Original Article

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Retrospective Analysis of the Clinical Usefulness of a Strut-Adjusted Volume Implant in a Single Center

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ABSTRACT

Objective: Reports demonstrating the effectiveness and safety of strut-adjusted volume implants (SAVI) in Japan are limited. Therefore, this study aimed to compare the treatment outcomes of SAVI and whole-breast irradiation (WBI) at a single facility.

Materials and Methods: Data were retrospectively extracted from the medical records of patients treated with SAVI or WBI following partial mastectomy (Bp). Patients undergoing Bp, sentinel lymph node biopsy, and SAVI spacer insertion followed by brachytherapy with the SAVI device were compared to those followed with WBI. Local recurrence was assessed annually by physical examination, bilateral mammography, and breast ultrasonography.

Results: The SAVI and WBI groups comprised 53 and 113 patients, with a median age of 55 and 52 years, respectively; among them, 47 and 91 patients had a pathological tumor diameter ≤2 cm and six and 22 had a pathological tumor diameter >2 cm, respectively. Recurrence events, acute adverse events, and late adverse events were observed in the SAVI and WBI groups in 1 and 3 (p = 0.726), 24 and 79 (p = 0.01), and 24 and 18 patients (p = 0.00002), respectively, with median observation periods of 60.0 and 47.8 months, respectively. All adverse events were grades 1–2, with dermatitis being the most common in the acute phase. In the late phase, pigmentation was common in both groups.

Conclusion: The local recurrence rate does not differ between SAVI and WBI within the relatively short-term follow-up period. Longer follow-up is required to confirm our results in the Japanese population.

Keywords: SAVI; accelerated partial breast irradiation; Japanese; breast cancer; local recurrences

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Key Points

- The strut-adjusted volume implant (SAVI) and whole breast irradiation (WBI) groups showed similar local recurrence rates within the relatively short-term follow-up period (p = 0.726). The median follow-up periods in the SAVI and WBI groups were 60.0 and 47.8 months, respectively.
- Fewer adverse events were observed in the SAVI group than in the WBI group in the acute phase.
- In the late stage, patients in the SAVI group experienced more adverse events than those in the WBI group; however, most of them were grade 1, with no significant difference in grade 2 or higher events compared to WBI.
- In the future, tumor control, adverse events, and cosmetic outcomes in the SAVI and WBI groups should be observed and compared over a longer period.

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Introduction

Whole-breast irradiation (WBI) is the standard treatment for local control after partial mastectomy (Bp) for breast cancer, which has been shown to reduce the risk of local recurrence and contribute to survival rates in meta-analyses of previous clinical trials (1). However, WBI usually requires long-term outpatient treatment for 5–6 weeks or even 3–4 weeks for hypofractionation, and most patients experience adverse events, primarily radiodermatitis. A clinical trial demonstrated that approximately 70% of local recurrences in the preserved breast after Bp occurred near the original tumor bed, with recurrences from other areas resembling contralateral breast cancer occurrences in terms of timing and frequency (2, 3). Therefore, control of local recurrence in the preserved breast by targeting only the tumor bed with radiation therapy may be possible.

Accelerated partial breast irradiation (APBI) is a modality that enables an increase in the per-fraction dose and a reduction in treatment duration by narrowing the irradiation target volume to only the tumor bed using several methods, including brachytherapy, intraoperative irradiation, and external irradiation. Brachytherapy involves the insertion of small, sealed sources containing radioactive isotopes into the body to directly irradiate cancerous tissues, allowing minimal damage to the surrounding normal tissues, which is a standard treatment for cervical and prostate cancers. For breast cancer, brachytherapy methods include interstitial irradiation using the multicatheter method and intracavitary irradiation using the balloon catheter method (MammoSite®) or a strut-adjusted volume implant (SAVI).

