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Dose–volume thresholds and smoking status for the risk of treatment-related pneumonitis in inoperable non-small cell lung cancer treated with definitive radiotherapy[☆]

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Abstract

Purpose—To identify clinical risk factors and dose–volume thresholds for treatment-related pneumonitis (TRP) in patients with non-small cell lung cancer (NSCLC).

Methods and materials—Data were retrospectively collected from patients with inoperable NSCLC treated with radiotherapy with or without chemotherapy. TRP was graded according to Common Terminology Criteria for Adverse Events, version 3.0, with time to grade ≥ 3 TRP calculated from start of radiotherapy. Clinical factors and dose–volume parameters were analyzed for their association with risk of TRP.

Results—Data from 576 patients (75% with stage III NSCLC) were included in this study. The Kaplan–Meier estimate of the incidence of grade ≥ 3 TRP at 12 months was 22%. An analysis of dose–volume parameters identified a threshold dose–volume histogram (DVH) curve defined by V_{20} 25%, V_{25} 20%, V_{35} 15%, and V_{50} 10%. Patients with lung DVHs satisfying these

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constraints had only 2% incidence of grade ≥ 3 TRP. Smoking status was the only clinical factor that affected the risk of TRP independent of dosimetric factors.

Conclusions—The risk of TRP varied significantly, depending on radiation dose–volume parameters and patient smoking status. Further studies are needed to identify biological basis of smoking effect and methods to reduce the incidence of TRP.

Keywords

Treatment-related pneumonitis; Non-small cell lung cancer; Smoking; Dose; volume histogram

Lung cancer has the highest incidence and mortality rate of all cancers in the United States [1], and patients often have advanced-stage disease at the time of diagnosis. The standard of care for locoregionally advanced non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy. However, treatment success is constrained by poor local control and post-therapy toxicity. Treatment-related pneumonitis (TRP) is one of the most commonly occurring adverse effects because lung tissue is extremely sensitive to radiation and possibly chemotherapy.

Numerous studies have investigated predictive factors for TRP and identified clinical factors that may influence risk, including performance status [2], pulmonary function before radiotherapy [2], chronic obstructive pulmonary disease (COPD) [3], tumor location [4], concurrent chemotherapy [4], total radiation dose [5], dose per fraction [5], smoking status [6] and induction chemotherapy with mitomycin [3]. In addition, many studies have shown that dosimetric factors from the lung dose–volume histogram (DVH), such as the mean lung dose (MLD) [6–13] and the percent lung volume receiving more than a threshold radiation dose (V_{Dose}) [6,9–10,12,14–18], are important in predicting TRP risk.

In earlier publications [19,20], we evaluated the risk of grade ≥ 3 TRP in patients with inoperable NSCLC who received three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) concurrently with platinum-based chemotherapy at The University of Texas M.D. Anderson Cancer Center (UTMDACC). None of the clinical factors investigated were found to be associated with the risk of TRP. However, numerous dosimetric factors, including MLD and V_5 – V_{65} , the lung volumes treated to doses higher than 5–65 Gy (in increments of 5 Gy), were significantly associated with the incidence of severe TRP. These dosimetric factors were shown to be highly correlated with one another ($p < 0.0001$) [19,20], making it challenging to determine the relative importance of the individual parameters.

As a sequel to our previous work, we expanded our dataset to include patients with NSCLC who were treated with definitive chemoradiotherapy more recently, as well as patients treated with radiotherapy with or without chemotherapy. In the combined dataset, we sought to further assess patient-, disease-, and treatment-related factors for potential associations with TRP, with the goal of developing treatment-planning guidelines to help curtail the incidence of TRP. To our knowledge, this is the largest study, to date, of TRP risk among patients with lung cancer receiving radiotherapy without surgery. Using this large cohort, we

have identified a “threshold” DVH associated, in our patient population, with a very low risk of TRP after definitive radiotherapy for NSCLC.

Methods and materials

Patients

We retrospectively reviewed the medical and radiation records of patients with NSCLC who had radiotherapy at UTMDACC between 1999 and 2005. The inclusion criteria were as follows: newly diagnosed and pathologically confirmed NSCLC; treatment without surgery; radiotherapy with either definitive 3D-CRT or IMRT with or without chemotherapy; lung DVH recoverable from institutional archives; and available radiographic images and symptom assessments for determining the occurrence and grade of TRP.

