

Clinicopathological Characteristics of Triple-negative Breast Cancers in the Northeast Region of Turkey

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Background: Triple-negative (TN) breast cancer is a subtype of breast cancer characterised by a loss of estrogen receptor (ER), progesterone receptor (PR) expression, and the absence of human epidermal growth factor (HER2) overexpression.

Aims: To identify the relationships between clinicopathological characteristics of TN breast cancers in the northeast region of Turkey and disease free survival (DFS) and overall survival (OS).

Study Design: Retrospective clinical study.

Methods: Seven hundred and eighty non-metastatic breast cancer patients were enrolled in this study. The relationships between TN breast cancer and other breast cancers with respect to clinicopathological characteristics, as well as DFS and OS, were studied.

Results: The triple-negative phenotype was detected in 204 patients (27.1%). Patients with triple-negative breast cancer had more grade 2-3 tumours compared to those with other types of breast cancer (92.5% versus 84.3%, $p=0.004$). Invasive ductal carcinoma histology, on the other hand, was less prevalent in patients with TN breast cancer

(77% versus 84.5%, $p=0.016$). No significant differences were identified between the groups in other clinicopathological variables. Relapse and mortality rates were higher in the TN group during the follow-up of both groups [57 (27.9%) versus 89 (16.2%), $p<0.001$ for relapse; 27 (13.2%) versus 37 (6.8%), $p=0.005$ for mortality]. The univariate analysis demonstrated shorter DFS and OS for patients with TN breast cancer compared to those with other types of breast cancer. In the multivariate analysis, patients with TN breast cancer were 2.21 times more likely to develop relapse, while the likelihood of death increased 3.21-fold ($p<0.001$ and $p<0.001$).

Conclusion: Triple-negative breast cancers demonstrate a more aggressive clinical course compared to other breast cancers. More effective strategies should be developed for the treatment of this subgroup of breast cancer.

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Key Words: Breast neoplasms, disease free survival, overall survival

Breast cancer is the most common malignancy among women and a leading cause of cancer-related deaths in the general population. On the other hand, both incidence and mortality rates decreased over the past 10-15 years (1). Different clinical courses observed in cancer patients during the same stage suggest that this disease has a heterogeneous nature.

Breast cancer has been categorised into 5 subtypes based on gene expression techniques (luminal A, luminal B, basal-like, human epidermal growth factor (HER2)-overexpressing, and normal breast like) (2-5). Estrogen receptor (ER), progesterone receptor (PR), and HER2 receptors are negative in basal-like tumours, as in the case of triple-negative (TN) tumours. Because anti-keratin antibodies, used to identify the basal-like phenotype, are not routinely analysed during daily practice, the terms TN and basal-like are often used interchangeably. This, however, is not precisely accurate. DNA analyses and

immunohistochemical assays have demonstrated that 85% of TN tumours were basal-like. Basal-like tumours have a shorter disease free survival (DFS) and poorer prognosis and are associated with BRCA-1 (2, 4, 5). The clinical behaviour of TN tumours is also similar to basal-like tumours and these tumours both have poor prognosis (4-7).

Triple-negative tumours account for 10.6-29.5% of all breast cancers (8-12). As proven by the results of previous studies, standard treatment protocols used for breast cancer management have not yielded the expected successful results in this subgroup to date. Therefore, the accurate identification of clinicopathological characteristics of TN breast cancer, as well as its prognostic and predictive factors, will provide guidance in developing effective treatment strategies for the patients in this subgroup with complicated management.

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The aim of this study is to identify the relationships between clinicopathological characteristics of TN breast cancers and DFS and overall survival (OS) in the northeast region of Turkey.

MATERIAL AND METHODS

Patients

Nine hundred and sixteen patients with diagnosed breast cancer presenting to the Karadeniz Technical University Faculty of Medicine Medical Oncology out-patient' clinic between January 2003 and December 2008 were scheduled to enroll in the study. However, 136 patients were excluded since they were at the metastatic stage at the time of diagnosis or were lost to follow-up; therefore, 780 patients were included in the study. The present retrospective study was approved by the Institutional Ethics Committee.

