The role of high-resolution computed tomography in the follow-up of diffuse lung disease

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ABSTRACT High-resolution computed tomography (HRCT) of the lung is a key component of the multidisciplinary approach to diagnosis in diffuse lung disease (DLD). HRCT also plays an important role in the follow-up of patients with established DLD. In this respect, serial HRCT examinations may provide valuable information that cannot be determined from clinical history and other diagnostic tests, such as pulmonary function tests. Important roles of HRCT in this context include assisting in determining prognosis, monitoring for the efficacy of treatment, detecting progression of disease or complications, and evaluating patients with worsening or acute symptoms. Both clinicians and radiologists should be aware of the expected evolution of HRCT changes in a variety of DLDs. The goals of this paper are to discuss: 1) the expected evolution of HRCT findings over time in common DLDs; 2) the role of serial HRCT examinations in formulating an initial diagnosis; and 3) the role of HRCT in the follow-up of patients with known DLD.

Introduction

High-resolution computed tomography (HRCT) of the lung is well established in its role in formulating an initial diagnosis in patients with diffuse lung disease (DLD); however, its ability to monitor patients with serial examinations may be equally important. Patients with DLD often undergo multiple HRCT examinations at various stages in their disease. This longitudinal imaging data often provides significant additional information compared with a single time point and may be used in a variety of ways, including: 1) increasing the accuracy of initial diagnosis; 2) assisting in the estimation of prognosis; 3) identifying

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progression of disease; 4) detecting new processes in patients with acute or worsening symptoms; and 5) detecting other abnormalities or complications, such as lung cancer. In the future, quantitative imaging techniques that can more accurately characterise and measure the extent of lung affected by disease may routinely complement visual assessment by radiologists. Clinicians and radiologists should be aware of the role of serial imaging and understand the expected progression of DLDs over time. The goal of this paper is to define the role that longitudinal HRCT plays in patients with DLD.

HRCT technique

There are several issues specific to longitudinal imaging in patients with DLD that may affect the selection of a preferred HRCT technique. The most important of these is the decision to use volumetric or spaced axial scans. Spaced axial imaging performed at 0.5–2 cm intervals imparts a lower radiation dose and usually provides adequate sampling of the lung parenchyma that is representative of the overall process when compared to volumetric computed tomography [1] and histopathology obtained from lung biopsy [2]. As several series (supine, prone, expiratory) are often obtained contemporaneously in patients with DLD, spaced axial imaging provides an incremental reduction in overall radiation dose compared with multiple volumetric acquisitions.

On the other hand, volumetric imaging is superior in its ability to image the entirety of the lung parenchyma. This may be particularly advantageous in the serial follow-up of DLD. Subtle changes in disease extent may be easier to appreciate when the whole lung is imaged, whereas the sampling error intrinsic to spaced axial images may significantly limit the assessment of longitudinal changes. In the near future, quantitative lung imaging may be used routinely in the evaluation of DLD. Quantitative computed tomography is not only able to evaluate extent of lung affected by disease, but is also able to distinguish different computed tomography findings based upon computerised textural analysis. Utilising these techniques, quantitative computed tomography may contribute to estimating prognosis on initial imaging and determining progression of disease on serial imaging. This represents another significant advantage of volumetric imaging over spaced axial scans, given that quantitative computed tomography has been studied primarily in the context of volumetric datasets. Last, spaced axial scans may miss focal abnormalities such as pneumonia or lung cancer. Patients with DLD have reduced pulmonary reserve, thus the detection of active lung processes, such as pneumonia, is important so that early treatment may be instituted. The incidence of lung cancer is significantly higher in patients with DLD. Lung cancer may have a significant impact on mortality and transplant candidacy in these patients.

The advantage of spaced axial scans over volumetric acquisitions has diminished as radiation reduction techniques have become more sophisticated. Model-based iterative reconstruction techniques can reduce effective dose by as much as 80% compared to older reconstruction techniques, without an associated reduction of diagnostic accuracy [3]. Additionally, the risks and benefits of higher-dose volumetric computed tomography techniques should be considered in the context of each individual patient. Given the delay between radiation exposure and the onset of most adverse effects, radiation is less of a concern in older patients or patients whose lifespan is reduced by their DLD. For all of the reasons detailed above, volumetric acquisitions have become the standard protocol at many institutions except for selected patient subgroups in which radiation exposure is a significant concern.

Prone and expiratory images are often helpful in establishing an initial diagnosis, but may be less important on follow-up imaging. Prone imaging may provide a superior assessment of findings in the posterior subpleural lung, particularly in early DLD, whereas expiratory imaging is important in detecting airways obstruction. For many diseases, however, these series are not required after an initial diagnosis has been established.

Expected evolution of findings over time on HRCT

Longitudinal imaging of DLD may be helpful in both establishing an initial diagnosis and in the follow-up of patients after a diagnosis has been established. Before discussing the role of serial HRCT in these contexts, it is important to have a fundamental understanding of the expected temporal evolution of findings for specific diseases (table 1 and figure 1). Data on serial HRCT changes are sparse in the literature. For this reason, conclusions regarding the evolution of diseases over time are often based on small series or inferred from serial clinical and pulmonary function test (PFT) data.

Temporal evolution of DLD varies greatly and is affected by the complex relationship between the nature of the inciting insult, the resulting immune reaction, and the treatment that is administered. Certain diseases, such as cryptogenic organising pneumonia, may resolve completely without significant residual abnormalities while other diseases, such as idiopathic pulmonary fibrosis (IPF), are irreversible and typically progress despite treatment.

