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Breast Cancer

Hormone Receptor Subtype in Ductal Carcinoma in Situ: Prognostic and Predictive Roles of the Progesterone Receptor

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Breast neoplasms • Ductal carcinoma in situ • Estrogen receptor • Hormone receptor subtype • Progesterone receptor

Abstract

Background. We investigated the prognostic and predictive roles of the hormone receptor (HRc) subtype in patients with ductal carcinoma in situ (DCIS). We focused on identifying the roles of the progesterone receptor (PR) independent of estrogen receptor (ER) status.

Methods. Nationwide data of 12,508 female patients diagnosed with DCIS with a mean follow-up period of 60.7 months were analyzed. HRc subtypes were classified as ER−/PR−, ER−/PR+, ER+/PR−, and ER+/PR+ based on ER and PR statuses. The Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results. The ER+/PR+ group showed better prognoses than the ER+/PR− and ER−/PR− groups in the patients who received tamoxifen therapy ($p = .001$ and $p = .031$, respectively). HRc subtype was an independent prognostic factor ($p = .028$). The tamoxifen therapy group showed better survival than the patients who did not receive tamoxifen, but only in the ER+/PR+ subgroup ($p = .002$). Tamoxifen therapy was an independent prognostic factor (HR, 0.619; 95% CI, 0.423−0.907; $p = .014$). PR status was a favorable prognostic factor in patients with DCIS who received tamoxifen therapy ($p < .001$), and it remained a prognostic factor independent of ER status (HR, 0.576; 95% CI, 0.349−0.951; $p = .031$).

Conclusion. The HRc subtype can be used as both a prognostic and predictive marker in patients with newly diagnosed DCIS. Tamoxifen therapy can improve overall survival in the ER+/PR+ subtype. PR status has significant prognostic and predictive roles independent of ER status. Testing for the PR status in addition to the ER status is routinely recommended in patients with DCIS to determine the HRc subtype in clinical settings. ***The Oncologist*** 2021;26:e1939–e1950

Implications for Practice: The hormone receptor (HRc) subtype was an independent prognostic factor, and the estrogen receptor (ER)+/progesterone receptor (PR)+ subtype showed a better survival in patients with ductal carcinoma in situ (DCIS) who received tamoxifen therapy. PR was an independent prognostic factor independent of ER, and PR was a favorable prognostic factor in patients with DCIS who received tamoxifen therapy. The HRc subtype could be used as both a prognostic and predictive marker in patients with newly diagnosed DCIS. Testing of PR status in addition to ER status is routinely recommended for patients with DCIS to determine the HRc subtype in clinical settings.

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Introduction

According to the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines, a routine test to assess the estrogen receptor (ER) status in ductal carcinoma in situ (DCIS) is recommended to determine the potential benefit of endocrine therapy for the risk reduction of subsequent breast cancer [1]. However, testing DCIS for progesterone receptor (PR) status remains optional because there are no solid data supporting the prognostic or predictive value of PR independent of ER. The current National Comprehensive Cancer Network (NCCN) guidelines also recommend testing for only ER status, not PR status, in DCIS to determine the benefits of adjuvant endocrine therapy or risk reduction. Thus, the prognostic and predictive roles of PR status, independent of ER status, in DCIS must be validated.

Furthermore, the prognostic benefits of tamoxifen therapy in DCIS remain uncertain. The ASCO/CAP guidelines acknowledge that no current evidence supports any survival benefits from endocrine therapy in women with DCIS, even in women with ER-positive (ER+) DCIS [1]. However, a previous study proposed a possible survival benefit of tamoxifen therapy in DCIS [2]. The current NCCN guidelines recommend considering endocrine therapy for 5 years in patients who have been treated with lumpectomy and/or radiation therapy, particularly for those with ER+ DCIS, to reduce the risk of ipsilateral breast cancer recurrence. The prognostic role of tamoxifen therapy according to the receptor status in DCIS must be validated.

The hormone receptor (HRc) subtype in breast cancer can be classified into four categories according to the statuses of ER and PR: ER-negative (ER−)/PR-negative (PR−), ER−/PR-positive (PR+), ER+/PR−, and ER+/PR+. A wealth of previous studies has revealed the prognostic and/or predictive roles of the HRc subtype in invasive breast cancer [3–5]. However, little is known about the prognostic or predictive roles of the HRc subtype in DCIS because the independent role of PR has not been elucidated. An investigation of the impact of the HRc subtype in patients with DCIS could be useful to understand the roles of PR and the prognostic role of tamoxifen therapy.

In this study, we investigated the prognostic and predictive roles of the HRc subtype in patients with newly diagnosed DCIS using the Korean Breast Cancer Registry (KBCR) database [6]. We particularly focused on the prognostic and predictive values of PR status independent of ER status. The prognostic impact of tamoxifen therapy in DCIS according to the HRc subtype was also investigated.

Institutional review boards approved this study (Seoul Metropolitan Government Seoul National University Boramae Medical Center, 07-2017-6).

Subjects, Materials, and Methods

Patients

In our previous study, data on 14,944 female patients diagnosed with pure DCIS who underwent curative surgery between January 1, 2000, and December 31, 2014, were analyzed using the KBCR database [2]. In this study, the 2,436 patients who lacked complete information on ER or PR status were further excluded from the data of our previous study. Thus, 12,508 female patients diagnosed with pure DCIS with complete information on their ER and PR statuses were enrolled in this study. The last update regarding overall survival was performed on December 31, 2014.

Clinicopathologic Parameters

Patient age was defined as the age when the diagnosis of DCIS was made. The ER and PR statuses were defined based on the results of the immunohistochemical test [1, 7]. HRc was defined as positive (HRc+) when the immunohistochemical test for either ER or PR was positive, and it was defined as negative (HRc−) when both ER and PR tests were negative. Human epidermal growth factor receptor 2 (HER2) status was defined as positive or negative based on the immunohistochemical results and the in situ hybridization test [8]. The statuses of ER, PR, and HER2 were determined from the pathology reports which were evaluated in the treating hospital in accordance with the ASCO/CAP guidelines in place at the time [1, 7–13]. Before 2010, the recommended cutoff for ER and PR positivity was 10%. In 2010, the guidelines were updated, and the cutoff was changed to 1% [7]. Body mass index (BMI) was calculated as the ratio of body weight (in kilograms) to height (in square meters). Operation period is classified into three groups with interval of 5 years: 2000–2004 (early operation period), 2005–2009 (middle operation period), and 2010–2014 (late operation period). Data on management were extracted from the KCBR registry, and patients were managed in accordance with local center guidelines.

