Relationship between diseased lung tissues on computed tomography and the motion of the fiducial marker near a lung cancer

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Short running title:

Tumor motion in diseased lung

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Conflict of interest:

Authors do not have any conflict of interest to declare.

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Abstract

BACKGROUND: For lung cancer patients with poor pulmonary function due to emphysema or fibrosis, it is important to predict the amplitude of internal tumor motion to minimize the irradiation of the functioning lung tissue before receiving stereotactic body radiotherapy.

MATERIALS AND METHODS: Two board-certified diagnostic radiologists independently assessed the degree of pulmonary emphysema and fibrosis on computed tomography (CT) in 71 patients with peripheral lung tumors before real-time tumor-tracking radiotherapy (RTRT). The relationships between CT findings of the lung parenchyma and the motion of the fiducial marker near the lung tumor were investigated. Thirty patients had normal pulmonary function. Twenty-nine patients had obstructive pulmonary dysfunction (FEV1/FVC < 70%), 6 patients had constrictive dysfunction (%VC < 80%), and 16 had mixed dysfunction.

RESULTS: The upper region was associated with smaller tumor motion, as expected ($p=0.0004$), and presence of fibrosis ($p=0.088$) and pleural contact of the tumor ($p=0.086$) were weakly associated with the tumor motion. The presence of fibrotic change in lung tissue was associated with smaller tumor motion in the upper region ($p<0.05$) but not in the lower region. The findings of emphysema and

pulmonary function tests were not associated with tumor motion.

CONCLUSIONS: Tumors in the upper region of lungs with fibrotic changes have smaller motion than those in the upper region of lungs without fibrotic changes. Tumor motion in the lower lung region was not significantly different between patients with and those without lung fibrosis. Emphysema was not associated with the amplitude of tumor motion.

Key words: lung tumor motion, lung fibrosis, emphysema, real-time tumor-tracking radiotherapy

Introduction

Focused, high-dose radiotherapy is increasingly indicated for inoperable peripheral lung cancers (1-3). Inoperable patients with such tumors often have moderate to severe pulmonary function impairment due to morphological changes of the diseased lung such as pulmonary emphysema, inflammatory changes, and fibrosis with our without history of previous thoracic surgery. It is crucial to minimize the irradiation volume of the functioning lung tissue for these patients. Accordingly, it is important to predict the amount of tumor motion from clinical and radiological findings before treatment in order to determine adequate internal margins for the clinical tumor volume during radiotherapy for these patients.

Previous studies have shown that simple pulmonary function, as assessed by such parameters as vital capacity and forced vital capacity, does not have predictive value for tumor motion (4, 5). In addition, these simple tests have recently been shown to be inadequate for the assessment of obstructive disease, and more precise criteria of pulmonary function have been recommended instead (6). On the other hand, morphological changes of the lung tissue around the tumor as measured using high resolution computed tomography (CT), which is known to be useful for the evaluation of obstructive, inflammatory, or fibrotic changes of the lung, may be useful

for predicting tumor motion (7, 8). Therefore, in this study, we compared two parameters with respect to their efficacy in predicting tumor motion: the global standard of pulmonary function of obstructive lung disease and morphological changes of the diseased lung around the tumor. These two parameters were compared with the trajectory of the fiducial marker near the tumor as measured during real-time tumor-tracking radiotherapy (RTRT) which has been shown to be useful to estimate the amplitude of the tumor (9 - 12).

Materials and Methods

After inserting a fiducial marker near the lung cancer, planning CT scan was performed while patients hold their breath at the end of expiration. We used an RTRT system that can track a gold marker in the body of a patient during actual irradiation of therapeutic beam as reported before (9, 10). Patients were asked to relax on the treatment table, and no additional method was used to control the patient's respiration during actual radiotherapy. The advantage of RTRT is that the motion of the fiducial marker can be automatically detected by pattern recognition method during the delivery of treatment beam every 0.033 seconds (9). The linac is gated to irradiate the tumor only when the fiducial marker is within gating window, usually ± 2.0 mm, from its planned position. Therefore, even if the magnitudes of

tumor motion between CT planning, initial set-up, and during treatment are different, we do not need to re-plan or to expand/contract internal margin at a different time in treatment. Treatment time may prolong if the magnitude of tumor motion increase since linac must wait longer the fiducial marker coming into the gating window at the end of exhale. If the baseline of the tumor motion changes during irradiation, then we adjust the table position for the trajectory of the marker position coming into the gating window (10).

