Dosimetric Comparison of Treatment Techniques: Brachytherapy, Intensity-Modulated Radiation Therapy, and Proton Beam in Partial Breast Irradiation

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Abstract

Purpose: To perform a dosimetric comparison of 3 accelerated partial breast irradiation techniques: catheter-based brachytherapy (BT), intensity-modulated radiation therapy (IMRT), and proton beam therapy (PBT).

Patients and Methods: Twelve patients with left-sided breast cancer treated with SAVI (Strut-Adjusted Volume Implant) were selected in this study. The original BT plans were compared with optimum plans using IMRT and PBT for 34 Gy (RBE) with 1.1 RBE in 10 fractions using identical parameters for target and organs at risk.

Results: Significant reduction in maximum dose to the ipsilateral breast was observed with PBT and IMRT (mean 108.58% [PBT] versus 107.78% [IMRT] versus 2194.43% [BT], $P = .001$ for both PBT and IMRT compared to BT). The mean dose to the heart was 0%, 1.38%, and 3.85%, for PBT, IMRT, and BT, respectively ($P < .001$ and $P = .026$). The chest wall mean dose was 10.07%, 14.65%, and 29.44% for PBT, IMRT, and BT, respectively ($P = .001$ and .013 compared to BT). The PBT was superior in reducing the mean ipsilateral lung dose (mean 0.04% versus 2.13% versus 5.4%, $P = .025$ and $P < .001$). There was no statistically significant difference in the maximum dose to the ipsilateral lung, chest wall, 3-mm skin rind or in the mean ipsilateral breast $V_{50\%}$ among the 3 techniques ($P = .168$, .405, .067, and .780, respectively). PBT exhibited the greatest mean dose homogeneity index of 4.75 compared to 7.18 for IMRT ($P = .001$) and 195.82 for BT ($P < .001$). All techniques resulted in similar dose conformality ($P = .143$).

Conclusion: This study confirms the dosimetric feasibility of PBT and IMRT to lower dose to organs at risk while still maintaining high target dose conformality. Though the results of this comparison are promising, continued clinical research is needed to better define the role of PBT and IMRT in the accelerated partial breast irradiation treatment of early-stage breast cancer.

Keywords: partial breast irradiation, brachytherapy, intensity-modulated radiation therapy, proton beam therapy

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Introduction

Breast conservation therapy consisting of lumpectomy followed by adjuvant whole-breast irradiation has become standard of care as an alternative to mastectomy for most women with early-stage breast cancer after confirmation of equivalent disease-free survival and overall survival in several prospective randomized trials [1–3]. Further, it has been found that most ipsilateral breast tumor recurrences occur in close proximity to the site of the original tumor [2, 4]. Such findings, along with a desire to increase the efficiency of adjuvant therapy while minimizing the volume of breast treated and thus decrease normal tissue effects, led to the development of accelerated partial-breast irradiation (APBI) also known as partial-breast irradiation. There are now several partial-breast irradiation techniques available to clinicians, including brachytherapy (BT) using single-lumen and multi-lumen catheter devices, external beam radiation therapy, and electronic and intraoperative therapy. The selection is based primarily on the personal choice of the surgeon and radiation oncologist.

In an effort to further minimize the dose to nontarget breast tissue and surrounding organs at risk (OARs), several techniques have been explored including respiratory gating, prone patient positioning, and using more sophisticated, advanced radiation technologies such as intensity-modulated radiation therapy (IMRT). Livi et al [5] reported their results of a prospective randomized trial comparing APBI with IMRT to whole-breast irradiation. At a median follow-up of 5 years, they reported no statistically significant difference in ipsilateral breast tumor recurrence rate or 5-year overall survival between the 2 arms, noting that the APBI group had significantly improved acute and late toxicities and cosmesis. Furthermore, a phase I/II study by Bergom et al [6] evaluated the feasibility of external beam APBI in the prone position, using image-guided IMRT.

Proton beams provide unique dose distribution governed by the maximum range of the beam. There is no dose beyond the range; hence, the undesirable dose to normal tissues could be significantly reduced in proton beam therapy (PBT). Proton therapy differs from photon-based modalities owing to the finite range of dose deposition within tissue. With protons, radiation is delivered to the selected depth of the target, thus limiting exposure to normal tissues beyond the target [7]. The finite range of the proton beam makes it suitable for use in the treatment of many sites including breast where lung and heart are critical structures to avoid. Theoretically, PBT may reduce the late toxicities of radiation treatment, especially in the left breast where cardiac toxicities are of high importance [8–14]. Given these potential benefits, PBT has been attempted for breast treatment with success in reducing ipsilateral breast, heart, and lung dose [15–18]. With availability of proton beam in every part of the country, the role of PBT in the treatment of breast cancer is currently being evaluated. Bush et al [19] reported their 5-year results of a phase II trial of PBT using multiple fields treated daily and skin-sparing techniques to deliver partial breast treatment. They reported an ipsilateral breast tumor recurrence-free survival of 97%, disease-free survival of 94%, and overall survival of 95% with no cases of grade 3 or higher acute skin reactions and with 7 cases of grade 1 telangiectasia. Overall cosmesis was good to excellent in 90% of patients [19].

