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Poor Baseline Pulmonary Function May Not Increase the Risk of Radiation Induced Lung Toxicity

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Summary

This analysis of 260 patients showed that poor baseline pulmonary function (PF) did not increase the risk of RILT, suggesting that poor PF may not be a contraindication to definitive radiation therapy. The combined model including age, MLD and FEV1 may improve the predictability of RILT as compared to that with MLD alone.

Purpose—Poor pulmonary function (PF) is often considered a contraindication for definitive radiotherapy for lung cancer. This study investigates whether baseline PF is associated with radiation induced lung toxicity (RILT) in patients with non-small cell lung cancer (NSCLC) receiving conformal radiation therapy (CRT).

Patients and Methods—NSCLC patients treated with CRT and tested for PF at baseline were eligible. Baseline predicted values of FEV1, FVC and DLCO were analyzed. Additional factors including age, gender, smoking status, KPS, coexisting COPD, tumor location, histology, concurrent chemotherapy, radiation dose and MLD were evaluated for RILT. The primary endpoint was symptomatic RILT (SRILT) including grade 2 radiation pneumonitis and fibrosis.

Results—There were a total of 260 patients and SRILT occurred in 58 (22.3%) of them. Mean FEV1 for SRILT and non-SRILT patients were 71.7% and 65.9% ($p = 0.077$). Under univariate analysis, risk of SRILT increased with MLD ($p = 0.008$), the absence of COPD ($p = 0.047$), and FEV1 ($p = 0.077$). Age (65 split) and MLD were significantly associated with SRILT in

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multivariate analysis. The addition of FEV1 and age to the MLD based model slightly improved the predictability of SRILT (Area under curve from 0.63 to 0.70, $p=0.088$).

Conclusions—Poor baseline PF does not increase the risk of SRILT and combining FEV1, age and MLD may improve the predictive ability.

Keywords

Radiation induced lung toxicity; Non-small cell lung cancer; Pulmonary function

Introduction

Lung cancer is the leading cause of cancer deaths worldwide. Approximately two thirds of lung cancer patients receive radiation therapy (RT) during the course of treatment with either definitive or palliative intent. Biological and clinical evidence suggest that higher radiation dose could provide better local control and may prolong survival in patients with non-small cell lung cancer (NSCLC) (1, 2). However, delivery of higher radiation dose tends to incur greater risk of radiation related damage to normal tissue. Symptomatic radiation induced lung toxicity (SRILT), presenting as pneumonitis or fibrosis, is one of the most important dose-limiting factors for RT in patients with thoracic cancer. The incidence of SRILT from the three dimensional conformal radiation therapy (3D-CRT) has been reported as 2% to 37% (1-3). An accurate predictive model could help stratify patients' risk of SRILT and allow dose escalation to patients with a low risk of toxicity. Studies have examined clinical, dosimetric, biological and functional imaging characteristics to determine their predictive ability for SRILT, but an ideal model does not yet exist (4-7). Pulmonary function tests (PFTs) are essential before considering thoracic surgery and definitive radiation. Baseline pulmonary function (PF) can predict the risk of pulmonary complications after thoracotomy and patients with very poor PF are generally considered unfit for surgery. Likewise, poor PF is often considered a contraindication for definitive radiation therapy in clinical practice and clinical trials. However, evidence about the impact of baseline PF on the risk of SRILT has not been well-documented.

This study aimed to investigate (1) whether baseline PF is correlated with SRILT in patients with NSCLC treated with 3D-CRT, and (2) whether PF can provide additional information to the conventional model in the prediction of SRILT.

