JBUON 2014; 19(4): 872-878
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Outcome of 561 non-metastatic triple negative breast cancer patients: Multi-center experience from Turkey

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Summary

Purpose: *Triple-negative breast cancers account for 15% of breast carcinomas and, when present as early-stage disease, they are associated with higher rates of recurrence and early distant metastasis risk when compared to hormone receptor positive and human epidermal growth factor receptor (HER-2) positive breast cancers. In this study we aimed to explore the basic clinicopathological characteristics, prognostic factors and recurrence patterns of non-metastatic triple negative breast cancer patients.*

Methods: *In this study 561 non-metastatic triple-negative breast cancer female patients admitted to 8 different cancer centers in Turkey between 2000 and 2010 were retrospectively evaluated through their medical records, to identify the basic clinico-pathological characteristics, prognostic factors and recurrence patterns.*

Results: *The ratio of triple-negative breast cancer was 12%. The median age of patients was 48 years, of whom 311 (55.4%) were premenopausal. The majority had early-stage breast cancer at the time of diagnosis (16.8% stage I, 48.1% stage II, 35.1 % stage III) and the most commonly identified variant was invasive ductal carcinoma (84.1%). Grade II and III tumors were 27.1 and 48.5%, respectively. Adjuvant chemotherapy was administered to 90.5% of women and adjuvant radiotherapy to 41.2%. Median patient follow up was 28 months (range 3-290). During the follow up period 134 (23.8%) patients developed metastatic disease. In most of these cases, metastatic sites were bone, soft tissue, and lung. Factors affecting disease free survival (DFS) and overall survival (OS) were age (both p<0.001), lymph node involvement (both p<0.001), lymphovascular invasion (LVI) (p<0.001 and p=0.004, respectively), tumor stage (both p<0.001), adjuvant administration of anthracycline-based chemotherapy (both <0.001) and type of surgery (not significant for DFS but p=0.05 for OS). Three-year DFS and OS were 72.0 and 93.0%, respectively.*

Conclusion: *Age, lymph node involvement, LVI, stage, and adjuvant chemotherapy were determined as prognostic factors for DFS and OS. The most common recurrence sites were bone, soft tissue and the lung. Further prospective randomised trials are needed to confirm the prognostic and predictive factors identified in this study.*

Key words: *breast cancer, prognosis, treatment, triple negative*

Introduction

Triple-negative breast carcinomas compose a relatively rare subtype of breast cancers and are defined as tumors lacking estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2). Triple-negative breast cancers account for nearly 15% of breast carcinomas and are associated with poor prognosis [1]. Early-stage triple-negative breast carcino-

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Received: 20/04/2014; Accepted: 06/05/2014

mas have a higher risk of recurrence [2] and early distant metastasis [3] when compared to hormone receptor positive and HER-2 positive breast cancers. Basal-like tumors account for 10-25% of breast carcinomas and 50-75% of this subgroup have triple-negative phenotype [4]. Currently, chemotherapy is the preferred treatment modality. Studies have shown that complete pathological responses with neoadjuvant anthracycline- and taxane-based regimens are quite high (45%) [5,6]. Alternatively, platin-based chemotherapy may be used. In a study, neodjuvant platin-based regimens resulted in 21% complete pathological response [7].

In this study, we aimed to evaluate the prevalence of triple-negative breast cancers in Turkey and to study the treatment modalities and prognosis of this subtype in our regional population.

Methods

Patients from 8 oncology centers in Turkey were included in the study. Those with histologically proven, non-metastatic breast cancer were evaluated between 2000 and 2010. Data including patient characteristics, laboratory values, treatment outcomes and toxicity, were reviewed and analyzed retrospectively from the patients' medical records.

Of 5,610 non-metastatic breast cancer patients admitted to 8 different cancer centers in Turkey between 2000 and 2010, 561 (10%) were identified to have triple-negative disease, and were retrospectively analysed. Patients with immunohistochemically (IHC) negative hormone receptor expression (ER and PR) plus HER-2 score 0 or 1 with IHC staining or fluorescent *in situ* hybridisation (FISH) negative expression were defined as triple-negative.

Statistics

For data analysis the Statistical Package for Social Sciences (SPSS v15.0, SPSS Inc., Chicago, IL, USA) software was used. Survival plots were generated with the Kaplan-Meier method and log rank test was used for comparison between groups. For analysis of factors affecting survival, univariate and multivariate Cox regression analysis was used. All p values were two-sided, and statisticall significance was set at $p<0.05$.

