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VMAT Planning With Xe-CT Functional Images Enables Radiotherapy Planning With Consideration of Lung Function

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Abstract. *Background/Aim: The most severe adverse event of radiotherapy in lung cancer is radiation pneumonitis (RP). Some indices commonly used to prevent RP are evaluated based on the anatomical lung volume. The irradiation dose may be more accurately assessed by using functional lung volume. We evaluated the usefulness of computed tomography (CT) incorporating functional ventilation images acquired by the inhalation of xenon (Xe) gas (Xe-CT functional images). Patients and Methods: Two plans were created for twelve patients: volumetric modulated arc therapy (VMAT) planning using conventional chest CT images (anatomical plans) and VMAT planning using Xe-CT functional images (functional plans), and the dosimetric parameters were compared. Results: Compared to the anatomical plans, the functional plans had significantly reduced V_{20Gy} in the high-functional lungs (p=0.005), but significant differences were not seen in the moderate-functional and low-functional lungs. Conclusion: The incorporation of Xe-CT functional images into VMAT plans enables radiotherapy planning with consideration of lung function.*

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Lung cancer is the fourth most prevalent malignancy in men and the third most prevalent in women in Japan (1). Approximately 14% of patients with non-small-cell lung carcinoma (NSCLC) at the first visit have stage III disease (1). Chemoradiotherapy is standard therapy for inoperable locally advanced NSCLC of stages IIIA and IIIB; however, the therapeutic outcome of chemoradiotherapy for stage III NSCLC is poor. The five-year survival rate is 15.1% (2) and the average overall survival is 16-30 months. Although dose escalation for improving the therapeutic outcomes of radiotherapy for lung cancer has been attempted, the increase in adverse events due to high irradiation doses is a significant issue. In an attempt to reduce adverse events, the use of intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) has increased. The most severe adverse event of radiotherapy for lung cancer is radiation pneumonitis (RP). Following chemoradiotherapy for locally advanced lung cancer, symptomatic RP occurs in 5-50% of patients and leads to fatal pneumonia in 1-2% of patients. It has been reported that development of RP is dependent on the irradiated volume and the irradiation dose of the lungs. V_{20Gy} (percentage of total lung volume irradiated with 20 Gy or higher), VS_{5Gy} (absolute lung volume spared from a dose of 5 Gy or higher), and mean lung dose are used as dose evaluation indices (3-7). However, these indices are evaluated based on the anatomical lung volume by computed tomography (CT) images, not considering lung function. However, some patients with lung cancer have pulmonary diseases such as chronic obstructive pulmonary disease (COPD). Therefore, the irradiation dose may be more accurately assessed in radiotherapy planning by using functional lung volume rather than anatomical lung volume. Regarding the correlation between lung function and the occurrence of adverse events, Robnett *et al.* and Warner *et al.* reported that patients with poor pretreatment respiratory function tended to present with

