ORIGINAL REPORT

Triple-Negative Breast Cancer Survival in Iranian Patients

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Abstract- This study focused on triple-negative breast cancer (TNBC) that is characterized by the lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2). The primary goal of this study was to describe the relation between triple-negative receptor status and survival. This is the first study about triple-negative breast cancer in our community of the 1541 patients diagnosed with breast cancer between 2002 and 2007 at the Cancer Institute (Tehran, Iran). 107 patients were identified as TNBC and 107 patients were randomly selected as non-TNB. HER-2, ER and PR status were assessed by immunohistochemistry (IHC). Analyses of their collected data were performed retrospectively and then clinical and pathologic parameters were compared between two groups. In multivariate analysis, a significantly decreased overall survival was observed for patients with TNBC compared with non-TNBC (55.7 months *versus* 60.7 mounts; 95%CI: 51.1-60.3 and 57.9-63.5 for TNBC and non-TNBC respectively, *P*=0.0008). The 2- and 5-year estimates for overall survival were 69.8% and 62.3% for TNBC, and 90% and 83% for non-TNBC, respectively. During the study period, 36 (33.6%) patient of TNBC and 14 (13.1%) of non-TNBC presented local recurrence. Significantly decreased disease-free survival was also observed for patients with TNBC compared with non-TNBC (*P*=0.0004). The 2- and 5-year estimates for disease-free survival were 68% and 63% for TNBC; and 89% and 82% for non-TNBC, respectively. Significantly decreased distant metastasis free survival was also observed for patients with TNBC compared with non-TNBC (54.4 mounts *versus* 61.7 mounts; 95%CI: 49.8-59.0 and 59.1-64.4 for TNBC and non-TNBC respectively, *P*=0.0004). Triple negative breast cancer has a biologic aggressive behavior and poor prognosis. Therefore aggressive treatment and regular follow-up in early stage of diagnosis can be a significant impact on their prognosis.

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Keywords: Breast cancer; Iran; Survival, Triple negative

Introduction

Breast cancer is a heterogeneous disease with a different characteristics such as age, tumor stage, lymph node involvement and pathologic grade (1) which are associated with disease prognosis (2,3). Also it is a common disease and its incidence is increasing all over the world (4). During the past three decades the mortality rate of this cancer is decreased due to screening (5,6), follow-up (7) and progress in systemic adjuvant therapy specially targeted therapy (8). Triple-negative breast cancers (TNBCs) are defined as the lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) (9).

These cancers occur in approximately 10% to 25% of all patients with breast cancer (10-12). As the patients with TNBC lack the appropriate targets for molecular treatments, they do not benefit from modern drugs such as trastuzumab.

Recently, by gene expression profiling, breast cancer has been shown to be classifiable into five major biologically distinct intrinsic subtypes (13-16): luminal A, luminal B, HER2-overexpressing, basal-like and normal-like. Because of poor prognosis of TNBC, many scientists are trying to achieve improvement in survival of these patients.

As we do not have enough data to investigate the proportion of TNBC and its outcome in Iran, in this study we evaluated survival and clinicopathologic

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characteristics in patients with TNBC in comparison with non-TNBC patients.

Patients and Methods

Patients and data

Data used for analysis from cancer registry database for 1541 patients with breast cancer who were treated between March 2002 and February 2007 in the Cancer Institute (an institute in Tehran affiliated with Tehran University of Medical Sciences). 281 patients were excluded for analysis due to lack of tumor staging, grading, ER, PR, HER2 receptor status or inappropriate follow-up. The rest (1260) of patients had surgery (mastectomy or breast saving) and adjuvant chemotherapy or radiotherapy. Patients with negative staining for ER, PR and HER2 in immunohistochemistry (IHC) were defined as TNBC and patients with positive in one of these receptors were defined as non-TNBC. Clinical and histological characteristics of all patients were obtained from medical documents and entered retrospectively into a questionnaire. Overall survival (OS) was measured from the date of surgery to the date of last follow-up or death. Disease-free survival (DFS) was measured from the date of surgery to the date of disease relapse that confirmed by imaging or biopsy. Distant metastasis-free survival (DMFS) was measured from the date of surgery to the date of clinical or radiologic sign of distant metastasis.

