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CLINICAL TRIAL

Four-year clinical update from a prospective trial of accelerated partial breast intensity-modulated radiotherapy (APBIMRT)

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Abstract This prospective Phase II single-arm study gathered data on the use of intensity-modulated radiotherapy (IMRT) to deliver accelerated partial breast irradiation (APBI). Four-year efficacy, cosmesis, and toxicity results are presented. Between February 2004 and September 2007, 136 consecutive patients with Stage 0/I breast cancer and negative margins $\geq$0.2 cm were treated on protocol. Patients received 38.5 Gy in 10 equal fractions delivered twice daily. Breast pain and cosmesis were rated by patient, and cosmesis was additionally evaluated by physician per Radiation Therapy Oncology Group (RTOG) criteria. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v3.0) was used to grade toxicities. 136 patients (140 breasts) with median follow-up of 53.1 months (range, 8.9–83.2) were evaluated. Population characteristics included median age of 61.9 years and T*is* (13.6 %), T1a (18.6 %), T1b (36.4 %), and T1c (31.4 %). Kaplan–Meier estimates at 4 years: ipsilateral breast tumor recurrence 0.7 %; contralateral breast failure 0 %; distant failure 0.9 %; overall survival 96.8 %; and cancer-specific survival 100 %. At last follow-up, patients and physicians rated cosmesis as excellent/good in 88.2 and 90.5 %, respectively; patients rated breast pain as none/mild in 97.0 %. Other observations included edema (1.4 %), telangiectasia (3.6 %), five cases of grade 1 radiation recall (3.6 %), and two cases of rib fractures (1.4 %). This analysis represents the largest cohort and longest follow-up of APBI utilizing IMRT reported to date. Four-year results continue to demonstrate excellent local control, survival, cosmetic results, and toxicity profile.

Keywords Accelerated partial breast irradiation · Breast cancer · Breast-conserving therapy · Intensity-modulated radiotherapy · Adjuvant radiotherapy

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Introduction

Breast-conserving therapy (BCT) of lumpectomy followed by radiotherapy has disease-free and overall survivals comparable to those of mastectomy, for ductal carcinoma in situ (DCIS) and early stage invasive breast cancer [1–4]. The 5–7 weeks required for the current standard of care whole breast irradiation (WBI) can be a significant deterrent for patients who would otherwise be good candidates for BCT [5–7]. Studies have investigated delivering a biologically equivalent radiation dose to the involved region over a shortened time frame [8–44]. The rationale for irradiating only a partial breast volume, including observations that a majority of ipsilateral breast tumor recurrences (IBTR) developed at or in the area of the tumor bed, has been

thoroughly elaborated elsewhere [8, 9]. This alternative treatment approach is commonly known as accelerated partial breast irradiation (APBI).

Various techniques for APBI delivery have been explored over the past decade, including interstitial (multicatheter) brachytherapy [10–15], single-entry brachytherapy using intracavitary devices such as MammoSite [16–20], external beam radiotherapy (EBRT) utilizing photons [21–37] or protons [38, 39], and intraoperative radiotherapy (IORT) delivered as a single fraction at the time of definitive surgery [40–43]. EBRT, specifically EBRT utilizing 3-dimensional conformal planning (3D-CRT), has gained popularity due to its noninvasive nature, decreased procedural trauma to the breast, ease of adoption for most radiation treatment facilities, and its suitability for most cases (in terms of tumor location and breast volume) [8, 9, 44]. APBI using EBRT is associated with a lower risk of seroma formation and infection than APBI delivered by brachytherapy [44]. Compared to brachytherapy and IORT techniques, 3D-CRT offers the best target coverage and the most homogenous dose distribution (i.e., minimizing "hot spots," the amount of breast tissue receiving radiation doses markedly exceeding the prescription dose); potential drawbacks of 3D-CRT include radiation exposure to a larger volume of the uninvolved ipsilateral breast, heart, and lung tissue (to account for tumor motion and setup variability), leading to a higher integral dose (total energy deposited in the patient) [8, 44].

While 3D-CRT relies on physical wedges (also known as blocks) to reduce the dose delivered by each treatment beam to adjacent healthy tissue, intensity-modulated radiotherapy (IMRT), a technique that might be considered the next generation of 3D-CRT, enables rapid re-blocking while the patient is being treated, thus allowing the radiation oncologist to vary the size and intensity of treatment beams to deliver spatially nonuniform doses that result in a homogenous dose distribution at the target site. The high precision and customizability afforded by IMRT has led to superior clinical outcomes and reduced toxicities in prostate (and other organs) irradiation compared to 3D-CRT [45–53]; accordingly, IMRT has been adopted as a new standard of care in prostate, head and neck, and central nervous system irradiation. Several studies utilizing IMRT to deliver WBI (including randomized, nonrandomized, and single-arm prospective studies compared to historical controls) have demonstrated dosimetric advantages of IMRT over 3D-CRT with accompanying decreases in incidence, duration, and severity of toxicities such as dermatitis, pruritus, moist desquamation, edema (both acute and chronic), and hyperpigmentation [48–53].

Despite the potential advantages of IMRT over 3D-CRT, relatively few groups have investigated the use of IMRT to deliver APBI. Among the pending large randomized clinical trials directly comparing WBI to adjuvant APBI (including GEC-ESTRO interstitial brachytherapy, IMPORT Low, NSABP B-39/RTOG 0413, and RAPID), only the British IMPORT Low study makes use of IMRT. Since one key advantage of BCT over mastectomy is the potential preservation of the appearance and sensation of the breast, recent institutional reports of adverse cosmesis and toxicity from APBI using 3D-CRT [30, 32] have been received with concern. Early 3D-CRT toxicities from B-39 were reassuringly low [27], leading many to suppose that the adverse outcomes reported were due to institutional practices or small sample size. However, the Canadian-based RAPID study has now reported interim toxicity and cosmesis results, showing that APBI delivered with 3D-CRT was associated with worse cosmetic outcomes and late radiation changes at 3 years compared to WBI [29].

