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Feasibility of Intraoperative Radiotherapy Tumor Bed Boost in Patients with Breast Cancer after Neoadjuvant Chemotherapy

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Purpose: This study aimed to assess the feasibility and safety of administering intraoperative radiotherapy (IORT) as a boost during breast-conserving surgery (BCS) following neoadjuvant chemotherapy for patients at high risk of breast cancer recurrence.
Materials and Methods: Patients who underwent neoadjuvant chemotherapy received a single 20-Gy dose of IORT during BCS, followed by external beam radiotherapy 4–6 weeks after surgery.
Results: The median follow-up duration was 31.0 months (range, 18.0–59.0 months). Initial tumor sizes had a median of 2.6 cm (range: 0.8–5.3 cm), reducing to 0.3 cm (range: 0–4.0 cm) after neoadjuvant chemotherapy. The most common neoadjuvant chemotherapy regimen was doxorubicin and cyclophosphamide, followed by paclitaxel (n=42, 73.7%). Among 57 patients who received neoadjuvant chemotherapy before BCS and IORT, 2 patients (3.5%) required secondary surgery to achieve negative resection margins due to initially positive margins. Regional lymph node irradiation was performed in 37 (64.9%) patients. There was no grade 3 or higher adverse events, with 4 patients (7.0%) experiencing grade 2 acute radiation dermatitis and 3 (5.3%) having less than grade 2 breast edema. Binary correlation analysis did not reveal statistically significant associations between applicator size or radiation therapy modality and the risk of treatment-related toxicity. Furthermore, chi-square analysis showed that the grade of treatment-related toxicity was not associated with the fractionated regimen (p=0.375).
Conclusion: Most patients successfully received IORT as a tumor bed boost after neoadjuvant chemotherapy. Thus, IORT may be a safe and feasible option for patients with advanced-stage breast cancer receiving neoadjuvant chemotherapy.

Key Words: Breast neoplasms, intraoperative, neoadjuvant therapy, radiotherapy, safety

INTRODUCTION

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).[1] The TARGeted Intraoperative Radiotherapy Alone (TARGIT-A) trial reported the non-inferiority of intraoperative radiotherapy (IORT) compared to WBI using external beam radiation therapy (EBRT) in select patients with early breast cancer.[2] Furthermore, a randomized comparison of the use of IORT boost with post-

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operative WBI followed by EBRT boost is currently underway in the TARGeted Intraoperative Radiotherapy Boost (TARGIT-B) trial.

Currently, IORT is mainly used in patients with low-risk features. IORT has several advantages, including the "same-day approach" settings and increased patient convenience. IORT allows increased skin-sparing, reduces the possibility of tumor repopulation between the completion of surgery and the initiation of radiotherapy, and allows for a more accurate assessment of the size of the tumor bed, which may reduce the irradiated target volume. Moreover, IORT allows precise identification of the tumor bed location, which reduces the risk of missed targets.[3]

Limited studies have investigated the feasibility and efficacy of using IORT as a boost, particularly in patients with advanced-stage breast cancer who require neoadjuvant chemotherapy. The rationale for neoadjuvant chemotherapy is to facilitate the use of BCS instead of mastectomy. Furthermore, the in vivo sensitivity to chemotherapy can be evaluated.[4] Therefore, the number of patients treated with neoadjuvant chemotherapy has been increasing. However, patients who eventually require neoadjuvant systemic therapy have a higher risk of local recurrence and distant metastasis due to their tumor biology compared to those who do not require neoadjuvant treatment. We hypothesized that IORT can be administered to high-risk patients without increasing toxicity. Therefore, in this study, we aimed to investigate the safety and feasibility of IORT boost after neoadjuvant chemotherapy in patients with advanced-stage breast cancer.

