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Original Article

Effect of Estrogen Receptor Expression Level and Hormonal Therapy on Prognosis of Early Breast Cancer

Kyung-Hwak Yoon[1], **Yeshong Park**[1], **Eunyoung Kang**[1], **Eun-Kyu Kim**[1], **Jee Hyun Kim**[2], **Se Hyun Kim**[2], **Koung Jin Suh**[2], **Sun Mi Kim**[3], **Mijung Jang**[3], **Bo La Yun**[3], **So Yeon Park**[4], **Hee-Chul Shin**[1]

Departments of [1]Surgery, [2]Internal Medicine, [3]Radiology, and [4]Pathology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

Purpose Estrogen receptor (ER) expression in breast cancer plays an essential role in carcinogenesis and disease progression. Recently, tumors with low level (1%-10%) of ER expression have been separately defined as ER low positive (ER^{low}). It is suggested that ER^{low} tumors might be morphologically and behaviorally different from tumors with high ER expression (ER^{high}).

Materials and Methods Retrospective analysis of a prospective cohort database was performed. Patients who underwent curative surgery for early breast cancer and had available medical records were included for analysis. Difference in clinicopathological characteristics, endocrine responsiveness and five-year recurrence-free survival was evaluated between different ER subgroups (ER^{high}, ER^{low}, and ER-negative [ER^{-}]).

Results A total of 2,162 breast cancer patients were included in the analysis, Tis and T1 stage. Among them, 1,654 (76.5%) were ER^{high}, 54 (2.5%) were ER^{low}, and 454 (21.0%) were ER^{-} patients. ER^{low} cases were associated with smaller size, higher histologic grade, positive human epidermal growth factor receptor 2, negative progesterone receptor, and higher Ki-67 expression. Recurrence rate was highest in ER^{-} tumors and was inversely proportional to ER expression. Recurrence-free survival was not affected by hormonal therapy in the ER^{low} group (p=0.418).

Conclusion ER^{low} breast cancer showed distinct clinicopathological features. ER^{low} tumors seemed to have higher recurrence rates compared to ER^{high} tumors, and they showed no significant benefit from hormonal therapy. Future large scale prospective studies are necessary to validate the treatment options for ER^{low} breast cancer.

Key words Breast neoplasms, Hormone receptor, Estrogen receptor, Hormonal therapy

Introduction

Breast cancer, the most common malignancy in women worldwide, is considered a heterogeneous disease with high degree of diversity [1]. Risk stratification for recurrence after surgery depends on various clinicopathological factors including patient age, tumor size, lymph node involvement, and hormone receptor expression [2]. Since the discovery of hormone receptors in the 1960s, estrogen receptor (ER) and progesterone receptor (PR) expression has remained essential in the decision-making algorithm for breast cancer treatment [3].

ER positivity is closely associated with major hormonal risk factors of breast cancer [4]. At the same time, ER-positive (ER^{+}) disease exhibits distinct clinicopathological features such as older age, smaller size, lower grade, and most importantly, favorable prognosis [5,6]. Yet the hallmark of ER expression is its predictive role in hormonal therapy response; adjuvant tamoxifen therapy for ER^{+} breast cancer has led to a significant decrease in recurrence and mortality [7].

It is undebatable that ER-negative (ER^{-}) patients do not benefit from hormonal therapy; however, defining ER positivity with a clear cutoff point remains challenging [8]. The traditional cutoff value for ER^{+} disease was over 10% of cells staining, which was later lowered to 1%; however, a recent update in the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guideline recommends defining samples with low level (1%-10%) of ER expression separately as ER low positive (ER^{low}) [9]. Recent reports in the literature suggest that ER^{low} tumors might be morphologically and behaviorally different from tumors with high ER expression (ER^{high}) [10-12]. In the present study, we aim to compare ER^{high}, ER^{low}, and ER^{-} subtypes of early breast cancer in terms of clinicopathological characteristics, endocrine responsiveness, and prognosis.

Correspondence: Hee-Chul Shin
Department of Surgery, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
Tel: 82-31-787-7097 Fax: 82-31-787-4055 E-mail: dradam77@naver.com
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*Kyung-Hwak Yoon and Yeshong Park contributed equally to this work.

Materials and Methods

1. Study population

Retrospective analysis was performed on a prospective cohort of 2,411 patients who underwent curative surgery for early stage breast cancer between January 2005 and December 2015 at Seoul National University Bundang Hospital. The inclusion criteria for the current study were as follows: (1) histologically confirmed stage 0 of ductal carcinoma *in situ* (DCIS) or stage I of invasive ductal carcinoma (IDC), (2) available surgical records and pathology reports, and (3) available immunohistochemistry (IHC) staining results on ER, PR, human epidermal growth factor receptor 2 (HER2) and Ki-67. Patients with contralateral advanced stage breast cancer were excluded from the study. A total of 2,162 patients were included for analysis.

