ORIGINAL RESEARCH

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Survival Analysis of Patients with Triple-Negative Breast Cancer: A Single-Center Experience

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ABSTRACT Objective: We determined the prognostic factors of patients with triple-negative breast cancer. **Material and Method:** Two hundred thirteen female patients with triple-negative breast cancer (TNBC) followed in the medical oncology unit of Kartal Doctor Lütfi Kırdar City Hospital between 2005 and 2020 were evaluated retrospectively. Patients' clinical and demographic features, laboratory findings, and treatments were investigated and their effect on mortality was analyzed. **Results:** The median age of patients was 52 years. Relapse was observed in 46 (26.6%) patients, 127 patients were followed without progression. During the follow-up period, 57 patients died and 156 patients survived. The median overall survival was 137.2 months in patients with tumor size <2 cm, 109.9 months in patients with ≥2 cm and <5 cm, and 90.5 months in patients with ≥5 cm (p=0.02). Tumor diameter, lymph node positivity, menopausal status, and whether receiving neoadjuvant chemotherapy were determined as factors affecting the overall survival. **Conclusion:** In accordance with the literature, patients with TNBC showed more aggressive characteristics. Our findings support that TNBC is a heterogeneous disease and highlight the need to define molecular subclasses. We believe that demographic and prognostic data studies with large patient series and determining molecular markers will guide the follow-up and treatment of patients with TNBC.

Keywords: Breast cancer; triple-negative; prognosis

Breast cancer is the most common type of cancer in women worldwide.[1] In parallel with the developments in the field of cancer genetics, breast cancer gene expression profiles have been revealed and divided into 4 main groups.[2] Among these, basal cell-like breast cancer, which is negative for estrogen receptor (ER), progesterone (PR), and HER-2, has the worst prognosis.[2-4] Nearly 70% of triple-negative breast cancers (TNBC) are basal cell-like breast cancer types, and 15 to 34% show non-basal cell-like features and constitute 15% of all breast cancers.[5-7] Because the tumor diameter is large, axillary lymph node positivity rate and histological grade are higher, with a tendency to reach a more advanced stage.[8] Despite the availability of several prognostic factors, classical prognostic factors, such as tumor size and lymph node involvement, are still considered important for the management of breast cancer.[9,10]

When the pathological diagnoses of TNBC patients were examined, invasive ductal carcinoma (IDC) was found in the first place with a rate of approximately 90%, and it had a high histological grade. Compared to other types (luminal or HER2 positive), the risk of recurrence of TNBC is higher in the first 5 years.[11] More prognostic factors and strengthening of treatment strategies are needed to prolong the survival in patients with TNBC.

Demographic, clinical, and pathological characteristics of patients with TNBC who had received adjuvant or neoadjuvant therapy were examined and their effects on progression and survival were investigated to determine the prognostic factors of patients with TNBC.

MATERIAL AND METHODS

A total of 213 female patients diagnosed with TNBC who applied to the Medical Oncology Unit of Kartal Doctor Lütfi Kırdar City Hospital between 2005 and 2020 were included in the study. Age over 18 years and ER, PR, and HER-2 negativity were the inclusion criteria. Patients with positive ER and/or PR

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and/or HER-2 were excluded from the study. The cut-off value was taken as 1% in ER and PR negativity. Those with immunohistochemical HER-2 negative or 1 (+) staining and HER-2 (+) staining were defined as HER-2 negative if they were found negative by the silver-enhanced in situ hybridization method. Biopsy dates were considered diagnosis dates. The date of first recurrence or metastasis after surgery was considered the date of progression. Patients were evaluated for progression by being called for follow-up every 3 months for the first 2 years, every 6 months between the 3rd and 5th years, and subsequently once a year. The data were statistically evaluated using the SPSS 22.0 software (SPSS Inc., Chicago, Illinois). Chi-square and Fisher's exact tests were used for comparative data. Numerical variables between 2 independent statuses were analyzed by student's *t*-test under a normal distribution and by Mann-Whitney U test, if otherwise. Overall survival (OS) was defined as the time from diagnosis of primary breast cancer to death or last contact. Kaplan-Meier analysis was used to estimate the effect of clinical and pathological characteristics on OS. Determiners related to survival were reviewed using multivariate cox regression analysis. The significance limit was determined as 0.05. The study was started after obtaining permission from the Kartal Doctor Lütfi Kırdar City Hospital Ethics Committee (date: March 30, 2022, no: 2022/514/222/21). This study was performed following the principles of the Declaration of Helsinki.

