Idiopathic Pulmonary Fibrosis: The Importance of Qualitative and Quantitative Phenotyping

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Summary

During the past decade, imaging has become of paramount importance in the diagnosis of patients with interstitial lung disorders. In addition, the quantification of radiographic features at the time of diagnosis gives important prognostic information and changes in these features over time may prove to be useful outcome variables in the study of new treatments and monitoring of patients' response to therapy. In this chapter, we review the classification of interstitial lung diseases focusing on the role of high-resolution computed tomography (HRCT), particularly as it pertains to the need for obtaining a surgical lung biopsy. We also discuss the role of baseline and longitudinal semi-quantitative and quantitative measurement of HRCT features in assessment of patients with idiopathic pulmonary fibrosis (IPF).

Classification of interstitial lung diseases

Interstitial lung diseases are a diverse group of disorders that involve the pulmonary parenchyma. In 2002, the American Thoracic Society and European Respiratory Society published an international consensus statement describing an approach to the classification of patients with interstitial lung diseases, also called diffuse parenchymal lung diseases (Fig. 1) (1). In this statement, patients were grouped into those with a known cause (drug exposure, connective tissue disease, etc.), granulomatous diseases (such as sarcoid), idiopathic interstitial pneumonias (IIPs) and a small group of others (such as pulmonary alveolar proteinosis, pulmonary langerhans cell histiocytosis/histiocytosis X, lymphangiomyomatosis and eosinophilic pneumonia). The IIPs were subdivided into IPF [also called cryptogenic organizing pneumonia (COP)], non-specific interstitial pneumonia (NSIP), respiratory bronchiolitis interstitial lung disease (RBILD), COP/ bronchiolitis obliterans organizing pneumonia, lymphocytic interstitial pneumonia, acute interstitial pneumonia and desquamative interstitial pneumonia. Of the IIPs, IPF is the most common and unfortunately has the worst prognosis (2–7) (Fig. 2).

## Approach to diagnosis for patients with suspected interstitial lung disease

The diagnosis of interstitial lung disease requires the integration of clinical information, radiographic findings and histopathologic patterns (1). For example, the diagnosis of IPF requires idiopathic disease and a histopathologic pattern on surgical lung biopsy of usual interstitial pneumonia (UIP). Histopathologic pattern alone is inadequate for diagnosis as the same histopathologic pattern, such as UIP, can be seen in patients with idiopathic disease (thus IPF) or patients with rheumatoid arthritis (thus confirming the diagnosis of rheumatoid lung). The most common exam findings are cough, progressive dyspnoea and fine basilar inspiratory crackles. These features are present in many ILDs and are not specific or helpful in separating diseases (8). Thus, the primary role of the clinical exam is to raise suspicion that ILD is present and to search for clues as to a potential cause (drugs, environmental exposures, connective tissue disease, etc.). A more detailed discussion of the clinical features, pulmonary function characteristics and histopathologic features is beyond the scope of this article but can be found in several recent reviews (6, 9, 10).

