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Prognostic Factors in Patients with Triple Negative Breast Cancer Undergoing Adjuvant Radiotherapy: A 10-Year Single Center Experience

Berrin B. Yavuz*[a], Meryem Aktan[a], Gul Kanyilmaz[a]

[a]*Department of Radiation Oncology, Meram Medical School, Necmettin Erbakan University, Konya, Turkey*

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ABSTRACT

Background: Triple negative breast cancer (TNBC) is the most aggressive and worst prognosis group among breast cancer molecular subtypes. This retrospective study aimed at determining the prognostic factors affecting survival in the TNBC group.

Methods: Between 2010 and 2020, patients with invasive ductal carcinoma who received curative radiotherapy were included in the study. The patients were divided into two groups as TNBC and non-TNBC. Clinicopathological and treatment parameters of both groups were compared. Survival rates were evaluated using the Kaplan Meirer method.

Results: One hundred ten (11.1%) of 992 patients were triple negative. The TNBC group showed more grade 2-3 tumors (95.8% vs 87.8%, P=0.019), a higher ki-67 value (72.7% vs 44.9%, P<0.001), more metastasis presence (28.2% vs 16.2%, P=0.002) and more exitus (28.2% vs 14.5%, P<0.001) than the non-TNBC group. Brain metastasis was observed more frequently in the TNBC group. In the TNBC group, being ≥70 years of age (P=0.05), having the T3-4 disease (P=0.040), the presence of perineural invasion (P=0.022), the presence of metastasis (P<0.001), and the presence of brain metastasis (P=0.049) had a negative effect on OS in univariate analysis. Having TNBC was determined as an independent variable that negatively affected both overall and disease-free survival in multivariate analysis.

Conclusion: This single-center study showed that having TNBC had a negative impact on survival. The treatment in TNBC patients should be determined by considering all factors affecting recurrence and survival and should be individualized.

INTRODUCTION

Breast cancer (BC) is the most common type of cancer in women in the world, and it is the 2nd most common cause of cancer-related deaths.[1] Breast cancer is a heterogeneous disease and is divided into 4 molecular groups: Luminal A, Luminal B, human epidermal growth factor receptor-2 (HER-2) positive and triple negative subtypes according to hormone receptor status.[2] Triple negative breast cancer (TNBC) consists of subgroups in which estrogen receptor (ER) and progesterone receptor (PR) stain less than <1% and HER-2 is negative.[3]

TNBC accounts for approximately 10-15% of all breast cancers.[4,5] The risk of TNBC increases with young menarche, young first birth, non-breastfeeding, and abdominal obesity.[6] It is more common in young women, obese people and BRCA-1 carriers.[7] TNBC is a heterogeneous group and has at least six different genetic subtypes.[8] It has a histopatho-

***Address for correspondence:**
Berrin Benli Yavuz, M.D., PhD,
Necmettin Erbakan University, Meram Medical School, Department of Radiation Oncology, Konya, Turkey
Phone: +505 5150093
E-mail: berrinyavuz77@gmail.com

logically high grade, increased mitotic activity, a high nuclear cytoplasmic ratio and an accelerated tumor proliferation rate.[6] We observe a larger tumor size[1], less nodal involvement,[7] more distant metastasis,[6] poor prognosis,[9] and increased mortality,[4] in this group of patients. It was observed that distant metastases are more common three years after the diagnosis,[10] and lung and that brain metastases are more common than bone metastases.[11,6] Mortality rates in the first 5 years after diagnosis are 40%.[10] Their 5-year survival rate is less than the subtype with the best prognosis at 8-16%.[6]

