Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2007 June 1; 68(2): 562–571. doi:10.1016/j.ijrobp.2007.01.044.

REDUCTION OF NORMAL LUNG IRRADIATION IN LOCALLY ADVANCED NON SMALL CELL LUNG CANCER PATIENTS USING VENTILATION IMAGES FOR FUNCTIONAL AVOIDANCE

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Abstract

Purpose: To investigate the ability of four-dimensional computed tomography (4D CT)-derived ventilation images to identify regions of highly functional lung for avoidance in intensity-modulated radiotherapy (IMRT) planning in locally advanced non-small cell lung cancer (NSCLC).

Methods and Materials: The treatment planning records from 21 patients with stage III NSCLC were selected. Ventilation images were generated from the 4D CT sets, and each was imported into the treatment-planning system. Ninety percentile functional volumes (PFV90), constituting the 10% of the lung volume where the highest ventilation occurs, were generated. Baseline IMRT plans were generated using the lung volume constraint on V20 (<35%), and two additional plans were generated using constraints on the PFV90 without a volume constraint. Dose-volume (DVH) and dose-function (DFH) histograms were generated and used to evaluate the PTV coverage, lung volume, and functional parameters for comparison of the plans.

Results: The mean dose to the PFV90 was reduced by 2.9 Gy, and the DFH at 5 Gy (F5) was reduced by 9.6% (SE=2.03%). The F5, F10, V5, and V10 were all significantly reduced from the baseline values. We identified a favorable subset of patients for whom there was a further significant improvement in the mean lung dose.

Conclusions: 4D CT-derived ventilation regions were successfully utilized as avoidance structures to reduce the DVH and DFH at 5 Gy in all the cases. In a subset, there was also a

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Presented at the 48th Annual Meeting of the American Society for Therapeutic Radiation Oncology (ASTRO), November 5–9, 2006, Philadelphia, Pennsylvania.

Conflict of Interest Notification

The authors have no commercial or financial interests related to this study to disclose.

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reduction in the F10 and V10 without a change in the V20, suggesting that this technique could be safely used.

Keywords

Thoracic radiation; IMRT; Ventilation; Pulmonary injury; Computed tomography

INTRODUCTION

Lung cancer is the leading cause of cancer death in both men and women in the United States, with 174,470 new cases and 162,460 deaths from lung cancer expected in 2006 alone 1. Part of the reason for these dismal statistics is that lung cancer is difficult to eradicate with current treatments, including radiotherapy. Tumor control probability model calculations estimate the dose required to achieve a local progression free survival of 50% at 30 months as 84.5 Gy 2. The present standard radiotherapy dose of 60 Gy used in NSCLC was established in a randomized trial, RTOG 7301, initiated more than thirty years ago 3. Several institutions have explored radiation dose escalation using 3D conformal radiotherapy. In a phase I radiation dose escalation study performed at the University of Michigan, higher radiation dose was found associated with improved overall survival 4. Other trials such as RTOG 9311 5 and single institution dose escalation trials 6, 7 confirm that higher doses are possible. These studies suggest that higher radiation doses are achievable for those patients whose tumor size, disease distribution, and lung size allow escalation of the dose without exceeding present standard treatment planning lung volume constraints.

The present treatment planning dosimetry constraints for the lung are based on studies which assume lung tissue is homogeneous in its response to toxicity, irrespective of its location or underlying function. The terminology and grading systems for pulmonary toxicity are summarized by Kong 8 and a description of the latest National Cancer Institute Common Toxicity Criteria (version 3.0) is given by Trotti 9. The total lung volume irradiated to more than 20 Gy (V_{20}) 10 and the mean lung dose (MLD) 11 have gained wide use in treatment plan evaluation because they can be readily identified across 3D treatment-planning systems. However, lung function is not distributed uniformly especially in diseased lung. In a prospective study, those patients whose irradiated lung regions had locally reduced function before treatment were found to have less reduction in their carbon monoxide diffusion capacity after treatment 12. This finding suggests a strategy for image-guided radiotherapy utilizing physiological images in radiotherapy treatment planning for image guidance to avoid the irradiation of highly functional regions and minimize the injury and/or loss following radiotherapy 13, 14. However, pulmonary function imaging based on single photon emission tomography (SPECT) is not broadly available for treatment planning in radiation oncology clinics. An ideal functional imaging method would utilize the imaging equipment already present in radiation oncology clinics for the treatment planning process.