Role of HRCT is the diagnosis of IPF

Over the past decade, HRCT has become critical in the evaluation of patients with suspected ILD. In a diagnostic algorithm, HRCT sits between the clinical evaluation where the presence of ILD is raised and the ultimate decision of whether or not a biopsy is required. Interpretation of HRCT involves identifying features that are present and their distribution (Table 1). From there, a differential diagnosis can be assembled. For example, peripheral distribution is typical of IPF, NSIP and connective tissue disease related ILD while central disease is more suggestive of sarcoid. Similarly, IPF, NSIP and
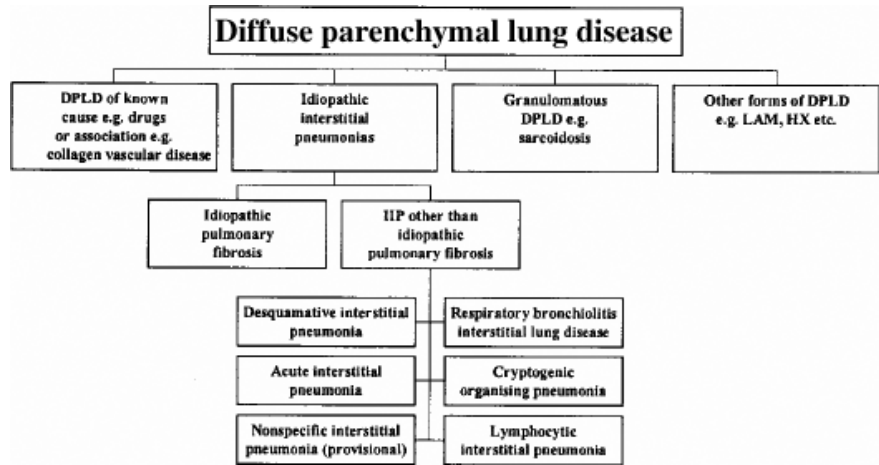
Fig. 1. Classification of diffuse parenchymal lung diseases [from (1) with permission].
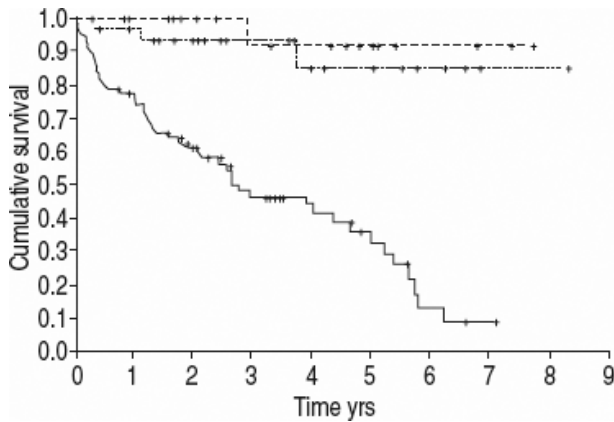
Fig. 2. Kaplan–Meier survival curves in patients with idiopathic pulmonary fibrosis (bottom curve solid line, N = 106), non-specific interstitial pneumonia (dotted line, N = 33) and respiratory bronchiolitis interstitial lung disease (dashed line, N = 22) grouped by diagnosis (P < 0.00001). [adapted from (4) with permission].

■ **Table 1:** Features and distribution of disease patterns on high-resolution computed tomography in patients with interstitial lung disease

Disease pattern	Distribution
Honeycombing	Craniocaudal
Reticulation	Upper
Ground glass opacity	Lower
Peribronchial thickening	Diffuse
Micronodules	
Consolidation	Axial
Mosaic attenuation	Central
Air trapping	Peripheral
Traction bronchiectasis	Diffuse
Emphysema	
Cysts	

connective tissue disease-related ILD are more common in the lower lung fields while sarcoid, pneumoconiosis, eosinophilic pneumonia and hypersensitivity pneumonia tend to be upper lobe predominant.

Within the IIPs, IPF is the most common, the most difficult to treat and associated with the worst prognosis. Idiopathic pulmonary fibrosis is more common with advanced age (11) and many patients have comorbid illness that increases the risk of a surgical lung biopsy. A key question in the evaluation of patients with suspected IPF is which patients actually need a surgical lung biopsy for diagnosis. Numerous studies have evaluated the role of HRCT for the diagnosis of IPF. A typical classification scheme that has been used in clinical trials for patients with IPF is highlighted in Table 2, Figs 3–5. It is clear that the identification of honeycomb change, in the absence of features that suggest an alternative diagnosis, is critical to a definite HRCT diagnosis of IPF. The importance of honeycomb change in establishing a diagnosis of IPF comes from several studies. Hunninghake evaluated 91 patients with suspected IPF. All patients underwent a surgical lung biopsy and 54 confirmed cases of IPF were identified. The presence of lower lobe honeycomb change was a significant predictor of IPF compared with an alternative diagnosis (odds ratio 5.36, 95% CI 1.58–18.22, $P = 0.007$) (12). The sensitivity was 74%, specificity 81%
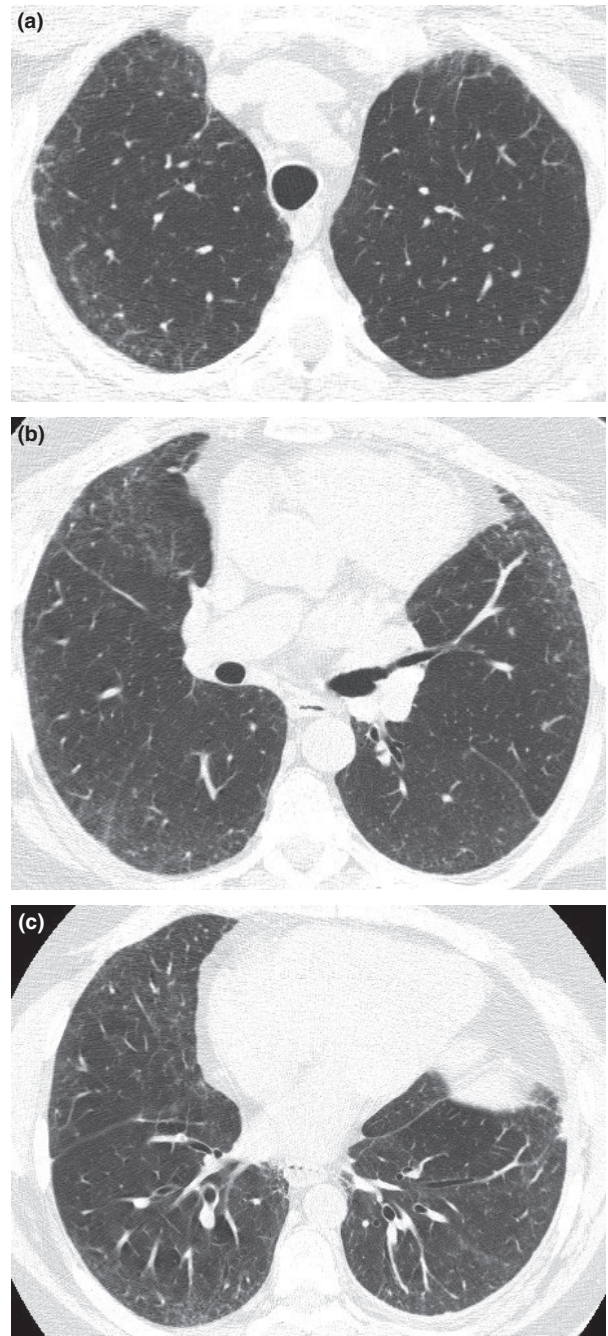
■ **Table 2:** High-resolution computed tomography diagnostic categories for usual interstitial pneumonia (UIP)