Treatment approaches in TNBC include surgery, radiotherapy (RT) and chemotherapy (CT). Surgery may be in the form of mastectomy or lumpectomy.[7] Standard systemic treatment is still anthracycline and taxane-containing chemotherapy regimens.[12] TNBC responds well to neoadjuvant CT (NAC) and the results have been found to be better in patients who a show complete pathological response. Capecitabine is often used as an adjuvant therapy in groups who do not show a complete pathological response.[13] The difficulty in treatment management is the absence of hormonal and target treatments in this group of patients.[14] Adjuvant RT plays an important role in BC. RT is applied after breast protective surgery (BCS), chest wall+/- regional nodal irradiation in high-risk patients after mastectomy, recurrence of disease and palliative purposes in metastasis.[11] RT reduces local recurrence and overall mortality.[2] EBCTCG (Early Breast Cancer Trialists' Collaborative Group) meta-analysis revealed that 10-year locoregional recurrence (LRR) and 20-year breast cancer mortality decreased with postmastectomy RT (PMRT) in patients with 1-3 lymph node positivity.[15] PMRT is recommended for patients whose 1-3 or 4 and more lymph nodes are positive in the National Comprehensive Cancer Network's clinical practice guideline.[16] However, RT is not recommended according to molecular subtypes in studies and NCCN guidelines.

We observed in our clinical practice that TNBC patients progress faster and survival is lower despite all treatments. Therefore, with respective study, we aimed to show patients and treatment characteristics and survival differences between TNBC and non-TNBC in patients undergoing adjuvant radiotherapy in our clinic.

MATERIALS AND METHODS

Patient selection

Nine hundred ninety-six patients who underwent curative radiotherapy between January 2010 and November 2020 in our clinic were included in the study. Female patients over 18 years of age with pathologically invasive tumors and at least 12 months follow-up were included in the study. Patients with bilateral breast cancer, metastatic disease, a second malignancy, and male patients were not included. Patients data and treatment characteristics were obtained from medical records and the hospital system. Patients were classified according to American Joint Committee on Cancer (AJCC), Version 8.17 The patients receiving neoadjuvant therapy were staged according to the pre-treatment imaging methods, and the patients receiving adjuvant therapy according were staged to the postoperative pathology data and preoperative imaging.

ER and PR status and HER-2 were evaluated immunohistochemically. If ER and PR were below 1%, they were accepted as negative. HER-2 was considered negative if 1(+) in IHC and positive if 3(+). HER-2 amplification was evaluated by fluorescence in situ hybridization (FISH) method in the two (+) group. Breast cancer subtypes were grouped as luminal A (ER/PR (+), HER-2 (-)), luminal B (ER/PR (+), HER-2 (+)), HER-2 (+) (ER/PR (-), HER-2 (+)) and triple negative (ER/PR/HER-2 (-)) according to the hormone status in IHC. The patients were categorized into two groups as TNBC and non-TNBC. Patients and tumor characteristics of both groups were obtained from the records. Clinicopathological characteristics of the patients (histological type, stage, tumor size, lymph node involvement, grade, perineural invasion (PNI), lymphovascular invasion (LVI), extracapsular invasion (ECE), ER/PR/HER-2 status, ki-67), and treatments (type of surgery, chemotherapy, radiotherapy) were evaluated separately for both groups. Ethics committee approval was obtained before starting the study. The principles in the latest version of the Helsinki Declaration were followed. No informed consent was obtained from the patients due to the retrospective nature of the study.

Treatments

Patients underwent BCS or modified radical mastectomy (MRM), sentinel lymph node dissection (SLND) or axillary dissection. Chemotherapy was administered as adjuvant or neoadjuvant in the form of 4 cycles of cyclophosphamide and adriamycin +/- 12 weeks or 4 cycles of taxanes. Radiotherapy was administered in the presence of T3-4, lymph node involvement, LVI, PNI, ECE after MRM. After BCS, adjuvant RT was given to all of the patients. Nodal irradiation was performed in those who were node positive. Nodal irradiation was administered to the axillary and supraclavicular region. Mammary interna lymphatics were included in the treatment area if the number of involved lymph nodes was large and mammary interna lymph nodes were positive in

tumors located in the inner and middle quadrant. Treatment was administered using a 3D conformal technique and the standard two parallel opposing tangential field technique. Then, 50 Gy RT was applied to the chest wall/ breast tissue of the patients. A boost was added to the 10-16 Gy tumor bed in patients who underwent BCS. All patients were treated with Eclipse treatment planning system (Varian Medical Systems Inc. Palo Alto, CA). No treatment was planned as part of the protocol of this study.

