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Proton versus Photon Breath-Hold Radiation for Left-Sided Breast Cancer after Breast-Conserving Surgery: A Dosimetric Comparison

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Abstract

Purpose: Radiation to breast, chest wall, and/or regional nodes is an integral component of breast cancer management in many situations. Irradiating left-sided breast and/or regional nodes may be technically challenging because of cardiac tolerance and subsequent risk of long-term cardiac complications. Deep inspiratory breath-hold (DIBH) technique physically separates cardiac structures away from radiation target volume, thus reducing cardiac dose with either photon (Ph) or proton beam therapy (PBT). The utility of combining PBT with DIBH is less well understood.

Methods and Materials: We compared photon-DIBH (Ph-DIBH) versus proton DIBH (Pr-DIBH) for different planning parameters, including target coverage and organ at risk (OAR) sparing. Necessary ethical permission was obtained from the institutional review board. Ten previous patients with irradiated, intact, left-sided breast and Ph-DIBH were replanned with PBT for dosimetric comparison. Clinically relevant normal OARs were contoured, and Ph plans were generated with parallel, opposed tangent beams and direct fields for supraclavicular and/or axillae whenever required. For proton planning, all targets were delineated individually and best possible coverage of planning target volume was achieved. Dose-volume histogram was analyzed to determine the difference in doses received by different OARs. Minimum and maximum dose (D_{min} and D_{max}) as well as dose received by a specific volume of OAR were compared. Each patient's initial plan (Ph-DIBH) was used as a control for comparing newly devised PBT plan (Pr-DIBH). Matched, paired *t* tests were applied to determine any significant differences between the 2 plans.

Results: Both the plans were adequate in target coverage. Dose to cardiac structure subunits and ipsilateral lung were significantly reduced with the proton breath-hold technique. Significant dose reduction with Pr-DIBH was observed in comparison to Ph-DIBH for mean dose (D_{mean}) to the heart (0.23 Gy versus 1.19 Gy; $P < .001$); D_{mean} to the left ventricle (0.25 Gy versus 1.7 Gy; $P < .001$); D_{mean}, D_{max}, and the half-maximal dose to the left anterior descending artery (1.15 Gy versus 5.54 Gy; $P < .003$; 7.7 Gy versus 22.15 Gy; $P < .007$; 1.61 Gy versus 4.42 Gy, $P < .049$); D_{max} of the left circumflex coronary artery (0.13 Gy versus 1.35 Gy; $P < .001$) and D_{mean}, the volume to the ipsilateral lung receiving 20 Gy and 5 Gy (2.28 Gy versus 8.04 Gy; $P < .001$; 2.36 Gy

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versus 15.54 Gy, $P < .001$; 13.9 Gy versus 30.28 Gy; $P = .002$). However, skin dose and contralateral breast dose were not significantly improved with proton.

Conclusion: This comparative dosimetric study showed significant benefit of Pr-DIBH technique compared with Ph-DIBH in terms of cardiopulmonary sparing and may be the area of future clinical research.

Keywords: breast radiation; proton; photon; breath hold

Introduction

Radiation to the breast, chest wall, and regional nodes is an integral component of breast cancer management. Whole-breast radiation, with or without boost to tumor cavity, is an integral component of breast-conserving therapy [1]. Increasingly, patients with advanced tumors or node-positive tumors are being treated with nodal irradiation that includes the axilla, supraclavicular fossa, and internal mammary node [2, 3].

With improving survival, long-term radiation complications for patients with breast cancer have become an area of increasing concern. In one of the initial analyses by the Early Breast Cancer Trialists' Collaborative Group, the risk of increased cardiac mortality was estimated to be as high as 5.6% for specific groups of patients [4]. It is now quantitatively documented that every 1-Gy increase in radiation dose to the heart increases the relative risk of long-term cardiac mortality by 7.4% [5]. Irradiating the left-sided breast and/or regional nodes is technically challenging because of cardiac tolerance and concern for this risk of long-term cardiac complications. Techniques and treatment modalities are being searched for to reduce late complications. Radiation pneumonitis, although not frequently seen or measured, is also an area of concern and, more so, in patients receiving nodal radiation. In a recent study, incidence of overall pulmonary toxicity was found to be 10.6% using multi-field intensity-modulated radiation therapy (IMRT) for patients with node-positive breast cancer receiving regional nodal irradiation [6]. However, the overall incidence of grade 2 or greater pulmonary toxicity in patients receiving nodal irradiation in the MA.20 trial was only 1.2% [2].

