

Scientific Article

Effect of Deep Inspiration Breath Hold on Normal Tissue Sparing With Intensity Modulated Radiation Therapy Versus Proton Therapy for Mediastinal Lymphoma



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Abstract

Purpose: Intensity modulated radiation therapy delivered with deep-inspiration breath hold (IMRT-BH) provides favorable normal tissue dosimetric profiles when treating patients with mediastinal lymphoma. However, it is unclear if IMRT-BH plans are comparable to free breathing (FB) proton plans. We performed a retrospective, comparative dosimetric study between IMRT-BH and FB passive scatter proton therapy (P-FB) or intensity modulated proton therapy (IMPT-FB). Hypothesizing that BH would provide superior normal tissue sparing when added to proton therapy, we also compared plans to passive scatter BH (P-BH).

Methods and Materials: For 15 patients who received involved-site RT with “butterfly” IMRT-BH, 3 additional proton plans (P-FB, IMPT-FB, P-BH) were optimized to deliver 30.6 Gy/Gy relative biological effectiveness. Dosimetric variables (mean dose, V30, V25, V15, and V5) for organs at risk (OARs) were calculated and compared using nonparametric Wilcoxon signed-rank tests.

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Results: Of 57 studied OAR parameters, IMRT-BH plans were comparable in 37 (65%) parameters with P-FB plans, 32 (56%) of IMPT-FB parameters, and 30 (53%) of P-BH parameters. Doses to breasts were generally equivalent among plans while esophageal dosing was worse with IMRT-BH. Mean doses and V5 of the total lung and heart were the highest with IMRT-BH; however, IMRT-BH resulted in comparable coronary and superior lung V30 relative to proton plans. The addition of BH with proton therapy resulted in the greatest lung sparing, with mean lung dose reductions of 11% to 38%.

Conclusions: The use of BH with IMRT reduces the disparity in OAR doses with equivalence achieved in nearly two-thirds of OAR metrics compared with P-FB and 50% compared with IMPT-BH. Because each modality exhibited unique benefits, personalization of modality selection is recommended. Proton therapy via BH provides additional benefits in heart and lung sparing.

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Introduction

Lymphoma affects significant proportions of men and women with subtypes such as Hodgkin lymphoma (HL) generally presenting as supradiaphragmatic lymphadenopathy in young adults.¹⁻³ High cure rates can be achieved for patients with early-stage lymphoma, but lymphoma in young patients with mediastinal involvement necessitates careful consideration of the benefits versus risks of late toxicity from systemic therapy and radiation therapy (RT).

Deintensification of chemotherapy regimens and reduction of RT fields have both been shown to reduce late side effects while preserving survival outcomes.^{4,5} Advances in RT planning, such as use of photon-based “butterfly” intensity modulated radiation therapy (IMRT) over conventional anteroposterior and posteroanterior directed photon beams⁶ or the delivery of RT using deep-inspiration breath hold (BH),⁷ can improve pulmonary and cardiac dosimetry. BH, in particular, increases total lung volumes, thereby reducing lung exposure and minimizing respiratory-induced motion to allow for smaller target volumes. It also leads to inferior cardiac displacement, which is favorable for patients with superior mediastinal target volumes.^{6,8,9}

Proton beam therapy also offers advantages for treating mediastinal disease.¹⁰ Compared with photons that exhibit an exit dose, the dose distribution of protons forms a Bragg peak with the maximum dose deposited at a finite tissue depth followed by a sharp dose falloff with virtually no exit dose.¹¹ Common proton modalities include passive scattering proton therapy (P) and intensity modulated proton therapy (IMPT). Given their physical properties, protons have been shown to provide dosimetric benefits over 3-dimensional (3D) or IMRT free-breathing–based plans when treating the mediastinum.¹²⁻¹⁵

Although BH can significantly improve doses to the heart and lungs,^{7,8,16,17} it is unclear whether the benefit afforded by BH when used with IMRT is comparable to or can exceed the desirable physical properties of protons when treating patients with mediastinal lymphoma in free breathing (FB). We therefore performed a detailed

dosimetric analysis comparing IMRT-BH to proton therapy administered in FB with passive scatter (P-FB) and IMPT (IMPT-FB). Finally, hypothesizing that proton plans administered with BH would offer superior normal tissue sparing, we compared passive scatter proton therapy via BH (P-BH) to the other techniques.

Methods and Materials

Patient selection

In this single institution retrospective dosimetric analysis, 15 patients were selectively included if they had a diagnosis of HL or non-Hodgkin lymphoma involving the mediastinum, were treated with IMRT-BH between 2013 and 2016, and had 4-dimensional (4D) computed tomography (CT) scans available. Bulky disease was defined as a nodal conglomerate measuring ≥ 10 cm axially. Disease extending ≥ 3 cm below the carina was considered to be whole mediastinal involvement; superior disease was classified as upper mediastinal involvement.^{7,8} All patients received 2 or more cycles of chemotherapy and underwent positron emission tomography/CT scans to confirm complete response to systemic therapy (defined as a score of 1-3 on a 5-point scale) before receiving RT.¹⁸

IMRT-BH planning

For simulation, patients were placed in the supine position with arms down and immobilized with an upper Vac-Lok bag (CIVCO Medical Solutions, Orange City, IA) and a facemask. A 10° to 15° incline board was used to inferiorly displace breast tissue (women) and improve heart sparing.⁶ Three serial BH scans using real-time position management with biometric feedback were acquired with patients in the treatment position. Clinical target volumes (CTVs) encompassed prechemotherapy sites of disease, according to the International Lymphoma Radiation Oncology Group involved-site RT guidelines.¹⁹ CTV volumes were verified on all BH scans, and planning target volumes (PTVs) comprised the CTV plus a uniform 5-mm expansion to account for motion and setup uncertainties.

IMRT-BH plans were created with a Pinnacle Treatment Planning System (Philips Healthcare, Andover, MA) for a 6-MV beam energy linear accelerator (Varian Medical Systems, Palo Alto, CA). Plans were optimized to deliver 30.6 Gy in 17 fractions to the PTV using a “butterfly” technique.⁶ All plans underwent rigorous optimization to achieve >98% CTV coverage with the prescribed dose while meeting normal-tissue dose constraints. IMRT was given with step-and-shoot multileaf collimation. Daily low-dose CT-on-rails (Varian Medical Systems) was used to verify reproducibility of the patient’s BH and to ensure accurate target localization.

