



# Role of imaging in progressive-fibrosing interstitial lung diseases

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**Imaging techniques, particularly HRCT, are the cornerstone for ILD diagnosis and new approaches to analysing HRCT images, including machine-learning technology, are being developed**  
<http://ow.ly/1R1e30mOqhn>

**Cite this article as:** Walsh SLF, Devaraj A, Enghelmayer JI, *et al.* Role of imaging in progressive-fibrosing interstitial lung diseases. *Eur Respir Rev* 2018; 27: 180073 [<https://doi.org/10.1183/16000617.0073-2018>].

**ABSTRACT** Imaging techniques are an essential component of the diagnostic process for interstitial lung diseases (ILDs). Chest radiography is frequently the initial indicator of an ILD, and comparison of radiographs taken at different time points can show the rate of disease progression. However, radiography provides only limited specificity and sensitivity and is primarily used to rule out other diseases, such as left heart failure. High-resolution computed tomography (HRCT) is a more sensitive method and is considered central in the diagnosis of ILDs. Abnormalities observed on HRCT can help identify specific ILDs. HRCT also can be used to evaluate the patient's prognosis, while disease progression can be assessed through serial imaging. Other imaging techniques such as positron emission tomography-computed tomography and magnetic resonance imaging have been investigated, but they are not commonly used to assess patients with ILDs. Disease severity may potentially be estimated using quantitative methods, as well as visual analysis of images. For example, comprehensive assessment of disease staging and progression in patients with ILDs requires visual analysis of pulmonary features that can be performed in parallel with quantitative analysis of the extent of fibrosis. New approaches to image analysis, including the application of machine learning, are being developed.

## Introduction

Interstitial lung diseases (ILDs) may be differentiated by combining data from clinical history and exposures, laboratory data, radiological imaging, and pathological findings [1, 2]. Chronic progressive fibrosis occurs in varying proportions of patients with ILDs, and in all patients with idiopathic pulmonary fibrosis (IPF). Terminology recently used to describe patients with fibrosing ILDs that may present a

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Provenance: Publication of this peer-reviewed article was sponsored by Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA (principal sponsor, *European Respiratory Review* issue 150).

Received: Aug 14 2018 | Accepted after revision: Nov 01 2018

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progressive phenotype is “progressive-fibrosing ILD” (PF-ILD) [3]. Patients with IPF and other fibrosing ILDs with a progressive phenotype may share a number of similar clinical features [4]. Information on the diagnosis of ILDs that may present a progressive-fibrosing phenotype will be discussed in the article by COTTIN *et al.* [5] in this issue of *European Respiratory Review*.

Here we highlight the various imaging techniques used in the diagnosis of ILDs that may present a progressive-fibrosing phenotype, along with their benefits and limitations. Other than IPF, there are limited data specific for each different ILD that may present a progressive-fibrosing phenotype. As such, we have drawn on experience in IPF.

### Imaging techniques in ILDs

Imaging techniques encompassing chest radiographs and high-resolution computed tomography (HRCT) represent an essential component of the ILD diagnostic process [6]. Imaging techniques are generally considered to be noninvasive, and can provide insights into both diagnosis and prognosis, with serial imaging having the potential to assess disease progression. The different imaging techniques that can be used in ILDs, with particular reference to IPF and other ILDs potentially associated with a progressive-fibrosing phenotype, are described in more detail below.

#### *Chest radiographs*

Chest radiographs may be useful in identifying patients with ILDs [1] (and are frequently the initial indicator of an ILD). Comparison of a patient’s previous chest radiographs to the current one can be important in helping to identify radiological abnormalities and confirm the presence of a progressive lung disease [1]. A diffuse reticulonodular pattern and/or ground-glass opacities are the most common findings in patients with ILDs [7]; the patterns and locations of the radiographic abnormality are nonspecific but can help to diagnose specific ILDs. Decreased lung volumes may be associated with IPF, idiopathic nonspecific interstitial pneumonia (iNSIP) or connective tissue disease (CTD), micronodules may be indicative of hypersensitivity pneumonitis or sarcoidosis, while abnormalities in the lower lung zone may be associated with IPF or iNSIP [1].