Patients and Methods

Study population

This study was based on populations pooled from two centers: Institute A and Institute B. The motivation of the pooled analysis was to increase study power and to test whether there was similar trend of results between two centers. Eligible patients had histologically proven stage I-III NSCLC, received 3D-CRT between 2001 and 2009, and had spirometry with measurements of diffusion capacity for carbon monoxide (DLCO) prior to treatment. One third of RILT events in Institute A were prospectively banked and PFTs were retrospectively collected. Institute B patients had all data collected prospectively through clinical studies. The COPD was assessed based on patient's report which was often per diagnosis of pulmonary service rather than central evaluation by a single pulmonologist. Both Institute A and Institute B studies were approved by respective Institutional Review Boards (IRB).

Treatment regimen

All patients received definitive RT with or without concurrent chemotherapy. CT-based treatment planning was applied to all patients and IV contrast CT was implemented

whenever possible. Institute A patients were simulated in treatment position under free-breathing. The majority of Institute B patients underwent simulation CT scans with respiratory motion assessment techniques and active breathing control was used when motion was larger than 1 cm for those who could tolerate it. Tumor delineation was performed using ICRU report 62 criteria (8). Mean lung dose (MLD) was computed from dose-volume histograms (DVH) for total volume of both lungs minus GTV. Tissue inhomogeneity corrections were applied on all plans. Three concurrent chemotherapy regimens were generally used in Institute A; paclitaxel and carboplatin (PC), etoposide and cisplatin (EP) and topotecan alone (TPT). All Institute B patients had uniform regimen of concurrent chemotherapy of PC.

Toxicity evaluation

In the past decades, three toxicity grading systems have been widely applied for classifying RILT; SWOG, RTOG and NCI-CTC 3.0. Although specific grading definitions differ, the presence of clinically significant pulmonary symptoms is consistently graded as 2 throughout all systems (Symptomatic RILT, SRILT). Since a substantial portion of lung cancer patients present with significant pulmonary symptoms deriving from tumor or comorbidities prior to treatment, it is often difficult to identify the true causes of post-treatment symptoms. To adjust for the influence of pre-existing symptoms on the diagnosis of SRILT, we adopted a modified criteria combining RTOG/SWOG/CTC 3.0, the details of which are described in our previous publications (5, 9). Advent of grade 2 SRILT served as the primary endpoint (non-SRILT vs. SRILT), and was defined as either new development of pulmonary symptoms, or worsening by at least one grade over pre-RT levels without evidence of tumor progression or other specific etiology.

Factors considered for SRILT risk

Baseline PF parameters included percent predicted value of forced expiratory volume at 1 second (FEV1), forced vital capacity (FVC) and diffusion capacity of lung for carbon monoxide (DLCO). Additional factors evaluated for the risk of SRILT included age, gender, smoking status, Karnofsky Performance Status (KPS), coexisting COPD, clinical stage (AJCC 6th edition), tumor location, histology, concurrent chemotherapy, MLD and physical dose.

Statistical analysis

Data were presented as mean $\pm$ standard deviation (SD) unless otherwise specified. Chi square and Mann-Whitney *U* test were adopted for general data comparison between groups. Optimal cutoff points for dichotomizing continuous variables were determined by Youden index in Receiver Operating Characteristic (ROC) analysis. Area under the curve (AUC) determined by ROC analysis was employed to evaluate the predictive ability of covariates for SRILT. AUCs between ROC curves were compared using Hanley & McNeil method. Logistic regression was used for univariate analysis of SRILT and a *p* value of 0.20 was defined as the threshold to select parameters for multivariate analysis.

Results

Patient characteristics and incidence of SRILT

Two hundred and sixty patients including 184 from Institute A and 76 from Institute B were analyzed and the general characteristics are shown in Table 1. The median follow up was 20.1 months. Among the entire population, 83% were male and the median age was 65. Twenty eight percent of patients had COPD and 91% had stage III disease. The median radiation dose was 60 Gy and one half of these patients underwent concurrent

chemotherapy. Institute B patients seemed older, more commonly presented with COPD, and more frequently treated with concurrent chemoradiation. Institute B administered higher RT dose than Institute A, largely resulting from individualized dose escalation. Both Institute A and B datasets had normal Gaussian distribution. At the last follow-up, grade 2 SRILT was observed in 25.5% (47/184), 14.5% (11/76) and 22.3% (58/260) of patients for the Institute A, B and combined dataset, respectively ($p = 0.051$). The incidence of grade 3 SRILT was 7.6% (14/184), 5.3% (4/76) and 6.9% (18/260), respectively ($p = 0.498$).

