

ORIGINAL ARTICLE

Proton beam versus photon beam dose to the heart and left anterior descending artery for left-sided breast cancer

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ABSTRACT

Purpose. The purpose of this study was to compare the dose to heart, left anterior descending (LAD) artery and lung between proton and photon beam irradiation for left-sided early stage breast cancer.

Material and methods. Ten women with early stage left-sided breast cancer were treated with breast conserving surgery and radiation. Whole breast radiation was delivered for actual treatment via a tangential technique with deep inspiration breath hold (DIBH) utilizing inverse planned intensity-modulated radiation therapy (IMRT). Each patient was replanned on an Institutional Review Board (IRB)-approved prospective study using en face proton beam radiation with both uniform scanning (US) and pencil beam scanning (PBS) techniques.

Results. Both PBS (0.011 Gy) and US (0.009 Gy) proton plans resulted in a significantly lower mean heart dose compared to IMRT (1.612 Gy) ($p < 0.05$ for PBS vs. IMRT and US vs. IMRT). The Dmean, Dmin, Dmax, and D0.2cm³ of the LAD with either proton technique were significantly lower ($p = 0.005$) compared to IMRT. Both US and PBS reduced the mean dose to the lungs compared to IMRT. The coverage of the breast planning target volume was comparable between photon and proton plans.

Conclusions. The dose to whole heart was relatively low in this study of patients treated under conditions of DIBH. However, proton beam radiation was associated with lower minimum, maximum, and dose to 0.2 cm³ of the LAD, which is the critical structure for late radiation therapy effects, compared to even the most optimized photon beam plan with DIBH and IMRT.

Post-lumpectomy radiation is the standard of care for the majority of women with early stage breast cancer undergoing breast conserving surgery [1]. Post-lumpectomy radiation has been proven in large, prospective randomized trials to be associated with both reduced local recurrence in the breast and increased breast cancer-specific and overall survival [2]. However, in the 2011 meta-analysis by The Early Breast Cancer Trialists' Collaborative Group of prospective randomized trials of post-lumpectomy radiation, there remained a difference in the rates of breast cancer-specific versus overall survival long-term after radiation. The improvement in overall survival with radiation was approximately 1% lower than would be expected from the improvement in cause-specific

survival with radiation. This difference is mostly attributed to an increase in late cardiac mortality from radiation.

Techniques for delivering whole breast radiotherapy have evolved over the last several decades with improved photon techniques and newer proton techniques which have been shown to reduce dose to heart and lung compared to photon beam radiation [3,4]. The standard practice in the US remains to try and limit dose to the heart and the lung as expressed by a mean dose or dose to the whole organ [5]. The mean whole heart dose has been associated with the risk for late cardiac effects [6]. However, the dose to the whole heart, where the heart is considered a homogenous whole organ, may not be the best

measure of determining the risk of late cardiac disease. The risk for late cardiac disease and death after radiation is mostly associated in the modern era with disease of the coronary arteries. In a study of 72 134 women diagnosed with breast cancer in Denmark or Sweden during 1976–2006, left-sided radiation increased the risk for acute myocardial infarction, angina, pericarditis, and valvular heart disease [7]. This may have included older radiation techniques with higher dose to cardiac structures than modern tangential radiation. For example, the 15-year cumulative hospital-related morbidity after tangential radiation for early stage breast cancer that excluded internal mammary irradiation was most related to arrhythmias, atherosclerosis, and acute myocardial infarction [8]. Based on these studies, the coronary arteries are likely the critical structure for late cardiac events in most cases in the modern era and not the blood, muscle, conduction tissue, valves, etc. within the whole heart organ. The proximate location of the left anterior descending (LAD) to the tangential radiation field in breast cancer may contribute to its importance as a critical avoidance structure [9].

The purpose of our study was to analyze the dose to the whole heart, LAD, and lung from left-sided radiation therapy with photon versus proton techniques with deep inspiration breath hold (DIBH). We hypothesized that proton beam radiation, using two different methods of uniform scanning (US) and pencil beam scanning (PBS), can reduce dose to LAD compared to the most advanced photon beam intensity-modulated radiation therapy (IMRT) technique.

