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CLINICAL TRIAL

Survival benefit of postoperative radiotherapy for ductal carcinoma in situ after breast-conserving surgery: a Korean population-based cohort study

Byoung Hyuck Kim[1] · Byung Kyun Ko[2] · Jeoung Won Bae[3] · Seokjin Nam[4] · Min Ho Park[5] · Joon Jeong[6] · Hyouk Jin Lee[7] · Ji Hyun Chang[1] · Suzy Kim[1] · Ki-Tae Hwang[8]

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Abstract

Purpose It has been accepted that radiation therapy (RT) for ductal carcinoma in situ (DCIS) has no survival benefit despite increasing local control. However, a recent large database study reported a small but significant benefit. Using a Korean population-based large database, we examined the survival benefit of RT for DCIS after breast-conserving surgery (BCS) and analyzed which subgroup might derive benefit from it.

Methods Data from 6038 female DCIS patients who underwent BCS with or without RT between 1993 and 2012 were included in this study. We used propensity score analysis to control for differences in baseline characteristics.

Results Before adjusting, patients who received RT were more likely to have a large-sized tumor, poor histologic grade, poor nuclear grade, and less hormone receptor positivity. Ten-year overall survival (OS) rates were 95.0% in the non-RT group and 97.1% in the RT group ($p < 0.001$). After adjusting, previously noted differences of characteristics were substantially reduced, and then ten-year OS rates were 94.3% in the non-RT group and 97.6% in the RT group ($p = 0.001$). When examining the benefit of RT according to proposed prognostic scores, patients with a score of 0 showed no difference in OS by adding RT after BCS, whereas those with high scores demonstrated a significant benefit.

Conclusions We demonstrated the significant OS benefit of postoperative RT after BCS based on a large database, and for the first time beyond the western population. The omission of RT for selected patients to prevent overtreatment needs to be more elaborately studied.

Keywords Postoperative radiotherapy · Ductal carcinoma in situ · Breast-conserving surgery

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✉ Ki-Tae Hwang
kiterius@snu.ac.kr

[1] Department of Radiation Oncology, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Republic of Korea

[2] Department of Surgery, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea

[3] Department of Surgery, Korea University Anam Hospital, Seoul, Republic of Korea

[4] Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[5] Department of Surgery, Chonnam National University Medical School, Kwangju, Republic of Korea

[6] Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

[7] Breast and Thyroid Clinic, Segyero Hospital, Pusan, Republic of Korea

[8] Department of Surgery, Seoul Metropolitan Government Seoul National University Boramae Medical Center, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Republic of Korea

Introduction

Ductal carcinoma in situ (DCIS) accounts for 15–20% of newly diagnosed breast cancer, and its incidence is increasing now that mammographic screenings are widely performed [1]. Mastectomy or breast-conserving surgery (BCS) followed by whole breast radiation therapy (RT) is an accepted standard treatment; sometimes lumpectomy alone is performed in low-risk patients. Because it is not an invasive carcinoma, the ten-year overall survival (OS) shows very good therapeutic results over 95% of the time. Thus, considerable efforts have been made to find a favorable subgroup that can safely omit RT, but there is no clear indication yet [2–4].

However, these approaches may have different meanings depending on the clinical benefit of RT. Despite its routine use, it has been accepted that RT for DCIS has no OS benefit. Well-known randomized controlled trials (RCTs) have shown there is no difference in survival rate whether or not RT is administered, although both invasive and DCIS recurrence were reduced by approximately a half from RT after BCS [5–8]. The total number of patients from the above studies was about one thousand, which might have precluded the detection of small differences in mortality rates. In addition, because those studies mostly used conventional RT techniques before 2000, late RT-induced toxicity may have offset the survival benefit. Consequently, a collective meta-analysis of DCIS trials by the Early Breast Cancer Trialists Collaborative Group reported that RT had no effect on breast cancer mortality (~4%), other-cause mortality (~5%), or all-cause mortality (~8%) [9]. Nowadays, RCT comparing RT or no-RT after BCS will not be performed, so there is a high possibility that there will be no updates concerning OS benefit of RT for time being. However, a recent large database study based on Surveillance, Epidemiology, and End Results Program (SEER) reported a small but significant increase in OS in this setting [10]. They also suggested that the magnitude of the survival difference with RT correlated significantly with the prognostic score. Therefore, we thought that the effect of RT on survival rate in DCIS should be re-evaluated using various independent large cohorts.

