UIP Possibile e Probabile

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ReW
Respiratory
Workshop

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Boehringer Ingelheim
Pfizer

Current definition of IPF

- IPF is a distinct type of chronic fibrosing interstitial pneumonia
- Unknown cause
- Limited to the lungs
- Has typical HRCT findings
- Associated with a histologic pattern of usual interstitial pneumonia (UIP)

ATS/ERS Consensus Statement. *Am J Respir Crit Care Med*. 2002;165:277-304

ATS/ERS Consensus Statement. *Am J Respir Crit Care Med*. 2000;161:646-664

Importance of early diagnosis of IPF

- Begin evaluation for lung transplant earlier
- Allows for earlier referral and enrollment in clinical trials (which are generally limited to patients with mild to moderate disease)
- Emerging evidence regarding response to therapy
- Exclude other more treatable diseases

Approach to the diagnosis of IPF

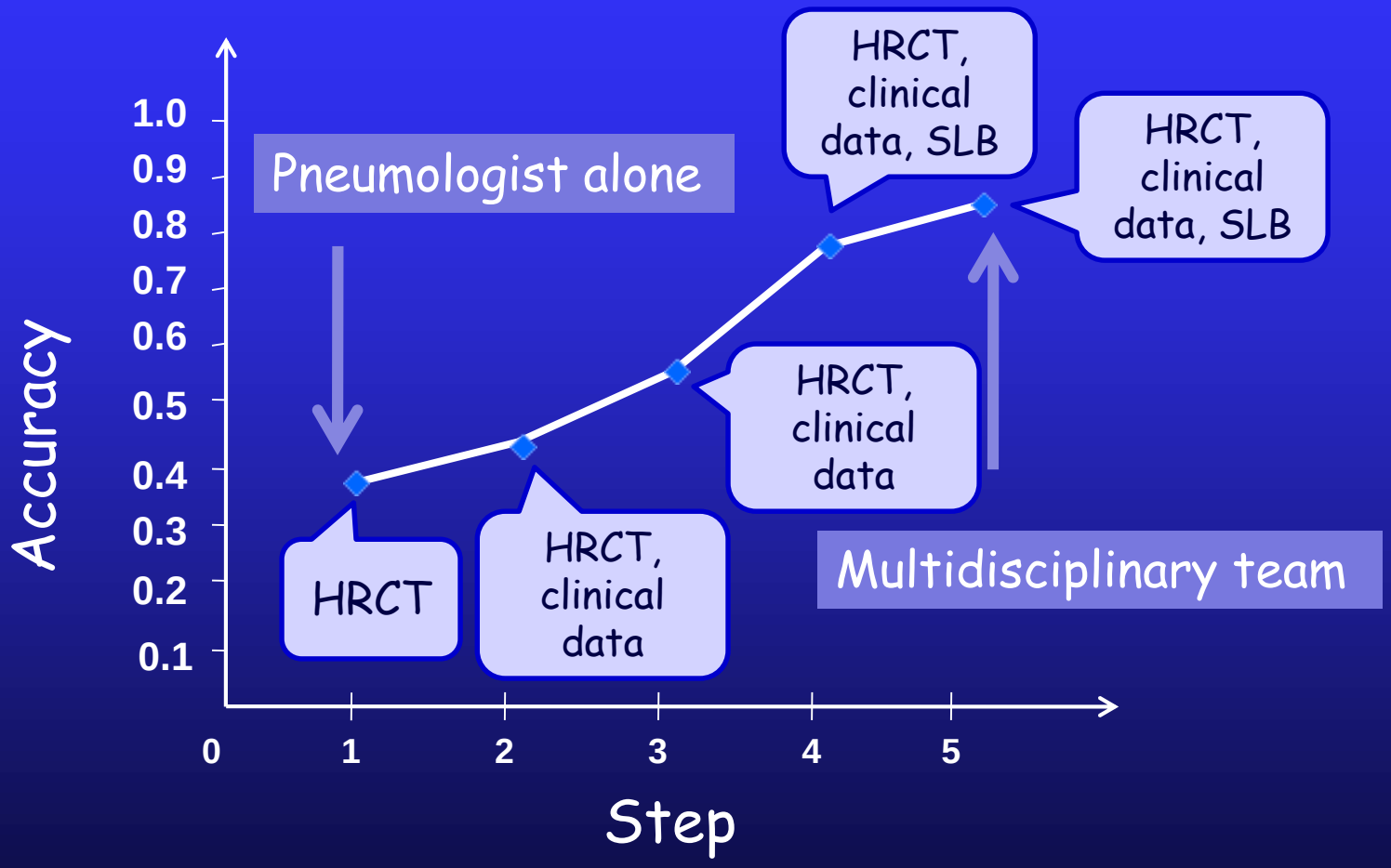
Clinical	*Radiology*	*Pathology*
• History • Physical • Laboratory • PFTs	• Chest X-ray • HRCT	• Surgical lung biopsy
Primary care physicians	Pulmonologists	Radiologists	Pathologists