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| --- |
| Definite UIP |
| Subpleural, basal distribution |
| Honeycomb ± traction bronchiectasis |
| Reticular abnormalities |
| Traction bronchiectasis |
| Absence of features suggesting an alternative diagnosis |
| Consistent with UIP |
| Subpleural, basal distribution |
| Reticular abnormalities |
| Absence of features suggesting an alternative diagnosis |
| Suggestive of alternate diagnosis |
| Upper/mid/peribronchovascular distribution |
| Ground glass > reticular abnormality |
| Profuse micronodules |
| Discrete cysts away from areas of honeycombing |
| Diffuse air trapping/mosaic attenuation |
| Areas of consolidation |
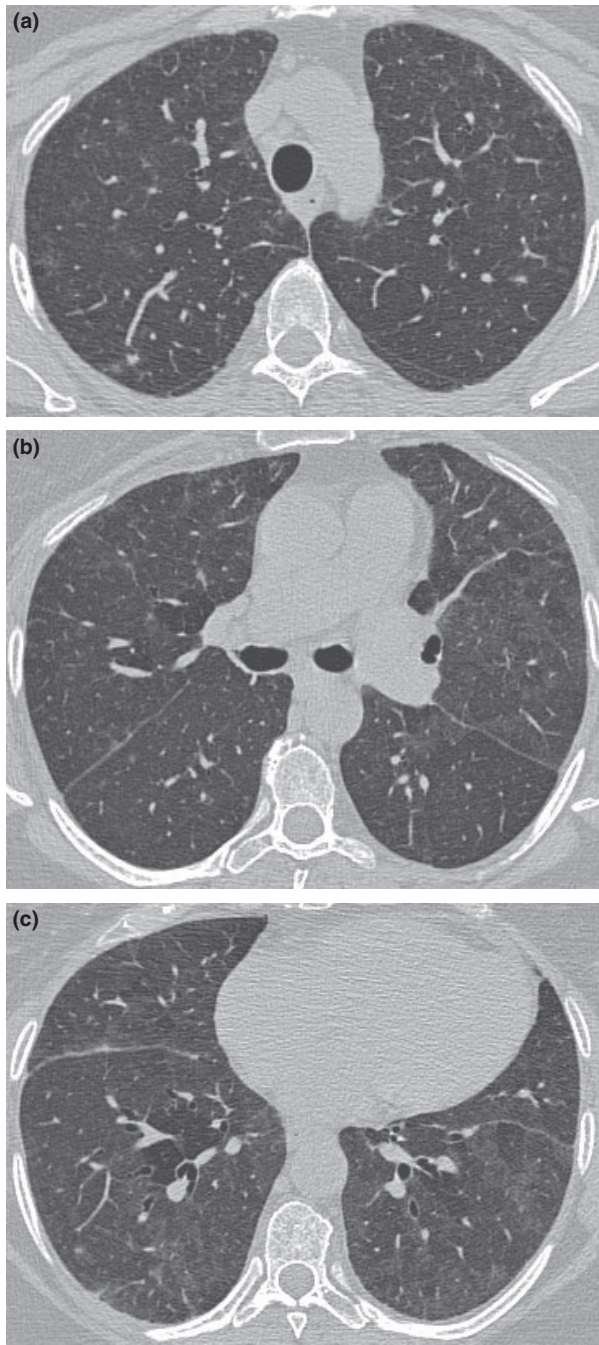
■ **Fig. 3.** High-resolution computed tomography (HRCT) images from a 68-year-old male with hypersensitivity pneumonia. The HRCT demonstrates diffuse ground glass attenuation with air-trapping (mosaic attenuation). Hazy ground glass nodules are present in the upper lobes. There is no significant reticulation or honeycombing. This CT is typical of hypersensitivity pneumonia and from Table 2 would be classified as suggesting an alternative diagnosis from idiopathic pulmonary fibrosis.