Material and methods

The study population consisted of 10 women with early stage left-sided breast cancer who were treated with breast conserving surgery and whole breast radiation at the University of Pennsylvania. All patients met eligibility for, gave informed consent, and were enrolled on a prospective study approved by the hospital Institutional Review Board (IRB). All women were treated with DIBH and photon beam radiation for their left-sided breast cancer. This study involved using the computed tomography (CT) datasets from their radiation simulation to retrospectively design proton beam radiation plans (not used for treatment) and compare these plans to photon beam plans.

All patients were simulated utilizing an angled wing board (Q-Fix, Avondale, PA, USA) so that the sternum was parallel to the couch and immobilized in a vac lock bag. Prior to simulation, patients were coached on the use of the SDX Spirometric Motion Management System (Qfix) for DIBH. The SDX system is spirometer based and controls breathing by

monitoring the volume of air inspired in the lung between breaths, allowing a more reproducible position of the breast and chest wall during treatment and greater distance between the heart and chest wall in order to reduce radiation dose. Wire was placed around the palpable breast tissue to assist in contouring and defining a clinical target volume (CTV) and planning target volume (PTV). Patients underwent three CT scans without contrast: 1) a free breathing scan; 2) a DIBH scan; and 3) a 4D CT scan as part of the IRB approved study, though only the DIBH scans were used for this particular analysis. Patients were scanned from the base of skull to at least 2 cm below the inframammary fold with a slice thickness of 3 mm. Patients were given anterior and lateral chest tattoos for more accurate positioning against lasers mounted in the treatment room on the walls and ceiling for better straightening and rotation on a daily basis. The CT simulation images were then exported to the Eclipse (Varian, Palo Alto, CA, USA) treatment planning software.

To reduce CT artifacts during planning process, the surface metal ball bearings (BBs) and wires placed during simulation had the CT-numbers overridden by $HU = -1000$ to approximate air density. Internal artifacts, such as fiducial markers or surgical clips, were also contoured and overridden with the average HU of the surrounding breast tissue. Contours were made of the whole heart, lungs, and breast CTV and PTV using RTOG guidelines [10]. A PTV_{eval} structure was created for use in radiation planning by cropping PTV 3 mm from the skin surface and 5 mm from the lung/chest wall interface. To limit interobserver variability, the LAD was contoured by a single individual, a certified radiologist/radiation oncologist (SV), as per Feng et al. [11]. The delineation of the LAD artery was performed for each axial slice without contrast enhancement using a window level range of 50–150 to help the visualization of the vessels. The LAD was contoured based on its location originating from the left coronary artery and running in the interventricular groove (Supplementary Figure 1, to be found online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1011756>). The LAD may move significantly with cardiac motion, so 3D reconstructions of the entire LAD artery were performed using a linear interpolation when the artery was not seen on contiguous slices due to motion artifact [12]. Non-contrast CT DIBH scans was used to delineate the LAD, following the ATLAS guideline as reported by Feng et al. [13]. Using contrast is not necessary, invasive and not routinely performed for breast simulation in RT. The maximum, minimum, mean and standard deviations of the volumes obtained from contouring the PTV_{eval}, heart and lungs are shown

in Supplementary Table I (to be found online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1011756>).

Three treatment plans were generated for each patient. Figure 1 shows an example of comparison of plans for a single patient for each of the three techniques with the radiation dose shown in a color wash. Whole breast radiation was delivered via opposed tangential medial and lateral beams, utilizing DIBH (SDX[®]), 6 MV and inverse planning and sliding window IMRT (Eclipse[™]). Each patient was replanned using an en face PBS and US proton beam. For US, an en face beam was employed to try and maintain an equal air gap separation from source to skin distance. A multi-leaf collimator margin of 1.5 cm was added around PTV to obtain an acceptable coverage. A 0.4 cm proximal margin and 0.5 cm distal margin were used to account for range uncertainties. The compensator smearing radium (SR) was used as defined by Moyers et al. 2001 [14]:

$$SR = \sqrt{\{(IM + SM)^2 + (0.03 \times range)^2\}}$$

The first term corrects for internal motion and setup uncertainties whereas the second term accounts for proton scattering ($0.03 \times range$). The manual editing of the compensator in order to increase the 95% isodose line (IDL) was done by adding a uniform thickness material to the compensator to decrease the dose at the chest wall/lung interface. For the PBS plan, an en face angle was also used. A 7 cm bolus was placed over the patient's skin in order to improve the superficial dose distribution of the target volume. This bolus acts as a range shifter and is not placed directly on the skin but rather as a bridge between the patient and the snout.

