Advances in Radiation Oncology (2020) **5**, 459-465

advances
in radiation oncology

www.advancesradonc.org

Scientific Article

Variations Between Dose-Ventilation and Dose-Perfusion Metrics in Radiation Therapy Planning for Lung Cancer

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Received 7 August 2019; revised 20 February 2020; accepted 5 March 2020

Abstract

Purpose: Currently, several active clinical trials of functional lung avoidance radiation therapy using different imaging modalities for ventilation or perfusion are underway. Patients with lung cancer often show ventilation-perfusion mismatch, whereas the significance of dose-function metric remains unclear. The aim of the present study was to compare dose-ventilation metrics with dose-perfusion metrics for radiation therapy plan evaluation.

Methods and Materials: Pretreatment 4-dimensional computed tomography and ^{99m}Tc-macroaggregated albumin single-photon emission computed tomography perfusion images of 60 patients with lung cancer treated with radiation therapy were analyzed. Ventilation images were created using the deformable image registration of 4-dimensional computed tomography image sets and image analysis for regional volume changes as a surrogate for ventilation. Ventilation and perfusion images were converted into percentile distribution images. Analyses included Pearson's correlation coefficient and comparison of agreements between the following dose-ventilation and dose-perfusion metrics: functional mean lung dose and functional percent lung function receiving 5, 10, 20, 30, and 40 Gy (fV_5, fV_{10}, fV_{20}, fV_{30}, and fV_{40}, respectively).

Results: Overall, the dose-ventilation metrics were greater than the dose-perfusion metrics (ie, fV_{20}, 26.3% ± 9.9% vs 23.9% ± 9.8%). Correlations between the dose-ventilation and dose-perfusion metrics were strong (range, r = 0.94-0.97), whereas the agreements widely varied among patients, with differences as large as 6.6 Gy for functional mean lung dose and 11.1% for fV_{20}. Paired t test indicated that the dose-ventilation and dose-perfusion metrics were significantly different.

Conclusions: Strong correlations were present between the dose-ventilation and dose-perfusion metrics. However, the agreement between the dose-ventilation and dose-perfusion metrics widely varied among patients, suggesting that ventilation-based radiation therapy plan evaluation may not be comparable to that based on perfusion. Future studies should elucidate the correlation of dose-function metrics with clinical pulmonary toxicity metrics.

Sources of support: This work was supported by the Clinical Research Fund of Tokyo Metropolitan Government under grant number H290303006 and JSPS KAKENHI under grant number JP17K10478.

Disclosures: none.

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https://doi.org/10.1016/j.adro.2020.03.002

Introduction

Lung cancer radiation therapy, particularly for locally advanced disease, can result in substantial pulmonary toxicity.[1,2] Symptomatic (ie, grade ≥2) radiation pneumonitis (RP) is a common toxicity that occurs in approximately 30% of patients who undergo radiation therapy for lung cancer and is fatal in approximately 2% of cases.[1,2] The current radiation therapy paradigm is based on anatomic imaging and assumes that normal tissue undergoes a homogeneous radiation dose response. Radiation therapy that selectively avoids radiation to highly functional lung regions may reduce pulmonary toxicity; this hypothesis has been supported by several studies demonstrating that lung dose-function metrics improved the predictive power for pulmonary toxicity compared with dose-volume metrics, which are the current clinical standard.[3-9] For example, the correlation with grade ≥3 RP was stronger for dose-ventilation metrics than for dose-volume metrics.[10] Furthermore, information regarding regional lung function, such as defects, was reportedly beneficial in predicting toxicity.[11-13]

Several modalities are available for pulmonary ventilation and perfusion imaging, including single-photon emission computed tomography (SPECT),[14] magnetic resonance imaging,[15,16] positron emission tomography,[17] and dual-energy computed tomography (CT).[18,19] Moreover, ventilation images can be acquired using an emerging technique based on 4-dimensional (4D) CT and image processing/analysis,[20,21] also referred to as CT ventilation imaging. Several active clinical trials of functional lung avoidance radiation therapy using different imaging modalities for ventilation or perfusion are ongoing, including NCT02308709, NCT02528942, NCT02843568, NCT03077854, NCT02773238, and NCT02002052. Under normal conditions, regional ventilation and perfusion are tightly matched, yielding efficient gas exchange. However, under pathologic conditions, the normal distributions dramatically change for both regional ventilation and perfusion, leading to a ventilation-perfusion mismatch and inefficient gas exchange.[22] For example, Yuan et al[23] reported that 39% of patients with lung cancer exhibited ventilation-perfusion mismatch; however, the potential significance of ventilation-perfusion mismatch in dose-function metrics is not well known. Therefore, the purpose of the present study was to compare dose-ventilation metrics with dose-perfusion metrics to quantify the impact of ventilation-perfusion mismatch on lung avoidance radiation therapy plan evaluation.

