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Characteristics and Prognosis of Estrogen Receptor Low-Positive Breast Cancer

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Conflict of Interest
The authors declare that they have no competing interests.

ABSTRACT

Purpose: The updated American Society of Clinical Oncology/College of American Pathologists guideline for estrogen receptor (ER) testing recommends that breast cancer with ER expression in 1–10% of tumor cells should be reported as ER-low positive (ER^{low}), although limited data are available on the overall benefits of endocrine therapy. We investigated the clinicopathological characteristics and clinical outcomes of ER^{low} breast cancer and to compare them with those of ER-negative (ER^{neg}) and ER-high (> 10% of tumor cells, ER^{high}) breast cancers.
Methods: Consecutive patients with invasive breast cancer who underwent curative surgery between November 2007 and December 2014 were included. Clinicopathological characteristics and disease-free survival (DFS) of ER^{low} tumors were compared with those of ER^{neg} and ER^{high} tumors.
Results: Of the 2,309 cases included, 46 (2%), 643 (27.8%), and 1,620 (70.2%) were ER^{low}, ER^{neg}, and ER^{high}, respectively. ER^{low} tumors were associated with no special type of histology (p = 0.011), advanced pT (p = 0.017), pN (p = 0.009) and anatomic stages (p < 0.001), high grade (p < 0.001), negative/low progesterone receptor (PR) status (p < 0.001), human epidermal growth factor receptor 2 positivity (p < 0.001), high Ki-67 (p < 0.001), and recurrence (p = 0.006) compared to ER^{high} tumors. DFS was significantly dependent on ER status, and ER^{low} tumors showed poorer DFS than ER^{high} tumors (p = 0.001), however, there was no significant survival difference between ER^{low} and ER^{neg} tumors. Furthermore, DFS in ER^{high} patients was affected by hormone therapy (p < 0.001), while it was not affected in ER^{low} patients.
Conclusion: Patients with ER^{low} breast cancer have clinicopathological characteristics that differ from those with ER^{high} tumors. Although this study was limited by the small sample size of the ER^{low} group, no benefit from hormone therapy was observed in the ER^{low} group compared with the ER^{high} group.

Keywords: Breast Neoplasms; Estrogen Receptor; Immunohistochemistry; Prognosis

INTRODUCTION

Breast cancer is a heterogeneous disease in biology and behavior and is the most common malignancy among females worldwide and in Korea [1,2]. Invasive breast cancers (IBCs) can be grouped into biomarker-defined subtypes for treatment purposes based on the status

Author Contributions

Conceptualization: Bae YK; Data curation: Kim MC, Park MH, Choi JE, Kang SH; Formal analysis: Kim MC, Park MH, Choi JE, Kang SH, Bae YK; Supervision: Bae YK; Writing - original draft: Kim MC, Park MH, Bae YK; Writing - review & editing: Choi JE, Kang SH, Bae YK.

of hormone receptors (HRs) (estrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor receptor 2 (HER2) [3]. Therefore, an assessment of HR and HER2 status is mandatory in all IBC cases.

ER is an important prognostic and predictive marker for the benefit of endocrine therapy. According to Korean Breast Cancer Society data from 2002 to 2018 [2], the incidence of HR-positive breast cancer has increased by more than 1% annually since 2002, 58.2% of breast cancers were ER-positive in 2002, and 78.9% displayed ER positivity in 2018 [2]. Threshold changes in ER-positive expression, advances in immunohistochemistry (IHC) techniques, and the development of highly sensitive antibodies probably contributed to this increase in ER-positive tumors. IHC has been the gold standard method for ER determination in surgical specimens, and a 10% cutoff was widely used to define ER positivity until the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) released guidelines for ER and PR testing of breast cancer in 2010 [4,5]. Subsequently, ≥ 1% tumor cell immunoreactivity for ER or PR was interpreted as positive, according to the ASCO/CAP guidelines. However, a recently updated ASCO/CAP guideline recommends that cases with 1%–10% tumor cell staining should be reported as ER-low positive (ER^{low}), with a comment explaining that there is limited data on the overall benefit of endocrine therapy, although these patients may benefit [6]. Approximately 2%–3% of breast cancers have been reported to be ER^{low}, which are known to be heterogeneous in terms of their biological behavior and clinicopathological characteristics [7-9].