and positive predictive value 85%. Similarly we evaluated a cohort of 168 patients with biopsy confirmed IPF, NSIP and RBILD. The presence of honeycomb change in at least one lobe predicted UIP/IPF with a sensitivity of 90%, specificity of 86% and positive predictive value of 85% (4).

■ **Fig. 4.** (a–c) High-resolution computed tomography from a 49-year-old male. The study would be consistent with idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP) demonstrating reticulation in a peripheral and lower lobe distribution. The study is not definite for IPF/UIP as there is no honeycombing. At biopsy the pathology demonstrated UIP.

Other studies in varied clinical settings have found similar results. Raghu and colleagues evaluated 59 patients referred with new onset ILD. The HRCT diagnosis of IPF, using biopsy as a gold standard, was made with a sensitivity of 78% and specificity of 90% (13). Within the IIPs, the HRCT features of IPF and NSIP are the most similar with the primary difference being the absence of
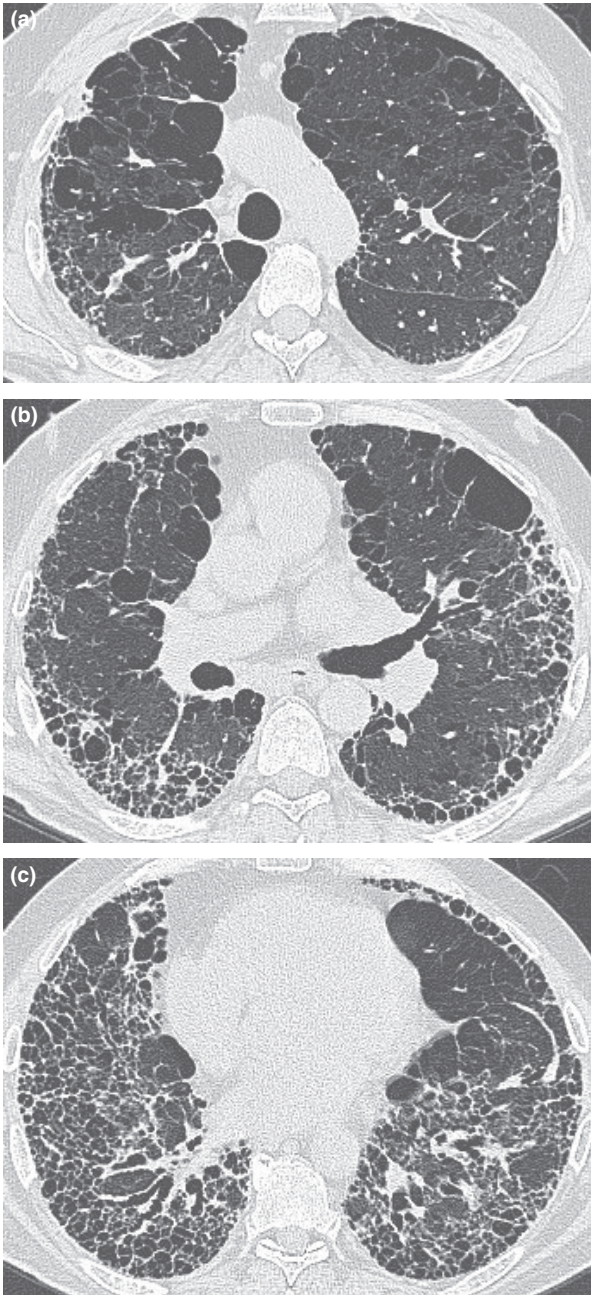
■ **Fig. 5.** (a–c) High-resolution computed tomography from a 68-year-old male demonstrating features of definite idiopathic pulmonary fibrosis/usual interstitial pneumonia. Honeycombing is present in a peripheral and lower lobe distribution. There is no significant ground glass attenuation or other features such as nodules to lead to the potential of an alternative diagnosis. Emphysema is present in the upper lobes consistent with the patients 40 pack year history of smoking.

