What predicts better prognosis in elderly breast cancer patients?

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Purpose: As we enter an aging society, the number of elderly patients with breast cancer is increasing. We assessed the prognostic factors for breast cancer recurrence or metastasis in patients over the age of 65 years by analyzing tumor characteristics and long-term clinical outcomes.

Methods: In this retrospective study, the data of 286 breast cancer patients aged 65 years and older, who underwent treatment at the Pusan National University Hospital and Pusan National University Yangsan Hospital from 2008 to 2014, were analyzed. The patients were divided into two groups: those with recurrence or metastasis and those without. Cox-regression model was used to analyze the risk factors for recurrence or metastasis. Kaplan-Meier method was used to analyze survival rates by the log-rank test.

Results: Among the 286 patients with invasive breast cancer, 43 patients (15.0%) had recurrence or distant metastasis during a median follow-up period of 61 months. Advanced stages of breast cancer and patients who are not adapted to endocrine therapy were associated with poor prognosis.

Conclusion: In this study, advanced stages of breast cancer and endocrine therapy were the prognostic factors for breast cancer recurrences or metastases. Early detection of elderly breast cancer generally increases the possibility of diagnosis at an earlier stage, which can lead to a better prognosis. Moreover, endocrine therapy should be administered to elderly patients who manifest favorable intrinsic subtypes of breast cancer.

Keywords: Breast neoplasms, Elderly, Clinical characteristics, Prognosis

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INTRODUCTION

The Ministry of Health and Welfare and the National Cancer Center in South Korea announced that the incidence rate of breast cancer was 62.6 per 100,000 women in 2016, up 14.4% from 54.7 per 100,000 in 2014. While the rates for most cancers, such as thyroid cancer, stomach cancer, and colorectal cancer, are decreasing, breast cancer rates are increasing every year in Korea. In all cases of breast cancer, the proportion of those aged 65 and older increased from 12.04% in 2007 to 16.29% in 2016. This increase is attributed to the growth in the elderly population. As a convention, a person aged 65 years or more is referred to as “elderly” [1,2]. Based on these data, we defined a person aged 65 years or more as “elderly” in this study. Elderly patients with breast cancer, however, tend to be reluctant to undergo treatments due to comorbidities and deterioration in quality of life and socioeconomic status. In addition, elderly patients often miss optimal treatment due to delay while seeking alternative medicine. Therefore, we assessed the tumor

characteristics and long-term clinical outcomes of breast cancer patients over the age of 65 to provide evidenced-based data for the treatment and prognosis of elderly patients.

METHODS

Patients

The patients in this study were diagnosed with primary breast cancer and treated at the Pusan National University Hospital and Pusan National University Yangsan Hospital between 2008 and 2014. The patients were treated with surgery and adjuvant or neoadjuvant chemotherapy, adjuvant hormonal therapy, or radiation therapy. Patients with ductal carcinoma *in situ*, recurrent breast cancer, metastases, or previous chemotherapy before 2008 were excluded.

Age at breast cancer diagnosis was used to analyze the survival period. We assessed the type of surgery, body mass index, histology, tumor size, lymph node status, histologic grade of tumor, status of chemotherapy, endocrine therapy and radiation therapy. The cancers were staged according to the breast cancer guidelines recommended by the 8th American Joint Committee on Cancer.

The hormone receptor status was graded using Allred scoring, and scores of 3 to 8 were considered positive. The human epidermal growth factor receptor 2 (HER2) was analyzed immunohistochemically using antibodies targeting HER2/neu (rabbit monoclonal). The results were scored on a scale of 0, 1+, 2+, and 3+. The 0 and 1+ were considered negative, 2+ was considered equivocal, and 3+ was considered strongly positive. When the result was equivocal, silver *in situ* hybridization (SISH) was performed. Detection of HER2 amplification by SISH was considered as HER2 positive. The intrinsic subtypes were classified as follows: luminal A, luminal B, HER2 over-expressing, and triple-negative breast cancer (TNBC). The luminal A type included tumors suggesting that hormone receptor was positive but HER2 was negative. The luminal B type included tumors testing positive for hormone receptor and HER2. The HER2-over expressing type included tumors that tested negative for hormone receptor but positive for HER2. TNBC included tumors negative for both hormone receptor and HER2.

Clinical follow-up was performed every three to 6 months during the first 5 years after primary therapy and annually thereafter. The data and cause of death were obtained from the medical records of the deceased patients.

This study was approved by the Institutional Review Board of Pusan National University, Korea (IRB No. 05-2019-141). Informed consent is not needed for this study.

Statistical analyses

Disease-free survival (DFS) was measured from the date of breast cancer diagnosis to the date of breast cancer recurrence or distant metastasis. Overall survival (OS) was measured from the date of diagnosis until the date of death or date the patient last visited the outpatient clinic. Breast cancer-specific survival (BCSS) was defined as death from breast cancer itself. The demographics and tumor characteristics were compared using chi-squared tests. The Kaplan-Meier method was used to determine the survival rates (DFS, OS, and BCSS) by log-rank test and a P-value less than 0.05 was considered significant. The Cox proportional hazards model was used to select significant covariates. The data were analyzed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

RESULTS

There were 286 patients aged 65 or older diagnosed with invasive breast cancer between 2008 and 2014 in this study, including 212 patients from Pusan National University Hospital and 74 from Pusan National University Yangsan Hospital.

