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<tr>
<td><strong>Author(s)</strong></td>
<td>Kimura, Tomoki; Nishibuchi, Ikuno; Murakami, Yuji; Kenjo, Masahiro; Kaneyasu, Yuko; Nagata, Yasushi</td>
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Functional Image-Guided Radiotherapy Planning in Respiratory-Gated Intensity-Modulated Radiation Therapy (IMRT) for Lung Cancer Patients with chronic obstructive pulmonary disease (COPD)

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Conflict of Interest Notification: none

Short running title: Functional Image-Guided Radiotherapy Planning in Respiratory- Gated IMRT for Lung Cancer
Abstract

(Purpose) To investigate the incorporation of functional lung image-derived low attenuation area (LAA) based on four-dimensional computed tomography (4D-CT) into respiratory-gated intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) in treatment planning for lung cancer patients with chronic obstructive pulmonary disease (COPD).

(Materials and Methods) Eight lung cancer patients with COPD were the subjects of this study. LAA was generated from 4D-CT data sets according to CT values lower than -860 Hounsfield units (HU) as a threshold. The functional lung image was defined as the area where LAA was excluded from the image of the total lung. Two respiratory-gated radiotherapy plans (70 Gy/35 fr) were designed and compared in each patient as follows: 1) Plan A: anatomical IMRT or VMAT plan based on the total lung 2) Plan F: functional IMRT or VMAT plan based on the functional lung. Dosimetric parameters (V20: the percentage of total lung volume irradiated with ≥ 20 Gy, MLD: mean dose of total lung) of the two
plans were compared.

(Results) V20 was lower in Plan F than in Plan A (mean 1.5 %, p= 0.025 in IMRT, mean 1.6 %, p= 0.044 in VMAT) achieved by a reduction in MLD (mean 0.23 Gy, p= 0.083 in IMRT, mean 0.5 Gy, p= 0.042 in VMAT). No differences were noted in target volume coverage and organ-at-risk doses.

(Conclusions) Functional image-guided radiotherapy planning based on LAA in respiratory-guided IMRT or VMAT appears to be effective in preserving a functional lung in lung cancer patients with COPD.

【Key Words】 functional imaging, 4D-CT, IMRT, COPD
INTRODUCTION

One of the most severe complications in radiation therapy for lung cancer is radiation pneumonitis (RP). Reduction of the incidence of severe RP requires a reduction of the lung dose, such as V20 which is defined as the percentage of pulmonary volume irradiated to $\geq 20$ Gy. It is also one of the significant dosimetric risk factors for the incidence and severity of RP (1). Chronic obstructive pulmonary disease (COPD) is a recognized risk factor for RP (2). There has been a worldwide increase of the prevalence of COPD and as the population ages, the incidence of COPD is expected to increase (3). Pulmonary emphysema (PE) is a subtype of COPD, and defined pathologically as a group of diseases that demonstrate anatomic alterations in the lung, characterized by enlargement of airspaces distal to the terminal bronchioles, accompanied by destructive changes of alveolar walls (4). These lesions are seen as low-attenuation areas (LAAs) on CT scans, and are established findings on the imaging diagnosis of COPD (5, 6). Kimura et al reported a correlation between the incidence of RP and the extent of LAAs in the
whole lung fields (7). From these results, the functional lung image-derived LAA based on four-dimensional computed tomography (4D-CT) was developed for planning of radiation treatment to reduce the risk of RP in patients with COPD.

Several authors have described functional imaging modalities for planning of radiation treatment, such as ventilation imaging with 4D-CT (8) and single-photon emission computed tomography (SPECT) lung perfusion imaging (9). All of these authors showed that functional lung regions could be identified with imaging and then avoided with IMRT treatment planning techniques. Matsuoka (6) suggested that paired inspiratory and expiratory CT imaging can be used to define LAA volumes in patients with COPD. Therefore, these two approaches were combined in order to address the respiratory problem. This study investigated the ability of functional lung image-derived LAA based on 4D-CT, and its incorporation into respiratory-gated intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) in treatment planning for lung cancer patients with COPD.
Materials and Methods

Patient background

In this study, eight male patients with lung cancer were enrolled who had undergone 4D-CT scanning and definitive radiation therapy at Hiroshima University from 2009 to 2010. Pathological diagnosis, stage (UICC 7th edition), and the primary tumor location are summarized in Table 1. All patients received $[^{18}F]$ fluorodeoxyglucose-positron emission tomography (FDG-PET) for staging.