Definition of Hormonal Receptor Subtypes

HRc subtypes were classified into four groups based on ER and PR statuses: ER−/PR−, ER−/PR+, ER+/PR−, and ER+/PR+ [3]. HRc subtypes were additionally classified into three groups: double-positive (ER+/PR+), single-positive (ER−/PR+ or ER+/PR−), and double-negative (ER−/PR−).

Statistical Analysis

Pearson's χ^2 test was used to determine differences in clinicopathologic characteristics between groups. All survival analyses were performed with respect to overall survival. Overall survival was defined as the time from the initial diagnosis to death from any cause. The Kaplan-Meier estimator was used to analyze survival rates. The log-rank test was used to determine the significance of differences between two or more survival curves. Cox proportional hazards models were used for the univariable and multivariable analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. All statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY). All tests were two-sided. A p value of less than .05 was considered statistically significant.

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Results

Clinicopathologic Characteristics of the Study Subjects

Of the 12,508 total subjects, the mean age was 49.5 ± 10.1 years (median, 48.0 years; range, 5–87 years). The mean follow-up period was 60.7 ± 40.6 months (median, 56.0 months; range, 0–179 months), and there was a total of 170 deaths (1.4%) during this period. A total of 2,629 (21.0%), 359 (2.9%), 1,212 (9.7%), and 8,308 (66.4%) patients were classified as ER−/PR−, ER−/PR+, ER+/PR−, and ER+/PR+, respectively. The clinicopathologic features of the study subjects according to HRc subtypes are summarized in Table 1. Compared with the ER−/PR− group, the ER+/PR+ group had higher proportions of patients with a younger mean age, HER2-negative status, low nuclear grade, age ≤ 50 years, low BMI, a more recent operation period, lumpectomy, radiation therapy, and tamoxifen therapy. The clinicopathologic characteristics of the study subjects according to tamoxifen therapy are summarized in supplemental online Table 1.

Prognostic and Predictive Roles of Estrogen Receptor and Progesterone Receptor

The ER+ and PR+ groups showed better prognoses than the ER− and PR− groups, respectively ($p = .009$ and $p = .001$, respectively; Fig. 1A, 1B). ER status lost prognostic significance in the subgroups of patients with or without tamoxifen therapy. Although PR status lost prognostic significance in the subgroup of patients without tamoxifen therapy, the prognostic significance became more prominent in the subgroup of patients with tamoxifen therapy ($p < .001$; Fig. 1F). The HRc + group showed a superior prognosis compared with the HRc − group ($p = .024$; supplemental online Fig. 1). HRc status also lost prognostic significance in the subgroups of patients with or without tamoxifen therapy, similar to ER status. Detailed overall survival rates according to ER and PR statuses are described in supplemental online Table 2.

Prognostic and Predictive Roles of the Hormone Receptor Subtype

The ER+/PR+ group showed better prognoses compared with the ER+/PR− and ER−/PR− groups, respectively, according to Kaplan-Meier analysis ($p = .004$ and $p = .003$, respectively; Fig. 2A). The ER+/PR+ group showed a superior prognosis than the ER−/PR− group according to the Cox proportional hazards model ($p = .003$; Fig. 2B). Although the HRc subtype lost its prognostic significance in the subgroup of patients without tamoxifen therapy, its significance was maintained in the subgroup of patients with tamoxifen therapy according to both Kaplan-Meier analysis ($p = .001$ for ER+/PR+ vs. ER+/PR−, $p = .031$ for ER+/PR+ vs. ER−/PR−; Fig. 2E) and the Cox proportional hazards model ($p = .041$; Fig. 2F). The double-positive HRc group showed better survival than the single-positive or double-negative HRc groups according to Kaplan-Meier analysis ($p = .002$, $p = .003$, respectively; supplemental online Fig. 2A). The double-positive HRc group showed a superior survival than the double-negative HRc group according to the Cox proportional hazards model ($p = .003$; supplemental online Fig. 2B). These significances were lost in the no tamoxifen subgroup, but the significances were maintained in the tamoxifen subgroup. Detailed overall survival rates according to HRc statuses are described in supplemental online Table 3.

Survival Analysis According to Tamoxifen Therapy

The tamoxifen therapy group showed better survival than the no tamoxifen group in all subjects according to Kaplan-Meier analysis ($p < .001$; Fig. 3A) and the Cox proportional hazards model ($p < .001$; Fig. 3B). This significance was only valid in the ER+/PR+ subgroup ($p = .002$; Fig. 3F) and not in the ER−/PR, ER−/PR+, or ER+/PR− subgroups. The tamoxifen therapy group showed a superior prognosis compared with the no tamoxifen group in the ER+, PR+, and HRc + subgroups ($p < .001$, $p = .001$, $p < .001$, respectively; supplemental online Fig. 3B, 3D, 3F), but there were no significant differences among the ER−, PR−, and HRc − subgroups. Detailed overall survival rates according to tamoxifen therapy in each HRc subgroup are described in supplemental online Table 4.

Subgroup Analysis in Terms of Tamoxifen Therapy

In all subjects, patients who received tamoxifen therapy had a significantly lower mortality compared with those who did not receive tamoxifen therapy (HR, 0.487; 95% CI, 0.350−0.677; Fig. 4). The patients who received tamoxifen had a significantly lower mortality than the patients who did not receive tamoxifen in the ER+/PR+, ER+, PR+, HRc +, double-positive HRc, HER2-negative, low nuclear grade, operation periods of 2005 − 2009 and 2010 − 2014, and mastectomy subgroups. In particular, the tamoxifen group showed a better prognosis regardless of the subgroups according to age, BMI, and radiation therapy. There were no significant differences in prognosis among the ER−/PR−, ER−/PR+, ER+/PR−, ER−, PR−, HRc−, double-negative or single-negative HRc, HER2-positive, high nuclear grade, operation period of 2000 − 2004, and lumpectomy subgroups.

