

Original Article



Comparison of Recurrence Rate Between Re-Excision With Radiotherapy and Radiotherapy-Only Groups in Surgical Margin Involvement of *In Situ* Carcinoma

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ABSTRACT

Purpose: Surgical margin status is a surrogate marker for residual tumors after breast-conserving surgery (BCS). A comparison of ipsilateral breast tumor recurrence (IBTR) rates between re-excision combined with radiotherapy (excision with RTx) and RTx alone, following the confirmation of ductal carcinoma *in situ* (DCIS) in the resection margin after BCS, has not been reported previously. Therefore, in the present study, the clinical characteristics of DCIS involvement in the surgical resection margin between excision with RTx and RTx alone were investigated, and the IBTR rate was compared.

Methods: We analyzed 8,473 patients treated with BCS followed by RTx between January 2013 and December 2019. Patients were divided into 2 groups based on surgical resection margin status in permanent pathology, and superficial and deep margins were excluded. Patients who underwent re-excision with DCIS confirmed in the resection margin were identified and the IBTR rate was examined.

Results: Among 8,473 patients treated with BCS, 494 (5.8%) had positive surgical resection margins. The median follow-up period was 47 months. Among the 494 patients with a positive resection margin, 368 (74.5%) had residual DCIS at the surgical resection margin in the final pathology. Among those with confirmed DCIS at the resection margin, 24 patients (6.5%) were re-excised, and 344 patients (93.5%) underwent RTx after observation. The IBTR rates were 4.2% and 1.2% in the re-excision and observation groups, respectively. IBTR-free survival analysis revealed no significant difference between the excision with RTx and RTx-only groups ($p = 0.262$).

Conclusion: The IBTR rate did not differ between the excision with RTx and RTx-only groups when DCIS was confirmed at the resection margins. This suggests that RTx and close observation without re-excision could be an option, even in cases where minimal involvement of DCIS is confirmed on surgical resection.

Keywords: Carcinoma, Intraductal, Noninfiltrating; Margins of Excision; Mastectomy, Segmental; Radiotherapy; Recurrence

Jeong Eon Lee <https://orcid.org/0000-0003-0037-2456>Seok Won Kim <https://orcid.org/0000-0002-6130-7570>Seok Jin Nam <https://orcid.org/0000-0003-1072-8954>Byung Joo Chae <https://orcid.org/0000-0003-1564-0978>**Conflict of Interest**

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Chae BJ; Investigation: Lee H, Bang YJ; Supervision: Lee JE, Kim SW, Nam SJ; Visualization: Ryu JM, Lee SK, Yu J; Writing - original draft: Lee JH.

INTRODUCTION

Breast-conserving surgery (BCS) with radiation therapy is the treatment option of early breast cancer. BCS followed by radiotherapy (RTx) decreases ipsilateral breast tumor recurrence (IBTR) and improves overall survival [1,2].

Complete excision of the tumor and clear surgical resection margins are required when performing BCS. Frozen biopsies are routinely examined to identify the presence of residual tumor to prevent recurrence because residual disease increases the risk of IBTR [3,4]. The absence of ink on the tumor is a well-known principle of surgical margin status, and when the final pathology confirms the involvement of invasive cancer in the margin, re-excision of the involved margin should be considered [5,6]. Like invasive cancer, when ductal carcinoma *in situ* (DCIS) confirmed in the resection margin of the final pathology, the principle so far is to do complete excision of DCIS involved margin through reoperation [7]. In other words, the current international guideline recommends additional resection if there is a tumor in the margin regardless of in situ or invasive cancer.

However, if DCIS is confirmed in the final resection margin, there still remains controversy among surgical oncologists as to whether additional resection should be performed [8-11]. In cases where additional excision of the margin is performed during reoperation, accurate re-excision is difficult because of the effects of adhesions and breast reshaping. RTx is an effective alternative option when DCIS is involved because it minimizes side effects and maximizes therapeutic effects. In addition, Tamburelli et al. [12] reported that residual tumor was found in less than 50% of reoperation specimens after margin re-excision. Conversely, the IBTR rate also increased when a margin was involved in DCIS. However, few studies have compared IBTR rates between re-excision combined with RTx (excision with RTx) and RTx alone in cases where DCIS was confirmed in the resection margin after BCS.

In the present study, the clinical characteristics of DCIS involvement in the surgical resection margin between excision with RTx and RTx-only approaches were investigated, and the IBTR rate was compared based on the re-excision of margins treated with BCS followed by RTx.

METHODS

The medical records of patients who underwent BCS followed by RTx at Samsung Medical Center between January 2013 and December 2019 were retrospectively reviewed. From final pathologic reports, the pathologic stage, histologic and nuclear grade, multiplicity, extensive intraductal component, lymphatic invasion, hormone receptor status, human epidermal growth factor receptor 2 (HER2) status, lateral parenchymal resection margin width in 4 directions (superior, inferior, medial, and lateral), and superficial or deep resection margin width were investigated. Age, median follow-up duration, and adjuvant chemotherapy data were obtained from the medical records (**Table 1**).

