

## Single-institution Comparison of Accelerated Partial Breast Irradiation and Whole Breast Irradiation in Breast Cancer Patients with Unfavorable Parameters by the American Society for Radiation Oncology Guidelines

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### ABSTRACT

**AIM:** The American Society for Radiation Oncology (ASTRO) issued guidelines regarding patients that were suitable for accelerated partial breast irradiation (APBI) following breast-conserving surgery (BCS) as an alternative to whole breast irradiation (WBI). However, the suitability criteria may not be based on updated data concerning the risk of ipsilateral breast tumor recurrence (IBTR) with APBI. We reviewed the experience of APBI and WBI in patients that would be characterized in the unfavorable categories based on the ASTRO guidelines.

**METHODS:** Patients in both APBI and WBI cohorts were categorized into one of the three groups based on the ASTRO guidelines on ABPI: suitable, cautionary, or unsuitable. Consecutive patients who underwent BCS followed by APBI or WBI were

examined to compare and determine patterns of treatment failures.

**RESULTS:** Since November 2007, 203 patients receiving APBI and 132 receiving WBI were analyzed. Mean follow-up was longer than 3 years. In the APBI cohort (17 suitable, 87 cautionary, and 99 unsuitable patients), IBTR or regional recurrence was observed in 1 (5.9%), 1 (1.1%), and 3 (3.0%) patient, respectively. In the WBI cohort (14 suitable, 30 cautionary, and 88 unsuitable patients), IBTR or regional recurrence was observed in 0 (0%), 1 (3.3%), and 4 (4.5%) patients, respectively. When APBI patients were stratified according to the ASTRO category, there was no statistically significant difference in the local control rates.

**CONCLUSIONS:** The clinical efficacy of APBI was comparable with that of WBI for local control after BCS in patients considered cautionary or unsuitable for APBI following the ASTRO guidelines.

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**Key words:** Breast Cancer; Accelerated Partial Breast Irradiation; Whole Breast Irradiation; Ipsilateral Breast Tumor Recurrence; The American Society for Radiation Oncology guidelines

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### INTRODUCTION

Breast-conserving surgery (BCS) followed by whole breast irradiation (WBI) has been established as an acceptable alternative to mastectomy for patients with early-stage breast cancer<sup>[1,2]</sup>. However, it takes 5-6 weeks of frequent visits to the radiation centers; therefore, at least 25% or more patients fail to receive sufficient radiation after

BCS<sup>[3,4]</sup>. Accelerated partial breast irradiation (APBI) allows the delivery of radiation therapy after BCS in 1 week or less via several techniques, which offer decreased overall treatment time and several theoretical advantages over WBI.

The efficacy and feasibility of APBI as an alternative to WBI have been evaluated in many phase II and III trials<sup>[5-9]</sup>, which showed that APBI with proper patient selection and quality assurance yields similar results to those achieved with standard WBI. Therefore, APBI is increasingly being used with a 10-fold increase between 2002 and 2007<sup>[10]</sup>, and in recent years more than 30,000 patients have been treated worldwide outside of clinical trials<sup>[11]</sup>.

With the increased use of APBI, evidence-based guidelines are necessary to guide physicians regarding appropriate patient evaluation and selection. In the United States, several professional societies including the American Brachytherapy Society and the American Society of Breast Surgeons base these recommendations primarily on patient age, tumor size, and margin status. In 2009, the American Society for Radiation Oncology (ASTRO) Health Services Research Committee developed a consensus statement regarding patient selection criteria to identify suitable candidates and best practices for the off-protocol use of APBI before the availability of results from randomized clinical trials<sup>[11]</sup>. These guidelines proposed 3 groups of APBI appropriateness: “suitable,” “cautionary,” and “unsuitable,” based on patient characteristics and clinical and pathological factors.

In our institution, since October 2008 we have initiated a prospective observational study on APBI using multicatheter brachytherapy after BCS. Data regarding the long-term efficacy of this technique indicated some instances of local recurrence and a low rate of adverse events<sup>[12-14]</sup>. We started APBI immediately following lumpectomy with simultaneous multicatheter insertion during primary surgery. Therefore, we could not follow the ASTRO guidelines that require candidates to be selected without the final pathology, which is similar to intraoperative radiotherapy technique.

In this study, we reviewed our single-institution experience of APBI in patients selected using our wider enrollment criteria than the ASTRO suitable group to determine whether the ASTRO guidelines are useful in patients with breast cancer in Japan.

