Radiotherapy and Oncology 100 (2011) 210–214

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Partial breast irradiation

Twelve-year clinical outcomes and patterns of failure with accelerated partial breast irradiation versus whole-breast irradiation: Results of a matched-pair analysis

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ARTICLE INFO

Article history:
Received 20 December 2010
Received in revised form 15 March 2011
Accepted 20 March 2011
Available online 15 April 2011

Keywords:
Breast cancer
Breast-conserving therapy
Accelerated partial breast irradiation
APBI
Brachytherapy
Local recurrence

ABSTRACT

Background and Purpose: To compare 12-year outcomes of accelerated partial breast irradiation (APBI) versus whole-breast irradiation (WBI) in patients treated with breast conservation.
Materials and Methods: A matched-pair analysis was performed using 199 patients receiving WBI and 199 patients receiving interstitial APBI. Match criteria included tumor size, age, nodal status, ER status, and the use of adjuvant hormonal therapy. Patterns of failure and efficacy of salvage treatments were examined.
Results: No differences were seen in the 12-year rates of local recurrence (3.8% vs. 5.0%, $p = 0.40$), regional recurrence (0% vs. 1.1%, $p = 0.15$), disease free survival (DFS) (87% vs. 91%, $p = 0.30$), cause-specific survival (CSS) (93% vs. 95%, $p = 0.28$), or overall survival (OS) (78% vs. 71%, $p = 0.06$) between the WBI and APBI groups, respectively. The rate of distant metastases was lower in the APBI group (10.1% vs. 4.5%, $p = .05$). Following LR, no difference in outcome was seen between the two groups with 5 year post-LR rates of DFS (80% vs. 86%, $p = 0.55$), CSS (88% vs. 75%, $p = 0.77$), and OS (88% vs. 75%, $p = 0.77$), respectively.
Conclusions: With 12-year follow-up, APBI produced outcomes equivalent to WBI. Following LR, patients treated with APBI also had similar failure patterns to those managed with WBI.
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With the publication of multiple phase III randomized trials with long-term follow-up demonstrating the equivalence of mastectomy and breast-conserving therapy (BCT), lumpectomy followed by adjuvant radiation has become a mainstay in the treatment of early-stage breast cancer. One of the concerns with the use of BCT, however, is the protracted six to seven week course of adjuvant radiation therapy with studies finding that up to 20% of patients do not receive adjuvant radiation therapy [1–2]. One strategy that has been studied to shorten the course of radiation therapy, while delivering biologically equivalent doses, is accelerated partial breast irradiation (APBI). This technique limits the radiation target to the volume surrounding the surgical cavity with a variable margin and reduces treatment time to one week or less.

Accelerated partial breast irradiation can be delivered utilizing interstitial catheters, applicator-based brachytherapy treatment (including intra-operative radiation), or external beam radiotherapy (i.e., 3D-CRT) and has been shown not only to be feasible, but also associated with excellent clinical outcomes with 5–10 years of follow-up [3–10]. Currently, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413 phase III trial is enrolling patients with Stage I–II invasive ductal carcinoma (IDC) or ductal carcinoma in situ (DCIS) and randomizing them to either adjuvant whole breast irradiation or APBI delivered via interstitial, 3-D conformal, or balloon-based brachytherapy. Results from this trial, however, will not be available for several years. As a result, a previous matched-pair analysis from our institution was performed and found comparable clinical outcomes between a cohort of 199 women who received whole-breast radiation (WBI) and 199 women who received interstitial-based APBI [11]. Since our initial publication, results from a meta-analysis of 1041 patients have suggested an increase in local and axillary recurrences with APBI [12]. The purpose of this study was to update the results of our initial matched-pair analysis with 12-year follow-up and to compare outcomes with salvage treatment following local failures in APBI and WBI patients.

