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Validating the efficacy of single-stage breast-conserving therapy using multicatheter partial-breast brachytherapy based on updated ASTRO guidelines

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ABSTRACT

Based on the accumulating evidence for equivalent results of partial-breast irradiation (PBI) and whole-breast irradiation (WBI) in breast-conserving therapy (BCT), the American Society for Radiation Oncology (ASTRO) updated the consensus statement (CS) to expand the range of potential candidates for PBI outside clinical trials. Of the various techniques, PBI using multicatheter interstitial brachytherapy (MCB) is the oldest and has long-term data. In this study, the efficacy of single-stage BCT using MCB-PBI achieved by an intraoperative catheter placement was validated on updated ASTRO guidelines. We retrospectively examined patients undergoing BCT using MCB-PBI or WBI. The updated CS distinguished patients aged 40–49 years with ER+, tumor ≤2 cm, and margin ≥2 mm from unsuitable patients in the previous CS. We compared the ipsilateral breast tumor recurrence (IBTR) rate in MCB-PBI with that in WBI patients with suitable or cautionary (S/C) categories on the updated CS. Between November 2007 and September 2017, 641 patients with 647 lesions underwent BCT (MCB-PBI, 407; WBI, 240). At the median follow-up time of 54.4 months, we observed 8 (1.97%; 95% CI: 0.62–3.31%) and 7 (2.92%; 95% CI: 0.79–5.05%) IBTRs, respectively. Updating the CS increased the S/C patients receiving MCB-PBI from 232 patients (57.0%) to 319 (78.4%). Comparison of clinical outcomes at the 12-month minimum follow-up between 291 MCB-PBI and 103 WBI in S/C patients showed no significant differences in the 4-year rate of IBTR-free (100% vs 98.9%; $P = 0.29$) and disease-free survival (98.7% vs 95.5%; $P = 0.24$). Overall, single-stage BCT using MCB-PBI offered similar tumor control rates, compared with WBI, on the updated ASTRO CS.

Keywords: breast cancer; breast-conserving treatment; partial-breast irradiation; multicatheter interstitial brachytherapy; ASTRO guideline

INTRODUCTION

Breast-conserving surgery (BCS) followed by 5–7 weeks of daily whole-breast irradiation (WBI) is the preferred breast-conserving therapy (BCT) for patients with early-stage breast cancer [1, 2]. Although hypofractionated WBI is considered an effective, safe, and shorter treatment schedule than an adjuvant WBI [3], which needs 15–16 daily treatments, normal tissue toxicities, such as toxicities of the lung and coronary arteries, should be still considered [4]. Hence, partial-breast irradiation (PBI), which radiates a limited breast field, has been practised, using several techniques, to reduce the burden of WBI.

Based on the limited number of Phase III trials comparing the efficacy and safety of PBI and WBI, the American Society for Radiation Oncology (ASTRO) Health Services Research Committee developed a consensus statement (CS) regarding patient selection criteria for off-protocol PBI use in 2009. These guidelines categorized

patients on the basis of PBI appropriateness, regardless of the technique group—suitable, cautionary or unsuitable [5]—that had been produced by traditional clinicopathological risk factors of ipsilateral breast tumor recurrence (IBTR) with BCT using WBI, and were not able to be considered for PBI because of the scarce evidence. Recently, a randomized trial conducted by the Groupe European de Curietherapie–European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) demonstrated the non-inferior efficacy, similar late toxicities, and equal or better cosmetic outcomes of PBI using multicatheter brachytherapy (MCB) compared with WBI with a tumor-bed boost after BCS [6, 7]. Such growing evidence from Phase III trials led the ASTRO to update guidelines and expand the candidates for PBI, especially using MCB-PBI [8].

At our institution, PBI is initiated immediately after surgery with intraoperative multicatheter insertion as 'single-stage BCT,' which is a comparatively less invasive procedure and has an accurate placement of catheters [9]. This study aims to review our registry data of single-stage BCT using MCB-PBI to validate the efficacy using the updated ASTRO CS.

