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Long-term outcomes of intraoperatively-placed applicator brachytherapy for rapid completion of breast conserving treatment: An analysis of a prospective registry data

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ABSTRACT

Background and purpose: To evaluate the long-term outcome of accelerated partial breast irradiation utilizing intraoperatively placed applicator-based brachytherapy (ABB) in early-stage breast cancer.
Materials and methods: From our prospective registry, 223 patients with pTis-T2, pN0/pN1mic breast cancer were treated with ABB. The median treatment duration including surgery and ABB was 7 days. The prescribed doses were 32 Gy/8 fx BID (n = 25), 34 Gy/10 fx BID (n = 99), and 21 Gy/3 fx QD (n = 99). Endocrine therapy (ET) adherence was defined as completion of planned ET or ≥ 80% of the follow-up (FU) period. Cumulative incidence of ipsilateral breast tumor recurrence (IBTR) was estimated and influencing factors for IBTR-free survival rate (IBTRFS) were analyzed.
Results: 218/223 patients had hormone receptor-positive tumors, including 38 (17.0%) with Tis and 185 (83.0%) with invasive cancer. After a median FU of 63 months, 19 (8.5%) patients had recurrence [17 (7.6%) with an IBTR]. Rates of 5-year IBTRFS and DFS were 92.2% and 91.1%, respectively. The 5-year IBTRFS rates were significantly higher for post-menopausal women (93.6% vs. 66.4%, $p = 0.04$), BMI < 30 kg/m^2 (97.4% vs. 88.1%, $p = 0.02$), and ET-adherence (97.5% vs. 88.6%, $p = 0.02$). IBTRFS did not differ with dose regimens.
Conclusions: Postmenopausal status, BMI < 30 kg/m^2, and ET- adherence predicted favorable IBTRFS. Our results highlight the importance of careful patient selection for ABB and encouragement of ET compliance.

Introduction

Accelerated partial breast irradiation (APBI) shortens treatment duration by increasing the dose per fraction and provides excellent local control in patients with low-risk breast cancer [1]. Several randomized controlled trials have shown that ipsilateral breast tumor recurrence (IBTR) rates are comparable between APBI and whole breast irradiation (WBI), when APBI was administered with optimal methods to well-selected patients [1]. To guide selecting patients suitable for APBI, several groups of experts have provided consensus guidelines [2–5] The guidelines consistently suggest that optimal candidates for APBI are patients with old age (≥45 or 50 years) and favorable surgical-pathologic features (small size, absent lymph nodes metastases, and negative resection margins). Given the effectiveness and efficiency of

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APBI, it has been used for more than 5,000 patients per year since 2008, according to the National Cancer Database of the United States [6].

Three major types of radiotherapy have been applied for APBI: brachytherapy, external beam radiotherapy, and intraoperative radiotherapy. Of the methods, brachytherapy is the most commonly used approach for APBI, accounting for more than 70% of APBI modalities [6]. Brachytherapy enables the administration of high-dose radiation focusing on the target while minimizing radiation to adjacent normal organs including surrounding breast tissue. Among various techniques for delivering brachytherapy, applicator-based brachytherapy (ABB) allows easy handling and good reproducibility [7]. Moreover, we have previously published that conformal target PTV_{eval} coverage (D90% greater than 90%) is achieved using our intraoperatives strut applicator placement technique [8]. The major advantages of our intraoperatively placed ABB technique are patient convenience and compliance to adjuvant radiotherapy and 3D planning that allows dosimetric evaluation of the target and organs at risk which is a limitation in intraoperative radiotherapy with electrons or low photon energy.