Patient and treatment factors and SRILT

Viewed as categorical data, age (65 split), physical dose (60 Gy split), gender, KPS (80 split), smoking status, stage, location, histology and concurrent chemoradiation were not correlated with SRILT. Among the entire study population, COPD patients had a lower incidence of SRILT (13.9% vs. 25.5%, $p = 0.04$). This difference was significant in the Institute B (5.1% with COPD vs. 24.3% without COPD, $p = 0.02$) but was not significant in Institute A (24.2% vs. 25.8%, $p = 0.85$).

PFT and SRILT

Baseline FEV1 and FVC data were available for all patients whereas DLCO was attainable for only 223 patients (86%). The mean FEV₁, FVC and DLCO for the pooled population were 67.2%, 76.4% and 65.0%, respectively. Institute A patients had higher FEV1 and DLCO than Institute B patients (Table 1). PFT parameters were significantly correlated with each other ($p < 0.001$).

Table 2 shows the correlation between PFTs and SRILT. In Institute A, SRILT patients had marginally higher FVC than those without SRILT (81.7% vs. 75.1%, $p = 0.054$). Similar tendency was also seen with respect to FEV1 (73.4% vs. 69.5%, $p = 0.245$) and DLCO (70.4% vs. 66.6%, $p = 0.222$), though the differences were not statistically significant. Institute B data also showed a higher FEV1 for SRILT group (64.5% vs. 58.3%, $p = 0.348$). In the pooled population, patients with SRILT had marginally higher FEV1 than those without (71.7% vs. 65.9%, $p = 0.077$). Likewise, SRILT patients seemed to have higher FVC or DLCO than non-SRILT patients, though the difference did not reach significant level. Under ROC analysis, the optimal cutoff points for FEV1, FVC and DLCO were 65.1%, 72.1% and 65.8%, respectively. Using these discriminators to dichotomize entire patients into respective groups, all SRILT groups showed significant better PF than corresponding non-SRILT groups. Table 3 showed that no significant PFTs difference between grade 3 and grade < 3 SRILT groups.

Correlation between MLD and SRILT

MLD data were available for 247 patients. The median MLD was 15.3 Gy, 14.6 Gy and 15.1 Gy for Institute A, B and the combined population ($p = 0.52$). SRILT patients from Institute A received higher mean MLD than non-SRILT patients (16.8 Gy vs. 14.5 Gy, $p = 0.001$), whereas no significant difference was seen among Institute B patients (14.6 Gy vs. 14.8 Gy, $p = 0.829$). In the combined cohort, MLD was significantly associated with SRILT (16.4 Gy for SRILT vs. 14.8 Gy for non-SRILT, $p = 0.004$). Based on the 17.4 Gy cutoff identified by ROC, the incidence of SRILT was 17.6% and 38.7% for low and high MLD groups ($p = 0.001$).

Univariate analysis

Table 4 displays results of univariate analysis of patient and treatment related factors. PFTs and dosimetric indices were analyzed as continuous variables while other factors were analyzed as categorical covariates. Age, gender, histology, location, total radiation dose and

use of concurrent chemotherapy were not significantly correlated with the development of SRILT. Compared to non-chemotherapy, various chemo-regimens were not associated with SRILT. The rates of SRILT for non-chemo, PC, EP and TPT alone (only 10 patients) were 25.0%, 15.3%, 29.2% and 40.0%, respectively ($p = 0.12$).

