Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2013 June 1; 86(2): . doi:10.1016/j.ijrobp.2013.01.004.

Use of 4-Dimensional Computed Tomography-Based Ventilation Imaging to Correlate Lung Dose and Function With Clinical Outcomes

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Abstract

Purpose—Four-dimensional computed tomography (4DCT)-based ventilation is an emerging imaging modality that can be used in the thoracic treatment planning process. The clinical benefit of using ventilation images in radiation treatment plans remains to be tested. The purpose of the current work was to test the potential benefit of using ventilation in treatment planning by evaluating whether dose to highly ventilated regions of the lung resulted in increased incidence of clinical toxicity.

Methods and Materials—Pretreatment 4DCT data were used to compute pretreatment ventilation images for 96 lung cancer patients. Ventilation images were calculated using 4DCT data, deformable image registration, and a density-change based algorithm. Dose—volume and ventilation-based dose function metrics were computed for each patient. The ability of the dose—volume and ventilation-based dose—function metrics to predict for severe (grade 3+) radiation pneumonitis was assessed using logistic regression analysis, area under the curve (AUC) metrics, and bootstrap methods.

Results—A specific patient example is presented that demonstrates how incorporating ventilation-based functional information can help separate patients with and without toxicity. The logistic regression significance values were all lower for the dose—function metrics (range $P=$.093-.250) than for their dose—volume equivalents (range, $P=$.331-.580). The AUC values were all greater for the dose—function metrics (range, 0.569-0.620) than for their dose—volume equivalents (range, 0.500-0.544). Bootstrap results revealed an improvement in model fit using

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Conflict of interest: This work was partially funded by the National Institutes of Health through an NIH Director's New Innovator Award DP2OD007044 (E.C., R.C., T.G.).

dose—function metrics compared to dose—volume metrics that approached significance (range, $P=.118-.155$).

Conclusions—To our knowledge, this is the first study that attempts to correlate lung dose and 4DCT ventilation-based function to thoracic toxicity after radiation therapy. Although the results were not significant at the .05 level, our data suggests that incorporating ventilation-based functional imaging can improve prediction for radiation pneumonitis. We present an important first step toward validating the use of 4DCT-based ventilation imaging in thoracic treatment planning.

Introduction

A new and exciting form of functional imaging has been proposed in the form of 4-dimensional computed tomography (4DCT)-based ventilation. Guerrero et al (1) proposed to use phase-resolved CT images (2) to calculate pulmonary ventilation. Because 4DCTs are acquired as part of routine clinical care for lung cancer patients, calculating ventilation maps comes at no extra dosimetric or monetary cost. Recent studies have reported on the methodology (3), validation (3-5), and different clinical uses of 4DCT-based ventilation (6, 7). Castillo et al (3) compared different methodologies of calculating ventilation. Validation studies have looked at comparing 4DCT-based ventilation to xenon CT (5), using single-photon emission computed tomography (SPECT) perfusion images (3), and evaluating the reproducibility of 4DCT ventilation (4). Vinogradskiy et al (6) evaluated changes in lung function throughout the course of treatment using 4DCT-based ventilation, whereas Yamamoto et al (7) used 4DCT-ventilation to investigate lung function of emphysema patients.

Another proposed use of 4DCT-based ventilation is to optimize radiation treatment plans for lung cancer patients (8-10) based on ventilation functional avoidance maps. The idea is to design the treatment plan using information gained from the ventilation image. The idea of designing treatment plans that account for lung function has previously been proposed using perfusion imaging (11-14). The added benefit of using 4DCT-based ventilation over SPECT for treatment planning purposes is that the functional information is available from the patient's 4DCT simulation and no additional imaging studies are required. However, the clinical benefit of using ventilation images in treatment planning remains to be tested. The purpose of the current work was to test the potential benefit of using ventilation in treatment planning by evaluating whether dose to highly ventilated regions results in increased incidence of clinical toxicity. We computed dosimetric and ventilation-based functional metrics for 96 non-small cell lung cancer (NSCLC) patients and evaluated the relationship between dose—volume and function with severe radiation pneumonitis.