Patients were excluded if they had an unknown stage of NSCLC, unspecified chemotherapy regimen, a treatment break of more than 7 days during radiotherapy, or a total radiation dose of <50.4 Gy. These inclusion and exclusion criteria were similar to those used in our previous studies [19,20] except that the earlier studies included only patients receiving concurrent chemoradiation. This study was approved by the UTMDACC institutional review board.

Treatment

All patients had radiotherapy simulation on regular or four-dimensional (4D) computed tomography (CT) simulators in a supine position and were immobilized with a T-bar, wing board, and customized Vac-lock cradle. CT scans were obtained with 3-mm-thick slices from the mandible to lower edge of the liver. When 4D-CT simulation was used, respiratory cycles were monitored and recorded using a real-time position-management system (Varian Oncology Systems, Palo Alto, CA).

The gross tumor volume (GTV) was defined as the total volume of the primary and nodal tumor masses visualized on any radiographic image. For patients who did not have 4D-CT, the clinical target volume (CTV) was defined as the GTV plus a 0.8-cm margin, and the planning target volume (PTV) as the CTV plus a 1- to 1.5-cm margin to account for setup uncertainty and respiratory motion. With 4D-CT, the internal target volume (ITV) encompassed the CTV on all phases of each respiratory cycle evaluated by the 4D-CT simulation scan, and the PTV was the ITV plus a 0.8-cm margin. The regional lymph nodes were not electively irradiated. All patients' treatment plans were designed with a commercial treatment-planning system (Pinnacle, Philips Medical Systems, Andover, MA) to deliver the prescribed dose to 95% of the PTV. For 3D-CRT, four or five fields were usually used in the treatment plans, typically anterior–posterior beams in combination with oblique beams. In IMRT plans, five to seven beam angles were usually used for dose optimization. With a few exceptions, fraction sizes were 1.2 Gy for twice-daily treatment and 1.8–2.0 Gy for once-daily irradiation. A tissue heterogeneity correction was applied to all dose calculations using a convolution/superposition algorithm.

Patients' chemotherapy regimens, if any, were determined by attending medical oncologists according to institutional standards.

DVH parameters

Normal lung was defined as the total lung excluding GTV, trachea, and main bronchi. DVHs for normal lung were computed from the 3D dose distributions and were exported from treatment plans. The percentages of lung volume that received more than a threshold dose of radiation (V_{Dose}) were calculated, where the values of threshold dose ranged from 5 to 75 Gy in increments of 5 Gy (V_5 to V_{75}).

Evaluation of TRP

All patients were examined weekly by their attending radiation oncologist during radiotherapy and 4–6 weeks after completing treatment. Patients were then examined every 3 months for the first 3 years and every 6 months thereafter unless they had symptoms that required immediate examination and/or intervention. Chest radiographic examination was performed at each follow-up visit after treatment. For this analysis, we reviewed all relevant clinical notes that were dictated by attending physicians and all radiographic images for every patient. TRP was diagnosed according to clinical symptoms and any of the following radiographic abnormalities: ground-glass opacity, attenuation, or consolidation changes within the radiation field. TRP was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 [21], as follows: pneumonitis was considered grade 3 when it was symptomatic and interfered with daily activities or when the patient required oxygen, grade 4 when the patient required assisted ventilation, or grade 5 if the patient died from TRP.

Statistical analysis

The end point for this analysis was grade ≥ 3 TRP. Time to grade ≥ 3 TRP was calculated from start of radiotherapy and was censored at last follow-up for patients not experiencing the end point. Kaplan–Meier analysis was used to calculate freedom from TRP in subgroups as a function of time. Incidence levels of TRP were calculated as 1 minus the Kaplan–Meier estimate of freedom from TRP.

The log-rank test was used to perform univariate analyses of differences in time to grade ≥ 3 TRP in subgroups of patients defined by patient-related factors (age, sex, smoking history, COPD, cardiovascular disease, and Karnofsky performance status), disease-related factors (tumor histology, location, and stage), treatment-related factors (radiation dose, number of dose fractions per day, and induction or concurrent chemotherapy), and radiation technology factors (4D-CT simulation and treatment with IMRT), collectively referred to as clinical factors. For the subset of patients who had pulmonary function tests (PFTs) prior to radiotherapy, univariate analyses were also performed to assess the relationship between FVC, FEV1 and DLCO and freedom from severe TRP. Multivariate analyses were performed using the Cox proportional hazards model. The Kruskal–Wallis test was used to investigate differences in the results of pre-radiotherapy PFTs by patient smoking status.