At our institution, we have chosen to use the SAVI (Strut-Adjusted Volume Implant, Cianna Medical, Aliso Viejo, California) device for APBI. This device consists of a central catheter surrounded by 6, 8, or 10 peripheral catheters that can be differentially loaded to allow shaping of the dose distribution to patient anatomy and therefore maximize tumor bed dose while minimizing normal tissue dose. Given the promising results of the abovementioned studies, we performed a direct dosimetric comparison of 3 APBI techniques—BT using the SAVI device, IMRT, and PBT—to explore the potential for further reducing dose to the ipsilateral nontarget breast tissue and surrounding OARs while still maintaining high dosimetric conformality. We specifically focused on left-sided breast cancer owing to increased radiation exposure to the heart in patients with breast cancer treated with radiation therapy [8, 13]. Herein, we report our dosimetric findings comparing 3 techniques: SAVI-BT, IMRT, and PBT.

Materials and Methods

Under institutional review board exempt status, 12 patients with early-stage left-sided breast cancer treated with APBI using the SAVI device at our institution from December 2012 to October 2014 were retrospectively selected for inclusion in this study. At the time of initial treatment planning, the SAVI device surface was defined as the structure represented by a contour created by directly connecting each strut. The PTV_{Eval} was then defined, per the Radiation Therapy Oncology Group (RTOG) 0413 protocol, as a 1-cm uniform expansion of the device surface contour less the volume of the device surface contour. This volume was cropped off the chest wall musculature, ribs, and/ or 5 mm from the skin surface as necessary. OARs were also contoured per the RTOG 0413 protocol and included the heart, ipsilateral breast, ipsilateral chest wall, ipsilateral lung, and 3-mm skin rind. The ipsilateral breast contour included all tissue volume, excluding lung and any nonbreast structure deep to the lung-rib interface, within the boundaries of the standard whole breast tangential fields. Only the SAVI device surface contour

(and not the PTV_{Eval}) was excluded from the ipsilateral breast volume. Patients were treated with 34 Gy in 10 fractions given twice daily with at least 6 hours between fractions over a 5-day period, based on treatment plans generated by the BrachyVision-v11 (Varian Medical Systems, Palo Alto, California) treatment planning system.

For IMRT and proton beam, a new PTV was defined that consisted of the SAVI device surface contour with a 1-cm expansion. At some institutions, if patients were to be treated with protons or IMRT, the treated volume would be much smaller than the volume described here owing to expansion of the lumpectomy cavity as a result of expansion of the struts. The air cavity and metallic component related image artifacts were modified to water equivalent density. Separate IMRT and PBT plans for each patient were created by using this modified PTV. The IMRT plans used a 5-field noncoplanar technique with 6-MV photons individualized for patient anatomy. The IMRT plans were performed with dose calculation algorithm (analytical anisotropic algorithm, AAA from Eclipse, version 11 software [Varian Medical Systems Inc, Palo Alto, CA]) correcting for inhomogeneity. Similarly, the proton plans used a 3-field coplanar technique individualized for patient anatomy. For target coverage, it was required that 90% of the PTV receive 100% of the prescription dose. Eclipse version 11 software was used for proton treatment planning using our uniform scanning proton beam with standard 3.5% proton range uncertainty. The identical dose prescription to that of SAVI (34 Gy in 10 fractions) was used except in proton beam dose, which was multiplied by 1.1 to account for relative biological effectiveness. The calculation grid size in all cases was 2.5 mm. It is well known that most brachytherapy plannings do not use inhomogeneity correction, which was the case in this study too.

