

Original Article

# The effect of escalating the boost dose for patients with involved resection margin after breast-conserving surgery

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## Abstract

**Background:** This study aims to investigate the impact of boost dose escalation on ipsilateral breast tumor recurrence (IBTR) in breast cancer patients with involved resection margins following breast-conserving surgery.

**Methods:** Between January 1998 and December 2010, 192 patients were treated with a boost dose of over 10 Gy for involved resection margins. We retrospectively analyzed outcomes in 192 patients who underwent whole breast irradiation of 50.4 Gy followed by a median boost dose of 15.0 Gy (range, 12–16 Gy). Boost doses of 12.5 Gy and 15 Gy were delivered to patients with carcinoma *in situ* and invasive carcinoma, respectively, at the positive margins. We evaluated the impact of the boost dose on the IBTR rate.

**Results:** Median follow-up duration was 6.7 years (0.4–15.6 years). The 5-year cumulative risk of IBTR as a first event was 5.0%. IBTR occurred as a first recurrence in 13 of 192 patients. In-boost-field recurrences were found in 11 patients (85%). Five patients (39%) experienced out-of boost field recurrences, and three experienced both types of recurrences. In multivariate analysis, age (<40 years), pT stage, and positive radial resection margin were prognostic factors for IBTR ( $P = 0.029$ ,  $P = 0.024$  and  $P = 0.035$ , respectively).

**Conclusions:** A median boost dose of 15 Gy might be insufficient in patients younger than 40 years, with tumor size greater than 2 cm, or with involved radial resection margins. On the other hand, in cases of positive superficial or deep margins, dose-escalated boost or re-excision may not be necessary.

**Key words:** breast-conserving surgery, breast neoplasms, local recurrence, margins of excision, radiotherapy

## Introduction

Several randomized trials with long-term follow-up have conclusively established that breast-conserving therapy (BCT) (breast-conserving surgery [BCS] and radiation therapy) is considered the standard of care for patients with Stage I and II breast cancer, and that it has survival equivalent to that of mastectomy (1–3). However, BCS has been associated with a higher risk of local recurrence than mastectomy (1), and one of the most important factors for local recurrence after BCS is resection margin status (4–7). Moreover, the resection margins of the

first lumpectomy were found to show tumor involvement in ~15% of patients (8,9). National Comprehensive Cancer Network (NCCN) guidelines recommend further surgery in cases of positive margins, either a re-excision to achieve a negative margin or a mastectomy. In most cases to date, re-excision has been performed, and this procedure has considerable psychological and physical effects on patients, together with a potential economic impact and delays in adjuvant therapy. Moran et al. demonstrated that the effects of a positive margin do not appear to be negated by the use of either adjuvant chemotherapy

or endocrine therapy (10). Meanwhile, van Limbergen et al. demonstrated the dose-dependency of local control, suggesting a two-fold decrease in the local recurrence rate for every 15 Gy increase in dose (11). Against this background, the European Organisation for Research and Treatment of Cancer (EORTC) launched a subsequent prospective randomized trial (EORTC 22881-10882 'boost' trial), investigating the relevance of a boost dose to the primary tumor site following lumpectomy and whole breast irradiation (12). The EORTC trial demonstrated that an additional boost dose of 16 Gy targeting the tumor bed after microscopically complete tumor removal and whole breast radiation therapy (WBRT) significantly reduced the rate of ipsilateral breast tumor recurrence (IBTR). The overall cumulative incidence of IBTR at 10 years was 10.2% (95% confidence interval [CI], 8.7–11.8%) without a boost and 6.2% (95% CI, 4.9–7.5%) with a boost dose of 16 Gy ( $P < 0.001$ ) (8,9). In the small subset of 251 patients who had positive margins and received a boost, the cumulative incidence of IBTR at 10 years was 17.5% (95% CI, 10.4–24.6%) with 10 Gy and 10.8% (95% CI, 5.2–16.4%) with 26 Gy ( $P > 0.10$ ), although the difference was not significant, probably due to the small population sample (12). These data suggest that, although a boost provides a degree of reduction in IBTR when the margins are microscopically positive, the absolute benefit is insufficient to reduce the rate of

IBTR to that observed with negative margins and the use of a boost. Whether the higher risk of local recurrence following incomplete tumor excision can be completely counterbalanced by increasing the boost dose has not been clearly demonstrated. The high local recurrence rate in cases of positive surgical margins probably depends on patient characteristics (T stage, age and hormone status, among others). Therefore, the aim of the present study was to analyze the outcome of boost dose escalation in patients with incomplete local margin control. We used a moderate boost dose escalation regimen that was lower than the 10–26 Gy used in previous trials, including the EORTC 22881-10882 trial (12–15). However, as fibrosis was noted much more frequently in patients treated with the high boost dose over 20 Gy (12,14), we thought that a moderate-dose boost could be a realistic alternative if a similar IBTR rate could be achieved while lowering the toxicity.