TABLE 1 Expected course of common diffuse lung diseases, including a list of high-resolution computed tomography (HRCT) findings for each disease that are typically reversible *versus* irreversible

Disease or pattern	Expected course	HRCT findings	
		Typically reversible	Typically irreversible
Idiopathic pulmonary fibrosis	Progression is typical	None GGO may evolve into reticulation	Reticulation Honeycombing Traction bronchiectasis Architectural distortion
Hypersensitivity pneumonitis	Depends on antigen removal and the presence of fibrosis on HRCT	Findings of acute or subacute hypersensitivity pneumonitis (GGO, consolidation and centrilobular nodules)	Findings of chronic hypersensitivity pneumonitis (reticulation, honeycombing, traction bronchiectasis, emphysema)
Respiratory bronchiolitis ILD	Almost always improves with smoking cessation	GGO Centrilobular nodules	Reticulation (rare as a significant finding) GGO that remains after smoking cessation/treatment may represent microscopic fibrosis
Desquamative interstitial pneumonia	Majority of patients improve with smoking cessation and/or corticosteroids	GGO (if the patient doesn't stop smoking this may evolve into fibrosis or cystic lucencies)	Cystic lucencies Reticulation Honeycombing GGO that remains after smoking cessation/treatment may represent microscopic fibrosis
Langerhans cell histiocytosis	Findings may improve or resolve with smoking cessation	Nodules (if patient doesn't stop smoking these may cavitate and evolve into cysts) Thick-walled cavities	Thin-walled cavities Cysts
NSIP	Evolution depends on subtype (cellular *versus* fibrotic) and is hard to predict on imaging	Findings of cellular NSIP, namely GGO (however this finding is not specific for reversible disease in NSIP)	Findings of fibrotic NSIP (reticulation and traction bronchiectasis)
Sarcoidosis	Progression from nodules to fibrosis is rare	Nodules Interlobular septal thickening GGO and consolidation more commonly evolve to fibrosis	Reticulation Honeycombing Cystic airspaces
Organising pneumonia	Highly responsive to steroids; relapse may occur	Consolidation GGO	Findings may progress to fibrosis, commonly in an NSIP pattern

ILD: interstitial lung disease; NSIP: nonspecific interstitial pneumonia; GGO: ground glass opacity.

Usual interstitial pneumonia

Usual interstitial pneumonia (UIP) is a histopathological pattern of injury that is most commonly caused by IPF. IPF is a progressive fibrotic lung disease with a median survival of approximately 3–4 years [4, 5]. Over time, patients demonstrate worsening pulmonary symptoms, decline in PFT abnormalities and increase in the extent of fibrosis on HRCT. It is important to note that there is significant variation in the rate of progression. After diagnosis, some patients remain stable for prolonged periods of time, while others show rapid progression to death [6]. Additionally, lead time bias may factor into apparent differences in the rates of progression as there is a subclinical radiological precursor to symptomatic disease that may be discovered as an incidental finding on imaging performed for non-pulmonary symptoms.

Early IPF may demonstrate findings on HRCT that are not highly specific. Initially, subpleural irregular reticulation with or without traction bronchiectasis/bronchiolectasis may be seen in the absence of honeycombing. According to the 2011 consensus paper by Raghu *et al.* [7] this would be classified as "possible UIP" and would not be considered diagnostic of IPF. If honeycombing is not present initially, it may develop on serial imaging as the disease becomes more severe. In one study, 53% of patients with a "possible UIP" pattern at baseline developed honeycombing on subsequent imaging during the 3-year follow-up period [8]. At this point, the pattern can be considered "definite UIP" and diagnostic of IPF. Evolution to a more diagnostic HRCT pattern over time is particularly relevant for patients who are not candidates for a surgical lung biopsy.

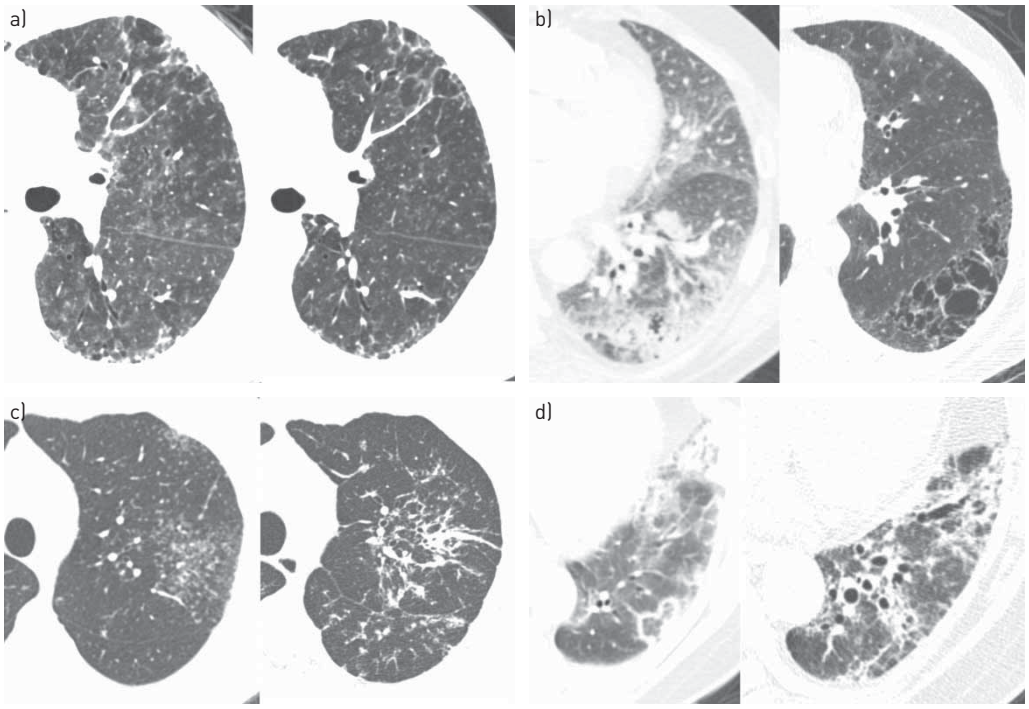

FIGURE 1 a-d) Typical changes over time in different diffuse lung diseases. a) Subacute hypersensitivity pneumonitis: baseline (left) and 6-month follow-up (right) high-resolution computed tomography (HRCT). Ground glass opacity and centrilobular nodules demonstrate significant interval decrease after antigen removal with mild persistent abnormality remaining including reticulation. b) Desquamative interstitial pneumonia: baseline (left) and 3-year follow-up (right) HRCT. Subpleural ground glass opacity seen on the baseline HRCT has evolved into cystic lucencies in a patient who continued to smoke. The cystic lucencies may represent emphysema surrounded by fibrosis. c) Sarcoidosis: baseline (left) and 4-year follow-up (right) HRCT. Perilymphatic nodules on the initial HRCT evolve into fibrosis as evidenced by reticulation, architectural distortion, and mild bronchiectasis. d) Organising pneumonia: baseline (left) and 2-year follow-up (right) HRCT. Ground glass opacity, consolidation, and the reversed halo sign on the initial HRCT evolves to fibrosis after treatment with corticosteroids.