Results

The prevalence of triple-negative breast carcinoma was 12%. Patient and tumor characteristics are shown on Table 1. All patients were women with median age 48 years (range 20-87). Three hundred and eleven (55.4%) of the patients were premenopausal and 250 (44.6%) were postmenopausal. Modified radical mastectomy (MRM) was more frequently performed than breast-conserving surgery (BCS) (448 patients/79.9%, and 113 patients/20.1%, respectively).

Table 1. Basic patient and disease characteristics

Characteristics	*N*	*%*
Mean age, years (range)	48 (20-87)	
Menopausal status		
Premenopausal	311	55.4
Postmenopausal	250	44.6
Histology		
Invasive ductal	472	84.1
Invasive lobular	15	2.7
Other	74	13.2
Histological grade		
I	34	6.1
II	152	27.1
III	272	48.5
Unknown	103	18.4
Stage		
I	94	16.8
II	270	48.1
III	197	35.1
Type of surgery		
MRM	448	79.9
BCS	113	20.1

MRM: modified radical mastectomy, BCS: breast conserving surgery

Most of the patients were diagnosed with invasive ductal carcinoma (472 patients, 84.1%) and 15 (2.70%) with invasive lobular carcinoma. Other histopathological subtypes such as medullary and mixed invasive subtypes were rarely observed. Grade II and III tumors were more common than grade I (27.1, 48.5 and 6.1%, respectively). The majority of the patients had early-stage disease at the time of diagnosis (94/16.8% stage I, 270/48.1% stage II, and 197/35.1% stage III). Axillary lymph nodes were not involved in 142 (25.3%) of the patients. As adjuvant systemic treatment 257 (45.8%) patients received anthracycline-based chemotherapy whereas 251 (44.7%) received anthracyclines in addition to taxane-based chemotherapy and 21 (3.1%) did not receive any adjuvant chemotherapy. Adjuvant radiotherapy was delivered to 231 (41.1%) patients.

The median follow-up period was 28 months (range 3-290). During this period 134 patients (23.8%) developed recurrent disease; the most common recurrence sites were bone, soft tissue and lung. The adjuvant treatment modalities and sites of recurrence are summarized in Table 2.

Most of the recurrences (74%) were seen in the first 3 years of follow-up. Factors affecting the recurrences were axillary lymph node involve-

Table 2. Treatment modalities and sites of recurrence

	N	%
Adjuvant treatment		
Chemotherapy	529	94.3
Anthracycline	257	45.8
Anthracycline and taxane	251	44.7
Radiotherapy	231	41.2
Recurrence site(s)		
Bone and/or lymph node	52	9.3
Lung	43	7.7
Liver	18	3.2
Brain	15	2.7
Other	6	1.0

ment, LVI and high histological grade. Figure 1 illustrates the patterns of recurrences and factors that affected recurrence (Fig 1A: all patients, Fig 1B: N status, Fig 1C: histological grade, Fig 1D: lymphovascular invasion).

For the treatment of recurrences, single agents including taxanes and capecitabine (23.6%) or combination chemotherapy regimens (19.7%) were used. Second-line chemotherapy including cisplatin or vinorelbine as single agents or as part of combination chemotherapy regimens were utilized in 12.2 % of the patients. Only 5.7% of the patients received third-line chemotherapy regimens. Overall, median DFS was 82 months (range 3-114) and the 3-year DFS was 72%. Patient DFS and OS are shown in Figure 2 A,B.

Menopausal status, histological subtype, grade of tumor and the site of recurrence did not signifantly impact DFS (p=0.6, p=0.2, p=0.2 and p=0.26, respectively). Older age at diagnosis, lymph node involvement, LVI and higher tumor stage were significantly related with shorter DFS (p<0.001, p<0.001, p<0.001 and p<0.001, respectively). The type of operation and adjuvant radiotherapy application were found not to have statistical impact on DFS. Interestingly, anthracycline-based adjuvant chemotherapy was associated with longer DFS rather than taxane-based regimens (p<0.001), however selection bias could account for this difference.