Log-rank analyses were also performed to test the association between TRP and a grid of dose–volume parameters from DVH curves. Specifically, for choices of threshold dose (Dose) and percent lung volume (% V), freedom from TRP was compared in subsets of patients with $V_{\text{Dose}} \leq \% V$ versus $V_{\text{Dose}} > \% V$. Threshold doses ranged from 5 Gy (V_5) to 75

Gy (V_{65}) in increments of 5 Gy, and lung volumes (% V) ranged from 5% to 95% in increments of 5%. Analyses were limited to those DVH points for which there were ≥ 25 patients in each patient subgroup to ensure robustness of the results. To limit the possibility of finding spurious significant associations because of the large number of analyses performed, a Bonferroni correction was applied to the nominal p -values; comparisons were considered significant only if p was $< 0.05/n$, where n was the total number of dose–volume parameters tested.

Results

Patient characteristics and univariate analyses of clinical factors

We identified 576 eligible patients for this study, including 291 patients from our previous analyses [19,20]. The crude incidence of grade ≥ 3 TRP in this cohort was 117 (20%); six of these were grade 4, and 3 were grade 5. The Kaplan–Meier estimate of incidence of grade ≥ 3 TRP at 12 months was 22% (95% confidence interval [CI], 19–26%). No cases of grade ≥ 3 TRP occurred later than 10 months after initiation of radiotherapy.

Table 1 shows the distribution of clinical and patient factors and their association with time to grade ≥ 3 TRP. The factor most strongly associated with TRP was smoking status. Patients who had never smoked (“non-smokers”) had the highest incidence of grade ≥ 3 TRP (37% at 1 year; 95% CI, 24–53%), whereas patients who reported being smokers at the time of diagnostic workup (“smokers”) had the lowest incidence (14% at 1 year; 95% CI, 9–20%). Individuals who had stopped smoking before diagnosis (“former smokers”) had an intermediate incidence of TRP (23% at 1 year; 95% CI, 19–28%). Other factors associated with significantly lower incidence of TRP by univariate analysis were negative node status, use of 4D-CT simulation, and treatment with IMRT. Pre-radiotherapy PFT values, which were available for only a subset of the patients, were not significantly associated with differences in the risk of severe TRP, and were also found not to vary significantly with patient smoking status.

Dose–volume parameters

Fig. 1 shows the results of a comprehensive analysis of DVH parameters. Each symbol represents a dose–volume combination (Dose, % V) for which freedom from grade ≥ 3 TRP was compared in the patient subgroups with $V_{\text{Dose}} \leq \% V$ versus $V_{\text{Dose}} > \% V$. Comparisons were performed only if the corresponding subsets included at least 25 patients each.

Points marked with an “x” in Fig. 1 represent dose–volume combinations for which freedom from grade ≥ 3 TRP was not significantly different in the corresponding patient subgroups (e.g., $V_5 \leq 50\%$ versus $V_5 > 50\%$, $p = 0.166$). Open circles represent comparisons that were significant at the $p < 0.05$ level (e.g., $V_{10} \leq 40\%$ versus $V_{10} > 40\%$, $p = 0.015$). Closed circles represent comparisons that remained significant if a stricter criterion of $p < 0.00056$ ($= 0.05/89$) was used to define statistical significance, as required by a Bonferroni adjustment of the p -value to take into account the multiple ($n = 89$) analyses performed. For example, the comparison between patients with $V_{40} \leq 15\%$ and patients with $V_{40} > 15\%$ ($p = 0.00004$) met this strict criterion.