Univariable and Multivariable Analyses

The univariable analysis identified nine significant prognostic factors: HRc subtype, ER status, PR status, age, BMI, operation period, operation, radiation therapy, and tamoxifen therapy (Table 2). Multivariable analyses were performed using three different models (Table 2). In model 1, HRc subtype was an independent prognostic factor after being adjusted for five factors (age, BMI, operation period, operation, and radiation therapy) that were significant in the univariable analysis ($p = .028$). In model 2, tamoxifen therapy remained an independent factor after adjustment (HR, 0.619; 95% CI, 0.423−0.907). In model 3, PR status was a significant independent factor after adjustment (HR, 0.576; 95% CI, 0.349−0.951), but ER status lost its significance after adjustment.

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Table 1. Baseline characteristics of study subjects according to hormone receptor subtypes

Characteristics	Hormone receptor subtypes				*p* value	Total, *n* (%)
	ER−/PR−, *n* (%)	ER−/PR+, *n* (%)	ER+/PR−, *n* (%)	ER+/PR+, *n* (%)		
All	2,629 (21.0)	359 (2.9)	1,212 (9.7)	8,308 (66.4)		12,508 (100)
Mean age (years)	52.7 ± 9.9	48.1 ± 9.9	51.8 ± 9.7	48.2 ± 9.9		49.5 ± 10.1
HRc					<.001	
Negative	2,629 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)		2,629 (21.0)
Positive	0 (0.0)	359 (100.0)	1,212 (100.0)	8,308 (100.0)		9,879 (79.0)
HER2					<.001	
Negative	627 (23.8)	166 (46.2)	536 (44.2)	5,642 (67.9)		6,971 (55.7)
Positive	1,591 (60.5)	129 (35.9)	418 (34.5)	926 (11.1)		3,064 (24.5)
Unknown	411 (15.6)	64 (17.8)	258 (21.3)	1,740 (20.9)		2,473 (19.8)
Nuclear grade					<.001	
1, 2	527 (20.0)	109 (30.4)	404 (33.3)	4,110 (49.5)		5,150 (41.2)
3	964 (36.7)	67 (18.7)	237 (19.6)	850 (10.2)		2,118 (16.9)
Unknown	1,138 (43.3)	183 (51.0)	571 (47.1)	3,348 (40.3)		5,240 (41.9)
Age (years)					<.001	
≤50	1,049 (39.9)	230 (64.1)	511 (42.2)	5,498 (66.2)		7,288 (58.3)
>50	1,531 (58.2)	124 (34.5)	689 (56.8)	2,684 (32.3)		5,028 (40.2)
Unknown	49 (1.9)	5 (1.4)	12 (1.0)	126 (1.5)		192 (1.5)
Body mass index (kg/m^2)					<.001	
≤25	1,506 (57.3)	222 (61.8)	774 (63.9)	5,035 (60.6)		7,537 (60.3)
>25	540 (20.5)	60 (16.7)	247 (20.4)	1,553 (18.7)		2,400 (19.2)
Unknown	583 (22.2)	77 (21.4)	191 (15.8)	1,720 (20.7)		2,571 (20.6)
Operation period (year)					<.001	
2000–2004	303 (11.5)	65 (18.1)	157 (13.0)	757 (9.1)		1,282 (10.2)
2005–2009	1,060 (40.3)	197 (54.9)	395 (32.6)	3,031 (36.5)		4,683 (37.4)
2010–2014	1,266 (48.2)	97 (27.0)	660 (54.5)	4,520 (54.4)		6,543 (52.3)
Operation					<.001	
Lumpectomy	1,345 (51.2)	191 (53.2)	714 (58.9)	5,244 (63.1)		7,494 (59.9)
Mastectomy	1,220 (46.4)	157 (43.7)	445 (36.7)	2,718 (32.7)		4,540 (36.3)
Unknown	64 (2.4)	11 (3.1)	53 (4.4)	346 (4.2)		474 (3.8)
Radiation therapy					<.001	
No		151 (42.1)	433 (35.7)	3,074 (37.0)		4,792 (38.3)
Yes	1,241 (47.2)	169 (47.1)	666 (55.0)	4,471 (53.8)		6,547 (52.3)
Unknown	254 (9.7)	39 (10.9)	113 (9.3)	763 (9.2)		1,169 (9.3)
Tamoxifen therapy					<.001	
No	2,022 (76.9)	62 (17.3)	180 (14.9)	1,168 (14.1)		3,432 (27.4)
Yes	268 (10.2)	253 (70.5)	929 (76.7)	6,522 (78.5)		7,972 (63.7)
Unknown	339 (12.9)	44 (12.3)	103 (8.5)	618 (7.4)		1,104 (8.8)

Abbreviation: ER−, estrogen receptor negative; ER+, estrogen receptor positive; HER2, human epidermal growth factor receptor 2; HRc, hormone receptor; PR−, progesterone receptor negative; PR+, progesterone receptor positive.

Discussion

This study used the nationwide data of 12,508 patients newly diagnosed with pure DCIS and investigated the prognostic and predictive influences of the HRc subtype in DCIS. In particular, this study focused on the roles of PR status independent of ER status. This study also investigated the prognostic role of tamoxifen therapy in DCIS according to HRc subtype.

Two representative phase III clinical trials have investigated the impact of tamoxifen therapy in patients with DCIS [14, 15]. Wapnir et al. analyzed combined data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial and the NSABP B-17 trial [16–18]. They reported that the addition of tamoxifen therapy was effective in reducing the risk of invasive ipsilateral breast tumor recurrence in both the NSABP B-24 trial (HR, 0.68; 95% CI,