In this study, we aimed to investigate the clinicopathological characteristics and prognosis of ER^{low} breast cancer and to compare them with those of ER-negative (< 1% of tumor cells positive, ER^{neg}) and ER-high (> 10% of tumor cell positive, ER^{high}) breast cancers.

METHODS

This study included 2,309 consecutive cases with primary IBC who underwent curative surgery at Yeungnam University Hospital between November 2007 and December 2014. IHC staining for ER, PR, HER2, and Ki-67 was performed routinely in all primary and recurrent breast cancers. Patients with metachronous contralateral advanced stage breast cancer, microinvasive carcinoma, or those who received neoadjuvant chemotherapy were excluded. Patients' clinicopathological information (age at diagnosis, sex, date and method of operation, extent of axillary dissection, tumor size, histological grade, histological type, lymphovascular invasion, pathological T and N stages, IHC results for ER, PR, HER2, and Ki-67, and clinical outcomes) were obtained from medical records and pathology reports. Since December 2008, SP1 monoclonal antibody has been used for ER staining. The percentages of cells positive for ER or PR estimated by visual assessment under a microscope were recorded in pathology reports. Ki-67 result was expressed as the percentage of positively staining cells among the total number of tumor cells by counting of at least 500 invasive cancer cells. In cases with equivocal HER2 IHC results, the presence or absence of gene amplification was routinely confirmed by *in situ* hybridization according to the ASCO/CAP guidelines [10].

The cases were classified into 3 groups: ER^{neg} (< 1% of tumor cells positive), ER^{low} (1%–10% of tumor cells positive), and ER^{high} (> 10% of tumor cells positive) based on IHC results for ER. Ki-67 results were classified as low (< 20%) or high (≥ 20%) [11]. Disease-free survival

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(DFS) was defined as the time from the date of diagnosis to the date of first recurrence (local recurrence or distant metastasis).

Statistical analysis was performed using SPSS version 25.0 for Windows (IBM, Armonk, USA). Comparisons of group clinicopathological characteristics were made using the χ^2, Fisher's exact, Kruskal-Wallis, and Mann-Whitney tests. Survival analysis was performed using the Kaplan-Meier method, and group survival differences were compared using the log-rank test. Univariate and multivariate Cox regression analyses were performed to determine the prognostic impact of variables on recurrence. The significant variables identified in the univariate analysis were further analyzed by multivariate analysis using backward stepwise selection. Adjusted hazard ratios and associated 95% confidence intervals were calculated for each variable. The *p*-values of < 0.05 were considered statistically significant.

This study was approved by the institutional review board of Yeungnam University Medical Center (YUMC2022-01-005), which waived the requirement for informed consent.

RESULTS

Of the 2,309 patients with IBC, 2,304 were females, and 5 were males. A total of 1,267 (54.9%) patients underwent breast-conserving surgery, while 1,042 (45.1%) patients underwent mastectomy. Axillary lymph node dissection was performed in 813 (35.2%) patients and 1,487 (64.4%) patients underwent sentinel lymph node biopsy alone. Nine patients (0.4%) did not undergo a sentinel lymph node biopsy or axillary lymph node dissection. There were 46 (2%), 643 (27.8%) and 1,620 (70.2%) cases of ER^{low}, ER^{neg} and ER^{high}, respectively. The clinicopathological characteristics of the patients stratified by ER expression status are summarized in **Table 1**. Compared to ER^{neg} or ER^{high} tumors, ER^{low} tumors were more likely to be invasive carcinoma of no special type ($p = 0.041$ and $p = 0.011$, respectively), more frequently presented in advanced pN ($p = 0.042$ and $p = 0.009$, respectively) and anatomic ($p = 0.017$ and $p < 0.001$, respectively) stages and were more likely to be HER2-positive ($p = 0.002$ and $p < 0.001$, respectively). Furthermore, these tumors were present more frequently in advanced pT ($p = 0.017$) and were associated with a higher grade ($p < 0.001$), negative/low PR status ($p < 0.001$) and high Ki-67 status ($p < 0.001$) than ER^{high} tumors. Patients with ER^{low} tumors received chemotherapy more frequently ($p < 0.001$) but less frequently received hormone therapy ($p < 0.001$) than those with ER^{high} tumors. ER^{low} tumors were more strongly associated with lymph node metastasis ($p = 0.008$) and PR positivity ($p < 0.001$) than ER^{neg} tumors.

