Impact of 3D Conformal Radiotherapy on Lung Function of Patients with Lung Cancer: A Prospective Study

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Key Words

Lung cancer · Radiotherapy · Lung function tests · Radiation pneumonitis

Abstract

Background: The development of three-dimensional conformal radiotherapy (3D-RT) has enabled the restriction of the dose to normal lung, limiting radiation-induced lung injury. **Objectives:** This study was designed to describe the time course of lung function until 7.5 months after 3D-RT in patients with lung cancer, and assess the relationship between lung function changes and dose-volume histogram (DVH) analysis or computed tomography scan changes. Radiation doses were optimized according to recent guidelines. **Methods:** Sixty-five lung cancer patients treated with 3D-RT agreed to participate in this prospective, hospital-based study. Lung volumes, forced expiratory volume in 1 s (FEV₁) and diffusing capacity of the lung for carbon monoxide (DLCO) were measured before radiotherapy (RT), 10 weeks, 4 and 7.5 months after the beginning of 3D-RT. **Results:** Eleven lung cancer patients (17%) developed grade 2–3 respiratory symptoms after RT. At 7.5 months, vital ca-

capacity (VC) was $96 \pm 2\%$, total lung capacity (TLC) $95 \pm 2\%$, FEV₁ $93 \pm 2\%$ and DLCO $90 \pm 2\%$ of the initial value. Only 15% of patients showed pulmonary function reduction >20%. Patients with FEV₁ or DLCO <60% before RT did not show significant changes after RT. There were weak correlations between reduction of VC, TLC, FEV₁ or DLCO and radiation dosimetric parameters and between reduction of VC or FEV₁ and radiation-induced pneumonitis images. **Conclusions:** In lung cancer, the reduction of lung function within 7.5 months after 3D-RT was small and correlated, albeit weakly, with DVH parameters. Patients with initially impaired lung function showed tiny changes in spirometry and DLCO values.

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Introduction

Injury to the lung is a common complication after radiation therapy of chest malignancies. High radiation doses improve tumor control but also increase pulmonary toxicity, which is a dose-limiting side effect of radiotherapy. The development of three-dimensional confor-

mal radiotherapy (3D-RT) has enabled the calculation of dose-volume histograms (DVH) to fit the dose distribution to the planning target and restrict the dose to normal lung [1]. Several DVH-based factors have been strongly associated with lung toxicity, with a rapid increase in risk with increasing DVH parameters [2–5]. No threshold below which there is no risk could be defined. However, according to these results, it has been recommended to reduce the highest radiation doses used in clinical practice in order to limit lung toxicity [4]. In recent studies it has been attempted to keep the mean lung dose (MLD) under 20 Gy and the maximum fraction of the irradiated lung volume receiving more than 20 Gy (V20) or 30 Gy (V30) set at 30–35 and 20%, respectively [6]. As a result, weaker associations have been found between dosimetric parameters and dyspnea in later studies [7]. Whether or not appliance of these dosimetric criteria has also limited the loss of lung function remains to be investigated. The question is of particular relevance in lung cancer patients, who frequently present with altered lung function due to smoking habits. Indeed, finding small radiation-induced decreases in lung function would encourage the extension of this therapeutic option to patients with significantly impaired lung function who are currently often excluded from radiotherapy (RT) protocols.

We designed this study to evaluate the loss of lung function in lung cancer patients after 3D irradiation, with restricted MLD, V20 and V30, combined or not with chemotherapy. The main aims were: (i) to describe the time course of lung function parameters until 7.5 months after 3D-RT; (ii) to assess the relationship between lung function changes and DVH analysis, and (iii) to assess the relationship between lung function and computed tomography (CT) scan changes after 3D-RT. In addition, we assessed the relationship between symptoms and either lung function loss or CT scan image changes.