Functional lung image-derived LAA based on 4D-CT

At first, 4D-CT scans were acquired with 2.5-mm-thick slices using multi detector-row CT (MDCT; LightSpeed, GE Medical systems, Waukesha, WI) in cine mode with the Varian Real-time Position Management (RPM) Respiratory Gating system (Varian Medical Systems, Palo Alto, CA). Following image acquisition, the CT image data set was sorted into 10-phase bins of the respiratory cycle, and phase by phase evaluation was performed on a workstation (AdvantageSim, GE Healthcare, Princeton, NJ). The 10-phase set consisted of 0 to
90% in steps of 10%, and 0 or 90% was in the end-inspiratory phase and 50% in
the end-expiratory phase. All 10-phase CT data sets were imported into the Eclipse
treatment planning system (Varian Medical Systems, Palo Alto, CA). Several
authors reported that the threshold CT value for the detection and quantification of
LAA ranged from -850 to -950 HU (10, 11). Matsuoka et al concluded that the
threshold of -860 HU correlated closely with airway dysfunction in COPD on
paired inspiratory and expiratory CT (6). Therefore LAAs were generated from
10-phase 4D-CT data sets according to CT values lower than -860 Hounsfield units
(HU) as a threshold on Eclipse.

For respiratory gated planning in this study, three expiratory phases (40-60%)
were selected with the phase gating method. Fig 1 shows the three steps involved in
making the functional lung image-derived LAA based on 4D-CT of case 1.

1) Acquisition of LAA at each phase (the threshold of -860HU).

2) Fusion of LAA at three expiratory phases (40-60%), and trimming the ROI as
LAA image (40-60%).
3) The functional lung image was defined as the area where LAA image (40-60%) was excluded from fusion images of the total lung volumes on each of the 40-60% phases.

This technique did not employ any sort of deformable image registration algorithm in any of the steps.

Respiratory Gated IMRT and VMAT planning with functional lung image

In this simulation study, two respiratory-gated radiotherapy plans were designed and compared for each patient as follows: 1) Plan A: anatomical IMRT or VMAT plan based on the total lung; 2) Plan F: functional IMRT or VMAT plan based on the functional lung. RapidArc (Varian Medical Systems, Palo Alto, CA) was used as VMAT. In this study, IMRT was defined as fixed, non-rotational IMRT, and VMAT was defined as rotational IMRT. All dose calculations were done on the full expiration (50%) phase.

For target delineation of each plan, a physician delineated the target volume on each 10-phase CT image. Gross tumor volume (GTV) included the primary tumor
and metastatic lymph nodes, and clinical target volume (CTV) margin of 3-5 mm
was added to GTV according to the pathology. Elective nodal irradiation was
omitted (so-called “involved-field”). Internal target volume (ITV) was defined as
the sum of CTV at three expiratory phases (40-60%) in this respiratory gated
planning. A planning target volume (PTV) margin of 5-10 mm was added allowing
for reproducibility of respiratory motion and setup error to ITV.

The IMRT plans consisted of five coplanar fixed beams with gantry angles of
20°, 320°, 240°, 180°, and 135° at the right lung, and 340°, 40°, 120°, 180°, and
215° at the left lung. The VMAT plans consisted of two coplanar arcs with gantry
angles were moved 220° from 180° to 40° in the right lung, and from 180° to 320°
in the left lung in clockwise and counter clockwise directions. Treatment plans
were delivered using 6-MV photons generated by a linear accelerator (Clinac iX,
Varian Medical Systems, Palo Alto, CA) with continuous changes in the gantry
speed, multi-leaf collimator position, and dose rate. The collimator angle was fixed
at 45° throughout the arc. The same beam arrangements were used for both plans.
A total dose of 70 Gy in 35 fractions to 95% of the PTV was prescribed. The prescribed dose was calculated with a heterogeneous dose calculation algorithm (the Eclipse anisotropic analytical algorithm; AAA). Table 2 shows the dose constraints for each structure. The constraints on the total lung were used in Plan A, and those on the two functional lung regions were used in Plan F. V20 or functional V20 (fV20) was calculated by lung-PTV and its dose constraints were defined as less than 10-30%. Therefore the background of patients included all stages. The minimal value of V20 which could be achieved in the anatomical plan of each patient was selected according to the field size of each patient, and the value of fV20 was also the same. Several IMRT and VMAT plans were made to maintain clinical acceptability, and the plans which most suitably satisfied the dose constraints in Table 2 were selected for Plans A and F.