The balloon catheter method (MammoSite®) is a single-lumen balloon-type applicator, whereas the SAVI has a cage-like structure surrounding the center catheter with multiple outer catheters, which are expanded post-insertion to adhere to the resection cavity post-lesion excision. The SAVI was approved by the Food and Drug Administration in 2006 and received pharmaceutical approval in Japan in 2013.The local recurrence rate of post-irradiation using the SAVI is approximately 3.6%, showing no significant difference in treatment outcomes compared with standard treatment. It shows excellent tumor control, comparable to that of APBI, and survival with low toxicity (4). Recently, the preliminary results of a prospective clinical trial on the usefulness of brachytherapy using SAVI for Japanese patients with breast cancer have been reported (5). In this report, 44 patients were included, and Grade 2 acute toxicities were observed in 18% of the patients. This report mainly focused on dosimetry and acute adverse events; thus, clinical information regarding the local recurrence and late adverse event rates in this population is limited. Health insurance covers brachytherapy for breast cancer, including the SAVI device in Japan; however, this coverage includes brachytherapy treatments beyond those using the SAVI device. The insurance approval is not specifically focused on brachytherapy using the SAVI device, which may be a barrier to expanding brachytherapy with SAVI and might be one reason for the limited use of the SAVI device in Japan. Therefore, the clinical efficacy, usefulness, and side effects of brachytherapy with SAVI in the Japanese population should be clarified.

In this study, we compared the treatment outcomes and adverse events of SAVI with those of WBI by retrospectively examining cases of WBI and SAVI use at our institution in a single-facility setting. This study aimed to clarify the clinical data, such as local recurrence and acute/late adverse event rates, which would contribute to the new insurance coverage specifically focused on brachytherapy with the SAVI device.

Materials and Methods

Study Design

This retrospective observational study extracted data from medical records of patients treated with SAVI or WBI following breast-conserving therapy at Showa University Hospital from February 2014 to June 2019. This trial was conducted with ethical approval from Showa University Research Ethics Review Board Committee (approval no: 22-170-B, date: 17.11.2022).

Participants

Treatment was performed according to the American Society for Radiation Oncology guidelines for brachytherapy (6). The inclusion criteria were: patients aged >40 years; clinically single lesions of ≤3 cm in diameter; N0 stage ductal (invasive/non-invasive), mucinous, medullary, tubular, or lobular (invasive/non-invasive) carcinoma; no previous radiation or chemotherapy; no prior breast cancer; no synchronous bilateral breast cancer; performance status of 0–1; and the provision of informed consent and voluntarily requesting SAVI treatment. Luminal A was defined as Ki-67 ≤20% and Luminal B as Ki-67 >20%.

The SAVI treatment schedule is shown in Figure 1. The SAVI spacer was placed within the cavity and at the time of Bp and sentinel lymph

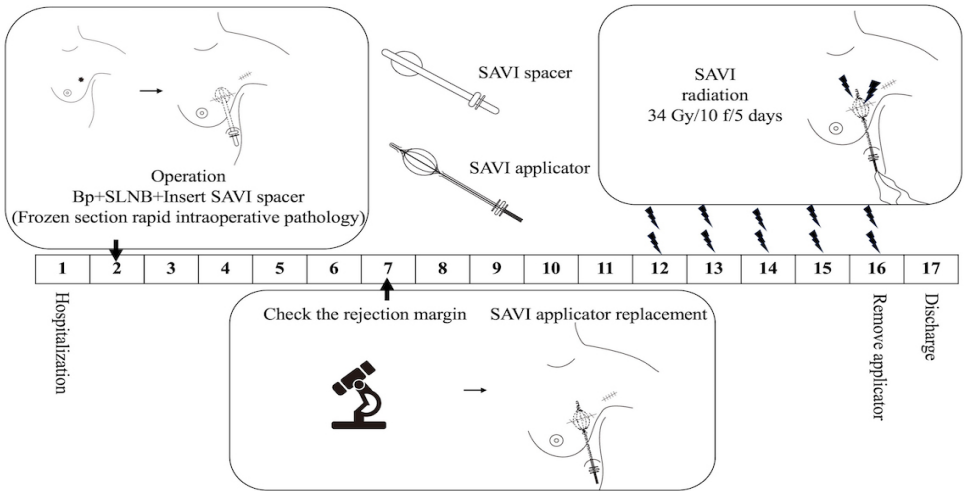

Figure 1. Treatment schedule

Bp: Partial mastectomy; SAVI: Strut-adjusted volume implant; SLNB: Sentinel lymph node biopsy