This prospective, hypothesis-generating Phase II single-arm study gathered dosimetric data and clinical outcomes of APBI delivered with IMRT (APBIMRT). We previously compared 56 APBIMRT plans from this trial to 3D-CRT plans following B-39 dose constraints retrospectively constructed on the same cases [34]; IMRT improved normal tissue sparing in the ipsilateral breast without compromising treatment target coverage. This report presents the 4-year disease control, cosmesis, and toxicity outcomes for the first 140 breasts treated on this Phase II study at our institutions.

Materials and methods

Patient population

Between February 2004 and September 2007, 150 consecutive patients with Stage 0/I breast cancer were prospectively enrolled on an Institutional Review Board-approved study of APBIMRT. Subsequently, 14 patients were not treated with APBIMRT: 2 due to patient choice, 1 due to insurance concerns, and 11 due to technical ineligibility. Of the 11 ineligible patients, 1 was ineligible because the lumpectomy cavity could not be visualized on planning scans for contouring, and the remaining either had lumpectomy cavities deemed too large for APBI or the cavities were so medial in location that the dose constraints for the heart or the contralateral breast could not be met. The remaining 136 patients (4 with bilateral disease) were treated at 6 facilities in Colorado, USA. Internal retrospective review showed that 2/136 did not meet all eligibility criteria but were treated according to protocol and therefore included in this analysis.

The eligibility requirements were initially age $\geq$45 years, Stage T1N0M0 (as defined by AJCC Cancer Staging Manual, 6th edition), and negative margins

≥2 mm after final surgery (re-excision permitted). The protocol was later amended to include patients ≥40 years old and pure DCIS.

IMRT planning and treatment

Treatment technique, target volume and normal tissue contouring, and dose constraints have been previously reported in detail [34] and summarized here. The first 8 patients were treated to the prescribed dose of 34 Gy, and the remaining patients to 38.5 Gy. Patients were treated while supine in 10 equal fractions delivered twice daily (with 6-h interfractional minimum) over 5 consecutive days; 1 patient received treatment over 6 days and 2 over 9 days due to unplanned linear accelerator maintenance or inclement weather. The clinical target volume (CTV) was initially defined as the lumpectomy cavity +2 cm for the patients treated to 34 Gy, then decreased to lumpectomy cavity +1 cm when the prescribed dose was increased to 38.5 Gy; the planning target volume (PTV) was defined as CTV +1 cm. No respiratory gating or active breathing control was used. The CTV was at least 0.5 cm from the chest wall and the skin surface. The PTV/ipsilateral breast volume ratio was generally limited to ≤20 %. Plans were optimized so ≥95 % of the PTV received ≥95 % of the prescribed dose. Heart exposure was limited to ≤5 % organ volume receiving >5 % of the prescribed dose. Ipsilateral lung exposure was initially limited to ≤15 % receiving >30 % of the prescribed dose ($n = 8$), then reduced to ≤10 % receiving >30 % of the prescribed dose ($n = 123$), and eventually to ≤10 % receiving >20 % of the prescribed dose for the remaining cases in this series after we gained more experience with image-guided radiotherapy (IGRT). IGRT utilizing nonmigrating fiducial markers [35] was adopted after more than 100 cases and used to treat 32 breasts in this cohort. For breasts treated without IGRT, treatment was set up to skin tattoos and verified with orthogonal pair MV imaging, approved prior to the first treatment and confirmed intermittently throughout the treatment course. APBIMRT was completed prior to any chemotherapy.

Cosmesis and toxicities

Cosmesis and toxicities were evaluated 4–6 weeks after treatment completion, then every 3–4 months for 2 years; protocol was later amended to encourage yearly follow-up beyond 2 years. Patients were asked to rate breast pain as none, mild, moderate or severe, and cosmesis as excellent, good, fair or poor without further instructions. Cosmesis was additionally evaluated by physician per RTOG criteria; (presumed) surgical effects on cosmesis were not excluded. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v3.0) was used to grade toxicities. Rib fractures were confirmed by 2D plain films.

Statistical methods

Time intervals were calculated from completion of APBI unless noted otherwise. IBTRs were defined as the recurrence of cancer in the treated breast. Treatment failures were dated to pathologic diagnosis of recurrence. Univariate analysis was performed with the two-sample t test (age and volumetric data were analyzed as continuous variables) and the χ^2 test for independent observations and the paired t test for repeated measures. Equality of variance was verified with the F test to insure applicability of two-sample t tests. Multivariate analysis was performed with repeated measures ANOVA. Statistical significance was defined as $p \leq 0.05$ with $\alpha = 0.05$, p values were one-sided (following standard χ^2 and F distributions).

Results

Patients

136 patients (140 breasts) were evaluated. The median follow-up from APBI completion (for recurrence and survival) was 53.1 months (8.9–83.2).

MRI scanning

Bilateral MRI to rule out occult disease was not required but was performed for the majority of patients. All 19 cases with DCIS (100 %), 5 with invasive lobular (100 %), 3 with mixed invasive ductal and lobular histologies (100 %), and 83 with invasive ductal histology with accompanying DCIS component (80.7 %) had MRI scanning.

Patient and treatment-related characteristics

Patient characteristics (Table 1) were generally favorable, with median age of 61.9 years, median Tumor size of 0.95 cm, 76.4 % with a closest margin >0.5 cm, and 90.7 % estrogen receptor (ER) positive. Of note, over half of the cases are classified as either "unsuitable" for APBI outside of a clinical trial ($n = 17$, 16/17 cases were diagnosed at <50 years old, 2/17 cases of microscopically multifocal DCIS spanning >3 cm) or "cautionary" ($n = 66$, 47/66 cases were diagnosed at ages 50–59, 11/66 ER negative) according to the APBI consensus guidelines published in 2009 by the American Society for Radiation Oncology (ASTRO) [44].