Therefore in this study, using a Korean population-based database, we examined the survival benefit of RT for DCIS after BCS and tried to analyze which subgroup could derive benefit from it.

Methods

Study design and data source

After obtaining Institutional Review Board approvals (No. 07-2017-6), we searched for eligible patients from the Korean Breast Cancer Society database. As the data were de-identified in the Korean Breast Cancer Society database, the Ethics Committee approved that the requirement of informed consent was waived. We identified 124,584 patients diagnosed with breast cancer between January 1993 and December 2012. Of these patients, 112,104 patients were excluded because their stages were not TisN0-xM0. After further exclusion of 28 male patients, 277 patients diagnosed with lobular carcinoma in situ, and 111 with Paget's disease, 12,064 female patients with pure DCIS remained. In addition, a total of 4727 patients who underwent mastectomy or an unknown operation and 1299 patients with unknown adjuvant RT status were also excluded. Finally, 6038 female DCIS patients who underwent BCS with known RT status were included in this study. Figure 1 illustrates the above patient selection process.

Clinicopathologic parameters, definition of molecular subtypes, and treatment details

Estrogen receptor (ER) and progesterone receptor (PR) status were determined using immunohistochemistry tests. HER2 status was defined as negative when immunohistochemistry results were negative or 1+ and as positive when results were 3+. When 2+, HER2 status was determined according to the results of in situ hybridization. Molecular subtypes were classified into one of the following four categories: Luminal A (ER or PR+, and HER2−), Luminal B (ER or PR+, and HER2+), HER2 (ER and PR−, and HER2−), and triple negative (TN) (ER, PR, and HER2−). Patients whose hormone receptor or HER2 status could not be defined were classified as an unknown subtype. For hormonal therapy, oral tamoxifen was usually prescribed at a dose of 20 mg/day for 5 years. Details of RT (total dose, boost dose, radiation energy, or extent of field) were not available in this nation-wide database.

Propensity score matching

Since RT assignment might not have been random, a commonly used multivariate Cox regression model alone might not properly adjust for the many confounding factors and possible selection bias. Therefore, we used propensity score analysis to control for differences in the baseline characteristics between patients who did and did not receive RT,