The diagnostic accuracy of chest radiographs in suspected ILDs is ~80% [8]; however, chest radiographs can appear normal in patients with ILD and are considered inferior to HRCT in the diagnosis and prognosis of patients with ILDs [9]. A “normal” chest radiograph should not eliminate the possibility that an ILD is present in the appropriate clinical context [9]. Given the lack of specificity and sensitivity of the radiograph, it is mostly used as a method of initial diagnostic approach to the patient with shortness of breath, and to rule out other diseases such as left heart failure, infection or cancer.

#### *High-resolution computed tomography*

HRCT is a more sensitive modality for the detection of ILD than chest radiography or conventional chest computed tomography (CT), and is considered central in the diagnosis of ILD, as per the recommendations of the most recent American Thoracic Society/European Respiratory Society clinical practice guidelines for the diagnosis of IPF [1, 10, 11]. HRCT allows for the recognition of abnormalities, which may not be apparent on chest radiographs and may lead to earlier diagnosis of ILDs. HRCT may be used to identify sites for bronchoalveolar lavage and lung biopsy, guide treatment strategies and predict treatment outcomes [1]. Additionally, outcomes of HRCT may preclude the need for invasive diagnostic and/or prognostic techniques [1, 2, 10, 12–15]. Surgical lung biopsy is unfeasible in many patients and, consequently, efforts are being made to minimise the need for this assessment when making a diagnosis (*e.g.* by considering clinical as well as radiographic features) [16, 17].

The pattern of the radiographic abnormalities on HRCT can help identify specific ILDs. The pattern of usual interstitial pneumonia (UIP) (also observed in IPF) is characterised by subpleural and basal, bilateral and peripheral predominance, reticular opacities, honeycombing with or without traction bronchiectasis or bronchiolectasis, architectural distortion, focal ground-glass attenuation and the absence of features inconsistent with UIP [10, 18, 19]. Classic features of hypersensitivity pneumonitis on imaging may include poorly defined centrilobular nodules, ground-glass opacities, mosaic attenuation and absence of lower lung zone predominance [20, 21]. For CT scans, the Fleischner Society defines honeycombing as clustered, thick-walled cystic spaces of similar diameters, generally measuring between 3 and 5 mm, but occasionally up to 25 mm in size; honeycombing can consist of several stacked layers of cysts or a single subpleural layer of two or three adjoining cysts [22]. Honeycombing is a characteristic of established fibrosis and is considered as an important criterion when diagnosing UIP and IPF, although recent evidence suggests that honeycombing may not be required for an HRCT-based diagnosis of IPF in selected patients [16, 22–24]. This highlights the importance of considering the presence/absence of multiple features of fibrosis when examining HRCT images.

HRCT is central in the diagnosis and prognosis of IPF, with the identification of a UIP pattern on HRCT being one of the main diagnostic criteria for this ILD [1, 10, 19]. The positive predictive value of a HRCT diagnosis of UIP is ~90–100% [10]. UIP is characterised on HRCT by the presence of reticular opacities, often associated with traction bronchiectasis and honeycombing [10]. UIP distribution is usually basal and peripheral and is often patchy [10]. The presence of micronodules, significant mosaic attenuation or air trapping, nonhoneycomb cysts, and extensive ground-glass opacities should lead to consideration of an alternative diagnosis [10].

HRCT can be used to identify different types of ILDs, even to the level of subclassification of CTD-ILDs and staging of early *versus* progressive disease (figure 1) [25–27]. A UIP pattern can be observed in some patients with fibrotic ILD that may present a progressive phenotype, including patients with idiopathic interstitial pneumonia (IIP), CTD-ILD, interstitial pneumonia with autoimmune features or hypersensitivity pneumonitis. Patients presenting with a UIP pattern have a worse prognosis than those without, highlighting the potential importance of identifying this HRCT pattern [15, 27–33]. CTD-associated ILDs and hypersensitivity pneumonitis can also present with an iNSIP pattern on HRCT assessments [34]. It is important to note that there are potential differences in interpretation of HRCT patterns between thoracic radiologists [35, 36]. However, these differences seem to be in general within a clinically acceptable range of observer variation and can be partially mitigated by review of difficult cases at ILD referral centres [35–37].