Statistical analysis

Tumors negative for ER, PR, and HER-2 were classified as TNBCs and compared with tumors with any receptor positivity (non-TNBC). Parameters assessed included age at the time of diagnosis, tumor histology, nuclear grade, lymphovascular invasion, perineural invasion, tumor size, pathologic tumor (T) and nodal (N) score, OS, DFS, DMFS and type of surgery.

Data were entered into SPSS. Demographic and clinical data were analyzed descriptively as means, medians, or proportions. We used Chi-squares statistics to determine associations between tumor characteristics and TNBC. Survival curves were generated using the Kaplan-Meier graph.

Results

Of 1260 patients evaluated in this study, 122 identified as TNBC (9.6%), but only 107 who had enough follow-up were evaluated for data analysis. 107 non-TNBC cases, were randomly selected from the rest of the cases and the following comparisons were considered in two groups.

Prevalence of receptor positivity in non-TNBC patients

In non-TNBC patients, 79 (73.8%) were PR positive, 81 (75.7%) were ER positive, 51 (47.7%) were HER2 receptor positive, 78 (72.89%) ER and PR positive, 25 (23.36%) ER and HER2 receptor positive, 23 (21.45%) PR and HER2 receptor positive and 22 (20.56%) were triple-receptor positive.

Comparison of clinicopathologic characteristics between TNBC and non-TNBC patients

There were no significant differences in histologic subtypes, nodular involvement, perineural invasion, and surgical treatment method and chemo-radiotherapy between the two groups of patients (all of the patients had received chemo-radiotherapy) (Table 1 and Table 2).

In other characteristics the two groups were significantly different (Table 1); the mean age of patients in the TNBC group was significantly lower than patients in the non-TNBC group; Overall 60% of patients with TNBC were under 50 years of age as compared to 46% of patients in the other group. The mean tumor size in the TNBC group was significantly higher than the other group. The grade III tumor was more frequently observed in the TNBC group than in the other group and so was lymphovascular invasion.

Comparison of disease-free, metastasis-free and overall survival between TNBC and non-TNBC patients

A Kaplan-Meier survival analysis was performed for comparing the DMFS, DFS and OS in the two groups.

The mean time of follow-up of the patients after the end of the treatment was 38.24 ± 13.07 months.

34 patients (31.8%) of the TNBC group and 12 patients (11.2%) of the non-TNBC group died during follow-up. Overall survival was significantly different between the two groups (the *P*-value of log-rank test was 0.0008); mean overall survival time was 55.7 months (95% Confidence Interval: 51.1-60.3) in the TNBC group and 60.7 months (95% Confidence Interval: 57.9-63.5) in the non-TNBC group. The 2-year overall survival was 69.8% in the TNBC group *versus* 90% in the non-TNBC group and the 5-year OS was 69.8% in the TNBC group *versus* 90% in the non-TNBC group (Figure 1).

26 patients (24.3%) of the TNBC group and 9 patients (8.4%) of the non-TNBC group had distant metastasis during follow-up. DMFS was significantly different between the two groups (the *P*-value of log-rank test was 0.0022); mean DMFS time was 54.4 months (95% Confidence Interval: 49.8-59) in the TNBC group and 61.7 months (95% Confidence Interval: 59.1-64.4) in the non-TNBC group. The 2-year DMFS was 77.9% in the TNBC group *versus* 90.8% in the non-TNBC group and the 5-year DMFS was 72.6% in the TNBC group *versus* 90.8% in the non-TNBC group (Figure 2).

36 patients (33.6%) of the TNBC group and 14 patients (13.1%) of the non-TNBC group had recurrence during follow-up. DFS was significantly different between the two groups (the *P*-value of log-rank test was 0.0004); mean DFS time was 49.3 months (95% Confidence Interval: 44.2-54.3) in the TNBC group and 59.1 months (95% Confidence Interval: 55.7-62.5) in the non-TNBC group. The 2-year DFS was 68% in the TNBC group *versus* 89% in the non-TNBC group and the 5-year DFS was 63% in the TNBC group *versus* 82% in the non-TNBC group (Figure 3).

Table 1. The parameters of clinicopathologic characteristics with significant difference.