Multidimensional and multidisciplinary

The gold-standard of IIP diagnosis

Diagnosis is multidisciplinary

Modified from: Flaherty et al. Am J Respir Crit Care Med 2004; 170:904



Requires pulmonologists, radiologists and pathologists working together

Don't stop with "pulmonary fibrosis"

- Reason for a specific diagnosis:
  - many forms are treatable
  - treatments depend on diagnosis
  - prognosis varies
  - clinical trial eligibility requirements

In idiopathic interstitial pneumonia, diagnosis is prognosis

Systematic approach to CT

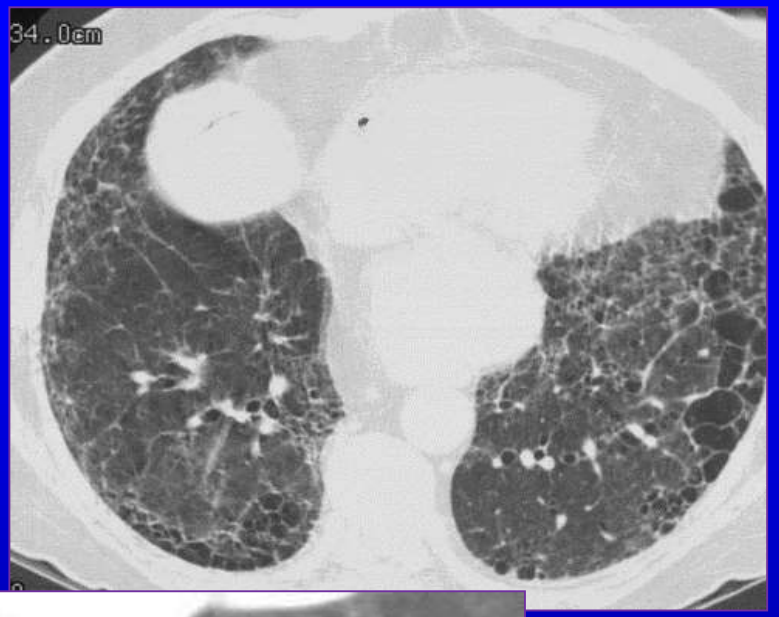
- Evaluation of image quality
- Precise description of specific disease features using standard terminology
- Disease distribution
- Is it a fibrotic ILD or non-fibrotic ILD?
  - If so, is it definite UIP?
  - If no, is possible or inconsistent?
  - what are the alternatives (e.g. fibrotic sarcoid, CPFE etc.)?

