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Cardiac-Sparing and Breast-Sparing Whole Lung Irradiation Using Intensity-Modulated Proton Therapy

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Abstract

Purpose: Whole lung irradiation (WLI) is indicated for certain pediatric patients with lung metastases. This study investigated whether WLI delivered as intensity-modulated proton therapy (IMPT) could significantly spare the heart and breasts when compared with conventional WLI delivered with anteroposterior/posteroanterior photon fields and with intensity-modulated photon therapy (IMRT) WLI.

Materials and Methods: Conventional, IMRT, and IMPT plans were generated for 5 patients (aged 5-22 years). The prescription dose was 16.5 GyRBE in 1.5-GyRBE fractions. Conventional plans used 6-MV photons prescribed to the midline and a field-in-field technique to cover the planning target volume (the internal target volume [ITV] + 1 cm). IMRT plans used 6-MV photons with a 7-beam arrangement with dose prescribed to the planning target volume. IMPT plans used scenario-based optimization with 5% range uncertainty and 5-mm positional uncertainty to cover the ITV robustly. Monte Carlo dose calculation was used for all IMPT plans. Doses were compared with paired Student *t* test.

Results: The ITV Dmean was similar for the IMPT, conventional, and IMRT plans, but the IMPT plans had a lower Dmin and a higher Dmax at tissue interfaces than conventional plans (Dmean ratio: 0.96, $P > .05$; Dmin ratio: 0.9, $P < .001$; Dmax ratio: 1.1, $P = .014$). Dmeans for breast and heart substructures were lower with IMPT plans than with conventional/IMRT plans (heart ratios, 0.63:0.73; left ventricle ratios, 0.61:0.72; right ventricle ratios, 0.45:0.57; left atrium ratios, 0.79:0.85; right atrium ratios, 0.81:0.86; left breast ratios, 0.40:0.51; right breast ratio, 0.46:0.52; all $P < .05$).

Conclusions: IMPT resulted in comparable ITV coverage and lower mean doses to the heart and breasts when compared with other techniques. Whole lung irradiation delivered as IMPT warrants prospective evaluation in pediatric patients.

Keywords: whole lung irradiation; proton therapy; cardiac-sparing; breast-sparing

Introduction

Contemporary European and North American treatment protocols require whole lung irradiation (WLI) for certain pediatric patients with pulmonary metastases. Specific indications for WLI include Wilms tumor with persistent lung metastases or relapsed lung metastases [1], Ewing sarcoma with lung metastases [2] or pleural disease, and rhabdomyosarcoma with lung or large pleural metastases [3, 4]. Whole lung irradiation is

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conventionally delivered via opposed anteroposterior-posteroanterior (AP/PA) photon fields, which include nontarget organs such as the mediastinum and breasts. Both the mediastinum and breasts receive the full dose of radiation, which can range from 10.5 to 16.5 Gy. Whole lung irradiation can also be delivered via intensity-modulated radiation; however, breast and cardiac substructures typically fall within the low-dose spill. The long-term effects of cardiac and breast irradiation in this young population are not negligible; they can include potentially fatal cardiac events [5], an overall increase in cardiac comorbidities [6], secondary breast cancers [6, 7], breast hypoplasia [8], and decreased lactation [8].

Advances in radiation therapy (RT) have enabled more sophisticated delivery techniques with the potential to spare adjacent organs. Kalapurakal et al [9] reported on a phase II trial of photon therapy that compared intensity-modulated radiation therapy (IMRT) with the conventional AP/PA technique, demonstrating that IMRT was feasible and resulted in a reduced cardiac dose. The breast doses were not reported. Siddiqui et al [10] conducted a dosimetry study on non-4D datasets and found volumetric modulated arc therapy (VMAT) to be superior to the conventional technique for cardiac sparing, although breast sparing was minimal. Although IMRT and VMAT are advanced photon therapy techniques that can carve high-dose regions out of adjacent normal structures, they are associated with low-dose spill into adjacent organs.

