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Functional image-based radiotherapy planning for non-small cell lung cancer: A simulation study

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Abstract

Background and purpose: To investigate the incorporation of data from single-photon emission computed tomography (SPECT) or hyperpolarized helium-3 magnetic resonance imaging (³He-MRI) into intensity-modulated radiotherapy (IMRT) planning for non-small cell lung cancer (NSCLC).

Material and methods: Seven scenarios were simulated that represent cases of NSCLC with significant functional lung defects. Two independent IMRT plans were produced for each scenario; one to minimise total lung volume receiving 20 Gy (V_{20}), and the other to minimise only the functional lung volume receiving 20 Gy (FV_{20}). Dose–volume characteristics and a plan quality index related to planning target volume coverage by the 95% isodose (V_{PTV95}/FV_{20}) were compared between anatomical and functional plans using the Wilcoxon signed ranks test.

Results: Compared to anatomical IMRT plans, functional planning reduced FV_{20} (median 2.7%, range 0.6–3.5%, $p = 0.02$), and total lung V_{20} (median 1.5%, 0.5–2.7%, $p = 0.02$), with a small reduction in mean functional lung dose (median 0.4 Gy, 0–0.7 Gy, $p = 0.03$). There were no significant differences in target volume coverage or organ-at-risk doses. Plan quality index was improved for functional plans (median increase 1.4, range 0–11.8, $p = 0.02$).

Conclusions: Statistically significant reductions in FV_{20} , V_{20} and mean functional lung dose are possible when IMRT planning is supplemented by functional information derived from SPECT or ³He-MRI.

Keywords

Intensity-modulated radiotherapy; Non-small cell lung cancer; SPECT; Hyperpolarized helium-3 MRI; Radiotherapy treatment planning

Radical radiotherapy plays a significant role in the curative management of medically or surgically inoperable non-small cell lung cancer patients, with 5-year survival rates of 29–42% for stage I–II disease [1,2] and 5–14% for locally advanced stage IIIA–B tumours [3,4]. Dose escalation may improve tumour control and survival [5,6], but is limited by the

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incidence of radiation pneumonitis, a dose- and volume-dependent effect that correlates with the mean lung dose (MLD) and the volume of lung receiving a dose of at least 20 Gy (V_{20}). This risk of radiation pneumonitis can be reduced by up to 10% using intensity-modulated radiotherapy (IMRT), without compromise in tumour dose delivery [7,8].

IMRT planning has traditionally been performed with the assumption that functional activity is distributed homogeneously throughout the lung. However, a significant proportion of NSCLC patients have defects in regional lung function caused either by local tumour effects or by concurrent pulmonary disease [9–12]. This observation has prompted investigations of functional image-based radiotherapy planning, utilising physiological information from either single-photon emission computed tomography (SPECT) [10–13], four-dimensional X-ray computed tomography (4D-CT) [14] or hyperpolarized helium-3 magnetic resonance imaging (^3He -MRI) [15,16].

The use of perfusion SPECT in facilitating lung radiotherapy treatment planning has been investigated over a number of years, with results demonstrating that incorporation of SPECT functional information into standard conformal radiotherapy planning can allow reductions in the V_{20} for functional lung (FV_{20}) of 3–17% in individual cases, particularly where discrete non-functional regions of significant size are detected [10,17]. In addition, the combination of SPECT imaging data with IMRT techniques has shown the potential to improve functional lung avoidance when compared to both SPECT-based 3D conformal plans [11], and standard anatomical IMRT plans [12,13], permitting average reductions in FV_{20} of 3–10.6% in patients with locally advanced disease, although this benefit has not been demonstrable in early stage patients [11–13].

