IJBC 2017; 9(1): 18-23

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir

ORIGINAL ARTICLE

Clinicopathological Features of Non-metastatic Triple Negative Breast Cancer

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ARTICLE INFO

Article History:
Received: 28.10.2016
Accepted: 17.12.2016

Keywords:
Breast cancer
Overall survival
Disease free survival
Prognostic factors
Triple negative
Estrogen receptor
Progesterone receptor
HER2 receptors

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ABSTRACT

Background: Triple negative breast cancer (TNBC) is reported to be associated with a high risk of recurrence, poor overall survival (OS), and disease-free survival (DFS) rates. This study evaluated the clincopathological features and survival of non-metastatic TNBC women in the capital of Iran compared with other areas of the world.
Methods: In a retrospective study, 119 women with TNBC based on the criteria were analyzed in this study during 2007-2015. A number of clinicopathological variables, OS and DFS were determined in all patients. The mean follow-up was 38 months, which 6 patients lost to follow-up and 16 died of the disease and therefore were censored from the study.
Results: The mean age at diagnosis was 44.9 years (range: 21-85 years). 31.9% were older than 50 years. The 2- and 5-years OS rates were 96% and 88.1%, respectively; whereas, the 2- and 5-years DFS rates were 87% and 74.1%, respectively. Right breast tumor and lymph node involvement were more common in patients younger than 50 years, but vascular invasion was more observed in patients aged ≥50 years. There was no significant difference between menopause status, age and Ki-67 index for OS or DFS.
Conclusion: The prevalence of TNBC was more common in women younger than 50 years. Ki-67 index, menopausal status and age could contribute to prognosis and survival of patients.

Please cite this article as: Najafi S, Mozaffari HR, Sadeghi M. Clinicopathological Features of Non-metastatic Triple Negative Breast Cancer. IJBC 2017; 9(1): 18-23.

Introduction

Breast cancer (BC) is the most common malignancy and the leading cause of death among women.[1,2] This cancer is a common health problem in Iranian women,[3] and occurs about a decade earlier than women in western countries.[4] Triple negative breast cancer (TNBC) is defined by the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)[5] receptors. Therefore, patients with TNBC do not benefit from hormone or trastuzumab-based therapies.[6] TNBC accounts for 10-17% of all BCs.[5,7] Risk of developing TNBC varies with age, race, genetics, breastfeeding patterns and parity. Some of TNBCs are very chemosensitive and most patients treated for TNBC will never relapse.[8] Proliferative index reflected by Ki-67, is a key characteristic feature of malignant tumors and could be one of the major factors associated with prognosis.[9,10] TNBC is characterized by a typical ductal histology, high grades, and high proliferation and mitotic rates.[11] It is associated with a high rate of local recurrence and poor disease-free survival (DFS).[12] We aimed to evaluate the clinicopathological features and survival of

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non-metastatic TNBC women in Tehran, Iran, compared with other areas of the world.

Materials and Methods

In this retrospective study, out of all patients with breast cancer referred to a Private Clinic, Tehran, Iran, 2007-2015, 119 patients with TNBC were selected for this study. Age, laterality of the tumor, tumor size, lymph node involvement, vascular invasion, perineural invasion, stage, type of pathology, grade, margin involvement, Ki-67 index, menopausal status, radiation therapy, OS and DFS were determined in all patients. The mean follow-up was 38 months During this period, 16 women died and 6 were lost to follow-up. We included women with breast cancer with ER, PR and HER2 negativity (TNBC) aged over 18 years. We excluded women with TNBC with HER2 2+/FISH+ and metastatic TNBC at diagnosis. The characteristics of the included women such as age, laterality, tumor size, menopause status, vascular invasion, lymph node involvement, tumor grade, pathology, receiving radiotherapy, and marginal involvement were assessed.

All patients were treated with adjuvant chemotherapy. The OS was defined as from the date of diagnosis until death from any cause and DFS as the time from diagnosis to either relapse, second cancer, or death from any cause. ER and PR negativity was defined as less than 10% positive tumor cells with nuclear staining and HER2 2+ was tested by fluorescence in situ hybridization (FISH).[13,14] Meanwhile, Ki-67 index was divided into ≤20% and >20%.

