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Four-year results using balloon-based brachytherapy to deliver accelerated partial breast irradiation with a 2-day dose fractionation schedule

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ABSTRACT

PURPOSE: We present 4-year results from a Phase I/II trial using balloon-based brachytherapy to deliver accelerated partial breast irradiation in 2 days.

MATERIALS/METHODS: Forty-five patients received breast-conserving surgery followed by adjuvant radiation therapy using a balloon-based brachytherapy applicator delivering 2800 cGy in four fractions over 2 days. Outcomes analyzed include toxicities scored using the NCI Common Toxicity Criteria v3.0 scale, ipsilateral breast tumor recurrence, regional nodal failure, distant metastasis, disease-free survival, cause-specific survival, and overall survival.

RESULTS: Median age was 66 years (range, 48−83 years) and median tumor size was 0.6 cm (range, 0.2−2.3 cm). Five percent of patients were node positive ($n = 2$), whereas 73% was estrogen receptor positive ($n = 33$). Median followup was 3.7 years (2.4−7.0 years) with greater than 2 years of followup for all patients. Only Grades 1 and 2 chronic toxicities were noted with fat necrosis (18%) and asymptomatic seromas (42%) being the most common toxicities. Seven percent of patients developed ipsilateral rib fractures ($n = 3$), although this was not statistically associated with maximum rib dose ($p = 0.31$). Ninety-eight percent of patients had a good or excellent radiation-related cosmetic outcome at the time of last followup. There were no ipsilateral breast tumor recurrences or regional nodal failures; however, 2 patients developed distant metastases. Four-year actuarial disease-free survival, cause-specific survival, and overall survival were 96%, 100%, and 93%, respectively.

CONCLUSIONS: Treatment of early-stage breast cancer patients with breast-conserving therapy using a 2-day radiation dose schedule resulted in acceptable chronic toxicity and similar clinical outcomes as standard 5-day fractionation.

Keywords: APBI; Hypofractionation; Partial breast irradiation; IORT; Breast cancer

Introduction

Adjuvant radiation to the whole breast after breast-conserving surgery has been established as a standard of care in the treatment of early-stage breast cancer in multiple prospective randomized trials (1, 2). Beginning in the early 1990s, an accelerated schedule of radiation delivery to the portion of the breast at highest risk for local failure (e.g., accelerated partial breast irradiation [APBI]) was developed to improve the option for breast conservation by reducing the overall treatment time and potentially improving the quality of life of patients (3, 4). Gradually, this technique has been made available to larger groups

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of carefully selected women with low-risk disease. Phase I/II studies with 5- and 10-year followup using interstitial brachytherapy techniques to deliver APBI have documented acceptable rates of cosmesis, toxicity, and local control (4–6). Balloon- or applicator-based brachytherapy and three-dimensional conformal radiation therapy have become the most common methods for APBI in the United States (7, 8). Several groups (including a national registry trial) (9–13) have published results using the MammoSite Radiation Therapy System (RTS) (Hologic, Inc., Bedford, MA, USA) showing excellent rates of local control with adequate early and late toxicity.

Although varied radiation fractionation schedules exist in the literature to deliver APBI, the radiation dose schedule used in the United States has been fairly uniform. Patients who receive interstitial brachytherapy or applicator-based brachytherapy traditionally receive a total dose of 34 Gy divided into 10, twice-daily fractions with a minimum interfraction interval of 6 hours. Patients who are treated with the three-dimensional conformal radiation therapy technique of APBI typically receive 38.5 Gy also divided into 10 fractions using a twice-a-day dose–delivery schedule.

Over the past 5 years, there has been increasing interest in further shortening the treatment length for patients receiving APBI. Hypofractionated APBI can vary from one to four fractions and has been studied using a variety of delivery techniques (14–17). We present an update of our previously published results of a Phase I/II trial using a balloon-based catheter to deliver APBI in four fractions over 2 days.

Materials and methods

Investigational review board approval was granted in 2004 for this Phase I/II, nonrandomized, prospective pilot trial using a balloon-based brachytherapy device (the MammoSite RTS) to deliver adjuvant radiation after lumpectomy in 2 days (investigational review board #2004-007).