MATERIALS AND METHODS

Patient selection

All data were prospectively collected in a phase II study (NCT02213991) conducted according to the Conditional Approval System of Health Technology and approved by the Ministry of Health and Welfare of Korea (CAS-2017-4-1). Five hundred and ninety-six patients diagnosed with breast cancer were treated with a single dose of 20 Gy IORT as a tumor bed boost between August 2014 and February 2020. All patients were required to have a biopsy-proven diagnosis of breast cancer along with clinical, radiographic, and pathological assessments for staging purposes. Imaging studies including breast ultrasound, mammography, and breast magnetic resonance imaging (MRI) were performed for initial clinical staging. IORT was administered to patients aged ≥20 years, with biopsy-proven breast cancer undergoing BCS, and with a maximum tumor size <5 cm. Patients who presented with an initial tumor size >2 cm or initial lymph node metastases on axillary imaging and/or biopsy were treated with neoadjuvant chemotherapy.

After BCS, specimens were sent to the pathology department, and pathological tumor staging was performed, according to the American Joint Committee on Cancer 8th edition TNM staging system. The estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 (HER-2) statuses were also analyzed. This study was approved by the Institutional Review Board of Gangnam Severance Hospital (IRB No. 3-2023-0059) and adhered to the principles of the Declaration of Helsinki.

Treatment scheme

The most frequently used neoadjuvant chemotherapy regimen was Adriamycin (doxorubicin) and cyclophosphamide, followed by paclitaxel (AC+T). The docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) regimen was used in patients with HER-2-positive breast cancer. After the completion of neoadjuvant chemotherapy, imaging studies including mammography, ultrasound, and/or breast MRI were performed for response evaluation to determine eligibility for BCS. Breast surgery was performed by experienced surgeons, and sentinel lymph node biopsy or axillary nodal dissection were performed according to institutional protocols. Frozen sections were sent to the Department of Pathology immediately after tumor excision. Additional margin excision was performed in cases with positive resection margins on frozen-section analysis.

After tumor excision, patients who provided informed consent were administered IORT. In some cases, IORT was delivered before pathological confirmation of negative margins. IORT was planned and delivered by a radiation oncologist. A single dose of 20 Gy IORT was administered at the surface of the applicator using the mobile 50 kV X-ray source (INTRABEAM, Zeiss, Oberkochen, Germany), with attenuation of the dose to approximately 5 Gy at 1 cm from the edge of the excision cavity (Supplementary Figs. 1 and 2, only online). A spherical applicator with an appropriate diameter (ranging from 3.0–4.5 cm in 0.5 cm increments) was selected based on the size of the tumor cavity and placed inside the cavity following mass excision. A purse-string suture was used to tightly pull the walls of the tumor cavity around the surface of the applicator. Optically stimulated, luminescent dosimeter chips were attached to the skin to measure the skin dose. The superior, inferior, medial, and lateral doses were measured, each at 5 mm from the skin edge. As for the skin dose, which was measured at 1 cm from the edge of the excision cavity, the dose constraint was 5 Gy. Skin dose measurements were performed as previously described.[5]

At 4–6 weeks after the surgery, patients underwent EBRT. The ipsilateral whole breast, including the tumor bed, was delineated for determining the target volume, and WBI with 46 Gy in 23 fractions was performed. Hypofractionated radiation therapy (RT) with 40.05 Gy in 15 fractions has been approved in our institution since 2019. For patients with initial node metastases, the regional lymph nodes were irradiated. In these patients, the axillary, supraclavicular, and internal mammary lymph nodes were included in the target volume. As for supraclavicular lymph nodes, the target volume was contoured ac-

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cording to European Society for Radiotherapy and Oncology (ESTRO) nodal target volume guidelines in patients with initial clinical N1 disease, and the target volume was contoured according to Radiation Therapy Oncology Group (RTOG) nodal target volume guidelines in patients with initial clinical N2 disease or higher. Patients who received regional node irradiation were administered a dose of 50.4 Gy in 28 fractions. In patients with left-sided breast cancer, RT was administered using the deep inspirational breath-hold technique. Patients were administered intensity-modulated RT (IMRT) or three-dimensional conformal RT (3D-CRT). Breast ultrasonography, mammography, and/or breast MRI were performed every 6 months following WBI. Adjuvant chemotherapy and endocrine therapy were administered based on the current guidelines.