Parameter	TNBC (n=107)	Non-TNBC (n=107)	*P*-value
Age (mean ± SD, yrs)	46.7±11.1	50.4±9.6	0.009
Tumor Size (mean ± SD, cm)	3.9±1.7	3.2±1.5	0.001
Histological grade			
Grade1	3 (2.8)	9 (8.4)	0.000
Grade2	19 (17.8)	47 (43.9)	
Grade3	85 (79.4)	51 (47.7)	
Tumor score			
T1	17 (15.9)	30 (28)	0.01
T2	55 (51.4)	59 (55.1)	
T3	35 (32.7)	18 (16.8)	
Lymphovascular invasion			
Positive	62 (57.9)	42 (39.3)	0.006
Negative	45 (42.1)	65 (60.7)	

Table 2. The parameters of clinicopathologic characteristics with no significant difference.

Parameter	TNBC (n=107)	Non-TNBC (n=107)	*P*-value
Histological subtype			
Invasive ductal carcinoma	93 (86.9)	83 (77.6)	
Invasive lobular carcinoma	2 (1.9)	5 (4.7)	
Medullary carcinoma	9 (8.4)	9 (8.4)	0.357
Ductal in situ carcinoma	1 (0.9)	2 (1.9)	
Papillary	1 (0.9)	4 (3.7)	
Tubular carcinoma	1 (0.9)	4 (3.7)	
Nodular Involvement			
Positive	52 (48.6)	45 (42.1)	0.336
Negative	55 (51.4)	62 (57.9)	
Number of involved lymph node	2.3	2.32	0.978
Involved lymph node/Dissected lymph node	0.26	0.22	0.404
Perineural invasion			
Positive	39 (36.4)	31 (29)	0.244
Negative	68 (63.6)	76 (71)	
Surgical treatment method			
Breast conservation surgery	25 (23.4)	24 (22.4)	0.871
Modified radical mastectomy	82 (76.6)	83 (77.6)	

Table 3. Comparison of survival times between the two groups at each stage.

	TNBC	non-TNBC	*P*-value
Stage I: (N=34)			
No. of death/ No. of patients	1/12	0/22	
Mean overall survival time Mean (95% CI)	64.5(57.8-71.1)	-	0.178
5-year overall survival (%)	90	100	
No. of recurrence/ No. of patients	2/12	0/22	
Mean DFS time Mean (95% CI)	59.8 (49.2-70.3)	-	0.05
5-year DFS (%)	81	100	
No. of distant metastasis/ No. of patients	0/12	0/22	
Mean DMFS time Mean (95% CI)	-	-	-
5-year Metastasis-free overall survival (%)	100	100	
Stage II: (N=108)			
No. of death/ No. of patients	15/57	5/51	
Mean overall survival time Mean (95% CI)	59.4 (53.9-64.9)	60.6 (56.1-65.2)	0.08
5-year overall survival (%)	72	83	
No. of recurrence/ No. of patients	12/57	2/51	
Mean DFS time Mean (95% CI)	53.5 (48.2-58.8)	64.1 (61.4-66.7)	**0.01**
5-year DFS (%)	78	96	
No. of distant metastasis/ No. of patients	7/57	2/51	
Mean DMFS time Mean (95% CI)	58.2 (54.1-62.2)	64.1 (61.4-66.7)	0.143
5-year DMFS (%)	87	96	
Stage III: (N=72)			
No. of death/ No. of patients	18/38	7/34	
Mean overall survival time Mean (95% CI)	40.7 (34.1-47.4)	51.8 (47-56.5)	**0.01**
2-year overall survival (%)	57	84	
5-year overall survival (%)	41	73	
No. of recurrence/ No. of patients	22/38	12/34	
Mean DFS time Mean (95% CI)	32.2 (24.4-40)	44.7 (38.2-51.2)	**0.03**
2-year DFS (%)	50	71	
5-year DFS (%)	37	55	
No. of distant metastasis/ No. of patients	19/38	7/34	
Mean DMFS time Mean (95% CI)	36.1 (28.3-44)	50.2 (44.3-56.1)	**0.008**
2-year Metastasis-free overall survival (%)	57	78	
5-year Metastasis-free overall survival (%)	45	78	

Comparison of survival times between TNBC and non-TNBC patients at each stage

We also compared the disease-free, metastasis-free and overall survival between the two groups at each stage. Table 3 shows the results of this comparison. There was no significant difference in the baseline characteristics between the two groups at any stage.

