Six-Year Results From a Phase I/II Trial for Hypofractionated Accelerated Partial Breast Irradiation Using a 2-Day Dose Schedule

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Background: To report 6-year outcomes from a phase I/II trial using balloon-based brachytherapy to deliver APBI in 2 days.

Methods: A total of 45 patients with early-stage breast cancer received adjuvant APBI in 2 days with high-dose rate (HDR) brachytherapy totaling 2800 cGy in 4 fractions (700 cGy BID) using a balloon-based applicator as part of a prospective phase I/II clinical trial. All patients had negative margins and skin spacing $\geq$8 mm. We evaluated toxicities (CTCAE v3) as well as ipsilateral breast tumor recurrence (IBTR), regional nodal failure (RNF), distant metastasis, disease-free survival, cause-specific survival, and overall survival.

Results: Median age and tumor size were 66 years old (48 to 83) and 0.8 cm (0.2 to 2.3 cm), respectively. Four percent of patients were N1 (n = 2) and 73% were estrogen receptor (ER) positive (n = 32). Median follow-up was 6.2 years (2.4 to 8.0 y). Nearly all toxicities at 6 years were grade 1 to 2 except 1 instance of grade 3 telangiectasia (2%). Eleven percent (n = 5) of patients had chronic asymptomatic fat necrosis whereas asymptomatic seromas were noted on mammogram in 13% of cases (n = 6). Cosmesis at last follow-up was good or excellent in 91% of cases (n = 40) and fair in 9% (n = 4). Two of the previously reported rib fractures healed with conservative measures. There were no IBTR or RNF (6 y IBTR/RNF rate 0%); however, 2 patients experienced distant metastasis (4% at 6 y). The 6-year actuarial disease-free survival, cause-specific survival, and overall survival were 96%, 100%, and 93%, respectively.

Conclusions: Hypofractionated 2-day APBI using brachytherapy resulted in excellent clinical outcomes with acceptable chronic toxicities.

Key Words: accelerated partial breast irradiation, APBI, hypofractionation, breast cancer, brachytherapy

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Accelerated partial breast irradiation (APBI) has been in clinical use for over 20 years[1,2] allowing patients to complete the adjuvant radiotherapy component of breast conserving therapy in $\leq$5 days with twice-daily brachytherapy[3] or external beam radiotherapy.[4] For appropriately selected patients, retrospective analyses and 4 prospective randomized trials have shown APBI to have similar efficacy and cosmetic outcomes as whole breast irradiation (WBI).[5–9] Interest in minimizing the length of therapy and exploiting the reported low α-β ratio of breast carcinoma has led to many shortened schedules of breast radiotherapy.[10] Hypofractionated WBI has been shown to be safe and effective at 10 years in 3 international clinical trials[10,11] and is now offered to many women with early-stage breast cancer. Ultra-hypofractionated partial breast techniques delivered at the time of surgery (intraoperative radiotherapy [IORT]) are limited by the lack of margin status[12,13] and may use a nonstandard dose to the clinical target volume.[13] The purpose of this paper is to provide 6-year results of a phase I/II clinical trial testing a novel hypofractionated APBI 2-day dose schedule biologically similar to WBI with a lumpectomy cavity boost.

METHODS

A total of 45 patients with early-stage breast cancer were enrolled as part of a single-institution Investigational Review Board (IRB)-approved phase I/II clinical trial evaluating hypofractionated APBI (HIC#: 2004-007). Complete accrual was met during an enrollment period of March 2004 to August 2007. Eligibility criteria for this protocol, which has been previously published,[14,15] was based on general suitability for breast conserving therapy including age >40, tumor size less $\leq$3 cm, $\leq$3 pathologically-staged positive lymph nodes, and negative margins per National Surgical Adjuvant Breast and Bowel Project (NSABP) criteria. Additional technical factors included skin spacing $\geq$8 mm, balloon volume between 4 and 6 cm, corresponding with a balloon fill volume between 35 and 125 cc.

The breast brachytherapy device used in this trial was the original MammoSite (Hologic Inc., Bedford, MA) single-lumen radiation therapy system. The prescribed dose was 2800 cGy in 4 fractions (700 cGy BID) using high-dose rate (HDR) brachytherapy with a biologic effective dose similar WBI plus lumpectomy cavity boost (60 Gy). The prescription point was 1 centimeter from the surface of the balloon/lumpectomy cavity interface and delivered using either 1or 3-dwell positions. The interfraction time was a minimum of 6 hours. All patients were treated in contiguous days with a maximum time between fractions 2 and 3 of 18 h or less (ie, requiring all 4 fractions to be delivered on consecutive treatment days).