Four-dimensional CT (4D CT) imaging, which was developed to provide tumor motion information to improve radiotherapy targeting 15-17, is becoming widely available and has shown great promise for treatment planning. In addition to tumor motion, the 4D CT image set also contains the changes in the pulmonary parenchyma that result from the changes in air content due to breathing. These changes in the local air content may be extracted to obtain pulmonary ventilation images 18, 19. An advantage of these 4D CT derived ventilation images is that since they are derived from the treatment-planning 4D CT there is no separate imaging sessions required. In comparison, SPECT imaging is not available in radiation oncology clinics hence patients are sent to the nuclear medicine clinic for an

additional imaging session. The resulting images must be retrieved, imported into the treatment planning system, and registered with the treatment planning CT.

These 4D CT derived ventilation images are still an experimental imaging study. There is uncertainty regarding the use of deformable image registration in the generation of the ventilation images which limits the spatial resolution of the CT ventilation images to 9 mm 18. Phantom studies have found the uncertainty in our deformable image registration on the order of the voxel dimensions 20. Validation studies show good correlation between the ventilation image estimates of tidal volume and tidal volumes measured directly from the CT images 18, 19. Hence, the functional heterogeneity of the lungs could be taken into account using these images, which may reduce normal tissue complications.

In this study, we evaluated 4D CT-derived ventilation images to identify regions of high function for conformal avoidance with intensity modulated radiotherapy (IMRT) in a radiotherapy treatment planning study. In brief, we generated treatment plans with and without the use of the ventilation images, evaluated the plans with traditional volumetric metrics as well as with ventilation dose-function histograms 21, and calculated the normal tissue complication probabilities (NTCPs) 22.

MATERIALS AND METHODS

Patient and CT data

Consecutive stage III non-small cell lung cancer 23 cases treated in the Department of Radiation Oncology at The University of Texas M. D. Anderson Cancer Center were screened for use in this study, those with incomplete coverage of the thorax on their 4D CT were excluded. Twenty-one cases were selected from the department patient database for this study (Table 1). The patient identifiers were removed from the image data in accordance with the retrospective study protocol approved by our Institutional Review Board. The patients were all immobilized in a vac-lock bag, wing board, and tee-bar in the supine position with their arms above their head 24. All CT images were obtained at a 2.5-mm slice thickness on a PET/CT scanner (Discovery ST; GE Medical Systems, Waukesha, WI) with a 70-cm bore. Feedback guidance was given to patients as the 4D CT images were acquired during normal resting breathing.

Ventilation image determination

Simon 25 reported a relationship between CT average regional values (in Hounsfield units, [HU], designated HU_{ex} and HU_{in}) and the regional volume change

$$\frac{\Delta V}{V_{ex}} = 1000 \frac{(HU_{in} - HU_{ex})}{HU_{ex} (1000 + HU_{in})}, \quad (1)$$

where $\Delta V = V_{in} - V_{ex}$ is the local volume change due to inspiration. This equation is derived from a model that assumes the voxel content is composed of a combination of water-like material with a CT value of zero (in HU) and air-like material with a CT value of -1000 HU. In this study, a deformable image registration algorithm was utilized to link tissue elements between CT image volumes of the thorax representing exhale and inhale phases obtained from components of the 4D CT image set. This link should relate the location of each underlying tissue element represented in each voxel in the first image (maximum exhalation) to that in the second image (maximum inhalation). We have previously reported on the calculation of ventilation images from breath-hold CT 18 and from 4D CT 19 images. In this study, a ventilation image was calculated using the maximum expiratory and inspiratory 4D CT image pair for each case.