Methods and Materials

Patients

From October 2005 to February 2010, 65 patients with confirmed unresectable lung cancer agreed to participate and provided informed consent prior to registration in this study, approved by the Institutional Review Board (HUS No. 3492). Stage I–III lung cancer patients treated with either exclusive RT, sequential or concurrent chemotherapy, with or without prior lung resection, were eligible. Patients were ineligible if they were younger than 18 years, had an ECOG performance status >2, history of prior RT to the thorax, active systemic or pulmonary infection, or synchronous malignancy within 2 years of entry.

Radiotherapy Modalities

Patients were immobilized in a supine position with arms above the head. Target volumes were delineated on planning CT scan with 2.5-mm slices. The gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV) were delineated according to the definitions of the International Commission on Radiation Units and Measurements [8], the GTV including tumor and nodes visualized on CT and positron emission tomography (PET)-CT scan. CTV was defined as the GTV with a 5-mm margin for the mediastinal areas and a 5- to 8-mm margin for the primary tumor according to the tumor histology. PTV (including set-up margin and internal target volume) was obtained by a 2- to 10-mm 3D expansion from CTV. In case of induction chemotherapy, the post-chemotherapy volume of the primary tumor was considered as the GTV of the primary tumor, and the pathological lymph node areas positive on the pretreatment PET scan were included in the GTV. After surgery, the CTV included the scar or residual tumor, the pathological lymph node areas and lymph node areas just above and below the pathological one. Irradiation was applied with two to four 6–25 MV photon beams from accelerators with multileaf linear collimators. Portal imaging for set-up control was performed daily. The irradiation dose was delivered with conventional fractionation (2 Gy per fraction, 5 fractions per week) up to 66 Gy. After lung resection, the dose was 54 Gy for R0 resection and no nodal capsular rupture. If resection was not R0 or nodal capsular rupture was diagnosed, the dose was increased up to 66 Gy.

DVH Parameters

Doses were calculated to account for tissue density heterogeneity. The lungs were automatically contoured, excluding the GTV. MLD (average dose to the CT-defined total lung volume, excluding the GTV), V5, V13, V20 and V30 (percentage of lung volume receiving at least 5, 13, 20 or 30 Gy) were calculated from the lung DVH. As often as possible, dosimetric goals were optimized according to previously published data, i.e. less than 30 and 20% of irradiated lung volume receiving more than 20 and 35 Gy, respectively [2, 6]. The mean pericardium dose and the volume of the heart receiving more than 30 Gy were also calculated [9].

Lung Toxicity

Significant lung toxicity ('symptomatic patients') was indicated by post-treatment cough or dyspnea grade 2 or higher according to the Common Terminology Criteria of Adverse Events (CTCAE) v3.0, or a significant increase in symptoms for patients with underlying lung disease.

CT Scan Changes after Radiotherapy

CT scans were performed within 4 weeks before, and 10 weeks, 4 and 7.5 months after the beginning of RT and reviewed at the same time for each patient by the same radiologist experienced in CT of the thorax. The system used to score the extent of emphysema on the CT scans was adapted from prior work by Goddard et al. [10]. Each CT section was assessed individually and the right and left lungs were graded separately according to the percentage area that demonstrated changes suggestive of radiation pneumonitis. These changes were ground-glass opacity, consolidation, fibrosis, traction bronchiectasis, scarring and volume loss. Radiation-induced manifestations were scored in the right and left lung, independently, as follows:

Fig. 1. CT scan images of radiation pneumonitis. **a** Grade <1 (minimal radiographic findings). **b** Grade 1 (changes with estimated proportion of ipsilateral lung volume of <1/3). **c** Grade 2 (changes with estimated proportion of ipsilateral lung volume of >1/3 and <2/3). **d** Grade 2.5 (changes with estimated proportion of ipsilateral lung volume of >1/3 and <2/3 and <1 in contralateral lung). Only one slice per patient is displayed, but all the slices were examined to evaluate the proportion of lung volume affected by radiation pneumonitis.

- 0: none;
- <1: minimal radiographic findings, volume <1 cm³;
- 1: changes with estimated proportion of lung volume of <1/3;
- 2: changes with estimated proportion of lung volume of >1/3 and <2/3;
- 3: changes with estimated proportion of lung volume of >2/3.

