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Prognostic factors affecting survival in breast cancer patients age 40 or younger

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Abstract

The aims of this study were to identify the factors affecting survival and disease-free survival (DFS) in invasive breast cancer patients who underwent surgery for breast cancer age 40 or younger. Medical records of 216 women with breast carcinoma at age 40 or younger who underwent surgery at our Institution between October 2005 and May 2017 were retrospectively reviewed. One hundred and eighty eight invasive breast cancer patients that were eligible were categorized according to their clinical and pathological features. Univariate analyses of survival and DFS were performed by the Kaplan–Meier method and the log-rank test. Independent prognostic and predictive factors affecting survival and DFS were assessed by Cox regression proportional hazard method. 10-year survival and DFS were 85 and 74%, respectively. Axillary involvement, pathologic tumor size, HER 2 + subtype and Triple Negative subtype were found to be the prognostic factors that independently affected survival and DFS. The prognosis is worse in patients with axillary involvement, tumors larger than 2 cm, and HER 2+ and Triple Negative subtypes. These adverse prognostic factors should be considered during treatment and follow-up of patients age 40 or younger.

Keywords: breast cancer, prognosis, survival, disease-free survival, breast neoplasms

1. Introduction

Breast cancer is the most common cancer in women and is an important public health problem that causes approximately 2.088.000 new cases and 627.000 deaths worldwide each year (1). Although majority of patients (88.4%) are diagnosed over the age of 40, the 11.6% of patients are at age 40 or younger (1). In a study published from our country, 17.2% of patients diagnosed with breast cancer were found to be younger than 40 years old (2). Despite these high rates, there are few studies examining breast cancer and prognostic factors affecting survival or disease-free survival (DFS) in women at the age of 40 or younger (3-6).

Risk factors, clinical outcomes, and tumor biology could differ in women aged 40 or younger and may present more aggressive behaviour and worse prognosis (7, 8). It has been reported that the disease is at an advanced stage during the presentation in cases of breast cancer at the age of 40 or younger (9-11). These suggestions raise the question that prognostic factors for survival and disease-free survival in patients≤ 40 years old could be different than the older patients. Therefore, prognostic factors for survival and DFS have been investigated inpatients aged 40 or younger. Positive axillary lymph nodes, hormone receptors, HER2 status, molecular subtypes, tumor size, grade, age, and type of surgery have been defined as independent prognostic factors but controversies about prognostic factors still exist (3-6, 12, 13).

The aim of our study is to show the prognostic and predictive factors affecting survival and disease-free survival of invasive breast cancer patients age 40 years or younger.

2. Material and Methods

The procedures followed were in accordance with the ethical standards of the institutional or regional responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. Informed consent was obtained from participants in the study and our Institution's ethics committee approved the study.

This study was conducted with the approval of our hospital's ethics committee (Approval number: 2019/663, approval date:17.10.2019). Medical records of 216 women with breast carcinoma age 40 or younger who underwent surgery at Ondokuz Mayis University School of Medicine, Department of General Surgery between October 2005 and May 2017 were retrospectively reviewed.

Two hundred and sixteen patients included in the present

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study were selected among 1587 patients who underwent surgery during this period (13.6%). Pathological and clinical data and follow-up information were retrieved from the medical records. Patients with pure ductal carcinoma in-situ (DCIS), with T4 tumor and patients who received neoadjuvant chemotherapy and patients whose postoperative examination, follow-up and treatment data were not available were not eligible and excluded from the study.

Prognostic and predictive factors for survival and DFS were analyzed for 188 invasive breast cancer patients. If 3 months elapsed after the last regular examination time during follow-up, recent status of patients was also updated by phone call. The follow-up times of the survivors continued to March 2019. All patients were followed up with 3-6 months' intervals for the first three years and every 6 months during years 4 and 5.

