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Clinical imaging

A potential to reduce pulmonary toxicity: The use of perfusion SPECT with IMRT for functional lung avoidance in radiotherapy of non-small cell lung cancer

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Abstract

***Background and purpose*: The study aimed to examine specific avoidance of functional lung (FL) defined by a single photon emission computerized tomography (SPECT) lung perfusion scan, using intensity modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3-DCRT) in patients with non-small cell lung cancer (NSCLC).**

***Materials and methods*: Patients with NSCLC underwent planning computerized tomography (CT) and lung perfusion SPECT scan in the treatment position using fiducial markers to allow co-registration in the treatment planning system. Radiotherapy (RT) volumes were delineated on the CT scan. FL was defined using co-registered SPECT images. Two inverse coplanar RT plans were generated for each patient: 4-field 3-DCRT and 5-field step-and-shoot IMRT. 3-DCRT plans were created using automated AutoPlan optimisation software, and IMRT plans were generated employing Pinnacle^3 treatment planning system (Philips Radiation Oncology Systems). All plans were prescribed to 64 Gy in 32 fractions using data for the 6 MV beam from an Elekta linear accelerator. The objectives for both plans were to minimize the volume of FL irradiated to 20 Gy (fV_{20}) and dose variation within the planning target volume (PTV). A spinal cord dose was constrained to 46 Gy. Volume of PTV receiving 90% of the prescribed dose (PTV_{90}), fV_{20}, and functional mean lung dose (fMLD) were recorded. The PTV_{90}/fV_{20} ratio was used to account for variations in both measures, where a higher value represented a better plan.**

***Results*: Thirty-four RT plans of 17 patients with stage I—IIIB NSCLC suitable for radical RT were analysed. In 6 patients with stage I—II disease there was no improvement in PTV_{90}, fV_{20}, PTV/fV_{20} ratio and fMLD using IMRT compared to 3-DCRT. In 11 patients with stage IIIA—B disease, the PTV was equally well covered with IMRT and 3-DCRT plans, with IMRT producing better PTV_{90}/fV_{20} ratio (mean ratio — 7.2 vs. 5.3, respectively, $p = 0.001$) and reduced fMLD figures compared to 3-DCRT (mean value — 11.5 vs. 14.3 Gy, $p = 0.001$). This was due to reduction in fV_{20} while maintaining PTV coverage.**

***Conclusion*: The use of IMRT compared to 3-DCRT improves the avoidance of FL defined by perfusion SPECT scan in selected patients with locally advanced NSCLC. If the dose to FL is shown to be the primary determinant of lung toxicity, IMRT would allow for effective dose escalation by specific avoidance of FL.**
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Keywords: Non-small cell lung cancer; Intensity modulated radiotherapy; Radiation pneumonitis; Radiotherapy treatment planning; Functional imaging

Lung cancer is the leading cause of cancer related mortality worldwide [1]. The principal curative treatment in patients with non-small cell histology (NSCLC) which represents over three-quarters of primary lung cancer is surgery. Patients with locally advanced NSCLC and those unsuitable for surgery due to comorbidity are appropriately treated with radiotherapy (RT) [2]. Despite radical RT, the 5-year survival rate is 18—36% in patients with early stage medically inoperable disease [3—7] and 5—14% in patients with locally advanced stage IIIA—B disease [8—10].

Although survival can be improved by intensifying radiotherapy [11], attempts at dose escalation are limited by radiation damage of normal lung in the form of radiation pneumonitis. The incidence of pneumonitis is dose and volume dependent, and is related to lung volume receiving >20 Gy (V_{20}) and mean lung dose (MLD) with a risk of pneumonitis of over 10% when V_{20} exceeds 30% [12—14]. V_{20} reduction using three-dimensional conformal radiotherapy (3-DCRT) may allow dose escalation with a potential impact on survival in selected patients with NSCLC [15,16]. A bene-

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fit of 3-DCRT can be enhanced in some cases with intensity modulated radiotherapy (IMRT), which may allow for improved planning target volume (PTV) coverage and better selective avoidance of normal tissues, particularly when the targets are of complex shape lying in close proximity to critical structures. In IMRT, intensity modulation within individual beam inlets is designed on the basis of the target prescription and a set of dose constraints for organs at risk using inverse planning algorithms. Recently published data report a 6–15% absolute decrease of V_{20} when using IMRT compared to 3-DCRT [17–19]. However, the role of IMRT in treating NSCLC remains uncertain owing to the concern that significant areas within the PTV may be underdosed due to failure in controlling tumour motion. There are also concerns over the low, yet potentially damaging, dose that IMRT can deliver to a significant volume of normal lung [20].