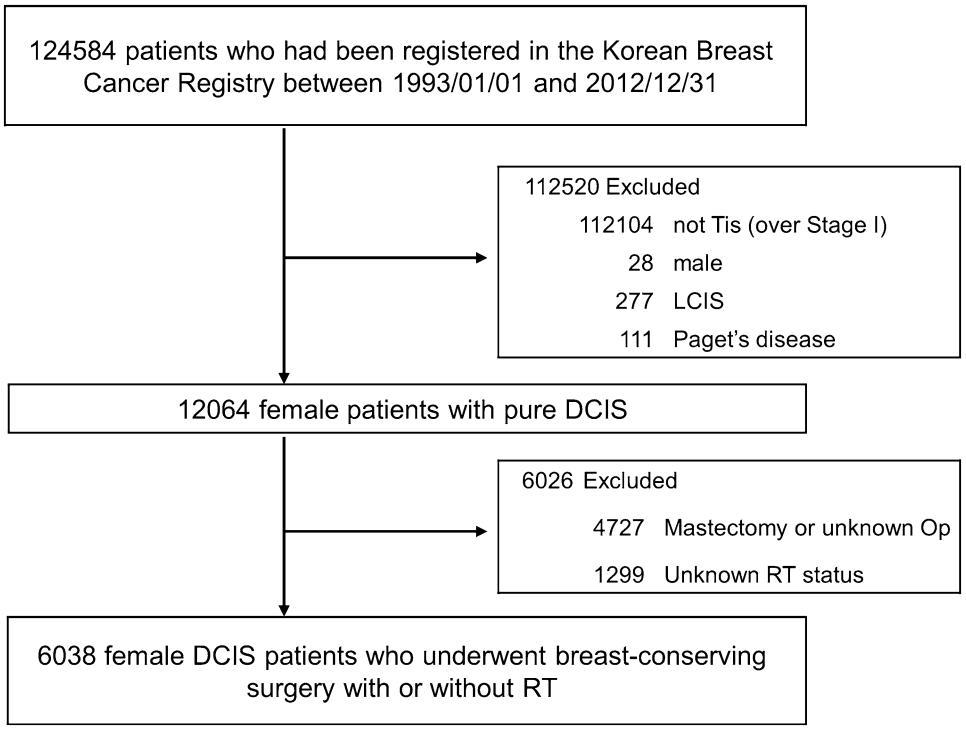


Fig. 1 Patient selection process. *DCIS* ductal carcinoma in situ, *LCIS* lobular carcinoma in situ, *Op* operation, *RT* radiation therapy

consequently to observe the adjusted effects of RT. Logistic regression was used to calculate propensity scores for RT from baseline patient characteristics including age, operation period, laterality, tumor size, ER, PR, HER2 status, and hormonal therapy. Because the number of patients in the non-RT group was relatively small ($n = 1023$), OS events were too few to be adequately analyzed after propensity score matching, thus matching results could not be analyzed. Instead, an inverse probability of treatment weighting (IPTW) analysis was performed using a pre-matched cohort [11]. Inverse probability weight was calculated using the following equation: 'weight = z/ps + (1 − z)/(1 − ps),' where 'z' indicates whether or not the patient was treated with RT while 'ps' represents the conditional probability of receiving RT [12].

Statistical analysis

The differences in clinical and tumor characteristics between the non-RT and RT groups were compared using the standardized mean difference (SMD) method, which measures the distance between two group means in terms of one or more variables [13]. OS was defined as the interval from the date of diagnosis to the date of death or last follow-up. The Kaplan–Meier method was used for univariate survival analysis with the log-rank test. In the IPTW cohort, propensity score-weighted log-rank tests and the Cox proportional hazard model were used. To examine the consistency of our results, we conducted a separate multivariate analysis before and after adjusting the propensity score. In addition, we used two Cox proportional hazard models for multivariate analysis. Lastly, the effect of RT on OS was evaluated in various subgroups according to characteristics and prognostic scores. All statistical data analyses were performed with R software version 3.3.0.

Results

Patient characteristics

The total number of analyzable patients was 6038. Table 1 shows overall patient and tumor characteristics. Median age at diagnosis was 48 years (range 16–87). About two-thirds of patients underwent surgery between 2008 and 2012. Information about histologic grade was largely unavailable. Luminal A (50.2%) was the most common subtype, followed by Luminal B (9.5%), HER2 (8.4%), and TN (4.8%). Of this initial cohort, 5015 (83.1%) patients received RT and 1023 (16.9%) did not. The number of patients who received hormonal therapy was 4317 (71.5%). During the follow-up period, the total number of deaths was 112 (1.9%).