MATERIALS AND METHODS

Patients

In this retrospective chart review, we examined consecutive patients who underwent BCS followed by adjuvant radiotherapy. Patients with tumor diameter ≤3.0 cm who can achieve an acceptable cosmesis with a 1 cm-negative margin after surgery are candidates for BCS. After obtaining approval from our Institutional Review Board for an observational study of MCB-PBI, we applied it as an option for radiation treatment other than WBI since October 2008. The criteria for MCB-PBI being added to BCS were age ≥40 years, unifocal disease, negative margins on intraoperative specimen mammography, and no evidence of metastasis on sentinel nodes. We excluded patients receiving neoadjuvant chemotherapy from this study.

Radiotherapy techniques

The details of our MCB-PBI technique have been published previously [9]. We inserted the catheters for the ^{192}iridium wires under a template guidance using preoperative CT simulation by the Nucletron PLATO Treatment Planning System (Version UPS: 11.3; Nucletron Trading BV, Veenendaal, the Netherlands). We performed a dose distribution analysis on postoperative CT. The planning target volume (PTV) was provided by delineation of the surgical cavity with a 10-mm margin. The maximum dose to the skin and chest wall was <75% of the prescription dose. Furthermore, interstitial brachytherapy was performed just after surgery in single-stage fashion, with a dose of 32 Gy in eight fractions over 5–6 days.

For WBI, patients received external beam radiotherapy over the entire breast, with a total dose of 50 Gy in 25 fractions using the Pinnacle 3 Treatment Planning System (Philips, Fitchburg, WI). The decision regarding the radiation field was at the discretion of radiation oncologists. Patients with risk factors such as positive margins and young age (<40 years) received a subsequent 10-Gy boost to the tumor bed using electrons. The boost PTV contained the surgical scar with an overall margin of 10 mm in all directions. In addition, regional nodal irradiation was added in patients with ≥4 positive nodes.

Assessment of outcomes

The follow-up policy was physical examination every 3–4 months with annual mammography. In addition, a contrast-enhanced breast MRI scan was performed every 12 months for the first 5 years. IBTRs were classified by location in relation to the lumpectomy cavity [10]. True recurrence was defined as recurrence on the primary tumor bed or adjacent to the lumpectomy cavity. Failure elsewhere was defined as recurrence several centimeters away from the primary site and was considered a new primary cancer.

First, we compared the clinical outcomes of MCB-PBI with WBI in the two cohorts with respect to the rate of IBTRs and illustrated the patterns of treatment failures in patients experiencing IBTR. Second, patients in the MCB-PBI and WBI cohorts were categorized into three groups (i.e. suitable, cautionary or unsuitable), and the distributions of the suitable/cautionary (S/C) group were evaluated based on the former and updated ASTRO CS. Finally, we compared the clinical outcomes of MCB-PBI with WBI in the S/C group, with a minimum follow-up of 12 months regarding the IBTR-free survival (IBTR-FS) and disease-free survival (DFS).

Statistical analysis

We used the χ^2 test to analyze the correlation between categorical variables. Student's unpaired *t*-test was used to assess differences between the means of continuous variables. We considered $P < 0.05$ as statistically significant. Furthermore, StatView 5.0 (SAS Institute Inc., Cary, NC) was used for statistical analyses. We obtained written informed consent from all patients, and the Institutional Review Board of our institution approved this study.

RESULTS

From November 2007 to September 2017, we examined 635 Japanese (99.1%) and 6 Asian patients (0.9%) who underwent BCT, of whom 403 and 238 consecutive patients with 407 and 240 lesions were treated with BCT using MCB-PBI and WBI, respectively. The number of lesions was calculated per patient. Table 1 presents the patients' characteristics and demographics. In the entire cohort, patients receiving WBI had a longer follow-up period ($P < 0.005$), were significantly younger ($P < 0.001$), and had more margin positivity and nodal involvement ($P < 0.0001$) than MCB-PBI because of our protocol. At a median follow-up of 54.4 months (4.5–123.0 months), IBTR was observed in 8 (1.97%; 95% CI: 0.62–3.31%) and 7 patients (2.92%; 95% CI: 0.79–5.05%) in MCB-PBI and WBI patients, respectively. Table 2 summarizes the characteristics of patients experiencing IBTR. Notably, of patients with IBTR, MCB-PBI patients (50%) tended to present more recurrences elsewhere than WBI patients (14.3%).

