



PILOT™ MISSION STATEMENT

PILOT™ is a national education initiative designed to provide physicians with a comprehensive continuing medical education program that focuses on the early and accurate diagnosis of idiopathic pulmonary fibrosis (IPF), while addressing educational objectives critical to optimizing disease intervention and management.



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IDIOPATHIC INTERSTITIAL PNEUMONIA TO BIOPSY OR NOT TO BIOPSY: EMERGING INSIGHTS REGARDING AN AGE-OLD DILEMMA

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Idiopathic interstitial pneumonias (IIP) are a group of acute and chronic interstitial lung diseases with unknown etiology.¹ Of the IIPs, idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP) occur more frequently than cryptogenic organizing pneumonia, respiratory bronchiolitis interstitial lung disease, desquamative interstitial pneumonia, acute interstitial pneumonitis, and lymphocytic interstitial pneumonia. Assigning an accurate diagnosis is critical given the varied prognoses²⁻⁹ and treatment options. The "gold standard" for diagnosing an IIP involves an interaction between the clinician, radiologist, and pathologist;^{1,10} however, not all patients may require a surgical lung biopsy to establish a diagnosis. This article discusses recent data highlighting the role of high resolution computed tomography (HRCT) and surgical lung biopsy (SLB) in the diagnosis of IIP, particularly in the identification of IPF.

General diagnostic approach

The signs and symptoms of patients with IIP are non-distinct. Most patients present with a history of dyspnea, cough, and restrictive pulmonary physiology. The clinical evaluation is critical in confirming that there are not features (drug/environmental exposures, systemic illnesses, etc.) which could account for the patient's pulmonary disease and remove them from the realm of IIP. Similarly, physiologic testing supports the suspicion of IIP when restrictive physiology and impaired gas exchange are present. At this point in the

evaluation radiographic studies assume paramount importance. Although a chest radiograph can confirm the presence of interstitial infiltrates, it lacks the sensitivity and specificity of HRCT. It is with HRCT that the pulmonologist, along with a thoracic radiologist, further refine the differential diagnosis and ultimately make a decision regarding the need for a surgical lung biopsy.

Importance of confirming the presence of idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis is a distinctive type of chronic fibrosing interstitial pneumonia of unknown cause limited to the lungs and associated with a surgical lung biopsy showing

a histopathologic pattern of usual interstitial pneumonia (UIP).¹ Patients with IPF have the greatest risk of mortality with a median survival of 2 to 6 years.²⁻⁹ Baseline features such as the presence of honeycombing on HRCT may be correlated with survival.¹¹ There is no treatment with proven efficacy for IPF,¹² although as the pathogenesis of this disease is unraveled, exciting potential therapies are being investigated.¹³ The lack of effective treatment, the grave prognosis, and the potential for enrollment into clinical trials highlight the importance of an accurate diagnosis of IPF.

Role of HRCT in the diagnosis of IPF

High resolution computed tomography uses thin collimation, 1–2 mm, to obtain resolute images of the lung. Conventional computed tomography, with collimation typically around 10 mm, lacks adequate resolution to reliably identify and classify patients with interstitial lung disease. The HRCT features of IPF are described in Table 1.¹² Similarly, it is possible to assemble a list of clinical and radiographic features that predict the presence of IPF in the absence of a surgical lung biopsy with a high degree of confidence (Table 2).

Several studies have addressed the ability of HRCT to predict IPF/UIP confirmed by surgical lung biopsy (Table 3).^{11,14,15} In general, the presence of consistent clinical and radiographic features is associated with a high positive predictive value. However, the absence of such features does not necessarily preclude a diagnosis

**TABLE 1.
HRCT FEATURES OF IPF¹²**

Features suggestive of IPF
Distribution of disease in a lower-lobe, subpleural pattern
Reticular abnormalities with honeycombing
Ground-glass opacities are not a major feature
Traction bronchiectasis
Mild lymph node enlargement
Features suggestive of a diagnosis other than IPF
Pleural thickening/effusion
Predominance of ground glass opacities
Significant mediastinal/hilar lymph node enlargement
Central lobular nodules and cysts

HRCT = high resolution computed tomography; IPF = idiopathic pulmonary fibrosis

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TABLE 2.
ATS/ERS CRITERIA FOR THE DIAGNOSIS OF
IPF IN THE ABSENCE OF A SURGICAL LUNG BIOPSY¹²

Major Criteria

Exclusion of other known causes of interstitial lung disease such as drug toxicities, environmental exposures, and connective tissue diseases

Abnormal pulmonary function studies that include evidence of restriction and impaired gas exchange

Bibasilar reticular abnormalities with minimal ground-glass opacities on HRCT

Transbronchial lung biopsy or bronchoalveolar lavage showing no features to support an alternative diagnosis

Minor Criteria

- Age > 50 years
- Insidious onset of otherwise unexplained dyspnea on exertion
- Duration of illness > 3 months
- Bibasilar, inspiratory crackles (dry or "Velcro" type in quality)

ATS = American Thoracic Society; ERS = European Respiratory Society;
IPF = idiopathic pulmonary fibrosis; HRCT = high resolution computed tomography

IPF/UIP. Furthermore, although an HRCT may suggest the diagnosis of a non-IPF IIP, SLB is required to confirm an alternative diagnosis.