Prescription dose to the whole breast was 50 Gy in 2 Gy fractions. Beams were optimized such that the breast PTV_{eval} was encompassed by the 95% IDL, while maintaining a hot spot of less than 110%. Normal whole organ dose guidelines were used for limiting dose to the lungs and heart and plan approval including V20 lung < 15% and V20 heart < 5%. Dose to LAD was not specifically calculated or restricted during the planning process of the patient's treatment but retrospectively calculated. A conformity index (CI) and homogeneity index (HI) were defined to describe the quality of coverage of the target: $CI = V_{47.5} \text{ Gy} / PTV_{eval}$ (or $CI = V_{95\%} / PTV_{eval}$), where V47.5 Gy represents the volume receiving 47.5 Gy (or volume encompassed by the 95% IDL, since 47.5 is 95% of the prescribed 50 Gy) and $HI = D_{5\%} / D_{95\%}$ with D5%, D95%, as doses of 5% and 95% of PTV_{eval} volume as previously described [15,16]. For lung and heart doses, the following parameters were analyzed: V20, V10, V5 and mean dose (Dmean) for heart; V20, V5 and Dmean for

lungs; and Dmean, maximum dose (Dmax), minimum dose (Dmin) and dose to 0.2cm³ (D0.2cm³) for LAD as this may be a more clinically relevant volume of tissue [17]. Figure 2 shows a dose volume histogram for a single patient comparing DVHs of the breast PTV, heart, lung and LAD for the different techniques. The Wilcoxon matched-pair signed-rank test was used to compare the results among all three different techniques (IMRT vs. PBS, IMRT vs. US, PBS vs. US, significance level: $p < 0.05$). A Bonferroni correction was applied to adjust for multiple comparisons ($n = 3$), such that a significant p-value was: $p < 0.05/3$ or 0.0167.

Results

The dose volume parameters for the heart, lung, LAD, and breast CTV and PTV are outlined in the Supplementary Table I to be found online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1011756>. Both PBS (0.011 Gy) and US (0.009 Gy) protons plans had a significantly lower whole heart mean dose compared to IMRT (1.612 Gy) but PBS was not significantly different from US. The V5, V10, and V20 had a similar pattern where proton by either PBS or US was superior to IMRT but the two proton techniques were not significantly different from each other for the whole heart structure.

The Dmean, Dmin, Dmax, and D0.2cm³ of the LAD with either protons PBS or US were statistically significantly lower compared to IMRT (Table I). When compared to each other, the two proton techniques were not significantly different for any of these endpoints. Looking specifically at Dmin to the LAD, we observed that IMRT had no sparing of any length of LAD so that the minimum dose was 1.093 Gy, whereas portions of the LAD were spared all dose by protons PBS or US with Dmin of 0. Figure 3 shows a dose volume histogram of the near complete sparing of LAD by protons PBS or US, but the large shoulder and low dose given to the entire contoured LAD by IMRT.

Results demonstrate that both US and PBS proton beam reduced the average dose to the lungs compared to IMRT (Dmean = 0.875 Gy for PBS, Dmean = 1.505 Gy for US, Dmean = 7.313 Gy for IMRT) (Table I). PBS significantly reduced the mean dose compared to IMRT and US. For volumes of lung receiving low doses (V5) or higher doses (V20) of radiation, a higher sparing of dose was also achieved with PBS and US compared to IMRT. PBS had a significantly better V5 and V20 than those achieved with US or IMRT (V5 = 4.7% and V20 = 0.0% for PBS; V5 = 7.5% and V20 = 2.5% for US; and V5 = 25.2% and V20 = 12.5% for IMRT).

