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Original article

Adjuvant radiation therapy in small ductal carcinoma in situ

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ABSTRACT

Background: The objective of this study was to evaluate ipsilateral breast tumor recurrence (IBTR) rates in patients with small (≤1 cm) ductal carcinoma in situ (DCIS) who were followed up for more than 15 years.

Methods: We identified 209 patients with primary small (≤1 cm) DCIS without invasion who received curative excision with and without adjuvant radiation therapy (RT) from 1996 to 2009. IBTR rates and prognostic factors in all patients were estimated by univariate and multivariate analyses.

Results: With a median follow-up of 104 months, eight (53.3%) had DCIS recurrence and seven (46.7%) had recurrence of invasive ductal carcinoma. IBTR rate of all patients was 7.5% at 10 years and 12.1% at 15 years. In univariate analysis, age and subtypes were significant factors for IBTR. In multivariate analysis, resection margin, adjuvant RT, and endocrine therapy were significant factors for IBTR.

Conclusions: IBTR rate of small (≤1 cm) DCIS following excision with or without adjuvant RT was 12.1% at 15 years. Adjuvant RT and endocrine therapy were associated with lower IBTR rate in small DCIS.

1. Background

Incidence of ductal carcinoma in situ (DCIS) has increased as screening programs are widely implemented [1,2]. Given the increasing proportion of screening-detected tumors, physicians are encountering DCIS with size of 1 cm or smaller more often than in the past. Although adjuvant radiation therapy (RT) following excision of DCIS is proven to reduce ipsilateral breast tumor recurrence (IBTR) rates, the use of adjuvant RT remained optional for these patients, due to the absence of survival benefit and concerns about radiation complications [3]. A number of clinical and pathological factors have been suggested to predict the risk of recurrence and individualize the use of adjuvant RT in DCIS patients [4–7]. Although tumor size has been previously demonstrated to be one of the most powerful risk factors, the prognostic significance of tumor size in DCIS remains unclear, particularly in low-risk patients.

We have previously reported that adjuvant RT following excision could be omitted in small DCIS with size less than 1 cm [8]. However, a recent update of Eastern Cooperative Oncology Group (ECOG) trial has shown that the IBTR rate continuously increased without plateau in those receiving excision alone for low to intermediate risk DCIS [9]. That trial suggested that tumors that we considered to have low risk of IBTR might not actually have low IBTR rate. Instead, they may have more delayed IBTR compared to so called “high risk” tumors [9]. The authors of that trial have emphasized that longer follow-up periods of more than 12 years are necessary to estimate the effect of RT in low to intermediate risk DCIS. Accordingly, the objective of the present study was to evaluate IBTR rate of small size (≤1 cm) DCIS with a long-term follow-up period. Furthermore, we compared IBTR rates of those who did receive adjuvant RT for small size DCIS and those who did not.

2. Methods

We identified 209 patients with primary DCIS with size of 1 cm or less without invasion who received curative partial mastectomy at Samsung Medical Center from 1996 to 2009. Adjuvant RT was recommended mainly for high risk patients with close resection margin, high nuclear grade, and/or comedo-type histology. It was ultimately determined after discussion between physicians and patients. Lymph node evaluation with sentinel lymph node biopsy or axillary dissection was performed for 53 patients. RT dose to the whole breast was 45–54 Gy by 1.8–2.0 Gy per fraction. Primary tumor bed boost was applied to 17 (8.1%) patients, mainly those with close resection margins. RT dose for tumor bed boost was 9–18 Gy by 1.8–3.5 Gy per fraction. Molecular subtypes were

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determined according to results of immunohistochemical (IHC) staining for estrogen receptor (ER), progesterone receptor (PR), and HER2. HER2-positive was defined as a staining score of three in IHC.

Distributions of categorical variables between patients who did receive RT and those who did not were compared using Chi-square tests. Time to IBTR was defined as the time between the date of surgery and the date of IBTR. We used the Kaplan-Meier method to estimate cumulative incidence of ITBR and generate survival curves. Cumulative incidence curves were compared using a Log-rank test. Cox proportional hazards model was used to control confounding factors and to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). All the factors that included in univariate analysis were entered in the multivariate analysis simultaneously. A P value < 0.05 was considered statistically significant. All analyses were conducted using SPSS Statistics version 20 (SPSS Inc., IBM, Armonk, NY, USA) and STATA statistical software version 11.0 (STATA, College Station, TX, USA).

