THE INCORPORATION OF SPECT FUNCTIONAL LUNG IMAGING INTO INVERSE RADIOThERAPY PLANNING FOR NON-SMALL CELL LUNG CANCER

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**Background and purpose**

Patients with non-small cell lung cancer (NSCLC) requiring radiotherapy treatment often have smoking-related lung damage. Lung perfusion single photon emission computed tomography (SPECT) scans have been accurately co-registered with radiotherapy planning computed tomography (CT) scans to design radiotherapy treatments which limit the dose to areas of healthy ‘perfused’ lung.

**Materials and Methods**

Patients undergoing radiotherapy planning for localised NSCLC had CT and SPECT scans accurately co-registered in the planning system. The SPECT images were used to define a new volume of perfused ‘functioning’ lung (FL). Inverse planning software was used to create four 4-field 3D-conformal plans for each patient. The planning objective was either to minimise the dose to whole lungs (WL) or to minimise the dose to FL. The percentage volume of functioning lung receiving ≥ 20 Gy (FLV$_{20}$) and volume of the PTV covered by the 90% isodose (PTV$_{90}$) were the primary endpoints.

**Results**

Four plans were created for each of six patients. The mean difference in volume between WL and FL was 1011.7 cm$^3$ (range 596.2 – 1581.1cm$^3$). One patient with bilateral upper lobe perfusion deficits had a 16% reduction in FLV$_{20}$. The remaining patients had inhomogeneous perfusion deficits such that inverse planning was not able to sufficiently optimise beam angles to avoid functioning lung.
Conclusion

SPECT perfusion images can be accurately co-registered with radiotherapy planning CT scans in planning systems. These images are likely to be most helpful in creating treatment plans in patients with large areas of perfusion deficit.
Introduction

Radiotherapy has been transformed with the incorporation of three-dimensional imaging into treatment planning software. With the vast amount of dose-distribution data that can now be generated, dose-volume histograms (DVHs) have become a useful method of reducing the volume of information into a two-dimensional display, upon which an assessment of a plan can be made. However, in creating a DVH, there is an implied assumption that homogeneity of function exists for a particular volume of an organ. In patients undergoing radiotherapy for NSCLC who have frequent pre-existing lung damage, lung function is far from uniform.

For a lung to function, the alveoli require both ventilation and perfusion at the same time. If one of these is absent, gaseous exchange at the alveolar diffusion membrane does not occur in that area. Lung cancer may cause permanent change, where a tumour has destroyed an area of lung tissue or a temporary change [4] where tumour-associated atelectasis becomes aerated and tumour infiltrates are reduced in response to successful radiotherapy.

Three dimensional single photon emission computed tomography (SPECT) lung perfusion imaging provides information about the functioning of pulmonary vascular/alveolar subunits where $^{99m}$Tc labelled albumin adheres to the functioning vasculature of the pulmonary vessels. SPECT imaging studies have most commonly compared the functional lung changes in the pre and post radiotherapy setting. Several authors have shown that a reduction in lung perfusion occurs after radical doses of radiotherapy and that these changes are dose-dependent [5,7,8,15].

The aim of thoracic radiotherapy for non-small cell lung cancer (NSCLC) is to maximise dose to the tumour whilst keeping the dose to the surrounding lungs and other organs to a minimum. The development of radiation pneumonitis is usually seen
as the main dose-limiting end-point and the dose parameters, $V_{20}$ (the volume of lung to receive greater than 20 Gy) and MLD (mean lung dose) are commonly used as predictors of pneumonitis. However, the reduction in pulmonary function, short of severe pneumonitis, is also a complication of thoracic radiotherapy which may seriously impact upon quality of life.

Due to the complexity of assessing pulmonary function in this group of patients, who often have other co-existing cardio-pulmonary disease, dose-volume statistics are not reliable predictors of a long-term reduction in lung function in comparison to the prediction of pneumonitis, where correlation is better. The extent of lung damage, due to smoking related disease e.g. chronic obstructive pulmonary disease (COPD), cannot be easily assessed on CT scan images and these patients frequently have inhomogeneous lung perfusion. In one study hypoperfusion in regions separate from the tumour were most common in patients with poor pulmonary function and COPD [10]. When SPECT images were matched with the CT images, perfusion defects adjacent to and separate from the tumour had corresponding CT abnormalities in only 50% and 20% of patients, respectively [10]. Using functional information in the optimisation of radiotherapy plans to spare the well-perfused regions of lung may result in less damage to well functioning lung and consequently, potential for better lung function after treatment [14].