Data were analyzed with SPSS version 19 software and survival data were plotted with GraphPad Prism 5 (Kaplan Meier curves and Log-rank test for analysis). P<0.05 was considered statistically significant.

Results

Mean age at diagnosis was 44.9 years (range, 21-85 years); 31.9% of patients were older than 50 years of age (table 1). Out of 119 patients with TNBC, 44.5% had right breast involvement, 47.9% showed lymph node involvement, 18.5% vascular invasion, 7.6% perineural invasion, 7.6% margin involvement and 27.7% had Ki-67≤20% and 87.4% received radiotherapy. 18.5%, 62.2% and 19.3% of the patients were diagnosed with stage I, II and III, respectively. 10.9%, 42% and 47.1% of patients had grade I, II and III tumors, respectively. Ductal carcinoma was the most common histological type (89.99%), followed by medullary carcinoma (9.2%) and lobular carcinoma (0.8%). Tumor size was <2 cm, 2-5 cm and > 5cm in 26.9%, 58% and 15.1% of the patients, respectively.

The correlation between a number of variables and age is shown in table 2. There was a significant correlation between laterality of tumor, lymph node involvement and vascular invasion with age (P=0.015, P=0.012 and P=0.003, respectively). Therefore, right breast involvement and positivity for lymph nodes were more common in patients less than 50 years old, but vascular invasion was more observed in patients ≥50 years.

Figure 1 shows the OS and DFS for all TNBC patients. The 2- and 5-years OS rates (the means) were 96% (22 months) and 88.1% (34.2 months), respectively. Also, the 2- and 5-years DFS rates (the means) were 87% (21.5 months) and 74.1% (33.5 months), respectively.

Figure 2 shows the 5-year OS and DFS in terms of Ki-67

Table 1: The characteristics of the patients with triple negative breast cancer (n=119)

Variables	N (%)	Variables	N (%)
Age group, years		Type of pathology	
≥50	38 (31.9)	Ductal carcinoma	107 (89.9)
<50	81 (68.1)	Medullary carcinoma	11 (9.2)
Laterality		Lobular carcinoma	1 (0.8)
Right	53 (44.5)	Grade	
Left	66 (55.5)	I	13 (10.9)
Tumor size, cm		II	50 (42)
<2	32 (26.9)	III	56(47.1)
2-5	69 (58)	Radiotherapy	
>5	18 (15.1)	Yes	104 (87.4)
Lymph node involvement		No	15 (12.6)
Yes	57 (47.9)	Margin involvement	
No	62 (52.1)	Yes	9(7.6)
Vascular invasion		No	110(92.4)
Yes	22 (18.5)	Ki-67, %	
No	97 (81.5)	≤20	33 (27.7)
Perineural invasion		>20	86 (72.3)
Yes	9 (7.6)	Menopausal status	
No	110 (92.4)	Premenopausal	80 (67.2)
Stage		Postmenopausal	39 (32.8)
I	22 (18.5)		
II	74 (62.2)		
III	23 (19.3)		

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Table 2: The correlation between a number of variables and age in triple negative breast cancer patients (n=119)

Variables	Age<50 N=81	Age≥50 N=38	P value
Laterality (right)	42(51.9)	11(28.9)	0.015
Tumor size, cm (<2, 2-5)	24(29.6), 46(56.8)	8(21.1),23(60.5)	0.557
Lymph node involvement (yes)	45(55.6)	12(31.6)	0.012
Vascular invasion (yes)	9(11.1)	13(34.2)	0.003
Perineural invasion (yes)	4(4.9)	5(13.2)	0.115
Stage (I, II)	16(19.8),47(58)	6(15.8),27(71.1)	0.363
Type of pathology (DC*, MC**)	72(88.9), 0	35(92.1), 1(2.6)	0.210
Grade (I, II)	11(13.6),36(44.4)	2(5.3),14(36.8)	0.184
Margin involvement (yes)	73(90.1)	37(97.4)	0.153
Ki-67, % (≤20)	20(24.7)	13(34.2)	0.194
Menopausal status (Premenopausal)	56(69.1)	24(63.2)	0.328