3. Results

3.1. Patient characteristics

Patient and tumor characteristics are summarized in Table 1. The median age was 47 years (range, 23–81 years) and the median tumor size was 0.6 cm (range, 0.05–1.0 cm). The most frequent histologic type was cribriform-type (n = 59, 28.2%), followed by comedo-type (n = 36, 17.2%) and solid-type (n = 25, 12%). Most tumors (82.1%, n = 146) presented low-to-intermediate nuclear grade. Hormone receptor-positive and HER2-negative subtype (70.8%, n = 148) was the most frequent subtype, followed by hormone receptor-positive and HER2-positive subtype (6.7%, n = 14). Of all patients, 144 (69.9%) received endocrine therapy. Among them, 132 patients were hormone receptor-positive and 12 patients had unknown subtype. Adjuvant whole breast RT was performed for 103 (49.3%) patients. No patient received adjuvant trastuzumab therapy.

Table 1
Characteristics of all patients.

Median size (range)	0.6 (0.05–1.0) cm
Age	
< 40 years	38 (18.2%)
≥ 40 years	171 (81.8%)
Histologic types	
Cribriform	59 (28.2%)
Solid	25 (12%)
Micropapillary	13 (6.2%)
Comedo	36 (17.2%)
Mixed w/o comedo	37 (17.7%)
Unknown	39 (18.7%)
Nuclear grade	
Low-intermediate	146 (82.1%)
High	32 (18.0%)
Subtypes	
HR +, HER2 +	14 (6.7%)
HR +, HER2 -	148 (70.8%)
HR-, HER2+	2 (1%)
HR-, HER2-	12 (5.7%)
Unknown	33 (15.8%)
Necrosis	
Absent	154 (73.7%)
Present	55 (26.3%)
Resection margin	
< 2 mm	25 (12%)
≥ 2 mm	184 (88%)
Multifocal tumor	
No	173 (83.2%)
Yes	35 (16.8%)
Adjuvant RT	
No	106 (50.7%)
Yes	103 (49.3%)
Endocrine therapy	
No	65 (31.1%)
Yes	144 (69.9%)

Abbreviation; RT, radiation therapy; HR, hormone receptor.

3.2. Ipsilateral breast recurrence and prognostic factors

After a median follow-up of 104 months, 15 patients developed IBTR. Cumulative IBTR rate was 7.5% at 10 years and 12.1% at 15 years (Fig. 1). Of these 15 patients, eight (53.3%) recurred as DCIS whereas seven (46.7%) patients showed recurrence of invasive ductal carcinoma. Salvage mastectomy was done for 12 patients while two patients received breast-conserving therapy for salvage treatment. One patient was lost to follow-up. No patient died from breast cancer among all 15 patients with IBTR.

Factors including size of tumor, age, histologic type, molecular subtype, nuclear grade, necrosis, resection margin, multifocality, adjuvant RT, and adjuvant endocrine therapy were included to identify prognostic factors for IBTR. In univariate analysis, age <40 years ($p = 0.033$) and hormone-positive and HER2-negative subtype ($p < 0.001$) were associated with higher IBTR rates (Table 2). In multivariate analysis including all the factors, resection margin ≥2 mm (HR: 0.156, 95% CI: 0.029–0.852, $p = 0.032$), adjuvant RT (HR: 0.104, 95% CI: 0.015–0.712, $p = 0.021$), and endocrine therapy (HR: 0.144, 95% CI: 0.024–0.849, $p = 0.032$) were related to lower IBTR rates (Table 3).

3.3. Effect of adjuvant RT in those who received endocrine therapy

To identify the effect of adjuvant RT in the setting of standard treatment, we evaluated IBTR rates in subset of patients who had hormone receptor-positive tumor and received endocrine therapy (n = 132). Among these 132 patients, 57 (43.2%) received adjuvant RT while 87 (65.8%) received excision alone. The IBTR rate in the adjuvant RT group was significantly lower than that in the RT-omitted group (28.8% vs. 1.8% at 12 years, $p = 0.020$).