Dose-volume histogram analysis was performed to compare conformality, dose homogeneity, and normal tissue avoidance. Specifically, the maximum dose point, maximum dose in 1 cm^3 volume, and mean dose to the heart, ipsilateral breast, ipsilateral lung, ipsilateral chest wall, and skin, the ipsilateral breast $V_{50\%}$ (percentage volume of the ipsilateral normal breast receiving 50% of the prescription dose), $V_{95\%}$ (percentage volume of the PTV that received 95% of the prescription dose), $V_{100\%}$ (percentage volume of the PTV that received 100% of the prescription dose), $D_{2\%}$ (dose covering 2% volume of PTV), $D_{98\%}$ (dose covering 98% volume of PTV), D_{mean} (the ratio of mean dose to the PTV to the prescription dose), homogeneity index (HI) ($[D_{2\%} - D_{98\%}]/D_{mean}$), and the conformality index ($V_{95\%}$ or $V_{100\%}$/PTV volume), as defined in ICRU-83 [20], were determined for each plan. One-way analysis of variance was used to compare dosimetric differences among plans in parameters using the 3 techniques with significance defined as a $P < .05$. Statistical analysis was performed with SPSS version 20 (IBM Corp, Armonk, New York).

Results

Figure 1 shows an example of comparative treatment planning for a patient treated with APBI included in this study. The dose distribution in all 3 planes is visually clear, indicating a possible advantage of proton beam. The dosimetric results are summarized in **Table 1**. For intercomparison, doses are reported as a percentage of the prescription dose. BT resulted in a significantly higher maximum dose to the ipsilateral breast than both proton and IMRT (mean 2194.43% [BT] versus 108.58% [PBT] and 107.78% [IMRT], $P = .001$ for both BT versus PBT and BT versus IMRT) and a higher maximum heart dose than PBT (mean 16.35% [BT] versus 0.43% [PBT], $P < .001$). The IMRT plan resulted in a significantly lower maximum skin surface dose than BT and PBT (mean 45.37% [IMRT] versus 83.10% [BT] and 84.98% [PBT], $P < .001$ for both IMRT versus BT and IMRT versus PBT) owing to controlled optimization of the IMRT plan, although the accuracy of skin dose calculation could be questionable as reported by Akino et al [21]. There was no statistically significant difference in the maximum dose to the ipsilateral lung, chest wall, 3-mm skin rind or in the ipsilateral breast $V_{50\%}$ among all 3 techniques ($P = .168$, .405, .067, and .780, respectively).

Similarly, BT resulted in a significantly higher dose to 1 cm^3 volume of the ipsilateral breast than both PBT and IMRT (mean 433.81% [BT] versus 104.40% [PBT] and 105.15% [IMRT], $P < .001$ for both BT versus PBT and BT versus IMRT) and higher dose to 1 cm^3 volume of heart than PBT (mean 14.23% [BT] versus 0% [PBT], $P < .001$). The BT also resulted in a significantly higher dose to 1 cm^3 volume of ipsilateral lung than PBT and IMRT (mean 41.82% [BT] versus 10.55% [PBT] and 20.74% [IMRT], $P = .001$ for BT versus PBT and 0.024 for BT versus IMRT). There was no statistically significant difference in the dose to 1 cm^3 volume of chest wall among the 3 techniques ($P = .605$).

Additionally, BT resulted in a significantly higher mean dose to the heart and ipsilateral chest wall than both PBT and IMRT (heart mean 3.85% [BT] versus 0% [PBT] and 1.38% [IMRT], $P < .001$ for BT versus PBT and $P = .026$ for BT versus IMRT; and ipsilateral chest wall mean 29.44% [BT] versus 10.07% [PBT] and 14.65% [IMRT], $P = .001$ for BT versus PBT and 0.013 for BT versus IMRT). The PBT resulted in a significantly lower mean dose to the ipsilateral breast than BT and IMRT (mean 14.85% [PBT] versus 24.93% [BT] and 25.33% [IMRT], respectively, $P = .004$ for PBT versus BT and 0.003 for PBT versus