Proton therapy is associated with a sharp distal fall-off as a result of the Bragg peak; therefore, it does not have the low-dose spill characteristic of IMRT and VMAT plans. There is an entrance dose within the beam path, but this is minimized when superficial targets are being treated. We investigated the feasibility of reducing the dose to the heart and breasts via intensity-modulated proton therapy (IMPT), using 2 posterior oblique beams to deliver WLI. We hypothesized that in appropriately selected patients, IMPT would significantly reduce the dose to the breasts and heart. There have been no published cardiac and breast dosimetric comparisons of IMPT versus AP/PA WLI or IMRT WLI. Given the challenges of motion management and accurate dose calculation inherent to lung tissue, we limited our analysis to patients with minimal respiratory motion and used both pencil-beam analytic algorithm (PBA) and Monte Carlo (MC) dose calculations. Eliminating the cardiac and breast dose for young patients will have long-lasting effects on cardiovascular health and will reduce the incidence of secondary breast cancers.

Materials and Methods

Four-dimensional computed tomography (CT) datasets from previously treated female patients who had received WLI were selected to provide samples representing an age spectrum. Patients were eligible for inclusion if their respiratory motion was regular and the amplitude was not excessive (defined as less than 5 mm in the superior-inferior direction at the level of the diaphragm and in the anterior-posterior direction on a 4D cine loop). The internal target volume (ITV) was delineated to include the maximum volume of lung tissue, using the minimum-intensity projection CT dataset in a lung window. The heart and breasts were contoured on the average CT dataset in a soft tissue window. Cardiac subregions were contoured according to an atlas by Feng et al [11] and the breasts were contoured only in postpubertal patients [12]. IMPT and conventional photon plans were generated with an Eclipse treatment planning system (Varian Medical Systems, Palo Alto, California). The prescription dose was 16.5 GyRBE in 1.5-GyRBE fractions, with the minimal coverage being specified as a dose to 100% of the target (D100%) of 15 GyRBE and a vertebral dose of at least 80% of the prescription dose to prevent differential bone growth. A dose of 16.5 GyRBE was chosen as based on ESTF13, a Ewing sarcoma protocol (Clinicaltrials.gov: NCT01946529), with the understanding that WLI doses can vary according to disease and protocol. This study was approved by the institutional review board at St. Jude Children's Research Hospital.

For conventional photon and IMRT plans, the planning target volume was a 1-cm isometric expansion of the lung ITV, minus 3 mm from skin. Conventional photon plans were devised by using 6-MV beams arranged in an AP/PA configuration and prescribed to the midplane, with a field-in-field technique used to improve dose homogeneity. IMRT plans were devised by using sliding window technique and a 7-beam arrangement. Organ-at-risk dose constraints from the Children's Oncology Group IMRT WLI study by Kalapurakal et al [9] were used. Specifically, plans were designed such that the maximum dose to the spinal cord, heart, and liver were $<$107%, $<$110%, and $<$110%, respectively.

IMPT plans were created with a multifield optimization technique and 2 posterior oblique fields that were 30° off-axis in both the left and right directions. A contour of a 3.9-cm-thick polymethyl methacrylate (PMMA) range shifter board was added posteriorly to the patient to mimic the range shifter device that would be needed in the treatment of these patients. The use of a range shifter is necessary to reduce the range of the proton beam ensuring coverage of superficial lung. IMPT was planned to target the ITV with spot spacing of 4 mm. Plans were first calculated and optimized with 5-mm range and 5% positional uncertainty on free-breathing datasets with the PBA. Final dose calculations were performed with an automated pipeline [13] modeling our clinical beamline and using TOPAS [14] MC code.