Alternative functional imaging approaches that have been utilised in this setting include emerging forms of MRI in which inert hyperpolarized helium-3 gas is inhaled to demonstrate regional lung function by selective display of ventilated air spaces, with signal voids corresponding to non-ventilated regions. ^3He -MRI avoids the need for additional radiation exposure whilst providing ventilation distribution images comparable to nuclear medicine techniques, and can be co-registered with conventional CT for radiotherapy treatment planning [15,16,18]. Evaluation of lung ventilation has also been proposed through observation of changes in the pulmonary parenchyma across the respiratory cycle using 4D-CT [14]. Both ^3He -MRI and 4D-CT have been combined with IMRT planning, allowing reductions in FV_{20} of between 1% and 3% in preliminary studies [14,18].

Existing studies have identified the potential utility of functional imaging in radiotherapy planning, but have provided differing suggestions as to the situations where it may be most useful. Early SPECT studies using conformal planning concluded that the greatest benefits were observed in patients with large localised defects in lung function [10,17], a view supported by the findings of a more recent study using IMRT [12]. However, another recent study comparing SPECT-based IMRT with functional 3D conformal planning failed to identify significant benefits in this group, suggesting instead diffuse inhomogeneity of lung function as the most favourable setting for the use of this combined technique [11,19].

The aim of this study was to investigate the impact of incorporating ventilation and perfusion data in the design of IMRT plans for the radical treatment of NSCLC. Specifically, the objective was to use simulated functional image data to investigate which patient groups may benefit most from functional image-based planning. To achieve this, we compared IMRT plans produced with and without the inclusion of functional data for a number of clinical scenarios that represent cases of locally advanced lung cancer with significant functional lung deficits.

Materials and methods

Simulated clinical scenarios

A breath-hold CT image volume from a patient participating in a related ^3He -MRI lung planning study [20] was chosen as a base to generate the NSCLC simulations. The selected CT demonstrated essentially normal pulmonary and mediastinal anatomy, without extensive distortion due to pathology or primary tumour. The CT was imported into AdvantageSim treatment planning software (GE Healthcare, Princeton, NJ, USA) for contouring, and was used to create seven scenarios using simulated functional imaging data representing locally advanced NSCLC of stage IIIA–B, covering a range of primary tumours sites and involved nodal groups. Each scenario considered a central primary tumour location in which the presence of regional lobar or multi-lobar functional deficits in distal or adjacent lung could be expected. The seven simulated cases are summarised in Fig. 1.

For each scenario, a gross tumour volume (GTV) was delineated on the CT images to include the simulated primary tumour and involved nodal groups. This was then expanded by 5 mm in all dimensions to arrive at the clinical target volume (CTV), and then further expanded by 10 mm circumferentially and 15 mm in the cranio-caudal direction to define the planning target volume (PTV), as per local protocols. In addition, the spinal cord, oesophagus, heart, and external patient contours were outlined, and the total lung volume was contoured as the entire ipsilateral and contralateral lung volume excluding the GTV.

A further structure was then created for each simulation to represent the functional lung volume. This used anatomical lobar boundaries identified on the CT dataset to simulate lobar or multi-lobar functional defects congruous with the primary tumour characteristics. Finally, a “normal tissue” structure was defined, using the PTV subtracted from the external patient contour, to generate an avoidance structure for use in limiting normal tissue low-dose irradiation. Once contoured, all simulation scenarios were reviewed prior to use in IMRT planning by a clinical oncology consultant experienced in the management of lung cancer and with knowledge of ^3He -MRI distributions, to ensure clinical relevance and realism, plus congruence of GTVs with simulated defects.

IMRT planning

All simulations were imported into the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA) for IMRT planning. Plans were created using five isocentric, coplanar, non-opposing beams, with manually optimised incident beam angles and arrangements for each individual anatomical or functional plan. Inverse planning was performed to generate treatment beam fluence intensity maps using the Eclipse Dose-Volume-Optimiser module, with planned IMRT delivery via the dynamic MLC method.