#### *HRCT as a prognostic tool*

In addition to diagnosis, HRCT can be used to evaluate prognosis in ILDs. The extent of honeycombing and reticulation has been used as a predictor of mortality in patients with IPF [15]. In both chronic hypersensitivity pneumonitis and CTD-related fibrotic lung disease, the severity of traction bronchiectasis and the extent of honeycombing have been reported as predictors of mortality [36, 38]. Identification of the extent of fibrosis may be indicative of a poor prognosis for patients with fibrotic ILDs, including fibrotic IIP with little honeycombing [39–41]. Mortality is often not feasible as an end-point for diseases with chronic progressive fibrosis (such as IPF), therefore change in disease extent on HRCT represents a potential means of assessing treatment response [42].

In contrast with this, some studies have questioned the prognostic value of HRCT findings. Data from a large group of patients with IPF or CTD-UIP showed that clinical but not radiological features are predictive of survival [43]. In another study, the progression of ILD and reticulation were not associated with subsequent change over time in diffusing capacity of the lungs for carbon monoxide, among patients with systemic sclerosis-associated ILD (SSc-ILD) [44].

#### *Disease progression and serial imaging*

ILD progression can be assessed through serial imaging. Serial CT or HRCT can reveal changes in the extent of honeycombing and reticulation, allowing identification of a progressive, more fibrosing disease correlated with poorer survival (figure 2) [36, 45, 46]. Other studies have shown that honeycombing does

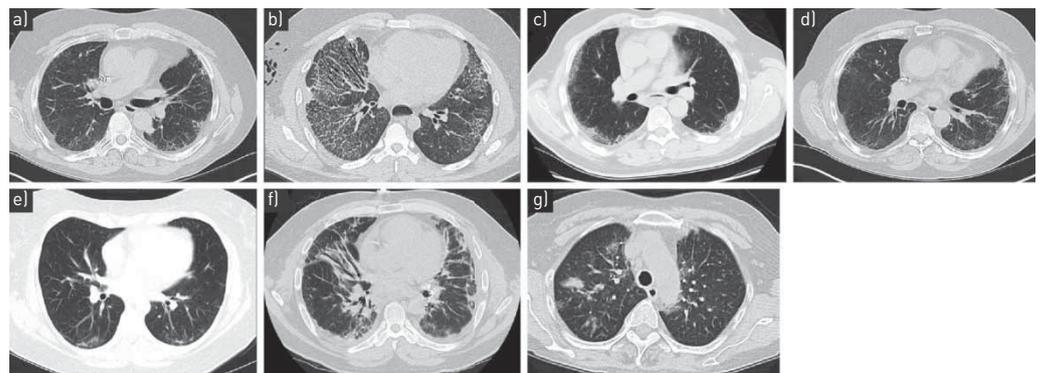


FIGURE 1 Use of high-resolution computed tomography imaging to diagnose different connective tissue disease-associated interstitial lung diseases (ILDs), and to differentiate between stable and progressive disease. a) Scleroderma with stable reticular opacities. b) Scleroderma with rapidly progressive ILD and pulmonary hypertension; oesophageal dilatation is seen. c) Scleroderma with reticular changes and oesophageal dysmotility with food in the oesophagus. d) Scleroderma with minimal reticular changes. e) Jo-1 associated antisynthetase syndrome presenting with organising pneumonia. f) PL-7 associated antisynthetase syndrome with acute respiratory failure. g) Cystic changes in Sjögren's syndrome, probably secondary to lymphocytic interstitial pneumonitis. Reproduced from [25] with permission.

