

# Emphysema quantification on computed tomography and its value in predicting radiation pneumonitis in lung cancer treated by stereotactic body radiotherapy

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## ABSTRACT

A large portion of patients with early-stage non-small-cell lung cancer (NSCLC) who are receiving stereotactic body radiation therapy (SBRT) are medically inoperable due to compromised pulmonary function, and among these patients pulmonary emphysema (PE) is common. However, the relationship between PE and radiation-induced lung injuries remains unclear. In this study, we aimed to describe the full spectrum of computed tomography (CT) features after SBRT for NSCLC, and to explore their relationship with variables, including PE and dosimetric factors. In all, 71 patients were enrolled. PE was quantified as the percentage of low attenuation area [attenuation values of <−860 Hounsfield units (HU)] within the radiation field (%LAA-860). Spearman's correlation and logistic regression were used to explore factors related to radiological features and radiation pneumonitis (RP). At the 1-year follow-up, acute radiological changes included: (i) diffuse consolidation, 11.3%; (ii) patchy consolidation and ground-glass opacities, 42.3%; and (iii) patchy ground-glass opacity, 14.1%. Late morphological changes occurred in 61.9% of patients (50.7% with a modified conventional pattern, 5.6% with a mass-like pattern and 5.6% with a scar-like pattern). Lower %LAA-860 was the only factor that was significantly associated with consolidation changes at 6 months after SBRT [odds ratio (OR), 0.008;  $P = 0.009$ ], and it was also a significant predictor for Grade  $\geq 2$  RP (OR, 0.003;  $P = 0.04$ ). Our study showed that patients with PE can benefit from SBRT on the condition that good control of dose–volume constraints is achieved.

**Keywords:** CT-lung; lung injury; pneumonitis; radiation

## INTRODUCTION

Stereotactic body radiotherapy (SBRT) is a proven effective treatment for early-stage non-small-cell lung cancer (NSCLC). Clinically, a large portion of patients with early-stage NSCLC who are receiving SBRT are inoperable due to compromised pulmonary function, and among these patients pulmonary emphysema (PE) is common. PE involves gradual damage to the lung tissue (e.g. thinning and

destruction of the alveoli or air sacs), and patients with emphysematous lungs are often very concerned about radiation-induced lung damage (RILD) after SBRT [1]. Appropriate evaluation of the influence of PE on treatment outcome is important in the management of these lung cancer patients.

PE is usually diagnosed and graded by one or two doctors based on the pretreatment computed tomography (CT) scan, and subjective

errors can occur [2–4]. However, recent studies have shown that PE can be graded by calculating the percentage of low attenuation area (%LAA), which is an objective quantitative measurement [5–7]. The %LAA has been defined as the percentage of LAA-860 or LAA-960 in the whole lung in most studies. SBRT is a novel technique that can deliver a high dose to the tumor, while minimizing the radiation dose to the surrounding normal tissue [8]. During the treatment, a large portion of lung receives a low or no dose of radiation; therefore, it is more reasonable to focus on the emphysematous changes within the radiation field.

Clinically, SBRT can be delivered via helical tomotherapy (HT-SBRT). In HT-SBRT, the patient moves into the machine while the radiation source continuously revolves around the patient [9]. The fan beam irradiates the target volume, slice by slice, making it feasible to focus on the radiated region. Having used HT-SBRT for a long time in our institution, we decided to investigate the predictive role of %LAA-860 with regard to the radiological changes and radiation pneumonitis (RP) after SBRT. It was hoped that such study might provide us with further insights into the role of PE in lung SBRT.