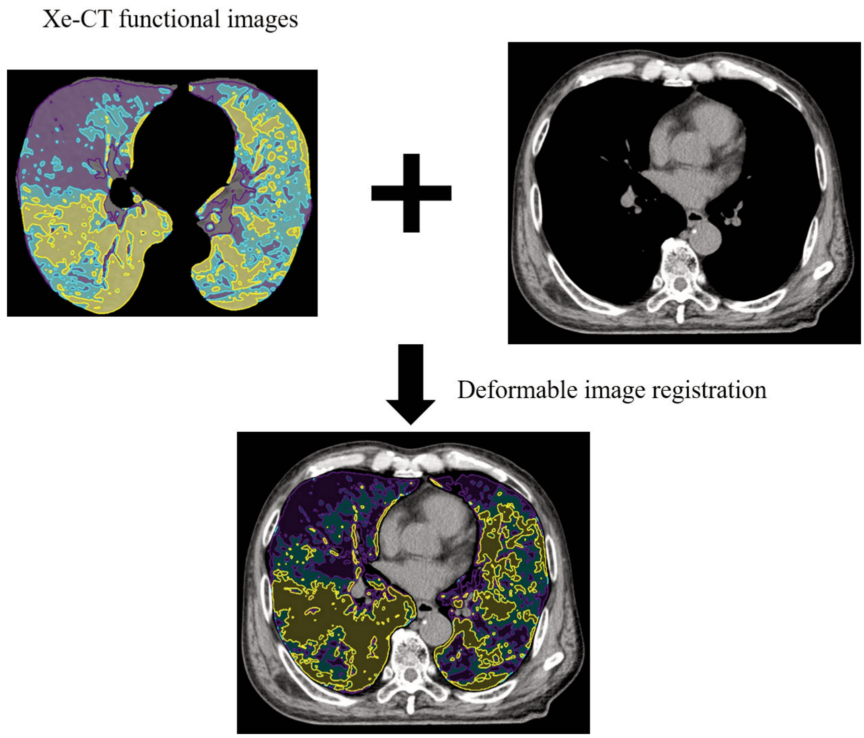

Figure 1. *Fusion of Xenon (Xe)-computed tomography (CT) functional images and radiotherapy planning CT images. Xe-CT functional images acquired during maximal inhalation were fused with the conventional radiotherapy planning CT images acquired during regular breathing.*

symptoms of pulmonary impairment after radiotherapy (8, 9). Yorke *et al*. demonstrated that irradiation dose to the lower portion of the lungs was more important than that to the upper portion of the lungs for prediction of adverse events of the lungs after radiotherapy (10). Therefore, radiotherapy planning in consideration with lung function has been attempted in recent years. Several methods of acquiring functional ventilation images for radiotherapy planning have been reported such as the technique of using low attenuation areas (LAAs) on CT images (11, 12), and the use of four-dimensional CT (4D-CT) (13-17) and 99 mTc-macroaggregated albumin (MAA) single photon emission CT (SPECT) (15, 18-21). In this study, we focused on acquiring chest CT images with patients inhaling xenon (Xe). Inhalation of Xe raises the CT value and the extent of the increase reflects the distribution of Xe. Unlike the LAA method or 4D-CT, this method, established by Honda *et al*. (22), evaluates lung ventilation directly. Moreover, the advantage of this method over SPECT is that higher-resolution images are obtained. To date, there has been no study on the use of chest CT images acquired by Xe inhalation (Xe-CT functional images) and evaluation of lung ventilation for radiotherapy planning. In this study, we investigated a technique to create VMAT planning using Xe-CT functional images (functional plans). In addition, we compared it with VMAT planning using conventional chest CT images (anatomical plans) and evaluated the usefulness of functional radiotherapy planning using Xe inhalation.

Patients and Methods

The present study was approved by the Ethics Committee of the Saitama Medical Center, Saitama Medical University (1191-II~V). Twelve patients with lung cancer who underwent radiotherapy between April 2017 and March 2018 were enrolled in this study. We obtained written informed consent from all patients. This study was a treatment planning study and the method developed in this study was not used in actual clinical practice.

The participants inhaled Xe and Xe-CT functional images were acquired with a dual-energy (tube voltages of 80 kV and 140 kV/Sn) CT scanner, Somatom Definition Flash (Siemens Healthcare, Forchheim). The patients were placed in a supine position with the upper limbs lifted, which is the same position maintained during CT scans for radiotherapy planning. A face mask (King Systems, Nobelsville, Ind) was fixed by a strap to cover the mouth and nose of the patient and was connected to an outlet and inlet of a xenon control system Az-726 V Xetron VI (Anzai Medical). The patients were scanned in dual-energy mode during breath hold after a vital-capacity inspiration of a mixture of 35% xenon and 65% oxygen using the xenon control system. The density of Xe-54 was 5.9 kg/m^3 (standard condition), approximately 4.6 times the density of air. The ventilated lung regions showed a high CT value. Since details of the method for obtaining Xe-CT functional images have been already

Table I. *Dose constraints for volume modulated arc therapy (VMAT).*

		Anatomical plan			Functional plan		
Structure	Constraint type	Dose (Gy)	Volume (%)	Weight	Dose (Gy)	Volume (%)	Weight
PTV	Minimum DVH	60	95	100	60	95	100
	Minimum dose	57		60	57		60
	Maximum dose	63		60	63		60
	Minimum DVH	60	98	10	60	98	10
	Maximum DVH	61.2	10	10	61.2	10	10
Heart	Maximum DVH	40	50	20	40	50	20
	Maximum DVH	40	25	1	40	25	1
Spinal cord PRV	Maximum dose	45		50	45		50
Esophagus PRV	Maximum DVH	55	30	40	55	30	40
	Maximum DVH	40	30	1	40	30	1
Total lung minus GTV	Maximum DVH	20	30	20			
	Maximum DVH	20	15	1			
High-functional lung minus GTV	Maximum DVH				18	30	50
	Maximum DVH				18	10	30
Moderate-functional lung minus GTV	Maximum DVH				18	30	5
Low-functional lung minus GTV	Maximum DVH				18	30	1

