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Research Article

Investigation of Factors Predicting Disease Recurrence and Survival in Triple-Negative Breast Cancer Patients

Aysun Fatma Akkuş,[1] Osman Köstek,[2] Muhammet Bekir Hacıoğlu,[1] Bülent Erdoğan,[1] İrfan Çiçin,[3] Sernaz Topaloğlu[1]

[1]Department of Medical Oncology, Trakya University Faculty of Medicine, Edirne, Türkiye
[2]Department of Medical Oncology, Marmara University Faculty of Medicine, Istanbul, Türkiye
[3]Department of Medical Oncology, İstinye University Faculty of Medicine, Istanbul, Türkiye

Abstract

Objectives: This retrospective study aimed to identify factors influencing disease recurrence and survival in patients with triple-negative breast cancer (TNBC).

Methods: The study included 69 patients who were admitted to the medical oncology clinic of Trakya University between January 1, 2012, and March 1, 2019. Clinicopathological characteristics, recurrence, survival factors, and treatment approaches were evaluated. Univariate and multivariate analyses were performed. Data were expressed as mean±SD, with comparisons made using the independent t-test for parametric variables and Chi-square test for non-parametric variables. Survival was analyzed using Kaplan-Meier and Cox regression, with a significance level of $p<0.05$.

Results: Of the 69 patients, 11 received neoadjuvant therapy, and 58 received adjuvant therapy. The median disease-free survival was 50.2 months, and the median overall survival was 123.1 months. Disease-free survival was shorter in patients with Ki-67 >30% (p=0.006). Advanced age (>60 years) and neoadjuvant therapy were independent predictors of disease-free survival, with overall survival being lower in patients over 60.

Conclusion: Genetic counseling for BRCA mutation testing is recommended for this patient group. No significant findings were observed for other clinical and demographic factors. Due to the retrospective nature and small sample size, further studies with larger patient groups are needed.

Keywords: Triple negative breast cancer, overall survival, disease-free survival

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Breast cancer is the most common cancer type in women. In breast cancer classification, 10-20% of cases fall into the triple-negative breast cancer (TNBC) group.[1] Triple-negative breast cancer (TNBC) is a subtype of breast cancer that does not express estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), which are molecular markers used for classification. TNBC tends to behave more aggressively compared to other breast cancer types.[2] When compared to other types of breast cancer, TNBC is frequently diagnosed as aggressive, invasive, high-grade, and with lymph node positivity, which serves as an increased prognostic factor for mortality and morbidity.[3]

Approximately 35% of TNBC patients have BRCA1 mutations, and 8% have BRCA2 mutations.[4, 5] In contrast, less than 6% of all breast cancers are associated with a BRCA mutation. Based on this finding, it is recommended that any patient with TNBC be referred to a genetic counselor

Address for correspondence: Aysun Fatma Akkuş, MD. Department of Medical Oncology, Trakya University Faculty of Medicine, Edirne, Türkiye
Phone: +90 538 812 01 36 **E-mail:** aysunfatmadogan@gmail.com

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for BRCA genetic mutation testing.[6] The basal-like subtype is typically ER– and HER2– and exhibits some characteristics of mammary myoepithelial cells. It has been shown that the basal-like subtype has the highest proliferation rates and poor clinical outcomes, and is also associated with carcinomas related to BRCA1.[7] Overall, very little is known about the development and prevention of these aggressive tumors.[8]

In 90% of TNBC cases, the pathological diagnosis is invasive ductal carcinoma with a high histological grade. They often have central necrotic zones and frequent lymph node involvement.

For patients with TNBC with tumor size >0.5 cm or positive lymph node pathology (independent of tumor size), adjuvant therapy is standard. For tumors smaller than 0.5 cm and negative lymph nodes, the prognosis of TNBC is generally good. Therefore, the benefit of adjuvant chemotherapy is debated, considering its side effects. The response to chemotherapy (CT) is worse compared to non-TNBC types, and the risk of recurrence within five years is higher.[6] Therefore, to increase survival in TNBC, a more detailed identification of prognostic factors and stronger treatment strategies are needed.