Raghu et al evaluated the role of a clinical/HRCT IPF/UIP diagnosis compared with SLB findings in 59 cases of new onset interstitial lung disease.¹⁵ A minority of cases (19/59, 32%) met clinical/radiographic criteria for IPF; a diagnosis of IPF/UIP was confirmed in 18/19 (95%). Alternatively, the majority of cases (40/59, 68%)

were not believed to be consistent with IPF/UIP. In these cases, 11/40 (28%) were diagnosed with IPF/UIP on the basis of pathologic findings. Overall, 38% of the cases displayed non-diagnostic clinical/radiographic characteristics for IPF. Similarly, Hunninghake et al evaluated 91 cases of suspected IPF from 8 tertiary referral centers; 46 (51%) cases met the criteria for a confident clinical/radiographic diagnosis of IPF. Of these cases, 37/46 (80%) were confirmed by SLB. Of the 45/91 (49%) cases without a confident

clinical/radiographic diagnosis of IPF, 17/45 (31%) were identified as IPF/UIP at SLB. Overall, 31% of the cases did not display diagnostic clinical/radiographic characteristics of IPF.

Of the IIPs, UIP and NSIP occur more frequently and they are the most difficult to separate clinically, radiographically, and histopathologically. Flaherty et al evaluated the ability of HRCT characteristics to identify histopathologically confirmed cases of UIP or NSIP in 96 consecutive cases.¹¹ A minority of cases (27/96, 28%) had HRCT results that were felt to be diagnostic of IPF/UIP; all 27 were confirmed by SLB. Interestingly, the majority of cases not felt to be diagnostic of IPF/UIP (46/69, 67%) were confirmed as IPF/UIP by SLB. Only a minority (23/69, 33%) of the cases felt to be NSIP by HRCT were confirmed by SLB. This study¹¹ and others¹⁶ highlight the difficulty of using clinical/HRCT criteria to make a diagnosis of NSIP, and suggest that a clinical/radiologic diagnosis of NSIP should prompt the clinician to consider obtaining a surgical lung biopsy to rule out the presence of UIP.

Role of Surgical Lung Biopsy in the Diagnosis of IIP

Surgical lung biopsy is required to confirm the diagnosis of non-IPF IIP; however, use of SLB findings is not without difficulty. Histopathologic classification of IIP is difficult, particularly the separation of IPF/UIP from NSIP.¹⁷ The utility of SLB is further complicated because individual patients may display features of both IPF/UIP and NSIP in different lung biopsy specimens. Flaherty et al evaluated 109 patients with suspected IIP that had an SLB obtained from more than one lobe. Of these patients, 28 (26%) had a pattern of UIP in one lobe and NSIP in another lobe.³ Importantly, the prognoses for patients with discordant UIP (lobes with a

TABLE 3.
TEST CHARACTERISTICS FOR A CLINICAL/HRCT DIAGNOSIS OF IPF COMPARED TO
CLINICAL/HRCT/SLB^{11,14,15}

Study	# of Patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Raghu, et al	59	78	90	88	82
Hunninghake, et al	91	74	81	86	67
Flaherty, et al	96	37	100	100	33

HRCT = High resolution computed tomography; IPF = Idiopathic pulmonary fibrosis; SLB = Surgical lung biopsy; PPV = Positive predictive value; NPV = Negative predictive value

mixture of UIP and NSIP) and concordant UIP (all lobes with UIP) were similar. These findings have been confirmed by others through the examination of patients with suspected IIP¹⁸ and by the examination of explanted specimens at the time of lung transplantation.¹⁹

Conclusion

The idiopathic interstitial pneumonias comprise a number of distinct clinicopathologic entities that are sufficiently different from one another to be designated as separate disease entities, but sufficiently similar in their clinical presentation to pose a significant diagnostic challenge for the clinician. In all cases, however, a multidisciplinary approach with ongoing dialogue between the appropriate specialists is essential for facilitating an accurate diagnosis.

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PILOT™ RESOURCE HUB

Approach to the Diagnosis of IPF

Clinical

- History
- Physical
- Laboratory
- PFTs

Radiology

- Chest X-ray
- HRCT

Pathology

- Surgical lung biopsy

Primary care physicians

Pulmonologists

Radiologists

Pathologists

Multidimensional and multidisciplinary

- The early recognition of IPF starts with a high level of clinical suspicion
- The approach to the diagnosis of IPF requires a multidisciplinary effort (pulmonologist, radiologist and pathologist)
- A better understanding of histologic and pathologic findings can help distinguish the ILDs
- Differentiating IPF from other ILDs can direct the management and predict the prognosis of these patients