For each simulated scenario, two independent treatment plans were produced. Firstly, an anatomical plan was created, with beam angles and beamlet fluence optimised with the intention of mini-mising the total lung volume receiving 20 Gy (V_{20}). Secondly, a functional plan was generated that minimised the volume of identified functional lung receiving 20 Gy (FV_{20}). Additional constraints were included in all inverse planning optimisations to produce plans meeting the requirements detailed in Table 1, with sequential priority given to achieving planning target volume coverage, limiting spinal cord dose, achieving lung dose–volume optimisation goals, and remaining within normal tissue dose-constraints.

Following optimisation, forward dose calculation was performed for each plan to generate an accurate dose distribution, using the eclipse anisotropic analytical algorithm (AAA) with inhomogeneity correction [21]. All plans were designed for delivery using 6 MV photons, to

a prescribed CHART dose of 54 Gy in 36 fractions [22]. In addition to standard dose distributions, dose–volume histograms were created for all plans to aid assessment of dose–volume parameters.

For each plan, the following were calculated and recorded:

- V_{PTV95} (percentage volume of the PTV covered by the 95% isodose)
- minimum and maximum doses within the PTV
- maximum spinal cord dose
- V_{20} (percentage of total lung volume receiving ≥ 20 Gy)
- FV_{20} (percentage of functional lung volume receiving ≥ 20 Gy)
- MLD (mean lung dose for total lung in Gy)
- MFLD (mean functional lung dose in Gy)
- V_{45} for heart (percentage volume of heart receiving ≥ 45 Gy)
- V_{55} for oesophagus (percentage of oesophageal volume receiving ≥ 55 Gy)
- maximum normal tissue dose
- monitor units (MUs) required to deliver the IMRT plan on a Varian linear accelerator.

Where there was a choice between two or more clinically acceptable alternative plans, the ratio of $V_{PTV95}:V_{20}$, or $V_{PTV95}:FV_{20}$, was used to select the “best” overall arrangement for anatomical or functional plans, respectively, with a higher ratio representing a “better” plan that has proportionally less lung irradiation for a given level of PTV coverage.

Data analysis and statistical methods

Data collected for the two plan groups were summarised using the median and range, and differences between the two groups were assessed for significance using the Wilcoxon signed ranks test. All statistical analysis was performed using SPSS for Windows (SPSS Version 15.0; Chicago, IL, USA). A *p* value less than 0.05 was considered statistically significant.

Results

The characteristics of the seven scenarios generated for use in treatment planning simulation are outlined in Table 2. The median PTV for simulated NSCLC scenarios was 599.8 cm³ (range 361.4–669.2 cm³) with a median functional lung deficit comprising 25.0% (19.4–55.2%) of the total lung volume.

Clinically acceptable plans that fulfilled the criteria for limitation of dose to lung, heart, oesophagus, spinal cord, and normal tissue were achieved for all scenarios using both the anatomical and functional optimisation strategies. All plans met the requirements for target volume dose prescription as previously described, with dose–volume characteristics for the anatomical and functional plan groups as summarised in Table 3.

In all seven scenarios, the inclusion of functional information in the optimisation process resulted in reduced dose–volume parameters for functional lung when compared to plans produced with anatomical information alone, with reductions in the FV_{20} for each case, and a median reduction in FV_{20} of 2.7% (range 0.6–3.5%, *p* = 0.02). Furthermore, a small but

statistically significant reduction in the mean functional lung dose (MFLD) of 0.4 Gy (0–0.7 Gy, $p = 0.03$) was observed in favour of the functional plan group.

In addition to the demonstrated reduction in functional lung irradiation volume, plans optimised using both anatomical and functional information showed a reduction in the total lung V_{20} (median reduction 1.5%, range 0.5–2.7%, $p = 0.02$) when compared to purely anatomical plans. However, this did not translate into reduced mean total lung doses, with median values of 13.8 Gy for both plan groups.