Several prognostic factors, both tumor-dependent and tumor-independent, have been defined in breast cancer.. In this single-center study, the clinical and pathological characteristics of triple-negative breast cancer were examined, and prognostic risk factors were identified.

Methods

In this single-center study, patients diagnosed with triple-negative breast cancer who were admitted to the Medical Oncology Clinic of Trakya University Medical Faculty between 2012 and 2019 were retrospectively evaluated. The study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the Trakya University Ethics Committee (TUTF-BAEK 2019/03).

Before the study, the medical records of 1100 breast cancer patients were reviewed. A total of 110 patients diagnosed with triple-negative breast cancer were identified. Sixty-nine patients who were diagnosed with triple-negative breast cancer and had complete medical records were included in the study. Forty-one patients were excluded from the study due to incomplete medical records. During data collection, the Medical Oncology archive records, hospital files, and Trakya University Medical Faculty Hospital's automation system were utilized. For patients whose last follow-up was more than 6 months ago, they were contacted by phone to obtain information about their current status. For patients without a diagnosis date, pathological diagnosis date, or pre-operative diagnosis, the date of surgery was used as the reference. Patient files were scanned, and the following data were recorded for all patients: age, primary tumor location, age at menarche, ECOG performance status, age at first delivery, obstetric history, postmenopausal status, presence of comorbidities, primary surgery, family history, germline BRCA mutation status, tumor histopathology, clinical TNM stage, pathological stage, grade, Ki-67 status, presence of lymphovascular invasion, presence of in situ components, treatment group, and those who received neoadjuvant and adjuvant therapy.

During data recording, disease-free survival (DFS) was defined as the time from diagnosis to the first progression, and overall survival (OS) was defined as the time from diagnosis to death.

Univariate and multivariate analyses were performed. Standard deviation (±) was used. The intergroup comparisons of the variables were performed using the independent t-test. The relationships between non-parametric variables were evaluated using the Chi-square test. Kaplan-Meier analysis was used for survival analysis. Cox regression analysis was performed for multivariate analysis. A confidence interval of 95% and a p-value <0.05 were considered statistically significant. All data were encoded and entered into the SPSS 22.0 program.

Results

A total of 69 patients were included in the study, and the descriptive characteristics of the population are presented in Table 1. The median follow-up time of the patients was 33.8 months (minimum 1.0 – maximum 139.6). The median disease-free survival (DFS) of the patients was 50.2 months (24.3 – 76.0) (Table 3). The median overall survival (OS) of the patients was 123.1 months (100.5 – 145.7).

Factors that statistically significantly increased the disease-free survival rate included: diagnosis age <60 years, invasive ductal carcinoma histological type, neoadjuvant treatment, Ki-67 ≥30 (p=<0.001, p=0.04, p=0.008, p=0.06, respectively).

In the multivariate analysis, the prognostic impact of Ki-67 ≥30% showed only borderline significance (p=0.06).

The group that received neoadjuvant treatment consisted of 11 patients, while the group that received adjuvant treatment consisted of 58 patients. The fact that only 11 out of 69 patients received neoadjuvant therapy may limit the statistical power of the subgroup analysis. Their demographic and clinical characteristics were compared in Table 2. Statistically significant factors identified included: clinical axillary lymph node status (p=0.04) and clinical stage (p=0.01).

