

Clinical Investigation: Breast Cancer

Accelerated Partial Breast Irradiation With Low-Dose-Rate Interstitial Implant Brachytherapy After Wide Local Excision: 12-Year Outcomes From a Prospective Trial

Jona A. Hattangadi, M.D.,^{*} Simon N. Powell, M.D., Ph.D.,[†]
Shannon M. MacDonald, M.D.,[‡] Thomas Mauceri, M.S.,[‡] Marek Ancukiewicz, Ph.D.,[‡]
Phoebe Freer, M.D.,[§] Brian Lawenda, M.D.,[¶] Mohamed A. Alm El-Din, M.D.,^{†, #}
Michele A. Gadd, M.D.,^{||} Barbara L. Smith, M.D., Ph.D.,^{||} and
Alphonse G. Taghian, M.D., Ph.D.[‡]

^{}Harvard Radiation Oncology Program, Boston, MA; [†]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY; Departments of [‡]Radiation Oncology, [§]Radiology, and ^{||}Surgical Oncology, Massachusetts General Hospital, Boston, MA; [¶]21st Century Oncology, Las Vegas, NV; and [#]Department of Clinical Oncology, Tanta University Hospital, Tanta, Egypt*

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Summary

We report 12-year outcomes from a prospective, dose-escalating phase I/II trial of low dose rate (LDR) interstitial implant brachytherapy (IB) alone after wide local excision for T1N0 breast cancer. LDR IB provides acceptable local control in select patients, but higher doses are associated with worse long-term treatment-related toxicity and cosmesis.

Purpose: To evaluate the long-term toxicity, cosmesis, and local control of accelerated partial breast irradiation with implant brachytherapy after wide local excision for Stage T1N0 breast cancer (BCa).

Materials and Methods: Between 1997 and 2001, 50 patients with Stage T1N0M0 BCa were treated in a Phase I-II protocol using low-dose-rate accelerated partial breast irradiation with implant brachytherapy after wide local excision and lymph node surgery. The total dose was escalated in three groups: 50 Gy (n = 20), 55 Gy (n = 17), and 60 Gy (n = 13). Patient- and physician-assessed breast cosmesis, patient satisfaction, toxicity, mammographic abnormalities, repeat biopsies, and disease status were prospectively evaluated at each visit. Kendall's tau (τ_b) and logistic regression analyses were used to correlate outcomes with dose, implant volume, patient age, and systemic therapy.

Results: The median follow-up period was 11.2 years (range, 4–14). The patient satisfaction rate was 67%, 67% reported good-excellent cosmesis, and 54% had moderate-severe fibrosis. Higher dose was correlated with worse cosmetic outcome (τ_b 0.6, $p < .0001$), lower patient satisfaction (τ_b 0.5, $p < .001$), and worse fibrosis (τ_b 0.4, $p = .0024$). Of the 50 patients, 35% had fat necrosis and 34% developed telangiectasias ≥ 1 cm². Grade 3–4 late skin and subcutaneous toxicities were seen in 4 patients (9%) and 6 patients (13%), respectively, and both correlated with higher dose (τ_b 0.3–0.5, $p \leq .01$). One patient had Grade 4 skin ulceration and

Reprint requests to: Alphonse G. Taghian, M.D., Ph.D., Department of Radiation Oncology, Massachusetts General Hospital, 100 Blossom St., Boston, MA 02114. Tel: (617) 726-6050; Fax: (617) 726-3603; E-mail: ataghian@partners.org

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fat necrosis requiring surgery. Mammographic abnormalities were seen in 32% of the patients, and 30% underwent repeat biopsy, of which 73% were benign. Six patients had ipsilateral breast recurrence: five elsewhere in the breast, and one at the implant site. One patient died of metastatic BCa after recurrence. The 12-year actuarial local control, recurrence-free survival, and overall survival rate was 85% (95% confidence interval, 70–97%), 72% (95% confidence interval, 54–86%), and 87% (95% confidence interval, 73–99%), respectively.

Conclusion: Low-dose-rate accelerated partial breast irradiation with implant brachytherapy provides acceptable local control in select early-stage BCa patients. However, treatment-related toxicity and cosmetic complications were significant with longer follow-up and at higher doses. © 2012 Elsevier Inc.

Keywords: Accelerated partial breast irradiation, Implant brachytherapy, Early-stage breast cancer, Low-dose-rate, Long-term cosmesis

Introduction

Accelerated partial breast irradiation (APBI) is an alternative to whole breast irradiation for early-stage breast cancer (BCa), involving treatment to only the involved portion of breast over a shorter time period (1). APBI has several modalities—interstitial implant brachytherapy, balloon-brachytherapy devices, highly conformal external beam techniques, and intraoperative radiotherapy. APBI with interstitial implant brachytherapy (APBI-IB) was the first of these and has the most mature data.

Randomized clinical trials investigating the effectiveness and safety of APBI compared with whole breast irradiation are ongoing, but the long-term results are not yet available (1). Several Phase I-II APBI-IB studies using high-dose-rate (HDR) or low-dose-rate (LDR) techniques have been published (1–11). In 1997, we initiated a dose-escalating prospective Phase I-II protocol using LDR APBI-IB after wide local excision for patients with Stage T1N0M0 invasive BCa. The rationale for dose escalation was based on evidence from the European Organization for Research and Treatment of Cancer breast boost trial showing that a higher dose might improve local control (12). Detailed dose–volume analyses of the toxicities and outcomes at 23 months of follow-up were previously published (12). Herein, we report the complete and updated results of this study with extended median follow-up of 134 months (11.2 years).