2. Data collection

Demographic information of study participants was obtained through review of medical records. Surgical records were reviewed for operation date, method, and extent of axillary dissection. Information on tumor size, histological type, histological grade, lymphovascular invasion, lymph node metastasis, and pathological stage was retrieved from pathology reports. IHC staining was routinely performed for ER, PR, HER2, and Ki-67. Follow-up data was collected until each patient's last visit to the hospital and included adjuvant therapy (radiation therapy, hormonal therapy, chemotherapy), recurrence status (date of recurrence, initial recurrence site, additional treatment), and survival status (date and cause of death). 5-Year recurrence-free survival (RFS) was analyzed by censoring events at 5 years.

3. Immunohistochemistry staining

Hormone receptor status was determined by our pathologists who are fully dedicated to breast cancer pathology. Patients were separated into three groups based on IHC result of ER staining: (1) ER^{high}, when ≥ 10% of tumor cell nuclei were immunoreactive, (2) ER^{low}, with 1%-9% of cells staining, and (3) ER^{-}, if less than 1% of tumor cells showed IHC staining for ER.

4. Statistical analysis

All statistical analyses were performed using SPSS ver. 23.0 (IBM Corp., Armonk, NY). Continuous variables were compared using Student's t test; categorical variables were compared using chi-square test or Fisher exact test. Survival analysis was conducted using Kaplan-Meier method and log-rank test. Hazard ratio for recurrence was obtained through Cox regression analysis. Subgroup analysis was performed for DCIS and IDC patients separately. All p-values were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Among the 2,162 patients included in the study, 1,654 (76.5%) were ER^{high}, 54 (2.5%) were ER^{low}, and 454 (21.0%) were ER^{-}. Clinicopathological characteristics of the study participants are summarized in Table 1. When compared to ER^{high} cases, ER^{low} patients were associated with higher grade, negative PR, positive HER2, and higher Ki-67 expression. When compared to ER^{-} cases, ER^{low} patients were associated with younger age, lower grade, positive PR, positive HER2, and lower Ki-67 expression. ER^{low} breast cancer was smaller in size than both ER^{high} and ER^{-} groups ($p < 0.001$ and $p=0.010$, respectively).

Postoperative treatment data was available for all cases. Eighty seven point one percentage (1,441/1,654) of ER^{high} patients, 68.5% (37/54) of ER^{low} patients, and 4.4% (20/454) of ER^{-} patients received hormonal therapy ($p < 0.001$ between all groups). Hormonal therapy included selective ER modulators and aromatase inhibitors. 22.6% (373/1,654) of ER^{high} patients, 38.9% (21/54) of ER^{low} patients, and 53.3% (242/454) of ER^{-} patients received adjuvant chemotherapy ($p < 0.001$ between all groups).

Follow-up information was available for 2,161 patients (mean follow-up of 6.59 years; range, 0.01 to 15.79 years). Five-year recurrence rate was 5.1% (84/1,654), 7.4% (4/54), and 9.7% (44/454) in ER^{high}, ER^{low}, and ER^{-} groups, respectively ($p < 0.001$). Recurrence data included local recurrence, regional recurrence, and systemic recurrence. When two groups were compared to each other independently, RFS was significantly worse in ER^{-} cases compared to ER^{high} cases ($p < 0.001$), but there was no statistically significant difference between ER^{low} and ER^{high} cases ($p=0.597$) or ER^{low} and ER^{-} cases ($p=0.400$) (Fig. 1). Similar results were found in subgroup analysis of IDC patients; only ER^{-} patients showed worse RFS compared to ER^{high} patients ($p < 0.001$), and no significant difference in recurrence was observed between ER^{low} and ER^{high} patients ($p=0.613$) or ER^{low} and ER^{-} patients ($p=0.385$) (Fig. 2).

To evaluate endocrine responsiveness of ER^{high} and ER^{low} patients, 5-year RFS was compared between patients with our without hormonal therapy (Fig. 3). ER^{-} patients were excluded from this analysis as hormonal therapy was routinely not included in their treatment plan. ER^{high} patients showed significantly worse prognosis when hormonal therapy was omitted ($p=0.020$). This difference was not observed in ER^{low} cases; there was no difference in recurrence between-patients who received hormonal therapy and those who did not receive the treatment ($p=0.418$).