Scores obtained in the right and the left lung were then summed to provide the grade for the whole lung. This yielded maximum possible scores of 3 for either side, for a maximum possible total score of 6. Examples of CT scan image grades are presented in figure 1.

Lung Function Tests

Lung volumes, flow-volume curves and single-breath diffusion capacity of the lung for carbon monoxide (DLCO) tests were measured using an MS-pulmonary function test (PFT) device (Jaeger USA Masterscreen Diffusion, VIASYS Healthcare), following the American Thoracic Society and European Respiratory Society (ERS) recommendations [11–13]. Functional residual capacity was determined using the helium dilution technique [13]. DLCO values were corrected for hemoglobin. Reference equations were those published by the ERS (1993). Equipment and protocols were unchanged during the 4.5-year period and tests were performed by experienced technicians.

Statistical Analysis

CT scan and lung function tests were performed within 4 weeks before, and 10 weeks, 4 and 7.5 months after the beginning of RT. Characteristics of the patients or lung function values were compared using t test or χ^2 test depending on the variable being continuous or qualitative. Changes in lung function values with time were evaluated using linear mixed models with unstructured variance-covariance matrices. The influence of DVH parameters was assessed by including these parameters as covariates in the mixed models. Correlation at each time between lung func-

tion values and grade of CT scan image was computed using Pearson's or Spearman's correlation coefficient. Values are expressed as mean and standard deviation (SD). The significance level was set at $\alpha = 0.05$. Computations were done with SAS 8.0 (PROX MIXED) and R 2.11.

Results

Patients' Characteristics

Patients' characteristics are reported in table 1. Twenty patients had either lung V20 >35% or V20 >20%, and 3 had MLD >20 Gy. Five patients (8.3%) had a mean heart dose >26 Gy and 2 (4.6%) had a heart V30 >46% [9].

Lung Function Test Changes after Radiotherapy

Analyses demonstrated significant linear decrease with time of vital capacity (VC), functional residual capacity, total lung capacity (TLC), forced expiratory volume in 1 s (FEV₁) and DLCO (slopes: –0.18, –0.26, –0.22, –0.21, –0.72, respectively, $p < 0.001$). A significant quadratic effect was detected in DLCO time trend ($p < 0.01$; fig. 2). Hence, the lowest spirometric values were observed at 7.5 months and the lowest DLCO values at 4 months (table 2). At 7.5 months, VC was $96 \pm 5\%$, TLC $95 \pm 16\%$, FEV₁ $93 \pm 14\%$ and DLCO $90 \pm 12\%$ of the baseline value. At 7.5 months, in 60% of patients, the variations of spirometric parameters and DLCO compared to pre-RT values were within the range of the year-to-year variability [14], e.g. $\pm 10\%$ (table 3). Four-

Table 1. Patients' characteristics

Lung cancer patients (n = 65)		
Mean age (SD), years	61 (11)	
Males/females	48/17	
Smoking history		
Current smoker	13 (20% of patients)	
Ex-smoker	49 (75% of patients)	
Never-smoker	3 (5% of patients)	
Histology and stage		
	NSCLC: 52	
	Squamous: 32	Stage I: 1
	Adenocarcinoma: 12	Stage II: 4
	Large cell: 4	Stage III: 47
	Unspecified: 4	
	SCLC: 13	Limited
Treatment		
Sequential chemotherapy	21 (13 carboplatin-paclitaxel; 4 cisplatin-vinorelbin; 4 carbo- or cisplatin-etoposide)	
Concurrent chemotherapy	40 (10 carboplatin-paclitaxel; 14 cisplatin-vinorelbin; 10 carbo- or cisplatin-etoposide; 6 others)	
No chemotherapy	4	
Previous lung resection	14 (4 pneumonectomies)	
Mean DVH (SD)		
	Lung:	Heart:
	V5: 45% (15%)	
	V13: 31% (12%)	
	V20: 24% (10%)	
	V30: 17% (8%)	V30: 11% (2.2%)
	MLD: 12.9 Gy (4.6 Gy)	MHD: 11.2 Gy (1.3 Gy)
Pulmonary function tests		
Normal spirometry	15 (23% of patients)	
Obstructive pattern	37 (57% of patients)	
Restrictive pattern	13 (20% of patients)	
Decreased DLCO	49 (75% of patients)	
(N)SCLC = (Non-)small cell lung cancer; MHD = mean heart dose.

