Should regional ventilation function be considered during radiation treatment planning to prevent radiation-induced complications?

Fujun Lan and Jean Jeudy  
Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, Maryland 21201

Suresh Senan and J. R. van Somsen de Koste  
Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, Maryland 21201

Warren D’Souza, Huan-Hsin Tseng, Jinghao Zhou, and Hao Zhang  
Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, Maryland 21201

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Purpose: To investigate the incorporation of pretherapy regional ventilation function in predicting radiation fibrosis (RF) in stage III nonsmall cell lung cancer (NSCLC) patients treated with concurrent thoracic chemoradiotherapy.

Methods: Thirty-seven patients with stage III NSCLC were retrospectively studied. Patients received one cycle of cisplatin–gemcitabine, followed by two to three cycles of cisplatin–etoposide concurrently with involved-field thoracic radiotherapy (46–66 Gy; 2 Gy/fraction). Pretherapy regional ventilation images of the lung were derived from 4D computed tomography via a density change–based algorithm with mass correction. In addition to the conventional dose–volume metrics (V20, V30, V40, and mean lung dose), dose–function metrics (fV20, fV30, fV40, and functional mean lung dose) were generated by combining regional ventilation and radiation dose. A new class of metrics was derived and referred to as dose–subvolume metrics (sV20, sV30, sV40, and subvolume mean lung dose); these were defined as the conventional dose–volume metrics computed on the functional lung. Area under the receiver operating characteristic curve (AUC) values and logistic regression analyses were used to evaluate these metrics in predicting hallmark characteristics of RF (lung consolidation, volume loss, and airway dilation).

Results: AUC values for the dose–volume metrics in predicting lung consolidation, volume loss, and airway dilation were 0.65–0.69, 0.57–0.70, and 0.69–0.76, respectively. The respective ranges for dose–function metrics were 0.63–0.66, 0.61–0.71, and 0.72–0.80 and for dose–subvolume metrics were 0.50–0.65, 0.65–0.75, and 0.73–0.85. Using an AUC value = 0.70 as a cutoff value suggested that at least one of each type of metrics (dose–volume, dose–function, dose–subvolume) was predictive for volume loss and airway dilation, whereas lung consolidation cannot be accurately predicted by any of the metrics. Logistic regression analyses showed that dose–function and dose–subvolume metrics were significant (P values ≤ 0.02) in predicting volume airway dilation. Likelihood ratio test showed that when combining dose–function and/or dose–subvolume metrics with dose–volume metrics, the achieved improvements of prediction accuracy on volume loss and airway dilation were significant (P values ≤ 0.04).

Conclusions: The authors’ results demonstrated that the inclusion of regional ventilation function improved accuracy in predicting RF. In particular, dose–subvolume metrics provided a promising method for preventing radiation-induced pulmonary complications. © 2016 American Association of Physicists in Medicine.

Key words: regional ventilation function, radiation fibrosis, nonsmall cell lung cancer

1. INTRODUCTION

Two-thirds of patients with lung cancer will receive radiation therapy during the course of their treatment. Survival rates for lung cancer are low (average five-yr survival across all stages = 14%). The delivery of higher doses of radiation (74 vs 60 Gy) in a recent trial (RTOG 0617) showed reduced survival rates for the 74 Gy arm, potentially due to increased toxicity. Thus, attempts to decrease toxicity, such as radiation pneumonitis (RP) and/or radiation fibrosis (RF) are important, particularly as RF may lead to chronic respiratory insufficiency. These radiation-induced complications, in turn, can lead to substantial negative consequences in both clinical outcomes (e.g., therapy interruptions and quality of life detriments) and resource utilization (e.g., hospitalization, emergency department visits, and increased staff time). It would thus be beneficial to establish specific guidelines for dose escalation that can be employed for controlling the risk of toxicity.