Study participants

Between March 2004 and August 2007, 45 patients with early-stage breast cancer were enrolled onto a Phase I/II clinical trial and received breast-conserving surgery followed by adjuvant radiation therapy using a single-lumen balloon-based brachytherapy applicator. Eligibility for this trial included age >40, ≤ 3.0 cm tumor size, ≤ 3 pathologically positive lymph nodes, and negative margins (per National Surgical Adjuvant Breast and Bowel Project [NSABP] criteria).

Prescribed radiation dose and placement techniques

An equivalent dose to standard whole breast irradiation (45 Gy in 25 fractions) with lumpectomy cavity boost (16 Gy in 8 fractions and 61 Gy in total) was estimated using the linear quadratic model. An alpha/beta ratio for tumor control of 4.0 was used to calculate a dose and fractionation pattern of four fractions of 700 cGy to a total dose of 28 Gy delivered over 2 days. This calculated dose was prescribed to a distance of 1.0 cm beyond the surface of the balloon. Minimum interfraction time for all patients was 6 hours. Our device placement and treatment-planning techniques using the MammoSite RTS have been previously described (9, 15). All patients met dosimetric criteria specified by the NSABP B-39/Radiation Therapy Oncology Group 0413 Phase III trial. Acceptable balloon fill volumes were 35–125 mL corresponding to device diameters between 4 and 6 cm. The prescription dose was delivered by connecting the applicator's central port to an afterloader equipped with an iridium-192 source. After completion of the fourth fraction, the radiation oncologist removed the brachytherapy applicator.

Outcome measures and toxicity analysis

Our primary objective was to measure both clinical effectiveness and rates of toxicity using our 2-day fraction schedule. Toxicities were evaluated using the National Cancer Institute Common Toxicity Criteria for Adverse Events v3.0 scale. Methods of analysis for both acute and late toxicity for this trial have also been previously described (15). Patients were followed every 3 months for the first 2 years by the radiation oncologist or the breast surgeon and then every 6 months thereafter. Cosmesis was scored by the physician using the Harvard Criteria (18) at each followup encounter beginning with the 6-month visit. Mammograms were obtained annually, and additional imaging studies were ordered at the discretion of the radiologist, radiation oncologist, or surgeon. Clinical outcomes evaluated include ipsilateral breast tumor recurrence (IBTR), regional nodal failure (RNF), distant metastasis (DM), disease-free survival (DFS), cause-specific survival (CSS), and overall survival (OS).

Statistical analysis

The estimated likelihood for IBTR, RNF, DM, DFS, CSS, and OS were calculated using the Kaplan–Meier method. Microsoft Excel was used to calculate data counts, mean, median, and ranges for patient characteristics and toxicity rates. Statistical significance of toxicity levels as compared with radiation dose and clinical outcomes were established using linear regression, a Pearson chi-square test, and two sample T tests. Statistical analyses were performed using Systat version 11.0 (Systat Software, Inc., Chicago, IL), and all statistical tests were two sided.

Results

Clinical and treatment-related characteristics

Patient characteristics are summarized in Table 1. Of the 45 women treated, the median age was 66 years (range, 48–83 years) with a median tumor size of 0.6 cm (range,

Table 1
Patient, tumor, and treatment-related characteristics ($n = 45$)

Characteristic	Findings (n, %)
Patient/tumor-related characteristics	
Followup (y)	
Median	3.7
Range	2.4–7.0
Length of followup (y)	
≥2	45 (100)
≥3	38 (85)
≥4	18 (40)
Age (y)	
Median	66
Range	48–83
Race	
African American	6 (13)
Caucasian	37 (83)
Other	2 (4)
Stage	
0	6 (13)
I	37 (83)
II	2 (4)
Tumor size (mm)	
Median	6
Range	2–23
≤10	33 (74)
11–20	10 (22)
>20	1 (2)
Unknown	1 (2)
Nodes	
Nx	6 (13)
(−)	37 (82)
(+)	2 (4)
(1 positive node)	1 (2)
(2–3 positive nodes)	1 (2)
Histologic grade	
Grade I	15 (33)
Grade II	20 (44)
Grade III	10 (23)
Receptor status	
ER positive	33 (73)
PR positive	28 (62)
Treatment-related characteristics	
Margins (mm)	
Negative (≥2)	26 (58)
Close (>0, <2.0)	19 (42)
Systemic treatment	
Hormone therapy	25 (61)
Chemotherapy	8 (18)
Placement technique	
SET	6 (13)
Lateral	39 (87)
Trocar used	9 (20)
Balloon size (cm)	
Small (4–5)	33 (73)
Large (5–6)	12 (27)
Balloon volume (mL)	
Median	60
Range	35–110
Skin spacing (mm)	
Median	12
Range	8–24
<10	9 (20)
Dwell positions	
One	35 (78)
Three	9 (20)
Five	1 (2)

ER = estrogen receptor; PR = progesterone receptor; SET = scar entry technique.

