

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 ≥ 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 ≤ 5 days with twice-daily brachytherapy³ 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 ≤ 3 cm, ≤ 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 ≥ 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 1 or 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 Statement¹⁷ 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 an additional 3 to 5 weeks of therapy to the entire breast (even if disease is limited to the peritumpectomy 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)

Toxicity	n (%)			
	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 (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	Telangiectasia
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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REFERENCES

- King TA, Bolton JS, Kuske RR, et al. Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for T(is,1,2) breast cancer. *Am J Surg.* 2000;180:299–304.
- Vicini FA, Chen PY, Fraile M, et al. Low-dose-rate brachytherapy as the sole radiation modality in the management of patients with early-stage breast cancer treated with breast-conserving therapy: preliminary results of a pilot trial. *Int J Radiat Oncol Biol Phys.* 1997;38:301–310.
- Benitez PR, Keisch ME, Vicini F, et al. Five-year results: the initial clinical trial of MammoSite balloon brachytherapy for partial breast irradiation in early-stage breast cancer. *Am J Surg.* 2007;194:456–462.
- Baglan KL, Sharpe MB, Jaffray D, et al. Accelerated partial breast irradiation using 3D conformal radiation therapy (3D-CRT). *Int J Radiat Oncol Biol Phys.* 2003;55:302–311.

- Shah C, Antonucci JV, Wilkinson JB, et al. Twelve-year clinical outcomes and patterns of failure with accelerated partial breast irradiation versus whole-breast irradiation: results of a matched-pair analysis. *Radiother Oncol.* 2011;100:210–214.
- Polgár C, Fodor J, Major T, et al. Breast-conserving treatment with partial or whole breast irradiation for low-risk invasive breast carcinoma - 5-year results of a randomized trial. *Int J Radiat Oncol Biol Phys.* 2007;69:694–702.
- Rodriguez N, Sanz X, Dengra J, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys.* 2013;87:1051–1057.
- Meattini I, Saieva C, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy technique compared to whole breast irradiation for patients 70 years and older: subgroup analysis from a randomized phase 3 trial. *Breast Cancer Res Treat.* 2015;153:539–547.
- Stmad V, Ott OJ, Hildebrandt G, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase-3, non-inferiority trial. *Lancet.* 2016;387:229–238.
- Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.* 2013;14:1086–1094.
- Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med.* 2010;362:513–520.
- Veronesi U, Orecchia R, Luini A, et al. Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons. *Breast Cancer Res Treat.* 2010;124:141–151.
- Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomized trial. *Lancet.* 2014;383:603–613.
- Wallace M, Martinez A, Mitchell C, et al. Phase I/II study evaluating early tolerance in breast cancer patients undergoing accelerated partial breast irradiation treated with the mammosite balloon breast brachytherapy catheter using a 2-day dose schedule. *Int J Radiat Oncol Biol Phys.* 2010;77:531–536.

