Textural analysis demonstrates heterogeneous [^{18}F]-FDG uptake in radiologically normal lung in patients with idiopathic pulmonary fibrosis

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Running title: Textural analysis of FDG-PET in IPF

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Textural analysis demonstrates increased heterogeneity of [18F]-FDG uptake in normal lung (on CT) in patients with IPF. Molecular imaging of the lungs using PET can be used to study early disease in IPF before CT abnormalities are apparent.

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ABSTRACT

Positron Emission Tomography (PET) scanning in idiopathic pulmonary fibrosis (IPF) has revealed increased [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) uptake in areas of the lungs that appear normal on high resolution computed tomography (HRCT). We hypothesised that 'microscopic' disease identified using PET would be heterogeneous because IPF is characterised histologically by patchy fibrosis. We applied textural analysis to PET scans to evaluate heterogeneity of [^{18}F]-FDG uptake in lung regions that appeared normal on HRCT. We identified six textural features that demonstrated significantly more heterogeneous [^{18}F]-FDG uptake in radiologically normal lung in IPF patients compared with controls. Textural analysis of lung PET-CT imaging is a novel approach to study early changes in IPF before HRCT abnormalities are apparent.

INTRODUCTION

Recently, Positron Emission Tomography-Computerised Tomography (PET-CT) imaging in IPF has revealed increased [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) uptake both in fibrotic lung and areas of lung with normal radiological appearance on HRCT [1 2]. IPF is characterised by heterogeneous fibrosis at the tissue level, so to gain insight into the early 'microscopic' disease process we used established textural features [3 4] to evaluate heterogeneity of [^{18}F]-FDG uptake in radiologically normal lung in patients with IPF.

METHODS

Patients with IPF diagnosed according to international guidelines and who had undergone PET-CT imaging for concomitant cancer diagnosis or staging were identified retrospectively in a single interstitial lung disease (ILD) tertiary referral centre. Controls comprised patients without ILD who had undergone PET-CT imaging for lung cancer (control group 1) or extra-thoracic malignancy (control group 2).

PET-CT images were analysed by two experienced radiologists. Four 10mm diameter regions of interest (ROIs) were placed manually in areas of lung with normal CT appearance, confirmed by measuring lung density. ROIs were placed away from areas of high FDG uptake (concomitant tumour, mediastinum, diaphragm) to avoid spill-over. [^{18}F]-FDG uptake (standardized uptake values (SUV)) and textural features were extracted within each ROI using XD™ (Mirada Medical Ltd, UK) and proprietary software [5]. Mean and maximum SUV were normalised using body weight. Twenty textural features were extracted from each ROI, including First Order Statistics (FOS) derived from the grey-level intensity distribution, a measure of grey-level uniformity derived from the Laplacian of Gaussian (LoG) technique for a range of filter sizes (mm), and Laws Texture features using two dimensional convolution masks [3-5]. Paired t-tests were used to compare fibrotic and normal lung in IPF patients. Unpaired t-tests were used to compare normal lung in IPF and controls, using a Bonferroni-corrected alpha of .0025 (.05/20). Results are expressed as mean (SD).

RESULTS

Forty-nine PET-CT scans were identified from 16 patients with IPF (13 men, 3 women; mean (SD) age 74.1 (10.2); percent predicted FVC 87 (12); percent predicted TLco 46 (14)), 17 lung cancer controls (10 men, 7 women; age 61.3 (16.4)), and 16 extra-thoracic malignancy controls (9 men, 7 women; age 64.5 (12.4)). Lung cancer was the most common reason for PET-CT imaging in IPF patients (11/16). Most extra-thoracic malignancy controls had lymphoma or melanoma (11/16).

Areas of radiologically established fibrosis in IPF patients exhibited higher SUV compared to radiologically normal lung in the same patient (maximum SUV 2.1 (0.5) vs 1.0 (0.3), $p<.001$; mean SUV 1.3 (0.4) vs 0.8 (0.3), $p<.001$).

Radiologically normal lung on CT was confirmed by measuring lung density, showing identical Hounsfield units in IPF and controls (data not shown). There were no differences between the two control groups in maximum or minimum SUV in radiologically normal lung. On PET imaging, the SUV in radiologically normal lung in IPF patients was significantly higher than normal lung in pooled controls (maximum SUV 1.0 (0.3) vs 0.7 (0.2) respectively, p=.002; mean SUV 0.8 (0.3) vs 0.6 (0.2), p=.001).

We found significant differences in heterogeneity of the PET [^{18}F]-FDG signal in normal lung between IPF patients and controls in six textural features (Figure 1): LoG Uniformity with a 3.84mm filter (0.77 (0.12) vs 0.92 (0.10) respectively, p<.0001); LoG Uniformity with a 6.19mm filter (0.87 (0.12), 0.98 (0.05), p<.0001); Laws Tex L5E5 mean (5.9 (2.8) x10^4, 2.8 (1.4) x10^4, p<.0001); LawsTex L5L5 standard deviation (std) (2.3 (1.5) x10^6, 1.1 (0.6) x10^6, p<.001); Laws Tex L5E5 std (2.1 (1.2) x10^4, 1.0 (0.52) x10^4, p<.0001); FOS std (310 (199), 139 (77), p<.0001). These textural features indicate higher variability in signal intensities within the ROIs in radiologically normal lung in IPF.

DISCUSSION

IPF is a patchy disease at the tissue level, with areas of new and established fibrosis interspersed with histologically normal lung. As IPF progresses over time, fibrosis spreads to involve previously unaffected lung. Increased [^{18}F]-FDG uptake in radiologically normal lung in patients with IPF [2] has been proposed to reflect increased metabolism in inflammatory cells, erythrocytes, or fibroblasts in early injury or fibrosis before structural lung changes become apparent on HRCT [6 7 8]. Our finding of heterogeneous [^{18}F]-FDG uptake demonstrated by textural analysis in radiologically normal lung in IPF patients supports use of PET imaging to non-invasively identify early 'microscopic' disease. We cannot say whether the heterogeneous [^{18}F]-FDG signal represents early injury, inflammation, fibrosis, or other processes which would require histological correlation. Redistribution of pulmonary blood flow to normal lung is an unlikely explanation for our findings because there was no increase in CT density, the IPF patients did not have severe disease, and we would not expect blood flow to generate a heterogeneous PET signal. A limitation of the present study was the relatively small (10mm) ROIs which were necessary to avoid spill-over effect and to target only lung that was normal on CT. Our results require confirmation in other populations with early pulmonary fibrosis, including patients with rheumatological disease or subjects in CT screening studies with 'interstitial lung abnormalities'. Textural features derived from [^{18}F]-FDG PET are increasingly applied in oncology, and tumour heterogeneity is associated with response to therapy [4]. Textural analysis of lung PET-CT imaging is a novel approach that could be used to study early events in IPF pathogenesis, identify early disease, aid prognostication, or predict response to therapy.

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Figure legend

Figure 1. Textural analysis of PET [^{18}F]-FDG signals from normal lung in IPF patients and two control groups. Four examples showing significant differences in textural features: A) Laplacian of Gaussian (LoG) Uniformity with a 3.84mm filter ($p<0.0001$, IPF vs pooled controls), B) Laws Tex L5E5 mean ($p<.0001$), C) Laws Tex L5E5 std ($p<.0001$), D) First Order Statistics (FOS) std ($p<.0001$).