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Changes in Functional Lung Regions During the Course of Radiation Therapy and Their Potential Impact on Lung Dosimetry for Non-Small Cell Lung Cancer

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Abstract

Purpose—To study changes in functional activity on ventilation (V)/perfusion (Q) single-photon emission computed tomography (SPECT) during radiation therapy (RT) and explore the impact of such changes on lung dosimetry in patients with non-small cell lung cancer (NSCLC).

Methods and Materials—Fifteen NSCLC patients with centrally located tumors were enrolled. All patients were treated with definitive RT dose of 60 Gy. V/Q SPECTCT scans were performed prior to and after delivery of 45 Gy of fractionated RT. SPECT images were used to define temporarily dysfunctional regions of lung caused by tumor or other potentially reversible conditions as B3. The functional lung (FL) was defined on SPECT by 2 separate approaches: FL1, a threshold of 30% of the maximum uptake of the patient's lung; and FL2, FL1 plus B3 region. The impact of changes in FL between initiation of RT and delivery of 45 Gy on lung dosimetry were analyzed.

Results—Fourteen patients (93%) had larger FL2 volumes than FL1 pre-RT ($P < .001$). Dysfunctional lung became functional in 11 patients (73%) on V SPECT and in 10 patients (67%) on Q SPECT. The dosimetric parameters generated from CT-based anatomical lung had significantly lower values in FL1 than FL2, with a median reduction in the volume of lung receiving a dose of at least 20 Gy (V_{20}) of 3%, 5.6%, and mean lung dose of 0.95 and 1.55 on V and Q SPECT respectively.

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Conflict of interest: none.

Conclusions—Regional ventilation and perfusion function improve significantly during RT in centrally located NSCLC. Lung dosimetry values vary notably between different definitions of functional lung.

Introduction

Definitive radiation therapy (RT) plays an important role in the curative management of medically or surgically untreatable non-small cell lung cancer (NSCLC) patients with 5-year survival rates of 29% to 42% for stage I-II disease (1-2) and 5% to 14% for locally advanced stage IIIA-B tumors (3-4). Current RT is limited by the risk of radiation pneumonitis, a dose- and volume-dependent toxicity that correlates with mean lung dose (MLD) and the volume of lung receiving a dose of at least 20 Gy (V_{20}). Currently, computed tomography (CT) lung-based dosimetric parameters are the most significant factors associated with radiation-induced lung toxicity. However, we and other investigators have demonstrated that such factors are suboptimal in predictive accuracy and thus may not be reliable in practice (5, 6).

Conventional RT planning of NSCLC using CT data considers the lung a uniform organ, regardless of regional difference in function. Local functional lung (FL) assessment by ventilation (V) and perfusion (Q) single-photon emission computed tomography (SPECT) provide estimates of patient tolerance to local RT. Function-guided RT planning may avoid or minimize exposure of FL, potentially reducing pulmonary toxicity and allowing effective dose escalation in patients with NSCLC (7-13). In fact, a significant proportion of NSCLC patients have defects in regional lung function caused by either local tumor effects or concurrent pulmonary disease (14). Tumor-related functional defects are often reversible through radiation (15). Because functionally defective regions are more resistant to radiation damage, functional lung dose-volume histograms (fDVHs) based on SPECT may be more accurate in predicting radiation lung toxicity than DVH models based on pretreatment CT. We have demonstrated that lung cancer patients often have multiple defects on V or Q SPECT at baseline and that such defects change during radiation (16). However, the significance on lung dosimetry is not clear. This study aimed to quantify the changes of functional lung regions during the course of RT and the potential impact of changes in these functional lung regions on MLD and V_{20} .

Methods and Materials

Study population

Patients with centrally located tumors were selected from those enrolled in institutional review board–approved prospective studies (UMCC2003-376 and 2006-040), who had V/Q scans performed before and during the course (approximately 45 Gy) of RT between 2008 and 2009. Written informed consent was obtained from all subjects before enrolment. Adult patients with histologically confirmed stage I to III NSCLC (American Joint Committee on Cancer, 2003) were treated with a conventionally fractionated 3-dimensional conformal RT dose of 60 Gy, with or without chemotherapy based on stage of disease and medical condition, and RT was planned on pretreatment CT scans. For this pilot study, patients with centrally located tumors defined as 2 cm from the proximal bronchus tree were eligible.