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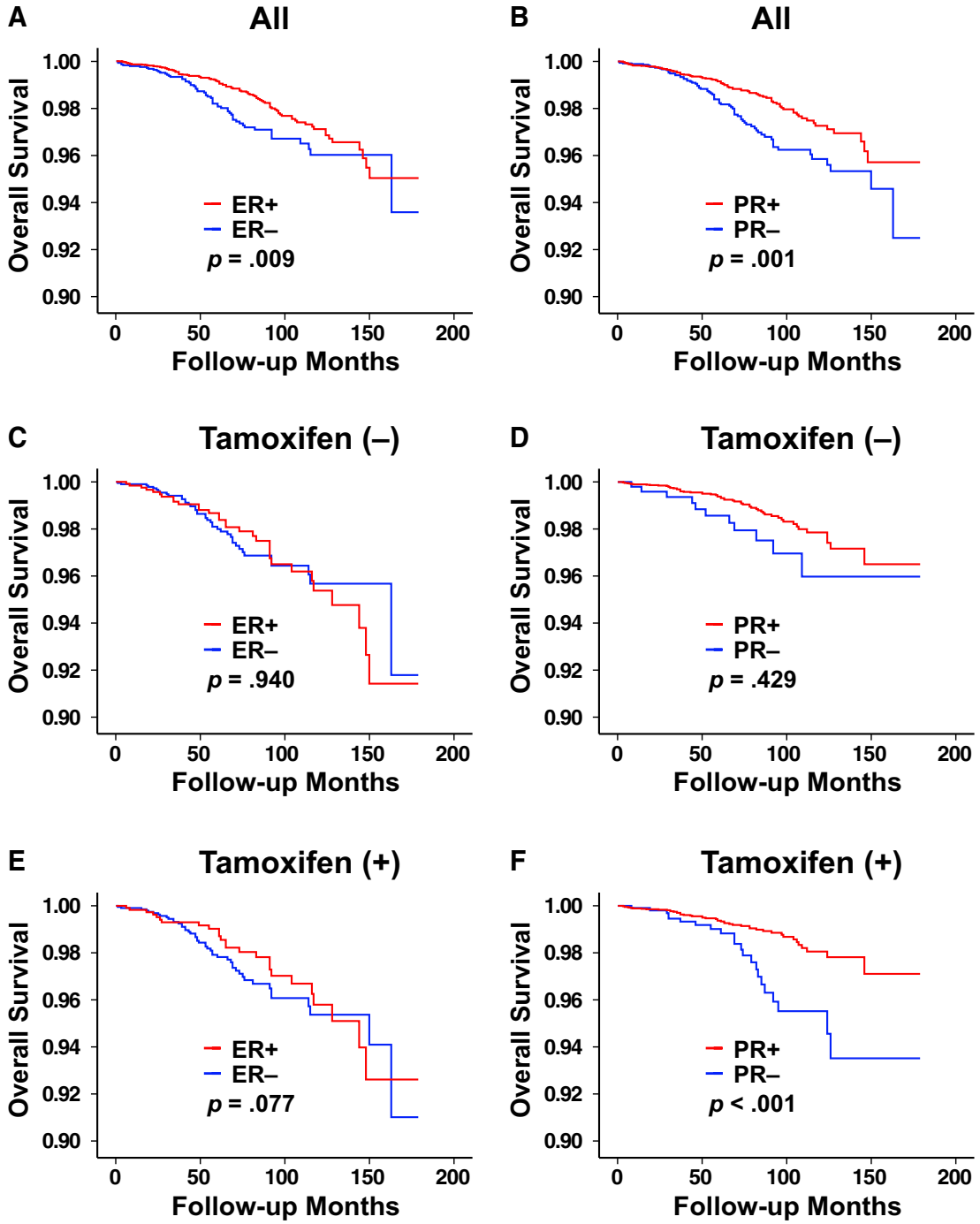

Figure 1. Overall survival curves according to ER and PR statuses. Overall survival curves in all subjects according to ER status **(A)** and PR status **(B)**. Overall survival curves in patients who did not receive tamoxifen therapy according to ER status **(C)** and PR status **(D)**. Overall survival curves in patients who received tamoxifen therapy according to ER status **(E)** and PR status **(F)**.
Abbreviation: ER, estrogen receptor; PR, progesterone receptor.

0.49–0.95) and in the combined trials (HR, 0.30; 95% CI, 0.21–0.42) [14]. The addition of tamoxifen therapy reduced the risk of contralateral breast cancer recurrence (HR, 0.68; 95% CI, 0.48–0.95) in the NSABP-24 trial. The U.K., Australia, and New Zealand (UK/ANZ) DCIS trial initially reported that tamoxifen therapy did not reduce the ipsilateral, contralateral, or overall breast cancer risks even in subgroup analyses stratified by radiation therapy; it only reduced the risk of overall DCIS recurrence (HR, 0.45; 95% CI, 0.49–0.96) [19]. Cuzick et al. reported follow-up results showing that tamoxifen therapy reduced the risk of all new breast events (HR, 0.71; 95% CI, 0.58–0.88), ipsilateral DCIS recurrence (HR, 0.70; 95% CI, 0.51–0.86), and contralateral tumors (HR, 0.44; 95% CI, 0.25–0.77) [15]. A meta-analysis of these two trials reported a reduced risk of breast cancer recurrence in the tamoxifen therapy group [20]. Although the NSABP B-24 trial and the UK/ANZ DCIS trial revealed the benefits of tamoxifen therapy in terms of recurrences,

