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ORIGINAL ARTICLE – BREAST ONCOLOGY

Redefining Eligibility by Analyzing Canceled Intraoperative Radiotherapy as a Boost for Patients Undergoing Breast-Conserving Treatment

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ABSTRACT

Background. Intraoperative radiotherapy (IORT) with a 50-kV x-ray is used for a tumor bed boost during breast-conserving surgery. This study evaluated the anatomicosurgical factors associated with cancellation of planned IORT.

Methods. Patient eligibility for the study included age of 20 years or older, compatibility for lumpectomy, and ductal carcinoma in situ or stages 1–3 invasive carcinoma. All the patients underwent magnetic resonance imaging (MRI) and multidisciplinary team evaluations. Resection margins were assessed by frozen pathology. Pre- and intraoperative variables were compared between the IORT and IORT-cancellation groups.

Results. A total of 434 patients underwent surgeries for IORT between August 2014 and December 2017. For 90 of these patients, IORT was canceled because of repeated positive margins leading to a large cavity or total mastectomy (n = 27), insufficient cavity-skin distance (n = 14), satellite lesions leading to a large cavity or total mastectomy (n = 12), MRI findings of a large primary tumor or uncertain margins leading to a large cavity (n = 6), cavity geometry unsuitable for IORT (n = 6), subareolar tumor extension (n = 6), tumor abutting the pectoralis muscle (n = 3), patient refusal (n = 5), intraoperative confirmation of bilateral breast cancer (n = 3) or benign pathology (n = 3), device malfunction (n = 3), or scheduling difficulty (n = 2). A tumor larger than 2 cm (P = 0.014) and the presence of satellite lesions (P = 0.014) were independent predictors of IORT cancellation.

Conclusions. Surgical procedures resulting in large cavities were the leading cause of IORT cancellation. Multidisciplinary evaluations using MRI were critical for completion of IORT procedures.

Whole-breast irradiation (WBI) followed by a tumor bed boost is the standard radiation treatment for patients with breast cancer undergoing breast-conserving surgery (BCS). Intraoperative radiotherapy (IORT) using low-energy (50 kV) x-rays delivers high-dose radiation to the tumor cavity while sparing normal breast tissue.

When used as a boost to the tumor bed, IORT can potentially reduce the risk of missing the target volume, which can be as high as 20–90% when external-beam radiotherapy (EBRT) is used[1,2]; shorten the interval between the surgery and the beginning of radiotherapy; and eliminate 1–2 weeks of EBRT boost delivery time.[3]

The ongoing TARGeted Intraoperative radioTherapy as a tumor bed Boost (TARGIT-B) trial was designed to test whether a tumor bed boost administered intraoperatively is superior to a tumor bed boost administered via EBRT for patients with breast cancer undergoing BCS followed by WBI (https://clinicaltrials.gov/ct2/show/NCT01792726).

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The eligibility criteria for the TARGIT-B trial are quite broad, including patients who can undergo BCS even with more than one tumor in the breast as long as the tumors can be removed through a single specimen. Unlike other trial protocols involving radiation treatment, which often include a detailed description of radiotherapy techniques and constraints to be met, the TARGIT-B protocol simply states that the skin must be at least 1 cm away from the applicator and protected from the radiation such that no delay in wound healing occurs.

Our breast cancer multidisciplinary team at Gangnam Severance Hospital has been using IORT as a boost for Korean patients with breast cancer since August 2014 and has treated more than 400 patients. In our experience, approximately 20% of the patients who met the eligibility criteria at our multidisciplinary team discussions ultimately failed to complete the IORT procedure.

We previously reported the results of an in vivo dosimetry study conducted during the IORT procedure based on the first 55 patients. The initial breast volume, the ratio of the applicator diameter to breast volume, and the distance between the tumor margin and the skin were significantly correlated with maximum skin dose.[4]

The current study aimed to report the reasons that lead to cancellation of planned IORT procedures and to determine the pre- and intraoperative factors associated with IORT cancellation.