Free-breathing proton planning

Available 4D CT simulation data sets were transferred into an Eclipse Treatment Planning System (Varian Medical Systems), which was used to generate 2 proton-FB plans per patient: P-FB and IMPT-FB. CTVs were delineated on the maximum intensity projection scan, which reflects the highest density value by pixel throughout the respiratory cycle, while organs at risk (OAR) were contoured on the average intensity scan. A uniform 5-mm expansion was applied to create the PTV. Two or 3 anterior beams were used with gantry angles ranging from 340° to 20°, and if the CTV extended to the neck, caudal “couch kicks,” which entail moving the couch so that the gantry is closer to the patient’s feet, were used to avoid irradiating the mandible. Cranial couch kicks, which position the couch so that the gantry is closer to the patient’s head, were often used to minimize dose to the breasts. Beam angles were the same for the P-FB and IMPT-FB plans for each patient. For P-FB plans, the distal margin was calculated as $\text{range} \times 3.5\% + 2$ mm. The proximal margin was set to 0 mm. Compensator smearing was set to 6 mm (set-up uncertainty + 1 mm). IMPT-FB was planned to the PTV to facilitate comparison with IMRT. Range shifters and apertures were added to the IMPT plans after single-field optimization with a lateral margin similar to that used for the P-FB plans. P-FB and IMPT-FB plans were designed to deliver 30.6 Gy relative biological effectiveness (RBE) in 17 fractions on the average intensity projection scan.²⁰ All plans were optimized until they met OAR constraints while achieving greater than 98% coverage of the CTV by the prescription dose.

Breath-hold proton planning

The FB and BH scans used to create the original IMRT-BH plans were also uploaded into Eclipse to create passive scatter P-BH plans. The same individualized, anterior beam arrangements and couch kicks that resulted in the most optimal P-FB plans per patient were used for

P-BH planning. Apertures and compensators were then refitted to optimize target coverage and OAR sparing using the same constraints as specified for the IMRT-BH planning.

Delineation of organs at risk

Normal tissues contoured included the lungs, total heart, left ventricle (LV), left main/left anterior descending artery, right coronary artery, bilateral breasts (for women), thyroid gland, spinal cord, and upper body. The total lung volume (in mL) included the entire lung (without exclusion of the CTV or PTV). The heart and cardiac substructures were delineated according to a contouring atlas.²¹ The upper body contour was outlined from the base of skull to L1, encompassing the full length of the lungs to maintain consistency of range between the serial BH scans and 4D CT scans.

Statistical analysis

CTV and PTV coverage as well as dose sparing of OARs using IMRT-BH, P-FB, IMPT-FB, or P-BH plans were analyzed. Specifically, for OARs, the mean values and standard deviations for the following parameters are reported using data from all patient plans per treatment planning technique: mean dose (Gray), V5, V15, V20 (total lung), V25, and V30. Statistical comparisons of all dosimetric variables were performed using nonparametric Wilcoxon signed-rank methods. A *P* value of < .05 was considered statistically significant, and multiple comparisons statistics were reported. Percent changes in heart and lung V5, V30, and mean doses per patient were evaluated using a waterfall plot analysis for P-BH versus IMRT-BH, P-FB versus IMRT-BH, and IMPT-FB versus IMRT-BH. All analyses were completed in R and JMP Pro 12 (SAS, Cary, NC).

Results

Patient characteristics

Characteristics of the 15 patients in this study are summarized in Table 1. The median patient age was 32 years (range, 24-44 years); 9 (60%) were women. The most common diagnosis was HL (*n* = 12, 80%). Twelve patients (80%) had stage I/II disease, 6 (40%) had bulky mediastinal disease, and 13 (87%) had whole mediastinal involvement. Twelve patients had pericardial disease with right sided-heart involvement (75%) more prevalent than left-sided (25%).

Effect of deep-inspiration breath-hold on lung volumes

The median lung volume for all 15 patients was 2372.2 mL³ (range, 2076.5–3436.5 mL³) during free-breathing and 4101.93 mL³ (range, 3002.9–7604.52 mL³) using BH. Therefore, the median and mean percentage increase in lung volume secondary to BH was 47.7% and 64.4%, respectively (range, 38.0–133.5%).

Dosimetric analysis

Coverage of the CTV was excellent in all 4 plans, with a mean CTV (D99%) of 30.4 Gy with IMRT-BH, 30.6 Gy (RBE) with P-FB and P-BH, and 30.7 Gy (RBE) with IMPT-FB (Table 2). Representative dose distributions achieved for 1 patient with mediastinal lymphoma using IMRT-BH and all 3 proton plans are shown in Figure 1.

Dose parameters per treatment plan are shown in Table 2 with color scales of their associated *P* values in Figure 2. Overall, IMRT-BH plans were comparable in 37 of the 57 (65%) studied OAR variables from P-FB plans, 32 (56%) of IMPT-FB, and 30 (53%) of P-BH parameters. When comparing only the mean dose OAR parameters per plan (11 metrics), IMRT-BH was comparable in 5/11 (45%) with P-FB, 3/11 (27%) with IMPT-FB, and 5/11 (45%) with P-BH. With regards to the 6 lung dosimetric parameters, IMRT was equivalent or superior in 4 (67%), 3 (50%), and 2 (33%) parameters compared with P-FB, IMPT-FB, and P-BH. For total heart dosimetry (5 parameters), IMRT-BH was equivalent in 3 (60%), 3 (60%), and 1 (20%) parameters, respectively. Combining all coronary arteries (15 parameters) resulted in an IMRT-BH equivalent rate of 87%, 100%, and 67% compared with P-FB, IMPT-FB, and P-BH, respectively.

Lung parameters showed the greatest variations among plans despite all of them achieving a mean lung dose (MLD) of ≤ 13.5 Gy and V5 $\leq 55\%$. Although the mean MLD value was low with IMRT-BH, it was significantly higher than all proton plans as was the lung V5 (low dose bath). IMRT-BH, however, improved high dose conformity with an equivalent mean V20 compared with P-FB and IMPT-FB (20.2% vs 20% vs 18.5%; $P > .05$) and a superior mean V30 compared with P-FB, IMPT-FB, and P-BH (7.1% vs 11.7% vs 8.7% vs 8.6%; $P < .001$). The contrasting percent changes in MLD, lung V5, and lung V30 using proton plans relative to IMRT-BH are shown in Figure 3. Among BH plans, the combination of protons with BH significantly improved all lung parameters compared with IMRT-BH, with the exception of lung V25 and V30. P-BH plans significantly reduced the MLD by 11% and 17% compared with P-FB and IMPT-FB, respectively, although the absolute doses differences were small at < 1.2 Gy.