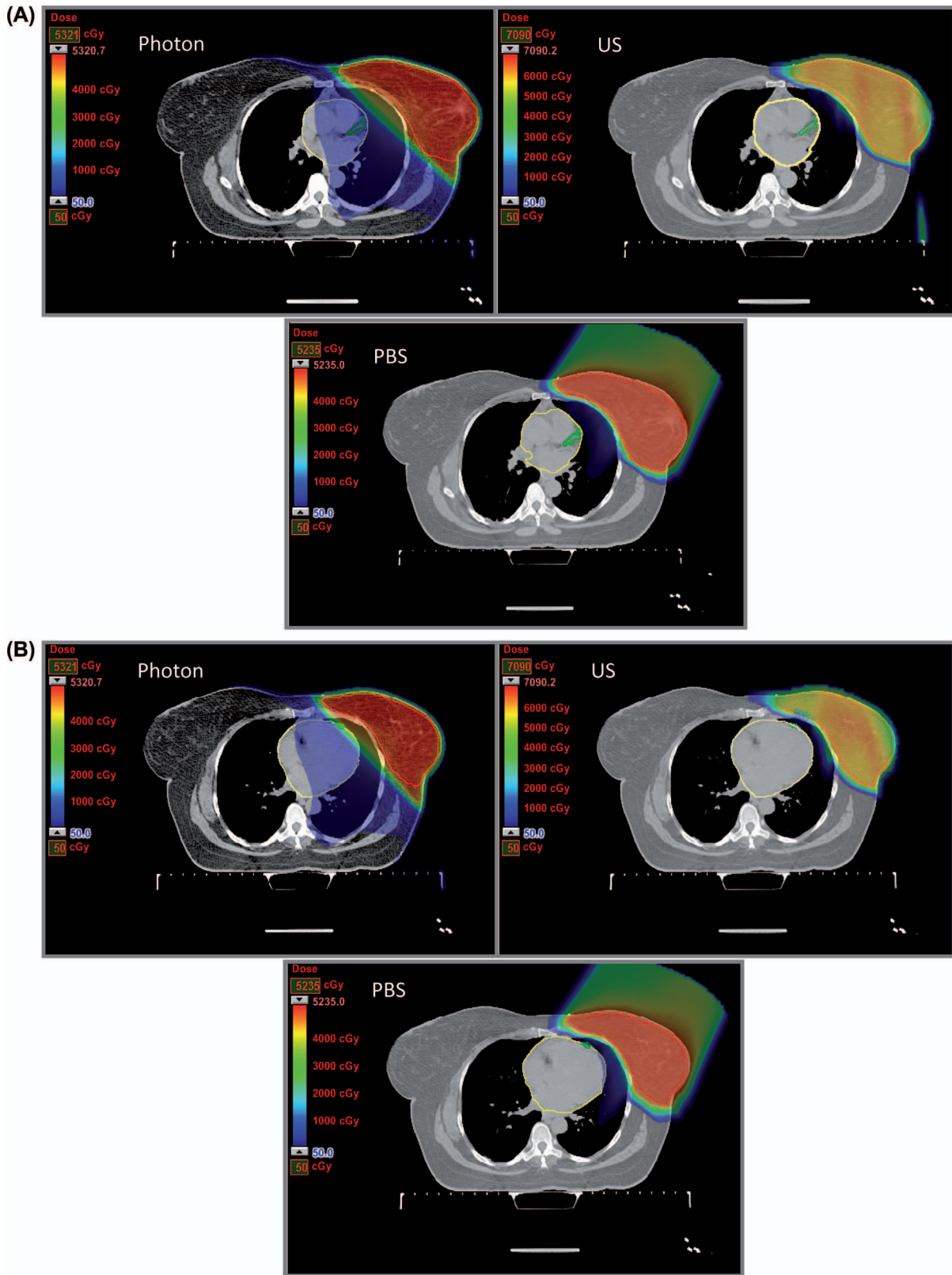


Figure 1. Photon, uniform scanning and pencil beam scanning plans in low dose (0.5 Gy) colorwash at two different axial CT slices through the heart: (A) slice -3.2 – LAD dose when farther away from PTV and (B) slice -5.6 – LAD dose when in close proximity to PTV. The LAD is contoured in green, heart in yellow and PTV in red.