Each ventilation image volume was mapped to a percentile ventilation image (to facilitate use of the auto-contouring tools in the Pinnacle treatment planning system) as follows: If the ventilation image consisted of N voxels with values in the range $V_i \in [0, p_{\max}]$, then the cumulative distribution function (of voxel values) is given by:

$$F(p) = \frac{\#V_i \in [0, p]}{N} \quad (2)$$

The percentile ventilation image is produced by mapping the voxel values of the ventilation image, $V(\vec{x})$, using the above function and scaling to the range $[0, 100]$, as follows:

$$V_{\text{percentile}}(\vec{x}) = 100 \cdot F(V(\vec{x})) \quad (3)$$

Only the percentile ventilation images were utilized during inverse planning in the Pinnacle-3 treatment-planning system (Philips Medical Systems, Andover, MA). The auto-segmentation feature of this system was used to define regions of interest within the lung that represented the 10% of lung volume with the highest pulmonary function by segmenting all voxels with a value greater or equal to 90. The 90 percentile functional volume (PFV90) was chosen as the avoidance structure based on a review of the distribution of percentile volumes (Figure 1). The PFV90 separated the highly functional lung away from the remaining lung.

IMRT planning

The gross tumor volume (GTV) was delineated on each phase of the breathing cycle. An internal target volume (ITV) 26 was formed by adding an 8-mm margin isotropically to the composite GTV, which allowed for microscopic tumor spread 27. The planning target volume (PTV) was obtained by adding a 5-mm margin to the ITV, which accounted for setup error 24. The Pinnacle-3 treatment planning system version 7.6c was used. The isocenter was placed at the centroid of the PTV, and nine equally spaced coplanar beam angles were used. The beam arrangement was similar to other IMRT treatment planning studies for NSCLC 28-30. The initial field size for each beam was obtained from a 5-mm expansion of the PTV projection. Three separate IMRT plans were generated for each case in this study: a volume-constrained baseline plan and two ventilation-constrained plans. Esophagus, heart, spinal cord, and total lung minus GTV (designated TL) were contoured as volumes of interest (VOIs) for optimization and plan evaluation.

The tumor and normal tissue treatment-planning parameters employed in this study are summarized in Table 2 24. Although 50 iterations were specified for the optimization step, a small fraction of plans were stopped early because the objective function achieved its minimum value before the 50 iterations were reached. The direct machine optimization option, with settings for a Varian 21EX machine and a 120 multi-leaf collimator, was chosen to generate a deliverable plan for each plan. The radiation dose distributions used in this study were calculated using the collapsed-cone convolution algorithm 31.

A baseline IMRT plan was then calculated using the lung volumetric criteria summarized in Table 2 10, 11, 24, 32. The PTV coverage planning goal was to achieve 95% coverage of the PTV with the 70 Gy isodose volume. Two IMRT plans were created using the PFV90 volumes as avoidance structures (Table 2) rather than the lung volumetric criteria. Ventilation Constrained Plan 1 (VENT1) represented a stringent attempt to protect the most highly functioning lung (PFV90). Ventilation Constrained Plan 2 (VENT2) was less stringent in its avoidance of functioning lung and increased the PTV coverage weighting. A PTV homogeneity index was calculated as the ratio of the dose providing 99% coverage of

the PTV to the dose providing 1% coverage of the PTV 33. For each case, one of the two plans (VENT1 or VENT2) was selected to join a third set called the optimal set based on PTV coverage and homogeneity.

Evaluation of plans

We compared the optimal plans with the corresponding baseline plans, looking for reductions in TL DVH, TL DFH, mean lung dose (MLD), PFV90 DVH, and mean dose to PFV90. In some of the cases, the ventilation-constrained plan (VENT1 or VENT2) resulted in a reduction in each of the dosimetric parameters studied as well as a reduction in the MLD from the baseline plan. This group was called the favorable subset.