A mean dose of 60 Gy in 30 fractions was prescribed to the PTV. The constraints on the total lungs were used in the anatomical plans, and those of the three functional lung regions were used in the functional plans, with the greatest weight given at the high functional lungs. PTV: Planning target volume; DVH: dose volume histogram; PRV: planning organ at risk volume; GTV: gross tumor volume.

described (22, 23), only a brief explanation is given herein. Syngo Multimodality Workplace (Siemens Healthcare) software was used for the distinction of Xe on CT images. Following this, using the Velocity (Varian Medical Systems) software platform, CT value histograms of Xe in Xe-CT images were acquired. The upper limit of the small peak on the left tail of the pixel-value histograms of Xe-CT images of the whole lung was detected and it was applied as a threshold to remove the pulmonary arteries and veins from the Xe-CT images, and then Xe-CT functional images were created. We divided the area of the CT-value histograms showing functional lungs into three equal areas based on volume. The three equal areas were termed high-functional, moderate-functional, and low-functional lungs from the lung regions showing high CT values. CT images for radiotherapy planning were acquired using an Optima CT 660 Pro Advance scanner (GE Healthcare). For the fusion of Xe-CT functional images and radiotherapy planning CT images, deformable image registration (DIR) was performed using Velocity software. Xe-CT functional images acquired during maximal inhalation were fused with the radiotherapy planning CT images acquired during regular breathing (Figure 1).

Eclipse (Varian Medical Systems) software was used for VMAT planning. The gross tumor volume, clinical target volume, planning target volume (PTV), and organs at risk (OARs), including the heart, spinal cord, esophagus, and lungs, were contoured on radiotherapy planning CT images. The spinal cord and esophagus were expanded by 5 mm to generate the planning organ at risk volumes (PRVs). Anatomical plans and functional plans were created for all 12 patients. We prescribed a mean dose of 60 Gy in 30 fractions to the PTV. Table I lists the dose-volume constraints for each structure in both plans. Except for the lungs, the parameters of the anatomical plans and the functional plans were set to be the same for comparison. The difference between the two plans lied in how the dose was constrained to the lungs. In the anatomical plans, dose constraints were set uniformly over the entire lung, whereas in the functional plans, dose constraints were set in each of the three areas of high-functional, moderate-functional, and low-functional lungs. The weight of the dose constraint for V_{18Gy} was set so that the high-functional lungs were prioritized over the moderate-functional and low-functional lungs with the greatest weight for the high-functional lungs.

The following items were evaluated: (1) among the lung domains, (a) the mean dose to the high-functional, moderate-functional, low-functional, and total-functional lungs (Gy); and (b) the V_{5Gy}, V_{20Gy}, V_{40Gy}, and V_{50Gy} of the high-functional lungs and the V_{20Gy} of the moderate-functional and low-functional lungs (%) (V_{xGy}: percentage of volume receiving ≥ x Gy); (2) among the PTV domains, (a) the homogeneity index (H.I.) of the PTV (H.I.=[D2%-D98%]/D50%, DX%; dose covering X% of the PTV) and (b) the conformity index (C.I.) of the PTV (C.I.=the total volume covered by the prescription isodose/PTV); (3) among the OARs, (a) the V_{40Gy} of the heart (%), (b) the maximum dose to the spine cord (Gy), and (c) the mean dose to the esophagus (Gy); and (4) the monitor units. Dose-volume metrics were calculated using functional CT images. For analysis of the correlation between the two plans, the Wilcoxon signed-rank test was used for each index. Statistical significance was defined as $p<0.05$. SPSS for Windows version 23 software (IBM) was used for all statistical analyses.

Results

Patient characteristics are shown in Table II. The tumors were distributed in the upper or middle lobes, and no tumors were seen in the lower lobes. Sufficient inhalation of Xe during the acquirement of Xe-CT functional images was confirmed in all patients, and no adverse events due to Xe-CT scanning were noted. Suitable fusion of the Xe-CT functional images and radiotherapy planning CT images was performed for all patients; thus, creating both the anatomical and functional plans.