Table 1. Clinicopathological characteristics according to ER expression in early breast cancer patients

	ER				p-value		
	ER^{-} (n=454)	ER^{low} (n=54)	ER^{high} (n=1,654)	Total (n=2,162)	Total	ER^{low} vs. ER^{-}	ER^{low} vs. ER^{high}
Age (yr)							
Mean±SD	54.0±11.1	48.9±10.5	51.2±11.0	51.7±11.1	< 0.001	0.001	0.570
Median (range)	54 (25-85)	49 (29-72)	49 (25-88)	50 (25-88)			
Sex							
Female	454 (100)	54 (100)	1,644 (99.4)	2,152 (99.5)	0.326	-	> 0.99
Male	0	0	10 (0.6)	10 (0.5)			
Operation							
Breast conserving surgery	281 (61.9)	30 (55.6)	1,217 (73.6)	1,528 (70.7)	< 0.001	0.366	0.003
Total mastectomy	173 (38.1)	24 (44.4)	437 (26.4)	634 (29.3)			
Axillary dissection							
Not done	40 (8.8)	9 (16.7)	299 (18.1)	348 (16.1)	< 0.001	0.130	0.482
Sentinel lymph node biopsy	399 (87.9)	43 (79.6)	1,324 (80.0)	1,766 (81.7)			
Axillary lymph node dissection	15 (3.3)	2 (3.7)	31 (1.9)	48 (2.2)			
Size (cm)							
Mean±SD	1.0±0.7	0.8±0.6	1.2±0.6	1.1±0.6	< 0.001	0.010	< 0.001
Median (range)	1.1 (0.1-2.0)	0.6 (0.1-2.0)	1.2 (0.0-2.0)	1.1 (0.0-2.0)			
Type							
Ductal carcinoma *in situ*	86 (18.9)	13 (24.1)	457 (27.6)	556 (25.7)	0.001	0.404	0.870
Invasive ductal carcinoma	357 (78.6)	39 (72.2)	1,131 (68.4)	1,527 (70.6)			
Others	11 (2.4)	2 (3.7)	66 (4.0)	79 (3.7)			
T category							
Tis	86 (18.9)	13 (24.1)	457 (27.6)	556 (25.7)	< 0.001	0.270	< 0.001
T1mic	81 (17.8)	13 (24.1)	81 (4.9)	175 (8.1)			
T1a	41 (9.0)	6 (11.1)	117 (7.1)	164 (7.6)			
T1b	56 (12.3)	8 (14.8)	325 (19.6)	389 (18.0)			
T1c	190 (41.9)	14 (25.9)	647 (40.7)	878 (40.6)			
N category							
Nx	41 (9.0)	8 (14.8)	297 (18.0)	346 (16.0)	< 0.001	0.249	0.904
N0	408 (89.9)	45 (83.3)	1,311 (79.3)	1,764 (81.6)			
N1mic	5 (1.1)	1 (1.9)	46 (2.8)	52 (2.4)			
Stage							
0	86 (18.9)	13 (24.1)	457 (27.6)	556 (25.7)	< 0.001	0.579	0.877
IA	363 (80.0)	40 (74.1)	1,152 (69.6)	1,555 (71.9)			
IB	5 (1.1)	1 (1.9)	45 (2.7)	51 (2.4)			

(Continued to the next page)