Survival Analysis

The primary endpoint of the study was to found the survival differences between the TNBC and non-TNBC groups. The secondary aim was to find the prognostic factors affecting overall survival (OS) and disease-free survival (DFS). OS was defined as the time from the date of diagnosis to death or last control. DFS was defined as the time from the date of diagnosis to the date of the first occurrence of metastasis/local-regional recurrence /death.

The patients were followed up retrospectively from the records until March 2022 or death. During this period, they were routinely followed up once every 3 months for the first 2 years, once every 6 months for up to 5 years, and then once a year.

Statistics

The patients' characteristics were summarized as n (%) for categorical variables and continuous variables as median. Patients and tumor characteristics in both groups were evaluated by chi-square test and Mann Whitney u test. Survival rates were evaluated using the Kaplan Meirer method. Survival differences between the two groups were evaluated using the log-rank test. All statistical survival analyses were performed using SAS University Edition 9.4 program. The First's correction was used in multivariable cox regression. P<0.05 was considered statistically to be significant.

RESULTS

Patient and treatment characteristics

One hundred ten (11.1%) of the 992 patients were triple negative. The median age was 50 (27-87) and 50 (27-83) in the TNBC and non-TNBC groups, respectively. The median follow-up was 73.57 months (12.32-153.49). Also, 47.4% of our patients were postmenopausal. The characteristics of the patients and the treatments are summarized in Table1 and Table 2. The most common histology in the TNBC group was invasive ductal carcinoma (74.5%). The medullary carcinoma subtype was observed more frequently than non-TNBC group. The TNBC group had more grade 2-3 tumors (95.8% vs 87.8%, P=0.019), a higher ki-67 value (72.7% vs 44.9%, P<0.001), more metastasis presence (28.2% vs 16.2%, P=0.002) and more exitus (28.2% vs 14.5%, P<0.001) than the non-TNBC group. Also, local recurrence was higher in the TNBC group, although it was not statistically significant. When the patients with metastases were evaluated, visceral and bone metastases were not different between the groups, while brain metastases were observed to be more common in the TNBC group (51.6% vs 21.7%, P=0.001) (Table-3).

Survival

During the median follow-up of 73.57 months, 883 of 992 patients (84%) were alive and 174 of 992 (17.5%) had distant metastasis. While the mean survival rate was 131.978 months in the whole group, it was 117.7 and 132.2 months in the TNBC and non-TNBC groups, respectively. In addition, 2, 5 and 10-year overall survival (OS) was 91.8%, 75.8%, 64% and 98.5%, 91.3% and 76.2%, respectively in the TNBC and non-TNBC groups (Figure-1). The median of DFS was 52.37 months in the non-TNBC group while it was 29.7 months in the TNBC group. Additionally, 2, 5 and 10-year DFS were 65.3%, 27.3%, 0% and 78.4%, 44.3% and 3.2%, respectively (Figure-1).

When evaluated as a whole group, factors like receiving neoadjuvant CT (P<0.001), suffering from TNBC (P<0.001), being ≥70 years of age (p<0.001), being postmenopausal (P=0.010), having grade 2-3 (P=0.019), having ki-67>20 (P=0.014), having the T3-4 disease (P<0.001), having the N2-3 disease (P<0.001), the presence of ECE (P<0.001), the presence of PNI (P=0.014), the presence of LVI (P<0.001), the presence of metastasis (P<0.001), the presence of brain (P<0.001) and visceral (P=0.011) metastasis and the presence of local regional recurrence (P=0.004) were found to have a negative effect on OS in univariate analyses. Receiving neoadjuvant CT (P=0.017), having the N2-3 disease (P=0.026), and the presence of ECE (P=0.049) had a negative effect on DFS.