0.2–2.3 cm). Four percent of patients were node positive ($n = 2$), whereas 73% were estrogen receptor positive ($n = 33$). Sixty one percent of patients received hormonal therapy ($n = 25$), whereas only 18% received chemotherapy ($n = 8$), which was administered after brachytherapy. Median followup in surviving patients was 3.7 years (range, 2.4–7.0 years).

Median skin to balloon distance was 12 mm (range, 8–24 mm). The most common number of dwell positions was one ($n = 35$), with 9 patients treated with three dwell positions and 1 patient treated with five dwell positions. Mean balloon fill volume was 60 cc (range, 35–110 cc). The average length of time from implantation of the balloon to removal after completion of radiation therapy in this trial was 4.8 days (range, 3–10 days). This is compared with our institutional average for traditional balloon-based brachytherapy patients of 8.6 days (range, 6–14 days), the difference of which was found to be statistically significant ($p < 0.001$). Additional treatment-related characteristics are outlined in Table 2.

Chronic toxicity and cosmetic outcomes

With greater than 2 years of followup for all patients, only Grade 1 and Grade 2 late effects were noted (Table 3). Asymptomatic fat necrosis developed in 29% of patients ($n = 13$), which was more common in those who had an infection ($p = 0.02$) and patients with higher balloon fill volumes ($p = 0.002$). Seromas were noted on mammogram in 58% of patients ($n = 26$) and were also associated with increased fill volume ($p = 0.01$). These maximum rates of toxicity have decreased to 18% ($n = 8$) and 41% ($n = 18$), respectively, as of the most recent followup visit. Only 3 patients had symptoms from their seromas (7%), all of which were treated with aspiration, which resolved the associated discomfort entirely in each case. Nine percent of patients had Grade 1 telangiectasia ($n = 4$), and 4% had Grade 2 telangiectasia ($n = 2$) after treatment, which increased from 7% ($n = 3$) Grade 1 telangiectasia at our 3-year interim analysis. At 3 years after APBI, 36% ($n = 16$) and 2% ($n = 1$) of patients had Grade 1 and Grade 2 breast induration/fibrosis, which increased slightly to 44% ($n = 20$) and 7% ($n = 3$) at the time of our 4-year analysis. Cosmesis was scored as good or excellent in 98% of patients with only 1 patient rated as having a fair cosmesis at the time of their last followup (Table 4).

Table 2
Acute and chronic toxicities (at last followup, all pts ≥2 y)