The deep inspiratory breath-hold (DIBH) technique physically separates cardiac structures away from the radiation target volume and helps reduce cardiac dose. This is particularly suitable for left-sided breast tumors [7]. The method has also been described to effectively reduce cardiac dose in patients with mediastinal lymphoma [8, 9]. Proton beam therapy (PBT) has generated significant interest and enthusiasm for its clinical utility because of its Bragg peak effect. However, data of the DIBH technique combined with PBT is sparse in literature for left-sided breast-cancer planning, particularly with an intact breast that requires nodal irradiation. We compared photon DIBH (Ph-DIBH) versus proton DIBH (Pr-DIBH) in 10 patients who underwent breast-conserving surgery with left-sided breast cancer, who required whole-breast radiation alone or with nodal irradiation covering the supraclavicular, axillary, and internal mammary lymph nodes.

Materials and Methods

Patient Selection

Ten consecutive patients who received radiation as part of breast-conserving therapy were included in this comparative dosimetric study after obtaining necessary institutional review board approval. All patients (10 of 10; 100%) underwent lumpectomy; 9 of 10 patients (90%) underwent sentinel lymph node biopsy and 1 patient (10%) underwent axillary lymph node dissection. All patients (10 of 10; 100%) were planned with opposed tangent beams with the DIBH technique as described below.

Simulation

Patients were explained in detail about the procedure and DIBH methods. Simulations were done in the supine position with arms over the head using a breast board. Computed tomography (CT) scans with 3-mm-slice thickness were obtained with both free breathing and DIBH. The DIBH was performed with the help of RPM software (Varian Medical Systems, Palo Alto, California). Patients were required to hold breath for 20 seconds. Scans were obtained from below the mandible to the midabdomen. Markers were used to define the clinical breast volume. Images were transferred to the Varian Eclipse V11.0 treatment planning software.

Table 1. Cardiac subunits and delineation.

Cardiac subunit	Description
Heart	The entire heart, with its pericardium, was contoured. Superiorly, it started at the lower border of the pulmonary trunk, where it crossed the midline, and inferiorly, it blended with the diaphragm. The entire pericardial sac was contoured. Care was exercised not to include the left lobe of the liver.
LV	Superiorly, contouring was from the mitral valve down to the apex. Medially, it was fused with the right ventricular wall; 1 cm of septal wall was included inside the LV structure.
LCA	Contouring was from the left lateral ascending aorta to the bifurcation into left anterior descending and circumflex coronary arteries.
RCA	Contouring was from the anterior aspect of the ascending aorta to the apex running in the posterior interventricular groove to the tip of the apex.
LCx	Contouring was from the end of the left main coronary artery running in the left atrioventricular groove.
LAD	Contouring was from the end of the main LCA and continued into the interventricular groove until the apex.

Abbreviations: LV, left ventricle, LCA, left coronary artery; LCx, left circumflex coronary artery; LAD, left anterior descending coronary artery.

Organ and Target Delineation

The body was contoured with autosegmentation software and verified by manual editing whenever required. The soft tissue window available with the software was used to verify the outer surface of the body and the autosegmented body. Ipsilateral and contralateral lungs were contoured individually in all its extension. After autosegmentation, manual editing was done to make sure all the lung parenchyma was contoured, particularly at the superior most and inferior most extent. The trachea was edited off the lung volume. The entire heart with its pericardium was contoured, which started superiorly at lower border of pulmonary trunk when it crossed the midline and inferiorly in blended with the diaphragm. During the contouring of the heart, care was exercised not to include the left lobe of liver. Additional cardiac subunits (**Table 1**) contoured were the left ventricle (LV), the left coronary artery (LCA), the right coronary artery (RCA), the left circumflex coronary artery (LCx), and the left anterior descending coronary artery (LAD).

Skin of ipsilateral breast was contoured as an organ at risk (OAR). A 3-cm area around the ipsilateral breast with 5-mm skin thickness was contoured from the most superficial layer of the skin inward as seen on the CT scan images. These were contoured with autosegmentation software followed by manual editing with the help of a contouring brush of 5-mm diameter to avoid any unwanted autosegmentation error.

Cardiac subunits

Table 1 describes details of cardiac subunit contouring. The different cardiac subunits contoured included the heart, the LV, the LCA, the RCA, the LCx, and the LAD. These are shown in **Figure 1**.