## METHODS

### APBI with multicatheter brachytherapy and WBI techniques after BCS

A prospective observational study has been conducted to evaluate the efficacy of APBI using multicatheter brachytherapy in patients with breast cancer. The following are criteria for the inclusion: patient age  $\geq 40$  years, pathologically proven breast cancer, unifocal disease, tumor diameter  $\leq 3.0$  cm, and negative margins and sentinel node metastasis by frozen section analysis. Neoadjuvant chemotherapy was not allowed. A written informed consent was obtained, and the institutional review board of our hospital approved the study.

The technique of multicatheter brachytherapy with APBI was previously reported<sup>[12]</sup>. The procedure involves the insertion of applicators and the subsequent delivery of doses of radiation simulated by preoperative computed tomography (CT) using the Nucletron PLATO treatment planning system (Version UPS: 11.3; Nucletron Trading BV, Veenendaal, The Netherlands). The planning target volume was determined as the lumpectomy cavity defined by hemoclips plus 20-mm. Dose distribution analysis using dose-volume histograms was performed based on postoperative CT. The dose for APBI was 32 Gy in 8 twice-daily fractions with a minimum 6 hour

interval.

For WBI, patients received a total dose of 50 Gy in fractions of 2 Gy delivered to the entire breast. Patients with risk factors, such as positive margins and young age, also received a 10-Gy boost to the tumor bed. The combination of regional nodal irradiation (RNI) with WBI after BCS was performed in patients with  $\geq 4$  positive nodes. The follow-up after treatment was planned as follows: clinical examination every 3-4 months, an annual mammography, and contrast-enhanced breast magnetic resonance imaging (MRI) were performed every year to detect ipsilateral breast tumor recurrence (IBTR) and regional nodal failure for the first 5 years.

### Classification by ASTRO guidelines

First, the distribution of suitable, cautionary, and unsuitable patients between the APBI and WBI treatment groups was evaluated. Patients in the APBI and WBI cohorts were categorized into one of the 3 groups (suitable, cautionary or unsuitable) using the criteria outlined in the ASTRO guidelines on APBI. There were no patients referred for BRCA 1/2 testing. The suitable, cautionary, and unsuitable patients in the APBI with WBI cohorts were compared to determine patterns of breast cancer treatment failures. IBTR was classified into “tumor-bed recurrence” and “treatment failure elsewhere” based on the location of the tumor. Tumor-bed recurrence was considered as a true recurrence located within or immediately adjacent to the lumpectomy cavity. Treatment failure elsewhere was generally regarded as a new primary cancer located several centimeters from the cavity.

### Statistics

The chi-square test was used to analyze associations among categorical variables with treatment groups. Student’s unpaired *t* test was used to analyze differences between 2 sample means of continuous variables. A *p* value  $< 0.05$  was considered to indicate statistical significance. Statview 5.0 (SAS Institute Inc. Cary, NC, USA) was used to perform statistical analyses.

## RESULTS

### ASTRO guidelines assignments

A total of 343 consecutive patients who underwent BCS followed by radiotherapy from November 2007 to September 2013 were analyzed, and a prospective multicatheter brachytherapy study was initiated in October 2008. Patients who received neoadjuvant chemotherapy were excluded from the study.

All patients eligible for our observational study were offered the option of APBI after BCS. They were informed of the experimental nature of the treatment. Patients who have not met the eligibility criteria declined WBI but were willing to receive APBI were included in the study. A consort diagram is shown in figure 1, and table 1 lists the clinical, pathological, and treatment-related characteristics of APBI and WBI groups. The mean age of the APBI patients (56.0 years) was significantly higher than that of the WBI patients (51.2 years,  $p < 0.05$ ). The mean follow-up was 36.6 months for APBI and 42.7 months for the WBI cohort, which was statistically different ( $p < 0.05$ ). APBI patients were less likely to be node-negative (87.7% vs 75.8%, respectively; not significant). A total of 170 patients (83.7%) in the APBI cohort and 85 (64.4%) in the WBI cohort met the enrollment criteria for the registry study, which was moderately different but not significant.

