A comparative study of the clinical characteristics and outcomes of HR-positive HER2-negative breast cancer patients over and under 65 years old

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Purpose: The purpose of this study was to compare the clinical characteristics and outcomes of hormone receptor-positive (HR+) human epidermal growth factor 2-negative (HER2-) breast cancer among elderly patients (over 65 years old) and younger patients.

Methods: This was a retrospective cohort study of 328 patients who were treated for breast cancer at Pusan National University Yangsan Hospital between January 2009 and December 2014. Tumor characteristics, surgical methods, and survival outcomes were compared between the two age groups (<65 and ≥65 years old). Kaplan-Meier curves for disease-free survival (DFS) and overall survival (OS) were also constructed according to the age groups.

Results: Among the 328 patients with HR+ HER2- breast cancer, 184 (56.1%) were <65 years old and 144 (43.9%) were ≥65 years old. Breast cancer stages were similar between the two age groups, but the older patients were treated less often with chemotherapy (81% vs. 66%, $P=0.002$). During the follow-up period, 17 deaths and 36 cases of recurrence or metastasis were reported. There was no difference in DFS between the two groups ($P=0.840$); however, the OS of the older age group was significantly lower than that of the younger age group ($P=0.015$).

Conclusion: This study suggested that HR+ HER2- breast cancer patients belonging to the two age groups had no significant difference in DFS. However, older age is an independent factor affecting OS rate. Therefore, even if patients are old, but their physical condition is satisfactory, standard and active treatment may be necessary, similar to that given to younger patients.

Keywords: Aged, Breast neoplasm, Receptor, ErbB-2

INTRODUCTION

In Korea, breast cancer rates are increasing, whereas the rates of

other cancers are decreasing annually [1]. In general, Korean women in their forties have a high breast cancer incidence rate, unlike the rate in Western countries [1,2]. However, despite the country having an aging society, with the proportion of those aged 65 and older increasing, studies on elderly breast cancer patients remain insufficient.

Elderly patients have often been excluded from clinical trials, and prospective studies are usually inadequate, making it difficult to establish an appropriate treatment [3,4]. In addition, compared with younger patients, elderly patients are more unlikely to receive active treatments such as breast-conserving surgery, endocrine therapy, radiotherapy, or chemotherapy [5].

Breast cancer in elderly patients is frequently of the luminal type, with a less aggressive pathology [6,7]. In this study, we compared the clinical characteristics, prognostic factors, and long-term outcomes of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer among elderly patients (over 65 years old) and younger patients.

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METHODS

Study population

In this retrospective study, we analyzed the data of 328 patients who were treated for invasive breast cancer between January 2009 and December 2014 at Pusan National University Yangsan Hospital and Pusan National University Hospital. The patients were divided into two age groups: < 65 and $\geq$ 65 years old.

We classified a total of 328 patients with estrogen receptor-positive or progesterone receptor-positive HER2- breast cancer as having luminal type A breast cancer. Immunohistochemistry (IHC) staining permits the detection and localization of estrogen receptor/progesterone receptor within sections from formalin-fixed, paraffin-embedded tissues. Staining of > 20% of tumor cell nuclei is considered positive. Staining of 5% to 19% of tumor cell nuclei is considered borderline. Staining of < 5% of tumor cell nuclei is considered negative. HER2 proteins, our study considers IHC result of 0 to 1+ as negative and 3+ as positive. A Her2/neu result of 2+ is considered a negative result unless verified by silver *in-situ* hybridization.

The basic clinical characteristics of the patients were obtained using electronic medical records. We analyzed the clinicopathologic factors affecting prognosis in both age groups. The data included age at diagnosis, body mass index (BMI; kg/m²), T stage, N stage, histologic grade, Ki-67 status, and the type of surgery, chemotherapy, radiotherapy, and endocrine therapy. The breast cancer stage was classified using the 7th edition of the American Joint Committee on Cancer guidelines. The Ki-67 cutoff value was set at 15%. For detection of local and distant recurrence, clinical follow-up was performed every 3–6 months for the first 5 years after primary therapy.

This study was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (IRB No. 05-2021-023). Informed consent was not required for this study.

Statistical methods

Overall survival (OS) was defined as the time from the date of curative surgery to the date of death or last follow-up, whereas disease-free survival (DFS) was measured from the date of curative surgery to the date of local recurrence or distant metastasis. Five-year DFS and OS curves of the two age groups were calculated using the Kaplan-Meier method and were compared using the log-rank test. Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The median ages of the younger and older groups were 49 years (range, 25–64 years) and 70 years (range, 65–87 years), respectively. The proportion of patients with a high BMI was higher in the older group than that in the younger group ($P < 0.001$) (Table 1). Distribution of pathologic tumor stage was different in the two groups ($P = 0.041$) (Table 1). However, there was no statistically significant difference in the TNM final stage between the two groups. As expected, the incidence of comorbidity was greater among the older age group than younger age group ($P < 0.001$) (Table 1).