honeycombing in NSIP (14). It is also important to highlight that many patients with IPF also lack honeycombing (15) and require a surgical lung biopsy for diagnosis. This was highlighted by Flaherty and colleagues in their examination of 96 patients with IPF/UIP or NSIP as defined by biopsy. Overall 73 patients had IPF/UIP although the diagnosis could only be made by HRCT

(using criteria similar to those found in Table 2) in 27 cases correlating to a sensitivity of only 37% (15). On the other hand, no cases of NSIP were called IPF/UIP by HRCT leading to a specificity and positive predictive value of 100% (Fig. 6). Similar data were seen by Sumikawa et al., where a HRCT pattern of definite IPF/UIP was present in only 33/98 (34%) of biopsy proven IPF/UIP cases and 29/98 (30%) had a HRCT felt to represent NSIP (16). These data highlight that HRCT findings of definite IPF/UIP have excellent correlation with surgical pathology and thus these patients do not require a biopsy for diagnosis. Furthermore, many patients with biopsy proven IPF/UIP do not have definite HRCT features and thus require a biopsy for diagnosis.

Role of HRCT in predicting prognosis and response to therapy

Patients with a definite diagnosis of IPF/UIP by HRCT have a shorter survival compared with other IPF/UIP patients. In the study by Flaherty and colleagues, the patients with a HRCT diagnosis of IPF/UIP had a median survival of 2.08 years compared with a median survival of 5.76 years for IPF/UIP patients who lacked honeycombing and had HRCT diagnoses of either indeterminate or NSIP (15). Sumikawa found similar results in that IPF/UIP patients with a definite HRCT study had a median survival of 35 months compared with 112 months when NSIP was suspected (16). Gay and colleagues also found a worse survival in IPF/UIP patients that had honeycombing compared with those that did not (17). The reason for the differential survival is unknown but could relate to lead-time bias and more established disease in patients with honeycomb change.

It is also possible that HRCT features could predict response to therapy. Early studies by Wells and colleagues highlighted that ground glass was more likely to resolve following steroid therapy compared with reticular change (18). Some of these patients may have had NSIP. In a more recent study, King and colleagues reported the results of a placebo controlled trial of bosentan for patients with IPF. The primary outcome (change in 6-min walk distance) was negative. Interestingly, in a *post hoc* analysis, patients that underwent a surgical lung biopsy were less likely to meet a
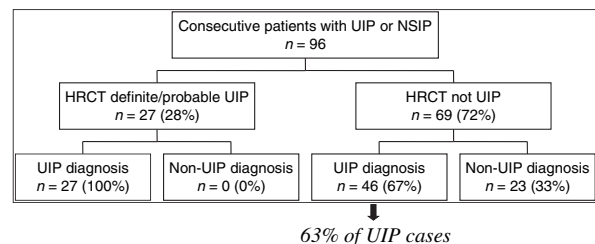
■ **Fig. 6.** Diagnosis of idiopathic pulmonary fibrosis/usual interstitial pneumonia or NSIP by high-resolution computed tomography and surgical lung biopsy [adapted from (15)].

composite endpoint of death or progression of disease by pulmonary function (HR 0.315, 95% CI 0.126–0.789, $P = 0.009$) (19). It is likely that the patients undergoing biopsy were patients without honeycomb change on HRCT. Although not conclusive these data are intriguing in that HRCT features could potentially be able to aid in the identification of patients likely to respond to treatment.

Role of quantitative HRCT analysis

The course of IPF is characterized by progressive fibrosis of the lung parenchyma leading to increased disability and eventual death. There is no cure for IPF. Mortality can be argued as the most important and easily definable endpoint for clinical trials of novel therapeutic agents. Unfortunately, the size, duration and cost of mortality-powered trials are prohibitive. As an example, a recent Industry sponsored trial for patients with IPF that used mortality as an endpoint required 81 centres in Europe, Canada and North America to enrol 826 patients. Even with this large number of sites accrual took 28 months (20). The difficulties with mortality powered trials have led investigators to actively pursue identification of surrogate endpoints that can be easily measured and predict future mortality.