Mean dose of the high-functional, moderate-functional, low-functional, and total functional lungs in the two plans are shown in Figure 2. Compared to the anatomical plans, the functional plans had significantly reduced mean doses to the high-functional, moderate-functional, low-functional, and total functional lungs (p=0.002, p=0.003, p=0.002, and p=0.002, respectively), and the corresponding differences were 0.32, 0.27, 0.20, and 0.27 Gy, respectively.

The V_{5Gy}, V_{20Gy}, V_{40Gy}, and V_{50Gy} of the high-functional lungs and the V_{20Gy} of the moderate-functional and low-functional lungs in the anatomical and functional plans are shown in Figure 3. Compared to the anatomical plans, the functional plans had significantly reduced V_{5Gy}, V_{20Gy}, V_{40Gy}, and V_{50Gy} of the high-functional lungs (p=0.005, p=0.005, p=0.002, and p=0.006, respectively), and the corresponding differences were 0.7%, 1.3%, 0.3%, and 0.1%, respectively. Although the V_{20Gy} was reduced by 0.7% and 0.5% in the moderate-functional and low-functional lungs, respectively, upon comparison between the functional and anatomical plans, a significant difference was not seen.

The dosimetric parameters of PTV, OARs, and monitor units in the anatomical and functional plans are shown in Table III. H.I. was significantly increased in the functional plans compared to that in the anatomical plans (p=0.002). In contrast, no significant difference was seen in the C.I. among the two plans. In comparison to that in the anatomical plans, a significant reduction in the V_{40Gy} of the heart was observed in the functional plans (p=0.007). Significant differences were not observed in the maximum doses to the spinal cord or the mean doses to the esophagus. Compared to the anatomical plans, the functional plans showed a significant reduction in monitor units (p=0.050).

Table II. *Characteristics of the study participants.*

Patient backgrounds	
Age (years)	
≥75	4
<75	8
Median	69 (58-82)
Gender	
Male	11
Female	1
ECOG performance status	
0	12
Pathology	
Non-small-cell carcinoma	10
Small-cell carcinoma	2
Stage	
I	1
II	1
III	10
IV	0
Prescription dose (Median)	60 Gy (45-64 Gy)
Primary site	
Right upper lobe	7
Right middle lobe	3
Left upper lobe	2
$FEV_{1.0\%}$ (Median)	59.2% (41.1-77.8%)

ECOG: Eastern Cooperative Oncology Group; $FEV_{1.0\%}$: forced expiratory volume 1.0 (s) %.

Discussion

In Japan, Xe inhalation is only approved for use in Xe/CT cerebral-blood-flow evaluation. The maximum concentration of Xe allowed is 35%; therefore, the concentration used in this study is within the approved levels. Acquisition of Xe-CT functional images without any adverse events related to Xe inhalation was possible in our study.

In this study, the Velocity software was used for DIR of the Xe-CT functional images and radiotherapy planning CT images. Regarding the validation of DIR, we visually confirmed that the accuracy conformed to the guidelines (24, 25). There are simple quantitative evaluations such as the dice coefficient and more accurate quantitative evaluations as further evaluations. However, since the tumors were distributed in the upper or middle lobes with relatively little respiratory movement in this study, we only confirmed that visually suitable fusion images were obtained that could be used for radiotherapy planning.

Compared to that in the anatomical plans, the mean dose in the functional plans was reduced from 13.04 Gy to 12.72 Gy and the V_{20Gy} was reduced from 25.9% to 24.6% in the high-functional lungs. Although significant reductions were observed in the mean doses to the high-functional, moderate-functional, and low-functional lungs, the difference was the largest in the high-functional lungs. For IMRT and VMAT planning, Kimura *et al.* used the LAA method for acquiring functional images, and a radiotherapy dose of 70 Gy was prescribed; in the high-functional lungs, a mean dose reduction of 0.3 Gy was reported in the IMRT plans and of 0.5 Gy was reported in VMAT plans, and a significant reduction in V_{20Gy} was also reported (11). Yamamoto *et al.* used 4D-CT for lung functional imaging and prescribed a radiotherapy dose of 74 Gy; in the high-functional lungs, the mean dose reduced from 13.4 Gy to 11.6 Gy in the IMRT plans and from 15.9 Gy to 13.9 Gy in the VMAT plans, and a reduction in V_{20Gy} was also reported (13). Huang *et al.* used 4D-CT for lung functional imaging and prescribed a

