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Magnetic resonance imaging biomarkers of chronic obstructive pulmonary disease prior to radiation therapy for non-small cell lung cancer

Khadija Sheikh [a,b,1], Dante P.I. Capaldi [a,b,1], Douglas A. Hoover [c], David A. Palma [c], Brian P. Yaremko [c], Grace Parraga [a,b,c,*]

[a] *Imaging Research Laboratories, Robarts Research Institute, London, Canada*
[b] *Department of Medical Biophysics, The University of Western Ontario, London, Canada*
[c] *Department of Oncology, The University of Western Ontario, London, Canada*

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Abstract

Objective: In this prospectively planned interim-analysis, the prevalence of chronic obstructive lung disease (COPD) phenotypes was determined using magnetic resonance imaging (MRI) and X-ray computed tomography (CT) in non-small-cell-lung-cancer (NSCLC) patients.

Materials and methods: Stage-III-NSCLC patients provided written informed consent for pulmonary function tests, imaging and the 6-min-walk-test. Ventilation defect percent (VDP) and CT lung density (relative-of-CT-density-histogram <−950, RA_{950}) were measured. Patients were classified into three subgroups based on qualitative and quantitative COPD and tumour-specific imaging phenotypes: (1) tumour-specific ventilation defects (TSD), (2) tumour-specific and other ventilation defects without emphysema (TSD_V), and, (3) tumour-specific and other ventilation defects with emphysema (TSD_{VE}).

Results: Seventeen stage-III NSCLC patients were evaluated (68 ± 7 years, 7 M/10 F, mean $FEV_1 = 77\%_{pred}$) including seven current and 10 ex-smokers and eight patients with a prior lung disease diagnosis. There was a significant difference for smoking history ($p = .02$) and FEV_1/FVC ($p = .04$) for subgroups classified using quantitative imaging. Patient subgroups classified using qualitative imaging findings were significantly different for emphysema (RA_{950}, $p < .001$). There were significant relationships for whole-lung VDP ($p < .05$), but not RECIST or tumour-lobe VDP measurements with pulmonary function and exercise measurements. Preliminary analysis for non-tumour burden ventilation abnormalities using Reader-operator-characteristic (ROC) curves reflected a 94% classification rate for smoking pack-years, 93% for FEV_1/FVC and 82% for RA_{950}. ROC sensitivity/specificity/positive/negative likelihood ratios were also generated for pack-years, (0.92/0.80/4.6/0.3), FEV_1/FVC (0.92/0.80/4.6/0.3), RA_{950} (0.92/0.80/4.6/0.3) and RECIST (0.58/0.80/2.9/1.1).

Conclusions: In this prospectively planned interim-analysis of a larger clinical trial, NSCLC patients were classified based on COPD imaging phenotypes. A proof-of-concept evaluation showed that FEV_1/FVC and smoking history identified NSCLC patients with ventilation abnormalities appropriate for functional lung avoidance radiotherapy.

Keywords: Lung; Cancer; COPD; Phenotype; Radiotherapy; Functional magnetic resonance imaging

1. Introduction

The current standard of care for patients with non-small cell lung cancer (NSCLC) relies on radiation therapy that focuses the radiation dose to the tumour, sparing healthy lung tissue. However, the current standard approach for radiation therapy planning uses four-dimensional computed tomography (4DCT) to delineate the target volume and this does not take into account lung function heterogeneity. This is an important consideration, especially in ex-smokers with chronic obstructive pulmonary disease (COPD) or other underlying lung disease. In these patients, pulmonary functional imaging has been used to characterize large functional deficits of poorly and unventilated lung [1,2] which is typically very spatially heterogeneous. Moreover,

* Corresponding author at: Imaging Research Laboratories, Robarts Research Institute, 1511 Richmond St N, London, Canada N6A 5K7.
Tel.: +1 519 913 5265; fax: +1 519 913 5238.
E-mail address: gparraga@robarts.ca (G. Parraga).
[1] Co-first authors who contributed equally to this work.

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such functional defects cannot be easily predicted by smoking history or other pulmonary function measurements, including the forced expiratory volume in 1 second (FEV_1) [1,3,4]. Ideally, radiation treatment planning should derive improvements from pulmonary imaging measurements that differentiate the functioning from non-functioning lung, with attention focused on the non-functioning part of the lung, independent of tumour burden.