Histopathological subtypes were classified according to World Health Organization criteria as invasive ductal, invasive lobular carcinoma, or as pure special features such as medullary, tubular, mucinous, papillary, scirrhous, apocrine and adenoid cystic carcinoma. ER and PR status were defined by immunochemistry and staining of 1% of tumor cells was accepted ER or PR positive. Molecular subtypes of breast cancer were determined according to the classification on the St. Gallen International Expert Consensus in 2011 (14) .Adjuvant radiation therapy was applied to the breast of patients who underwent breast conserving surgery, and patients who underwent mastectomy and had pT3 tumor or had ≥ 4 axillary lymph node involvement received adjuvant radiotherapy to the chest wall. Patients with axillary involvement who did not undergo axillary lymph node dissection received axillary radiation therapy. Adjuvant radiotherapy was given also to the supraclavicular and internal mammary fields of the patients who had ≥ 4 positive axillary lymph nodes (15). Adjuvant chemotherapy was given to all patients except three patients whose tumors were classified as Luminal A subtype, had a tumor less than 1cm, and grade 1 tumor, and had not axillary lymph node involvement. All patients with ER and/or PR positive tumors were given adjuvant hormonotherapy. Patients with HER2+ status had trastuzumab treatment (16-22)

Potential prognostic and predictive factors included in this study were age (20-30, 31-40), type of surgery performed (BCS, mastectomy), axillary lymph node metastasis (pN0, pN+ and pN0, pN1, pN2, pN3), histopathological type (invasive ductal carcinoma, invasive lobular carcinoma, other), pathological tumor size (pT1, pT2, pT3), pathological grade (1, 2, 3), estrogen, progesterone, and HER2 status (Negative, Positive), molecular subtypes (Luminal A, Luminal B, HER2 +, Triple Negative) and lymphovascular invasion (LVI) (Yes, No)(Table 1).

Table 1. 10-year survival and disease-free survival by characteristics of patients

	No (%)	10-year OS %	p (log rank)	10-year DFS %	p (log-rank)
Age					
<31	32 (17)	87		63	NS
31-41	156 (83)	84	N	76	
Type of surgery					
BCS	98 (52)	89		80	
Mastectomy	90 (48)	81	0.062	70	NS
Axillary involvement					
pN0	89 (47)	91		80	
pN+	99 (53)	80	0.028	69	NS
Axillary involvement					
pN0	89 (47)	91	0.	80	0.05
pN1 (1-3 positive nodes) LN)LN)	62 (33)	79		68	
pN2 (4-9 positive nodes) LLNLLLLN)LN) nodes	28 (15)	82		73	
pN3 (≥10 positive nodes)	9 (5)	78		56	
Histopathological Type					
Invasive ductal	173 (92)	85		76	
Invasive lobular	7 (4)	86	NS	86	NS
Other	8 (4)	88	NS	49	NS
Pathological Tumor Size					
pT1	66 (35)	96		93	
pT2	95 (51)	80	0.029	66	0.00
pT3	27 (14)	60	0.027	49	0.00
Grade					
1	17 (9)	91		91	
2	95 (51)	89	NS	77	NS

3	76 (41)	66	0.054	64	NS
Estrogen Receptor					
Positive	152 (81)	88		78	
Negative	38 (19)	73	0.061	61	0.02
Progesterone Receptor					
Positive	129 (69)	88		77	
Negative	59 (31)	77	NS	67	NS
HER2					
Positive	75 (40)	87		79	
Negative	113 (60)	80	NS	67	NS
Molecular Subtype					
Luminal A	73 (39)	90		88	
Luminal B	79 (42)	92	NS	71	0.025
HER2+	12 (6)	68	0.004	54	0.001
Triple Negative	24 (13)	54	0.021	53	0.009
Lymphovascular Invasion					
Yes	75 (40)	82	NS	71	NS
No	113 (60)	91		81	

2.1. Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 15.0 program was used for statistical analysis. The follow-up interval calculated in months and defined as the time between the date of surgery and the date of event (death, local, regional or distant recurrence, or contralateral breast cancer) or last follow-up. The first documented recurrence of disease or occurrence of contralateral breast cancer, whichever occurred earlier was defined as event of endpoint for DFS, and death was defined as event of endpoint for survival. Descriptive statistical methods (Median) were used while evaluating the data regarding age, follow-up and recurrence time. The ca0tegorical data were expressed as numbers and percentages, and the continuous data and the follow-up time were expressed as median (range). Comparisons of categorical data were made with the Chi-square test. Kaplan Meier method and Log Rank test were used in survival analysis. Stepwise Cox Regression Proportional Hazards model was used to assess the independent prognostic and predictive factors affecting survival and DFS. Variables that were found to have a significant effect on OS or DFS at univariate analysis were included in the multivariate analysis. The results were evaluated in the 95% confidence interval and P values of less than 0.05 were considered significant.