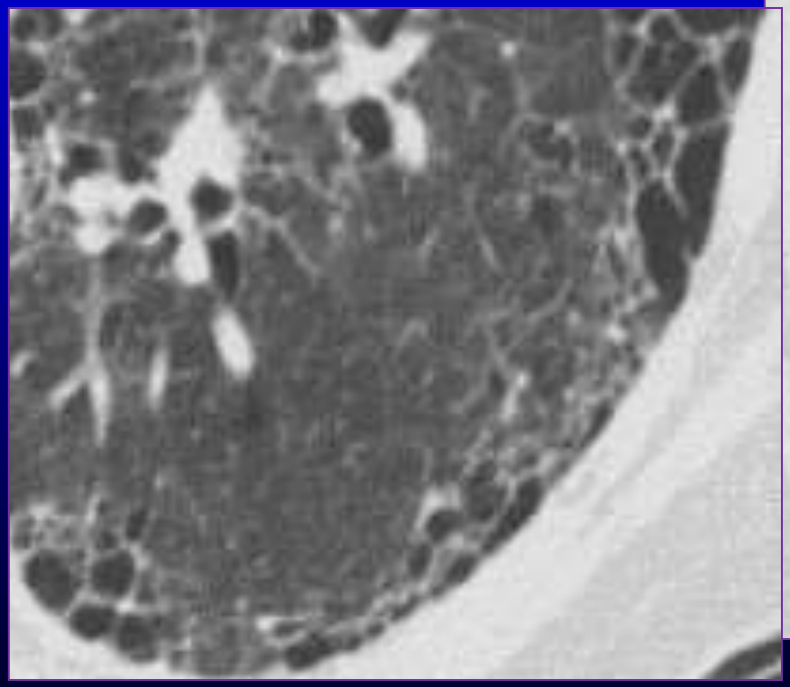
HRCT

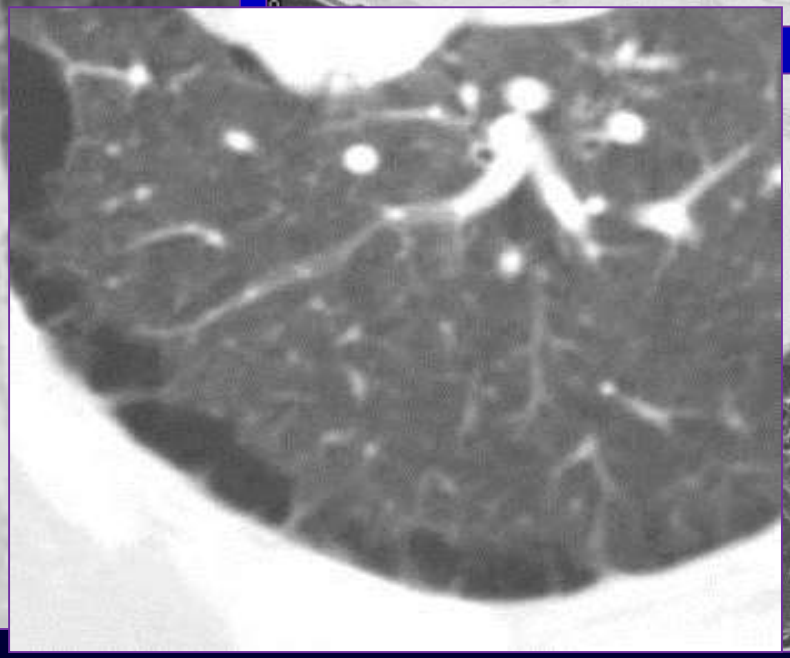
features of fibrosis,

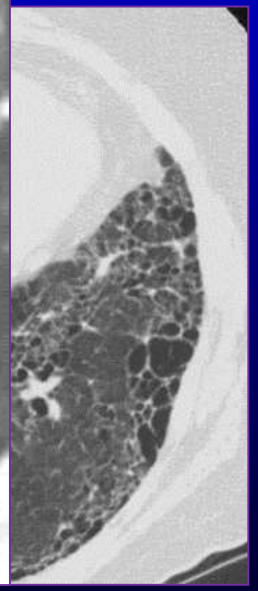
Intra-lobular and inter-lobular septal thickening, walled cysts representing honeycombing,

may be associated traction bronchiectasis









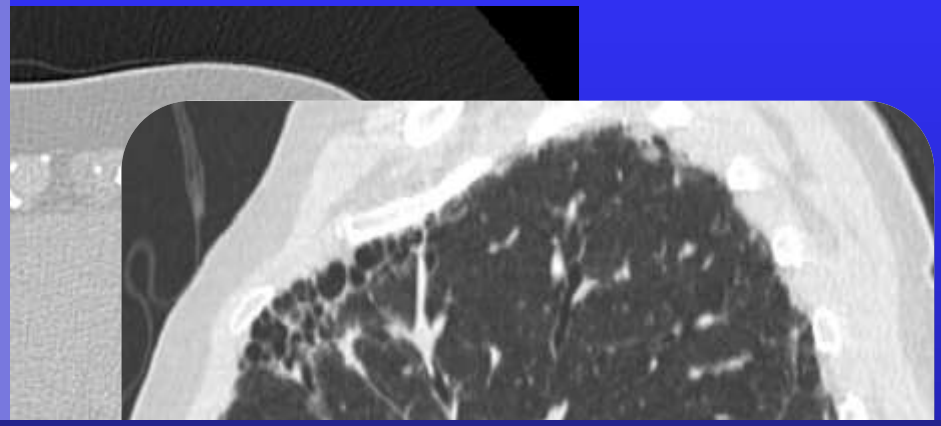
UIP pattern (all four):