No effect on DFS was found while factors like being ≥70 years of age (P=0.05), having the T3-4 disease (P=0.040), the presence of PNI (P=0.022), the presence of metastasis (P<0.001), and the presence of brain metastasis (P=0.049) had a negative effect on OS in univariate analysis in the TNBC group (Table 4). In the non-TNBC group, receiving neoadjuvant CT (P=0.001), being ≥70 years old (P<0.001), being postmenopausal (P=0.002), having a grade 2-3 disease (p=0.026), having the T3-4 disease (P<0.001), the having N2-3 disease (P<0.001), the presence of ECE (P<0.001), the presence of LVI (P<0.001), the presence of

metastasis (P<0.001), the presence of brain (P<0.001) and visceral (P=0.014) metastasis and the presence of local regional recurrence (P=0.021) were found to have a negative effect on OS (Table 4). When evaluated in terms of DFS, having the N2-3 disease (P=0.026) had a negative effect on the results of univariate analysis.

In the results of multivariate analysis, suffering from TNBC, having the N2-3 disease, being ≥70 years old, being postmenopausal, and the presence of metastasis were found to be factors affecting OS negatively in the whole group. Being ≥70 years old, suffering from TNBC, having the T3-4 disease, and having the N2-3 disease were independent prognostic factors for DFS (Table 5).

Table 1. Characteristics of the patients and tumors

Characteristics	TNBC N (%)	Non-TNBC N (%)	P value
Patients	110 (11.1)	882 (88.9)	
Age (median)	50 (27-87)	50 (27-83)	0.340
Menopausal status			
Premenopausal	59 (53.6)	463 (52.5)	0.821
Postmenapausal	51 (46.4)	419 (47.5)	
Stage			
Stage I-II	63(57.3)	529(60)	0.842
Stage III	41(37.3)	304(34.5)	
Nx	6(5.5)	49(5.6)	
Tumor stages			
T0-1-2	87 (79.1)	735 (83.3)	0.266
T3-4	23 (20.9)	147 (16.7)	
Lymph node stages			
N0-1	67 (65)	581 (69.5)	0.357
N2-3	36 (35)	255 (30.5)	
Pathology			
Ductal	82 (74.5)	727 (82.4)	<0.001*
Lobular	2 (1.8)	63 (7.1)	
Mixt	4 (3.6)	30 (3.4)	
Medullar	20 (18.2)	11 (1.2)	
Others	2 (1.8)	51 (5.8)	
Grade			
Grade 1	4 (4.2)	97 (12.2)	0.019*
Grade 2-3	92 (95.8)	699 (87.8)	
ECE			
Yes	29 (33)	271 (37.5)	0.406
No	59 (67)	452 (62.5)	
PNI			
Yes	25 (27.5)	243 (31.7)	0.413
No	66 (72.5)	524 (68.3)	
LVI			
Yes	38 (41.8)	382 (49.4)	0.167
No	53 (58.2)	391 (50.6)	
Ki-67			
≤20	15 (27.3)	295 (55.1)	<0.001*
>20	40 (72.7)	240 (44.9)	

ECE: extracapsular extension, LVI: lymphovascular invasion, PNI: perineural invasion
*statistically significant

DISCUSSION

According to 2020 GLOBOCAN data, 2.3 million new cases each year (11.7% of all cancers) are expected to have BC.[18] Today, not only the TNM stage but also the hormone status are effective in the process of deciding on the treatment of this global problem. TNBC, on the other hand, is difficult to manage because hormonal and target treatments cannot be administered. Improved demonstration of clinicopathological and prognostic factors is important in terms of treatment planning in this group. The TNBC and non-TNBC groups were compared over 10 years in this retrospective study. In our clinic, 11.1% of breast cancers treated for curative purposes in the last 10 years had triple negative histology, showing that mortality and metastasis rates were worse in the TNBC group than in the non-TNBC group.