Patients with NSCLC have frequent smoking related comorbidity and this further limits the use of radical RT. The lung cancer itself may cause regional variation in pulmonary perfusion resulting in altered function of different parts of lung. Conventional RT planning (RTP) of NSCLC using CT data assumes the lung as a uniform organ, where radiation is distributed to different parts regardless of their function. A single photon emission computerized tomography (SPECT) perfusion scan using ^{99m}Tc labelled macroaggregated albumin provides 3-D information on the distribution of pulmonary blood flow, where perfused areas equate with normal functioning lung (FL) [21,22]. SPECT can be accurately co-registered with conventional CT images [23,24]. It is possible to advance a hypothesis that specific avoidance of FL with greater deposition of lung dose to non-functioning regions of lung, defined by a SPECT perfusion scan, may allow for greater dose escalation [22]. We attempted to establish whether the use of modern RT delivery techniques can result in better functional avoidance. We have previously shown that it is possible to avoid SPECT-defined FL in patients with large uniform perfusion defects using conventional 3-DCRT [25,26]. In this study we have assessed an additional value of IMRT over 3-DCRT in larger cohort of patients with the aim of minimizing irradiation of FL.

Patients and methods

Patient population and ethical concern

The study protocol was approved by the Ethics Committee of Royal Marsden NHS Foundation Trust. Seventeen patients undergoing radical radiotherapy for NSCLC were consented for entry to the study. Patient characteristics are shown in Table 1. Six patients had medically inoperable stage I–II disease and other 11 patients had locally advanced stage IIIA–B disease with extension to mediastinum.

Imaging and image co-registration

Patients underwent CT scanning (General Electrics Hi-Speed QX/i scanner) in the treatment position using a lung immobilization board. Prior to the CT-scan, to facilitate image co-registration, 8–10 disc-shaped markers containing ^{57}Co (Isotope Products Laboratories, Valencia, CA) were positioned on bony landmarks over the antero-lateral surface of the patient's chest. CT slice thickness was set at 5 mm. Following CT, an intravenous injection of 200 MBq of ^{99m}Tc labelled macroaggregated albumin was given and lung perfusion SPECT scan was acquired in the same position using low energy, high resolution collimators of (Philips Medical Systems ForteTM dual-head gamma-camera system). Projections were acquired at discrete 3° angular intervals with each camera head rotating through 180°. The approximate duration of the SPECT scan was 15 min. The spatial resolution of the reconstructed SPECT images was 15–20 mm. All scans were carried out with free breathing, and had sufficient coverage to include the total lung volume. The CT and SPECT scans were co-registered manually in the Pinnacle^3 planning system (Philips Radiation Oncology Systems, Milpitas, CA). A correction algorithm was applied to the SPECT images to compensate for photon attenuation as reported previously [27]. Accuracy of the co-registration was externally validated and described in further detail by Partridge et al. [24].

Table 1
Patient characteristics

Variable	Patient #
Stage (patient number)	
I–II	6
IIIA–B	11
Tumour localisation (patient number)	
Upper lobes	10
Lower lobes	2
Hilar areas	5

Radiotherapy volume definition

Gross tumour volume (GTV), body outline, whole lung (WL) as a single organ (excluding GTV), and spinal cord were outlined. The planning target volume (PTV) was created using a 1 cm uniform margin around the GTV. A ''normal volume'' was created using a 3 cm uniform margin around the PTV and subtracting this volume from the body outline, to define the anatomical areas where low doses of radiation were expected.

The SPECT data were viewed as a multicoloured image in the spectrum colour setting to allow accurate volume contouring around a predefined colour. The threshold level was adjusted individually for each patient in order to match the size of the SPECT image within the lung volumes defined on CT. A new contour of FL was created from the SPECT images using a threshold of 60% of the maximum uptake for each patient.

