ORIGINAL ARTICLE

Özgün Araştırma

Clinicopathological Features and Survival Outcomes Of Very Young Women Aged 30 and Under With Breast Cancer

Otuz Yaş Altı Meme Kanserli Kadınların Klinikopatolojik Özellikleri ve Sağkalım Sonuçları

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ABSTRACT

Objective:

The purpose of this study was to evaluate the clinicopathological feautures and prognostic factors of breast cancer (BC) patients aged 30 years and younger.

Materials and Methods:

We retrospectively evaluated the clinical and pathological data of the patients from their file records.

Results:

The median age of 50 patients included in this study was 28 (20-30). At diagnosis, 5 (10%) patients had metastatic disease, 2 (4%) patients had a pregnancy, 5 (10%) patients had breast-feeding. The patients had pathological features such as node positivity (66%), grade 2 (50%), lymphovascular invasion (LVI) (38%), and perineural invasion (PNI) (26%). Luminal A was the predominant molecular subtype (44%). 12% of patients had HER2-like and 16% had triple-negative disease. In 45 non-metastatic patients, the median follow-up was 59.9 months, the 5-year disease-free survival (DFS) and overall survival (OS) were 61.4% and 95.5%, respectively. During the follow-up, 5 (11.4%) of 45 patients died, 3 (6.8%) had local recurrence and 17 (38.7%) developed distant metastatic disease. Adjuvant radiotherapy was determined as a positive predictor for DFS in Cox regression analysis.

Conclusions:

In our study, HER-2-like and triple-negative BC rates were higher in women aged 30 years and younger than in the older population, consistent with the literature. In addition, our patients had a better 5-year OS rate than reported in previous studies, and the independent prognostic factor for DFS was adjuvant radiotherapy.

Key Words:

Breast cancer, Prognosis, Young women

ÖZ

Amaç:

Bu çalışmanın amacı 30 yaş ve altı meme kanserli hastaların klinikopatolojik özelliklerini ve prognostik faktörlerini değerlendirmektir.

Gereç ve Yöntemler:
Hastaların klinik ve patolojik verilerini dosya kayıtlarından retrospektif olarak değerlendirdik.

Bulgular:
Çalışmaya dahil edilen 50 hastanın ortanca yaşı 28 (20-30) idi. Tanıda 5 (%10) hasta metastatikti, 2 (%4) hasta gebe, 5 (%10) hasta emziriyordu. Luminal A, moleküler olarak baskın alt tip idi (%44). Hastaların %12' si HER2-like ve %16' sı triple negatif hastalık idi. Metastatik olmayan 45 hastada medyan takip süresi 59,9 aydı, 5 yıllık hastalıksız sağ kalım (DFS) ve genel sağ kalım (OS) sırasıyla %61,4 ve %95,5 idi. Takipte, 45 hastanın 5 (%11,4)'i öldü, 3 (%6,8) 'ünde lokal nüks ve 17 (%38,7)'sinde uzak metastaz gelişti. Cox regresyon analizlerinde, adjuvan radyoterapi DFS'nin olumlu bir prediktörü olarak saptandı.

Sonuç:
Çalışmamızda literatürle uyumlu olarak 30 yaş ve altındaki kadınlarda HER2-like ve triple negatif meme kanseri oranları yaşlı popülasyona göre daha yüksekti. Ek olarak, hastalarımız önceki çalışmalarda bildirilenden daha iyi 5 yıllık OS oranına sahipti ve adjuvan radyoterapi DFS için bağımsız prognostik faktör idi.

Anahtar Kelimeler:
Meme kanseri, Prognoz, Genç kadın

INTRODUCTION

Breast cancer (BC) is the most common cancer in women and the second most common cause of cancer-related death in women. It has been calculated that approximately 276.480 new cases of invasive BC will be diagnosed, and 42.170 women will die from BC in 2020 (1). Although BC often begins to appear after the 5th decade, it has recently started to occur more frequently in young women. The definition of 'young woman' for BC is still not standardized, but most of the literature refers to women ≤ 40 years of age as young women. Breast cancer is generally rare in young women, and young women constitute less than 7% of all BC cases; and these patients have adverse clinicopathological features of BC such as more advanced disease at diagnosis and more aggressive subtype compared to older women. In addition, survival among younger women is worse than among older (2,3).