Table 1 Patient characteristics

| Characteristic | Patient no. (%) |
|----------------------------|-----------------|
| Age, years, median (range) | 32 (24–44) |
| Sex | |
| Male | 6 (40) |
| Female | 9 (60) |
| Lymphoma subtype | |
| Hodgkin | 12 (80) |
| Marginal zone | 1 (7) |
| PMBCL | 1 (7) |
| T cell | 1 (7) |
| Disease stage | |
| IB | 1 (7) |
| IIA | 6 (40) |
| IIB | 5 (33) |
| IIIB | 1 (7) |
| Other | 2 (13) |
| Bulky disease | |
| Yes | 6 (40) |
| No | 9 (60) |
| Pericardial disease | |
| Yes | 12 (80) |
| No | 3 (20) |
| Right-sided heart disease | |
| Yes | 9 (60) |
| No | 6 (40) |
| Left-sided heart disease | |
| Yes | 3 (20) |
| No | 12 (80) |
| Superior disease extent | |
| Hyoid/larynx | 6 (40) |
| Thyroid | 9 (60) |
| Inferior disease extent | |
| Middle third sternum | 10 (67) |
| Lower third sternum | 5 (33) |
| Mediastinal involvement | |
| Upper mediastinum only | 2 (13) |
| Whole mediastinum | 13 (87) |
| Chemotherapy | |
| ABVD | 12 (80) |
| R-CHOP | 1 (7) |
| Other | 2 (13) |
| No. of cycles | |
| 2 | 1 (7) |
| 4 | 4 (27) |
| 6 | 8 (53) |
| ≥ 7 | 2 (13) |

Abbreviations: ABVD = adriamycin, bleomycin, vinblastine, dacarbazine; PMBCL = primary mediastinal B cell lymphoma; R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone.

Similar findings (ie, worse mean dose and V5 but comparable high-dose organ sparing) with IMRT-BH versus proton plans were seen for the heart (Fig 2) and LV. P-BH was associated with the lowest heart parameters that were significantly improved compared with IMRT-BH and IMPT-FB only. When combining all OAR

Table 2 Dosimetric comparison for IMRT-BH, P-FB, IMPT-FB, and P-BH plans

| | IMRT-BH | P-FB | IMPT-FB | P-BH |
|--------------------------------------|-------------|-------------|--------------|-------------|
| CTV D ₉₉ , Gy or Gy (RBE) | 30.38 ± 0.5 | 30.60 ± 0.3 | 30.66 ± 0.2 | 30.63 ± 0.3 |
| PTV D ₉₅ Gy or Gy (RBE) | 29.65 ± 1.2 | 30.36 ± 0.4 | 30.34 ± 0.2 | 30.31 ± 0.4 |
| Total lung | | | | |
| V ₅ , % | 42.9 ± 8 | 33.3 ± 7 | 32.5 ± 8 | 30.3 ± 6 |
| V ₁₅ , % | 25.6 ± 7 | 23.8 ± 7 | 22.2 ± 6 | 19.7 ± 5 |
| V ₂₀ , % | 20.2 ± 6 | 20 ± 6 | 18.5 ± 5 | 15.6 ± 4 |
| V ₂₅ , % | 14.7 ± 5 | 16.8 ± 5 | 14.4 ± 5 | 12.8 ± 3 |
| V ₃₀ , % | 7.1 ± 3 | 11.7 ± 4 | 8.7 ± 3 | 8.6 ± 2 |
| D _{mean} , Gy or Gy (RBE) | 9.01 ± 1.9 | 7.64 ± 1.9 | 7.23 ± 1.9 | 6.49 ± 1.4 |
| Total heart | | | | |
| V ₅ , % | 44.1 ± 18 | 31.6 ± 13 | 35.7 ± 13 | 6.1 ± 4 |
| V ₁₅ , % | 32 ± 13 | 26.8 ± 11 | 28 ± 11 | 3.9 ± 3 |
| V ₂₅ , % | 26 ± 11 | 22.3 ± 10 | 21.7 ± 10 | 1 ± 2 |
| V ₃₀ , % | 20.1 ± 9 | 19 ± 9 | 16.7 ± 9 | 0.7 ± 1 |
| D _{mean} , Gy or Gy (RBE) | 11.19 ± 4.2 | 8.52 ± 3.6 | 8.97 ± 3.6 | 1.10 ± 0.9 |
| Left ventricle | | | | |
| V ₅ , % | 21.1 ± 19 | 8.7 ± 11 | 12.3 ± 12 | 5.3 ± 5 |
| V ₁₅ , % | 8.1 ± 10 | 5.9 ± 8 | 6.9 ± 8 | 3.3 ± 4 |
| V ₂₅ , % | 4.7 ± 7 | 3.9 ± 6 | 3.7 ± 5 | 2.1 ± 2 |
| V ₃₀ , % | 2.4 ± 4 | 2.7 ± 4 | 1.9 ± 3 | 1.3 ± 2 |
| D _{mean} , Gy or Gy (RBE) | 4.29 ± 3.2 | 1.95 ± 2.5 | 2.49 ± 2.6 | 1.15 ± 1.2 |
| Left main-LAD | | | | |
| V ₅ , % | 43.9 ± 16 | 46.2 ± 22 | 45.8 ± 19 | 40.9 ± 21 |
| V ₁₅ , % | 34.2 ± 19 | 39 ± 24 | 38.3 ± 24 | 34.5 ± 23 |
| V ₂₅ , % | 30.3 ± 20 | 33.2 ± 25 | 32.2 ± 23 | 28.6 ± 24 |
| V ₃₀ , % | 26.5 ± 21 | 28.2 ± 23 | 23.7 ± 23 | 25.2 ± 24 |
| D _{mean} , Gy or Gy (RBE) | 12.08 ± 5.4 | 12.51 ± 7.5 | 11.97 ± 6.8 | 11.08 ± 7.4 |
| Left circumflex | | | | |
| V ₅ (%) | 81.1 ± 23 | 34.1 ± 39 | 54.9 ± 37 | 29.7 ± 33 |
| V ₁₅ (%) | 45.4 ± 35 | 29.7 ± 41 | 42.1 ± 39 | 25.4 ± 32 |
| V ₂₅ (%) | 36.6 ± 34 | 28.1 ± 41 | 30 ± 41 | 22.6 ± 31 |
| V ₃₀ (%) | 27.1 ± 31 | 26.9 ± 40 | 23.5 ± 35 | 19.7 ± 29 |
| D _{mean} , Gy or Gy (RBE) | 16.62 ± 8.5 | 9.95 ± 12.9 | 13.17 ± 11.3 | 8.39 ± 10.2 |
| RCA | | | | |
| V ₅ , % | 52.3 ± 28 | 51.8 ± 30 | 49.2 ± 31 | 51.6 ± 25 |
| V ₁₅ , % | 41.2 ± 30 | 46.6 ± 31 | 42.5 ± 32 | 46.9 ± 25 |
| V ₂₅ , % | 35.7 ± 31 | 42.1 ± 32 | 37.5 ± 32 | 39.9 ± 27 |
| V ₃₀ , % | 30.8 ± 32 | 38.4 ± 32 | 30.1 ± 31 | 33.7 ± 29 |
| D _{mean} , Gy or Gy (RBE) | 13.98 ± 8.9 | 14.92 ± 9.9 | 13.38 ± 9.9 | 14.59 ± 8.4 |
| Esophagus | | | | |
| V ₅ , % | 74.7 ± 12 | 56.8 ± 13 | 59.6 ± 12 | 56.9 ± 12 |
| V ₁₅ , % | 65.6 ± 11 | 53.2 ± 14 | 53 ± 12 | 53.4 ± 14 |
| V ₂₅ , % | 59.1 ± 11 | 49.2 ± 14 | 47.3 ± 13 | 49.7 ± 16 |
| V ₃₀ , % | 50.5 ± 16 | 44.6 ± 15 | 41.2 ± 14 | 45.5 ± 17 |
| D _{mean} , Gy or Gy (RBE) | 20.83 ± 3.4 | 16.69 ± 4.3 | 16.69 ± 3.9 | 16.82 ± 4.6 |
| Left breast (n = 9) | | | | |
| V ₅ , % | 4.7 ± 3 | 5.3 ± 5 | 3.6 ± 4 | 6.1 ± 4 |
| V ₁₅ , % | 2.2 ± 2 | 3.1 ± 3 | 1.8 ± 2 | 3.9 ± 3 |
| V ₂₅ , % | 0.5 ± 1 | 1 ± 1 | 0.3 ± 0 | 1 ± 2 |
| V ₃₀ , % | 0.1 ± 0 | 0.6 ± 1 | 0 ± 0 | 0.7 ± 1 |
| D _{mean} , Gy or Gy (RBE) | 1.32 ± 0.6 | 0.96 ± 0.9 | 0.59 ± 0.6 | 1.10 ± 0.9 |
| Right breast (n = 9) | | | | |
| V ₅ , % | 5.6 ± 7 | 3.5 ± 3 | 2.6 ± 3 | 5.7 ± 5 |
| V ₁₅ , % | 1.7 ± 3 | 1.9 ± 2 | 1 ± 2 | 3.0 ± 4 |
| V ₂₅ , % | 0.1 ± 3 | 0.5 ± 1 | 0.2 ± 1 | 0.8 ± 2 |
| V ₃₀ , % | 0 ± 0 | 0.4 ± 1 | 0 ± 0 | 0.6 ± 1 |
| D _{mean} , Gy or Gy (RBE) | 1.21 ± 1.1 | 0.61 ± 0.6 | 0.40 ± 0.6 | 0.96 ± 1 |

