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Diagnosing fibrotic lung disease: When is high-resolution computed tomography sufficient to make a diagnosis of idiopathic pulmonary fibrosis?

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF), a progressive and fatal diffuse parenchymal lung disease, is defined pathologically by the pattern of usual interstitial pneumonia (UIP). Unfortunately, a surgical lung biopsy cannot be performed in all patients due to comorbidities that may significantly increase the morbidity and mortality of the procedure. High-resolution computed tomography (HRCT) has been put forth as a surrogate to recognize pathological UIP. The quality of the HRCT impacts the ability to make a diagnosis of UIP and varies based on the centre performing the study and patient factors. The evaluation of the HRCT includes assessing the distribution and predominance of key radiographical findings, such as honeycomb, septal thickening, traction bronchiectasis and ground glass attenuation lesions. The combination of the pattern and distribution is what leads to a diagnosis and associated confidence level. HRCT features of definite UIP (subpleural, basal predominant honeycomb with septal thickening, traction bronchiectasis and ground glass attenuation lesions) have a high specificity for the UIP pathological pattern. In such cases, surgical lung biopsy can be avoided. There are caveats to using the HRCT to diagnose IPF in isolation as a variety of chronic pulmonary interstitial diseases may progress to a UIP pattern. Referral centres with experience in diffuse parenchymal lung disease that have multidisciplinary teams encompassing clinicians, radiologists and pathologists have the highest level of agreement in diagnosing IPF.

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal diffuse parenchymal lung disease with unclear pathophysiology and no clear consensus on treatment. The incidence of IPF has been reported as 6–42 per 100 000 persons but increases with age to more than 200 per 100 000 persons in those older than age 75 years.[1–4] The median survival for IPF is poor, between 2–3 years. From an American Thoracic Society/European Respiratory Society (ATS/ERS) consensus statement on the idiopathic interstitial pneumonias (IIP), IPF is definitively diagnosed when lung pathology shows a usual interstitial pneumonia (UIP) pattern in the absence of a plausible aetiology.[1] Several studies have shown that in a prescribed clinical setting, high-resolution computed tomography (HRCT) of the chest with certain features can be used as a surrogate to recognize the pathological pattern of UIP with high degrees of confidence. This is attractive given the possibility of acute exacerbations and high 30-day mortality following lung biopsy in patients with resting hypoxemia, pulmonary hypertension, immune-suppression or suffering an acute deterioration.[5–7] Because UIP can be found with many diffuse parenchymal lung diseases, such as hypersensitivity pneumonitis, collagen vascular disease, occupational exposures etc., a careful multidisciplinary approach to exclude these is essential to yielding an accurate diagnosis of IPF.

DEFINITION OF HIGH-RESOLUTION COMPUTED TOMOGRAPHY

The ability to make a diagnosis of UIP in part depends on the quality of the HRCT examination. Unfortunately, there are significant differences in HRCT

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Table 1 American College of Radiology practice guideline for performing a high-resolution computed tomography examination[8]

No i.v. iodinated contrast material
High-spatial-frequency reconstruction algorithm
Slice thickness
≤2 mm for non-helical CT
≤1.5 mm for helical CT
Patient positioning
Supine
Prone
Respiration
End inspiration
End expiration
Gantry rotation time ≤1 second

Table 2 Diagnostic categories and high-resolution computed tomography (HRCT) features

Definite usual interstitial pneumonia
Subpleural, basal distribution
Predominant honeycomb
Interlobular septal thickening
Traction bronchiectasis
No predominant ground glass attenuation
Consistent with usual interstitial pneumonia
Subpleural, basal distribution
Minimal or equivocal honeycomb
Interlobular septal thickening
Traction bronchiectasis
No predominant ground glass attenuation
Suggestive of alternate diagnosis
No honeycomb
With one or more of the following as the predominant HRCT finding:
Upper or mid lung distribution
Peribronchovascular distribution
Ground glass attenuation
Micronodules
Discrete cysts
Air trapping
Consolidation

technique as each institution that performs HRCT scans defines its own technique. Therefore, the quality and the utility of a particular HRCT scan may be subjective. Understanding the capability of local imaging centres may help to reduce or avoid unnecessary repeat HRCT scans and radiation exposure. CT technology has changed rapidly through the years and with that, expert opinion as to what constitutes a satisfactory quality HRCT scan. Table 1 highlights the current American College of Radiology recommendations for the performance of a HRCT scan.[8]