Recurrence included locoregional and distant metastasis. During a median follow-up period of 99 months (range, 1–165 months), recurrence occurred in 266 (11.5%) patients. The recurrence rate for ER^{low} tumors was higher than that for ER^{high} tumors ($p = 0.006$). DFS was significantly influenced by ER status ($p < 0.001$, **Figure 1A**). Pairwise comparisons showed that ER^{high} tumors were associated with better DFS than ER^{neg} ($p = 0.001$) and ER^{low} ($p = 0.001$) tumors, but DFSs of ER^{neg} and ER^{low} tumors were not significantly different ($p = 0.105$). Similar results were found in patients who received hormone therapy (n = 1,658) (**Figure 1B**).

Anti-HER2 therapy affects the survival outcomes of patients with HER2- positive breast cancer. Because our study population was heterogeneous regarding indications for anti-HER2 therapy, we performed a survival analysis in patients who underwent surgical

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Table 1. Clinicopathological characteristics and biomarkers according to ER expression in invasive breast carcinomas

Clinicopathologic factor	ER expression				*p*-value		
	Total (n = 2,309)	Negative (n = 643)	Low (n = 46)	High (n = 1,620)	All	Negative vs. Low	Low vs. High
Age (yr)	50 (26–90)	52 (26–90)	49.5 (30–73)	49 (26–87)	< 0.001	0.087	0.812
Tumor size (cm)	1.8 (0.2–12)	2 (0.2–12)	2.2 (0.4–6.9)	1.7 (0.2–12)	< 0.001	0.313	0.003
Histologic type					0.001	0.041	0.011
IC-NST	2,055 (89)	591 (91.9)	46 (100)	1,418 (87.5)			
Others	254 (11)	52 (8.1)	0 (0)	202 (12.5)			
LN metastasis					0.003	0.008	0.072
Absent	1,388 (60.3)	416 (65)	21 (45.7)	951 (58.9)			
Present	912 (39.7)	224 (35)	25 (54.3)	663 (41.1)			
pT					< 0.001	0.577	0.017
1	1,430 (61.9)	343 (53.3)	20 (43.5)	1,067 (65.9)			
2	791 (34.3)	270 (42)	24 (52.2)	497 (30.7)			
3	84 (3.6)	28 (4.4)	2 (4.3)	54 (3.3)			
4	4 (0.2)	2 (0.3)	0 (0)	2 (0.1)			
pN					< 0.001	0.042	0.009
0	1,388 (60.3)	416 (65)	21 (45.7)	951 (58.9)			
1	593 (25.8)	128 (20)	12 (26.1)	453 (28.1)			
2	175 (7.6)	40 (6.3)	6 (13)	129 (8)			
3	144 (6.3)	56 (8.8)	7 (15.2)	81 (5)			