Fig. 1 shows that multiple dose–volume parameters were significantly associated with differences in freedom from grade ≥ 3 TRP. Of interest, the lower “edge” of the set of solid symbols in Fig. 1 traces a “threshold DVH” ranging from 20 to 65 Gy. In Fig. 2, a curve is drawn (curve A) connecting the most stringent of these DVH constraints: $V_{20} \leq 25\%$, $V_{25} \leq 20\%$, $V_{35} \leq 15\%$, and $V_{50} \leq 10\%$. The incidence of TRP among patients whose DVHs met these stringent constraints (Group A) was extremely low (2% at 1 year), as shown in Fig. 3. When the constraints were relaxed by 10% each, i.e., $V_{20} \leq 35\%$, $V_{25} \leq 30\%$, $V_{35} \leq 25\%$, and $V_{50} \leq 20\%$, as illustrated in Fig. 2 by curve B, the incidence of grade ≥ 3 TRP among patients meeting these constraints but not the more stringent constraints (Group B) was 16% (Fig. 3). As the constraints were relaxed still further by another 10%, i.e., $V_{20} \leq 45\%$, $V_{25} \leq 40\%$, $V_{35} \leq 35\%$, and $V_{50} \leq 30\%$ (curve C in Fig. 2), the 1-year incidence of TRP in patients whose DVHs met these constraints but not the previous ones (Group C) was 25%. Patients whose lung DVHs violated one or more of the constraints defined by curve C (Group D) had a 1-year incidence of grade ≥ 3 TRP of 36%.

Multivariate analyses

To investigate whether the effects of smoking status and other important clinical factors could be explained by their association with dose–volume effects, we performed a multivariate analysis in which clinical factors were considered as candidate factors in addition to DVH groups A–D defined above (Figs. 2 and 3). Smoking status retained significance independent of dose–volume effects; Table 2 lists Kaplan–Meier estimates of the 1-year incidence of grade ≥ 3 TRP in subgroups of patients according to smoking status and DVH. However, 4D-CT and IMRT were not significant after taking dose–volume parameters into account, suggesting that these clinical factors may have influenced the risk of TRP through associated DVH effects.

Chemotherapy

Of the 576 patients, 92 received radiotherapy alone, 63 received induction chemotherapy without concurrent radiotherapy, 260 received concurrent chemoradiation without induction therapy, and 157 received induction therapy and concurrent chemoradiotherapy. The numbers of patients in these groups who subsequently received adjuvant chemotherapy were 4, 3, 37, and 23, respectively. Carboplatin plus taxane was the most common regimen used for concurrent chemotherapy (238 of 417 [57%]), followed by cisplatin plus etoposide (14%).

By univariate analyses, we found no evidence that either induction chemotherapy or concurrent chemotherapy affected the risk of grade ≥ 3 TRP (Table 1). In multivariate analyses, there was still no detectable effect from either induction or concurrent chemotherapy after accounting for dose–volume effects and/or smoking status.

Although the number of patients treated with adjuvant chemotherapy was small, univariate and multivariate analyses showed no association of this factor with risk of grade ≥ 3 TRP. The effect of adjuvant chemotherapy was also investigated in patients who survived at least 3.5 months after starting radiotherapy. This analysis was performed to avoid the possibility of selection bias, since patients with shorter survival would not have received adjuvant

chemotherapy, which is typically started 4–6 weeks after completion of radiotherapy. However, there was still no detectable effect of adjuvant chemotherapy by either univariate or multivariate analysis.

Finally, we also investigated the effects of specific chemotherapeutic agents: cisplatin, carboplatin, etoposide, gemcitabine or taxanes. However, none of these agents, given as part of either induction or concurrent therapy, was found to be significantly associated with the risk of severe TRP.

Discussion

This study was an extension of our previous investigations of the incidence of TRP among patients with NSCLC [19,20]. The present study comprised a much larger number of patients ($N = 576$) treated with or without chemotherapy over a span of 7 years. Consistent with published results from our own and other institutions, our present analyses indicate that radiation dose–volume parameters are significantly associated with the risk of TRP. Furthermore, we found smoking status to be predictive of differences in risk of severe TRP, independent of dosimetric effects.

In our previous study [19], we noted very high correlations among relative volumes of lung exposed to various dose thresholds. In this study, we therefore investigated a comprehensive list of DVH parameters rather than individual dose–volume constraints. Our results indicate that if lung DVH met a set of “threshold” constraints, i.e., $V_{20} \geq 25\%$, $V_{25} \geq 20\%$, $V_{35} \geq 15\%$, and $V_{50} \geq 10\%$, the incidence of grade ≥ 3 TRP was extremely low – only 2% at 1 year. Until the effects of different dose levels on lung toxicity are better understood, we propose using the shape of the DVH curve, rather than a single point on DVH, to limit incidence of TRP.