The median age of the patients was 70 years (range, 65-92 years). Among these patients, 43 (15.0%) had a local recurrence or distant metastasis with a median follow-up period of 61 months (range, 14-134 months). Loco-regional recurrences occurred in 15 patients: one in ipsilateral axillary lymph node, five in supraclavicular lymph nodes, and nine involving breast and chest wall. There were 37 patients with distant metastasis: 15 involving lung, 13 involving bone, 10 related to liver, and four cases of brain metastasis.

Two of the 286 patients were male patients and two patients underwent surgery, followed by neoadjuvant chemotherapy. Hypertension was diagnosed in 172 patients, and 73 were diagnosed with diabetes mellitus. During the follow-up period, 32 patients were diagnosed with cancers involving other organs.

We found that pathologic node stage, the final stage, and the status of endocrine therapy varied significantly between patients with and without local recurrence or distant metastasis (Tables 1, 2). However, there were no differences in the pathologic tumor stage, grade, lymphovascular invasion, and intrinsic subtype (Table 1). Also, no differences were found between treatments with different types of surgery, chemotherapy, or radiotherapy (Table 2).

In multivariate Cox-regression analysis, pathologic nodal stage and the status of endocrine therapy were identified as prognostic factors for DFS. Stage and status of endocrine therapy were significant risk factors for OS and BCSS (Table 3).

Although obesity was not a risk factor for DFS, OS, or BCSS, it was related to luminal A and B type tumors. The chi-square test showed that overweight and obesity were correlated with positive

Table 1. Characteristics of patients with and without recurrence or distant metastasis

Variable	Patients without events (n = 243)	Patients with events (n = 43)	P-value
pT			0.340
1	118 (48.6)	6 (14.0)	
2	105 (43.2)	24 (55.8)	
3	11 (4.5)	9 (20.9)	
4	9 (3.7)	4 (9.3)	
pN			0.008
0	163 (67.1)	15 (34.9)	
1	54 (22.2)	13 (30.2)	
2	17 (7.0)	8 (18.6)	
3	9 (3.7)	7 (16.3)	
Stage			0.001
I	98 (40.3)	2 (4.6)	
IIA	75 (30.9)	14 (32.6)	
IIB	33 (13.6)	8 (18.6)	
IIIA	20 (8.2)	8 (18.6)	
IIIB	8 (3.3)	4 (9.3)	
IIIC	9 (3.7)	7 (16.3)	
Histologic grade			0.173
Unknown	11 (4.5)	1 (2.3)	
1	56 (23.0)	4 (9.3)	
2	116 (47.7)	14 (32.6)	
3	60 (24.7)	24 (55.8)	
Multiplicity			0.837
Yes	31 (12.8)	5 (11.6)	
No	212 (87.2)	38 (88.4)	
Lymphovascular invasion			0.698
Yes	68 (28.0)	19 (44.2)	
No	175 (72.0)	24 (55.8)	
Estrogen receptor			0.304
Positive	161 (66.3)	25 (58.1)	
Negative	82 (33.7)	18 (41.9)	
Progesterone receptor			0.934
Positive	126 (51.9)	22 (51.2)	
Negative	117 (48.1)	21 (48.8)	
HER2			0.030
Positive	44 (18.1)	14 (32.6)	
Negative	199 (81.9)	29 (67.4)	
Ki-67 (%)			0.051
≤ 14	126 (51.9)	17 (39.5)	
> 14	117 (48.1)	26 (60.5)	
Intrinsic subtype			0.098
Luminal A	147 (60.5)	19 (44.2)	
Luminal B	16 (6.6)	7 (16.3)	
HER2	28 (11.5)	7 (16.3)	
Triple-negative	52 (21.4)	10 (23.3)	

Values are presented as number (%).

pT, pathologic tumor stage; pN, pathologic node stage; HER2, human epidermal growth factor receptor 2.

Table 2. Differences in therapy between patients with and without local recurrence or metastasis

Therapy	Patients without events (n = 243)	Patients with events (n = 43)	P-value
Surgery			0.165
Mastectomy	148 (60.9)	31 (72.1)	
Breast conservation	95 (39.1)	12 (27.9)	
Chemotherapy			0.453
Adjuvant	160 (65.8)	30 (69.8)	
Neoadjuvant	1 (0.4)	1 (2.3)	
No chemotherapy	82 (33.7)	12 (27.9)	
Radiotherapy			0.211
Provided	116 (47.7)	25 (58.1)	
Not provided	127 (52.3)	18 (41.9)	
Endocrine therapy (n = 190)			0.009
Provided	161 (98.2)	23 (88.5)	
Not provided	3 (1.8)	3 (11.5)	
Target therapy (n = 58)			0.228
Provided	27 (61.4)	11 (78.6)	
Not provided	17 (38.6)	3 (21.4)	

Values are presented as number (%).

hormone receptors, with a P-value of 0.003 (Table 4).