Table 1 Patient characteristics

Characteristic	All patients ($n = 140$ breasts)	Stage I ($n = 121$ breasts)	Stage 0 ($n = 19$ breasts)
Age at diagnosis (*y*)			
Median (range)	61.9 (37.2–96.8[a])	61.6 (37.2–96.8[a])	62.4 (41.9–72.8)
Menopausal status at study entry (*n*)			
Pre/Perimenopausal	26 (18.6 %)	22 (18.2 %)	4 (21.0 %)
Postmenopausal	114 (81.4 %)	99 (81.8 %)	15 (79.0 %)
Primary histology (*n*)			
Ductal carcinoma in situ	19 (13.6 %)		19
Invasive ductal carcinoma	116 (82.9 %)	116 (95.9 %)	
Invasive lobular carcinoma	5 (3.6 %)	5 (4.1 %)	
Tumor grade (*n*)		Histologic grade	Nuclear grade
Low		61 (50.4 %)	5 (26.3 %)
Intermediate		40 (33.1 %)	7 (36.85 %)
High		16 (13.2 %)	7 (36.85 %)
Unavailable		4 (3.3 %)	
Size of invasive tumors (cm)			
Median (Range)		0.95 (0.1–2)	
Presence of central necrosis (*n*)			
Yes			10 (52.6 %)
No			9 (47.4 %)
Total span of DCIS (cm)			
Median (Range)			0.5 (0.1–4)
Multifocal DCIS (*n*)			
Yes			5 (26.3 %)
No			14 (73.7 %)
Margin size (cm)			
Median (Range)	0.8 (0–2.1[a])	0.9 (0–2.1[a])	0.8 (0.2–1.5)
Estrogen receptor status (*n*)			
Positive	127 (90.7 %)	111 (91.7 %)	16 (84.2 %)
Negative	13 (9.3 %)	10 (8.3 %)	3 (15.8 %)
HER2/neu status (*n*)			
Positive	14 (10.0 %)	13 (10.0 %)	1 (5.2 %)
Negative	102 (72.9 %)	102 (84.3 %)	0 (0 %)
Unknown	24 (17.1 %)	6 (5.0 %)	18 (94.7 %)
ER negative and HER2 negative (*n*)	7 (5.0 %)	7 (5.8 %)	0 (0 %)
Sentinel nodes sampled (*n*)			
Median (Range)	2 (0–11)	2 (1–11)	0 (0–3)
Total nodes sampled (*n*)			
Median (Range)	2 (0–14)	3 (1–14)	0 (0–7)
T stage (*n*)			
T*is*	19 (13.6 %)		19 (100 %)
T1mic	6 (4.3 %)	6 (5.0 %)	
T1a	20 (14.3 %)	20 (16.5 %)	
T1b	51 (36.4 %)	51 (42.1 %)	
T1c	44 (31.4 %)	44 (36.4 %)	
N stage (*n*)			
N0	136 (97.1 %)	117 (96.7 %)	19 (100 %)
N0(i+)	4 (2.9 %)	4 (3.3 %)	0 (0 %)
Bilateral breast MRI prior to enrollment (*n*)	117 (83.6 %)	98 (80.1 %)	19 (100 %)

Table 1 continued

Characteristic	All patients ($n = 140$ breasts)	Stage I ($n = 121$ breasts)	Stage 0 ($n = 19$ breasts)
ASTRO APBI Consensus [44] Category (*n*)			
Suitable	57 (40.7 %)	57 (47.1 %)	0 (0 %)
Cautionary	67 (47.9 %)	51 (42.1 %)	16 (84.2 %)
Unsuitable	16 (11.4 %)	13 (10.7 %)	3 (15.8 %)
Adjuvant Treatment (*n*)			
RT only	24 (17.1 %)	15 (12.4 %)	9 (47.4 %)
RT + endocrine therapy (no chemotherapy)	97 (69.3 %)	87 (71.9 %)	10 (52.6 %)
RT + chemotherapy (no endocrine therapy)	8 (5.7 %)	8 (6.6 %)	
RT + chemotherapy + endocrine therapy	11 (7.9 %)	11 (9.1 %)	
Time from end of RT to beginning of chemotherapy (month)			
Median (Range)		0.4 (0.1–2.4)	
Time from end of RT to beginning of endocrine therapy (month)			
Median (Range)	0.5 (−1.9 to 4.6)	0.5 (−1.9 to 4.6)	0 (−0.9 to 2.0)

[a] As mentioned in the Materials/Methods section, 2 patients that did not meet all eligibility criteria but were treated on protocol were included in the analysis and account for the age and margin size values listed in this table outside the range specified by the protocol

Table 2 Cosmesis and pain outcomes

Visit[a]	Patient-rated cosmesis		Physician-rated cosmesis		Patient-rated pain	
	n[b]	Excellent/good	n[b]	Excellent/good	n[b]	None/mild
12 months	121	118 (97.5 %)	120	118 (98.3 %)	130	127 (97.7 %)
24 months	100	93 (93.0 %)	101	98 (97.1 %)	113	110 (97.7 %)
36 months	77	67 (87.0 %)	80	72 (90.00 %)	91	87 (95.6 %)
48 months	72	62 (86.1 %)	74	66 (89.2 %)	83	82 (98.8 %)
60 months	39	35 (90.8 %)	41	36 (87.8 %)	46	44 (95.7 %)

[a] From end of RT, closest follow-up within ±180 days to time point specified

[b] Breasts with evaluated cosmesis/pain

Treatment efficacy

Kaplan–Meier estimates of efficacy at 4 years: IBTR 0.7 %; contralateral breast failure 0 %; distant failure 0.9 %; overall survival 96.8 %; and cancer-specific survival 100 %. The one patient with subsequent IBTR was originally diagnosed at age 44 with a 0.2 cm high-grade DCIS tumor with comedonecrosis, margins ≥0.5 cm, and ER and PR negative (HER2/neu not tested). The IBTR (diagnosed ∼ 14 months after treatment completion) was also high-grade DCIS, located at ≥3.7 cm from the original tumor by one author's (T. K.) review of diagnostic imaging, and verified to be outside the treatment volume (referencing the fiducial markers placed for IGRT), and therefore an "elsewhere" failure [14, 54]. No true recurrence/marginal miss or ipsilateral nodal failures were observed.