Methods and Materials

Patients

This prospective study, which was approved by the institutional review board of our hospital, used imaging data from 60 patients with lung cancer enrolled in a prospective study, including 47 patients with non-small cell lung cancer and 13 patients with small cell lung cancer. The patients had clinical stage IB to IIIB cancer, with Eastern Cooperative Oncology Group Performance Status scores ranging from 0 to 2. The median age was 65 years (range, 33-79 years), and no patient had a history of therapy (including chemotherapy, surgery, radiation therapy, and immune therapy) or had undergone 4D-CT or SPECT perfusion scans. A previous report[24] detailed the characteristics of all patients included in the present study. The patients were treated with radiation therapy, with a median total dose of 74 Gy (range, 66-74 Gy) for non-small cell lung cancer and 45 Gy (range, 45-54 Gy) for small cell lung cancer. Patients were followed up at our hospital. Radiation therapy plans were designed solely on the basis of anatomic and geographic considerations and not upon the spatial arrangement of the functional lung regions. Three-dimensional conformal radiation therapy was used in all patients. Intensity modulated radiation therapy was used as local boost irradiation for patients in whom it was difficult to avoid the spinal cord because of vertebral invasion or lymph node metastasis to the bilateral mediastinum.

Pretreatment 4D-CT and SPECT perfusion images were acquired with the patients in the same position; the median time interval between the scans was 4 days. Ventilation images were obtained by CT ventilation imaging. SPECT ventilation scans were not acquired because a ventilation tracer could not be obtained.

CT ventilation imaging

CT ventilation images were created by deformable image registration (DIR) of the 4D-CT image sets, and quantitative image analysis for changes in regional volume was performed as a surrogate for ventilation. Using nonparametric volume-based DIR, the peak-inhalation 4D-CT image (moving) was spatially mapped to the peak-exhalation image (fixed), yielding a displacement vector field using Elastix, an open source software, for image registration.[25] The DIR parameter settings were the same as the Parameter Set 2 reported in a study by Kanai et al,[26]

which validated the geometric accuracy with a target registration error of <1.3 mm. Regional volume changes were quantified using Hounsfield unit (HU)-based[20,21,27] metric. HU-based ventilation (V_{HU}) was defined by the following formula:

$$V_{HU}(x,y,z) = \frac{HU_{ex}(x,y,z) - HU_{in}\{x+u_x(x,y,z), y+u_y(x,y,z), z+u_z(x,y,z)\}}{[HU_{in}\{x+u_x(x,y,z), y+u_y(x,y,z), z+u_z(x,y,z)\} + 1000]}\rho_{scaling} \quad (1)$$

where HU is the HU value and $u(x, y, z)$ is a displacement vector mapping the voxel at location (x, y, z) of the peak-exhalation image (ex) to the corresponding location of the peak-inhalation image (in). $\rho_{scaling}$ is the CT density scaling factor; $\rho_{scaling} = (HU_{ex} + 1024)/774$, which is a value ranging from 0 for the voxel with the lowest lung CT density (−1024 HU) to 1 or the voxel with the highest density (−250 HU) to transform a purely mechanical model of regional ventilation based on volume change alone to a more physiologic model, in a manner similar to that described by Hegi-Johnson et al.[28] As described by Guerrero et al,[21] mass correction was applied to HU_{in} to account for the difference in lung mass between peak-exhalation and peak-inhalation phases. To reduce the influence of CT noise, a median filter with a kernel width of 7 × 7 × 7 voxels[3] was applied before calculating V_{HU}, as described by Hegi-Johnson et al.[28] The ventilation images and deformation maps were visually inspected to check for any major errors.