The purpose of this study is to evaluate the clinicopathological features and prognostic factors of breast cancer (BC) patients aged 30 years and younger.

MATERIALS and METHODS

Patients:

Patients treated and followed up in our hospital between 2004 and 2019 were included in this study. All female patients diagnosed with pathologically invasive BC and aged 30 years or younger at diagnosis were recruited. All data were obtained from patients' medical records. Patients' age, pregnancy and breastfeeding history, family history of BC, performance status, location of the primary tumor, TNM stage, disease onset (metastatic or non-metastatic), surgical procedures (breast-conserving surgery (BCT) or mastectomy) and adjuvant/neoadjuvant treatments (chemotherapy (CT), radiation therapy (RT), and endocrine therapy (ET)) were recorded. In addition, pathological characteristics were collected from the final pathology reports. The positivity for estrogen receptor (ER) and progesterone receptor (PR) was defined as 1% or more nuclear staining by immunohistochemical (IHC) technique. human epidermal growth factor receptor 2 (HER2) status was determined by the IHC technique or fluorescent in situ hybridisation (FISH) analysis. Based on ER, PR, and HER2 results, tumors were grouped into four molecular subtypes: 1) luminal A: ER (+) and/or PR (+), HER2 (-), 2) luminal B: ER+ and/or PR (+), HER2 (+), 3) HER2-like: ER (-), PR (-), HER2 (+), 4) triple-negative: ER (-), PR (-), HER2 (-).

This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the Meram Medical Faculty Ethical Committee, Necmettin Erbakan University (approval number: 2020/2347).

Statistical Analyses:

Primary statistical analysis has included descriptive statistics of the patients presented as median (min-max) and mean±-standart deviations. Overall survival (OS) was defined as the time from initial diagnosis of BC to the time of death from any cause. Disease-free survival (DFS) was defined as the time from the diagnosis of BC to the development of any regional recurrence, distant metastatic disease, or death from any cause. Locoregional recurrence was defined as a recurrent tumor in the ipsilateral breast, axillary region, or chest wall. The Kaplan–Meier method was used for survival analysis. For nonmetastatic patients, 5-year DFS and OS rates were calculated, and Cox proportional-hazard regression models were used for univariate and multivariable analysis of DFS and OS. p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinicopathological feautures

A total of 50 patients were evaluated. The median age of the patients at diagnosis was 28 (20-30) years, and all were premenopausal. Two patients (4%) were pregnant, and five patients (10%) were breastfeeding at diagnosis. Three patients (8%) had a first-degree relative with a history of BC. %88 of the patients presented with a palpable mass in the breast. The most common primary tumour location was the left breast (56%).

Five patients (10%) had metastatic disease at diagnosis. The remaining 45 patients (90%) had a non-metastatic disease: two patients (4%) had stage-1, 27 patients (54%) had stage-2, and 16 patients (32%) had stage-3 disease. Primary tumor surgery was performed only on non-metastatic patients: the BCS was performed in 14 of them (31.1%), and mastectomy

was done in the other 31 patients (68.9%). Sentinel lymph node biopsy (SLNB) was performed in seven patients (15.9%), and axillary lymph node dissection was performed in 38 patients (84.1%). The mean tumour diameter was 3.4±1.7 centimetres (cm). Twenty-two patients (44%) had luminal A, 14 patients (28%) had luminal B, six patients (12%) had HER2-like, and eight patients (16%) had triple-negative disease. The clinicopathological feautures of the patients were shown in Table I.

Table I: Demographic characteristics of all patients at the time diagnosis.