Toxicity	Time	None	Grade 1	Grade 2	Grade 3
		n (%)	*n* (%)	*n* (%)	*n* (%)
Radiation dermatitis	Acute	17 (38)	24 (53)	4 (9)	0 (0)
	Chronic				
	Max	33 (73)	12 (27)	0 (0)	0 (0)
	Current	37 (82)	6 (13)	2 (4)	0 (0)
Breast pain	Acute	20 (45)	13 (29)	6 (13)	6 (13)
	Chronic				
	Max	33 (73)	10 (22)	2 (4)	0 (0)
	Current	35 (78)	9 (20)	1 (2)	0 (0)
Breast edema	Acute	29 (64)	15 (34)	1 (2)	0 (0)
	Chronic				
	Max	38 (84)	7 (18)	0 (%)	0 (0)
	Current	39 (87)	6 (13)	0 (%)	0 (0)
Hyperpigmentation	Acute	30 (67)	14 (31)	1 (2)	0 (0)
	Chronic				
	Max	33 (73)	11 (25)	1 (2)	0 (0)
	Current	36 (80)	8 (18)	1 (2)	0 (0)
Induration (fibrosis)	Acute	33 (73)	11 (25)	1 (2)	0 (0)
	Chronic				
	Max	22 (49)	20 (44)	3 (7)	0 (0)
	Current	22 (49)	20 (44)	3 (7)	0 (0)
Telangiectasia	Acute	44 (98)	0 (0)	1 (2)	0 (0)
	Chronic				
	Max	39 (87)	4 (9)	2 (4)	0 (0)
	Current	39 (87)	4 (9)	2 (4)	0 (0)
Hypopigmentation	Acute	42 (93)	3 (7)	0 (0)	0 (0)
	Chronic				
	Max	44 (98)	1 (2)	0 (0)	0 (0)
	Current	44 (98)	1 (2)	0 (0)	0 (0)
Volume loss (due to RT)	Acute	43 (96)	2 (4)	0 (0)	0 (0)
	Chronic				
	Max	41 (91)	4 (9)	0 (0)	0 (0)
	Current	41 (91)	4 (9)	0 (0)	0 (0)
Fat necrosis	Acute	45 (100)	0 (0)	0 (0)	0 (0)
	Chronic				
	Max	32 (71)	13 (29)	0 (0)	0 (0)
	Current	37 (82)	8 (18)	0 (0)	0 (0)
Infection	Acute	39 (87)	6 (13)	0 (0)	0 (0)
	Chronic				
	Max	43 (96)	2 (4)	0 (0)	0 (0)
	Current	45 (100)	0 (0)	0 (0)	0 (0)
Seroma on mammogram	Acute	42 (93)	3 (7)	0 (0)	0 (0)
	Chronic				
	Max	19 (42)	23 (51)	3 (7)	0 (0)
	Current	27 (60)	18 (40)	0 (0)	0 (0)
Rib fracture	Acute	43 (96)	0 (0)	2 (4)	0 (0)
	Chronic				
	Max	42 (93)	0 (0)	3 (7)	0 (0)
	Current	45 (100)	0 (0)	0 (0)	0 (0)

RT = radiation therapy.

Seven percent of patients developed ipsilateral rib fractures ($n = 3$), all of which were symptomatic (Grade 2). None of the rib fractures were displaced, and all three were treated with prescription pain medication and healed with no additional interventions. Rib fracture was not statistically associated with maximum rib dose ($p = 0.31$), although two of the fractures occurred in patients with a per-fraction dose to the rib exceeding 160% of the prescription dose. This dose

Table 3
Cosmetic score with ≥2 y followup ($n = 45$)

Cosmetic result	% (n)
Excellent	36 (16)
Good	62 (28)
Fair	2 (1)
Poor	0 (0)

was calculated as the highest point dose contained within the contour of the rib closest to the balloon. The volume of rib treated was not considered in treatment planning or our analysis. Table 5 lists maximum rib dose divided into groups of dose relative to the per-fraction prescription dose correlated with the number of fractures associated with each dose level, although interpretation of these data are limited because they are based on a relatively few number of events.

Treatment outcome

There were no IBTR or RNF; however, 2 patients experienced DM. Two patients died from preexisting renal and pulmonary disease, which was unrelated to their breast cancer. Based on a 4-year actuarial analysis, DFS was 96% with a CSS of 100% and OS of 93%. Most patients treated (64%, $n = 29$) fall into the ''cautionary'' category of the American Society for Radiation Oncology consensus statement for APBI, whereas 27% are considered ''suitable'' ($n = 12$) and only 9% are categorized as ''unsuitable'' ($n = 4$). Assignment to a consensus statement group did not correlate with development of a distant metastasis or any other clinical outcome.

Discussion

The current report provides an update on the use of a novel hypofractionated dose of APBI using 2800 cGy delivered in four fractions of 700 cGy over 2 consecutive days with balloon-based brachytherapy. With a median followup of 3.7 years in 45 patients, no IBTRs were noted. Cosmetic results were judged to be good-to-excellent in 98% of patients, and acceptable rates of chronic toxicities (similar to those observed with a standard five-day schedule) were observed. These findings support the continued investigation

Table 4
Max rib dose per fraction

Prescription dose to rib, % (cGy)	No fracture n (%)	(+) Fracture n (%)	p-Value
≤100 (≤700)	28 (62)	0 (0)	0.31
101–120 (701–840)	2 (4)	1 (33)	
121–140 (840–1000)	4 (9)	0 (0)	
141–160 (1000–1160)	3 (7)	0 (0)	
>160 (>1160)	8 (18)	2 (67)	

Table 5
Clinical outcomes ($n = 45$)

IBTR	RNF	DM	DFS	CSS	OS
% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
0 (0)	0 (0)	4 (2)	96 (43)	100 (45)	93 (42)

IBTR = ipsilateral breast tumor recurrence; RNF = regional nodal failure; DM = distant metastasis; DFS = disease-free survival; CSS = cause-specific survival; OS = overall survival.

of these novel hypofractionated APBI schemes delivered in an adjuvant setting.