Comparison of characteristics between the non-RT and RT group using propensity score weighting

Before adjusting using propensity score, patients who received RT were more likely to have undergone surgery

Table 1 Overall patient and tumor characteristics ($n = 6038$)

Characteristics	No. of patients (%)
Median age at diagnosis (year)	48 (16–87)
Body mass index (kg/m^2)	
< 25	3506 (58.1)
≥ 25	1055 (17.5)
Unknown	1477 (24.5)
Marital status	
Single	315 (5.2)
Married	3893 (64.5)
Unknown	1830 (30.3)
Operation period (years)	
1993–2002	362 (6.0)
2003–2007	1681 (27.8)
2008–2012	3995 (66.2)
Laterality	
Left	2900 (48.0)
Right	2708 (44.8)
Both	11 (0.2)
Unknown	419 (6.9)
Tumor size (cm)	
< 2.0	3366 (55.7)
≥ 2.0	1247 (20.7)
Unknown	1425 (23.6)
Histologic grade	
1, 2	352 (5.8)
3	131 (2.2)
Unknown	5555 (92.0)
Nuclear grade	
1, 2	2568 (42.5)
3	833 (13.8)
Unknown	2637 (43.7)
Estrogen receptor	
Positive	4320 (71.5)
Negative	1130 (18.7)
Unknown	588 (9.7)
Progesterone receptor	
Positive	3966 (65.7)
Negative	1480 (24.5)
Unknown	592 (9.8)
HER2 status	
Positive	1082 (17.9)
Negative	3324 (55.1)
Unknown	1632 (27.0)
Subtype	
Luminal A	3031 (50.2)
Luminal B	572 (9.5)
HER2	508 (8.4)
TN	291 (4.8)
Unknown	1636 (27.1)
Radiation therapy	
Yes	5015 (83.1)
No	1023 (16.9)
Hormonal therapy	
Yes	4317 (71.5)
No	1486 (24.6)
Unknown	235 (3.9)

HER2 human epidermal growth factor receptor 2, *TN* triple negative

in 2008–2012, a large-sized tumor, poor histologic grade, poor nuclear grade, less ER+, less PR+, more HER2+, less Luminal A subtype, and received more hormonal therapy, as shown in Table 2. After IPTW adjusting, the weighted number of patients in the non-RT and RT groups was 4201 and 4163, respectively. Previously noted differences in characteristics were substantially reduced after weighting, with the exception of tumor size and histologic grade of which SMD still exceeded 0.1.

Survival benefit of RT before and after adjusting propensity scores

The results of baseline univariate and multivariate analyses for OS before propensity score adjusting are listed in Supplemental Table 1. Four factors appeared to be associated with OS in univariate analysis: age, body mass index (BMI), RT, and hormonal therapy. In multivariate model 1, age, BMI, and RT were significant factors for OS. In multivariate model 2, further including operation period and tumor subtype, only RT remained as a significant factor. Ten-year OS rates were 95.0% in the non-RT group and 97.1% in the RT group ($p < 0.001$, Fig. 2, dotted line).

In the IPTW cohort, propensity score-weighted univariate and multivariate analyses for OS were performed (Table 3). All factors except RT were not associated with OS using weighted log-rank tests. After multivariate analysis using the same characteristics before weighting, RT was a unique prognostic factor which showed statistical significance. After weighting, ten-year OS rates were 94.3% in the non-RT group and 97.6% in the RT group ($p = 0.001$, Fig. 2, solid line).

Investigation of survival benefit of RT according to each characteristic and prognostic score

Overall, Supplemental Fig. 1 plotted hazard ratio and 95% confidence intervals comparing OS according to the receipt of RT for each subgroup using every characteristic. The tendency of RT showing a significant OS benefit was not much different in most subgroups.

Table 2 Comparison of patient characteristics by the receipt of radiotherapy before and after propensity score weighting