Sub-pleural, basal predominance

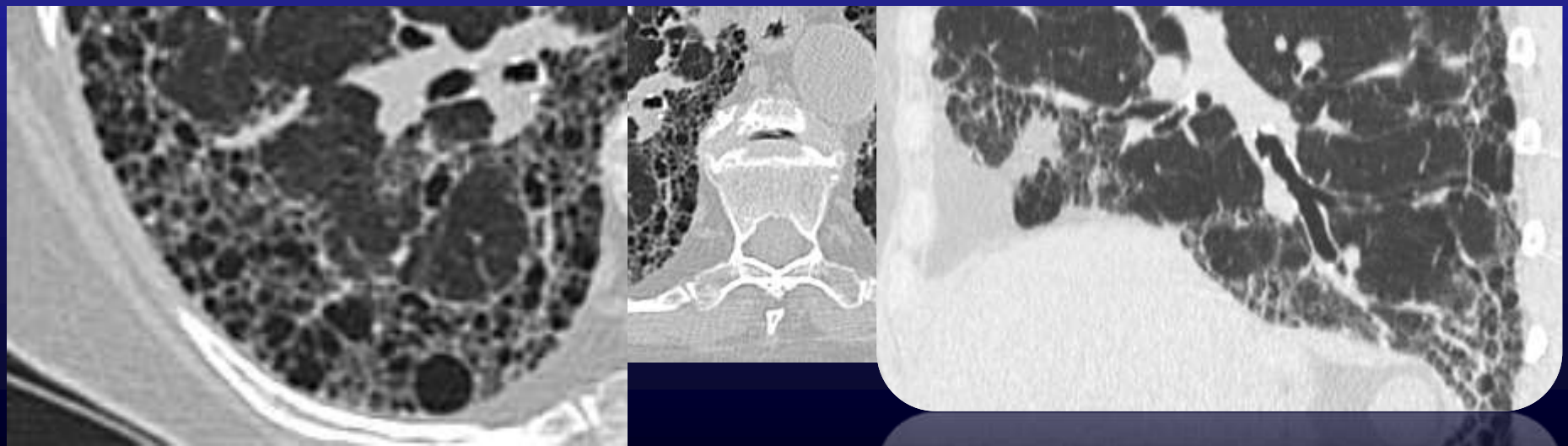
Reticular abnormality

Honeycombing with or without traction bronchiectasis

Absence of features listen as inconsistent with UIP



***Am J Respir Crit Care Med* 2011; 183: 788-824**



*An **early** and **accurate** diagnosis of IPF is **critical**, particularly with the advent of novel specific treatments that may have the potential to reduce disease progression*

Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis

Cordier JF, Cottin V Eur Respir J 2013; 42: 916

- IPF is a relatively recent disease linked to the tobacco epidemics
- IPF is a disease of ageing
- Earlier diagnosis of IPF could be obtained by recognizing the value of velcro crackles

  and
- by promoting the screening for IPF as a by-product of low-dose CT screening for lung cancer