The literature includes numerous studies that relate dose–volume parameters, such as V20 (percentage of lung volume receiving ≥20 Gy) and mean lung dose (MLD), to the incidence of RP. These parameters are generally found...
to be significantly correlated with RP. In an attempt to reduce the risk of radiation-induced lung injury, clinical practice has routinely used V20 and MLD to define safety levels for limiting doses delivered to the lung. However, these studies implicitly assume a spatially uniform function within the lung, despite the fact that this assumption may not be valid for patients with lung cancer. Because lung function requires both perfusion and ventilation of alveoli, both single-photon emission computed tomography (SPECT) perfusion imaging and the more recent 4D computed tomography (4DCT)–based ventilation imaging have been proposed to quantify functional variation within the lung and have been suggested as independent surrogates for lung function.

The majority of research that incorporates functional heterogeneity of the lung is performed either to contour the functional lung region as a new avoidance structure in treatment planning or to define a dose–function histogram (DFH), which is utilized to derive dose–function metrics such as functional V20 (fV20) and functional mean lung dose (fMLD). Dose–function metrics have been employed for the purposes of treatment planning and treatment evaluation. In addition, results from several studies that related dosimetric and functional parameters to RP suggested that dose–function metrics are more predictive of toxicity than dose–volume metrics.

Relatively few studies have reported on predictive factors for RF. Here we attempt to incorporate nonhomogeneous lung function in predicting RF. In addition to dose–function metrics, we compute the conventional dose–volume metrics on a functional lung region and refer to these as dose–subvolume metrics. The functional lung is quantified as the lung region with certain percentage of the maximum regional ventilation function value. Note that the concept of dose–subvolume metrics is not necessarily new. These have been utilized for plan generation and evaluation in several studies dealing with functional image-based treatment planning. To the best of our knowledge, our current study appears to be the first that used dose–subvolume metrics as potential predictors for toxicity. The dose–function and dose–subvolume metrics were compared to the dose–volume metrics (on the entire lung) in their ability to predict for hallmark characteristics of RF [lung consolidation, volume loss, and airway dilation (AD)].

2. METHODS AND MATERIALS

2.A. Patient population and endpoints

This retrospective study included data on 37 patients with stage III nonsmall cell lung cancer (NSCLC). Patients received one cycle of cisplatin–gemcitabine, followed by two to three cycles of cisplatin–etoposide concurrently with involved-field thoracic radiotherapy (46–66 Gy). For each patient the dose was delivered at 2 Gy/daily fraction, five fractions/week. Patients were evaluated for RF at six months after treatment using common terminology criteria for adverse effects (CTCAE) scoring based on lung consolidation, volume loss, and AD. Table I lists the details of the grading system. After grading was done by an experienced radiologist/physician, binary endpoints for each symptom were obtained using toxicity grade >2 as criteria. The number of patients graded as toxicities and the patient characteristics are listed in Table II. All patients underwent planning 4DCT prior to treatment.

### Table II. Patient characteristics.

| Characteristic               | Number of cases or mean | Percentage or range |
|------------------------------|-------------------------|---------------------|
| Age (yr)                     | 61                      | 41–74               |
| Gender                       |                         |                     |
| Male                         | 27                      | 73%                 |
| Female                       | 10                      | 27%                 |
| Smoking history              |                         |                     |
| Yes                          | 34                      | 92%                 |
| No                           | 3                       | 8%                  |
| COPD                         |                         |                     |
| Yes                          | 4                       | 11%                 |
| No                           | 33                      | 89%                 |
| Lung consolidation           |                         |                     |
| Grade ≤ 2                    | 20                      | 54%                 |
| Grade > 2                    | 17                      | 46%                 |
| Volume loss                  |                         |                     |
| Grade ≤ 2                    | 33                      | 89%                 |
| Grade > 2                    | 4                       | 11%                 |
| Airway dilation              |                         |                     |
| Grade ≤ 2                    | 25                      | 68%                 |
| Grade > 2                    | 12                      | 32%                 |

2.B. Fractional regional ventilation

Using the 4DCT image dataset, which includes CT images corresponding to ten phases that were equally spaced in time over the full respiratory cycle, a fractional regional ventilation (FRV) image was calculated via a density change–based algorithm with mass correction for each patient. Lungs
were segmented on the CT images at the inhale and exhale phases of respiration. The images at these two phases were matched to each other on a voxel-by-voxel basis using a “Demons” deformable image registration technique with a multiresolution scheme from ITK (http://www.itk.org). The FRV for a given voxel is estimated by

\[ \frac{V_{IN} - V_{EX}}{V_{EX}} = \frac{k \rho_{EX} - \rho_{IN}}{\rho_{IN}}, \]  