We have investigated the accurate co-registration of CT and SPECT images within a treatment planning system and the use of this data in radiotherapy planning. This has allowed the creation of a new ‘organ at risk’ volume – that of functioning lung. Inverse planning techniques for 3D-CRT, have been used to design a series of coplanar and non-coplanar plans comparing the reduction in dose to functioning lung
possible when perfusion information is taken into account during radiotherapy planning.
Materials and methods

Imaging and image co-registration

Eight patients undergoing radical radiotherapy for Stage IA - IIIB NSCLC were consented for entry to the study. Prior to the radiotherapy planning CT scan, approximately 10 spherical markers filled with Barium chloride and aqueous $^{99m}$Tc were positioned on bony landmarks over the antero-lateral surface of the patient’s chest. Patients underwent CT scanning (Siemens Somatom Plus 4 CT scanner) in the treatment position using a lung treatment board to improve reproducibility of positioning. CT slice thickness was set at 5mm intervals. Immediately following CT, an intravenous injection of 200 MBq of $^{99m}$Tc labelled macroaggregated albumin was given and two SPECT scans were acquired (Philips Medical Systems Forte$^\text{TM}$ gamma camera) using low energy, high resolution collimators: the first was a rapid “marker scan” to allow co-registration (see Figure 1), following which the markers were removed and a lung perfusion SPECT scan (approximate time for both SPECT scans was 25 minutes). All scans were carried out during quiet free breathing, without breath-holds. All scans had sufficient coverage to include the total lung volume. The CT and SPECT scans were co-registered manually in the Pinnacle$^3$ version 6.0m (Philips Radiation Oncology Systems, Milpitas, CA) planning system. Accuracy of the co-registration algorithm has been externally validated [12].

Target volume definition

The following areas were outlined for each patient on the planning system; GTV, body outline, whole lungs (WL) as a single organ, excluding GTV, and spinal cord. CT windows were set at a width of 120 and at a level of 250. The PTV was created using a 1 cm uniform margin around the GTV. For the purposes of inverse planning a
further volume, the Normal Volume, was created using a 3 cm uniform margin around the PTV and subtracting this volume from the body outline, thus creating the annulus used to define the anatomical areas where low doses of radiation were expected. The SPECT data was viewed in the spectrum colour setting. This produced a multicoloured image which allowed more accurate volume contouring around a chosen colour. The threshold level was adjusted individually for each patient in order to match the size of the SPECT image to within the lung volumes defined on CT. A new contour of ‘Functional lung’ (FL) was created from the SPECT images. FL outlines drawn using the SPECT images, were assessed by a radiologist expert in functional imaging.

**Radiotherapy planning**

The inverse planning software AutoPlan was then used to create a series of four plans for each patient. AutoPlan has been developed in-house at the Royal Marsden Hospital, using an algorithm to specifically reduce the computational intensity [1-3]. Ranges of gantry, couch and collimator angles are supplied as search limits for the program. The algorithm then carries out a random search over the space of beam orientations, weights and wedge angles, in a manner equivalent to fast simulated annealing with zero temperature [11]. At each iteration, dose is calculated using a fast convolution algorithm. AutoPlan is used in conjunction with Pinnacle³ planning system. Patient CT scans and outline sets can be read from the Pinnacle³ database, optimisation is then carried out within AutoPlan, and the resulting optimal parameters are entered back into Pinnacle³. This facilitates a final dose calculation using Pinnacle³’s accurate collapsed cone convolution algorithm.
The main objective for each plan was to minimise the volume of either FL or WL
receiving $\geq 20$ Gy. Dose constraints and objectives are described in Tables 1 (a) and
(b).
Two 4-field coplanar plans were created for each patient using the planning objectives
and constraints described in Table 1 (a) and (b). This produced two plans, one where
functional information had been taken into account – Plan 1 and the other where only
CT data was available – Plan 2. The same process was repeated for two 4-field non-
coplanar plans, to create Plans 3 and 4.

**Data collection and assessment of plans**

The primary endpoint of this study was to compare the dose to FL for all four plans.
This would assess whether adding functional information to inverse planning for
NSCLC could bring about a significant reduction in the dose to the FL. It would also
assess the use of non-coplanar beams in the avoidance of FL.