Patients with a positive surgical resection margin in the final pathology were identified, and DCIS involvement with margin status was examined. Patients with invasive ductal carcinoma at the surgically involved margin and those with a superficial or deep margin involvement of DCIS were excluded. Finally, patients with lateral parenchymal margin involvement in DCIS were included.

Table 1. Demographic and baseline clinical characteristics between re-excision combined with RTx and RTx only for ductal carcinoma *in situ* margin involvement

Characteristics	Excision with RTx (n = 24)	RTx only (n = 344)	p-value
Age (yr)	48.2 (26–62)	50.7 (28–78)	0.129
Follow-up duration (mo)			0.223
Median	52	50	
Mean ± SD	51.60 ± 3.25	48.70 ± 0.97	
Tumor size (cm)			0.856
≤ 2	19 (79.2)	285 (82.8)	
> 2	5 (20.8)	59 (17.2)	
Node metastasis			0.414
Negative	14 (58.3)	236 (68.6)	
Positive	10 (41.7)	108 (31.4)	
Histologic grade			0.166
1/2	18 (75.0)	201 (58.4)	
3	6 (25.0)	143 (41.6)	
Nuclear grade			0.393
1/2	20 (83.3)	257 (74.7)	
3	4 (16.7)	87 (25.3)	
Multiplicity			1.000
None	18 (75.0)	262 (76.2)	
Yes	6 (25.0)	82 (23.8)	
EIC			0.620
Absent	16 (66.7)	204 (59.3)	
Present	8 (33.3)	140 (40.7)	
Lymphatic invasion			0.071
None	23 (95.8)	269 (78.2)	
Yes	1 (4.2)	75 (21.8)	
Hormone receptor			1.000
Negative	4 (16.7)	63 (18.3)	
Positive	20 (83.3)	281 (81.7)	
HER2			0.540
Negative	20 (83.3)	260 (75.6)	
Positive	4 (16.7)	84 (24.4)	
Adjuvant chemotherapy			0.197
None	19 (79.2)	220 (64.0)	
Yes	5 (20.8)	124 (36.0)	

RTx = radiotherapy; SD = standard deviation; EIC = extensive intraductal component; HER2 = human epidermal growth factor receptor 2.

In addition, we investigated whether re-excision was performed after margin involvement or after RTx alone without re-excision. Whether to re-excise the involved margin or to observe was at the surgeon's discretion or on shared decision-making with patients after confirming DCIS involvement at the surgical resection margin in the final pathology report. The dose generally administered to the whole breast was 50–50.4 Gy in 25–28 fractions or 42.4 Gy in 16 fractions using 2 tangential photon beams with an electron beam boost to the tumor bed. If the safety margin exceeded 3 mm, a boost of 3 Gy in 3 fractions was applied to the tumor bed. If re-excision was not performed, a total radiation boost dose of 15 Gy (3 Gy in 5 fractions) was additionally applied to the positive margin site that could be checked with a clip. If the residual tumor was close to the margin (within 3 mm), an additional 3.5 Gy in a 3-fraction regimen (total boost dose, 10.5 Gy) was applied to the tumor bed region.

IBTR and survival were compared between the excision with RTx group and RTx-only group (**Figure 1**). IBTR was defined as recurrent invasive carcinoma and/or DCIS in either the skin or parenchyma of the ipsilateral breast after BCS, in the absence of clinical and radiological evidence of regional or distant metastases.