Table 1. Demographic and Clinical Data

	All Patients (n=69)
Age, years	
Mean±SD	52±11
Primary Tumor Location, n (%)	
Right Breast	34 (49.2)
Left Breast	35 (50.8)
Age at Menarche, years	
Mean±SD	13±1
Age at First Birth, years	
Mean±SD	22±3
History of Childbirth, n (%)	58 (81.6)
Postmenopausal Status, n (%)	44 (62.0)
ECOG Performance Score, n (%)	
0	3 (4.2)
1	66 (93.0)
>2	2 (2.8)
Presence of Comorbidities, n (%)	38 (53.5)
Primary Surgery, n (%)	
Modified Radical Mastectomy	34 (47.8)
Breast-Conserving Surgery	35 (49.2)
Family History, n (%)	
Breast or Gynecological Malignancy	18 (25.3)
Other Malignancies	13 (18.3)
gBRCA Mutation, BRCA 1/2, n (%)	16/1, 17 (23.9)
Histology, n (%)	
Invasive Ductal Carcinoma	61 (88.4)
Invasive Lobular Carcinoma	1 (1.6)
Other*	7 (10.1)
Clinical T Stage, n (%)	
cT1	40 (57.9)
cT2	21 (30.4)
cT3	6 (8.69)
cT4	1 (1.4)
Unknown	1 (1.4)
Clinical N Stage, n (%)	
cN0	37 (53.6)
cN1	10 (14.5)
cN2	5 (7.0)
cN3	7 (9.9)
Unknown	10 (14.1)
Clinical TNM Stage, n (%)	
Stage IA	25 (36.6)
Stage IIA/IIB	10 (15.5) / 10 (14.1)
Stage IIIA/IIIB/IIIC	6 (8.5) / 1 (1.4) / 7 (9.9)
Stage IV	1 (1.4)
Unknown	9 (12.7)

*Other: Mucinous, Medullary, and Small Cell Differentiation Types. SD: Standard Deviation.

Univariate and multivariate analyses (Table 4) were performed to predict factors affecting progression-free survival (PFS). According to the results, advanced age (p=0.001) and neoadjuvant treatment (p=0.01) were found to be independent predictors of progression-free survival. Furthermore, it was observed that patients with Ki-67 levels over 30% tended to have shorter progression-free survival (HR 4.52, 95% CI 0.96-21.19, p=0.006).

Overall survival was found to be lower in older patients (>60 years) (Fig. 1). No significant results were found when survival times were analyzed with other clinical and demographic characteristics.

Discussion

Breast cancer is the most commonly diagnosed cancer in women and is a leading cause of cancer-related deaths. Triple-negative breast cancer (TNBC) has a worse prognosis compared to other breast cancer subtypes. Identifying clinical and pathological factors that affect the prognosis of patients is important. In our study, we found that overall survival was worse in the older population. Additionally, we identified factors affecting disease-free survival, such as age, neoadjuvant treatment, and non-invasive ductal carcinoma pathology. We found no significant differences in tumor location, age at menarche, age at first delivery, ECOG performance status, comorbidities, or pathological stage classification in our study.

TNBC is more frequently seen in younger patient groups compared to other subtypes. Carey K. Anders et al.[9] showed that TNBC is more invasive in patients under 40 years of age. Wenji Zhu et al.[10] demonstrated that patients over 70 years old have higher mortality and morbidity rates in the first two years after treatment. Judith Nisan Malmgren et al.[11] showed that 18% of patients over 75 years old die from causes other than breast cancer, but disease-free survival significantly does not change. In our study, patients over 60 years old had significantly lower disease-free survival and overall survival. This may be related to the higher number of comorbid diseases in older patients.

TNBC is more common in premenopausal patients.[12] Asaga et al.[13] showed that the postmenopausal group accounted for a higher percentage in 135 TNBC patients. In our study, a higher proportion of postmenopausal patients was also found. No effect of premenopausal or postmenopausal status on disease-free survival or overall survival was observed.