METHODS

Patients

The eligibility criteria specified women 20 years old or older who were eligible for lumpectomy and had ductal carcinoma in situ (DCIS) or stages 1–3 invasive carcinoma. Patients treated with neoadjuvant chemotherapy and those who required BCS for bilateral breast cancer were excluded.

The current study included the 215 patients enrolled in a phase 2 trial of IORT boost followed by WBI for patients undergoing BCS. The phase 2 trial was registered with ClinicalTrials.gov, NCT02213991, and an early report on acute toxicity has been recently published.[5] The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by our institutional review board.

Pretreatment Evaluation and Treatments

Ultrasound-guided biopsy or mammography-guided stereotactic breast biopsy confirmed the diagnosis of breast malignancy. All patients underwent ultrasonography (US) and magnetic resonance imaging (MRI) evaluation of the breast, and the eligibility for breast-conserving treatment and IORT were evaluated in a multidisciplinary conference consisting of breast surgeons, diagnostic radiologists, and radiation oncologists. Patients who had a tumor located in close proximity (< 1 cm) to the skin or confirmed bilateral breast cancers requiring BCS for both breasts were excluded from the study during the multidisciplinary discussion. Patients who met the preoperative eligibility evaluation proceeded to BCS and IORT. The causes of cancellation were recorded for cases in which the planned IORT procedure was canceled.

To minimize the number of false-positive cases, a second-look US was recommended for incidental suspicious lesions detected on MRI and shown to be occult on both mammography and the initial US. For nonpalpable breast lesions, patients undergo preoperative US-assisted wire-guided localization of the breast lesion.[6]

Two experienced breast surgeons performed all of the surgical procedures. During the operations, frozen sections of shaved margins in four directions (superior, inferior, lateral, and medial) were sent to the Department of Pathology. A reexcision was performed for patients in whom positive resection margins were observed on the frozen examinations.

After a successful lumpectomy, IORT procedures were performed by a team of breast surgeons and radiation oncologists. A spherical applicator with the best-fitting diameter (ranging from 1.5 to 5.0 cm in 0.5-cm increments) was selected according to the size of the lumpectomy cavity, and a purse-string suture was used to pull the tumor cavity tightly against the applicator surface. The stitch should be taken deep to the edges of the whole cavity through the breast tissue and not in the subcutaneous tissues such that with tightening of the purse string, the skin is not pulled too close (< 1 cm) to the applicator. At the same time, with pulling of the purse-string, the breast tissue should be apposed to the surface of the applicator and wrap around it.

After a minimum distance of 5–10 mm between the applicator surface and the skin was ensured by everting the incision margins, a single fraction of 20 Gy was delivered to the surface of the post-lumpectomy cavity using the mobile 50-kV x-ray source (Intrabeam; Carl Zeiss, Oberkochen, Germany).

Detailed IORT procedures have been described previously.[4,7] The IORT procedure was followed by WBI of 46–50.4 Gy in 23–28 fractions. For WBI planning, a computed tomography (CT) scan was performed for all the patients, placed in the supine position with the ipsilateral arm in abduction on a customized immobilization device. The acquired CT images with 5-mm spacing were transferred to MIMVISTA 6.3.3 (MIM Software Inc, Cleveland, OH, USA) for contouring radiotherapy (RT) target

volumes according to the Radiation Therapy Oncology Group Breast Cancer Atlas for Radiation Therapy Planning[8] and for measurement of the ipsilateral breast volume (Fig. S1).

Statistical Analysis

Pre- and intraoperative variables were compared between the patients undergoing IORT and those whose planned IORT was canceled. The Chi square test was used to test the correlation between two categorical variables. Variables with *P* values lower than 0.05 in the univariate analysis were applied to a multivariate logistic regression analysis for evaluation of their association independently of the confounding factors.

RESULTS

The eligibility criteria were met by 434 patients, who underwent surgeries for IORT between August 2014 and December 2017. The IORT procedure was completed for 344 patients, and these patients received WBIs of 46–50.4 Gy in 23–28 fractions without additional boosts to the tumor beds. The remaining 90 patients did not undergo the planned IORT due to anatomic (n = 74), pathologic (n = 6), and nonsurgical (n = 10) reasons and received WBI of 50.4 Gy in 28 fractions followed by tumor bed boosts of 9 Gy in 5 fractions (Fig. 1).