Methods and Materials

Patient and tumor characteristics

Between 1997 and 2001, 50 patients with Stage T1N0M0 BCa were treated on an institutional review board-approved Phase I-II protocol using LDR APBI-IB after wide local excision and lymph node surgery. The study details, including eligibility criteria, were described previously (12). The patient and tumor characteristics are listed in Table 1.

Treatment

At definitive wide local excision or re-excision, 16-gauge flexible catheters were inserted, evenly spaced 1–1.5-cm apart, through the target volume (12). Placement depended on the breast geometry, and the catheters were not necessarily aligned in different

planes. A median of 14 catheters (range, 10–17) were placed in three planes. The target volume included a 3-cm circumferential margin around the tumor cavity with full breast thickness in the anteroposterior direction (12).

Orthogonal X-rays were used to reconstruct three-dimensional images of the catheters for dose planning. A computer model determined ribbon placement and activities for adequate coverage of the planning target volume and homogeneous dose distribution. Three days after planning, LDR iridium-192 ribbons, with 1.0-cm seed spacing were loaded. The dose rate was 0.5 Gy/h prescribed to an isodose volume ≥ 0.5 cm around the implanted area in a plane through the center of the implant and perpendicular to the direction of the catheters. Total dose was escalated in three cohorts: 50 Gy in 20 patients, 55 Gy in 17 patients, and 60 Gy in 13 patients. According to the linear quadratic model, with an α/β ratio of 3 Gy and tissue repair half-time of 3 h for late effects (13), this translated to corresponding biologically effective doses for late effects of 118, 131, and 143 Gy, respectively. For local control (α/β ratio of 10 Gy), the corresponding biologically effective doses were 71, 78, and 85 Gy, respectively. The goal for patient accrual was ≥ 15 patients in each dose group; however, only 13 patients were accrued to the 60-Gy dose group.

Acute complications and toxicities were monitored closely. There was no second planning session after treatment initiation to account for catheter displacement. Adjuvant systemic therapy was given at the discretion of the treating physician (Table 1).

Prospective follow-up and evaluation

The patients were seen in follow-up after 6 weeks, 6 months, and 12 months of treatment and yearly thereafter. At each visit, the physician (radiation and/or surgical oncologist) completed a detailed questionnaire (12) on cosmesis, edema, breast pain, pigmentation changes, fibrosis, fat necrosis, telangiectasias, and late skin and subcutaneous tissue toxicity. Breast imaging and pathologic findings were reviewed for disease status and local recurrence. Patients also reported on cosmesis, treatment satisfaction, breast size and swelling, breast pain, pigmentation changes, and fibrosis. Questionnaires were based on those used in the Radiation Therapy Oncology Group 95-17 study (6). Skin and subcutaneous tissue toxicities were scored according to the Radiation Therapy Oncology Group morbidity schema, and telangiectasias according to the Late Effects Normal Tissue Task Force (14).

Table 1 Baseline patient and treatment characteristics (*n* = 50)

Characteristic	No. of patients (%)
Age (y)	
Median	60
Range	35–82
Race	
White	48 (96)
Black	1 (2)
Asian	1 (2)
Menopause status	
Premenopausal	6 (12)
Perimenopausal	6 (12)
Postmenopausal	38 (76)
Histologic feature	
IDC	42 (84)
Mucinous	4 (8)
ILC	3 (6)
Tubular	1 (2)
Grade	
1	23 (46)
2	19 (38)
3	7 (14)
Unknown	1 (2)
Margin status	
Negative (>2 mm)	46 (92)
DCIS near (<2 mm) margin	4 (8)
ER status	
Positive	40 (80)
Negative	4 (8)
Unknown	6 (12)
PR status	
Positive	39 (78)
Negative	4 (8)
Unknown	6 (12)
HER-2neu status	
Positive	3 (6)
Negative	16 (33)
Unknown	30 (61)
Lymph node surgery	
SLN biopsy	14 (28)
AxLND	36 (72)
APBI-IB dose (Gy)	
50	20 (40)
55	17 (34)
60	13 (26)
Implant volume (cm ³)	
61–127	11 (22)
128–164	13 (26)
165–203	13 (26)
≥204	13 (26)
Systemic treatment	
None	7 (14)
CMT	1 (2)
HT	41 (82)
CMT + HT	1 (2)

Abbreviations: IDC = infiltrating ductal carcinoma; ILC = infiltrating lobular carcinoma; ER = estrogen receptor; PR = progesterone receptor; SLN = sentinel lymph node; AxLND = axillary lymph node dissection; CMT = chemotherapy; HT = hormonal therapy.

Baseline mammograms were performed within 6 months after APBI-IB, every 6 months for 60 months, and yearly thereafter. For suspicious lesions, the decision to biopsy (repeat biopsy) was based on interpretation of the mammogram and discussion by the radiologist, surgical oncologist, and radiation oncologist.