At our institution, we have established a protocol in which an applicator was placed at the time of lumpectomy based on frozen pathology followed by brachytherapy initiation within one postoperative weekday after the surgery in selected patients with early-stage breast cancer [9]. As an ABB applicator, a Strut Adjusted Volume Implant (SAVI®) device (Cianna Medical Inc., Aliso Viejo, CA, USA) was used. The SAVI device has multiple strut configurations including a central strut surrounded by multiple peripheral strut, which enables radiation dose modulation with a single entry [7]. In analyses of early results of the protocol, we found that patient-reported outcomes and cosmesis were excellent with minimal toxicities after ABB [10,11]. In the current analysis, we evaluated the long-term oncologic results of our ABB protocol and assessed factors influencing disease control outcomes. Through this analysis, we aimed to determine optimal criteria for patient selection that incorporating patient's hormonal-metabolic status and get insight for future improvements in oncologic outcomes of ABB.

Materials and methods

Patients and treatments

Patients with newly diagnosed stage 0 – II breast cancer who met the criteria for our institutional registry as previously published [9] were prospectively enrolled at our institution since October 2012. ABB suitability was determined after consultation with breast surgeons and radiation oncologists. This study was approved by the institutional review board of the Mayo Clinic and all patients provided written informed consent before study registration.

For diagnostic staging work-up, all patients underwent mammography. Additional studies including breast tomosynthesis, breast ultrasonography, or breast magnetic resonance imaging (MRI) were completed on a case-by-case basis. Breast-conserving surgery (BCS) and ABB were performed according to the institutional protocol, as described in our previous reports [9,10]. Briefly, the SAVI device was placed intraoperatively in the lumpectomy bed after confirming negative resection margins and nodes (when applicable) by intraoperative frozen section pathology assessment. ABB was initiated at a median of two days post-operatively following computed tomography-based three-dimensional treatment planning and confirmation of negative margins and sentinel nodes on final pathology. Individual patient ABB plans were optimized to adequately cover the planning target volume (PTV), which included the lumpectomy bed plus 1 cm margin, while excluding the chest wall and the first 5 mm beneath the skin surface. Every plan was modulated to ensure that more than 90% of the PTV receives greater than 90% of the prescription dose. The prescribed radiation dose regimens were as follows: 32 Gy in 8 twice-daily (32 Gy/8 fx, BID), 34 Gy in 10 BID, or 21 Gy in 3 once-daily (21 Gy/3 fx, QD). Until 2015, two types of regimens of 32 Gy/8 fx, BID or 34 Gy/10 fx, BID were used. Beginning in 2015, 3-fraction ABB was offered as part of MC1532, a non-randomized trial evaluating 3-fraction photon, proton, and brachytherapy APBI [9,10]. Three, eight, or ten fractions of ABB continued to be used at the discretion of the treating providers after MC1532 enrollment was complete in 2017. On the last day of ABB, the applicator was removed by an attending radiation oncologist. After completion of ABB, adjuvant endocrine treatment (ET) was administered according to the hormone receptor-positivity status (HR +) of the tumor. Five years of tamoxifen (TAM) or aromatase-inhibitor (AI) were prescribed depending on the patient's characteristics and preference after medical oncology consultation. Each patient's menopausal status was assessed by menstrual history or measuring levels of gonadotropins and estrogen in the blood.

Follow-ups and outcome evaluation

Patients were evaluated by history and physical exams at 3 months and 12 months after ABB completion, and then annually. Mammography was performed on an annual basis or as clinically indicated. The ET adherence was retrospectively assessed at the time of data analysis after reviewing the medical records of the patient registry. To assess ET adherence, we categorized patients into one of the following four groups based on prior studies [12,13]: ET-none, if the patient did not ever initiate ET; ET-discontinued, if the patients stopped taking ET within 6 months after the first ET prescription; ET-adherent, if the patient completed the planned ET course or continued ET for $\geq$ 80% of the follow-up duration; ET-non-adherent, if the patient took ET for more than 6 months but <80% of the follow-up duration or planned ET schedule. In addition, underlying patient comorbidities were graded at the time of data analysis, according to the Charlson Comorbidity Index (CCI) [14]. Body mass index (BMI) was calculated based on the patient's weight and height as measured within a month before surgery.