Three to four fiducial markers with a diameter of 1.5 mm were inserted through a bronchial fiberscope near the lung tumor (11). Coordinates of one of the markers nearest to the tumor were recorded in log files at intervals of 0.033 s using the RTRT system (12). To measure marker movement, log files of the RTRT system were analyzed using a previously described computer program (10).

In this study, the *x*, *y*, and *z* directions were consistent with the left-right, cranio-caudal, and ventro-dorsal directions, respectively. We assumed the motion of fiducial markers nearest to the tumor, usually within 1 cm from the tumor boundary, as the actual tumor motion in the *x, y*, and *z* directions. The amplitude of the fiducial marker differed patient by patient and also fluctuated even in the same patient during treatment. Therefore, we have randomly sampled respiratory cycles from each

patient. Mean ± standard deviation (SD) of sampling numbers of respiratory cycle was 79 ± 53 for one patient. The variations in sampling numbers of respiratory cycle were due to the length of treatment time but not due to researchers' preference. We first measured the mean amplitude and SD of the amplitude during treatment for each patient to represent our data series. Since it is important to know the distance that the actual tumor is likely to move in the thoracic space during radiotherapy, we also measured the maximum three-dimensional amplitude during treatment for each patient.

The three-dimensional maximum movement was estimated from the following formula using the mean plus one SD of the amplitude along each direction:

estimated three-dimensional maximum movement (in mm) = $\sqrt{x^2 + y^2 + z^2}$.

Thus, one patient has only one "estimated three-dimensional maximum movement".

Chest CT images were acquired to plan the radiation treatment for all patients within 1 week after the insertion of gold markers and within 1 week before the start of radiotherapy. We used a 4-detector acquisition high resolution CT (Aquilion Multi Toshiba, Tokyo, Japan) for the evaluation of morphological changes of the lung tissue. In all cases, we scanned the entire lung in the exhaled position. Contrast medium was not used for the chest CT scan. All scan data were reconstructed

using voxels of 1 x 1 x 1 mm.

Two board-certified diagnostic radiologists independently interpreted the CT images to assess the presence of fibrotic changes. Grossly speaking, a diagnosis of fibrotic changes was made when non-segmental reticular abnormalities and ground-glass attenuation were observed in the lung parenchyma (Fig. 1). The percentage of low attenuation volume (%LAV) was used to quantify pulmonary emphysema objectively (13-15). The %LAV was calculated as the area under the curve (AUC) under the cut-off-line low attenuation value at -950HU divided by total AUC using the Virtual Place Advanced software package (AZE, Tokyo, Japan) and workstation according to the following formula:

%low attenuation volume (%LAV) = 100 x AUC of under -950HU / total AUC of total CT density distribution.

The location of the tumor was categorized into two groups as follows: the upper region (n = 41), for tumors restricted to the right or left upper lobes without lingual segment; the lower region (n = 30), for tumors involving the middle and right lower lobe and for tumors in the lingual segment and left lower lobe. The presence of pleural contact of the tumor, which could be a sign of fixation of the tumor to the chest wall and reduction of tumor motion, was also diagnosed on the same CT. The

maximum diameter of the tumor on the transaxial CT planes was defined as the tumor size.

The pulmonary functions and body mass index of all patients were assessed before radiotherapy. The ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1.0/FVC ×100 = FEV1/FVC) and the percent vital capacity (%VC) were evaluated (6).