When the ASTRO guidelines were used to segregate these patients into the 3 groups, the distributions were as follows: in the

APBI cohort, 17 (8.4%), 87 (42.9%), and 99 (48.7%) patients were suitable, cautionary, and unsuitable, respectively, compared with 14 (10.6%), 30 (22.7%), and 88 (66.7%) in the WBI cohort, respectively. Therefore, 186 APBI patients (91.6%) and 118 WBI patients (89.4%) were regarded as cautionary or unsuitable for APBI therapy based on the ASTRO guidelines (Table 2).

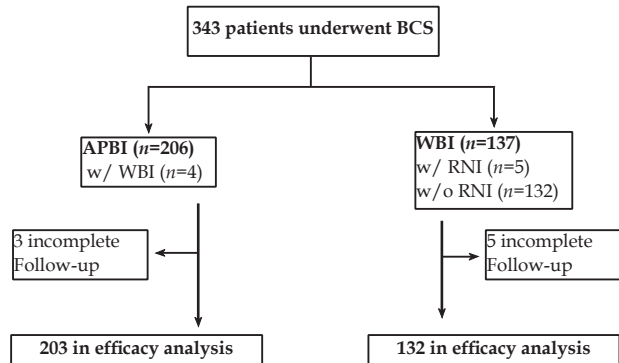


Figure 1 CONSORT diagram of radiotherapy after breast-conserving surgery.

Table 1 Clinical, pathological, and treatment-related characteristics of the 2 radiation treatment groups.

	APBI (n = 203)	WBI (+RNI) (n = 132)	p value
Age, years (mean)	56.0 (30-92)	51.2 (31-84)	<0.05
<50	74 (36.5%)	63 (47.7%)	
50-59	48 (23.6%)	40 (30.3%)	
≥60	81 (39.9%)	29 (22.0%)	
Follow-up time (mean)	36.6 months	42.7 months	<0.05
Mean pathological diameter	12.0 mm (0-38 mm)	12.1 mm (0-27 mm)	n.s.
Tis	19 (9.4%)	20 (15.2%)	
T1	171 (84.2%)	102 (77.3%)	
T2	13 (6.4%)	10 (7.5%)	
Margin negative	174 (85.7%)	101 (76.5%)	n.s.
Grade II-III	32 (15.8%)	26 (19.7%)	n.s.
ER-positive	183 (90.1%)	113 (85.6%)	n.s.
HER2 overexpressed	20 (9.9%)	18 (13.6%)	n.s.
Node negative	178 (87.7%)	100 (75.8%)	<0.05
Adjuvant chemotherapy	54 (26.6%)	47 (35.6%)	n.s.
Met enrollment criteria (%)	170 (83.7%)	85 (64.4%)	n.s.

Table 2 The ASTRO category for APBI and WBI patients.

ASTRO category	APBI (n = 203)	WBI (n = 132)	p value
Suitable (%)	17 (8.4%)	14 (10.6%)	n.s.
Cautionary (%)	87 (42.9%)	30 (22.7%)	<0.05
Unsuitable (%)	99 (48.7%)	88 (66.7%)	n.s.

### Clinical outcomes by ASTRO guidelines

Next, locoregional and distant recurrence between the 2 treatment cohorts were examined among the 3 different ASTRO categories. In the suitable group, there were no IBTR patients in either the APBI or WBI cohort, and regional-only recurrence was observed in only 1 patient (5.9%) in the APBI cohort (Table 3). In the cautionary group, there was 1 patient with regional-only recurrence (1.1%) in the APBI cohort, and 1 IBTR patient (3.3%) in the WBI cohort. There was 1 patient with distant recurrence (3.3%) only in the WBI cohort (Table 3). In the unsuitable group, there were 2 IBTR patients (2.0%) in the APBI cohort, and 3 (3.4%) in the WBI cohort. Although there were no obvious differences in locoregional recurrence in the APBI and WBI cohorts, there were 4 patients (4.5%) with distant recurrence only in the WBI cohort (Table 5).

Table 3 The ASTRO suitable group (n = 31).

	APBI (n = 17)	WBI (+RNI) (n = 14)
Locoregional recurrence		
Local only (IBTR)	0	0
Tumor bed recurrence	0	0
Failure elsewhere	0	0
Regional only	1 (5.9%)	0
Distant recurrence		
First or concurrent	0	0
After locoregional	0	0
Death	1	1 (other cause)

Table 4 The ASTRO cautionary group (n = 117).