The NTCP was estimated for each plan generated from differing sets of constraints using the MLD model 11, a special application of the Lyman-Kutcher-Burman model 34. This model uses two parameters: the median toxic dose (TD50) and the steepness parameter (m). The NTCP is given by the equation:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-\frac{x^2}{2}} dx \quad (4)$$

where $t = \frac{MLD - TD_{50}}{m \cdot TD_{50}}$ and x is a variable used for integration. The parameters from Seppenwoolde (TD50 = 30.8 Gy, m = 0.37) 22 were used to provide the NTCP estimates. The average NTCP (averaged over all patients) was calculated for the baseline plan set, the optimal set of plans (i.e. VENT1 or VENT2; n=21) and the favorable subset of plans (n=10). The average NTCP calculated for the optimal set and favorable subset were compared with that from the baseline plan set.

Statistical methods

Observed differences in volumetric parameters (V5, V10, V20), functional parameters (F5, F10, F20), mean TL dose, and mean dose to PFV90 were assessed for statistical significance using the Wilcoxon signed rank test. An ANOVA analysis was performed to determine whether characteristics of the PTV, PFV90, or TL influenced the observed differences in these dosimetric parameters. The NTCP estimates for each group were compared with the baseline estimates for each group using a two-sided, paired t-test with a level of significance of $\alpha = 0.05$.

RESULTS

Patient and CT data

From the 4D CT datasets the average maximum expiration lung volume was 2975 mL (SE = 42 mL), the average maximum inspiration lung volume was 3428 mL (SE = 43 mL), the average tidal volume was 453 mL (SE = 36 mL), and the average pulmonary CT intensity change from expiration to inspiration was -30.4 HU (4.16 HU). The ipsilateral lung, the side with the primary tumor, had an average tidal volume of 205.5 mL (23.21 mL) and an average CT intensity change of -28.1 HU (4.58 HU). The contralateral lung had a larger average tidal volume of 255.7 mL (24.93 mL) and an average CT intensity change of -35.5 HU (5.47 HU).

The average TL volume was 3354.7 mL, the average PTV volume was 671.3 mL, and the average PFV90 volume was 418.5 mL. Average ratios of these parameters were determined, which showed that the average ratio of PFV90 to TL was 0.13, the average ratio of PFV90 to PTV was 0.71, and the average ratio of PTV to TL was 0.21. The difference in average

TL volume between the ipsilateral and contralateral lungs was assessed using a paired t-test. The two means differed at a level of significance of $p=0.10$, implying a trend toward a significant reduction in ventilation on the ipsilateral side.

IMRT planning

Dosimetric results from all treatment plans are given in Tables 3 and 4. Overall PTV coverage was much better for VENT2 than for VENT1 (Table 4), enabling acceptable coverage of the PTV in all 21 patients; VENT1 enabled acceptable coverage in only 11 of 21 patients. The homogeneity requirement (Table 4) was also much better satisfied by VENT2 (all 21 patients), with the calculated homogeneity index and standard error similar to those of the baseline plan. In 7 patients the homogeneity requirements (Table 2) were satisfied using the constraints VENT1. All seven VENT1 plans with acceptable homogeneity also had acceptable minimal coverage of the PTV. Therefore, the optimal set of 21 minimally covering plans consisted of seven plans constrained according to VENT1 conditions and 14 plans constrained according to VENT2 conditions. The isodose distribution from an example case is illustrated in Figure 2. The coronal section through the isocenter illustrates the sparing of the regions of high ventilation in the contralateral lung in the VENT1 plan dose distribution (Figure 2d) versus the baseline plan (Figure 2c). The DVH for PTV, TL, and PFV90 are shown for this case in Figure 3a, and the ventilation DFH for TL is shown in Figure 3b.