Patients were followed up in the surgery department every 3–6 months for the first 2 years, followed by annual visits thereafter. Seroma was defined as repeated aspiration ≥5 times or >50 cc of fluid aspirated at one time; cases of minimal aspiration volume (<5 cc) were excluded. Acute radiation dermatitis was assessed by the treating radiation oncologist as part of the standard weekly assessment during RT and 1 month after RT. Individual indices of acute skin toxicity, including erythema and desquamation, were also noted. Late toxicity was assessed at least 3 months after radiotherapy and every 3–6 months thereafter. Fibrosis, edema, and hyperpigmentation were recorded as late skin toxicities. Acute toxicities were scored according to the RTOG/European Organization for Research and Treatment of Cancer (EORTC) toxicity scale associated with radiation and delayed toxicities according to the late effects of the normal tissue-subjective objective management analytical scale.[6]

Primary endpoint and statistical analysis

The primary endpoints were acute and late treatment-related toxicities. Secondary endpoints were overall survival (OS), local recurrence-free survival (LRFS), and distant metastasis-free survival. All endpoints were defined from the date of IORT to the pertinent event. The Kaplan–Meier method was used to calculate survival times. Binary correlation analysis using Spearman's rank correlation was used to examine the impact of various determinants, particularly, the applicator size, fractionated regimen, or RT modality, on toxicities. *p*-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

Of the 596 patients referred for IORT, 58 were treated with neoadjuvant chemotherapy; of the 58, one patient did not undergo IORT because the excision cavity was too large, which precluded finding an applicator of an appropriate size. Therefore, 57 patients received neoadjuvant chemotherapy before BCS and IORT (Fig. 1), and were included in the analysis. These patients received IORT between December 2016 and February 2020. The clinical characteristics of the study population are shown in Table 1. The median patient age was 50 years (range, 33–74 years). The most common histological type was invasive ductal carcinoma (96.5%), and the median tumor size was 2.6 cm (range 0.8–5.3 cm) at the initial diagnosis and 0.3 cm (range 0–4.0 cm) after neoadjuvant chemotherapy. Most patients had T2 (n=47, 82.5%), 8 (14.0%) had T1, and 2 (3.5%) had T3 initial clinical staging. The majority of patients (n=39, 68.4%) had regional node metastases at the initial diagnosis; N1 disease was the most common (n=27), followed by N0 (n=18). Among the luminal subtypes, 26 patients (45.6%) had triple-negative breast cancer, followed by luminal A (22.8%), HER-2 (21.1%), and luminal B (10.5%) subtypes. ypT0 was diagnosed in 26 patients (45.6%), ypT1 in 28 (49.1%), and ypT2 in 3 (5.3%). ypN0 was diagnosed in 39 patients (68.4%), ypN1 in 13 (22.8%), ypN2 in 3 (5.3%), and ypN3 in 1 (1.8%). Pathological complete response was achieved in 24 patients (42.1%) following neoadjuvant chemotherapy. A total of 49.1% of the patients achieved tumor downstaging, and 5% presented with stable disease. No patient showed disease progression during the course of neoadjuvant chemotherapy.

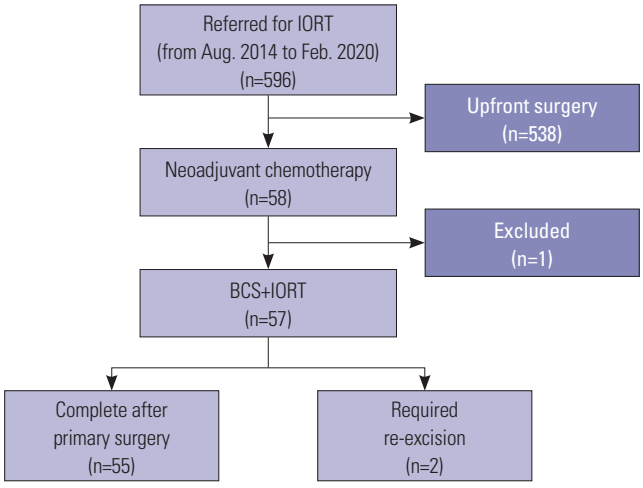

Fig. 1. Flow chart of patient selection. IORT, intraoperative radiotherapy; BCS, breast-conserving surgery.