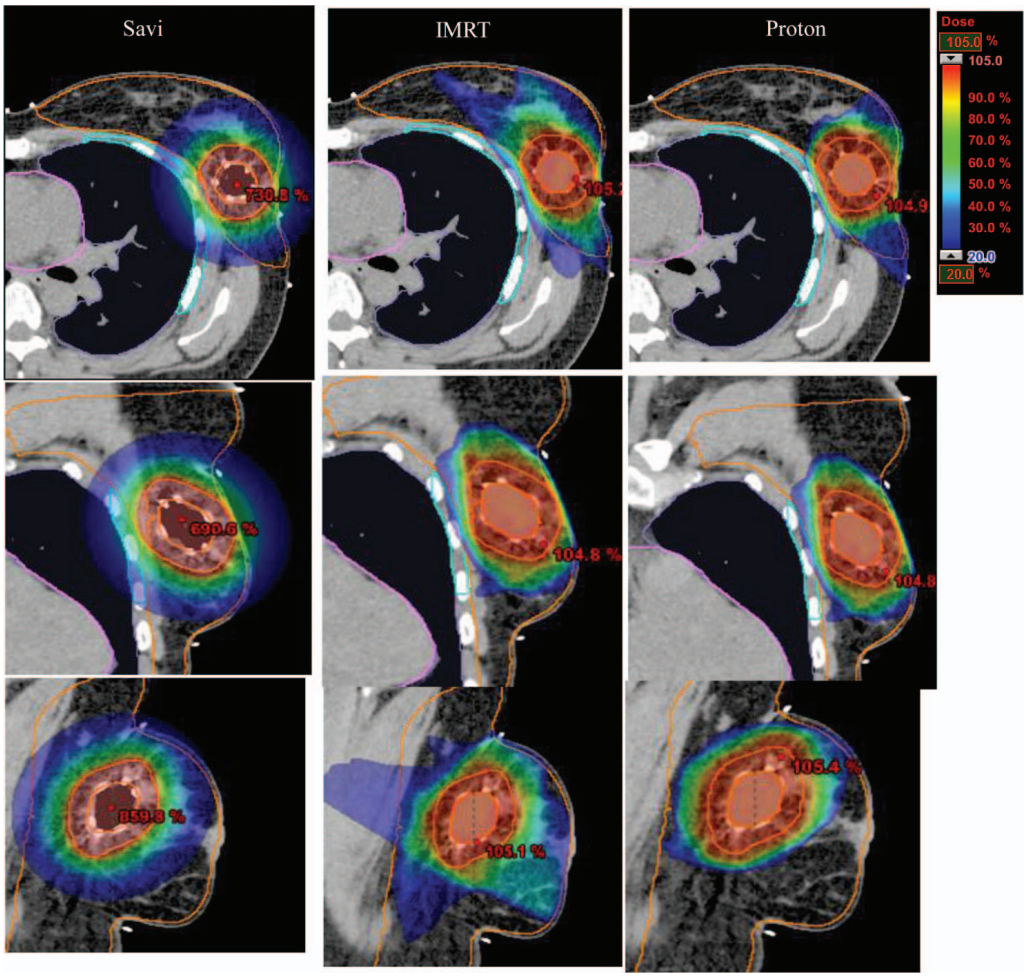

Figure 1. Comparative accelerated partial breast irradiation treatment planning for a patient included in this study. The patient was treated by using the SAVI device (left). Separate intensity-modulated radiation therapy (middle) and proton beam therapy (right) plans were created with equivalent D (RBE) of 34 Gy (RBE) for dosimetric comparison. All 3 plans are shown for comparison. The color wash indicates the percentage dose values. Abbreviation: SAVI, Strut-Adjusted Volume Implant.

IMRT). The mean ipsilateral lung dose was 5.40% for BT, 2.13% for IMRT, and 0.04% for PBT. This was significantly different among all techniques ($P = .001$ for BT versus IMRT, $P < .001$ for BT versus PBT, and $P = .025$ for IMRT versus PBT).

Dose HI was significantly different among all techniques, with PBT exhibiting the greatest homogeneity with a HI of 4.75 compared to 195.82 for BT and 7.18 for IMRT (mean $P = .001$ for BT versus IMRT, $P < .001$ for BT versus PBT, and $P = .025$ for IMRT versus PBT). All techniques resulted in similar conformality ($P = .143$).

On multivariate analysis, all parameters remained significant with the exception of maximum dose to the skin surface (**Table 2**).

Discussion

We performed a direct dosimetric comparison of 3 APBI techniques—BT using the SAVI device, IMRT, and proton beam—specifically focusing on patients with left-sided breast cancer. The purpose of this comparison was to evaluate the potential for further reducing dose to the ipsilateral nontarget breast tissue and surrounding OARs with IMRT and/or PBT, compared to our institutional practice of treating early-stage breast cancers with APBI using the SAVI device. Further, we aimed to achieve this reduction in dose to normal tissues while still maintaining the high conformality afforded by brachytherapy-based APBI.

Our results show that compared to BT, PBT resulted in a significantly reduced maximum dose, dose to 1 cm^3 volume, and mean dose to the ipsilateral breast and heart, a reduced mean dose to the ipsilateral lung and chest wall, and a reduced dose to 1 cm^3 volume to the ipsilateral lung. Similarly, IMRT resulted in a significantly reduced maximum dose and dose to 1 cm^3 volume to the ipsilateral breast, a reduced mean dose and dose to 1 cm^3 volume to the ipsilateral lung, and a reduced mean dose to the heart. In comparing PBT and IMRT, PBT was better than IMRT in reducing mean dose to the ipsilateral breast and lung, while IMRT was superior in reducing the maximum dose to the skin surface, although this parameter did not maintain significance on multivariate analysis.