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doi:10.1016/j.radonc.2011.03.011

Materials and methods

Patient population

A total of 221 patients with invasive early-stage breast cancer were prospectively treated at William Beaumont Hospital with APBI, receiving interstitial brachytherapy to the tumor bed as part of their BCT from October 1992 to November 2001. This population included a total of 158 women who were prospectively enrolled on one of three IRB-approved APBI protocols. Our inclusion and exclusion criteria have been previously published [13]. Treatment techniques included a low-dose rate implant which delivered 50 Gy over 96 h at 0.52 Gy/h and a high-dose rate (HDR) implant that delivered either 32 Gy in 8 fractions BID or 34 Gy in 10 fractions BID. For the WBI patients selected for this study, there were a total of 1861 women with invasive early-stage breast cancer who were treated with whole-breast irradiation (WBI) at our institution between December 1992 and November 1996. This group served as the basis for the WBI cohort. Follow up was complete through August 2010.

Matched-pair analysis and outcomes

In order to evaluate clinical outcomes between comparable groups of patients, each APBI patient was matched with one WBI patient. Patients were matched according to tumor size (±5 mm), nodal status (negative vs. 1–3 positive), ER status (positive vs. negative vs. unknown), the use of adjuvant hormonal therapy (yes vs. no), and age (±10 years) as per the previous matched-pair analysis [11]. A total of 199 matches were made. Clinical outcomes that were analyzed include local recurrence (LR) (ipsilateral breast tumor recurrence), regional recurrence (RR), distant metastases (DM), disease free survival (DFS), cause-specific survival (CSS), and overall survival (OS). Local recurrence was defined as a recurrence of cancer in the treated breast before or at the same time as a regional or distant failure. These local recurrences were examined and were defined as either a true recurrence/marginal miss or an elsewhere failure based on previously published criteria [14]. A true recurrence/marginal miss consists of a failure within or immediately adjacent to the treated volume whereas an elsewhere failure was a failure a few centimeters or more away from the treated volume. Regional recurrence was defined as a failure within the regional lymphatics (axillary, supraclavicular, or internal mammary nodes). Distant metastases were determined by a combination of clinical, radiographic, and pathologic factors. Disease-free survival was defined as survival without a LR, RR, or DM. Cause-specific survival was defined as any death that could be attributed to breast cancer while overall survival was defined as death secondary to any cause. Patient characteristics for each group in the matched-pair analysis were analyzed including age, tumor size, receptor status, margin status, lymph node status, adjuvant hormonal therapy, adjuvant chemotherapy, and follow up. Rates of LR were analyzed by ASTRO consensus group [15]. Univariate analysis of LR was performed in order to analyze the impact of age, tumor size, receptor status, margin status, nodal status, hormonal therapy and chemotherapy. Patterns of failure following LR were analyzed following a chart review of patients who developed a LR in order to determine the efficacy of salvage treatments following interstitial APBI and WBI. Rates of DFS, CSS and OS were calculated following LR for both APBI and WBI patients.

Statistical analyses

The rates of LR, RR, DM, DFS, CSS and OS were determined by utilizing the Kaplan–Meier method while the statistical significance of differences between the arms of the matched-pair analyses was calculated using a log-rank test. All time intervals were calculated utilizing the date of radiation therapy (RT) completion. The association of categorical variables by treatment group for both matched-pair analyses was performed utilizing Pearson's Chi-Square test. The differences between two sample means of continuous variables were analyzed utilizing Student's unpaired *t*-test. Regression analysis was performed using the Cox proportional hazards model. The analysis was designed to exclude with 90% power at a 5% significance level, an increase in the 12-year rate of local recurrence of 2%. This required 135 patients to be analyzed [16,17]. A *p*-value of $\leqslant 0.05$ was considered statistically significant. Statistical analyses were performed utilizing SYSTAT version 13 (SYSTAT Software, Chicago, IL) and all statistical tests were two-sided.