Outcomes and statistical analysis

Cosmetic outcomes and toxicities were recorded using ordinal scales. Kendall's tau (τ_b) coefficient was used to evaluate the nonparametric correlation between these variables and total dose and implant volume. Kendall's tau (sb) coefficient was also used to examine the correlation between patient and physician assessments. The correlations were tested using Kendall's test of $\tau_b = 0$. Next, ordinal logistic regression analysis was used to study the effect of age and systemic therapy on the outcomes, accounting for dose or implant volume if significant on the univariate analysis. For patients who underwent mastectomy, the evaluations immediately preceding mastectomy were used for the analyses. For 37 patients, the treatment plans were unarchived, and skin and subcutaneous doses estimated at 1 cm and 1.5 cm from the most superficial catheters. These values were tested for correlation with cosmetic and toxicity outcomes. Cox regression analysis was used to test the association between clinical outcomes (overall survival [OS], recurrence-free survival [RFS], and local control [LC]) and dose and implant volume.

Ipsilateral breast tumor recurrence (IBTR) was defined as histologic confirmation of cancer in the treated breast. Each IBTR was reviewed by a dedicated breast radiologist (PF) and defined as elsewhere if it was ≥ 5 cm from the primary site. The actuarial rates of LC, RFS, and OS were estimated using the Kaplan-Meier method. Patient death and mastectomy competed with IBTR in analyses of LC and RFS. All intervals were from the date of APBI-IB catheter placement. A *p* value $< .05$ established statistical significance, and all statistical tests were two-sided. The R project for statistical computing (r-project.org) was used for the analyses.

Results

Acute/subacute complications

The median follow-up was 134 months (range, 43–167). Most patients (*n* = 40, 80%) experienced no acute treatment complications. Four patients had mild erythema or edema at the catheter site that resolved within 2 weeks. Three patients had hematomas in the implant site after catheter removal requiring cautery or surgical evacuation. Two patients experienced subacute fibrosis and inflammation in the catheter site after 8 months, and one developed an abscess at the catheter site 10 months after treatment requiring incision and drainage. No correlation was found between the acute/subacute complications and the implant volume or dose.

Long-term results: cosmesis and toxicity

Statistically significant correlations were found between patient and physician assessments of cosmesis ($\tau_b = 0.60$, *p* < .0001) and fibrosis ($\tau_b = 0.32$, *p* = .01).

Patient- and physician-reported outcomes and toxicities for all patients and stratified by dose group, with Kendall's τ_b for correlation between outcome and dose are listed in Table 2. The

Table 2 Long-term cosmetic outcomes and treatment-related toxicities: Correlation with dose

Outcome	Dose (Gy)			All patients* (n = 46)	Kendall's $\tau_b^{\dagger}$	p
	50 (n = 19)	55 (n = 16)	60 (n = 11)			
Cosmesis (patient)					0.47	.0003
Excellent	9 (47)	5 (31)	1 (9)	15 (33)		
Good	9 (47)	5 (31)	2 (18)	16 (35)		
Fair	1 (5)	6 (38)	5 (46)	12 (26)		
Poor	0 (0)	0 (0)	3 (27)	3 (7)		
Satisfaction (patient)					0.46	.0009
Total	16 (84)	13 (81)	2 (18)	31 (67)		
Unsatisfied, would choose APBI-IB again	3 (16)	2 (13)	6 (55)	11 (24)		
Unsatisfied, would not choose APBI-IB again	0 (0)	1 (6)	3 (27)	4 (9)		
Breast pain at implant site (patient)					NC	NS
None	13 (68)	14 (88)	8 (73)	35 (76)		
Mild	5 (26)	1 (6)	2 (18)	8 (17)		
Moderate	1 (5)	1 (6)	1 (9)	3 (7)		
Change in breast size (patient)					0.35	.01
Same size	11 (58)	7 (44)	1 (9)	19 (41)		
Different size	8 (42)	9 (56)	10 (91)	27 (59)		
Fibrosis (patient)					0.40	.0024
None	8 (42)	4 (25)	1 (9)	13 (28)		
Mild	6 (32)	5 (31)	1 (9)	12 (26)		
Moderate	5 (26)	6 (38)	6 (55)	17 (37)		
Severe	0 (0)	1 (6)	3 (27)	4 (9)		
Cosmesis (physician)					.59	<.0001
Excellent	6 (32)	1 (6)	0 (0)	7 (15)		
Good	12 (63)	11 (69)	1 (9)	24 (52)		
Fair	1 (5)	4 (25)	8 (73)	13 (28)		
Poor	0 (0)	0 (0)	2 (18)	2 (4)		
Breast edema (physician)					NC	NS
None	17 (90)	15 (94)	9 (82)	41 (89)		
Mild	1 (5)	1 (6)	2 (18)	4 (9)		
Moderate	1 (5)	0 (0)	0 (0)	1 (2)		
Severe	0 (0)	0 (0)	0 (0)	0 (0)		
Breast color change (physician)					NC	NS
None	12 (63)	11 (69)	5 (46)	28 (61)		
Mild	6 (32)	4 (25)	1 (9)	11 (24)		
Moderate	1 (5)	1 (6)	5 (46)	7 (15)		
Severe	0 (0)	0 (0)	0 (0)	0 (0)		
Telangiectasia					NC	NS
None	8 (42)	9 (56)	4 (36)	21 (46)		
<1 cm ²	6 (32)	3 (19)	0 (0)	9 (20)		
1–4 cm ²	5 (26)	4 (25)	5 (46)	14 (30)		
>4 cm ²	0 (0)	0 (0)	2 (18)	2 (4)		
Fibrosis (physician)					0.54	<.0001
None	2 (11)	1 (6)	0 (0)	3 (7)		
Mild	13 (68)	4 (25)	1 (9)	18 (39)		
Moderate	4 (21)	9 (56)	6 (55)	19 (41)		
Severe	0 (0)	2 (13)	4 (36)	6 (13)		
Fat necrosis (physician)					NC	NS
Absent	13 (68)	12 (75)	5 (46)	30 (65)		
Present	6 (32)	4 (25)	6 (55)	16 (35)		
Late skin toxicity (physician)					0.33	.01
None	9 (47)	7 (44)	2 (18)	18 (39)		
Grade 1	5 (26)	5 (31)	0 (0)	10 (22)		
Grade 2	5 (26)	4 (25)	5 (46)	14 (30)		
Grade 3	0 (0)	0 (0)	3 (27)	3 (7)		
Grade 4	0 (0)	0 (0)	1 (9)	1 (2)		