Table 2. Characteristics of the treatment and recurrences

Charecteristics	TNBC N (%)	Non-TNBC N (%)	P value
Neoadjuvant CT			
Yes	12 (10.9)	77 (8.7)	0.451
No	98 (89.1)	805(91.3)	
Chemotherapy			
Yes	105 (95.5)	797 (90.4)	0.080
No	5 (4.5)	85 (9.6)	
Surgery type			
BCS	40 (36.4)	362 (41)	0.346
MRM	70 (63.6)	520 (59)	
Radiotherapy			
Chest Wall	43 (39.1)	278 (31.5)	0.277
Chest Wall+RNI	62 (56.4)	560 (63.5)	
Chest Wall+RNI+MI	5 (4.5)	44 (5)	
Metastasis			
Yes	31 (28.2)	143 (16.2)	0.002*
No	79 (71.8)	739 (83.8)	
Local relaps			
Yes	4 (3.6)	14 (1.6)	0.129
No	106 (96.4)	868 (98.4)	

CT: Chemotherapy, BCS: breast conserving surgery, MRM: modified radical mastectomy, LNI: regional nodal irradiation, MI: Internal mammary lymph node
*statistically significant

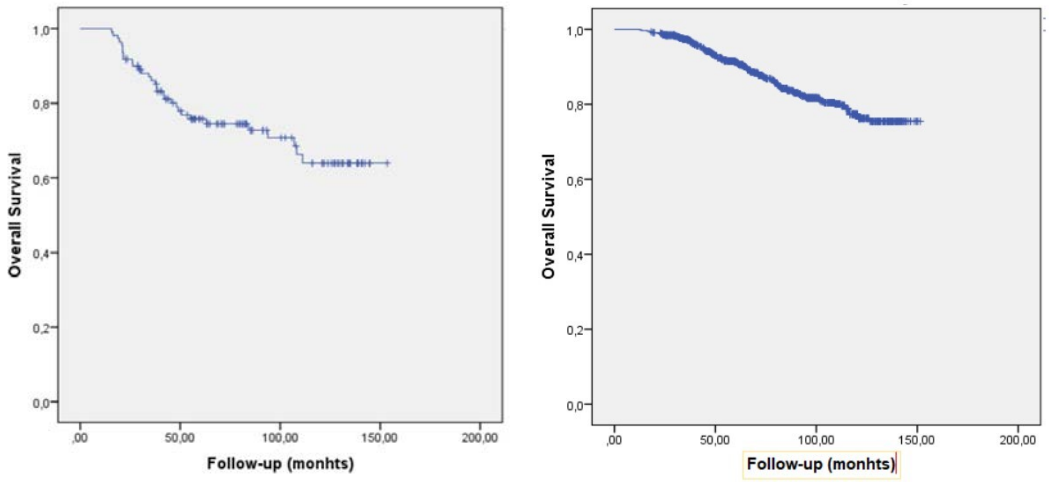

Figure 1. Overall survival curves in TNBC (a) and non-TNBC groups (b).

Table 3. Characteristics of metastasis

Charecteristics	TNBC N(%)	Non-TNBC N(%)	P value
Brain metastasis			
Yes	16 (51.6)	31 (21.7)	0.001*
No	15 (48.4)	112 (78.3)	
Visseral metastasis			
Yes	26 (83.9)	99 (69.2)	0.100
No	5 (16.1)	44 (30.8)	
Bone metastasis			
Yes	14 (45.2)	90 (62.9)	0.067
No	17 (54.8)	53 (37.1)	

*statistically significant

The majority of the patients had invasive ductal carcinoma. They had a higher-grade cancer and higher Ki-67 values. TNBC is a subgroup associated with poor prognosis, and high recurrence rates in the first 3 years and higher mortality rates in the first 5 years.[2] In previous research, 5-year OS and DFS were found to be 75.8% and 27.3% in the TNBC group, and 91.3% and 44.3% in the non-TNBC group, in accordance with the literature in our data. Having TNBC was determined as an independent variable that negatively affected both OS and DFS in multivariate analysis results. The risk of death in those with triple negative disease was found to be 1.8 times higher than in the other group (HR: 1.8, 95%, Cl: 1.2-2.7, P=0.0044).