Ipsilateral breast tumor recurrence (IBTR) was defined as a biopsy-confirmed recurrent tumor in the treated breast regardless of location within the breast. Ipsilateral breast tumor recurrence-free survival (IBTRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) were calculated from the date of surgery to the dates of IBTR, distant metastasis, any recurrence, and death, respectively. Treatment-related toxicities were assessed by the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0).

Statistical analyses

Continuous variables were dichotomized according to a median value, cut-off points indicated by a receiver operating characteristics analysis, or researcher's discretion. IBTRFS, DMFS, and DFS were estimated by cumulative incidence function, with death as a competing risk. OS was calculated by Kaplan-Meier analysis. Comparisons of IBTRFS between groups were conducted by Gray's test and the Fine and Gray model. Variables with a significance level of $p < 0.05$ on univariate analyses were included for multivariable analysis. All statistical analyses were performed using R statistical software (version 4.1.2, R Core Team 2021, Vienna, Austria) and SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Between October 2012 and September 2019, 226 patients were enrolled in the ABB registry. Among them, 223 patients were included in this analysis, excluding three patients who were lost to follow-up within 3 months after ABB completion. The median patient age was 65 years (range, 42–83). 218/223 patients had HR + tumors, including 38 (17.0%) with Tis and 185 (83.0%) with invasive cancers. Operation consisted of wide local excision with sentinel lymph node biopsy in 14 (36.8%) patients with ductal carcinoma in-situ (DCIS) (n = 38) and 176 (95.1%) patients with invasive cancer (n = 185), while wide local

excision alone was performed in 24 (63.2%) with DCIS and 9 (4.9%) patients with invasive cancer. Ninety-nine patients were treated with 10 fractions, 25 with 8 fractions, and 99 with 3 fractions. All locoregional treatments, including both surgery and ABB, were completed within 11 days. Among patients treated with the regimen of 21 Gy/3, all treatments were completed within a median of 6 days. ET was prescribed to 136 (60.9%) patients. Of the ET prescribed patients, 13 (9.5%) had switched ET regimens because of adverse effects of drugs. Further details of patients' characteristics and treatments are shown in Table 1 and Table 2, respectively.

A total of 8 patients (3.6%) developed grade 2 or higher treatment-related complications, all within 9 months of ABB completion: five (2.2%) had grade 2 infection, one (0.5%) had grade 3 infection, and 2 (0.9%) had grade 3 wound dehiscence.

After a median follow-up of 63 months (interquartile range, 42–81 months), 19 (8.5%) patients experienced a recurrence, including 17 (7.6%) with an IBTR. The IBTR developed a median of 32 months after ABB completion (range, 8–83 months). Five patients developed IBTR within 2 years after ABB completion while 12 IBTR occurred beyond 2 years after ABB completion. Among the patients with IBTR, 12 (70.5%) had a recurrent tumor within or adjacent to their previous lumpectomy bed. The IBTR presented as invasive cancer in 13 (5.8%) patients and as carcinoma in-situ in 4 (1.7%). Site of the first recurrence was IBTR alone in 15 patients, simultaneous IBTR/regional/distant metastasis (DM) in 2, isolated regional recurrence in 1, and isolated DM in 1 patient. Additionally, three (1.3%) patients developed contralateral breast cancer and one (0.4%) patient showed secondary primary breast cancer presenting as follicular lymphoma in the treated breast. For salvage treatment for IBTR, 14 (6.2%) patients underwent surgery ± systemic treatment, 1 (0.4%) received systemic treatments, and 2 declined any further treatments. The salvage surgery included mastectomy (n = 8) or repeat wide local excision (n = 6). Of the 15 patients who underwent salvage treatment for IBTR, 12 (80.0%) patients remained without evidence of disease, 2 (13.3%) were alive with disease, and 1 (6.7%) had died of breast cancer, after a median follow-up of 15 months following the salvage treatment.