Radiotherapy planning

Two coplanar inverse RT plans were generated: a 4-field 3-DCRT plan and a 5-field step-and-shoot IMRT plan (Fig. 1). Dose constraints and objectives are shown in Table 2. The principal objectives for each plan were to minimize the volume of FL irradiated to 20 Gy (fV_{20}) and a dose variation within the PTV. The plans were prescribed to 64 Gy in 32 fractions at isocentre using the 6 MV X-ray beam data from an Elekta linear accelerator (Elekta Oncology systems, Crawley, UK). This was purely a planning study, so no patients were treated using the plans produced.

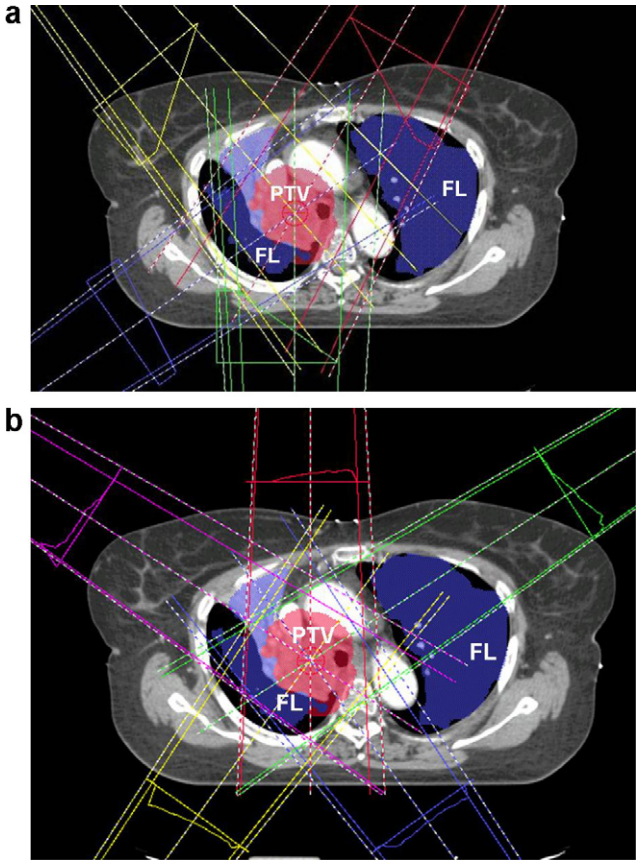

Fig. 1. Beam orientation of 3-DCRT (a) and IMRT (b) plan of the same patient.

Table 2
Inverse planning objectives and constraints

Objectives/constraints	
PTV	Uniform dose 64 Gy Minimal dose >60 Gy
FL	V_{20} < 20%
Spinal cord	Maximal dose <46 Gy
Normal volume	Maximal dose <60 Gy

PTV, planning target volume; FL, functioning lung.

The inverse 4-field 3-DCRT plans were created with AutoPlan planning software developed at the Royal Marsden Hospital [28,29] which carries out a random search of beam orientations, weights and wedge angles. At each iteration, dose is calculated using a fast convolution algorithm. AutoPlan was used in conjunction with the Pinnacle^3 planning system to facilitate a final dose calculation using an accurate collapsed-cone convolution algorithm for a clinically usable plan.

Step-and-shoot 5-field IMRT plans were produced with Pinnacle^3 planning system. The beams were oriented manually to avoid FL. After calculating intensities, beam segmentation was performed using the method described by Niotsikou et al. [30], setting error tolerance at 5% and aiming to reduce the number of segments. The mean number of segments was 5 per field (range 3–8) and 25 per plan (range 18–32).

Data collection and assessment of plans

The primary endpoint of this study was to compare the dose to PTV and FL. The volume of the PTV, WL and FL were recorded for each of the IMRT and 3-DCRT inverse plans. PTV volume covered by 90% isodose (PTV_{90}), fV_{20}, and functional MLD (fMLD) were calculated. The PTV_{90}/fLV_{20} ratio accounted for variations in both measures, where a higher ratio represented a better plan. Data mean values were compared using unpaired Student's t test [31]. Wilcoxon matched-pair signed rank test was used to compare dose/volume data for individual patients [32].