Approximately 35% of patients with triple-negative breast cancer (TNBC) have gBRCA1 mutations, and 8% have gBRCA2 mutations.[4, 5] In the study by Bayraktar et al.,[14] a gBRCA mutation was detected in 21% of patients, whereas our study found a rate of 23.9%. No significant relationship was found between disease-free survival (DFS) and overall survival (OS) when comparing the gBRCA-mutant and non-

Table 2. Clinical and Demographic Characteristics of Triple-Negative Breast Cancer Patients by Treatment Group

Variable	Neoadjuvant Group (n=11)	Adjuvant Group (n=58)	p
Age, years			
Median (Interquartile Range)	53 (40-59)	52 (46-58)	0.82
Primary Tumor Location, n (%)			
Right Breast	6 (54.5)	28 (48.3)	0.75
Left Breast	5 (45.5)	30 (51.7)	
Age at Menarche, years			
Median (Interquartile Range)	12 (11-14)	13 (12-13)	0.80
Age at First Birth, years			
Median (Interquartile Range)	21 (20-22)	21 (20-24)	0.53
ECOG Performance Score, n (%)			
0	1 (9.1)	2 (3.4)	0.41
1	10 (90.9)	56 (96.6)	
Presence of Comorbidities, n (%)	3 (27.3)	32 (55.2)	0.11
Primary Surgery, n (%)			
Modified Radical Mastectomy	9 (90)	24 (42.9)	0.01
Breast-Conserving Surgery	1 (10)	32 (57.1)	
Clinical T Stage, n (%)			
cT1	4 (36.3)	36 (62.1)	0.07
cT2	4 (36.3)	17 (29.3)	
cT3	1 (9.1)	5 (8.6)	
cT4	1 (9.1)	0 (0)	
Unknown	1 (9.1)	0 (0)	
Clinical N Stage, n (%)			
cN0	1 (9.1)	36 (62.1)	0.04
cN1	3 (27.3)	7 (12.0)	
cN2	1 (9.1)	4 (6.8)	
cN3	2 (18.2)	5 (8.6)	
Unknown	4 (9.1)	6 (10.3)	
Clinical TNM Stage, n (%)			
Stage IA	0	26	0.01
Stage IIA/IIB	1/2	8/8	
Stage IIIA/IIIB/IIIC	1/1/2	5/0/5	
Unknown	4	6	
Pathological Stage, Tumor Size (pTn), n			
Tx-1-2	8 (72.7)	50 (86.2)	0.26
T3-4	3 (27.3)	8 (13.8)	
Pathological Stage, Lymph Nodes (Ln), n			
Nx-0	8 (72.7)	32 (55.2)	0.37
N1	0 (0)	12 (20.7)	
N2	1 (9.1)	7 (12.1)	
N3	2 (18.2)	7 (12.1)	
Grade, n (%)			
Grade 1	2 (18.2)	4 (6.9)	0.18
Grade 2	2 (18.2)	26 (44.8)	
Grade 3	7 (63.6)	28 (48.3)	
Ki-67 Status, n (%)			
≤15	1 (9.1)	2 (3.4)	0.43
15-30	1 (9.1)	15 (25.9)	
30-60	5 (45.5)	15 (25.9)	
>60	0 (0)	4 (6.9)	
Unknown	4 (36.4)	22 (37.9)	