Rates of 5-year IBTRFS, DMFS, DFS, and OS were 92.2%, 98.2%, 91.1%, and 97.8%, respectively. In multivariate analysis, the IBTRFS rates were significantly associated with the following factors: menopausal status (HR 0.26, 95% CI 0.08 – 0.83, $p = 0.02$), BMI < 30 kg/m^2 (HR 0.32, 95% CI 0.12–0.88, $p = 0.02$), and ET-adherence (HR 0.19, 95% CI 0.04 – 0.83, $p = 0.02$). The 5-year IBTRFS was significantly higher for post-menopausal women (93.6% vs. 66.4%, $p = 0.04$), BMI < 30 kg/m^2 (97.4% vs. 88.1%, $p = 0.02$), and ET-adherence (97.5% vs. 88.6%, $p = 0.02$) (Table 3). Notably, the favorable effect of ET-adherence was only found in post-menopausal women, not in pre-menopausal patients, albeit the number of pre- and *peri*-menopausal women in this registry was quite small due to selection criteria including age: among post-menopausal women, the 5-year IBTRFS was significantly higher in the ET-adherent group than among non-ET-adherent patients (100% vs. 90.1%, $p < 0.01$); whereas, among pre- and *peri*-menopausal women (n = 17), IBTRFS did not differ significantly with ET-adherence (77.8% vs. 62.5%, $p = 0.69$, 95% CI 48.7–63.2% vs. 53.9–61.7%). Additional details of the analyses on factors influencing IBTR are shown in Table 3.

Table 1
Patient's characteristics.

Characteristics		Number of patients (%)
Age (years, median 65, range 42–83)	<50	5 (2.2)
	≥50	218 (97.8)
Menopausal status	Peri- or pre-menopause	17 (7.6)
	Postmenopause	206 (92.4)
BMI (kg/m^2, median 28.5)	<30	131 (58.7)
	≥30	92 (41.3)
Charlson Comorbidity Index	<5	122 (54.7)
	≥5	101 (45.3)
Laterality of breast cancer	Right breast	114 (51.1)
	Left breast	109 (48.9)
Resection margin (cm, median 0.5)	<0.5, >0	70 (31.4)
	≥0.5	137 (61.4)
	Negative, margin width not specified	16 (7.2)
pT stage	DCIS	38 (17.0)
	T1 and T1mic	179 (80.3)
	T2	6 (2.7)
Tumor size (cm, median 0.9, range 0.1–4.5)	<1.0	120 (53.8)
	≥1.0	103 (46.2)
Histologic grade	1–2	206 (92.4)
	3	12 (5.4)
	unknown	5 (2.2)
Tumor subtype	ER+/or PR+	218 (97.8)
	ER-/PR-	5 (2.2)
Ki-67 (%) of breast tumor	<15%	128 (57.4)
	≥15%	45 (20.2)
	unknown	50 (22.4)
pN stage	pN0	219 (98.2)
	pN0(i +) or pN1mic	4 (1.8)

Abbreviations: BMI, body mass index; MMG, mammography; US, ultrasonography; MRI, magnetic resonance image; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor.

Table 2
Details of treatments.

Details		Number of patients (%)
Axillary management in invasive cancer	None	9 (4.9)
	Sentinel lymph node biopsy	176 (95.1)
Axillary management in DCIS	None	24 (63.2)
	Sentinel lymph node biopsy	14 (36.8)
Adjuvant endocrine therapy [1)]	None	87 (39.0)
	Early discontinued	9 (4.0)
	Non-adherence	31 (13.9)
	Adherence	96 (43.0)
Endocrine therapy regimen	Not done	87 (39.0)
	Tamoxifen (TAM)	33 (14.8)
	Aromatase-inhibitors (AI)	96 (43.0)
	TAM & AI	7 (3.1)
Adjuvant chemotherapy	None	221 (99.1)
	Yes	2 (0.9)
Radiation dose/schedule	7 Gy × 3 fx (QD)	99 (44.4)
	3.4 Gy × 10 fx (BID)	99 (44.4)
	4 Gy × 8 fx (BID)	25 (11.2)
Treatment duration [2)] (Median 7 days, range 3–11)	≤7 days	115 (51.6)
	8–11 days	108 (48.4)