(1)

where \( V_{IN} \) and \( V_{EX} \) are the inhale and exhale volumes for the voxel, and \( \rho_{IN} \) and \( \rho_{EX} \) are the voxel densities at the inhale and exhale phases. Treating the lung as a composite of mainly air and tissue, the density of a voxel is approximated by

\[ \rho_{VOX} = \frac{\rho_{AIR} V_{AIR} + \rho_{TISSUE} V_{TISSUE}}{V_{VOX}}, \]  

(2)

where \( \rho_{AIR} \sim 0.001 \) g/cm\(^3\) and \( \rho_{TISSUE} \sim 1.1 \) g/cm\(^3\). The parameter \( \kappa \) in Eq. (1) is introduced to account for the tissue-based mass changes that occur over the respiratory cycle. This parameter can be roughly interpreted as the ratio of the entire lung mass at the inhale phase to that at the exhale phase.

Before calculating any function metrics, the FRV values were normalized \((0 \leq f \leq 1)\) so that other type of function images (other than FRV images) can also be easily utilized.

2.C. Dose–volume and dose–function metrics

For each patient, the 3D dose matrix for the entire lung region was used to compute a dose–volume histogram (DVH), MLD, \( V_{20} \), \( V_{30} \), and \( V_{40} \). Incorporating the lung function information given by the FRV image into the dose distribution, DFH, fMLD, and fV\(_{20} \), fV\(_{30} \), and fV\(_{40} \) were calculated.

Before introducing the dose–subvolume metrics, we first review the formal definitions of \( V_{20} \), MLD, fV\(_{20} \), and fMLD. Let \( R \) denote the set of voxels in the entire lung region. Denote by \( v_i \) and \( D_i \) the volume and dose, respectively, received for voxel \( i \in R \), and let \( R_{20} \) be the set of voxels receiving a dose level 20 Gy (i.e., \( R_{20} = \{ i \in R : D_i \geq 20 \} \)). Then,

\[ V_{20} = \frac{\sum_{i \in R_{20}} v_i}{\sum_{i \in R} v_i}, \quad \text{MLD} = \frac{\sum_{i \in R} v_i D_i}{\sum_{i \in R} v_i}, \]  

(3)

Note that the volume \( v_i \) is usually the same for each voxel \( i \). Now let \( f_i \) denote the FRV function for voxel \( i \). fV\(_{20} \) and fMLD are expressed as

\[ fV_{20} = \frac{\sum_{i \in R_{20}} f_i}{\sum_{i \in R} f_i}, \quad \text{fMLD} = \frac{\sum_{i \in R} f_i D_i}{\sum_{i \in R} f_i}. \]  

(4)

Note that Eq. (4) is obtained by replacing the voxel volume \( v_i \) in Eq. (3) with the corresponding voxel function \( f_i \).

2.D. Dose–subvolume metrics

Instead of working with the dose distribution for the entire lung region as in the dose–volume metrics, we propose to analyze dose distributions in the functional lung region, which is quantified as the lung region with a certain percentage of the maximum regional ventilation function value. Dose–subvolume metrics are defined as the conventional dose–volume metrics computed on a subregion of interest (sROI), which is the functional lung in this study.

Let \( R_f \) denote the functional lung that consists of only the lung voxels with a FRV value above a certain threshold \( f \) \((0 \leq f \leq 1)\) (i.e., \( R_f = \{ i \in R : f_i \geq f \} \)). The 3D dose matrix restricted to \( R_f \) was used to compute the dose–subvolume metrics, including a dose–subvolume histogram (DsVH), subvolume MLD (sMLD), subvolume \( V_{20} \) \((sV_{20}) \), \( V_{30} \), and \( V_{40} \). Formally, \( sV_{20} \) and sMLD are expressed as

\[ sV_{20} = \frac{\sum_{i \in R_f} v_i}{\sum_{i \in R_f} v_i}, \quad \text{sMLD} = \frac{\sum_{i \in R_f} v_i D_i}{\sum_{i \in R_f} v_i}. \]  

(5)

Note that Eq. (5) is obtained by replacing \( R \) in Eq. (3) with \( R_f \). The dose–subvolume metrics are clearly dependent on the choice of the functional threshold \( f \). They reduce to the conventional dose–volume metrics when \( f = 0 \).

