Comparing Proton Beam to Intensity Modulated Radiation Therapy Planning in Esophageal Cancer

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Abstract

Purpose: To compare passive-scatter proton beam therapy (PBT) versus intensity-modulated radiation therapy (IMRT) for reducing heart/lung dose in esophageal cancer, and to identify anatomy and treatment planning parameters that can lead to suboptimal proton plans.

Patients and Methods: Passive-scatter PBT versus IMRT mean doses and coverage to the lung/heart were evaluated for 55 patients with esophageal cancer from 2007 to 2010. Geometric relationships between the tumor (distance from planning target volume to carina, and percentage of uninvolved heart) and doses to the lung/heart, respectively, were used to predict expected doses to these normal tissues. Cross-comparisons of heart versus lung dose and proton versus photon mean lung/heart dose were used to identify suboptimal proton dosimetry.

Results: Dose–volumetric analysis showed that, for the lung and heart, although protons resulted in smaller volumes receiving lower doses (5–30 Gy), photons achieved smaller volumes receiving higher doses (40–50 Gy). Both distance from planning target volume to carina and percentage of uninvolved heart were linearly associated with IMRT and PBT mean lung/heart doses and can, therefore, be used to estimate expected mean heart/lung doses. Compared with IMRT, initial PBT plans had lower mean lung doses in 100% of cases but only lower mean heart doses in 92% of cases. Reasons for initial suboptimal proton plans with unexpectedly high mean heart doses included poor beam arrangements (ie, AP/PA) and weighting and/or unique patient anatomy. Reoptimization of these initially suboptimal proton plans using a left lateral/PA beam with 1:2 weighting resulted in significantly improved heart doses in most cases, except with patients who had unique anatomies. Nevertheless, after reoptimization, PBT was consistently superior to IMRT in lowering mean lung/heart doses in 100% of the cases, despite suboptimal anatomy.

Conclusion: Compared with IMRT, passive-scatter PBT using a left lateral/PA beam approach with 1:2 weighting can further reduce mean lung/heart dose in esophageal cancer.

Keywords: proton planning; esophageal cancer

Introduction

Preoperative or definitive radiation in the management of nonmetastatic esophageal cancer has led to significant improvements in survival outcomes [1–5]. However, thoracic...
radiation is also associated with substantial late, treatment-related, cardiopulmonary morbidity and mortality. Among patients with Hodgkin lymphoma and breast cancer treated with radiotherapy, cardiovascular disease is now the most common nonmalignant cause of death [6–9] despite the lower relative radiation doses used for treatment. Moreover, thoracic irradiation from the treatment of breast cancer, bronchopulmonary malignancies, and mediastinal lymphomas have been associated with risk of acute radiation pneumonitis and late lung fibrosis [10]. In these cancers, toxicity is a primary concern of thoracic irradiation because dose-limiting toxicities to the heart and lung can offset the survival benefit of radiation.

Although studies on cardiopulmonary complications of thoracic radiation are the most prevalent in survivors of lymphoma and breast cancer, the toxicity of thoracic radiation for the treatment of esophageal cancers cannot be underestimated. In several clinical studies of patients with esophageal carcinomas treated with chemoradiation, the incidence of late cardiopulmonary toxicities was as high as 29% [11] and 33% [12], with 2 deaths (out of 139 patients) reported secondary to myocardial infarction [12]. Results on long-term outcomes with 3-dimensional conformal radiation therapy (3D-CRT) versus intensity-modulated radiation therapy (IMRT) for esophageal cancer also showed an increased cumulative incidence of cardiac deaths and deaths from indeterminate causes in the 3D-CRT group compared with the IMRT group [13].