Most patients with IPF show worsening of the severity and extent of imaging findings over time. In the study by Nishiyama *et al.* [9], 89% of IPF patients showed progression of HRCT findings during the mean 4-year follow-up period. Specific findings of worsening disease include increase in extent of irregular reticulation and honeycombing [10], development of more pronounced architectural distortion, and decrease in ground glass opacity (GGO). Patients may show either a consistent progression of lung fibrosis over time or a more step-wise progression of stability alternating with worsening.

Acute exacerbation of IPF may lead to a rapid worsening of clinical symptoms and decline in lung function. In a recent meta-analysis, this occurred with a frequency of 41 cases per 1000 patient–years [11]. HRCT is often obtained in the work-up of IPF patients with acute symptoms. Its main role is to identify findings compatible with an acute exacerbation and to exclude alternative causes of worsening symptoms, such as infection, pneumothorax, pulmonary embolism, heart failure, *etc.* [12]. Typical findings of IPF exacerbations on HRCT include new bilateral GGO superimposed upon pre-existing fibrosis [13].

There are little data on the natural history of HRCT findings in non-IPF causes of UIP, such as connective tissue disease (CTD), drug toxicity and asbestosis; however, a comparison of mortality data among the different causes of UIP pattern gives some insight into the expected rate of progression of findings. In general, IPF has a worse prognosis than non-idiopathic UIP. In the study by Park *et al.* [14], the 5-year mortality of IPF *versus* CTD-associated UIP was 82% *versus* 45% respectively. In a study of patients with early asbestosis, another cause of a UIP pattern, the mean decline in forced vital capacity (FVC) over an average 4.8 year follow-up period was only 0.2 L (5% change) [15], whereas in IPF a decline in FVC of 0.2 L·year^{-1} is typical.

Hypersensitivity pneumonitis

As opposed to IPF, hypersensitivity pneumonitis has a much greater variability in its clinical presentation, radiographic findings and pathological findings. This variability stems from the fact that patients may

present with disease that is inflammatory, fibrotic or both. In general, the inflammatory subtype corresponds to the acute and subacute forms of hypersensitivity pneumonitis, whereas the fibrotic subtype corresponds to the chronic form of hypersensitivity pneumonitis. The expectations for changes on longitudinal imaging vary depending upon the predominant pattern present.

Remy-Jardin *et al.* [16] studied serial HRCTs in patients with subacute and chronic hypersensitivity pneumonitis due to bird exposure. In the group with subacute hypersensitivity pneumonitis, the primary findings on the baseline HRCT were diffuse micronodules and GGO, which dramatically improved in all patients after antigen removal (figure 1a). This was associated with a concomitant improvement in clinical symptoms. This trend was confirmed in another study of hypersensitivity pneumonitis patients exposed to avian antigens [17] in which all patients with GGO and centrilobular nodules showed an interval decrease in the extent of findings on serial HRCTs. In the subgroup with subacute hypersensitivity pneumonitis, the average extent of lung involved decreased from 50% to 25% on interval follow-up. Considering these two studies, it appears that GGO and micronodules in patients with subacute hypersensitivity pneumonitis likely represent the active, inflammatory and potentially reversible component of disease. After withdrawal of the antigen, patients should show significant clinical and radiographic improvement, although some persistence of abnormality is common.

In patients with chronic hypersensitivity pneumonitis, the primary findings on baseline HRCT in the study by Remy-Jardin *et al.* [16] were honeycombing or emphysema associated with GGO and micronodules. After antigen removal, the honeycombing and emphysema remained unchanged; however, the GGO and micronodules showed significant improvement. However, chronic hypersensitivity pneumonitis patients showed no change in clinical status or pulmonary function parameters following antigen removal. Thus, as with subacute hypersensitivity pneumonitis, it appears that the GGO and micronodules in chronic hypersensitivity pneumonitis represent a potentially reversible component of disease although their improvement on serial HRCTs had little impact on functional status because of the presence of coexistent fibrosis or emphysema.

Smoking-related lung disease

Respiratory bronchiolitis, desquamative interstitial pneumonia (DIP) and Langerhans cell histiocytosis are the most common forms of DLD related to cigarette smoking. All patterns may be associated with a variety of histopathological changes including inflammation, fibrosis and emphysema. The evolution of findings over time primarily depends upon the predominant histopathological changes present and the ability of patients to adhere to smoking cessation.

Respiratory bronchiolitis is a common histopathological finding in smokers and, when symptomatic, is called respiratory bronchiolitis interstitial lung disease (RB-ILD). Respiratory bronchiolitis is not a significant cause of mortality or morbidity *per se*, but may represent a precursor to the subsequent development of centrilobular emphysema. Typical HRCT findings include small centrilobular nodules, GGO and air trapping. In patients who are able to stop smoking, serial HRCTs will demonstrate a significant improvement of the nodules and GGO in almost all patients [18]. Residual abnormalities persist, however, in the majority of patients, likely representing microscopic regions of fibrosis. Irregular reticulation is an uncommon finding in respiratory bronchiolitis and, when seen, does not tend to show significant change over time.

DIP is a more severe pattern of injury in the same spectrum as respiratory bronchiolitis and may evolve in several ways. In patients with predominantly inflammatory (non-fibrotic) disease, manifested by peripheral GGO on HRCT, the cessation of smoking will be associated with significant improvement or resolution of the abnormalities [19, 20]. Corticosteroid therapy may be used in conjunction with smoking cessation. This results in stabilisation or improvement in the majority of patients [21]. Residual GGO after treatment is common and may represent microscopic fibrosis as with respiratory bronchiolitis. Improvement of the HRCT findings does not occur in all patients, however. In the study by Kawabata *et al.* [22], 16% of DIP patients showed temporal progression of HRCT findings as evidenced by the development of honeycombing and/or thin-walled cysts (figure 1b). These thin-walled cysts demonstrated a different morphology than honeycombing, potentially representing emphysema surrounded by fibrosis [19].