The 3-year OS was 93.4%. Older age at diagnosis, lymph node involvement, LVI and tumor stage were significantly related with shorter OS (p<0.001, p<0.001, p<0.004 and p<0.001, respectively). The type of operation had a borderline ef-

Table 3. Factors related or not-related to disease free survival and overall survival

Variables	*3-Year DFS (%)*	*p value*	*3-Year OS (%)*	*p value*
Age, years				
≤48	66	<0.001	93	<0.001
>48	80		94	
Menopausal status				
Premenopausal	68	0.6	93	0.7
Postmenopausal	78		93	
Histological grade				
I	85		100	
II	73	0.2	94	0.7
III	71		91	
Lymphovascular invasion				
Yes	64	<0.001	88	0.004
No	91		98	
Lymph node involvement				
N0	94	<0.001	99	<0.001
N1-3	85		90	
Stage of disease				
I	93		99	
II	91	<0.001	98	<0.001
III	78		83	
Adjuvant radiotherapy				
Yes	85	0.7	96	0.9
No	95		93	
Preferred surgical approach				
BCS	75	0.2	97	0.05
MRM	73		94	

MRM: modified radical mastectomy, BCS: breast conserving surgery

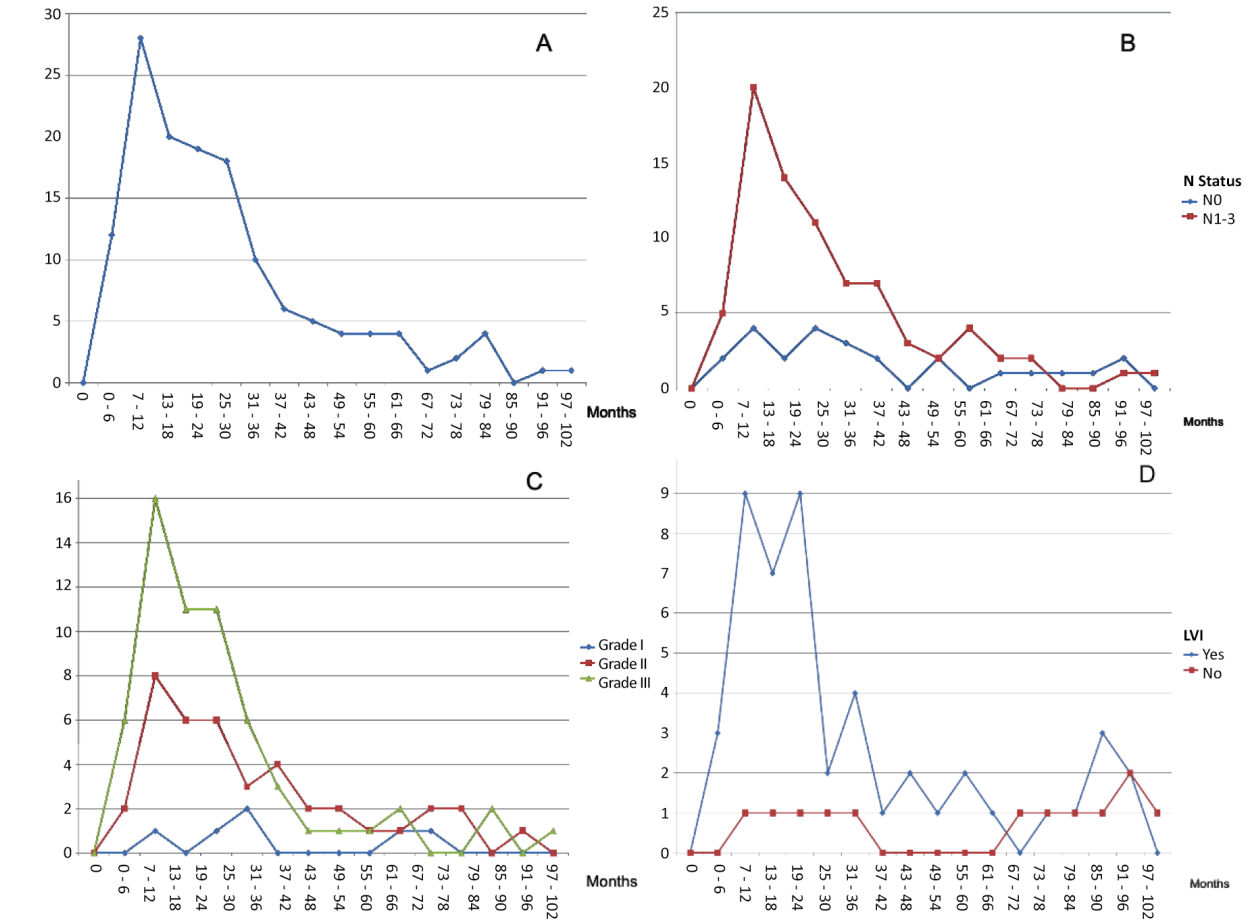

Figure 1. Recurrence patterns of patients. **A:** All patients; **B:** according to lymph node status; **C:** according to histological grade; **D:** according to lymphovascular invasion status.