The CT ventilation images were down-sampled to match the spatial resolution of the SPECT perfusion images and converted into percentile distribution images in a manner similar to that described by Vinogradskiy et al.[6]

SPECT perfusion imaging

SPECT perfusion images were acquired with a commercial scanner (BrightView XCT; Philips Healthcare, Cleveland, OH) after intravenous administration of 185 MBq of ^{99m}Tc-labeled macroaggregated albumin (MAA). SPECT projections were acquired in a 128 × 128 matrix with a pixel size of 3.19 × 3.19 mm^2 and a slice spacing of 3.19 mm. Details of the SPECT perfusion imaging were described previously.[24]

The SPECT perfusion images were converted into percentile distribution images in a manner similar to that performed for CT ventilation imaging.

Comparisons of dose-ventilation and dose-perfusion metrics

To quantify the impact of ventilation-perfusion mismatch on lung avoidance radiation therapy plan evaluation, we compared dose-ventilation metrics with dose-perfusion metrics. Ventilation-based and perfusion-based dose-function histograms (DFHs)[29] were computed from the ventilation and perfusion images, respectively. Six previously described lung function metrics were calculated: (1) functional mean lung dose (fMLD; mean lung dose weighed by regional function) and (2-6) percent lung function receiving 5, 10, 20, 30, and 40 Gy (fV_5, fV_{10}, fV_{20}, fV_{30}, and fV_{40}, respectively).[6,9] We quantified the relationship between the dose-ventilation and dose-perfusion metrics using Pearson's correlation coefficient as well as linear regression slope coefficients. We also evaluated agreements between the dose-ventilation and dose-perfusion metrics using the Bland-Altman method.[30] Statistical analyses were performed to assess the differences between dose-ventilation and dose-perfusion metrics using a paired t test with a significance level set at .01.

Results

Figure 1 shows the ventilation and perfusion images for 3 representative cases. Patient 55 exhibited the smallest difference (1.0%) and patients 21 and 13 exhibited the largest differences (11.2% and −4.3%, respectively) in lung fV_{20} between the dose-ventilation and dose-perfusion metrics. Patient 55 had a good ventilation-perfusion match in the irradiated region, resulting in only slight differences between the ventilation-based and perfusion-based DFHs (fMLD, 11.0 vs 10.6 Gy; fV_{20}, 19.8% vs 20.8%, respectively). Patients 21 and 13, in contrast, had a ventilation-perfusion mismatch. Patient 21 showed normal ventilation and reduced perfusion in the irradiated region, resulting in a large difference between the ventilation-based and perfusion-based DFHs (fMLD, 14.3 vs 7.6 Gy; fV_{20}, 23.4% vs 12.2%, respectively). Conversely, patient 13 showed reduced ventilation and normal perfusion in the irradiated region, resulting in a difference between the ventilation-based and perfusion-based DFHs (fMLD, 19.3 Gy vs 21.0 Gy; fV_{20}, 34.8% vs 39.1%, respectively).

Figure 2 shows the relationship between the dose-ventilation and dose-perfusion metrics, including fMLD, fV_5, fV_{10}, fV_{20}, fV_{30}, and fV_{40}. The correlations between the dose-ventilation and dose-perfusion metrics were strong (range, r = 0.94-0.97), and the slopes of linear regression were close to unity (range, 0.92-0.97). Figure 3 shows the Bland-Altman plot comparing the dose-ventilation and dose-perfusion metrics, including fMLD,