HRCT should be performed without i.v. iodinated contrast material so as to prevent lung parenchymal enhancement that may confuse ground glass attenuation (GGA) lesions with normal lung tissue, especially if situated adjacent to areas of structural abnormality, such as emphysema and atelectasis. Reconstructing HRCT images with a high-spatial-frequency algorithm (bone algorithm) enhances the sharpness of lung structural abnormalities by increasing the contrast between adjacent structures that have only minor attenuation differences. Traditionally, HRCT has been performed in an incremental fashion that limited sampling to a series of 1- to 2-mm thin sections separated every 10 or 15 mm, excluding 90% or more of the lung parenchyma. Current HRCT using multi-detector helical scanners can provide a volumetric dataset with narrow slice thickness images of the entire lungs obtained during a single breath hold. Contiguous HRCT images make it feasible to confidently distinguish honeycomb and lung cysts from traction bronchiectasis, as well as lung nodules from vascular structures or mucus impaction in small airways.

Ideally, HRCT of the lungs should include supine end-inspiratory, supine end-expiratory and prone end-inspiratory images. Prone HRCT images may help to evaluate for early UIP changes at the posterior lung bases, which may be either mimicked or obscured by atelectasis on supine images. End-expiratory images may reveal air trapping seen in patients with hypersensitivity pneumonitis. To reduce a patient's radiation dose, expiratory and prone scanning may be performed in an incremental fashion.

Patient characteristics may also affect HRCT image quality and must be taken into account before scanning. An acutely ill, tachypneic patient may have significant respiratory motion artefact interfering with the illustration of the lung pathology. Patients may not be able to lie prone for scanning due to their dyspnea. Pulmonary oedema enhances interlobular septal thickening and generates GGA that can simulate alveolitis. Morbid obesity can reduce HRCT scan signal-to-noise ratio to the extent of obscuring subtle changes of interstitial lung disease.

Radiation dose is a concern for volumetric HRCT scans and is variable based on patient factors, type of CT scanner, scan parameters and HRCT protocol. The radiation dose has a linear relationship with CT scanner tube current. Radiation dose reduction is achieved by adjusting tube current; however, lowering tube current will decrease signal-to-noise ratio.[9,10] Hence, it is important to obtain diagnostic quality HRCT images using as low as reasonably achievable (ALARA principle) radiation dose. At our institution, radiation dose for the current volumetric HRCT technique is approximately 13 versus 9 mSv for an incremental HRCT. For reference, the radiation dose for the current two view digital chest radiography examination is 0.05 mSv.

RADIOGRAPHICAL EVALUATION OF IDIOPATHIC PULMONARY FIBROSIS

The approach to evaluating the HRCT images relies on evaluation of the predominant findings and their distribution (Table 2). A level of radiographical confidence in diagnosing UIP can then be applied. The findings most often associated with UIP include

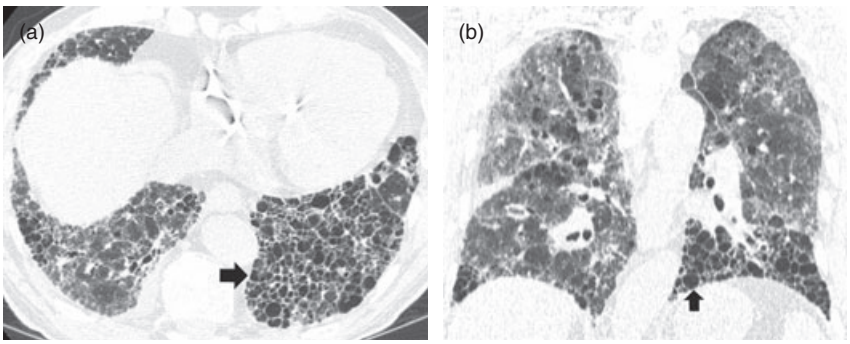

Figure 1 Definite usual interstitial pneumonia. A 92-year-old man with progressive dyspnea on exertion. Axial high-resolution computed tomography image (a) acquired at the lung base reveals extensive honeycomb (arrow). Coronal reformatted image (b) illustrates the peripheral subpleural and lower lung dominant distribution of honeycomb.