Data analysis and Statistical methods

The dosimetric parameters of Plans A and F using respiratory guided IMRT and VMAT planning were evaluated by examining the following:
1) Lung V5-30 and fV5-30: the percentage of total or functional lung volumes irradiated with \( \geq 5-30 \) Gy

2) Lung MLD and functional MLD (fMLD): mean dose to total or functional lung

3) Mean dose, homogeneity index (HI), and conformity index (CI) of PTV

\[
HI = \frac{\text{maximum dose of PTV}}{\text{minimum dose to PTV}}
\]

\[
CI = \frac{\text{Treated Volume}}{\text{PTV}}; \text{ it is implied that Treated Volume completely encompasses the PTV}
\]

4) Mean or maximum dose of organ-at-risk (heart, esophagus, and spinal cord)

5) Monitor units of each plan

For comparison of statistical significance the Mantel-Haenzel \( \chi^2 \) or t tests were used. All statistical analysis was performed using StatMate for Windows (StatMate ver 4.01; ATMS, Tokyo, Japan). Statistical significance was defined as \( p<0.05 \).

**Results**

*Details of target characteristics*
The details of target characteristics used in both plans are presented in Table 3.

Comparison of dosimetric parameters for lung

Figs 2A and B show the mean percentage volumes of total lung (A) or functional lung (B) receiving \( \geq 5 \), \( \geq 10 \), \( \geq 20 \) and \( \geq 30 \) Gy (V5, V10, V20, V30, and fV5, fV10, fV20, fV30, respectively) for both IMRT and VMAT. Compared with Plan A, Plan F reduced V20 in IMRT (mean 1.5 %, \( p=0.025 \)), in VMAT (mean 1.6 %, \( p=0.044 \)), V30 in IMRT (mean 1.0 %, \( p=0.026 \)), in VMAT (mean 1.3 %, \( p=0.048 \)) and fV30 in IMRT (mean 1.3 %, \( p=0.048 \)). Small reductions were noted in MLD (mean 0.23 Gy, \( p=0.083 \) in IMRT, mean 0.5 Gy, \( p=0.042 \) in VMAT) and fMLD (mean 0.3 Gy, \( p=0.106 \) in IMRT, mean 0.5 Gy, \( p=0.092 \) in VMAT).

On the other hand, compared with IMRT, VMAT reduced fV20 in Plan A (mean 2.0 %, \( p=0.027 \)), and in Plan F (mean 1.3%, \( p=0.027 \)), but increased V5 in Plan A (mean 16.4 %, \( p=0.027 \)), in Plan F (mean 15.1%, \( p=0.005 \)); V10 in Plan A (mean 8.4 %, \( p=0.021 \)), in Plan F (mean 7.7 %, \( p=0.040 \)); fV5 in Plan A (mean 19.0 %, \( p=0.001 \)), in Plan F (mean 18.7 %, \( p=0.001 \)) and fV10 in Plan A (mean 9.3 %,
p=0.025), in Plan F (mean 8.4 %, p=0.045). Significant increases were also seen in
MLD (mean 1.1 Gy, p= 0.013 in Plan A, mean 0.8 Gy, p= 0.010 in Plan F) and
fMLD (mean 1.1 Gy, p= 0.037 in Plan A, mean 0.9 Gy, p= 0.002 in Plan F).

Fig 3 shows V5 and fV5 in IMRT and VMAT of Plan F according to PTV.

Compared with PTV < 250 cc, IMRT and VMAT significantly increased V5 and
fV20 in PTV ≥ 250 cc. Additionally, compared with IMRT, VMAT also increased
V5 and fV5 in PTV ≥ 250 cc significantly (P=0.0096 in V5, p= 0.0032 in fV5).