### Methods

Between January 1998 and December 2010, 4265 patients with breast cancer were treated with BCT at our institution. Patients with clear resection margins, pure carcinoma *in situ* (CIS), multiple tumor foci in more than one quadrant, or a history of other malignant

**Table 1.** Patient and treatment characteristics ( $n = 192$ )

Characteristic	<i>n</i> (%)	Characteristic	<i>n</i> (%)
Age (years)		Hormone therapy	
<35	19 (9.9)	Yes	157 (81.8)
35–40	36 (18.8)	No	35 (18.2)
41–50	94 (48.9)	Histological type	
51–60	29 (15.1)	Invasive ductal carcinoma	166 (86.5)
>60	14 (7.3)	Invasive lobular carcinoma	13 (6.8)
Menopausal status		Mucinous carcinoma	8 (4.2)
Unknown	4 (2.0)	Papillary carcinoma	1 (0.5)
Premenopausal	156 (81.3)	Other	4 (2.1)
Menopausal	32 (16.7)	Extensive intraductal component	
Pathologic tumor staging		Yes	69 (35.9)
pT stage		No	108 (56.3)
T1	132 (68.8)	Not assessed	15 (7.8)
T2	59 (30.7)	Vascular invasion	
T3	1 (0.5)	Yes	47 (24.5)
pN stage		No	136 (70.8)
N0	139 (72.4)	Not assessed	9 (4.7)
N1	44 (22.9)	Histologic grade	
N2	5 (2.6)	1	11 (5.7)
N3	4 (2.1)	2	126 (65.6)
Hormone receptor status		3	45 (23.4)
ER+, PR+	139 (72.4)	Not assessed	10 (5.2)
ER+, PR–	15 (7.8)	Nuclear grade	
ER–, PR+	4 (2.1)	1	7 (3.6)
ER–, PR–	33 (17.2)	2	123 (64.1)
Missing	1 (0.5)	3	47 (24.5)
HER-2		Not assessed	15 (7.8)
Positive	49 (25.5)	Resection margin	
Negative	141 (73.4)	Superficial	80 (41.7)
Missing	2 (1.0)	Deep	39 (20.3)
Systemic treatment		Radial	73 (38.0)
Neoadjuvant chemotherapy		Unavailable	12 (6.3)
Yes	3 (1.6)	Multiplicity	
No	189 (98.4)	Yes	23 (12.0)
Adjuvant chemotherapy		No	169 (88.0)
Yes	93 (48.4)		

ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

disease were ineligible for the present study. Eligible patients included 194 with involved resection margins following BCS. Among these, 192 patients were enrolled in the present study; the exceptions were two patients with breast cancer in both breasts. All patients were treated with boost dose escalation over 10 Gy. This study was approved by the institutional review board of Asan Medical Center (2017-0744), and the need for informed consent was waived because of the retrospective nature of the study.

Patient and treatment characteristics are summarized in Table 1. The median age was 46 years (range, 25–73 years). One hundred eighty-two patients (94.8%) had Stage I to II cancer, and 10 patients (5.2%) had Stage III breast cancer.

Surgery preceded patient referral for radiotherapy and consisted of excision of the primary tumor, with a 1–2 cm margin of macroscopically normal tissue as well as sentinel lymph node biopsy and/or axillary lymph node dissection. A positive resection margin was defined as ‘ink on the tumor’, from the 2014 Surgical Oncology-American Society for Radiation Oncology Consensus Guideline on Margins (10).