These results not only suggest that thoracic radiation for esophageal cancer remains a concern because of its potential cardiopulmonary toxicities but also that the dosimetric advantages of advanced radiation technologies may better spare heart/lungs from irradiation and thus offer a method of limiting toxicity. Although previous studies have demonstrated improved heart and lung sparing with IMRT (especially using a modified firefly technique consisting of posterior-lateral hemispheric beams) compared with 3D-CRT [14, 15], questions remain regarding the potential superiority of proton beam therapy (PBT) versus IMRT. Charged particles, such as protons, have a minimal exit dose beyond the target volume and, thus, could theoretically result in greater sparing of surrounding normal tissues, such as the heart/lung. However, although a few limited studies have addressed the dosimetric advantages of PBT in comparison to IMRT for esophageal cancers [16, 17], PBT does not always prove to have the best dosimetric results. The goal of our study was to assess whether passive-scatter PBT versus IMRT can further reduce normal tissue toxicity to the heart and lung in esophageal cancer and to identify any anatomic or treatment planning parameters that can lead to suboptimal proton plans so as to learn how proton planning techniques can be further enhanced.

**Methods**

**Generation of Proton Beam Therapy and Comparison Intensity-Modulated Radiation Therapy Plans**

This was an institutional review board–approved, retrospective study that compared passive scatter PBT against IMRT for 55 patients with distal (N = 42), mid (N = 11), and proximal (N = 2) esophageal cancer. All patients were initially treated with proton plans to 50.4 cobalt gray equivalents in 28 fractions from 2007 to 2010. The clinical target volume (CTV) was defined as gross tumor volume (GTV; esophageal tumor plus involved nodes), plus elective coverage of the first echelon nodes and sometimes the celiac axis for distal tumors, plus 3- to 4-cm superior/inferior margin, plus 1.0- to 1.5-cm radial margin.
Additional proximal, distal, and lateral margins for proton treatment planning were included per details described below under “Proton Treatment Planning.” All CTVs were initially delineated by the treating radiation oncologist on the proton planning treatment system (with the same contours exported to Pinnacle [Philips Healthcare, Andover, MA] for IMRT planning) at the time of consultation and were not modified for the purposes of this dosimetric study.

Contoured targets and avoidance structures from the proton plans that were actually used for radiation treatment in the Eclipse treatment planning system version 9.6 software (Varian, Palo Alto, California) were then exported to the Pinnacle treatment planning system version 9.4 through DICOM (Philips), so that the IMRT plans could be generated for comparison. The dose volume constraints used for both PBT and IMRT planning included maximum dose to the spinal cord < 45 Gy, mean lung dose ≤ 20 Gy with V20 ≤ 35% if receiving chemoradiation and preferably V20 ≤ 30% if receiving chemoradiation before surgery, lung V5 < 55%, heart V30 ≤ 45% with a heart mean dose < 26 Gy, and liver V30 ≤ 40% with a liver mean dose < 30 Gy.

**Intensity-Modulated Radiation Therapy Treatment Planning**

Plans for IMRT were generated using a standardized IMRT class solution [15] and static beams. The CTV was already contoured by the treating radiation oncologist as described. The planning target volume (PTV) was generally a 0.5-cm expansion of the CTV. The standardized IMRT beam arrangement used for planning consisted of posterior and lateral beam entries (SupraFirefly technique: 60°, 80°, 120°, 140°, 160°, 180°, and 200°), which were previously found to further reduce cardiac doses compared with traditional hemispheric (350°, 30°, 70°, 100°, and 180°) and butterfly (350°, 25°, 130°, 165°, and 195°) IMRT beam arrangements [15]. The main priorities/constraints used for IMRT planning included ensuring that 95% of the PTV should be covered by the prescription dose of 50.4 Gy and that all organs at risk should meet our normal tissue dose constraints as described above.

**Proton Treatment Planning**

Four-dimensional computed tomography (CT)–based planning was used for all cases to account for respiratory motion. A diaphragm structure was created from the T0 and T50 phases. Its density was then overridden with the average Hounsfield Units of the Maximum Intensity Projection scan to increase the water equivalent thickness in the path of the beams. This enabled the compensator to be designed to ensure adequate coverage to the distal margin (DM) with respiratory motion.

