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PET adapted lung IMRT

High-resolution pulmonary ventilation and perfusion PET/CT allows for functionally adapted intensity modulated radiotherapy in lung cancer

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ABSTRACT

Background and purpose: To assess the utility of functional lung avoidance using IMRT informed by four-dimensional (4D) ventilation/perfusion (V/Q) PET/CT.

Materials and methods: In a prospective clinical trial, patients with non-small cell lung cancer (NSCLC) underwent 4D-V/Q PET/CT scanning before 60 Gy of definitive chemoradiation. Both "highly perfused" (HPLung) and "highly ventilated" (HVLung) lung volumes were delineated using a 70th centile SUV threshold, and a "ventilated lung volume" (VLung) was created using a 50th centile SUV threshold. For each patient four IMRT plans were created, optimised to the anatomical lung, HPLung, HVLung and VLung volumes, respectively. Improvements in functional dose volumetrics when optimising to functional volumes were assessed using mean lung dose (MLD), V5, V10, V20, V30, V40, V50 and V60 parameters.

Results: The study cohort consisted of 20 patients with 80 IMRT plans. Plans optimised to HPLung resulted in a significant reduction of functional MLD by a mean of 13.0% (1.7 Gy), $p = 0.02$. Functional V5, V10 and V20 were improved by 13.2%, 7.3% and 3.8% respectively (p-values < 0.04). There was no significant sparing of dose to functional lung when adapting to VLung or HVLung. Plan quality was highly consistent with a mean PTV D95 and D5 ranging from 60.8 Gy to 61.0 Gy and 63.4 Gy to 64.5 Gy, respectively, and mean conformity and heterogeneity index ranging from 1.11 to 1.17 and 0.94 to 0.95, respectively.

Conclusion: IMRT plans adapted to perfused but not ventilated lung on 4D-V/Q PET/CT allowed for reduced dose to functional lung whilst maintaining consistent plan quality.

Damage to normal pulmonary tissues is a recognised dose-limiting toxicity associated with localised irradiation of non-small cell lung cancer (NSCLC). Pneumocytes and the vascular endothelium are considered to be the most radiation sensitive tissues in the lungs [1]. Complex inflammatory molecular responses to ionising radiation in these tissues result in both bronchoalveolar fibrosis and vascular endothelial effects, which can cause pulmonary ventilation and perfusion deficits [2]. Imaging modalities capable of assessing ventilatory function and blood perfusion have demonstrated that these deficits can be observed and are associated with the clinical risk of toxicity [3–6]. Planar scintigraphy using ^{99m}Tc-labelled macroaggregated albumin (MAA) is a long-established imaging standard for functional ventilation/perfusion evaluation. Single positron emission computed tomography (SPECT), and the subsequent advent of hybrid SPECT/CT devices have improved diagnostic accuracy by enabling anatomic characterisation of scintigraphic abnormalities [7]. These imaging modalities can be used to identify the most functional areas of the lung and facilitate avoidance of these regions. Perfusion SPECT/CT has been demonstrated to allow for functional lung avoidance during lung radiotherapy planning by several groups [8–10]. Recently, ventilation SPECT/CT has also been explored as a potential tool for functional lung avoidance by Munawar et al. [11].

PET/CT offers a further opportunity to improve the image quality and accuracy of contemporary functional lung imaging [12].

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Our group has demonstrated superior sensitivity of PET in the detection of radioactive substances, respiratory gating capability, and both higher spatial and temporal resolution [13,14]. Unlike SPECT/CT, PET/CT is fully quantitative. Additionally, respiratory gating (4D) allows for accurate attenuation correction which improves imaging accuracy and allows for accurate anatomical co-registration [13]. The purpose of this study is to assess the utility of radiotherapy optimisation to functional lung volumes using state-of-the-art gated V/Q-PET/CT acquisition technology. The study population consists of patients with NSCLC receiving definitive radiotherapy undergoing pre-treatment four-dimensional (4D) V/Q PET/CT. The primary hypothesis is that dose to functional regions of the lung can be reduced through adaptation of radiotherapy plans optimised to these functional volumes. In this study, both perfusion and ventilation datasets are acquired contemporaneously allowing for comparison of the value of either modality in functionally adaptive planning. As radiotherapy plan quality can dramatically impact dosimetric evaluation, particular attention is paid to a rigorous intensity modulated radiotherapy (IMRT) planning methodology.

Material and methods

Patient selection

This work was part of an observational prospective clinical trial (Universal Trial Number U1111-1138-4421) of patients undergoing curative intent radiotherapy for NSCLC. This study received institutional review board approval by the Peter MacCallum Cancer Centre. All patients had pre-treatment pulmonary function testing (PFTs) with testing for diffusing capacity of the lung for carbon monoxide (DLCO). All patients were planned to receive 60 Gy in 30 fractions of external beam radiotherapy, 5 fractions per week with or without concurrent chemotherapy using a departmental cone-beam CT image guidance protocol.