We previously identified V_5 as an important predictive factor for TRP [19]. The dose constraint of V_5 , in addition to MLD ≥ 20 Gy and $V_{20} \geq 35\%$, has been incorporated into the evaluation criteria for clinical acceptability of a treatment plan at our institution. With updated information from the current study, we believe an optimal treatment plan should result in a lung DVH curve defined by multiple dose–volume constraints including V_{20} , V_{25} , V_{35} , and V_{50} , along with MLD. However, we expect that the proposed DVH constraints will be essentially equivalent to defining a sequence of MLD constraints. Our current clinical constraint is MLD = 20 Gy; the average (standard deviation) MLD for patient groups A–D defined in Fig. 3 is 8.3 (± 2.9), 16.1 (± 2.6), 22.3 (± 2.2) and 28.3 (± 3.7) Gy, respectively. However, we realize that our study is a single institution retrospective analysis and the findings need to be validated using other comparable dataset(s) from other institution(s).

Besides dose–volume effects clearly other clinical and biologic factors play a role in pulmonary complications. Although earlier studies have suggested a link between TRP and smoking status [6,22,23], data from our cohort more conclusively illustrate the association. The results should in no way be taken to encourage patient smoking; rather, further investigations on underlying causes for the smoking effect should be undertaken. Possible explanations include a decreased inflammatory reaction among smokers [22,23]; smoking-associated hypoxia; effect of glutathione in preventing oxidant injury to the lungs [24–26]; a

compromised capacity to repair DNA damage in non-smoking patients who develop lung cancer, predisposing them to increased lung toxicity after radiotherapy [27], or differences in tumor location, and hence lung sensitivity, between smokers and non-smokers. The subjectivity of the toxicity grading system may also play a role; because smokers frequently have a history of cough or COPD, they may be less likely to notice and report symptoms of TRP than non-smokers and former smokers. This possibility underscores the importance of developing more quantitative and objective methods of measuring TRP, such as by use of imaging studies of lung function.

Our study did not identify any effects of chemotherapy on risk of TRP, although this subject is highly controversial. In breast cancer patients, for example, tamoxifen, oxaliplatin, and paclitaxel have been found to enhance the effects of radiation in inducing lung injury [28]. In our recent study of patients with esophageal cancer treated with concurrent radiotherapy and chemotherapy, induction chemotherapy was associated with an increased rate of pneumonitis [29]. Possibly, the conflicting results can be explained by the doses of radiation and/or chemotherapy used. The radiation dose administered in breast and esophageal cancers (45–50 Gy) is lower than that used in treating NSCLC, which leads to a reduced dose–volume of treated lung and reduced incidence of TRP; in such patients, therefore, the adverse effects of chemotherapy might be more evident than the effects of radiation. In addition, different chemotherapeutic agents are likely to affect the risk of TRP differently. However, in our patient cohort, with carboplatin plus taxanes and cisplatin plus etoposide being the most common chemotherapeutic regimens, we were not able to detect any differences in TRP rates among agents.

Because of changes in radiotherapy technology in the past 5 years, a number of patients with NSCLC have undergone 4D-CT simulation and IMRT. Although the number of patients in this study was small, the effects of using these new technologies on reducing risk of TRP were apparent and consistent with the findings of an earlier report [20]. Further investigations are being carried out at our institution to confirm the effect of technologic advancement using IMRT and 4D-CT on outcomes in patients with locally advanced NSCLC.

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Fig. 1.

Dose–volume histogram (DVH) parameters tested for their ability to define patient cohorts with different rates of grade ≥ 3 pneumonitis. Open circles represent DVH parameters for which freedom from TRP was significantly different ($p < 0.05$) in the patient subgroups with $V_{\text{Dose}} \leq \% V$ versus $V_{\text{Dose}} > \% V$. Closed circles represent dose–volume combinations that remained significant when a stricter criterion of $p < 0.00056 = 0.05/89$ was used to determine statistical significance, as required by a Bonferroni adjustment of the p -value to take into account the 89 analyses performed. Dose–volume combinations marked with “x” indicate a comparison (≥ 25 patients per group) that did not reach statistical significance ($p \geq 0.05$).

Fig. 2.