Improvements in FV_{20} were achieved without necessitating compromise of target volume coverage, with no significant differences in V_{PTV95} observed between the anatomical and functional plan groups, with median values of 91.8% (range 90.4–93.2%) and 91.4% (range 90.2–93.2%), respectively ($p = 1.00$). Use of the $V_{PTV95}:FV_{20}$ ratio as an overall plan quality index showed a benefit in favour of the functionally optimised plans, with higher ratios recorded for the functional group, indicating more favourable plans (median increase in ratio 1.4, range 0–11.8, $p = 0.02$).

There were no significant differences in the number of monitor units required to deliver the anatomically and functionally optimised plans (median 556 MU vs. 592 MU, $p = 0.55$) nor were significant variations seen in maximum spinal cord dose (median 37.2 Gy vs. 24.3 Gy, $p = 0.3$), V_{45} volume for heart (median 3.8% vs. 3.8%, $p = 0.7$), or the oesophageal V_{55} volume (medians 22.9% vs. 21.1%, $p = 0.2$).

Discussion

Functional imaging modalities such as SPECT and ^3He -MRI can be accurately co-registered to standard CT planning images to provide combined datasets for treatment planning, and previous studies suggest potential improvements in functional lung dose–volume parameters when this information is utilised in IMRT planning. However, these techniques are not yet widely available in the UK, and routine application to clinical practice would carry significant resource implications. Therefore, identification of the patient groups who are most likely to benefit from these new and evolving techniques is important, to help direct resources appropriately.

The principal aim of this study was to assess the impact of incorporating functional information into IMRT planning for the radical treatment of NSCLC on lung dose–volume parameters. Seven scenarios using simulated functional imaging data representing locally advanced NSCLC have demonstrated that inclusion of functional information in IMRT plan optimisation allowed improved avoidance of functional lung, as assessed by FV_{20} and the MFLD, compared to anatomical IMRT alone. The median reduction in FV_{20} of 2.7% demonstrated in this simulation study is in keeping with that observed previously by Ireland et al of 3.1% (range 0.4–5.1%) [18] when using ^3He -MRI data, although it is less than the 5–6% absolute median reductions in FV_{20} observed in selected SPECT literature examining functional versus anatomical IMRT [12,13].

Observed improvements in FV_{20} and MFLD were achieved without compromise in target volume coverage, with an overall increase in the plan quality index for the functional plan group. In addition, there were no significant changes in the doses received by critical normal structures such as heart, spinal cord, and oesophagus. This indicates that this technique could be safely applied to patient treatments, without exceeding known normal tissue tolerances or compromising anti-tumour efficacy.

In addition to improvements in functional lung dose–volume parameters observed in this study, small improvements in total lung V_{20} volumes were identified, which have also been

found by previous groups investigating functional radiotherapy planning [12,18]. A possible explanation for this improvement in V_{20} may be an increased degree of freedom allowed to the planning algorithm when only functional lung doses are constrained, permitting distribution of total lung dose into not only low-dose zones, but also zones of non-functional lung where the 20 Gy threshold has already been exceeded, due to calculation of cost functions in inverse planning via an “area under the curve” method.

The largest improvements in FV_{20} and plan quality ratio ($V_{PTV95}:FV_{20}$) were seen in Scenarios 3, 5, 6 and 7, with observed reductions of 2.7–3.5%, as compared to smaller differences of 1.4% in other case simulations. Examination of the characteristics of these simulations suggests that the size of the functional deficit identified could be an important factor in determining the value of the functional information in treatment planning, with scenarios where defects exceeded approximately 25% of the total lung volume showing larger potential reductions in FV_{20} . This is in keeping with the findings of previous SPECT studies, such as that performed by Seppenwoolde et al. [10], who demonstrated greater improvements in functional lung irradiation parameters with large functional deficits, hypothesising that larger non-functional volumes allow greater potential to select beam arrangements that enter or exit through a non-functional “window” of lung.