Table 1. Summary of dosimetric comparisons among APBI techniques.

Parameters	BT (SAVI)	IMRT	PBT	*P* value
Maximum heart dose, %	16.35	12.60	0.43	<.001, BT vs. PBT
Maximum ipsilateral breast dose, %	2194.43	107.78	108.58	.001, BT vs. IMRT and BT vs. PBT
Maximum ipsilateral lung dose, %	50.43	28.97	34.41	.168
Maximum chest wall dose, %	89.97	67.38	68.01	.405
Maximum skin surface dose, %	83.10	45.37	84.98	<.001 for BT vs. IMRT and IMRT vs. PBT
Maximum skin 3-mm rind dose, %	121.91	95.49	99.65	.067
Mean heart dose, %	3.85	1.38	0.00	.026, BT vs. IMRT; .001, BT vs. PBT
Mean ipsilateral breast dose, %	24.93	25.33	14.85	.004, BT vs. PBT; .003 for IMRT vs. PBT
Mean ipsilateral lung dose, %	5.40	2.13	0.04	.001, BT vs. IMRT; <.001, BT vs. PBT, .025, IMRT vs. PBT
Mean chest wall dose, %	29.44	14.65	10.07	.013, BT vs. IMRT; .001, BT vs. PBT
Dose to 1 cm^3 volume of heart, %	14.23	9.55	0.00	<.001, BT vs. PBT
Dose to 1 cm^3 volume of ipsilateral breast, %	433.81	105.15	104.40	<.001, BT vs. IMRT and BT vs. PBT
Dose to 1 cm^3 volume of ipsilateral lung, %	41.82	20.74	10.55	.024, BT vs. IMRT; .001, BT vs. PBT
Dose to 1 cm^3 volume of chest wall, %	66.10	51.58	54.84	.605
Ipsilateral breast $V_{50\%}$, %	12.58	14.08	12.67	.780
$V_{95\%}$, %	93.83	99.45	99.84	.001, BT vs. IMRT and BT vs. PBT
$V_{100\%}$, %	89.35	90	90.00	.837
$D_{2\%}$, %	426.68	105.21	103.61	<.001 for all comparisons
$D_{98\%}$, %	90.02	97.86	98.81	.001, BT vs. IMRT and BT vs. PBT; 0.038, IMRT vs. PBT
D_{mean}, %	169.49	102.28	101.18	<.001 for all comparisons
Homogeneity index	195.82	7.18	4.75	<.001, BT vs. IMRT and BT vs. PBT; .001, IMRT vs. PBT
Conformality index, 95%	1.35	1.06	1.07	.143
Conformality index, 100%	1.29	0.96	0.96	.061
PTV volume, cm^3	74.81	104.63	104.63	.062

Dose is reported as a percentage of the prescription dose.

Abbreviations: APBI, accelerated partial-breast irradiation; BT, brachytherapy; SAVI, Strut-Adjusted Volume Implant; IMRT, intensity-modulated radiation therapy; PBT, proton beam therapy; $V_{50\%}$, percentage volume of the ipsilateral normal breast receiving 50% of the prescription dose; $V_{95\%}$, percentage volume of the PTV that received 95% of the prescription dose; $V_{100\%}$, percentage volume of the PTV that received 100% of the prescription dose; $D_{2\%}$, dose covering 2% volume of PTV; $D_{98\%}$, dose covering 98% volume of PTV; D_{mean}, the mean dose to the PTV compared to the prescription dose; PTV, planning target volume.

Table 2. Multivariate analysis of dosimetric parameters.

Parameters	*P* value
Maximum heart dose	.001
Maximum ipsilateral breast dose	<.001
Maximum skin surface dose	.855
Mean heart dose	<.001
Mean ipsilateral breast dose	.002
Mean ipsilateral lung dose	<.001
Mean chest wall dose	<.001
Dose to 1 cm^3 volume of heart	<.001
Dose to 1 cm^3 volume of ipsilateral breast	<.001
Dose to 1 cm^3 volume of ipsilateral lung	<.001
$V_{95\%}$	<.001
$D_{2\%}$	<.001
$D_{98\%}$	<.001
D_{mean}	<.001
Homogeneity index	<.001

Abbreviations: $V_{95\%}$, percentage volume of the PTV that received 95% of the prescription dose; $D_{2\%}$, dose covering 2% volume of PTV; $D_{98\%}$, dose covering 98% volume of PTV; D_{mean}, the mean dose to the PTV compared to the prescription dose.