Dose-volume histogram (DVH) constraints. Curve A: The most stringent set of lung DVH constraints, with V_{20} 25%, V_{25} 20%, V_{35} 15%, and V_{50} 10%. Curve B: Constraints of curve A relaxed by 10% each: V_{20} 35%, V_{25} 30%, V_{35} 25%, and V_{50} 20%. Curve C: Constraints of curve B relaxed by a further 10% each: V_{20} 45%, V_{25} 40%, V_{35} 35%, and V_{50} 30%.

Fig. 3.

Freedom from grade ≥ 3 treatment-related pneumonitis in patients stratified by the lung dose-volume histogram (DVH) constraints defined by curves A–C defined in Fig. 2. Group A: Patients with lung DVHs satisfying the constraints of curve A. Group B: Patients with DVHs satisfying the constraints of curve B but not of curve A. Group C: Patients with DVHs satisfying the constraints of curve C but not of curve B. Group D: Patients whose DVHs fail to meet one or more of the constraints of curve C.

Table 1

Distribution of clinical and patient factors and their association with freedom from grade ≥ 3 treatment-related pneumonitis

Characteristic	No. of patients (%) (N = 576)	p-Value
<i>Age (y)</i>		0.943
60	190 (33)	
>60	386 (67)	
<i>Sex</i>		0.410
Male	303(53)	
Female	273 (47)	
<i>COPD</i>		0.899
Yes	145 (25)	
No	431 (75)	
<i>CVD</i>		0.697
Yes	293 (51)	
No	283 (49)	
<i>KPS</i>		0.399
60–70	98 (17)	
80–90	478 (83)	
<i>Smoking history</i>		0.001
Smoker	156 (27)	
Former smoker	374 (65)	
Non-smoker	46 (8)	
<i>Tumor type</i>		0.308
Adenocarcinoma	202 (35)	
Squamous	174 (30)	
NOS	200 (35)	
<i>Affected lung</i>		0.621
Left	241 (42)	
Right	328 (57)	
Mediastinum	7 (1)	
<i>Tumor location</i>		0.273
Upper lobe	350 (61)	
Middle lobe	54 (9)	
Lower lobe	172 (30)	
<i>Clinical stage</i>		0.315
I	76 (13)	
II	36 (6)	
III	434 (75)	
IV	30 (5)	
<i>Node status</i>		0.031
Positive	469 (81)	

Characteristic	No. of patients (%) (N = 576)	p-Value
Negative	107 (19)	
<i>Radiation dose</i>		0.928
<63 Gy	107 (19)	
63–66 Gy	379 (66)	
>66 Gy	90 (16)	
<i>Radiation fractionation</i>		0.530
Once daily	503 (87)	
Twice daily	73 (13)	
<i>Use of 4D-CT</i>		0.039
Yes	119 (21)	
No	457 (79)	
<i>Use of IMRT</i>		0.033
Yes	90 (16)	
No	486 (84)	
<i>Induction chemotherapy</i>		0.297
Yes	220 (38)	
No	356 (62)	
<i>Concurrent chemotherapy</i>		0.979
Yes	417 (72)	
No	159 (28)	
<i>Pretreatment PFT (N = 239)*</i>		
<i>FVC</i>		0.867
2.7 (L)	120 (50.2)	
>2.7 (L)	119 (49.8)	
<i>FEV1</i>		0.894
<1.8 (L)	120 (50.2)	
>1.8 (L)	113 (47.3)	
<i>DLCO-HB</i>		0.820
<14.5 (ml/min/mmHg)	76 (31.8%)	
>14.5 (ml/min/mmHg)	75 (31.4%)	

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular diseases; KPS, Karnofsky performance status; NOS, not otherwise specified; 4D-CT, four-dimensional computed tomography; IMRT, intensity-modulated radiotherapy; PFT, pulmonary functional test.

* Total 239 patients had pretreatment PFT. The PFT values have been divided approximately at the median of the available values and the percentage in this category is the proportion of the total 239 patients who had pretreatment PFT available.

Table 2

One-year incidence (%) of grade ≥ 3 treatment-related pneumonitis (TRP) according to DVH group (defined in Figs. 2 and 3) and smoking status

Smoking status	DVH group			
	A	E	C	D
Smokers	0	8(3–22)	18 (11–30)	21 (8–53)
Former smokers	4(1–23)	18 (12–27)	27 (21–34)	35 (24–51)
Non-smokers	0	18 (5 – 55)	39(23–72)	70(37–96)

Note: 95% confidence intervals are shown in parentheses.