Langerhans cell histiocytosis shows a typical progression of findings over time. The initial manifestation is nodules which represent localised collections of Langerhans cells surrounding airways. Over time, these nodules develop lucencies at their centres, shown to coincide with focal areas of airway dilation [23] on pathological sections, and evolve into thick-walled cysts. Eventually thin-walled cysts develop, reflecting emphysema surrounded by fibrosis. On longitudinal imaging the nodules and thick-walled cysts may improve or resolve with smoking cessation, whereas the thin-walled cysts and emphysema represent irreversible disease and may even progress [24].

Nonspecific interstitial pneumonia

Nonspecific interstitial pneumonia (NSIP) is a histopathological pattern of injury that may be idiopathic or due to CTD, hypersensitivity pneumonitis or drug toxicity. NSIP may be cellular, fibrotic or a combination of both types. In an analysis of the 10-year survival rates of patients with idiopathic NSIP, survival with the cellular type was 100% whereas survival with the fibrotic type was 40% [25]. Unfortunately, it is difficult to accurately distinguish the various forms of NSIP with HRCT when compared with histology [26, 27]. Most patients with NSIP do not undergo surgical lung biopsy, particularly in the setting of CTD, making the distinction between cellular and fibrotic subtypes even more challenging. Serial HRCTs often provide significant information in this context. Radiographic improvement after treatment suggests a significant cellular component whereas a lack of change favours a predominantly fibrotic pattern.

On longitudinal imaging, patients with NSIP show different trajectories. In the serial follow-up of patients with biopsy-confirmed NSIP (median follow-up of 72 months) Akira *et al.* [28] demonstrated improvement in 38%, worsening in 22% and no significant change in the remaining 40%. As with other patterns of injury, it would be reasonable to surmise that GGO and consolidation represent findings with a significant reversible component, and several papers have demonstrated that these findings decrease in extent after treatment [28–30]. Additionally, at least one study has shown improvements in FVC and diffusing capacity of the lungs for carbon monoxide (*D*LCO) associated with the decrease in GGO [31]. On the other hand, Sumikawa *et al.* [27] showed significant discordance between imaging and pathological findings with respect to the presence of inflammation or fibrosis. In that series, the presence of GGO on HRCT did not necessarily correlate with reversible findings on pathology but rather corresponded to fibrosis in some patients.

Conversely, it would be expected that HRCT findings of fibrosis, such as irregular reticulation, traction bronchiectasis and honeycombing would not resolve but rather could worsen over time. Accordingly, Akira *et al.* [28] demonstrated an increase in the coarseness of fibrosis and traction bronchiectasis over time while Silva and colleagues [30] showed an increase in reticulation on serial HRCTs in NSIP patients over a median 61 months of follow up. A subset of patients (28%) was also shown to evolve from an NSIP pattern to a UIP pattern over time. While bronchiectasis is typically a finding of fibrosis in NSIP, it may rarely resolve as was demonstrated by Nishiyama *et al.* [32].

In summary, HRCT findings in NSIP, when evaluated in isolation, do not consistently predict the presence of reversible or irreversible changes. GGO is typically associated with reversible disease but may, in some cases, indicate microscopic fibrosis. Change in extent of disease on HRCT over time is likely the best predictor of the presence of reversible *versus* irreversible changes in patients with NSIP.

Sarcoidosis

Similar to hypersensitivity pneumonitis, sarcoidosis demonstrates wide variability in its manifestations over time. Granulomatous infiltration of lymph nodes and pulmonary lymphatics represents the more active and potentially reversible phase of disease. Irreversible fibrosis may eventually develop in areas previously involved by granulomas (figure 1c). Changes on longitudinal imaging have been studied predominantly using the Scadding staging system on chest radiographs [33]. Progression from stages I–III (nodules and/or lymphadenopathy) to stage IV (fibrosis) is uncommon. The long-term rate of progression to stage IV based upon the initial stage is as follows: stage I (1%), stage II (6%) and stage III (6%) [34].

Longitudinal changes on HRCT are not as well studied. Akira *et al.* [35] analysed findings on serial HRCTs in 40 patients with pulmonary sarcoidosis. Most patients with nodules showed resolution or decrease in the extent of parenchymal abnormalities over time. In contrast, patients with GGO and consolidation on the baseline computed tomography were more likely to progress to honeycombing. Murdoch *et al.* [36] also evaluated serial HRCTs in patients with pulmonary sarcoidosis. Nodules, GGO, irregular linear opacities and interlobular septal thickening represented potentially reversible findings whereas architectural distortion and cystic airspaces were predominantly irreversible abnormalities in that series.

It is important to note that nodular lung disease may be below the threshold for detection on PFTs. For this reason, HRCT may be the diagnostic test of choice to detect changes over time in this subset of patients with mild disease. Gafá *et al.* [37] assessed serial HRCTs in 14 consecutive sarcoidosis patients. On follow-up imaging, 58% of patients demonstrated worsening findings; however, in half of these patients, the worsening HRCT findings were not accompanied by a significant change in FVC. HRCT also plays an important role in the detection of complications of sarcoidosis such as aspergillomas.

Organising pneumonia

Organising pneumonia is a histopathological pattern of injury that may be cryptogenic or may be associated with a variety of insults including drug exposures, CTDs, graft *versus* host disease, *etc*. From a

clinical perspective, organising pneumonia is a highly steroid-responsive disease, with clinical improvement in many patients days to weeks after corticosteroid treatment [38]. Although relapse is common, seen in nearly 60%, recurrence is not associated with increased mortality [39]. The most typical HRCT findings are patchy bilateral peribronchvascular and subpleural consolidation [40].