(continued on next page)

Table 2 (continued)

Outcome	Dose (Gy)			All patients* (n = 46)	Kendall's $\tau_B^\dagger$	p
	50 (n = 19)	55 (n = 16)	60 (n = 11)			
Late subcutaneous toxicity (physician)					0.46	.00004
None	8 (42)	5 (31)	0 (0)	13 (28)		
Grade 1	7 (37)	3 (19)	1 (9)	11 (24)		
Grade 2	3 (16)	7 (44)	6 (55)	16 (35)		
Grade 3	1 (5)	1 (6)	3 (27)	5 (11)		
Grade 4	0 (0)	0 (0)	1 (9)	1 (2)		

Abbreviations: NC = not correlated; NS = not significant.

Percentages might not sum to 100 because of rounding.

* Of 50 patients, 46 had completed patient and physician evaluations.

† Kendall's τ_B coefficient for correlation of outcome and total dose: $\tau_B > 0$ positively correlated, $\tau_B < 0$ inversely correlated.

patient- and physician-assessed evaluations were not completed for 4 patients, although they were followed prospectively for disease status. There was no indication that this was related to treatment dissatisfaction or poor outcome. Overall, 67.4% of patients reported good-excellent cosmesis, and 67.4% were totally satisfied with their treatment. Four patients (8.7%) were dissatisfied and reported that they would not choose APBI-IB again. Increasing dose was associated with poorer cosmesis ($\tau_B = 0.47$, $p = .0003$) and worse patient satisfaction ($\tau_B = 0.46$, $p = .0009$). Overall, 58.7% of the patients reported a change in breast size, and a higher dose was associated with a different size ($\tau_B = 0.35$, $p = .01$). Moderate/severe fibrosis

was reported by 45.7% of patients and correlated with higher dose ($\tau_B = 0.40$, $p = .0024$).

The physician-assessed good/excellent cosmesis rate was 67.4%, and higher dose was associated with worse cosmesis. Telangiectasias ≥ 1 cm² were seen in 34.7% of patients with no dose correlation. Physician-assessed moderate/severe fibrosis was seen in 54.3% of patients, and higher dose correlated with worse fibrosis ($\tau_B = 0.54$, $p < .0001$). Radiographic or clinically palpable fat necrosis was documented in 34.7% of the patients. Grade 3–4 late skin and late subcutaneous tissue toxicity developed in 4 patients (8.7%) and 6 patients (13%), respectively; both correlated with higher dose. Implant volume was not significantly