Results

WBI versus Interstitial APBI

A total of 199 matched-pairs were made between the two groups. Table 1 lists clinical, pathologic, and treatment related characteristics between the two groups. The median follow-up was 14.5 years (0.7–25.5 years) for the WBI patients and 10.7 years (0.1–16.9 years) for the interstitial APBI patients ($p < 0.001$). For surviving patients, the median follow-up was 15.3 years (7.5–25.5) for the WBI group and 12.2 years (2.0–16.7) for the interstitial group. The two groups were well balanced with respect to age, tumor size, receptor status, and T stage. However, patients in the APBI cohort received adjuvant hormonal therapy less frequently (40% vs. 57%, $p < 0.001$) and adjuvant chemotherapy more frequently (4% vs. 13%, $p < 0.001$). Further, the APBI patients were more likely be node positive (2% vs. 12%, $p < 0.001$), and less likely to have negative margins (99.5% vs. 97.0%, $p = 0.05$).

Treatment outcomes for the matched-pair analysis are displayed in Table 2. With 12-year follow-up, clinical outcomes between the two groups were similar. The rate of local recurrence was 3.8% (95% Confidence Interval (CI): 1.5–6.1%) in the WBI group compared with 5.0% (95% Confidence Interval (CI): 2.4–7.6%) in the

Table 1
Clinical, pathologic and treatment related characteristics for the WBI and APBI patients.

	WBI ($n = 199$)	Interstitial APBI ($n = 199$)	*p*-value
Age at diagnosis, mean (years)	63.5	65.1	0.11
Tumor size (mm)	12.3	11.7	0.31
ER+	85%	86%	0.85
PR+	67.5%	69.4%	0.73
Margins			0.05*
Negative	99.5%	97.5%	
Positive	0.5%	0%	
Close	0%	2.5%	
T-Stage			0.10
T1	86.9%	92.0%	
T2	12.6%	8.0%	
T3	0.5%	0%	
Lymph node status			<0.001*
Node negative	88.4%	88.4%	
Node positive	2.0%	11.6%	
Unknown	9.5%	0%	
Adjuvant hormonal therapy	57.3%	39.7%	<0.001*
Adjuvant chemotherapy	3.5%	12.6%	<0.001*
Follow up (years)	14.0	10.4	<0.001*

Abbreviations: WBI = whole-breast irradiation and APBI = accelerated partial breast irradiation.
* Statistically significant.

Table 2
Twelve-year outcomes between WBI and APBI patients.

12-year actuarial	WBI (%)	Interstitial APBI (%)	*p*-Value
LR	3.8	5.0	0.40
RR	0	1.1	0.15
DFS	87	91	0.30
DM	10.1	4.5	0.05*
CSS	93	95	0.28
OS	78	71	0.06

Abbreviations: WBI = whole-breast irradiation, APBI = accelerated partial breast irradiation, LR = local recurrence, RR = regional recurrence, DFS = disease-free survival, DM = distant metastases, CSS = cause-specific survival and OS = overall survival.
* Statistically significant.

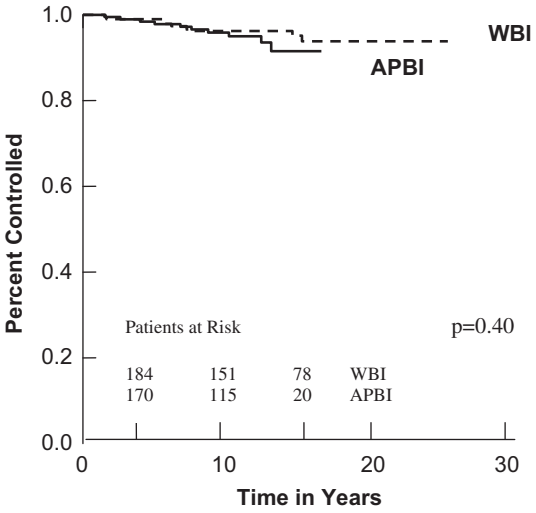

Fig. 1. Freedom from local failure for APBI and WBI patients. APBI = accelerated partial breast irradiation and WBI = whole breast irradiation.