Receiving hormone therapy was not different in both groups, but there were significant differences between the two groups in terms of surgical method ($P < 0.001$), chemotherapy ($P = 0.002$), and radiation therapy ($P < 0.001$) (Table 2).

The majority of patients in the younger age group (81.5%) underwent breast-conserving surgery but older patients did not (40.3%) ($P < 0.001$).

In terms of treatment, for the younger age group, 81.0%, 89.1%, and 98.8% of patients received chemotherapy ($P = 0.002$), radiotherapy ($P < 0.001$), and hormone therapy ($P = 0.257$) respectively, whereas the older patients were less likely to have received chemotherapy or radiotherapy.

During the follow-up period, 17 deaths and 36 cases of recurrence or metastasis were reported in both groups (Table 3).

In the younger group, 20 of 184 patients (10.8%) had recurrence or metastasis. Local recurrences were observed in 10 of 184 patients (5.4%): six in the remnant breast, one in the chest wall, two in the axillary lymph, and one in multiple recurrences (remnant breast and axillary lymph). Metastasis occurred in 10 of 184 patients (5.4%): two in the lung, one in the bones, one in the liver, four in the brain, and two in multiple metastases (lung and bone).

In the older age group, the rate of locoregional recurrence or metastasis was not significantly different when compared to that of the younger group. Sixteen of 144 patients (11.1%) had recurrence or metastasis. Local recurrences were observed in five of 144 patients (3.4%), all in axillary lymph nodes. Metastasis occurred in 11 of 144 patients (7.6%): three in the lung, four in the bones, three in the liver, and one in multiple metastases (lung and bone).

The total number of deaths was 17, five of 184 patients (2.7%) in the younger age group and 12 of 144 patients (8.3%) in the older age group. There were 10 deaths from metastasis, two of five patients (40%) in the younger group and eight of 10 patients (66.7%) in the elderly. Two of older patients and one of younger patients were deaths from other cancer.

Univariate and multivariate analyses were performed to identify

Table 1. Characteristics of patients with estrogen receptor-positive breast cancer according to age

Variable	Overall (n = 328)	Age < 65 years (n = 184)	Age ≥ 65 years (n = 144)	P-value
BMI (kg/m ²)				< 0.001
Underweight (< 18.5)	6 (1.8)	3 (1.6)	3 (2.1)	
Normal weight (18.5 to < 23)	112 (33.9)	80 (43.5)	32 (22.2)	
Overweight (23 to < 25)	79 (24.1)	45 (24.5)	34 (23.6)	
Obesity (25 to < 30)	105 (32.0)	45 (24.5)	60 (41.7)	
Severe obesity (> 34)	26 (7.9)	11 (6.0)	15 (10.4)	
pT				0.041
1	166 (51.0)	95 (51.6)	71 (49.3)	
2	130 (40.0)	73 (39.7)	57 (39.6)	
3	23 (7.0)	15 (8.2)	8 (5.6)	
4	9 (3.0)	1 (0.5)	8 (5.6)	
pN				0.971
0	192 (58.5)	106 (57.6)	86 (59.7)	
1	90 (27.4)	51 (27.7)	39 (27.1)	
2	28 (8.5)	16 (8.7)	12 (8.3)	
3	18 (5.5)	11 (6.0)	7 (4.9)	
Stage				0.520
I	136 (41.5)	81 (44.0)	55 (38.2)	
II	137 (41.7)	72 (39.1)	65 (45.1)	
III	55 (16.8)	31 (16.8)	24 (16.7)	
Tumor grade				0.560
1	110 (33.5)	66 (35.9)	44 (30.6)	
2	164 (50.0)	90 (48.9)	74 (51.4)	
3	54 (16.5)	28 (15.2)	26 (18.1)	
Ki-67				0.340
< 15%	221 (67.4)	128 (69.3)	93 (64.6)	
≥ 15%	107 (32.6)	56 (30.4)	51 (35.4)	
Comorbidity				
HTN				< 0.001
Yes	117 (35.7)	29 (15.8)	88 (61.1)	
No	211 (64.3)	155 (84.2)	56 (38.9)	
DM				< 0.001
Yes	50 (15.3)	12 (6.5)	38 (26.4)	
No	278 (84.7)	172 (93.5)	106 (73.6)	

Values are presented as number (%).

BMI, body mass index; HTN, hypertension; DM, diabetes mellitus.

the prognostic factors for OS and DFS. The significant factors included age, BMI, type of surgery, tumor size, hormone therapy and Ki-67 in univariate analyses for OS. Multivariate analysis revealed that age, tumor size, hormone therapy and Ki-67 were significant factors for OS (Table 4). Table 5 shows that tumor size, node stage, TMN stage, nuclear grade, and Ki-67 were the significant factors for DFS in univariate analyses. Only tumor size was the significant factor for DFS in multivariate analyses. In multivariate analyses, tumor size had influence on OS and DFS.