Anatomic stage					< 0.001	0.004	< 0.001
I	1,092 (47.5)	270 (42.1)	13 (28.3)	809 (50.1)			
II	867 (37.7)	269 (42)	18 (39.1)	580 (35.9)			
III	329 (14.3)	98 (15.3)	13 (28.3)	218 (13.5)			
IV	13 (0.6)	4 (0.6)	2 (4.3)	7 (0.4)			
Grade					< 0.001	0.768	< 0.001
1	357 (15.5)	3 (0.5)	0 (0)	354 (21.9)			
2	623 (27)	42 (6.5)	4 (8.7)	577 (35.6)			
3	1,329 (57.6)	598 (93)	42 (91.3)	689 (42.5)			
LVI					< 0.001	0.206	0.982
Absent	1,268 (54.9)	396 (61.6)	24 (52.2)	848 (52.3)			
Present	1,041 (45.1)	247 (38.4)	22 (47.8)	772 (47.7)			
PR					< 0.001	< 0.001	< 0.001
Negative	856 (37.1)	620 (96.4)	36 (78.3)	200 (12.3)			
Positive	1,453 (62.9)	23 (3.6)	10 (21.7)	1,420 (87.7)			
HER2					< 0.001	0.002	< 0.001
Negative	1,845 (79.9)	411 (63.9)	19 (41.3)	1,415 (87.3)			
Positive	464 (20.1)	232 (36.1)	27 (58.7)	205 (12.7)			
Ki-67					< 0.001	0.140	< 0.001
Low (< 20%)	793 (34.3)	45 (7)	6 (13)	742 (45.8)			
High (≥ 20%)	1,516 (65.7)	598 (93)	40 (87)	878 (54.2)			
Hormone therapy					< 0.001	< 0.001	< 0.001
No	651 (28.2)	603 (93.8)	18 (39.1)	30 (1.9)			
Yes	1,658 (71.8)	40 (6.2)	28 (60.9)	1,590 (98.1)			
Chemotherapy					< 0.001	0.608	< 0.001
No	820 (35.5)	87 (13.5)	5 (10.9)	728 (44.9)			
Yes	1,489 (64.5)	556 (86.5)	41 (89.1)	892 (55.1)			
Recurrence					< 0.001	0.078	0.006
No	2,043 (88.5)	551 (85.7)	35 (76.1)	1,457 (89.9)			
Yes	266 (11.5)	92 (14.3)	11 (23.9)	163 (10.1)			

Values are presented as median (range) or number (%).
ER = estrogen receptor; IC-NST = invasive carcinoma of no special type; LN = lymph node; LVI = lymphovascular invasion; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.

treatment during the period in which trastuzumab was approved as an adjuvant treatment for HER2-positive breast cancer. Of the 1,811 patients who underwent surgical treatment after July 2009 (483 ER^{neg}, 38 ER^{low}, and 1,290 ER^{high}), 360 (19.9%) had HER2-positive breast cancer (176 ER^{neg}, 22 ER^{low}, and 162 ER^{high}). Of these, 288 patients with lymph node metastasis or tumors > 1 cm were eligible for adjuvant anti-HER2 therapy according to the Korean medical