Results

Imaging FL

Thirty-four RT plans of 17 patients were available for analysis. Co-registered CT and SPECT images demonstrated either large uniform perfusion defects adjacent to tumour (Fig. 2a and Table 3) or inhomogeneity of FL often due to pre-existing lung dysfunction because of underlying lung disease (Fig. 2b and Table 3). All patients had smaller FL volume than anatomical WL. The mean FL/WL ratio was 0.65 for early stage disease and 0.68 for locally advanced disease (Table 3).

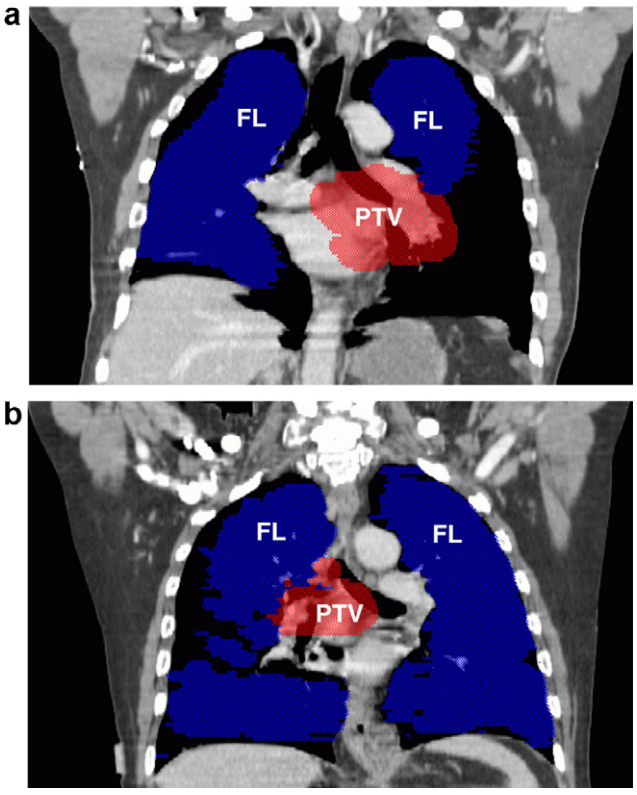

Fig. 2. Radiotherapy volumes delineated on combined CT/SPECT images (coronal reconstruction). Functioning lung (FL) contour demonstrates either single uniform perfusion defect close to planning target volume (PTV) (a) or general heterogeneous hypoperfusion (b).

Table 3
Perfusion defects and radiotherapy volumes

Variable	Stage	
	I–II (n = 6)	IIIA–B (n = 11)
Perfusion defect (patient number)		
Large uniform defect adjacent to tumour	3	3
Non-uniform heterogeneous hypoperfusion	3	8
Radiotherapy volumes (mean ± SD)		
PTV (cm^3)	118 ± 56	284 ± 87
WL (cm^3)	3905 ± 1440	3822 ± 1088
FL (cm^3)	2587 ± 1176	2502 ± 1052
WL/FL	0.65 ± 0.11	0.68 ± 0.16

n, patient number; SD, standard deviation; WL, whole lung; PTV, planning target volume; FL, functioning lung.

Stage I–II patients

The dose/volume parameters of 6 patients with stage I–II disease are shown in Table 4. There was no difference in PTV coverage and fV_{20}, PTV/fV_{20} ratio and fMLD values between IMRT and 3-DCRT in all individual patients. There was no clear relationship between PTV_{90}, fLV_{20}, PTV_{90}/fV_{20} ratio and fMLD from one side and absolute volume of PTV and FL/WL ratio from the other side.

Stage IIIA–B patients

The dose/volume parameters of 11 patients with stage IIIA–B disease are shown in Table 4. There was no significant difference between IMRT and 3-DCRT in terms of individual and mean PTV_{90} values. The mean fV_{20} (p = 0.007; 95% CI = −12.6 to −2.8), PTV_{90}/fV_{20} (p = 0.001; 95% CI = 1.1–2.8) and fMLD (p = 0.001; 95% CI = −3.8 to −1.5) were better for IMRT compared to 3-DCRT. This was also seen for individual patients.