To achieve a clinically acceptable dose distribution that ensured coverage of the target volume, additional margins from the CTV were used to account for range uncertainties. The DM was defined as $DM = 0.035 \times \text{Distal range} + 0.3$ cm; and, the proximal margin (PM) was defined as $PM = 0.035 \times (\text{Proximal range-tumor thickness}) + 0.3$ cm. Aperture block margins (or lateral margins) were expanded from the CTV based on the 95% to 50% penumbra plus setup motion [18]. The penumbra is dependent on the range of the beam (the larger the range of the beam, the larger the penumbra), but is on average 7 mm. The average uncertainty is 5 mm. The smear radius, defined as $\sqrt{(0.03 \times \text{Range})^2 + (\text{Setup uncertainty})^2}$ [18] was used to physically modify the compensator device attached to the treatment machine to shape the dose distally [19].

Robustness was tested by transferring the proton plan calculated on the average CT scan to the T0 (inhaleation) and T50 (exhalation) scans with the same parameters. The
dose and dose-volume histogram were evaluated for coverage. The parameters—distal margin, proximal margin, and smear value or aperture margin—were adjusted accordingly in the treatment plan if the target volume was underdosed or one of the critical structures exceeded their tolerances on either one of the robustness scans.

Various beam angles and weighting were used in the original proton plans because of changes in techniques over time. Because some historic proton plans resulted in less than ideal doses to normal organs at risk, we tried to improve those identified suboptimal proton plans with alternative beam arrangement and weighting approaches to see whether lower doses to normal tissue structures could be achieved. For reoptimization of those initially suboptimal proton plans, a standard 2-beam technique with a left lateral or slight left posterior oblique and a posterior-anterior (PA) or slight right posterior oblique beam with 1:2 weighting was used. All final analyses compared only optimized IMRT plans against optimized PBT plans in terms of both mean heart/lung doses and dose-volume histogram parameters.

**Dosimetric Comparison of Passive-Scatter Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy**

In terms of mean dose analysis, 2 geometric parameters (distance from PTV to carina [DPC], and percentage of uninvolved heart [%UIH]) were correlated with mean doses to the heart and lung, respectively, using the Pearson product-moment correlation coefficient. Mean doses and coverage to the targets (GTV, CTV, and PTV) and normal tissue structures (lung, heart, liver, cord) were then evaluated for both modalities, with \( P \) values determined using Wilcoxon paired \( t \) tests. To identify potentially suboptimal plans with unexpectedly high mean heart or lung doses relative to the other, heart mean doses were plotted against lung mean doses for each modality. After reoptimization of any identified suboptimal plans, comparison of proton versus photon mean lung and heart doses were then used to identify the superiority of one modality to the other on a case-by-case basis. Similarly, IMRT versus optimized PBT DVHs were then generated for both the heart and lung using Eclipse and Pinnacle treatment planning systems.

**Results**

**Identifying Intensity-Modulated Radiation Therapy and Proton Beam Therapy Dosimetric Statistical Outliers**

We identified 2 geometric parameters with the ability to predict expected lung and heart mean doses. The first is the DPC, which was found to be highly associated with total lung mean dose for both IMRT and PBT, with correlations values of −0.83 (photons) and −0.8 (protons; Figure 1A). The second is the %UIH, defined as %\( UIH = (Heart - PTV \text{ volume})/Heart \text{ volume} \) (%), which was found to be significantly associated with the heart mean dose (Figure 1B) with correlation values of −0.8 (photons) and −0.71 (protons). The DPC and %UIH can thus be used to estimate expected lung and heart mean doses, respectively, and to identify any dosimetric outliers for both PBT and IMRT plans.

Initial mean dose analysis of the treated PBT and comparative IMRT plans showed that both techniques had similar coverage to the PTV (Table 1); thus, differences in doses to organs at risk from PBT versus IMRT were not due to excessive coverage or underdosage of the PTV to spare normal tissues. Overall, mean doses for the lung, heart, and liver were
statistically lower for PBT versus IMRT for proximal, mid, and distal esophageal cancers ($P < 0.05$; Table 1). Similarly, lung V5/V10/V20 and heart V10/V20/V30 were lower for PBT versus IMRT ($P < 0.05$; Table 1). However, on a case-by-case comparison, protons had lower lung mean doses in 100% of the cases but only lower heart mean doses in 93% (39 of 42) and 91% (10 of 11) of the distal and proximal esophageal cancer cases, respectively.