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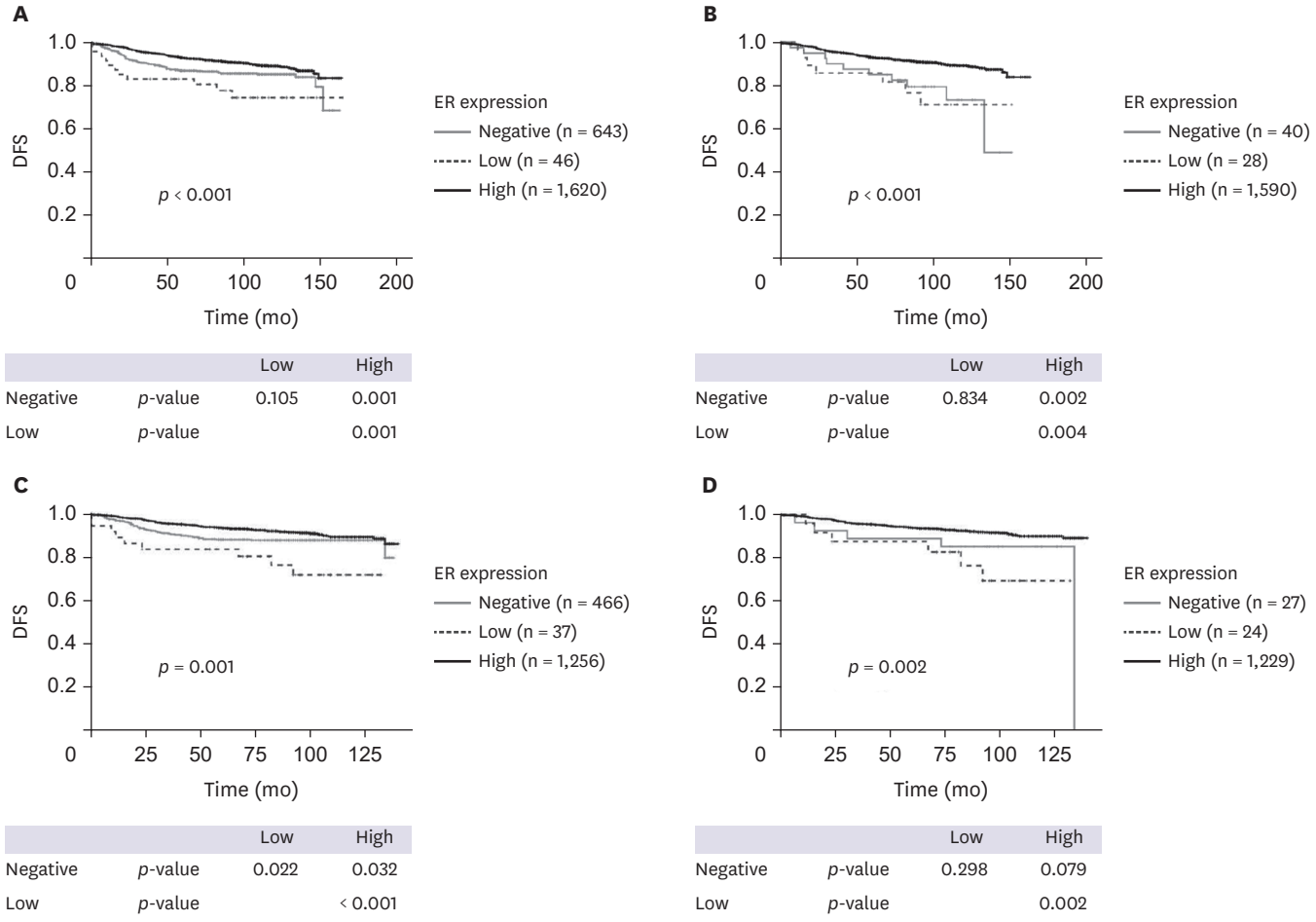

Figure 1. DFS according to ER status in (A) 2,309 patients with IBC and (B) 1,658 patients with IBC who received hormone therapy. DFS according to ER status in (C) 1,759 patients with IBC who underwent surgical treatment during the period when trastuzumab was available as adjuvant therapy for HER2-positive breast cancer and (D) 1,280 patients with IBC who received hormone therapy among the 1,759 patients.
DFS = disease-free survival; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IBC = invasive breast cancer.

insurance guidelines, and 236 of them received trastuzumab treatment. After excluding 52 HER2-positive breast cancer patients who did not receive trastuzumab (17 ER^{neg}, 1 ER^{low}, and 34 ER^{high}), 1,759 of the 1,811 patients were finally included in the survival analysis. In this cohort, the ER^{low} group showed the worst DFS among the 3 groups ($p = 0.001$) and there were significant differences in the DFSs of ER^{neg} and ER^{low} tumors ($p = 0.022$), ER^{low} and ER^{high} tumors ($p < 0.001$), and ER^{neg} and ER^{high} tumors ($p = 0.032$) (**Figure 1C**). In a cohort of 1,759 patients, 1,280 received hormone therapy, of which ER^{high} tumors had better DFS than ER^{low} tumors ($p = 0.002$) (**Figure 1D**).