Characteristics	(n:50) (%)
Median age, years (range)	28 (20-30)
Family breast cancer history	3 (6%)
Pregnancy	2 (4%)
Breastfeeding	5 (10%)
Childbirth	1.48±1.05 (mean) median 2 (0-3)
Affected side	
Right	22 (44%)
Left	28 (56%)
Histologic type	
Invasive ductal	43 (86%)
Invasive lobular	2 (4%)
Other	5 (10%)
Histologic grade	
I	3 (6%)
II	25 (50%)
III	22 (44%)
T stage	
1	16 (32%)
2	27 (54%)
3	6 (12%)
4	1 (2%)
N stage	
0	17 (34%)
1	17 (34%)
2	12 (24%)
3	4 (8%)
Overall stage	
1	2 (4%)
2	27 (54%)
3	15 (30%)
4	6 (12%)
Ki67, median (range)	35 (5-95)
LVI	
Yes	19 (38%)
No	31 (62%)
PNI	
Yes	13 (26%)
No	37 (74%)
Molecular subtypes	
Luminal A	22 (44%)
Luminal B	14 (28%)
HER2 like	6 (12%)
Bazal/Triple negative	8 (16%)
Type of breast surgical procedure	
No	5 (10%)
BCS	14 (28%)

Among 45 patients with non-metastatic disease, ten patients (22.2%) received neoadjuvant CT, 31 patients (68.9%) received adjuvant CT, and four patients (8.9%) did not receive any CT. In 3 of 10 patients who received neoadjuvant CT, a complete pathological response was obtained. Thirteen patients received adjuvant trastuzumab therapy because of HER2-positive disease for one year. Adjuvant RT was indicated for 32 patients (72.7%) due to different reasons, including BCS, lymph node involvement, and T3 disease. Adjuvant ET was administered to HR-positive patients. Seven patients (15.9%) received tamoxifen, 25 patients (56.8%) received tamoxifen+gonadotropin-releasing hormone analogue (GnRH-a), and 1 patient (2.3%) received aromatase inhibitor+GnRH-a (Table II).

Table II: Treatments of patients with non-metastatic disease.

	Number of patients (n:44) (%)
Neoadjuvant chemotherapy	
Yes	10 (22.7%)
No	34 (77.3%)
Adjuvant chemotherapy	
Yes	31 (70.5%)
No	13 (29.5%)
Adjuvant radiotherapy	
Yes	32 (72.7%)
No	12 (27.3%)
Adjuvant hormonotherapy	
Tamoxifen	7 (15.9%)
Tamoxifen+GnRH analog	25 (56.8%)
Aİ+GnRH analog	1 (2.3%)

During the follow-up period, five patients (11.1%) died, three patients (6.6%) developed local recurrence, and 17 patients (37.7%) developed distant metastatic disease. In patients who were not initially non-metastatic but later developed metastases, the most common sites of metastasis were liver (20%, 9/45), lung (6.6%, 3/45) and bones (4.4%, 2/45).

Outcomes

The median follow-up of 45 non-metastatic patients was 59.9 months, and 5-year DFS and OS rates were 61.4% and 95.5%, respectively (Figure 1, 2).

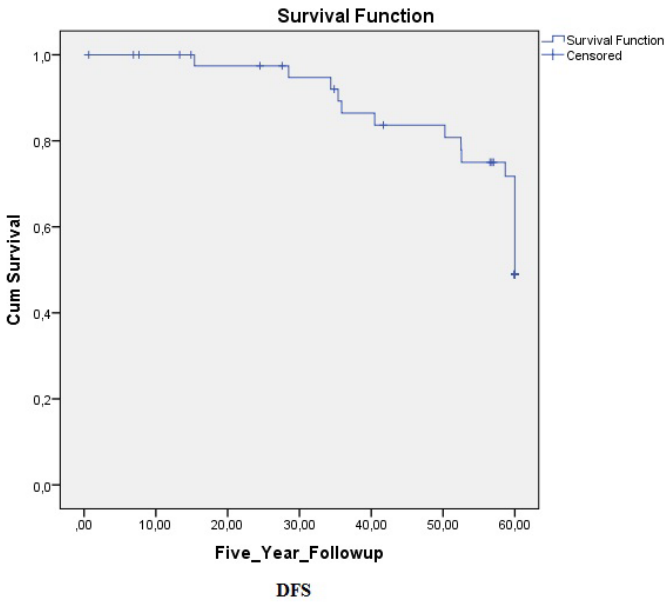

Figure 1: Kaplan-Meier curve of DFS for all patients.