Characteristics	Unadjusted			Adjusted		
	No-RT ($n=1023$)	RT ($n=5015$)	SMD	No-RT ($n=4201$)	RT ($n=4163$)	SMD
Age (years)	49.0 ± 11.2	48.5 ± 9.2	0.052	49.5 ± 10.7	49.0 ± 9.5	0.025
Body mass index (kg/m^2)	23.0 ± 3.2	23.0 ± 3.2	0.004	23.0 ± 3.2	23.1 ± 3.2	0.029
Married	599 (92.0%)	3294 (92.6%)	0.022	2273 (92.1%)	2676 (92.5%)	0.014
Operation period (years)			0.324			0.047
1993–2002	122 (11.9%)	240 (4.8%)		140 (3.3%)	131 (3.1%)	
2003–2007	337 (32.9%)	1344 (26.8%)		1082 (25.7%)	991 (23.8%)	
2008–2012	564 (55.1%)	3431 (68.4%)		2980 (70.9%)	3041 (73.1%)	
Laterality			0.047			0.073
Left	509 (53.1%)	2391 (51.3%)		2179 (53.4%)	2018 (51.5%)	
Right	447 (46.6%)	2261 (48.5%)		1878 (46.0%)	1890 (48.3%)	
Both	3 (0.3%)	8 (0.2%)		22 (0.6%)	7 (0.2%)	
Tumor size (cm)	1.4 ± 1.4	1.8 ± 1.4	0.325	1.5 ± 1.6	1.6 ± 1.3	0.234
Histologic grade			0.431			0.561
1, 2	80 (87.0%)	272 (69.6%)		362 (88.5%)	219 (65.8%)	
3	12 (13.0%)	119 (30.4%)		47 (11.5%)	114 (34.2%)	
Nuclear grade			0.174			0.004
1, 2	375 (81.7%)	2193 (74.5%)		1716 (75.3%)	2027 (75.1%)	
3	84 (18.3%)	749 (25.5%)		563 (24.7%)	672 (24.9%)	
Estrogen receptor			0.162			0.047
Negative	123 (15.4%)	1007 (21.7%)		958 (22.8%)	865 (20.8%)	
Positive	677 (84.6%)	3643 (78.3%)		3244 (77.2%)	3295 (79.2%)	
Progesterone receptor			0.156			0.030
Negative	171 (21.4%)	1309 (28.2%)		1197 (28.5%)	1132 (27.2%)	
Positive	627 (78.6%)	3339 (71.8%)		3002 (71.5%)	3031 (72.8%)	
HER2 status			0.217			0.019
Negative	532 (83.0%)	2792 (74.2%)		3136 (74.7%)	3137 (75.5%)	
Positive	109 (17.0%)	973 (25.8%)		1062 (25.3%)	1018 (24.5%)	
Subtype			0.250			0.069
Luminal A	501 (78.3%)	2530 (67.3%)		2903 (69.1%)	2866 (68.9%)	
Luminal B	57 (8.9%)	515 (13.7%)		517 (12.3%)	548 (13.2%)	
HER2	51 (8.0%)	457 (12.1%)		545 (13.0%)	470 (11.3%)	
TN	31 (4.8%)	260 (6.9%)		236 (5.6%)	278 (6.7%)	
Hormonal therapy			0.341			0.003
No	383 (38.5%)	1103 (22.9%)		977 (23.3%)	983 (23.6%)	
Yes	613 (61.5%)	3704 (77.1%)		3217 (76.6%)	3182 (76.4%)	

% Calculated only in available cases

HER2 human epidermal growth factor receptor 2, *RT* radiation therapy, *SMD* standardized mean difference, *TN* triple negative

In addition, we stratified patients by two simple prognostic scores using three or four factors which are commonly considered to be prognostic and also available in our dataset (age, BMI, tumor size, or ER status). Prognostic scores were defined as the number of risk factors (age ≥ 50, BMI ≥ 25, tumor size ≥ 2 cm, and ER−). When examining the benefit of RT based on proposed prognostic scores, we found that OS in the RT group was significantly better than that in the non-RT group only for patients with a prognostic score greater than 0 (having at least one risk factor) both using three or four factors (Fig. 3).