*Ductal carcinoma, **Medullary carcinoma

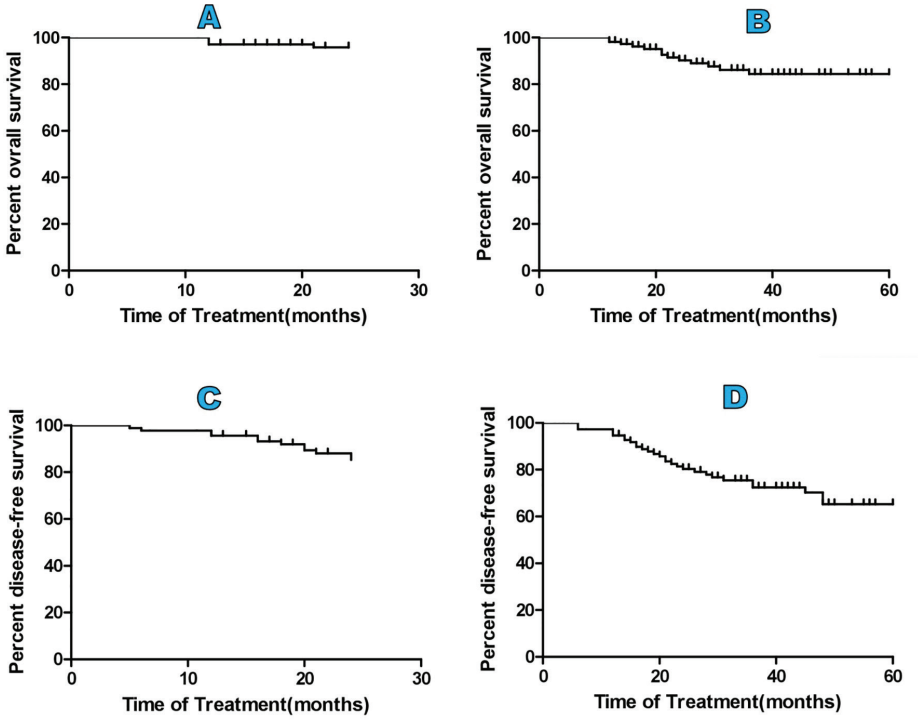


Figure 1: The overall survival rate for all patients: (A) 2-year (B) 5-year, and disease-free survival for all patients: (C) 2-year (D) 5-year

index and menopausal status in all patients. The OS and DFS rates (the means) for the patients with Ki-67≤20% were 86.7% (38.9 months) and 86.2% (38.1 months), respectively; whereas for patients with Ki-67>20% were 85% (32.6 months) and 71.6% (32.3 months), respectively. Therefore, there was no significant difference between Ki-67 index and OS (hazard ratio [HR] 0.77, 95%CI 0.26-2.24; P=0.63) or DFS rates (HR 0.48, 95%CI 0.21-1.12; P=0.09).

Also, the OS and DFS rates (means) for the patients of premenopausal were 82.9% (39.4 months) and 67.1% (35 months), respectively; whereas for the patients of postmenopausal the corresponding figures were 91.1% (32.5 months) and 85.3% (31.2 months), respectively. Therefore, there was no significant difference between menopause status and OS (HR 1.41, 95%CI 0.45-4.41; P=0.54) or DFS (HR 1.85, 95%CI 0.84-4.10; P=0.12). The OS and DFS rates (means) for the patients younger than 50 years were 87% (37.1 months) and 76.6% (34.2 months), respectively; whereas for the patients older than 50 years were 84.2% (30.1 months) and 68.4% (30.1 months), respectively. Therefore, there was no significant difference between age and OS (HR 0.62, 95%CI 0.21-1.87; P=0.40) or DFS (HR 0.62, 95%CI 0.28-1.37; P=0.24).