RESULTS

All 213 patients included in the study were women and the median age was 52 (range: 27-93 years) years. The most common primary tumor location was the left breast. In addition, 1 patient had bilateral breast cancer. The median tumor diameter was 2.5 cm (0.3-12 cm). The pathological subtype of more than 80% of the patients was found to be IDC, the pathological subtype of 19 patients could not be classified, and the most common subtype after IDC was a mixed and metaplastic type, with seven patients each. Four patients had inflammatory breast cancer. Although 33% of the patients were in Grade 2, 65.9% of them were in Grade 3. The disease relapsed in 26.6% of patients. Forty-six patients received neoadjuvant chemotherapy, whereas 156 patients received adjuvant chemotherapy. Of the patients who received adjuvant chemotherapy, 147 received anthracycline-based chemotherapy and/or taxane chemotherapy. For nine patients, carboplatin was added to the adjuvant treatment. While the number of patients who underwent breast-conserving surgery was 110, modified radical mastectomy was performed on 83 patients. Adjuvant radiotherapy was applied to 145 patients. The demographic and clinical characteristics of patients are shown in Table 1.

BCS: Breast-conserving surgery; MRM: Modified radical mastectomy.

The median overall survival (mOS) was 137.2 months in patients with tumor size <2 cm, 109.9 months in patients with tumor size ≥2 cm and <5 cm, and 90.5 months in patients with tumor size ≥5 cm (p=0.02). Relapse was observed in 46 (26.6%) patients, 127 patients were followed without progression, and 40 patients were discontinued. During the follow-up period, 57 patients died and 156 patients survived. A study of survival according to age revealed that the mOS of patients aged 45 years and younger was statistically significantly better than those over the age of 45 years (123.4 months compared to 102.2 months, p=0.045) (Figure 1).

As the tumor diameter increased, the mOS decreased statistically significantly (p=0.02). The mOS was 137.2 months in tumors less than 2 cm in diameter, 90.5 months in tumors 5 cm and above, and 109.9 months in tumors between 2 and 5 cm in diameter (Figure 2).

Patients with locally advanced disease who required neoadjuvant therapy had worse survival data than those with earlier stages who did not require neoadjuvant therapy. Accordingly, the mOS for those who received neoadjuvant treatment was 57.3 months and 119.7 months for those who did not (p<0.001) (Figure 3).

Considering the factors affecting survival, a significant OS relationship with patient age, menopause status, tumor diameter, and lymph node status was observed. This result indicated that menopause increased the risk of death by 1.76 times (p=0.047). Similarly, the risk of death increased as the tumor di-

TABLE 1: General characteristics of patients.