By updating the ASTRO CS, the number of S/C patients for MCB-PBI and WBI increased from 232 (57.0%) and 75 (31.3%) to 319 (78.4%) and 108 (45.0%), respectively. We compared the clinical outcomes at the 12-month minimum follow-up of 291 patients receiving MCB-PBI with those of 103 patients receiving WBI in the

Table 1. Patient demographics and tumor characteristics in the entire cohort

	MCB-PBI ($n = 407$)	WBI ($n = 240$)	*P*
Medium follow-up (months)	51.0 (4.8–112.2)	58.3 (4.5–123.0)	<0.005
Mean age (years)	56.9 (30–92)	53.4 (26–84)	<0.001
Mean invasive diameter (mm)	12.1 (0–38)	12.0 (0–50)	n.s.
pTis	40 (9.8%)	43 (17.9%)	
pT1	336 (82.6%)	168 (70.0%)	
pT2	29 (7.1%)	29 (12.1%)	
NR	2 (0.5%)	0 (0%)	
Margin positive	39 (9.6%)	47 (19.6%)	<0.001
Grade II–III	58 (14.3%)	36 (15.0%)	n.s.
ER-negative	59 (14.5%)	39 (16.3%)	n.s.
HER2 overexpressed	46 (11.3%)	34 (14.2%)	n.s.
Node positive	25 (6.1%)	81 (33.8%)	<0.0001
Adjuvant chemotherapy	138 (33.9%)	103 (42.9%)	<0.05

Table 2. Characteristics of patients experiencing IBTR

	Age (years)	pT (cm)	Positive nodes	Margin status	Failure type	Adjuvant chemotherapy	Distant metastases	Time to event (months)
MCB-PBI								
1	41	micro	1	Positive	True	No	No	18.7
2	48	2.0	0	Positive	Elsewhere	No	No	12.6
3	38	0.7	0	Negative	True	No	Yes	71.7
4	58	1.0	1	Negative	True	No	Yes	50.0
5	38	1.7	0	Positive	Elsewhere	No	No	13.3
6	43	1.0	0	Negative	Elsewhere	No	No	61.9
7	46	3.0	0	Positive	Elsewhere	No	No	44.5
8	41	micro	1	Positive	True	No	No	18.7
WBI								
1	41	micro	1	Positive	True	No	No	18.7
2	48	2.0	0	Positive	Elsewhere	No	No	12.6
3	38	0.7	0	Negative	True	No	Yes	71.7
4	58	1.0	1	Negative	True	No	Yes	50.0
5	38	1.7	0	Positive	Elsewhere	No	No	13.3
6	43	1.0	0	Negative	Elsewhere	No	No	61.9
7	46	3.0	0	Positive	Elsewhere	No	No	44.5

S/C group (Table 3). Although the number of eligible patients increased, only 1 patient with IBTR was present in this study, based on the updated ASTRO guidelines. Hence, no significant difference was observed in the 4-year rate of IBTR-FS (100% vs 98.9%; $P = 0.29$) or DFS (98.7% vs 95.5%; $P = 0.24$) between MCB-PBI and WBI patients (Figs 1 and 2).

DISCUSSION

Although this study is not a prospective randomized clinical trial comparing the efficacy of MCB-PBI with that of WBI, it demonstrates the excellent 4-year rate of IBTR-FS and DFS by single-stage BCT using MCB-PBI in S/C patients based on the retrospective chart review. Almost all cases examined in the study were Japanese patients. The findings could be validated on updated ASTRO guidelines that extended the candidature to relatively young Japanese patients with favorable tumor factors.