Toxicities were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE), version 3 at the time of follow-up by the treating physician. Typical follow-up intervals consisted of short-term toxicity evaluations every 3 to

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4 months for the first 2 years following treatment succeeded by annual evaluations thereafter. Clinical end points studied 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). Surveillance for recurrences was performed using clinical exam and appropriate diagnostic imaging with histologic confirmation required for all suspected recurrences. Cosmesis was evaluated by the treating physician using the Harvard scale.[16] Cases were divided into "suitable," "cautionary," and "unsuitable" categories according to the American Society for Radiation Oncology (ASTRO) Consensus Statement[17] paper for additional analysis.

The estimated likelihood for IBTR, RNF, DM, DFS, CSS, and OS were calculated using the Kaplan-Meier method. Microsoft Excel (Microsoft Corporation, Redmond, WA) was used to calculate data counts, mean, median, and ranges for patient characteristics. A P-value of < 0.05 was considered significant. Statistical analyses were performed using SYSTAT 13 (Systat Software Inc., Chicago, IL), and all statistical tests were 2-sided.

RESULTS

The median age and tumor size was 66 years old (range, 48 to 83 y) and 6.5 mm (range, 2 to 23 mm) (Table 1), respectively. Four percent of cases were lymph node positive (n = 2) and 73% were ER positive (n = 32). Median follow-up was 6.2 years (range, 2.4 to 8.0 y). Median skin distance was 12 mm (range, 8 to 24 mm) and mean balloon volume was 60 cc (range, 35 to 110 cc) (Table 2). Most patients (61%, n = 25) received hormonal therapy and 18% received chemotherapy (n = 8).

Acute and initial chronic toxicities for this patient cohort have been previously reported. The vast majority of toxicities at the 6-year time interval were grade 1 and grade 2 events (Table 3) except for 1 patient (2%) with grade 3 telangiectasia (Table 3). Chronic asymptomatic fat necrosis was present in 11% of women (n = 5), which was associated with prior infection ($P = 0.02$) or high balloon fill volume (> 70 cc) as a continuous variable ($P = 0.002$). Asymptomatic seromas were noted on mammogram in 13% of cases (n = 6) and also associated with higher fill volume ($P = 0.01$). Although grade 2 seromas were not evident in long-term follow-up, 1 patient (2%) experienced symptomatic fat necrosis. Grade 1 or 2 telangiectasia were seen in 22% and 9% (n = 10, 4) of cases, whereas most women (64%) had some level of fibrosis on exam (grade 1, 32%; grade 2, 32%; n = 16, each). Other grade 2 skin toxicities were minimal (4%). Two of the 3 previously reported symptomatic rib fractures in this patient cohort (grade 2, n = 3, 7%) resolved with nonsurgical management, with 1 case requiring additional long-term narcotic analgesic medication.

There were no IBTRs or RNFs (6 y IBTR/RNF rate 0%) (Table 4); however, 2 patients experienced DM (4% at 6 y). The 6-year actuarial DFS, CSS, and OS were 96%, 100%, and 93%, respectively. For the 2 patients who developed DM, 1 was N0 and 1 was N1 at diagnosis. Both of these patients are alive and have not had progression of disease aside from their initial metastasis. The 3 patients who died (OS 93%) did not die from breast cancer and had no evidence of disease at the time of their death. Reasons for assignment to the ASTRO Consensus Statement "cautionary" group included age between 50 and 59, ER negative histology, or close margin, whereas "unsuitable" assignment (9%) was for young age and lymph node positivity.

TABLE 1. Patient/Tumor-related Characteristics (Current Trial, N = 45)

Characteristics	Findings (n [%])
Age (y)	
Median	66
Range	48-83
Race	
African American	6 (13)
White	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)

ER indicates estrogen receptor; PR, progesterone receptor.

Although a majority of patients included in this trial had a "cautionary" or "unsuitable" demographic or histologic feature, the clinical outcomes were excellent and ASTRO CS grouping did not correlate with local/regional recurrence (no events) or DM ($P = 0.31$).