## MATERIALS AND METHODS

### Patients

The study was approved by the Zhongshan Hospital Ethics Committee, and institutional review board protocols were followed after informed consent was obtained from each patient. Patients receiving HT-SBRT at our institution between January 2011 and March 2017 were assessed for their eligibility. Inclusion criteria were as follows: (i) patient received HT-SBRT for primary Stage I NSCLC; (ii) availability of follow-up CT at 3 months, 6 months and 12 months after the treatment. Patients were excluded if: (i) they had interstitial lung disease; (ii) they had more than one target treated at the same time; or (iii) they received thoracic treatment or chemotherapy during follow-up. Patients were diagnosed pathologically or by a multidisciplinary team composed of experts from departments of radiology, radiation oncology, and pulmonary and thoracic surgery. Lung cancer stage was classified according to the TNM eighth edition by the American Joint Committee on Cancer on the basis of CT imaging and PET/CT using F-18 fluorodeoxyglucose (FDG-PET/CT). In some patients, for whom biopsy

**Table 1. Patient characteristics**

Parameter	Total (71)	Low %LAA-860 (36)	High %LAA-860 (35)	<i>P</i> value
Median age	73	72	75	0.004
(range)	(40–89)	(40–83)	(62–89)	
Median tumor diameter	2.30	2	2.5	0.568
(range)	(0.40–5.00)	(1.0–5.0)	(0.4–4.0)	
Median PTV (cm <sup>3</sup> )	26.06	32.09	44.39	0.165
(range)	(4.97–193.98)			
Gender				0.001
Male	52	20	32	
Female	19	16	3	
Smoking				<0.01
No	29	22	6	
Yes	42	14	29	
Histologic type				0.008
Squamous cell carcinoma	11	1	10	
Adenocarcinoma	37	23	14	
Clinically diagnosed	23	12	11	
Tumor location				
Central/peripheral	12/59	4/32	8/27	0.187
Upper, middle/lower	44/27	22/14	22/13	0.537

PTV = planning target volume.

is dangerous, a clinical diagnosis of lung cancer was made based on consistent CT findings and a pathological uptake value (SUVs) on PET scan. In all, a total of 71 patients were eligible for the study (Table 1).

### Treatment planning

The technique and treatment planning used for HT-SBRT patients has been described in previous reports [10]. At first, 4D-CT scans, which covered the entire breathing cycle, were obtained using a Big Bore CT Scanner (Siemens Somatom CT, Sensation Open; Siemens Healthcare, Munchen, Germany). The respiratory cycle was divided into 10 phases, which were labeled as T0%, T10%,... 90%. We defined T0% as end-inhalation and T50% as end-exhalation. These DICOM (Digital Imaging and Communications in Medicine) images were then transferred to XiO (version 4.8.01, Elekta, Sweden) for gross tumor volume (GTV) and internal target volume (ITV) contouring. The primary tumor in the enhanced CT was delineated as the GTV. The ITV was generated after including the extension of GTVs at all phases of the respiratory cycle on the 4D-CT scanning. The delineation of the planning target volume (PTV) and organs at risk (OARs) was performed on the Pinnacle<sup>3</sup> version 9.10 (Philips Radiation Oncology Systems, Fitchburg, WI). The PTV extended a margin of 0.5 cm from the ITV to account for set-up errors and residual tumor motion. All the information was subsequently transferred to the TomoTherapy (Hi-Art version 4.2.1, Accuray Inc., Madison, WI, USA) for SBRT planning. Fractionation schemes were 6 Gy × 10 fractions for tumors that were centrally