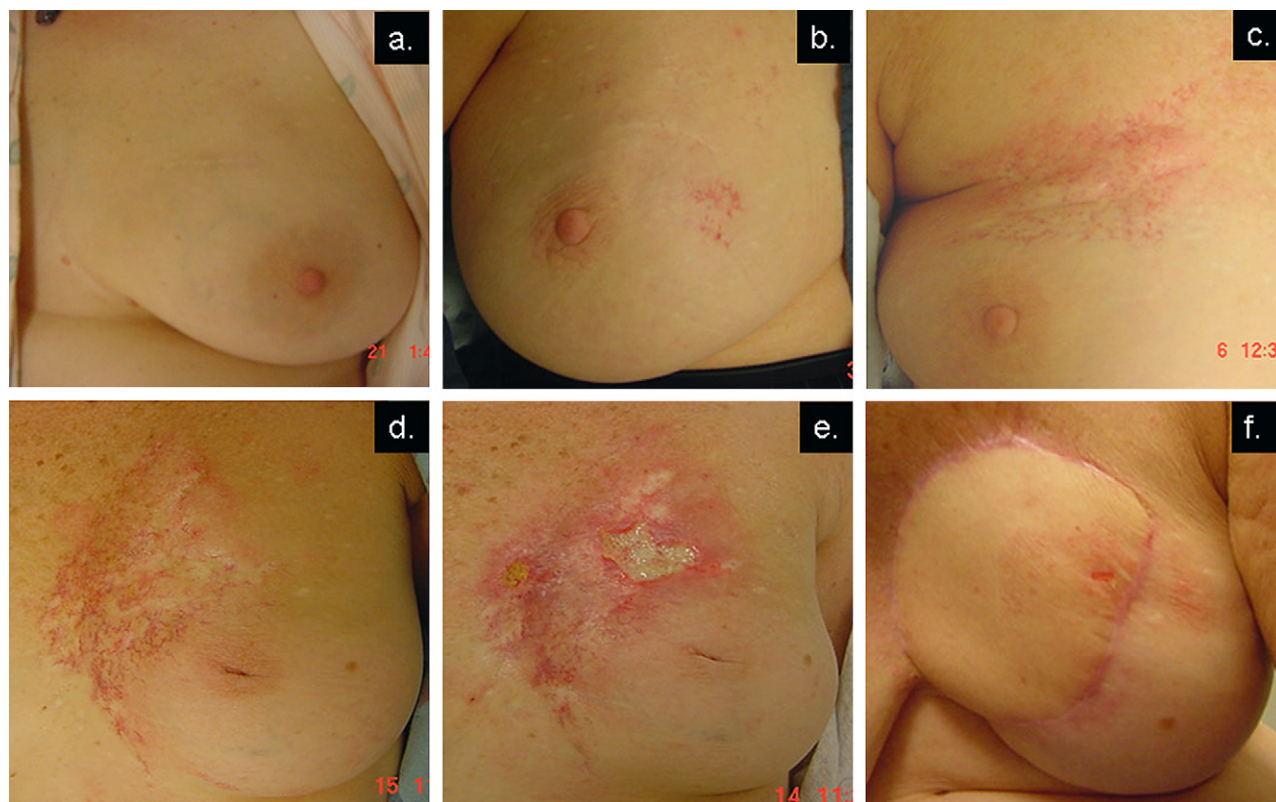


Fig. 1. Patient images showing (a) excellent cosmesis, (b) good cosmesis with mild (Grade 1) telangiectasia, and (c) fair cosmesis with Grade 3 telangiectasia and fibrosis. One patient who received 60 Gy developed Grade 3 skin toxicity at 7 years (d), which progressed to ulceration (Grade 4) at 8 years (e), requiring partial mastectomy and reconstruction with pedicle latissimus myocutaneous flap (f).

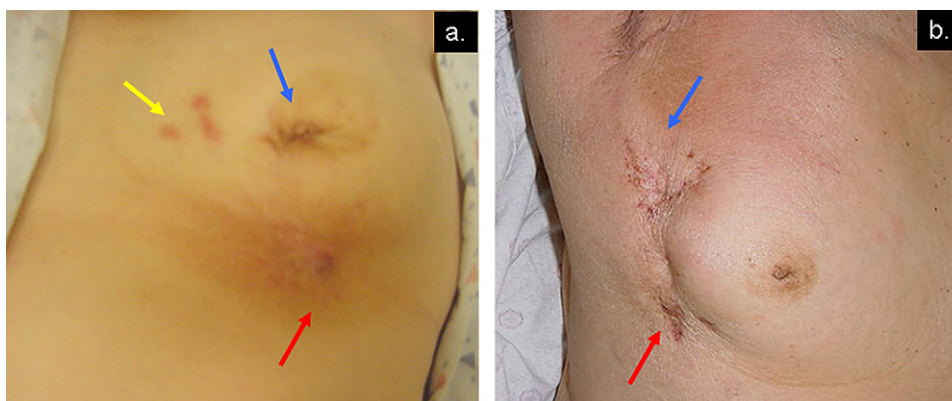


Fig. 2. Ipsilateral breast tumor recurrences. (a) True dermal recurrence at implant site (red arrow), with large tumor burden resulting in nipple inversion (blue arrow), and tumor infiltration through catheter tracts (yellow arrow). (b) Elsewhere recurrence in upper outer quadrant (blue arrow), >6 cm from original primary/implant site (red arrow). Patient refused mastectomy and was treated with lumpectomy and repeat fractionated partial breast irradiation, shown after treatment completion.

correlated with cosmesis or treatment-related toxicity. Figure 1 shows examples of excellent, good, and fair cosmesis and Grade 4 toxicity requiring partial mastectomy.

The median estimated skin/subcutaneous dose at 1 cm and 1.5 cm from the superficial catheters was 43 Gy (range, 35–54) and 32 Gy (range, 27–41), respectively. A higher estimated skin dose at 1.5 cm from the superficial catheters correlated with worse patient satisfaction ($\tau_\beta = 0.30$, $p = .03$), physician-rated cosmesis ($\tau_\beta = 0.36$, $p = .007$), fibrosis ($\tau_\beta = 0.35$, $p = .007$), and late skin toxicity ($\tau_\beta = 0.40$, $p = .002$). A greater estimated dose 1 cm from the superficial catheters correlated with worse patient satisfaction ($\tau_\beta = 0.33$, $p = .014$), fibrosis ($\tau_\beta = 0.32$, $p = .016$), physician-rated cosmesis ($\tau_\beta = 0.37$, $p = .005$), and late subcutaneous toxicity ($\tau_\beta = 0.27$, $p = .035$).

Ordinal logistic regression analyses showed that older age was associated with less breast edema (odds ratio [OR], 0.80; 95% confidence interval [CI], 0.66–0.97; $p = .026$), hyperpigmentation (OR, 0.91; 95% CI, 0.85–0.98; $p = .01$), fibrosis (OR, 0.94; 95% CI, 0.88–1.0; $p = .036$), and late subcutaneous toxicity (OR, 0.94; 95% CI, 0.88–0.99; $p = .024$) after adjusting for dose. Use of chemotherapy or hormonal therapy were not associated with clinical outcomes after accounting for dose.

Mammography and rebiopsy

Sixteen patients (32%) had abnormal mammographic findings during their follow-up period. Of these 16 patients, 15 underwent rebiopsy of the suspicious areas, of which 11 (73.3%) were benign and 4 showed recurrent breast cancer. No correlation was found between the mammographic abnormalities or rebiopsy findings and dose or implant volume. The median interval to the detection of a mammographic abnormality was 41 months (range, 12.2–130). One patient elected mastectomy with reconstruction because of difficulties with fibrosis and several benign rebiopsies of mammographic abnormalities in her treated breast.