Following treatment, most patients show rapid decrease in the size of lung opacities. In a study of 22 patients with cryptogenic organising pneumonia, changes on the follow-up HRCTs included compete resolution in 27%, improvement in 68% and no change in only 5% [41]. Lee *et al.* [42] investigated the HRCT findings on initial imaging that were associated with radiographic improvement *versus* worsening. Patients with consolidation as the predominant abnormality were more likely to demonstrate resolution or improvement of radiographic abnormalities, whereas those with reticulation or GGO as an initial manifestation were more likely to demonstrate worsening on serial HRCTs. It is important to note, however, that consolidation seen on the initial HRCT may evolve to GGO as the abnormalities improve. Residual fibrosis may remain after treatment and, when involving a significant portion of the lung, often resembles fibrotic NSIP (figure 1d).

Role of longitudinal imaging in establishing a primary diagnosis

A major emphasis of the literature on DLD has been to define findings and patterns on HRCT that are specific for certain diseases or histopathologic patterns of injury. These studies are typically conducted using a single point in time, often at initial presentation. However, the accuracy of HRCT for predicting

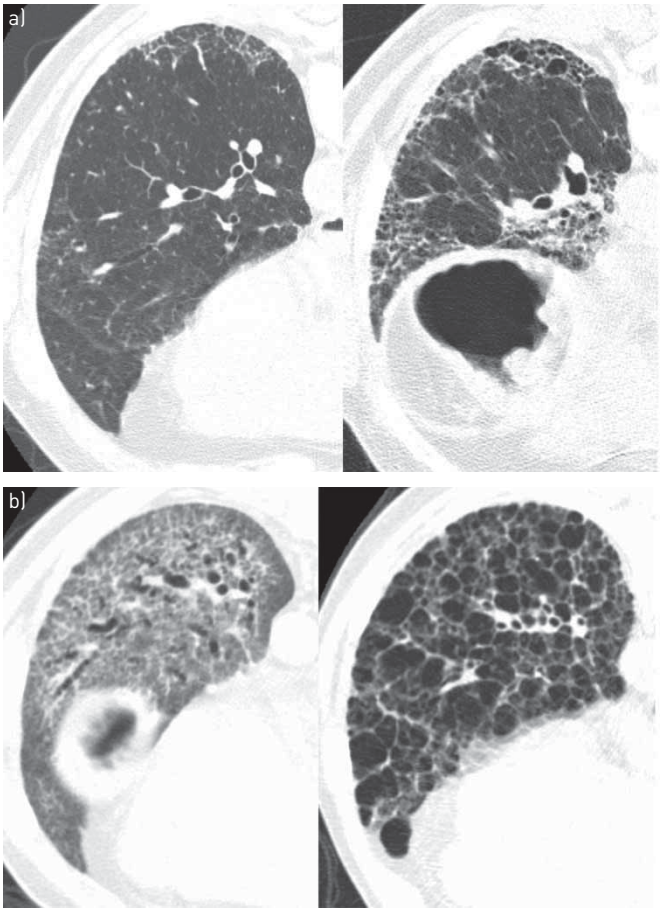

FIGURE 2 Changes in high-resolution computed tomography (HRCT) pattern over time. a) Idiopathic pulmonary fibrosis (IPF), increased specificity over time. Initial HRCT in a patient with early IPF (left) shows mild subpleural reticulation without honeycombing. 3 years later (right) honeycombing has developed. While the initial study is nonspecific, the follow-up HRCT would be considered a "definite usual interstitial pneumonia" pattern and diagnostic of IPF in the appropriate clinical setting. b) Nonspecific interstitial pneumonia (NSIP), change in pattern over time. Baseline prone HRCT image (left) in a patient with rheumatoid arthritis demonstrates reticulation and traction bronchiectasis with subpleural sparing compatible with NSIP. 8 years later (right) there is diffuse honeycombing that would be compatible with a usual interstitial pneumonia pattern.

the correct primary diagnosis is improved by the availability of several imaging studies spaced over time, as a single HRCT from one time point may not be representative of the true nature of DLD. For example, diseases with a significant inflammatory component may wax and wane over time. HRCT performed at the height of disease activity is typically, although not always, the most representative of the underlying disease. The presence and direction of temporal changes in HRCT findings may also give insight into the nature of the underlying disease. Findings that improve on serial HRCT examinations suggest an infiltrative or inflammatory component, and thus when significant improvement is seen, predominantly fibrotic diseases such as IPF, are unlikely.

While early disease on HRCT is often nonspecific with regards to aetiology, HRCT patterns may become more specific as the disease progresses (figure 2a). Yamauchi *et al.* [8] demonstrated that 53% of IPF patients with a nonspecific pattern on the initial HRCT went on to develop findings that would subsequently be considered diagnostic of IPF. This increase in the specificity of the HRCT pattern over time is particularly relevant in patients who are not candidates for a surgical lung biopsy. On the other hand, it is also possible for the HRCT pattern to become less diagnostic over time or for the initial pattern to change in a manner that is not suggestive of the underlying aetiology (figure 2b). Silva *et al.* [30] demonstrated that 28% of patients with biopsy proven NSIP evolved to a UIP pattern over serial HRCT examinations.

Role of longitudinal imaging in the follow-up of established DLD

After initial diagnosis, HRCT may be used in several ways (table 2 and figure 3) including: 1) assisting in the determination of prognosis; 2) monitoring for the efficacy of treatment; 3) detecting progression of disease or complications; or 4) evaluating patients with worsening or acute symptoms. The exact role of HRCT compared to PFTs is not clear; however, these two modalities are complimentary and are both important in the follow-up of DLD patients. Some of the important roles of HRCT in the follow-up of established DLD are discussed below.