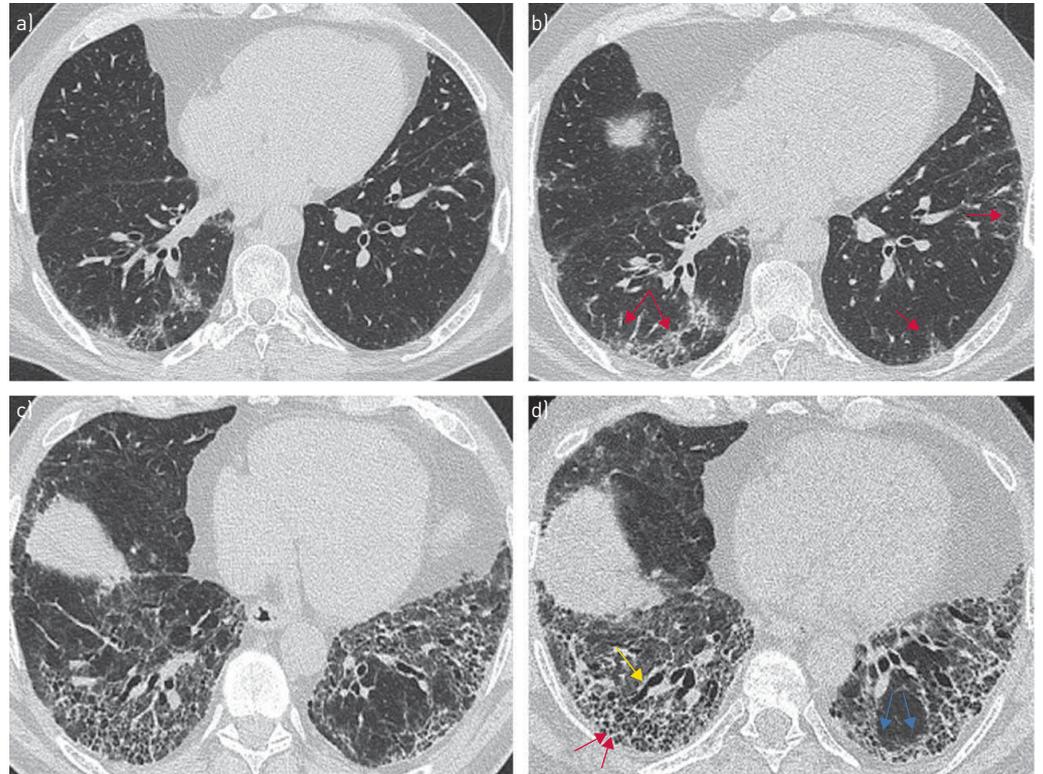


FIGURE 2 Serial computed tomography (CT) imaging for monitoring disease progression in patients with idiopathic pulmonary fibrosis. Axial CT images of two patients at baseline (a and c) and at 12 months (b and d), showing progressive reticulation in both of the lower lobes (red arrows in b) and progressive traction dilation of the airways (red and yellow arrows in d) and reticulation in both lower lobes (blue arrows in d). Reproduced from [47] with permission.

not show prognostic value as there is no significant difference in survival between patients with or without honeycombing [48], highlighting the lack of consensus and need for additional studies to address the impact of serial CT imaging in monitoring the progression and general prognosis of ILDs [47]. However, these studies were all limited by the use of qualitative (*i.e.* visual) CT assessment. As will be discussed later, quantitative HRCT analysis paired with visual analysis may reduce variability in results. Serial CT scans may allow detection of changes/progression that are consistent with the different syndromes in the various fibrotic ILDs that may present with a progressive phenotype; with the prospect of yearly CT scans, cancer could also be detected in these patients. It is still possible, however, to have a progressive-fibrosing phenotype, demonstrated by deterioration in clinical parameters, with a stable CT appearance. As well as being an essential component for ILD diagnosis and follow-up, HRCT also enables the detection of comorbidities associated with lung fibrosis, such as lung cancer [49].

#### **Other imaging techniques**

Other imaging techniques such as positron emission tomography (PET)-CT and magnetic resonance imaging (MRI) have been tested and have shown variable efficacy/use in IPF and other ILD that may present a progressive-fibrosing phenotype. Drawbacks with these methods (*e.g.* MRI has a poor signal-to-noise ratio in the lung; use of PET can require an onsite cyclotron and radioisotope with short half-life) mean that they are not commonly used, and are currently overshadowed by HRCT as the imaging technique of choice for ILD diagnostic and prognostic purposes [47, 50, 51].

#### **The importance of imaging in ILDs that may present a progressive-fibrosing phenotype**

While imaging techniques are fundamental in diagnosing ILDs and their progression, deeper insight into the disease itself and patient conditions is provided by combining imaging outcomes with clinical, physiological and pathological outcomes of different tests, as well as testing for biomarkers. The prognostic value of imaging tools remains to be fully elucidated as, at present, no clinical trial has used visual HRCT scores as a hard study end-point, and no visual scoring biomarker has yet been validated, as visual scores are inconsistent and relatively irreproducible. A combination of HRCT data with other

biomarkers may make for a more powerful diagnostic tool for ILDs that may present a progressive-fibrosing phenotype [36, 52, 53].