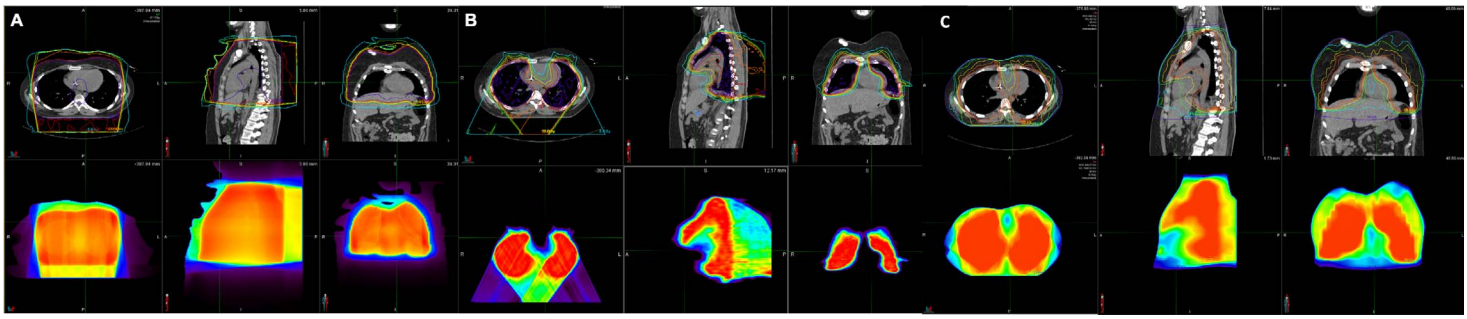

Figure 1. Axial, sagittal, and coronal images showing beam configuration and fluence for (A) conventional AP/PA photon, (B) IMPT, and (C) IMRT plans. Isodose lines: teal, 5 GyRBE; green, 8 GyRBE; yellow, 10 GyRBE; orange, 12 GyRBE; red, 15 GyRBE; purple, 16.5 GyRBE. Abbreviations: AP/PA, anteroposterior-posteroanterior; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy.

Dosimetry endpoints were the mean (Dmean), minimum (Dmin), and maximum (Dmax) doses and the volumes receiving 50%, 95%, and 110% of the prescription dose (V50%, V95%, and V110%, respectively). IMPT plans and conventional plans were compared by calculating the ratios of the IMPT dose parameters to the corresponding conventional dose parameters. The PBA and the MC methods were compared by calculating the ratios of the PBA-calculated dose parameters to the corresponding MC-calculated dose parameters. A paired Student *t* test was used to compare aggregate values for the IMPT and conventional plans, as well as IMPT and IMRT plans. Boxplots of the Dmean, Dmax, and Dmin were generated from aggregate values. Statistical analysis and visualization were performed with base packages from RStudio (Integrated Development for R, RStudio Inc, Boston, Massachusetts).

Results

Five 4D datasets from patients aged 5 to 22 years were used. Breast tissue was only assessable in postpubertal patients ($n = 3$). **Figure 1** shows the isodose lines and beam fluence above 5 GyRBE in the axial, sagittal, and coronal sections for the conventional photon, IMRT, and IMPT plans for a postpubertal patient. The average body Dmean was 5 GyRBE for IMPT versus 8.1 GyRBE for conventional plans (ratio: 0.62, $P = .002$) and 6.9 GyRBE for IMRT (ratio: 0.72, $P = .04$) (**Figure 2**).

Whole Lung Coverage

When MC-calculated IMPT plans were compared with conventional photon and IMRT plans, the lung ITV Dmeans were similar (ratio: 0.96 and 0.99, respectively; both $P > .05$) but the IMPT plan doses were more heterogeneous than conventional plan doses (Dmin ratio: 0.87, $P < .001$; Dmax ratio: 1.12, $P = .014$). Compared to IMRT, and IMPT ITV Dmax was higher (Dmax ratio: 1.16, $P = .009$) but ITV Dmin was similar (Dmin ratio: 0.84, $P > .05$) (**Figure 2**, **Table 1**). Hotspots from IMPT plans were small and were located at tissue interfaces (**Figure 3**). There was no significant difference in V110% for IMPT and conventional photon plans (0.5% versus 0.4%, respectively; $P > .05$) and for IMPT and IMRT plans (0.5% versus 0%, respectively; $P > .05$) (**Table 2**).

When IMPT doses calculated by using the PBA were compared with MC-calculated doses, the ITV Dmin and Dmax were higher and lower, respectively, with the PBA (ITV Dmin ratio: 1.17, $P = .005$; ITV Dmax ratio: 0.90, $P = .032$) (**Supplemental Table 1**). The breast Dmax was lower with the PBA (ratio: 0.74 for the left breast, $P = .012$; 0.94 for the right breast, $P = .013$) (**Supplemental Table 1**). **Supplemental Figure 1** shows a dose-volume histogram (DVH) comparing the PBA and MC dose calculations for 1 patient.