JMP version 7.0.1 (SAS Institute Japan, Tokyo) was used for statistical analysis. Since the estimated three-dimensional maximum movements do not necessarily have normal distribution, we use the median of the estimated three-dimensional maximum movement in the following analysis and used non-parametric statistical analysis. A correlation coefficient (Spearman's correlation coefficient by rank test) was calculated between the effects of various factors and estimated three-dimensional maximum tumor movement. Mann-Whitney *U* test was used to compare the median values between two groups. A probability value of less than 0.05 was considered statistically significant.

Results

Seventy-one patients (52 male, 19 female) treated from 2001 to 2006 were entered into the study (Table 1). All patients were subjects for stereotactic

hypofractionated high-dose small-field irradiation using RTRT system. The median patient age was 73 years (range, 36 to 85 years). Fifty-six patients with primary lung cancer and six patients with a metastatic lung tumor from other organs were included. The other nine patients had unknown pathology. The maximum tumor diameter ranged from 0.5 to 7.4 cm with a median of 2.7 cm. Four patients had a history of surgical lobectomy. No patients had thoracic nodal involvement in radiological examinations.

Twenty patients had normal pulmonary function. Twenty-nine patients had obstructive pulmonary dysfunction (FEV1/FVC < 70%), six patients had constrictive dysfunction (%VC < 80%), and sixteen patients had mixed dysfunction. The mean ± standard deviation values of FEV1/FVC and %VC were 62.5 ± 16.9% and 94.9 ± 25.7%, respectively. There was a significant negative correlation between FEV1/FVC and log %LAV (correlation coefficient, -0.494. $p<0.0001$) confirming that %LAV has morphometric value for pulmonary emphysema (Fig. 2).

The mean ± SD of mean amplitudes among the 71 patients was 3.7 ± 4.6, 6.7 ± 6.2, and 4.4 ± 4.8 mm along right-left, cranio-caudal, and antero-posterior directions, respectively. The mean ± SD of SD of amplitudes among the 71 patients was 1.2 ± 2.2 mm, 1.8 ± 2.8 mm, and 1.1 ± 1.5 mm along each direction, respectively.

The mean plus one SD of the amplitude of the fiducial marker among 71 patients distributed from 0.2 to 32.1 mm, from 0.2 to 31.2 mm, and from 0.5 to 34.8 mm along right-left, cranio-caudal, and antero-posterior directions, respectively. The estimated three-dimensional maximum movements were calculated using these data for each patient. The median and range of estimated three-dimensional maximum movements of 71 patients was 11.9 mm (1.79 mm - 50.38 mm).

The relationship between each factor and the estimated three-dimensional maximum movement, which we used as the surrogate of the tumor motion in this study, is shown in Table 2. The presence of fibrosis was weakly associated with the tumor motion, but this association did not reach the level of statistical significance ($p = 0.088$). The pulmonary emphysema estimated by %LAV was not associated with the tumor motion. The median of the estimated three-dimensional maximum movement in the lower regions of the lung was significantly larger than that in the upper regions, as expected ($p=0.0004$). The presence of pleural contact of the tumor was weakly associated with the tumor motion, but this association did not reach the level of statistical significance ($p=0.086$). Tumor size was not associated with tumor motion. The body surface area and the results of the pulmonary function tests, FEV1/FVC and %VC, were also not associated with tumor

motion. The median of the estimated three-dimensional maximum movement in the four postoperative patients was smaller than that of the patients with no prior surgery ($p = 0.001$).

Next, we examined the influence of fibrotic change on tumor motion in the upper region and on tumor motion in the lower region (Figure 3). In the upper region, tumor motion was significantly smaller in the lungs with fibrotic change than in those without fibrotic change ($p<0.05$). In the lower region, there was no significant influence of fibrotic change on tumor motion.

An estimated three-dimensional maximum movement of more than 20 mm was recognized in 10 patients. In contrast to the general tendency of smaller tumor motion in the upper region, 6 of the 10 tumors that showed more than 20 mm of movement were located in the upper region.