Variable	n (%)
Gender	
Female	213 (100)
Age	
Median (minimum-maximum)	52 (27-93)
Localization	
Left	110 (51.5)
Right	102 (48.1)
Bilateral	1 (0.4)
Neoadjuvant chemotherapy	
Yes	36 (16.2)
No	187 (83.8)
Surgery types	
BCS	110 (49.3)
MRM	83 (37.2)
Pathological subtypes	
Invasive ductal	169 (80.9)
Invasive lobular	4 (1.9)
Mixed	7 (3.3)
Mucinous	1 (0.5)
Micropapillary	2 (1.0)
Metaplastic	7 (3.3)
Ungraded	19 (9.1)
Inflammatory breast cancer	
Inflammatory	4 (2.5)
Non-inflammatory	157 (97.5)
Histological grade	
Grade 1	2 (1.1)
Grade 2	116 (65.9)
Grade 3	58 (33.0)
Ki-67 (%)	
≤50	50 (49.5)
>50	51 (50.5)
Lymph node involvement	
Node positive	59 (26.4)
Node negative	117 (52.5)
Adjuvant chemotherapy	
Yes	156 (70.0)
No	31 (13.9)
Adjuvant chemotherapy choice	
Anthracycline-based chemotherapy and/or taxanes	147 (65.9)
Anthracycline-based chemotherapy+taxanes+carboplatin	9 (4.0)
Adjuvant radiotherapy?	
Yes	145 (65.0)
Disease relapse	
Yes	46 (26.6)
No	127 (73.4)

BCS: Breast-conserving surgery; MRM: Modified radical mastectomy.

ameter increased, and the risk of death was 4.99 times higher in patients with a tumor diameter of 5 cm and above than in those with a tumor diameter of less than 2 cm (p=0.09). Similarly, the OS was shorter in patients with lymph node involvement. A 2.43-, 2.92-, and 3.60-fold increased risk of death was found in patients with N1, N2, and N3 lymph node involvement, respectively, compared to patients without lymph node involvement (p=0.03, 0.012, and 0.004, respectively). Multivariate cox regression analysis revealed that menopause status, tumor size, whether she received neoadjuvant therapy, and lymph node status correlated with survival (p=0.015, 0.023, 0.001, and 0.032, respectively). The factors affecting survival are shown in Table 2.

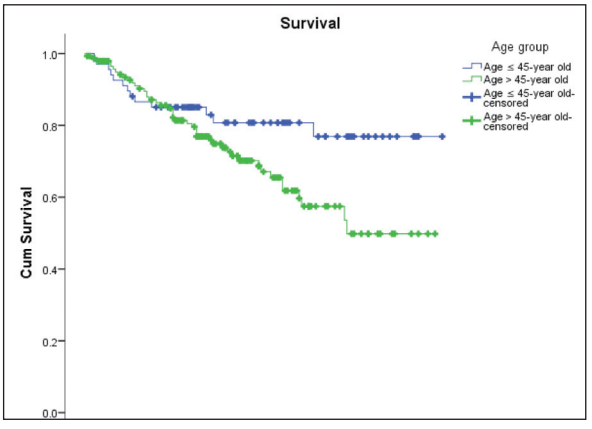

FIGURE 1: Survival curve by age groups of patients.

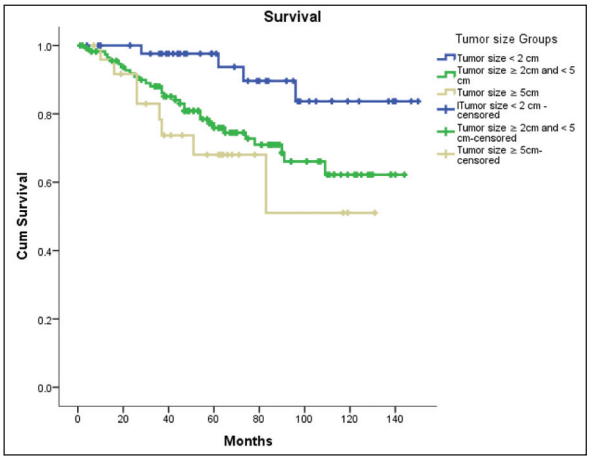

FIGURE 2: Survival curve of patients by tumor size groups.