Cardiac Avoidance

Overall, IMPT improved cardiac dose metrics. When MC-calculated IMPT plans were compared with conventional plans, the Dmean ratios for different cardiac regions were as follows: cardiac (entire): 0.63 ($P = .008$); left ventricle: 0.61 ($P = .004$); right ventricle: 0.45 ($P = .003$); left atrium: 0.79 ($P = .004$); right atrium: 0.81 ($P = .008$) (**Figure 2**, **Table 1**). When MC-calculated IMPT plans were compared with IMRT plans, the Dmean ratios for different cardiac regions were as follows: cardiac (entire): 0.73 ($P = .01$); left ventricle: 0.72 ($P = .001$); right ventricle: 0.57 ($P = .002$); left atrium: 0.85 ($P = .013$); right atrium: 0.86 ($P = .016$) (**Figure 2**, **Table 1**). The cardiac V50% was lower with IMPT for the left and right ventricles and the entire heart, but

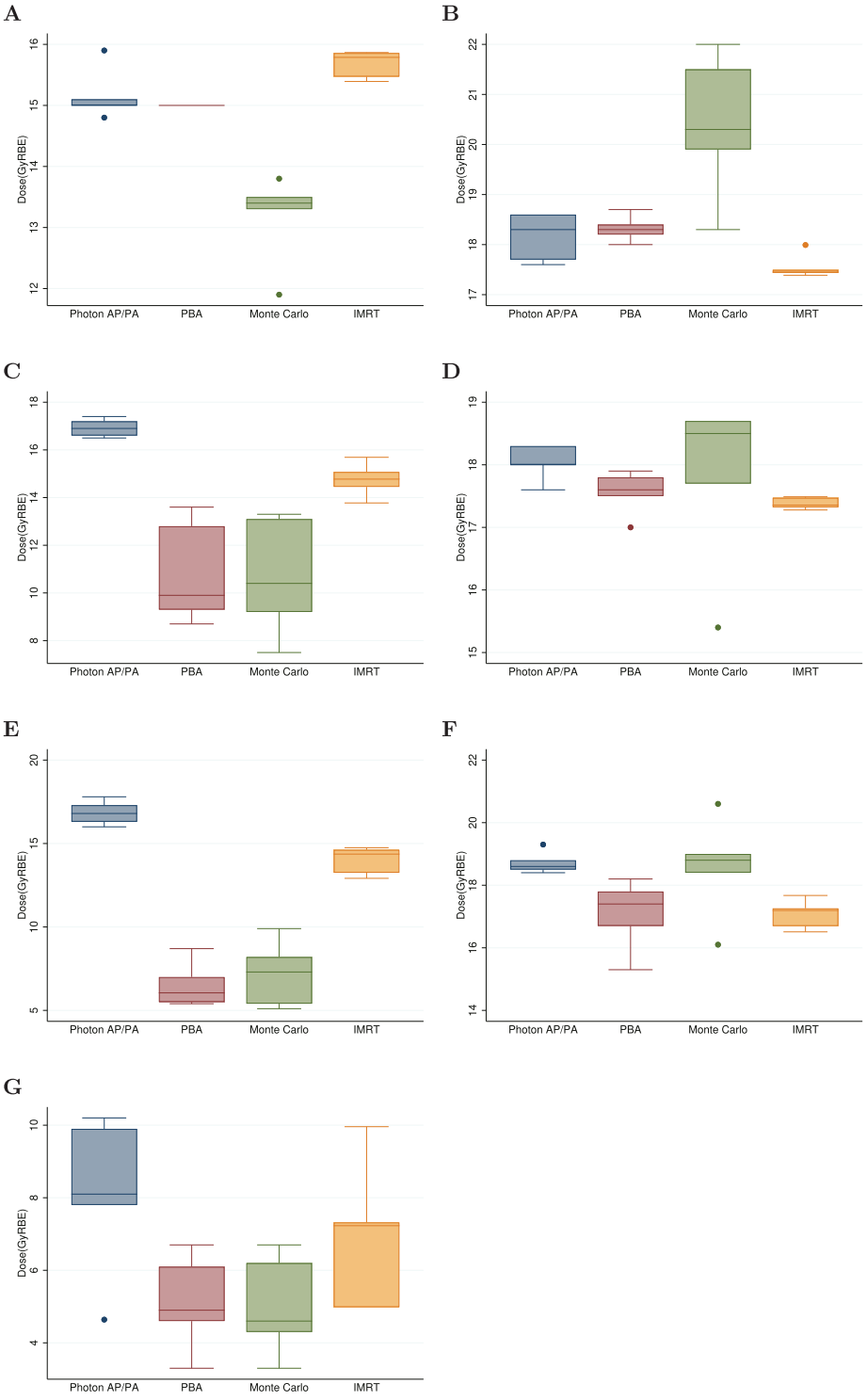

Figure 2. Boxplots summarizing (A) ITV Dmin, (B) ITV Dmax, (C) heart Dmean, (D) heart Dmax, (E) breast Dmean, (F) breast Dmax, and (G) body Dmean for conventional AP/PA PBA-calculated IMPT plans, Monte Carlo–calculated IMPT plans, and IMRT plans. Abbreviations: AP/PA, anteroposterior-posteroanterior; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy; ITV, internal target volume; PBA, pencil beam algorithm.

not for the left and right atria. The cardiac V95% was lower for the entire heart, left atrium, right atrium, and left ventricle (all $P < .05$) (**Table 2**). With respect to the right ventricle V95%, IMPT plan doses were lower than conventional plan dose, but not IMRT plan dose. There was considerable interpatient variation in the heart DVH (**Figure 4**). The Dmax did not differ between planning techniques for the heart as a whole or for any of the cardiac substructures.

Table 1. Comparison of average doses delivered with IMPT, IMRT, and conventional plans.

Parameter	No. of patients	IMPT	AP/PA	Ratio[a]	*P* value	IMRT	Ratio[b]	*P* value