APBI group ($p = 0.40$) (Fig. 1). Regional recurrence rates were 0% in the WBI cohort and 1.1% (95% Confidence Interval (CI): −0.7–2.9%) in the APBI group ($p = 0.15$). No differences were seen in DFS (87% (95% Confidence Interval (CI): 84.2–90.2%) vs. 91% (95% Confidence Interval (CI): 88.2–94.0%), $p = 0.30$) between the WBI and APBI patients. There was a trend for improved OS with the WBI group (78% (95% Confidence Interval (CI): 74.5–81.3%) vs. 71% (95% Confidence Interval (CI): 67.4–74.6%), $p = 0.06$); however, there was no difference in CSS between the groups CSS (93% (95% Confidence Interval (CI): 90.4–95.8%) vs. 95% (95% Confidence Interval (CI): 92.5–97.7%), $p = 0.28$) (Fig. 2). Distant metastases were lower in the APBI group (10.1% (95% Confidence Interval (CI): 7.2–13.0%) vs. 4.5% (95% Confidence Interval (CI): 2.0–7.0%), $p = 0.05$) with freedom from DM displayed in Fig. 3.

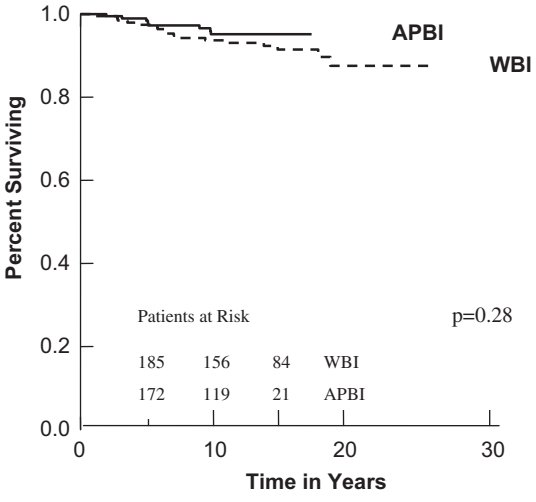

Fig. 2. Cause-specific survival for APBI and WBI patients. APBI = accelerated partial breast irradiation and WBI = whole breast irradiation.

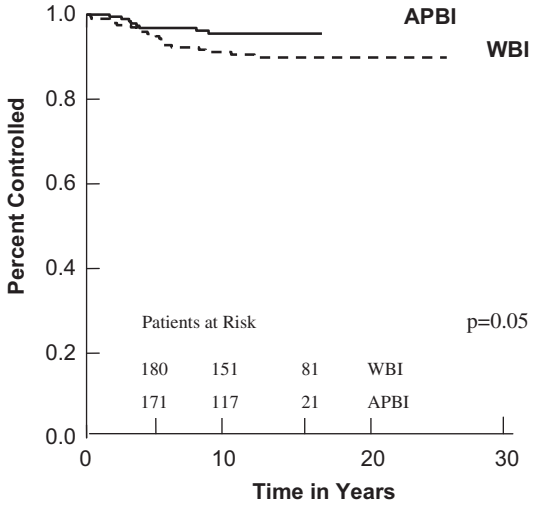

Fig. 3. Freedom from distant metastases for APBI and WBI patients. APBI = accelerated partial breast irradiation and WBI = whole breast irradiation.

Local control analysis

The APBI cohort of patients ($n = 199$) were grouped by the ASTRO consensus panel statement with 95 patients (47.7%) in the suitable group, 63 patients (31.7%) in the cautionary group, and 41 patients (20.6%) in the unsuitable group. The 12-year rates of LR were 4.4%, 7.4%, and 2.4% for the suitable, cautionary, and unsuitable groups, respectively ($p = 0.61$). Of note, 2 of the 10 LR in the APBI group occurred after 12 years, one in the suitable group and one in the unsuitable group.