The patients were invited to the clinic at three-month intervals during the first two years following adjuvant treatment, in six-month intervals during the next two years, and then annually. During each visit, physical examinations were carried out and the patients were asked to undergo blood analyses (complete blood count, routine biochemical tests, and tumour markers), annual mammography and/or breast USG, annual abdominal USG or BT and additional examinations including bone profile and bone scintigraphy, if indicated; all of the patients were monitored for relapse/metastasis.

In this study, ER-, PR- and HER2- negative patients were considered to have TN breast cancer, while patients who were positive for any of these markers were defined as "other breast cancers". Breast cancer stage at diagnosis was defined by the American Joint Committee on Cancer Staging Manual 6th edition (13). Modified Black's nuclear grading system was used for nuclear grading of pathology preparations (14).

Disease free survival was described as the period (months) from the time of patient's diagnosis until determining a local relapse or metastasis. Overall survival was defined as the period (months) from the time of the patient's diagnosis until the last visit or death.

Immunohistochemical (IHC) staining

Immunohistochemical (IHC) staining was performed using an automated staining system (Nexes IHC, Ventana (15, 16). ER (Clon SP1; NeoMarkers, California, USA), PR (Clon SP2, NeoMarkers, California, USA), and HER2 (Clon e2-4001+3B5, NeoMarkers, California, USA) were used as the primary antibodies. For ER and PR, >10% nuclear staining of cells was considered positive expression (17, 18). For HER2, grades from 0 to +3 were given based on the degree of membranous staining; staining with grades 0 to +1 were deemed negative, grade +2 staining was considered borderline, and grade +3 staining was considered positive. Patients displaying grade +2 staining pattern underwent FISH and those with HER2 gene <2 copies were considered negative (7, 8).

Statistical analysis

Statistical evaluations were performed on computers using the SPSS 13 (SPSS Inc., Chicago, IL, USA) (License no: 31133001) sta-

tistics software. Chi-square test was used for comparisons between TN and non-TN groups for relationships with respect to clinicopathological characteristics (diameter, lymph node involvement, presence of menopause, histological type, etc.), while comparisons of means (age and tumour diameter) were carried out using the Student's t test. Relationships between the variables to DFS and OS were assessed by the Kaplan-Meier survival analysis. For the variables which were statistically significant in univariate analysis, multivariate Cox regression analysis was used. The level of significance was established as $p < 0.05$.

RESULTS

Of the 780 patients enrolled, 752 (96.4%) had receptors for all three hormones (ER, PR and HER2), while at least one receptor was unknown in 28 patients (3.6%). TN phenotype was detected in 204 patients (27.1%). The median follow-up was 36 months (range, 5-77 months).

Clinicopathological characteristics of 752 patients with known hormone receptor status are shown in Table 1. No statistically significant relationships were identified between TN and non-TN breast cancer groups in terms of the studied parameters, which included mean age at the time of diagnosis, tumour diameter, lymph node involvement, disease stage, lymphovascular invasion, and the presence of menopause. Moderately and poorly differentiated tumours were more common in patients with TN breast cancer compared to patients with other breast cancers (92.5% versus 84.3%, $p=0.004$). Invasive ductal carcinoma histology was less common in patients with TN breast cancer (77% versus 84.5%, $p=0.016$). On the other hand, both relapse and mortality was noted with a higher rate in the TN group during the follow-up period [57 (27.9%) versus 89 (16.2%), $p < 0.001$ for relapse; 27 (13.2%) versus 37 (6.8%), $p=0.005$ for mortality].

The impact of the studied variables on DFS and OS, as demonstrated by the univariate analysis, is presented in Table 2. Patients with TN breast cancer had shorter DFS and OS compared to patients with other breast cancers (57.1 months versus 63.8 months, $p=0.004$ for DFS and 66.8 months versus 71.2 months, $p=0.024$ for OS) (Figure 1a, b). Results of the multivariate analysis carried out for variables with p values lower than 0.05 in the univariate analysis are shown in Table 3. The patients with TN breast cancer were 2.21 times more likely to develop relapse, while the likelihood of death was increased 3.21-fold ($p < 0.001$ and $p < 0.001$).