Radiotherapy was initiated not more than 6 weeks after BCS unless patients received adjuvant chemotherapy first. Irradiation of the whole breast was performed using a pair of opposed tangential fields arranged across the chest. Twenty-five patients (13%) treated prior to 2005 were treated with the 2D technique and from that date forward, 167 patients (87%) underwent three-dimensional conformal radiotherapy (3D-CRT). All 192 patients received whole breast irradiation of 50.4 Gy, followed by a boost for breast cancer with involved resection margins. A total dose of 50.4 Gy over a 5-week period, with a dose of 1.8 Gy per fraction, was delivered for whole breast irradiation. The boost volume was assessed from the location of the tumor within the removed specimen localized by pre-operative magnetic resonance imaging (MRI), scar position, surgical clip, the orientation of positive margin(s) within the specimen and tissue induration. The boost volume was described as the site of the primary tumor bed with a margin of 2.0–2.5 cm to the field borders including the surgical clips and the scar. When electrons were employed, the energy was selected to encompass the volume to the anterior chest wall within the 80–90% isodose line. Otherwise, a mixture of electron and photon beams was used.

Prior to 2004, a boost dose of 12–16 Gy was delivered with 1.5–2.0 Gy per fraction, regardless of the pathologic features of the involved margins. However, thereafter, the boost dose was varied according to the pathologic features of the involved resection margins. A boost dose of 12.5 Gy (2.5 Gy/fraction) was delivered to patients with ductal carcinoma *in situ* (DCIS) at the positive margins. A boost dose of 15 Gy (2.5 Gy/fraction) was delivered to patients with invasive carcinoma at the positive resection margins. Patients received a median boost dose of 15.0 Gy (range, 12–16 Gy). Generally, in patient with DCIS, it is standard therapy to irradiate the whole breast using around 50 Gy without boost because boost has been shown to have no significant impact on recurrence (16,17). However, in general, patients with invasive carcinoma are recommended to receive ~10–16 Gy of boost to the tumor bed (8,13,14). Considering this, the same principle was applied to the postoperative margin status, which led to the development of the regimen used in our center. Therefore, different boost doses were delivered depending on whether the resection margin was DCIS or invasive carcinoma owing to the belief that DCIS could also be controlled with a lower boost dose. That is why we applied the moderate dose regimens of 12.5 Gy or 15 Gy for patients with positive resection margins.

Neoadjuvant chemotherapy was performed for three patients (1.6%). Adjuvant chemotherapy was delivered to 93 patients

(48.4%). One hundred fifty-seven patients (81.8%) underwent systemic hormone therapy.

## Statistics

All events were measured from the date of the surgery to the date of occurrence or the last follow-up visit. Local recurrence was defined as IBTR, which was defined as recurrent tumor occurring after BCS plus radiotherapy in either the breast parenchyma or skin of the ipsilateral breast in the absence of regional or distant metastatic disease. Regional relapse was defined as any regional lymphatic recurrence. Distant metastasis was defined as any recurrence in a systemic organ. Overall survival (OS), distant metastasis-free survival (DMFS), regional recurrence-free survival (RRFS), disease-free survival (DFS) and local recurrence were determined by Kaplan–Meier method. Survival curves were compared using the log-rank test. Univariate and multivariate survival analysis was performed with Cox proportional hazards model. Hazard ratios (HR) were estimated by Cox proportional hazards regression analysis. A  $P$  value of  $<0.05$  was considered statistically significant. Statistical analyses were performed using SPSS Version 18.0 (SPSS Inc., Chicago, IL, USA).

## Results

The median patient age was 46 years (range, 25–73 years), 81.3% patients were premenopausal, 82.8% presented with cN0 tumors and 72.4% had pN0 tumors. Among the patients who underwent adjuvant chemotherapy, six (1.4%) received a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), 45 (10.5%) received doxorubicin and cyclophosphamide (AC) and 39 (9.3%) received AC followed by paclitaxel (T). Tamoxifen and aromatase inhibitors (AIs) alone were administered to 51 (12.2%) and 20 (4.8%) patients, respectively. Trastuzumab was used in nine patients (2.1%). The median follow-up duration for all patients was 6.7 years (0.4–15.6 years).

IBTR occurred as the first recurrence in 13 of the 192 patients. The 5-year cumulative risk of IBTR as a first event was 5.0%, as shown in Fig. 1. In-boost-field recurrences were observed in 11 patients (85%), five patients (39%) experienced out-of-boost field recurrences, and three patients had both types of recurrences.