node biopsy (SLNB), where rapid pathological diagnosis confirmed a negative sentinel lymph node (SLN) metastasis. The spacer was replaced with an applicator under ultrasound guidance on postoperative day 5 after a pathological check confirmed that the surgical resection margins were free and there was no extensive intraductal spread. After computed tomography (CT)-based simulation for treatment planning, an accelerated partial irradiation dose of 34 Gy was delivered in 10 fractions, administered twice daily on 5 treatment days, starting on postoperative day 10. The planning target volume (PTV) was defined as a 1 cm expansion from the cavity's edge, which corresponds to the outer boundary of the SAVI applicator. The PTV_EVAL was subsequently determined by subtracting the volumes occupied by the chest wall, cavity, and subcutaneous tissue within 2 mm below the skin surface from the PTV. Several dosimetric constraints were established for quality assurance. These included ensuring that at least 90% of the prescribed dose covered 90% or more of the PTV_EVAL (V90% ≥90%), limiting the volume of breast tissue receiving 150% of the prescribed dose (V150%) to no more than 50 cm^3, restricting the volume of breast tissue receiving 200% of the prescribed dose (V200%) to under 20 cm^3, and maintaining the dose delivered to 1 cm^3 (D1 cm^3) of the skin within 110% of the prescribed dose. To ensure accurate treatment delivery, the position of the applicator was verified by measuring the distance between the skin and the applicator's hub, as well as through anterior-posterior and lateral CT scout views, prior to each irradiation session. If displacement of the applicator was observed, it was confirmed by CT and re-planned at the discretion of the radiologists. The applicator was removed after irradiation, and discharge was scheduled for the following day. All cases in the SAVI group had a fixed hospital stay of 17 days for surgery and brachytherapy with the SAVI device. Post-irradiation, whether using chemotherapy, hormonal therapy, or both, was at the discretion of the treating medical oncologist, based on the pathological results of each patient. The patients were followed up annually by physical examination, bilateral mammograms, and breast ultrasound to assess recurrence.

Patients with the same eligibility criteria and treated with WBI post-Bp during the same period were grouped into the WBI group, and their treatment outcomes were compared. WBI was used to deliver doses of 50 Gy in 25 total fractions or 42.56 Gy per day in 16 fractions. Boost therapy (10 or 10.64 Gy) was permitted at the discretion of the radiation oncologist.

The primary endpoint was recurrence rates, and the secondary endpoint was acute and late adverse events. Adverse events were assessed using the Common Terminology Criteria for Adverse Events version 4.0. at 1, 3, and 6 months after the end of irradiation and every six months thereafter until five years. Adverse events occurring from the end of irradiation to within three months after treatment were considered acute adverse events, and those occurring later were considered late adverse events. The maximum adverse events in each case are summarized in this study.

Statistical Analysis

For comparison between the two groups, the χ^2, Mann-Whitney U, log-rank, and Fisher's exact probability tests were performed. Statistical analyses were performed using GraphPad Prism version 7.0e (GraphPad Software, San Diego, CA, USA).

Results

The process of patient selection is illustrated in Figure 2. Sixty-one patients were subjected to Bp, SLNB, and SAVI spacer insertion. Two patients were switched to postoperative WBI treatment due to confirmation of positive SLN metastasis by frozen section. Three patients were excluded owing to positive resection margins, two patients had early removal of the SAVI after postoperative hemorrhage/infection, and one patient was ineligible because of post-augmentation mastopexy.

Fifty-three patients completed postoperative radiation treatment with the SAVI and received pharmacotherapy based on their individual pathological results. Concurrently, 143 patients underwent WBI after breast-conserving surgery. Thirteen patients were excluded owing to positive margins and 17 owing to a tumor diameter >3 cm, leaving 113 patients in the WBI group. The total radiation doses were 42.56 Gy in 68 patients and 50 Gy in 45 patients, with additional boost irradiation performed in 30 patients, including 10 Gy in seven patients and 10.64 Gy in 23 patients.