Discussion

This study evaluated a number of associated factors and also the OS and DFS in women with non-metastatic TNBC. In a retrospective analysis,[14] 296 patients with TNBC had a median age of 55 years old (range, 23–88.5)

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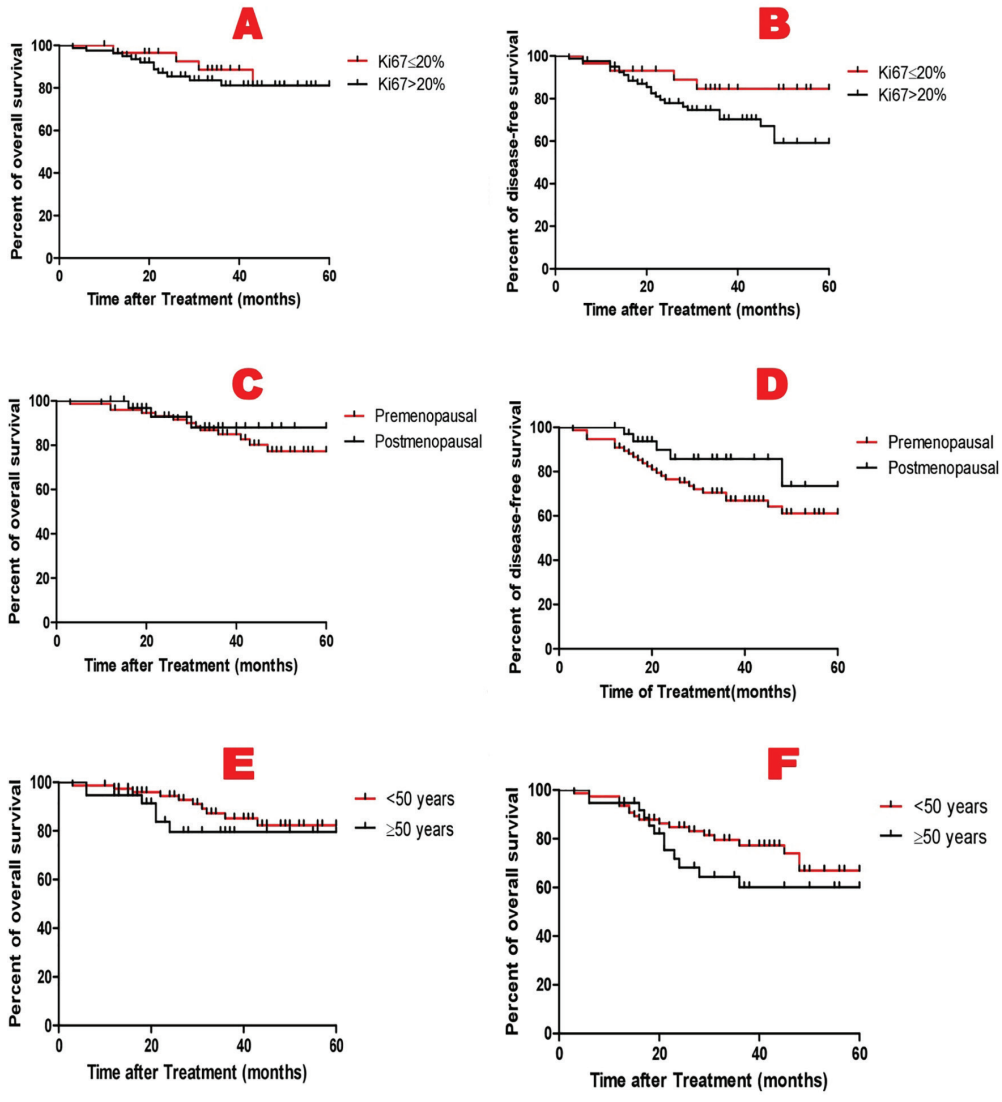


Figure 2: (A) 5-year overall survival and (B) 5-year disease free survival based on percentage of Ki-67; (C) 5-year overall survival and (D) 5-year disease free survival based on menopausal status; (E) 5-year overall survival and (F) 5-year disease free survival based on age group

at diagnosis. The median age of non-metastatic TNBC in the study of Yue et al.[15] was 57 years old (range, 28-92 years). The median age of TNBC patients at diagnosis in another research was 54.5 years old (range, 24-86).[16] The results were almost similar and showed that the mean age of patients with TNBC approximately is reported over 45 years of age in most studies. Ovcaricek et al.[14] reported that non-metastatic TNBC patients were more likely to have grade III tumors (82.5%), tumor size >2 cm was reported in almost two third of the patients. At least one axillary lymph node was positive in 46.1% of patients and one third of the tumors were positive for lymphovascular invasion and most women were postmenopausal at the presentation (60.3%). Pogoda et al.[16] showed that 4% of patients with TNBC had an evidence of metastases at initial diagnosis and 55% had axillary lymph node involvement at presentation. The most common histological type in their study was ductal carcinoma (81%).[16]