In stage I, there was no significant difference in survival times between the two groups.

In stage II, DFS of the TNBC patients was significantly lower than non-TNBC patients.

In stage III, the two groups were significantly different in all of the survival times; In TNBC patients, disease-free, metastasis-free and overall survival was significantly lower than non-TNBC patients.

Cox proportional hazard analysis in the subgroups of patients

Analyses according to the Cox proportional-hazards model were performed in the subgroups to determine the prognostic role of TNBC. In the subgroups, patients with TNBC were at increased risk of death; in the node-positive patients, TNBC increased the risk of death by 2.57 times and in node-negative patients, by 3.48 times. In the stage III cancer, TNBC increased the risk of death by 2.8 times and in the other stages, by 3.18 times. Among menopausal women, TNBC increased the risk of death about 4.46 times.

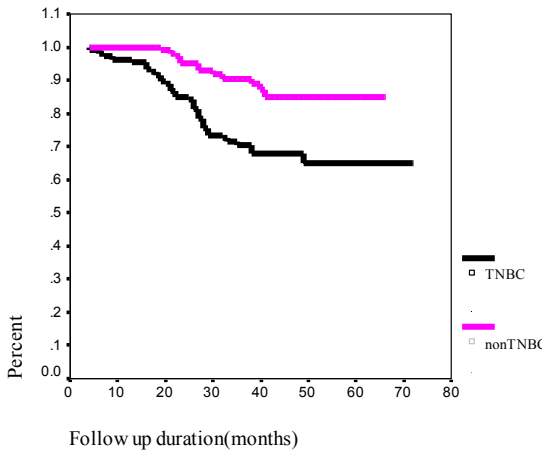

Figure 1. Overall survival in patients with TNBC and non-TNBC.

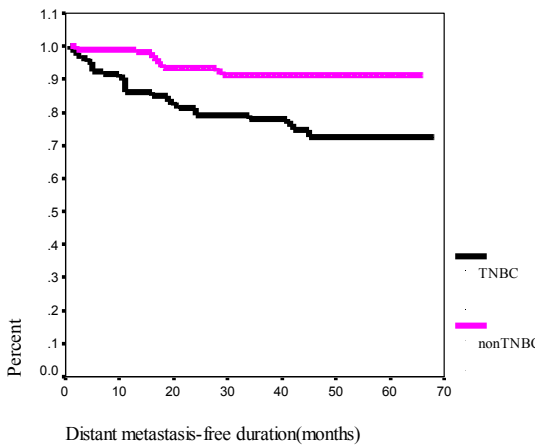

Figure 2. Distant metastasis-free survival in patients with TNBC and non-TNBC.

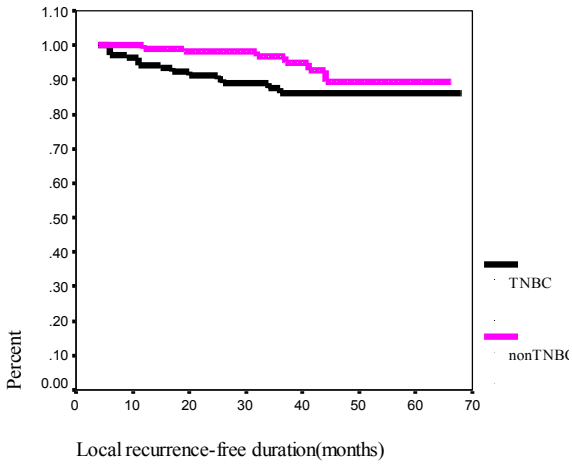

Figure 3. Disease-free survival in patients with TNBC and non-TNBC.