The proportion of the patients whose IORT was omitted among the total number of patients undergoing BCS for IORT was 23.8% in 2014/2015, 20.9% in 2016, and 19.3% in 2017. Table 1 shows the reasons for omission of the planned IORT. The anatomicosurgical reasons (n = 74) included repeated positive margins leading to a large tumor cavity or total mastectomy (n = 27), insufficient cavity-to-skin distance (n = 14), satellite lesions leading to a large tumor cavity or conversion to total mastectomy (n = 12), large primary tumor or uncertain tumor margins on the MRI resulting in a large tumor cavity (n = 6), tumor cavity geometry unsuitable for IORT (n = 6), subareolar extension of the tumor (n = 6), and tumor abutting the pectoralis muscle (n = 3). The non-anatomic reasons (n = 16) were patient refusal (n = 5), intraoperative confirmation of bilateral breast cancer (n = 3) or benign pathology (n = 3), device malfunction (n = 3), and scheduling difficulty (n = 2). When these categories of cancellation were divided according to the year of surgery, "conversion to mastectomy after repeated positive margins" decreased from seven cases in 2014/2015 to one case in 2016 and another case in 2017. No other categories showed a significant decrease during the study period.

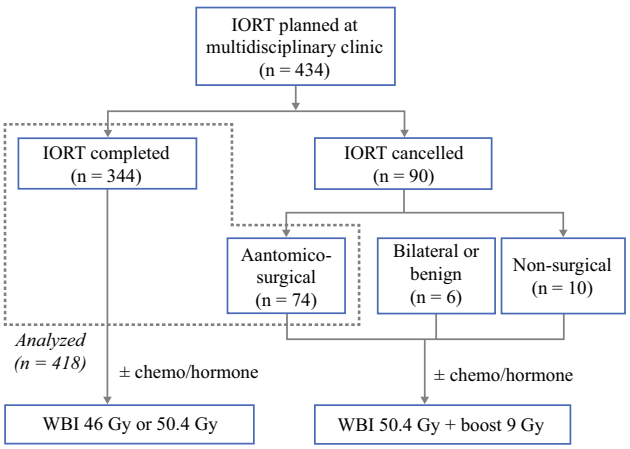

FIG. 1 Patients selected for a comparison between completion and cancellation of intraoperative radiotherapy

Figure 2 shows six cases in which the planned IORT was canceled, described as follows:

(A) An 80-year-old woman had a diagnosis of invasive ducal carcinoma (IDC) at the 11 o'clock position in the right breast. The maximum diameter of the tumor was 4.2 cm on the MRI and 4.5 cm on the surgical specimen. However, with additional resection margins in four directions for frozen analysis, the size of the tumor cavity exceeded the size of the largest applicator (5 cm), and IORT had to be aborted.

(B) A 60-year-old woman had a diagnosis of biopsy-proven IDC at the 6 o'clock position in the right breast measuring 2.8 cm, with three satellite nodules in the vicinity of the main mass. After one of the satellite nodules was located with US guidance, BCS was performed, and frozen analysis of the satellite nodule showed a 2-mm fibroinflammatory nodule. However, the tumor cavity exceeded the size of the largest applicator.

(C) A 25-year-old woman had a diagnosis of biopsy-proven IDC at the 2 o'clock position in the left breast. The MRI showed a tumor with speculated margins measuring 1.5 × 1.9 cm and a 1.1-cm linear non-mass enhancement (NME) extended from the tumor in the anterior direction. The size of the entire surgical specimen was 5.0 × 4.5 cm, and the surgical cavity exceeded the size of the largest applicator.