Abbreviations: DCIS, ductal carcinoma in-situ.
[1)] None, if the patient did not initiate ET ever; early discontinue, if the patient stopped taking ET within 6 months after the first ET prescription; non-adherence, if the patient continued to take ET more than 6 months after ET initiation but no longer than 80% of follow-up duration or planned ET schedule; adherence, if the patient completed planned ET course or continued to have ET prescription for ≥ 80% of follow-up duration.
[2)] Time from date of operation through completion of adjuvant radiotherapy.

Discussion

In this prospective registry study including 223 patients with early-stage breast cancer, we evaluated long-term outcomes and related prognostic factors after BCS and ABB. With our institutional ABB protocol utilizing intraoperative SAVI device placement, all treatments, including surgery and radiotherapy, were completed within 11 days. After ABB completion, 61% of our patients agreed to take ET, of whom

Table 3
Factors influencing ipsilateral breast tumor recurrence-free survival.

Characteristics		No. of patients (%)	No. of events (%)	5-yr (%)	Univariate	Multivariate*	HR (95% CI)
Age (years)	<50	5 (2.2)	0 (0.0)	100.0	0.51		
	≥50	218 (97.8)	17 (7.8)	92.1			
Menopause	Peri- or premenopause	17 (7.6)	3 (17.6)	66.4	0.04	0.02	0.26 (0.08–0.83)
	Postmenopause	206 (92.4)	14 (6.8)	93.6			
BMI	≥30 kg/m^2	92 (41.3)	11 (11.9)	88.1	0.04	0.02	0.32 (0.12–0.88)
	<30 kg/m^2	131 (58.7)	6 (4.6)	97.4			
CCI	<5	122 (54.7)	8 (6.6)	92.0	0.82		
	≥5	101 (45.3)	9 (8.9)	92.3			
Side of breast	Right	114 (51.1)	5 (4.4)	94.5	0.07		
	Left	109 (48.9)	12 (11.9)	90.0			
Pathology	DCIS	38 (17.0)	3 (7.9)	87.3	0.79		
	Invasive Ca	185 (83.0)	14 (7.5)	91.4			
Tumor size	<1.0 cm	120 (53.8)	8 (6.7)	93.4	0.67		
	≥1.0 cm	103 (46.2)	9 (8.7)	90.9			
Histologic grade	1–2	206 (92.4)	16 (7.7)	91.7	0.09		
	3	12 (5.4)	1 (8.3)	64.5			
	unknown	5 (2.2)	0 (0.0)	100.0			
Hormone receptor	ER+/or PR+	218 (97.7)	17 (7.8)	90.4	0.48		
	ER-/PR-	5 (2.3)	0 (0.0)	100.0			
ET adherence[1)]	Other than adherence	127 (57.0)	15 (11.8)	88.6	0.02	0.02	0.19 (0.04–0.83)
	Adherence	96 (43.0)	2 (2.1)	97.5			
Radiotherapy regimen	7 Gy × 3 fx (QD)	99 (44.4)	4 (4.0)	95.1	0.16		
	3.4 Gy × 10 fx (BID)	99 (44.4)	8 (8.1)	93.3			
	4 Gy × 8 fx (BID)	25 (11.2)	5 (20.0)	78.7			

Abbreviations: HR, hazard ratio; BMI, body mass index; CCI, Charlson Comorbidity Index; DCIS, ductal carcinoma in-situ; ER, estrogen receptor; PR, progesterone receptor. ET, endocrine treatment.
[1)] ET adherence is defined if the patient completed the planned ET course or continued to have ET prescription for ≥ 80% of follow-up duration.