Cosmetic and pain results

Table 2 and Fig. 1 present the patient- and physician-rated cosmesis as well as patient-rated pain in this study population over time.

Patient- and physician-rated cosmesis outcomes assessed at the same time points were categorized into excellent/good and fair/poor and analyzed for agreement. There was 97 % agreement ($n = 116$) at 12 months and 92.2 % ($n = 77$) at 24 months.

Univariate analysis

Univariate analysis showed no relationship between age at diagnosis, re-excision, use of IGRT, ipsilateral breast volume (IB), PTV, and PTV/IB ratio to patient- or MD-rated cosmesis or patient-reported pain at last follow-up. The

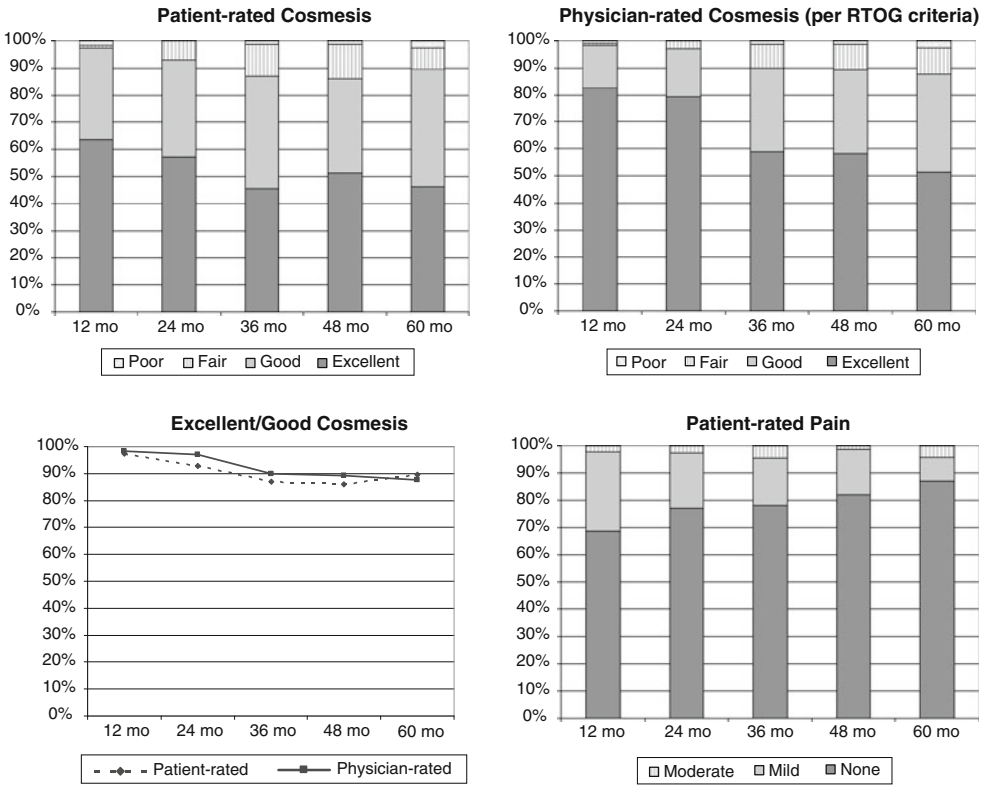

Fig. 1 Cosmesis and pain outcomes, legend: cosmesis: *marbled gray* poor, *striped gray* fair, *solid light gray* good, *solid dark gray* excellent, pain: *striped gray* moderate, *solid light gray* mild, *solid dark gray* none, excellent/good cosmesis: *dotted line with diamond markers* patient-rated, *solid line with square markers* physician-rated

Table 3 Treatment toxicities (highest grade reported for each breast)

	Grade 0	Grade 1	Grade 2	Grade 3
Breast edema ($n = 138$)	12 (90.6 %)	11 (8.0 %)	2 (1.4 %)	0 (0 %)
Telangiectasia ($n = 138$)	129 (93.5 %)	7 (5.1 %)	2 (1.4 %)	0 (0 %)
Radiation recall ($n = 139$)	134 (96.4 %)	5 (3.6 %)	0 (0 %)	0 (0 %)
Rib fracture ($n = 139$)	137 (98.6 %)	0 (0 %)	2 (1.4 %)	0 (0 %)

lack of relationship between PTV and pain contrasts our prior report [37]. However, the current analysis corroborates the statistically significant relationship between the volume of the chest wall receiving >35 Gy and patient-reported pain as previously discussed (results not shown).

Patients who reported moderate/severe pain at any point during follow-up were proportionally more likely to report fair/poor cosmesis at last follow-up ($p = 0.008$).

Patients who received endocrine therapy were proportionally less likely to report pain at last follow-up ($p = 0.003$). Patients who received endocrine therapy exhibited a non-significant trend toward reporting excellent/good cosmesis at last follow-up ($p = 0.068$).