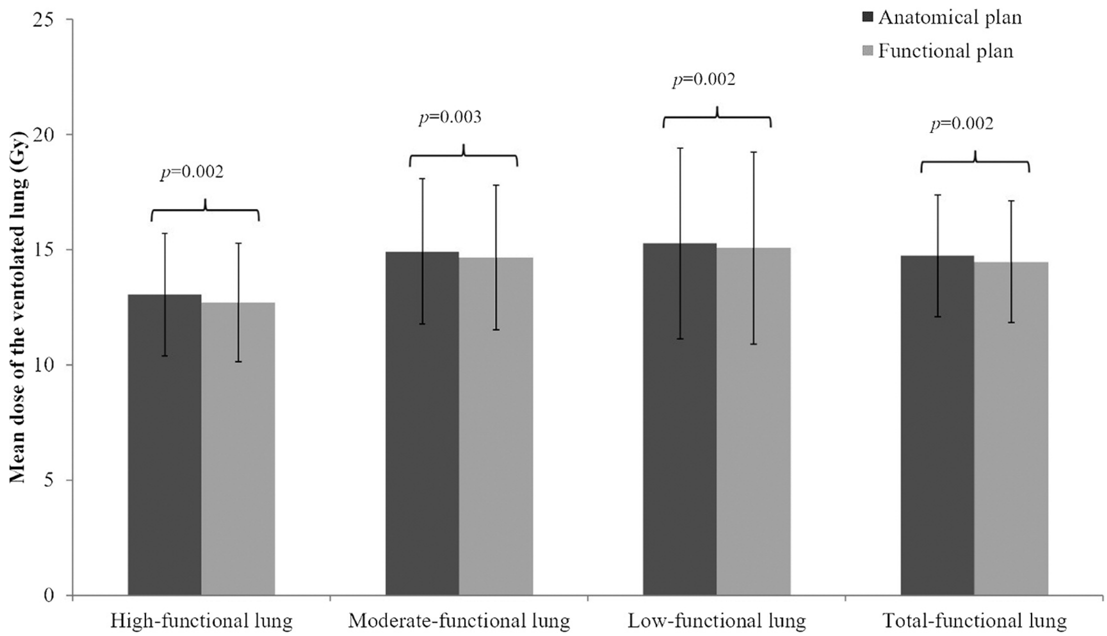

Figure 2. *Comparison of the mean dose of irradiation (mean±standard deviation) to the high-functional, moderate-functional, low-functional, and total-functional lungs between the anatomical and functional plans. Compared to the anatomical plans, the functional plans had significantly reduced mean doses to the high-functional, moderate-functional, low-functional, and total functional lungs (p=0.002, p=0.003, p=0.002, and p=0.002, respectively).*