(D) A 44-year-old woman had a diagnosis of IDC in the left breast after a mammotome excision. The post-mammotome MRI showed a residual tumor measuring 1 cm in the subareolar area, with the tumor extent uncertain due to post-mammotome changes. A frozen analysis of the subareolar resection margin after the initial lumpectomy showed pagetoid extension of the DCIS, and additional central lumpectomy with resection of the nipple–areolar complex showed

TABLE 1 Reasons for omission of planned intraoperative radiotherapy (IORT) (n = 90)

Reasons to abort IORT	Patients n (%)
Anatomicosurgical	
Large cavity after repeated positive margins	18 (20.0)
Conversion to mastectomy after repeated positive margins	9 (10.0)
Insufficient cavity-to-skin distance (< 1 cm)	14 (15.6)
Large cavity after removal of satellite lesions	6 (6.7)
Conversion to mastectomy after removal of satellite lesions	6 (6.7)
Large cavity after removal of large primary tumor	3 (3.3)
Larger cavity after removal of tumor with uncertain margin on MRI	3 (3.3)
Cavity geometry unfit for IORT	6 (6.7)
Subareolar tumor extension	6 (6.7)
Tumor abutting pectoralis muscle	3 (3.3)
Other pathology	
Confirmation of contralateral breast cancer	3 (3.3)
Benign pathology confirmed during surgery	3 (3.3)
Nonsurgical	
Patient refusal	5 (5.6)
Device malfunction	3 (3.3)
Scheduling difficulty	2 (2.2)

MRI magnetic resonance imaging

a close negative margin. The IORT was aborted to boost the tumor bed including the overlying skin with EBRT.

(E) A 65-year-old woman had a diagnosis of IDC at the 4 o'clock position in the right breast measuring 2.4 cm, and MRI showed the tumor abutting the pectoralis muscle. After negative resection margins including that of the chest wall were achieved, the base (chest wall side) of the tumor cavity was so large that the purse-string suture failed to bring the breast tissue tightly against the surface of the applicator.

(F) The MRI of a biopsy-proven IDC in the right breast of a 49-year-old woman showed an oval-shaped tumor at the 1 o'clock position measuring 1.1 cm. The IORT procedure was attempted after lumpectomy, but the remaining breast tissue did not provide enough space for an applicator of an appropriate size, so the IORT was aborted. The volume of the right breast measured in the simulation CT was 269 ml.

Pre- and intraoperative variables including age, tumor histology, tumor location, breast volume, presence of satellite nodule or nodules, and positive frozen section were correlated with whether the planned IORT was successfully completed or not (Table 2). For this analysis, we excluded the 16 patients who did not undergo IORT because they failed to meet the inclusion criteria due to non-anatomicosurgical reasons, leaving 344 patients who completed IORT and 74 patients whose planned IORT was canceled.

The median age of the patients was 52 years (range 24–79 years). In 61 patients (14.6%), DCIS was detected. The median breast volume was 515 ml (range 130–2892 ml), and the median tumor size was 1.6 cm (range 0.3–5.0 cm). A satellite nodule or nodules were found in 12 patients (2.9%), and 103 patients (24.6%) had positive resection margins in one or more frozen section analyses. The largest proportion of patients had tumors located in the upper-outer quadrant (31.3%), followed by the upper-inner quadrant (23%), the upper-middle quadrant (13.9%), and the outer-middle quadrant (10.8%).

In the univariate analysis, a primary tumor larger than 2 cm (P = 0.033), a satellite nodule or nodules ($P < 0.0001$), and positive frozen section (P = 0.013) were significantly associated with omission of planned IORT, whereas breast volumes of 510 ml or less on CT scans showed a tendency toward failure of a planned IORT (P = 0.066). In a multivariate analysis, only primary tumor size (P = 0.014) and presence of a satellite nodule or nodules (P = 0.014) were independent predictors of omission of planned IORT.