Fig. 2. Time course of lung function parameters after 3D-RT in lung cancer patients [mean (SEM)]. A small but significant decrease in lung function parameters with time was observed.**Table 2.** Time course of lung function parameters (expressed as percentage of predicted values) after radiotherapy in lung cancer patients

	Before	10 weeks	4 months	7.5 months
n	65	61	54	50
VC%				
mean $\pm$ SD	97.4 $\pm$ 23.9	98.0 $\pm$ 26.3	94.9 $\pm$ 25.3	94.6 $\pm$ 27.5
range	55.8 – 159.0	46.2 – 160	58.8 – 164.9	52.3 – 158.9
TLC%				
mean $\pm$ SD	94.2 $\pm$ 18.2	93.5 $\pm$ 18.9	89.4 $\pm$ 15.9	88.5 $\pm$ 20.0
range	57.7 – 147.4	48.9 – 133.3	44.9 – 121.0	45.4 – 142.5
FEV ₁ %				
mean $\pm$ SD	83.0 $\pm$ 26.6	82.7 $\pm$ 28.0	81.1 $\pm$ 26.6	80.0 $\pm$ 29.4
range	25.2 – 157.9	33.5 – 160.2	28.9 – 157.2	26.0 – 154.7
DLCO%				
mean $\pm$ SD	66.4 $\pm$ 17.2	60.9 $\pm$ 17.4	59.0 $\pm$ 15.0	60.5 $\pm$ 15.6
range	25.8 – 100.1	19.1 – 99.5	21.6 – 99.1	17.7 – 100.2

teen patients showed a decrease >20% in at least one lung function parameter [3 females/11 males, age 61 (± 13) years, 4 current, 9 ex- and 1 non-smoker, 7 sequential/6 concurrent chemotherapy]. There was no correlation between the baseline lung function and the loss of lung function. Lung function changes of patients with sequential chemotherapy did not differ from those of patients with concurrent chemotherapy [FEV₁: 4.7% (13.4) vs. 8.3% (11); VC: 3.0% (14.6) vs. 7.0% (12.1); TLC: 6.3% (15.0) vs. 4.6% (17.0); DLCO: 8.1% (7.5) vs. 7.3% (7.5)].

Lung Cancer Patients with Significantly Impaired Lung Function (<60% of Predicted Value) before RT, or with Respiratory Symptoms

The DVH parameters of these patients did not differ from those of other patients. In patients with impaired pretreatment lung function, FEV₁ and DLCO did not change significantly after RT (table 4). Eleven patients (17%) developed respiratory symptoms. In the 9/11 symptomatic patients who completed the tests at 7.5 months, the loss of VC, FEV₁ and DLCO were 7.9% (14.5), 10.2% (11.8) and 9.1% (10.6), respectively. This was not different from the 3.8% (13.6), 6.0% (13.9) and 7.5% (7.0) of patients without symptoms, but the number of symptomatic patients was low.

Relationship between DVH Parameters and Lung Function Changes

For lung DVH parameters, the mixed model demonstrated significant interactions between time effect and dosimetric effect on TLC, VC and FEV₁. These interactions were significant for V13, V20, V30 and MLD ($p < 0.05$). Correlation coefficients are given in table 5 and figure 3. The interaction between time and dosimetric effects on DLCO tended to be significant for V20 ($p = 0.09$) and in the univariate analysis at 7.5 months the change in DLCO tended to correlate with V20 ($p = 0.055$). There was no correlation between cardiac DVH parameters and lung function changes.