Dmean, GyRBE								
ITV	5	16.3	17.0	0.96	NS	16.5	0.99	NS
Left ventricle	5	10.5	17.1	0.61	.004	14.6	0.72	.001
Right ventricle	5	7.6	16.8	0.45	.003	13.4	0.57	.002
Left atrium	5	13.0	16.5	0.79	.004	15.3	0.85	.013
Right atrium	5	13.6	16.7	0.81	.008	15.9	0.86	.016
Heart	3	10.7	16.9	0.63	.008	14.6	0.73	.01
Left breast	3	6.8	16.9	0.40	.006	13.4	0.51	.003
Right breast	3	7.6	16.7	0.46	.012	14.7	0.52	.02
Body	5	5.0	8.1	0.62	.002	6.9	0.72	.04
Dmin, GyRBE								
ITV	5	13.2	15.2	0.87	<.001	15.7	0.84	NS
Dmax, GyRBE								
ITV	5	20.4	18.2	1.12	.014	17.6	1.16	.009
Left ventricle	5	17.4	17.9	0.97	NS	17.3	1.00	NS
Right ventricle	5	16.6	17.7	0.94	NS	17.2	0.97	NS
Left atrium	5	16.4	17.5	0.94	NS	17.0	0.96	NS
Right atrium	5	17.0	17.7	0.96	NS	17.3	0.98	NS
Heart	5	17.8	18.0	0.99	NS	17.4	1.02	NS
Left breast	3	19.3	18.8	1.0	NS	16.7	1.16	NS
Right breast	3	18.0	18.6	0.97	NS	17.1	1.05	NS

Abbreviations: IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy; AP/PA, anteroposterior-posteroanterior; ITV, internal target volume; NS, not significant.

[a]Ratio is calculated by dividing the IMPT dose parameter by the conventional dose parameter.

[b]Ratio is calculated by dividing the IMPT dose parameter by the IMRT dose parameter.

Breast Avoidance

The breast Dmean was lower with IMPT than with conventionally planned therapy (ratios: 0.40 for the left breast, $P = .006$; 0.46 for the right breast, $P = .012$) and with IMRT (ratios: 0.51 for the left breast, $P = .003$; 0.52 for the right breast, $P = .02$) (**Table 1**). The V50% and V95% of all cardiac substructures favored IMPT except for V95% right ventricle (**Table 2**). The V50% was lower for both breasts with IMPT (**Table 2**). The V95% was lower for the left breast with IMPT. With respect to the right breast, there was a significant reduction in V95% when comparing IMPT to conventional treatment (3.9% versus 91.2%,