The combination of FEV1/FVC and log %LAV was not effective for predicting tumor motion (Figure 2). The combination of %VC and $\%FEV_1$/FVC was also ineffective for this purpose (Figure 4).

Discussion

Fibrotic or emphysematous changes of lung tissue are known to produce dynamic changes in respiratory function. Hyperinflation of the lung can affect the motion of

the diaphragm (16) and can result in so-called “paradoxical” motion (17). Pleural adhesion of lung cancers can also be associated with restricted tumor motion (10). Also, cardiopulmonary function affects the tumor mobility and respiration patterns to a certain degree due to the difference in cardiac beat, ejection fraction, and tidal volume (10).

Our results demonstrated that tumor motion is significantly smaller in the upper region of lungs with fibrotic change than in those without fibrosis. In the lower region of the lungs, the presence of fibrosis did not significantly influence the tumor motion, probably because the motion in this region is dominantly affected by the motion of the diaphragm. On the other hand, among the 10 tumors with an estimated three-dimensional maximum movement of more than 20 mm, 6 were located in the upper lung region. This conflicting finding suggests the difficulty of predicting the internal margin for individual patients (16).

It is well known that the diaphragmatic motion often decreases in patients with emphysematous lung (17). Tumors in the normal lung move mostly in a cranio-caudal direction due to diaphragmatic motion (18). We therefore hypothesized that pulmonary emphysema could be a cause of reduced tumor motion. We are certain that %LAV is a reasonable parameter to estimate the severity of

emphysema since %LAV was significantly associated with FEV1.0/FVC in this study, and such an association has also been suggested by other authors (13, 15). However, the present study showed no significant reduction in tumor motion with the increase in %LAV. Recent studies have shown that the diaphragm sometimes exhibits so-called "paradoxical" motion. (17,19). Emphysema may cause complex tumor motion resembling the complex motion of the diaphragm, rather than simply causing a reduction in tumor motion.

We have previously shown that neither VC alone nor FEV_1 alone was associated with tumor motion (5). However, pulmonologists suggested us that %VC and FEV_1/FVC should be used instead of VC and FEV_1 to assess its pathological meaning (6). We therefore used these combined parameters in the present study, but found that the variables still had no significant value for predicting tumor motion even in this form.

The present results suggested usefulness and limitation of CT assessment before radiotherapy in general. Moreover, as we published previously (18), the speed and amplitude of the tumor motion was variable even in the same patient at different treatment day. In other words, assessment of tumor motion at the initial treatment day may not be applicable in the second treatment day. Stereotactic body frame

and rhythm generators were shown to be not useful to reduce these uncertainties in a recent study (20). Image-guided radiotherapy using on-board cone-beam CT (21), four-dimensional cone beam CT guidance(22), a margin model based on the internal motion(23), or gating based on external signals (24) are useful to reduce daily set-up error and lung motion uncertainties to some extent, but still have limitation for intra-fractional variation of tumor motion.

Treatment results of RTRT for T1N0M0 non-small cell lung cancer were shown to be encouraging using 48 Gy in 4 fraction (25). In RTRT, as long as the position of the marker relative to the tumor mass is not different from its planned position at the end of exhale phase, irregularity in the tumor trajectory does not affect the accuracy of irradiation. Therefore, we are not customizing margins for each patient when we use RTRT system. We use 5-mm PTV margin in RTRT to cover possible residual errors such as discrepancy in respiratory phase between the planning and actual treatment, minor displacement of the fiducial marker, and shrinkage of the tumor during 1-week treatment. However, when we cannot insert fiducial markers near the tumor, we use individualized internal margin for each tumor by taking CT scans at three different respiratory phases (26). From the findings in the present study, we would be able to reduce the internal margin for tumors at upper lobe with fbrotic

changes but not for tumors at upper lobe without fibrotic changes when we treat the patients without fiducial markers. In RTRT using treatment time longer than 1-week, re-plan or margin expansion/contraction may be required since the distance between the tumor and the fiducial marker can be different from its planned position.