DISCUSSION

Breast cancer is a heterogeneous disease. Survival may differ even among individuals with similar prognostic factors and in the same disease stage. Treatment strategies for the

TABLE 1. Characteristics of patients with triple negative and other breast cancer groups

Variable	Other (n:548) n (%)	TN (n:204) n (%)	p
Mean age at diagnosis (y)	52.01	51.23	0.448
<35 years	33 (6)	14 (6.9)	
≥35 years	515 (94)	190 (93.1)	0.672
Mean tumour size	3.72	3.70	0.922
≤5 cm	458 (83.7)	165 (80.9)	
>5 cm	89 (16.3)	39 (19.1)	
Missing	1	0	0.356
Lymph node status			
Negative	200 (37.5)	86 (43)	
Positive	333 (62.5)	114 (57)	
Missing	15	4	0.176
Stage			
Early stage (I-II)	330 (62)	130 (65.3)	
Locally advanced (III)	202 (38)	69 (34.7)	
Missing	16	5	0.411
Tumour grade			
I	77 (15.7)	13 (7.5)	
II-III	415 (84.3)	160 (92.5)	
Missing	56	31	0.004
Lymphovascular invasion			
Negative	47 (9.2)	11 (12.8)	
Positive	198 (80.8)	75 (87.2)	
Missing	303	118	0.180
Localisation			
Right	268 (48.9)	90 (44.1)	
Left	280 (51.1)	114 (55.9)	0.242
Histological type			
Ductal	463 (84.5)	157 (77)	
Non-ductal	85 (15.5)	47 (23)	0.016*
Menopause status			
Pre-menopause	274 (50.3)	107 (52.5)	
Post-menopause	271 (49.7)	97 (47.5)	
Men	3	0	0.596
Nux			
Absent	459 (83.8)	147 (72.1)	
Present	89 (16.2)	57 (27.9)	<0.001*
Ex			
Absent	511 (93.2)	177 (86.8)	
Present	37 (6.8)	27 (13.2)	0.005*
Adjuvant chemotherapy			
Yes	476 (88.8)	195 (96.1)	
No	60 (11.2)	8 (3.9)	
Unknown	12	1	0.002*
Adjuvant radiotherapy			
Yes	304 (56.9)	104 (51.5)	
No	230 (43.1)	98 (48.5)	
Unknown	14	2	0.185
Adjuvant hormone therapy			
Yes	460 (86)	11 (5.4)	
No	75 (14)	192 (94.6)	
Unknown	13	1	<0.001*

*Statistically significant

TN: triple-negative

non-TN population include chemotherapy, hormonotherapy, and HER2-targeted treatments (trastuzumab), whereas patients with TN breast cancer may only use the chemotherapy option among these agents. Better insight and more effective treatment choices are required for this subgroup with a disease that has an aggressive course and limited treatment strategies. However, clinical data on TN breast cancers are very limited in Turkey. No relevant studies have been conducted so far in the Northeast region of Turkey, where the present study was carried out.

Triple-negative tumours were identified at a rate of 27.1% in our study, which is at the upper limit compared to the data from previous studies and may be explained by ethnic and geographical differences. In a study by Lund et al. (12), in three different states of the United States, the frequency of TN was 46.6% in African Americans and 21.8% in Caucasians. However, there is no standard cut-off value for ER, PR, and HER2 receptor positivity among studies on TN breast cancer. While some studies adopt >10% staining as positivity criterion for ER and PR (6, 17-21), others use a limit of > 5% (7, 8), and some others accept any degree of staining as positive (12, 22). Similarly, +3 staining is accepted as positive for HER2 in some studies (8, 19), while others use ≥+2 staining and positivity criterion (12, 21). In two studies carried in the same city, Aksoy et al. (8) identified the TN prevalence to be 10.6%, whereas the prevalence reported by Mersin et al. (11) was 24.8%. These data indicate that it is likely to obtain diverse prevalence values for TN in patients with breast cancer residing in the same geographical region, if different cut-off values are adopted for immunohistochemical staining.