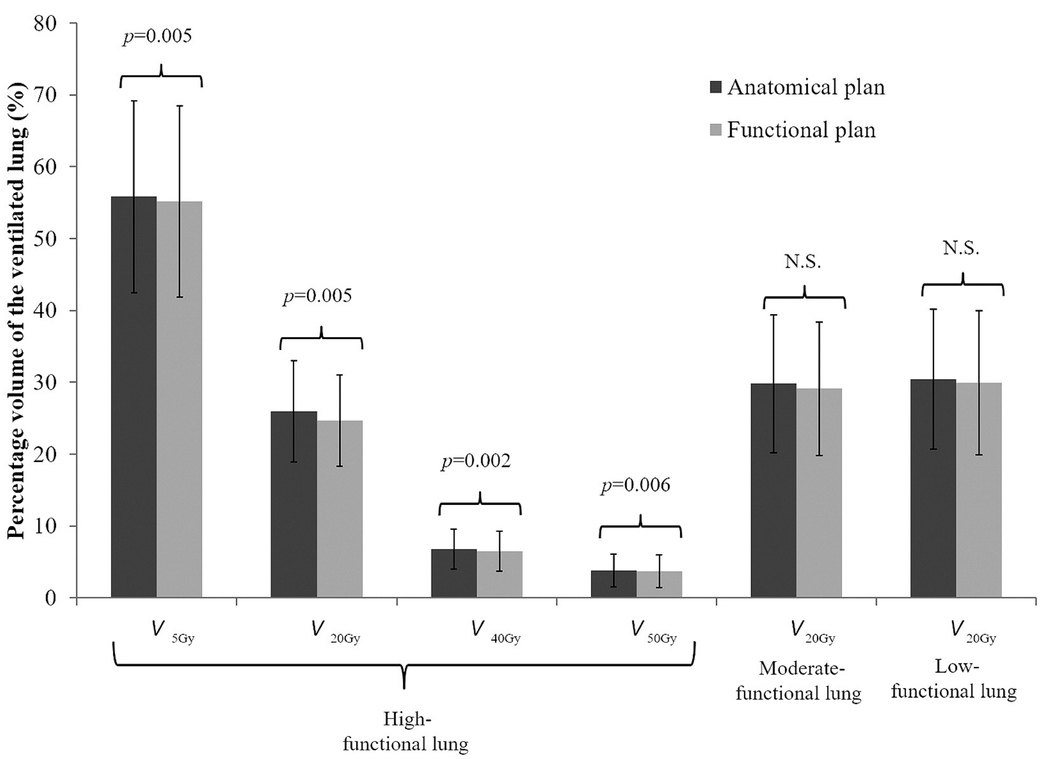

Figure 3. *Comparison of the percentage volume of the ventilated lung receiving irradiation doses ≥5, ≥20, ≥40, or ≥50 Gy (V_{5Gy}, V_{20Gy}, V_{40Gy}, or V_{50Gy}, respectively) (mean±standard deviation) in the high-functional, moderate-functional, and low-functional lungs between the anatomical and functional plans. Compared to the anatomical plans, the functional plans had significantly reduced V_{5Gy}, V_{20Gy}, V_{40Gy}, and V_{50Gy} of the high-functional lungs (p=0.005, p=0.005, p=0.002, and p=0.006, respectively). In the moderate-functional and low-functional lungs, a significant difference was not seen on comparing between the functional and anatomical plans. N.S.: Not significant.*

Table III. *Summary of PTV, organs at risk, and monitor units in the anatomical and functional plans (mean±standard deviation).*

Metric	Anatomical plan	Functional plan	*p*-Value
PTV			
Homogeneity index	0.15±0.02	0.17±0.02	0.002
Conformity index	0.58±0.02	0.58±0.01	0.782
Heart			
V_{40Gy} (%)	3.3±4.1	3.1±4.1	0.007
Spinal cord			
Maximum dose (Gy)	37.1±7.0	37.6±6.9	0.480
Esophagus			
Mean dose (Gy)	21.8±6.1	22.1±6.2	0.919
Monitor units	490±23	486±28	0.05

Homogeneity index was significantly increased in the functional plans compared to that in the anatomical plans (p=0.002). In contrast, no significant difference was seen in the conformity index among the two plans. In comparison with that in the anatomical plans, a significant reduction in the V_{40Gy} of the heart was observed in the functional plans (p=0.007). Significant differences were not observed in the maximum doses to the spinal cord or the mean doses to the esophagus. Compared to the anatomical plans, the functional plans showed a significant reduction in monitor units (p=0.050). PTV: Planning target volume; V_{40Gy}: the percentage volume of the heart receiving irradiation doses ≥40 Gy.

radiotherapy dose of 50-74 Gy; in the high-functional lungs, the mean dose reduced from 8.61 Gy to 7.38 Gy and the V_{20Gy} reduced from 15.22% to 12.57% in the IMRT plans (14). Thus, adding dose restrictions to conventional radiotherapy planning and considering lung function by using Xe-CT functional images improved dose distribution in the lungs, especially in the high-functional lungs. In PTV analysis, although a significant increase was noted in the H.I. in the functional plans, no significant difference was seen in the C.I. In another study, Kimura *et al*. reported no significant changes in the H.I. or C.I. in their functional plans (11). In contrast, Yamamoto *et al*. reported a significant increase in the H.I. and a significant decrease in the C.I. in their functional plans (13). Compared to the anatomical plans, the functional plans showed a significantly reduced V_{40Gy} of the heart (a difference of 0.2%), and no significant differences were seen between the two plans in the maximum dose to the spinal cord and the mean dose to the esophagus. Kimura *et al*. and Yamamoto *et al*. reported no significant changes in the average and maximum doses to OARs other than the lungs in their functional plans (11, 13). We believe that our technique of radiotherapy planning considering lung function reduced the absorbed dose of the high-functional lungs and maintained the dose distribution of the PTV and OARs at a similar level with that in the anatomical plans.