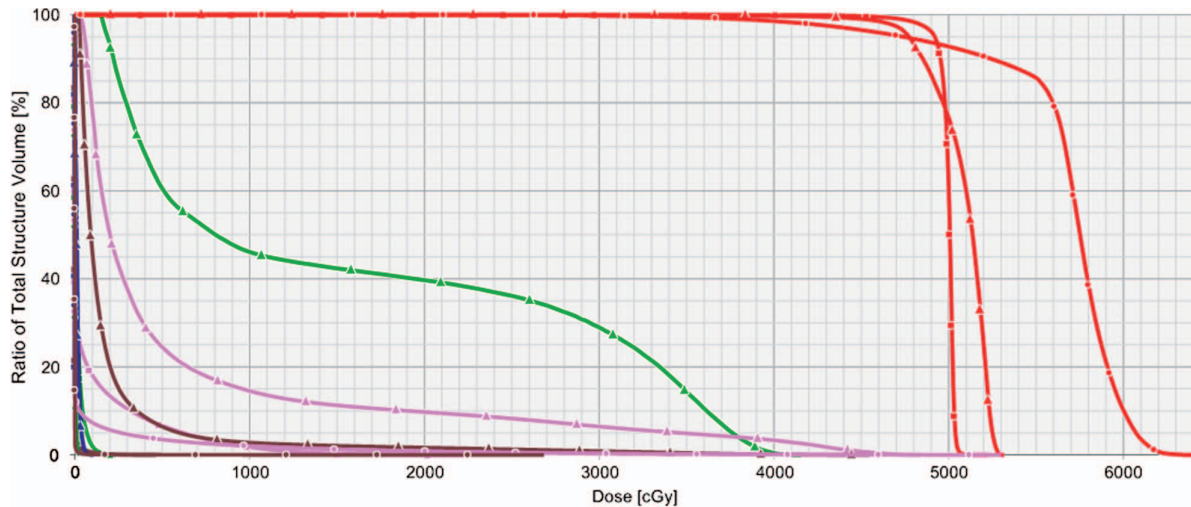


Figure 2. DVH of breast PTV (red), left lung (purple), right lung (blue), heart (brown), LAD (green). Triangle – photon, circle – US, square – PBS.

All plans met the planning goal of 95% of the PTV receiving at least 95% of the prescribed dose (Table I). The D95% was comparable among all three modalities, extending from a minimum value of 47.5 Gy for PBS to a maximum value of 48.1 Gy for IMRT, without statistically significant differences. The V107 was also determined with each technique with the V107 for US found to be significantly worse with than with either PBS or IMRT. V107 between IMRT and PBS were not significantly different.

There was no significant difference in CI between the three techniques. For homogeneity, PBS plans (HI = 1.06) were significantly superior to both IMRT (HI = 1.10) and US (HI = 1.21) as outlined in Table I. There was no significant difference in CI between PBS and IMRT. For homogeneity, both proton plans

were superior to IMRT, and PBS was significantly superior to both IMRT and US.

Discussion

Our results demonstrate that with IMRT using DIBH technique, doses to the whole heart are very low. We further show that even with DIBH, doses to the whole heart and LAD could be significantly lowered with either proton beam radiotherapy technique compared to IMRT for women with early stage breast cancer. Even with IMRT, portions of the LAD may be in the tangential radiotherapy field. With protons, however, the field choice is en face and protons due to its physical characteristics can reduce exit dose. As we observed the mean, D0.2cm³, and max doses to the LAD were very low with either proton technique.

Table I. Dose volume parameters to the PTV, heart, lung and LAD and breast CTV.

Modality	PTV		Index		Heart				Lung			LAD			
	D95 (Gy)	V107 (%)	CI	HI	V20 (%)	V10 (%)	V5 (%)	Mean (Gy)	V20 (%)	V5 (%)	Mean (Gy)	Mean (Gy)	Min (Gy)	Max (Gy)	D0.2cc (Gy)
IMRT (median)	48.1	0.0	0.97	1.10	0.7	1.6	4.3	1.6	12.5	25.2	7.3	5.6	1.1	31.8	10
US (median)	47.6	25.6	0.95	1.21	0.0	0.0	0.0	0.009	2.5	7.5	1.5	0.015	0.0	0.045	0.012
PBS (median)	47.5	0.07	0.96	1.06	0.0	0.0	0.0	0.011	0.0	4.7	0.88	0.031	0.0	0.71	0.052
p-Value PBS vs. IMRT	>0.1	>0.1	>0.1	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167
p-Value US vs. IMRT	>0.1	<0.0167	>0.1	>0.1	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167	<0.0167
p-Value PBS vs. US	>0.1	<0.0167	>0.1	<0.0167	>0.1	>0.1	>0.1	>0.1	<0.0167	<0.0167	<0.0167	>0.1	>0.1	>0.1	>0.1

IMRT, intensity modulated radiation therapy; PBS, pencil beam scanning; US, uniform scanning. p-Values are reported as not significant (>0.1) or significant (<0.0167 or <0.05/3) considering Bonferroni's correction.