Although the reductions in FV_{20} and MFLD observed in the study simulations are statistically significant, it is not clear whether such reductions in FV_{20} volume would have clinical relevance in terms of reduction of the risk of pulmonary morbidity for patients. In addition, there is currently a lack of outcome data correlating functional lung dose–volume parameters with pulmonary toxicity endpoints, and no generally accepted functional lung planning constraints exist in the literature. This is clinically relevant as evidence suggests that a proportion of functional deficits identified prior to radiotherapy may undergo recovery after successful treatment of the primary tumour [9], for example restoration of perfusion or ventilation to a segment of lung previously impaired by compression due to local tumour. Such recovery could conceivably diminish the toxicity of standard anatomically planned treatments that limit the dose to total lung V_{20} , but may not be possible if the potentially recoverable lung had received a higher radiation dose due to classification as non-functional on pre-treatment imaging. Ongoing work at this institution aims to address these issues, with long-term follow-up of a preliminary patient cohort for whom functional lung dose–volume parameters are known, with assessment of lung function and morbidity outcomes after radical radiotherapy treatment, and comparison of baseline and follow-up functional ^3He -MRI scans.

In this study, a limited number of simulated functional defects were examined, each consisting of a relatively large, localised lobar or multi-lobar functional deficit that correlated with the simulated tumour position. These defects were selected to represent a subgroup of situations in NSCLC that could be potentially favourable for functional planning based on previous published work, and are not representative of the entire NSCLC patient spectrum. A previous radiotherapy planning series utilising perfusion SPECT has demonstrated that such localised functional deficits are present in a significant proportion of patients undergoing radiotherapy for NSCLC, with even large deficits such as hypo-function of the entire ipsilateral lung present in 16% of cases [10]. However, a significant number of patients had defects only at the target tumour itself, or varied patterns of inhomogeneous function spread throughout the lung, and therefore whilst it is likely that these simulations correspond to patterns present in real NSCLC patients, they may only be a small subset of the population as a whole.

Considerable further work is required before this technique could be considered for routine application. The first step would be application of ^3He -MRI- or SPECT-based planning to a

larger cohort of NSCLC patients undergoing radiotherapy, to assess if reductions in functional lung dose–volume parameters can be consistently achieved in real patients. This could also allow analysis of the potential factors that may predict the utility of functional planning and allow patient selection, such as the size of functional defects, PTV, tumour stage, or even pre-treatment pulmonary function test parameters. In addition, work is required to demonstrate that reductions in functional lung dose parameters will translate into clinical benefits for NSCLC patients.

Conclusion

This study demonstrates that reductions in FV_{20} , V_{20} and MFLD are possible for a subset of locally advanced NSCLC patients when standard IMRT planning techniques are supplemented by simulated functional lung imaging information such as that derived from ^3He -MRI or SPECT. The greatest benefits may be seen in patients who have larger localised functional defects.

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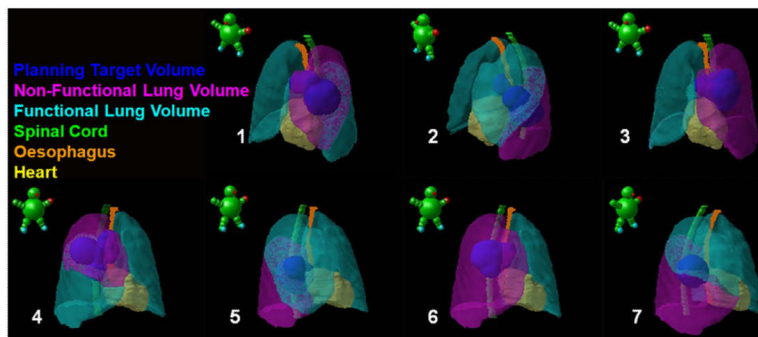


Fig. 1. Summary of simulated non-small-cell lung cancer scenarios. The figures demonstrate the target and normal tissues contours for the seven simulated scenarios, demonstrating structures as indicated by the colour key. Scenarios incorporated non-functional lung regions comprising: (1) left upper lobe; (2) left lower lobe; (3) whole left lung; (4) right upper lobe; (5) right lower lobe; (6) whole right lung; and (7) right middle and lower lobe (simulating primary lesion of bronchus intermedius.).