3. Results

Median age was 36 years (range, 22-40) and the median follow-up was 75 months (range, 8 - 166). Ninety-eight patients underwent sentinel lymph node biopsy (SLNB) and 90 underwent axillary lymph node dissection (ALND) with or without SLNB. There were 18 deaths due to breast carcinoma. Total number of events was 34. Median recurrence time was 32 months (range, 4-114). Ten-year survival was 85% and 10-year disease-free survival was 74%. Characteristics of patients and the factors that are potentially affecting survival or DFS were shown in Table 1.

Local, regional recurrence or distant metastasis were found in 2 (1%), 2 (1%) and 19 (10%) patients, respectively. Single organ metastasis and multiple distant metastases were detected in 9 and 10 of those 19 patients, respectively. Out of 33 organ metastasis bone, lung, brain and liver metastases were found in 11, 11, 6 and 5 patients, respectively. Two patients had contralateral breast cancer.

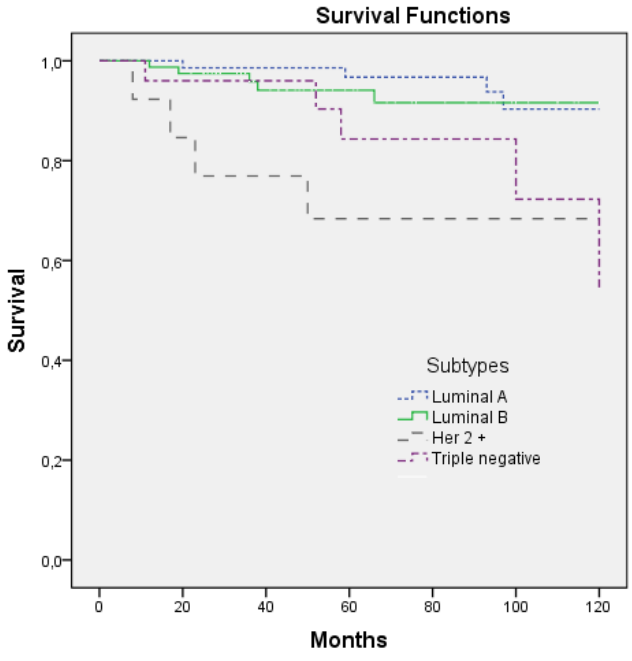

Fig.1. Overall survival by molecular subtypes (p=0.011)

Among the prognostic and predictive variables entered into the univariate analysis axillary involvement (pN0, pN+), pathological tumor size and molecular subtype (Fig.1) correlated with survival. Pathological tumor size (pT), ER status and molecular subtype (Fig. 2) were found to be associated with DFS (Table 1).

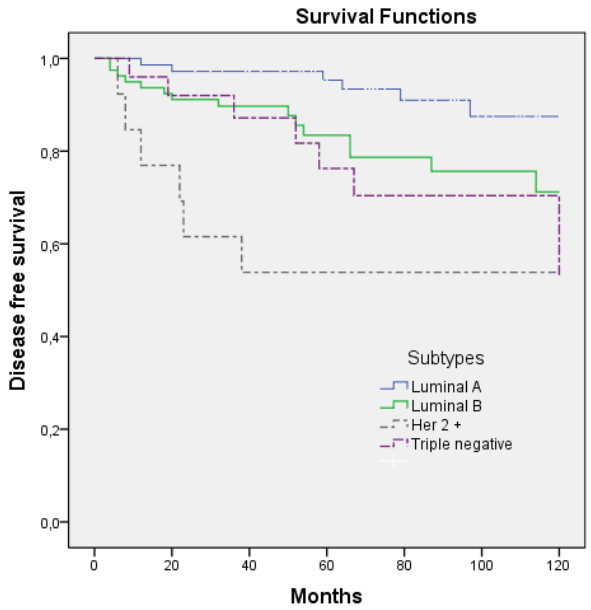

Fig. 2. Disease free survival by molecular subtypes (p=0.004)

Multivariate analysis revealed that axillary lymph node involvement (pN0, pN+), (HR (95% CI): 4.05 (1.30-12.64), p = 0.016), HER2 + subtype (HR (95% CI): 5.83 (1.44- 23.60), p = 0.013) and Triple Negative subtype (HR (95% CI): 5.63 (1.48-21.41), p = 0.011) were independent prognostic factors affecting 10-year survival (Table 2). pT2 (HR (95% CI): 3.51 (1.20-10.28), p = 0.022) and pT3 (HR (95% CI): 4.85 (1.44-16.23), p = 0.010), HER2 + molecular subtype (HR (95% CI): 5.33 (1.70-16.64), p = 0.004) and Triple Negative subtype (HR (95% CI): 3.04 (1.02-9.12), p = 0.047) were found as independent prognostic factors for 10-year DFS (Table 3).