MLD and COPD were significantly, while FEV1 was marginally correlated with the occurrence of SRILT. Risk of SRILT escalated with the increase of MLD and FEV1 as well as the absence of COPD. As a single factor to predict the probability of SRILT, MLD and FEV1 had AUC of 0.63 [95% confidence interval (CI), 0.56 to 0.69] and 0.58 (95% CI, 0.50 to 0.66), respectively ($p = 0.43$).

Figure 1 shows the relationship between baseline FEV1 and MLD, indicating no significant linear correlation between these two parameters ($R^2 = 0.01$). Survival analysis demonstrated that better baseline FEV1, as either a continuous ($p = 0.04$) or a binary (65% cutoff, $p = 0.03$) variable, had a significant correlation with prolonged overall survival. There was no significant difference in follow-up ($p = 0.26$) or survival ($p = 0.3$) between SRILT and non-SRILT groups.

Multivariate analysis

Under multivariate analysis including MLD and PF parameters as continuous variables, age (65 split) and MLD were significantly associated with SRILT, with odds ratios (OR) of 2.95 (95% CI, 1.41 to 6.18) and 1.13 (95% CI, 1.02 to 1.25), respectively. Under multivariate analysis viewing MLD (17.4 split) and PF parameters (optimal cutoffs split determined by ROC) as categorical variables, age (OR = 2.89) and MLD (OR = 3.59) still presented significant correlation with SRILT. Neither analysis indicated significant correlation between PF parameters and SRILT.

Based on 247 patients with complete data, ROC curves in figure 2 displayed that the addition of age to MLD based model did not enhance the predictability for SRILT (AUC 0.63 vs. 0.64, $p = 0.65$). However, the combination of age and the dichotomized MLD (17.4 Gy split) and FEV1 (65% split) can marginally improve the predictive efficacy of SRILT than that of MLD alone (AUC = 0.70, $p = 0.088$).

Risk stratification of SRILT

Two hundred and forty seven patients with complete data of age and MLD were stratified into three risk groups; low risk (age ≤ 65 and MLD ≤ 17.4 Gy $n = 97$), moderate risk (age > 65 or MLD > 17.4 Gy, $n = 122$) and high risk (age > 65 and MLD > 17.4 Gy, $n = 28$), corresponding to the SRILT incidence of 16.5%, 20.5% and 53.6%, respectively ($p < 0.001$). The addition of FEV1 (65% split) could further distinguish patients with lowest SRILT risk from those with higher probability of SRILT, resulting in an incidence of 8.3% for the abovementioned low risk subgroup with FEV1 $< 65\%$ and 57.1% for the high risk subgroup with FEV1 $\geq 65\%$ ($p < 0.001$).

Discussion

In this combined analysis, we investigated the effect of patient and treatment related factors on the development of SRILT in NSCLC patients treated with CRT. As expected, age and MLD served as robust predictors for SRILT. In contrast to conventional thinking, poor PF did not increase the risk of SRILT in this large cohort of patients from two institutions.

PFTs have been investigated in numerous studies for their ability to predict risk of SRILT. A few studies reported better baseline PFTs predicted lower risk of SRILT whereas some studies did not show any correlation between PFTs and SRILT (10-13). However, it should