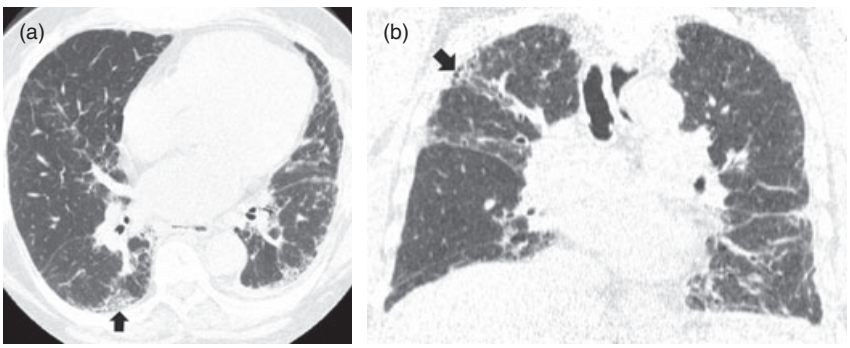

Figure 2 Consistent with usual interstitial pneumonia. A 74-year-old man with dyspnea on exertion and progressive cough. Axial high-resolution computed tomography image (a) acquired at the lung base reveals patchy, minor, focal honeycomb (arrow). Coronal reformatted image (b) illustrates the peripheral and patch distribution along with interlobular septal thickening.

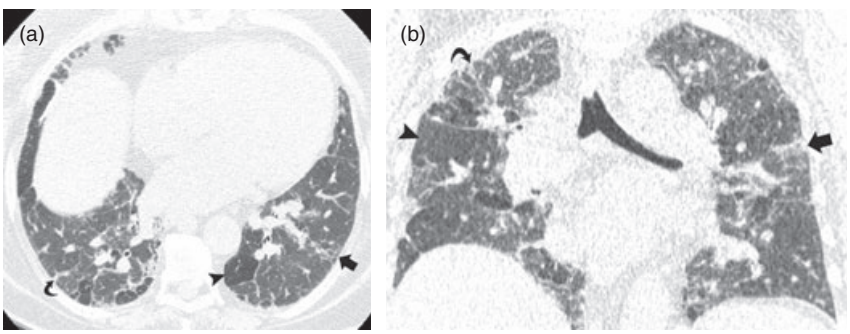

Figure 3 Suggestive of alternate diagnosis. A 72-year-old woman with limited exertional capacity due to worsening breathlessness. Axial high-resolution computed tomography image (a) acquired at the lung base reveals patch subpleural reticulation (arrow), irregular interlobular septal thickening (curved arrow) and areas of lobular sparing (arrow head). Coronal reformatted image (b) reveals diffuse and patch distribution. The appearances suggest possible non-specific interstitial pneumonitis or chronic hypersensitivity pneumonitis.

honeycomb, traction bronchiectasis, irregular interlobular septal thickening and GGA. The distribution is typically basal and peripheral.

In our institution, we interpret HRCT studies of patients suspected to have IPF as definite UIP, consistent with UIP or suggestive of alternate diagnosis (Figs. 1–3). Categories listed in Table 2 have been used in clinical trials for patients with IPF; however, prospective validation of their impact on prognosis or response to treatment are lacking. A HRCT diagnosis of definite UIP is defined as a peripheral and basal distribution of honeycomb with traction bronchiectasis, irregular interlobular septal thickening and minimal GGA. Honeycomb is a prerequisite for definite UIP diagnosis. In a study of 54 biopsy-proven UIP patients, the hazard ratios for basal honeycomb and upper lobe interlobular septal thickening were 5.4 and 6.3, respectively.[11] Honeycomb in at least one lobe was found to indicate UIP with a 90% sensitivity and 86% specificity in 106 patients with biopsy-proven UIP.[12]

To achieve a HRCT diagnosis of consistent with UIP, there may be questionable, scant or patchy honeycomb, with traction bronchiectasis and irregular interlobular septal thickening in a peripheral distribution. Features such as absent honeycomb, prominent GGA, nodules, cysts, mosaicism and/or if the distribution is uncharacteristic, such as upper lobe predominance, classify the HRCT as suggestive of alternate diagnosis.