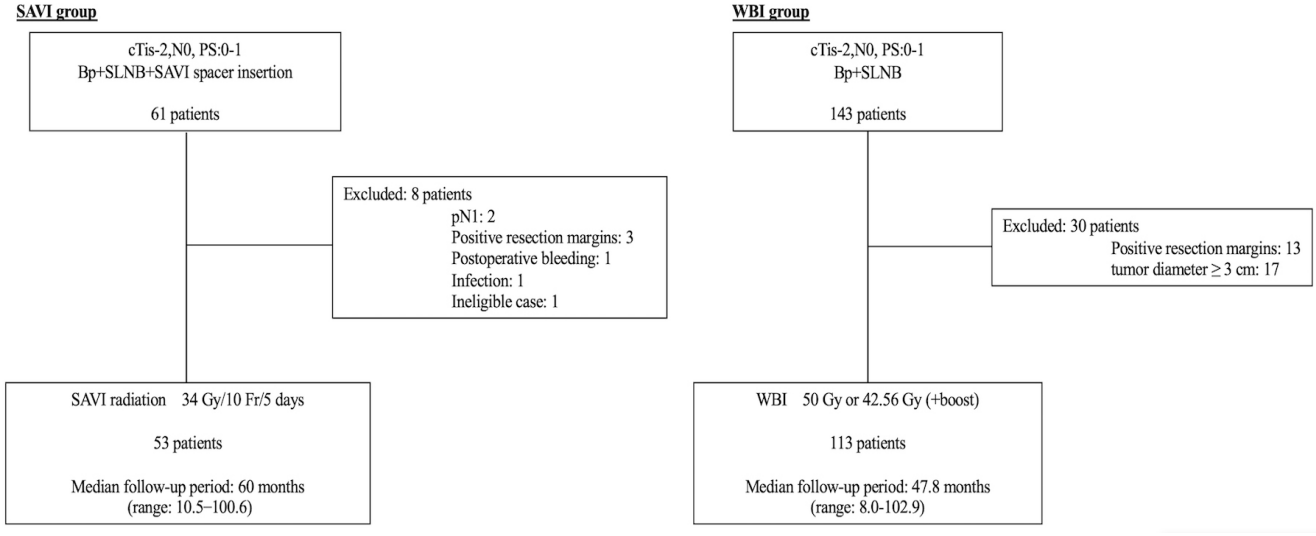

Figure 2. Trial profile

Bp: Partial mastectomy; SAVI: Strut-adjusted volume implant; SLNB: Sentinel lymph node biopsy; WBI: Whole breast irradiation

The patient demographics of each group are shown in Table 1. The median ages of the patients were 55 (range: 39–85) years and 52 (range: 40–72) years in the SAVI and WBI groups, respectively. In the SAVI group, pStage0, stage IA, stage IB, stage IIA, and stage IIB were observed in 6, 43, 1, 2, and 1 patient(s), respectively. In the WBI group, pStage0, stage IA, stage IIA, and stage IIB were observed in 11, 93, 8, and 1 patient(s), respectively.

The pathological tumor diameters (including noninvasive parts) were ≤2 cm and >2 cm in 47 (89%) and 6 (11%), as well as 91 (81%) and 22 (19%) patients in the SAVI and WBI groups, respectively. In the SAVI group, the subtypes were luminal A, luminal B, and triple-negative in 36, 8, and 1 patient(s), respectively. In the WBI group, luminal A, luminal B, estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2)+, ER+ and HER2+, and triple-negative subtypes were observed in 76, 16, 1, 6, and 1 patient(s), respectively.

Postoperative pathology showed micro-lymph node metastasis in two patients (0.3–2 mm) in the SAVI group and two patients (unknown) in the WBI group, with no significant differences in age, pStage, tumor diameter, subtype, and pN between the two groups.

Efficacy of SAVI and WBI

The Kaplan-Meier curves for local recurrence, including ipsilateral breast and lymph node recurrences, are shown in Figure 3. The median follow-up periods in the SAVI and WBI groups were 60.0 (range: 10.5–100.6) and 47.8 (range: 8.0–102.9) months, respectively. The SAVI group included one case each of local and distant recurrences, whereas the WBI group included three cases (two cases of local recurrence and one case of supraclavicular lymph node recurrence). Of note, there was no significant difference in recurrence rates between the two groups (p = 0.726).

Adverse Events After SAVI and WBI

The adverse event results of SAVI and WBI are shown in Table 2. In the SAVI group, 25 (47%) patients experienced grade 1–2 acute adverse events (within 3 months of radiotherapy start), and 25 (47%) patients experienced late adverse events (beyond 3 months), with no events of grade 3 or above. The most common adverse events were dermatitis in the acute phase and pigmentation in the late phase. Two patients experienced dermatitis of grade 2 or higher, which was improved after dermatological consultations. Two patients required antibiotic treatment due to infection of grade 2 or higher. One patient