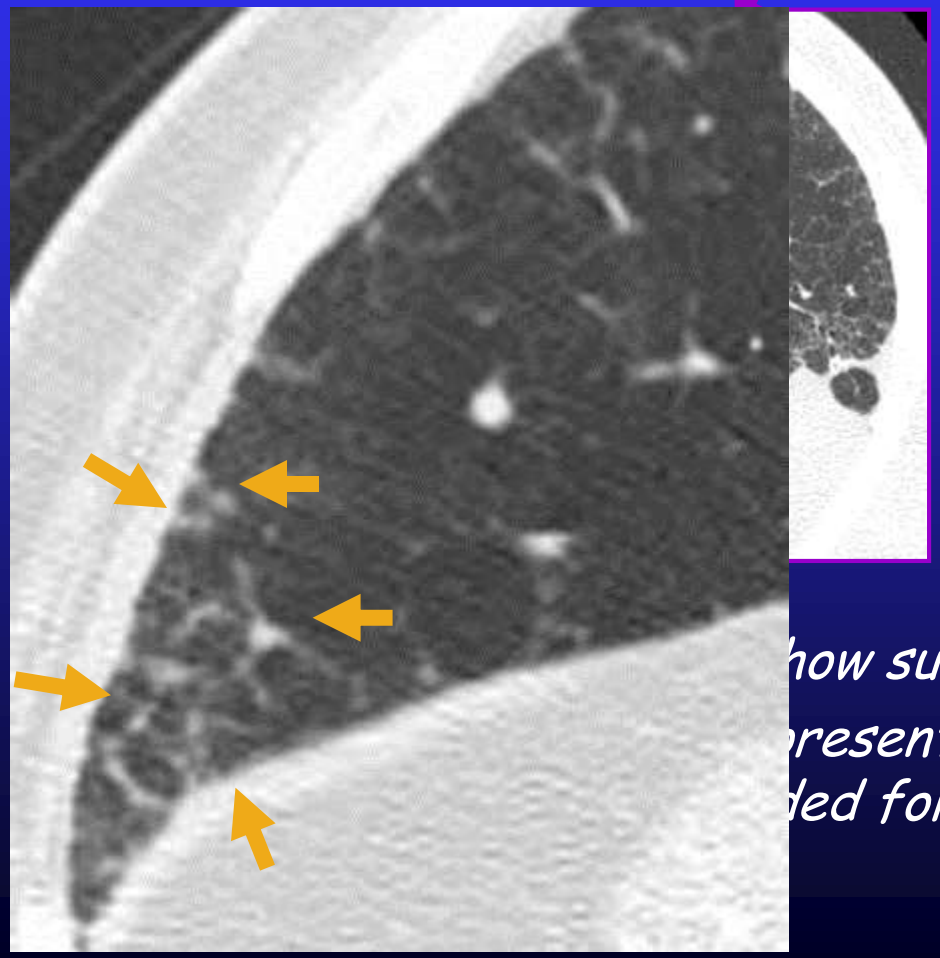
Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate

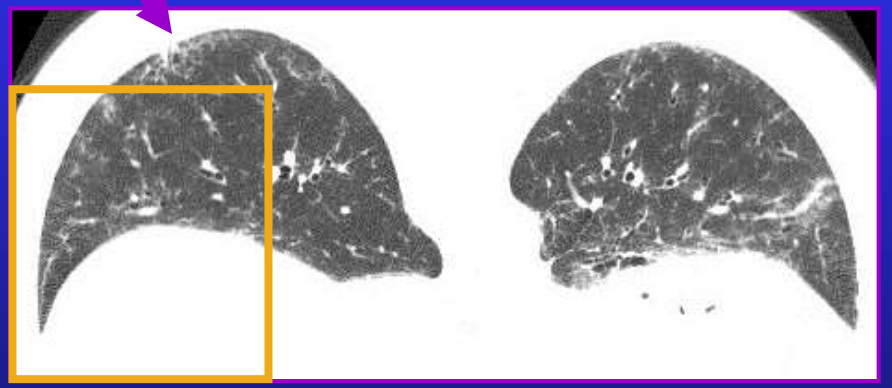
Lynch D et al. Radiology 2013; 268: 563

- In a population of current and former smokers with at least 30 p/y, 55-74 years of age fibrotic interstitial lung disease was present at systematic CT in ~ 2% of patients, 37% of whom had progressive fibrotic disease on 2-year follow-up CT
- Low dose CT scan appropriately detect subclinical fibrotic ILD likely corresponding to IPF at an early stage