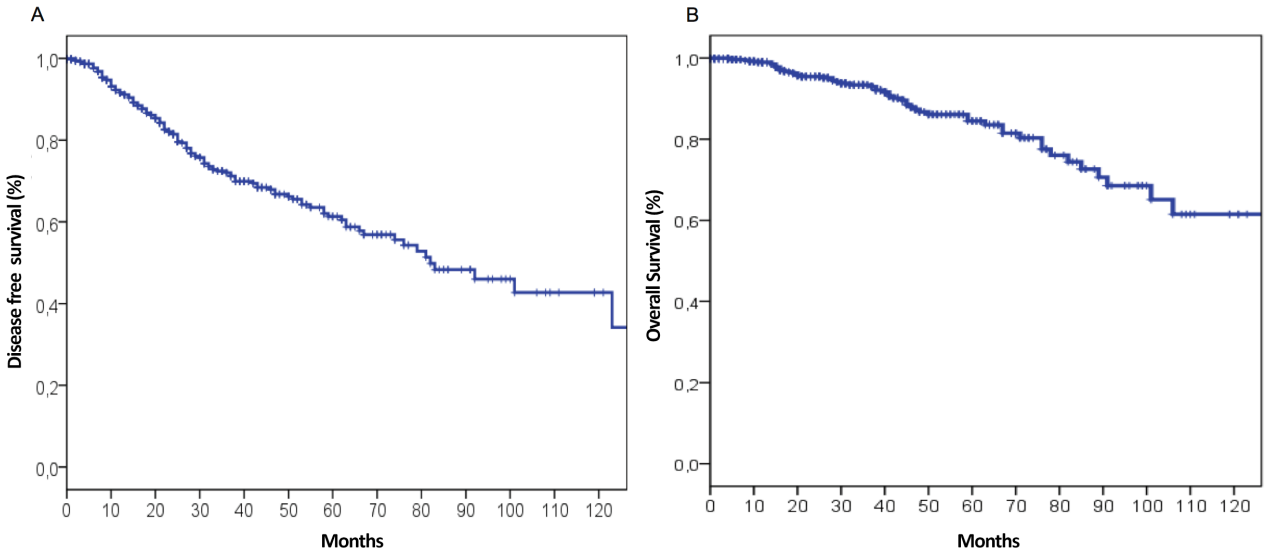

Figure 2. Disease free survival **(A)** and overall survival **(B)** of triple-negative breast carcinoma patients.

fect on OS (p=0.057). Patients who had undergone BCS lived longer than those with MRM (p<0.05). Anthracycline-based adjuvant chemotherapy was associated with longer OS when compared to anthracycline and taxane-based combination regimens (p=0.003). Menopausal status, histological subtype, grade of the tumor, adjuvant radiotherapy and the site of recurrence were found not to have statistically significant effect on OS (p=0.7, p=0.07, p=0.7, p=0.9 and p=0.8, respectively). Factors affecting DFS and OS are illustrated on Table 3.

Discussion

Triple-negative breast carcinomas are defined as tumors lacking ER, PR and HER-2 expression. Basal-like breast cancer is one of the 5 subgroups of breast cancer, defined by using microarray gene technology. This variant has very little or no ER expression and is HER-2 negative. Most triple-negative breast cancers overlap with basal-like phenotype features when studied by microarray technology [8]. However, triple-negative and basal-like breast cancers are not identical, since 10% of basal-like tumors are HER-2 positive and 12% are ER-positive. Most basal-like breast carcinomas have histological grade III (84%) [9]. In the literature the prevalence of triple-negative breast cancer is 15% [10], however in our study the prevalence was 12%.