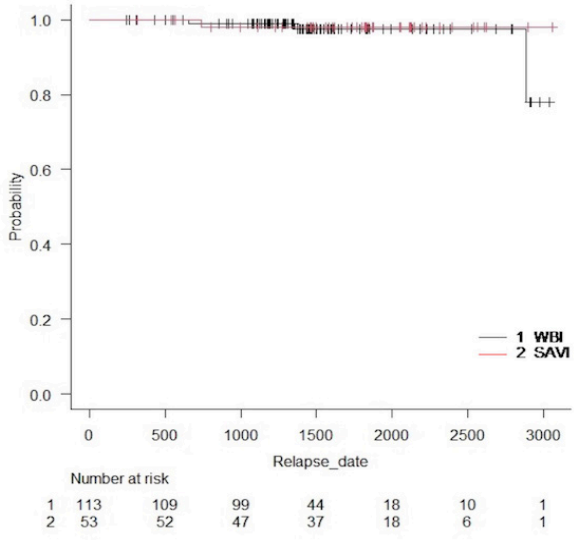

Figure 3. Kaplan-Meier curves of breast tumor recurrence

SAVI: Strut-adjusted volume implant; WBI: Whole breast irradiatio

Table 1. Patient characteristics

		SAVI group	WBI group	*p*
Number		53	113	
Age (y)		55 (39–85)	52 (40–72)	0.1
pStage	0	6 (11%)	11 (10%)	0.59
	IA	43 (81%)	93 (82%)	
	IIB	1 (2%)	0	
	IIIA	2 (4%)	8 (7%)	
	IIB	1 (2%)	1 (1%)	
Tumor diameter	≤2 cm	47 (89%)	91 (81%)	0.19
	>2 cm	6 (11%)	22 (19%)	
Subtype	Luminal A	36 (68%)	76 (67%)	0.17
	Luminal B	8 (15%)	16 (14%)	
	ER- HER2+	0	1 (1%)	
	ER+ HER2+	0	6 (5%)	
	Triple-negative	1 (2%)	1 (1%)	
pN	0	51 (96%)	111 (98%)	0.33
	Micro meta	2 (4%)	2 (2%)	
	1	0	0	

ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; SAVI: Strut-adjusted volume implant; WBI: Whole breast irradiation

Table 2. Toxicity assessment results

None		SAVI group			WBI group			*p*
		Grade 1	Grade 2	None	Grade 1	Grade 2		
Acute	Any acute adverse events	28 (53%)	23 (43%)	3 (6%)	34 (30%)	70 (62%)	9 (8%)	0.01
	Dermatitis	31 (58%)	20 (38%)	2 (4%)	34 (30%)	70 (62%)	9 (8%)	0.001
	Skin hyperpigmentation	50 (94%)	3 (6%)	0	111 (98%)	2 (2%)	0	0.33
	Dry skin	52 (98%)	1 (2%)	0	111 (98%)	2 (2%)	0	>0.99
	Skin infection	52 (98%)	0	2 (2%)	113 (100%)	0	0	0.32
	Pain	47 (89%)	6 (11%)	0	113 (100%)	0	0	0.001
	Malaise	52 (98%)	1 (2%)	0	113 (100%)	0	0	0.32
	Localized edema	52 (98%)	1 (2%)	0	113 (100%)	0	0	0.32
	Telangiectasia	53 (100%)	0	0	112 (99%)	1 (1%)	0	0.03
Late	Any late adverse events	28 (53%)	24 (45%)	1 (2%)	95 (84%)	17 (15%)	2 (2%)	0.00002
	Skin hyperpigmentation	36 (68%)	17 (32%)	0	100 (88%)	13 (12%)	0	0.002
	Superficial soft tissue fibrosis	37 (70%)	15 (28%)	1 (2%)	112 (99%)	1 (1%)	0	<0.0001
	Pain	48 (91%)	5 (9%)	0	113 (100%)	0	0	0.003
	Telangiectasia	50 (94%)	3 (6%)	0	113 (100%)	0	0	0.03
	Breast atrophy	51 (96%)	2 (4%)	0	113 (100%)	0	0	0.1
	Dry skin	52 (98%)	1 (2%)	0	109 (96%)	4 (4%)	0	>0.99
	Localized edema	52 (98%)	1 (2%)	0	113 (100%)	0	0	0.32
	Nipple deformity	52 (98%)	1 (2%)	0	113 (100%)	0	0	0.32
	Fracture	52 (98%)	1 (2%)	0	112 (99%)	1 (1%)	0	0.53
	Pneumonitis	53 (100%)	0	0	110 (97%)	1 (1%)	2 (2%)	0.55