The treatment-related parameters are listed in Table 2. All of the patients underwent neoadjuvant chemotherapy. The most commonly used regimen was AC+T (n=42, 73.7%). The TCHP regimen was used in all HER-2-positive patients (n=12, 21.1%). Trastuzumab/letrozole was administered to 2 patients (3.5%). Most patients underwent sentinel lymph node biopsy (n=56, 98.2%), and one underwent axillary lymph node dissection.

Two patients (3.5%) required secondary surgery for initially positive margins, and IORT was performed during the first surgery in these cases. Negative resection margins were achieved after re-excision. The median actual beam-on time was 18 min (range, 12–35 min), depending on the applicator diameter. An applicator with a diameter of 3 cm was used in 19 patients

Table 1. Patient Characteristics (n=57)

Characteristics	Value
Age	
≥50 years	30 (52.6)
<50 years	27 (47.4)
Laterality	
Left	26 (45.6)
Right	31 (54.4)
Pathology	
Invasive ductal carcinoma	55 (96.5)
Invasive lobular carcinoma	1 (1.8)
Others	1 (1.8)
Clinical T stage	
T1	8 (14.0)
T2	47 (82.5)
T3	2 (3.5)
Clinical N stage	
N0	18 (31.6)
N1	27 (47.4)
N2	10 (17.5)
N3	2 (3.5)
Histologic grade	
I	1 (1.8)
II	36 (63.2)
III	20 (35.1)
Luminal subtype	
Luminal A	13 (22.8)
Luminal B	6 (10.5)
HER-2	12 (21.1)
TNBC	26 (45.6)
Proliferation index	
Ki-67 <14%	26 (45.6)
Ki-67 ≥14%	18 (31.6)
Unknown	13 (22.8)
Pathologic T stage	
T0	26 (45.6)
T1	28 (49.1)
T2	3 (5.3)
Pathologic N stage	
N0	39 (68.4)
N1	13 (22.8)
N2	3 (5.3)
N3	1 (1.8)
Lymphovascular invasion	
Absent	49 (86.0)
Present	8 (14.0)
Perineural invasion	
Absent	55 (96.5)
Present	2 (3.5)

HER-2, human epidermal growth factor receptor-2; TNBC, triple-negative breast cancer.
Data are presented as n (%).

Table 2. Treatment Characteristics (n=57)

Characteristics	Value
Neoadjuvant CTx regimen	
AC+Taxol	42 (73.7)
TCHP	12 (21.1)
Trastuzumab/Letrozole	2 (3.5)
Response to neoadjuvant CTx	
Complete response	24 (42.1)
Partial response	28 (49.1)
Stable disease	5 (8.8)
Progression of disease	0 (0.0)
Sentinel node biopsy	
Yes	56 (98.2)
No	1 (1.8)
IORT applicator size	
3 cm	19 (33.3)
3.5 cm	18 (31.6)
4 cm	9 (15.8)
4.5 cm	11 (19.3)
EBRT dose	
46 Gy/23 fx	15 (26.3)
40.05 Gy/15 fx	5 (8.8)
50.4 Gy/28 fx	37 (64.9)
RT modality	
IMRT	45 (78.9)
3D-CRT	12 (21.1)
RT field	
Whole breast	20 (35.1)
Whole breast and regional LN	37 (64.9)
Adjuvant CTx regimen	
None	33 (57.9)
Trastuzumab	12 (21.1)
Capecitabine	8 (14.0)
HP	4 (7.0)
Hormone treatment	
Tamoxifen	13 (22.8)
Aromatase inhibitor	10 (17.5)
None	34 (59.6)

CTx, chemotherapy; AC, adriamycin and cyclophosphamide; TCHP, docetaxel, carboplatin, trastuzumab, and pertuzumab; IORT, intraoperative radiotherapy; EBRT, external beam radiation therapy; Fx, fractions; RT, radiation therapy; IMRT, intensity-modulated radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; LN, lymph node; HP, trastuzumab and pertuzumab.
Data are presented as n (%).