**Table 1.** Dosimetric analysis of protons versus intensity-modulated radiation (IMRT) therapy.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Lung</th>
<th>Cord</th>
<th>Liver</th>
<th>Heart</th>
<th>PTV</th>
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<tr>
<td>All, n = 55</td>
<td>Mean, cGy</td>
<td>V5 %</td>
<td>V10 %</td>
<td>V20 %</td>
<td>Max, cGy</td>
</tr>
<tr>
<td>IMRT</td>
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<td>47.2</td>
<td>31.4</td>
<td>16.9</td>
<td>3972</td>
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<tr>
<td>Protons</td>
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<td>26.9</td>
<td>21.7</td>
<td>12.7</td>
<td>3125</td>
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<tr>
<td>Diff $^a$</td>
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<td>$-20.3^b$</td>
<td>$-9.7^b$</td>
<td>$-4.2^b$</td>
<td>$-847^b$</td>
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<td>21.2</td>
<td>12.2</td>
<td>3095</td>
</tr>
<tr>
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<td>$-20.1^b$</td>
<td>$-8^b$</td>
<td>$-3.2^b$</td>
<td>$-786^b$</td>
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<tr>
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<td>$-545^b$</td>
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<td>2756</td>
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<tr>
<td>Diff $^a$</td>
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<td>$-1701$</td>
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</tbody>
</table>

**Abbreviations:** PTV, planned treatment volume; cGy, centigray; max, maximum; diff, difference; prox, proximal.

$P < 0.05$.

$^a$Diff – Protons – IMRT.

$^b$Protons.

$^c$IMRT.

$^d$Sample size too small for $P$ value.
The average difference for the heart mean dose between IMRT versus PBT was 722 centigray (cGy) when PBT was superior but only 88 cGy when IMRT was superior.

Identifying Suboptimal Proton Dosimetry

To assess why some of the initial PBT plans were inferior to IMRT plans for mean heart doses, a plot of heart mean dose versus lung mean dose was generated for each modality as a method of identifying potential suboptimal plans secondary to compromise of either the heart or the lungs to spare the other. Using this analysis, 10 suboptimal proton plans with mean heart doses above the IMRT best-fit line (and, therefore, those that had higher-than-expected heart mean doses relative to lung mean doses) were identified (Figure 2).

To assess whether those 10 plans truly represented suboptimal proton dosimetry, we plotted PBT heart mean dose against IMRT heart mean dose for each case (Figure 3). The grey line in Figure 3 represents PBT and IMRT equivalency. Thus, if IMRT and PBT modalities were identical, the data points would fall along the grey line. If PBT was able to achieve lower mean heart doses compared with IMRT, then the data points would fall below the grey line. Conversely, if PBT resulted in higher mean heart doses compared with IMRT, then the data points would fall above the grey line. As shown in Figure 3, 10 proton plans (denoted by clear boxes with black frames) either straggled or fell above the grey line defining PBT and IMRT equivalency. These represent the same 10 suboptimal proton plans with unexpectedly high mean heart doses as identified in Figure 2.

Reexamination of those 10 suboptimal PBT plans revealed that the reasons for the suboptimal proton dosimetry included (1) nonstandard beam arrangements using an AP/PA or AP/PA/Left lateral approach, (2) 1:1 beam weighting of left lateral/PA beam, and/or (3) unique patient anatomy (ie, too generous CTV extending into the heart or the CTV...
wrapping anteriorly around the heart). Figure 4 shows a representative proton case that did not meet the estimated heart dose expectations because of a generous CTV contour.

**Intensity-Modulated Radiation Therapy Versus Proton Beam Therapy Comparison After Reoptimization of Suboptimal Proton Beam Therapy Plans**

Figure 3 shows the results after the initially suboptimal proton plans were reoptimized (denoted as green dots) and the remaining proton plans that already used standard beam/weighting techniques and were thus never required reoptimization (denoted as blue boxes). As shown in Figure 3, reoptimization of the initial 10 suboptimal proton plans (using a more-standard left lateral/PA beam approach with 1:2 weighting as described in the “Methods”) yielded significantly improved mean heart doses (reduced from 2132 to 1519 cGy) with minimal increase in mean lung doses (from 560 to 603 cGy) in five of the 10 cases. The remaining 5 cases (denoted as green dots circled in red) represented proton cases that were reoptimized, but little change in mean heart dose was seen. This appeared to be because of the too-generous CTV contours that either extended into or wrapped around the heart (Figure 4). Of note, those CTV contours were the same for both proton and photon plans.