A total of 448 non-Hispanic black and white women were identified which 57% were premenopausal and 89% had grade III tumors. Stage II (47%) was the most frequent stage at diagnosis followed by stage III (28%); 32% had lymphovascular invasion. The 5-year OS and DFS rates were 68% and 60% for blacks and 65% and 63% for whites, respectively.[17] The results of this study and other studies suggest that considering various clinicopathological features in TNBC patients, genetic factors and geographical area could have a significant impact on these factors.

Christiansen et al.[18] enrolled women with different ethnics with stage I-III TNBC who had received adjuvant chemotherapy (African Americans vs. non-African Americans). Among the patients, 42.6% were African American. The African American patients had a significantly lower 5-year DFS rate (45.2% vs. 79.7%) and a higher 5-year recurrence rate (42.5% vs. 7.0%; P=0.0005), compared with the non-African American patients. In a study from Lithuania,[19] consisting of 99 TNBC patients, the OS of these patients was 97.0%, 84.9% and 66.5% following 10, 30 and 60 months of diagnosis, respectively. The study of Kaplan et al.[20] showed that 5-year relapse-

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free survival and OS in TNBC patients were 84 and 81%, respectively. Aghili et al.[21] evaluated 107 patients with TNBC and found 2 and 5-year DFS rates of 68% and 63%, respectively. A study from Slovenia,[14] reported the 5-year DFS and OS rate of 68.2% and 74.5%. Van Roozendaal et al.[22] in the Netherlands, showed a 5-year DFS of 78.7% and OS of 82.3%. In a study from Poland,[16] 6-year DFS and OS rates were 68% and 62%, respectively.

Our current study identified the 2- and 5-year OS rates were 96% and 88.1%, respectively; whereas the 2- and 5-year DFS rates were 87% and 74.1%, respectively. These figures assume to be superior in comparison to studies from other areas; however, the kind of treatments the patients receive could have a contribution on the outcome. Therefore, the correlation between genetic or race with survival in TNBC patients is yet to be defined.

Kassam et al.[23] reported that TNBC patients younger than 50 years of age had an inferior outcome. In another study, age was not related to prognosis.[24] On the other hand, Ovcaricek et al.[14] showed that age>65 years was an independent prognostic factor for DFS and that the risk of recurrence was around 2-fold higher in older patients.[16] Yue et al.[15] retrieved 192 consecutive non-metastatic TNBC patients who had undergone the resection of a primary tumor that the multivariate Cox analysis identified three significant variables for survival: Ki-67, tumor stage, and nodal involvement. Proliferation marker Ki-67 was an important variable for survival in the study of Keam et al.[25] and the high Ki-67 index was associated with a higher histological grade, larger tumor size, presence of axillary lymph node metastasis, and worse outcome. Since TNBCs typically exhibit higher grades and high proliferation rates, the expression of Ki-67 was usually higher in most of TNBC patients.[15] In this study, patients older than 50 years had a poor outcome compared with younger patients, but this difference was not statistically significant. Right breast and lymph node involvement were more common in patients younger than 50 years compared with older patients. Vascular invasion was reported more commonly in patients older than 50 years. In current study; however the difference of DFS rates for Ki-67 index (≥20% vs. <20%), menopausal status (post vs. pre) and age (≥50 years vs. <50 years) was not significant, but its rate was higher in the group of patients with Ki-67<20%, postmenopausal women and those younger than 50 years old. Therefore, these variables may have a significant impact on survival of TNBC patients. In addition, age can be suggested a determining factor besides other clinicopathological factors.

Conclusion

The prevalence of TNBC was more common in women younger than 50 years of age. It might be suggested that Ki-67 index, menopausal status and age could have a contribution on prognosis and survival of TNBC patients besides geographical and ethnic factors. To confirm this, future studies with larger samples and careful analysis in the same geographical areas are needed.

Conflict of Interest: None declared.

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