Discussion

Since post-BCS RT is regarded as a standard treatment, future RCT to demonstrate a survival benefit of RT cannot be ethically implemented. Plus, it is difficult to assess OS

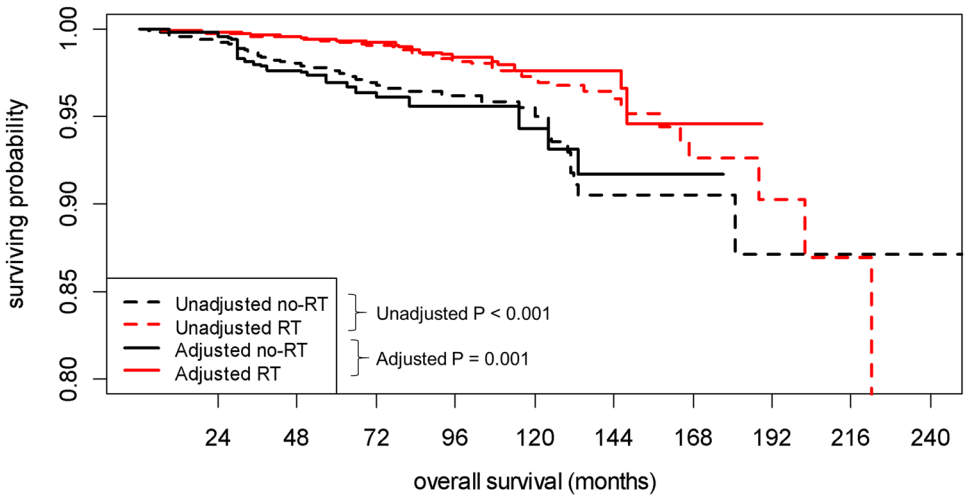


Fig. 2 Propensity score unadjusted and adjusted overall survival curve by the receipt of radiation therapy. *RT* radiation therapy

differences in DCIS using a small number of patients due to the low mortality rate. Thus, we used large population-based data to evaluate the role of RT after BCS with regard to survival rate and propensity score analysis to obtain a less-biased comparison. As a result, we were able to demonstrate small but significant OS differences. It would be not completely accurate to say that there was no OS benefit from RT in DCIS based on the results of rather old RCTs. Recently, mostly using SEER data, researchers demonstrated a significant reduction in breast cancer mortality associated with RT after BCS [10, 14]. Notably, Sagara et al. stated that survival gain from RT was only observed in patients with high prognostic scores consisting of nuclear grade, age, and tumor size [10]. Our study showed similar results, but for the first time, we validated it through independent cohort beyond the western population.

There are several hypotheses that explain the potential OS benefit from RT. First of all, we believe that there is a connection between the reduction in local recurrence (LR) and OS gain. Without RT, even in the selected patients with favorable characteristics and treated with BCS alone, the increased risk of developing LR was observed through more than 10 years of prospective follow-up, without plateau [15]. Overall, RT after BCS in DCIS is known to reduce invasive LR by about numerically 10% [9, 16]. Meanwhile, it is also a well-known breast cancer fact that about one cancer-related death can be avoided for every four LR avoided in the first 5 years [17]; this could be proven by using a large number of patients in several RCTs for invasive breast cancer. Long-term results of NSABP B-17 and B-24 trials also showed that invasive LR was associated with a significantly higher risk of death in patients with DCIS [16]. Assuming the same 1:4 ratio from the meta-analysis applies to DCIS after BCS, RT might be expected to reduce breast cancer mortality by an absolute amount of about 2.5%, which is similar to around 3% reduction noted in our results (unadjusted 2.1%/adjusted 3.3% reduction in 10 years).

Second, inevitable patient selection bias might have affected survival outcomes in our study due to its retrospective nature. Patients receiving RT might have a high social–economic status, less comorbidity, or other unknown hidden bias. But, it was necessary to consider that there was no significant relationship between the presence of patient comorbidities and the receipt of RT after BCS in the setting of DCIS from a previous National Comprehensive Cancer Network study [18]. In that study, the only factor significantly associated with a reduction in the use of RT was having a low/intermediate grade tumor (OR = 0.19; $p < 0.001$), which was also noticed in our cohort (Table 2). Rather, the presence of more high-grade patients in the RT group may have dropped the survival rate of patients who underwent RT because this factor was not fully accounted even after IPTW adjustment due to the high percentage of missing values. Another SEER data-based study also reported that the cost of RT and transportation to an RT facility were not reported to be influential factors when considering the omission of RT [19]. Collectively, we believe that the OS benefit is largely attributable to the effect of RT itself and may not be confounded by the baseline characteristic imbalances.