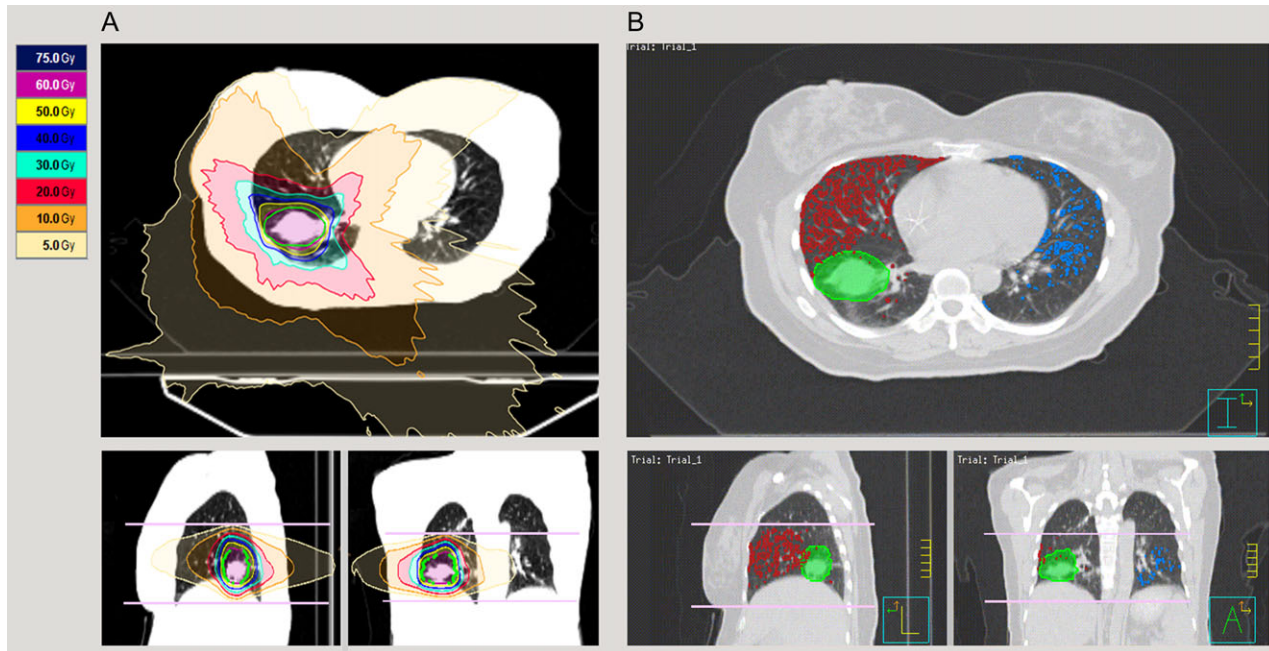
located or extensively adhered to the chest wall, and 10 Gy × 5 for other peripherally located tumors. At least 90% (95% in most cases) of the PTV received the prescribed dose. Doses to the OARs were limited according to the accepted standards of the Japan Clinical Oncology Group (JCOG) study 0403 [11].

### Percentage of low attenuation area measurements

Measurement of the low attenuation area was performed on the Pinnacle<sup>3</sup>. It was reported that the threshold of -860 Hounsfield Units (HU) correlated closely with airway dysfunction in chronic obstructive pulmonary disease (COPD) patients [7]. In another study, the cut-off value of average HU for predicting RP was determined as -850 HU [12]. Therefore, in this study, the lung field area with attenuation values < -860 HU was considered as the LAA. The Lung\_T was defined as the subvolume of lung being radiated. The Lung\_of\_interest (LOI) was defined as the affected side (tumor side) of the lung\_T without the GTV and central airway (i.e. the airway from the trachea to the lobar bronchi). The LAA-860 was defined as the lung area with attenuation of -860 HU or lower, and the %LAA-860 was the percentage of LAA-860 in the LOI. Figure 1 is an illustration of the measurement of %LAA-860.

### Follow-up and CT evaluation

Routine follow-up occurred at 3, 6 and 12 months after the treatment for the first year and every 6 months thereafter, with a diagnostic chest CT performed at each visit. If a recurrent cancer was suspected, FDG-PET/CT would be carried out.



**Fig. 1.** Illustration of treatment plan and emphysema quantification. (A) An SBRT treatment plan with isodose curve distribution are displayed for a NSCLC patient. (B) Color-coded display of abnormal emphysematous regions in both lungs. Lung\_T refers to the region between the two purple lines. Emphysematous regions with attenuation values < -860 HU within Lung\_T are shown in red (tumor side) and blue (opposite side). The Lung\_of\_interest (LOI) was defined as the affected side of lung\_T without the GTV and central airway. In this study, %LAA-860 refers to the percentage of red area in the LOI.