Local recurrence and survival outcomes

Six patients (12%) developed IBTR after APBI-IB (12-year actuarial IBTR rate 14.6%). Of these, 1 patient developed a dermal recurrence at the catheter site (Fig. 2a) 117 months after APBI-IB.

Although this was considered a true recurrence, the pathologic findings were different from the primary tumor. Five patients (10%) developed elsewhere recurrences, all were ≥ 5 cm from the primary site. The median interval to elsewhere recurrence was 91.1 months (range, 26.1–131.3). Of the 6 patients with IBTRs, 5 underwent salvage mastectomy but 1 patient refused and underwent repeat lumpectomy and fractionated external beam partial breast irradiation (Fig. 2b). The 12-year actuarial LC rate was 85.4% (95% CI, 70.4–97.3%) and was not associated with radiation dose (Fig. 3a.) Of the 5 patients with elsewhere recurrences, 3 had received 50 Gy and 2 had received 55 Gy. The patient who developed a dermal true recurrence had received 60 Gy APBI-IB. Age, tumor margins, hormone receptor status, estimated skin doses, and systemic therapy use were not associated with IBTR.

Three patients (6%) developed contralateral BCa, with a median interval to detection of 37 months (range, 18.4–115). The 12-year actuarial RFS rate was 71.5% (95% CI, 54.1–86.3%) and also did not vary with the dose (Fig. 3b).

Of the six patients with IBTR, one patient died of metastatic BCa seven years after elsewhere recurrence. One other patient was alive with disease at the last follow-up visit. Overall, 44 patients (88%) were alive with no evidence of disease at the last follow-up visit. Four patients had died of other causes: one of pulmonary fibrosis, one of metastatic colon cancer, and two of congestive heart failure. The 12-year actuarial OS rate was 87% (95% CI, 73.3–99.3%) and did not correlate with dose (Fig. 3c).

Discussion

Given the protracted course and excellent cure rate of early-stage BCa, long-term results from APBI studies are critical in this population. The present dose-escalating Phase I-II study of Stage T1N0M0 BCa patients has the longest follow-up of all published APBI-IB series (134 months). Our results show acceptable local control but a significant rate of treatment-related toxicity and poor cosmetic outcomes at higher doses.

With respect to disease control, only two other studies have reported outcomes at ≥ 10 years. The William Beaumont series reported a 10-year actuarial IBTR rate of 5% (15) and the Hungarian series a 12-year actuarial IBTR of 9.3% (16). Our rate of IBTR was slightly greater than the Hungarian series (Table 3).