Patients with small cell lung cancer or mixed small cell and non-small cell histology or pericardial effusion or who were pregnant or lactating were excluded. Patients had to be able to lie flat for the duration of V/Q SPECT.

V/Q SPECT CT imaging

V/Q SPECTs were performed with a Symbia T6 SPECTCT system (Siemens Medical Solutions, Hoffman Estates, IL) before radiation therapy, with the patient in the treatment position, using a flat thoracic board. Each patient inhaled aerosolized Tc-99m diethylene triamine pentaacetic acid (DTPA) from a 50 mCi reservoir, for V scanning. After the V scan, the patients were given 185 MBq of Tc-99m-labeled macroaggregated albumin particles intravenously. The Tc-99m-labeled macroaggregated albumin dose was thoroughly shaken immediately before intravenous administration.

Each V and Q SPECT was acquired in 60 projections over 360° by means of the step-and-shoot method. The SPECT scans were acquired using a noncircular orbit and step-and-shoot mode over a 360° arc in 128 frames, 19 seconds/frame, at 3° angles in 128 × 128 matrices. After attenuation and scatter correction, the SPECT slices were reconstructed using 3-dimensional ordered subset expectation maximization iterative reconstruction with resolution, scatter, and attenuation correction.

SPECT images coregistered with low-dose x-ray CT scans were obtained with the patient in the same position. Accuracy of the coregistration algorithm has been externally validated and is similar to that described by Partridge et al (17). The CT slice thickness was set at 5 mm, and CT imaging did not use oral or intravenous contrast administration or diagnostic collimation. Scans were carried out at the end of exhale when the patient was treated under free breathing or at 75% of vital capacity at inhale when patients were simulated and treated under an active breathing control device.

Classifications of local lung regions

Local lung regions were classified according to underlying cause and their potential application in guiding RT, as previously prescribed (16). In brief, type A regions refers to dysfunction caused directly by the tumor. These tumor occupying lung regions were targets of RT. Type B1 regions were defined as completely functionally defective due to chronic lung condition such as chronic obstructive pulmonary disease (COPD) or other unrecoverable disease. These regions, with unrecoverable nonfunctioning lung, can be given high-dose RT without causing changes in global lung function. SPECT data were viewed as a multicolored images in the spectrum of color setting to allow accurate volume contouring around a predefined color. The threshold level was adjusted individually for each patient in order to match the size of the SPECT image within the lung volumes defined on CT. Using a threshold of 60% of the maximum uptake of normal lung of each scan, scan artifacts such as aerosol deposits were excluded with the assistance of a nuclear medicine physician according to comprehensive analysis of SPECT and CT. Defects (types A and B1) were defined as those displaying less than 30% of the maximum uptake of normal functional lung. Type B2 regions were defined as reduced lung function from chronic lung condition, with thresholds of 30% to 60% of the maximum uptake of normal lung. Type B3 regions were

those with temporarily reduced function due to tumor and other potentially reversible conditions, defined below the threshold of 60% of the maximum uptake of normal lung. Type C regions consisted of the remaining normal functioning lung. Type C was contoured by the threshold of 60% of the maximum uptake of the lung (12). For this study, the functional lung was described on Vor Q SPECT in 2 different ways: (1) FL1, a threshold of 30% of the maximum uptake for each patient without consideration of malignancy classification, as per previously performed studies; and (2) FL2, FL1 plus type B3 region (Fig. 1).

Data collection and statistical analysis

The following structures were contoured for each patient in the planning system for dosimetric consideration: gross tumor volume (GTV), whole lungs (WL) as a single organ, with exclusion of the GTV. The planning target volume (PTV) was created using a 1.5-cm uniform margin around the GTV. SPECT data were viewed in the spectrum color setting. The threshold level was adjusted individually for each patient in order to match the size of the SPECT image to within the lung volumes defined on CT. Clinically acceptable plans that fulfilled the criteria for limitation of doses to lung, heart, esophagus, spinal cord, and normal tissue were achieved for all patients by using anatomical strategies. RT plans were generated without knowledge of V/Q scans. Dose-volume characteristics for the anatomical and functional lung groups are summarized in Table 3. Descriptive statistics and Student *t* tests were used to summarize the data and examine the potential impact on lung dosimetry. Differences were considered significant when the *P* value was $<.05$. Analysis was performed using the Statistical Package for Social Sciences (version 13.0 Chicago, IL).