In conclusion, tumor location remained an important parameter, as expected, but tumor motion larger than 20 mm was seen as often in the upper region as the lower region. Although conventional static CT images and pulmonary function tests were still inadequate for predicting the internal margins, the fibrotic change of the lung and the pleural contact of the tumor were weakly associated with the tumor motion. In particular, fibrotic change of lung was associated with the motion of tumors in the upper region. The presence of emphysema as estimated by %LAV on CT was not associated with the tumor motion. At present, we do not have any simple way to predict the tumor motion based on pulmonary pre-treatment tests and CT images in order to avoid resulting potential target volume miscoverage. This study suggested an additional guide avoiding miscoverage of the target volume and a caution for simple stratification of the patients into upper and lower lung region in the determination of internal margin.

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Figure legends

Figure 1. An example of a lung tumor in the left upper region in a patient with fibrotic change of the lung. The mean±SD amplitudes in the x, y, and z directions were 2.4±0.3, 4.1±0.8, and 2.8±0.2 cm, respectively. The tumor was treated by RTRT and controlled well.

Figure 2. Distribution of tumor motion according to FEV1/FVC and log (%LAV). The blue area in the CT image is the area for which the CT value is lower than the threshold of - 950 HU and was used for the estimation of %LAV. The sizes of the circles indicate the estimated three-dimensional maximum movement of the tumors in the lung with the log (%LAV) value in the patients with the FEV1/FVC value.

Figure 3. Relationship between tumor motion and presence of fibrosis by region. The black symbols indicate tumors with fibrosis, and the white symbols tumors without fibrosis. There was a significant difference in the amount of tumor motion in the upper region between tumors with fibrosis and those without fibrosis, while there was a significant difference in the amount of tumor motion between the upper region

and lower region. There was no significant relationship between tumor motion and the presence of fibrosis in the lower region.

Figure 4. Distribution of tumor motion according to FEV1/FVC and %VC

There was no statistically significant correlation between FEV1/FVC and %VC.

Table 1. Patients characteristics

Gender male : female	52 : 19
Age	median 75, 36 – 85
Body surface area(m^2)	median 1.57, 1.22 – 2.19
Post-operative lung (yes or no)	4 : 67
Pulmonary function tests	
FEV1/FVC	median 63.0, 31.4 – 96.0
%VC	median 95.3, 40.1 – 153.8
Morphological change of the lung	
Presence of fibrosis (yes or no)	27 : 44
%LAV	median 0.4, 0.0 – 45.2
Histopathological diagnosis	
Adenocarcinoma	35
Squamous cell carcinoma	20
Large cell carcinoma	1
Metastasis	6

unknown	9		
Tumor location			
upper or lower	41 : 30		
right or left	39 : 32		
right upper or right lower	21 : 18		
left upper or left lower	15 : 17		
Tumor size (mm)	median 27,	5 – 74	
Presence of pleural contact (yes or no)	49 : 22		
Nodal involvement (yes or no)	71 : 0		

Table 2 Relationship between each factor and tumor motion

	C.C.	P value
Body surface area	0.128	0.296
Post-operative lung (yes or no)	4:67	0.001
Pulmonary function tests		
FEV1/FVC	-0.157	0.196
%VC	0.162	0.184
Morphological change of the lung		
Presence of fibrosis (yes or no)		0.088
%LAV	0.021	0.858
Tumor characteristics		
Tumor location		
upper or lower		0.0004

right or left		0.326
right upper or right lower		0.026
left upper or left lower		0.057
Tumor size	-0.021	0.859
Presence of pleural contact (yes or no)		0.086

