

This study was presented as a poster presentation at the 8<sup>th</sup> European Breast Cancer Conference in

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