Table 4. Factors affecting overall survival in univariate analysis

Variables	TNBC Median OS	P value	Non-TNBC Median OS	P value
Age				
<70	120.872	0.050	134.120	<0.001*
≥70	80.512		101.766	
Menopausal status				
Premenopausal	114.933	0.538	136.707	0.002*
Postmenapausal	111.402		126.102	
Tumour stages				
T0-1-2	122.922	0.040*	134.530	<0.001*
T3-4	94.253		117.145	
Lymph node stages				
N0-1	127.463	0.062	139.586	<0.001*
N2-3	102.016		117.446	
Grade				
Grade 1	121.314	0.756	136.795	0.026*
Grade 2-3	119.041		131.466	
ECE				
Yes	104.908	0.070	123.897	<0.001*
No	120.756		137.453	
PNI				
Yes	85.746	0.022*	126.547	0.063
No	119.055		132.831	
LVI				
Yes	98.302	0.109	124.972	<0.001*
No	113.278		136.197	
Ki-67				
≤20	102.058	0.143	131.796	0.129
>20	83.510		115.756	
Neoadjuvant chemotherapy				
Yes	82.881	0.142	104.803	0.001*
No	120.225		133.305	
Metastasis				
Yes	63.477	<0.001*	83.606	<0.001*
No	139.191		144.820	
Brain metastasis				
Yes	36.665	0.049*	60.536	<0.001*
No	79.905		92.894	
Visceral metastasis				
Yes	64.239	0.978	78.730	0.014*
No	57.961		100.110	
Bone metastasis				
Yes	66.044	0.930	87.171	0.594
No	59.932		82.004	

ECE: extracapsular extension, LVI: lymphovascular invasion, PNI: perineural invasion
*statistically significant

Nodal status is one of the most important prognostic factors in BC. In some studies, nodal disease was found to be a prognostic factor in TNBC patients.[19] In our study, the N2-3 disease had a negative effect on OS in both TNBC and non-TNBC groups. Also, in multivariate analysis, having the N2-3 disease had a negative effect on OS and DFS. The risk of death has been found to increase 1.6 times in those who have the N2-3 disease (HR: 1.6, 95, Cl%: 1.1-2.3, P=0.0049).

Lymph node involvement was less common compared to the non-TNBC group (55.2% vs 65.4%, P=0.041). The poor prognosis in the TNBC group is thought to be due to hematogenous metastasis rather than lymph node metastasis.[11] The brain metastasis was observed more frequently in TNBC, while no difference was observed between the groups in visceral organ metastasis and bone metastases in our study.

In our study, the rate of local recurrence was 3.6%. In another study examining 2007 TNBC patients, local recurrence and distant metastasis were found to be 31.9% and 51.4%, respectively, after 10 years of observation, and the rate of brain metastasis was 9.6%.[4] However, it is thought that stage IV patients who received radiotherapy in 50.4% of the case group in this study showed increased local recurrence rates. In a meta-analysis including

Table 5. Factors affecting overall survival and disease-free survival in multivariate analysis