Prognosis

Morbidity and mortality from DLD is affected by several factors including diagnosis, comorbidities, extent of lung involvement, presence of reversible or inflammatory disease and rate of progression of disease. In general, progression of HRCT abnormalities is associated with increased mortality. In an analysis of nearly 2000 patients in the Framingham heart study [43], 6% were found to have worsening interstitial lung abnormalities on serial computed tomographies, which was associated with increased mortality (hazard

TABLE 2 The most common roles of longitudinal high-resolution computed tomography (HRCT) data in the evaluation of patients with diffuse lung disease (DLD)

HRCT role	Notes
Initial diagnosis	Pattern may become more diagnostic over time Resolved or improved findings suggest an inflammatory or infiltrative component (*e.g.* not IPF)
Prognosis	Worsening abnormalities or rapid progression suggest a worse prognosis
Routine follow-up	Particularly helpful when PFTs may be inaccurate: patient unable to cooperate with PFTs; multifactorial restrictive disease (*e.g.* both fibrosis and pleural disease); mixed interstitial and airways disease; or early disease (below threshold of PFTs) Distinguish inflammation/infiltration from fibrosis on baseline HRCT
Detection of disease progression	Particularly helpful in patients with worsening symptoms and/or PFTs HRCT may be used as endpoint in clinical drug trials Quantitative analysis may provide a more objective analysis of findings and extent of lung involved
Evaluation of patients with acute lung symptoms	Distinguish progression of DLD *versus* a superimposed process (*e.g.* infection) Detection of acute exacerbation
Detection of complications	Detection of lung cancer, pulmonary hypertension and other abnormalities associated with DLD

IPF: idiopathic pulmonary fibrosis; PFT: pulmonary function test.

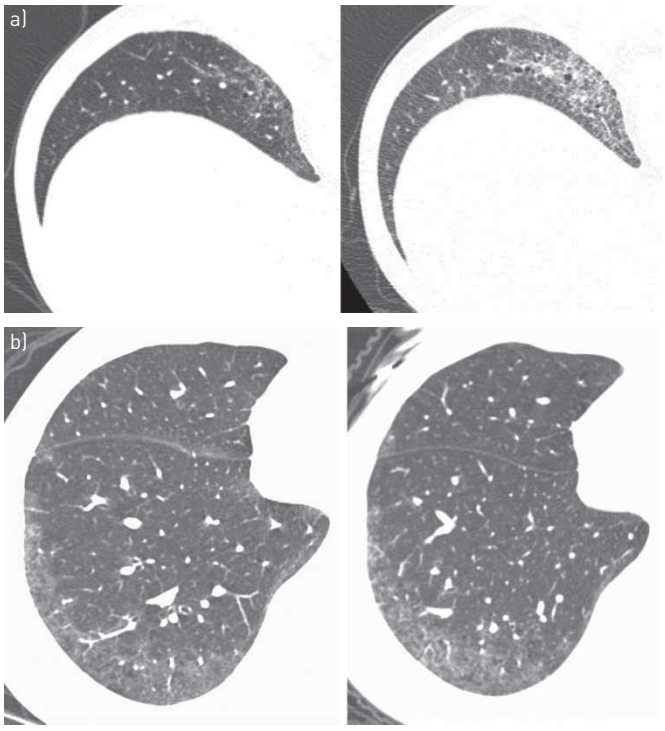

FIGURE 3 Longitudinal imaging after initial diagnosis. a) Nonspecific interstitial pneumonia (NSIP), early changes not detected by pulmonary function tests. In a patient with scleroderma and normal pulmonary function tests, prone high-resolution computed tomography (HRCT) (left) demonstrates early ground glass opacity and reticulation. 1 year later, a repeat HRCT (right) shows worsening of the lung disease; however, this was not accompanied by a significant change in pulmonary function tests. b) NSIP, microscopic fibrosis. Baseline HRCT (left) in a patient with scleroderma shows subpleural ground glass opacity suggestive of cellular NSIP. A repeat HRCT (right) 1 year later after immunosupression shows no significant change. In this case, the ground glass opacity represented microscopic fibrosis that was irreversible.

ratio of 3.9). Serial HRCTs may be able to identify a subset of patients with more rapid progression of disease. Oda *et al.* [44] used a semi-quantitative score of fibrosis in patients with IPF at baseline and at 6 months. A significant increase in the fibrosis score at the 6-month HRCT compared with the baseline predicted an increased risk of mortality and continued progression of disease. This held true even in the subset of patients who had no change in FVC between 0 and 6 months. Additionally, specific findings on the initial HRCT, for example scores of the amount of fibrosis, in patients with established DLD may aid in the prediction of mortality for diseases such as IPF [45, 46], hypersensitivity pneumonitis [47] and others.

Routine follow-up of known DLD

Clinical symptoms and PFTs are the most common diagnostic tools used to evaluate longitudinal changes in patients with DLD. Declines in FVC or *D*LCO are the most commonly used PFT metrics, and are typically obtained at 3–6 month intervals after initial diagnosis. In the absence of new or worsening symptoms, HRCT is not usually obtained for routine follow-up, despite its ability to provide an accurate anatomical assessment of the extent and severity of findings. It is unclear what incremental data HRCT provides over routine PFTs, particularly given that agreement between HRCT and PFT changes over time is moderate at best [48, 49].

There are several limitations of PFTs that suggest potential roles for HRCT in this context. First, PFTs are highly effort dependent and may vary significantly between different labs. Second, abnormalities on PFTs are nonspecific with regards to aetiology. For example, PFTs may not be able to distinguish the effects of fibrotic lung disease from pleural abnormalities or muscle weakness. A combination of interstitial lung disease (ILD) and emphysema may cause a "pseudo-normalisation" of PFT findings and will significantly impair the ability of PFTs to accurately detect and quantify the severity of lung disease. Finally, the presence of early DLD may be below the threshold for detection on PFTs. In a study of early asbestosis [15], spirometic parameters were shown to be insensitive in the detection of disease, with only 6% of patients with HRCT abnormalities having an abnormal FVC. Spirometry was also very insensitive in detecting worsening of HRCT abnormalities over time. Tsushima *et al.* [50] found that early interstitial changes were present on

lung cancer screening computed tomography in 2.5% of patients. 44% of these patients who were followed with serial imaging demonstrated worsening of the imaging findings over time; however, PFTs during this follow-up period were not significantly different (figure 3a).