After reoptimization, passive-scatter PBT proved consistently superior to IMRT in lowering mean doses to the heart in 100% of the cases, despite suboptimal anatomy (CTV...
extending into or wrapping around the heart; Figure 4). Suboptimal anatomy resulted in both suboptimal IMRT and PBT plans, but the proton plans were still better compared with photon plans. Similarly, comparison of PBT versus IMRT total lung mean dose for each case showed that proton plans had superior mean lung doses 100% of the time (data not shown). Comparison of average IMRT and average PBT DVH parameters showed that optimized passive-scatter proton plans resulted in smaller volumes receiving lower doses (5 to 20 Gy), but photons achieved smaller volumes receiving higher doses (40 to 50 Gy) for both the heart and lung (Figure 5). Specifically, paired t-test analyses showed that there was less dose to the heart with proton plans compared with photon plans at the V5 Gy.
Discussion

Thoracic radiation in esophageal cancer can be associated with significant cardiopulmonary morbidity and mortality [11, 12, 20]. In our study of 55 patients with esophageal cancers treated with chemoradiation, passive-scatter PBT resulted in lower mean heart and lung doses than did IMRT.

Studies of advanced radiation technologies such as PBT are needed because tumor control rates improve, and concerns about the consequences of normal tissue toxicity arise. In esophageal cancer, radiation has been associated with a higher prevalence of inferior left ventricular ischemia [21]. In a study of patients with thoracic esophageal carcinomas treated with chemoradiation, the 2-year cumulative incidence of late grade 3 or greater cardiopulmonary toxicities for patients 75 years or older was as high as 29% [11]. In another retrospective series of 139 esophageal cancer patients treated with definitive chemoradiation, grade 3 or greater cardiopulmonary complications occurred in 33% of the patients who achieved complete remission, with 2 deaths secondary to myocardial infarction [12]. These potential acute and delayed side effects of radiation are important because they can not only adversely affect quality of life but also shorten patients’ life spans despite cancer cure.

An increasing number of clinical studies suggest that dosimetric factors (eg, V20, V30, mean lung/heart dose, among others) should be considered for limiting the risk of lung and cardiac toxicity. Improvements in radiation techniques should thus provide one theoretic method of helping to better spare the heart and lungs. Although 3D-CRT remains the current standard beam arrangement for the treatment of esophageal cancer, IMRT (versus 3D-CRT) has been shown to improve mean heart and lung dose in esophageal cancers [14, 15]. Further improvements in normal tissue can be accomplished with PBT, which has fundamental physical advantages over photon beams. In particular, the sharp lateral penumbras, Bragg peak properties, and finite penetration ranges of proton beams allow increased ability to deliver uniform doses to the tumor while sparing nearby healthy tissues.

Previous studies have compared the dosimetric effects of protons with photons. A recent study by Zhang and colleagues [17] incorporated 4D-CT–based planning to compare IMRT with 2-beam (AP/PA) and 3-beam (AP/2 posterior oblique beams) PBT for 15 patients with distal esophageal cancers. Although the proton plans were found to improve median lung volumes exposed to the 5, 10, and 20 Gy and mean lung doses, there was no improvement in heart sparing using either the 2-beam or 3-beam PBT plan compared with IMRT. Another dosimetric study [16] of intensity-modulated proton therapy (IMPT) did find reduced doses to both the heart and lungs with PBT versus IMRT. However, most patients with esophageal cancer who undergo proton therapy in the United
States are treated with a passive-scatter technique not with IMPT, which may limit the applications/generalizability of an IMPT method.