The 5-year OS and DFS rates in the younger age group (n = 184) were 97.8% and 92.6%, respectively, whereas in the older age group, were 90.6% and 91.3%, respectively, with a median follow-up peri-

od of 64 months. Figs. 1 and 2 shows the OS and DFS Kaplan-Meier curves according to the age groups. No difference in DFS (P = 0.840) was observed between the two age groups (Fig. 1); however, the OS in the older age group was significantly lower than in the younger age group (P = 0.015) (Fig. 2).

DISCUSSION

Almost 50% of women diagnosed with breast cancer in the United States are ≥ 65 years old, and the median age of diagnosis is 61 years [8,9]. Due to the growing population of people aged over 65 years owing to Korea's increasing life expectancy, the number of

elderly breast cancer patients is also increasing.

We investigated the differences in OS and DFS between older and younger patients with HR+ HER2– breast cancer, which is the most frequent subtype, and its incidence is increasing compared to

other cancers among females.

Conventionally, “elderly” has been defined as ≥ 65 years old, and most developed countries have accepted the chronological age of 65 years as the definition of “elderly” or an older person [10]. Accordingly, the age group in our study was divided into the fol-

Table 2. Treatment of patients with estrogen receptor-positive breast cancer according to age

Variable	Overall (n = 328)	Age < 65 years (n = 184)	Age ≥ 65 years (n = 144)	P-value
Surgery				< 0.001
Breast conservation	208 (63.4)	150 (81.5)	58 (40.3)	
Mastectomy	120 (36.6)	34 (18.5)	86 (59.7)	
Chemotherapy				0.002
Adjuvant	244 (74.3)	149 (81.0)	95 (66.0)	
No chemotherapy	84 (25.7)	35 (19.0)	49 (34.0)	
Radiotherapy				< 0.001
Yes	235 (71.6)	164 (89.1)	71 (49.3)	
No	93 (28.4)	20 (10.9)	73 (50.7)	
Hormone therapy				0.257
Yes	322 (98.2)	182 (98.9)	140 (97.2)	
No	6 (1.8)	2 (1.1)	4 (2.8)	

Values are presented as number (%).

Table 3. Difference of locoregional recurrence or metastasis according to age

Variable	Overall (n = 328)	Age < 65 years (n = 184)	Age ≥ 65 years (n = 144)
Recurrence	15 (4.57)	10 (5.43)	5 (3.47)
Remnant breast	6 (1.83)	6 (3.26)	0
Axillary lymph	7 (2.14)	2 (1.09)	5 (3.47)
Chest wall	1 (0.30)	1 (0.54)	0
Multiple	1 (0.30)	1 (0.54)	0
Metastasis	21 (6.40)	10 (5.43)	11 (7.64)
Lung	5 (1.52)	2 (1.09)	3 (2.08)
Bones	5 (1.52)	1 (0.54)	4 (2.78)
Liver	4 (1.22)	1 (0.54)	3 (2.08)
Brain	4 (1.22)	4 (2.18)	0
Multiple	3 (0.91)	2 (1.09)	1 (0.70)
Death	17 (5.18)	5 (2.72)	12 (8.33)

Values are presented as number (%).

Table 4. Univariate and multivariate Cox regression analyses for overall survival

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
pT				
T1	Reference		Reference	
T2	2.54 (1.14–5.72)	0.024	2.54 (–1.13–5.71)	0.024
T3	9.11 (3.34–24.81)	< 0.001	9.11 (3.34–24.82)	< 0.001
T4	10.04 (2.68–37.54)	0.001	10.04 (2.68–37.54)	0.001
pN				
N0	Reference			
N1	2.24 (1.04–4.84)	0.040		
N2	3.72 (1.31–10.61)	0.140		
N3	5.66 (1.96–16.14)	0.001		
TNM stage				
1	Reference			
2	2.49 (1.03–6.07)	0.040		
3	6.89 (2.69–17.62)	< 0.001		
Nuclear grade				
1	Reference			
2	2.19 (0.88–5.49)	0.090		
3	4.23 (1.53–11.75)	0.006		
Ki-67				
< 15%	Reference			
$\geq 15\%$	2.28 (1.18–4.41)	0.014		

HR, hazard ratio; CI, confidence interval.

lowing two groups: <65 and ≥65 years old.

In this study, BMI was relatively high among the elderly ($P < 0.001$) because as people get older, basal metabolic rate, physical activity, and social activity are decreased; post-menopausal women experience numerous metabolic changes due to changes in female hormones, and, especially at this time, women are at high risk for

obesity due to increased body fat [11].