Some ER^{low} and ER^{high} patients did not receive hormone therapy due to the different thresholds of ER positivity (10%) applied in earlier cases and treatment refusal. When the DFSs of patients who received or did not receive hormone therapy-were compared to evaluate endocrine responsiveness, ER^{high} patients who received hormone therapy had significantly better DFS ($p = 0.001$) (**Figure 2A**). However, the DFS of ER^{low} patients who received or did not receive hormone therapy were similar ($p = 0.979$) (**Figure 2B**).

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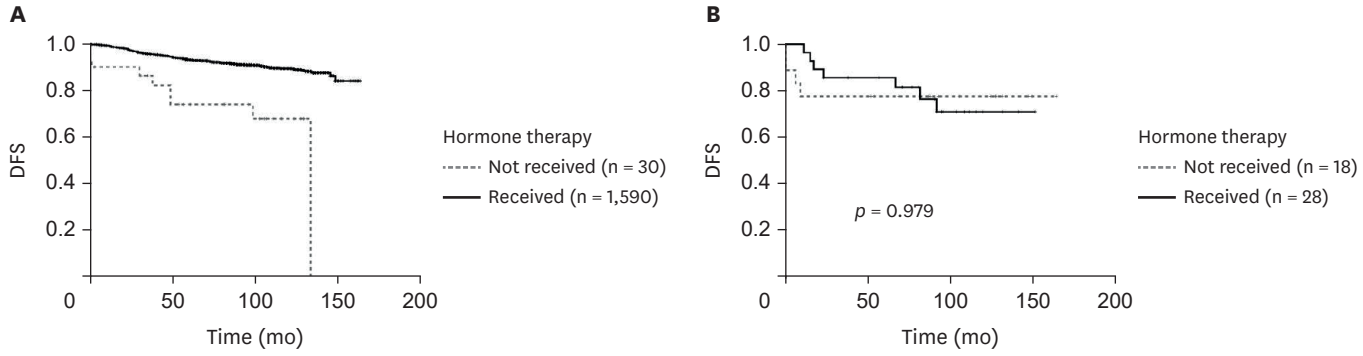

Figure 2. DFS according to hormone therapy in patients with (A) ER^{high} or (B) ER^{low} breast cancer.
DFS = disease-free survival; ER^{high} = estrogen receptor-high; ER^{low} = estrogen receptor-low positive.

In addition to ER status, histological grade 3, large tumor size (≥ 2 cm), lymph node metastasis, lymphovascular invasion, PR negative, HER2 positive, high Ki-67, chemotherapy status, and omission of hormone therapy were found to be associated with a higher risk of recurrence in univariate analyses. However, in the multivariate analysis, ER status was not an independent factor for DFS, but histological grade 3, large tumor size (≥ 2 cm), lymph node metastasis, lymphovascular invasion and PR negativity were independently significant factors for poorer DFS (**Table 2**).

Table 2. Univariate and multivariate analyses of clinicopathologic factors affecting disease-free survival

Clinicopathologic factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
ER expression		< 0.001		
Positive	Reference			
Negative	1.548 (1.199–1.999)	0.001	-	-
Low positive	2.593 (1.407–4.777)	0.002	-	-
Histologic grade				
1 & 2	Reference		Reference	
3	2.988 (2.221–4.021)	< 0.001	1.915 (1.380–2.656)	< 0.001
Tumor size				
≤ 2 cm	Reference		Reference	
> 2 cm	2.573 (2.015–3.287)	< 0.001	1.515 (1.161–1.978)	0.002
LN metastasis				
Absent	Reference		Reference	
Present	2.538 (1.981–3.250)	< 0.001	1.405 (1.051–1.879)	0.022
LVI				
Absent	Reference		Reference	
Present	3.243 (2.483–4.237)	< 0.001	2.247 (1.648–3.065)	< 0.001
PR expression				
Positive	Reference		Reference	
Negative	1.651 (1.298–2.101)	< 0.001	1.369 (1.054–1.777)	0.019
HER2 status				
Negative	Reference			
Positive	1.382 (1.046–1.826)	0.023	-	-
Ki-67				
Low (< 20%)	Reference			
High (≥ 20%)	2.377 (1.743–3.241)	< 0.001	-	-
Chemotherapy				
No	Reference			
Yes	2.360 (1.735–3.212)	< 0.001	-	-
Hormone therapy				
No	Reference			
Yes	0.640 (0.498–0.823)	< 0.001	-	-