The $\chi 2$ tests were performed on the two groups with no adverse events and those with Grade 1 and 2 adverse events, and p-values were calculated; SAVI: Strut-adjusted volume implant; WBI: Whole breast irradiation

had a rib fracture on the operated side but showed no worsening during the asymptomatic follow-up. In the WBI group, 79 (70%) patients experienced grade 1–2 acute adverse events, and 18 (16%) patients experienced late adverse events, with no events of grade 3 or higher. The most common adverse events were dermatitis in the acute phase and pigmentation in the late phase. Two patients experienced grade 2 pneumonia, of whom one showed improvement during follow-up observation, and the other required steroid treatment. One patient had a rib fracture on the operated side but showed no worsening during the asymptomatic follow-up. The χ^2 tests were performed, and *p*-values are listed in Table 2.

Discussion and Conclusion

The SAVI and WBI groups showed similar local recurrence rates. During the acute phase, significantly fewer adverse events were observed in the SAVI group than in the WBI group, whereas in the late stage, patients in the SAVI group experienced significantly more adverse events than those in the WBI group.

Comparison of Efficacy (Treatment Outcomes) and Safety Between APBI and WBI

A summary of phase III trials comparing the treatment outcomes of APBI and WBI is presented in Table 3. APBI methods, including brachytherapy, three-dimensional conformal radiation therapy (3DCRT or IMRT), and intraoperative radiation, were compared to WBI, mostly showing non-inferiority of APBI in terms of ipsilateral breast tumor recurrence (IBTR). In the National Surgical Adjuvant Breast and Bowel Project B-39/Radiation Therapy Oncology Group 0413 trial, multiple methods, such as multicatheter, 3DCRT, SAVI, and balloon catheter methods (MammoSite®), were compared to WBI. The difference in the 10-year IBTR results was not equivalent but was <1% (7). In the IMPORT LOW trial comparing intensity-modulated radiation therapy (IMRT) with WBI, the 5-year IBTR rates were 0.5 and 1.1% (IMRT and WBI), respectively, showing non-inferiority (8). Similarly, in the Florence trial comparing IMRT and WBI, the 10-year IBTR rates were 3.9 and 2.6% (IMRT and WBI), respectively, with no significant difference (9). In our study, the IBTR rate was 1.96% during a median follow-up of 60.0 months, with no significant difference from that in the WBI group, which was similar to previous reports despite different detailed conditions.

Table 4 summarizes the previous reports on SAVI. The proportion of adverse events during the acute phase was significantly lower in the SAVI group than in the WBI group, particularly dermatitis, which was observed in approximately 70% of the patients in the WBI group compared to 42% in the SAVI group. Previous research found the occurrence rate of skin complications of grade 2 or higher within 24 months post-brachytherapy with the SAVI device to be 7% (10). In the present study, the occurrence rate of adverse events of grade 2 or higher in the acute phase was equivalent to that reported previously (6%), and the severity was low grade, which was manageable on an

Table 3. Summary of phase III trials of APBI

Clinical trial	Sample size	Duration	Patient background	Treatment	APBI radiation dose/days	WBI radiation dose/ fraction	Result	Conclusions
NSABPB-39/ RTOG0413 (7)	4.214	2005–2013	≧18 years, Stage 0, I, II LN meta: 0–3 Tumor diameter ≦3 cm	Multicatheter/ MammoSite® SAVI Contura/ 3DCRT	34 Gy/10 f/5 d 34 Gy/10 f/5 d 38.5 Gy/10 f/5 d	50 Gy/25 f	10 years IBTR APBI: 4.6% *vs.* WBI: 3.9%	Not equivalent (10 years IBTR) (but the difference was <1%)
IMPORT LOW (8)	2.018	2007–2010	≧50 years, Tumor diameter ≦3 cm pT1-2, N0-1	IMRT	40 Gy/15 f/15 d	40 Gy/15 f 36 Gy/15 f	5 years IBTR IMRT: 0.5% *vs.* WBI: 1.1%	Non-inferiority (5 years IBTR)
APBI-IMRT-Florence (9)	520	2005–2013	≧40 years Tumor diameter ≦2.5 cm	IMRT	30 Gy/5 f/5 d	50 Gy/25 f (+10 Gy boost)	10 years IBTR IMRT: 3.9% *vs.* WBI: 2.6%	Non-inferiority (10 years IBTR, 10 years OS)
RAPID (11)	2.128	2006–2011	≧40 years, DCIS or N0 early-stage cancer	3DCRT	38.5 Gy/10 f/5 d	50 Gy/25 f 42.5 Gy/16 f	8 years IBTR APBI: 3.0% *vs.* WBI: 2.8%	Non-inferiority (8 years IBTR)
ELIOT (12)	1.305	2000–2007	48–75 years Tumor diameter ≦2.5 cm cN0	Electron (IORT)	21 Gy/1 f/1 d	50 Gy/25 f (+10 Gy boost)	15 years IBTR APBI: 12.6% *vs.* WBI: 2.4%	Inferiority (15 years IBTR, 15 years OS)