Fig. 1 shows the Kaplan-Meier curves for DFS, OS, and BCSS according endocrine therapy status. Patients who received endocrine therapy had a better 5-year DFS rate than those who did not receive endocrine therapy (91.9% vs. 80.1%, endocrine therapy vs. no endocrine therapy, respectively; $P = 0.007$). In addition, the group, which was treated with endocrine therapy, had superior 5-year OS and BCSS rates compared with the group, which was not exposed to endocrine therapy (92.1% vs. 80.9%, $P = 0.005$; 93.7% vs. 81.8%, $P = 0.005$, respectively).

DISCUSSION

Korean women in their forties have a high breast cancer incidence rate unlike the rate in Western countries [3,4]. As mentioned earlier, however, the proportion of patients over the age of 65 is gradually increasing. Of all breast cancer patients, 16.29% were aged 65 or older in 2016, more than double since 2007. The increase in elderly breast cancer patients is significantly correlated with overweight status and obesity, especially in hormone receptor-positive cancers [5-8]. Mammographies are performed in women over 40 years old every 2 years in Korea. Mammography alone is highly sensitive in patients over 65 years of age due to the age-related reduction in breast density and may be responsible for the higher rates of breast cancer diagnosis. In this study, advanced stage was a

Table 3. Multivariate Cox-regression model

Variable	DFS		OS		BCSS	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
pN	1.84 (1.32–2.56)	< 0.001	-	-	-	-
Stage	-	-	1.67 (1.14–2.06)	< 0.001	1.78 (1.39–2.27)	< 0.001
Endocrine therapy	0.07 (0.02–0.25)	< 0.001	0.04 (0.01–0.15)	< 0.001	0.04 (0.01–0.20)	< 0.001

DFS, disease-free survival; OS, overall survival; BCSS, breast cancer-specific survival; HR, hazard ratio; CI, confidence interval; pN, pathologic node stage.

Table 4. Correlation of BMI with hormone receptor status

BMI	Hormone receptor status		Total
	ER-negative and PR-negative	ER-positive or PR-positive	
Underweight or normal	35 (12.24)	46 (16.08)	81 (28.32)
Overweight or obese	61 (21.33)	144 (50.35)	205 (71.68)
Total	96 (33.57)	190 (66.43)	286 (100)

Values are presented as number (%).

BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor.

significant risk factor for OS and BCSS. Therefore, appropriate examination should be conducted to increase early detection of breast cancer. We performed breast conservation surgery in 107 patients (37.4%) and found that the type of surgery was not related to DFS, OS, or BCSS. Early detection of breast cancer increases the possibility of breast-conserving surgery, which could lead to improved quality of life in elderly patients.

The pathologic nodal stage was a significant risk factor for local recurrence or distant metastasis in this study. When metastasis is detected in axillary lymph nodes, chemotherapy must be considered, followed by surgery. In general, patients over 65 years of age are more likely to manifest adverse events than younger patients [9–11]. Dose-reduction chemotherapy is common in elderly patients and may reduce treatment efficacy [12,13]. When administering chemotherapy, the effectiveness of treatment must be balanced against the possible side effects.

In our study, 65.6% of HER2-positive patients were treated with adjuvant trastuzumab. Elderly patients are often excluded from targeted therapy because they cannot withstand chemotherapy before adjuvant trastuzumab can be administered. Patients also discontinue with targeted therapy in the middle of treatment due to cardiotoxicity, which is a common side effect of trastuzumab.

Our findings are consistent with other studies that recommend endocrine therapy for elderly patients with luminal A or B type breast cancer [9,14–17].

The group treated with endocrine therapy showed longer survival and prevention of local recurrence or distant metastasis, suggesting that 66.1% of these patients have been diagnosed with luminal A or B type and were treated with endocrine therapy.

Fig. 1. Disease-free survival (A), overall survival (B), and breast cancer-specific survival (C) according to the availability of endocrine therapy.

A limitation of this study was that all intrinsic subtypes of breast cancer were included. Chemotherapy, targeted therapy, and radiotherapy might be underestimated because optimal treatment varies according to the intrinsic subtype. Despite this limitation, our results were similar to previous studies. Therefore, tailored therapy is indicated for elderly patients based on their individual situation.

In conclusion, elderly patients manifested favorable intrinsic subtypes of breast cancer. Therefore, endocrine therapy is recommended elderly patients with breast cancer carrying luminal A or B type tumors. Advanced stages of breast cancer are related to poor prognosis in elderly patients with breast cancer. Elderly patients tend to stop treatment more easily than younger patients with advanced stage breast cancers. Therefore, early detection of breast cancer is especially beneficial in elderly patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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