Images were evaluated on the institutional Picture Archiving and Communication Systems (GE Healthcare, Milwaukee). All the post-treatment CT scans were read and categorized by one radiation oncologist and one pulmonary radiologist in consensus. Patients' post-treatment images were divided into three periods based on the follow-up time: (i) Period 1: CT images obtained within 3 months after radiotherapy; (ii) Period 2: CT images obtained between 3 and 6 months after radiotherapy; (iii) Period 3: CT images obtained between 6 and 12 months after radiotherapy. In accordance with previous studies, CT scans performed within 6 months after the treatment were used to assess acute radiological injuries. Lung injuries occurring after 6 months were defined as radiation fibrosis. The features of acute radiological injuries were categorized according to Palma's report as follow: (i) diffuse consolidation; (ii) patchy consolidation and ground-glass opacities (GGOs); (iii) diffuse GGOs; (iv) patchy GGOs; or (v) no evidence of increasing density [13]. Radiation fibrosis was recorded based on Koenig's report: (i) modified conventional pattern

(including bronchiectasis, consolidation, and volume loss); (ii) mass-like pattern; (iii) scar-like pattern; or (iv) no findings [14].

RP was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Acute RP refers to RP that happens within 90 days from the beginning of radiotherapy, whereas late RP refers to RP that happens after 90 days from the beginning of radiotherapy.

### Statistical analysis

The categorical comparison was performed using Pearson's chi-squared test for discrete data and Student's *t*-test for continuous data. Univariate and multivariate logistic regression analysis were performed to explore factors associated with consolidation findings and RP. All *P* were 2-sided, and *P* < 0.05 was regarded as statistically significant. Statistical analyses were performed using the SPSS 23.0 (SPSS Inc. Chicago, IL, USA).

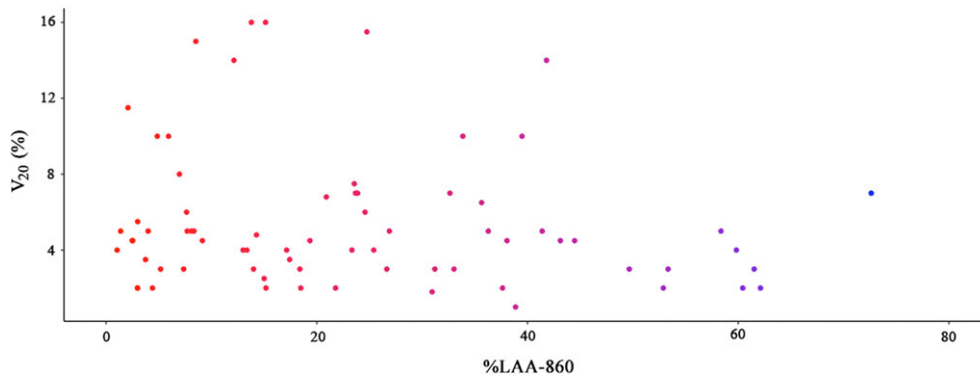


Fig. 2. Scatter plots illustrating information regarding each patient's %LAA-860 and its corresponding V<sub>20</sub>.

Table 2. Comparison of dosimetric parameters between patients with low and high %LAA-860

Parameter	Low %LAA-860 (Mean ± SD)	High %LAA-860 (Mean ± SD)	<i>P</i> value
MLD (Gy)	4.66 ± 3.07	4.64 ± 2.83	0.978
V <sub>2.5</sub> (%)	28.79 ± 13.30	28.57 ± 10.81	0.939
V <sub>5</sub> (%)	18.43 ± 9.57	17.86 ± 8.37	0.791
V <sub>10</sub> (%)	10.12 ± 6.42	10.08 ± 6.26	0.977
V <sub>20</sub> (%)	5.76 ± 4.08	5.16 ± 3.29	0.499
V <sub>30</sub> (%)	3.68 ± 3.00	3.03 ± 2.38	0.320
V <sub>40</sub> (%)	2.03 ± 2.07	1.83 ± 1.89	0.677
V <sub>50</sub> (%)	1.03 ± 1.49	0.81 ± 1.36	0.510
V <sub>60</sub> (%)	0.36 ± 0.81	0.21 ± 0.79	0.443

MLD = mean lung dose, V<sub>2.5</sub>, V<sub>5</sub>, V<sub>10</sub>, V<sub>20</sub>, V<sub>30</sub>, V<sub>40</sub>, V<sub>50</sub> and V<sub>60</sub> = percentage of normal lung receiving at least 2.5, 5, 10, 20, 30, 40, 50 and 60 Gy.