Third, the potential systemic effects of RT might have affected the OS benefit. Several recent studies on invasive breast cancer have suggested that BCS plus RT is superior to mastectomy in terms of OS despite similar LC rates [20–23]. Although it has not been studied much to date, RT may have contributed to the OS benefit possibly through immune modulatory or systemic effects of a micrometastatic niche. Lastly, in a modern RT era, it is also possible that the development of RT technology has reduced radiation-induced toxicity such as an ischemic heart disease [24, 25]. For example, a variety of heart-sparing techniques has already been used

Table 3 Univariate and multivariate survival analyses in the IPTW cohort

Characteristics	Univariate		Multivariate model 1		Multivariate model 2	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)						
≥ 50 versus < 50	1.019 (0.387–2.685)	0.970	0.833 (0.268–2.587)	0.752	0.777 (0.276–2.183)	0.632
Body mass index (kg/m^2)						
≥ 25 versus < 25	1.246 (0.435–3.565)	0.682	1.301 (0.455–3.721)	0.623	1.251 (0.415–3.771)	0.691
Marital status						
Married versus single	3.182 (0.672–15.067)	0.145				
Operation period (years)						
1993–2002	1				1	
2003–2007	2.050 (0.726–5.787)	0.175			1.870 (0.277–12.623)	0.520
2008–2012	0.639 (0.195–2.090)	0.459			0.728 (0.119–4.441)	0.731
Laterality						
Right versus left	2.178 (0.880–5.387)	0.092				
Tumor size (cm)						
≥ 2 versus < 2	0.669 (0.232–1.929)	0.457				
Nuclear grade						
3 versus 1, 2	2.095 (0.353–12.456)	0.416				
Estrogen receptor						
(+) versus (−)	0.446 (0.132–1.502)	0.192				
Progesterone receptor						
(+) versus (−)	0.443 (0.153–1.285)	0.134				
HER2 status						
(+) versus (−)	1.661 (0.448–6.156)	0.448				
Subtype						
Luminal A	1				1	
Luminal B	0.527 (0.222–1.251)	0.147			0.444 (0.145–1.357)	0.154
HER2	3.008 (0.656–13.794)	0.156			7.467 (0.592–94.175)	0.120
TN	1.238 (0.324–4.735)	0.755			1.571 (0.134–18.385)	0.719
Radiation therapy						
Yes versus no	0.288 (0.137–0.607)	0.001	0.241 (0.097–0.600)	0.002	0.276 (0.137–0.558)	< 0.001
Hormonal therapy						
Yes versus no	0.758 (0.320–1.794)	0.528	1.019 (0.375–2.764)	0.971	3.904 (0.349–43.738)	0.269

CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IPTW, inverse probability treatment weighting; TN, triple negative

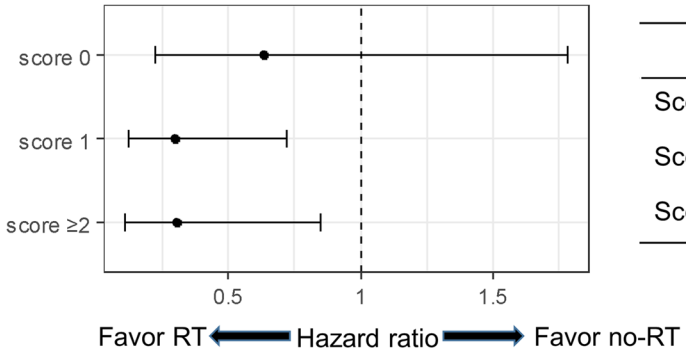
in clinical practice and will continue to have a large impact on the reduction of RT-induced late side effects [26, 27].