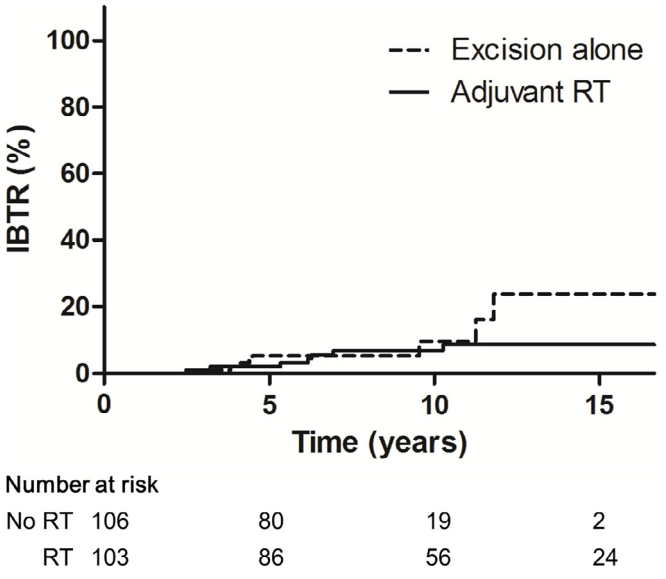

Fig. 1. Ipsilateral breast tumor recurrence in all patients.

Table 2
Univariate analysis of prognostic factors for ipsilateral breast tumor recurrence.

Characteristics	10-year IBTR rate (%)	15-year IBTR rate (%)	P −value[a]
Tumor size			
< 0.5 mm	7.7%	7.7%	*0.903*
≥ 0.5 mm	7.3%	13.2%	
Age			
< 40 years	9.7%	32.6%	*0.033*
≥ 40 years	5.5%	7.0%	
Comedo type			
No	8.5%	12.8%	*0.565*
Yes	2.9%	8.3%	
Nuclear grade			
Low-intermediate	9.5%	15.2%	*0.289*
High	3.4%	3.4%	
Subtypes			*<0.001*
HR +, HER2 +	8.3%	8.3%	
HR +, HER2 -	8.7%	14.6%	
HR-, HER2+	0	0	
HR-, HER2-	0	0	
Unknown	3.1%	8.8%	
Necrosis			
Absent	9.3%	15.0%	*0.098*
Present	2.0%	2.0%	
Resection margin			
< 2 mm	14.4%	21.5%	*0.140*
≥ 2 mm	6.5%	10.5%	
Multifocal tumor			
No	6.4%	10.6%	*0.093*
Yes	13.4%	19.2%	
Adjuvant RT			
No	9.4%	23.5%	*0.359*
Yes	7.0%	8.7%	
Endocrine therapy			
No	12.1%	15.5%	*0.248*
Yes	5.6%	11.4%	

Abbreviation; IBTR, ipsilateral breast tumor recurrence; RT, radiation therapy.
[a] P-value by log-rank test.

Table 3
Multivariate analysis of prognostic factors for ipsilateral breast tumor recurrence.

Characteristics		HR (95% CI)	P -value
Tumor size	<0.5 mm ≥0.5 mm	11.756 (0.374–8.232)	*0.922*
Age	<40 years ≥40 years	10.345 (0.082–1.457)	*0.148*
Comedo type	No Yes	11.112 (0.133–9.269)	*0.922*
Nuclear grade	Low-intermediateHigh	10.001 (0.001–10^2)	*0.965*
Subtypes	HR +, HER2 + [a]	1	*0.442*
	HR +, HER2 -	0.145 (0.013–1.682)	
	Unknown	0.029 (0.001–1.060)	
Necrosis	AbsentPresent	10.263 (0.026–2.668)	*0.259*
Resection margin	<2 mm≥2 mm	10.156 (0.029–0.852)	*0.032*
Multifocal tumor	NoYes	11.612 (0.292–8.886)	*0.583*
Adjuvant RT	NoYes	10.104 (0.015–0.712)	*0.021*
Endocrine therapy	NoYes	10.144 (0.024–0.849)	*0.032*

Abbreviation; HR, hazard ratio; CI, confidence interval; RT, radiation therapy.
[a] Hazard ratios of HR-/HER2+ and HR-/HER2- subtypes could not be calculated since no event occurred in these groups.