Our study not only confirms the dosimetric promise of using PBT versus IMRT to spare the heart/lungs as shown in previously published articles but also extends those prior results by identifying potentially modifiable parameters that may lead to suboptimal PBT dosimetry. These parameters included poor beam arrangements (AP/PA beam), equal beam weighting, and unique anatomy (extension of CTV into or around the heart). Although AP/PA beams spare the lung, it does so at the expense of the heart; thus, any passive-scatter PBT plan that uses an AP/PA beam approach or heavier weighting of AP/PA, as opposed to lateral beam, may result in higher-than-ideal doses to heart. This difference in proton beam arrangement—left lateral/PA with 1:2 weighting in our study—versus AP/PA and AP/2 posterior oblique beams in the Zhang et al [17] article—may account for the contrary findings in heart sparing with PBT. When unique anatomy is present (CTV extending into or wrapping around the heart to the right), our study further suggests that an optimal PBT plan with minimal heart dose may not be possible. In those cases, evaluation of CTV margins around the heart before the start of proton planning may be warranted, and customized beam arrangements should be considered. Although the use of IMPT and the addition of more beams may further improve high-dose conformality to the target, IMPT will also increase uncertainties because of motion (and thus decrease plan robustness), and the use of additional beams may spread the low doses more.

One major limitation to this study was the lack of contour quality and consistency, which impaired dosimetry for both modalities. Those contours were initially delineated by the treating radiation oncologists at the time of consultation and were not modified for the purposes of this dosimetric study; however, because the IMRT plans were generated from the PBT plans actually used for treatment, the CTV contours were the same for both proton and photons plans. Therefore, although the CTV contours extending into or around the heart may have contributed to poor dosimetry, the contribution was equal for both proton and photon plans and did not bias one modality over the other. We chose not to adjust the contours to highlight the potential impact of suboptimal contouring on dosimetry; however, it may be a worthwhile evaluation in the future to see whether both proton and photon dosimetry can be further improved if the contours were corrected before planning. Another limitation was using historic proton plans over a relatively long period of time (2007–2010); we did not know some of those plans were suboptimal until we were able to identify the outliers based on our statistical analyses. When we analyzed the reasons for the outliers, we discovered that the suboptimal results were often due to changes in treatment planning techniques during this period because of increasing knowledge regarding how to optimally plan for and deliver proton therapy during the past several years. For example, an AP/PA approach was formerly used to limit the range uncertainties of perpendicular beams (ie, left lateral) through the diaphragm. Now, however, we can use a left lateral/PA beam to improve cardiac dosimetry while still accounting for the dosimetric effect of diaphragm motion (using 4D-CT planning, adequate margins, and verifications plans).

Nevertheless, historic proton plans (some of which were later found to be suboptimal based on outlier statistical analyses) were still included in our study to highlight the effect of poor dosimetry on critical structure doses, to learn from those cases so that treatment planning techniques could be further enhanced, and to serve as cautionary hurdles for other proton centers to avoid. However, we did ultimately replan all historic proton plans deemed to be “suboptimal” based on outlier analysis, such that the final analyses only compared optimized proton plans to
optimized photon plans (please see section under “Results” labeled “IMRT Versus PBT Comparison After Reoptimization of Suboptimal PBT Plans”).

In conclusion, our study suggests that passive-scattering PBT using a left lateral/PA beam approach with 1:2 weighting is superior to IMRT for lowering both mean heart and lung doses and should be considered as a treatment planning approach for reducing radiation-induced cardiopulmonary toxicities in esophageal cancer. However, IMRT may be superior to PBT for smaller normal tissue volumes receiving higher doses of radiation. Thus, future studies evaluating which dosimetric parameters (V5, V40, or mean heart/lung dose, among others) have the greatest effect on late cardiopulmonary morbidity are needed to determine whether IMRT versus PBT should be used on an individualized patient basis. Long-term clinical data on pulmonary/cardiac toxicities are also needed to validate these theoretic dosimetric advantages.

**ADDITIONAL INFORMATION AND DECLARATIONS**

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

Acknowledgments: Funding was provided in part by the University of Texas MD Anderson Cancer Center and by the National Cancer Institute Cancer Center support grant CA016672.

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