Dose volume parameters of patients with stage IIIA–B disease in relation to the type of perfusion defect are shown in Table 5. Three patients had large uniform perfusion defect adjacent to the primary tumour. This resulted in a minimal amount of the FL close to PTV (Fig. 2a). Effective FL avoidance was therefore possible with 3-DCRT, and there was no significant reduction of fV_{20}, PTV_{90}/fV_{20} ratio and FMLD using IMRT (Fig. 3a and Table 5). In contrast, 8 patients with locally advanced disease had non-uniform perfusion defects scattered within both lungs resulting in larger amount of FL close to PTV (Fig. 2b). Using IMRT in these patients resulted in relative reduction of mean fV_{20} (p = 0.02; 95% CI = −14.9 to −8.0), PTV_{90}/fV_{20} ratio (p = 0.03; 95% CI = 1.3–3.5) and fMLD (p = 0.04; 95% CI = −4.5 to −2.4) by about one-third (Fig. 3b and Table 5). This was also noted for individual patients.

Discussion

The aim of modern radical RT of NSCLC is to improve target coverage while minimizing the dose of radiation to normal tissue, with lung as the principal dose limiting organ at risk. An increase of PTV_{90}/V_{20} ratio may allow for dose escalation and potential improvement in tumour control and survival. While the majority of studies evaluate the normal tissue sparing effect of modern RT techniques by

Table 4
Dose/volume parameters of intensity modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3-DCRT) of patients with non-small cell lung cancer

Parameter	Stage I–II (n = 6)				Stage IIIA–B (n = 11)			
	IMRT	3-DCRT	p	95% CI	IMRT	3-DCRT	p	95% CI
PTV_{90} (%)								
Mean*	99.2	98	0.24	−6.4 to 0.7	99.3	98.9	0.23	−0.8 to 0.1
Range**	95–100	92–98.9	0.14		97–100	96.5–100	0.09	
fV_{20} (%)								
Mean*	12.8	14.7	0.16	−0.2 to 5.5	16.8	24.5	0.007	−12.6 to −2.8
Range**	10.3–15	10.5–16.9	0.28		8.1–29.1	10.1–45.8	0.002	
PTV_{90}/fV_{20}								
Mean*	7.8	7.2	0.22	−2.3 to 0.5	7.4	5.3	0.001	1.1 to 2.8
Range**	6.3–9.3	5.8–9.1	0.12		3.4–11.2	2.2–10.7	0.0008	
fMLD (Gy)								
Mean*	6.4	6.6	0.5	−1.3 to 0.1	11.5	14.1	0.001	−3.8 to −1.5
Range**	5.9–7.5	5.4–7.4	0.46		3.6–19.9	4.2–24.8	<0.0001	

n, number of patients; 95% CI, 95% confidence interval of difference in means; PTV_{90}, percentage of the planning target volume receiving 90% of a prescribed dose; fV_{20}, percentage of functioning lung volume irradiated to 20 Gy; fMLD, functioning lung mean dose; p values calculated using *unpaired t test and **Wilcoxon matched pair signed rank test.

Table 5
Dose/volume parameters of intensity modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3-DCRT) of stage IIIA–B patients with non-small cell lung cancer related to a type of perfusion defect

Parameter	Large uniform defect adjacent to tumour (n = 3)				Non-uniform heterogeneous hypoperfusion (n = 8)			
	IMRT	3-DCRT	p	95% CI	IMRT	3-DCRT	p	95% CI
PTV_{90} (%)								
Mean*	99.4	98.7	0.54	−5.1 to 0.5	99.2	98.9	0.31	−1.6 to 0.1
Range**	98.6–99.9	96.5–99.8	n/a		97–100	98.1–100	0.12	
fV_{20} (%)								
Mean*	9.7	11.2	0.28	−1.2 to 6.3	18	29.5	0.02	−14.9 to −8.0
Range**	8.1–11.8	10.1–14	n/a		11.6–29.1	18.6–45.8	0.008	
PTV_{90}/fV_{20}								
Mean*	9.7	9.1	0.7	−4.2 to 0.3	6.2	3.9	0.03	1.3–3.5
Range**	8–11.2	7.5–10.7	n/a		3.4–8.6	2.2–6	0.008	
fMLD (Gy)								
Mean*	6.8	7.4	0.8	−5.8 to −0.7	13.1	16.7	0.04	−4.5 to −2.4
Range**	3.6–8.7	4.2–9.5	n/a		8.8–19.9	12.3–24.8	0.006	