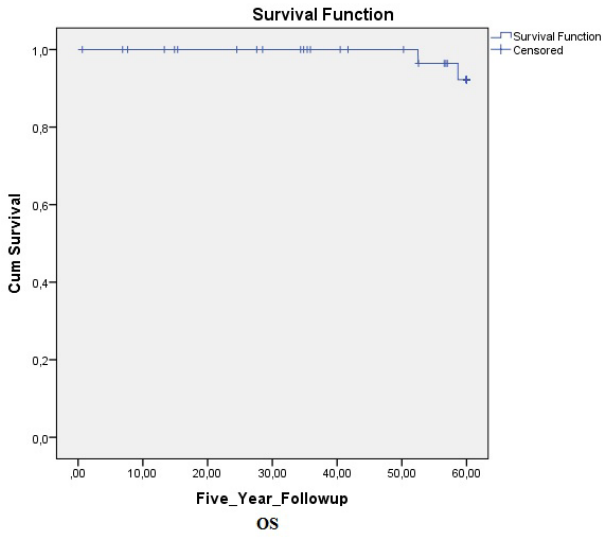

Figure 2: Kaplan-Meier curve of OS for all patients.

In univariate analysis, adjuvant RT was the only significant factor affecting DFS (yes vs. no: 65.6% vs. 50.0%, p:0.024). T stage, N stage, number of positive axillary lymph nodes, histological type, histological grade, ki67 proliferation index, LVI and PNI, molecular subtypes, adjuvant GnRH-a, adjuvant and neoadjuvant CT were not significant prognostic factors for DFS (all of p>0.05). Besides, the type of breast surgical procedure trended to be significant for DFS (BCS vs. mastectomy: 78.6% vs. 53.3%, p:0.06). No significant factor affecting OS was found in univariate analysis (Table III).

Table III: Univariable analysis of different variables affecting DFS and OS.

Variables	DFS HR (%95 CI)	p value	OS HR (%95 CI	p value
T stage (T1-2 vs. T3-4)	0.63 (0.15-2.65)	0.78	0.23 (0.01-3.73)	0.32
N stage (N0-1 vs. N2-3)	0.53 (0.21-1.33)	0.18	0.92 (0.15-5.54)	0.92
Number of positive axillary lymph nodes (0, 1-3, ≥4)	0.34 (0.10-1.17)	0.20	0.76 (0.29-1.98)	0.58
Histologic type (invazive ductal vs. other)	0.57 (0.18-1.74)	0.32	0.88 (0.0-7.89)	0.91
Histologic grade	1.44 (0.56-3.70)	0.43	0.54 (0.09-3.26)	0.50
PNI	1.23 (0.35-4.25)	0.74	0.68 (0.15-1.15)	0.51
LVI	0.59 (0.23-1.49)	0.26	3.04 (0.33-27.34)	0.32
Ki67	0.98 (0.96-1.01)	0.34	1.04 (0.99-1.09)	0.09
Molecular subtype	10.57 (0.18-1.74)	0.32	1.12 (0.12-10.08)	0.91
Type of breast surgical procedure	0.34 (0.10-1.19)	0.06	0.03 (0.01-6.1)	0.44
Adjuvant GnRH analog	2.03 (0.77-5.34)	0.14	1.95 (0.32-11.76)	0.46
Adjuvant chemotherapy	1.58 (0.62-4.03)	0.33	1.69 (0.28-10.18)	0.56
Adjuvant radiotherapy	3.44 (1.17-10.09)	0.024	2.32 (0.38-14.12)	0.35
Neoadjuvant chemotherapy	0.90 (0.32-2.53)	0.84	1.17 (0.13-10.49)	0.88

Adjuvant RT was also the only significant independent favourable prognostic factor for DFS in multivariate analysis (p=0.02) (Table IV).