Table 1. Continued

	ER				p-value		
	ER⁻ (n=454)	ER^{low} (n=54)	ER^{high} (n=1,654)	Total (n=2,162)	Total	ER^{low} vs. ER⁻	ER^{low} vs. ER^{high}
Grade							
G1	3 (0.7)	5 (9.3)	418 (25.3)	426 (19.7)	< 0.001	< 0.001	0.017
G2	88 (19.4)	17 (31.5)	513 (31.0)	618 (28.6)			
G3	221 (48.7)	12 (22.2)	200 (12.1)	433 (20.0)			
Unknown	142 (31.3)	20 (37.0)	523 (31.6)	685 (31.7)			
Lymphovascular invasion							
Present	41 (9.0)	1 (1.9)	184 (11.1)	226 (10.5)	0.055	0.057	0.056
Absent	284 (62.6)	31 (57.4)	959 (58.0)	1,274 (58.9)			
Unknown	129 (28.4)	22 (40.7)	511 (30.9)	662 (30.6)			
Progesterone receptor							
Positive	16 (3.5)	22 (40.7)	1,491 (90.1)	1,529 (70.7)	< 0.001	< 0.001	< 0.001
Negative	438 (96.5)	32 (59.3)	163 (9.9)	633 (29.3)			
HER2							
Negative	102 (22.5)	9 (16.7)	584 (35.3)	695 (32.1)	< 0.001	0.269	< 0.001
Equivocal	0	0	4 (0.2)	4 (0.2)			
Positive	66 (14.5)	12 (22.2)	71 (4.3)	149 (6.9)			
Not done	286 (63.0)	33 (61.1)	995 (60.2)	1,314 (60.8)			
Ki-67 (%)							
Mean±SD	26.7±19.0	18.1±13.9	9.1±9.0	13.0±13.9	< 0.001	< 0.001	< 0.001
Median (range)	20 (0-90)	15 (5-60)	5 (0-70)	7 (0-90)			
Radiotherapy							
Done	263 (57.9)	27 (50.0)	1,138 (68.8)	1,428 (66.0)	< 0.001	0.508	0.009
Not done	186 (38.8)	25 (46.3)	488 (29.5)	689 (31.9)			
Unknown	15 (3.3)	2 (3.7)	28 (1.7)	45 (2.1)			
Hormonal therapy							
Done	20 (4.4)	37 (68.5)	1,441 (87.1)	1,498 (69.3)	< 0.001	< 0.001	< 0.001
Not done	434 (95.6)	17 (31.5)	213 (12.9)	664 (30.7)			
Chemotherapy							
Done	242 (53.3)	21 (38.9)	373 (22.6)	636 (29.4)	< 0.001	0.045	0.005
Not done	212 (46.7)	33 (61.1)	1,281 (77.4)	1,526 (70.6)			
Recurrence							
Yes	44 (9.7)	4 (7.4)	84 (5.1)	132 (6.1)	0.001	0.587	0.357
Local	16 (3.5)	2 (3.7)	34 (2.1)	52 (2.4)			
Regional	7 (1.5)	0	5 (0.3)	12 (0.6)			
Systemic	13 (2.9)	1 (1.9)	21 (1.3)	35 (1.6)			

Values are presented as number (%) unless otherwise indicated. ER, estrogen receptor; ER⁻, estrogen receptor negative; ER^{high}, estrogen receptor high positive; ER^{low}, estrogen receptor low positive; HER2, human epidermal growth factor receptor 2; SD, standard deviation.