We and others have demonstrated that 6- and 12-month decline in forced vital capacity (FVC) of ≥10% is associated with an increased risk of subsequent mortality (21–24). Although the best current surrogate marker for subsequent mortality, decline in FVC is unable to correctly predict mortality in all patients as many patients die acutely prior to demonstrating a decline in FVC (25) while others can survive for extended periods of time despite large losses of lung function (26).

As highlighted above, baseline HRCT features are predictive of prognosis in retrospective series. Unfortunately, change in HRCT features on long-term prognosis for patients with IPF has received little attention. Available series involve small numbers of patients with variable length of follow-up and different scoring methodology. In general, progression has been suggested in areas of ground glass opacification (GGO), irregular linear opacities and honeycombing (27) (28), with the latter loosely associated with survival (29). A recently published trial comparing pirfenidone with placebo noted that 15% (10/65) of patients on pirfenidone had 'improved patterns of the HRCT images' compared with 7% (2/29) of patients treated with placebo, $P = 0.092$ between baseline and 6 months of follow-up (30). Methodology for classifying HRCT scans was not detailed.

Computer-derived indexes, such as mean lung attenuation, skewness and kurtosis can be obtained from frequency histograms of HRCT scans of the lung. Mean lung attenuation represents the average global attenuation value of the lung and reflects the relative proportions of air and soft tissue in a given image pixel. Skewness describes the degree of asymmetry of a histogram; a histogram with a long tail to the right has a positive skewness, and a perfectly symmetric distribution has a value of zero. Kurtosis describes how sharply peaked a histogram is; a histogram that is more peaked than a normal distribution has a positive kurtosis. A normal distribution has a kurtosis of zero.

Recently investigators demonstrated that measures of HRCT densitometry, compared with semi-quantitative visual scoring, had better inter-rater agreement and better correlation with pulmonary function (31). Good correlation has also been reported between baseline HRCT data and pulmonary function from 144 subjects enrolled in the placebo arm of a controlled trial evaluating interferon beta 1a for the treatment of IPF at 30 centres (32). Thus, computer-aided analyses may have better agreement in scoring and may have better correlation with functional parameters compared with visual assessment. Furthermore, quantitative measures that correlate with pulmonary function can be obtained from CT data obtained from multiple centres.

The Adaptive Multiple Feature Method (AMFM) is a texture-based computer assisted method capable of characterizing parenchymal patterns in reconstructed CT data sets (33, 34). A potential advantage of this method is the utilization of all the data that are acquired during CT scan as opposed to only using the data visually appreciated on images. This approach has also been shown to be better than simple density based measures for recognition of normal, emphysema, sarcoidosis and IPF (34, 35). Initial applications of the AMFM used 2D analysis. The emergence of multidetector row CT now allows for the ability to obtain high quality volumetric images of the lung during a single breath hold. Utilization of 3D analysis is likely to improve accuracy over 2D analysis as the lung is a complex 3D structure. An example is the difficulty in distinguishing a honeycomb cyst from traction bronchiectasis on a single 2D image. It is much easier to distinguish these features on a volumetric dataset that allows scrolling up and down to identify if the structure seen on a single image is a cyst (honeycomb) or a tube (bronchiectasis) cut in cross section. Recent data from the University of Iowa evaluated the ability of 3D AMFM to recognize patterns of emphysema, GGO, honeycombing, normal smokers and normal non-smokers in 20 subjects. Using Bayesian classifying methodology, the sensitivity for detecting honeycombing was 93% with 99% specificity (36). This is significantly improved compared with 2D AMFM.

It is clear that technology is evolving to allow for the quantitative scoring of HRCT features. Further study is required to better define the potential role in the care of patients as well as for potential use as outcome variables in clinical trials of novel therapy.

Conclusion

High-resolution computed tomography has assumed a critical role in the evaluation of patients with suspected

ILD, especially IPF. In some patients, HRCT is diagnostic and can supplant the need for a surgical lung biopsy. Qualitative analysis of features, such as honeycombing, can provide prognostic information and may give insight on the probability of response to therapy. Computer-aided techniques that can recognize and quantify HRCT features are being developed. It is possible that these techniques may be able to detect changes that have clinical implications and aid in the management and study of patients with ILD.

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