be noted that these studies involved relatively small cohorts of patients and lacked baseline symptoms for comparison. To the best of our knowledge, the present study included the largest number of patients with complete PFT data. Under our modified SRILT criteria, we found that patients with lower pre-RT PF did not increase the risk of SRILT. Interestingly, lower FEV1 may be associated with reduced risk of SRILT. To some extent this was consistent with findings of an early prospective study, which reported that patients with better (> 50%) baseline FEV1 tended to lose significant PF after RT, while most of those with poor FEV1 prior to RT underwent only a mild decrease or even an improvement in PF (14). This phenomenon may be explained by the following hypotheses. First, better PF is subject to higher level of cellular oxygenation, which might result in greater radiation sensitivity of alveolar cells and more significant lung injury. Our functional imaging study observed a similar phenomenon that single photon emission computed tomography (SPECT) based ventilation and perfusion function decreased remarkably after 45Gy of RT in initially functional regions whereas improved in previously defective regions (15). Second, patients with poor baseline PF are more likely to experience significant pulmonary symptoms prior to treatment. For those whose symptoms have already reached or approached a nadir, the post-RT score would be less likely to decrease by one grade, therefore SRILT could not be diagnosed on our criteria. Third, bronchial obstruction or compression by tumor is a common cause of low FEV1 level. Tumor shrinkage after treatment could alleviate airway occlusion and improve ventilation function, which may translate into symptom lessening (16). Forth, most of the patients in this cohort with low FEV1 were probably emphysema patients, though we did not grade the emphysema score for every single patient. Since emphysema is anatomically equivalent to the lack of lung tissue, one would expect less risk of lung toxicity if there is less lung tissue to injure. It would be logical to further categorize patients by potential causes of low FEV1 and investigate whether greater radiographic emphysema is resistant to SRILT.

Numerous studies have investigated the predictive efficacy of other clinical factors on the risk of SRILT, though an effective model has not been achieved. Patient related characteristics such as age, gender, smoking status, KPS and tumor location (4, 7, 10) have been reported to be associated with the development of SRILT. Treatment factors including chemotherapy, radiation dose, normal tissue complication probability (NTCP) and DVH metrics (6, 13, 17, 18) showed association with SRILT as well. Nonetheless, most of these factors have not been consistently demonstrated across studies. In our study, no relationship was detected between SRILT and the factors of: gender, smoking status, KPS, stage, tumor location, histology, physical RT dose and concurrent chemotherapy.

Since the introduction of 3D-CRT planning, DVH metrics have been extensively investigated and reported to be associated with SRILT. As for conventional dose delivery, MLD seems to be the most widely recognized and definite SRILT related parameter. By reviewing 12 publications assessing the relationship between DVH and radiation pneumonitis, Rodrigues et al. summarized that MLD provided more consistent results across studies in terms of raising SRILT rate with increasing MLD bin/quartile (OR, 2.02 to 5.66) than Vdose (OR, 1.41 to 13.2) and NTCP (OR, 1.93 to 11.18) (19). Previously, by pooling data from 5 SRILT studies, our group generated a MLD-based exponential formula for SRILT prediction and yielded a R^2 of 0.82, corresponding to the sigmoid shape of the dose-response relationship (6). Considering the dramatic linear correlation between Vdose and MLD, we selected MLD as the representative DVH parameter for the risk of SRILT and verified that MLD was a robust predictor among patient and treatment specific factors. In recent years, dose-escalation RT has emerging as a promising direction for NSCLC treatment. Current RT dose prescription is often individualized to a fixed lung dose limit causing most of the patients to have similar lung dosimetry such as MLD, which consequently mitigates the predictive value of dosimetric indices. Under such

circumstances, patient-based factors including general characteristics, biological markers as well as functional imaging parameters may play more important roles in the prediction of SRILT.

Considering the possible bias that physicians may reduce total dose delivery or assign more stringent constraints in lung for patients with poor PF, we examined the correlation between PFTs and MLD to determine whether the effect of FEV1 on SRILT was actually explained by its association with MLD. Our scatter plot did not show a significant correlation between FEV1 and MLD, indicating that there was no interaction between the two factors. As expected, in the present study, lower FEV1 was correlated with worse OS. However, SRILT correlated with neither follow-up time nor the OS, indicating that the follow-up time or survival was not a competing factor for the relationship between FEV1 and SRILT.

There are several limitations in this study. Some data from Institute A were retrospectively reviewed and inevitably subject to multiple biases. Even though we used relatively objective criteria for SRILT, there was no central case review and the determination of SRILT was mainly dependent on records per treating physician's individual assessment.