71% were adherent to ET while 29% showed early ET discontinuation or ET-non-adherence. After 63 months of median follow-up, 5-year IBTRFS was 92.2% and the grade 3 acute toxicity rate was 1.3%. Of note, IBTRFS was significantly better in post-menopausal patients, patients who were ET-adherent, and those with a BMI < 30 kg/m^2. Given these results, we provide important insight on ET-adherence in a real clinical practice setting and ascertain patient factors relating to favorable IBTRFS after ABB. The results of our study suggest that optimal patient selection and enhancing ET adherence will further improve IBTRFS in patients treated with BCS and ABB for early-stage breast cancer.

APBI, which provides favorable local control with minimal toxicities, has emerged as an appropriate alternative treatment to WBI in patients with early-stage breast cancer [15]. In trials of brachytherapy-based APBI, researchers applied various criteria for patient selection and used different radiation dose regimens. Regarding dose schedules, the most common approach has been a twice-daily treatment for 8 or 10 fractions [16–25]. Similarly, we administered twice-daily treatment initially. In recent years, we and others have investigated ABB delivered in 3 fractions or less. Long-term results of ultra-accelerated APBI trials are eagerly awaited, but these preliminary results suggest that APBI shortened to 3 days may be safe and feasible [11]. Among prior studies of brachytherapy, long-term IBTRFS were mostly available in trials utilizing interstitial brachytherapy or balloon brachytherapy. Rates of IBTR in studies containing more than 100 patients were reported between 0.5% and 6.2%, with a median follow-up duration of over 3 years [16–19,21,22,24–28].

In the current study, the cumulative IBTR rate was 7.8% at 5-years after ABB. Although it is difficult to directly compare our results with the literature since various methods for APBI were adopted among other studies, the IBTR rate in our study is higher than some other reports (Table 4). This may be explained by our very complete and relatively long-term follow-up period. Besides, it is possible that there was learning curve effect on oncologic outcome when ABB procedure was implemented in the initial phase of our study. The regimen of 32 Gy/8 fx (BID) was the very first scheme of our ABB protocol. After the 32 Gy/8 fx (BID) regimen was used, other fractionation schedules, 34 Gy/10 fx (BID) or 21 Gy/3 fx (QD) were adopted later period of our study. Considering that patients with 32 Gy/8 fx (BID) showed non-significantly higher IBTR rate than those with 34 Gy/10 fx (BID) or 21 Gy/3 fx (QD), it may be possible that less skilled ABB performance could have partially affected on the outcome. Another plausible cause for the relatively frequent IBTR is an insufficient margin in PTV construction in our ABB protocol. For target volume delineation, PTV was set at tumor bed with 1 cm margin in our study. Given that margins of 1.5 – 2 cm were added to lumpectomy cavity in studies using multi-catheter brachytherapy [17,18], our margin of 1 cm seems to be insufficient to cover risky area.

In addition, the IBTR outcome is likely attributed to the relatively low proportion of patients recommended for or adhering to prescribed adjuvant ET. Among women included in this study, <61% initiated ET after ABB. Considering that patients undergoing ET accounted for 61–100% of the study cohort in other brachytherapy studies [16–19,21,22,24–26], the proportion of patients taking ET in our study is lower than that of other studies. Adjuvant ET reduces breast cancer recurrence and breast cancer mortality [29]. Even though the efficacy of ET has largely been evaluated in patients treated with conventional whole breast irradiation, it can be also presumed that ET has a significant impact on improving local control in patients treated with APBI for low-risk HR + breast cancer. We found that ET-adherence was significantly associated with a lower risk of IBTR in our ABB cohort: women adherent to prescribed ET had an IBTR rate of 2.5% at 5-years while those non-adherent to ET were nearly 5 times more likely to have an IBTR at 5 years (11.4%). This finding provides further evidence of the value of adjuvant ET in patients treated with ABB for low-risk early-stage breast cancer. Previous studies have shown that approximately 87% of patients with HR + breast tumors do initiate ET, and about 38–70% of them adhere to the medication [12,30]. In our study, 71% of patients who started to take ET were adherent to the prescription. Such suboptimal drug adherence raises the necessity to promote adherence to ET in breast cancer management, even for low-risk breast cancer. In this regard, individualized supporting systems and protocols for enhancing ET-adherence are needed to be implemented. Furthermore, supportive care for relieving ET-related side effects should be properly provided for patients undergoing ABB and adjuvant ET.