DISCUSSION

In this analysis, we have demonstrated excellent treatment efficacy using a hypofractionated accelerated partial breast technique for early-stage invasive breast cancer as part of breast conserving therapy. Despite several adverse pathologic features including many included patients with younger age (50 to 59), high-grade histology, and ER negative receptor status, clinical outcomes from our trial show no IBTRs or RNFs with a median follow-up of 6 years. In addition, nodal involvement did not predict for DM or disease-related death in this cohort of patients. When compared with other reports on APBI in the literature, our series seems to match reported rates of local, regional, and distant control (Table 5).

An important feature about this trial, aside from the excellent local control, is that we have demonstrated the ability to safely deliver HDR brachytherapy to the breast with acceptable side effects in only 2 days. Before this study, APBI had been traditionally delivered using 8 to 10 fractions over a period of 4 to 5 days. Although shorter than either hypofractionated or standard WBI, a standard APBI fractionation pattern of 5 days typically requires a patient to keep the APBI applicator in the breast over at least one weekend (which may place a patient at risk for added complications) and can create

TABLE 2. Treatment-related Characteristics (Current Trial, N = 45)

Characteristics	Findings (n [%])
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)
Trochar 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	
1	35 (78)
3	9 (20)
5	1 (2)

SET indicates scar entry technique.

inconvenience for women who work or live at an extended distance from a radiation oncology center.

In contrast to intraoperative radiotherapy (IORT), hypofractionated APBI offers clinicians and patients distinct advantages including a known margin and lymph node status (before treatment) as well as a biologically effective dose similar to WBI,[27] whereas still allowing the option to complete therapy within the same week of surgery. In the case of a close or positive surgical margin, patients being treated with hypo-APBI can still be appropriately managed with reexcision of the circumferential cavity or only the margin in question. For patients receiving IORT with a positive or close margin, the delivered dose becomes (in many cases) a boost treatment and the case is converted to external beam radiotherapy requiring at an additional 3 to 5 weeks of therapy to the entire breast (even if disease is limited to the perilumpectomy site).

An additional significant advantage of this hypo-APBI technique is the ability to accurately demonstrate (using image guidance) the delivery of an accurate radiation dose to the target volume (dosimetric verification). Some of the current IORT techniques have significant limitations in the ability to

TABLE 3. Chronic Toxicities (Current Trial, N = 43)

	n (%)			
Toxicity	**None**	**Grade 1**	**Grade 2**	**Grade 3**
Hyperpigmentation	28 (65)	14 (33)	1 (2)	0 (0)
Hypopigmentation	28 (88)	5 (12)	0 (0)	0 (0)
Telangiectasia	28 (65)	10 (23)	4 (9)	1 (2)
Induration (fibrosis)	15 (34)	14 (33)	14 (33)	0 (0)
Seroma	37 (86)	6 (14)	0 (0)	0 (0)
Fat necrosis	39 (91)	3 (7)	1 (2)	0 (0)
Breast pain	29 (67)	13 (30)	1 (2)	0 (0)
Breast edema	36 (84)	7 (16)	0 ()	0 (0)
Rib fracture	42 (93)	0 (0)	1 (2)	0 (0)

TABLE 4. Clinical Outcomes (Current Trial, N = 45)

	Control Rate (n [%])
Ipsilateral breast tumor recurrence	0 (0)
Regional nodal failure	0 (0)
Distant metastasis	2 (4)
Disease-free survival	43 (96)
Cause-specific survival	45 (100)
Overall survival	42 (93)

demonstrate (objectively) that the target volume received the prescribed dose. This, in part, may be one of the factors responsible for the suboptimal results recently reported in published phase III trials testing IORT (see below). In the past 3 years, the 2 largest series of patients treated with IORT (TARGIT-A and ELIOT) have reported higher rates of local recurrence as compared with standard WBI.[13,25] In contrast, the initial Phase III trials comparing image-guided APBI (with a suitable biologic dose) to WBI have shown equivalent rates of local control.[6–9]

With regard to toxicities, this trial demonstrates stability and improvement in chronic toxicities over time following applicator-based brachytherapy using a 2-day fractionation pattern. Most notably, the rate of asymptomatic seromas detected by mammography in our prior analysis was 42%,[15] which has now decreased to 13% of patients. As previously reported, some side effects with this dose-fractionation schedule have been slightly higher than expected including skin hyperpigmentation in some patients and rib fractures in 3 women within 18 months of treatment. A partial explanation of this is that the breast brachytherapy device available at the time of this trial was a single-lumen, balloon-based system. Although this catheter has provided excellent outcomes for thousands of women,[23] cases with close skin or chest wall spacing may benefit from dose modulation using a traditional interstitial implant, multilumen balloon,[28] or strut-based applicator.[29] Previously under-appreciated dose constraints of the skin and chest wall (Dmax <100% and 125%, respectively) are now routinely employed in both hypofractionated and standard APBI cases in the United States. When contrasted to other published reports of cosmesis and chronic toxicities (Tables 6, 7), this trial favors well especially when the novel, high-dose fractionation scheme is considered.