Comparison of dosimetric parameters for PTV and organ-at-risk

Table 4 (A) shows the dosimetric parameters for PTV, organ-at-risk and monitor
units (MU) between Plans A and F. There were no differences of PTV mean dose,
HI, CI, mean or maximum dose to organ-at-risk, such as heart, esophagus and
spinal cord and MU between Plans A and F in both IMRT and VMAT.

Table 4 (B) shows the dosimetric parameters for PTV, organ-at-risk and MU
between IMRT and VMAT. Compared with IMRT, VMAT improved HI and CI of
PTV, especially in Plan F (p=0.040) without change in mean dose to PTV. However,
there was no difference in mean or maximum doses to heart and spinal cord between IMRT and VMAT, and VMAT increased mean dose to esophagus (mean 3.9 Gy, p=0.002 in Plan A, mean 3.6 Gy, p=0.003 in Plan F) in both Plans A and F. However, IMRT resulted in greater MU than in VMAT in both Plans A and F (p=0.008 and 0.003).

Fig 4 shows dose distribution of case 4.

**Discussion**

This study showed that planning of functional image-guided radiotherapy based on LAA can improve the dosimetric parameters for lung without a major change of PTV coverage and increasing other organ-at-risk doses. IMRT appears to be a good treatment planning based on favorable outcomes and in maintaining dosimetric predictors of toxicity at acceptable levels for patients who have larger tumors with difficult geometry in critical locations (12). However, in as much as reductions in MLD, V20 and V10 have been shown by IMRT, it can also increase the volume of
lung receiving low doses, such as V5, which may potentially increase lung toxicity (13, 14). For delivering safe IMRT for lung cancer, it is important for dosimetric factors to be carefully considered. In fact, severe radiation pneumonitis may be easily induced by a lower dose in patients with COPD, which is seldom comprised of normal lung tissue (7). It is especially in these patients that the functional IMRT described here may contribute to minimize the effect of lower doses.

Several authors have reported on functional imaging modalities for planning of radiation treatment. Ventilation imaging is one of the modalities, which is generated from CT image volumes of the thorax representing exhale and inhale phases obtained from components of the 4D-CT sets using a deformable image registration algorithm (8, 15). Yaremko et al reported generation of high functional regions, comprised of 90 percentile functional volume, and constituting 10 % of the lung volume where the highest ventilation occurred. IMRT plans were generated using constraints on the high functional regions. This method led to the result in which the mean dose to the high functional region was reduced by 2.9 Gy (8). Yamamoto et al
also reported the effectiveness of the ventilation imaging-based functional planning (15). In their study, functional lung was divided into high-, moderate- and low-functional regions, and the average reductions of the mean dose in the high-functional lung were 1.8 Gy for IMRT and 2.0 Gy for VMAT. This was achieved by using constraints on each region, for patients who had high-function lungs adjacent to the PTV.

SPECT lung perfusion imaging is the other functional imaging modality, which provides information about the function of pulmonary vascular and alveolar subunits. Shioyama et al reported that the functional plans reduced the median dose of the 50- and 90-percentile hyperperfusion lung to 2.2 and 4.2 Gy, respectively, compared with anatomic plans by incorporating perfusion information in IMRT planning (9).

An advantage of these modalities is that several degrees of functional regions can be described according to the degree of its regional volume change or perfusion distribution. However, the regional physiologic accuracy has not been validated in
the ventilation imaging because of the uncertainty regarding the use of deformable image registration. Additionally, the use of SPECT lung perfusion imaging is limited by the need for separate imaging sessions or fusions in radiotherapy planning.