In addition, menopausal status was found to be significantly associated with IBTR risk in this analysis. As known for decades, estrogen plays an essential role in cancer development, progression, and

Table 4
Previous studies on brachytherapy-based accelerated partial breast irradiation.

Studies	Sample size	Accrual years, Median FU	Type of brachytherapy	Dose regimens	Inclusion criteria	% pts receiving ET	% of menopause	IBTR rate
Randomized								
Budapest trial [16] (PBI vs. WBI)	258	1998 – 2004, 122 months	Interstitial (n = 88)or electron Tx (n = 40)	36.4 Gy/7 fx, BID	Age > 40, tumor ≤ 2 cm, RM (-) pN0 or pN1mic, grade 1–2	81% (90% had HR +)	78.9%	10-year, 5.9%
GEC-ESTRO [17] (PBI vs. WBI)	1,184	2004 – 2009, 79.2 months	Interstitial (n = 655)	32 Gy/8 fx (BID) or 30.1 Gy/7 fx (BID)	Age ≥ 40, invasive or DCIS, tumor ≤ 3 cm, pN0 or pN1mic, clear RM ≥ 2 mm	87% (89% had HR +)	83.0%	5-year, 1.38%
NSABP B-39/ RTOG 0413 [18] (PBI vs. WBI)	4,216	2005 – 2013, 122.4 months	InterstitialApplicator (MammoSite, Contura, or SAVI)	34 Gy/10 fx, BID	Age > 19, early-stage breast cancer (stage 0, I, II), tumor ≤ 3 cm, RM (-)	85% (81% had HR +)	61.0%	10-year, 4.6%
Prospective								
NRG oncology/ RTOG 9517 [26]	98	1997 – 2000 145 months	Interstitial	45 Gy/3.5–6 days LDR or 34 Gy/10 fx, BID	Unicentric invasive cancer < 3 cm, RM (-), pN0-N1	64% (74% had HR +)	79.6%	10-year, 6.2%
Mammosite registry [19]	1,449	2002 – 2004, 63.1 months	Applicator (MammoSite)	34 Gy/10 fx BID	Early breast cancer, based on ABS guideline	60.4% (61% had HR +)	NA	5-year, 3.8%
William Beaumont Hospital [20]	45	2004–2007, 74 months	Applicator (MammoSite)	28 Gy/4 fx, BID	Age > 40, tumor ≤ 3 cm, pN0-N1	61% (73% had HR +)	NA	6-year, 0%
TRIUMPH-T [21]	200	2015 – 2017, 19 months	InterstitialApplicator (SAVI or Contura)	22.5 Gy/3 fx, QD	Age ≥ 45, invasive or DCIS ≤ 3 cm, RM (-), LN (-), HR+	91.5% (98% had HR +)	NA	Crude rate, 0.5%
SiFEBI [22]	26	2012 – 2014, 63 months	Interstitial	16 Gy/1 fx	Age ≥ 70, "low-risk" according to the GEC-ESTRO guideline	100%	100.0%	5-year, 0%
Lattore [23]	20	2014 – 2016, 24 months	Interstitial	18 Gy/1fx	Age ≥ 50, invasive or DCIS ≤ 3 cm, RM (-), LN (-), HR (+)	100%	100.0%	Crude rate, 0%
Retrospective								
Hannoun-Levi [28]	157	2004 – 2018, 97 months	Interstitial	34 Gy/10 fx BID or 16 Gy/1 fx	Age ≥ 70, low-risk breast cancer	86.2% (89.8% had HR +)	100.0%	6-year, 1.3%
Contura registry [24]	342	2008 – 2011, 36 months	Applicator (Contura)	34 Gy/10 fx (BID)	Age ≥ 50, invasive or DCIS ≤ 3 cm, HR (+), RM (-), pN0	NA	94.6%	3-year, 2.2%
Yashar [25]	250	2007 – 2010, 59.5 months	Applicator (SAVI)	34 Gy/10 fx (BID)	Early breast cancer	65% (90% had HR +)	87%	4-year, 3.6%
The current study	223	2012 – 2019, 63 months	Applicator (SAVI)	− 32 Gy/8 fx (BID) − 34 Gy/10 fx (BID) − 21 Gy/3 fx (QD)	Age > 40, invasive or DCIS < 5 cm, RM (-), pN0 or pN1mic	60.9% (97% had HR +)	92.4%	5-year, 7.8% (In ET-adherence [1]: 2.5%)