(continued on next page)

Table 2 (continued)

| | IMRT-BH | P-FB | IMPT-FB | P-BH |
|---|--------------|--------------|--------------|--------------|
| Thyroid | | | | |
| V ₅ , % | 66.4 ± 40 | 64.8 ± 33 | 54.6 ± 38 | 71.8 ± 34 |
| V ₁₅ , % | 56.3 ± 41 | 55.7 ± 38 | 47.6 ± 40 | 62.2 ± 38 |
| V ₂₅ , % | 48.9 ± 40 | 46.7 ± 40 | 37.1 ± 36 | 52.6 ± 40 |
| V ₃₀ , % | 40.6 ± 37 | 32.9 ± 35 | 23 ± 27 | 42.2 ± 38 |
| D _{mean} , Gy or Gy (RBE) | 18.32 ± 11.9 | 17.28 ± 11.3 | 14.34 ± 11.7 | 19.44 ± 11.4 |
| Upper body | | | | |
| V ₅ , % | 19 ± 5 | 8.4 ± 3 | 8.7 ± 3 | 9.5 ± 2 |
| V ₁₅ , % | 12.1 ± 4 | 6.6 ± 2 | 6.6 ± 2 | 7.1 ± 2 |
| V ₂₅ , % | 6.9 ± 3 | 5.1 ± 2 | 4.8 ± 2 | 5.2 ± 2 |
| V ₃₀ , % | 4 ± 1 | 4.1 ± 2 | 3.4 ± 2 | 4.2 ± 1 |
| D _{mean} , Gy or Gy (RBE) | 6.24 ± 2 | 2.09 ± 0.8 | 2.12 ± 0.8 | 2.28 ± 0.6 |
| Cord D _{max} , cGy or Gy (RBE) | 30.55 ± 2.4 | 12.93 ± 9 | 23.11 ± 6.2 | 12.18 ± 6.7 |

Abbreviations: CTV = clinical target volume; IMPT-FB = intensity modulated proton therapy while free breathing; IMRT-BH = intensity modulated photon radiation therapy with breath-hold; IMRT-DIBH = intensity modulated radiation therapy while using deep-inspiration breath-hold; Left Main-LAD = left anterior descending artery; P-BH = passive proton therapy using breath-hold; P-FB = passive proton therapy while free breathing; PTV = planning target volume; RCA = right coronary artery; RBE = relative biological effectiveness. All values are reported as means of the entire cohort with corresponding standard deviation.

parameters pertaining to the heart and its substructures (total heart, LV, left anterior descending artery [left-main LAD], left circumflex, right coronary artery [RCA]; 25 OAR parameters per plan), IMRT-BH was equivalent in 19/25 (76%) parameters in P-FB, 22/25 (88%) in IMPT-FB, and 13/25 (52%) in P-BH plans. Dose variables pertaining to the left main-left anterior descending artery and right coronary artery were roughly equivalent among plans. For women, all plans resulted in low mean doses to the breast (≤ 1.3 Gy) and a V₂₅ and V₃₀ of $\leq 1\%$. With respect to the esophagus, all dosimetric parameters were significantly higher with IMRT-BH compared with proton plans, and grossly equivalent among the proton plans (IMPT-FB was superior to P-FB for esophageal V₂₅ and V₃₀). The thyroid was best spared using IMPT-FB (V₃₀ = 23%), with significantly lower doses compared with the BH plans (IMRT-BH and P-BH V₃₀: 40.6% and 42.2%, respectively; $P < .001$). However, IMRT-BH was able to produce equivalent thyroid sparing compared with P-FB and P-BH. Average dosimetric parameters for the total lung, total heart, and heart substructures by treatment planning technique are shown in Figure 4.