Conclusions

In summary, in 260 patients with complete baseline pulmonary function data from two centers, age and MLD were independently correlated with SRILT. Lower baseline pulmonary function did not increase the risk of SRILT and might even be associated with lower probability of SRILT, which suggested that poor PF should not be a contraindication to definitive RT. The addition of FEV1 may help improve the risk prediction for SRILT.

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Figure 1.
Individual based scatter plot indicates no linear correlation between MLD and FEV1.

	AUC	95% CI	P value comparing to MLD
MLD	0.63	0.56 to 0.69	---
MLD+AGE(65)	0.64	0.58 to 0.70	0.654
MLD(17.4)+AGE(65)+FEV1(65%)	0.70	0.64 to 0.75	0.088
AGE 65 = dichotomizing age using 65 as cutoff; MLD17.4 = dichotomizing MLD using 17.4 Gy as cut off; FEV1r = dichotomizing FEV1 using 65% as cut off.			

Figure 2.
The combination of age, FEV1 and MLD displays mild improvement in prediction of SRILT as compared with MLD alone.

Summary of patient characteristics

Table 1

Characteristic	No. of patients	Pooled dataset	Institute A	Institute B	p
Age (median, range)	260	65 (25, 88)	64(25, 88)	68 (43, 87)	0.001 [†]
Gender (male/female)	260	217/43	157/27	60/16	0.208 [†]
Smoking history (yes/no)	260	199/61	137/47	62/14	0.218 [†]
KPS (80 vs. <80)	253	212/41	154/30	58/11	0.944 [†]
COPD (yes/no)	260	72/188	33/151	39/37	<0.001 [†]
Stage (I/II/III)	260	15/8/237	0/0/184	15/8/53	<0.001 [†]
Histology (SCC vs. Adeno vs. Others)	258	141/53/64	120/40/24	21/13/40	<0.001 [†]
Location (upper [#] vs. lower)	239	181/58	138/44	43/57	0.953 [†]
Concurrent chemotherapy regimen (no vs. PC vs. EP vs. TPT)	260	128/98/24/10	107/43/24/10	21/55/0/0	<0.001 [†]
FEV1	260	67.2±22.0	70.5±20.4	59.2 ± 23.9	<0.001 [*]
FVC	260	76.4±18.8	76.8±18.7	75.4± 19.0	0.391 [*]
DLCO	223	65.0 ± 20.0	67.6 ± 19.5	58.6 ± 19.8	0.001 [*]
Physical dose (Gy)	259	62.6 ± 6.5	61.0 ± 5.0	66.5 ± 8.1	<0.001 [*]
MLD (Gy)	247	14.5 ± 3.9	14.7 ± 3.3	14.0 ± 5.0	0.518 [*]

Abbreviations: PUMC = Peking Union Medical College Cancer Hospital; UMMC = University of Michigan Medical Center; KPS = Karnofsky performance status; COPD = chronic obstructive pulmonary disease; SCC = squamous cell carcinoma; Adeno = adenocarcinoma; PC = Paclitaxel and carboplatin; EP = etoposide and cisplatin; TPT = topotecan alone; FEV1 = percent predicted value of forced expiratory volume at 1 second; FVC = percent predicted value of forced vital capacity; DLCO = diffusion capacity of lung for carbon monoxide; MLD = mean lung dose.

[#] Including both upper and middle lobes for right lung.

^{*} Results from Mann-Whitney *U*-test.

[†] Results from Chi-square test.