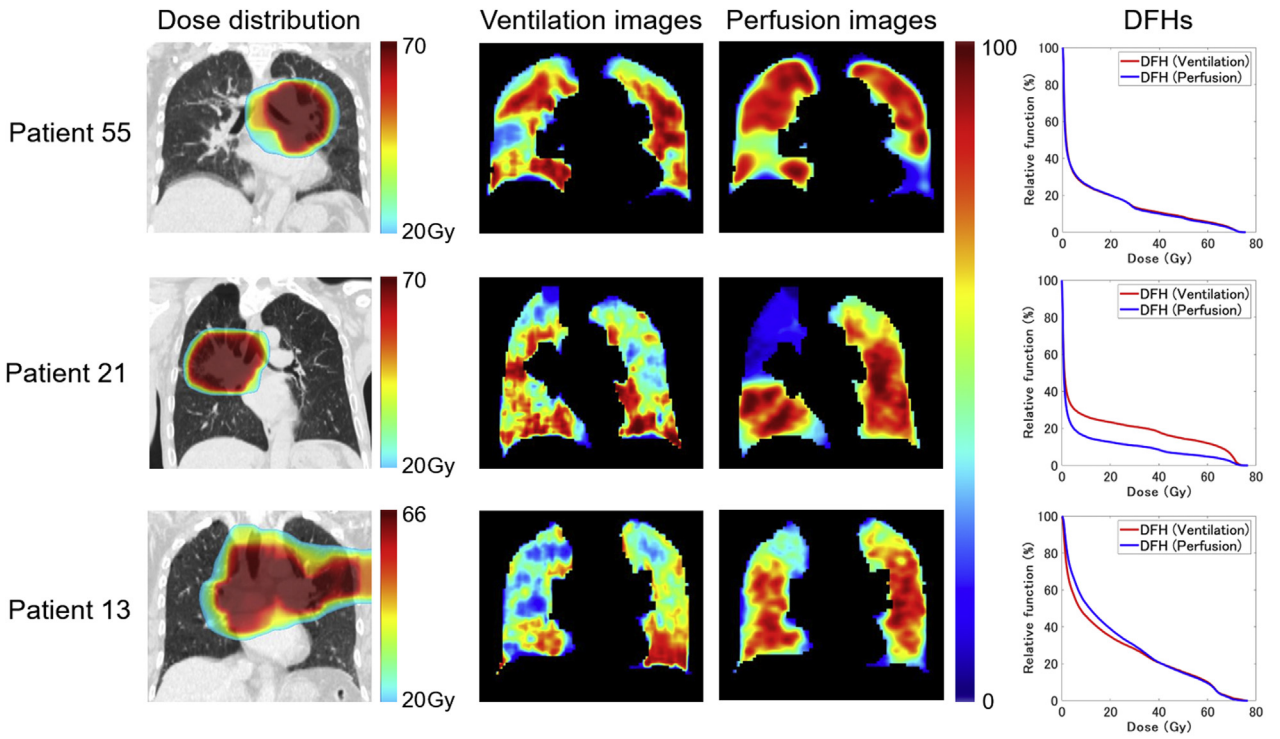

Figure 1 Three representative cases showing the dose distribution, ventilation images, perfusion images, dose-volume histograms (DVHs), and dose-functional histograms (DFHs). Patient 55 showed good agreement of dose-ventilation and dose-perfusion metrics. Patient 21 showed dose-ventilation metrics greater than dose-perfusion metrics. Patient 13 showed dose-perfusion metrics greater than dose-ventilation metrics.