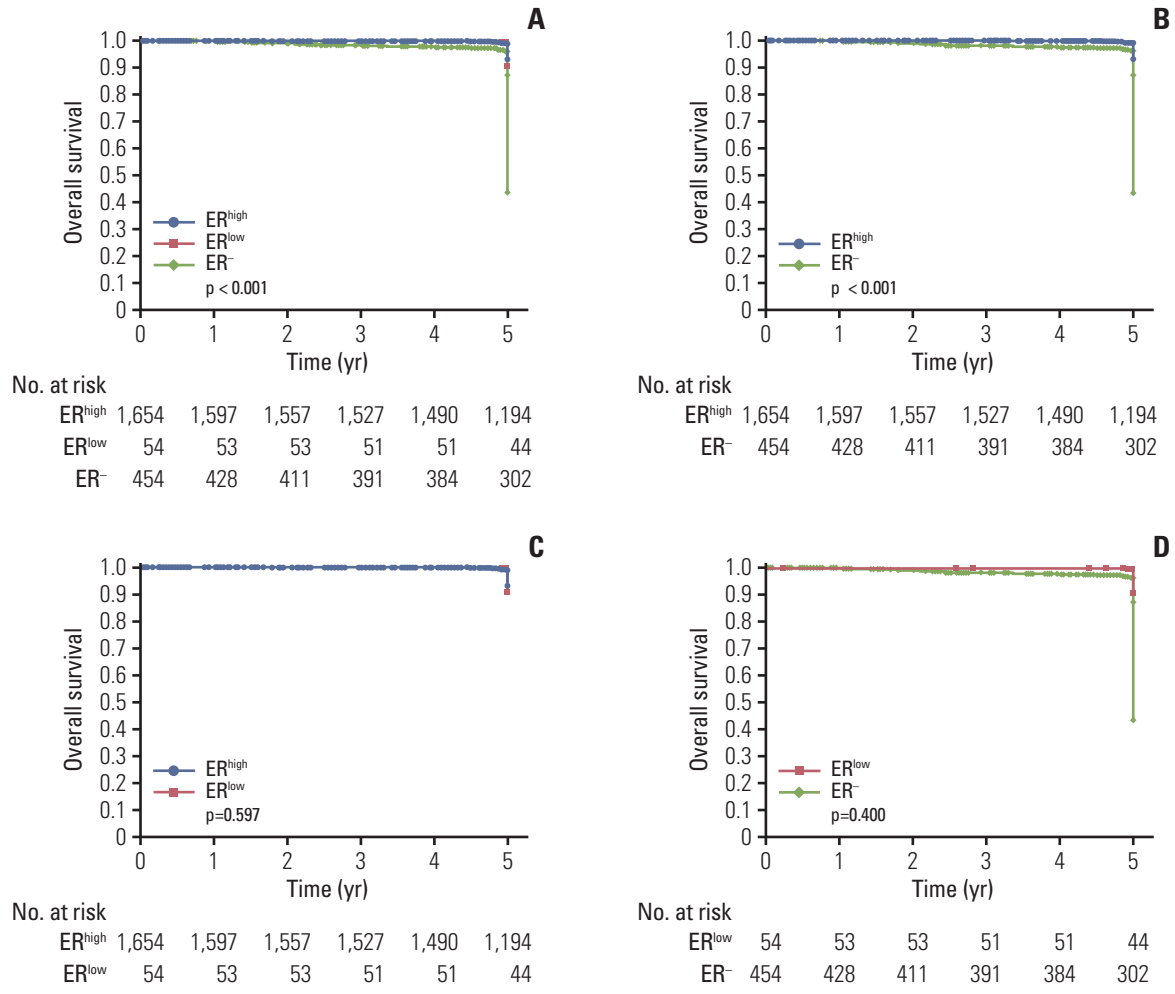

Fig. 1. Survival analysis between different estrogen receptor (ER) subgroups in early breast cancer patients. Difference in 5-year recurrence-free survival between ER^{high}/ER^{low}/ER^- (A), ER^{high}/ER^- (B), ER^{high}/ER^{low} (C), and ER^{low}/ER^- (D) patients. ER^-, estrogen receptor negative; ER^{high}, estrogen receptor high positive; ER^{low}, estrogen receptor low positive.

Risk factors for recurrence in the study population were analyzed by Cox proportional regression (Table 2). In univariate analysis, younger age, higher grade, ER^- status, higher Ki-67 expression, and omission of hormonal therapy were associated with increased risk of recurrence. In multivariate analysis, all factors except ER^- status and Ki-67 expression remained statistically significant. Subgroup analysis was performed for DCIS and IDC patients. In the DCIS group, only age was associated with recurrence (p=0.007). In the IDC group, univariate analysis revealed that younger age, higher grade, ER^- status, lower PR expression, higher Ki-67 expression, and omission of hormonal therapy were associated with higher recurrence rate. In multivariate analysis, only age and hormonal therapy remained statistically significant.

Discussion

ER plays an important role in the signaling pathway for breast cancer carcinogenesis and disease expression [13]. Hormonal therapy targeting ER including selective ER modulators, aromatase inhibitors, ER down-regulators, and ovarian suppression has led to significant improvement in the clinical outcome of breast cancer treatment [7]. ER^+ tumors show excellent response to hormonal therapy, and therapeutic effect depends on the proportion of ER expression [14,15]. In contrast, ER^- tumors show no response to hormonal therapy; however, these tumors respond relatively better to chemotherapy compared to ER^+ tumors [16]. Therefore, it is critical to set an optimal cutoff point for ER positivity to properly select patients eligible for individualized treatment options [17].