Relationship between CT Scan Images of Radiation-Induced Pneumonitis and DVH or Lung Function Changes

Fifty, 53 and 49 patients' CT scans could be evaluated at 10 weeks, 4 and 7.5 months. Most patients' (90, 74 and 76%, respectively) CT scan images scored 1.5 or less. At 10 weeks, 4 and 7.5 months, respectively, 4, 9 and 6% of patients had scores of 3 or more. The lung DVH parameters correlated with the grade of radiation-induced CT

Table 3. Changes in lung function 7.5 months after the beginning of radiotherapy

	VC%	FEV ₁ %	DLCO%
Total patients	50	50	48
Gain >10%	4 (8%)	3 (6%)	0
-10 to +10%	31 (62%)	29 (58%)	28 (58%)
Loss >10%	15 (30%)	18 (36%)	20 (42%)
Loss >20%	7 (14%)	6 (12%)	7 (15%)
Loss >30%	4 (8%)	3 (6%)	3 (6%)

Table 4. Changes in lung function of lung cancer patients with significantly impaired lung function (<60% predicted) before RT

	Before	10 weeks	4 months	7.5 months
FEV ₁ % <60% before RT				
n	11	11	9	7
Mean $\pm$ SD	48.8 $\pm$ 9.7	51.6 $\pm$ 8.4	52.2 $\pm$ 12.4	47.6 $\pm$ 12.9
Range	25.2 – 59.3	33.5 – 61.8	28.9 – 66.6	26.0 – 62.0
DLCO% <60% before RT				
n	23	22	20	15
Mean $\pm$ SD	48.9 $\pm$ 10.1	46.2 $\pm$ 9.5	46.8 $\pm$ 10.7	46.4 $\pm$ 11.5
Range	25.8 – 59.2	28.5 – 61.3	21.6 – 69.9	17.7 – 58.4

FEV₁ and DLCO are expressed as percentage of predicted values. Dosimetric parameters did not differ between patients with impaired lung function and other patients.

scan images at 4 months (r from 0.31 to 0.41, $p < 0.05$) and 7.5 months (r from 0.45 to 0.54, $p < 0.001$). Correlation coefficients between loss of lung function and grade of CT scan images are given in table 5 and figure 3. Chemotherapy given concomitantly to RT may alter the relationships between these parameters. Therefore, an analysis was performed in the concurrent chemotherapy group, the results of which are presented in table 5.

Relationship between Symptoms and Lung Function Loss or CT Scan Image Changes

There was no correlation between loss of VC, FEV₁, TLC, DLCO and CTCAE grade of dyspnea at the various time points. In contrast, significant correlations were found between dyspnea grade and CT scan image scores at 4 months ($r = 0.37$, $p < 0.01$) and at 7.5 months ($r = 0.36$, $p < 0.05$). Figure 4 shows the distribution of radiological changes seen on 7.5-month CT scans, according to symptoms.

Table 5. Correlations between loss of lung function and DVH parameters or grade of radiation-induced CT scan images