Clinical target volume in photon breath-hold plan

The entire breast was covered adequately by the tangent beams. This was essentially clinically marked. Two parallel, opposed beams were used to cover the clinically marked area adequately keeping the OAR dose within tolerance limits.

Clinical target volume in proton breath-hold plan

For proton beam planning, the entire breast was contoured as whole-breast clinical target volume (CTV) as seen in the planning CT scan. The superior and inferior extents of the whole-breast CTV for the proton plan were adjusted to match that of the photon plan CTV. This was done to avoid confounding issues arising out of the difference in the extent of the effective planning target volume (PTV) for both the planning.

Nodal clinical target volume (for both techniques)

Whenever required, nodal contouring for axilla (levels I–III), and the supraclavicular field and internal mammary lymph node (IMN) was performed after RADCOMP contouring atlas [10].

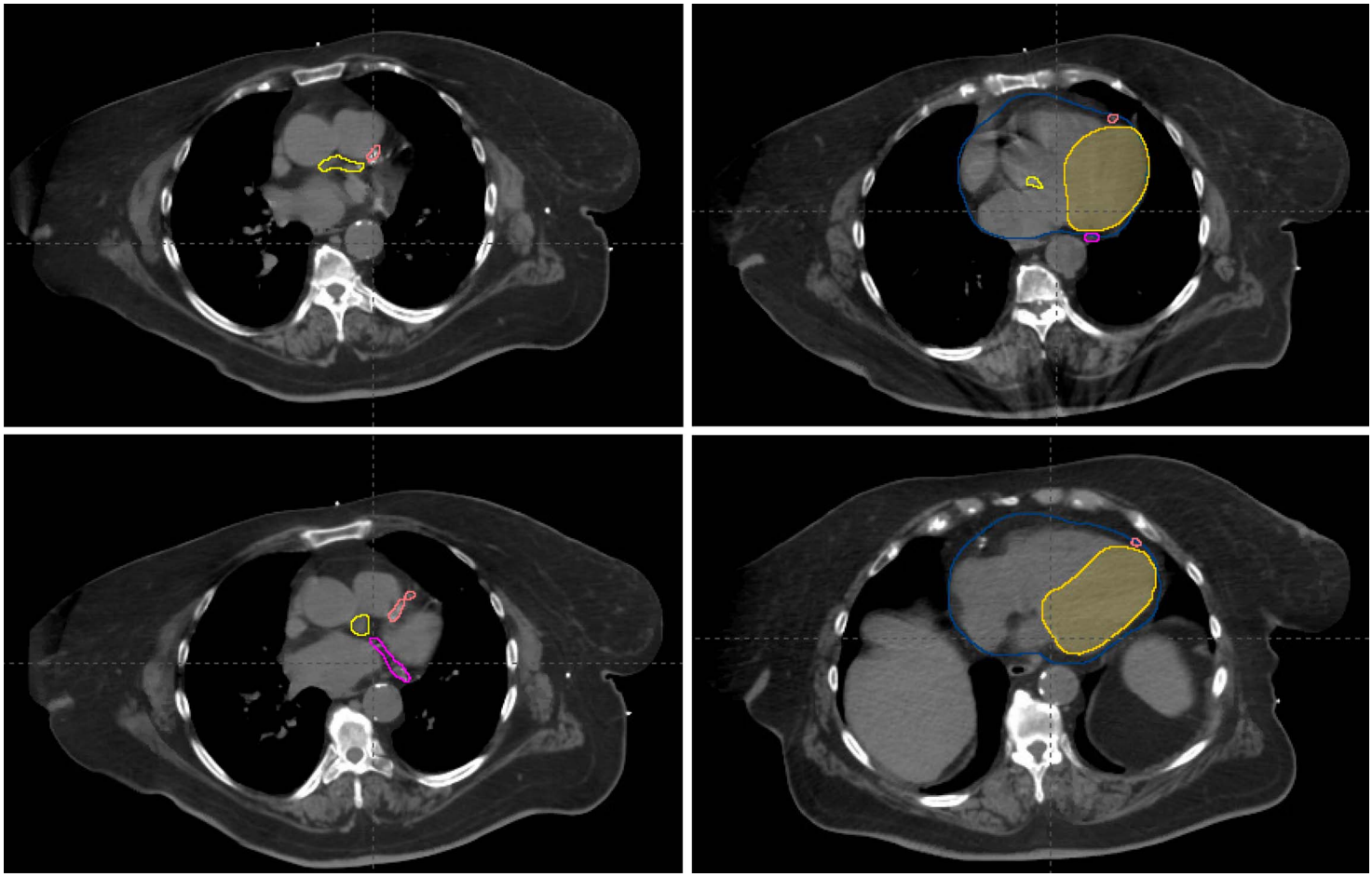

Figure 1. Contouring of different subunits of the heart as organs at risk.