4. Discussion

This study revealed that adjuvant RT was associated with lower IBTR rate in small DCIS (<1 cm). The benefit of adjuvant RT for small DCIS is still controversial. Hughes et al. have suggested that IBTR risk is high (12.7%) even in DCIS < 1 cm if they are high grade [10]. Rakovitch et al. have also reported that excision alone for DCIS with size less than 1 cm might not be safe [11]. Our previous study has shown that the IBTR rate of small size DCIS (≤1 cm) following excision is acceptable without adjuvant RT (5-year IBTR rate: 6.1%) after a median follow-up of 58 months [8]. However, with a median follow-up of 91.5 months, the IBTR rate following excision alone was much higher (23.5% at 15 years) in this study. This IBTR rate was similar to that in the ECOG study (24.6% at 12 years) [9].

It has been proven that endocrine therapy can reduce the risk of DCIS and invasive cancer of the breast following surgical resection of DCIS [12–14]. The National Comprehensive Cancer Network guideline recommends 5-year endocrine therapy following surgical resection for patients with ER-positive DCIS regardless of tumor size [15]. In this study, 18.5% of hormone receptor-positive patients omitted endocrine therapy and most of whom were treated in earlier periods of this study between late 1990s and early 2000s when adjuvant endocrine therapy had not been completely established yet. Interestingly, adjuvant RT and endocrine therapy were both significant factors for IBTR in multivariate analysis after controlling other confounding factors.

In this study, high risk factors such as high nuclear grade, comedo type, and close resection margin (<2 mm) were more frequent in the adjuvant RT group than those in the RT-omitted group (data not shown). This suggests that the decision to use adjuvant RT might have been made based on these factors in small DCIS. However, higher IBTR rate in RT-omitted group implies that current risk stratifications are missing a few patients who would be able to avoid IBTR if they have received adjuvant RT. A recent Korean Radiation Oncology Group 16-02 study has reported that, among those with low to intermediate risk, age and margin width are the most significant factors for recurrence [16]. In their next study, they confirmed that RT could diminish the risk of IBTR in those younger than 50 years who had margin width of less than 1 cm [17]. The Radiation Therapy Oncology Group (RTOG) 9804 trial aims to investigate the role of adjuvant RT in low-risk DCIS having a size less than 2.5 cm, low or intermediate nuclear grade, and margin width of more than 3 mm. Long-term results of RTOG 9804 will offer more information regarding the role of RT in low to intermediate risk DCIS [18]. Recently, biomarkers such as Oncotype DX, COX-2, or p51 have been reported to have association with IBTR risk [19]. Further development of reliable biomarkers is expected to predict recurrence risk and the effect of adjuvant RT in DCIS.

This study has a few limitations due to its retrospective nature. First, the number of patients was too small to draw a significant result. Second, diagnostic and surgical approaches might have been changed during the long study period. Moreover, tumor characteristics differed between those who did receive adjuvant RT and those who did not, which implies that there might be a selection bias. However, although unfavorable factors such as high nuclear grade and close resection margin (<2 mm) were more frequent in the RT group than those in the RT-omitted group, IBTR was higher in RT-omitted patients than that in the adjuvant RT group. Furthermore, median follow-up period was shorter for the RT-omitted group than that for the RT group, suggesting that IBTR rate in the RT-omitted group could increase after a longer follow-up. Nevertheless, clinical impact of adjuvant RT on small DCIS remains obscure considering a still relatively small number of IBTR events (15/209) after 15 years of follow up without cancer-related death. The necessity of adjuvant RT for low-risk DCIS needs to be confirmed by larger prospective trials.

In conclusion, the IBTR rate of small DCIS with size of 1 cm or less was 12.1% at 15 years. Adjuvant RT and endocrine therapy were favorable factors for lower IBTR rate in small DCIS (≤1 cm). Larger studies are warranted to elucidate the role of adjuvant RT in low risk DCIS patients.