Univariate analysis for LR was performed on all patients, including separate analyses for the APBI and WBI groups (Table 3). Analysis of the entire group found only younger age to be significantly associated with LR ($p = 0.02$) with no impact of tumor size, receptor status, hormonal therapy, adjuvant chemotherapy, lymph nodes status, or margin status. In the WBI cohort, younger age was the

Table 3
Univariate analysis of factors potentially associated local recurrence.

Characteristic	All patients	APBI	WBI
Age	0.02*	0.66	0.003*
ER status	0.07	0.09	0.42
PR status	0.39	0.12	0.73
Her-2 status	–	0.31	–
Tumor size	0.74	0.53	0.92
Hormonal therapy	0.42	0.03*	0.16
Chemotherapy	0.96	0.96	0.97
Margins	0.64	0.96	0.98
Nodal status	0.73	0.85	0.74
ASTRO consensus group	–	0.88	–

Abbreviations: WBI = whole-breast irradiation and APBI = accelerated partial breast irradiation.
* Statistically significant, –: not applicable or available.

only variable associated with LR. Age, receptor status, tumor size, adjuvant chemotherapy, nodal status, and margins were not found to be associated with LR in the APBI; however, the use of hormonal therapy was found to be significant ($p = 0.03$).

Salvage therapy following local recurrence

A total of 10 LR's occurred in the cohort of 199 APBI patients and 9 LR's in the cohort of WBI patients. In the APBI patients, 70% (7/10) of the LR were deemed to be elsewhere breast failures based on clinical, radiographic, and pathologic data. This is similar to the WBI patients where 5 of the 9 (55.6%) patients had elsewhere breast failures. The median time to LR was 6.8 years for all 19 failures. The median time to LR was 7.2 years (range: 1.5–13.2 years) for the APBI patients and 6.2 years (1.6–15.3 years) for WBI patients ($p = 0.98$). The median time to LR for the suitable, cautionary, and unsuitable interstitial patients was 8.9 (range: 5–13.2 years), 5.4 (range: 2.6–8.8 years), and 7.0 years (range: 1.5–12.5 years), respectively ($p = 0.53$). Following LR, the mean follow-up for the APBI and WBI groups was 4.9 (range: 1.8–8.9 years) and 8.7 years (range: 1.0–16.8 years) ($p = 0.08$), respectively. In the APBI group, eight patients underwent mastectomy following LR and two patients received a lumpectomy with adjuvant balloon-based brachytherapy. For all patients who developed a LR, the 5 year post-LR DFS, CSS and OS rates were all 81%. No difference was noted in the 5 year post-LR DFS for the APBI and WBI patients (80% vs. 86%, $p = 0.55$). In addition, no difference in CSS (88% vs. 75%, $p = 0.77$) or OS (88% vs. 75%, $p = 0.77$) was found between the APBI and WBI patients.

Discussion

The results of this study demonstrate that with 12 years of follow-up, clinical outcomes between APBI patients matched with an equivalent group of WBI patients were comparable. In addition, no differences were noted in patterns of failure between the two groups. Despite a recent meta-analysis suggesting increased rates of LR and RR with APBI, the results of this matched-pair analysis do not support this conclusion and add to the growing body of literature supporting the use of APBI in appropriately selected patients with early-stage breast cancer [3–12].

Published results with APBI

Multiple retrospective, single institution experiences have been published addressing the use of APBI in relatively low risk patients. Various APBI techniques have been employed including interstitial brachytherapy, balloon and applicator-based brachytherapy, single-fraction intra-operative RT (IORT), and 3D-CRT. Despite the excellent results seen in the majority of these analyses, very little phase III data are available comparing APBI versus a standard regimen of 6 weeks of WBI.