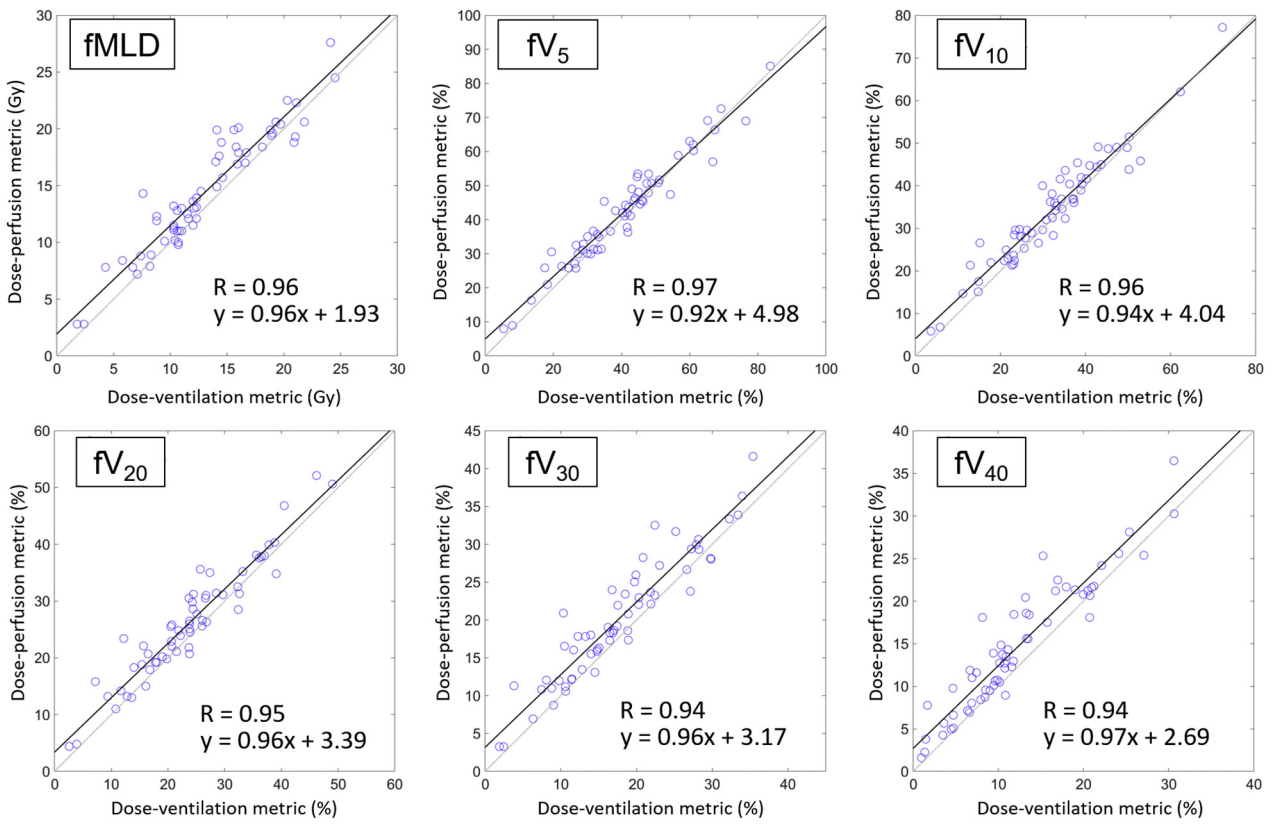

Figure 2 Scatter plot comparing dose-ventilation and dose-perfusion metrics (fMLD, fV_5, fV_{10}, fV_{20}, fV_{30}, and fV_{40}) for 60 patients.