(33.3%), 3.5 cm in 18 (31.6%), and 4 cm in 9 (15.8%). A maximum dose of 6.76 Gy was recorded at 5 mm from the skin edge, with a median dose of 3.07 Gy (range, 0.29–6.76 Gy). Most patients (n=37, 64.9%) received conventional fractionation radiotherapy, and the median time from BCS to radiotherapy was 1.3 months (range, 1.2–6.8 months); IMRT was the most frequent modality (n=45, 78.9%), with 3D-CRT applied to the remainder of patients. WBI and regional node irradiation with

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50.4 Gy in 28 fractions were administered to all patients with node-positive disease: pN1 (n=14), pN2 (n=3), and pN3 (n=1).

Table 3 shows the toxicity profiles of the study population. No patient experienced grade 3 or higher adverse events. No patient experienced surgical complications, such as infection or delayed wound healing. Grade 2 acute radiation dermatitis occurred in 4 (7.0%) patients; all of these dermatitis events occurred in breast outside the tumor bed during the EBRT phase and were resolved after conservative care. Tumor bed fibrosis occurred in 14 patients (24.6%), breast edema ≤grade 2 in 3 patients (5.3%), and skin pigmentation in 4 patients (7.0%). Twenty-four (42.1%) patients underwent repeat aspiration for seroma formation. Finally, binary correlation analysis did not reveal statistically significant associations between any particular variable (applicator size or RT modality) and the risk of treatment-related toxicity (Supplementary Tables 1 and 2, only online). Logistic regression analysis was performed to analyze the correlation between seroma and tumor/treatment-related factors. No particular variable was significantly associated with the occurrence of seroma (Supplementary Table 3, only online). In addition, the grade of treatment-related toxicity was not significantly associated with the fractionated regimen in chi-square analysis (p=0.375) (Table 4). However, all grade 2 treatment-related toxicity [radiation dermatitis (n=4) and breast edema (n=1)] was observed in the 50.4 Gy/28 fx arm.

No death occurred during the follow-up period, with a median follow-up of 31.0 months (range, 18.0–59.0 months). No recurrence was observed in the ipsilateral or contralateral breast. One patient developed brain metastasis 12 months after IORT.

DISCUSSION

There is a paucity of data regarding the feasibility of IORT as a tumor bed boost, especially in patients with advanced-stage breast cancer receiving neoadjuvant chemotherapy. However, increasing evidence has suggested that IORT boost has several advantages over EBRT boost in patients with breast cancer undergoing BCS.[7] Immediate irradiation after tumor removal may reduce the chances of tumor cell repopulation, and direct placement of the applicator in the tumor cavity may reduce targeting errors.[8-11] Moreover, the steep dose fall-off enabled by IORT allows an increased dose to the tumor bed while sparing adjacent normal tissues, including the skin, contralateral breast, heart, and lungs.[12]

Vaidya, et al.[13] reported that lumpectomy and TARGIT boost combined with WBI showed superior local tumor control compared to the interventions in the EORTC boost or the Standardization of Breast Radiotherapy (START-B) trials. Furthermore, Blank, et al.[14] reported a single-center experience using the IORT boost, resulting in a 5-year OS of 91.3% and a 5-year LRFS of 97.0%. TARGIT-B, an ongoing trial, compares the IORT and EBRT boosts in high-risk patients. However, few studies have evaluated the feasibility of IORT in patients with advanced-stage breast cancer receiving neoadjuvant chemotherapy. Kolberg, et al.[4] reported the treatment outcomes of IORT in patients undergoing BCS after neoadjuvant chemotherapy. In their retrospective analysis with a median follow-up of 49 months, IORT as a tumor bed boost after neoadjuvant chemotherapy was not worse than the EBRT boost in terms of treatment outcomes, including the OS, LRFS, disease-free survival, and breast cancer mortality. In the current study, we focused on the safety and feasibility of the treatment, specifically its toxicity.