EVIDENCE FOR DIAGNOSING IDIOPATHIC PULMONARY FIBROSIS BY HIGH-RESOLUTION COMPUTED TOMOGRAPHY

Numerous studies have evaluated the agreement between the clinical/radiographical diagnosis and the final diagnosis reached after including histopathological information. The types of patients included in these studies as well as the clinical settings vary. Raghu and colleagues prospectively evaluated 59 sequential patients referred to a tertiary care centre with new onset interstitial lung disease.[13] The cases were reviewed by a single clinician, radiologist and pathologist independently with the pathological interpretation used as the gold standard for diagnosis. The sensitivities for making a correct clinical and HRCT diagnosis of IPF were 62% and 78.5%, respectively. However, the specificities were respectively 97% and 90%. In a subsequent study, Flaherty *et al.* examined 96 patients with either UIP or nonspecific interstitial pneumonitis (NSIP) based on surgical lung biopsy results. The HRCT interpretation of definite UIP had 100% specificity, although the sensitivity was low at 37%.[14] In an even more restrictive study, Sumikawa *et al.* evaluated the HRCT characteristics of 98 patients with pathologically proven UIP. A HRCT pattern of definite UIP was seen in only 33 cases (34%). Twenty-nine cases (30%) had a HRCT suggestive of an alternate diagnosis, namely NSIP.[15] These studies substantiate that HRCT can be used to diagnose UIP; however, the sensitivity to detect all cases of UIP is low.

HRCT studies that are interpreted as UIP with a high level of confidence are more likely to be concordant with UIP on histopathology. In a blinded prospective evaluation of 91 patients with proven UIP on surgical lung biopsy, Hunninghake *et al.* found the specificity of a confident HRCT diagnosis of UIP was 95% (21/22 cases). A core of experienced pulmonologists reached a confident UIP/IPF diagnosis with an 87% positive predictive value and a core of radiologists had a 96% positive predictive value.[16] In a subsequent study investigators undertook a blinded review of 176 HRCT studies from patients enrolled in the Idiopathic Pulmonary Fibrosis International Group Exploring N-Acetylcysteine I Annual trial[17] and rendered three categories of diagnoses (unlikely, probable or very suggestive of UIP). These diagnoses represented 12.6%, 38.2% and 48.5% of HRCT scans, respectively.[18] The lung biopsy specimens were positive for UIP in 84.4% of those deemed probable UIP and 91.7% of those with the diagnosis of very suggestive of UIP. These data corroborate that the level of confidence in HRCT diagnosis correlates with pathological diagnosis.

HRCT appearance may also aid in determination of prognosis. In the series by Flaherty *et al.*, HRCT appearance of definite UIP was associated with a median survival of 2.08 years. In contrast, UIP patients where the HRCT was indeterminate or suggestive of an alternate diagnosis, namely NSIP, median survival increased to 5.76 years.[14] These findings are similar to the Sumikawa study where median survival was worse for patients with HRCT diagnosis of definite UIP (34.8 months), compared with patients with HRCT appearance suggestive of alternate diagnosis (112 months), although the results were not statistically significant.[15] Quantitative HRCT scoring of traction bronchiectasis and fibrosis was associated with mortality.

In aggregate, these studies highlight that HRCT has a high specificity for diagnosing UIP as verified by pathology, especially in the setting of a high-confidence interpretation. However, HRCT cannot rule out UIP, regardless of the confidence. Therefore, if the HRCT interpretation is other than definite UIP, surgical lung biopsy would be warranted to establish the diagnosis if the patient's clinical condition permits.