DISCUSSION

The IORT omission rates at our institution were maintained at approximately 20%, although the initial rate of 23.8% in the years 2014 and 2015 was slightly higher than the rates in the later years. Our results suggest that a multidisciplinary team approach was effective in minimizing the rate of IORT cancellation from the early part of

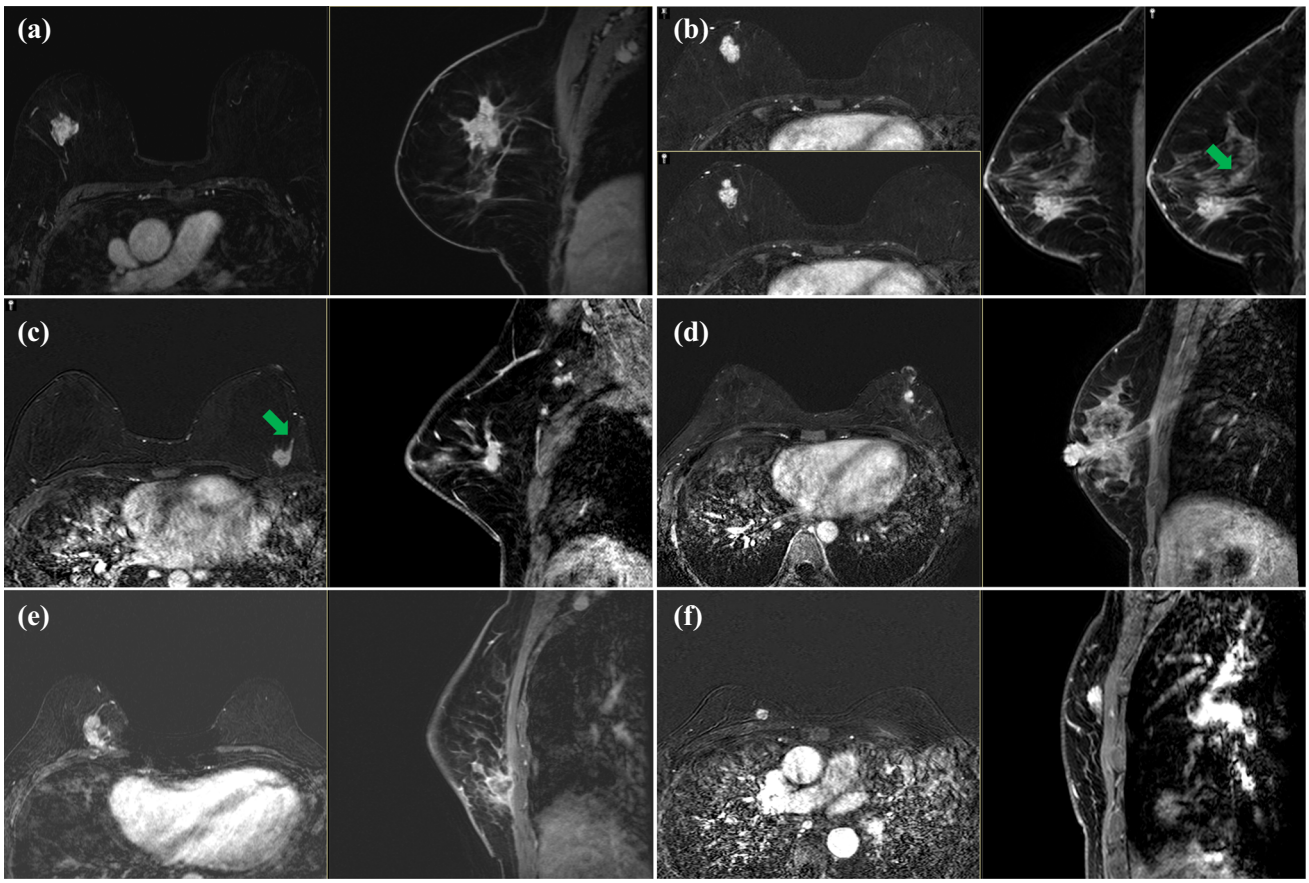

FIG. 2 Example cases in which planned intraoperative radiotherapies were canceled. **a** A large primary tumor leading to a cavity size exceeding the largest applicator diameter. **b** Presence of a satellite lesion (green arrow) leading to a large tumor cavity. **c** An uncertain tumor margin due to a linear enhancement (green arrow) leading to a large tumor cavity. **d** A subareolar tumor extension. **e** Tumor invasion of the pectoralis muscle leading to an ineffective purse-string suture. **f** A tumor located close to a margin of a small breast

its clinical application. However, a significant proportion of patients have pre- and intraoperative factors that eventually lead to their cancellation of IORT.