Radiological Diagnosis Inconclusive

Subpleural reticular opacities



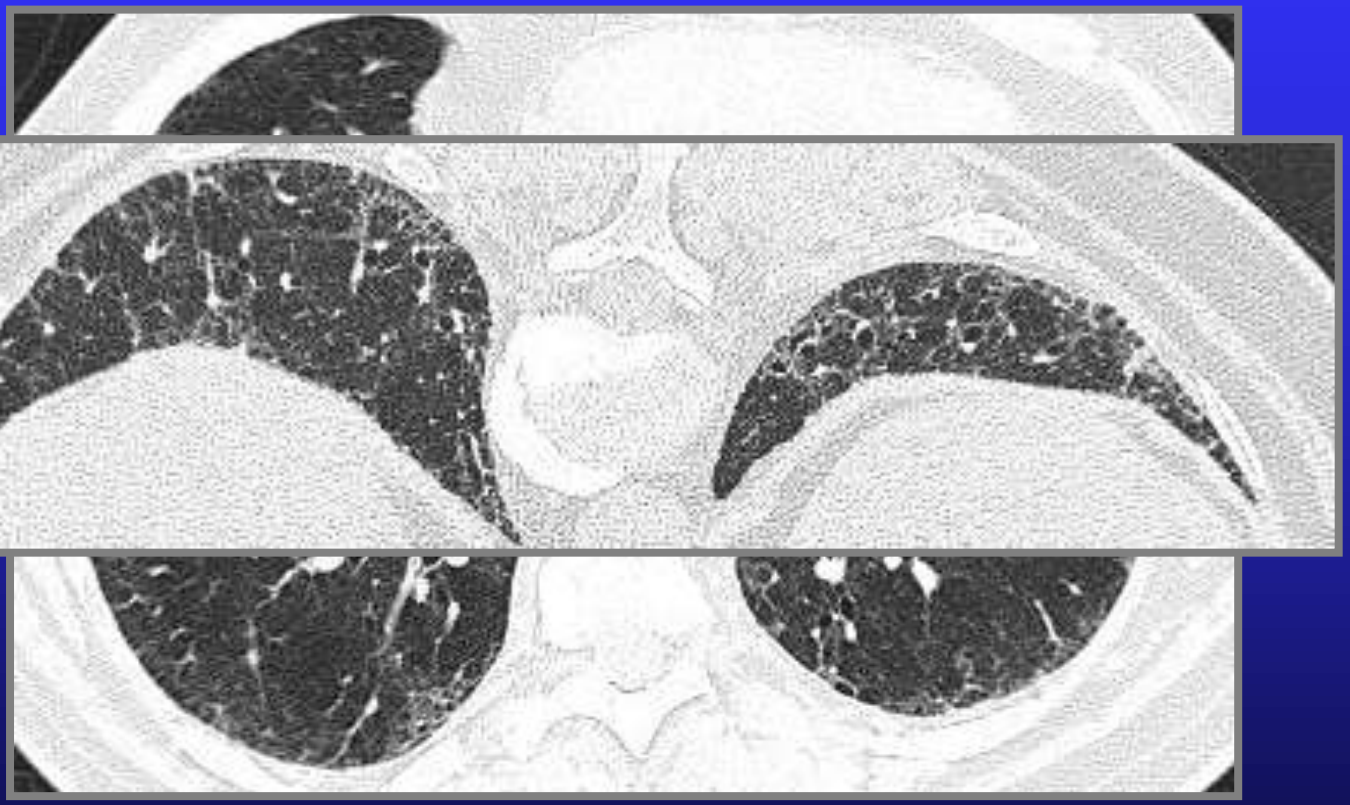


how subpleural reticulation.

resent early UIP/IPF or fibrotic NSIP.

ded for their differentiation.