In the present study, tumour grade was found to be higher in TN breast cancer compared to the non-TN group, which is consistent with several previous studies (6, 8, 19-21). On the other hand, no statistically significant difference was noted between TN and other breast cancers in other parameters including age, tumour diameter, lymph node involvement, stage, and menopausal state. Although there were no differences in terms of lymphovascular invasion, these data were unknown in the majority of subjects of the current study (421 subjects). Previous studies have reported larger tumour diameters (6, 17, 21-23) and more cases of lymph node metastases (17) and younger ages of diagnosis (7, 8, 19, 20, 23) in TN breast cancer compared to other breast cancers. On the other hand, some other studies have identified no significant differences between TN tumours and other breast cancers with regard to age (11, 22), diameter (8, 11, 20), and lymph node involvement (6, 11, 20, 21), consistent with the present study. Although lymph node metastases presented no statistical significance in the present study, it was more common in the TN group. However, higher occurrences of both relapse and death in the TN group indicate that TN cancers favour metastases in a hematogenous pattern. In a study by Zhang et al. (23), DFS

TABLE 2. Association between variables and survival in univariate analysis

Variables	DFS			OS		
	OR	(%95 CI)	p	OR	(%95 CI)	p
TN (presence vs. absence)	1.61	(1.16-2.25)	0.004 [‡]	1.76	(1.07-2.89)	0.024 [‡]
Age (<35 vs. ≥35 y)	0.76	(0.42-1.37)	0.351	1.56	(0.49-4.95)	0.450
Tumour size (≤5 cm vs. >5cm)	1.99	(1.39-2.84)	<.001 [‡]	1.87	(1.11-3.15)	0.017 [‡]
Lymph node status (positive vs. negative)	3.12	(2.06-4.73)	<.001 [‡]	3.37	(1.72-6.63)	<.001 [‡]
Stage (stage I-II vs. III)	4.08	(2.89-5.74)	<.001 [‡]	3.38	(2.00-5.70)	<.001 [‡]
Tumour grade (I vs. II-III)	1.96	(1.09-3.55)	0.023	2.37	(0.95-5.91)	0.057
Lymphovascular invasion (negative vs. positive)	1.82	(0.87-3.78)	0.105	1.18	(0.41-3.37)	0.760
Localisation (right vs. left)	0.95	(0.69-1.31)	0.753	0.86	(0.53-1.38)	0.521
Histological type (ductal vs. non-ductal)	1.56	(0.97-2.49)	0.063	1.49	(0.74-3.00)	0.265
Menopause status (pre-menopause vs. post-menopause)	0.87	(0.63-1.19)	0.378	1.09	(0.68-1.75)	0.714
Chemotherapy (yes vs. no)	2.59	(1.14-5.85)	0.018 [‡]	1.48	(0.54-4.07)	0.445
Radiotherapy (yes vs. no)	2.73	(1.88-3.95)	<.001 [‡]	2.74	(1.57-4.80)	<.001 [‡]
Hormonotherapy (yes vs. no)	0.48	(0.34-0.66)	<.001 [‡]	0.53	(0.32-0.87)	0.010 [‡]
ER (positive vs. negative)	0.46	(0.33-0.64)	<.001 [‡]	0.46	(0.27-0.77)	0.003 [‡]
PR (positive vs. negative)	0.58	(0.41-0.80)	0.001 [‡]	0.51	(0.30-0.85)	0.008 [‡]
HER2 (positive vs. negative)	1.80	(1.23-2.64)	0.002 [‡]	2.15	(1.25-3.70)	0.005 [‡]

[‡]Statistically significant

OR: odds ratio; TN: triple-negative; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor; DFS: disease free survival; OS: overall survival

TABLE 3. The effects of variables on disease-free survival and overall survival in multivariate analysis