Evaluation of plans

The average percentage reduction in total lung DVH, total lung DFH, and PFV90 DVH over the 21 cases of the optimal versus baseline treatment plans (versus dose) are shown in Figure 4a. In comparing the optimal versus baseline plans the observed benefit was greatest at the lowest doses (Figure 4a). There was no benefit or even a slight worsening for these parameters at higher doses. Specifically, the V5 was improved by 9.8% (1.28%), the V10 was improved by 3.4% (1.52%), and the V20 was worsened slightly by 2.6% (1.16%). The F5 was improved by 8.7% (1.12%), the F10 was improved by 3.5% (1.32%), and the F20 was worsened slightly by 2.2% (1.12%). For the PFV90, the observed benefit was larger than the benefit for the TL and the improvement extended over a much greater range of doses. The percentage of PFV90 receiving a dose of 5 Gy (herein called the PFV90-5) was improved by 16.6% (2.00%), the PFV90-10 was improved by 11.7% (1.93%), and the PFV90-20 was improved by 3.4% (1.32%). The mean dose to the TL was 21.8 Gy (0.71 Gy) for the baseline and 22.0 Gy (1.05 Gy) for the optimal subset. The mean dose to the PFV90 improved slightly from 22.2 Gy (1.76 Gy) for the baseline to 19.2 Gy (1.05 Gy) for the optimal subset. For the optimal set ($n=21$), the Wilcoxon ranked analysis demonstrated significant improvement in the volumetric parameters V5 ($p=6.4\times10^{-7}$) and V10 ($p=5.3\times10^{-3}$), functional lung parameters F5 ($p=3.2\times10^{-7}$) and F10 ($p=1.8\times10^{-3}$), and mean dose to PFV90 functional lung ($p=4.4\times10^{-6}$). There was a significant effect of the ratio PTV:TL on improvement in V20 ($p=0.03$), improvement in F20 ($p=0.05$), and decrease in MLD ($p=0.01$). The corresponding beta-coefficients for each of these effects were negative, implying that the benefit of ventilation-constrained planning was diminished as PTV increased in volume.

A subset of plans using ventilation avoidance (VENT1 or VENT2 criteria) which resulted in a reduction in all the plan evaluation parameters (TL DVH, TL DFH, MLD, and PFV90 DVH) were grouped as the favorable subset. For the favorable subset ($n=10$), the observed improvements were even more substantial (Figure 4b). There was a decrease in V5 of 12.7% (2.00%), a decrease in V10 of 7.8% (1.42%), and a slight decrease in V20 of 1.0% (1.39%). The F5 decreased by 11.1% (1.77%), the F10 decreased by 7.1% (1.3%), and the F20 decreased by 1.0% (1.42%). The PFV90-5 decreased by 17.4% (3.51%), the PFV90-10

decreased by 14.3% (2.6%), and the PFV90-20 decreased by 7.1% (1.69%). In contrast to the optimal set of 21 patients, the favorable subset of patients had both an improvement in mean dose to the TL of 1.5 Gy (0.32 Gy) and an improvement in the mean dose to the PFV90 of 4.3 Gy (0.46 Gy) relative to the volume-constrained baseline plan. For the favorable subset ($n=10$), Wilcoxon ranked analysis also showed a significant improvement in V5 ($p=1.3\times10^{-3}$), V10 ($p=1.3\times10^{-3}$), F5 ($p=6.5\times10^{-4}$), F10 ($p=1.3\times10^{-3}$), and mean dose to PFV90 functional lung ($p=6.5\times10^{-4}$). The corresponding box plots are presented in Figure 5. The mean dose to TL was not significantly changed relative to the baseline value for any of the plans in this study, either for the optimal set or for the favorable subset. There was a significant positive effect of the ratio PFV90:PTV on improvement in V5 ($p=0.022$) and F5 ($p=0.016$). There was also a significant negative effect of the ratio PFV90:TL on both improvement in V5 ($p=0.034$) and improvement in F5 ($p=0.020$). Otherwise, geometry appeared to play no role.

NTCP

For the baseline set ($n=21$), the average NTCP for grade 2 pneumonitis was 22.5% (1.8%). For the optimal set of plans ($n=21$), the average NTCP was 23.8% (2.6%). For the favorable subset ($n=10$), the average NTCP was 16.7% (2.7%). For the optimal set of plans ($n=21$), ventilation constrained treatment planning did not significantly change the NTCP relative to the volume constrained planning (22.5% baseline; 23.8% optimal set; $p=0.26$). However, for the favorable subset ($n=10$), there was a strong statistically significant reduction in NTCP (22.5% baseline; 16.7% optimal set; $p=0.0005$).