Multivariate analysis

Multivariate analysis including time from RT and use of endocrine therapy showed no relationship between either factor and patient-reported cosmesis or pain. There was a statistically significant decrease in physician-rated cosmesis over time ($p = 0.003$). This decrease remained significant when the model accounted for variations in endocrine therapy, re-excision, and age, and appeared to stabilize after 36 months from RT (Fig. 1; paired t test confirmed loss of statistically significant difference between physician-rated cosmesis at 36 and 48 months). Due to the small number of physician-evaluated cosmesis available at 60 months for comparison at this current time ($n = 29$), this apparent stabilization requires future confirmation.

Treatment-related toxicities

Table 3 details the highest grade of toxicities reported for each breast at any time following APBI. No grade 2+ acute skin toxicities and no heart or lung toxicities (of any grade) were observed. At last follow-up, toxicities reported were mild (1.4 %) edema, and mild (2.2 %) or moderate (1.4 %) telangiectasia. The adverse event "radiation recall" corresponded to dermatitis associated with chemotherapy

administered after completion of radiation, and was graded according to CTCAE v3.0.

Discussion

This report is an update to previous publications [34–37] and represents the largest cohort and longest follow-up of APBIMRT reported to date. Four-year results continue to demonstrate excellent local control, survival, cosmetic results, and toxicity profile and support the continued use and study of this technique. Table 4 offers an exploratory comparison between this study and representative adjuvant APBI studies that utilized brachytherapy, 3D-CRT, or IMRT techniques.

Comparison of clinical outcomes to other APBI reports

As EBRT techniques for APBI delivery have become more widely used, multiple institutions and cooperative groups have published varying rates of late toxicity (Table 4). One of the explanations offered by the RAPID study team for their 3D-CRT APBI cosmesis results was lack of conformality, i.e., the breast volume receiving high radiation doses did not correspond precisely enough to the treatment target volume. As we previously reported, in comparison to 3D-CRT, IMRT significantly increased conformality and correspondingly improved normal ipsilateral tissue sparing; the volume of ipsilateral lung and heart irradiated was small with both techniques but decreased with IMRT [36]. The clinical implications of these findings were further delineated by a later investigation demonstrating correlation between patient-reported pain after APBIMRT and chest wall volume receiving >35 Gy [37]. These findings led us to hypothesize that improved normal tissue sparing offered by IMRT may also improve clinical outcomes, such as pain or cosmesis. Accordingly, in October 2007 (after the entire patient series analyzed in this report had completed treatment), our institutional guidelines for APBI using IGRT were amended to further reduce the PTV. Leonard et al. [30] suggests that in the setting of larger radiation doses over shorter time frames (hypofractionation), small differences in prescribed dose and dose distribution may result in dramatic differences in normal tissue complication. Table 5 lists some key technical differences between representative external beam APBI studies, including the sizes of margin added to the lumpectomy cavity to form the PTV.

Both the Tufts and the University of Michigan studies have reported associations between dose-volume data and adverse clinical outcomes [30, 32]. Leonard et al. [30] demonstrated statistically significant associations between the percentage of breast volume receiving at least 100 % (V100) and 50 % (V50) of the prescribed dose to subcutaneous fibrosis ($p = 0.001$ and 0.01), cosmesis ($p = 0.02$ and 0.04), and grade 2+ toxicity ($p = 0.009$ and 0.003). Jagsi et al. [32] also reported a significant association between V100 and V50 to cosmesis ($p = 0.02$ and 0.002). These findings suggest that it is not enough to simply compare outcomes from different ABPI techniques (i.e., 3D-CRT vs. IMRT, EBRT vs. brachytherapy); subtle dosimetric considerations, e.g., differences between V100 and V50 reported by the 2 IMRT studies in Table 5, and other factors, such as immobilization techniques, timing of radiotherapy, the use of other adjuvant therapies, methodological differences in cosmesis assessment, statistical anomalies associated with small sample sizes and/or short follow-up, etc., may also contribute to variability in cosmesis and late toxicities.

The IBTR rate and clinical outcomes reported by this study are comparable to outcomes of other APBI series (Table 4). One theoretical concern regarding the improved tissue sparing offered by IMRT is a potential increase in marginal failures, but marginal failures were not observed in this study population. Whether IMRT offers clinical advantages such as less severe late toxicities over other APBI techniques still requires testing in a randomized setting.

MRI scanning in patient series

The role of MRI scanning in the management of breast cancer is highly controversial and variable throughout the world. Some studies have demonstrated that MRI identified ipsilateral and/or contralateral occult disease and changed APBI eligibility in 8.8 % [55] to 12.9 % [56] of prospectively screened clinical candidates. MRI scanning to confirm suitability for breast conservation was not required by this study but is commonly utilized by breast surgeons in our region. A detailed analysis for (or against) the routine use of MRI in determining APBI eligibility, including whether it is cost-effective, and whether it has a clinically significant impact on long term APBI outcomes, is outside the scope of this paper. Nevertheless, it may be worth noting that this study is the only one among published EBRT APBI studies [10, 21–37] to report extensive use of breast MRI scanning in the diagnostic workup of the patient series. The effect of MRI on patient selection could partially account for the low IBTR rate (0.7 %) we observed.