Since young age might be an independent risk factor for IBTR after BCT, the previous ASTRO CS on PBI categorized relatively young age as unsuitable for PBI. Updating the CS extended the candidature to patients with a relatively young age with certain factors, including patients aged 40–49 years with estrogen receptor–positive and <2.0 cm diameter tumor. Notably, this expansion was highly beneficial to Asian patients because one incidence peak of breast cancer was observed in Japanese patients in their forties; this trend was also observed in other East Asian countries [11, 12]. Recent advancements in preoperative imaging study and systemic treatment and the advantages of extending the radiation field to the entire breast have found utility in younger patients as well [13]. In fact, several studies have reported the excellent outcomes of PBI in relatively young Japanese patients [14, 15]. Although the clinical trial from GEC-ESTRO reported similar results for the local control rate at 40–50 years, it was only 17% of the entire cohort [6]. Hence, this updated CS categorized such patients as cautionary. In this study, some patients considered unsuitable based on the updated ASTRO CS underwent MCB-PBI because of our different protocol, with uncertain final pathology and compassionate grounds. We might consider further extension of the candidature for PBI based on the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413.

Reportedly, external beam PBI using 3D conformal radiation therapy (3D-CRT) [16] and intensity-modulated radiotherapy (IMRT) [17] is another attractive two-stage BCT technique because of its proven non-invasive, homogeneous dose delivery, and the final pathology. However, the PTV should be expanded from the clinical target volume by 1 to 2 cm because of inaccurate delineation of the target, set-up uncertainty, and cardiac and respiratory motion. The exposure of the large radiation volume to the healthy tissue in an accelerated manner accounted for late toxicity and worse cosmesis [18], especially in Japanese patients with relatively small breasts. Despite lacking knowledge about the final pathology, an intraoperative implant of a catheter or intraoperative radiation therapy (IORT) [19, 20] as a single-stage BCT is less invasive and can attain precise delineation of the target volume in order to control the residual tumor after lumpectomy. Compared with other techniques, the IORT technique can deliver the radiation to a small depth beyond the cavity and should achieve a more accurate delineation compared with the postoperative one. In the targeted intraoperative radiotherapy (TARGIT)-A trial, pre-pathological strata demonstrated the excellent local control rate compared with

Table 3. Demographics and tumor characteristics of S/C patients at the 12-month minimum follow-up

	MCB-PBI ($n = 291$)	WBI ($n = 103$)	P
Medium follow-up (months)	53.5 (12.0–112.2)	72.8 (12.3–123.0)	<0.0005
Mean age (years)	58.1 (40–84)	56.4 (40–92)	n.s.
Mean invasive diameter (mm)	11.3 (0–30)	9.4 (0–30)	n.s.
pTis	30 (10.3%)	29 (28.1%)	
pT1	248 (85.2%)	68 (66.0%)	
pT2	13 (4.5%)	6 (5.8%)	
NR	0 (0%)	0 (0%)	
Margin positive	0 (0%)	0 (0%)	n.s.
Grade II–III	30 (10.3%)	13 (12.6%)	n.s.
ER-negative	37 (12.7%)	14 (13.6%)	n.s.
HER2 overexpressed	34 (11.7%)	10 (9.7%)	n.s.
Node positive	0 (0%)	0 (0%)	n.s.
Adjuvant chemotherapy	82 (34.4%)	30 (29.1%)	n.s.