Table 3. Factors Associated with Disease-Free Survival Time

Variable	Median (95% CI)	p
Age, years		
<60	64.7 (34.1-95.4)	<0.001
>=60	14.6 (3.8-25.4)	
Primary Tumor Location, n (%)		
Right Breast	42.8 (23.5-62.1)	0.88
Left Breast	50.2 (1.0-106.9)	
Age at Menarche, years		
<13	64.7 (17.2-112.3)	0.31
>=13	35.9 (1.0-72.5)	
Age at First Birth, years		
<21	24.9 (1.0-56.5)	0.09
>=21	100.9 (22.6-179.2)	
History of Childbirth		
Yes	50.2 (11.0-89.3)	0.174
No	20.8 (16.1-25.5)	
Postmenopausal Status		
Yes	34.9 (16.1-53.7)	0.07
No	72.8 (16.1-129.5)	
Presence of Comorbidities		
Yes	61.3 (18.6-104.1)	0.34
No	42.8 (9.6-76.0)	
Primary Surgery		
Modified Radical Mastectomy	34.9 (6.9-62.8)	0.17
Breast-Conserving Surgery	72.8 (17.6-128.1)	
BRCA Mutation, BRCA 1/2		
Yes	14.6 (1.0-40.4)	0.13
No or Unknown	14.0 (8.3-19.6)	
Histology, n (%)		
Invasive Ductal Carcinoma	50.2 (21.1-79.2)	0.04
Other*	19.0 (7.8-20.1)	
Clinical T Stage, n (%)		
cT1	50.2 (20.7-79.7)	0.90
cT2-T4	43.0 (1.4-84.7)	
Clinical N Stage, n (%)		
cN0	100.9 (23.3-178.5)	0.12
cN (+)	43.0 (1.0-87.3)	
Clinical TNM Stage, n (%)		
Stage IA - IIA	30.3 (7.6-42.8)	0.6
Stage IIB - III	22.4 (6.7-30.8)	
Treatment Group, n (%)		
Neoadjuvant Treatment	15.1 (7.3-22.8)	0.008
Adjuvant Treatment	61.3 (32.1-90.6)	
Pathological Stage, Tumor Size (pTn)		
Tx-1-2	50.7 (20.9-80.6)	0.39
T3-4	20.8 (1.0-43.8)	
Pathological Stage, Lymph Nodes (Ln)		
Nx-0	100.9 (23.3-178.5)	0.12
N (+)	43.0 (1.0-87.3)	
Grade, n (%)		
Grade 1	33.0 (5.9-60.1)	0.77
Grade 2	50.2 (19.6-80.8)	
Grade 3	64.7 (10.8-118.7)	
Ki-67 Status, n (%)		
<30	77.9 (57.2-98.6)	0.04
>=30	44.4 (34.3-54.5)	
Presence of Lymphovascular Invasion		
Yes	50.2 (4.5-95.8)	0.61
No	50.7 (16.3-85.2)	
Presence of In Situ Component		
Yes	50.2 (24.8-75.5)	0.73
No	72.8 (60.7-84.9)	
Type of Treatment		
Neoadjuvant	15.1 (7.3-22.8)	0.008
Adjuvant	61.3 (32.1-90.6)	

mutant groups. Recent evidence underscores the prognostic and predictive significance of BRCA mutations in TNBC. Approximately 20% of patients with TNBC harbor germline BRCA1/2 mutations, which confer increased sensitivity to platinum-based chemotherapy and PARP inhibitors.[15, 16] The OlympiAD and EMBRACA trials showed significant improvements in progression-free survival with PARP inhibitors, while the OlympiA trial demonstrated a survival benefit in high-risk early-stage TNBC.[17] Thus, BRCA testing is essential for both prognosis and treatment selection.Given these findings, it is important that patients diagnosed with TNBC are referred to genetic counseling for gBRCA mutation testing.

A large proportion of TNBC cases are diagnosed as invasive ductal carcinoma (IDC).[13] In our study, the largest proportion of patients had IDC pathology. The longest disease-free survival was observed in IDC, while rarer histological subtypes were associated with the shortest disease-free survival. No significant statistical results were found related to overall survival.

Many early-stage TNBC patients are suitable for adjuvant treatment. However, neoadjuvant chemotherapy is the appropriate treatment approach for locally advanced breast cancer and candidates for breast-conserving surgery.[18, 19] In our study, a larger number of patients received adjuvant therapy compared to those who received neoadjuvant therapy. Among the 69 patients, only 11 (15.9%) received neoadjuvant therapy, a rate considerably lower than the 40–60% reported in the literature. This discrepancy can be explained by the stage distribution of the patients, the lim-