Boost clinical treatment volume (for both techniques)

Lumpectomy cavity, along with 1-cm margin all around, was contoured as a boost CTV. The definition of the lumpectomy cavity was guided by the presence of surgical clips, seroma, hematoma, or other surgery-induced changes considered part of the cavity.

Planning

Whole breast and boost were planned with a phased manner.

Photon breath hold

Photon plans were generated with conformal planning for TrueBeam with Eclipse external beam radiation planning software (version 11.0; Varian). Two parallel, opposed photon beams with multileaf collimator shaping and dynamic wedge were used to adequately cover the PTV. The isocenter was placed at the center of the opposed beams. Boost to the tumor cavity CTV was planned either with electron therapy of appropriate energy or with photon therapy depending on the depth of the tumor cavity from the skin surface.

Proton breath hold

Proton plans were generated for Mevion S250 (Mevion Medical Systems, Littleton, Massachusetts) with a double-scatter proton therapy technique. Range compensators are used to cover the proximal and distal margin of the PTV adequately. This was calculated using the formula to calculate range uncertainty and the limit used was per institutional protocol. Range was

Table 2. Different doses and fractions used in the patients.

Whole-breast dose, Gy	No. of fractions	Boost dose, Gy	No. of fractions	No. (%) of patients
50	25	10	5	3 (30)
42.56	16	10	4	4 (40)
36.63	11	13.32	4	2 (20)
36.63	11	0	—	1 (10)

defined for a particular proton beam with a spread-out Bragg peak. Both phases were planned with proton therapy for proton beam dosimetry. Different dose fractions schedules used are given in **Table 2**.

Statistical Analysis and Plan Comparison

Each patient's photon plan worked as a control for their own proton plan for comparison. Group means were compared using paired, 2-tailed *t* tests. For all comparisons, $\alpha = .05$ was used to determine statistical significance. All statistical analyses were performed with Prism software version 7.0d (GraphPad Software, San Diego, California).

Results

Ten patients were included, with an average age of 52.8 years (range, 35–74 years). Only 1 of 10 patients (10%) underwent axillary lymph node dissection, and all other patients (9 of 10; 90%) underwent sentinel lymph node biopsy. Six patients (60%) had stage I disease, whereas 4 (40%) had stage II disease. All patients (10 of 10; 100%) had ER^+ and $HER2/Neu^-$ disease. Three patients (3 of 10; 30%) received locoregional irradiation for node-positive tumor and 1 patient (10%) was treated with high tangent to treat lower axillary nodes. Six patients (60%) with node-negative, stage I disease were treated with whole-breast radiation. Locoregional irradiation included whole breast, axilla levels I–III, supraclavicular field and ipsilateral IMN. Different dose and fractionations to treat the whole breast were 50 Gy in 25 fractions, 42.56 Gy in 16 fractions, and 36.63 Gy in 11 fractions; for boost CTV, the rates were 10 Gy in 5 fractions, 10 Gy in 4 fractions, and 13.32 Gy in 4 fractions were used (**Table 2**).

Coverage of whole breast and lumpectomy PTV was satisfactory with both techniques. Maximum (D_{max}), minimum (D_{min}), mean dose (D_{mean}), and dose received by specific volumes (D_X) of an organ were assessed. The OAR dose statistics are summarized in **Table 3**.

Both the plans were adequate in target coverage. Doses to cardiac structures were significantly reduced by the proton breath-hold technique. The D_{mean} to the heart and the LV were reduced. When the dose received by cardiac vessels was analyzed, it was found that for all parameters, namely D_{max}, D_{mean}, and D_{50}, were significantly reduced by Pr-DIBH. The dose with Pr-DIBH was observed as being reduced in comparison to Ph-DIBH for D_{mean} to the heart (0.23 Gy versus 1.19 Gy; $P < .001$); D_{mean} to LV (0.25 Gy versus 1.7 Gy; $P < .001$); D_{mean}, D_{max}, and D_{50} to the LAD coronary artery (1.15 Gy versus 5.54 Gy; $P = .003$; 7.7 Gy versus 22.15 Gy; $P = .007$; 1.61 Gy versus 4.42 Gy, $P = .049$); and D_{max} of the LCx (0.13 Gy versus 1.35 Gy; $P < .001$).