	APBI (n = 87)	WBI (+RNI) (n = 30)
Locoregional recurrence		
Local only (IBTR)	0	1 (3.3%)
Tumor bed recurrence	0	1
Failure elsewhere	0	0
Regional only	1 (1.1%)	0
Distant recurrence		
First or concurrent	0	1 (3.3%)
After locoregional	0	0
Death	1 (other cause)	1 (3.3%)

Table 5 The ASTRO unsuitable group (n = 187).

	APBI (n = 99)	WBI (+RNI) (n = 88)
Locoregional recurrence		
Local only (IBTR)	2 (2.0%)	3 (3.4%)
Tumor bed recurrence	1	2
Failure elsewhere	1	1
Regional only	1 (1.0%)	1 (1.1%)
Distant recurrence		
First or concurrent	0	4 (4.5%)
After locoregional	0	0
Death	0	1 (3.3%)

## DISCUSSION

Breast cancer is the most common cancer in Japan<sup>[15]</sup>. After the introduction of mammography to screen patients for breast cancer, the number of patients who underwent BCS had been increasing, and this procedure has been the most common treatment for breast cancer since 2003<sup>[16,17]</sup>. Data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated not only a significant reduction in local recurrence but also an overall survival benefit with the use of adjuvant radiation therapy after BCS<sup>[18,19]</sup>. Nevertheless, 15%-30% of patients who undergo BCS refuse WBI<sup>[20-25]</sup> primarily due to the long-term daily visits that are required to the radiation centers. In fact, 20% of patients who underwent BCS in Japan did not receive WBI<sup>[26]</sup>, especially if they had complete pathologically negative margins. Our institution is located far from a metropolitan area; therefore, patients take a long time to travel for receiving radiation therapy. We started our registry program to introduce APBI particularly for patients living further from our institution, and almost all BCS patients received adjuvant radiation therapy. Therefore, we were able to enroll a large number of patients from a variety of backgrounds into this study. This is one of the first observational studies from Asia to demonstrate acceptable clinical outcomes of APBI for patients with unfavorable features based on the ASTRO guidelines.

Older patients exhibited a lower risk of IBTR than younger patients when treated with WBI<sup>[27,28]</sup> or MammoSite<sup>[29]</sup>, and the EBCTCG reported that WBI did not improve survival for women aged ≥60 years<sup>[18]</sup>. Therefore, the ASTRO guidelines have accepted APBI as an alternative to WBI for these older patients. However,

the incidence of breast cancer peaks between the ages of 45 and 49 years in Japan, whereas there is a continuous increase in the number of patients until 75-79 years in the United States<sup>[15]</sup>. Therefore, the indication of a suitable age group based on the ASTRO criteria could be too strict to allow Japanese patients to be considered for APBI. Most recent single-institution and registry studies examining patients treated with APBI stratified according to the ASTRO category revealed no statistically significant difference in the IBTR rates between the suitable, cautionary, and unsuitable groups<sup>[30]</sup>, and we need the guideline updates based on available APBI data.

There were 2 IBTR patients in the APBI cohort in our study. Although 1 patient did not match our enrollment criteria, APBI was performed for compassionate reasons. She received a second conserving surgery and remained in a disease-free condition. In the second patient, IBTR was identified using breast MRI during the 1 year follow-up period. Compared with the previous breast MRI, another focus near the primary lesion which had been recognized as benign cyst was revealed as mucinous carcinoma. Therefore, we treated her with nipple-sparing mastectomy, and she also remained disease free. It is essential that all mammographically occult breast cancer is detected to improve patient selection for APBI. Although the ASTRO task force does not support the routine use of MRI in an APBI setting, MRI should be strongly considered for proper patient selection from this case.

This study demonstrated that the clinical efficacy of APBI for local control after BCS was comparable with WBI in ASTRO-defined cautionary and unsuitable patients with breast cancer in Japan after approximately 3 years of follow-up. The limitations of this study were that it was not randomized, was based on only a small number of patients, and covered only a short follow-up period. The application of APBI, particularly in patients considered to be unfavorable based on the ASTRO guidelines, should still be carefully approached until mature phase III trial data are available.

#### List of abbreviations

BCS: breast-conserving surgery

WBI: whole breast irradiation

APBI: accelerated partial breast irradiation

ASTRO: American Society for Radiation Oncology

CT: computed tomography

RNI: regional nodal irradiation

MRI: magnetic resonance imaging

IBTR: ipsilateral breast tumor recurrence

EBCTCG: Early Breast Cancer Trialists' Collaborative Group

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## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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