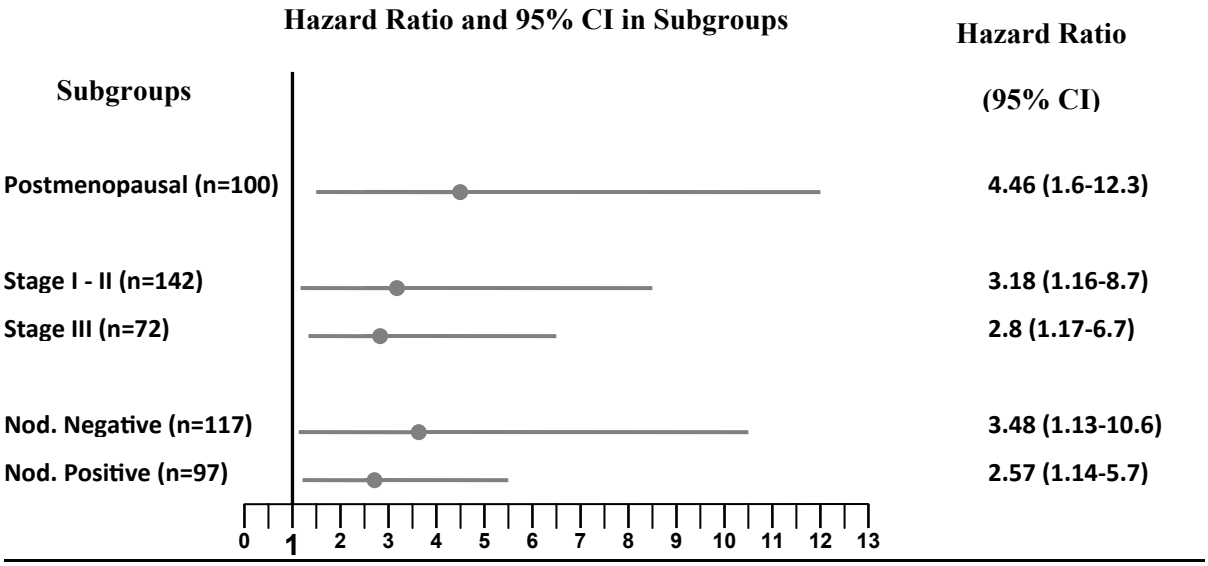

Figure 4. TNBC was associated with increased risk of death in the subgroups.

Discussion

International interest has been focused on TNBC, partly because of its poorer overall prognosis and lack of specific targeted therapies. We investigated clinicopathological features and survival rates of breast cancers in our patient population. Our data indicate that incidence of TNBC was 9.68%.the incidences of TNBC reported by Bauer *et al*. (12), Sanz *et al.* (18) and Dent *et al.* (19) were 12.5%, 6.4% and 11.2% respectively.

In our study, the mean age of patients with TNBC (46.7 years) was younger compared with non-TNBC (50.43 years). This rate was found to be 47.64 and 49.99 by Liedtke *et al.* (9) for TNBC and non-TNBC respectively. Also in studies by Ann *et al*. (20) and Lin *et al*. (21), similar results have been achieved.

Our study showed that the most percentage of TNBC were invasive ductal carcinoma (86.9%) and grade III (79.4%). Studies by Basu *et al*. (22), Rakh *et al*. (23) and Dent *et al.* (19) showed the same results. This study found relation between TNBC and tumor size. These patients had larger tumors so that more than two-thirds of them were greater than 2 cm. Dent *et al*. (19) and Ann *et al*. (20) found the same results. As the similar studies by Sanz *et al.* (18) and Rakh *et al.* (23) there was no significant association between these two groups and lymph node involvement in our study.

Our results also demonstrate that OS, DFS and DMFS are significantly lower in TNBC patients which corroborates with previous studies (12,18,19,23,24). As expected, poor prognostic factors (such as stage and grade) were also higher in TNBC and finally this may cause reduced survival.

It is therefore not surprising that patients with TNBC had a shorter survival compared to stages. It is important to know that in our study, most mortalities and recurrences occur in the first 3 years after diagnosis. Studies by Liedtke *et al.* (9) and Dent *et al.* (19) corroborated our results.

Our results are in agreement with the previous literature and demonstrate the associations between TNBC and its characteristics in our population. However it is important to recognize that breast cancer is a heterogeneous disease and extended between luminal A and HER-2. So, it is probably that our results not completely randomized. We know that our study has some limitations. Before 2008, most patients with positive HER-2, were not treated by Herceptin or any new chemotherapy regimen. In conclusion, triple negative breast cancer has a biologic aggressive behavior and poor prognosis. Therefore effective treatment and regular closed follow-up in this group, especially early stage of diagnosis, may have a significant impact on their prognosis.

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