Another significant improvement was reduction in lung dose with Pr-DIBH. All the parameters for the ipsilateral lung were improved, whereas the D_{mean} of the contralateral lung was improved with Pr-BH. D_{mean}, the volume receiving 20 Gy (V20), and the volume receiving 5 Gy (V5) to the ipsilateral lung were 2.28 Gy versus 8.04 Gy ($P < .001$) and was 2.36 Gy versus 15.54 Gy ($P < .001$) and 13.9 Gy versus 30.28 Gy ($P = .002$), respectively, for Pr-DIBH and Ph-DIBH. However, the D_{mean} to the contralateral lung was also negligible with Ph-DIBH, and the clinical significance of further reduction with Pr-DIBH is currently unknown.

However, skin dose and contralateral breast dose were not significantly improved with proton therapy.

Discussion

Radiation is an integral part of breast cancer management after breast-conserving surgery. Whole-breast radiation, with or without boost to the tumor cavity and/or nodal irradiation, is the standard of care. Irradiating left-sided breast and/or the nodal region is always challenging considering the proximity to the heart and other vital organs. Previous studies have demonstrated the importance of cardiac dose to late cardiac morbidity in patients receiving breast irradiation, particularly for left-sided breast

Table 3. Dose and dose-volume histogram (DVH) statistics.

Organ	Parameter	Ph-DIBH		Pr-DIBH		*P* value (Pr-DIBH versus Ph-DIBH)[a]
		Mean	Range	Mean	Range	
Heart	Mean, Gy	1.19	0.65-2.0	0.23	0.01-0.5	**<.001**
	Max Gy	25.58	0.65-39.7	18.68	2.5-44.0	.09
	V40, %	0	0.0-0.0	0.00	0.0-0.01	.34
	V25, %	0.12	0.0-0.38	0.04	0.0-0.21	.39
	V18, %	0.20	0.004-0.6	0.15	0.0-0.5	.70
	V5, %	2.23	0.29-6.3	1.0	0.0-2.97	.08
LV	Mean, Gy	1.70	0.98-2.32	0.25	0.01-0.84	**<.001**
	Max, Gy	22.41	7.5-37.37	12.16	1.93-43.0	.07
LAD	Mean, Gy	5.54	2.2-13.32	1.15	0.3-4.18	**.003**
	Max, Gy	22.15	6.36-39.27	7.7	2.81-26.8	**.007**
	D50, Gy	4.42	2.3-9.89	1.61	0.1-8.76	**.048**
LCx	Mean, Gy	0.99	0.45-1.41	0.07	0.002-0.22	**<.001**
	Max, Gy	1.35	0.64-2.1	0.13	0.003-0.53	**<.001**
	D50, Gy	0.94	0.44-1.38	0.07	0.001-0.22	**<.001**
LCA	Mean, Gy	0.87	0.45-1.27	0.05	0.002-0.2	**<.001**
	Max, Gy	1.25	0.54-1.82	0.09	0.2-0.23	**<.001**
	D50, Gy	0.87	0.46-1.36	0.12	0.001-0.77	**<.001**
RCA	Mean, Gy	0.55	0.23-1.05	0.02	0.002-0.11	**<.001**
	Max, Gy	0.81	0.42-1.78	0.04	0.00-0.22	**<.001**
	D_{50}, Gy	0.536	0.22-1.00	0.02	0.0-0.11	**<.001**
Skin	Mean, Gy	28.9	20.0-35.33	30	23.7-35.5	.43
	Max, Gy	52.69	40.0-63.39	53.9	44.73-66.0	.35
I/L Lung	Mean, Gy	8.04	3.4-15.82	2.28	0.9-3.91	**<.001**
	Max, Gy	45.88	36.27-56.39	40.83	30.52-53-2	**.01**
	V20, %	15.54	4.47-30.22	2.36	0.01-5.4	**<.001**
	V5, %	30.28	13.54-52.75	13.9	6.0-26.0	**.002**
C/L lung	Mean, Gy	0.16	0.03-0.25	0.02	0.002-0.13	**.04**
	Max, Gy	1.91	0.41-6.22	2.91	0.04-16.3	.61
	V5, %	0.002	0-0.002	0.49	0.0-4.3	.28
C/L breast	Mean, Gy	0.43	0.04-2.51	0.02	0.003-0.14	.12
	Max, Gy	10.86	2.06-54.37	4.8	0.01-21.3	.36

Abbreviations: Ph-DIBH, photon deep inspiratory breath hold; Pr-DIBH, proton deep inspiratory breath hold; Max, maximum dose; VXX, volume receiving XX Gy; LV, left ventricle; LAD, left anterior descending coronary artery; D_{50}, half-maximum dose; LCx, left circumflex coronary artery; LCA, left coronary artery.