Triple-negative breast cancers differ from other variants in their clinical course. They are diagnosed at earlier age and axillary lymph node involvement is infrequent when compared to other subtypes. Also, there is an increased tendecy for early recurrence (within 3 years of diagnosis) [11]. Recurrences are mostly seen in brain and/or lung in the triple-negative subgroup, whereas in the luminal type bone and/or visceral organ metastases predominate [12-15].

In the present study, the median patient age was 48 years, and axillary lymph node involvement was common. Time to recurrence was consistent with the literature. Recurrences were mostly seen within 3 years after the diagnosis of breast cancer and were higher in cases with lymph node positivity, high grade histology and LVI (Figure 2).

The recurrence sites were mostly the soft tissue and bone, quite similar to breast cancers of luminal type. Although lung metastasis was frequent as reported in the English literature, brain metastasis was rarer in this patient population. Kenecke et al. reported that the frequency of central nervous system (CNS) metastasis was 10% in the basal-like subtype and 7% in the non-basal triple-negative subgoup [3]. As our study was retrospective the prevalence of CNS metastasis could be expected to be lower since we might not know an asymptomatic brain metastasis without routine brain imaging.

Chemotherapy is the most efficacious and preferred treatment modality in triple-negative breast cancers [16-18]. Anthracycline - and taxane-based regimens are also reported to be effective. Relevant literature indicates high response rates in triple-negative cancers. Some studies have even reported pathological complete response (pCR) rates up to 45%, by utilizing combination chemotherapy including cyclophosphamide, anthracycline and 5-fluorouracil [5,6,19].

In a small retrospective study involving BRCA-1 carriers, neoadjuvant platinum-based regimens were associated with higher rates of pCR when compared to non-platinum-based regimens (83 vs 22%) [20]. The association of BRCA-1 and triple-negative breast cancer implies that triple-negative breast cancers are also sensitive to platinum-based chemotherapy. High pCR rates were reported with cisplatin and epirubicin [21] or cisplatin and paclitaxel combinations (40 and 65%, respectively) [22]. Although the literature about therapy of advanced triple-negative breast cancers with platinum-based chemotherapy supports our speculation, there are no standardized guidelines supporting the use of platinum-based chemotherapy in the adjuvant setting.

Poly-(ADP ribose)-polymerase (PARP) inhibitors have also been used successfully for the treatment of triple-negative breast cancers. PARP inhibitors are a new class of drugs and exert their effects by inhibiting DNA repair mechanisms. High response rates were reported with the PARP inhibitor *olaparib* (63%) in anthracycline - and taxane-resistant triple-negative breast cancer groups [23,24]. Prospective trials evaluating the efficacy of this new drug are underway.

Although adjuvant radiotherapy did not make any difference in DFS and OS, adjuvant chemotherapy managed to alter both DFS and OS. In our study, patients who received single-agent anthracycline chemotherapy had longer DFS and OS when compared to those who received taxane and anthracycline combination regimens. This result may be due to the fact that we used mostly taxane-based combinations in lymph node positive patients, whereas in lymph node negative ones, only anthracyclines were used because taxanes are reimbursed only in cases with lymph node positivity in Turkey.

Triple-negative breast cancer has been shown to have poorer DFS and OS than other breast cancer subtypes in various studies [6,10]. Dent et al., in a study with a median follow up of 8.3 years, have reported an 11% incidence of the triple-negative subtype and a recurrence rate of 42% for the triple-negative group; this is much higher in comparison to 28% noted in other subgroups. Median time to recurrence was 2.6 years in the triple-negative group and 5 years in the other subgroups [25]. In the same study, factors affecting surviv-

al were the patients' age, tumor size, and lymph node status.

In our study, median DFS was 82 months and factors affecting DFS were the patients' age, LVI, and tumor stage.

Dragun et al. have shown reduced local recurrence rates with radiotherapy administration in triple-negative patients [26]. However, in the present study, we did not find any effect of radiotherapy on local recurrence.

The type of surgical method (MRM and BCS) is not a defined factor affecting DFS and OS in the literature. In our study, however, patients who had undergone MRM had shorter DFS when compared to patients with BCS. The fact that MRM is usually preferred in higher risk breast cancer patients might explain this finding.

Triple-negative breast cancers have a poor prognosis. Treatment alternatives are also few. New treatment modalities and randomized controlled trials evaluating their efficacy are needed in triple-negative breast cancers.

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