For each patient, the volume of the PTV, FL and WL were collected. For each plan
the following data was calculated: PTV$_{90}$ (% volume of PTV covered by the 90%
isodose); FLV$_{20}$ and mean FL dose; WLV$_{20}$ (volume of whole lung to receive $\geq 20$
Gy) and mean WL dose. In addition, the Mean Perfusion Weighted Lung Dose
(MPWLD) was calculated, by considering the WL, but weighting each voxel,
according to functionality, ($p_i/p_{\max}$). Lung function is assumed to be linearly related
to the observed SPECT signal, up to a maximum of 80%, thus

$$MPWLD = \frac{1}{N} \sum_{i=1}^{N} d_i \frac{p_i}{p_{\max}}, \text{ for } p_i < 0.8p_{\max}$$

and

$$MPWLD = \frac{1}{N} \sum_{i=1}^{N} d_i, \text{ for } p_i \geq 0.8p_{\max}$$
where $d_i$ and $p_i$ is the dose and the perfusion value at the $i^{th}$ voxel respectively, $p_{max}$ is the maximum perfusion value observed in the whole volume with the summation performed over all N voxels of the WL. This approach assumes that any voxel that has a perfusion value of 80% or more of the maximum is considered to be totally functional.

For each plan the $PTV_{90}/FLV_{20}$ was calculated. As the high value isodoses cover the PTV more completely, the dose to the surrounding lung increases and hence $V_{20}$ increases. Comparison of $V_{20}$ alone might give inaccurate results as to which beam arrangement gave the ‘best’ overall plan. Therefore the $PTV_{90}/FLV_{20}$ ratio was used to account for variations in both measures. Quantile-quantile plots for $FLV_{20}$ and $PTV_{90}/FLV_{20}$ were constructed to ensure that the data was normally distributed and data was compared using a Student’s t-test.
Results

Eight patients were consented for the study; of these one patient declined the SPECT scan due to fatigue and one patient had CT data that could not be read by AutoPlan due to the large number of CT slices. Overall data from six patients was available for analysis. The mean PTV volume was 281.7 cm$^3$ (range 113.9 cm$^3$ – 438.6 cm$^3$). All patients had a reduction in volume of FL compared to the whole lung volume (WL) (Table 2). The mean difference between the total volume of lung and the whole volume of lung designated as ‘functioning’ was 1011.7 cm$^3$ (range 596.2 – 1581.1 cm$^3$). Tumour site and perfusion defects for each patient are shown in Table 3.

Perfusion was either non-uniform with considerable inhomogeneity of FL (Figure 2a) often due to pre-existing chronic lung dysfunction (due to old tuberculosis in patient 3 Fig 2a) or demonstrating specific defects usually due to local atelectasis and chronic obstructive pulmonary disease (Figure 2b).

Dose-volume data collected for each of the two four-field coplanar plans, Plans 1 and 2 are shown in Tables 4a and b. PTV$_{90}$ data was closely matched between the two sets of plans except for Patient 1 who had a small solitary peripheral tumour where the PTV dose-drop-off, due to the large relative lung-tumour interface, was a particular problem. Comparison of the PTV$_{90}$/V$_{20}$ between Plans 1 and 2 showed that the mean difference between them was 0.44 in favour of Plan 1 (95% C.I. –0.21 – 1.09), p = 0.14.

Dose-volume data for the non-coplanar Plans 3 and 4 is shown in Tables 5a and b. The mean PTV$_{90}$/V$_{20}$ difference between Plans 3 and 4 was 0.59, in favour of Plan 3 (95% C.I. –0.86 – 2.04), p = 0.34.

To test whether non-coplanar beams were able to reduce the dose to the FL compared to coplanar beams, Plans 1 and 3 were compared. There was a mean benefit in
$PTV_{90}/V_{20}$ of 0.43 in favour of Plan 1 (C.I. $-0.43$ – 1.29) which was not statistically significant ($p = 0.26$).
Discussion

The aim of this study was to establish a method of co-registering functional lung information with CT planning and then to establish what benefits, if any, could be gained in reducing the toxicity of radiotherapy by preferentially avoiding functioning lung. For the purposes of radiotherapy planning it was of crucial importance that the two sets of image data were accurately matched. Previous authors have matched images using a visual iterative manual technique [8] or have performed the scans on separate days using five external skin markers [14]. For this study a new couch insert was constructed for the curved gamma camera in order to match it to the flat CT couch. To ensure the same position for both scans, and treatment, an in-house-developed lung board, designed to fit both CT scanner and gamma camera, was used for patient immobilisation. To minimise error in co-registration the two sets of images were obtained consecutively, within an hour of each other on the same day.

The threshold settings for functional images when combined with CT images are uncertain. Finding the correct setting is crucial particularly when used for radiotherapy planning, as accurate volume definition is required. This study had taken a similar pragmatic approach as other authors by adjusting the threshold level to match the lung contours until the best fit is obtained [14]. Similar volume definition issues arise when FDG-PET is used in combination with CT for radiotherapy planning where the tumour size using PET may be over-estimated rather than under-estimated [6] although an attenuation-corrected method may be used to improve the accuracy of tumour measurements [16].