Hypofractionation for breast cancer

Shorter radiation schedules are currently being investigated to provide patients the option of breast conservation with radiation delivered in a more convenient and possibly less toxic fashion. These abbreviated radiation schedules have included treatment both to the whole breast volume and a partial breast target (e.g., APBI). In addition, significant recent interest has focused on the delivery of single-fraction intraoperative radiation dose in an effort to complete a patient's entire treatment course in only 1 day. Unfortunately, intraoperative radiation has several significant disadvantages (see below) including the inability to comprehensively and accurately define radiation dose coverage of the target in an optimal fashion and the fact that margin status is not frequently available in these patients until after the radiation treatment has been delivered. As a result, single-fraction intraoperative RT for breast cancer has met limited enthusiasm in many centers in the United States.

The current radiation technique in this study was designed to provide the logistical benefits of single-fraction intraoperative RT (minimal number of radiation fractions) but with the additional clinical and technical advantages of balloon-based brachytherapy. These include the fact that a patient's margin status is known before the treatment is delivered, the radiation dosimetry can be validated and optimized in all cases and that the implant technique has been shown to be well tolerated in thousands of women (many with over 5 years of followup) (13).

The hypofractionated dose of 2800 cGy in four fractions selected for this trial was designed to be biologically equivalent to standard whole breast irradiation (45 Gy in 25 fractions) combined with a boost to the lumpectomy bed (16 Gy in 8 fractions, 61 Gy total). As toxicity has been minimal at this dose level, a slightly higher fraction size while maintaining the fractionated regimen could be considered. In fact, Khan et al. have begun accrual to a Phase I/II dose escalation hypofractionated APBI clinical trial with an initial dose level of 2800 cGy in four fractions. Assuming no abnormal toxicity pattern is observed in the first phase of the new trial (30 patients followed a minimum of 6 months), two additional dose tiers of 2475 cGy in three fractions and 2100 cGy in two fractions are planned (Atif

Khan, M.D., Robert Wood Johnson University Hospital, written communication, March 2011).

Hypofractionation in whole breast irradiation

The U.K. Standardisation of Breast Radiotherapy (START) Trials have shown radiation can be delivered safely to the entire breast using a hypofractionated schedule with minimal toxicity and excellent local control rates. The START A Trial randomized 2215 patients to 50 Gy in 25 fractions vs. 41.6 or 39 Gy in 13 fractions. Fraction sizes were 2.0, 3.2, and 3.0 Gy with all dose levels delivered in 5 weeks. Local–regional relapse rates at 5 years were comparable between all arms with the 39-Gy arm showing evidence of a lower rate of late adverse skin effects (19). The START B Trial tested 40 Gy in 15 fractions delivered in 3 weeks vs. 50 Gy in 25 fractions given over 5 weeks. With a median followup of 6 years, the local control was similar between the two arms; however, the hypofractionated arm again had a lower rate of late breast toxicity (20).

With the longest followup of any randomized series on hypofractionation in early-stage breast cancer, Whelan et al. (21) have shown at 10 years that 42.5 Gy in 16 fractions is equivalent to standard fractionation of 50 Gy in 25 fractions. Alternate fractionation patterns and dose levels have been tested prospectively by other investigators, including Ortholan et al. (22) and Formenti et al. (23), who have also shown encouraging results using hypofractionated radiation with limited followup.

Intraoperative radiotherapy

In Milan, Veronesi et al. (14) have advocated the Intraoperative Radiotherapy with Electrons system that delivers a single fraction of 21 Gy to the 90% isodose line at the time of quadrantectomy. Other areas of Europe (and some centers in the United States) have also shown interest in single-fraction partial breast irradiation, including the recently published update to the TARGeted Intraoperative radiation Therapy (TARGIT) trial, where 20 Gy is prescribed to the surface of an intraoperative applicator using 50 kV X-rays (16). Collectively, these techniques are referred to as intraoperative radiotherapy (IORT).