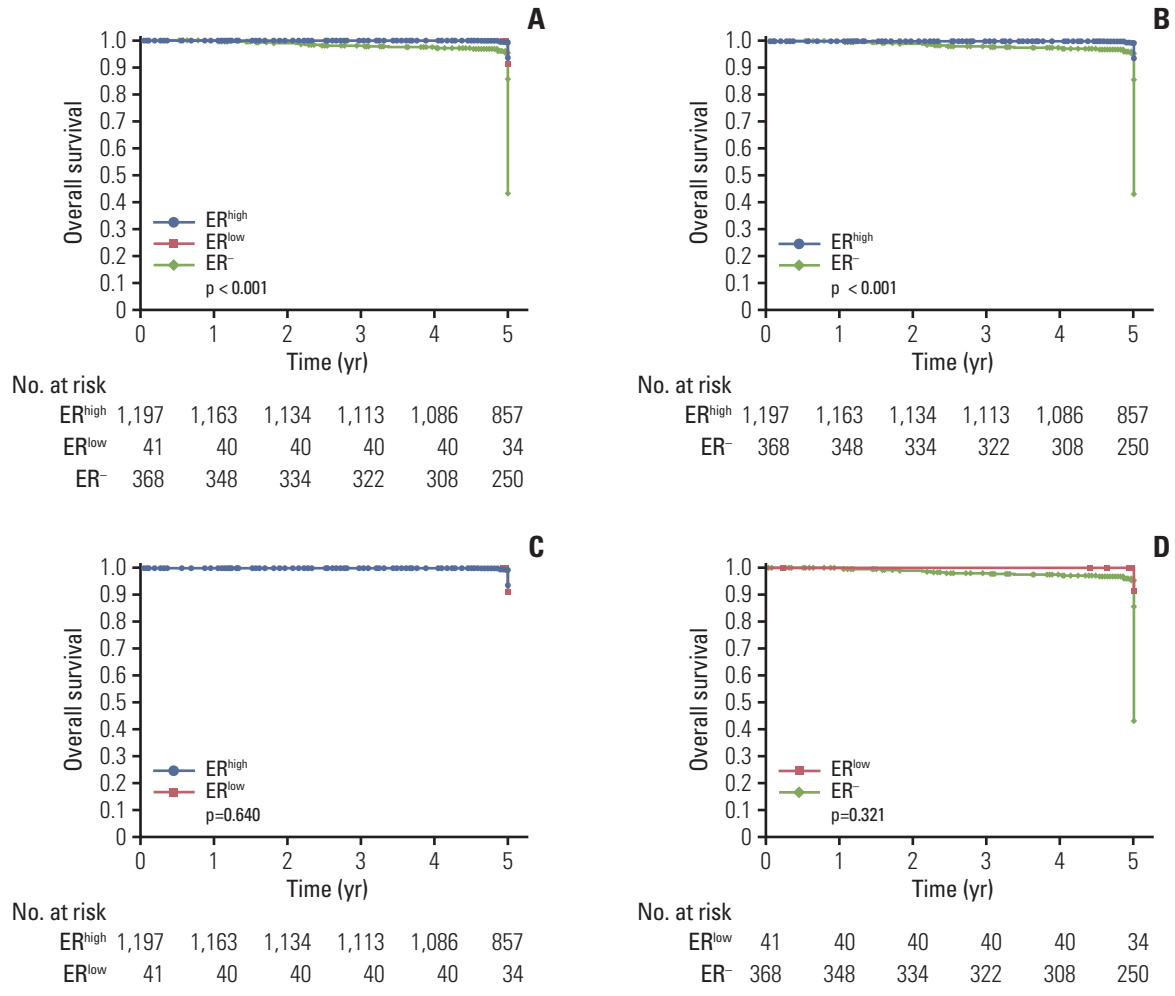

Fig. 2. Survival analysis between different estrogen receptor (ER) subgroups in early stage invasive ductal carcinoma patients. Difference in 5-year recurrence-free survival between ER^{high}/ER^{low}/ER^{-} (A), ER^{high}/ER^{-} (B), ER^{high}/ER^{low} (C), and ER^{low}/ER^{-} (D) patients. ER^{-}, estrogen receptor negative; ER^{high}, estrogen receptor high positive; ER^{low}, estrogen receptor low positive.

In 2010, the cutoff value for ER positivity was lowered to 1% from 10% by the ASCO/CAP guideline update [18]. Although the currently accepted cutoff is 1%, multiple studies have since reported that ER^{low} tumors with ER expression less than 10% show characteristics closer to ER^{-} tumors, including questionable response to hormonal therapy [10-12]. The latest recommendation of the ASCO/CAP guideline to report these tumors separately as ER low positive reflects this concern. If ER^{low} breast cancer is indeed a distinct disease subtype closer to ER^{-}, ER^{low} patients currently classified as ER^{+} will not only receive unnecessary hormonal treatment with potential side effects, but they might also fail to receive chemotherapy that is needed [17].

Several studies have addressed the clinicopathological features of ER^{low} tumors. Compared to ER^{high}, ER^{low} breast cancer is associated with younger age, advanced stage, larger tumor size, higher HER2 expression, and lower PR expression [19,20]. When morphologically analyzed, ER^{low} tumors exhibit features previously described for basal-like and triple-negative tumors, including higher grade, higher proliferation index, sheet-like growth pattern, intratumoral lymphocytic inflammatory infiltrate, and necrosis [12]. In our current study, we focused specifically on early stage breast cancer, a novel approach not presented in previous literature. ER^{low} tumors showed higher grade, positive HER2, negative PR, and higher proliferation index compared to ER^{high} tumors, which was consistent with previous studies. Age at diagnosis showed no statistically significant difference between ER^{low} and ER^{high} groups, and tumor size was smallest in the ER^{low} group compared to both ER^{high} and ER^{-} patients. Detailed morphological analysis was not performed in this study. Patients with ER^{high} tumors were more likely to