Methods and Materials

Patient cohort

The study used 96 NSCLC patients treated at our institution from 2004 to 2006. Seventy-six patients were taken from previous work, which is described and analyzed in detail by Jin et al (15). The additional 20 patients were selected from a more recent patient population (2006-2007) and were chosen to increase the number of toxicity cases in the entire patient cohort to improve modeling statistics. Patients in the study were treated with 3D conformal radiation therapy (RT) or intensity modulated RT with or without chemotherapy. We excluded patients from the study if they received <50.4 Gy, had doses per fraction that varied over treatment, or had breaks >7 days. The clinically significant end point used for analysis was severe (grade 3 or higher) radiation pneumonitis, which was determined using clinical presentation and radiographic findings. Grade 3 pneumonitis according to the

Common Terminology Criteria for Adverse Events (version 3.0) is defined as symptomatic, interfering with daily activities, or O₂ indicated. All patients in the study had a pretreatment 4DCT scan as part of their treatment simulation. The 4DCT images were acquired using cine mode on a multislice helical CT scanner (Discovery PET/CT; GE Healthcare, Waukesha, WI). The scans were acquired with a slice thickness of 2.5 mm and a cine duration of approximately 110% of the patient breathing cycle. Each patient's breathing trace was monitored using the Varian RPM system (Varian Medical Systems, Palo Alto, CA). The breathing trace was used to sort the images into 10 phases. A physicist was present during each 4DCT scan to make sure the patient's breathing was not erratic. Any patient scans that had significant breathing artifacts in their 4DCT were excluded from the study.

This study was approved by the Institutional Review Board at University of Texas MD Anderson Cancer Center.

Ventilation image calculation

A pretreatment ventilation image was calculated for each patient using the pretreatment 4DCT dataset. The lungs were segmented on the inhale and exhale data sets. Lung segmentation included delineating and excluding the trachea, main-stem bronchi, and pulmonary vasculature (3). A deformable image registration algorithm was used to link the lung voxel elements in the inhale phase to the exhale phase. The spatial accuracy of the deformation algorithm has been determined to be 1.25 mm (16). After spatial registration of the segmented lungs, corresponding Hounsfield units were input into a density change-based model, which can be mathematically written as:

$$\frac{V_{in} - V_{ex}}{V_{ex}} = 1000 \frac{HU_{in} - HU_{ex}}{HU_{ex}(1000 + HU_{in})}, \quad (1)$$

where V_{in} and V_{ex} are the inhale and exhale volumes and HU_{in} and HU_{ex} are the inhale and exhale Hounsfield units of the individual lung voxels. Equation 1 is derived from the assumption that CT voxel content is composed of a linear combination of water-like material with a CT value of 0 and air-like material with a CT value of -1000 (17). The left side of the equation represents the local change in air content and is referred to as specific ventilation. Equation 1 is applied on a voxel-by-voxel basis to produce a 3D map of ventilation (Fig. 1) in which the color map represents the local fractional volume change. Consistent with previous studies (3, 8), we normalized each ventilation map by converting it to a percentile image. All ventilation images and deformation maps were manually inspected for image artifacts and discontinuities, respectively. The ventilation images were assessed for self-consistency by comparing the total lung volume change calculated by summing the voxel ventilation to the lung volume change, calculated by taking the difference between lung volumes from exhale to inhale.

Dose—volume and dose—function metrics

Dose—volume and dose—function metrics were calculated using the 3D dose matrix and ventilation maps. For each patient, we computed a dose—volume histogram (DVH), mean lung dose (MLD), V_{20} (volume of lung receive 20 Gy), and the effective dose (D_{eff}). The effective dose was calculated using the following:

$$D_{eff} = \left[\sum_i v_i D_i^{1/n} \right]^n, \quad (2)$$

where D is the dose, v is the fractional volume, n is the volume parameter, and i loops over all the dose bins. Values of 0.25, 0.5, and 0.75 were used for n . Using methods previously proposed with perfusion imaging (12, 13, 18), we calculated dose—function metrics by replacing volume with ventilation-based function. We calculated dose—function histograms (DFHs) (18), functional MLD (fMLD) (13), functional V_{20} (fV₂₀), and functional Deff (fDeff) (12). The fMLD was calculated by weighting each dose voxel by its ventilation value, and the fV₂₀ was taken as the percentage of the total function (ventilation) contained within the volume receiving 20 Gy.