DISCUSSION

This study showed that ventilation images may be used to decrease the MLD, the V20, the F20, and the mean dose to the most highly functioning lung in at least a subset of patients without violating current standard treatment-planning parameters. To our knowledge, this is the first study to incorporate quantitative ventilation images into radiation treatment planning for locally advanced NSCLC. A particular advantage of our technique is that since 4D CT images are now routinely acquired at many institutions for ITV determination 16, 35-41, the calculation of ventilation images only requires an additional processing step 19.

The primary function of the lungs is to facilitate the exchange of gases between the blood and ambient air, providing oxygen to and extracting carbon dioxide from the blood. Ventilation, the diffusion of gases between the alveoli and pulmonary microvasculature, and pulmonary perfusion comprise the major components of lung function. Currently, SPECT imaging is available for the functional imaging of the ventilation and pulmonary perfusion components, but there is no standard imaging test for the diffusion component. In a study of SPECT perfusion images obtained prior to radiotherapy in 56 patients with NSCLC, perfusion defects were found at the tumor site in 94%, adjacent to the primary tumor in 74%, and separate from the tumor in 42% 42. In addition, many of the perfusion defects were not correlated with CT findings, in that CT showed normal regions in 49% of regions adjacent to the tumor that were found by SPECT to be hypoperfused. However, availability, multi-modality image registration, multiple imaging sessions, and patient preference are drawbacks to SPECT functional imaging for radiotherapy treatment planning.

Marked variations in regional perfusion have been found in lung cancer patients with poor pulmonary function before radiotherapy 43, 44. A linear relationship has been observed between the regional radiation dose and a reduction in regional pulmonary perfusion and ventilation at 3 months following radiotherapy 45, 46. Moreover, in a prospective study of 18 patients, those patients whose lungs showed reduced perfusion prior to radiotherapy were found to have a lower reduction in their carbon monoxide diffusion capacity after

radiotherapy 12. Therefore, reducing the amount of highly functional lung irradiated might reduce the post-radiotherapy loss in pulmonary function and normal lung tissue complications.

Prior studies of treatment planning have demonstrated the comparative ability of IMRT over 3D conformal radiotherapy (3D CRT) to spare the volume of normal lung irradiated 29. Christian *et al.* (15), who evaluated the use of SPECT perfusion images to define VOI avoidance structures for use with beam angle and weight optimization in six patients, found that this was able to reduce the amount of functional lung irradiated by 16% in only one patient. They were unable to optimize the beam angles to avoid functional lung in the remaining patients. Seppenwoolde *et al.* (43) utilized the mean perfusion weighted lung dose (MpLD) to perform beam-weight optimization on 3D CRT plans in one phantom and five selected patients. The MpLD optimization increased the beam weights through the relatively hypoperfused regions, resulting in plans with a reduced NTCP. McGuire *et al.* 30 developed a methodology to utilize SPECT perfusion images in thoracic IMRT treatment planning and reported on 5 cases. Their method utilized multiple overlapping regions of interest (ROIs), each with a progressively higher range of perfusion with cut-off values manually selected. These ROIs were utilized in place of lung volume in the inverse planning and plans were evaluated using DFH analysis.

In the present study, we utilized ventilation images and IMRT to optimize both the beam weights and the intensity distribution with constant beam angles (nine equally spaced coplanar beams) for each case. Regions with the most highly functional lung (PFV90) were identified and used as conformal avoidance structures in IMRT planning; the choice of cut-off (e.g. 90 versus 70 percentile) requires further study. Using this approach, we were able to significantly reduce the F5, F10, V5, V10, and mean dose to the most highly functional lung (PFV90) compared with the baseline plans in our set of 21 cases using the ventilation constraints. There was no statistically significant improvement in the calculated NTCP. However, present NTCP models assume uniform distribution of lung function and importance. Nonetheless, there was a favorable subset of patients in whom a further significant improvement in the MLD was identified. There was also a strongly statistically significant reduction in the NTCP in this subset.