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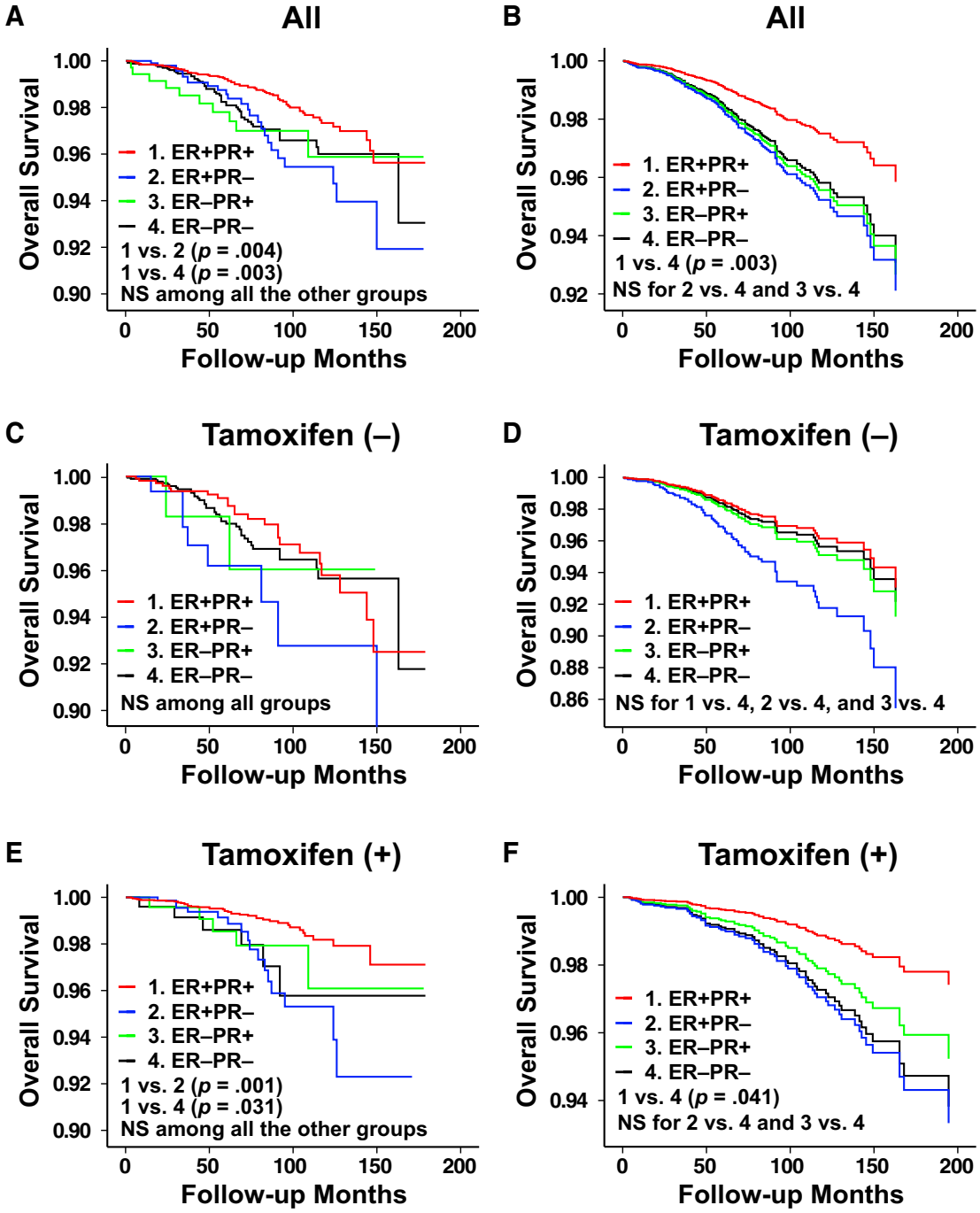

Figure 2. Overall survival curves according to hormone receptor subtypes. Overall survival curves in all subjects by Kaplan-Meier analysis **(A)** and by the Cox proportional hazards model **(B)**. Overall survival curves in patients who did not receive tamoxifen therapy by Kaplan-Meier analysis **(C)** and by the Cox proportional hazards model **(D)**. Overall survival curves in patients who received tamoxifen therapy by Kaplan-Meier analysis **(E)** and by the Cox proportional hazards model **(F)**. The Cox proportional hazards model was used with reference to the ER−/PR− group.
Abbreviation: ER, estrogen receptor; NS, not significant; PR, progesterone receptor.

no survival benefits were observed [14, 15]. Of note, at the time of accrual of these two trials, ER and PR statuses were not evaluated, even for the tamoxifen therapy group. Because there have been no other large prospective clinical trials regarding tamoxifen therapy in DCIS, little evidence is available to prove the prognostic role of tamoxifen therapy in DCIS according to ER and PR statuses. The U.K. Sloane project recently reported updated clinical outcomes of 11,337 patients with DCIS [21]. It reported that 7% of English patients developed ipsilateral breast cancer events and that contralateral breast events occurred in 5%. However, this population-based prospective cohort study did not analyze the treatment effect of endocrine therapy, as both ER and PR statuses were not routinely evaluated in this study.

To prove the prognostic role of PR status independent of ER status, using HRc subtypes is essential. This study

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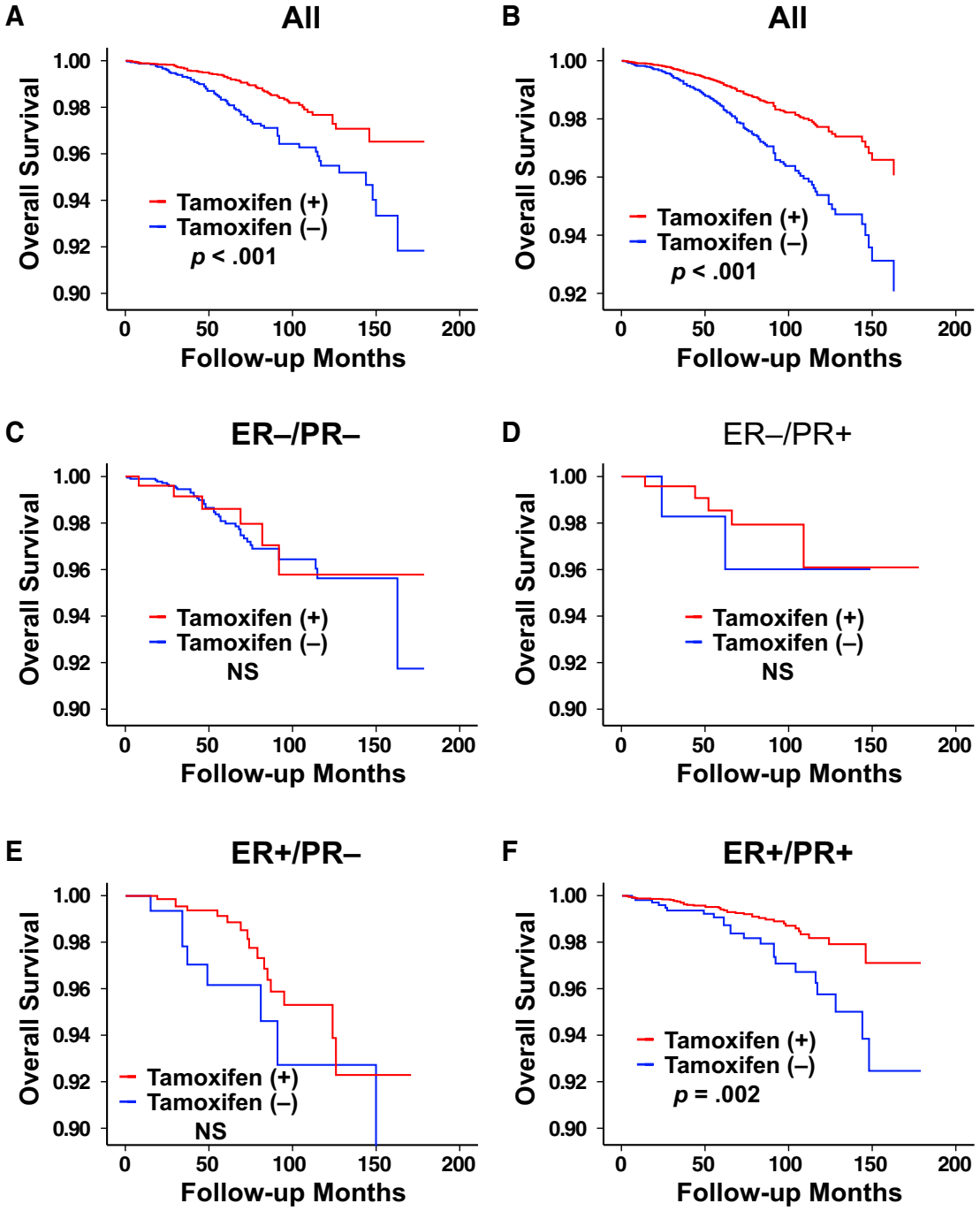