However, patients with a very low prognostic score still showed no difference in OS by adding RT after BCS in our results, whereas those with high scores demonstrated a significant benefit. As previously shown, variable risk subpopulations of patients with DCIS are mixed together. Still, it is debatable whether such a small OS benefit is large enough to warrant RT for all patients. The omission of RT according to prognostic score to prevent overtreatment needs to be studied further considering its potential OS detrimental effect.

The present study has several limitations. Although it may be a limitation of large-scale cohort studies, it is sometimes impossible to analyze essential factors. First, in terms of survival endpoint, only the OS could be analyzed without recurrence data and breast cancer-specific survival. Second, information about several important characteristics, such as surgical margin, tumor grade, and patient comorbidities was also not abundantly available. But margin-positive BCS rarely occurred, and even if the surgical margin was positive, a physician would be more likely to recommend RT then the benefit of RT being underestimated in this study. Lastly, as described in the "Methods" section, details of RT data (total dose, fractionation, technique, boost administration) were not available in this nation-wide database.

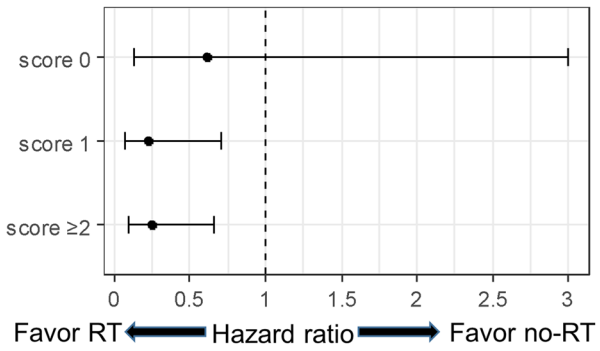
In conclusion, our results demonstrated that a significant OS benefit could be obtained by the addition of RT after BCS for DCIS. Nevertheless, it is known that the

A Score = Age (≥50) + BMI (≥25) + Size (≥2cm) ; each 1 point



	n	HR	95% CI	P value
Score 0	1234	0.634	0.226-1.780	0.387
Score 1	1379	0.301	0.126-0.724	0.007
Score ≥2	749	0.307	0.111-0.848	0.023

B Score = Age (≥50) + BMI (≥25) + Size (≥2cm) + ER (-) ; each 1 point



	n	HR	95% CI	P value
Score 0	970	0.617	0.127-2.994	0.549
Score 1	1121	0.228	0.074-0.708	0.011
Score ≥2	998	0.245	0.091-0.662	0.006

Fig. 3 Hazard ratio comparing overall survival between the radiation therapy group and the non-radiation therapy group according to prognostic scores. **a** Score by age, body mass index, and tumor size. **b** Score by age, body mass index, tumor size, and estrogen receptor positivity. *BMI* body mass index, *CI* confidence interval, *ER* estrogen receptor, *HR* hazard ratio, *RT* radiation therapy

exclusion of RT from the treatment plan is happening more than expected at the current clinics [19]. There is a steadfast concern regarding RT-related risks. However, along with technical advances, the risk is diminishing, and the small but clear survival benefits should not be overlooked. Therefore, more careful selection of patients will be needed to safely omit RT for better personalized therapy.

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Data availability The data that support the findings of this study are available from the Korean Breast Cancer Society but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the Korean Breast Cancer Society.

Compliance with ethical standards

Conflict of interest The authors declare that no actual or potential conflict of interest exists. The Institutional Review Boards approved this study (Seoul Metropolitan Government Seoul National University Boramae Medical Center, 07-2017-6).

Ethical approval All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

Research involving human participants and/or animals This article does not contain any studies with animals performed by any of the authors.

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