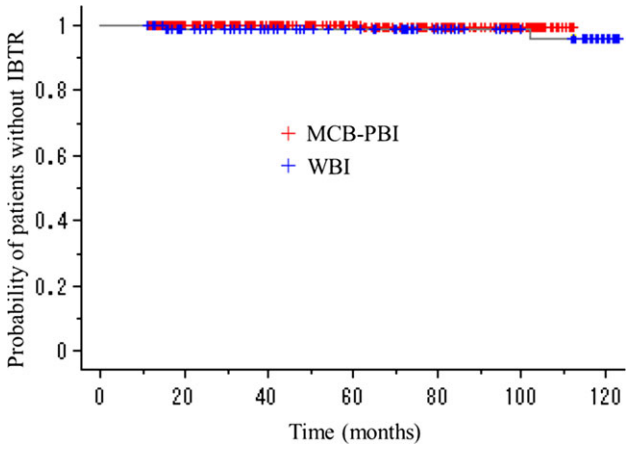

Fig. 1. A comparative study of the Kaplan–Meier estimates for IBTR-FS between MCB-PBI and WBI in updated S/C cohorts. MCB-PBI = multicatheter interstitial brachytherapy partial-breast irradiation, WBI = whole-breast irradiation, IBTR-FS = ipsilateral breast tumor recurrence–free survival.

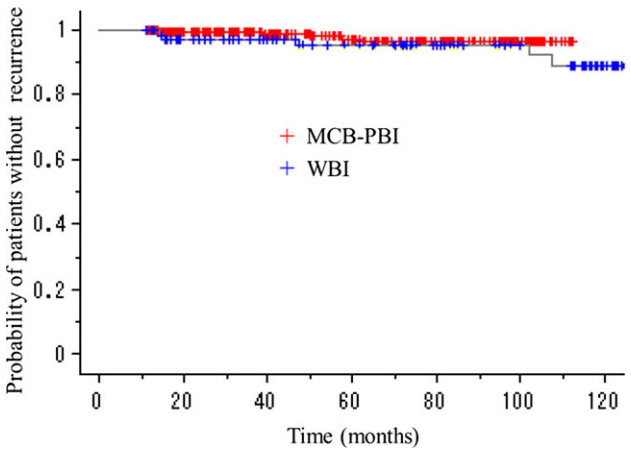

Fig. 2. A comparative study of the Kaplan–Meier estimates for DFS between MCB-PBI and WBI in updated S/C cohorts. DFS = disease-free survival, MCB-PBI = multicatheter interstitial brachytherapy partial-breast irradiation, WBI = whole-breast irradiation.

postoperative strata without the final pathology [21]. Hence, intraoperative insertion of a catheter that can deliver radiation at a moderate depth with a flexible implant might be the optimal technique.

In our series of patients, with diverse backgrounds, no additional benefit was observed from WBI with respect to local recurrence, compared with MCB-PBI. Interestingly, although the IBTR rate was similar to that in patients receiving WBI, half of the IBTRs were a new primary tumor, which could be observed in a non-radiation cohort after lumpectomy. Although WBI might be useful in eradicating subclinical breast cancer, PBI had an equal effect on primary tumor control to that of WBI. We raised two hypotheses about the excellent local control achieved by PBI. First, the effective systemic treatment affects the locoregional control after BCT, regardless of the margin status, and can dilute the additional local control effect of WBI [22]. Second, a breast tumor might have a lower α:β ratio than that reported. The tumor and late tissue sensitivity to fraction size have been based on data from squamous cell cancers, in which the α:β ratio of 10 Gy was assumed for tumor control and 3 Gy for healthy tissues [23]. Third, there is no delay in starting radiotherapy in an accelerated fashion for patients who need adjuvant chemotherapy. The evidence suggests that delay in radiotherapy increases the risk of local recurrence because delayed administration of radiation could foster the growth of cancer cells and the development of radio-resistance [24].

In conclusion, this study demonstrates the clinical efficacy of MCB-PBI in single-stage BCT in patients with breast cancer after a 4-year follow-up period. Although there was a relatively small number of patients and a shorter follow-up period, MCB-PBI demonstrated an adequate clinical efficacy. Nonetheless, the results of the NSABP B-39/RTOG 0413 trial evaluating the selection criteria and optimal technique for PBI should be awaited to see if they validate the findings of this study.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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None.

CLINICAL TRIAL REGISTRATION NUMBER

UMIN000029907

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