Table 2. Independent prognostic factors affecting overall survival in multivariate analysis

	Hazard ratio (confidence interval)	p
Axillary involvement	4.05 (1.30-12.64)	0.016
HER2 + Subtype	5.83 (1.44-23.60)	0.013
Triple Negative	5.64 (1.48-21.41)	0.011

Table 3. Independent prognostic factors affecting disease-free survival in multivariate analyzes

	Hazard ratio (confidence interval)	p
Pathologic Tumor Size (pT2)	3.51 (1.20-10.28)	0.022
Pathologic Tumor Size (pT3)	4.85 (1.44-16.23)	0.010
HER2+ Subtype	5.33 (1.70-16.64)	0.004
Triple Negative Subtype	3.04 (1.02-9.12)	0.047

4. Discussion

Breast cancer is the most common and most fatal form of cancer in women, leaving lung cancer behind. According to GLOBOCAN 2018 data, 25% of cancers in women and 15% of cancer-related women deaths are related to breast cancer. Approximately 11.6% of breast cancer patients newly diagnosed in 2018 are at the age of 40 or younger. This rate was determined as 6.2% in Europe, 5.6% in the USA and 16.6% in our country (1, 2). It was 13.6% in our center.

In the POSH study by Copson et al. which consists of 2956 patients at age ≤40, the median age was 36 years. 10.7% of patients were at 30 or younger, and 89.3% were at age 31-40 (3). The age groups in POSH study are similar to our findings (Table 1). Ten-year survival and disease-free survival were 85%, and 74%, respectively in our study. In the POSH study, 5-year survival, and disease-free survival were 81.9%, 76.6%, respectively (3). In the study of Thomas et al. based on the Surveillance, Epidemiology, and End Results (SEER) registries database, 10-year survival was 76% in 38.411 women with stage I-III breast cancer younger than 40 years (23). In a large series from SEER database, 10-year survival was 84% for stage I-II breast cancer (6). In our study, 10-year survival was found to be higher as 85%. We agree with Mahmood et al. (6) who reported that there was no significant difference in survival in 14.764 patients aged 20-39 years from SEER database who underwent BCS and mastectomy (83.5% vs 83.6% for BCS or mastectomy) and we agree also with the other two studies which reported that type of surgery was not an independent factor for survival (13, 17).

In the present study ten-year survival was significantly shorter in patients with pathological axillary involvement. Our findings are also compatible with the previous studies in literature which reported that survival and/or DFS decreases significantly in patients with axillary involvement (4, 6, 13, 24). However, Keegan et al. reported that it was not a significant factor for survival. (6) Our findings overlap with the studies which reported that survival and/or DFS decreases as tumor size increases in patients ≤ 40 years old, (4, 6, 24) but contrast with study by Yoshida et al (13).

Among the studies which analysed the molecular classification in patients younger than 40years old, Keegan et al. based on data for 5.331 breast cancers aged 15-39 years obtained from the California Cancer Registry reported that survival in HER2 + and Triple Negative subtypes was significantly shorter than in HR+/HER2- breast cancersubtype (5). Yoshida et al.also reported that survival was significantly shorter in patients with Triple Negative subtype (13). The findings of the present study are in agree with those studies.In our study, 10-year survivaland 10-year DFS were significantly shorter in the Triple Negative and HER2 + subtypes than in Luminal A, B subtypes. Fredholm et al. stated that Luminal B subtype has the worst breast cancer specific survival in compared with the other subtypes in patients under the age of 40. However, in that analysis it was stated that Luminal-HER2 (ER+ and Her2+, any PR or Ki67), and HER2-positive were combined (12).

The retrospective nature, the limited number of patients analysed in the present study and lack of details of the adjuvant treatments are some limitations of the present study.

Independent prognostic factors affecting 10-year survival and DFS in breast cancer patients ≤ 40 years old were determined as pT, axillary involvement, HER2 + and Triple Negative subtypes. Considering these adverse factors could play an important role in the course of the disease during the diagnosis, treatment and follow-up processes in patients aged 40 or younger.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: C.A., S.S.Y., Design: U.K., N.Ö., Data Collection or Processing: C.A., S.S.Y., Analysis or Interpretation: C.A., B.K., Literature Search: U.K., N.Ö., Writing: C.A., B.K.

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