The functional lung image-derived LAA based on 4D-CT of this study focused only on describing non-functional lung regions. The advantages of this method are: 1) Actual lung function may be easily recognized especially in patients with COPD by using LAA-based images. 2) Our LAA approach can be done simply, without the need of a sophisticated deformable image registration algorithm. 3) This method may be less affected by respiratory motion because of the respiratory-gated technique. Consequently, there was limited description of several degrees of functional regions. However, CT quantitation using LAA is already an established tool for in vivo assessment of COPD, and has been correlated with pulmonary function (10, 11). Especially in CT findings of patients with COPD, LAA appears as areas of decreased lung attenuation due to an air-trapping phenomenon, which is
characterized by progressive airway obstruction and airflow limitation that are not reversible with the administration of bronchodilator drugs (16). Therefore Zaporozhan et al reported that PE volumes measured from expiratory MDCT scans better reflect abnormalities in pulmonary function tests in patients with severe PE than in those from inspiratory scans (17). Considering the better reproducibility of lung motion, expiratory phases of 4D-CT were selected for this study. A problem remains in that 4D-CT data acquisition by this method is affected by respiratory motion. Thus, the proper thresholds of CT values for the detection and quantification of LAA and the correlations with pulmonary function using this method need to be evaluated. Nevertheless, the advantage of this respiratory gated method is that it can reduce not only the artifact of respiratory motion but also the total lung dose to a minimum.

Fixed-beam IMRT and VMAT plans were also compared. An advantage of VMAT over IMRT is the improvement of target conformity and the potential reduction in delivery time, especially in stereotactic body radiotherapy for lung
cancer which requires a large number of beams and monitor units (18). On the other hand, Schallenkamp et al reported that larger volumes of lungs treated with lower doses may be more critical in predicting adverse events than smaller volumes treated with higher doses, especially when using the IMRT technique which delivers low doses of radiation to large lung volumes (19). Yamamoto et al reported that functional IMRT and VMAT planning had a similar impact on each other for high-functional lung dose, PTV metrics, and doses to other critical organs (15). In our comparison with IMRT, although VMAT reduced fV20 and MU and improved HI and CI of PTV, VMAT increased the low dose areas in both plans, especially in patients with large PTV. Increasing the low dose area of lung using VMAT in patients with large PTV needs to be approached with caution.

The use of functional lung image-derived LAA into respiratory-gated IMRT or VMAT in planning for lung cancer patients may remove the uncertainties of quantifying LAA due to respiratory motion, and result in further reductions of total and functional lung doses in functional planning. However, several problems need
to be addressed for clinical use. Prospective clinical trials will be necessary to
determine whether treatment results, such as survival and complications, are
improved by using this functional avoidance treatment planning.

Conclusions

In conclusion, functional image-guided radiotherapy planning based on LAA in
respiratory-guided IMRT or VMAT appears to be effective in preserving a
functional lung in lung cancer patients with COPD. Further investigations are
needed, including those to clarify several technical problems mentioned above, and
to conduct prospective clinical trials.

REFERENCES


analysis for pneumonitis after 3D treatment for non-small cell lung cancer


**Figure legends**

[Fig 1] Fig 1 shows three steps to make the functional lung image-derived low attenuation area (LAA) based on four-dimensional computed tomography (4D-CT) of case 1.

[Fig 2] Comparison of V5-30 and fV5-30 in Plan A and F using IMRT and VMAT.
(mean ± SD). The p-values shown are only for statistically significant differences

[Fig 3] Comparison of V5 and fV5 in IMRT and VMAT of Plan F according to PTV. The p-values shown are only for statistically significant differences

[Fig 4] Dose distribution of case 4.

(A) IMRT plan A, (B) IMRT plan F, (C) VMAT plan A, and (D) VMAT plan F show isodose line $\geq 20$ Gy (blue) and functional lung area (green). The isodose line $\geq 20$ Gy was decreased at the functional lung in VMAT Plan F (red arrows).
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<th>tumor location</th>
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Table 2. Dose constraints for IMRT and VMAT

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#: functional lung
$^<$: low atenuation area
Table 3. Details of Target (PTV), Normal Tissue and Dosimetric Characteristics

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<th>Total lung volume (cm³)</th>
<th>Functional lung volume (cm³)</th>
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</tbody>
</table>
Table 4. Comparison of dosimetric parameters of PTV and normal tissue between anatomical and functional plans, for IMRT and VMAT (mean ± SD)