2.E. Statistical analysis

Logistic regression analysis and receiver operating characteristic (ROC) curve analysis were used to assess the predictive abilities of the dose–volume, dose–function, and dose–subvolume metrics for RF. The likelihood ratio test was used to compare logistic regression models when multiple types of metrics were combined as predictors.

3. RESULTS

Area under the receiver operating characteristic curve (AUC) values for the dose–volume metrics, dose–function metrics, and dose–subvolume metrics with \( f = 0.2, 0.4, 0.6, \) and \( 0.8 \) in predicting lung consolidation, volume loss, and AD are shown in Table III. Using an AUC value = 0.70 as cutoff value suggested that at least one of each type of metrics (dose–volume, dose–function, dose–subvolume) was predictive for volume loss and AD, whereas lung consolidation cannot be accurately predicted by any of the metrics. For AD, for example, the ranges of AUC values were 0.69–0.76, 0.72–0.80, and 0.73–0.85 for the dose–volume, dose–function, and dose–subvolume metrics, respectively.

For dose–subvolume metrics, when predicting volume loss and AD, AUC values were increasing in the lower functional threshold range \((f = 0.2–0.4)\) and reached the peak at \( f = 0.4 \). The AUC values stabilized in the higher functional threshold range \((f = 0.6–0.8)\). Thus, we report results associated with the dose–subvolume metrics for \( f = 0.6 \) only henceforth.
Mean and standard deviation values for the dose–volume, dose–function, and dose–subvolume metrics in the groups with and without AD, respectively, plus P values and coefficients from logistic regression analysis are shown in Table IV. All metrics on average were greater for the AD group than the non-AD group. P values for the dose–function and dose–subvolume metrics were generally smaller than those for the corresponding dose–volume metrics. In particular, P values reached statistical significance for the metrics fMLD, fV20, fV30, sMLD, sV20, sV30, and sV40 at the 0.05 level. The metrics were close for the groups with and without consolidation and with and without volume loss, which is shown in the Appendix (Table VIII).

AUC values for a combination of dose–volume, dose–function, and dose–subvolume metrics based on logistic regression analysis are reported in Table V. With respect to volume loss and AD, the addition of dose–function and/or dose–subvolume metrics generally improved the predictive ability of the dose–volume metrics alone. For example, in predicting volume loss, the AUC value was 0.57 for MLD, 0.80 for MLD+fMLD, 0.88 for MLD+sMLD, and 0.91 for MLD+fMLD+sMLD. Note that the inclusion of dose–subvolume metrics generally led to a larger increase in AUC values than inclusion of the corresponding dose–function metrics. For lung consolidation, the addition of dose–function or dose–subvolume metrics did not seem to have a major effect on the predictive ability of the dose–volume metrics alone. P values from likelihood ratio test (Table V) comparing logistic regression models with combined metrics to dose–volume metrics alone showed that most of the improvements of prediction accuracy on volume loss and AD were significant. The coefficients from logistic regression models with combined metrics are listed in Table VI, which demonstrated the importance of dose–subvolume metrics. Example ROC curves for individual and combinations of MLD, fMLD, and sMLD metrics in predicting AD are plotted in Fig. 1.