Figure 3. Overall survival curves according to tamoxifen therapy. Overall survival curves in all subjects by Kaplan-Meier analysis **(A)** and by the Cox proportional hazards model **(B)**. Overall survival curves in the ER−/PR− **(C)**, ER−/PR+ **(D)**, ER+/PR− **(E)**, and ER+/PR+ **(F)** groups.
Abbreviation: ER, estrogen receptor; NS, not significant; PR, progesterone receptor.

revealed that HRc subtype is a significant independent prognostic factor in patients with DCIS in terms of overall survival. Only the ER+/PR+ subtype had a better prognosis than the ER+/PR− and ER−/PR− subtypes in patients who received tamoxifen therapy. These effects were not valid in patients who did not receive tamoxifen therapy. There were no survival differences between the ER+/PR+ and ER−/PR+ subtypes and among the other subtypes such as ER−/PR−, ER−/PR+, and ER+/PR−. Of note, in ER+ DCIS, the ER+/PR+ subtype had a superior survival compared with the ER+/PR− subtype. This finding implies the prognostic role of PR status independent of ER status and demonstrates the necessity of routine testing for PR status in clinical settings. Allred et al. analyzed the role of ER and PR using data from the NSABP B-24 trial by retrospectively evaluating ER/PR status [22]. They reported that patients with ER+ DCIS who were treated with tamoxifen showed significant decreases in subsequent breast cancer at

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Characteristics		Subject Number	HR[a]	CI (95%)		p value
Total		11,303	0.487	0.350	0.677	<.001
Hormone receptor subtype	ER– /PR–	2,271	0.923	0.390	2.181	.854
	ER– /PR+	302	0.688	0.133	3.564	.656
	ER+/PR–	940	0.546	0.232	1.285	.166
	ER+/PR+	7,492	0.448	0.268	0.747	.002
ER	Negative	2,586	0.826	0.424	1.609	.575
	Positive	8,572	0.464	0.299	0.721	.001
PR	Negative	3,372	0.898	0.541	1.490	.677
	Positive	7,807	0.459	0.282	0.747	.002
HRc[c)]	Negative	2,271	0.923	0.390	2.181	.854
	Positive	8,887	0.472	0.309	0.721	.001
HRc subtype[d)]	Double negative	2,271	0.923	0.390	2.181	.854
	Single positive	1,256	0.558	0.262	1.188	.130
	Double positive	7,492	0.448	0.268	0.747	.002
HER2	Negative	6,332	0.431	0.275	0.674	<.001
	Positive	2,763	0.794	0.419	1.503	.478
	Unknown	1,971	0.333	0.143	0.774	.011
Nuclear grade	1,2	4,750	0.393	0.224	0.691	.001
	3	1,619	0.452	0.196	1.039	.062
	Unknown	4,539	0.594	0.366	0.963	.035
Age (years)	≤ 50	6,552	0.434	0.265	0.711	.001
	> 50	4,536	0.593	0.379	0.927	.022
Body mass index (kg/m^2)	≤ 25	6,929	0.473	0.308	0.727	.001
	> 25	2,164	0.484	0.258	0.907	.024
	Unknown	1,825	0.590	0.234	1.490	.265
Operation period (year)	2000-2004	1,084	0.627	0.378	1.037	.069
	2005-2009	4,184	0.514	0.319	0.829	.006
	2010-2014	5,593	0.249	0.081	0.760	.015
Operation	Lumpectomy	6,711	0.618	0.360	1.062	.081
	Mastectomy	4,096	0.449	0.279	0.724	.001
	Unknown	334	0.546	0.130	2.284	.407
Radiation therapy	No	4,591	0.645	0.424	0.982	.041
	Yes	6,288	0.418	0.238	0.734	.002
	Unknown	223	0.154	0.014	1.698	.126