DISCUSSION

This single-center study on a cohort of patients with TNBC revealed that nodal involvement, poor differentiation, and tumor size are the most important prog-

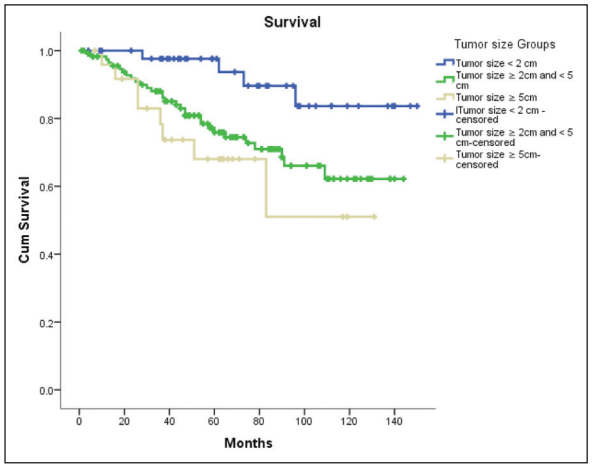

FIGURE 3: Survival curve of patients by neoadjuvant therapy status.

nostic factors determining cancer mortality. In addition, menopausal status and whether patients have received neoadjuvant therapy are significantly associated with overall survival. However, sentinel nodal involvement and Ki-67 expression are not associated with increased mortality.

Several studies have reported the mean age of patients with TNBC to range from 46 to 54 years. The mean age of patients in our study was 52.2 years, and the literature data were found to be consistent.[12-18] Although a significant relationship was observed between age and OS in our study, no significant relationship was found in the study by Costa et al.[18]

The histological grade is among the best established prognostic factors for breast cancer, and the majority of patients with TNBC have a high tumor grade.[5] Consistent with the literature, the majority of patients in our cohort also had a high tumor grade and their OS was worse, again similar to that reported in the literature.[12-18] Only a few other smaller studies have reported that grade has no role in determining survival outcomes.[17,19]

Certain studies have reported that tumor size and lymph node status are significantly associated with OS in patients with TNBC.[19-22] Consistently, we found a highly significant association between mortality and both tumor size and lymph node status in patients with TNBC. Among single TNM staging components, both tumor size and involvement of lymph nodes were independently and significantly associated with overall survival.

In addition to lymph node positivity and tumor diameter, menopausal status was determined as an independent variable affecting survival; premenopausal patients showed better survival. Moreover, survival was dependent on whether patients had received neoadjuvant therapy; the OS was longer in those who did not, which shows the association with the need for neoadjuvant therapies in patients with more advanced stages.

Certain studies have reported no association between Ki-67 expression and survival outcomes for TNBCs, whereas other larger studies have demonstrated a relatively high Ki-67 expression (≥10%) to be inversely associated with TNBC outcomes.[20,23-27] These results are in agreement with our findings,

TABLE 2: Cox regression analysis of factors and their effects on survival.

	Univariate analysis		Multivariate analysis	
Parameters	**Hazard ratio (95% CI)**	**p value**	**Hazard ratio (95% CI)**	**p value**
Ki 67 >50% vs. Ki 67 ≤50%	0.78 (0.32-1.93)	0.6		
Menopause vs. premenopause status	1.76 (1.07-3.10)	0.047	0.41 (0.20-0.84)	0.015
Tumor size, ≥2 cm and <5 vs. <2 cm	3.4 (1.19-9.66)	0.02	0.21 (0.05-0.81)	0.023
Tumor size, ≥5 cm vs. <2 cm	4.99 (1.50-16.66)	0.09	0.78 (0.3-2.06)	0.62
Neoadjuvant treatment, no vs. yes	0.23 (0.11-0.48)	<0.001	6.33 (2.03-19.67)	0.001
Sentinel lymph node involvement, yes vs. no	1.43 (0.17-11.53)	0.7		
Lymph node status, N1 vs. N0	2.43 (1.11-5.32)	0.03	0.32 (0.11-0.91)	0.032
Lymph node status, N2 vs. N0	2.92 (1.26-6.78)	0.012	0.86 (0.29-2.56)	0.78
Lymph node status, N3 vs. N0	3.60 (1.49-8.70)	0.004	0.92 (0.29-2.86)	0.88

CI: Confidence interval; numbers in bold represent statistically significant values.

showing that patients with TNBC and Ki-67 expression over 50% have a poorer prognosis, and the mortality increase with increasing expression of Ki-67.