<table>
<thead>
<tr>
<th>(A)</th>
<th>IMRT</th>
<th>VMAT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anatomical</td>
<td>Functional</td>
</tr>
<tr>
<td>PTV mean dose (Gy)</td>
<td>72.6 ± 1.2</td>
<td>72.9 ± 0.9</td>
</tr>
<tr>
<td>Homogeneity index#</td>
<td>1.52 ± 0.08</td>
<td>1.59 ± 0.08</td>
</tr>
<tr>
<td>Conformity index$</td>
<td>2.74 ± 0.72</td>
<td>3.17 ± 1.07</td>
</tr>
<tr>
<td>Heart mean dose (Gy)</td>
<td>19.7 ± 9.7</td>
<td>20.6 ± 10.6</td>
</tr>
<tr>
<td>Esophagus mean dose (Gy)</td>
<td>15.6 ± 11.4</td>
<td>15.6 ± 11.6</td>
</tr>
<tr>
<td>Spinal cord mean dose (Gy)</td>
<td>9.1 ± 6.3</td>
<td>9.2 ± 6.3</td>
</tr>
<tr>
<td>Maximum dose (Gy)</td>
<td>40.6 ± 21.2</td>
<td>40.6 ± 20.5</td>
</tr>
<tr>
<td>MU</td>
<td>786.8 ± 214.3</td>
<td>817.3 ± 203.1</td>
</tr>
<tr>
<td>(B)</td>
<td>Anatomical</td>
<td>Functional</td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td></td>
<td>IMRT</td>
<td>VMAT</td>
</tr>
<tr>
<td>PTV mean dose (Gy)</td>
<td>72.6 ± 1.2</td>
<td>72.2 ± 1.0</td>
</tr>
<tr>
<td>Homogeneity index¹</td>
<td>1.52 ± 0.08</td>
<td>1.51 ± 0.10</td>
</tr>
<tr>
<td>Conformity index⁵</td>
<td>2.74 ± 0.72</td>
<td>2.44 ± 0.49</td>
</tr>
<tr>
<td>Heart mean dose (Gy)</td>
<td>19.7 ± 9.7</td>
<td>19.1 ± 10.2</td>
</tr>
<tr>
<td>Esophagus mean dose (Gy)</td>
<td>15.6 ± 11.4</td>
<td>19.5 ± 13.1</td>
</tr>
<tr>
<td>Spinal cord mean dose (Gy)</td>
<td>9.1 ± 6.3</td>
<td>10.3 ± 5.4</td>
</tr>
<tr>
<td>Maximum dose (Gy)</td>
<td>40.6 ± 21.2</td>
<td>42.0 ± 14.6</td>
</tr>
<tr>
<td>MU</td>
<td>786.8 ± 214.3</td>
<td>496.5 ± 60.9</td>
</tr>
</tbody>
</table>

¹: maximum dose of PTV / minimum dose of PTV

⁵: irradiated volume which is covered by minimum dose of PTV / PTV
1) Acquisition of LAA at each phase (the threshold of -860HU)

2) Fusion of LAA at 40-60% phase and trimming the ROI

3) LAA image (40-60% phase) is excluded from total lung volume
Fig. 2 (A)

Percentage volume of total lung (mean ± SD %)

- V5
- V10
- V20
- V30

Anatomical IMRT
Functional IMRT
Anatomical VMAT
Functional VMAT

p-values:
- p=0.044
- p=0.048
- p=0.025
- p=0.026
- p=0.021
- p=0.040
- p=0.005
- p=0.027
- p=0.040
- p=0.026
- p=0.048
Fig. 2 (B)

- Percentage volume of functional lung (mean ± SD %)

- Comparison of different treatment techniques:
  - Anatomical IMRT
  - Functional IMRT
  - Anatomical VMAT
  - Functional VMAT

Significant p-values for comparisons between groups:
- fV5: p=0.001
- fV10: p=0.048
- fV20: p=0.025
- fV30: p=0.027
Fig. 3

Percentage volume of total lung (mean ± SD %)

- PTV <250cc
- PTV >250cc

V5
- p=0.0003
- p=0.0001
- p=0.0096
- p=0.0001

fV5
- p=0.0006
- p=0.0032

- Functional IMRT
- Functional VMAT
Fig. 4 (A-D)

(A) IMRT Plan A

(B) IMRT Plan F

(C) VMAT Plan A

(D) VMAT Plan F

20Gy isodose line

Functional lung (green)