## RESULTS

### Patient treatment and emphysema quantification

In all, 71 patients were included in the study. The characteristics of the patients are summarized in Table 1. In the studied group, the % LAA-860 ranged from 1.04% to 72.02%, and the median %LAA-860 was 19.35%, based on which patients were divided into the low % LAA-860 group (LAA\_low) and high %LAA-860 group (LAA\_high).  $V_{20}$ , an important variable in quality assurance, ranged from 1% to 16%. Figure 2 shows the detailed information for each patient's % LAA-860 and lung  $V_{20}$ .

### Comparison between patients with high and low %LAA-860

Patients in the LAA\_low and LAA\_high groups did not differ in tumor diameter or tumor location (Table 1). However, male gender, older age, and smoking history were more frequent in the LAA\_high group, and these characteristics also explained its higher percentage of squamous cell carcinoma. Dosimetric comparison showed that there was no difference regarding MLD or  $V_{2.5}$ - $V_{60}$  between the two groups (Table 2).

### Radiation-induced lung damage

Acute radiation injuries were observed more often in Period 2 than in Period 1 (67.6% vs 21.1%). CT appearance of acute RILD at 3 months was classified as follows: (i) patchy GGOs in 4 lesions; (ii) patchy consolidation and GGOs in 9 lesions; (iii) diffuse consolidation in 2 lesions; (iv) no evidence of increasing density in 56 lesions. CT appearance of acute RILD at 6 months was classified as follows: (i) patchy GGOs in 10 lesions; (ii) patchy consolidation and GGOs in 30 lesions; (iii) diffuse consolidation in 8 lesions; or (iv) no evidence of increasing density in 23 lesions. Late radiographic lung injuries were recorded as follows: 50.7% of lesions showed modified conventional pattern, 5.6% of lesions showed mass-like, 5.6% of lesions showed scar-like, and 38.1% showed no findings.

Regarding acute RP, most patients exhibited Grade 0–1 RP, 2 patients showed acute Grade 2 RP and 1 showed acute Grade 3 RP. Late Grade 0–1 and Grade 2 RP were observed in 52 (73.2%) and 13 (18.3%) patients, respectively. There were 6 patients (8.5%) who showed late Grade 3 RP.

### Analysis of factors related to radiological changes and radiation pneumonitis

We evaluated the relationship between various clinical factors and radiological changes after SBRT. The results of the univariate analysis can be seen in Table 3. Multivariate analysis (Table 4) showed that lower %LAA-860 was the only factor that was significantly associated with consolidation changes at 6 months after SBRT (odds ratio [OR], 0.008; 95% CI, 0.001–0.294;  $P = 0.009$ ). Figure 3 showed examples of radiological injuries in patients with low and high %LAA-860, respectively, with a color-coded display of %LAA-860.

Regarding the clinical factors associated with RP after SBRT, % LAA-860 and  $V_{2.5}$ - $V_{60}$  were found to be associated with Grade  $\geq 2$  RP (Table 5). Table 5 also showed that %LAA-860 was the only significant independent predictor of RP (OR, 0.003; 95% CI,

**Table 3. Univariate analysis of factors associated with consolidation changes after SBRT**

Parameter	Univariate <i>P</i> value	
	Consolidation changes at 3 months	Consolidation changes at 6 months
Sex (male vs female))	0.998	0.814
Age (years)	0.601	0.196
Tumor size (cm)	0.269	0.212
Histological		
Adenocarcinoma	1	1
Squamous cell carcinoma	0.058	0.852
Unknown	0.036	0.472
Tumor location		
Central vs peripheral	0.326	0.872
Upper, middle vs lower	0.428	0.448
Smoking (yes vs no)	0.658	0.430
%LAA-860	0.237	0.002
PTV (cm <sup>3</sup> )	0.065	0.274
MLD (Gy)	0.055	0.065
$V_{2.5}$ (%)	0.040	0.073
$V_5$ (%)	0.068	0.041
$V_{10}$ (%)	0.013	0.025
$V_{20}$ (%)	0.035	0.031
$V_{30}$ (%)	0.061	0.026
$V_{40}$ (%)	0.029	0.045
$V_{50}$ (%)	0.007	0.018
$V_{60}$ (%)	0.014	0.077