The most important limitations of the study were a retrospective design, not knowing the treatment of those receiving neoadjuvant therapy, and no knowledge of patients' *BRCA 1-2* or other *HRD* genes.

CONCLUSION

Based on the results, we conclude that our study provides an insight into the outcomes of patients with early-stage TNBC and highlights the major prognostic factors that may affect survival. Our findings support that TNBC is a heterogeneous disease and highlight the need to define molecular subclasses. We believe that demographic and prognostic data studies with large patient series and determining more effective molecular markers will guide the follow-up and treatment of patients with TNBC.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Akif Doğan, Murat Ayhan;* ***Design:*** *Akif Doğan, Murat Ayhan;* ***Control/Supervision:*** *Murat Ayhan;* ***Data Collection and/or Processing:*** *Murat Ayhan;* ***Analysis and/or Interpretation:*** *Murat Ayhan;* ***Literature Review:*** *Akif Doğan, Murat Ayhan;* ***Writing the Article:*** *Akif Doğan, Murat Ayhan;* ***Critical Review:*** *Murat Ayhan.*

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. [Crossref] [PubMed]
2. Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98(19):10869-10874. [Crossref] [PubMed] [PMC]
3. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A. 2003;100(14):8418-8423. [Crossref] [PubMed] [PMC]
4. Gusterson BA, Ross DT, Heath VJ, Stein T. Basal cytokeratins and their relationship to the cellular origin and functional classification of breast cancer. Breast Cancer Res. 2005;7(4):143-148. [Crossref] [PubMed] [PMC]
5. Rakha EA, El-Sayed ME, Green AR, Lee AH, Robertson JF, Ellis IO. Prognostic markers in triple-negative breast cancer. Cancer. 2007;109(1):25-32. [Crossref] [PubMed]
6. Fulford LG, Easton DF, Reis-Filho JS, et al. Specific morphological features predictive for the basal phenotype in grade 3 invasive ductal carcinoma of breast. Histopathology. 2006;49(1):22-34. [Crossref] [PubMed]
7. Gonçalves H Jr, Guerra MR, Duarte Cintra JR, Fayer VA, Brum IV, Bustamante Teixeira MT. Survival study of triple-negative and non-triple-negative breast cancer in a Brazilian cohort. Clin Med Insights Oncol. 2018;12:1179554918790563. [Crossref] [PubMed] [PMC]
8. Qiu J, Xue X, Hu C, et al. Comparison of clinicopathological features and prognosis in triple-negative and non-triple negative breast cancer. J Cancer. 2016;7(2):167-173. [Crossref] [PubMed] [PMC]
9. Soerjomataram I, Louwman MW, Ribot JG, Roukema JA, Coebergh JW. An overview of prognostic factors for long-term survivors of breast cancer. Breast Cancer Res Treat. 2008;107(3):309-330. [Crossref] [PubMed] [PMC]
10. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer. 1989;63(1):181-187. [Crossref] [PubMed]
11. Kinalis S, Nielsen FC, Talman ML, Ejlertsen B, Rossing M. Characterization of basal-like subtype in a Danish consecutive primary breast cancer cohort. Acta Oncol. 2018;57(1):51-57. [Crossref] [PubMed]
12. Bulut N, Aksoy S, Dizdar O, et al. Demographic and clinico-pathological characteristics in patients with triple-negative and non-triple-negative breast cancer. Med Oncol. 2011;28 Suppl 1:S75-79. [Crossref] [PubMed]
13. Akdeniz A, Altundağ ÖÖ. Üçlü negatif meme kanserlerinin klinik ve demografik verileri-tek merkez deneyimi [Clinical and pathological characteristics of triple-negative breast cancer patients: A single-center experience]. Mersin Univ Saglık Bilim Derg. 2019;12(3):478-488. [Crossref]
14. Haiderali A, Rhodes WC, Gautam S, et al. Real-world treatment patterns and effectiveness outcomes in patients with early-stage triple-negative breast cancer. Future Oncol. 2021;17(29):3819-3831. [Crossref] [PubMed]
15. Polley MC, Leon-Ferre RA, Leung S, et al. A clinical calculator to predict disease outcomes in women with triple-negative breast cancer. Breast Cancer Res Treat. 2021;185(3):557-566. [Crossref] [PubMed] [PMC]
16. Rapiti E, Pinaud K, Chappuis PO, et al. Opportunities for improving triple-negative breast cancer outcomes: results of a population-based study. Cancer Med. 2017;6(3):526-536. [Crossref] [PubMed] [PMC]