Likewise in the studies conducted by Christian *et al.* 14 and Seppenwoolde *et al.* 13, function-constrained plans led to a reduction in the risk of pulmonary complications (NTCP) in only a subset of patients versus the risk associated with lung volume-constrained plans. McGuire *et al.* 30 found improvements in dose function histogram parameters when incorporating perfusion SPECT into the treatment planning. In each of these studies the improvements were found in cases in which there was a favorable relative geometric distribution of both the PTV and the pulmonary function. Similarly, if the highly functional region, in our case the PFV90, is homogeneously distributed around the TL, then the constraints on PFV90 should be very similar to those for TL. However, if the PTV is remote from the PFV90, as in the example case presented earlier, then the beams may be directed along a route of comparatively low lung function. IMRT, which uses the optimization of beamlets, gave our study the advantage of requiring smaller regions of low function to achieve benefit versus the two previous studies 13, 14, which optimized beam weights or directions for 3D CRT and required hypoperfused regions of similar size to the treatment portals.

In this study, upper lobe lesions (PTV) generally had a more favorable geometry, with more ventilation occurring in the lower lobes than in the upper lobes, thereby facilitating effective avoidance of any superiorly lying PFV90. For the favorable subset of patients (those experiencing the greatest benefit from ventilation functional planning), the PTV was in the

upper lobe in seven of the 10 patients, the middle lobe in two, and the lower lobe in one. However, we found a trade-off between the PTV coverage dose and normal lung irradiated in most cases. In most cases VENT2 yielded better coverage and homogeneity of the PTV, but at the expense of a reduced benefit in terms of the PFV90. Validation of the 4D CT derived ventilation imaging with SPECT ventilation should be performed before clinical implementation of the techniques developed in this study proceed to clinical use. Then a clinical study will be necessary to determine whether patient outcome, including reduced treatment complications, is improved through the use of functional avoidance treatment planning.

CONCLUSIONS

In this study, a new method of functional inverse planning using 4D CT-derived pulmonary ventilation volumes as avoidance VOIs was assessed. Overall, the method was feasible, leading to substantial improvements in functional dosimetry. These improvements were primarily at the lower doses and were especially notable in a subset of patients whose tumor size, tumor location, and spatial distribution of functional lung made for a particularly good treatment plan. Overall, our data suggest that half of the patients with locally advanced NSCLC could benefit from the use of this method. Most importantly, our method can be applied in these patients without worsening standard volumetric planning criteria such as the V20, supporting its safe use in a clinical trial. It is hoped that the findings from this study will support the application of this novel treatment planning method, including its use in prospective clinical trials.

Acknowledgments

The University of Texas M. D. Anderson Cancer Center Physician-Scientist Program provided support for this project. We acknowledge the assistance of Kathleen Reyes in producing the ventilation contours (PFV90) used in this study. This work was partially supported by Grant R21 CA128230 from the National Cancer Institute and through a National Science Foundation VIGRE grant (NSF DSM 0240058).

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Figure 1. Ventilation Volumes of Interest (VOIs)

A coronal section through the treatment planning free-breathing CT image volume with VOIs generated from the ventilation image (90, 70, 50, and 30 percentile ventilation) is shown. The gross tumor volume (GTV) is shown in red and the planning tumor volume (PTV) in blue. There is a ventilation defect in the right upper lobe adjacent to the GTV seen as a lack of contours in that region. The defect fills in progressively with the lower percentile contours. The 90 percentile lines show a clear separation between the highly functional lung and the remaining lung.

Figure 2. Effect on isodose distribution

a) A coronal section through a 4D CT derived ventilation image is shown with 90 percentile volume of interest (PTV90) contours (light green), the GTV (red), and the PTV (blue). **b)** The same PTV90, GTV, and PTV contours are shown on the corresponding treatment planning CT coronal section. **c)** Same treatment planning CT coronal section shown in **a** & **b** with isodose distribution from the volume-constrained baseline plan. **d)** treatment planning CT coronal section with the isodose distribution from the ventilation-constrained plan, there is shifting of the 1000, 2000, and 3000 cGy isodose lines away from the PFV90 lung, sparing the regions of the normal lung with the highest function (PFV90).