Abbreviations: FU, follow-up; ET, endocrine therapy; IBTR, ipsilateral breast tumor recurrence; PBI, partial breast irradiation; WBI, whole breast irradiation; RM, resection margin; HR+, hormone-receptor-positive tumor; DCIS, ductal carcinoma in-situ; SAVI, a Strut Adjusted Volume Implant device; LDR, low-dose rate brachytherapy; NA, not-available; ABS, the American Brachytherapy Society.

[1] ET adherence is defined if the patient completed the planned ET course or continued to have ET prescription for ≥ 80% of follow-up duration.

recurrence in breast cancer [31]. In this respect, post-menopause is regarded as a favorable prognostic factor for breast cancer outcomes. Similarly, young age is known as a strong independent factor for predicting breast cancer recurrence [32]. Considering that menopausal status is closely related to patients' age, several clinical guidelines incorporate age into patient selection criteria in the determination of suitability for APBI [33]. Even if cut-off values for the age criteria vary across the guidelines, 45 or 50 years of age is often adopted for defining the low-risk group that is acceptable for APBI. Given that tumor occurring in younger women presents more aggressive biological characteristics [32,34], it would be reasonable to consider age as a selection criterion for APBI. However, in our analysis, age was not associated with IBTR risk. Rather, the menopausal status provided more statistically significant criteria for determining a favorable risk group in patients treated with our ABB protocol. Our findings suggest that ABB is less effective for premenopausal than postmenopausal women.

Obesity, defined by BMI ≥ 30 kg/m^2, is known as a strong negative prognostic factor for breast cancer recurrence and death [35]. In obese women, dysregulation of sex hormones, insulin/insulin-like growth factor, adipocytokines, and inflammatory cytokines are reported [36]. These dysregulated molecular mechanisms appear to promote radioresistance in breast cancer [37]. Likewise, in our study, obese patients showed inferior IBTRFS compared to non-obese women. Although there have been other reports showing a close association between obesity and locoregional recurrence, all these studies were performed in patients undergoing WBI [27,38]. In this regard, our study provides unique evidence that obesity is related to increased IBTR in women undergoing ABB and highlights the importance of lifestyle modification counseling.

Limitations of our study include that it was conducted in a single institution and included a relatively small number of pre- and *peri*-menopausal women. Consequently, the influence of menopausal status on IBTR might be under or overestimated. Additional studies including a larger number of pre-menopausal women would be required to assess the prognostic influence of menopause in patients treated with BCS and

ABB. Notwithstanding these limitations, the current study is valuable in providing long-term oncologic outcomes of intraoperatively placed SAVI utilizing ABB. Moreover, the IBTR-associated factors found in our study, menopausal status and BMI, can add practical guidance for the selection of patients who are suitable for ABB. Additional strengths of our work include granular data on ET adherence and lengthy follow-up.

In conclusion, intraoperative strut-based brachytherapy catheter placement followed by ABB is a favorable strategy for the delivery of APBI in optimally selected patients with early-stage HR + breast cancer. IBTRFS was most favorable for post-menopausal, non-obese, and ET-adherent women. Our data highlights the importance of multidisciplinary counseling with careful patient selection and encouragement of ET compliance in patients treated with ABB for breast cancer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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