No toxicities higher than grade 3 were reported in this study, the most common of which were radiation dermatitis, tumor bed fibrosis, and seroma formation. In particular, breast IORT did not result in significant skin toxicity in Asian (Korean) women with relatively small breast volumes. Burgos-Burgos, et al.[15] evaluated the acute toxicities and cosmetic outcomes of hypofractionated WBI after IORT. Hypofractionated WBI showed similar acute toxicities and cosmetic results to conventional fractionation RT in combination with IORT after BCS. However, hypofractionated RT has only been performed at our institution since 2019; therefore, only 5 patients (8.8%) treated with hypofractionated RT were included in this study. Thus, further studies on the safety and treatment outcomes according to fractionation in patients treated with IORT after neoadjuvant chemotherapy are warranted. In addition, toxicity was considered to be relatively rare, since a considerable proportion of patients (78.9%) were treated with IMRT. Nevertheless, the rate of seroma in the present study (42.1%) was relatively high com-

Table 3. Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Seroma		24 (42.1)		
Acute effects				
Radiation dermatitis	9 (15.7)	4 (7.0)	0	0
Late effects				
Tumor bed fibrosis	14 (24.6)	0	0	0
Breast edema	2 (3.5)	1 (1.8)	0	0
Pigmentation	4 (7.0)	0	0	0

Data are presented as n (%).

Table 4. Chi-Square Analysis for Grade of Treatment-Related Toxicity According to Fractionated Regimen

	40.05 Gy/15 fx (n=5)	46 Gy/23 fx (n=15)	50.4 Gy/28 fx (n=37)	Total (n=57)	p value
No treatment-related toxicity	5 (100)	12 (80.0)	26 (70.3)	43 (75.4)	0.375
Grade 1 treatment-related toxicity	0 (0)	3 (20.0)	6 (16.2)	9 (15.8)	
Grade 2 treatment-related toxicity	0 (0)	0 (0)	5 (13.5)	5 (8.8)	

Data are presented as n (%).

pared to that of previous reports (3.8%–25.5%).[16-20] There have also been various reports on the effect of IORT on seroma formation. Kraus-Tiefenbacher, et al.[21] analyzed the rate of seroma in patients treated with BCS+IORT vs. BCS-only and the rate of seroma was not different (IORT 23%; No-IORT 23%; p=0.933) between the two groups. In contrast, in a study including 93 patients by Gülçelik, et al.[19] assessing wound complications after IORT, seromas were observed in 25.5% of patients in the IORT group (compared to 6% in the BCS-only group). It was concluded that IORT could have a negative effect on seroma formation, and hence, the adverse effects of IORT on wound complications should be closely monitored. Unlike other previous studies, only patients who received neoadjuvant chemotherapy prior to BCS and IORT were included in our study; therefore, the high rate of seroma may have been due to the effect of chemotherapy. However, a firm conclusion cannot be drawn from this study alone, and further studies comparing the complication rates of the patients who were treated with or without neoadjuvant chemotherapy prior to IORT will have to be conducted.

In the present study, 2 patients (3.5%) underwent margin re-excision for initially positive margins and achieved negative resection margins. Appropriate margin status and the need for re-excision are important factors in IORT. Broman, et al.[22] compared the impact of pre- and post-IORT margin excisions on in-breast tumor recurrence and reported that taking additional pre-IORT margins and re-excising close/positive margins post-IORT improved margin clearance rates but had an unclear effect on in-breast tumor recurrence. Therefore, determining whether to return to surgery to re-excise positive margins after IORT remains controversial. Regarding lumpectomy with EBRT, two meta-analyses demonstrated that a greater margin distance did not lead to additional risk reduction beyond that conferred by margin-negative resection.[23,24] Meanwhile, a more conservative margin management strategy has been applied for partial breast irradiation (PBI).[25] Uncertainty exists in the appropriate margin status and the need for re-excision in the context of IORT, and future prospective studies are required to determine whether less strict criteria are appropriate for patients receiving IORT boost after neoadjuvant chemotherapy. In addition, several studies have reported a higher re-excision rate after neoadjuvant chemotherapy compared to primary operative management. Data from over 9000 patients in a nationwide network and registry of histology and cytopathology in the Netherlands showed an increased re-excision rate of 9.1% in patients treated with neoadjuvant chemotherapy and BCS compared to 5.3% in patients treated with primary operative management.[26] Moreover, Devane, et al.[27] reported that the re-excision rate after neoadjuvant chemotherapy was almost twice of that after upfront surgery. Therefore, it is necessary to confirm the results of the frozen section analysis when performing surgery after neoadjuvant chemotherapy.