Patient selection for APBI

APBI has gained popularity not only for its convenience to patients, but also with the increasing recognition that in cancer care, the more expansive treatment approach is not

Table 4 Summary of representative adjuvant APBI results

Study	Breasts treated with APBI (*n*)	Follow-up (*y*)	APBI delivery method	Fractionation scheme	Reported IBTR	IBTR/ year	Cosmesis good/excellent	Breast/chest wall pain	Toxicity (all grades)
Harvard Interstitial [11]	50	11.2 years (median)	Interstitial brachytherapy	LDR: 0.5 Gy/h to 50 Gy ($n = 20$), 55 Gy ($n = 17$), and 60 Gy ($n = 13$)	14.6 % at 12 years actuarial	1.21 %/ year	Patient-reported: 68 % (94 % for 50 Gy cohort, 62 % for 55 Gy cohort, 27 % for 60 Gy cohort); MD-reported: 67 % (95 % for 50 Gy cohort, 75 % for 55 Gy cohort, 9 % for 60 Gy cohort); follow-up time *NR* ($n = 46$)	Patient-reported: 24 % (26 % mild and 5 % moderate for 50 Gy cohort, 6 % mild and 6 % moderate for 55 Gy cohort, 18 % mild and 9 % moderate for 60 Gy cohort)	Breast edema (11 %) Pigmentation change (35 %) Telangiectasia (54 %) Fibrosis (93 % all grades, 54 % moderate/severe) Fat necrosis (65 %) Late skin toxicity (61 % all grades, 39 % grade 2+)
Hungary Interstitial [12]	45	10.75 (median for all patients); 11.1 (median for survivors)	Interstitial brachytherapy	HDR: 7 × 4.33 Gy ($n = 8$) or 5.2 Gy ($n = 37$) over 4 days	9.3 % at 12 years actuarial	0.78 %/ year	77.8 %, follow-up time *NR*	*NR*	Skin side effects (17.7 %) Fibrosis (42.2, 22.2 % grade 2+) Fat necrosis (37.8, 20 % grade 2+)
Beaumont Interstitial [13–15]	199	10.7 years (median for all patients); 12.2 (median for survivors)	Interstitial brachytherapy	LDR: 50 Gy over 96 h at 0.52 Gy/h ($n = 120$). HDR: 32 Gy in 8 fractions BID ($n = 71$) or 34 Gy in 10 fractions BID ($n = 8$)	5 % at 12 years actuarial	0.42 %/ year	98 % at ≥ 10 years ($n = 52$), 99 % at ≥5 years ($n = 163$)	9 % at ≥ 5 years ($n = 79$), 14 % at 2 years ($n = 128$), 27 % at ≤6 months ($n = 165$)	Infection (11 %, $n = 199$) 2 years ($n = 128$) unless noted as ≥5 years ($n = 79$): Breast edema (12 %) Erythema (11 %) Fibrosis (51 %) Hyperpigmentation (41 %) Hypopigmentation (34 %) Telangiectasia (23 % at 2 years, 35 % at ≥5 years) Fat necrosis (9 % at 2 years, 11 % at ≥5 years)
Hungary Randomized WBI vs. PBI [10]	87	5.5 (median)	Interstitial brachytherapy ($n = 88$) or 3D-RT for patients unsuitable for interstitial implantation ($n = 40$)	HDR: 7 × 5.2 Gy over 4 days. 3D-CRT: 50 Gy in 25 fractions, 5 fractions/week	4.7 % at 5 years actuarial	0.94 %/ year	HDR: 81.2 %, follow-up time NR ($n = 85$); EBRT: 70.0 %, follow-up time NR ($n = 40$)	*NR*	*NR*
MammoSite Prospective [16]	43	5.5 (median)	MammoSite	34 Gy in 10 fractions over 5 days	0 %	0 %	81.3 % at > 5 years ($n = 36$)	*NR*	Infection (9.3 %)Seroma formation (32.6 %)Telangiectasia (39.5 %)Retraction (20.9 %)

Table 4 continued

Study	Breasts treated with APBI (*n*)	Follow-up (*y*)	APBI delivery method	Fractionation scheme	Reported IBTR	IBTR/ year	Cosmesis good/excellent	Breast/chest wall pain	Toxicity (all grades)
MammoSite Registry [17–19]	1449	4.9 (median)	MammoSite	34 Gy in 10 fractions BID	3.5 % at 5 years actuarial	0.7 %/ year	90.4 % at > 5 years ($n = 260$), 93.3 % at 3 years ($n = 759$)	14.9 % at any time	At any time:Infection (9.5 %)Fibrosis (16.4 %)Any subcutaneous toxicity (33.1, 4.5 % grade 2 +)Seroma (28, 13 % grade 2 +)Fat necrosis (2.3 %)Rib fracture (0.3 %)
Beaumont MammoSite [20]	80	1.8 (median)	MammoSite	34 Gy in 10 fractions over 5–9 days	2.9 % at 3 years actuarial	0.97 %/ year	88.2 % at 3 years ($n = 17$), 96.9 % at 1 year ($n = 64$)	55.7 % at any time	Infection (11.3 %)Seroma (45, 10 % grade 2+)Fat necrosis (8.8 %)
Harvard 3D-CRT [21, 22]	99	5.9 (median)	3D-CRT	32 Gy in 8 fractions over 4-7 days (mixed photons and electrons $n = 63$, photons alone $n = 16$; protons $n = 20$)	5 % at 5 years actuarial	1 %/year	Patient-reported: 95 %; MD-reported: 97; at last follow-up (with median follow-up of 3 years)	Breast/chest wall pain NR; Rib tenderness (3.0 %); at last follow-up (with median follow-up of 3 years)	Rib fracture (1.0 %)At last follow-up (with median follow-up of 3 years):Telangiectasia (9.1 % grade 2 +)Moderate fibrosis (7.1 %)
NYU 3D-CRT prone [23]	99	5.3 (median)	3D-CRT prone	30 Gy in 5 fractions over 10 days	1 % at 5 years	0.20 %/ year	89 % at ≥3 years ($n = 74$); 90 % at ≥1 year ($n = 90$)	(LENT/SOMA criteria) 13 %; follow-up time NR	Pigmentation change (29 %)Edema (9 %)Telangiectasia (3 %)Fibrosis (8 %)Fat necrosis (19 %)
RTOG 0319 [24]	52	4.5 (median)	3D-CRT	38.5 Gy in 10 fractions over 5 days	6 % at 4 years actuarial	1.5 %/ year	*NR*	30.8 %; follow-up time NR	Dermatology/skin (75.0, 38.5 % grade 2+) Musculoskeletal/ soft tissue (25.0 %, 13.5 % grade 2+)
Beaumont 3D-CRT [25, 26]	192	4.8 (median)	3D-CRT	38.5 Gy ($n = 186$) or 34 Gy ($n = 6$) in 10 fractions over 5 days	0 % at 5 ($n = 91$) and 6 ($n = 77$) years actuarial, 1.8 % at 7 ($n = 46$) and 8 ($n = 28$) years actuarial	0.22 %/ year	81 % ($n = 192$) at last follow-up	41.3 % at 5 years ($n = 80$)	5 year ($n = 79$–87):Radiation dermatitis (25.0 %)Hyperpigmentation (43.8 %)Hypopigmentation (12.7 %)Breast edema (31.6 %)Induration/Fibrosis (75 %, 30 % grade 2 +)Volume reduction (35.6 %)Telangiectasia (25.3 %)
NSABP B-39/ RTOG 0413 [27]	1386	3.4 (mean); 974 cases ≥3 years	3D-CRT	38.5 Gy in 10 fractions over 5–10 days	*NR*	*NR*	*NR*	*NR*	Fibrosis (15 % grade 2+)
Canadian multicenter 3D-CRT [28]	87	3 (minimum)	3D-CRT	38.5 Gy ($n = 62$), 36 Gy ($n = 33$), or 35 Gy ($n = 9$) in 10 fractions over 5 working days	1 failure at 3 years	~0.38 %/ year	82 % at 3 years ($n = 85$); not statistically different from 86 % at baseline ($n = 104$)	23 % at 3 years ($n = 85$-87), 26 % at 1 year ($n = 88$–91)	1 year:Edema (16 %)Dermatitis (1 %)Hyperpigmentation (30 %)Hypopigmentation (10 %)2 years:Induration (39, 8 % grade 2+)Telangiectasia (20, 7 % grade 2+)