Conflicts of interest

The authors declare no conflicts of interest.

This study was approved by the Institutional Review Board at Samsung Medical Center (IRB No. 2017-09-060).

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References

[1] Smith BD, Smith GL, Buchholz TA. Controversies over the role of radiation therapy for ductal carcinoma in situ. Expert Rev Anticancer Ther 2008;8:433–41.
[2] Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst 2010;102:170–8.
[3] Correa C, McGale P, Taylor C, Wang Y, Clarke M, Davies C, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010;2010:162–77.
[4] Rudloff U, Jacks LM, Goldberg JI, Wynveen CA, Brogi E, Patil S, et al. Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ. J Clin Oncol 2010;28:3762–9.
[5] Silverstein MJ, Lagios MD, Craig PH, Waisman JR, Lewinsky BS, Colburn WJ, et al. A prognostic index for ductal carcinoma in situ of the breast. Cancer 1996;77:2267–74.
[6] Silverstein MJ. The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast. Am J Surg 2003;186:337–43.
[7] Sagara Y, Freedman RA, Vaz-Luis I, Mallory MA, Wong SM, Aydogan F, et al. Patient prognostic score and associations with survival improvement offered by radiotherapy after breast-conserving surgery for ductal carcinoma in situ: a population-based longitudinal cohort study. J Clin Oncol 2016;34:1190–6.
[8] Kim H, Noh JM, Choi DH, Lee J, Nam SJ, Lee JE, et al. Excision alone for small size ductal carcinoma in situ of the breast. Breast 2014;23:586–90.
[9] Solin LJ, Gray R, Hughes LL, Wood WC, Lowen MA, Badve SS, et al. Surgical excision without radiation for ductal carcinoma in situ of the breast: 12-year results from the ECOG-ACRIN E5194 study. J Clin Oncol 2015;33:3938–44.
[10] Hughes LL, Wang M, Page DL, Gray R, Solin LJ, Davidson NE, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2009;27:5319–24.
[11] Rakovitch E, Gray R, Baehner FL, Sutradhar R, Crager M, Gu S, et al. Refined estimates of local recurrence risks by DCIS score adjusting for clinicopathological features: a combined analysis of ECOG-ACRIN E5194 and Ontario DCIS cohort studies. Breast Canc Res Treat 2018;169:359–69.
[12] Fisher B, Dignam J, Wolmark N, Wickerham DL, Fisher ER, Mamounas E, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 1999;353:1993–2000.
[13] Allred DC, Anderson SJ, Paik S, Wickerham DL, Nagtegaal ID, Swain SM, et al. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. J Clin Oncol 2012;30:1268–73.
[14] Cuzick J, Sestak I, Pinder SE, Ellis IO, Forsyth S, Bundred NJ, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol 2011;12:21–9.
[15] National Comprehensive Cancer Network. NCCN clinical practice guidelines in Oncology: breast cancer. Version 1. 2018. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
[16] Kim K, Jung SY, Shin KH, Kim JH, Han W, Lee HB, et al. Recurrence outcomes after omission of postoperative radiotherapy following breast-conserving surgery for ductal carcinoma in situ of the breast: a multicenter, retrospective study in Korea (KROG 16-02). Breast Canc Res Treat 2017;162:77–83.
[17] Kim K, Kim JH, Kim YB, Suh CO, Shin KH, Kim JH, et al. Selective radiation therapy for ductal carcinoma in situ following breast-conserving surgery according to age and margin width: Korean radiation Oncology group 11-04 and 16-02 studies. J Breast Cancer 2017;20:327–32.
[18] McCormick B, Winter K, Hudis C, Kuerer HM, Rakovitch E, Smith BL, et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. J Clin Oncol 2015;33:709–15.
[19] Kerlikowske K, Molinaro AM, Gauthier ML, Berman HK, Waldman F, Bennington J, et al. Biomarker expression and risk of subsequent tumors after initial ductal carcinoma in situ diagnosis. JNCI J Natl Cancer Inst 2010;102:627–37.