Tuschy et al.[9] reviewed the data of 55 patients whose planned IORT was eventually canceled and reported that the main reasons for the IORT omission were insufficient tumor-skin distance (< 5–10 mm, 35.1%) an oversized wound cavity not suitable for the largest applicator of 5 cm (24.6%), or a combination of both (14%). In our practice, the main reasons for IORT cancellation were intraoperative factors including oversized tumor cavity (33.3%), conversion to total mastectomy (16.7%), and cavity geometry unfit for IORT (6.7%). These non-modifiable factors were difficult to anticipate preoperatively and needed to be verified during operation.

In our study, IORT was omitted due to insufficient cavity-to-skin distances in only 15.6% of the patients. All the patients who underwent breast MRI and those with tumor-to-skin distances less than 10 mm were excluded from participating in our study during the multidisciplinary discussion. Nonetheless, IORT had to be canceled for some of the participants because the surgical procedures resulted in insufficient cavity-to-skin distances, especially for those who had to undergo reexcision due to positive resection margin or margins.

In contrast, cancellation of IORT could have been avoided for six patients who had subareolar extension, and for three patients whose tumors were abutting the pectoralis muscle. These can be considered modifiable factors, so we currently put more emphasis on the preoperative discussions with diagnostic radiologists for such cases.

To determine predictive factors for the cancellation of planned IORTs, we compared clinical variables, including age, tumor histology, tumor location, breast volume, tumor size, presence of satellite nodule or nodules, and status of resection margin, between the patients who underwent IORT successfully and those who did not. Only tumor larger than 2 cm and presence of satellite nodule or nodules

TABLE 2 Factors influencing intraoperative radiotherapy (IORT) omission

	IORT completed (n = 344) n (%)	IORT omitted (n = 74) n (%)	Univariate P value	Multivariate P value
Age (years)			0.185	
≤ 52 years	182 (52.9)	44 (59.5)		
> 52 years	162 (47.1)	30 (50.5)		
Pathology			0.204	
IDC and other	291 (84.6)	66 (89.2)		
DCIS	53 (15.4)	8 (10.8)		
Quadrant			0.508	
Inner-middle	7 (2.0)	2 (2.7)		
Lower-inner	19 (5.5)	5 (6.8)		
Lower-middle	15 (4.4)	4 (5.4)		
Lower-outer	27 (7.8)	3 (4.1)		
Outer-middle	35 (10.2)	10 (13.5)		
Upper-outer	103 (29.9)	28 (37.8)		
Upper-middle	49 (14.2)	9 (12.2)		
Upper-inner	85 (24.7)	11 (14.9)		
Subareolar	4 (1.2)	2 (2.7)		
Breast volume on CT (ml)			0.066	0.075
> 510	172 (50.0)	20 (27.0)		
≤ 510	161 (46.8)	31 (41.9)		
Unknown	11 (3.2)	23 (31.1)		
Tumor size on MRI			0.033	0.014
≤ 2.0	258 (75.0)	47 (63.5)		
> 2.0	86 (25.0)	27 (36.5)		
Satellite nodule(s)			< 0.0001	0.014
No	340 (98.8)	66 (89.2)		
Yes	4 (1.2)	8 (10.8)		
Frozen section			0.013	0.541
Negative	268 (77.9)	47 (63.5)		
Positive	76 (22.1)	27 (36.5)		

IDC invasive ductal carcinoma, *DCIS* ductal carcinoma in situ, *CT* computed tomography, *MRI* magnetic resonance imaging

in the MRI scans were independent predictors of IORT cancellations for our patients. The largest diameter of the applicator available was 5 cm, and a larger tumor increased the risk of IORT cancellation during surgery. In a multivariate logistic regression, the smallest tumor size that independently predicted IORT cancellation was 2.1 cm, which is substantially smaller than the size of the largest applicator.