	4 months		7.5 months	
	all patients	concurrent chemotherapy	all patients	concurrent chemotherapy
Correlations between lung function and DVH parameters				
Loss in TLC	NS	NS	V20: $r = 0.32$, $p < 0.05$ V30: $r = 0.31$, $p < 0.05$ MLD: $r = 0.31$, $p < 0.05$	V30: $r = 0.40$, $p < 0.05$ MLD: $r = 0.43$, $p < 0.05$
Loss in VC	V13: $r = 0.31$, $p < 0.05$ V20: $r = 0.32$, $p < 0.05$	V13: $r = 0.40$, $p < 0.05$ V20: $r = 0.40$, $p < 0.05$	V13: $r = 0.37$, $p < 0.01$ V20: $r = 0.43$, $p < 0.01$ V30: $r = 0.44$, $p < 0.005$ MLD: $r = 0.44$, $p < 0.005$	V5: $r = 0.43$, $p < 0.05$ V13: $r = 0.48$, $p < 0.05$ V20: $r = 0.42$, $p < 0.05$ V30: $r = 0.41$, $p < 0.05$ MLD: $r = 0.49$, $p < 0.05$
Loss in FEV ₁	V13: $r = 0.27$, $p < 0.05$ V20: $r = 0.32$, $p < 0.05$	V20: $r = 0.40$, $p < 0.05$	V13: $r = 0.29$, $p < 0.05$ V20: $r = 0.40$, $p < 0.005$ V30: $r = 0.44$, $p < 0.005$ MLD: $r = 0.38$, $p < 0.01$	V13: $r = 0.40$, $p < 0.05$ V20: $r = 0.37$, $p = 0.05$ V30: $r = 0.37$, $p = 0.05$ MLD: $r = 0.40$, $p < 0.05$
Loss in DLCO	NS	NS	V20: $r = 0.33$, $p = 0.055$	V13: $r = 0.41$, $p < 0.05$ MLD: $r = 0.40$, $p < 0.05$
Correlations between lung function and concomitant CT scan image scores				
Loss in TLC	NS	NS	NS	NS
Loss in VC	NS	NS	$r = 0.29$, $p < 0.05$	$r = 0.36$, $p = 0.07$
Loss in FEV ₁	NS	NS	$r = 0.31$, $p < 0.05$	$r = 0.45$, $p < 0.03$
Loss in DLCO	NS	NS	NS	NS

Discussion

In this study, we have shown that in most lung cancer patients the loss of lung function within 7.5 months after RT, irrespective of pre-RT treatment used, was small and progressive. This reduction in lung function correlated weakly but significantly with dosimetric parameters derived from DVH and with the extent of radiation-induced pneumonitis in the CT images at 7.5 months. Interestingly, the decrease in lung function of patients with significantly impaired baseline lung function did not reach significance.

The progressive decline of lung volumes we observed in lung cancer patients contrasts with the significant recovery described in Hodgkin lymphoma patients [15]. Several treatment- and patient-related factors, especially preexisting lung disease, explain this difference. Nevertheless, the absence of fluctuations does not support performing serial measurements of pulmonary function after RT in lung cancer. TLC and VC showed reduction of 5 and 4%, respectively, and the mean loss of FEV₁ (−7%) and of DLCO (−11%) we observed were similar to those described at 3 and 18 months in two previous 3D-RT

studies [16, 17]. However, in these studies very few patients received combined chemo-radiotherapy, which has been found to increase lung toxicity compared to RT alone [18, 19]. Consequently, the mean loss of lung function of our lung cancer patients, who were treated with combined modalities, can be regarded as small. Approximately 15% of patients demonstrated reductions greater than 20%, confirming that the impact of 3D-RT on lung function was not deleterious in most patients.

Our patients with lower lung function values did not worsen their ventilatory or diffusing capacity defect after RT, and in the whole group there was no relationship between the initial lung function and the loss of lung function. These results were not explained by lower radiation doses prescribed in patients with initially compromised lung function. They are in line with those of two studies which reported no decrease in PFT values in patients with FEV₁ <50% of predicted [19, 20]. The number of patients with very impaired lung function included in our study was small, and consequently studies designed to measure lung function changes in these particular patients are required. Such data would be of interest given that today safe lower limits of respiratory function for RT, if any, re-

Fig. 3. Examples of relationships between DVH parameters (**a, b**) or grade of radiation-induced CT scan images (**c, d**) and lung function changes in lung cancer patients at 7.5 months. Loss of pulmonary function is the baseline PFT value (expressed as % predicted) minus the PFT value at 7.5 months. ● = Concurrent chemotherapy; ○ = sequential chemotherapy; △ = no chemotherapy.

main to be determined [21], and that RT is frequently not offered to patients with low functional values.