Variables	HR	OS 95% Cl	P value	HR	DFS95%Cl	P value
Age						
<70	1	1.2-3.3	0.0049*	1	1.3-3.2	0.002*
≥70	2.0			2.0		
Triple negative						
No	1	1.2-2.7	0.0044*	1	1.1-2.4	0.006*
Yes	1.8			1.6		
Menopausal status						
Premenopausal	1	1.4-2.8	<0.001*	1	0.7-1.4	0.67
Postmenapausal	2.0			1.0		
Tumour stages						
T0-1-2	1	0.9-2.1	0.058	1	1.3-2.1	0.006*
T3-4	1.4			1.5		
Lymph node stages						
N0-1	1	1.1-2.3	0.0049*	1	1.8-3.4	<0.001*
N2-3	1.6			2.5		
Metastasis						
No	1	10.3-22.0	<0.001*			
Yes	15.0					

22 studies, it was shown that recurrence and general mortality decreased with RT in 1 - 3, 4 or more node-positive patients. In node-negative patients, locoregional recurrence occurred in 16% of non-irradiated women before distant metastasis. RT reduced local recurrences but was not found to be effective in overall mortality and breast cancer mortality in this group.[15] In the Danish breast cancer group study, TNBC was found to be associated with increased overall mortality and distant metastasis, but this effect could not be observed in patients who underwent postmastectomy RT. Locoregional recurrence (LRR) was significantly increased in TNBC. [20] As the rate was 5% in the TNBC group and 2-3% in the hormone-positive group at 10 years after LRR, BCS and RT administration in early-stage BC.[21]

Thanks to neoadjuvant chemotherapy, the surgeons select breast-conserving surgery for a group of patients that were previously the candidate of total mastectomy.[16] Even if it is an operable disease, it is accepted as the standard approach in TNBC and HER-2 positive patients. If the pathological complete response is detected, significantly better DFS and OS are seen.[21] In our cases, NAC was administered to 10.9% of the TNBC group and 8.7% of the non-TNBC group. NAC administration was found to have a negative effect on OS and DFS in the whole group and on OS in the non-TNBC group. It was also negative in the whole group and non-TNBC group in the multivariate analysis results. Pathological complete response (pCR) occurred in 24.7% of patients receiving NAC. There was no statistical difference between the TNBC and non-TNBC groups (41.7% vs 22.1%, P=0.143). All patients receiving NAC had 2nd and 3rd stage diseases. The early-stage patients are usually treated with the first surgery in our hospital, and patients receiving NAC treatment are more frequently advanced stage patients. Besides, the NAC plan is not administered independently of the stage according to the hormone receptor status. The negative effect of NAC on OS and DFS is thought to be due to this.

Ki-67 is commonly used to evaluate the proliferative index in BC.[22] Cut-off values for Ki-67 vary in the literature. In the study carried on 1800 TNBC patients, Zhu *et al*. showed that Ki-67 was above 20% in 84.39% of the patients. Ki-67 values were found to be higher in TNBC than the luminal cancers. Shorter OS and DFS were shown in patients with Ki-67 values higher than 30%.[23] In our study, the median ki-67 value was 20 (range: 1-95). Similar to the literature, the high ki-67 value was more in the TNBC group compared to the non-TNBC group (72.7% vs 44.9%, p<0.001). The high Ki-67 levels in the whole group had a negative effect on OS in the univariate analysis.

The limitation of our study was its retrospective nature and partially the small number of patients. It is known that TNBC is more common in patients with BRCA mutation.[7] However, we did not know about BRCA mutations in this study. The strength of the study, on the other hand, was that since all patients treated in our clinic were evaluated, selection bias was minimal. All patients were treated in the same center with the same treatment protocols. Also, the median follow-up was 73.57 months.

CONCLUSION

This single-center study showed that having TNBC had a negative impact on OS and DFS. The TNBC group had more grade 2-3 tumors, higher ki-67 values, more metastasis, and more exitus than the non-TNBC group. The treatment in TNBC patients

should be determined by considering all factors affecting recurrence and survival and individualizing.

ETHICAL CONSIDERATIONS

Ethics committee of the institution has approved the protocol of the study before starting

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CONFLICT OF INTEREST

There are no conflicts of interest to be declared by the authors.

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