IORT, however, has limitations (as mentioned above). As radiation is delivered at the time of surgery, final evaluation of the lumpectomy margins is not always possible. Although frozen sections obtained within the operative setting may reduce the rate of reexcision (24), published reports continue to show that 3.8–11.3% of patients will require reexcision or mastectomy after obtaining an initial "negative" intraoperative margin (24–26). Discussion as to what additional therapy is needed for patients found to have positive margins after IORT ranges from reexcision to treating the intraoperative procedure as only a boost and supplementing with whole breast irradiation. Besides positive margins, other adverse histopathologic features may also warrant additional radiation treatment beyond the intraoperative TARGIT dose, including Grade 3 histology, extensive intraductal component, positive lymph nodes, and/or lymphovascular space invasion. In all, 14.3% of patients assigned to the TARGIT-only arm required additional adjuvant therapy (16).

Besides uncertain margin status and histology at the time of treatment, tissue conformance to the intraoperative applicator is another potential concern. Most of the adjuvant brachytherapy applicators are similar in shape to those used in the TARGIT trial; however, in the adjuvant setting, a postimplant CT is typically obtained to document tissue conformance. In many intraoperative techniques, true tissue conformance to the intraoperative applicator is unknown because three-dimensional imaging is not obtained after device placement and time to allow improvement in tissue conformance cannot be afforded, as the patient remains anesthetized until radiotherapy has been completed.

Logistical considerations aside, there have also been at least one report of increased toxicity with high-dose single-fraction IORT. Beal et al. tested intraoperative high-dose-rate brachytherapy using the Harrison–Anderson–Mick applicator prescribing a single fraction of 20 Gy at 1.0 cm from the surface of the applicator. The dose in their trial was subsequently decreased at the lateral edges of the applicator to 18 Gy after 5 of the first 18 patients developed significant fibrosis and skin retraction 6 months after completion of therapy (27). As with all new technologies, long-term followup is needed. Authors emphasize the potential cost savings of single-fraction techniques; however, patient safety and clinical efficacy must be proven before efforts to trim costs drive patient care into uncharted territory.

Limitations of current trial

Limitations of this analysis include a small sample size, a limited length of followup, and concerns over the development of rib fractures in 3 patients. Although women diagnosed with breast cancer are elderly, and thus at risk for osteoporosis and fracture, a 7% rib fracture is beyond what was expected in this trial. We conducted a dosimetric analysis and, although there was no statistical association between max rib dose and rib fracture, two of the three fractures occurred in women with a max rib dose greater than 160% of the prescription dose. This has created awareness within our group of a previously underappreciated normal tissue dose constraint where maximum dose to an ipsilateral rib should likely be limited to less than 160% of the prescription dose. This pilot trial was conducted before the availability of multilumen brachytherapy applicators and as such, it will be easier to meet this constraint with the new generation of applicator-based brachytherapy devices.

Compared with the published reports from our institution and others using standard-fractionated APBI, however, our current trial appears to be similar in regards to rates of

infection, telangiectasia, fibrosis, retraction, and breast pain. Seroma rates appear slightly higher than other published accounts; however, our reported rate of 58% represents patients who had a seroma identified at any point in time after 6 months of followup and does not reflect persistent seromas at the time of last followup. Very few of our patients experienced symptoms from the presence of the seroma or required aspiration. Without a Phase III study directly comparing a 2-day and 5-day fractionation pattern, it is not possible to say whether our current results differ statistically from current accounts of partial breast irradiation.

Finally, one of the primary goals of this trial is to reduce the length of time required for treatment using APBI. Because we used a 2-day fraction schedule, the balloon applicator was typically not required to remain in place over a weekend, as is common with 5-day applicator-based brachytherapy treatment regimens. As mentioned in our results section, we observed a mean total implant time of only 4.8 days. Compared with our institutional average for typical APBI cases of 8.6 days, this was a 79% reduction, which may translate into a decreased risk of infection and improved patient comfort and convenience.

Conclusions

Treatment of early-stage breast cancer patients using a 2-day dose schedule for balloon-based brachytherapy in a limited group of patients resulted in acceptable 4-year rates of chronic toxicity and similar clinical outcomes as a standard 5-day fractionation. Long-term followup with this patient cohort is necessary as this approach could offer improved patient convenience with optimal and verifiable dose delivery while eliminating the uncertainties of unknown margin status at the time of treatment.

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