Pulmonary functional imaging methods such as single photon emission computed tomography (SPECT) [5,6], 4DCT [7,8] and inhaled gas magnetic resonance imaging (MRI) [9,10], have been previously incorporated in functional imaging lung avoidance schemes, but this approach is not currently the standard clinical practice. The feasibility of function-based intensity modulated radiation therapy (IMRT) treatment planning [5,6,9], has been demonstrated, in addition to measurements of lung function before and after radiation treatment [7,11]. Importantly, when functional imaging was used to guide therapy in radiation planning studies, dose reductions to functioning lung were achievable [6,10]. Previous work also identified that functional lung avoidance plans can be optimized in patients with bullous lung disease and large perfusion defects [12,13].

While these thoracic imaging techniques provide a way to differentiate between functioning and non-functioning lung, there are a number of inherent limitations that have restricted the use of functional imaging for radiation therapy planning. For example, with SPECT imaging, artefacts stemming from radiolabelled tracers are typically observed in the major airways [14]. For 4DCT [15], lung function is indirectly measured over a time series of breaths and the resultant lung function maps require extensive image processing that is highly dependent on deformable image registration [16,17]. Fourier-decomposition 4D MRI is an alternative imaging method that indirectly measures lung ventilation and perfusion and correlates well with other pulmonary functional MR methods [18]. On the other hand, hyperpolarized noble gas MRI, although very sensitive to functional ventilation abnormalities, is limited because of its reliance on specialized MRI and polarization equipment. While the global quantities of ^{3}He are very limited and expensive, impeding its clinical uptake and translation, the sensitivity of this method may guide the use of other MR methods (e.g. Fourier decomposition, ^{129}Xe MRI, etc.). In addition, although MRI methods are well-tolerated, making them ideal for serial studies [19], until now, these methods have been limited to research applications only.

Therefore, in an interim analysis of a larger clinical trial [20], the objective of this proof-of-concept evaluation was to quantify imaging phenotypes of COPD in patients with NSCLC prior to concurrent chemo- and radiation therapy. We aimed to determine the utility of conventional and clinically available COPD measurements in stratifying patients for functional lung avoidance radiotherapy. We hypothesized that COPD phenotypes could be used to stratify NSCLC patients prior to radiotherapy planning as a first step towards personalizing treatment plans based on lung structural and functional measurements.

2. Materials and methods

2.1. Study participants

Study participants were evaluated in a prospectively planned interim analysis of a clinical trial in over 60 patients [20]. The logistical details of this clinical trial (NCT02002052) were previously published [20]; here we provide an interim analysis of the feasibility of acquiring and quantifying MRI phenotypes prior to randomization to standard or individualized functional lung avoidance radiation treatment. Volunteers with histologically confirmed non-resectable Stage IIIA or IIIB NSCLC and a smoking history of >10 pack-years provided written informed consent to this randomized controlled clinical trial which complied with the Health Insurance Portability and Accountability Act (HIPAA) and Personal Information Protection and Electronic Documents Act (PIPEDA), and approved by our local research ethics board and by Health Canada. Briefly, all subjects were required to be over 18 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance score between 0 and 2, $FEV_1 > 30\%_{pred}$, and able to undergo platinum-based chemotherapy as determined by his/her treating physicians. Those subjects with contradictions to the MRI (i.e. metal/electronic/magnetic implants, claustrophobia, etc.), serious co-morbidities, prior thoracic radiation, metastatic disease, or conflicts with routine radiotherapy were not considered suitable for the study. In addition to routine clinical care, in a two and a half hour visit, all study volunteers underwent additional pulmonary function tests, MRI, one additional low dose inspiratory CT, and the 6 min walk test (6MWT) [20].

2.2. Pulmonary function tests

Spirometry was used to acquire the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC according to American Thoracic Society (ATS) guidelines (Medgraphics Elite Series Plethysmograph, MedGraphics Corporation, St. Paul, MN, USA) [21]. Body plethysmography was also performed to measure lung volumes and the diffusing capacity of carbon monoxide (DL_{CO}) was also measured using the attached gas analyser (Medgraphics Elite Series Plethysmograph).

2.3. Image acquisition

MRI was acquired in the coronal plane using a whole body 3.0 Tesla Discovery MR750 (General Electric Health Care, Milwaukee, WI) system with broadband imaging capability. Polarization of the $^{3}He/^{129}Xe$ gas was performed using a polarizer system (HeliSpin/XeniSpin; Polarean, Durham, NC, USA) and achieved polarization levels of approximately 40%/8%. Hyperpolarized ^{3}He was diluted with medical-grade N_2 gas (Spectra Gases, NJ, USA) and ^{129}Xe was diluted with $^{4}He/N_2$ and administered in 1.0-L Tedlar® bags (Jensen Inert Products, FL, USA). Subjects were instructed to inhale a gas mixture from the bag from functional residual capacity (FRC) and image acquisition was performed under