If the relationship between dose-volume analysis and radiation pneumonitis symptoms is well established [4], only one study [16] out of three found an association between DVH parameters and pulmonary function changes in lung cancer [16, 17, 22]. In our series we found significant but weak correlations at 4 and 7.5 months, with DVH variations accounting only for 10–16% of the total variance of pulmonary function changes. The strongest relationships were observed between VC and FEV₁ and V20, V30 and MLD. These associations may be weaker in our study compared to others [16] since we limited radiation doses in order to reduce lung damage. Moreover, we found that the correlation between DLCO and MLD was only of borderline significance in our series. Since almost all our patients had chemotherapy, this may be explained by a stronger effect of chemotherapy on DLCO than on

Fig. 4. Bar chart showing the distribution of radiological changes seen on CT scans 7.5 months after radiotherapy. Black bar = patients with radiotherapy-induced respiratory symptoms, grey bar = patients without radiotherapy-induced respiratory symptoms.

spirometry parameters. Actually, the DLCO decline was found to correlate with radiation doses in a series including very few lung cancer patients treated with chemotherapy [16].

The large majority of our patients showed moderate RT-induced images in <1/3 of the ipsilateral lung volume. CT scan changes correlated with symptoms, as previously reported [23]. CT scan changes also correlated with variations of VC or FEV₁ at 7.5 months, indicating that the RT-induced loss of lung volumes can be broadly approached either through CT scan or spirometry [24]. In contrast, we did not find any association between CT scan images and changes in DLCO. In line with this result, the correlation coefficients between the pulmonary function reduction and either the reduction in regional perfusion or the increase in CT lung density have been found to be lower for DLCO than for FEV₁ [25]. DLCO may be more sensitive than spirometry to confounding factors, such as location of the tumor, chemotherapy, comorbidities and smoking history. DLCO may also be partially preserved as the consequence of a redistribution of the blood from the injured lung segments to the optimally ventilated ones.

Despite the heterogeneity of our population, which reflects the daily practice in lung cancer therapy [26], most patients showed small lung function changes. These changes were related to radiation doses, regardless of the heterogeneity in patients and treatments. An earlier study found that the use of chemotherapy concurrent with 3D-RT did not, as hypothesized, accentuate the development of radiation pneumonitis [27]. Adding to these results, we showed that pulmonary function impairment after concurrent chemotherapy was not significantly increased compared to sequential chemotherapy, and remained related to DVH parameters. Part of the symptoms reported by lung cancer patients after RT may be due to RT-induced heart toxicity, which is aggravated by tobacco smoking and cardiac disease history, and interacts with lung toxicity. The present study did not include an extended cardiac function assessment. However, it is unlikely that heart toxicity influenced PFT results. In most patients the heart radiation doses were below the recommended dose/volume limits, and did not correlate with lung function changes. Moreover, it has been shown that most radiation-induced cardiac effects occur from months (for pericarditis) to decades after RT [9, 28]. Because of the small proportion of patients who develop significant pulmonary function loss, identifying other potential predicting factors for lung function changes would require large population studies. Interestingly, these

patients are different from those developing respiratory symptoms, given that symptoms and pulmonary function changes did not correlate either in our study or in a previous one [16]. Whether or not the patient's characteristics are important, as they are for radiation pneumonitis symptoms or CT images [7, 23, 29], remains to be investigated.

Eventually, consistent with others [4], we observed a low incidence of radiation pneumonitis (with clinical and/or radiological impact). In terms of lung function, the RT-induced loss is far lower than that induced by a pneumonectomy, characterized by a 30% decrease in FEV₁ [30]. These results are likely due to advances in RT techniques. The development of 3D-RT, which has increasingly replaced conventional techniques, has especially led to a significant improvement of the therapeutic ratio. However, it remains sometimes impossible to deliver high radiation doses in large tumor volumes whilst keeping MLD and V20 below accepted limits. This precludes some patients from receiving radiation therapy and thus limits the therapeutic options offered to these patients. In the near future, intensity-modulated radiation therapy techniques may allow increasing the total radiation dose to large target volumes, without increasing the toxicity in organs at risk [31]. This new technique should also limit radiation-induced lung function impairment.

In conclusion, 3D-RT with optimized radiation doses induced small pulmonary function changes, which were weakly related to DVH parameters. The tiny changes in spirometry and DLCO values observed in subjects with significant impairment of baseline lung function should encourage initiating larger studies in these patients.

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