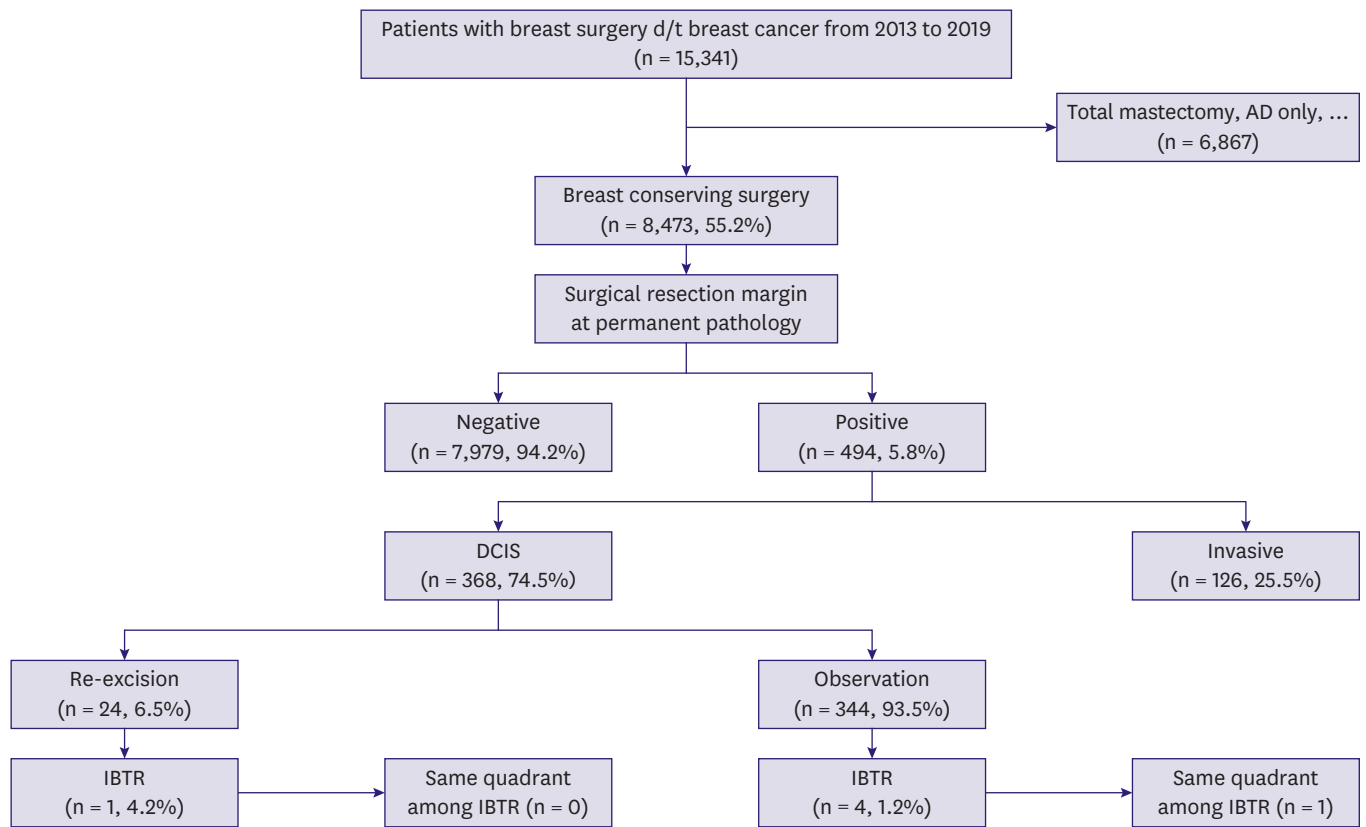


Figure 1. Study flow diagram.

AD = axillary dissection; DCIS = ductal carcinoma *in situ*; IBTR = ipsilateral breast tumor recurrence; d/t = due to.

A negative resection margin was defined as the lack of tumor cells on the inked resected margin of the specimen, and a positive resection margin was defined as a histologically positive margin in invasive or *in situ* breast carcinoma after lumpectomy. Re-excision was performed in patients with positive resection margins in the final pathology. All the patients underwent whole breast RTx after BCS. The radiation dose and technique did not differ between the 2 groups.

Statistical analysis

Patient characteristics were compared using independent *t*-tests for continuous variables and the χ^2 or Fisher's exact test for categorical variables. Values are reported as mean \pm standard deviation or median with range. Survival from the date of the first operation to the time of death was analyzed using the Kaplan-Meier method. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, USA).

Ethics

The study was approved by the Institutional Review Committee (IRB No. 2021-08-087) at Samsung Medical Center and was conducted according to the principles outlined in the Declaration of Helsinki.

RESULTS

Among the 15,341 patients who underwent surgery for breast cancer between January 2013 and December 2019 at Samsung Medical Center, 8,473 (55.2%) were treated with BCS (**Figure 1**). The surgical resection margins of 494 patients (5.8%) were positive in the final pathology, 368 patients (74.5%) had DCIS at the surgical resection margin, and 126 patients (25.5%) had invasive carcinoma at the surgical resection margin. Furthermore, 24 patients (6.5%) underwent additional margin re-excision followed by RTx and 344 patients (93.5%) underwent postoperative RTx without further margin re-excision. IBTR occurred in 1 (4.2%) of the 24 patients in the RTx with excision group and 4 (1.2%) of the 344 patients in the RTx-only group.

Baseline clinical characteristics between the RTx with excision and RTx-only groups in which DCIS was diagnosed at the final surgical resection margin are shown in **Table 1**. The median age of patients was 48.2 (26–62) years and 50.7 (28–78) years in the excision with RTx and RTx-only groups, respectively. The median follow-up duration in the excision with RTx and RTx-only groups was 52 (51.60 ± 3.25) months and 50 (48.70 ± 0.97) months, respectively; the differences between the 2 groups were not significant. Although the relative proportions of tumor size, nodal status, and multiplicity were higher in the excision with RTx group than in the RTx-only group, the differences between the 2 groups were not significant. In both the groups, > 80% of the patients were hormone receptor-positive and HER2-negative. In this study, DCIS was confirmed in the additional resected margin in 11 (47.8%) of the 24 patients in the final biopsy after re-excision.