Figure 3. Example case DVH and DFH

a) Example case dose volume histogram (DVH) of the resultant dosimetry for the baseline volume-constrained plan (broken lines) and the ventilation-constrained plan using PFV90 avoidance structures (solid lines). The DVH changes in the Total Lung, PFV90, and PTV are shown in this graph for the baseline and ventilation constrained plans. **b)** The change in Total Lung dose function histogram (DFH) is shown in this graph for the baseline and ventilation constrained plans.

Figure 4. Percentage improvements

a) The average improvement ($\pm$ SE) for the entire set ($n=21$) in the total lung DVH, total lung DFH, and PFV90 DVH. The improvement in the ventilation constrained plan versus the volume constrained plan was calculated on a case by case basis at each dose value then averaged. **b)** The average improvement ($\pm$ SE) for the favorable subset ($n=10$) in the total lung DVH, total lung DFH, and PFV90 DVH.

Figure 5. Effect of ventilation-constrained functional planning

There is a statistically significant difference in dosimetry between baseline and ventilation-constrained functional treatment plans for the favorable subset (n=10). The Boxplots show distribution of parameter values for each planning category.

Table 1

Patient demographics.

Structure	Volume Constrained (baseline) Mean Dose (SE) (Gy)
Age	
Median	69 y
Range	46 to 88 y
Gender	
Female	10 (48)
Male	11 (52)
Stage	
IIIA	13 (62)
IIIB	8 (38)
Location	
RUL	8 (38)
RML	3 (14)
RLL	4 (19)
LUL	4 (19)
LLL	2 (10)
PTV	
Median	698.4 mL
Range	260 to 2854 mL

Abbreviations: RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe, LUL = left upper lobe, LLL = left lower lobe, and PTV = planning target volume. Percentages are presented in parentheses.

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Table 2

IMRT planning goals and constraints.

Structure	Volume Constraints			Ventilation Constraints		
	Specification	Dose (Gy)	Coverage (%)	Specification	Dose (Gy)	Coverage (%)
PTV	MIN dose	70	100	MIN dose	70	100
	MAX dose	75	100	MAX dose	75	100
Total lung	MAX DVH	10	45			
	MAX DVH	20	35			
	MAX DVH	30	20			
Functional lung (PFV90)				MAX DVH	10	45
				MAX DVH	20	30
				MAX DVH	40	12.5
				MAX DVH	60	5
Esophagus	MAX DVH	50	50	MAX DVH	50	50
	MAX dose	66	Any point	MAX dose	66	Any point
Heart	MAX DVH	40	40	MAX DVH	40	40
Spinal cord	MAX dose	45	Any point	MAX dose	45	Any point

MAX = maximum
MIN = minimum
DVH = dose-volume histogram
PTV = planning target volume

Table 3

Mean dose to total lung and to PFV90 lung.

Structure	Volume Constrained (baseline)	Ventilation Constrained (VENT1)	Ventilation Constrained (VENT2)
	Mean Dose (SE) (Gy)	Mean Dose (SE) (Gy)	Mean Dose (SE) (Gy)
Total Lung	21.8 (0.71)	20.5 (0.87)	22.4 (1.05)
PFV90 lung	22.2 (1.76)	16.4 (1.07)	19.8 (1.44)

SE = standard error

Table 4

Analysis for minimum acceptable coverage and homogeneity

Parameter	Volume constrained (baseline)	Ventilation constrained-1 (VENT-1)	Ventilation constrained-2 (VENT-2)	MIN covering (VENT-1 or -2)
PTV 95% isodose	69.4 (0.17) Gy	60.8 (2.63) Gy	69.6 (0.16) Gy	69.0 (0.25) Gy
Homogeneity index	0.895 (0.006)	0.702 (0.042)	0.894 (0.008)	0.888 (0.008)