Table 4 continued

Study	Breasts treated with APBI (*n*)	Follow-up (*y*)	APBI delivery method	Fractionation scheme	Reported IBTR	IBTR/ year	Cosmesis good/excellent	Breast/chest wall pain	Toxicity (all grades)
RAPID [29]	1007	3 (median)	3D-CRT (IMRT allowed, % usage *NR*)	38.5 Gy in 10 fractions BID	*NR*	*NR*	Patient-reported: 73.8 %; nurse-reported: 68.5 %; digital photographs assessed by blinded radiation oncologist panel: 64.9 %; at 3 years ($n = 442$)	31.2 % (1.2 % grade 2 +) at 3 years ($n = 442$)	3 years:Telangiectasia (17.6 %, 4.6 % grade 2+)Induration/ Fibrosis (49.8 %, 8.8 % grade 2+)Fatty necrosis (3 %)
Tufts 3D-CRT [30]	80	2.7 (median)	3D-CRT	38.5 Gy in 10 fractions BID	1 % at last follow-up	~0.37 %/ year	81 %; follow-up time *NR*	*NR*	Subcutaneous fibrosis (64, 31 % grade 2 +)Fat necrosis (11 %)
Miami IMRT [31]	36	3.7 (median)	IMRT with respiratory gating	38 Gy in 10 fractions over 5 days	3 % at 3.7 years	0.81 %/ year	Patient-reported: 94 %; MD-reported: 97 %; at last follow-up	13.9 % acute (during treatment or ≤90 days from treatment completion)	Acute:Erythema (50.0 %)Hyperpigmentation (33.0 %)Late (>90 days from treatment completion):Breast edema (5.6 %)Fibrosis (16.7 %)Hyperpigmentation (2.8 %)Telangiectasia (2.8 %)Seroma (11.1 %)
UMich IMRT [32]	34	2.5 (median)	IMRT with deep-inspiration breath-hold	38.5 Gy in 10 fractions BID	0 %	0 %	78 % at ≥1.5 years ($n = 32$)	17.6 % acute (during treatment or ≤ 1 month from treatment completion); 11.8 % late (≥6 months from treatment completion)	Acute:Hyperpigmentation (55.9 %)Hypopigmentation (2.9 %)Breast edema (2.9 %)Rash (20.5 %)Late (≥90 days from treatment completion):Breast volume/ hypoplasia (79.4, 38.2 % grade 2+)Induration/Fibrosis (64.7, 8.8 % grade 2+)Telangiectasia (20.6 %)
Florence Randomized WBI vs. PBI IMRT [33]	131	*NR*	IMRT (no respiratory control)	30 Gy in 5 fractions	*NR*	*NR*	*NR*	*NR*	Skin toxicity (acute 5.8 %, no chronic skin damage at last follow-up)
Current study	140	4.4 (median)	IMRT (no respiratory control)	38.5 Gy ($n = 133$) or 34 Gy ($n = 7$) in 10 fractions over 5 days	0.7 % at 4 years actuarial	0.18 %/ year	Patient-reported: 88.2 %; MD-reported: 90.5 %; at last follow-up (median cosmesis follow-up 4.0 years)	Patient-reported: 26.3 % at last follow-up	Radiation recall (3.6 %)Rib fracture (1.4 %)At last follow-up (>6 months from treatment completion):Breast edema (1.4 %)Telangiectasia (4.3 %)

APBI accelerated partial breast irradiation, *WBI* whole breast irradiation, *IBTR* ipsilateral breast tumor recurrence (does not include cancer recurrence in the regional lymphatics), *NR* not reported/specified, *LDR* low-dose-rate, *HDR* high-dose-rate, *BID* twice daily, *LENT/SOMA* Late effects normal tissue task force subjective, objective, management and analytic system, *NSABP* National Surgical Adjuvant Breast and Bowel Project, *RTOG* Radiation Therapy Oncology Group