Figure 1

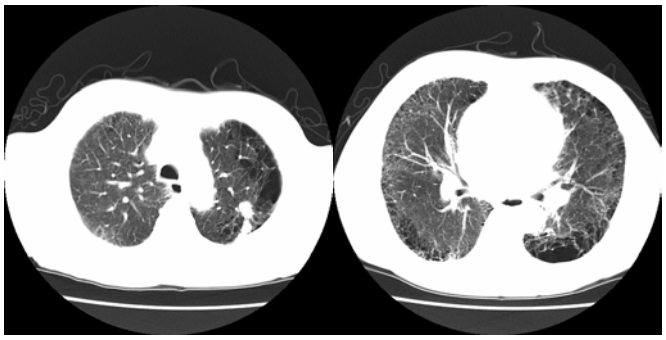


Figure 2

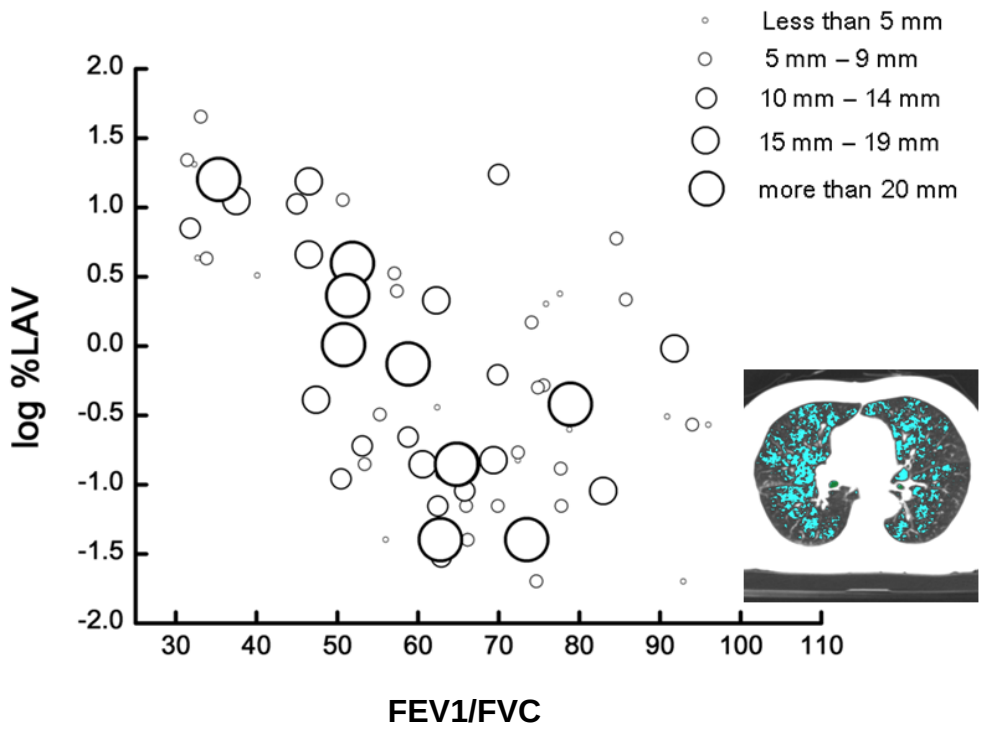

Less than 5 mm
5 mm – 9 mm
10 mm – 14 mm
15 mm – 19 mm
more than 20 mm
log %LAV
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
30
40
50
60
70
80
90
100
110
FEV1/FVC