For these reasons, PFTs and HRCT should be considered complimentary diagnostic tests. Changes in PFT abnormalities should be investigated with repeat imaging to determine the cause of these abnormalities. HRCT should be obtained in patients with worsening symptoms, even if there is not a significant change in PFT parameters. HRCT monitoring should be considered in cases for which the PFTs are thought to be inaccurate. Routine follow-up using HRCT may be particularly helpful in the following scenarios: patients who are unable to cooperate with pulmonary function testing; multifactorial restrictive disease (*e.g.* ILD, pleural disease, musculoskeletal disease, *etc.*); mixed interstitial and airways disease; and suspected early disease below the threshold of detection of PFTs.

On the other hand, HRCTs have several disadvantages compared with PFTs. In patients with moderate-to-severe lung disease, clinical symptoms and PFTs may be more sensitive than HRCT for subtle worsening. HRCT is insensitive for certain changes, particular airways and pulmonary vascular disease. In some cases, HRCT may be too sensitive for early interstitial changes. Copley *et al.* [51] demonstrated mild basilar reticulation in 65% of asymptomatic patients over the age of 75 years compared with 0% of patients aged below 55 years. It was thought that these early changes were a part of ageing and unlikely to cause clinically significant disease in the future.

Serial HRCTs can be helpful in distinguishing the presence of inflammatory *versus* fibrotic lung disease. As discussed above the ability of HRCT to predict which findings will be reversible or irreversible on a single baseline study is limited. GGO, a finding typically associated with inflammation or infiltration, does not always represent reversible lung disease, but rather in some cases may represent microscopic fibrosis (figure 3b). Irregular reticulation, a finding typically associated with fibrosis, can occasionally be reversible. The reversible component should improve or resolve on serial HRCTs after appropriate treatment, whereas the irreversible component should not.

Detection of disease progression in patients with worsening symptoms or PFTs

HRCT provides an accurate anatomical assessment of the nature of the lung disease and temporal progression. Thus, in patients with worsening clinical symptoms or PFT abnormalities, HRCT should be routinely obtained. As discussed, HRCT provides several advantages to PFTs and may be more sensitive to disease progression in certain scenarios. Dhariwhal *et al.* [52] investigated the effect of smoking cessation on PFT and HRCT abnormalities over time. They discovered micronodules, GGO or emphysema on HRCT in 58% of healthy, asymptomatic smokers despite normal forced expiratory volume in 1 s values. After smoking cessation, HRCT demonstrated a substantial decrease in micronodules and GGO without a corresponding change in the forced expiratory volume in 1 s. In another study of longitudinal data in patients with mixed connective tissue-related ILD, HRCT and *D*Lco were able to document progression of disease, whereas FVC showed no significant change over 10 years [53].

Findings on HRCT have also been used as independent endpoints in clinical drug trials. While typical endpoints in clinical trials include morality, declines in FVC and incidence of acute exacerbations [54, 55], HRCT is currently being utilised as an endpoint in multiple ongoing clinical drug trials with an emphasis on IPF patients. As an example, the ability of pirfenidone to slow the progression of fibrosis in treated IPF patients was recently confirmed using visual scores and quantitative analysis of HRCT images [49].

Quantitative lung imaging has the potential to provide a more objective evaluation of the extent of lung disease on initial and follow-up HRCTs. Quantitative techniques could provide a supplement to individual radiologists' impressions of change over time and could reduce errors inherent to the interobserver variability between radiologists. Several quantitative techniques have been described. Best *et al.* [56] used radiologists' visual estimates of the mean extent of abnormalities to the nearest 5% at three selected levels in patients with IPF and found that the mean fibrosis score (reticulation and honeycombing) at baseline computed tomography was a strong predictor of mortality. Elicker *et al.* [57] performed a more objective calculation by manually selecting regions of abnormality on axial images, summing the axial area measurements, and multiplying the sum of these serial area measurements by the distance between sections. Using this method, they were able to document decreased native lung volumes and increased extent of native lung fibrosis in single lung transplant patients with IPF. Computerised calculations provide a faster and easier method of determining lung volumes and percentage of lung affected by disease, and can also distinguish different HRCT abnormalities using textural analysis. To date, computerised quantitative computed tomography has been validated primarily using visual analysis and PFTs for comparison. For instance, Kim *et al.* [58] demonstrated that quantitative lung fibrosis was a sensitive marker for early changes (~7 months) in the severity of lung disease in IPF patients when compared with

FVC and *D*LCO. Further investigation is needed to determine the specific advantages of quantitative computed tomography over traditional methods of evaluating lung disease severity such as clinical symptoms and PFTs.

Evaluation of patients with acute symptoms

Another important role of longitudinal imaging of DLD patients is the evaluation of patients with new or worsening symptoms (figure 4). Progressive dyspnoea and other symptoms of worsening pulmonary disease may result from a variety of insults. Patients on immunosuppressive medications are susceptible to opportunistic infections (figure 4a). Drugs used to treat systemic disorders, such as methotrexate for CTD, may contribute pulmonary toxicity. DLDs may enter an accelerated phase of acute injury with more rapidly progressive symptoms. While PFTs give an accurate evaluation of overall lung function, they are limited in their ability to distinguish between these varied aetiologies and often are unable to differentiate the primary cause of deteriorating function. Thus HRCT is an important component of the evaluation of patients with acute lung symptoms.

Acute exacerbation of ILD is increasingly recognised as an important contributor to mortality in DLD. Exacerbations are best described in the setting of IPF but may be seen in most DLDs. The development of acute exacerbations is not uncommon, seen in one study in 9.6% of IPF patients within the first 2 years after diagnosis [59]. Acute exacerbation has a significant impact on mortality. In the follow-up of 112