[a]Bold values are statistically significant at $\alpha < .05$.

cancer. Darby et al [5] estimated that there is a 7.4% increase in the relative risk of late cardiac morbidity per 1-Gy increase in D_{mean} of the heart. With improvement in survival in patients with early breast cancer, cardiac morbidity and mortality are important considerations. Different techniques of breast radiation have evolved over years to reduce cardiac dose, which include half-beam blocker, conformal block, intensity modulation, DIBH, and various combinations of these [11]. Among these techniques, DIBH physically separates the cardiac structures from the chest wall and helps reducing cardiac dose [12].

With the PBT Bragg peak effect, the radiation dose becomes inconsequential (almost zero) once the beam crosses the desired depth of treatment [13]. This mechanism can help reduce cardiac dose. Thus, DIBH and PBT can individually reduce the cardiac dose. It is, therefore, anticipated that combined use of DIBH and PBT will reduce cardiac dose to a greater extent.

In a dosimetric comparative study from the University of Florida, Chera et al [14] compared 3 different planning techniques in patients with stage IIA–IIB Hodgkin lymphoma requiring radiation to the neck and or mediastinum and showed a significant dose reduction in nontarget healthy tissues (breast, lung, and total body) using 3-dimensional printing reprocessable thermosets. Dosimetric studies have been undertaken with proton therapy for postmastectomy radiation therapy in