Despite the addition of accurately co-registered functional information to the radiotherapy planning CT data, no significant reduction in the dose to the functioning lung was found when this was specified as the main objective during inverse
planning. All patients had a reduction in volume, when the whole lung volume was compared to the volume of the lung that was deemed ‘functioning’ on SPECT imaging. This implies that none of the SPECT images were entirely normal and in each patient it reflected a level of lung dysfunction, perhaps due to atelectasis or underlying chronic lung disease. Functional heterogeneity is known to occur in many patients with lung cancer and especially those with underlying COPD. Those with the poorest lung function often have the most non-uniform distribution on SPECT imaging [9]. This heterogeneity is accounted for explicitly in the MPWLD calculation, but less so in the MLD for FL, which could explain the ranking of different plans in terms of MPWLD apparently at variance with the ranking in terms of MLD for FL. A description of the perfusion defects is given in Table 3. Of note, Patient 1 appeared to have a greater reduction in FLV_{20} for coplanar Plan 1 when compared to Plan 2, than the other patients in the study. For this patient, an absolute reduction in FLV_{20} of 2.47 % represents an overall relative reduction of 16%. This patient was also the only patient to have single large areas of hypoperfusion of both upper lobes.

Without SPECT information available to the inverse planning system, Figure 3a shows the beams passing through a large area of functional contralateral lung (Plan 2). Incorporating functional lung data into the inverse planning protocol, as seen in Figure 3b, the area of functional lung can be avoided (Plan 1). For the rest of the patients however, perfusion defects were patchy and non-uniform. Seppenwoolde et al also found that patients with one large area of hypoperfused lung benefit most from radiotherapy planning that combines both CT and SPECT [13]. Although the small number of patients in our study makes it difficult to generate detailed conclusions about which patients are most likely to benefit from CT and SPECT fusion during
radiotherapy planning, it would seem reasonable that large defects allow the inverse planning system to find alternate sites of entry and exit for the radiotherapy beams. In the presence of multiple small defects it is usually not possible to find beam directions that can adequately avoid the functioning tissue and deliver dose through the non-functioning tissue.

The use of non-coplanar beams did not offer any clear benefit in FL PTV$_{90}$/V$_{20}$ over coplanar beams in patients with inhomogeneous perfusion defects. Again the perfusion defects were too patchy and too small to allow either coplanar or non-coplanar beams to find a satisfactory entry and exit route through which functioning lung tissue could be avoided.

We conclude that the routine use of SPECT imaging for all patients undergoing radiotherapy planning for localised NSCLC is not warranted however there remains a subgroup with bullous lung disease for whom SPECT imaging may provide useful information to optimise radiotherapy beam angles.
Acknowledgements

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References


Figures and Tables

Figure 1
Illustration of the co-registration method. CT greyscale and SPECT scan markers (spheres) are overlapping showing co-registration accuracy.
Figure 2  (a) Patient 3, CT images. FL volume = blue, PTV = purple, demonstrates non-uniform perfusion defects. (b) Patient 6, CT/SPECT fusion images (shown in spectrum) demonstrating reduced perfusion in areas of atelectasis.
Figure 3  (a) Patient 1, coplanar Plan 2 – where FL information has not been used for the inverse planning protocol. (b) Patient 1, coplanar Plan 1 – where FL information has been used for the inverse planning protocol. FL region = red volume, PTV = purple volume.
Table 1  (a) Inverse planning objectives when SPECT data is used to create the volume ‘functioning lung’ – used for Plans 1 and 3. (b) Inverse planning objectives when no SPECT information is used – used for Plans 2 and 4.
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<th>Volume WL (cm$^3$)</th>
<th>Volume FL (cm$^3$)</th>
<th>Volume PTV (cm$^3$)</th>
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Table 2  A summary of the whole lung volume (WL), the total volume of lung designated ‘functioning’ (FL) and the volume of PTV for the six study patients.
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<th>Perfusion defect</th>
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<td>Hypo-perfusion at site of tumour and general inhomogeneous perfusion</td>
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<td>LLL</td>
<td>LLL hypoperfusion (atelectasis) and general inhomogeneous perfusion</td>
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Table 3  A description of tumour sites and SPECT perfusion defects. RUL = right upper lobe, LLL = left lower lobe, R = right, L = left.
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<th>MLD FL (Gy)</th>
<th>FLV$_{20}$ (%)</th>
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Table 4  Dose-volume data (a) from coplanar Plans 1; (b) from coplanar Plans 2.
### Table 5

Dose-volume data (a) from non-coplanar Plans 3; (b) from non-coplanar Plans 4.

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