Multifocal disease has been identified previously as a risk factor for reexcision among patients undergoing BCS.[10–12] Although the presence of a satellite nodule or nodules was not common in our patients (2.9%), it still was a strong predictor of IORT cancellation. The presence of in situ carcinomas has been identified previously as a risk factor for margin involvement.[10,13,14] Because our institutional policy is to obtain negative resection margins through reexcision in cases of positive resection margin or margins, it was expected that the DCIS pathology would be associated with increased rates of IORT cancellation. However, in the current study, DCIS did not result in an increased IORT omission rate, and positive frozen analysis was not an independent predictor of IORT cancellation. Because Asian women have smaller breast volumes than Caucasian women,[15] the tumor location and the breast volume of our patients may have influenced whether IORT could be successfully completed or not. However, these anatomic factors did not correlate with IORT cancellation.

In the study by Tuschy et al.[9] an insufficient tumor-skin distance (i.e., less soft tissue around the excision cavity) was the main reason for non-implementation of IORT, and routinely implemented preoperative ultrasonic measurement of the tumor-skin distance was recommended. In our study, a tumor cavity unfit for the largest applicator (5 cm in diameter) was the main reason for IORT cancellation,

TABLE 3 Risk factors for omission of the planned intraoperative radiotherapy (IORT) procedure

Risk factors	Conditions required for IORT
Small cavity-to-skin distance (< 1 cm)	Overlying skin excision
Large cavity (> 5 cm)	
Satellite nodule(s) with high suspicion of malignancy	
Non-mass enhancement extending from tumor	
Radiologically uncertain tumor margins	
Tumor abutting or invading chest wall	Adequate purse-string suture
Subareolar tumor extension	NAC sacrifice
Bilateral breast cancers requiring bilateral BCS	EBRT boost for other breast
Repeated positive resection margins	
Elongated tumor cavity	

NAC nipple-areolar complex, *BCS* breast conserving surgery, *EBRT* external beam radiotherapy

and the importance of a preoperative imaging method for estimating the extent of resection during BCS cannot be overemphasized.

A previous study conducted at our institution evaluated preoperative MRI features, including tumor size, multifocality, pattern of enhancing lesions, and tumor characteristics (shape, margin, and internal enhancement characteristics), for correlations with positive resection margins. The findings demonstrated that NME with or without mass was an independent predictive factor.[16] We recommend the inclusion of irregular tumor margins and NME in estimating the volume of tumor cavities because these features must be removed together with the main mass during BCS. The presence of satellite lesions increases the extent of resection during BCS, but IORT still should be considered for patients with multifocality as long as the tumors can be removed through a single specimen.

Breast MRI has high sensitivity in breast cancer diagnosis [17,18] and is used routinely for preoperative planning at our institution. At detection of a satellite lesion on the MRI, second-look US allows for an additional confirmation and accurate localization of the lesion in spatial association with the main lesion.[19] We recommend the active use of second-look US-guided localization and biopsies for suspicious satellite lesions to minimize the extent of BCS.

The risk factors associated with the cancellation of IORT are summarized in Table 3. For patients with these factors, IORT still may be performed if certain conditions are met. Excising an ellipse of overlying skin may allow IORT for superficial tumors at a risk of poor cosmetic results. Tumors abutting the chest wall are a relative contraindication because the purse-string suture still may allow tight contract between the cavity wall and applicator surface. Central lumpectomy sacrificing the nipple–areolar complex may be performed with patient consent if subareolar tumor extension is suspected, analogous to excision of overlying skin for superficial tumors.

We did not enroll patients with bilateral breast cancer requiring BCS for both breasts because IORT could not be performed for both breasts, and different EBRT schedules for the two breasts were not desirable. Boosting one breast with IORT and the other breast with EBRT still may be considered, although the benefits of IORT in reducing the total treatment time is diminished.

In conclusion, IORT was canceled for patients primarily after surgical procedures leading to large surgical cavities. Tumor size and the presence of satellite lesions were independent predictors of IORT cancellation. A multidisciplinary team approach is important for the successful selection of IORT candidates, and careful evaluation of findings from MRI and US is critical for minimizing the number of patients whose IORT procedures are canceled during surgical procedures.

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DISCLOSURE The authors declare that they have no conflict of interest.

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