Results

Patient population

Fifteen patients (aged 57-86 years) with central primary tumors, stages I-III NSCLC requiring radiation-based therapy from 2008 to 2009 were included in this pilot study. All patients were scanned with V/Q SPECT between 0 to 14 days before the initiation of radiation and around delivery of 45 Gy during RT. Patients characteristic are shown in Table 1.

Baseline functional lung map

All 15 patients had functional defects (V or Q) at the tumor location; 11 of 15 patients had additional involvement of the adjacent lung, and 4 of 15 had defects from distant tumors, which are consistent with chronic conditions. WL on CT had greater volume than FL1 and FL2, defined on V and Q SPECTs both before and during-RT (both, $P<.001$, Table 2). Mean FL1/WL ratio was 0.35 and 0.60, and the mean FL2/WL ratio was 0.39 and 0.65 on pre-RT V and Q SPECT, respectively. Ventilation FL1 and FL2 were significantly smaller than perfusion FL1 and FL2 (both, $P<.001$), respectively. FL2 had a greater volume than FL1 in 14 of 15 patients, and few patients had equal FL2 volumes on V and Q SPECTs at pre-RT ($P<.001$, Table 2).

Changes of functional lung volumes during radiation therapy

The ipsilateral lung function of patients improved on both V SPECT and Q SPECT during RT. Type B3 regions were observed at pre-RT on V SPECT in 14 patients, 11 of whom improved and developed functional lungs (Fig. 2) during RT scan; 2 of 14 remained stable; and 1 of 14 worsened. Type B3 regions on Q SPECT were observed in 14 of 15 patients; 10 of 14 patients changed partially or totally to functional lung; and 3 of 14 remained stable, and 1 of 14 worsened.

Comparison between functional and anatomical lung dosimetry

Compared to V SPECT-based functional lung, CT-based WL anatomical dosimetry values had lower dose-volume parameters on FL1 than WL, with reductions in the V_{20} and MLD in 12 patients and a median reduction in V_{20} of 5.6% (range, 0.7%-29.6%, $P=.02$) and MLD of 1.1 (range, 0.4-12.8, $P=.22$). The same plans resulted in lower dose-volume parameters for FL2 than WL, with lower V_{20} in 9 patients and MLD in 4 patients, and a median reduction in V_{20} of 3% (range, 0-29.5%, $P=.03$) and MLD of 0.95 (range, 0.2-12.8, $P=.30$) (Table 3).

Compared to Q SPECT-based FL1, dosimetry based on the same CT anatomical lungs had significantly lower values in lung dose-volume parameters, with lower V_{20} in 13 patients and MLD in 10 patients and a median reduction in V_{20} of 8.2% (range, 0.7-23.6%, $P=.00$) and MLD of 2.35 (range, 0.8-7.3, $P=.02$). Similarly, dosimetry of FL2 was also significantly different from that of CT WL-based dosimetry, with lower V_{20} in 12 patients and lower MLD in 8 patients and a median reduction in V_{20} of 5.6% (range, 0.9-11.1%, $P=.002$) and MLD of 1.55 (range, 0.2-3.5, $P=.50$) Table 3.

Compared to FL2, all patients had lower dose-volume parameters (V_{20} and MLD) in FL1 on V and Q SPECTs at pre-RT (Table 3). Almost none of the patients had radiation-induced lung toxicity. Only 1 patient (no. 11) developed increasing shortness of breath, consistent with grade 1 radiation pneumonitis/fibrosis after 64 Gy RT. MLD and V_{20} were nearly 2 times higher in the FL2 than in the CT WL-based DVH in this patient (24.8 Gy vs 10.9 Gy and 42.6% vs 22.3% on V SPECT). However, the same treatment plans resulted in similar V_{20} and MLD for FL1 compared to WL. FL volume in this patient changed remarkably between before and during scans. Type B3 region was observed at pre-RT in the patient and changed to functional lung after 45 Gy of radiation.

Discussion

This study demonstrated that (1) remarkable differences in lung dosimetry defined on V and Q SPECT functional scan, and (2) significant changes occur in the regional function map on V/Q SPECT by the time a mean dose of 45 Gy had been delivered in patients with centrally located NSCLC. The type B3 region, recoverable functional defects, based on pre-RT V/Q SPECT were confirmed by V and Q scans obtained during RT.