On review of only dosimetric parameters, it would appear that PBT may be a preferred modality in terms of normal tissue sparing. However, it should be noted that there was no statistically significant difference in PTV volumes among the 3 techniques, likely relating to how the PTV was defined for the IMRT and PBT plans. In the RTOG 0413 protocol, the PTV used for the 3-dimensional conformal radiation therapy (3DCRT) APBI arm is created by uniformly expanding the lumpectomy cavity by 15 mm for the clinical target volume (CTV) with an additional uniform 10-mm expansion for the PTV to account for target motion and setup uncertainty. For this study, the decision was made to define the PTV as described in the "Materials and Methods" section, as the patients were initially scanned with the SAVI device in place, therefore distorting the architecture of the excision cavity. Had the PTV been defined per the RTOG 0413 protocol, the volumes would have likely been larger, resulting in increased dose to the normal tissues above what is reported in this study.

However, 2 studies examining PBT for APBI similarly found reduced doses to heart and ipsilateral lung, compared to other modalities. Moon et al [22] compared APBI with 3DCRT, IMRT, helical tomotherapy, and PBT techniques. They defined their PTV as a nonuniform expansion of the lumpectomy cavity by 1 to 2 cm. The average heart volume percentage receiving 20% and 10% of the prescription dose in 19 patients with left-sided breast cancer included in the analysis was significantly less for PBT than for other modalities, with values of 0% and 0% for PBT, 1.2% and 4.0 % for IMRT, 1.5% and 3.1% for 3DCRT, and 8.0% and 19.4% for tomotherapy, $P < .001$ [22]. In a study by Kozak et al [18] comparing proton and photon-electron 3DCRT, the use of protons resulted in a significant reduction in the radiation dose delivered to the ipsilateral lung and heart. They also used a 1.5- to 2-cm expansion of the lumpectomy cavity to define the PTV. Use of pencil beam scanning for postmastectomy patients has been described in a recent publication with significant advantage over scattered beam [23]. Using single pencil beam, improved nodal and breast dose coverage with significantly reduced cardiac structure dose was achieved. Additionally, a significant amount of treatment time was saved as compared to other techniques.

An additional concern with proton beam is limited availability and treatment cost. A potential solution to this is the use of IMRT, which is available in most radiation oncology practices. As noted above, in this analysis, use of IMRT also resulted in decreased dose to the heart, ipsilateral lung, and ipsilateral breast owing to proper optimization. Similarly, Rusthoven et al [24] showed significant improvement in the volume of ipsilateral lung ($V_{20Gy(RBE)}$ 1.2% versus 2.3%, $P < .01$) and heart ($V_{5Gy(RBE)}$ 0.6% versus 1.7%, $P = .04$) with the use of IMRT APBI compared to 3DCRT. Harsolia et al [25] also showed that IMRT provides superiority over 3DCRT in breast treatment.

Clinical studies, however, have raised concern for inferior cosmetic outcome in patients treated with IMRT. Liss et al [26] reported their final cosmetic results from a single-arm prospective clinical trial evaluating APBI using IMRT with active-breathing control. The trial was terminated prematurely secondary to the development of fair/poor cosmesis in 7 of 32 women at a median follow-up of 2.5 years. At median follow-up of 5 years, a further decline in cosmesis was noted with 26.7% of women having a fair to poor cosmetic result. A randomized Canadian trial showed that APBI has poor cosmesis at 3 years, compared to whole-breast irradiation [27]. Similar concerns regarding poor cosmesis and skin toxicity have been raised in prospective PBT partial breast studies, with recommendation for use of multiple fields treated daily to help improve cosmetic outcome [15, 28]. Bush et al [19] reported no cases of grade 3 or higher acute skin reactions, with 7 cases of grade 1 telangiectasia, and overall good to excellent cosmesis in 90% of patients at 5 years, using multiple fields treated daily and skin-sparing techniques to deliver proton APBI.

The dosimetric uncertainty in proton beam at the distal edge of the spread-out Bragg peak (SOBP) has been well studied [29–32]. Typically, range uncertainty of 3.5% is used, which has been recently verified by Monte Carlo simulation by Paganetti [29]. Multiple beam arrangements are commonly used to eliminate higher RBE at the distal edge as was done in this study with 3 fields. Using multiple (3 or more) fields where the distal edge of the SOBP falls in a different location is typically adequate to account for increased normal tissue risks related to uncertainty at the distal edge of the SOBP. Further, the use of a free breathing technique, and the associated movement of the target due to respiratory variability, could also help ameliorate concerns about dose at the distal edge of the SOBP. Although not used in proton plans in this study, a range feathering technique can be applied with variable range to 1 or more of the proton fields to further address the distal SOBP dose uncertainty [33]. The range feathering technique is particularly helpful when the distance between the target and critical structures are relatively small.