3DCRT: Three-dimensional conformal radiation therapy; APBI: Accelerated partial breast irradiation; IBTR: Ipsilateral breast tumor recurrence; IMRT: Intensity-modulated radiation therapy; LN: lymph node; OS: Overall survival; SAVI: Strut-adjusted volume implant; WBI: Whole breast irradiation

outpatient basis with antibiotics. In the present study, acute adverse events of grade 2 or higher within 3 months after brachytherapy with the SAVI device were not significantly different from those in recent reports on Japanese subjects (4). The RAPID Trial indicated fewer grade 2 or higher acute adverse events within 3 months post-treatment with APBI than it did with WBI, which is thought to be due to the total dose rather than the dose per session (11). Conversely, more grade 2 or higher late adverse events have been reported with APBI (12). In the present study, the incidence rates of hyperpigmentation, superficial soft tissue fibrosis, and telangiectasia were higher in the SAVI group than in the WBI group but most were grade 1, with no significant difference in grade 2 or higher events compared to WBI. The pain level was higher in the SAVI group in both the acute and late phases than in the WBI group, but it was grade 1 in all patients and controllable with analgesics. These observations suggested that SAVI showed lower acute adverse events and higher late adverse events than did WBI, and these results are comparable with the previous studies. An assessment of late adverse events of SAVI in Japanese patients has not been reported previously; therefore, this is the first report of its type.

In addition, following the results of the FAST-Forward trial (13), the European Society for Radiation Oncology (ESTRO) has recommended that an ultrafractioned dose of 26 Gy in five fractions can also be offered as standard of care or within a randomized trial or prospective cohort (14). However, the observation period has not been sufficiently long, and the outcomes of long-term follow-up and revalidation trials remain awaited. In the present study, we compared WBI in 16 or 25 fractions, the present standard of care in Japan. In terms of shortening treatment time, WBI such as ultrafractionation has similar advantages; however, APBI using the SAVI device can benefit patients such as older adults who live far from the hospital and have difficulty in making daily visits, as radiotherapy is completed during the same hospitalization period as the surgery. This suggests that APBI using the SAVI device is an alternative treatment choice for some patients. However, the application of the SAVI device remains limited for the following reasons: insurance approval is not specifically focused on brachytherapy using the SAVI device, and clinical data on brachytherapy using SAVI are limited. However, we believe that this study will contribute to evidence for the community of physicians who treat breast cancer and the expansion of APBI using the SAVI device. Going forward, we aim to compare these results with those of ultrafractionation and other APBI methods and evaluate the patient's treatment satisfaction, cosmetics, and long-term prognosis.

Comparison With Other Brachytherapy Applicators [Multicatheter and Balloon Catheter Methods (MammoSite®)]

The multicatheter method enables more precise treatment by adjusting the dose distribution according to the breast morphology, as numerous

Table 4. Summary of the previous reports on SAVI

Authors	Sample size	Duration	Patient background	Follow-up	Local recurrence rate	Adverse event (≧ grade 2)
Yashar et al. (4)	250	2007–2010	Tis-T2, N0-1	59.5 months	3.6%	Skin disorder 7% (<24 months) (erythema 2.6%, seroma 2.6%, etc.)
Amir Isbell et al.	50	2011–2015	≧18 years, Stage 0, I, II LN meta: 0–3 Tumor diameter ≦3 cm	45.6 months (3.48–56.3 months)	4%	Not observed
Yoshida et al. (5)	44	2016–2021	>40 years Tumor diameter ≦3 cm N0	Not described	Not described	Dermatitis 7% Skin infection 7% Chest wall pain 5% Breast pain 11%
Current study	53	2014–2019	>40 years Tumor diameter ≦3 cm N0	60.0 months	1.96%	Dermatitis 4% Skin infection 2% Superficial soft tissue fibrosis 2%