Statistical analysis

The goal of our analysis was to investigate how well dose and function within the lung correlate with clinical radiation pneumonitis. A quantitative analysis was performed by observing the DVH and DFH for patients with and without radiation pneumonitis. A discriminant analysis was used to separate patients into high- and low-risk toxicity groups using MLD and fMLD (14). Logistic regression analysis and logistic regression combined with receiver operating characteristic (ROC) curves were used to assess the predictive abilities of the dosimetric and functional parameters (14, 19). Finally, we fit the data to a normal tissue complication probability (NTCP) model and compared the quality of model fit using bootstrap methods. This technique is attractive because it allows assessment of how well dose—function can predict for radiation pneumonitis while accounting for dose—volume. The data were randomly sampled 1000 times and the sampled data were fit to a Lyman-Kutcher-Burman NTCP model using the dose and function parameters described in the previous section. Log-likelihood was calculated for both the dose and function metrics to assess model fit. For each simulation, we compared model fit of the dose—function metric to its dose—volume equivalent (fMLD to MLD, V₂₀ to fV₂₀, and Deff to fDeff).

Results

The dose distribution, ventilation map, DVH, and DFH are shown for 2 representative patients in Figure 2. Patient 1 (MLD = 19.6 Gy and V₂₀ = 29%) did not develop grade 3+ pneumonitis, whereas patient 2 (MLD = 23.2 Gy and V₂₀ = 41%) went on to develop grade 3 toxicity. Patient 1 received dose to nonfunctional portions of the lung, whereas patient 2 received dose to more ventilated regions (Fig. 2). Patient 1 had fMLD and fV₂₀ values of 11.8 Gy and 14%, respectively, whereas patient 2 had fMLD and fV₂₀ values of 25.9 Gy and 46%. The dose function metrics increased (compared to the dose—volume metrics) for the patient that developed toxicity and received dose to more-ventilated portions of the lung and decreased for the patient who did not develop toxicity and received dose to nonfunctional lung.

A scatter plot shows fMLD versus MLD according to whether the patient developed severe radiation pneumonitis (Fig. 3). The scatter plot shows that converting from MLD to fMLD spreads out the data (the points do not lie in a line), indicating that fMLD introduces new information and is not redundant with MLD. Discriminant analysis was used to fit a line to best separate the data. The data were separated into groups that had toxicity rates of 23.2% (10/43) and 13.2% (7/53).

All of the dose—volume and dose—function metrics analyzed are shown for the pneumonitis and nonpneumonitis groups (Table 1). Table 1 also shows the P value obtained using logistic regression and area under the curve (AUC) determined from ROC analysis. As expected, all of the dose—volume and dose—function metrics are greater for the pneumonitis group compared to the nonpneumonitis group. The P (logistic regression) values for the dose—function metrics (range, $P = .093$ –.250) approach significance and are smaller when compared to the P values for their dose—volume counterpart metrics (range,

$P=.340-.580$); although it should be noted that P values do not reach significance at the .05 level for either dose—volume or dose—function metrics. Similarly, the AUC values are greater for the dose—function metrics (range of AUC values, 0.569-0.620) when compared to the dose—volume equivalent metrics (range of AUC values, 0.500-0.544). The example ROC curves (Fig. 4) show an AUC of 0.500 for MLD, 0.569 for fMLD, and 0.618 for MLD combined with fMLD.

The results of the bootstrap analysis comparing model fit using dose—function and dose—volume metrics are shown in Table 2. The P values comparing each dose—function metrics to its dose—volume equivalent (MLD to fMLD, V_{20} to fV_{20} , and Deff to fDeff) range from 0.118 to 0.155. This indicates that the improvement in model fit using dose—function metrics over dose—volume metrics approaches statistical significance.