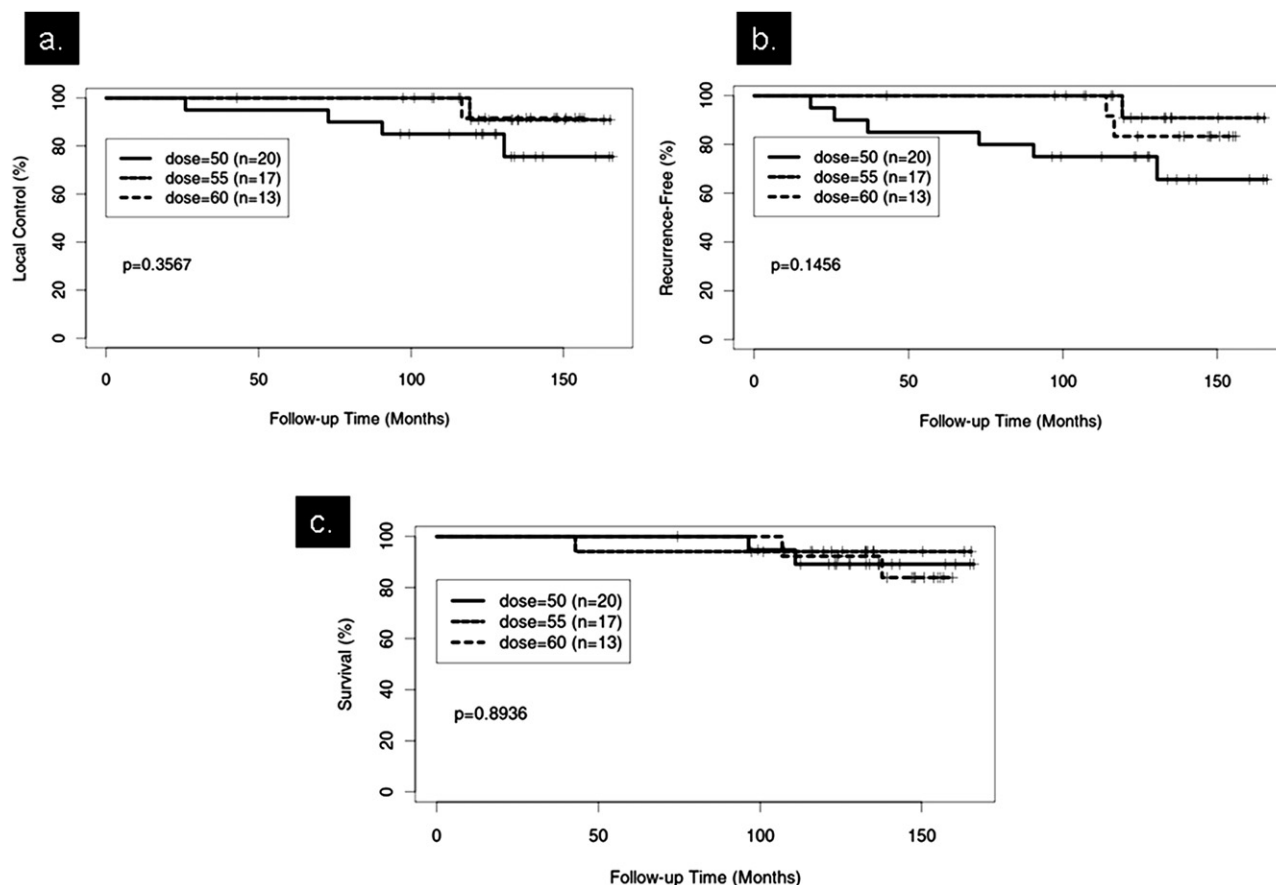


Fig. 3. Actuarial plots of (a) local control, (b) recurrence-free survival, and (c) overall survival.

Other studies reported lower IBTR rates but at much earlier follow-up. The two British and one Canadian study reported much greater IBTR rates but included patients with positive/close margins, extensive intraductal component (>25%), larger tumors, and positive nodes. (2, 3, 7). Similar to other series (4, 7–9, 11, 16), we found that most IBTRs were elsewhere recurrences. Radiation dose was not associated with local control but the present study lacked sufficient power to detect such differences. We found no regional nodal recurrences, likely reflecting patient selection of Stage T1N0 patients with adequate nodal surgery. Of the 6 patients with IBTRs, 5 were successfully salvaged. One patient developed recurrence in the chest wall after salvage mastectomy and ultimately died of metastatic disease. In our study, the 12-year actuarial RFS and OS rates were 71.5% and 87%, respectively, very similar to the Hungarian series (16).

Acute complications were minimal and similar to previous studies. Only one patient developed a postimplant infection, for a rate lower than the 3–7% in other studies (1, 9). Long-term cosmetic and toxicity results, however, were generally poor compared with those in previous studies. Good-excellent cosmesis was reported in 67% of patients compared with 75% to >95% in other studies (Table 3). Although 91% of patients would choose APBI-IB again, only 67% were totally satisfied with treatment. Three patients reported moderate breast pain at the last follow-up visit, slightly greater than that in other studies (4, 17), and 59% reported a change in breast size. Grade 2–3 telangiectasias were seen in 34% and moderate-severe fibrosis in 54% of patients, higher than that reported in other studies. Fat necrosis was seen in

35% of patients, a lower rate than that in the Tufts series (4). Grade 3–4 late skin and subcutaneous toxicity rates were generally within the range of other studies (Table 3), although 1 patient did have a severe complication requiring partial mastectomy (Fig. 1d–f). These long-term outcomes at 11+ years have significantly declined since the 2- and 5-year outcomes, highlighting the necessity for long-term follow-up.

Higher dose was associated with worse cosmesis, less patient satisfaction, and more fibrosis, late skin and subcutaneous toxicity, and change in breast size. Higher estimated skin doses also correlated with worse cosmesis and late skin and subcutaneous toxicity. This has not yet been reported in published studies, because previous APBI-IB series did not use differing dose levels. However, Wazer *et al.* (11) did report that dose hotspots were associated with worse cosmesis, more fat necrosis, and higher-grade skin toxicity. They also found that a larger implanted breast volume was associated with worse cosmesis. We did not find such correlations, given our small patient numbers and range of implant volumes. Older age was associated with less breast edema, hyperpigmentation, and fibrosis in our study, which has not previously been reported. Chemotherapy was not associated with cosmesis or toxicity as reported in other studies (11, 18).

There are several possibilities for the worse cosmesis and treatment-related toxicity in the present study. One might have been our use of LDR brachytherapy, which has been associated with higher odds of cosmetic-altering fibrosis and change in cosmesis after breast brachytherapy compared with HDR (18). In Radiation Therapy Oncology Group 95-17, 18% of patients