The median follow-up duration was 47.0 months. No differences were observed in IBTR rates between the excision with RTx and RTx-only groups ($p = 0.262$; **Figure 2**). The mean width of the involvement was also investigated. Lateral margin involvement in the excision with RTx and RTx-only groups were 3.180 (0.10–17.00) mm and 2.522 (0.10–35.00) mm, respectively; differences between the 2 groups were nonsignificant.

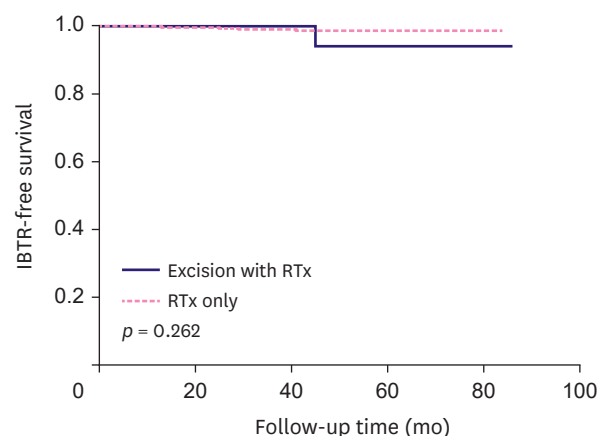


Figure 2. IBTR-free survival curve between re-excision combined with RTx and RTx alone for ductal carcinoma *in situ* margin involvement.

IBTR = ipsilateral breast tumor recurrence; RTx = radiotherapy.

DISCUSSION

In the present study, the IBTR rate did not differ between the excision with RTx and RTx-only groups when DCIS was confirmed at the resection margin after BCS. This result suggests that additional surgery, which places additional risk and burden on the patient, can be avoided in cases of minimal DCIS involvement. In addition, it is possible to avoid deformation of the breast shape because of additional partial breast tissue resection. It is also possible to avoid a decrease in compliance with patient-doctor relationship due to not performing reoperation in term of therapeutic effects.

Many studies have been conducted regarding the location of surgical margins and local recurrence. Some studies have suggested that superficial and deep margins may not have a significant impact on local recurrence and are not important predictors of IBTR [13,14]. In addition, further re-excision may not significantly influence local recurrence because radiation therapy had a significant effect on either the anterior or posterior margin location. Therefore, we focused on the positive involvement of the lateral parenchymal margin and analyzed the margin status except for superficial and/or deep margins.

Quadrants in which IBTR occurs after BCS have been investigated in several studies [15,16]. The location of recurrence can be a factor in determining whether radical surgery should be performed at the time of the initial operation. In the present study, the breast quadrant where IBTR occurred was investigated, which does not necessarily coincide with the initial surgical site. IBTR occurred in 1 (4.3%) of the 24 patients in the excision with RTx group, which did not coincide with the previous lumpectomy site. IBTR occurred in 4 (1.2%) of the 344 patients in the RTx-only group, and only one patient had IBTR in the same quadrant (**Figure 1**). Owing to the small number of cases of IBTR with DCIS involved in the resection margin that have been reported in other studies and the present study, the rate of IBTR cannot be conclusively considered to be reduced even if the surgical site is resected through reoperation.

The main limitation of this study is that it was a retrospective cohort study conducted at a single institution; therefore, further multicenter studies are needed. Selection bias related to surgeon decision-making regarding re-excision or observation may have existed; thus, the study results should be interpreted with caution. Because the median follow-up period was short, studies with long-term follow-up are needed to determine the effects of excision with RTx or RTx alone on IBTR. Re-excision was performed significantly less frequently than RTx alone when DCIS was present in the final margin; thus, comparison of IBTR between the 2 groups is also a limitation. Whether breast cancer subtypes affect margin involvement and re-excision has not been investigated because the presence of accompanying DCIS differs based on the subtype [17]. Despite some limitations, this study included a large cohort and the patient group was homogenous and enrolled from a single institution. IBTR usually occurs within 3 years after BCS; however, in the present study, IBTR was investigated over a 6-year period which adds strength to the study. The factors associated with IBTR in the excision with RTx and RTx-only treatment groups need to be investigated using multivariate analyses in future studies.

In conclusion, the IBTR rate did not differ between excision with RTx and RTx-only groups. This suggests that RTx and close observation without re-excision could be an option, even in cases where minimal involvement of DCIS is confirmed on surgical resection under the properly supported RTx boosting.

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