Several methods are available for shortening the duration of RT after BCS. In particular, the duration can be reduced using PBI or hypofractionated RT. The treatment outcomes of PBI and hypofractionated RT are also non-inferior to those of conventional fractionation RT; therefore, these techniques are widely used in patients with early breast cancer.[28-34] The total treatment period can also be reduced using the simultaneous integrated boost technique.[35,36] Fast-forward regimen, which is the latest trend in RT, can also shorten the treatment duration.[37] Nevertheless, IORT still remains compatible even in the era of fast-forward regimens and has several advantages of not only reducing the treatment duration but also improving tumor control by reducing geographic misses and applying higher doses of radiation to the tumor cavity.[8-12,35,36] Immediate irradiation after tumor removal may reduce the chances of tumor cell repopulation. IORT delivers radiation directly to the tumor site during surgery, allowing for highly targeted treatment with minimal exposure to surrounding normal tissues. In addition, IORT can help preserve normal breast tissue, and may potentially lead to improved cosmetic outcomes and breast preservation. Although there was no data available regarding the grade of the cosmetic outcomes in the present study, further studies will be conducted to analyze this factor in the future. Furthermore, IORT allows for immediate assessment of surgical margins, enabling additional treatment if necessary during the same surgery. Therefore, future studies are required to investigate the final oncological outcomes of this treatment strategy.

This study had several limitations. Patients were prospectively enrolled in this study; however, toxicity data were retrospectively collected from electronic medical records. Toxicity parameters are often influenced by numerous other uncontrollable factors; therefore, potential confounding factors could not be completely excluded. No local or regional recurrence occurred in this study; however, it is possible that the follow-up period was too short to analyze oncological outcomes. Furthermore, the small sample size may have obscured the results of data analysis. In addition, there was no data available regarding the grade of cosmetic outcomes. Therefore, future studies including the cosmetic results with longer follow-up periods and larger sample sizes are required. Moreover, the small number of patients treated with hypofractionated RT may be another limitation, since the recent trend is to undergo extensive hypofractionation regardless of the regional node irradiation. Nevertheless, these limitations do not diminish the potential of our findings or the clinical implications of IORT as a feasible modality for patients with advanced-stage breast cancer who undergo neoadjuvant chemotherapy. Furthermore, the hypothesis of systemic benefits of IORT will be assessed in the TARGIT-B international randomized trial, comparing the IORT boost to the EBRT boost in high-risk patients, including those who have received neoadjuvant chemotherapy. We anticipate that the results of this trial will help validate the conclusions of the current study.

In conclusion, our study is one of the first of its kind. We

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found that most patients included in this study successfully underwent IORT as a tumor bed boost during BCS following neoadjuvant chemotherapy, and that the overall treatment period was reduced by shortening the boost period, which did not result in significant toxicity. However, further follow-up is required to determine oncologic outcomes after IORT application. Overall, our findings indicate that IORT may be a safe and feasible option for patients with advanced-stage breast cancer receiving neoadjuvant chemotherapy.

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AUTHOR CONTRIBUTIONS

Conceptualization: Yeona Cho. Data curation: Gowoon Yang, Jun Won Kim, Ik Jae Lee, Joon Jeong, Sung Gwe Ahn, Soong June Bae, and Jee Hung Kim. Formal analysis: Gowoon Yang. Investigation: all authors. Methodology: Yeona Cho. Project administration: all authors. Resources: Jun Won Kim, Ik Jae Lee, Joon Jeong, Sung Gwe Ahn, Soong June Bae, Jee Hung Kim, and Yeona Cho. Software: Gowoon Yang. Supervision: Yeona Cho. Validation: all authors. Visualization: all authors. Writing—original draft: Gowoon Yang. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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