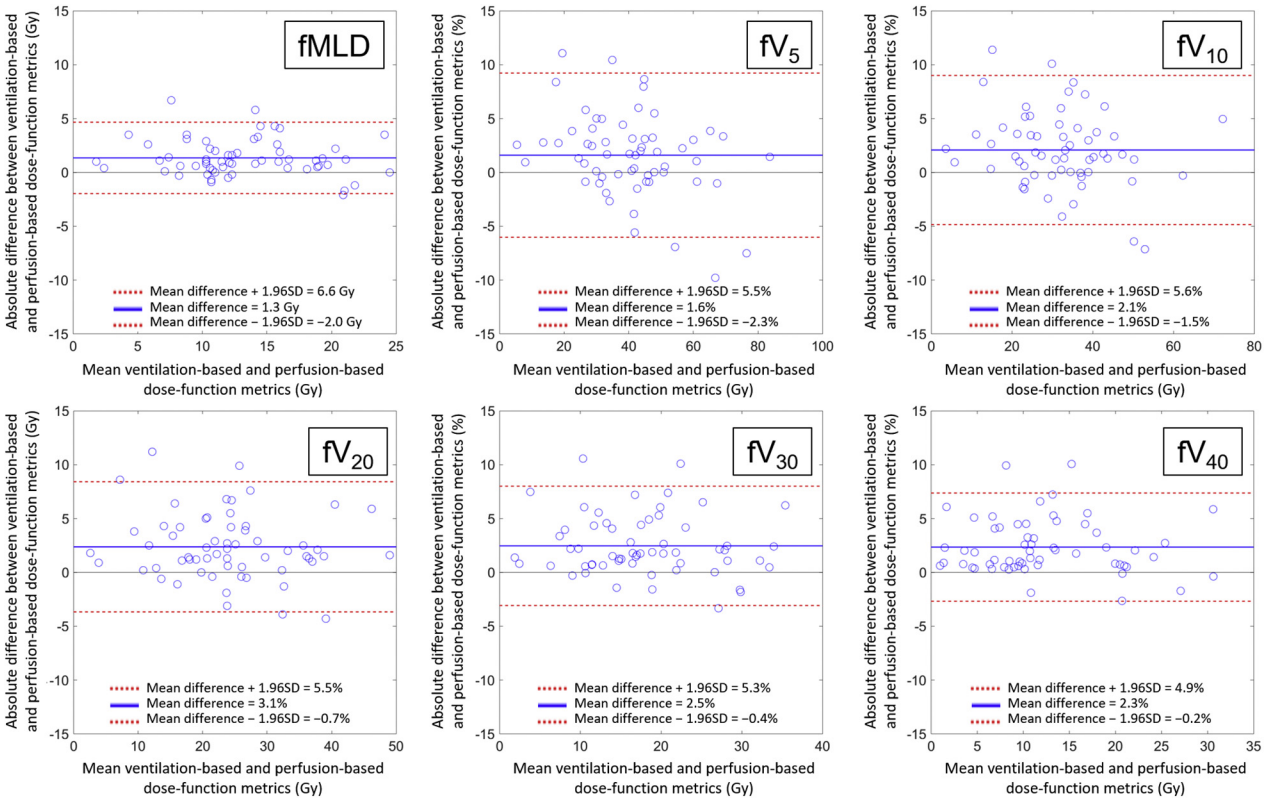

Figure 3 Bland-Altman plot comparing dose-ventilation and dose-perfusion metrics (fMLD, fV_5, fV_{10}, fV_{20}, fV_{30}, and fV_{40}) for 60 patients. The line of the mean relative difference (solid lines) and 95% limits of agreement (dashed lines) are also shown.

fV_5, fV_{10}, fV_{20}, fV_{30}, and fV_{40}. The mean differences were positive (ie, higher in the dose-ventilation metrics than in the dose-perfusion metrics). The agreement between the dose-ventilation and dose-perfusion metrics varied among the patients, with maximum values of 6.6 Gy, 11.1%, 11.4%, 11.1%, 10.6%, and 9.9% for fMLD, fV_5, fV_{10}, fV_{20}, fV_{30}, and fV_{40}, respectively. The 95% limit of agreement between the dose-ventilation and dose-perfusion metrics was 3.3 Gy for fMLD and 6.0% for fV_{20}.

Table 1 summarizes the dose-volume, dose-ventilation, and dose-perfusion metrics. Overall, the dose-ventilation metrics were greater than the dose-perfusion metrics. For example, the mean fV_{20} values with the dose-ventilation and dose-perfusion metrics were 26.3% and 23.9%, respectively. The analyses with the paired *t* test indicated that the dose-ventilation and dose-perfusion metrics were significantly different. Overall mean values of dose-volume metrics and dose-ventilation metrics were seemingly comparable, and the 95% limit of agreement between the dose-volume and dose-ventilation metrics was 2.9 Gy for MLD and 6.3% for V_{20}.

Discussion

This is the first study to compare dose-ventilation metrics with dose-perfusion metrics. Our analyses revealed that the agreement between dose-ventilation and dose-perfusion metrics varied widely among patients and that dose-ventilation and dose-perfusion metrics were significantly different. Overall, these findings suggest that ventilation-based and perfusion-based radiation therapy plan evaluations may not be comparable.

Several studies have reported that lung dose-function metrics improved the predictive power for pulmonary toxicity compared with dose-volume metrics, owing to variations in imaging modalities and definitions of metrics.[3-9] Kocak et al[5] reported that the predictive power for grade 2+ RP was improved by using ^{99m}Tc-MAA SPECT perfusion-based fMLD compared with MLD. Vinogradskiy et al[6] demonstrated that the predictive power of CT ventilation-based fV_{20} was better than that of V_{20} for grade 3+ RP. Hoover et al[7] showed that the predictive power for grade 2+ RP was improved by using ^{99m}Tc-Technegas SPECT ventilation-based fV_{20} alone and ^{99m}Tc-MAA SPECT perfusion-based fV_{20} alone compared with using V_{20}.