Discussion

Because protons have a rapid dose fall off beyond targets, it is often assumed that proton therapy will result in superior plans compared with photon-based therapy. However, continual advancements in the planning and delivery of RT make this a controversial topic that is highly influenced by patient characteristics as well as the extent and location of the targeted disease. In the current

dosimetric study, we found that photon plans using BH can be optimized to achieve comparable mediastinal target coverage and reasonable normal tissue sparing relative to most FB proton plans. Although low dose baths and mean doses to the heart and lungs were statistically lower using protons, IMRT-BH compensated by achieving relatively low doses to these organs and providing superior high-dose sparing. Proton therapy administered with BH, however, achieved maximal normal tissue reductions.

Our study is not the first to demonstrate that photon plans administered with BH can be largely comparable to FB proton plans. Rechner et al²² studied life-years lost (LYL) in 22 patients with early-stage HL within a data set that examined 4 treatment plans per patient: IMRT or passive scatter protons with and without BH. The LYL values were 2.1 years for IMRT-FB, 0.9 years for IMRT-BH, 1.3 years for P-FB, and 0.7 for P-BH. Although this value was the lowest with P-BH, no statistical difference in LYL was observed between P-FB and IMRT-BH. Our study complements their findings and provides additional robustness by incorporating 4D CT-based planning and providing a dosimetric comparative analysis between passive scatter and IMPT, the latter of which is the most advanced proton therapy technique to date.

A potentially dose-limiting toxicity to consider when planning irradiation of the lungs or mediastinum is radiation pneumonitis (RP). A mean lung dose ≥ 13.5 Gy and lung V₂₀ $\geq 33.5\%$ have been documented as potential RP risk factors for patients treated with 3D conformal RT for lung cancer or mediastinal lymphoma.^{23,24} In a more recent study, the RP incidence for patients with lymphoma treated with IMRT was found to significantly

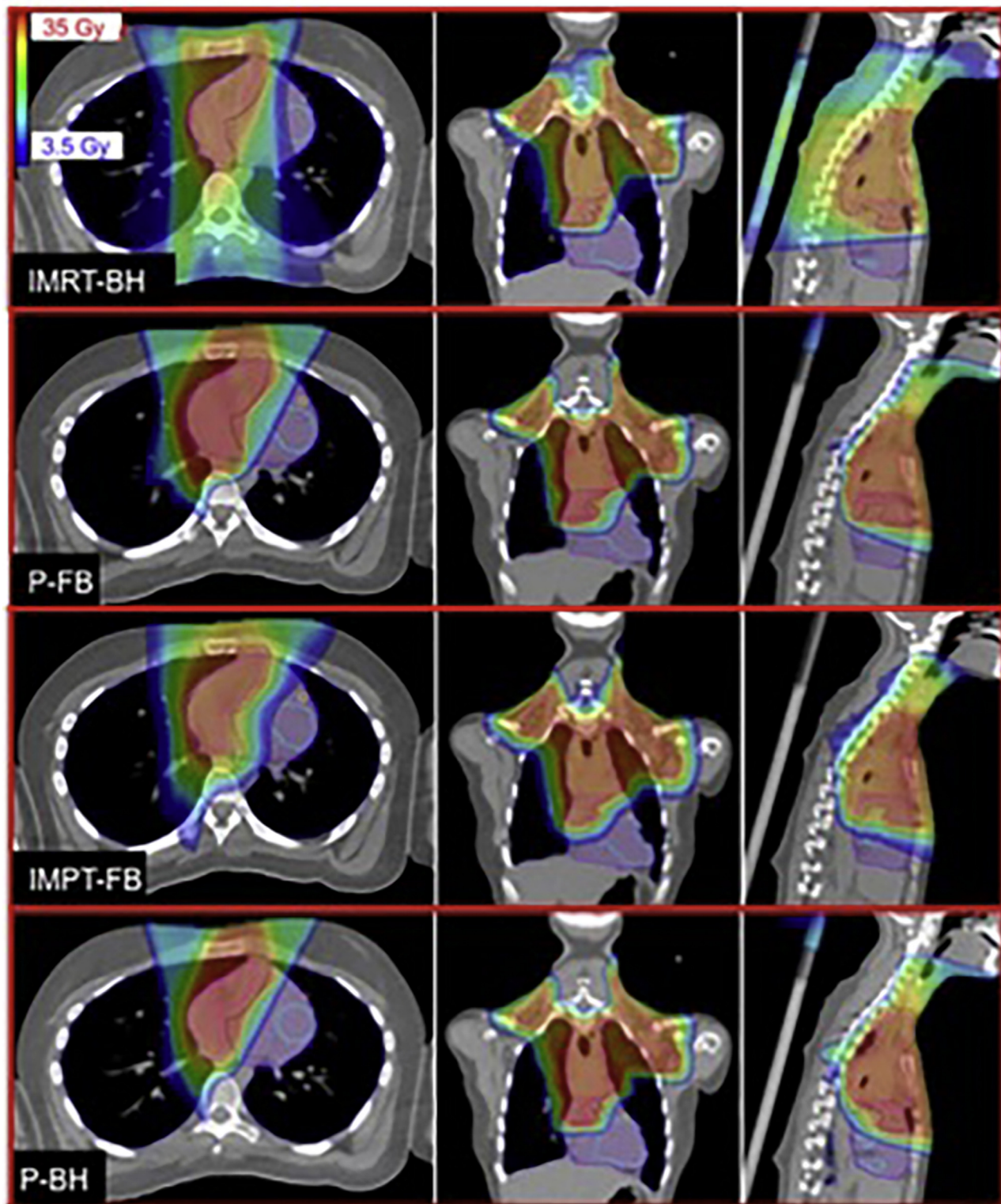


Figure 1 Axial, coronal, and sagittal treatment-planning images for intensity modulated photon radiation therapy with breath hold, passive scatter proton therapy with free breathing or breath-hold, and intensity modulated proton therapy with free breathing are shown for a patient with mediastinal lymphoma.