Table 1

IMRT plan constraints.

Structure	Constraint
Planning target volume (PTV)	Mean dose 54 Gy, and 90% of PTV receiving 95% or more of the prescribed dose
Spinal cord	Maximum point dose 40 Gy
Total ^a or functional ^b lung	Volume receiving 20 Gy less than 35%
Oesophagus	Volume receiving 55 Gy less than 35%
Heart	Volume receiving 45 Gy less than 50%
Normal tissue	Maximum point dose 60 Gy

^aFor anatomical plans.

^bFor functional plans.

Table 2

Characteristics of simulated non-small cell lung cancer scenarios.

Scenario	Stage ^a	Location of functional defect	Total lung volume (cm ³)	Functional lung volume (cm ³)	Defect size (as % of total lung volume)	PTV (cm ³)
1	T ₄ N ₂ M ₀ IIIB	Left upper lobe	7528.9	5804.4	22.9	651.1
2	T ₃ N ₂ M ₀ IIIA	Left lower lobe	7490.5	6040.9	19.4	663.4
3	T ₄ N ₂ M ₀ IIIB	Left lung	7508.3	4240.2	43.5	669.2
4	T ₂ N ₂ M ₀ IIIA	Right upper lobe	7560.4	5976.1	21.0	585.7
5	T ₃ N ₁ M ₀ IIIA	Right lower lobe	7497.2	5619.6	25.0	566.4
6	T ₃ N ₂ M ₀ IIIA	Right lung	7518.6	3368.4	55.2	599.8
7	T ₃ N ₁ M ₀ IIIA	Right lower and middle lobe	7512.0	4989.1	33.6	361.4

^aNSCLC staging as per tumour node metastasis (TNM) system.

Table 3

Comparison of dose–volume characteristics and plan parameters between functionally and anatomically optimised plans.

Scenario	V_{20}		FV_{20}		MLD		MFLD		V_{PTV95}		$V_{PTV95:FV_{20}}$	
	A	F	A	F	A	F	A	F	A	F	A	F
1	25.2	23.8	14.7	13.4	13.8	13.8	9.7	9.8	92.9	93.1	6.3	7.0
2	29.8	28.9	21.1	20.1	16.1	16.0	12.4	12.2	93.2	93.2	4.4	4.4
3	24.5	24.0	11.1	8.1	14.0	14.0	9.9	9.2	91.0	91.0	8.2	11.2
4	30.4	29.5	17.3	16.8	15.8	15.4	11.0	10.7	91.1	91.0	5.3	5.4
5	24.5	22.4	14.6	11.9	13.7	13.3	9.9	9.4	90.4	90.3	6.2	7.6
6	25.6	24.1	7.2	3.7	13.7	13.7	8.2	7.6	91.8	91.4	12.8	24.6
7	20.9	18.2	10.1	6.6	10.8	10.6	7.1	6.7	90.4	91.4	8.9	13.8
Median	25.2	24.0	14.6	11.8	13.8	13.8	9.9	9.4	91.8	91.4	6.3	7.6
p Value	0.02		0.02		0.07		0.03		1.00		0.02	

Data are presented for the most favourable plan generated using anatomical data (A), and with combined anatomical and functional data (F). Abbreviations: V_{20} , percent volume of lung receiving 20 Gy; FV_{20} , percent volume of functional lung receiving 20 Gy; MLD, mean lung dose in Gy; MFLD, mean functional lung dose in Gy; V_{PTV95} , percent volume of planning target volume (PTV) covered by the 95% isodose; $V_{PTV95:FV_{20}}$, plan quality index consisting of the ratio of V_{PTV95} to FV_{20} .