Lung function-guided planning based on pre-RT V and Q SPECT scans, particularly Q SPECT scans, has been used to guide treatment-planning beam arrangement for lung tumors to minimize dose to functional lung volume (7-13, 17). Pre-RT, V and Q functional image guided radiation therapy shows potential for preserving lung function and reducing radiation

lung toxicity. The findings from this study in functional defects are consistent with previous findings (7-13). The difference in functional lung of V or Q on pre-RT SPECT from this study validated the use of SPECT to optimize dose distribution.

It is critical to note that lung function changes remarkably during RT in many patients with central tumors. Dysfunctional lung defined on pre-RT SPECT may be recoverable. Thus, SPECT-guided RT plans based on pre-RT SPECT may actually target high-dose radiation to the potentially functional regions (B3), which improve during RT as a result of tumor response to treatment (15, 18). RT-induced tumor volume reduction may cause V/Q recovery because tumor shrinkage reduces pressure on the central airway and blood vessels. Understanding such changes during treatment may provide further useful guidance on RT planning to minimize radiation to function lung.

By further studying functional mapping on V/Q scans during RT, the current study validated to some degree our previous functional classification. Type B3 regions, potentially recoverable, were observed in 14 of 15 patients on pre-RT SPECT. V and Q function recovered in 11 of 14 and 10 of 4 of patients in these regions, accounting for 11 of 15 and 10 of 15 of patients respectively. This group of patients may benefit from V/Q SPECT scans acquired during RT for RT plan reoptimization for sparing of functional lung.

Interval changes in V and Q during RT have clinical significance. In this study, the type B3 region was observed pre-RT in patient no. 11, and that region changed to functional lung after 45 Gy radiation. The dose plan which did not consider function on V/Q scans resulted in higher dose-volume parameters for FL2 than the WL in this patient, with V_{20} and MLD nearly 2 times higher. This patient developed increasing shortness of breath consistent with grade 1 radiation pneumonitis/fibrosis. The observation of V/Q SPECT changes during RT suggests that there may be value in obtaining V/Q SPECT scans to reoptimize treatment plans in patients with centrally located tumors. V/Q function mapping using our recently proposed classification of pre-RT V/Q SPECT scans based on regional function level, cause of dysfunction, and potentially recoverability may guide applications of SPECT to RT planning. When local recovery takes place in a lung region during the course of RT, further radiation to the area in the late course of fraction RT should be avoided.

This study was limited first by the sample size of 15 patients, which may not be powerful enough to detect small differences in many functional endpoints. Second, all patients underwent V/Q SPECT scanning at approximately 45 Gy, but it is unclear whether 45 Gy is the right dose or the best time (generally this dose was given at week 4 of treatment) for V/Q rescans and replanning or if this dose made the damage irreversible. Studies focusing on quantitative analyses in more patients at different time points are being considered in our institution.

Conclusions

This study demonstrated that regional ventilation and perfusion functions improved remarkably at the 45-Gy dose point during RT. The potential changes in these functional

lung regions impact lung dosimetry. Adaptive planning based on V/Q SPECT scans during RT is ongoing, which may allow sparing of functional lung and improve therapeutic ratio.

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Summary

This study aimed to quantify the changes in functional lung regions during the course of radiation therapy and the impact of changes in these functional lung regions on lung dosimetry. We found significant changes occurred in the regional function map on single-photon emission computed tomography by the time a mean dose of 45 Gy had been delivered in patients with centrally located non-small cell lung cancer. Changes of functional lung volume and their impact on lung dosimetry had a remarkable interpatient heterogeneity.

Fig. 1.

Lung functional map schema lung functional map is shown on computed tomography (CT) (A) and ventilation single-photon emission computed tomography (V SPECT) (B) prior to radiation therapy (RT). Briefly the A region consists of functional defects corresponding to the location of tumor. B1 and B2 regions represent complete function defect induced by COPD or other unrecoverable disease. B3 region consists of temporarily dysfunctional lung induced by tumor. C region is normally functioning lung. Pre-RT V SPECT scans (C and D) show the delineation of FL1 (a threshold of 30% of the maximum uptake for each patient) and FL2 (FL1 combined with B3 region) respectively. In addition, the hot spot in the right central region in the V SPECT image is aerosol deposit, which is excluded for all analysis.

Fig. 2.