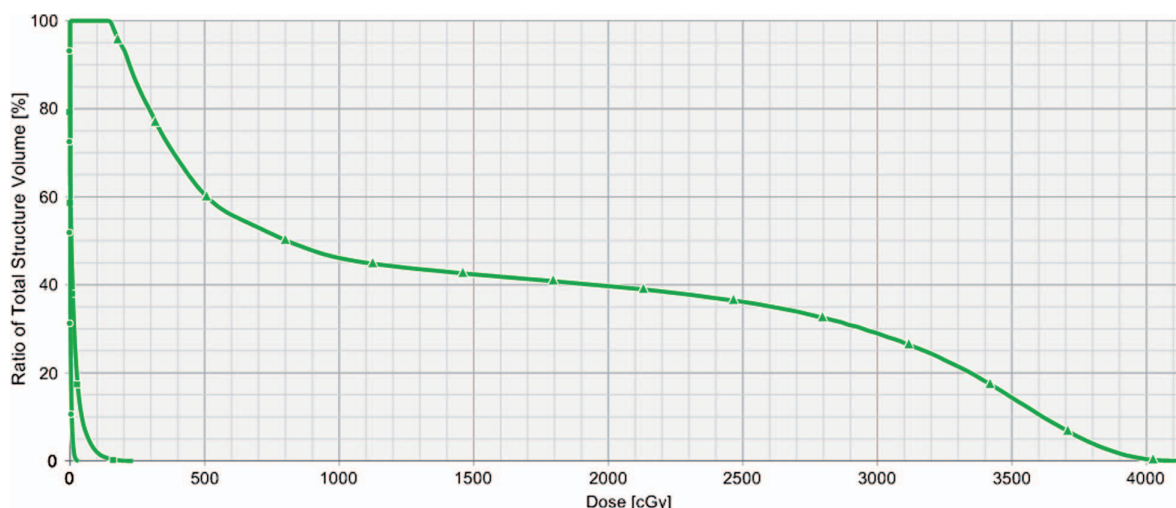


Figure 3. Photon versus PBS proton plan DVH of LAD. Triangle – photon, circle – US, square – PBS.

There is no question that there has been a risk of cardiovascular morbidity from left-sided radiation for breast cancer in most studies that have examined this endpoint for patients treated with photon irradiation up through the 20th century. In many older trials of postoperative radiation for breast cancer, the risk of death from radiation-related cardiac disease effaced the reduction in breast cancer mortality [18]. In a modern meta-analysis of post-lumpectomy radiation, the survival of women was also improved after post-lumpectomy radiation but the overall survival gain was slightly reduced compared to the breast cancer mortality due to late cardiac effects [2]. Darby et al. [5] reported a study of major coronary events in women treated with radiotherapy for breast cancer between 1958 and 2001. Individual CT-based information on the radiotherapy actually delivered was unavailable because this study period pre-dated 3D treatment planning. The authors estimated the mean heart dose and LAD artery dose from a process using diagrams and photographs from patient charts and a CT scan of a single woman with “typical” anatomy [19]. The mean heart dose correlated with excess relative risk of coronary events by 7.4% per 1 Gy. With modern techniques of photon tangential radiation being used in the past decade, long-term follow-up is needed to determine whether this risk remains an absolute 1–2% as seen in the data from the Early Breast Cancer Trialists’ Collaborative Group or has been further reduced [2].