n, number of patients; 95% CI, 95% confidence interval of difference in means; PTV_{90}, percentage of the planning target volume receiving 90% of a prescribed dose; fV_{20}, percentage of functioning lung volume irradiated to 20 Gy; fMLD, functioning lung mean dose; p values calculated using *unpaired t test and **Wilcoxon matched pair signed rank test.

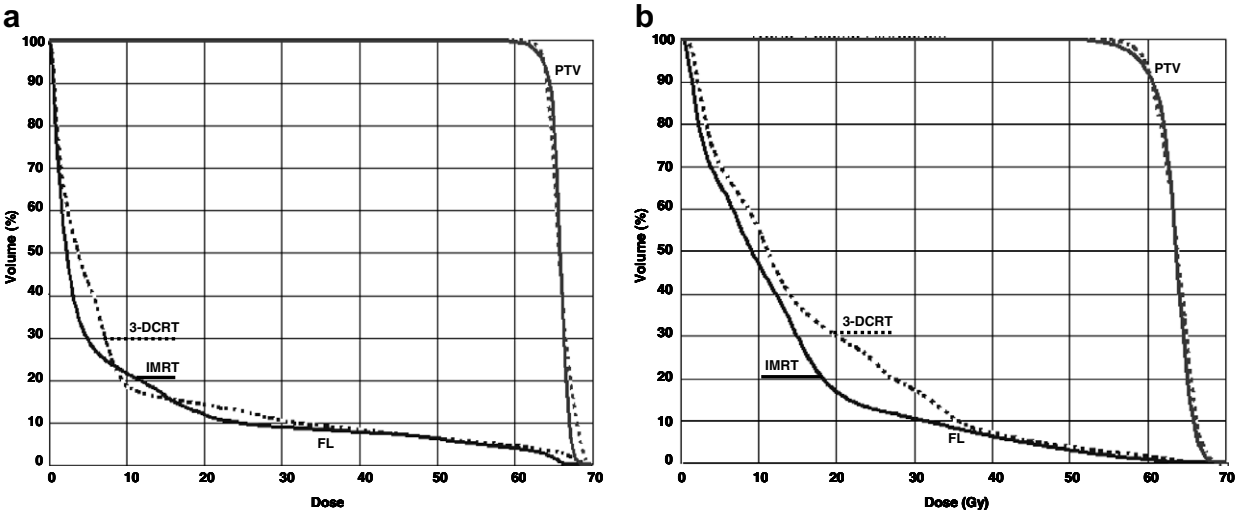

Fig. 3. Dose–volume histograms (DVH) for planning target volume (PTV) and functional lung (FL) of patient with stage III non-small lung cancer: (a) Equal PTV coverage for intensity modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3-DCRT) and marginal reduction of FL V_{20} (fV_{20}) using IMRT in patient with uniform perfusion defect close to tumour (see Fig. 2a); (b) equal PTV coverage for IMRT and 3-DCRT and significant reduction of fV_{20} using IMRT in patient with non-uniform heterogeneous hypoperfusion (see Fig. 2b).

looking at the whole lung, we chose looking at the lung as a functioning organ, aiming to reduce the volume of FL receiving significant radiation dose, where function is defined by the presence of lung perfusion on the SPECT scan.

We compared automated 4-field 3-DCRT plans with 5-field step-and-shoot IMRT plans in terms of PTV coverage and a volume of irradiated FL with both plans designed within same dose constraints. Our previous studies showed that increasing beam number over 4 in 3-DCRT plans did not improve PTV coverage and sparing of critical structures in patients with NSCLC [33–35]. In contrast, a minimum of 5 fields are typically required to give sufficient degree of freedom to allow IMRT plans to show an advantage [36].