| Plan 1: | IMRT-BH | | | IMPT-FB | P-BH | |
|--------------------|---------|---------|------|---------|------|---------|
| Plan 2: | P-FB | IMPT-FB | P-BH | P-FB | P-FB | IMPT-FB |
| CTV D99 | | | | | | |
| PTV D95 | | | | | | |
| Total Lung V5 | | | | | | |
| V15 | | | | | | |
| V20 | | | | | | |
| V25 | | | | | | |
| V30 | | | | | | |
| Mean Dose | | | | | | |
| Total Heart V5 | | | | | | |
| V15 | | | | | | |
| V25 | | | | | | |
| V30 | | | | | | |
| Mean Dose | | | | | | |
| Left Ventricle V5 | | | | | | |
| V15 | | | | | | |
| V25 | | | | | | |
| V30 | | | | | | |
| Mean Dose | | | | | | |
| Left Main-LAD V5 | | | | | | |
| V15 | | | | | | |
| V25 | | | | | | |
| V30 | | | | | | |
| Mean Dose | | | | | | |
| Left Circumflex V5 | | | | | | |
| V15 | | | | | | |
| V25 | | | | | | |
| V30 | | | | | | |
| Mean Dose | | | | | | |
| RCA V5 | | | | | | |
| V15 | | | | | | |
| V25 | | | | | | |
| V30 | | | | | | |
| Mean Dose | | | | | | |
| Esophagus V5 | | | | | | |
| V15 | | | | | | |
| V25 | | | | | | |
| V30 | | | | | | |
| Mean Dose | | | | | | |
| Left Breast V5 | | | | | | |
| V15 | | | | | | |
| V25 | | | | | | |
| V30 | | | | | | |
| Mean Dose | | | | | | |
| Right Breast V5 | | | | | | |
| V15 | | | | | | |
| V25 | | | | | | |
| V30 | | | | | | |
| Mean Dose | | | | | | |
| Thyroid V5 | | | | | | |
| V15 | | | | | | |
| V25 | | | | | | |
| V30 | | | | | | |
| Mean Dose | | | | | | |
| Body V5 | | | | | | |
| V15 | | | | | | |
| V25 | | | | | | |
| V30 | | | | | | |
| Mean Dose | | | | | | |
| Spinal Cord Dmax | | | | | | |

Figure 2 Color scale *P* value table for multiple comparisons among all treatment planning techniques. Green and red cells denote $P < .05$, with green representing an *improvement* in dose variable with plan 1 versus plan 2 and red representing a *worsening* in dose variable with plan 1 versus plan 2. Color gradients correlate with the significance of *P* values, with darker reds or greens representing

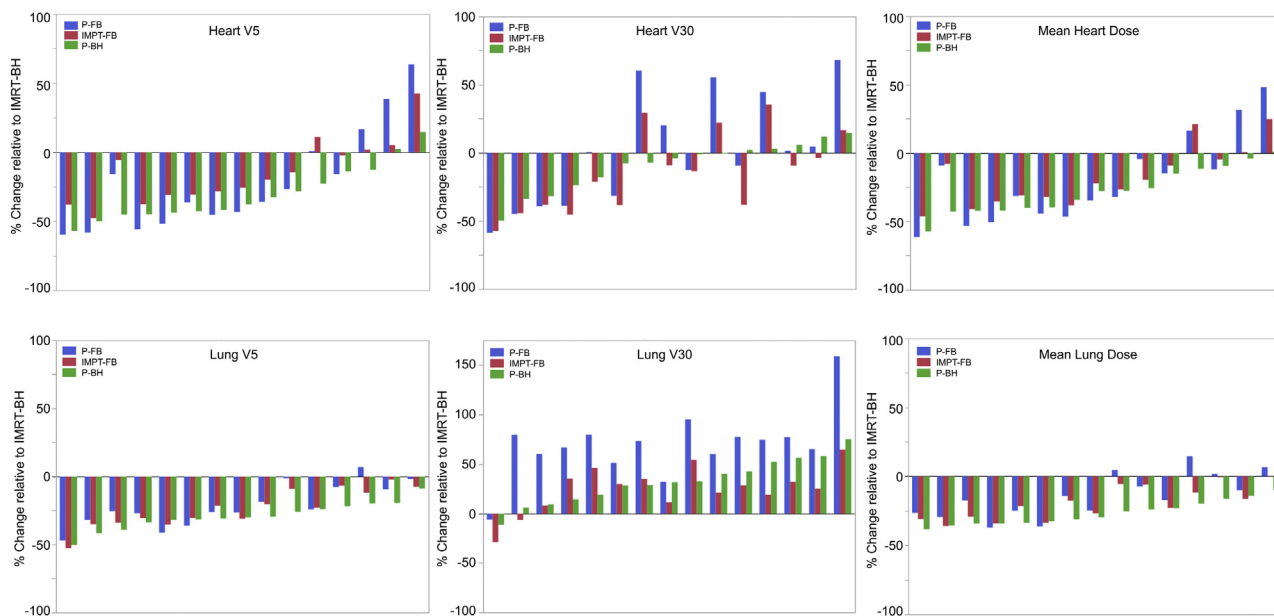


Figure 3 Waterfall plots of percent differences in heart and lung dose parameters for proton therapy relative to IMRT-BH plans. Differences (%) in heart V5, heart V30, mean heart dose, lung V5, lung V30, and mean lung dose for each patient are shown as green bars for P-BH, blue bars for P-FB, and red lines for IMPT-FB plans. Negative values (downward bars) indicate a dose reduction (and improvement) for proton therapy versus IMRT-BH, and positive values (upward bars) indicate a higher (and worse) average dose variable for proton therapy versus IMRT-BH. *Abbreviations:* IMPT-FB = intensity modulated proton therapy with free breathing; IMRT-BH = intensity modulated photon radiation therapy with breath-hold; P-BH = passive scatter proton therapy with breath-hold; P-FB = passive scatter proton therapy with free breathing.

increase when the MLD exceeded 13.5 Gy (50% vs 9.2%) and the lung V5 exceeded 55% (35% vs 7%).²⁵ In the current study, both IMRT and proton plans met and surpassed these criteria with a 33% to 52% and 22% to 45% reduction in MLD and lung V5, respectively. Improved lung sparing in our study may be multifactorial, including consistent use of an incline board for all women and advances in planning techniques (ie, incorporation of couch kicks). Further investigations are required to determine the clinical benefit associated with improved OAR sparing, and continued pushing of dose constraints is encouraged over time. Lastly, our dosimetric findings indicate that IMRT-BH can be an effective alternative to protons despite a particularly challenging population of patients with extensive mediastinal involvement and pericardial disease.