Limitations of this study include the fact that it is retrospective in nature with all the inherent biases in a retrospective analysis. For example, only the computed tomography scan done at the time of initial brachytherapy planning was available for IMRT and PBT treatment planning; thus, the PTV for the IMRT and PBT plans was defined differently than if a separate scan without the SAVI device in place had been available, given concern for distortion of the architecture of the excision cavity caused by placement of the device. Further, the clinical implications of the results of this study are unable to be determined, as

no patient from this study was ever treated with the PBT or IMRT plans. Nevertheless, this study represents an important contribution to the literature, as it is the first to our knowledge to compare these 3 techniques for APBI.

Conclusion

This study examines dosimetric endpoints for 3 different techniques for APBI. The results show that PBT and IMRT minimized dose to the ipsilateral breast, ipsilateral lung, and heart, compared to BT, with no significant difference in conformality. This study confirms the dosimetric feasibility of proton and IMRT to lower dose to surrounding OARs while still maintaining high conformality. Though the results of this comparison are promising, continued clinical research or a randomized trial is needed to better define the role of proton beam and IMRT in the treatment of early-stage breast cancer.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts to disclose.

References

1. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347:1233–41.
2. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, Aguilar M, Marubini E. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347:1227–32.
3. van Dongen JA, Voogd AC, Fentiman IS, Legrand C, Sylvester RJ, Tong D, van der Schueren E, Helle PA, van Zijl K, Bartelink H. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst*. 2000;92:1143–50.
4. Fowble B, Solin LJ, Schultz DJ, Rubenstein J, Goodman RL. Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment. *Int J Radiat Oncol Biol Phys*. 1990;19:833–42.
5. Livi L, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieva C, Paiar F, Scotti V, De Luca Cardillo C, Bastiani P, Orzalesi L, Casella D, Sanchez L, Nori J, Fambrini M, Bianchi S. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer*. 2015;51:451–63.
6. Bergom C, Prior P, Kainz K, Morrow NV, Ahunbay EE, Walker A, Allen Li X, White J. A phase I/II study piloting accelerated partial breast irradiation using CT-guided intensity modulated radiation therapy in the prone position. *Radiother Oncol*. 2013;108:215–9.
7. Schulz-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. *J Clin Oncol*. 2007;25:953–64.
8. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen MB, Nisbet A, Peto R, Rahimi K, Taylor C, Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368:987–98.
9. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, Cutter D, Davies C, Ewertz M, Godwin J, Gray R, Pierce L, Whelan T, Wang Y, Peto R. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378:1707–16.
10. Darby SC, Cutter DJ, Boerma M, Constine LS, Fajardo LF, Kodama K, Mabuchi K, Marks LB, Mettler FA, Pierce LJ, Trott KR, Yeh ET, Shore RE. Radiation-related heart disease: current knowledge and future prospects. *Int J Radiat Oncol Biol Phys*. 2010;76:656–65.
11. Taylor CW, McGale P, Darby SC. Cardiac risks of breast-cancer radiotherapy: a contemporary view. *Clin Oncol (R Coll Radiol)*. 2006;18:236–46.
12. Roychoudhuri R, Robinson D, Putcha V, Cuzick J, Darby S, Moller H. Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study. *BMC Cancer*. 2007;7:9.

13. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;366: 2087–106.
14. Correa CR, Das IJ, Litt HI, Ferrari V, Hwang WT, Solin LJ, Harris EE. Association between tangential beam treatment parameters and cardiac abnormalities after definitive radiation treatment for left-sided breast cancer. *Int J Radiat Oncol Biol Phys*. 2008;72:508–16.
15. Galland-Girodet S, Pashtan I, MacDonald SM, Ancukiewicz M, Hirsch AE, Kachnic LA, Specht M, Gadd M, Smith BL, Powell SN, Recht A, Taghian AG. Long-term cosmetic outcomes and toxicities of proton beam therapy compared with photon-based 3-dimensional conformal accelerated partial-breast irradiation: a phase 1 trial. *Int J Radiat Oncol Biol Phys*. 2014;90:493–500.
16. MacDonald SM, Patel SA, Hickey S, Specht M, Isakoff SJ, Gadd M, Smith BL, Yeap BY, Adams J, Delaney TF, Kooy H, Lu HM, Taghian AG. Proton therapy for breast cancer after mastectomy: early outcomes of a prospective clinical trial. *Int J Radiat Oncol Biol Phys*. 2013;86:484–90.
17. Taghian AG, Kozak KR, Doppke KP, Katz A, Smith BL, Gadd M, Specht M, Hughes K, Braaten K, Kachnic LA, Recht A, Powell SN. Initial dosimetric experience using simple three-dimensional conformal external-beam accelerated partial-breast irradiation. *Int J Radiat Oncol Biol Phys*. 2006;64:1092–9.
18. Kozak KR, Katz A, Adams J, Crowley EM, Nyamwanda JA, Feng JK, Doppke KP, Delaney TF, Taghian AG. Dosimetric comparison of proton and photon three-dimensional, conformal, external beam accelerated partial breast irradiation techniques. *Int J Radiat Oncol Biol Phys*. 2006;65:1572–8.
19. Bush DA, Do S, Lum S, Garberoglio C, Mirshahidi H, Patyal B, Grove R, Slater JD. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *Int J Radiat Oncol Biol Phys*. 2014;90:501–5.
20. Prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT): contents. *J ICRU*. 2010; 10:NP.
21. Akino Y, Das IJ, Bartlett GK, Zhang H, Thompson E, Zook JE. Evaluation of superficial dosimetry between treatment planning system and measurement for several breast cancer treatment techniques. *Med Phys*. 2013;40:011714.
22. Moon SH, Shin KH, Kim TH, Yoon M, Park S, Lee DH, Kim JW, Kim DW, Park SY, Cho KH. Dosimetric comparison of four different external beam partial breast irradiation techniques: three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, helical tomotherapy, and proton beam therapy. *Radiother Oncol*. 2009;90:66–73.
23. Depauw N, Batin E, Daartz J, Rosenfeld A, Adams J, Kooy H, MacDonald S, Lu HM. A novel approach to postmastectomy radiation therapy using scanned proton beams. *Int J Radiat Oncol Biol Phys*. 2015;91:427–34.
24. Rusthoven KE, Carter DL, Howell K, Kercher JM, Henkenberns P, Hunter KL, Leonard CE. Accelerated partial-breast intensity-modulated radiotherapy results in improved dose distribution when compared with three-dimensional treatment-planning techniques. *Int J Radiat Oncol Biol Phys*. 2008;70:296–302.
25. Harsolia A, Kestin L, Grills I, Wallace M, Jolly S, Jones C, Lala M, Martinez A, Schell S, Vicini FA. Intensity-modulated radiotherapy results in significant decrease in clinical toxicities compared with conventional wedge-based breast radiotherapy. *Int J Radiat Oncol Biol Phys*. 2007;68:1375–80.
26. Liss AL, Ben-David MA, Jagsi R, Hayman JA, Griffith KA, Moran JM, Marsh RB, Pierce LJ. Decline of cosmetic outcomes following accelerated partial breast irradiation using intensity modulated radiation therapy: results of a single-institution prospective clinical trial. *Int J Radiat Oncol Biol Phys*. 2014;89:96–102.
27. Peterson D, Truong PT, Parpia S, Olivotto IA, Berrang T, Kim DH, Kong I, Germain I, Nichol A, Akra M, Roy I, Reed M, Fyles A, Trotter T, Perera F, Balkwill S, Lavertu S, Elliott E, Julian JA, Levine MN, Whelan TJ. Predictors of adverse cosmetic outcome in the RAPID trial: an exploratory analysis. *Int J Radiat Oncol Biol Phys*. 2015;91:968–76.
28. Chang JH, Lee NK, Kim JY, Kim YJ, Moon SH, Kim TH, Kim DY, Cho KH, Shin KH. Phase II trial of proton beam accelerated partial breast irradiation in breast cancer. *Radiother Oncol*. 2013;108:209–14.
29. Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. *Phys Med Biol*. 2012;57:R99–117.
30. Paganetti H. Significance and implementation of RBE variations in proton beam therapy. *Technol Cancer Res Treat*. 2003; 2:413–26.

31. Paganetti H, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS, Suit HD. Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys*. 2002;53:407–21.
32. Anferov V, Das IJ. Biological dose estimation model for proton beam therapy. *Int J Med Phys Clin Eng Radiat Oncol*. 2015; 4:149–61.
33. Buchsbaum JC, McDonald MW, Johnstone PA, Hoene T, Mendonca M, Cheng CW, Das IJ, McMullen KP, Wolanski MR. Range modulation in proton therapy planning: a simple method for mitigating effects of increased relative biological effectiveness at the end-of-range of clinical proton beams. *Radiat Oncol*. 2014;9:2.