Table 3 Comparison of present study with other published APBI-IB studies

Series	Patients (n)	Median follow-up	Treatment modality/dose	Cosmesis/complications	Local control (IBTR)
William Beaumont Hospital, Royal Oak, MI (1, 15)	199	LC: 9.2 y Cosmesis: 6.4 y	HDR: 32–34 Gy in 8–10 fx LDR: 50 Gy in 4 d	Good/excellent cosmesis >95%; fat necrosis 11% after 5+ y; 11% infection rate (7% acute, 4% late)	10-y Actuarial IBTR 5% (3% TR, 2% ELR)
Ochsner Clinic, New Orleans, LA (5)	50	6.3 y (LC) Cosmesis: 1.7 y	LDR: 45 Gy over 4 days HDR: 32 Gy in 8 fx	8% Grade 3 toxicity requiring surgical intervention, 22% Grade 1–2 toxicity, 75% good/excellent cosmesis	Crude rate: 4 recurrences (8%)—1 IBTR (TR), 3 regional nodal recurrences
RTOG 95-17 (6)	99	2.7 y	LDR: 45 Gy in 3.5–5 d (n = 33) HDR: 34 Gy in 10 fx (n = 66)	Late Grade 3 toxicity: 18% (LDR), 6% (HDR); 70% fibrosis rate for LDR, 39% for HDR	Not stated
London Cancer Centre, London, ON, Canada (7)	39	7.6	HDR: 37.2 Gy in 10 fx	Cosmesis score (of 100): 90 (patient-assessed), 89 (physician-assessed); 13% fat necrosis	5-y actuarial IBTR 16.2%; crude: 6 IBTR (2 TR, 4 ELR); 10% ELR rate
Tufts Medical Center, Boston, MA (11)	75	6.1 y	HDR: 34 Gy in 10 fx	Good/excellent cosmesis in 91%; Grade 3–4 late subcutaneous toxicity 19%, Grade 4 fat necrosis 13%	4-y actuarial IBTR 3% (n = 1, ELR)
Tufts Medical Center, Boston, MA (4)	32	7 y	HDR: 34 Gy in 10 fx	Good/excellent cosmesis in 93% at 5 y; overall, 52% fat necrosis; Grade 2–3 late subcutaneous toxicity 36%	5-y actuarial IBTR 6.1% (n = 3, all ELR)
University of Kansas, Kansas City, KS (1)	24	3.9 y	LDR: 20–25 Gy in 24–48 h	Cosmesis very good to excellent	No disease recurrence
Guys Hospital, London, UK (3)	27	6 y	LDR: 55 Gy in 5 d	Local skin reaction and telangiectasia in 1 patient; no fibrosis	Crude IBTR: n = 10 (37%), 9 cases TR
Guys Hospital, London, UK (2)	49	6.3 y	LDR: 45 Gy in 4 d	Good/excellent cosmesis in 81%, 22% fibrosis, 65% altered breast texture, 12% telangiectasias	Crude IBTR: n = 9 (18%), 7 cases TR
National Institute of Oncology, Budapest, Hungary (16)	45	10.8 y	HDR: 30.3–36.4 Gy in 7 fx	Good/excellent cosmesis 78%; 4% Grade 3+ side effects: n = 1 Grade 3 fibrosis, n = 1 Grade 4 fat necrosis requiring surgery	12-y Actuarial IBTR 9.3%, crude IBTR n = 4 (all ELR) 12-y actuarial regional nodal failure 4.4%
National Institute of Oncology, Budapest, Hungary (8)	128	5.5 y	HDR 36.4 Gy in 7 fx or EBRT 50 Gy/25 fx	Good/excellent cosmesis 78% overall (81% HDR, 10% EBRT)	5-y Actuarial IBTR 4.7% (TR 1.6%, ELR 3.1%)

(continued on next page)

Table 3 (continued)

Series	Patients (n)	Median follow-up	Treatment modality/dose	Cosmesis/complications	Local control (IBTR)
German-Austrian Multicenter Trial, University Hospital, Erlangen Germany (9)	274	5.3 y	HDR: 32 Gy in 8 fx (36%) PDR 49.8 Gy in 83 fx in 5 d (64%)	Good/excellent cosmesis 90%; 3% acute infections; 30% fibrosis, 17% telangiectasias	Crude IBTR: n = 8 (3%)—3 TR, 5 ELR
Present study	50	11.2 y	LDR dose escalation: 50 Gy (40%), 55 Gy (34%), 60 Gy (26%) at 0.5 Gy/h for 5 d	Good/excellent cosmesis 67%; total patient satisfaction 67%; moderate/severe fibrosis 54%; 35% fat necrosis; 34% telangiectasias $\geq 1 \text{ cm}^2$; higher dose associated with worse cosmetic and toxicity outcomes	12-y Actuarial IBTR: 14.6% Crude: n = 6—1 TR (dermal recurrence at implant site), 5 ELR

Abbreviations: APBI-IB = accelerated partial breast irradiation with implant brachytherapy; IBTR = ipsilateral breast tumor recurrence; LC = local control; HDR = high dose rate; fx = fractions; LDR = low dose rate; TR = true recurrence; ELR = elsewhere recurrence; RTOG = Radiation Therapy Oncology Group; PDR = pulsed dose rate; EBRT = external beam radiotherapy.

treated with LDR had Grade 3 toxicity compared with 4% of HDR patients (6). Differences in outcomes between LDR and HDR might be because of greater dose inhomogeneity of LDR. Nevertheless, previous studies of LDR used doses of 45–55 Gy, and our results suggest that 60 Gy is too high and leads to greater complication rates. From the estimated skin doses, it appears that higher skin doses correlated with worse cosmetic outcomes and late skin and subcutaneous toxicity. Also, the study predated the advent of implant templates and new catheter placement techniques, which have improved target volume coverage and dose homogeneity compared with free-hand techniques (19). These cases were planned before three-dimensional computed tomography planning was available. It is very possible that modern brachytherapy techniques and the use of three-dimensional treatment planning might result in lower complication rates.

Mammographic abnormalities were detected in about one-third of the patients, most of which resulted in biopsy. Most (73%) of these rebiopsies were benign. It is important to consider the psychological effect of repeat biopsies. One patient underwent mastectomy and reconstruction because of this issue. Our group previously analyzed 32 mammograms from 19 patients who received APBI-IB (20). Mammographic distortions, density at the implant site, and skin thickening were common findings.

Conclusion

The present dose-escalation study is an important addition to the published data on APBI-IB, with its long and close, prospective follow-up and systematic patient and physician evaluations. We found an acceptable LC rate of 85% at 12 years, with predominantly elsewhere failures. However, poor cosmesis and significant treatment-related toxicity at higher doses suggest that LDR doses >50–55 Gy could lead to worse outcomes. Our toxicity outcomes have changed significantly from those reported previously, highlighting the need for long follow-up in studies of APBI (12). Finally, long-term data from ongoing Phase III prospective randomized trials are needed to establish whether APBI is equivalent to standard whole breast irradiation with respect to disease control and safety.

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