Table 4. Factors Associated with Progression-Free Survival

	Univariate		Multivariate	
	HR (%95 CI Lower-Upper Bound)	p	HR (%95 CI Lower-Upper Bound)	p
Age, years				
<60	1.00	<0.001	5.81 (2.07-16.23)	0.001
≥60	3.55 (1.83-6.85)			
Primary tumor location, n (%)				
Left breast	1.00	0.88		
Right breast	1.04 (0.55-1.96)			
Menarche age, years				
≥13	1.00	0.31		
<13	0.71 (0.37-1.37)			
Age at first birth, years				
<21	1.00	0.09		
≥21	0.54 (0.27-1.11)			
Obstetric history				
None	1.00	0.18		
Present	0.54 (0.22-1.32)			
Postmenopausal status				
No	1.00	0.07		
Yes	1.88 (0.93-3.80)			
Comorbidity status				
None	1.00	0.34		
Present	0.74 (0.40-1.37)			
Primary surgery				
Modified radical mastectomy	1.00	0.18		
Breast-conserving surgery	0.64 (0.33-1.22)			
BRCA mutation, BRCA ½				
Not present or unknown	1.00	0.13		
Present	0.46 (0.17-1.28)			
Histology, n (%)				
Invasive ductal/lobular carcinoma	1.00	0.04		
Other*	2.30 (1.01-5.28)		2.89 (0.73-11.38)	0.12
Clinical T stage, n (%)				
cT1	1.00	0.90		
cT2-T4	1.04 (0.54-1.99)			
Clinical N stage, n (%)				
cN0	1.00	0.13		
cN (+)	1.72 (0.84-3.50)			
Clinical TNM stage, n (%)/ n (%)				
Stage IA-IIB	1.00	0.16		
Stage IIB-III	1.66 (0.81-3.38)			
Treatment group, n (%)				
Neoadjuvant treatment	1.00	0.01		
Adjuvant treatment	0.35 (0.15-0.79)		0.17 (0.01-0.64)	0.009
Pathological stage, tumor size (pTn)				
Tx-1-2	1.00	0.40		
T3-4	1.42 (0.62-3.22)			

Table 4. Factors Associated with Progression-Free Survival (Cont.)

	Univariate		Multivariate	
	HR (%95 CI Lower-Upper Bound)	p	HR (%95 CI Lower-Upper Bound)	p
Pathological stage, lymph nodes (Ln)				
Nx-0	1.00	0.20		
N (+)	0.65 (0.34-1.26)			
Grade, n (%)				
Grade 1	1.00			
Grade 2	0.99 (0.33-2.95)	0.99		
Grade 3	0.79 (0.26-2.37)	0.68		
Ki-67 status, n (%)				
<30	1.00	0.06		
≥30	4.03 (0.92-17.65)		4.52 (0.96-21.19)	0.06
Lymphovascular invasion status				
Absent	1.00	0.61		
Present	1.19 (0.60-2.37)			
In situ component presence				
Absent	1.00	0.73		
Present	1.16 (0.48-2.79)			

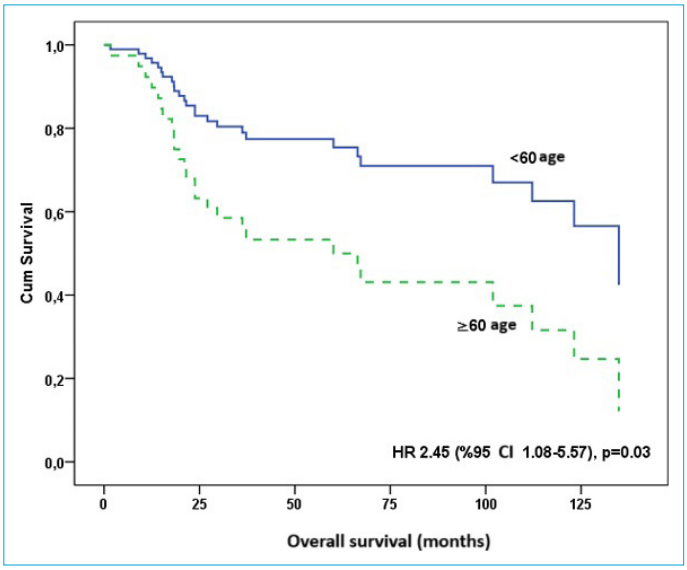

Figure 1. Overall survival (months).