Figure 3

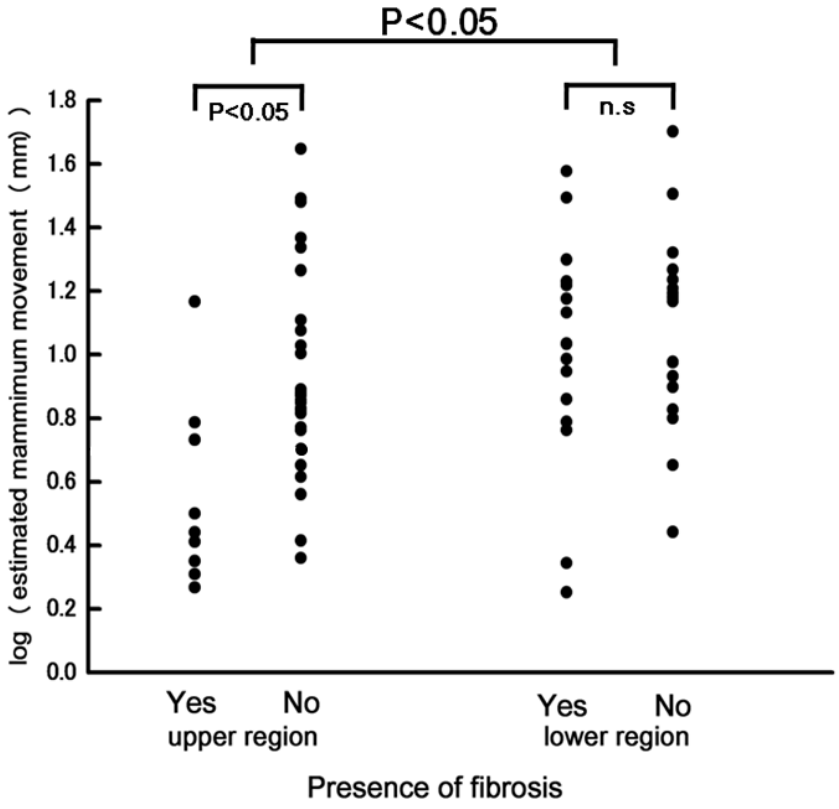
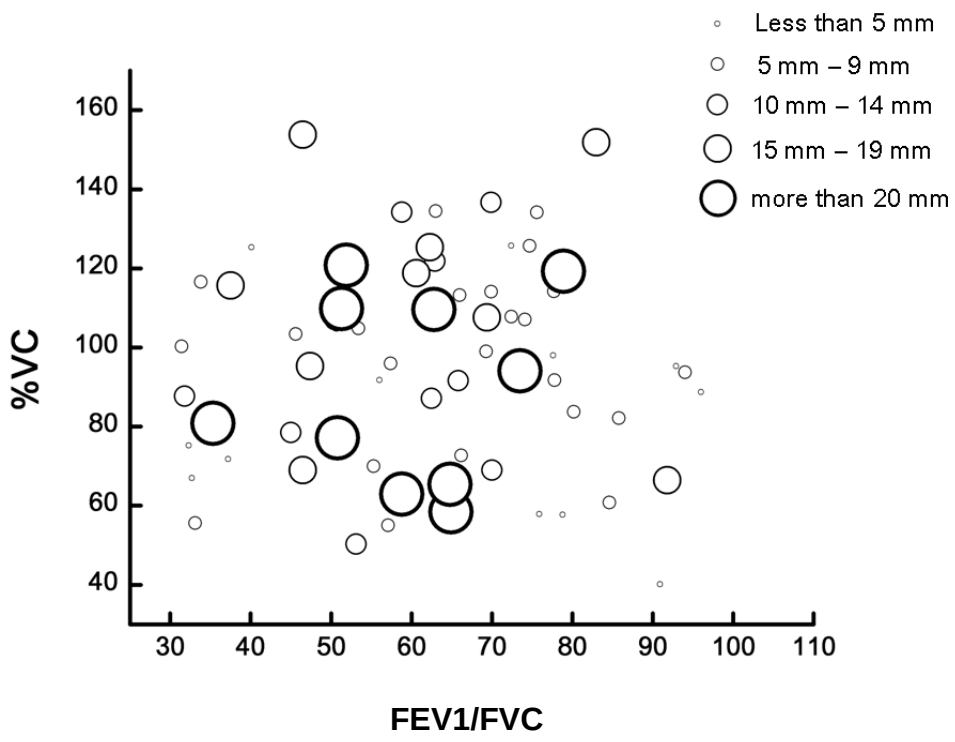

P<0.05
P<0.05
n.s
log（estimated mammimum movement（mm））
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Yes
No
upper region
Yes
No
lower region
Presence of fibrosis

Figure 4


Less than 5 mm
5 mm – 9 mm
10 mm – 14 mm
15 mm – 19 mm
more than 20 mm
%VC
160
140
120
100
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50
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70
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FEV1/FVC