On univariate analysis, age ( $P < 0.001$ ), cell type ( $P < 0.001$ ), pT stage ( $P = 0.002$ ), pN stage ( $P = 0.004$ ), extensive intraductal

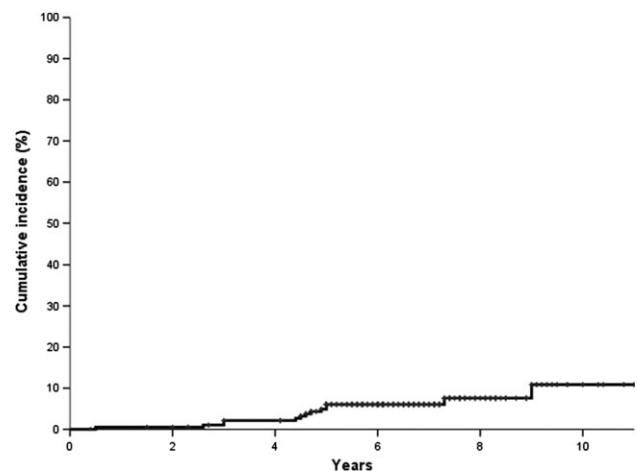


Figure 1. Cumulative incidence of ipsilateral breast tumor recurrence.

**Table 2.** Univariate analysis of prognostic factors for IBTR

Variables	<i>n</i>	5-year IBTR (%)	HR (95% CI)	<i>P</i> value	
Age (years)	<40	21	16.4	1	0.000
	≥40	171	3.7	0.173 (0.057–0.531)	
Histology	IDC	168	3.8	1	0.000
	ILC	12	7.7	1.138 (0.145–8.904)	
	Mucinous carcinoma	8	14.3	2.650 (0.336–20.873)	
	Papillary carcinoma	1		31.856 (3.774–268.857)	
	Other	3		0.000	
pT stage	pT1	132	2.5	1	0.002
	pT2	59	10.5	8.164 (2.242–29.724)	
	pT3	1	0	0.000	
pN stage	pN0	139	4.6	1	0.004
	pN1	44	2.4	0.635 (0.137–2.953)	
	pN2	5	40.0	8.601 (1.814–40.783)	
	pN3	4	0	0.000	
EIC	Yes	69	6.1	2.007 (0.539–7.475)	0.016
	No	108	1.9	1	
	Not assessed	15	21.4	6.424 (1.271–26.271)	
RM multiplicity	Multiple	23	4.4	3.512 (1.080–11.419)	0.026
	Single	169	8.9	1	
RM location	Radial RM	73	9.9	1	0.004
	Superficial or deep RM	119	1.8	0.240 (0.066–0.872)	

IDC, Invasive ductal carcinoma; ILC, Invasive lobular carcinoma; IBTR, ipsilateral breast tumor recurrence; EIC, extensive intraductal component; RM, resection margin; HR, hazard ratio; CI, confidence interval.

**Table 3.** Multivariate analysis of prognostic factors for IBTR

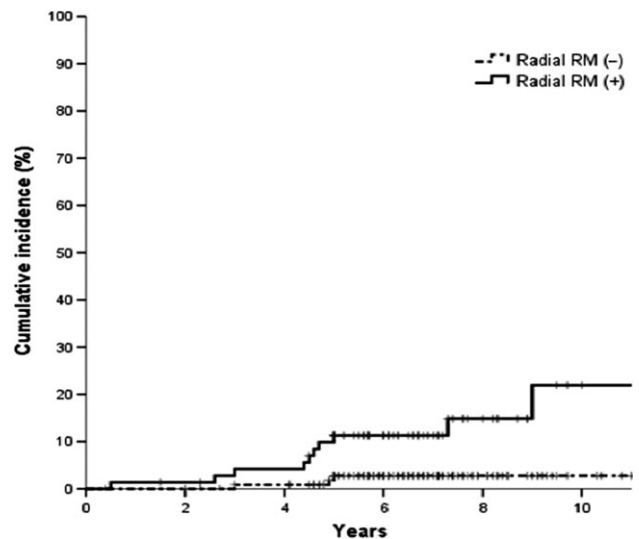
Variables	HR (95% CI)	<i>P</i> value	
Age (years)	<40	1	0.029
	≥40	0.273 (0.085–0.877)	
pT stage	pT1	1	0.024
	pT2	6.381 (1.684–24.181)	
	pT3	0.000	
RM location	Radial RM	1	0.035
	Superficial or deep RM	0.250 (0.069–0.908)	

IBTR, ipsilateral breast tumor recurrence; RM, resection margin; HR, hazard ratio; CI, confidence interval.

component (EIC) (*P* = 0.016), multiplicity of involved margins (*P* = 0.026) and margin location were prognostic factors for IBTR (*P* = 0.004), as shown in Table 2. On multivariate analysis, young age (<40 years), pT stage and positive radial resection margin were unfavorable prognostic factors for IBTR (*P* = 0.029, *P* = 0.024, and *P* = 0.035, respectively), as shown in Table 3. The cumulative incidence of local recurrence at 5 years was higher for patients with positive radial resection margins (9.9%) compared with patients who have negative radial margins (1.8%) as shown in Fig. 2 (*P* = 0.004; HR, 0.250; 95% CI, 0.069–0.908). The 5-year RRFs and DMFS rates were 95.1% and 97.3%, respectively. Two patients died as a result of breast cancer, and one patient died as a result of cerebral infarction. The 5-year DFS and OS rates were 91.0% and 97.9%, respectively.