Consider two representative patients, patient A and patient B. DVHs, DFHs, and DsVHs with functional thresholds f = 0.6 for these patients are plotted in Fig. 2. The associated metric values are reported in Table VII. Patient A did not develop RF, whereas patient B suffered lung consolidation, volume loss, and AD. For patient A, the DFHs and DsVHs were less than DVHs, and the dose–function and dose–subvolume metrics were smaller than the corresponding dose–volume metrics. In contrast, the DFHs and DsVHs were larger than the DVH for patient B, who had larger dose–function and dose–subvolume metrics than the corresponding dose–volume metrics. These results demonstrate that the incorporation of functional information by dose–function and dose–subvolume metrics better separates patients with and without toxicity. Also in this regard, the dose–subvolume metrics outperformed the dose–function metrics for these patients.
AUC values for combinations of dose–volume, dose–function, and dose–subvolume metrics. (P values reached statistical significance are marked in bold.)

| RF                      | Metric | DV | DV+DF | DV+DSV | DV+DSV+DSV |
|-------------------------|--------|----|-------|--------|------------|
|                         |        | AUC| AUC   | P value | AUC        | P value    |
| Lung consolidation      | MLD    | 0.65| 0.60  | 0.28   | 0.61       | 0.78       | 0.65       | 0.31       |
|                         | V_{50} | 0.67| 0.63  | 0.36   | 0.66       | 0.82       | 0.69       | 0.40       |
|                         | V_{30} | 0.68| 0.64  | 0.43   | 0.67       | 0.93       | 0.67       | 0.43       |
|                         | V_{20} | 0.69| 0.62  | 0.40   | 0.69       | 0.93       | 0.64       | 0.39       |
| Volume loss             | MLD    | 0.57| 0.80  | 0.04   | 0.88       | 0.01       | 0.91       | 0.04       |
|                         | V_{50} | 0.66| 0.80  | 0.03   | 0.88       | 0.01       | 0.90       | 0.03       |
|                         | V_{30} | 0.70| 0.77  | 0.05   | 0.85       | 0.02       | 0.86       | 0.05       |
|                         | V_{20} | 0.69| 0.72  | 0.09   | 0.85       | 0.02       | 0.85       | 0.04       |
| Airway dilation         | MLD    | 0.70| 0.77  | 0.01   | 0.83       | 0.001      | 0.84       | 0.005      |
|                         | V_{50} | 0.76| 0.80  | 0.01   | 0.83       | 0.001      | 0.84       | 0.006      |
|                         | V_{30} | 0.69| 0.75  | 0.02   | 0.82       | 0.002      | 0.82       | 0.007      |
|                         | V_{20} | 0.69| 0.75  | 0.02   | 0.84       | 0.001      | 0.85       | 0.005      |

Note: DV: dose–volume, DF: dose–function, DSV: dose–subvolume.

4. DISCUSSION

Dose–function and dose–subvolume metrics were proposed as a means to incorporate the 4DCT-based regional ventilation function into conventional dose–volume analysis. They were demonstrated to be more predictive than conventional dose–volume metrics with respect to volume loss and AD. In addition, dose–subvolume metrics were found to be competitive with, if not better than, dose–function metrics in this regard. In contrast, none of the metrics performed well in predicting lung consolidation.

Because of the limited number of patients available for this study, the P values from logistic regression analysis for the dose–subvolume metrics were close to, but did not reach statistical significance in predicting volume loss. However, the results are promising for the metrics to be included in clinical trials to further prove their value. The limited number of patients also affected the logistic regression prediction accuracy when multiple metrics were combined. Unlike methods such as the support vector machine, when metrics are added as predictors in logistic regression models, corresponding coefficients, which can degrade the estimates of coefficients (as shown in Table VI) related to “good” parameters need to be estimated. This factor may result in low accuracy when predicting lung consolidation.

A 2002 study that claimed to be the first to report applying ROC analysis to predictors of radiation-induced lung injury utilized SPECT lung perfusion images and reported AUC values of 0.61–0.72. A recent study that claimed to be the first to correlate ventilation function and dose to pulmonary toxicity reported AUC values of 0.50–0.54 and P values (logistic regression) of 0.33–0.58 for dose–volume metrics and corresponding values of 0.57–0.62 and 0.09–0.25 for dose–function metrics. Both of the studies used RP as endpoint. Compared to these results, we showed that the AUC

Table VI. Logistic regression coefficients for combinations of dose–volume, dose–function, and dose–subvolume metrics.