ited number of cases admitted to our center during that period, and the study timeframe (2012–2019). The neoadjuvant subgroup (n=11) was relatively small, which may limit the statistical power of subgroup analyses. Although acknowledged, this limitation should be considered when interpreting the survival outcomes associated with neoadjuvant treatment. Patients in the neoadjuvant group had a shorter disease-free survival compared to those in the adjuvant group. This could be attributed to a higher rate of axillary involvement in the neoadjuvant group. When examining clinical-demographic characteristics of the neoadjuvant and adjuvant groups, it was found that radical mastectomy was preferred in the neoadjuvant group (p=0.01). This was thought to be due to the higher prevalence of positive axillary lymph nodes in the neoadjuvant group, leading to the choice of radical mastectomy.

Although the TNM staging system remains widely used in treatment decision-making, its prognostic value appears to be limited in biologically aggressive subtypes such as Triple-Negative Breast Cancer (TNBC) . The AJCC 8th edition prognostic staging has not demonstrated a significant prognostic advantage over conventional TNM staging in patients with TNBC; in this subgroup, molecular and biological factors are suggested to play a more decisive role in predicting outcomes.[20-22] It is believed that in TNBC, prognostic factors may sometimes outweigh the significance of TNM staging.

Several studies have investigated the immunohistochemical expression of Ki-67 as a prognostic and predictive marker for breast cancer.[23-25] Ki-67 is a predictive factor for remission following neoadjuvant chemotherapy in breast cancer. Elevated Ki-67 levels after neoadjuvant chemotherapy indicate poor prognosis. In our study, patients with Ki-67 levels above 30% tended to have shorter progression-free survival. In our study, the association between high Ki-67 expression and survival did not reach statistical significance in multivariate analysis (p=0.06), indicating only

borderline prognostic value. Previous reports have shown that elevated Ki-67 levels (>30–40%) in TNBC are associated with poorer survival, although their independent prognostic impact remains limited.[26, 27] Meta-analyses further suggest that Ki-67 is more reliable as a predictive biomarker for pathological complete response (pCR) to neoadjuvant chemotherapy, rather than as a robust prognostic factor.[28] A major limitation of the present study is the small sample size, particularly in the neoadjuvant subgroup, which may impair the ability to detect statistically significant differences and should be considered when interpreting results.

Conclusion

In our study, there were no significant differences in tumor location, age at menarche, age at first delivery, ECOG performance score, comorbidities, or pathological stage classification among patients diagnosed with triple-negative breast cancer. Advanced age (>60 years) and neoadjuvant treatment were found to be independent predictors of disease-free survival. Overall survival was lower in patients over 60 years of age. This patient group should undergo genetic counseling for germline BRCA mutation testing. The presence of these mutations increases sensitivity to platinum-based chemotherapies and PARP inhibitors, playing a critical role in treatment planning. Moreover, it has clinical value in identifying individuals with a familial cancer risk and guiding genetic counseling. Therefore, germline BRCA testing in TNBC patients is important both prognostically and therapeutically.

Factors affecting disease-free survival included age, neoadjuvant treatment, and non-invasive ductal carcinoma pathology. The majority of patients had IDC pathology. No significant results were found when analyzing survival times in relation to other clinical and demographic data (age at menarche, primary tumor location, age at first birth, birth history, postmenopausal status, comorbidities, primary surgery, germline BRCA mutation, histology, clinical TNM stage, pathological stage, grade, lymphovascular invasion, or in situ component). Patients with Ki-67 levels above 30% tended to have shorter progression-free survival. Due to the retrospective nature of our study and the limited sample size, our data were insufficient. Further studies with larger patient groups are needed to develop more robust treatment strategies.

Disclosures

Ethics Committee Approval: The study was conducted in accordance with the Principles of the Declaration of Helsinki. The Ethics Committee of Trakya University approval was granted before the study (TUTF-BAEK 2019/123).

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Conflict of Interest: None declared.

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