This study demonstrated significant reduction of radiation dose to FL volume with IMRT in patients with stage IIIA–B NSCLC, but not in patients with stage I–II disease. The benefit of IMRT was seen in patients with non-uniform perfusion defects scattered within both lungs. Patients with locally advanced disease and non-uniform hypoperfusion may be candidates for future dose escalation studies using IMRT.

IMRT can improve an anatomical lung V_{20} and MLD values in patients with locally advanced NSCLC with hilar and mediastinal lymphoadenopathy [17–19]. Dose escalation to 95–100 Gy while maintaining V_{20} at 15–25% and MLD <16 Gy with IMRT is theoretically possible in selected patients with NSCLC [32]. However, the role of IMRT in

treating NSCLC remains uncertain owing to the concern that IMRT may deliver a low, yet damaging, dose to significant volume of normal lung, due to an increase in monitor units (MUs) to deliver and due to multi-leaf collimator leakage [20,22]. The biologic effect of the trade-off between a reduction of the high dose volume and an increase of the low dose volume is not clear. IMRT delivery with a step-and-shoot technique may require lower MUs compared with sliding window technique, and this may help to reduce the lung and normal tissue volumes receiving low doses [37].

Tumour motion with respiration introduces another level of complexity to IMRT with considerable variation between desired and delivered doses. There are two methods to ensure PTV and tumour coverage. RT may be planned and delivered at a specific phase of respiratory cycle by using either voluntary deep inspiration breath hold [38], or imposed breath hold applying active breathing control device (ABC) when inspiration breath hold is set at reproducible tidal lung volumes [39]. Alternatively, modern accelerators may allow RT delivery synchronized with respiratory cycle [40]. IMRT requires prolonged treatment time and multiple breath holds may not be tolerated by NSCLC patients with frequently compromised lung function. Methods of the RT delivery synchronized with breathing cycle are currently under evaluation [41,42].

Imaging lung function for RTP has not been addressed in studies of IMRT. Normal lung to function requires areas where both alveolar ventilation and perfusion occur. If one of these is absent, gaseous exchange does not occur in that part of lung. As previously noted, non-ventilated areas demonstrate compensatory reduction of perfusion [43], and imaging perfusion is likely to be sufficient to define FL volume. After radiotherapy, non-perfused areas on SPECT scan may regain perfusion transforming non-functioning lung to FL [22,44]. However, the pattern of reperfusion is difficult to predict and avoiding FL is likely to remain a reasonable approach.

The threshold settings for functional images combined with CT images are not clearly defined. Finding the correct setting is crucial particularly when used for accurate volume definition in RTP. We have taken a pragmatic approach used in other published studies, adjusting the lower threshold level for the SPECT perfusion map to remain contained within the CT lung contour [22,26]. Similar volume definition issues arise when FDG-PET is used in NSCLC in combination with CT for RTP where the tumour size using PET may be over-estimated rather than under-estimated [45]. The use of attenuation correction has been shown to improve tumour volume definition in FDG-PET [46], and hybrid PET/CT scanners now perform these corrections as default. Similar improvements in volume definition accuracy are also expected when applying attenuation correction to SPECT data [27].

The assumption that the radiation dose to FL is a determinant of radiation lung damage is a limitation of this study as the functional consequences of replacing WL volumes by FL volumes in RTP are not known. Seppenwoolde et al. reported that radiation pneumonitis incidence increased with mean perfusion-weighted lung dose (MpLD) [47]. However, validated predictive values of MpLD for pneumonitis or reliable parameters for NTCP-like models which explicitly include functional data are not available to date, due to a lack of data correlating functional imaging to clinical outcomes in radiotherapy. The comparative assessment of FL versus WL dose–volume parameters as predictors of postradiation pulmonary toxicity is required and this study is currently underway. At present SPECT-derived FL volume cannot be used for routine RTP of NSCLC.

We conclude that the use of IMRT improves the avoidance of FL defined by perfusion SPECT in selected patients with locally advanced non-small cell lung cancer. If the dose to FL is shown to be the primary determinant of lung toxicity, IMRT would allow for effective dose escalation.

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