Patient selection for APBI continues to be challenged despite respectable prospective and retrospective outcomes from both single and multi-institutional studies. Although our series did not identify any ipsilateral or regional nodal recurrences, commonly reported rates of IBTR range from 2% to 4% following breast conserving surgery and APBI.[2–6,15] The frequently cited ASTRO consensus statement groups for APBI have been retrospectively evaluated by multiple investigators and, although created with good intent, have not been demonstrated to predict for higher rates of IBTR following APBI.[24,32,33] The only factor that has been associated with higher rates of ipsilateral recurrence has been ER negative histology,[33] although this has not been universal.[34] When applied to our patient cohort, the ASTRO CS groups were not able to distinguish patients at higher risk for ipsilateral recurrence (no events), regional relapse within the axilla (no events), or DM ($P = 0.31$). In addition to patient selection, the decision of whether to withhold adjuvant radiotherapy in older women is often considered. Although there has been a push to omit breast radiotherapy for women over the age of 70 based on results of the randomized trial by Hughes et al,[35] many

TABLE 5. Treatment Outcomes for Standard and Hypofractionated APBI Regimens (5 Years)

	n	IBRT (%)	EF (%)	RNF (%)	CF (%)	DM (%)
2-day hypo-APBI trial (current analysis)	45	0	0	0	—	4
King et al[1]	51	2	—	6	—	—
Vicini et al[18]	199	1	0.6	—	—	—
Vicini et al[19]	1449	3.7	2.7	0.6	1.9	2.2
Rabinovitch et al[20] (RTOG 95-17)	98	—	—	—	—	—
Rodriguez et al[7]	102	0	—	0	—	0
Mózsa et al[21]	44	3.7	0	0	0	0
Galland-Girodet et al[22]	98	4.0	—	—	—	—
Shah et al[23]	1449	2.8	2.0	—	1.5	1.8
Wilkinson et al[24]	2127	2.8	1.9	0.6	1.7	1.6
Veronesi et al[25] (ELIOT)	651	4.4	—	—	—	—
Vargo et al[26]	157	2.5	—	1.9	—	0.6
Vaidya et al[13] (TARGIT)	1721	3.3	—	<2	—	—
Meattini et al[8]	117	1.9	—	—	—	—
Stmad et al[9] (GEC-ESTRO)	633	1.4	—	0.5	0.8	0.8

CF indicates contralateral failure; DM, distant metastasis; EF, elsewhere failure; IBTR, ipsilateral breast tumor recurrence; RNF, regional/nodal failure.

breast cancer physicians (and patients) would agree that a double-digit likelihood of local recurrence at 10 years remains high. In fact, including radiotherapy for patients over the age of 70 reduces the risk of subsequent mastectomy between 4% and 10% at 10 years, especially in patients with high-grade cancers.[36] An alternative to observation in these women would be hypofractionated APBI such as the technique used in this trial with a modern breast brachytherapy device. At the current time, the American Brachytherapy Society (ABS) has published updated guidelines suggesting APBI as an appropriate adjuvant treatment modality for women over the age of 50 with small tumors and adequate margins.[37]

Limitations of this study include the small sample size and the single-institutional design of this trial. Following the initial publication of 2-year outcomes, a multi-institution 2-day trial (Contura Overnight Trial) was developed and completed accrual of the initial dose level. In addition, a 3-fraction, multi-institutional phase II APBI trial (TRIUMPH: TRI-fraction Radiotherapy Utilized to Minimize Patient Hospital Trips) was initiated in 2015 using the either a multilumen balloon or strut-based partial breast applicator.[38] Combined analysis of these results and the eventual testing as part of a national cooperative group trial would add strength to the validity of this dose-fractionation schedule. An additional hurdle in the adoption of a 2-day APBI dose regimen may include reduced reimbursement and the general trend of declining use of interstitial breast brachytherapy. Reimbursement for radiation oncology services in the United States is currently based on the total number of fractions of brachytherapy; thus, a reduction in the number of fractions from 10 to 4 without a bundled payment solution for hypofractionated regimens will make this dose pattern more difficult to implement.