17. Urru SAM, Gallus S, Bosetti C, et al. Clinical and pathological factors influencing survival in a large cohort of triple-negative breast cancer patients. BMC Cancer. 2018;18(1):56. [Crossref] [PubMed] [PMC]
18. Costa REARD, Oliveira FTR, Araújo ALN, Vieira SC. Prognostic factors in triple-negative breast cancer: a retrospective cohort. Rev Assoc Med Bras (1992). 2021;67(7):950-957. [Crossref] [PubMed]
19. Kwon J, Eom KY, Koo TR, et al. A prognostic model for patients with triple-negative breast cancer: importance of the modified nottingham prognostic index and age. J Breast Cancer. 2017;20(1):65-73. [Crossref] [PubMed] [PMC]
20. Lee JA, Kim KI, Bae JW, Jung YH, An H, Lee ES; Korean Breast Cancer Society. Triple negative breast cancer in Korea-distinct biology with different impact of prognostic factors on survival. Breast Cancer Res Treat. 2010;123(1):177-187. [Crossref] [PubMed]
21. Ovcaricek T, Frkovic SG, Matos E, Mozina B, Borstnar S. Triple negative breast cancer-prognostic factors and survival. Radiol Oncol. 2011;45(1):46-52. [Crossref] [PubMed] [PMC]
22. He M, Zhang JX, Jiang YZ, et al. The lymph node ratio as an independent prognostic factor for node-positive triple-negative breast cancer. Oncotarget. 2017;8(27):44870-44880. [Crossref] [PubMed] [PMC]
23. Aleskandarany MA, Green AR, Benhasouna AA, et al. Prognostic value of proliferation assay in the luminal, HER2-positive, and triple-negative biologic classes of breast cancer. Breast Cancer Res. 2012;14(1):R3. [Crossref] [PubMed] [PMC]
24. Denkert C, Loibl S, Müller BM, et al. Ki67 levels as predictive and prognostic parameters in pretherapeutic breast cancer core biopsies: a translational investigation in the neoadjuvant GeparTrio trial. Ann Oncol. 2013;24(11):2786-2793. [Crossref] [PubMed]
25. Keam B, Im SA, Lee KH, et al. Ki-67 can be used for further classification of triple negative breast cancer into two subtypes with different response and prognosis. Breast Cancer Res. 2011;13(2):R22. [Crossref] [PubMed] [PMC]
26. Munzone E, Botteri E, Sciandivasci A, et al. Prognostic value of Ki-67 labeling index in patients with node-negative, triple-negative breast cancer. Breast Cancer Res Treat. 2012;134(1):277-282. [Crossref] [PubMed]
27. Abubakar M, Orr N, Daley F, et al. Prognostic value of automated KI67 scoring in breast cancer: a centralised evaluation of 8088 patients from 10 study groups. Breast Cancer Res. 2016;18(1):104. [Crossref] [PubMed] [PMC]