The present study revealed that the agreement between CT ventilation-based dose-ventilation and ^{99m}Tc-MAA SPECT perfusion-based dose-perfusion metrics varied among patients, although dose-ventilation metrics were in strong correlation with dose-perfusion metrics. These correlations may be strong because although dose-ventilation and dose-perfusion metrics differed to some

Table 1 Summary of dose-volume, dose-ventilation, and dose-perfusion metrics for 60 patients

	Dose-volume metrics	Dose-ventilation metrics	Dose-perfusion metrics	Difference between dose-ventilation and dose-perfusion metrics	Correlation between dose-ventilation and dose-perfusion metrics	*P* value
MLD/fMLD (Gy)	14.6 ± 4.8	14.5 ± 5.2	13.1 ± 5.1	1.3 ± 1.7	0.95	<.001
V_5/fV_5 (%)	43.3 ± 14.3	42.3 ± 15.1	40.7 ± 16.0	1.6 ± 3.9	0.97	.002
V_{10}/fV_{10} (%)	34.8 ± 11.5	34.0 ± 12.5	31.9 ± 12.8	2.1 ± 3.5	0.96	<.001
V_{20}/fV_{20} (%)	26.8 ± 8.8	26.3 ± 9.9	23.9 ± 9.8	2.4 ± 3.1	0.95	<.001
V_{30}/fV_{30} (%)	20.5 ± 7.4	20.3 ± 8.2	17.8 ± 8	2.5 ± 2.8	0.94	<.001
V_{40}/fV_{40} (%)	14.5 ± 6.9	14.6 ± 7.4	12.3 ± 7.2	2.3 ± 2.6	0.94	<.001

Abbreviations: fMLD = functional mean lung dose; fVx = percent lung function receiving > x Gy; MLD = mean lung dose; RP = radiation pneumonitis; Vx = percent volume receiving > x Gy.
Data are means ± SD,

extent in individual cases, overall, the dose-ventilation and dose-perfusion metrics increased with increasing irradiation dose. Because dose-ventilation metrics were in strong correlation with dose-perfusion metrics, the use of both dose-ventilation and dose-perfusion metrics may not improve the predictive power for pulmonary toxicity. Moreover, dose-ventilation and dose-perfusion metrics may not compete with one another during optimization, and functional avoidance planning may be simple. Conversely, in the present data set, the dose-ventilation metrics were significantly greater than the dose-perfusion metrics. Therefore, the use of the same dose-function constraints for both dose-perfusion and dose-ventilation during treatment planning may result in different dose distributions. These results suggest that determining the constraint for each metric is necessary when dose-ventilation and/or dose-perfusion metrics are used for treatment planning. In future studies with a larger number of cases, a dose-function constraint may be derived by analyzing the relationship between dose-volume and dose-function constraint.

There were several limitations to the present study. The main challenges were the small sample size and the heterogenous patient cohort. Second, several uncertainties associated with the ventilation and perfusion imaging should be acknowledged. CT ventilation imaging has inherent limitations, including imaging artifacts and noise,[31] poor-to-moderate reproducibility,[32,33] and uncertainties in DIR.[34] Third, ^{99m}Tc-MAA SPECT perfusion imaging, although a widely accepted, clinically standard method, provides images of limited quality because of its low resolution and motion blurring.[35,36] Differences in methodologies and characteristics between CT ventilation and SPECT perfusion imaging likely reflect systematic differences between the dose-ventilation and the dose-perfusion metrics rather than physiologic parameters. Future developments to improve the quality of CT ventilation[37,38] and SPECT perfusion[39] imaging may increase the accuracy of dose-ventilation and dose-perfusion metrics. Fourth, dose-ventilation and dose-perfusion metrics can vary depending on regional ventilation and perfusion, target size, location, and delivery technique. Future studies should use larger sample sizes with a broad spectrum of regional ventilation and perfusion patterns, target sizes, and locations to investigate the utility of ventilation and/or perfusion for predicting pulmonary toxicity.

Conclusions

The present study including 60 patients with lung cancer demonstrated that dose-ventilation and dose-perfusion metrics were strongly correlated. However, the agreement between the dose-ventilation and the dose-perfusion metrics varied widely among patients, suggesting that ventilation-based radiation therapy plan evaluation may not be comparable to perfusion-based radiation therapy plan evaluation. Further studies are needed to investigate the value of ventilation or perfusion for predicting pulmonary toxicity.

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