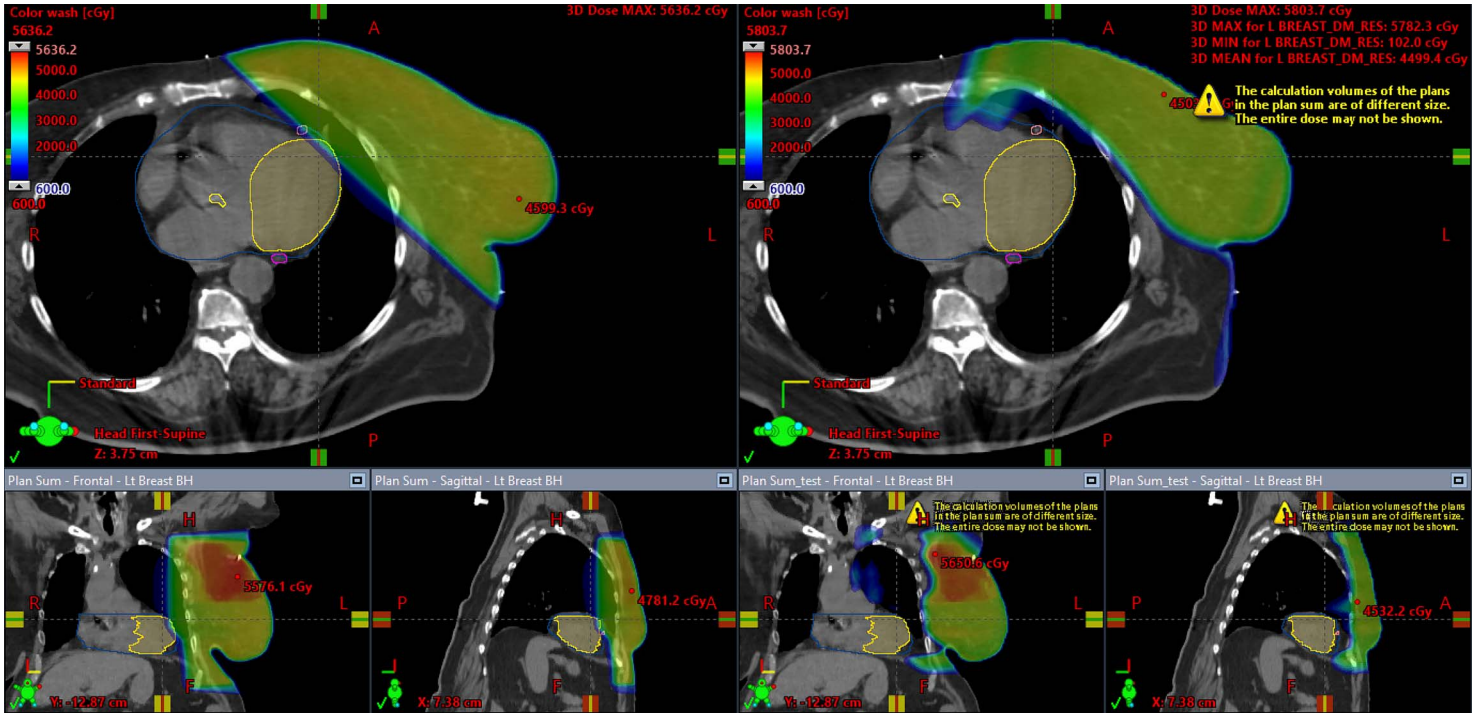

Figure 2. Axial, coronal, and sagittal views of comparative plans between photon deep inspiratory breath-hold (Ph-DIBH) versus proton (Pr) DIBH. The dose color wash shows sparing of the left ventricle and the left anterior descending coronary artery (LADCA) with proton therapy. In addition, note the significant reduction of irradiated lung volume with Pr-DIBH. Blue circle indicates LADCA, and yellow indicates the left ventricle.

combination with DIBH and showed significant reduction in cardiac dose. Studies with other mediastinal tumors have also shown reduction in cardiac dose with a combined PBT and DIBH approach.

Lin et al [15], from the University of Pennsylvania, published in 2015 the result of their comparative dosimetric analysis study for patients with early breast cancer who required whole-breast radiation. The study retrospectively used the CT data set of photon beam planning, similar to our study, and compared the results with PBT plan. In that article [15], the authors used both uniform scanning and pencil-beam scanning proton therapy and compared them with the IMRT plan. The D_{means} for the heart (0.009 and 0.011 Gy versus 1.612 Gy) and lung were significantly reduced by both uniform and pencil-beam scanning compared with IMRT plans. All dose constraints (D_{mean}, D_{max}, and D_{min}) for the LAD were significantly better with proton beam planning ($P < .005$). However, this study included only those patients requiring whole-breast radiation. Another important difference from our study is that the study conducted by Lin et al [15] analyzed the dose only to LAD among the cardiac structures.

In our study, different cardiac subunits were analyzed, including LCx artery. This is important because the LCx supplies a significant volume to the LV; 15% to 25% of the LV is supplied by the LCx in a right-dominant system and 40% to 50% in left-dominant systems [16]. The posterolateral part of the LV and the anterolateral papillary muscle are supplied by the LCx. In our study, we found significant reduction of D_{mean} to the heart as well as to the LV. All parameters for LAD, LCx, LCA, and RCA were significantly improved with Pr-DIBH (compared with Ph-DIBH) in our study.

In another comparative dosimetric study, Patel et al [17] compared proton versus photon for postmastectomy radiotherapy. In that study [17], the authors compared the dosimetry using both free breathing and DIBH techniques. Four different techniques were compared, including partially wide-tangent photon during DIBH, passive-scatter proton during free breathing, pencil-beam scanning proton during free breathing, and pencil-beam scanning during DIBH. When DIBH was considered, only photon and pencil-beam scanning proton therapy were used for comparison. The different metrics used for comparing cardiopulmonary dose were D_{mean} to the heart, D_{mean} to the LV, V20 to the LV, D_{max} to the LAD, D_{mean} to the lung, and V20 to the lung. In that study [17], proton plans showed significant improvement for all metrics when compared with photon therapy. This result is quite similar to our study; however, in our study, patients were treated after breast-conserving surgery that included the regional nodal area. Achieving dose constraints technically during comprehensive nodal irradiation is a bigger challenge. Patel et al [17] have also shown significant reduction in LV dose (mean, 3.72 versus 0.21 Gy radiobiological

equivalent [RBE]), V20 to the 0LV (2.73 versus 0), D_{max} to the LAD (46.14 versus 4.63 GyRBE), D_{mean} to the lung (13.30 versus 7.49 Gy RBE), and V20 to the lung (26.04 versus 14.43 GyRBE) when Ph-DIBH is compared with Pr-DIBH. However, D_{mean} to the LCx, the LCA, or the RCA contralateral breast and skin were not evaluated in that study [17]. In addition, in our study, we evaluated individual lung dose rather than evaluating both lungs as a single organ.