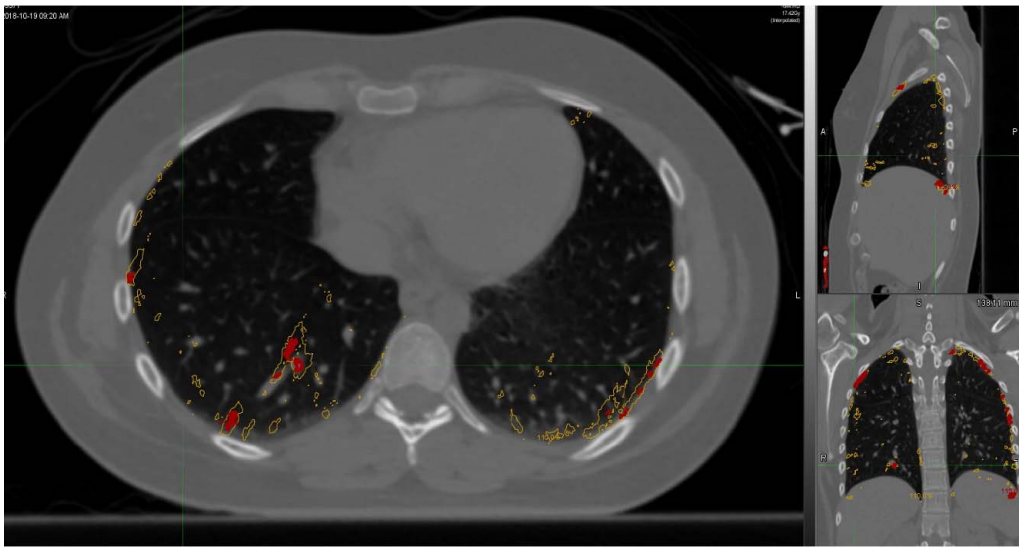

Figure 3. Axial image showing 110% (orange lines) and 120% (red fill) hot spots at tissue interfaces with an MC-calculated IMPT plan. Abbreviations: IMPT, intensity-modulated proton therapy; MC, Monte Carlo.

Table 2. Comparison of mean V50%, V95%, and V110% obtained with IMPT and IMRT plans across multiple structures.

	V50%					V95%					V110%				
Structure	IMPT, %	AP/PA, %	P^a	IMRT, %	P^b	IMPT, %	AP/PA, %	P^a	IMRT, %	P^b	IMPT, %	AP/PA, %	P^a	IMRT, %	P^b
ITV	100	100	NS	100	NS	99.1	99.8	NS	99.9	NS	0.5	0.4	NS	0.0	NS
Left ventricle	69.7	100	.041	100	.041	8.7	100	<.001	35.8	.002	-	-	-	-	-
Right ventricle	44.2	100	.024	98.9	.023	5.0	100	<.001	22.8	NS	-	-	-	-	-
Left atrium	98.6	100	NS	100	NS	7.62	99.9	<.001	35.2	.044	-	-	-	-	-
Right atrium	99.9	100	NS	100	NS	21.8	100	<.001	63.3	.006	-	-	-	-	-
Heart	71.0	100	.027	99.7	.027	13.6	99.8	<.001	44.0	.002	-	-	-	-	-
Left breast	25.9	96.7	.002	97.3	.004	2.4	90.7	.004	14.5	.015	-	-	-	-	-
Right breast	36.2	96.9	.008	99.6	.013	3.9	91.2	<.001	40.7	NS	-	-	-	-	-

Abbreviations: V50%, volume receiving 50% of the prescription dose; V95%, volume receiving 95% of the prescription dose; V110%, volume receiving 110% of the prescription dose; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy; AP/PA, anteroposterior-posteroanterior; ITV, internal target volume; NS, not significant.

[a]*P* Comparison of IMPT to AP/PA.

[b]*P* Comparison of IMPT to AP/PA.

$P = .015$), but not to IMRT (3.9% versus 40.7%, $P = .106$). Interpatient variation in the left breast DVH was minimal (**Figure 4**). The Dmax did not differ between planning techniques for the breasts.