HR = hazard ratio; CI = confidence interval; ER = estrogen receptor; LN = lymph node; LVI = lymphovascular invasion; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.

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DISCUSSION

ER status was incorporated into the 8th American Joint Committee on Cancer pathological prognostic stage (PPS) together with PR, HER2, and histological grade [12]. In PPS, IBC patients with a positive ER status (including ER^{high} and ER^{low}) were downstaged compared with the corresponding anatomic stage. Therefore, the biological behavior of ER^{low} cases needs to be clearly defined because downstaging ER^{low} cases can lead to undertreatment, even if they are biologically similar to ER^{neg} cases.

In the present study, ER^{low} cases constituted 2% (46/2,309) of all IBC cases and 2.8% (46/1,666) of ER-positive IBC cases, which is consistent with previous studies that reported ER^{low} cases accounted for 2%–5.1% of all IBC and 2.5%–7.4% of ER-positive IBC cases [6,7,9,13-15]. Some studies [9,13] have defined ER^{low} as 1%–9% positive staining instead of 1%–10% (the ASCO/CAP definition). Furthermore, a recent study that used tissue microarray IHC data reported a slightly higher incidence of ER^{low} cases (3% of all IBCs and 4.1% of ER-positive IBCs) [8].

Most ER^{low} cases (93.5%) in the present study and > 50% of ER^{low} cases in previous studies presented with low or negative PR expression [7-9], which may contribute to the lack of significant survival benefits of adjuvant hormone therapy for patients with ER^{low} IBC. Previous studies have reported HER2 positivity in 29%–60% of ER^{low} cases [7-9]. Furthermore, the current study revealed that ER^{low} IBCs are heterogeneous, with some cases similar to triple-negative breast cancer and others similar to HER2-positive breast cancer.

Regarding clinicopathological characteristics, ER^{low} cases were associated with younger age, larger tumor size, higher histological grade, higher pN, more advanced stage, higher Ki-67, and higher HER2 positivity and PR negativity than ER^{high} cases [7-9,14,16]. Our results are consistent with those of previous studies, as ER^{low} tumors presented with more advanced pT, pN, and anatomic stages, higher histological grade and Ki-67, and negative/low PR and positive HER2 statuses than ER^{high} tumors. Furthermore, ER^{low} cases were more associated with lymph node metastasis, advanced pN and anatomic stage, and positive PR and HER2 statuses than ER^{neg} cases. These findings are partially consistent with the observations of previous studies in which ER^{low} tumors frequently presented at a younger age, lower grade, more lymphovascular invasion, PR positivity, HER2 positivity, lower Ki-67, and lower basal marker expression than ER^{neg} tumors [7-9]. As shown in **Table 1** and as reported by Yu et al. [16], the difference in clinicopathological characteristics between ER^{low} and ER^{high} tumors was greater than the difference between ER^{low} and ER^{neg} tumors.