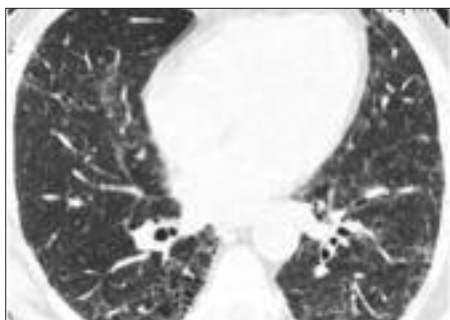
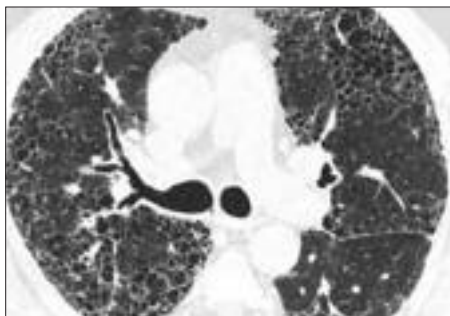
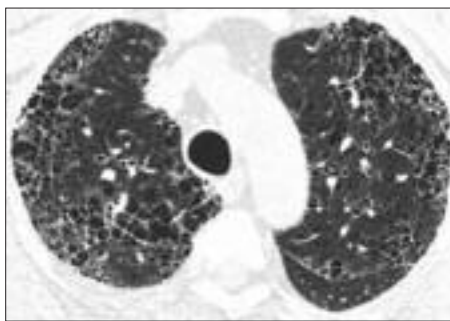
IN ALL CASES, HOWEVER, A MULTIDISCIPLINARY APPROACH WITH ONGOING DIALOGUE BETWEEN THE APPROPRIATE SPECIALISTS IS ESSENTIAL FOR FACILITATING AN ACCURATE DIAGNOSIS.

TO BIOPSY OR NOT TO BIOPSY BASED ON HRCT

The decision to biopsy a patient is based on whether a definite diagnosis can be obtained based solely upon clinical history and radiology. Presented below are two possible scenarios that are often encountered in the process of diagnosing a patient with IPF.

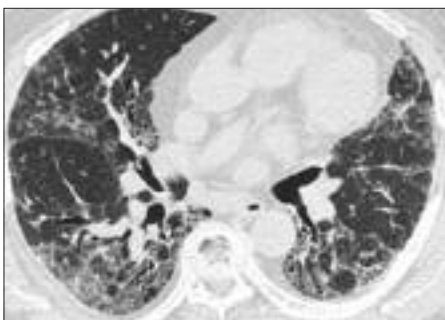
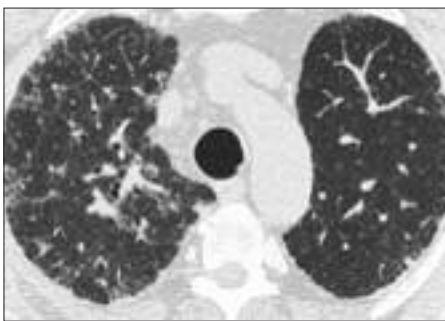
CASE SCENARIO 1.

High resolution computed tomography (HRCT) scan from a 57 year old male with surgical lung biopsy confirmed usual interstitial pneumonia. The HRCT demonstrates features typical for idiopathic pulmonary fibrosis/usual interstitial pneumonia such as peripheral honeycomb change without significant ground glass opacity.



CASE SCENARIO 2.

High resolution computed tomography scan from a 71 year old male with surgical lung biopsy confirmed usual interstitial pneumonia. The high resolution computed tomography was read as nonspecific interstitial pneumonia. Bilateral reticular infiltrates, traction bronchiectasis, and moderate ground glass opacities are present. Honeycomb change is not present.



UPCOMING CME EVENTS

PILOT™ CME DINNER MEETINGS: EMERGING PERSPECTIVES ON IPF: PRACTICAL STRATEGIES FOR DISEASE MANAGEMENT

July 7, 2005

San Diego, CA

Kevin O. Leslie, MD

July 11, 2005

Houston, TX

Paul W. Noble, MD

July 19, 2005

Jacksonville, FL

Baltimore, MD

Steven A. Sahn, MD

Charlie Strange, MD

July 20, 2005

San Antonio, TX

Marilyn Glassberg, MD

July 26, 2005

Birmingham, AL

Steven D. Nathan, MD

July 27, 2005

St. Louis, MO

Steven D. Nathan, MD

August 10, 2005

Athens, GA

Gerald Staton, MD

August 16, 2005

Shreveport, LA

Kevin O. Leslie, MD

August 17, 2005

Denver, CO

Sarasota, FL

Kevin O. Leslie, MD

Todd K. Horiuchi, MD

September 6, 2005

Rosemont, IL

Kevin O. Leslie, MD

Paul W. Noble, MD

September 7, 2005

Harlingen, TX

Steven D. Nathan, MD

September 14, 2005

Queens, NY

Santa Ana, CA

Craig T. Thurm, MD

Kevin O. Leslie, MD

September 15, 2005

Coral Gables, FL

San Jose, CA

Juan Mella, MD

Glenn D. Rosen, MD

September 20, 2005

Little Cottonwood, UT

Kevin O. Leslie, MD

September 27, 2005

Oakland, CA

Kevin O. Leslie, MD