Discussion

Whole lung irradiation is an important therapeutic strategy for certain pediatric patients with lung metastases [1–4, 15]. Our study showed that IMPT resulted in statistically significant reductions in the mean cardiac and breast doses when compared with conventional AP/PA photon and IMRT plans, but no reduction in Dmax. All of the cardiac substructures demonstrated significant reductions in Dmean, with the reduction being greater in the ventricles than in the atria. Whole lung irradiation plans using IMPT also resulted in a lower body Dmean, which is representative of a lower integral dose. However, IMPT plans were more heterogeneous, resulting in cold and hot spots in the ITV. Hot spots were small, and the V110% did not differ significantly between the modalities, with V110% being 0.5% with IMPT versus 0.4% with conventional photon plans and 0% with IMRT. The hot spots appeared largely at tissue interfaces as a result of differences in the stopping power ratio and increased proton scatter. These variations in target dose were underestimated when the PBA was used, as compared with the MC-calculated doses. For this study, we aimed to encompass the vertebral body with at least 80% of the prescription dose. We postulate that completely avoiding the vertebral body in skeletally mature patients may lower atrial doses.

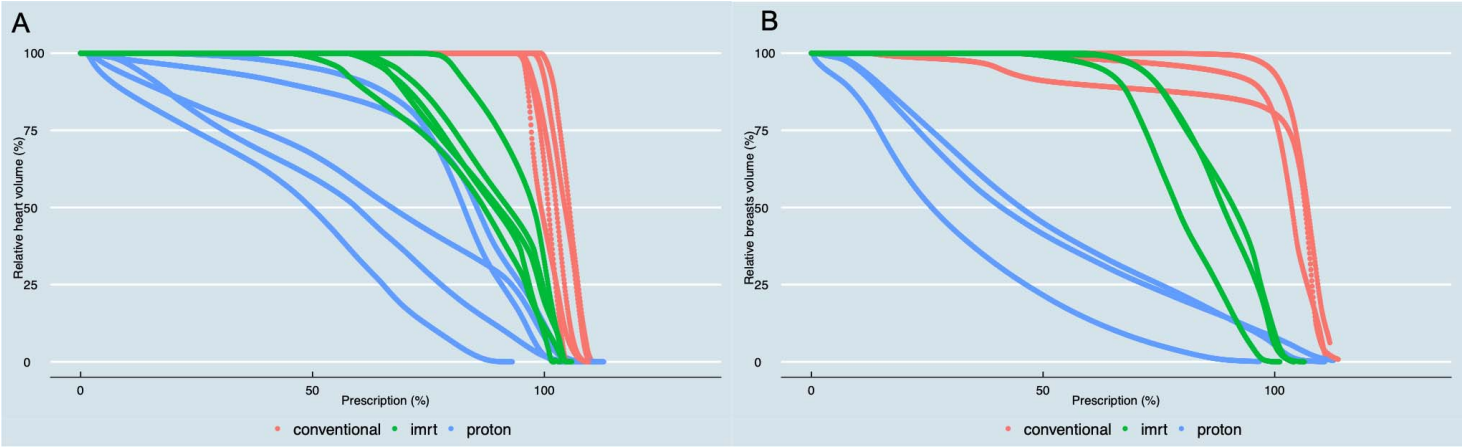

Figure 4. Dose-volume histogram for the (A) heart (n = 5) and (B) left breast (n = 3) for conventional AP/PA photon (pink), IMRT (green), and IMPT (blue) plans. Abbreviations: AP/PA, anteroposterior-posteroanterior; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy.

There is a paucity of data on the feasibility of using proton therapy and its comparison with photon therapy for WLI. One study [16] compared photon and proton therapy across different pediatric malignancies and concluded that there was no benefit to proton therapy with respect to WLI because the difference in the integral dose was less than 8%; however, no mention was made of specific normal organ dose differences. Cunningham et al [17] reported initial clinical outcomes of 7 patients treated with IMPT WLI with a median follow-up of 4.5 months and found that it was well tolerated.