Table 5 Key technical differences between representative external beam APBI studies

Study	Fractionation Scheme	Definition of PTV	Ipsilateral lung dose constraints		Mean V100 (%)	Mean V50 (%)	Good/ excellent cosmesis (%)
NSABP B-39/ RTOG 0413 [9, 27]	38.5 Gy in 10 fractions BID	Lumpectomy cavity +2.5 cm	<15 % receives >30 % of dose		*NR*	*NR*	*NR*
RAPID 3D-CRT [29]	38.5 Gy in 10 fractions BID	Lumpectomy cavity +2.0 cm	<10 % receives >30 % of dose; <20 % receives >10 % of dose		*NR*	*NR*	($n = 442$) 68.5
APBIMRT (present study) [36]	38.5 Gy in 10 fractions BID	Lumpectomy cavity +2.0 cm	<15 % receives >30 % of dose ($n = 8$); <10 % receives >30 % of dose ($n = 123$); <10 % receives >20 % of dose ($n = 9$)	($n = 56$)	9.4	42	($n = 140$) 90.5
Beaumont 3D-CRT [25, 26]	38.5 Gy in 10 fractions BID	Lumpectomy cavity +2.5 cm	Meets B-39 dose constraints (<15 % receives >30 % of dose)	($n = 94$)	24	49	($n = 192$) 81
Tufts 3D-CRT [30]	38.5 Gy in 10 fractions BID	Lumpectomy cavity + 2.5 cm	Meets B-39 dose constraints (<15 % receives >30 % of dose)	($n = 80$)	14	42	($n = 80$) 81
UMich IMRT [32]	38.5 Gy in 10 fractions BID	Lumpectomy cavity +1.5 cm	*NR*	All cases ($n = 34$)	17.5	37.7	($n = 34$) 78
				Acceptable cosmesis ($n = 25$)	15.5	34.6	
				Unacceptable cosmesis ($n = 7$)	23.0	46.1	
NYU 3D-CRT prone [23]	30 Gy in 5 fractions over 10 days	Lumpectomy cavity +2.0 cm	< 10 % in the treatment fields	($n = 100$)	26	47	($n = 99$) 89

APBI accelerated partial breast irradiation, *PTV* planning target volume, *V100* breast volume (as percentage of ipsilateral breast) receiving at least 100 % of prescription dose, *V50* breast volume (as percentage of ipsilateral breast) receiving at least 50 % of prescription dose, *NSABP* National Surgical Adjuvant Breast and Bowel Project, *RTOG* Radiation Therapy Oncology Group; *BID* twice daily, *NR* not reported/specified

always better. APBI has always—conceptually as well as in published data—relied on proper selection, typically of cases with clinicopathologic factors associated with low risk for recurrence, and encompass patients whose treatment options may include not only conventional WBI but observation as well (although it should be noted that a subgroup of patients in which RT does not reduce locoregional recurrence has yet to be identified [57, 58]). The optimal patient population for APBI remains controversial, as evidenced by the different sets of guidelines offered by ASTRO, The Groupe Européen de Curiethérapie and European Society for Therapeutic Radiology and Oncology (GEC-ESTRO), the American Society of Breast Surgeons, and the American Brachytherapy Society, as well as the numerous retrospective studies questioning the merits of these guidelines [44, 59–63].

The results reported here provide early confirmation of the importance of proper patient selection and also suggest that some patients deemed "cautionary" or even "unsuitable" may ultimately be appropriate for APBI. Although the ASTRO consensus guidelines established a population of patients "suitable" for APBI outside a clinical study [44], we continue to treat ~98 % of our institutional APBI cases on study and closely monitor the outcomes. Of note, this study is one of a few APBI studies utilizing EBRT to include synchronous (or metachronous) bilateral disease. Since the protocol limited the dose to the contralateral breast to less than 3 % of the prescribed dose, there was minimal dose overlap between the 2 breasts, and therefore bilateral treatment with APBIMRT was technically feasible.

The debate over the clinical role of APBI is not likely to be resolved until results are available from the large randomized clinical trials. Nevertheless, the favorable local control and late toxicity profiles detailed in this report continue to support APBIMRT as a promising treatment option worthy of further investigation. With the increasing attention to cost-effective health resource allocation, the greater cost of IMRT (relative to the 3D-CRT technique) may partially account for the lack of trials investigating the use of IMRT to deliver APBI. A careful comparison of outcomes from patients treated with APBI using 3D-CRT and IMRT—that specifically addresses whether the dosimetric advantages afforded by IMRT translates into meaningful clinical benefit—is a prerequisite for any meaningful cost-effectiveness analysis between 3D-CRT and IMRT. It should be noted, however, that APBIMRT has been shown to cost substantially less than single-catheter APBI techniques [64], and still remains attractive compared to conventional WBI over 6 weeks, or even hypofractionated WBI over 4 weeks, in terms of cost to payers [64], impact on departmental resources [65], and presumably overall societal cost, even more so when decreased transportation costs and time off from work are taken into account.

We previously demonstrated that IMRT provides excellent treatment target coverage while generally reducing the volume of ipsilateral breast, chest wall, lung, and heart exposed to high doses [36], and that increased pain correlated with larger chest wall and overall volumes receiving >75 % of the prescribed dose [37]. This report provides a significant update with a greater number of patients and longer follow-up that is especially relevant in the current context of discrepant cosmesis and toxicity reported by various APBI studies utilizing EBRT. Our currently enrolling Phase III randomized study will include a direct comparison of clinical outcomes of patients treated with APBI-using 3D-CRT and IMRT techniques.

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