| RF                      | Metric | DV+DF | DV+DSV | DV+DSV+DSV |
|-------------------------|--------|-------|--------|------------|
|                         |        | Coefficients | Coefficients | Coefficients |
| Lung consolidation      | MLD    | −0.15 | 0.21  | 0.05       | 0.02        | −0.38 | 0.54 | −0.11 |
|                         | V_{50} | −4.51 | 9.51  | 4.96       | 0.65        | −16.71 | 26.54 | −5.56 |
|                         | V_{30} | −3.37 | 9.05  | 5.65       | 0.31        | −20.05 | 30.97 | −7.19 |
|                         | V_{20} | −6.59 | 10.78 | 3.79       | 0.31        | −20.05 | 30.97 | −7.19 |
| Volume loss             | MLD    | −0.84 | 0.78  | −0.32      | 0.28        | −0.21 | −0.15 | 0.32 |
|                         | V_{50} | −48.22| 44.32 | −18.96     | 16.12       | −8.48  | −13.78 | 19.98 |
|                         | V_{30} | −39.61| 39.06 | −14.50     | 15.17       | −4.63  | −12.56 | 18.58 |
|                         | V_{20} | −32.07| 34.33 | −13.54     | 16.59       | 12.02  | −34.25 | 26.54 |
| Airway dilation         | MLD    | −0.51 | 0.61  | −0.14      | 0.24        | −0.05  | −0.12 | 0.27 |
|                         | V_{50} | −24.02| 31.23 | −3.75      | 12.20       | 4.03   | −9.87 | 14.71 |
|                         | V_{30} | −24.94| 30.47 | −7.39      | 13.34       | 3.18   | −14.16 | 17.18 |
|                         | V_{20} | −30.11| 34.15 | −11.12     | 15.83       | 0.46   | −15.94 | 20.24 |

Note: DV: dose–volume, DF: dose–function, DSV: dose–subvolume.
and $P$ values for dose–volume and dose–function metrics are more predictive for RF. Furthermore, the results listed in Tables III-V provide more compelling evidence of the proposed dose–subvolume metrics.

Three points on the dose–subvolume metrics should be noted. First, the dose–subvolume metrics were better predictors for AD and volume loss compared to the dose–volume and dose–function metrics. It was not the case for lung consolidation. The underlying causes remain to be investigated.

Second, the definition of the dose–subvolume metric relies on the availability of a sROI. Although the sROI is defined as the functional lung based on regional ventilation in this study, it can be similarly derived from other functional imaging modalities, such as SPECT perfusion imaging. It may even be created using a combination of anatomic and functional information. Thus, in addition to providing a promising alternative to dose–function metrics for incorporating functional information in relating dose to toxicity, the dose–subvolume metrics offer a convenient way to combine information from multiple sources including both anatomy and function. With more information, the accuracy of this type of metric in predicting toxicity is expected to be further improved.

If one chooses to use functional information on a structure to define the sROI, a question that naturally arises is what is the best functional threshold such that the resulting dose–subvolume metrics are most predictive? To answer this, note that different structures and imaging modalities may yield different ranges for measuring functional status; it is better, then, to use a relative threshold, such that the region having a functional status that is above a certain percentage of the maximum is considered to be highly functional. We used an absolute threshold in this study, because the fractional regional ventilation was already normalized so that the values lie between 0 and 1. In addition, this study suggested that dose–subvolume metrics with thresholds $f = 0.2, 0.4, 0.6,$ and $0.8$ yielded similar results. It remains to be tested whether this observation holds for more general studies and more patients in the future.

When choosing endpoints for radiation-induced lung toxicity, RP was the most frequently used. Although pneumonitis is commonly considered as an acute toxicity and fibrosis as a late toxicity, they are both limiting factors for improving the therapeutic ratio and affecting patient’s quality of life. The pathophysiology of both pneumonitis and fibrosis is a spectrum of abnormalities and is considered to be a dynamic process. It is also accepted that there are both reversible and irreversible components for RF and RP, and it is not easy to differentiate them in the clinical setting.23 The reversible component of fibrotic disease (more pneumonitis) may be explained by a shift in the process of extracellular matrix remodeling toward degradation. The irreversible component (more fibrosis) is thought to correspond
to the development of a “mature” scar. There is literature showing the correlation between the two and demonstrating common factors associated with both toxicities. There are also the notions of clinical and radiographic toxicity with clear differences between the two notions; the molecular mechanism(s) for radiation-induced lung damage remains unclear and there is no consensus on a standard to evaluate it. Most of the time, pneumonitis is used as a clinical toxicity endpoint and by definition the RF is a radiographic diagnosis. We believe the improvements achieved by dose–subvolume metrics in prediction of RF in this study could be applied to RP.