One significant advantage in treating young and relatively healthy individuals is their superior lung function compared with elderly patients. The favorable dosimetric changes associated with BH result largely from the increase in total lung volume. In a study of

patients with non-small cell lung cancer who underwent FB and BH planning for lung cancer, the mean increase in lung volume from BH was 37.8%.²⁶ This value is notably smaller than that in our young cohort (64%). Therefore, if treating patients with poor lung function who are incapable of BH, proton therapy via FB may result in a superior plan over a suboptimal IMRT-BH or standard IMRT-FB plan.

The combination of proton therapy with BH appears to be the most promising lung sparing advancement. In our study, P-BH was associated with absolute MLD reductions of 11% to 17% compared with proton FB plans and a 38% reduction compared with IMRT-BH. Our findings align with those of similar studies that have shown superior lung dose sparing with passive scatter proton therapy or IMPT delivered using BH compared with IMRT-BH.²⁷ When evaluating only proton plans, nearly all lung dose parameters were significantly improved with P-BH, thereby again demonstrating the dosimetric advantages of BH regardless of RT technique applied. Although statistically significant, the differences in lung V5 through V30 were relatively

← *P* values closer to $P \leq .001$ and lighter shades of red and green representing *P* values closer to $P = .05$. Gray cells denote $P > 0.05$. *Abbreviations:* IMPT-FB = intensity modulated proton therapy while free breathing; IMRT-DIBH = intensity modulated radiation therapy while using deep-inspiration breath-hold; Left Main-LAD = left anterior descending artery; P-BH = passive proton therapy using breath-hold; P-FB = passive proton therapy while free breathing; RCA = right coronary artery.

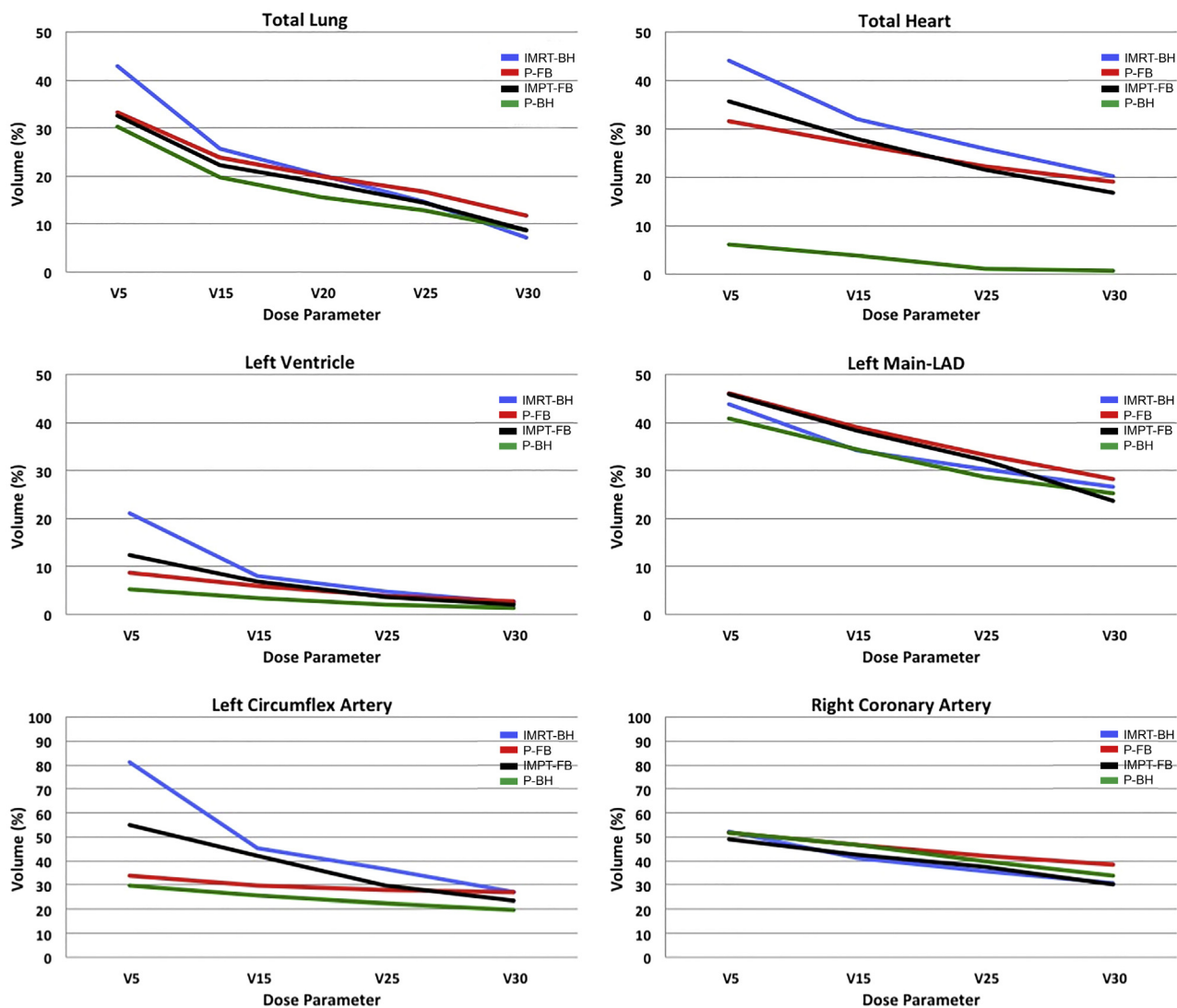


Figure 4 Comparison of dose volume parameters for IMRT-BH (blue), P-FB (red), P-BH (green), and IMPT-FB (black) for lung, heart, and coronary arteries. *Abbreviations:* IMPT-FB = intensity modulated proton therapy with free breathing; IMRT-BH = intensity modulated photon radiation therapy with breath-hold; Left Main-LAD = left anterior descending artery; P-BH = passive scatter proton therapy with breath-hold; P-FB = passive scatter proton therapy with free breathing.

small, at approximately 3% to 5% among proton plans, calling into question whether a clinically significant benefit will be seen in the future with P-BH over proton FB techniques. Additionally, the V20 through V30 with IMRT-BH were also within a 5% difference compared with P-BH, re-emphasizing the effective high dose sparing associated with IMRT-BH. Additional studies are warranted to determine whether reducing low-dose baths (proproton) or high-dose baths (pro-IMRT-BH) to the lungs is more clinically relevant when considering the risk for both RP and secondary lung cancers in patients with mediastinal lymphoma.