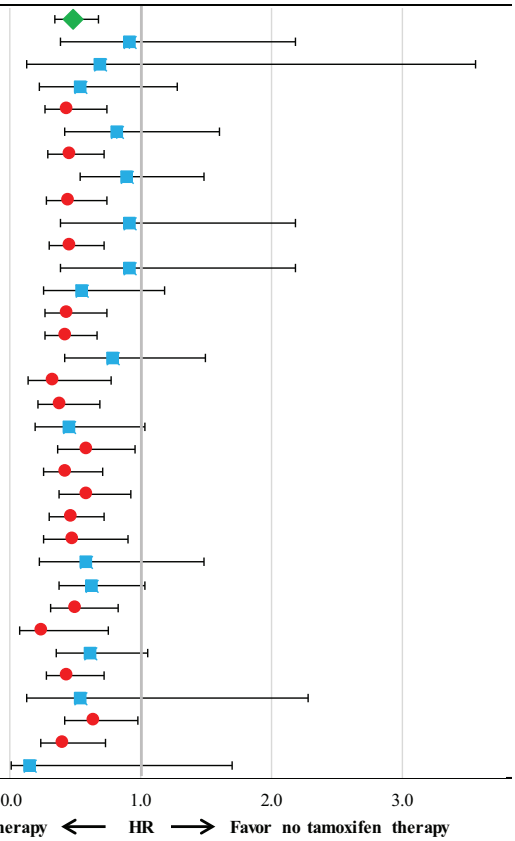

Figure 4. Subgroup analyses by the Cox proportional hazards model according to tamoxifen therapy. [a], HRs are the relative risks of the tamoxifen group with reference to the no tamoxifen group by the Cox proportional hazards model regarding overall survival. [b], In the forest plot, an HR value >1 favors the tamoxifen group against the no tamoxifen group. The red circles mean statistical significance, and the blue squares mean no statistical significance. The green diamond means the result of total subjects. [c], Hormone receptor status was defined as positive when the test for either ER or PR was positive, and it was defined as negative when both ER and PR were negative. [d], Hormone receptor status was classified into three groups: double positive (ER+/PR+), single positive (ER−/PR+, ER+/PR−), and double negative (ER−/PR−).
Abbreviation: CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HRc, hormone receptor; PR, progesterone receptor.

10 years of follow-up (HR, 0.49; $p < .001$) and throughout the overall follow-up period that lasted a median of 14.5 years (HR, 0.60; $p = .003$). The beneficial effect of tamoxifen was not observed in ER− DCIS. They also reported that the addition of PR status was not more predictive than ER status alone. Allred et al. reported the benefits of tamoxifen therapy in ER+ DCIS in terms of recurrence, but the survival benefit of tamoxifen therapy was not analyzed. A retrospective study analyzed the data of 693 patients with DCIS and reported that there was no difference in recurrence-free survival between ER+/PR+ and ER+/PR− subtypes [23]. It also reported that the ER−/PR− subtype had a significantly higher risk of recurrence compared with the ER+/PR+ subtype (HR, 3.7; 95% CI, 1.9–7.2). In ER+ DCIS, the group without endocrine therapy showed a higher risk of recurrence with the endocrine therapy group serving as the reference (HR, 2.2; 95% CI, 1.23–3.92). A phase III prospective randomized clinical trial analyzed 500 women with breast intraepithelial neoplasia [24]. It reported that a lower dose of tamoxifen (5 mg per day) and a shorter duration of treatment (3 years) can halve the incidence of new breast neoplastic events compared with placebo (HR, 0.48; 95% CI, 0.26–0.92). Tamoxifen was also reported to decrease contralateral breast events (HR, 0.25; 95% CI, 0.07–0.88). All of these previous studies have reported the impact of ER or PR statuses on the risk of recurrence, but no impact on survival was reported. Our current study presents the influence of HRc subtypes on survival in patients with DCIS. The poorer clinical outcomes of single HRc + tumors compared with double HRc + tumors in invasive breast cancers have been repeatedly reported [25–30]. However, little is known about the prognosis among single HRc+, double HRc+, and double HRc − tumors in DCIS. In this study, we also revealed that the double-positive HRc group showed better survival than the single-positive and double-negative HRc groups, particularly in the patients who received tamoxifen therapy. A previous study analyzed the data of 810,587 female patients with operable invasive breast cancer using the Surveillance, Epidemiology, and End Results database and reported that the frequencies of ER−/PR−, ER−/PR+, ER+/PR−, and ER+/PR+ subtypes were 18.6%, 1.6%, 11.9%, and 68.0%,

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Table 2. Univariable and multivariable analyses regarding overall survival

	Univariate analysis		Multivariate analysis					
			Model 1[a]		Model 2[b]		Model 3[c]	
Characteristics	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
HRc subtype		.003		.028				
ER−/PR−	Reference		Reference					
ER−/PR+	1.061 (0.538–2.093)	.864	1.097 (0.511–2.358)	.812				
ER+/PR−	1.144 (0.708–1.849)	.583	1.156 (0.668–2.003)	.604				
ER+/PR+	0.591 (0.417–0.838)	.003	0.606 (0.398–0.922)	.019				
ER, positive vs. negative	0.658 (0.480–0.901)	.009					1.142 (0.667–1.955)	.627
PR, positive vs. negative	0.594 (0.439–0.804)	.001					0.576 (0.349–0.951)	.031
HER2, positive vs. negative	1.143 (0.800–1.634)	.462						
Nuclear grade, 3 vs. 1, 2	1.272 (0.822–1.968)	.279						
Age, >50 vs. ≤50 (years)	2.031 (1.499–2.753)	<.001	1.655 (1.137–2.409)	.009	1.870 (1.278–2.737)	.001	1.695 (1.147–2.506)	.008
Body mass index, >25 vs. ≤25 (kg/m^2)	1.459 (1.028–2.070)	.034	1.285 (0.871–1.896)	.206	1.236 (0.825–1.853)	.304	1.251 (0.835–1.874)	.277
Operation period (year)		<.001		.001		<.001		<.001
2000–2004	Reference		Reference		Reference		Reference	
2005–2009	0.540 (0.382–0.765)	.001	0.516 (0.342–0.778)	.002	0.501 (0.328–0.765)	.001	0.503 (0.330–0.768)	.001
2010–2014	0.336 (0.188–0.601)	<.001	0.310 (0.156–0.618)	.001	0.271 (0.130–0.565)	<.001	0.270 (0.130–0.564)	<.001
Operation, mastectomy vs. lumpectomy	1.564 (1.143–2.139)	.005	1.061 (0.593–1.900)	.842	0.893 (0.494–1.615)	.709	0.880 (0.488–1.587)	.671
Radiation therapy, yes vs. no	0.574 (0.410–0.804)	.001	0.590 (0.322–1.083)	.089	0.564 (0.303–1.051)	.071	0.545 (0.293–1.013)	.055
Tamoxifen therapy, yes vs. no	0.487 (0.350–0.677)	<.001			0.619 (0.423–0.907)	.014	0.731 (0.468–1.140)	.167

Abbreviation: CI, confidence interval; ER, estrogen receptor; ER−, estrogen receptor negative; ER+, estrogen receptor positive; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HRc, hormone receptor; PR, progesterone receptor; PR−, progesterone receptor negative; PR+, progesterone receptor positive.

[a]Hormone receptor subtype was adjusted with five factors—age, body mass index, operation period, operation, and radiation therapy—which were significant factors by univariable analysis.

[b]Tamoxifen therapy was adjusted with five clinicopathologic factors, including age, body mass index, operation period, operation, and radiation therapy.