For large stage III NSCLC tumors, it had been shown that RF manifests as a consolidation, traction bronchiectasis, architectural distortion, and volume loss after the completion of radiation therapy. Park et al. have suggested that when using imaging features to evaluate the evolution of fibrosis due to radiation, volume loss, architectural distortion, bronchiectasis, and pleural thickening should be considered. They further suggest that in contrast to RP which usually occurs about 4–12 weeks after completion of radiation therapy, RF develops at six months after the completion of radiation therapy and remains stable after 2 yr. Since we evaluated the hallmark characteristics of RF as suggested by these studies, we picked six months after treatment as the evaluation point.

In Table II, other patient characteristics including age, gender, smoking history, COPD are provided. Some of these factors have been associated to radiation-induced lung toxicity as well. In this study, we only focused on dose–volume and dose–function metrics. Future study will involve the combinations of demographics, clinical parameters, and dose–function metrics.

5. CONCLUSION

Our results demonstrated that the inclusion of regional ventilation function improved accuracy in predicting RF. In particular, dose–subvolume metrics provided a promising method for preventing radiation-induced pulmonary complications.

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CONFLICT OF INTEREST DISCLOSURE

The authors have no COI to report.

APPENDIX: SUPPLEMENTAL TABLES

### Table VIII. Mean (standard deviation) values of the dose–volume, dose–function, and dose–subvolume metrics in groups with and without consolidation and volume loss.

| Metric          | Consolidation | No consolidation | P value | Volume loss | No volume loss | P value |
|-----------------|---------------|------------------|---------|-------------|----------------|---------|
| Dose–volume metrics |               |                   |         |             |                |         |
| MLD             | 19.48 (6.23)  | 17.89 (4.24)      | 0.35    | 18.31 (10.08)| 18.66 (4.61)  | 0.90    |
| V20             | 0.33 (0.09)   | 0.29 (0.07)       | 0.20    | 0.31 (0.19)  | 0.31 (0.07)   | 0.95    |
| V30             | 0.28 (0.09)   | 0.25 (0.06)       | 0.20    | 0.28 (0.17)  | 0.26 (0.06)   | 0.64    |
| V40             | 0.24 (0.10)   | 0.22 (0.06)       | 0.37    | 0.25 (0.14)  | 0.22 (0.07)   | 0.60    |
| Dose–function metrics |              |                   |         |             |                |         |
| fMLD            | 18.51 (6.71)  | 16.27 (4.47)      | 0.23    | 18.54 (10.64)| 17.15 (5.00)  | 0.64    |
| fV20            | 0.31 (0.11)   | 0.27 (0.08)       | 0.13    | 0.32 (0.20)  | 0.28 (0.08)   | 0.43    |
| fV30            | 0.26 (0.10)   | 0.22 (0.07)       | 0.15    | 0.29 (0.18)  | 0.24 (0.07)   | 0.27    |
| fV40            | 0.22 (0.10)   | 0.19 (0.06)       | 0.26    | 0.25 (0.15)  | 0.20 (0.07)   | 0.29    |
| Dose–subvolume metrics (f = 0.6) |       |                   |         |             |                |         |
| sMLD            | 14.52 (10.05)| 12.34 (6.27)      | 0.41    | 19.67 (12.05)| 12.57 (7.48)  | 0.12    |
| sV20            | 0.24 (0.18)   | 0.20 (0.12)       | 0.33    | 0.35 (0.24)  | 0.20 (0.13)   | 0.08    |
| sV30            | 0.20 (0.16)   | 0.17 (0.10)       | 0.39    | 0.31 (0.21)  | 0.17 (0.11)   | 0.06    |
| sV40            | 0.17 (0.14)   | 0.14 (0.09)       | 0.53    | 0.27 (0.18)  | 0.14 (0.10)   | 0.05    |
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