Table 2
Correlation between PFTs and G2 SRILT

Institutions	G2 SRILT	< G2 SRILT	<i>p</i> [*]
Institute A			
FEV1	73.4 ± 19.5	69.5 ± 20.7	0.245
FVC	81.7 ± 18.2	75.1 ± 18.7	0.054
DLCO	70.4 ± 21.3	66.6 ± 18.8	0.222
Institute B			
FEV1	64.5 ± 21.1	58.3 ± 24.4	0.348
FVC	70.1 ± 15.0	76.4 ± 19.5	0.408
DLCO	59.9 ± 14.1	58.4 ± 20.7	0.352
Pool			
FEV1	71.7 ± 20.0	65.9 ± 22.5	0.077
FEV1 < 65.1%	15.4%	84.6%	0.015
FEV1 65.1%	28.0%	72.0%	
FVC	79.5 ± 18.1	75.5 ± 18.9	0.180
FVC < 72.1%	15.5%	84.5%	0.023
FVC 72.1%	27.3%	72.7%	
DLCO	68.3 ± 20.4	64.0 ± 19.7	0.136
DLCO < 65.8%	16.4%	83.6%	0.016
DLCO 65.8%	29.9%	70.1%	

Abbreviations: FEV1 = percent predicted value of forced expiratory volume at 1 second; FVC = percent predicted value of forced vital capacity; DLCO = diffusion capacity of lung for carbon monoxide.

* Results from Mann-Whitney *U* test.

Table 3
Correlation between PFTs and G3 RILT

Institutions		G3 SRILT	< G3 SRILT	<i>p</i>[*]
Institute A				
	FEV1	75.1±19.0	70.1±20.5	0.343
	FVC	84.7±18.3	76.1±18.7	0.051
	DLCO	66.6±29.5	67.7±18.4	0.942
Institute B				
	FEV1	72.8±24.4	58.5±23.8	0.314
	FVC	66.8±18.4	75.9±19.0	0.325
	DLCO	54.3±11.1	58.9±20.1	0.757
Pool				
	FEV1	74.6±19.6	66.6±22.2	0.109
	FVC	80.7±19.4	76.1±18.7	0.232
	DLCO	64.3±27.2	65.1±19.3	0.947

Abbreviations: FEV1 = percent predicted value of forced expiratory volume at 1 second; FVC = percent predicted value of forced vital capacity; DLCO = diffusion capacity of lung for carbon monoxide.

* Results from Mann-Whitney *U* test.

Table 4
Logistic regression for analytical variables

Factors	OR	P
Actual age	1.010	0.442
FEV1	1.012	0.077
FVC	1.011	0.156
DLCO	1.011	0.174
Physical dose (Gy)	0.995	0.813
MLD (Gy)	1.126	0.008
Institutions (PUMC vs. UM)	0.493	0.051
Age (< 65 vs. ≥ 65)	1.501	0.175
Gender (male vs. female)	0.515	0.156
KPS (≥ 80 vs. < 80)	0.571	0.571
Smoking history (no vs. yes)	0.845	0.625
Coexisting COPD (no vs. yes)	0.470	0.047
Stage (I vs. II vs. III)	2.167 (II)/1.918 (III)	0.488 (II)/0.401 (III)
Histology (SCC vs. Adeno vs. Others)	0.984 (adeno)/0.561 (others)	0.966 (adeno)/0.144 (others)
Location (upper [#] vs. lower)	1.191	0.616
Concurrent chemotherapy (no vs. yes)	0.736	0.305
Chemotherapy regimen (no vs. PC vs. EP vs. TPT)	0.542 (PC)/1.235 (EP)/2.000 (TPT)	0.078 (PC)/0.668 (EP)/0.306 (TPT)

Abbreviations: OR = odds ratio; KPS = Karnofsky performance status; COPD = chronic obstructive pulmonary disease; SCC = squamous cell carcinoma; Adeno = adenocarcinoma; PC = Paclitaxel and carboplatin; EP = etoposide and cisplatin; TPT = topotecan alone; FEV1 = percent predicted value of forced expiratory volume at 1 second; FVC = percent predicted value of forced vital capacity; DLCO = diffusion capacity of lung for carbon monoxide; MLD = mean lung dose.

[#]Including both upper and middle lobes for right lung.