INTER-OBSERVER EXPERIENCE AND AGREEMENT

Numerous studies have evaluated the inter-observer agreement for diagnosing UIP by HRCT. [16,18–20] They demonstrate moderate levels of kappa (agreement beyond chance alone) that range from 0.40 to 0.55. There was less agreement between community-based versus academic-based radiologists (kappa 0.11–0.34).[20] Community-based physicians were more likely to assign a diagnosis of UIP/IPF compared with academic-based physicians.[20] The reason for the differences in interpretation between community- and academic-based radiologists is unclear. In either setting, use of a multidisciplinary approach involving a group of clinicians, radiologists and pathologists improved agreement.[20,21]

CAVEATS TO USING HIGH-RESOLUTION COMPUTED TOMOGRAPHY AS A SURROGATE

While all IPF by definition has UIP as its pathological correlate, not all UIP is IPF. Several diffuse parenchymal lung diseases can eventually lead to a UIP pattern on pathology. Clinical studies that evaluate the diagnostic process for IPF typically exclude patients known to have connective tissue disease or an occupational, environmental or medication exposure known to cause fibrosis. The capability of HRCT to unravel the original aetiology for the UIP pattern is unknown. Therefore, a comprehensive evaluation, including clinical history, physical, laboratory data and possibly bronchoscopy, is necessary to ensure that the patient's disease process is truly idiopathic. In some cases, the aetiology of a UIP appearance on HRCT may never be elucidated, such as in chronic hypersensitivity pneumonitis with an unknown antigenic exposure.[22] This process may be even more difficult to achieve with concomitant emphysema, which has been shown to confound the ability of thoracic radiologists to make a confident diagnosis of UIP.[23]

Applying the practices used in the aforementioned clinical trials may be difficult in a community health practice setting that lacks access to a specialist interpretation of HRCT images. Consistent and expert HRCT interpretation may be difficult to achieve in non-specialized centres due to a lower prevalence of diffuse parenchymal lung disease than in a referral population. The potential impact of the presence of a dedicated thoracic radiologist is highlighted by a recent survey of pulmonologists in the UK.[24] When queried about their management of diffuse parenchymal lung disease, 14% had no access to a thoracic radiologist. Half as many respondents in specialized cardiothoracic centres would recommend surgical lung biopsy in comparison with general hospital pulmonologists given the same clinical scenario. This discrepancy was thought to be due to the specialized imaging and radiologists available at the referral centres.

A MULTIDISCIPLINARY APPROACH

Given the moderate levels of inter-observer agreement between physicians and the caveats mentioned, an interactive multidisciplinary approach improves diagnostic certainty and confidence in regards to the IIPs and IPF. While HRCT features can accurately reflect a pathological diagnosis of UIP in some cases, arriving at a diagnosis of IPF is best supported by a team approach as outlined by the ATS/ERS consensus statement on IIP.[1]

For example, a study was conducted evaluating an interactive multidisciplinary process encompassing clinicians, radiologists and pathologists reviewing 58 consecutive cases of IIP.[21] The process involved each physician evaluating the cases alone, and finally in a process similar to a tumour board where all parties reviewed the information together. The consensus diagnosis often differed from the individual clinician, radiologist or pathologist. Inter-observer agreement improved from $\kappa = 0.39$ to $\kappa = 0.88$ as did diagnostic confidence. Although histopathological diagnosis had the greatest impact on final diagnosis, pathologists did consider data such as a history consistent with hypersensitivity pneumonitis or collagen vascular disease in determining a final diagnosis.[20,21] Inter-observer agreement improved among the multidisciplinary team when the pathologist took the clinical information into account.

CONCLUSIONS

HRCT can be used as a surrogate to identify the histopathological pattern of UIP under the appropriate conditions. Given the appropriate clinical scenario, this can yield a confident correct diagnosis of IPF. A consistent approach should be used to interpret HRCT for features consistent with UIP and to assign a level of confidence. A HRCT diagnosis of definite UIP is sufficient to preclude the need for lung biopsy. Biopsy would be required in other settings due to the low sensitivity of HRCT for UIP. A thorough evaluation and multidisciplinary approach with active discussion between clinicians, radiologists and pathologists can provide a high level of agreement for a diagnosis of IPF.

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