PTV = planning target volume, LAA = low attenuation area, MLD = mean lung dose,  $V_{2.5}$ ,  $V_5$ ,  $V_{10}$ ,  $V_{20}$ ,  $V_{30}$ ,  $V_{40}$ ,  $V_{50}$  and  $V_{60}$  = percentage of normal lung receiving at least 2.5, 5, 10, 20, 30, 40, 50 and 60 Gy, PE = pulmonary emphysema.

0.001–0.766;  $P = 0.04$ ), indicating the protective role of emphysematous changes for lung cancer patients receiving SBRT.

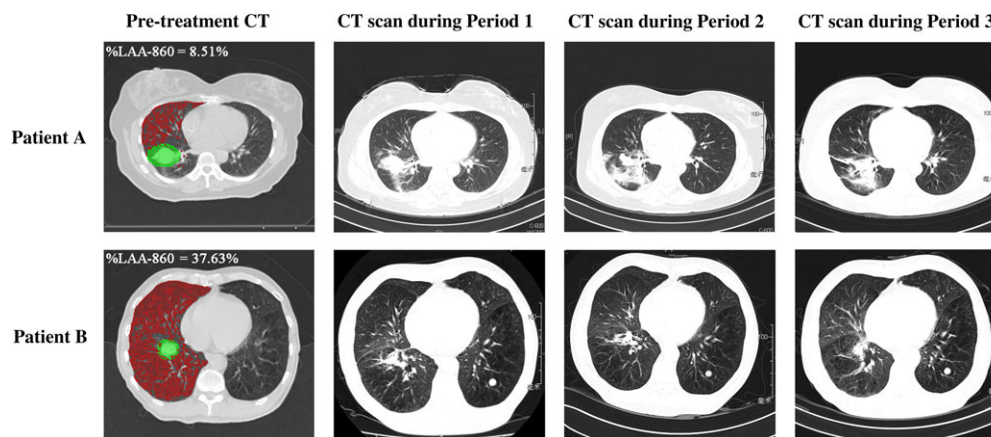
### Relationship between early radiological changes and radiation pneumonitis

We also explored the relation between radiological changes during Period 1 and late RP. Of the nine patients who showed

**Table 4. Multivariate analysis of factors associated with consolidation changes after HT-SBRT**

Parameter	Consolidation changes at 3 months		Consolidation changes at 6 months	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
<b>Histological</b>				
Adenocarcinoma	1	1		
SCC	6.723 (0.809–55.852)	0.078		
Unknown	3.418 (0.492–23.726)	0.214		
%LAA-860			0.008 (0.001–0.294)	0.009
$V_{2.5}$ (%)	1.009 (0.896–1.137)	0.883		
$V_5$ (%)			0.919 (0.757–1.115)	0.390
$V_{10}$ (%)	1.263 (0.784–2.035)	0.338	1.357 (0.848–2.172)	0.203
$V_{20}$ (%)	0.576 (0.212–1.561)	0.278	0.530 (0.161–1.740)	0.295
$V_{30}$ (%)			3.148 (0.675–14.675)	0.144
$V_{40}$ (%)	0.601 (0.129–2.807)	0.517	0.272 (0.060–1.238)	0.092
$V_{50}$ (%)	6.245 (0.760–51.296)	0.088	2.857 (0.724–11.271)	0.134
$V_{60}$ (%)	0.578 (0.101–3.296)	0.537		

$V_{2.5}$ ,  $V_5$ ,  $V_{10}$ ,  $V_{20}$ ,  $V_{30}$ ,  $V_{40}$ ,  $V_{50}$  and  $V_{60}$  = percentage of normal lung receiving at least 2.5, 5, 10, 20, 30, 40, 50 and 60 Gy.