The ability to reduce the cardiac and breast doses is clinically meaningful. Data from breast cancer survivors suggest that increasing the mean heart dose by 1 Gy increases the relative risk of severe cardiac events by 7% [5]. In our dataset, the mean heart dose decreased by 6 GyRBE when using IMPT compared to conventional photon therapy, suggesting a potential reduction of severe cardiac events by 42% if we extrapolate from the adult model. Furthermore, a Swedish study of breast cancer survivors who received coronary intervention found that the mean doses received by the left anterior descending artery (LAD) correlated with cardiac events [18]. With respect to the pediatric population, a 25-year follow-up study of patients with Wilms tumor from the Childhood Cancer Survivor Study [6] showed that left-flank irradiation and WLI increased cardiac comorbidities. In addition to cardiac events, secondary breast cancer is also a significant concern in the pediatric population. Lymphoma studies have shown that the risk of breast malignancies increases in young girls after they receive mediastinal RT, and mammograms are recommended for these patients starting at 25 years of age [19, 20]. According to a report from the Childhood Cancer Survivor Study [7], the incidence of breast cancer increased in women after they were treated for Ewing sarcoma, particularly in the group that received chest RT. Besides breast malignancies, breast hypoplasia and decreased lactation have also been reported in female patients after they received thoracic RT [8].

Other investigators have studied the feasibility of using advanced photon therapy modalities to spare normal organs during WLI. In the aforementioned phase II trial by Kalapurakal et al [9], although the cardiac V50% was significantly reduced with IMRT, as compared with conventional treatment, the effect size was only 4% (96% versus 100%) and is unlikely to be clinically meaningful. Our results similarly showed that the difference between IMRT and conventional cardiac V50% was only 0.3%. In comparison, IMPT was able to reduce the cardiac V50% by 30% when compared to both IMRT and conventional plans. The effect size for the reduction in cardiac V95% when compared to conventional treatment was also greater for IMPT (86.2%) than for IMRT (55.8%). It is also important to note that breast doses were lower in our study using IMPT than in the dosimetric study of VMAT by Siddiqui et al [10].

In a subset of patients who require WLI, some may warrant flank or whole-abdomen irradiation. A dose calculation study by investigators at the University of Pennsylvania [21] concluded that IMPT is feasible and provides dose sparing of abdominal organs. We suggest using gradients for field matching when performing concurrent flank and WLI with IMPT.

IMPT is not without its challenges financially, logistically, and technically. IMPT is more susceptible to interplay effects. To attempt to account for the effect of respiratory motion, we used 4D datasets to obtain the ITV and used 5% range uncertainty and 5-mm positional uncertainty [22]. The datasets were also assessed to ensure that lateral chest wall and diagrammatic motion was not excessive (all 5 patients had a maximum motion of less than 5 mm). For more accurate dose calculations, we ran MC simulations in TOPAS. Interplay effects are more significant when the effect of motion orthogonal to the beam is more than double the spot size. The chance of missing the target is higher when the tumor is small but comparatively less so when the fields are large, as in WLI. Motion-minimization techniques include breath-holding in cooperative patients (at the cost of increased time on the couch); using abdominal compression, which is more suitable for older patients; gating; and tracking. Other interplay-mitigation techniques include re-scanning, using larger spots, decreasing the distance between spots, and 4D optimization, although the latter is not yet commercially available [23, 24]. A full discussion of motion and its effect on IMPT is beyond the scope of this article.

This was a small retrospective study with limitations inherent to the study design. Because we selected patients with respiratory motion of less than 5 mm, our results might not be generalizable to patients with respiratory motion exceeding 5 mm. As none of the patients had contrast-enhanced CT scans, coronary vessels could not be clearly delineated. Although IMPT may potentially reduce dose to infradiaphragmatic organs such as the liver and stomach, these organs were not consistently imaged during CT simulation, limiting their dose-volume evaluation.

When delivering WLI, IMPT results in cardiac and breast mean doses that are lower than those delivered with conventional AP/PA plans or with IMRT plans or with IMRT plans. Prospective studies are needed to evaluate the efficacy and safety of delivering WLI with IMPT for patients who have a reasonable prognosis in order to potentially minimize long-term toxicities such as breast hypoplasia, malignancies, and cardiac morbidities. Techniques to mitigate physical uncertainties should be kept in mind.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: Sahaja Acharya, MD, received grant funding from the Conquer Cancer Foundation of the American Society for Clinical Oncology during the conduct of this study. The authors have no other relevant conflicts of interest to disclose.

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Ethical Approval: All patient data have been collected under internal review board (IRB)–approved protocol.

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