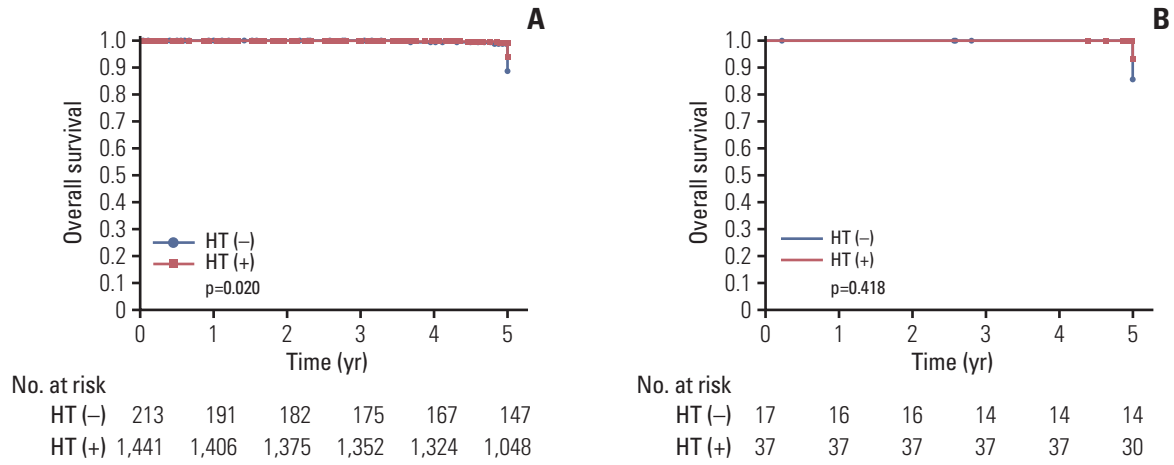

Fig. 3. Effect of estrogen receptor (ER) expression level on hormonal therapy (HT) response. (A) Difference in 5-year recurrence-free survival in ER^{high} patients. (B) Difference in 5-year recurrence-free survival in ER^{low} patients. ER^{high}, estrogen receptor high positive; ER^{low}, estrogen receptor low positive.

receive hormonal therapy compared to ER^{low} and ER^- groups; in contrast, a significantly small proportion of ER^{high} patients received chemotherapy in comparison to their ER^{low} or ER^- counterparts. This result was in concordance with previous literature [17,19,20].

Although limited data is available on the survival outcome of ER^{low} breast cancer, a few previous studies showed that ER^{low} patients exhibit significantly worse disease-free and overall survival rates compared to ER^{high} patients, but similar to those who are ER^- [11,21,22]. In the current study, the ER^{low} group had a slight, but not statistically significant, survival benefit over the ER^- group. At the same time, ER^{low} tumors showed worse prognosis compared to ER^{high} tumors, yet also with no statistical significance. Recurrence rate showed a proportional decrease with ER expression level. In multivariate regression analysis, we failed to prove the effect of ER expression level on recurrence. This study was confined to DCIS and stage I IDC, and the overall recurrence rate was low. It is possible that the low proportion of recurrent cases hindered to show a clear difference between ER subgroups. Future prospective studies with larger cohorts might validate the difference in survival outcome between ER^{low} and ER^{high} groups.

Most breast cancers exhibit either strong ER expression or its complete absence, and the number of patients in the ER^{low} subgroup is limited [23]. Therefore, prospective data on the endocrine responsiveness of ER^{low} tumors is scarce [19]. Yet many retrospective studies have suggested that primary breast cancer patients with low ER expression might not benefit significantly from hormonal therapy [17]. Viale et al. [21] compared disease-free and overall survival of ER^{low} and ER^- groups and reported that hormonal therapy had no effect on survival outcomes. In HER2-negative stage II/III breast cancer, ER^{low} tumors showed limited benefit from hormonal therapy and better response to neoadjuvant chemotherapy [24]. In our current study, we found that hormonal therapy had no effect on recurrence in ER^{low} patients; on the contrary, ER^{high} patients showed clear endocrine responsiveness. This suggests that hormonal therapy might have limited apparent benefit in early stage ER^{low} breast cancer.

ER^+ tumors have been subjected to multigene assays to identify more aggressive types that are expected to benefit from additional chemotherapy [12]. Our study sheds light on the possibility that early stage ER^{low} breast cancer might be a high risk subtype and potential candidate for chemotherapy. It is suggested that treatment options for ER^- tumors may be appropriate for some ER^{low} tumors; however, endocrine responsiveness of primary breast cancer patients with low ER expression needs to be further explored in prospective studies [20].

This study has certain limitations. First, the study was limited by its retrospective design, and treatment options were not assigned in a randomized manner. Second, although the current study was performed on a large cohort, the sample size of the ER^{low} group was relatively small. It is known that majority of breast cancers show either completely absent or strongly positive ER staining, and tumors with low ER expression are rare. Future studies with larger study populations could possibly overcome this limitation and provide more information on ER^{low} tumors.