Although not often discussed, an effective treatment is 1 where patients are willing to comply with and has the least disruption upon both their professional and private lives. Abbreviated treatment schedules, such as the 1 tested in this trial, allow patients to return to their lives earlier than standard fractionation pattern and, in the case of patients at extended distance from a radiotherapy center, may be the difference between completing breast conserving therapy versus forgoing adjuvant radiotherapy all together. Also, from a health care system cost perspective, fewer total fractions will mean less interaction with health care personnel during treatment. Because hypofractionated APBI requires fewer radiation oncology center visits, staff resources are made available for other patients, which should reduce cost at a system level (or make resources more available if they are scarce). An additional theoretical benefit of this fractionation pattern is

TABLE 6. Comparison of Internal Chronic Toxicities (At 5 Years)

	n	Seroma	Rib Fracture	Breast Pain	Fat Necrosis
2-day hypo-APBI phase I/II trial (current analysis)	43	14 (G1)	2 (G2)	30 (G1) 2 (G2)	7 (G1) 2 (G2)
Chen et al[30]	199	—	—	8 (G1) 1 (G2)	11 (G2)
Vicini et al[18]	1449	28 (G1) 13 (G2)	—	—	2.3
Khan et al[31]	1449	0.2	0	0	—
Shah et al[23]	1449	3.1 (G1) 0.6 (G2)	—	—	2.5
Rodriguez et al[7]	102	—	—	—	—
Mózsa et al[21]	44	—	—	2.3	14.0
Galland-Girodet et al[22]	98	—	—	15 (G2-G3)	11.0
Rabinovitch et al[20] (RTOG 95-17)	98	—	—	—	—
Vargo et al[26]	157	—	2.9	—	11.5
Meattini et al[8]	117	—	—	—	—
Stmad et al[9] (GEC-ESTRO)	633	—	—	1.1 (G2-G3)	—

TABLE 7. Comparison of Cosmesis and Skin-related Toxicities (At 5 Years)

	n	Excellent/Good Cosmesis	Induration (Fibrosis)	Erythema	Hyper/ HypoPigmentation	Telan-giectasia
2-day hypo-APBI phase I/II trial *(current analysis)*	43	91	33 (G1) 33 (G2)	0	45 (G1) 2 (G2)	23 (G1) 9 (G2) 2 (G3)
Chen et al[30]	199	99	46 (G1) 5 (G2) 1 (G3)	11.0	37.0	34 (G1) 1 (G2)
Vicini et al[19]	1449	91	—	—	—	—
Khan et al[31]	1449	—	0.3	—	38.0	—
Rabinovitch et al[20] (RTOG 95-17)	98	66	45.6	4.4	15.3	45.6
Rodriguez et al[7]	102	100	10 decreased elasticity	All skin effects: 11 (G1)		
Shah et al[23]	1449	91	—	—	—	13.0
Mózsa et al[21]	44	86	44.2 (G1) 7 (G2) 2.3 (G3-4)	—	11.6	—
Galland-Girodet et al[22]	98	88	—	—	22 (G2-G3)	20.0
Vargo et al[26]	157	93	—	—	—	33.4 (G1) 11.8 (G2)
Meattini et al[8]	117	90	2	—	—	—
Stmad et al[9] (GEC-ESTRO)	633	—	0 (G3)	—	—	—

G1, G2, G3 indicate Grades 1, 2, 3.

pairing a larger fraction size to the lower α-β ratio for carcinoma of the breast, which could contribute to a higher rate of tumor control probability. The encouraging results reported in our updated analysis, especially in light of the recently released results of the GEC-ESTRO randomized trial,[9] should make an APBI program using either a standard or hypofractionated dosing schedule (likely as part of a clinical trial) desirable at many centers.

CONCLUSIONS

Hypofractionated APBI using a 2-day dose/fractionation pattern is a safe and effective method to deliver adjuvant radiotherapy as part of breast conservation with acceptable toxicities that are comparable with 5-day treatment. Modern APBI devices including multilumen and strut-based applicators may allow for reduced toxicity using hypofractionated regimens. Additional study of hypofractionated APBI is warranted and currently ongoing.

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