**Discussion**

In general, positive margins after BCS are associated with an increased risk of IBTR, compared with negative margins. A meta-analysis including 19 studies of 13 081 patients with sufficient detail to separate negative, close, and positive margins found that the odds ratio (OR) for



**Figure 2.** Cumulative incidence of ipsilateral breast tumor recurrence by margin status.

positive versus negative margins was 2.44 (95% CI, 1.97–3.03) (10). Other published studies support the finding that the risk of IBTR in cases of positive margins is at least two-fold greater than that in cases of negative margins (18,19). Historically, in patients with incomplete tumor resection, re-excision was generally performed in order to obtain clear resection margins. Therefore, studies regarding boost dose escalation for the tumor bed have been limited.

Historical records showed administration of a boost dose of 10–16 Gy for negative resection margins. Patients with involved resection margins underwent a tumor bed boost of 10–26 Gy. The EORTC ‘boost trial’ was the only randomized controlled study that analyzed patients with involved margins. The researchers assessed

the impact of the boost dose in patients with involved surgical margins. At 10 years, the cumulative incidence of local recurrence was 17.5% versus 10.8% for the groups receiving 10 Gy and 26 Gy boost doses, respectively (hazard ratio [HR] = 0.83, Gray  $P > 0.1$ ) (12). Unfortunately, this sole randomized trial did not show any clinical significance. At this point in time, it is doubtful that application of an escalated boost dose alone could be performed instead of re-excision in patients with involved resection margins. Furthermore, it is unclear whether the increased risk of IBTR is nullified by escalating the boost dose of radiation. These questions led to the implementation of the present study.

The treatment principle at our institution is re-excision according to NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology) guidelines in cases of incomplete resection after BCS. However, we have performed boost dose escalation alone for patients who refuse additional surgery, or if mastectomy is required for re-operation. In these patients, the radiation dose was increased to 12.5 Gy or 15 Gy based on the presence of DCIS or invasive carcinoma. A median boost dose of 15 Gy reduced the IBTR, a finding comparable to previous results of research regarding boost following BCT (Table 4).

On the other hand, in the Netherlands, instead of re-excision, clinicians follow a policy of administering a high boost dose of 20–25 Gy. Recently, a Dutch group, Vos et al. (15) reported a 5-year IBTR rate of 2.9% when a boost dose of 20–25 Gy was delivered to patients with early-stage breast cancer with focally involved resection margins after BCS. When re-excision was performed, the 5-year IBTR rate (adjusted HR 0.30, 95% CI 0.11–0.82) was lower than that observed when an escalated boost dose was administered. In the Dutch study, even if a boost dose as high as 20–25 Gy was administered to patients with involved margins, the IBTR rate could not be lowered to levels similar to those observed with re-excision. In comparison, the IBTR rate in patients with radial margin positive early-stage breast cancer in our study was lower than that observed by Vos et al. (9.9% vs. 2.9%). This finding can be interpreted in two ways. First, there is a possibility that the boost dose (median 15 Gy) applied in our study was not high enough. Of course, it will be difficult to make a determination solely based on these comparisons. However, this interpretation can also be supported by the fact that the majority of the recurrences (85%) in our analysis were in-boost-field recurrences. One other interpretation of our findings is that boost dose escalation will not lower the IBTR rate to as great an extent as will re-excision. However, we conclude that higher

boost dose escalation or re-excision should be performed only in patients with positive radial margins because the IBTR rate differs significantly according to the location of the involved margins, as observed in the present study.