In conclusion, ER^{low} breast cancer shows distinct clinicopathological features compared to ER^{high} and ER^- types. ER^{low} tumors seem to have higher recurrence rates compared to ER^{high} tumors, although future large scale prospective stud-

Table 2. Cox regression model for risk factors of recurrence in early breast cancer

	Total				DCIS				IDC			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)												
< 50	Reference		Reference		Reference		Reference		Reference		Reference	
≥ 50	0.51 (0.35-0.73)	< 0.001	0.46 (0.32-0.66)	< 0.001	0.29 (0.12-0.72)	0.007	0.29 (0.12-0.72)	0.007	0.57 (0.38-0.86)	0.007	0.53 (0.36-0.80)	0.002
Type												
DCIS	Reference											
IDC	1.20 (0.80-1.80)	0.390	-	-	-	-	-	-	-	-	-	-
Grade												
1	Reference		Reference						Reference		Reference	
2	2.06 (1.10-3.87)	0.025	1.90 (1.00-3.61)	0.050	-	-	-	-	2.06 (1.10-3.87)	0.025	1.89 (0.99-3.61)	0.054
3	3.07 (1.65-5.73)	< 0.001	2.18 (1.05-4.52)	0.036	-	-	-	-	3.08 (1.65-5.73)	< 0.001	2.12 (0.99-4.54)	0.052
LVI												
No	Reference								Reference			
Yes	1.46 (0.90-2.37)	0.131	-	-	-	-	-	-	1.46 (0.90-2.37)	0.130	-	-
ER												
ER^{high}	Reference		Reference		Reference				Reference		Reference	
ER^{low}	1.34 (0.49-3.65)	0.571	0.95 (0.50-1.82)	0.882	1.31 (0.18-9.63)	0.793	-	-	1.36 (0.43-4.33)	0.606	1.09 (0.29-4.14)	0.897
ER^{-}	1.96 (1.35-2.85)	< 0.001	0.94 (0.34-2.64)	0.907	0.74 (0.23-2.46)	0.626	-	-	2.29 (1.52-3.44)	< 0.001	1.27 (0.36-4.44)	0.707
PR												
Positive	Reference				Reference				Reference		Reference	
Negative	1.20 (1.00-1.43)	0.054	-	-	0.81 (0.48-1.37)	0.426	-	-	1.62 (1.09-2.42)	0.018	0.52 (0.21-1.33)	0.175
HER2												
Positive	Reference								Reference			
Negative	0.76 (0.27-2.19)	0.613	-	-	-	-	-	-	0.77 (0.38-1.57)	0.477	-	-
Ki-67												
< 14	Reference		Reference		Reference				Reference		Reference	
≥ 14	1.66 (1.18-2.34)	0.004	1.00 (0.64-1.57)	0.989	1.13 (0.46-2.76)	0.794	-	-	1.79 (1.21-2.64)	0.003	0.99 (0.60-1.65)	0.971
HT												
No	Reference		Reference		Reference				Reference		Reference	
Yes	0.50 (0.35-0.70)	< 0.001	0.45 (0.25-0.79)	0.006	0.75 (0.37-1.54)	0.754	-	-	0.40 (0.27-0.59)	< 0.001	0.30 (0.12-0.77)	0.012
CT												
No	Reference								Reference			
Yes	1.06 (0.73-1.52)	0.777	-	-	-	-	-	-	1.00 (0.67-1.50)	0.985	-	-

CI, confidence interval; CT, chemotherapy; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; ER^{-}, estrogen receptor negative; ER^{high}, estrogen receptor high positive; ER^{low}, estrogen receptor low positive; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HT, hormonal therapy; IDC, invasive ductal carcinoma; LVI, lymphovascular invasion; PR, progesterone receptor.

ies are necessary. Similar to patients with ER- tumors, those with ER^{low} tumors do not appear to benefit from hormonal therapy. Treatment options for ER^{low} breast cancer should be reconsidered, including omission of hormonal therapy and addition of adjuvant chemotherapy.

Ethical Statement

This study was approved by the institutional review board of (blinded for review) (IRB No. B-2105-682-103). All procedures performed were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Author Contributions

Conceived and designed the analysis: Kang E, Kim EK, Shin HC.
Collected the data: Kim SM, Jang M, Yun BL, Park SY.
Contributed data or analysis tools: Yoon KH, Park Y.
Performed the analysis: Yoon KH, Park Y.
Wrote the paper: Yoon KH, Park Y.
Critical revision of the manuscript for important intellectual content: Kim JH, Kim SH, Suh KJ.
Study supervision: Shin HC.

ORCID iDs

Kyung-Hwak Yoon : https://orcid.org/0000-0002-6206-7767
Yeshong Park : https://orcid.org/0000-0002-0638-3001
Hee-Chul Shin : https://orcid.org/0000-0001-6512-2218

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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