The dose to the coronary arteries should be but is not currently a dose that is consistently measured and limited during the radiation therapy process for breast cancer to reduce this risk for cardiac disease. The cardiac mean dose may obscure the importance of a volume effect of critical portions of heart receiving high dose. The critical structures for late coronary

events, potentially life threatening, are the coronary arteries on the surface of the heart very close to the chest wall for left-sided breast cancer. Nilsson et al. observed a significant increase in stenosis in the mid and distal LAD in women who received left breast versus right breast radiotherapy. There is not an established dose that is safe for the coronary arteries. Previous study of photons used a measure of dose to 0.2 cm³ to LAD as an endpoint [17]. Therefore, our finding that protons significantly lowered the LAD dose compared to IMRT, including the minimum dose and dose to only 0.2 cm³, could be clinically significant for preventing late cardiac disease. Major coronary events can be caused by coronary stenosis of a vessel that is located within the dose range of photon beam radiation [9], whereas protons in our study were able to spare most of the length of the LAD, so that the Dmin was 0, and to the dose to 0.2 cm³ of LAD was very low overall.

Our study is unique in that we have compared two proton scanning techniques to IMRT using breath hold CT datasets to determine whether proton would offer any additional advantage with cardiac sparing to the best photon planning technique for cardiac sparing that we are aware of (IMRT with DIBH) [20]. Others have previously compared intensity-modulated proton therapy to IMRT [4], however, they have not looked specifically at doses to the LAD which may be the more clinically relevant structure particularly given the sharp fall off with proton radiotherapy and the field orientation.

We have found that proton beam radiation therapy, with either PBS or US, were able to match or improve target coverage of the PTV with 95% of the prescribed dose compared to IMRT. This would be expected, since the primary planning goal was achieving target coverage for each modality and plans

would not be accepted that did not meet the goal. However, PBS was superior to US for both homogeneity and conformity, and had better homogeneity than IMRT. Looking at the breast V107, there was no significant difference between IMRT and PBS plans, however, the median V107 for US plans was 25% which is significantly higher than for either IMRT or PBS. The V107 has been described by several groups as a potential predictor of radiation-induced toxicity [21,22]. One potential explanation for the larger V107 with US is that our protons have a field size limitation of 12 cm radius with multileaf collimators. Many of the patients on this study required a much larger field size to accommodate their breast size which made it difficult to meet the prescription goals with underdosage medially and laterally. As a result, not every patient will be a suitable candidate for proton beam therapy. The US plans are conformal distally but not proximally, compared to the PBS plans which are 3D conformal. Furthermore, lung doses with either PBS or US were significant lower than with IMRT.

A limitation of this study is that it is purely a dosimetric study with the goal of comparing IMRT and two proton planning techniques; all patients were actually treated with IMRT. There are other clinical issues that must be accounted for before clinical implementation of a program to utilize proton beam therapy for women with intact breast cancer including skin dose, breast swelling during therapy, and breast immobilization. Treating patients with PBS in breath hold positioning would likely require rescanning due to the time it takes to deliver PBS and may be limiting factor in the deliverability of these plans. Whether the generated PBS and US plans can be clinically deliverable is beyond the scope of this analysis. The comparison was made of protons to the best possible method of photons for cardiac sparing – using DIBH and IMRT. In this way, there was not an unfair advantage to protons by comparing them to out of date photon tangential techniques. Both DIBH and IMRT have been shown to lower dose to heart compared to conventional photon tangents [20]. Another potential limitation is that our study did not include regional node irradiation. Previous studies have demonstrated a dosimetric advantage to proton therapy for women requiring more complicated regional nodal irradiation or having complex geometry from breast reconstruction [4,23]. However, our study demonstrates that even women who require whole breast radiotherapy alone for early stage left-sided breast cancer could benefit from proton therapy with reduced doses to their heart and LAD compared to IMRT. Additionally, we did not use contrast with our CT scans which may have helped improve the contouring accuracy of the LAD

region. Cardiac-gated CT imaging which is typically used to investigate coronary vessels may have also facilitated more accurate localization of the LAD but it is a difficult procedure to use for routine clinical purposes [24].

In conclusion, our study demonstrates that with either US or PBS, significant sparing of the whole heart and LAD can be achieved compared to IMRT using DIBH. While US protons are now used clinically for breast cancer, there have been more challenging aspects to patient set-up, motion control and use of proton-specific bolus that have to be resolved before PBS may be safely used clinically at our institution. Future research will study the robustness of our PBS treatment plans. However, our results from this 10 patient study have confirmed that our goal will be to continue to develop PBS for clinical use at our institution.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Figure 1, Table 1 to be found online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1011756>.