15. Wilkinson JB, Martinez AA, Chen PY, et al. Four-year results using balloon-based brachytherapy to deliver accelerated partial breast irradiation with a 2-day dose fractionation schedule. *Brachytherapy*. 2012;11:97–104.
16. Harris JR, Levene MB, Svensson G, et al. Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. *Int J Radiat Oncol Biol Phys*. 1979;5:257–261.
17. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys*. 2009;74:987–1001.
18. Vicini FA, Kestin L, Chen PY, et al. Limited-field radiation therapy in the management of early-stage breast cancer. *J Natl Cancer Inst*. 2003;95:1205–1210.
19. Vicini FA, Beitsch P, Quiet C, et al. Five-year analysis of treatment efficacy and cosmesis by the American Society of Breast Surgeons MammoSite® breast brachytherapy registry trial in patients treated with accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys*. 2011;79:808–817.
20. Rabinovitch R, Winter K, Kuske R, et al. RTOG 95-17, a phase II trial to evaluate brachytherapy as the sole method of radiation therapy for stage I and II breast carcinoma—year-5 toxicity and cosmesis. *Brachytherapy*. 2014;13:17–22.
21. Mózsai E, Mészáros N, Major T, et al. Accelerated partial breast irradiation with external beam three-dimensional conformal radiotherapy. Five-year results of a prospective phase II clinical study. *Strahlenther Onkol*. 2014;190:444–450.
22. Galland-Girodet S, Pashtan I, MacDonald S, et al. Long-term cosmetic outcomes and toxicities of proton beam therapy compared with photon-based 3-dimensional conformal accelerated partial-breast irradiation: a phase I trial. *Int J Radiat Oncol Biol Phys*. 2014;90:493–500.
23. Shah C, Badiyan S, Wilkinson JB, et al. Treatment efficacy with accelerated partial breast irradiation (APBI): final analysis of the American Society of Breast Surgeons MammoSite(®) breast brachytherapy registry trial. *Ann Surg Oncol*. 2013;20:3279–3285.
24. Wilkinson JB, Beitsch PD, Shah C, et al. Evaluation of current consensus statement recommendations for accelerated partial breast irradiation: a pooled analysis of William Beaumont Hospital and American Society of Breast Surgeon MammoSite Registry Trial Data. *Int J Radiat Oncol Biol Phys*. 2013;85:1179–1185.
25. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol*. 2013;14:1269–1277.
26. Vargo JA, Verma V, Kim H, et al. Extended (5-year) outcomes of accelerated partial breast irradiation using MammoSite balloon brachytherapy: patterns of failure, patient selection, and dosimetric correlates for late toxicity. *Int J Radiat Oncol Biol Phys*. 2014;88:285–291.
27. Khan AJ, Dale RG, Arthur DW, et al. Ultrashort courses of adjuvant breast radiotherapy: wave of the future or a fool's errand? *Cancer*. 2012;118:1962–1970.
28. Shah C, Ghilezan M, Arthur D, et al. Initial clinical experience with multilumen brachytherapy catheters for accelerated partial breast irradiation. *Brachytherapy*. 2012;11:369–373.
29. Yashar CM, Scanderbeg D, Kuske R, et al. Initial clinical experience with the Strut-Adjusted Volume Implant (SAVI) breast brachytherapy device for accelerated partial-breast irradiation (APBI): first 100 patients with more than 1 year of follow-up. *Int J Radiat Oncol Biol Phys*. 2011;80:765–770.
30. Chen PY, Vicini FA, Benitez P, et al. Long-term cosmetic results and toxicity after accelerated partial-breast irradiation. *Cancer*. 2006;106:991–999.
31. Khan AJ, Arthur D, Vicini F, et al. Six-year analysis of treatment-related toxicities in patients treated with accelerated partial breast irradiation on the American society of breast surgeons MammoSite(®) breast brachytherapy registry trial. *Ann Surg Oncol*. 2012;19:1477–1483.
32. Vicini FA, Arthur D, Wazer DE, et al. Limitations of the American Society of Therapeutic Radiology and Oncology Consensus Panel guidelines on the use of accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys*. 2011;79:977–984.
33. Shaitelman SF, Vicini FA, Beitsch P, et al. Five-year outcome of patients classified using the American Society for Radiation Oncology consensus statement guidelines for the application of accelerated partial breast irradiation: an analysis of patients treated on the American Society of Breast Surgeons MammoSite Registry Trial. *Cancer*. 2010;116:4677–4685.
34. Wilkinson JB, Reid RE, Shaitelman SF, et al. Outcomes of breast cancer patients with triple negative receptor status treated with accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys*. 2011;81:e159–e164.
35. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol*. 2013;31:2382–2387.
36. Albert JM, Pan IW, Shih YC, et al. Effectiveness of radiation for prevention of mastectomy in older breast cancer patients treated with conservative surgery. *Cancer*. 2012;118:4642–4651.
37. Shah C, Vicini F, Wazer DE, et al. The American Brachytherapy Society consensus statement for accelerated partial breast irradiation. *Brachytherapy*. 2013;12:267–277.
38. Rutgers, The State University of New Jersey; National Cancer Institute. Accelerated partial breast radiation therapy using high-dose rate brachytherapy in treating patients with early stage breast cancer after surgery (TRIUMPH-T). *ClinicalTrials.gov [Internet]*. Bethesda (MD): National Library of Medicine (US); 2000. Available at: <https://clinicaltrials.gov/ct2/show/NCT02526498?term=TRI-fraction+Radiotherapy+Utilized+to+Minimize+Patient+Hospital+Trips&rank=1> NLM Identifier: NCT02526498. Accessed November 1, 2015.