Discussion

The technique of 4DCT-based ventilation is an emerging and attractive imaging technique, because routine clinical 4DCT simulation can provide data to assess lung function. Multiple studies are suggesting various clinical uses for 4DCT-based ventilation (6, 7), with a particular emphasis on using ventilation images to create thoracic functional avoidance regions in treatment planning (8-10). Before 4DCT-based ventilation is implemented in thoracic treatment planning, its clinical benefit needs to be assessed further. To our knowledge, this is the first study that attempts to correlate lung dose and ventilation-based function with clinical outcomes after radiation therapy. The specific patient example (Fig. 2) demonstrates how incorporating ventilation-based functional information can help to further separate patients with and without toxicity. The spread of the data in the scatter plot (Fig. 3) indicates that fMLD provides new and nonredundant information than what is contained within MLD. The logistic regression values for the dose—function metrics were all lower than their dose—volume equivalents. Similarly, the AUC values were greater for the dose—function metrics when compared to dose—volume metrics (Table 1) and combining dose—volume and dose—function improves the AUC further (Fig. 4). These results suggest that ventilation-based dose—function metrics can predict toxicity with greater accuracy than dose—volume metrics. However, it should be noted that the P values are not significant at the .05 level and the AUC values are modest. We used bootstrap methods to investigate whether dose—function can predict for toxicity while accounting for the dose—volume effect. The results showed that dose—function metrics produced a better model than dose—volume metrics in 85% (using fMLD) and 88% (using fV_{20}) of simulations, correlating with significance values of .15 and .13, respectively. Although the results do not reach significance at the .05 level, bootstrap simulations indicate that using dose—function metrics can improve prediction for toxicity while accounting for the dose—volume effect.

There is precedent for performing studies trying to correlate lung dose and function with thoracic toxicity using perfusion imaging (12-14, 18, 19). Initially, theoretical studies (12, 13, 18) proposed the idea of incorporating lung function into standard dose—volume metrics and using dose—function metrics such as fDeff to evaluate thoracic treatment plans. Lind et al (14) correlated dose and perfusion-based function to grade 2+ radiation pneumonitis. They reported AUC values of 0.56 for dose—volume metrics and AUC values in the range of 0.5 to 0.66 for metrics that combine dose—volume and perfusion-based function. Analyzing datasets from Duke University and The Netherlands Cancer Institute, Kocak et al (19) cite AUC values of 0.51 to 0.62 for dose—volume metrics and 0.54-0.72 for perfusion-based dose—function metrics. These results are in line with the AUC values reported in Table 1, using ventilation-based function. Seppenwoolde et al (20) used perfusion imaging to calculate global and regional dose, volume, and function metrics. They fit their dose—volume and dose—function data to an NTCP model predicting the rate of grade 2 radiation

pneumonitis. It should be noted that they observed a dependence of toxicity on superior—inferior tumor location and built this dependence into their model by introducing an offset parameter. Using binary logistic regression, they evaluated the significance of the relationship between dose—volume and dose—function metrics with toxicity. They report P values in the range of .002-.900 for various regional and global metrics; including P values of .02 using MLD and .01 using perfusion weighted mean lung dose. These significance values are lower than the logistic regression values that we report in Table 1. The data presented by Seppenwoolde et al (20) showed a clear dose—volume relationship, whereas we did not observe as strong a dose—volume correlation with toxicity. Because their study showed strong dose—volume dependence it is difficult to judge the improvement made in using dose—function values over dose—volume metrics. Furthermore, the addition of the offset parameter to account for superior—inferior position complicates the interpretation of the relationship between dose—function and toxicity. Our study using ventilation imaging and previous work with perfusion imaging show promising (albeit statistically limited) results, indicating that functional imaging can improve prediction for toxicity.

There is a need to test the clinical benefit of incorporating functional imaging into the thoracic treatment planning process. One way to test the clinical benefit is to study whether incorporating functional imaging improves prediction for clinical toxicity. However, predicting for toxicity is challenging. Our study using 4DCT-based ventilation for functional analysis and previous work using SPECT-based perfusion show promising data but are not able to conclusively demonstrate the relationship between dose—function and toxicity. The main challenge of predicting for toxicity is the limited number of patients available for the study. Our study was done using 96 patients, which is in line with previous work (14, 19, 20). The current study attempts to isolate dose—volume and function parameters and therefore does not incorporate additional factors in predicting for toxicity. Many factors beyond dose—volume and function have been shown to predict for toxicity, including spatial location, smoking status, chemotherapy status, and genetic data. In future work, we plan to combine dose—volume and function with other parameters, and we believe that this will improve our predictive statistics. It would be informative to combine ventilation and perfusion imaging, as these represent differing biological processes and could provide a more complete picture of lung function. Several studies have shown that current 4DCT ventilation calculation techniques can have limited accuracy and reproducibility (3, 4) which may have contributed to the insignificant P values. Work is still underway to improve methods of calculating 4DCT-based ventilation, with specific strategies being developed to account for uncertainties related to deformable image registration and 4DCT imaging artifacts. As calculation techniques and the quality of 4DCT imaging improves, more accurate and reproducible ventilation images may give a more precise picture of lung function and can enable better correlation between function-based metrics and clinical toxicity.