Variables	Disease free survival			Overall survival		
	RR	(95% CI)	p	RR	(95% CI)	p
TN	2.21	(1.48-3.29)	<.001 [‡]	3.21	(1.68-6.10)	<.001 [‡]
Tumour size	1.60	(1.07-2.40)	0.022 [‡]	1.34	(0.72-2.49)	0.350
Lymph node status	2.46	(1.59-3.83)	<.001 [‡]	2.35	(1.17-4.73)	0.016
Tumour grade	1.55	(0.85-2.83)	0.151	1.60	(0.63-4.08)	0.320
HER2	2.60	(1.66-4.09)	<.001 [‡]	3.46	(1.69-7.11)	<.001 [‡]

[‡]Statistically significant

TN: triple-negative; HER2: human epidermal growth factor; RR: relative risk

and OS was shorter, although lymph node involvement was less common in TN tumours compared to other breast cancers, which is supportive of this hypothesis.

The analyses demonstrated a higher impact of TN tumours on patient survival compared to other tumours. The univariate

analysis showed shorter DFS and OS, consistent with the data from previous studies (7, 19-21, 24). The presence of poor prognostic factors known for breast cancer describes shorter survival relative to other breast cancers. A study by Nishimura et al. (21) confirmed through multivariate analysis that a

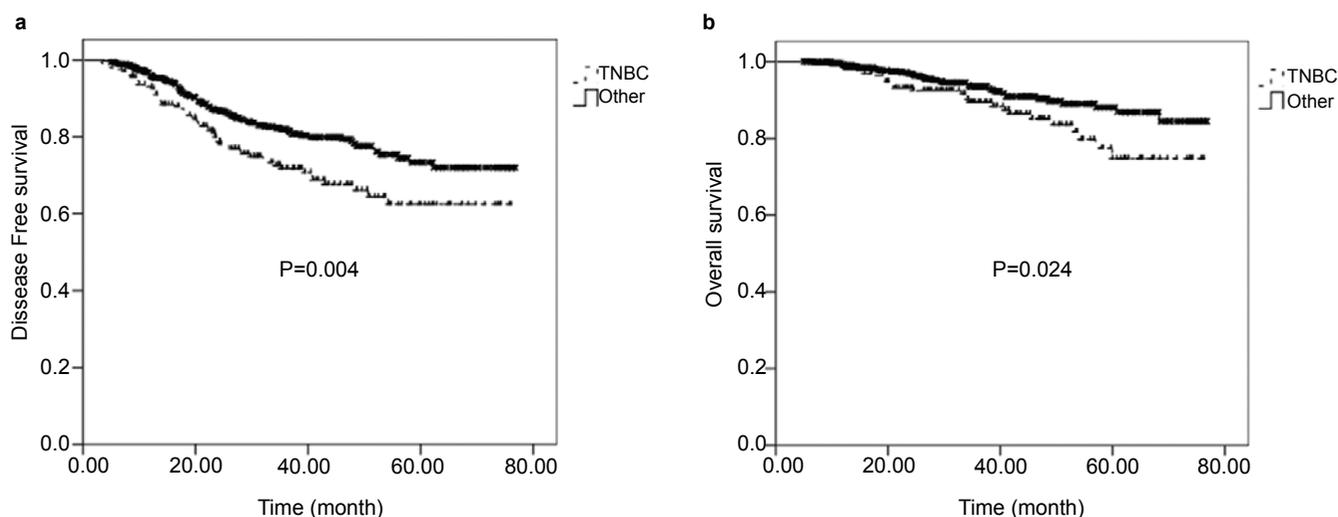


FIG. 1. a, b. Kaplan-Meier curves for disease free survival (a). Kaplan-Meier curves for overall survival (b).

TN tumour was an independent prognostic factor on both DFS and OS. Similarly, TN breast cancer, identified to be an independent prognostic factor, increased the risk of relapse 2.21-fold and the risk of death 3.21-fold in the multivariate analysis of the present study.

In conclusion, TN breast cancers have a substantial prevalence among breast tumours both in our region and in different geographies. Better insight into clinicopathological characteristics, as well as its prognostic and predictive factors, will provide guidance to clinicians in developing effective treatment strategies for this subgroup with high rates of relapse and mortality.

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