### Quantitative *versus* qualitative imaging

Semi-quantitative imaging techniques that depend in a large part on visual analysis are useful for general assessments of ILD but are limited in accuracy and restricted to descriptors such as mild, moderate or severe, or reporting imaging outcomes to the nearest 5, 10, 15, 20 or 25% [47, 54]. Numerous previous studies have used visual assessment to determine the extent of fibrosis at baseline, and have been shown to correlate with outcomes in a number of ILDs that may present a progressive-fibrosing phenotype (IPF, CTD-ILD, chronic hypersensitivity pneumonitis, IIP) including development and rate of progression of fibrosis, decline in pulmonary function and mortality [36, 40, 41, 55–59]. However, there are often difficulties in assessing subtle changes on serial CT scans due to the need to subjectively evaluate the entire thorax [60].

Quantitative imaging, including simple methods such as histogram analysis and complex textural-based analysis coupled to machine learning for optimal performance, is a new and promising approach in the field of ILD diagnosis and prognosis. Histogram-based measurements of mean lung attenuation and amount of skewness and kurtosis from CT images have been shown to correlate with measures of disease severity [61–63]. Automated textural analysis utilises a machine-learning approach to develop a predictive model for CT patterns and analyses, and can be used, for example, to quantify fibrosis based on textural patterns for ground-glass opacification, honeycombing and reticulation which was shown to be predictive of disease progression and patient survival [42, 47, 64–67].

Quantitative imaging is increasingly being used in ILD to identify pulmonary abnormalities and diagnose specific ILDs [42], with some studies showing that outcomes of computer-assisted imaging can be correlated with lung function tests and patient-centred measures of dyspnoea and functional disability [47, 68–71]. Computer-based CT analysis (CALIPER), in particular the assessment of pulmonary vessel volume, has been reported as a predictor of mortality and a prognostic marker in patients with CTD-ILD [72]. While quantitative imaging provides advantages over visual analysis, it does not replace it. In particular, many of the quantitative CT (QCT) tools available today were developed using some form of “feature engineering”, meaning they extract and quantify specific patterns after a period of training by expert radiologists. In addition, QCT has not been able to overcome some of the perceptual tasks that human radiologists find most challenging such as the separation of honeycombing from emphysema and traction bronchiectasis. A coupling of visual analysis of specific pulmonary features in parallel with quantitative analysis of the extent of fibrosis is likely to be the optimal approach to disease staging and outcome prediction in fibrosing ILDs that may present a progressive phenotype.

### Conclusions

Imaging techniques, particularly HRCT, are the cornerstone for ILD diagnosis, allowing for the initial differentiation between different ILDs. Imaging outcomes must be considered alongside the results of other diagnostic procedures to provide greater insight into the patient’s specific type of ILD, enabling an accurate diagnosis to be reached. Semi-quantitative and quantitative measures of fibrosis also correspond with physiological outcomes and prognosis in IPF and other ILDs that may present a progressive-fibrosing phenotype. New techniques for quantitative image analysis, including the use of machine learning, are being developed and provide a great deal of promise in the ILD field; such methods may be used together with visual analysis to obtain the most accurate diagnostic and prognostic information.

**Acknowledgements:** The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. Writing assistance was provided by Ken Sutor of GeoMed, an Ashfield company, part of UDG Healthcare plc, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). BIPI was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

**Conflict of interest:** S.L.F. Walsh has nothing to disclose. A. Devaraj reports personal fees from Boehringer Ingelheim, Roche and GSK, outside the submitted work. J.I. Enghelmayer reports personal fees, nonfinancial support and other funding from Boehringer Ingelheim, and personal fees and nonfinancial support from Roche, outside the submitted work. K. Kishi reports grants and personal fees from Boehringer Ingelheim, outside the submitted work. R.S. Silva has nothing to disclose. N. Patel has nothing to disclose. M.D. Rossman has nothing to disclose. C. Valenzuela has nothing to disclose. C. Vancheri reports grants and personal fees from Roche and Boehringer Ingelheim, outside the submitted work.

**Support statement:** The authors received no direct compensation related to the development of the manuscript. Writing assistance was contracted and funded by Boehringer Ingelheim Pharmaceuticals Inc. (BIPI).

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