**Fig. 3.** Pre-treatment and follow-up CT scans of two patients with low and high %LAA-860, respectively. Low attenuation areas on the tumor side are shown in red.

consolidation changes at 3 months after the treatment, three of them developed late Grade 3 RP, and five of them developed late Grade 2 RP. The Chi-Square test indicated that consolidation changes at 3 months after the treatment were significantly related to late Grade 3 and Grade  $\geq 2$  RP ( $P = 0.024$  and  $P < 0.001$ , respectively).

## DISCUSSION

SBRT has become the standard of care for inoperable, early-stage NSCLC patients [15]. At the same time, RP is one of the most frequent toxicities experienced by patients after SBRT, and severe RP can be fatal. For risk factors related to RP, lung mean dose and certain percentage volume limits have been well studied and are used

**Table 5. Analysis of factors associated with Grade  $\geq 2$  RP**

Parameter	Univariate analysis	Multivariate analysis	
	P value	OR (95% CI)	P value
Sex (male vs female)	0.777		
Age (years)	0.408		
Tumor size (cm)	0.132		
Histological			
Adenocarcinoma	1		
Squamous cell carcinoma	0.818		
Unknown	0.843		
Tumor location			
Central vs peripheral	0.407		
Upper, middle vs lower	0.759		
Smoking (yes vs no)	0.196		
%LAA-860	0.039	0.003 (0.001–0.766)	0.040
PTV (cm <sup>3</sup> )	0.153		
MLD (Gy)	0.067		
V <sub>2.5</sub> (%)	0.036	1.038 (0.908–1.186)	0.588
V <sub>5</sub> (%)	0.036	0.824 (0.614–1.104)	0.194
V <sub>10</sub> (%)	0.010	1.531 (0.923–2.541)	0.099
V <sub>20</sub> (%)	0.015	0.658 (0.189–2.288)	0.511
V <sub>30</sub> (%)	0.020	0.572 (0.104–3.149)	0.521
V <sub>40</sub> (%)	0.008	2.184 (0.347–13.761)	0.405
V <sub>50</sub> (%)	0.003	3.975 (0.658–24.006)	0.133
V <sub>60</sub> (%)	0.030	0.236 (0.045–1.231)	0.087

PTV = planning target volume, LAA = low attenuation area, MLD = mean lung dose, V<sub>2.5</sub>, V<sub>5</sub>, V<sub>10</sub>, V<sub>20</sub>, V<sub>30</sub>, V<sub>40</sub>, V<sub>50</sub> and V<sub>60</sub> = percentage of normal lung receiving at least 2.5, 5, 10, 20, 30, 40, 50 and 60 Gy, PE = pulmonary emphysema.

during treatment planning [16, 17]. However, being a local treatment modality, the influence of lung parenchyma features has been rarely studied. For patients with lung cancer who also have COPD, surgery often cannot be performed because of their low cardiopulmonary reserve. Thus PE, being a subtype of COPD, was common in patients receiving SBRT. The relationship between PE and RILD can be complex. On the one hand, emphysematous lung contains less lung parenchyma for radiation exposure. On the other hand, patients with PE are prone to having limited tolerance to any reduction in lung function, making them more vulnerable to RILD.

CT image-based quantitative analysis has been widely used in studying PE and pulmonary function, and has shown great clinical relevance [18, 19]. However, its value in lung radiotherapy has rarely been studied. Several studies have discussed the relationship

between PE and RILD. Our work is distinguishable from those studies in two respects. First, compared with visual grading of PE, which is highly dependent on the judgement of observers, we used %LAA-860, an objective quantitative measurement. Second, whereas in previous studies %LAA was defined as the percentage of LAA in the whole lung, we focused on the percentage of LAA in the radiated field.