There is a need to clinically validate the use of 4DCT-based ventilation imaging in thoracic treatment planning. To our knowledge, this is the first study to attempt to correlate lung dose and ventilation-based function with clinical outcomes after radiation therapy. Although the results were not significant at the .05 level, our data suggest that incorporating ventilation-based functional imaging improves prediction for radiation pneumonitis. Future work will incorporate a greater patient database and more factors to predict for toxicity. Our study presents an important first step toward validating the use of 4DCT-based ventilation in thoracic treatment planning.

References

1. Guerrero T, Sanders K, Castillo E, et al. Dynamic ventilation imaging from four-dimensional computed tomography. *Phys Med Biol.* 2006; 51:777–791. [PubMed: 16467578]
2. Rietzel E, Pan TS, Chen GTY. Four-dimensional computed tomography: image formation and clinical protocol. *Med Phys.* 2005; 32:874–889. [PubMed: 15895570]
3. Castillo R, Castillo E, Martinez J, et al. Ventilation from four-dimensional computed tomography: density versus Jacobian methods. *Phys Med Biol.* 2010; 55:4661–4685. [PubMed: 20671351]
4. Du K, Bayouth J, Cao K, et al. Reproducibility of registration-based measures of lung tissue expansion. *Med Phys.* 2012; 39:1595–1608. [PubMed: 22380392]
5. Reinhardt JM, Ding K, Cao K, et al. Registration-based estimates of local lung tissue expansion compared to xenon CT measures of specific ventilation. *Med Image Anal.* 2008; 12:752–763. [PubMed: 18501665]
6. Vinogradskiy YY, Castillo R, Castillo E, et al. Use of weekly 4DCT-based ventilation maps to quantify changes in lung function for patients undergoing radiation therapy. *Med Phys.* 2012; 39:289–298. [PubMed: 2225299]
7. Yamamoto T, Kabus S, Klinder T, et al. Investigation of four-dimensional computed tomography-based pulmonary ventilation imaging in patients with emphysematous lung regions. *Phys Med Biol.* 2011; 56:2279–2298. [PubMed: 21411868]
8. Yaremko BP, Guerrero TM, Noyola-Martinez J, et al. Reduction of normal lung irradiation in locally advanced non-small-cell lung cancer patients, using ventilation images for functional avoidance. *Int J Radiat Oncol Biol Phys.* 2007; 68:562–571. [PubMed: 17398028]
9. Yamamoto T, Kabus S, von Berg J, et al. Four-dimensional computed tomography-based pulmonary ventilation imaging for adaptive functional guidance in radiotherapy. *J Thorac Oncol.* 2009; 4:S959–S960.
10. Yamamoto T, Kabus S, von Berg J, et al. Impact of four-dimensional computed tomography pulmonary ventilation imaging-based functional avoidance for lung cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2011; 79:279–288. [PubMed: 20646852]
11. Munawar I, Yaremko BP, Craig J, et al. Intensity modulated radiotherapy of non-small-cell lung cancer incorporating SPECT ventilation imaging. *Med Phys.* 2010; 37:1863–1872. [PubMed: 20443508]
12. Miften MM, Das SK, Su M, et al. Incorporation of functional imaging data in the evaluation of dose distributions using the generalized concept of equivalent uniform dose. *Phys Med Biol.* 2004; 49:1711–1721. [PubMed: 15152926]
13. Nioutsikou E, Partridge M, Bedford JL, et al. Prediction of radiation-induced normal tissue complications in radiotherapy using functional image data. *Phys Med Biol.* 2005; 50:1035–1046. [PubMed: 15798307]
14. Lind PA, Marks LB, Hollis D, et al. Receiver operating characteristic curves to assess predictors of radiation-induced symptomatic lung injury. *Int J Radiat Oncol Biol Phys.* 2002; 54:340–347. [PubMed: 12243806]
15. Jin HK, Tucker SL, Liu HH, et al. Dose-volume thresholds and smoking status for the risk of treatment-related pneumonitis in inoperable non-small cell lung cancer treated with definitive radiotherapy. *Radiother Oncol.* 2009; 91:427–432. [PubMed: 18937989]
16. Castillo E, Castillo R, Martinez J, et al. Four-dimensional deformable image registration using trajectory modeling. *Phys Med Biol.* 2010; 55:305–327. [PubMed: 20009196]
17. Simon BA. Non-invasive imaging of regional lung function using X-ray computed tomography. *J Clin Monit Comput.* 2000; 16:433–442. [PubMed: 12580227]
18. Marks LB, Sherouse GW, Munley MT, et al. Incorporation of functional status into dose-volume analysis. *Med Phys.* 1999; 26:196–199. [PubMed: 10076973]
19. Kocak Z, Zhou S, Kahn D, et al. Prospective assessment of models to predict radiation pneumonitis based on dosimetric/functional parameters. *Int J Radiat Oncol Biol Phys.* 2005; 63:178–186. S388–S.