Table IV: Multivariable analysis of different variables affecting DFS.

Variables	DFS HR (%95 CI)	p value
Type of breast surgical procedure	0.33 (0.09-1.16)	0.08
Adjuvant radiotherapy	3.63 (1.20-10.97)	0.02

DISCUSSION

In this study, we documented the clinicopathological feautures and survival outcomes of patients with young BC. The 5-year DFS and OS rates of patients who were non-metastatic at diagnosis were 61.4% and 95.5%, respectively, and adjuvant RT was an independent favourable prognostic factor for DFS.

Although BC is a rare disease in young women (<40 years) in developed countries, 1 out of 220 women may develop the disease by the age of 30 (4). In previous studies, it has been reported that young women have more advanced-stage disease and have more aggressive disease including pathological features such as higher histological grade, higher Ki-67 proliferation index, higher ER and/or PR negativity, and higher HER2 positivity compared with BC occurring in the older population (5-7). Invasive ductal carcinoma has also been shown to be the most common subtype in both the entire BC population and in younger patients under 40 years of age (7,8). In contrast, at the time of diagnosis, most of our cohort had early-stage (stage-2) disease, low-grade (grade 2), and invasive ductal carcinoma and luminal disease.

Pregnancy-associated breast cancer (PABC) is defined as BC diagnosed during pregnancy or within one year after delivery. In addition, PABC has a more aggressive biological behavior, advanced stage, and poor prognosis (9). In a study comparing PABC and non-PABC, it has been found that the luminal B and HER2-like subtypes had poor prognosis in patients with PABC (10). Seven of our patients (14%) had PABC at diagnosis. 2 (28.6%) of them had stage-2, 1 (14.3%) stage-3, and 4 (57.1%) stage-4 disease. 2 patients (28.6%) had luminal A, 1 patient (14.3%) had luminal B, 2 patients (28.6%) had HER2-like, and 2 patients (28.6%) had triple-negative disease. The changes in the breast structure during pregnancy and lactation mask the recognition of the symptoms of BC developing during this period. Especially in women aged 30 and under, the delayed diagnosis of BC may be due to the higher incidences of pregnancy and lactation in this age group.

The patients with early-stage BC undergo primary surgery (BCT or mastectomy) to the breast and regional nodes; after that, the RT could be added or not. Prospective randomized studies reported no statistically significant difference in OS between modified radical mastectomy and BCT followed by breast irradiation (11-13). Although younger age is an independent risk factor for increased local recurrence, BCT is a safe and effective treatment option for young BC patients. Furthermore, SLNB indications and surgical management of

axillar lymph node are the same as in older patients (14-16). Similar to the older patients, there was no statistically significant difference between the BCT plus RT and mastectomy groups regarding BC specific survival and OS in women <40 years of age with early-stage BC (17,18). Nevertheless, recently, mastectomy rates have increased significantly to treat early-stage BC in women aged 40 and under (14-16). Although most of the patients in our cohort had early stage disease, the most preferred surgical method was mastectomy. DFS tended to be longer in our patients who underwent BCS, although it was not statistically significant.

The indications of CT, RT and HER2-targeted therapies in young women with BC and the contents of the treatment protocols are the same as in the treatment of BC in older women (19). Updated results of the SOFT and TEXT studies confirmed that tamoxifen alone remains the standard of care for adjuvant ET of women with hormone receptor (HR) positive premenopausal BC at low risk of relapse, defined by clinical and immunohistochemical parameters. Also, ovarian function suppression (OFS) with tamoxifen or exemestane, rather than tamoxifen alone is recommended for women with high-risk HR positive BC, including the presence of pathologically involved lymph nodes, tumour diameter >5 cm, high risk of recurrence based on a genomic assay, 35 years or younger at diagnosis, or other high-risk features for which the patient received CT (20). Our study demonstrated that patients with non-metastatic disease at diagnosis received 56.8% tamoxifen plus GnRH-a as adjuvant ET, 15.9% tamoxifen alone, and 2.3% aromatase inhibitor plus GnRH-a as adjuvant ET. In addition, the rates of receiving neoadjuvant therapy and anti-HER2 therapy were similar to older patients.