Polgar et al. have published their results from a small phase III trial investigating the use of APBI. In this study, 258 patients were randomized to receive either WBI (50 Gy/25 fractions) or APBI (36.4 Gy/7 fractions, twice daily) delivered with multi-catheter HDR (69%) or limited electron fields (31%). They found no difference in local control at 5 years (3.4% WBI vs. 4.7% APBI) and noted improved excellent/good cosmesis in the APBI patients (78% vs. 63%) [4]. Further, 12 year outcomes in a prospective trial from Hungary found the 5, 10, and 12-year rates of LR to be 4.4%, 9.3% and 9.3%, respectively, following interstitial APBI [18]. In addition, Vaidya et al. recently published their results using single-fraction IORT as an APBI technique. With 25-month follow-up, they found no difference in the rate of LR (IORT 1.2% vs. WBI 0.95%), with no significant difference in complications or toxicities between the two treatments [19].

To our knowledge, our study represents the largest set of APBI patients matched to comparable WBI patients. With a 12-year length of follow up, we have demonstrated excellent long-term rates of local control using interstitial APBI. Obvious limitations to this matched-pair analysis include the fact that patient groups differed with respect to length of follow-up and that the matched-pairs did not encompass all clinical, pathologic or treatment related characteristics, which could potentially affect outcome. Most notably, our APBI cohort had higher rates of nodal involvement and close margins. Nonetheless, short of phase III data, these results present relatively objective evidence demonstrating the long-term efficacy of this technique in appropriately selected patients.

Phase III trials addressing the efficacy of APBI

There are additional phase III trials that are either ongoing or have recently completed accrual addressing the use of APBI versus WBI using a variety of APBI techniques. The largest phase III trial using three different APBI techniques is NSABP B39/RTOG 0413 trial. In this study, eligible patients include those with Stage I–II IDC or DCIS. Patients are randomized to adjuvant whole breast irradiation or APBI delivered via interstitial, 3-D conformal, or intracavitary techniques. The enrollment goal for this study is 4300 patients. Because the trial is presently limited to only patients with higher-risk features (node positive, age less than 50, or ER negative), accrual is not expected to be completed until February 2013 with results not available until several years later [20]. Veronesi and colleagues at the European Institute of Oncology have also recently completed accrual to their phase III trial of single-fraction IORT (ELIOT) after quandrantectomy. Over 1300 patients have been enrolled and results of this trial are anticipated shortly. Currently, the Ontario Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) trial is accruing patients and seeks to compare hypofractionation (42.5 Gy/6 fractions) with APBI delivered with a 3D-CRT technique delivering 38.5 Gy in 10 fractions on a twice-daily basis. Eligible patients for this trial include those older than 40 with either DCIS or invasive cancer that are lymph node negative and have adequate surgical resection margins.

Patterns of failure following LR

The results of this study also suggest that following salvage for LR, patients who initially received APBI have outcomes comparable to those patients who had a LR after being initially treated with WBI. At 5 years following LR there was no difference in the rates of DFS, CSS, or OS between our two cohorts. Our 5-year survival rates following LR with APBI compare favorably to a previous series examining outcomes following LR with WBI patients. Fredriksson et al. examined outcomes in 391 patients who developed a LR following BCT. The 5-year rates of DFS and OS in their series were 84 and 85%, respectively, comparable to our results with interstitial APBI patients [21]. Recent reports; however, have also shown less-than encouraging results with 5-year DFS and OS following treatment of a LR after BCT to be between 51–65% and 60–81%, respectively [22–24], which is lower than the 5-year data for our WBI and interstitial patients treated for recurrence following breast conserving therapy.

Conclusion

With 12 years of follow-up, we found no difference in clinical outcome or patterns of failure in 199 patients treated with APBI matched with a comparable group of patients treated with WBI.

Following LR, WBI or APBI patients had equivalent 5-year outcomes with salvage therapies.

Conflict of interest statement

None declared.

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