[c]Multivariable analysis performed using eight clinicopathologic factors, including ER, PR, age, body mass index, operation period, operation, radiation therapy, and tamoxifen therapy.

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respectively [25]. In our study, the frequencies of ER−/PR−, ER−/PR+, ER+/PR−, and ER+/PR+ subtypes in patients with DCIS were 21.0%, 2.9%, 9.7%, and 66.4%, respectively; these results of DCIS are very similar to those of invasive breast cancer. This study showed a tendency for the progressive increase of ER+/PR+ DCIS and progressive decrease of ER−/PR− DCIS over time. Improved technology of immunohistochemical tests for ER/PR, introduction of automated staining platforms, and the change in cutoff for ER/PR positivity from 10% to 1% might partly explain this tendency [9].

Notably, the ER+/PR+ group of this study showed a younger mean age compared with the ER−/PR− subtype, which is contrary to the results of invasive breast cancers [3]. Further studies are needed to reveal the association between age and HRc positivity in patients with DCIS.

In the current study, we revealed that tamoxifen therapy could achieve a survival benefit in patients with DCIS; however, this effect was valid only in the ER+/PR+ subtype. There were no survival gains from tamoxifen therapy in the other subtypes including ER+/PR−, ER−/PR+, and ER−/PR−. Tamoxifen therapy was a significant independent prognostic factor in terms of overall survival. These findings support a higher risk of recurrence in patients with DCIS with the ER+/PR+ subtype who were not treated with tamoxifen therapy [1]. In our previous study, we reported that the tamoxifen therapy group showed a superior prognosis compared with the group that did not receive tamoxifen therapy, particularly in the HRc+/HER2-negative subtype (HR, 0.420; 95% CI, 0.250–0.705), with a mean follow-up period of 62.3 months [2]. We also reported that tamoxifen therapy was a significant independent factor in the multivariate analysis (HR, 0.538; 95% CI, 0.306–0.946). Although this was the first study to present the survival gains from tamoxifen therapy in patients with DCIS, we did not analyze the prognostic role of tamoxifen therapy according to the HRc subtype. In this study, we reported the significant prognostic role of tamoxifen therapy according to HRc status for the first time. According to the current guideline, tamoxifen therapy is not recommended for patients with ER− DCIS including both ER−/PR− and ER−/PR+. However, in real-world practice, some patients with ER−/PR− DCIS received tamoxifen therapy (10.2%). Furthermore, the majority of patients with ER−/PR+ DCIS received tamoxifen therapy (70.5%). On the contrary, some patients with ER+ DCIS did not receive tamoxifen therapy (14.9% and 14.1% of ER+/PR− and ER+/PR+, respectively). We could not analyze the reasons for these discrepancies with unavailability of related data. Previous studies tried to identify biologic markers associated with breast cancer recurrence after the diagnosis of DCIS [31, 32]. Although some markers were proposed as possible candidates to predict recurrence, further studies are needed to validate these markers.

In this study, ER, PR, and HRc statuses were significant favorable prognostic factors in unselected patients with DCIS. PR status was a significant prognostic factor in the tamoxifen therapy subgroup according to the subgroup analysis, but ER and HRc statuses lost their significance in the subgroup analyses according to tamoxifen therapy. The survival gains from tamoxifen therapy were observed in unselected patients with DCIS. The beneficial effect of tamoxifen therapy was observed only in the ER+, PR+, and HRc + subgroups but not in the ER−, PR−, and HRc − subgroups according to the subgroup analysis. PR status was a significant independent prognostic factor, particularly independent of ER status. Currently, the benefits of endocrine therapy for ER− DCIS have been unveiled. This study also showed that the beneficial effects of tamoxifen therapy were not observed in ER− DCIS including the ER−/PR− and ER−/PR+ subtypes. In ER+ DCIS, the beneficial effect of tamoxifen therapy was only observed in the ER+/PR+ subtype but not in the ER+/PR− subtype. Although previous studies have reported the clinical significance of PR status independent of ER status in invasive breast cancer [4, 5, 33–36], little on this topic was known in DCIS. Our current study is the first study to reveal the independent prognostic role of PR status in DCIS.

The group with more recent operation period showed relatively larger proportion of patients with ER+/PR+. This group showed smaller proportion of patients with ER− DCIS, especially for ER−/PR+ DCIS. This group also showed relatively higher proportion of patients who received tamoxifen therapy. These findings might explain the significantly lower HRs of the middle and late operation period groups with the reference of the early operation period group regarding both univariate and multivariate analyses. Tamoxifen therapy group showed significantly lower HRs compared with those who did not receive tamoxifen therapy in the middle and late operation period groups, but not in the early operation period group.

This study proposed the clinical usefulness of HRc subtypes and the necessity of PR testing by analyzing nationwide registry data of patients with DCIS, but it has several limitations. First, this study could not determine the direct association between HRc subtypes and potential subsequent cancer recurrences during the follow-up period because of the unavailability of recurrence data. Second, this study analyzed the prognostic impact of HRc in terms of overall survival only but not in terms of breast cancer–specific survival because of the unavailability of cause-specific death data. Third, this is a retrospective cohort study and thus it has potential biases. Fourth, data on surgical margin status were not available in this study, which is an important factor for local recurrence.

Conclusion

The HRc subtype was an independent prognostic factor in patients with DCIS. The ER+/PR+ subtype showed a better survival than the ER+/PR− and ER−/PR− subtypes in patients who received tamoxifen therapy. Tamoxifen therapy was an independent prognostic factor in patients with DCIS. Tamoxifen therapy demonstrated a survival benefit only in the ER+/PR+ subtype. The ER+ and PR+ groups showed better survival than the ER− and PR− groups, respectively, in unselected patients with DCIS, and only PR status was a favorable prognostic factor in DCIS patients who received tamoxifen therapy. PR status was an independent prognostic factor in patients with DCIS independent of ER status. The HRc subtype could be using as both a prognostic

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and predictive marker in patients with newly diagnosed DCIS. Tamoxifen therapy can improve overall survival in the ER+/PR + subtype. PR status has significant prognostic and predictive roles independent of ER status. Testing of PR status in addition to ER status is routinely recommended for patients with DCIS to determine the HRc subtype in clinical settings.

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Disclosures

The authors indicated no financial relationships.

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