20. Seppenwoolde Y, De Jaeger K, Boersma LJ, et al. Regional differences in lung radiosensitivity after radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2004; 60:748–758. [PubMed: 15465191]

Summary

Studies have proposed to use 4-dimensional computed tomography (4DCT)-based ventilation images for functional avoidance in treatment planning. Our study tests the clinical benefit of using ventilation imaging in thoracic treatment planning. Pretreatment 4DCT-based ventilation images were computed for 96 lung cancer patients and were used to calculate dose—volume and dose—function metrics. The relationship between dose-volume and dose—function with thoracic toxicity was evaluated. Our data suggests that incorporating ventilation-based functional imaging can improve prediction for radiation pneumonitis.

Fig. 1.

An example of a 4-dimensional computed tomography (4DCT)-based ventilation image overlaid over a coronal CT slice. Color map represents the local fractional volume change. Brighter colors represent the more functional regions of the lung, whereas the darker colors indicate ventilation defects.

Fig. 2. Specific patient examples showing the dose distribution, ventilation map, dose—volume, and dose—function histograms. Arrows highlight the high-dose areas and the corresponding ventilation in the region. Patient 1 did not develop pneumonitis, whereas patient 2 went on to develop grade 3 toxicity. The patient example demonstrates how dose—function metrics can help to better separate patients with and without toxicity.

Fig. 3.

Scatter plot showing the relationship between functional mean lung dose and mean lung dose. Line segregating patients into low- and high-toxicity risk groups was calculated using discriminant analysis.

Fig. 4. Example receiver operating characteristic (ROC) curves using mean lung dose (MLD), functional mean lung dose (fMLD), and MLD combined with fMLD. The AUC values were 0.500, 0.569 and 0.618 using MLD, fMLD, and fMLD combined with MLD, respectively.

Table 1
Dose—volume and dose—function metrics for the pneumonitis and nonpneumonitis groups, and statistical results indicating the ability of the metrics to predict for toxicity

Metric	Mean RP (SD)	Mean No RP (SD)	<i>P</i> value (logistic regression)	AUC
Dose—volume metrics				
MLD	21.13 (4.71)	20.47 (4.54)	.580	0.500
V ₂₀	35.41 (6.68)	33.41 (8.47)	.331	0.544
Deff n=0.25	43.18 (4.72)	42.13 (3.85)	.345	0.519
Deff n=0.5	31.67 (4.83)	30.52 (4.40)	.340	0.523
Deff n=0.75	25.16 (4.77)	24.19 (4.51)	.440	0.512
Dose—function metrics				
fMLD	20.86 (5.63)	19.21 (5.27)	.250	0.569
fV ₂₀	34.60 (9.13)	30.3 (9.13)	.093	0.620
fDeff n=0.25	42.31 (4.89)	40.26 (4.60)	.102	0.576
fDeff n=0.5	30.75 (5.43)	28.49 (5.31)	.114	0.593
fDeff n=0.75	24.25 (5.57)	22.27 (5.31)	.169	0.587

Abbreviations: AUC = area under the curve; Deff = effective dose; fDeff = functional Deff; fMLD = functional mean lung dose; MLD = mean lung dose; RP = radiation pneumonitis; SD = standard deviation.

Table 2
Bootstrap results comparing model fit using dose—volume and dose—function metrics

Dose and function metrics	Bootstrap <i>P</i> Value
MLD + fMLD	.154
$V_{20} + fV_{20}$	.118
Deff + fDeff (n=0.25)	.121
Deff + fDeff (n=0.5)	.149
Deff + fDeff (n=0.75)	.155

Abbreviations: Deff = effective dose; fDeff = functional Deff; fMLD = functional MLD; MLD = mean lung dose.