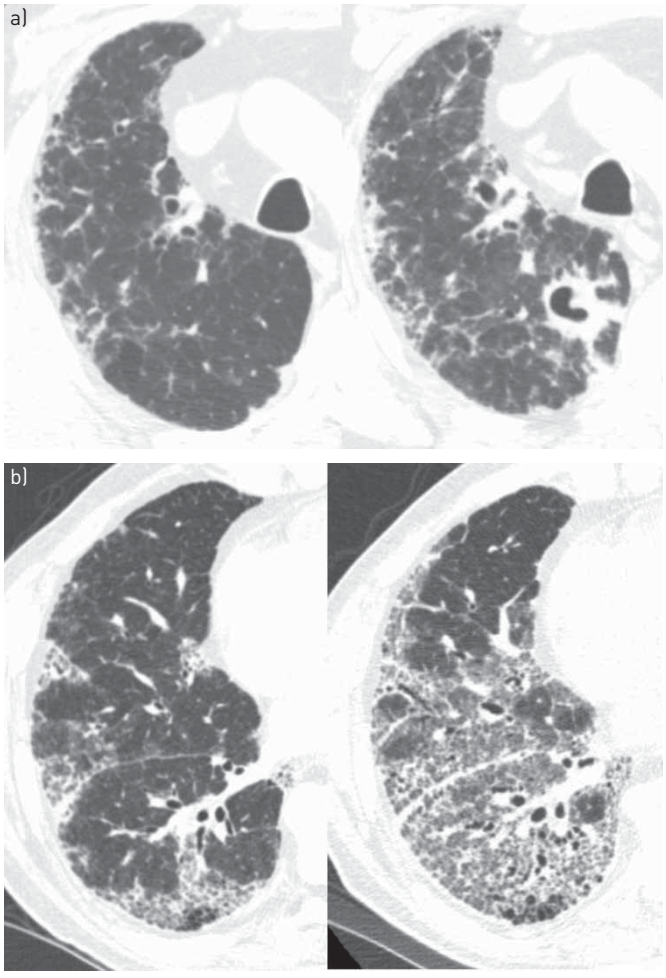

FIGURE 4 Evaluation of acute symptoms. a) Infection in the setting of idiopathic pulmonary fibrosis (IPF). Baseline high-resolution computed tomography (HRCT) (left) and follow-up HRCT after the development of acute symptoms (right) shows both worsening diffuse lung disease and a new cavitary lesion. Sputum cytology revealed atypical mycobacterial infection. b) Acute exacerbation of IPF. Baseline study (left) shows a usual interstitial pneumonia pattern of fibrosis with subpleural honeycombing and mild reticulation. 1 month later, the patient presented with acute respiratory distress and a new HRCT (right) shows both worsening fibrosis and diffuse ground glass opacity compatible with an acute exacerbation.

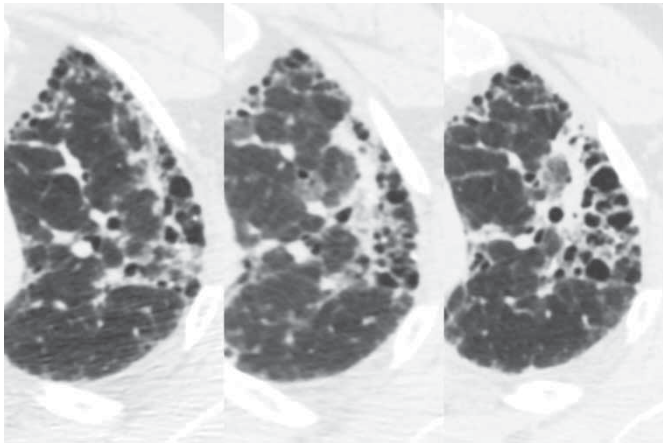

FIGURE 5 Evaluation of complications. Lung cancer in the setting of idiopathic pulmonary fibrosis. Baseline high-resolution computed tomography (left) shows a usual interstitial pneumonia pattern of fibrosis. A follow-up scan performed 9 months later (centre) shows a new, subtle band of ground glass and consolidation in the left upper lobe. A short-term follow up was performed 3 months later (right), which showed slight enlargement of the abnormality, and this was subsequently proven to represent lung adenocarcinoma.

patients with IPF, Okamoto *et al.* [60] showed a mean survival time of 0.9 months after an acute exacerbation compared to 3.1 years for all IPF patients. On pathology, acute exacerbation will show diffuse alveolar damage, organising pneumonia or progressive fibrosis. The HRCT findings of acute exacerbation include the interval development of bilateral GGO or consolidation superimposed on pre-existing signs of fibrosis [13] (figure 4b). The distribution of GGO may be peripheral, patchy or diffuse [61].

Evaluation of complications of DLD

DLDs place patients at risk for the development of other comorbidities. HRCT plays a significant role in the detection of these comorbid conditions, particularly when they are asymptomatic or unsuspected.

Bronchogenic carcinoma is one of the more common comorbid conditions that may be seen with a higher frequency in DLD patients. The association between DLD and bronchogenic carcinoma has been studied most frequently in IPF patients. Le Jeune *et al.* [62] demonstrated a five-times higher incidence of lung cancer in IPF patients compared with the general population. On HRCT, bronchogenic carcinoma in the setting of IPF appears as a solid nodule that is often located at the interface between fibrotic and normal lung. In the study by Oh *et al.* [63], nearly 20% of these cancers were misinterpreted as infection (figure 5) and more than 10% were not detected at all on the baseline computed tomography scan. Given the poor prognosis of IPF, the discovery of bronchogenic carcinoma may have little impact on overall mortality, particularly in patients with moderate-to-severe fibrosis. Suspected malignancy, however, does have a major impact upon the lung transplant candidacy given that cancer is considered a contraindication for transplant.

Pulmonary hypertension is another comorbidity that may be associated with increased mortality and worsening symptoms disproportionate to changes in lung volumes on PFTs. HRCT findings suggesting pulmonary hypertension include a main pulmonary diameter greater than the aorta, an absolute main pulmonary diameter $\geqslant$29 mm or right ventricular chamber enlargement. It is important to note that these findings are less sensitive in the setting of lung fibrosis compared with other causes of pulmonary hypertension [64]. While there are specific treatments for pulmonary hypertension, the use of these agents in the setting of DLD is mostly untested, thus the main advantage of identifying pulmonary hypertension would be to enrol patients in clinical trials.

Conclusion

Serial HRCT examinations play an important role in both the initial diagnosis and the follow-up of patients with DLD. When used in conjunction with clinical symptoms and PFTs, HRCT can enhance the detection and characterisation of temporal changes in DLD as well as identify acute abnormalities and complications. Both clinicians and radiologists should be aware of the role of HRCT in this context and the expected evolution of HRCT findings over time in a variety of DLDs.

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