While this study was undertaken to address the need for data, we are aware of certain limitations of our analyses. This was a single-center and retrospective study, making it difficult to draw conclusions. Moreover, the median follow-up duration of our study was 6.7 years, which is a relatively short follow-up duration for breast cancer. We compared the 5-year IBTR rate to historical studies because of the single-arm nature of the present study. To overcome these weaknesses, we compared studies that had similar characteristics to those of our study. In addition, we compared the results of patients who had negative margins after BCS performed at our institution. Furthermore, systemic therapy for breast cancer has changed drastically, with the use of treatments such as taxane-based chemotherapy, AIs and trastuzumab. At our institution, anthracycline-based chemotherapy began to be used in 2003 and taxane-based chemotherapy was initiated in mid-2005. Fifteen patients (7.8%) in the present study were treated before 2003, and 30 (15.6%) were treated before 2005. Correspondingly, 162 patients (84.4%) were treated with anthracycline-based or taxane-based chemotherapy. We analyzed the differences in the IBTR rate before and after 2003, but there was no significant difference between the two groups (3.1% vs. 6.7%, respectively,  $P = 0.354$ ).

In particular, we believe that toxicity analysis is essential in boost dose escalation studies such as the present study. However, owing to its retrospective nature, which is the biggest weakness of this study, a medical record review was conducted for all 192 included patients, but no mention or record of toxicity was found for most of the patients. Of the 12 patients for whom confirmation was possible, five had Grade 1 dermatitis but all were well recovered in follow-up recordings, and the remaining seven patients completed treatment without any specific skin toxicity.

A notable achievement of the present study is its demonstration that the location of a positive resection margin influences IBTR. Young age has been a well-known poor prognostic factor for IBTR. The difference in the IBTR rate according to the location of the positive resection margin is remarkable. A positive radial margin rather than a superficial or deep margin was found to be a poor prognostic factor for IBTR in the current study. Some surgeons have insisted that there is a high probability of a false positive with a positive superficial resection margin (20). Furthermore, the common surgical practice to not

**Table 4.** Selected studies of tumor bed boost after BCS

Trial	Year	Patient characteristics	Boost dose (Gy)	No. of patients	End point	RM status	IBTR rate (%)
EORTC 22 881-10 882	2009	T1-2:99.2%, N0:85.6%	26	251	10-yr actuarial	Positive	11
			10			18	
			26		5-yr crude rate	Positive	6
			10			10	
Budapest (Hungary)	2002	T1-2:100%, N0:77%	16	104	5.3-yr crude rate	Negative: 85.4%, Positive: 9.7%	6.7
			0			103	Negative: 88.5%, Positive: 6.7%
Lyon (France)	1997	T1-2:100%, N0:73%	10	1024	3.3-yr actuarial	Negative: 97.8%, Positive: 2.2%	3.6
			0			4.5	
Vos et al.* (Dutch)	2017	T1-2:98.4%, N0:66.1%	20–25	7820	5-yr actuarial	Negative	2.3
			20–25	492		Focally positive	2.9
			20–25	586		Focally positive + re-excision	1.1
Yi et al.* (Korea)	2009	T1:72.7%, T2-3:27.3%	10	578	5-yr crude rate	Negative: 93.3%, Positive: 5.7%	3.6

\*Retrospective study. BCS, breast-conserving surgery; RM, resection margin; IBTR, ipsilateral breast tumor recurrence.

re-excision positive anterior margins contradicts current guidelines that recommend obtaining negative margins to reduce the risk of IBTR. However, there is little evidence detailing the relationship between positive anterior margins and rates of IBTR (21). The results of the present study could constitute evidence to support the existence of a relationship. Our findings are thought to make an important contribution given the paucity of studies exploring the anatomical location of positive margins and the current lack of specific guidelines to approach the management of involved anatomically non-breast margins. In the current study, the 5-year IBTR rate was 9.9% when the radial resection margins were positive, but the recurrence rate was significantly reduced to 1.8% when the radial resection margins were negative ( $P = 0.004$ ; HR, 0.250; 95% CI, 0.069–0.908). These results suggest that the positive rate of superficial or deep margins will not significantly affect local recurrence, and this recurrence can be controlled with a median boost dose of 15 Gy. However, boost dose escalation or re-excision might be considered in high-risk patients (age < 40, tumor size > 2 cm, radial resection margin involvement). Conversely, if the superficial or deep margin is positive, boost dose escalation or re-excision might not be necessary. However, it is obviously a matter of some concern to perform neither re-excision nor boost dose escalation for patients with involved margins, even in cases of superficial or deep margins. We could not provide a definitive answer because we did not directly compare the patients in the standard-dose study with these groups because of the retrospective nature of the present study. However, at least in patients with superficial or deep margins without high risk factors, we think that it would be reasonable to consider applying standard-dose boost radiation without re-excision.

### Conflict of interest statement

None declared.

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