Appendix

Calculation of Percent Deviation from Homogeneity

Areas of functional defect were identified as regions with ventilation values below a calculated cutoff. The calculation of the cutoff value is based on a percent deviation from an ideal, homogeneous functional distribution within the lung. The theoretical ventilation value that corresponds to perfectly homogenous functionality is a mean of the average ventilation value in six lung regions, divided superior to inferior into thirds for both the left and right lung. The cutoff at which defects were identified is given in Equation A.1.

$$V_T = \left(\frac{100}{6}\right)\left(\frac{100-x}{100}\right)\sum_{i=1}^{6} V_{ave,i} \qquad \text{(A.1)}$$

Where x is the percent reduction from homogeneous function, and $V_{ave,i}$ is the average ventilation value of the ith third. All voxels with ventilation values greater than V_T were classified as functional lung and included in the functional lung contour used to calculate functional dose metrics.

Mathematically the values for x can span +100% to -500%. Realistically the range is much more limited as it is unlikely that all of a patient's ventilation occurs within a highly localized region (x = -500%) and in the limit that x approaches +100%, metrics would be derived for the entire lung and be equivalent to standard lung planning dose metrics. As an example, an input value of -50% would produce a ventilation threshold equal to 1.5 times theoretically homogeneous value. Likewise, an input of +50% means that the threshold value for identifying functional lung would be one half of the theoretically homogeneous value. In other words, in the latter case, all areas of the lung with ventilation values greater than 0.5 times the homogeneous ventilation value would be binned to the functional contour.

Modeling Results for Grade 2+ Radiation Pneumonitis

Grade 2+ Pneumonitis				
Model	**Metrics**	**Maximum AUC**	**p-Value**	**Threshold**
Percentile	V20Gy	0.73	<0.01	86th Percentile
	Mean	0.73	<0.01	69th Percentile
Percent Deviation	V20Gy	0.73	<0.01	-50
	Mean	0.73	<0.01	-15
Total Lung	V20Gy	0.55	0.36	N/A
	Mean	0.58	0.12	N/A

Table A.1: The predictive power (AUC) and significance of fit (p-Values) for NTCP models using different functional sub-volumes is presented for Grade 2+ radiation pneumonitis. For comparison, the normal means of evaluating lung dose from the total lung is reported for the examined patient cohort.

Grade 2+ Pneumonitis			
Model	**Metric**	**AUC**	**p-Value**
DFH	F10Gy	0.70	0.02
Sigmoidal Weighting	F20Gy	0.74	<0.01
Total Lung	V20Gy	0.55	0.36
	Mean	0.58	0.12

Table A.2: The predictive power (AUC) and significance of fit (p-Values) for NTCP models using different dose function histogram calculations is presented for Grade 2+ radiation pneumonitis. For comparison, the normal means of evaluating lung dose from the total lung is reported for the examined patient cohort.

Calculating the Dose-Function of Interest for Different Structure-Based Thresholds

Grade 3+ Pneumonitis			
Threshold	**AUC**	**p-Value**	**Metric**
Total Lung	0.55	0.290	Mean
5th	0.58	0.160	V30Gy
10th	0.61	0.111	V30Gy
15th	0.63	0.076	V30Gy
20th	0.64	0.055	V30Gy
25th	0.65	0.044	V20Gy
30th	0.66	0.036	V20Gy
35th	0.66	0.032	V20Gy
40th	0.67	0.029	V20Gy
45th	0.67	0.027	V20Gy
50th	0.68	0.035	V30Gy
55th	0.68	0.024	V20Gy
60th	0.68	0.023	V20Gy

65th	0.69	0.021	V20Gy
70th	0.69	0.020	V20Gy
75th	0.68	0.021	V20Gy
80th	0.69	0.024	V20Gy
85th	0.70	0.033	V20Gy
90th	0.68	0.062	V20Gy
95th	0.66	0.110	V20Gy

Table A.3: The dose metric providing the highest predictive power (AUC) for structure-based modeling is reported for different functional cutoff thresholds. The functional cutoff thresholds used were based on a percentile image of the ventilation values. For example, the 90^{th} percentile would treat the top 10% of all ventilation values as the functional sub-volume used for analysis.

Model Parameters for Non-Linear Weighting

Pneumonitis Grade	**Dose-Function Metric**	**h_c**	**m**	**AUC**	**p-Value**
Grade 2+	F20Gy	0.3	8	0.74	<0.01
Grade 3+	F20Gy	0.2	8	0.67	0.03

Table A.4: The model parameters for the sigmoidal weighting of ventilation values prior to DFH calculation are presented. These parameters provided the highest predictive power (as determined by AUC) while maintaining significance (p-Value < 0.05) with respect to predicting Grade 2+ and Grade 3+ radiation pneumonitis. Also presented are the dose-function metrics which provided the highest predictive power for the model. The parameter h_c corresponds to the relative position of the sigmoid and the parameter m represents the slope of the central region.

	Dose-Function Metric									
	V5Gy		V10Gy		V20Gy		V30Gy		Mean Dose	
Method	**AUC**	**p-Value**	**AUC**	**p-Value**	**AUC**	**p-Value**	**AUC**	**p-Value**	**AUC**	**p-Value**
% Deviation	0.55	0.78	0.60	0.25	0.70	0.02	0.68	0.02	0.66	0.04
Percentile	0.55	0.61	0.59	0.35	0.70	0.03	0.68	0.03	0.66	0.06

Table A.5: The highest AUCs and associated p-values are presented for all the structure-based dose-function metrics examined in the study.

	Dose-Function Metric							
	F5Gy		F10Gy		F20Gy		F30Gy	
Method	**AUC**	**p-Value**	**AUC**	**p-Value**	**AUC**	**p-Value**	**AUC**	**p-Value**
DFH	0.48	0.92	0.54	0.55	0.66	0.04	0.66	0.04
Non-Linear Weighting	0.53	0.75	0.57	0.39	0.67	0.03	0.65	0.04

Table A.6: The highest AUCs and associated p-values are presented for all the image-based dose-function metrics examined in the study.