Regarding survival outcomes for ER^{low} tumors, a previous large cohort study reported that ER^{low} tumors (n = 250) had poorer distant recurrence-free survival (DRFS), recurrence-free survival (RFS) and overall survival (OS) than ER^{high} tumors (n = 7,764) regardless of endocrine therapy, but DRFSs, RFSs and OSs were similar to ER^{neg} tumors (n = 1,625) [13]. Poon et al. [8] reported that the DFS of ER^{low} tumor (n = 54) was significantly worse than that of ER^{high} tumors (n = 1,266), but comparable to that of ER^{neg} tumors (n = 503). We also observed that DFS was poorer for ER^{low} tumors than ER^{high} tumors, and no significant differences were observed between DFSs of ER^{low} and ER^{neg} tumors. However, other studies have reported contradictory results. Fei et al. [7] reported that ER^{low} tumor (n = 97) had better RFS and disease-specific survival (DSS) than ER^{neg} tumors (n = 1,100), and no significant differences were observed between RFSs and DSSs of ER^{low} and ER^{high} (n = 2,982) tumors. These diverse

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clinical outcomes may be explained by different clinicopathological characteristics of ER^{low} tumors in the study population, such as PR positive rates (20%–75%) and proportions of patients who received hormone therapy (20%–66%) or chemotherapy (49%–97%) [7,8,13]. The HER2 positivity rate and the proportion of patients who received anti-HER2 therapy would also affect survival outcomes. In Korea, trastuzumab was first approved for metastatic HER2-positive breast cancer in September 2006, and its use was expanded in July 2009 as an adjuvant treatment for HER2-expressing node-positive breast cancer. Approximately a year later, it was also approved for use in node-negative breast cancer patients with tumors > 1 cm. Therefore, we performed a survival analysis on patients who underwent surgical treatment after July 2009, when trastuzumab administration was possible in the adjuvant setting. In this cohort (n = 1,759), ER^{low} tumors had poorer DFS than ER^{high} or ER^{neg} tumors. The worst survival in patients with ER^{low} tumors is probably due to advanced anatomic stage compared to those with ER^{high} or ER^{neg} tumors.

In addition to our study, a recent Korean study [9] also showed that adjuvant hormone therapy did not have an effect on DFS in patients with ER^{low} tumor, and that patients with ER^{high} tumors showed clear endocrine responsiveness. These results support the notion that hormone therapy has limited benefits for ER^{low} breast cancer patients. Cai et al. [15] recently reported that short-term endocrine therapy for 2–3 years might be an alternative for patients with ER^{low} breast cancer instead of standard 5 years of treatment because there was no significant difference in DFS between the 2 groups. We did not observe differences in DFS of patients with ER^{low} according to hormone therapy, although the comparison was made with a small number of patients. A meta-analysis of 6 studies also revealed a lack of benefit of endocrine therapy in patients with ER^{low} tumors because patients with ER^{low} tumors who received endocrine therapy showed a prognosis similar to those without endocrine therapy and those with ER^{neg} tumors who received endocrine therapy [16].

There are several limitations to this study. First, it is limited by its retrospective nature and the small number of patients (n = 46) with an ER^{low} tumor, which prevented the subgroup analysis according to adjuvant treatment options and pathologic features of ER^{low} tumors. However, to the best of our knowledge, the present study was conducted in the largest cohort of Korean IBCs (n = 2,309) with a long median follow-up of 99 months to elucidate the clinicopathological characteristics and survival outcomes after treatment of ER^{low} tumors. Second, most patients with an ER^{low} tumor received adjuvant chemotherapy or anti-HER2 therapy, which may have influenced the clinical outcomes of ER^{low} tumors, although it should be noted that all patients received standard treatment at the time of diagnosis. We suggest a large nationwide multicenter study to overcome these limitations and provide detailed information on the biological characteristics of ER^{low} breast cancer.

In summary, ER^{low} breast cancers are heterogeneous and have distinct clinicopathological features that differentiate them from ER^{high} and ER^{neg} breast cancers. Patients with ER^{low} tumors have poorer DFSs than those with ER^{high} tumors. Furthermore, no benefit from hormone therapy was observed in the ER^{low} group compared to the ER^{high} group, although this study was limited by the small sample size of the ER^{low} group.

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