In young women, BC has been reported to be associated with a higher risk of relapse and death. Young age reported to be an unfavourable independent prognostic factor for BC (21, 22). In the United States, the 5-year survival rate in women diagnosed with BC aged < 40 and aged > 40 was 85% and 90%, respectively (23). Women with stage I-III BC between 2000 and 2015, aged 20-49, were analyzed for 5- and 10-year survival rates through the SEER-18 registry database. 5 and 10-year survival rates were 85.6% and 74.6% in patients aged 20-29 years, were 87.9% and 78.9% in patients aged 30-39 years, and were 91.8% and 84.9% in patients aged 40-49 years, respectively (24). Another study involving 17.575 patients with early-stage BC showed that the mortality rate due to the BC was higher in women aged ≤ 40 years at diagnosis than in women aged > 40. When evaluated according to subtypes in this study, it has been found that in women aged ≤ 40 years was associated with significant increases of BC mortality in women with luminal A and luminal B subtypes, with borderline significance in women with triple-negative subtype but not in those with HER2-like subtype compared to women aged >40 years (25). However, in a recently published study, Dai et al. evaluated 33.968 patients with BC, and they reported that young age (<40 years) was an independent risk factor only for triple negative BC, but not for other subtypes (26). In another analysis of the SEER-18 registries of the United States database including 68.530 patients aged 20-49 years with stage I-III BC between 2010-2016, it has been found that with increasing age, HER2-/HR+ subtype rates increased, whereas HER2+/HR+, HER2+/HR-, and HER2-/HR- subtype rates decreased. This analysis showed increased incidence estimates for each receptor-based subtype among women 20-29 years except HER2-/HR+, for which incidence remained relatively stable, and the most significant increases in incidence were observed for HER2-/HR- women aged 20-29 years. Also, it has been found that the 5-year survival rates according to subtypes among women 20-29 years were 91.9%, 91.8%, 89%, and 79.3% for HER2+/HR+, HER2+/HR-, HER2-/HR+, and HER2-/HR-, respectively (27).

In contrast to the studies summarized herein, Zimmer et al. showed that young women with BC aged <40 had worse clinical features (higher grade, stage II and ER-negative disease) than the older women but had a similar OS rate to older women. This similarity in OS results was explained by the fact that women under 40 received more aggressive treatment and had less comorbidity than the older group (28). The 5-year OS rate of our cohort was 95.5% and was better than those reported in the above studies.

CONCLUSIONS

In our study, HER-2-like and triple-negative BC rates were higher in women aged 30 years and younger than in the older population, consistent with the literature. Moreover, we demonstrated that the 5-year OS rate in young women with non-metastatic BC is better than rates reported in previous studies. We also showed that mastectomy is the most preferred surgical method, even in early-stage disease. Furthermore, we found that mastectomy, although not statistically significant, was associated with lower DFS than BCS.

Ethics Committee Approval:
This research complies with all the relevant national regulations, institutional policies and is in accordance the tenets of the Helsinki Declaration, and has been approved by the Meram Medical Faculty Ethical Committee, Necmettin Erbakan University (approval number: 2020/2347).

Author Contributions:
Concept – M.K.E.; Design – M.K.E.; Supervision – M.A.; Resources – M.K.E, M.K.,M.K. Materials – M.K.E.; Data Collection and/or Processing - M.K.E, M.K.,M.K.; Analysis and/ or Interpretation - M.K.E, M.K.; Literature Search - M.K.E, M.K.; Writing Manuscript- M.K.E, M.K.,M.K.; Critical Review - M.A, M.K.E.

Conflict of Interest:
The authors have no conflict of interest to declare.

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