Changes in functional dose-volume histogram (DVH) on the lung dosimetry. Changes in the V SPECT from pretreatment (A) to during RT (B) are shown as example. (C) Lung DVHs based on V- and Q-defined functional lungs and CT-defined anatomic lungs, before (PRE) and during (DUR) RT. DVH = dose-volume histogram; Q = perfusion; V SPECT = ventilation single-photon emission computed tomography.

Table 1

Patient characteristics

Characteristic	No. of patients
Sex	
Male	11
Female	4
Age	
<70	9
>70	6
T stage	
T1	3
T2	3
T3	0
T4	9
Clinical stage	
II	3
III	12

Table 2

Summary of whole lung (WL) volume and total volume of functioning lung (FL) before (Pre-) and during (Dur-) RT for the 15 study patients

Patient	WL volume (cm ³)	V SPECT volume (cm ³)				Q SPECT volume (cm ³)			
		Pre-FL1	Pre-FL2	Dur-FL1	Dur-FL2	Pre-FL1	Pre-FL2	Dur-FL1	Dur-FL2
1	2557	1154	1460	975	1078	1134	1429	1430	1528
2	4456	1069	1131	1386	1414	2786	2813	2359	2381
3	3066	1961	1978	1999	2008	2361	2384	2225	2234
4	3301	1618	1659	1091	1122	2067	2108	1596	1621
5	4482	488	488	576	691	1820	1820	1347	1417
6	3925	369	1100	541	1562	710	2111	698	2002
7	2669	766	767	863	930	1571	1702	1141	1203
8	1997	974	1073	863	878	1400	1459	1188	1204
9	4280	409	538	2159	2202	1784	1840	2279	2312
10	5230	1328	1716	692	864	3283	3646	3081	3219
11	4100	427	545	1397	1467	3123	3147	3187	3205
12	2088	1007	1111	865	982	1427	1526	1220	1353
13	2644	1809	1827	1412	1426	1886	1903	1622	1631
14	2489	1148	1211	1612	1653	2009	2018	2202	2215
15	2279	938	953	488	515	1484	1499	1539	1542
<i>P</i> *	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001

Abbreviations: Q = perfusion; SPECT = single-photon emission computed tomography; V = ventilation.

* *P* values refer to FL1 and FL2 volumes as defined on V and Q SPECT pre-RT and during RT compared to WL volume of CT anatomic lung.

Table 3
Comparison of dose-volume characteristics between functional and anatomical lungs

Patient	V20						MLD (Gy)					
	FL1			FL2			FL1			FL2		
	WL	V	Q	V	Q	WL	V	Q	V	Q	V	Q
1	32.4	9.2	8.8	27.9	27.3	17.0	9.9	9.7	17.8	17.5		
2	19.2	12.8	12.4	17.3	13.2	9.8	8.4	7.5	10.1	7.8		
3	19.6	13.5	15.1	14.3	15.9	10.3	8.6	9.5	9.2	10.1		
4	25.2	20.2	17.0	22.2	18.6	13.2	11.8	10.8	13.0	11.8		
5	6.9	4.1	7.5	4.1	7.5	3.7	2.9	4.1	2.9	4.1		
6	28.7	32.12	30.0	34.4	32.2	16.8	19.0	17.8	20.0	19.4		
7	33.3	3.7	15.7	3.8	22.2	16.9	4.1	10.0	4.1	13.4		
8	33.9	26.6	22.5	32.6	25.6	14.5	14.0	12.3	16.8	13.8		
9	21.0	16.1	9.5	29.8	11.6	13.0	12.6	8.8	19.5	9.9		
10	22.3	19.8	12.7	35.8	20.4	12.5	11.8	10.5	18.0	13.2		
11	22.3	27.1	19.9	42.6	20.4	10.9	16.0	12.1	24.8	12.4		
12	31.9	19.3	19.2	25.2	23.2	13.4	11.6	11.0	14.3	12.9		
13	26.6	30.0	25.9	30.8	29.2	13.9	16.0	15.5	16.4	15.9		
14	34.2	30.6	33.0	34.2	33.3	16.5	16.0	17.0	18.0	17.2		
15	32.0	31.3	26.3	32.2	26.9	16.1	15.6	14.1	16.2	14.4		

Abbreviations are as in Table 2.

Values in boldface type indicate higher dosimetric parameters (V20 and MLD) in functional lung than in anatomical lung.