4D Ventilation/perfusion PET/CT acquisition

All scans were performed on a GE-Discovery™ 690 PET/CT scanner (GE Medical Systems Milwaukee, Wisconsin, USA). 4D V/Q PET/CT technique and acquisition protocol was performed as previously described in detail by our group [13,14]. In brief, ventilation imaging was performed following inhalation of Galligas, produced by substituting Gallium-68 instead of Technetium-99 m in a Technegas generator (Cyclomedica, Australia). Approximately 200 MBq of Galligas was added to the carbon crucible prior to inhalation. The patients were positioned supine on the PET/CT scanner in a default planning position using the radiotherapy palette and head rest with their arms raised. The patient breathing trace was tracked using the Varian RPM™ respiratory tracking system (Varian Medical Systems, Palo Alto, California). The patients were instructed to breathe freely for the duration of the scans. A contemporaneous low-dose chest 4D-CT acquisition was performed using 125 kVp energy photons at 10 mA and a slice thickness of 5 mm. The field of view for both 4D-PET and 4D-CT encompassed the entire lung fields. Ventilation-PET scan of the lungs was acquired (2 bed positions, 5 min per bed). Approximately 40 MBq of ^{68}Ga-MAA was subsequently administered intravenously, and 4D Perfusion-PET acquired over the same field-of-view (2 bed positions, 5 min per bed). The ventilation and perfusion PET scans were reconstructed as both gated and un-gated images. Phase matched attenuation correction with 5 and 10 respiratory bins was used to reconstruct the 4D-PET/CT scan. The free-breathing PET acquisition was subsequently co-registered with the average intensity projection of the 4D CT. Fig. 1 shows typical images for ventilation and perfusion scans.

4DCT simulation

Patients were simulated supine with arms located above the head and a bolster under the knees for comfort. A time resolved 4D CT scan for Radiotherapy planning purposes was performed on all patients using a 64-slice Big Bore Brilliance™ CT scanner (Koninklijke Philips Electronics, Amsterdam, The Netherlands). The pressure sensitive belt (Philips Bellows system) was used for respiratory-sorting and data binned into 10 phases for image reconstruction. The patients were scanned in helical mode, using 140 kVp, 3-mm slice thickness, 3-mm increment and 0.44-s rotation time. Images were reconstructed with $\sim$3.5 mm^3 voxel resolution (3-mm slice thickness $\times$ 1.0742-mm pixel spacing).

Volume marking/tumour delineation

From the respiratory-sorted imaging phases of the Radiotherapy planning scan, average (AVG) and maximum intensity projection (MIP) series were reconstructed. Target delineation was performed on an Elekta FocalSim™ (Crawley, UK) workstation. Standardised lung window/level settings (1700/−300) were used in the MIP image series. All volumes were delineated onto the AVG CT dataset for final dose calculation. An internal target volume (ITV) was delineated from the MIP series, with a further isotropic expansion of 5 mm used to generate the clinical target volume (CTV). A further 10 mm isotropic expansion from CTV was used to create the planning target volume (PTV). The anatomical lung volume was delineated using the planning CT dataset. A highly perfused lung volume (HPLung) and highly ventilated lung volume (HVLung) were delineated using a visually adapted 70th centile SUV threshold method, as recently described by our group [15,16] and others [17]. It was apparent that HVLung was considerably smaller than HPLung, so a ventilated lung volume (VLung) was created to approximate the HPLung volume using the 50th centile SUV threshold, a methodology previously reported by Munawar et al. [11]. Any clumping of Galligas was excluded from the volume using the method described by Kipritidis et al. [18], by which an upper threshold was set that removed voxels >4 standard deviations above the mean. Radiotherapy planning was completed on the 4D simulation dataset by employing a rigid registration method of image fusion with the 4D V/Q scans, allowing contours to be accurately transferred between the datasets. For each of the lung volumes, the organ at risk (OAR) for planning purposes was defined as the volume of both lungs minus the volume of the GTV.

Planning technique

A single qualified radiotherapy planner created a total of 80 IMRT plans for the anatomical, HP, HV and V lung volumes. Each plan was optimised using the planning 4DCT AVG dataset to the relevant lung volume, without being informed by the alternative lung volumes. Inverse IMRT planning was performed for each patient using Varian Eclipse treatment planning software (v11, Palo Alto, California USA). A 2.5 mm calculation grid was used to perform the dose calculation using an analytic anisotropic algorithm (AAA V.11.0.21). A sliding window IMRT technique was employed to prescribe 60 Gy to cover 95% of the PTV using 5–6 coplanar 6MV X-ray beams. The same beam arrangements were used in all four-treatment plans. Beam arrangements were defined by the position of the tumour volume, with the aim of limiting beam paths through the contralateral lung and without consideration of functional lung geometry. The organs at risk (OARs) optimised in the inverse planning process included; bony spinal canal, oesophagus, heart, as well as the lung volume relevant to each plan. A summary of the target volume and OARs as well as