LN: Lymph node

applicators can be placed independently. The Groupe Européen de Curiethérapie of the European Society for Radiotherapy and Oncology APBI Trial comparing APBI and WBI using a multicatheter showed non-inferiority in the 5-year IBTR rate (WBI: 0.92% *vs.* APBI: 1.44%) (15). The benefits of the multicatheter method, especially for Asian patients with a smaller breast size compared to that of Western patients, have been reported in Japan, showing good prognoses and cosmetic outcomes (16). However, the multicatheter method has drawbacks, including greater invasiveness owing to the insertion of multiple applicators and the requirement of considerable skill for correct placement. The balloon catheter method (MammoSite®) showed excellent results in a prospective trial with an ipsilateral breast recurrence rate of 2.8% at 5 years, excellent/good cosmetic outcomes >90%, acute adverse events <10%, and almost no late adverse events (17), similar to the findings of the present study. However, this approach has not yet been approved for use in Japan. Notably, it is deemed unsuitable for smaller breasts, such as those of Japanese patients, because it can only provide a concentric dose distribution around the catheter passing through the balloon center, making fine adjustment of the dose distribution impossible when inserted close to the skin or chest wall.

This study had some limitations. First, outcome differences between the two groups may be due to selection bias or other confounding factors. Patients in the SAVI group voluntarily requested SAVI treatment. However, there are several conditions regarding therapy choice. Our institution could not simultaneously perform brachytherapy using the SAVI device for multiple patients, which is an institutional limitation. In addition, when holidays fall on weekdays, choosing brachytherapy using the SAVI device is impossible. Therefore, we should consider that these limitations may have contributed to selection bias or other confounding factors and clinical outcomes. This limitation should not be ignored, and the present results should be cautiously interpreted. Furthermore, the results should be re-evaluated in future randomized controlled trials.

Second, the observation period differed between the two groups by one year. However, the observation period of the SAVI group was longer than that of the WBI group, which had little effect on demonstrating the non-inferiority of IBTR. Therefore, controlled groups with matched conditions are required to observe long-term outcomes. Third, the surgical techniques of lumpectomy may have differed between the two groups because of the presence of a lumpectomy cavity in the SAVI group. Therefore, direct comparisons of adverse events and cosmesis may be difficult. However, previous studies have compared adverse events between SAVI and WBI, and including differences in surgical technique was deemed acceptable. Indeed, our study findings also indicated that patients who underwent WBI experienced more acute events, while those who underwent SAVI experienced more late events. Importantly, no serious complications of grade 3 or above were observed in the SAVI group, aligning with earlier reports. Thus, we are confident that our results contribute valuable insights into the feasibility of SAVI. Fourth, the occurrence rate of late adverse events differed between the two groups. As the follow-up period in the Department of Radiation Oncology was shorter in the WBI group than in the SAVI group, it is possible that late adverse events in the WBI group were underestimated. In addition, the recurrence rates in this study were only comparable over a short period of 5 years. Therefore, tumor control and adverse events in both groups should be observed and compared for a longer period in the future.

In conclusion, as a treatment option, brachytherapy with the SAVI device was not inferior to conventional WBI in terms of therapeutic efficacy and is expected to shorten the treatment time and reduce acute adverse events. Late adverse events were more frequent with SAVI than with WBI, but they were low-grade and controllable. Results,

including long-term prognoses, the presence of late adverse events, and objective evaluation of the patient's quality of life, are required.

Ethics Committee Approval: This trial was conducted with ethical approval from Showa University Research Ethics Review Board Committee (approval no: 22-170-B, date: 17.11.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: A.A-S., T.K., M.K., H.S., K.M., A.N., N.K., M.M., Ha.S., Y.M., S.N., A.Y., M.I., K.T., H.M., T.S., N.H., Y.I., C.W., S.A-T., Se.N.; Concept: A.A-S., T.K.; Design: A.A-S., T.K.; Data Collection and/or Processing: A.A-S., T.K., M.K.; Analysis and/or Interpretation: A.A-S.; Literature Search: A.A-S., T.K.; Writing: A.A-S., T.K., H.S.

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