Extent of disease was not found to be associated with a dosimetric benefit from proton therapy, which was surprising given that 87% of our cohort had extensive mediastinal disease. Equipoise between IMRT-BH plans

and proton FB plans would not be surprising for cases of low disease burden located high within the mediastinum and superior to the heart. For this kind of disease, using involved-site RT principles to generate target volumes would be expected to generate minimal differences in the dose-volume histogram profile for the heart, lungs, and breast across techniques. However, for disease that extends more inferiorly in the mediastinum (as was the case for most patients in our study), the lack of consistent superiority of the FB proton plans further emphasizes the importance of BH.

The risk of breast cancer is known to be higher for women treated with thoracic RT than for women in the general population.^{28,29} Speculation that use of IMRT with multiple beam arrangements would result in

increased low-dose radiation to the breasts has been debunked by numerous retrospective analyses showing effective breast sparing with anteroposterior-posteroanterior weighted IMRT beam arrangements.^{6,8,13} However, some evidence suggests that BH may result in increased breast dose over FB approaches. In a study at Princess Margaret Hospital, deep-inspiration breath-hold (DIBH) was found to lead to a 0.6-Gy increase in mean breast dose (relative to FB) among 77% of women.⁸ In contrast, we found efficient sparing of both breasts using all RT techniques, with reported mean doses to either breast of ≤ 1.3 Gy and V30 $\leq 0.6\%$. This finding may be attributed to our use of a 10° to 15° incline board and highlights the importance of incorporating this basic tool into the treatment approach for women receiving RT to the mediastinum.³⁰

Limiting radiation exposure to the heart is also essential in planning thoracic RT. A landmark study following women who received RT for breast cancer from 1958 to 2001 showed that the risk of ischemic heart disease increased linearly with mean heart dose by 7.4% per Gy.³¹ This study is limited given that it was performed in the 3D-conformal RT era. Nowadays, with advances in high conformity planning techniques, a mean heart dose of less than 5 Gy is a desirable dosimetric constraint and often achievable in patients with superior mediastinal lymphoma. For patients with extensive lower mediastinal involvement, doses to the heart can vary significantly by radiation modality and technique. In our cohort, with all patients having disease extending inferiorly to the middle third of the sternum or beyond, a mean heart dose of < 5 Gy was only achievable using P-BH at 1.1 Gy (RBE) compared with 11.2 Gy with IMRT-BH, 8.5 Gy (RBE) with P-FB, and 9 Gy (RBE) with IMPT-FB. Other studies have also mirrored better reductions in mean heart dose using protons instead of IMRT.^{32,33} Specifically, Baues et al³⁴ achieved a mean heart dose of 4.1 Gy (RBE) with IMPT-BH over IMRT-BH (mean heart dose of 6.6 Gy [RBE]; $P < .01$) when designing plans for 21 patients with mediastinal HL (information regarding extent of mediastinal disease is unavailable). Although protons were more optimal in our study in limiting total heart mean dose and V5, IMRT-BH had high dose sparing rates comparable to protons with respect to coronary arteries. Another study found significantly improved coronary artery sparing with IMRT-BH compared with IMPT-FB (5.6 Gy vs 12.9 Gy [RBE]; $P < .05$).³³ Further studies are needed to determine whether coronary doses are more predictive of long-term cardiac toxicities than total heart mean dose and V5.

Our study has several limitations beyond the small number of patients. At the time of this study, we lacked robust optimization capabilities in Eclipse. Therefore, as a compensatory measure, range uncertainties and setup without robust optimization were considered in the PTV for IMPT-FB plans. Although this is a feasible approach

that adds to the variety of methods described in other dosimetric studies, it could lead to artificial inflation of radiation dose envelopes compared with IMRT-BH and as a result increased doses to OARs.^{27,33,34} Dose algorithms for proton planning did not incorporate neutron dose, and we could not evaluate the potential significance of variations in RBE.³⁵ Furthermore, our simulation setup (ie, use of incline boards), target coverage definitions, and planning directives (ie, planning to achieve $> 98\%$ target coverage) are institutional specific and may not be generalizable to all institutions. Although potentially interesting, we did not perform an additional comparison with IMPT-BH as we wanted to limit our study to only 1 theoretical scenario (ie, P-BH), and the feasibility of IMPT-BH is questionable at this time. Edvardsson et al³³ did, however, perform a large dosimetric study on 18 patients with mediastinal HL to compare 6 types of plans: 3D-conformal radiotherapy, volumetric modulated arc therapy (VMAT), and IMPT delivered using either FB or DIBH techniques. They found that IMPT-BH resulted in superior lung parameters compared with VMAT-BH and IMPT-FB, and equivalent mean heart doses compared with IMPT-FB. Finally, our data did not include a large proportion of patients with superior mediastinal disease only or include a discussion about cost or access limitations of techniques. Without evidence from randomized studies using standardized patient selection criteria and treatment planning considerations, continued reporting of unique dosimetric reports such as our study is important to enhance our decision-making process when choosing a specific RT modality for treating patients with mediastinal lymphoma.

In conclusion, we show here that patients with extensive mediastinal lymphoma can be treated with a variety of RT modalities, with each showing varying dosimetric advantages. Additional investigations and the ultimate realization of proton therapy delivery with BH should offer additional benefits with regard to mediastinal RT. Finally, careful assessment of individual patient anatomy, comorbid conditions, disease extent, and prior therapies (such as chemotherapy regimens) should be done to optimize radiation treatment selection and reduce the risk of treatment-related toxicity.

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