Our study showed that increased %LAA-860 was associated with a significantly lower rate of consolidation changes at 6 months after SBRT treatment. Some other studies have reported similar results [4, 5]. Emphysema is anatomically equivalent to a lack of lung tissue. It is reasonable to expect less risk of lung toxicity if there is less lung tissue to be injured. Defraene *et al.* reported that higher baseline lung density was related to higher  $\Delta$ HU<sub>max</sub> (Changes in

Hounsfield Units), which is also in line with our findings [20]. Another explanation for such a result might be the influence of smoking. Smoking is a well-known risk factor for PE. A pooled analysis conducted by Vogelius *et al.* showed that smoking had a protective effect against RILT [21]. It has also been suggested that those 'dead lungs' may not be as sensitive to RILD as healthy, well-perfused lung tissue [22], and the absorbed doses of normal lung tissues in patients with high %LAA-860 may be lower than those in patients with lower %LAA-860 or without PE.

In our study, lower %LAA-860 was also significantly related to Grade  $\geq 2$  RP. Some other studies have also reported PE as playing a protective role [2, 12, 23]. Saito *et al.* reported that the cut-off value of 50% in the %LAA-860 indicated the point at which risk for RP became significant [12]. Theoretically speaking, a lower probability of density changes after the treatment could lead to lower rates of RP. However, there are studies that suggest the opposite [24, 25], and Yamamoto *et al.* found no significant association between %LAA-860 and Grade 2–3 RP [5]. It should be pointed out that in all of these studies, %LAA-860 represents the percentage of LAA-860 in the whole lung, rather than the emphysematous changes within the radiation field. In addition, these studies used 3D-conformal radiation therapy or had treatment plans that differed from ours, which may have compromised both their accuracy and comparability. We consider that these conflicting results indicate there was heterogeneity in the patients with PE, as reported in previous studies [26, 27], and that the heterogeneity may have influenced the treatment outcome. Furthermore, we think that good control of  $V_{20}$  contributed to the validity of our results.  $V_{20}$  is a well-known significant predictor for RP [17, 28]. In this series, our median  $V_{20}$  was 4.5%, well below the limits required in RTOG protocols ( $V_{20}$  of  $<10\%$ ), and only two patients in the LAA-high group had a  $V_{20}$  of  $>10\%$ , which reduced the risk of respiratory compromise. Therefore, although the limit of  $V_{20}$  has been suggested to be 10%, we recommend it be as low as possible for NSCLC patients receiving SBRT.

In our study, more patients showed CT findings during Period 2 than during Period 1 (67.6% vs 21.1%); thus, we hypothesized that an early sign of radiological changes might indicate vulnerability to radiation damage. Further analysis confirmed that conjecture. Our results showed that an early appearance of consolidation changes was related to severer RP in the future. Although %LAA-860 did not show a relationship with early radiological changes, we think such results are worth mentioning, because they indicate the importance of regular follow-up after SBRT treatment. Genomics studies have confirmed that a portion of patients (e.g. ATM rs189037 variant, SNP rs10898880) may be more vulnerable to RP [29, 30]. Therefore, patients who show early signs of radiological changes should be warned against further infection and followed up carefully.

The present study had some limitations. First, it was a retrospective study conducted in a single institute with a limited sample size. Second, since a pulmonary function test was not mandatory for patients without compromised breathing, factors such as forced expiratory volume in 1 s and lung ventilation–perfusion data were not available. Further studies with a larger sample size and more detailed analysis are wanted to yield more confirmative results.

In conclusion, our study showed that pretreatment measurement of %LAA-860 could provide incremental information for clinicians, and will be useful in optimizing the therapeutic strategy for early-stage NSCLC patients receiving SBRT. Lower %LAA-860 is the only factor that was significantly associated with consolidation changes at 6 months after SBRT (OR, 0.008;  $P = 0.009$ ), and it was also a significant predictor for Grade  $\geq 2$  RP (OR, 0.003;  $P = 0.04$ ). Patients with PE could also benefit from SBRT on the condition that a good control of dose–volume constraints is achieved. Last, but not least, regular follow-up after SBRT for NSCLC is important, especially for those who show early signs of radiological changes.

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this study.

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