Moreover, obesity among these women is highly related to the development of lifestyle diseases, such as coronary artery and heart disease, stroke, diabetes, and hypertension, that increase mortality [11,12].

Similar to that in other countries, South Korea provides breast

Fig. 1. Disease-free survival according to age groups.

Fig. 2. Overall survival according to age groups.

Table 5. Univariate and multivariate Cox regression analyses for disease-free survival

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr)				0.037
< 65	Reference		Reference	
≥ 65	3.37 (1.19–9.59)	0.015	3.71 (1.08–12.79)	
BMI (kg/m ²)				
Underweight (< 18.5)	Reference			
Normal weight (18.5 to < 23)	0.11 (0.03–0.42)	0.001		
Overweight (23 to < 25)	0.04 (0.01–0.22)	< 0.001		
Obesity (25 to < 30)	0.05 (0.01–0.22)	< 0.001		
Severe obesity (> 34)	0.08 (0.01–0.73)	0.026		
Type of surgery				
Breast conservation	Reference			
Mastectomy	4.62 (1.64–13.18)	0.001		
pT				
T1	Reference		Reference	
T2	4.11 (1.11–15.15)	0.034	3.34 (0.83–13.46)	0.090
T3	9.32 (1.84–46.43)	0.006	9.79 (1.73–55.45)	0.010
T4	16.51 (2.75–99.13)	0.002	23.65 (3.33–167.78)	0.002
Hormone therapy				
No	Reference		Reference	
Yes	0.03 (0.01–0.11)	< 0.001	0.09 (0.02–0.53)	0.008
Ki-67				
< 15%	Reference		Reference	
≥ 15%	3.94 (1.46–10.65)	0.004	4.91 (1.36–17.72)	0.015

HR, hazard ratio; CI, confidence interval; BMI, body mass index.

cancer screening for women over the age of 40 years [13,14]. However, in the elderly population, examinations are not performed regularly, and high T stages are more commonly observed due to delayed diagnosis [15].

In our study, patients older than 65 years were more likely to be diagnosed with high T stage breast cancer than younger patients were ($P=0.041$); nevertheless, the difference in the overall stage was not significant. However, tumor stage is one of the risk factors for increased OS and DFS. Early detection is considered to be an important factor during breast cancer screening tests or self-examination.

Elderly women were more likely to undergo mastectomy (59.7%) than younger women were (18.5%) ($P<0.001$), and there was a tendency to omit postoperative radiation therapy. This difference in surgical methods can be attributed not only to the elderly being less sensitive to their body image or to cosmetic results but also to the high T stage at the time of diagnosis.

As reported in previous studies, receiving chemotherapy is closely related to the cancer stage and HR status [16,17]. Elderly patients less frequently receive systemic therapy, particularly chemotherapy. The reasons for this difference in treatment may be due to the higher rate of comorbidities, the patient's or family preferences, concerns about quality of life, and low life expectancy.

Hormonal therapy has been reported to be independent of age [15]. This is because it is easier for patients to adjust to the drug in the short term, but long-term compliance tends to decline; therefore, long-term outcomes require follow-up.

HR+ HER2- breast cancer is not aggressive [18], and elderly patients can be treated with hormones and have good compliance.

In this study, there was no difference in DFS between the two age groups; however, the OS in the older age group was significantly lower than that in the younger age group. The reasons for the decrease in OS in older patients include the high stage at the time of diagnosis, short life expectancy, high comorbidity rate, and lack of active treatment. In our study, both all-cause mortality and breast cancer-specific mortality were higher in the older age group. It was thought that comorbidity would affect both mortality rates. The proportion of lifestyle diseases such as hypertension and diabetes were significantly higher in the older (Table 1) and one of the older age group died from atrial fibrillation. Cancer incidence rate increases with age, and in this study, the incidence rate of other organ cancers was higher in the older age group than in the younger group.

The difference in overall stage between age groups was not significant, but a high T stage in old age is generally considered to affect the overall stage and prognosis. These factors are thought to be directly or indirectly responsible for the reduction of OS in old age

as they reduce compliance with postoperative recovery, chemotherapy, radiation therapy, and endocrine therapy.

Previously, many studies on similar subjects have already been reported, and this study has the limitation of being a retrospective study of a single institution. Also, accurate comparison through propensity score matching between the two groups is necessary, but the analysis is likely to be difficult due to the small number of target groups.

In conclusion, this study suggested that HR+ HER2- breast cancer patients belonging to the two age groups had no significant difference in DFS. However, older age is an independent factor affecting the OS rate. Therefore, even if patients are old, standard and active treatment may be necessary, similar to that in younger patients, for the older patients with satisfactory physical condition. For such active treatment to be achieved, early detection through continuous regular check-ups is necessary, even among the elderly.

CONFLICT OF INTEREST

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

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