All these dosimetric studies establish the role of proton therapy in reducing the dose to vital organs, such as the whole heart, LV, LAD, and lung. However, those studies do not analyze radiation dose to skin, LCA, RCA, or LCx.

Our study is different in many ways. First, skin dose was systematically assessed where skin was contoured as a vital OAR. Our study showed skin dose is higher with PBT when compared with photon therapy, although the difference was not statistically significant. We warrant caution in this regard and suggest patient counseling explaining the risk of equal or greater skin toxicity with PBT compared with photon therapy. Consequentially, cosmesis may be a significant concern in long-term survivors and will be a secondary endpoint in the toxicity profile of the ongoing RADCOMP trial [10]. In addition, we warrant caution in skin contouring because autocontouring tools available with commercial planners are not accurate enough to define this organ because of rapid changes in surface anatomy. We suggest manual editing with a 5-mm paint brush after autocontouring is used for skin contouring.

None of the existing dosimetric studies evaluating proton dose have, to our knowledge, contoured cardiac structures as extensively as was performed in the current study. We evaluated the dose to the entire heart, the LV, the LCA, the RCA, the LAD, and the LCx; details of which have been described in the Materials and Methods section [18–20]. Damage to the LCx in this population could potentially be clinically detrimental. Numerically, D_{mean} reduction to the entire heart, the LV, or the LAD was almost 1 Gy, 1Gy, and 4.4 Gy. This could lead to an estimated reduction in long-term cardiac mortality by at least 7% if we consider the Darby et al [5] results to be accurate, which is significant, considering number of patients diagnosed with breast cancer and treated every year. The D_{mean} to the LCx, LCA, and RCA were also low even with Ph-DIBH; and thus, the clinical significance of further dose reduction to these structures with Pr-DIBH is unknown at present.

The D_{max} to the contralateral breast was reduced, but that results was not statistically significant. That may be due to the few patients who received comprehensive nodal irradiation, including IMN radiation. However, every effort must be made to reduce all components of dose metrics to the contralateral breast considering its significant effect on second malignancy [21].

Ipsilateral lung dose was also significantly reduced. The absolute value of reduction in D_{mean}, V20, and V5 were approximately 6 Gy, 13%, and 17% and were significant. Unlike other thoracic primaries, there is no part of the target in the lung; therefore, lung dose constraints should be as low as reasonably achievable during breast cancer planning. Radiation pneumonitis in patients with breast cancer is relatively underevaluated. There is an association between a low dose received by the lung and long-term radiation pneumonitis as seen in patients with different primary tumors [22, 23]. Therefore, keeping the dose of radiation low, more specifically the V5 or V10 as low as possible, is necessary. Proton therapy with DIBH significantly reduced the dose, and clinically, this might have long-term benefits.

In the present study, D_{mean} to the heart with Pr-DIBH was lower than the study by Chera et al [14] (1.96 CGE versus 0.23 CGE). Even when the present study was done with a much higher dose, the cardiac D_{mean} was lower. This further reduction was possible with DIBH.

However, this study is a dosimetric comparison of Pr-DIBH in a group of patients who were already treated with Ph-DIBH. Therefore, it is not devoid of selection bias, and the advantages of a randomized trial are also lacking. As a result, there are a few limitations. We opine that, the clinical implications of the dosimetric advantage using PBT will require a properly conducted randomized study with a long term follow-up. In addition, the expected clinical toxicity profile from such proton treatment is currently difficult to anticipate because of the lack of adequate long-term clinical experience. We hope that the ongoing RADCOMP study will be able to answer such questions in coming few years. In addition, being a dosimetric study, only physical doses were compared between proton and photon plans, instead of actual biological dose-effect relationships. Finally, this study did not use any normal tissue complication probability model to predict the clinical toxicity profile, which was not part of the study intent or design.

Conclusion

Proton DIBH significantly reduces dose to vital OARs in comparison to Ph-DIBH in patients requiring whole-breast radiation and/or nodal irradiation. This may be the new standard of care in the future because of its significant long-term clinical benefits. Further randomized clinical studies do not, however, seem to be a near-term reality but are warranted to ascertain its actual clinical utility and cost effectiveness.

ADDITIONAL INFORMATION AND DECLARATIONS

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