The advantage of our technique is that functional images that directly evaluate the lung ventilation can be obtained as high-resolution images. The functional images by the LAA method and the method using 4D-CT are acquired by identifying functional lung regions with CT images, and their evaluation for lung function is indirect. The SPECT method can obtain functional images that directly evaluate lung function, but the resolution of the obtained functional images is low. Xe-CT functional images are acquired by actual Xe inhalation by the patients, so that lung ventilation is directly evaluated and also their resolution is high. In addition to this, our technique has another advantage of using VMAT for radiotherapy planning. VMAT is a technique which demonstrates favorable dose distribution and short treatment delivery time. Valakh *et al*. compared a single 360˚ coplanar arc VMAT plan with IMRT and a single 180˚ coplanar arc VMAT plan for a small lung nodule that was centrally located in close proximity to the mediastinal structures, and reported that VMAT improved esophageal sparing compared to IMRT and a single 180˚ coplanar arc VMAT plan had the highest dose conformity (26). In this study, IMRT planning was not assessed, however, better dose distribution could be obtained by VMAT planning compared to IMRT planning. On the other hand, in order to acquire Xe-CT functional images, there is a demerit that patients take CT images inhaling Xe. The LAA method and the method using 4D-CT use radiotherapy planning CT images to obtain functional images and they do not require taking additional images. Our technique has a disadvantage that additional CT scan, and the fusion of Xe-CT functional images and radiotherapy planning CT images are required.

Honda *et al*. reported uneven Xe distribution in Xe-CT functional images in one patient with COPD. In this patient, no abnormality was observed on conventional lung CT images acquired by breath-holding following maximal inhalation. They reported that the abnormality in ventilation could be detected on Xe-CT functional images but could not be detected using morphologic data. Further evaluation of the utility of this technique in these patients is required.

We acknowledge there are some limitations in this study. First, the number of cases is small. Second, there is a bias in the patient background. The subjects of this study had relatively good lung function enough to receive definitive radiotherapy. Coincidentally, the tumors were distributed in the upper or middle lobes with relatively little respiratory movement compare to lower lobes. Third, the functional lungs were divided into three areas based on the volume of each case, which was only classified by relative evaluation within the individual, and high-functional lungs were not defined with something like a threshold. Since the number of cases in this study was small and the purpose of this study was to develop a technique of radiotherapy planning using functional ventilation images acquired by Xe-CT, no patient selection criteria were set for lung function or tumor location, and we evaluated three areas based on the volume of each case for convenience. Even in such a patient background, it was confirmed that the high-functional lungs and the low-functional lungs could be separated into different doses. Further research is required for patients with lower lung function with COPD or lower lobe tumors, which might lead to dose difference of radiobiological significance. Moreover, by accumulating the number of cases, it might be possible to set an optimum threshold value to define high-functional lungs.

We devised a method of VMAT radiotherapy planning using functional images obtained by inhalation of Xe. This method has not been reported in any previous study. The plans that used this technique showed a reduction in absorbed doses, predominantly in the doses to the high-functional lungs. In addition, the dose distribution of the PTV or OARs were maintained at a similar level with that in the conventional anatomical plans. Thus, we believe that VMAT plans with Xe-CT functional images by the technique used in this study enable radiotherapy planning with consideration of lung function. Further research is required to identify patients who would benefit the most from this method.

Conflicts of Interest

The Authors have no financial relationships to disclose.

Authors' Contributions

T.T. and N.H. developed the concept. N.U., T.T., S.H., M.H., M.S., S.K., R.S., K. N., and T.Y. researched the data. N.U. wrote the manuscript. T.T., S.H., M. H., and M.S. contributed to the discussion of the manuscript. N.U., T.T., S.H., M.H., M.S., S.K., R.S., K. N., T.Y., W.W., M. S. and N.H. had full access to all the data in the study and reviewed the manuscript.

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