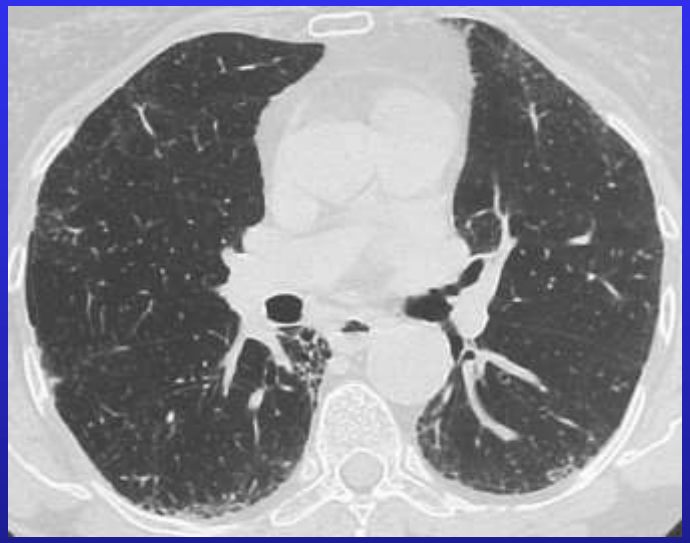
Use of prone Imaging



UIP: progression of fibrosis on CT

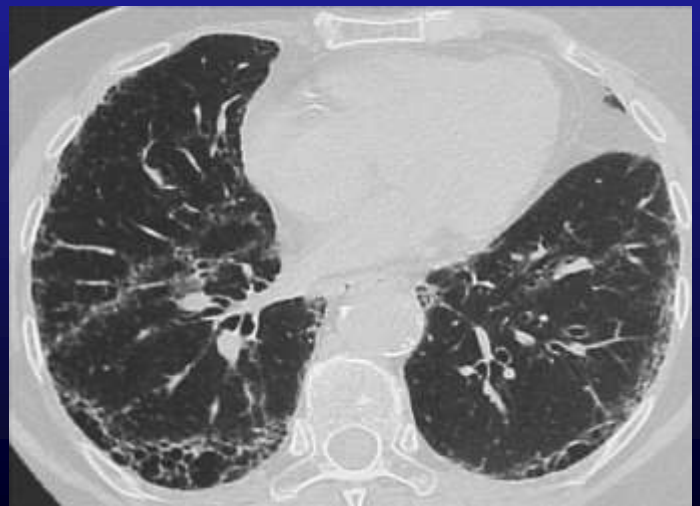
Early:

Reticular



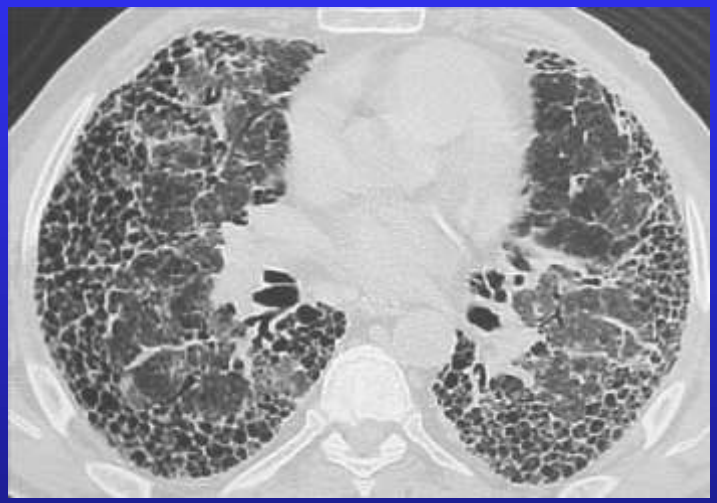
Midcourse:

Subpleural honeycombing

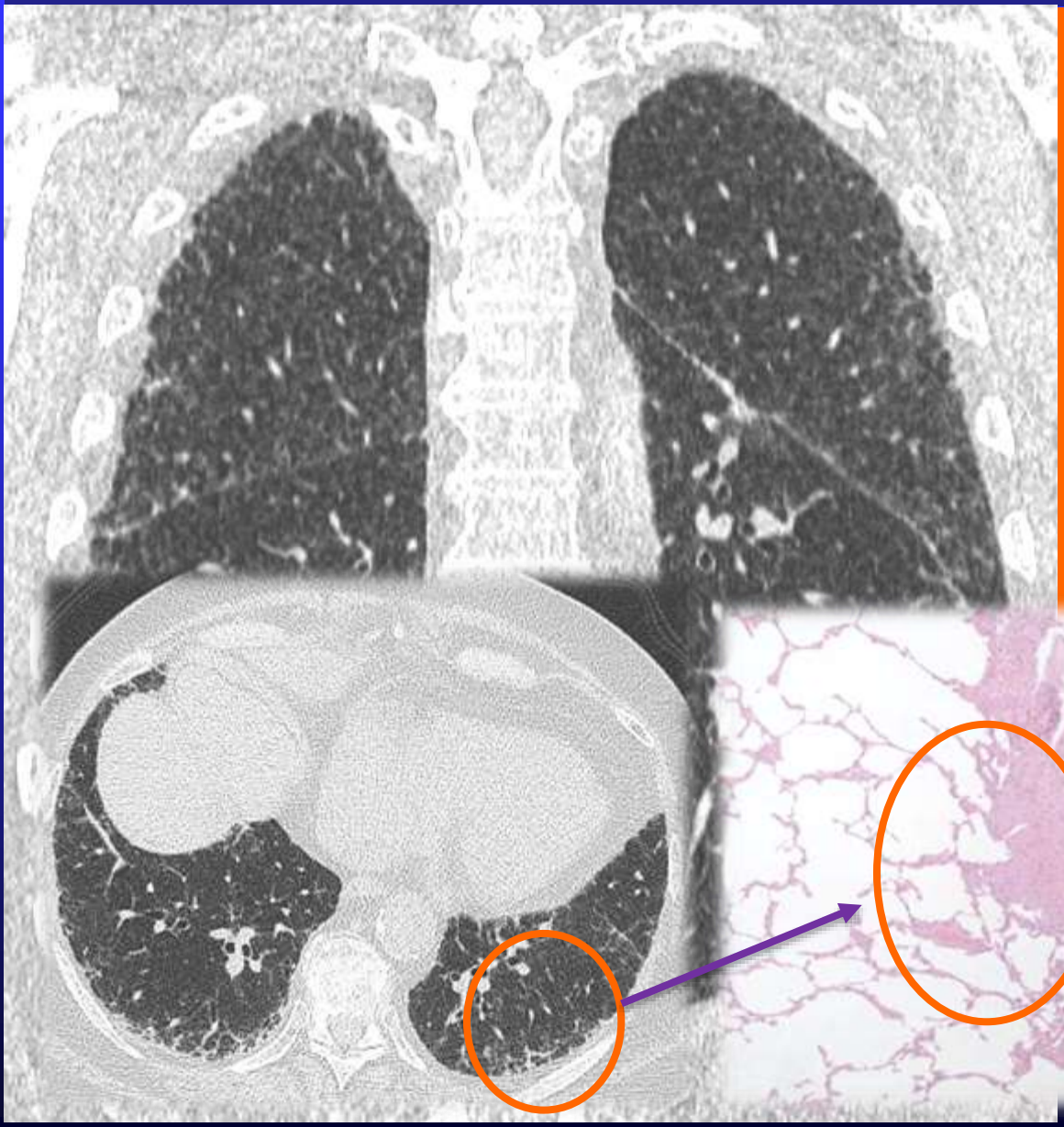


Late:

Diffuse honeycombing



Am J Respir Crit Care Med 2011; 183: 788-824

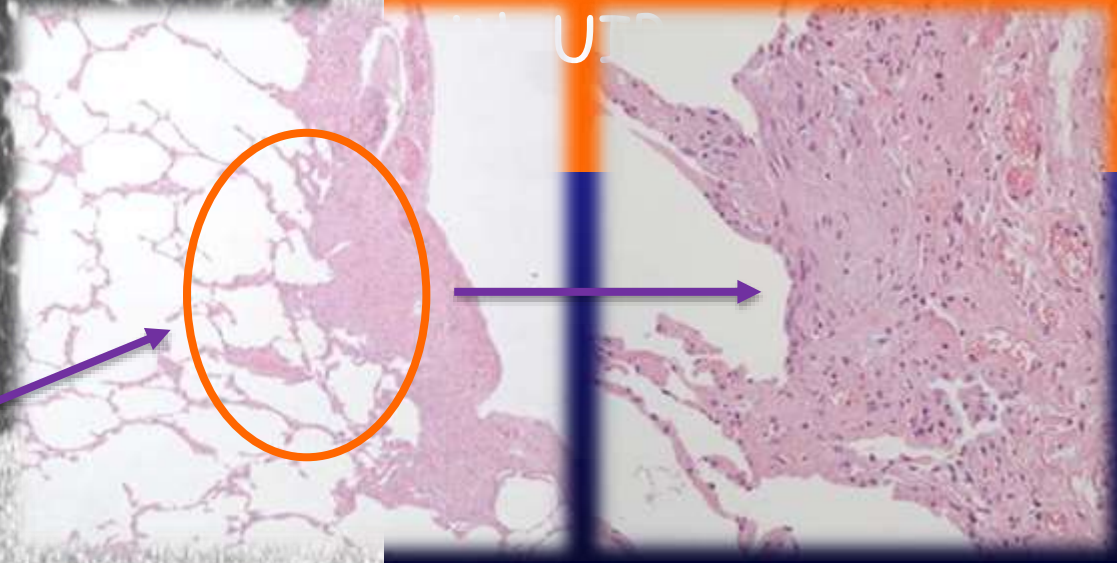


Possible UIP pattern (all three):

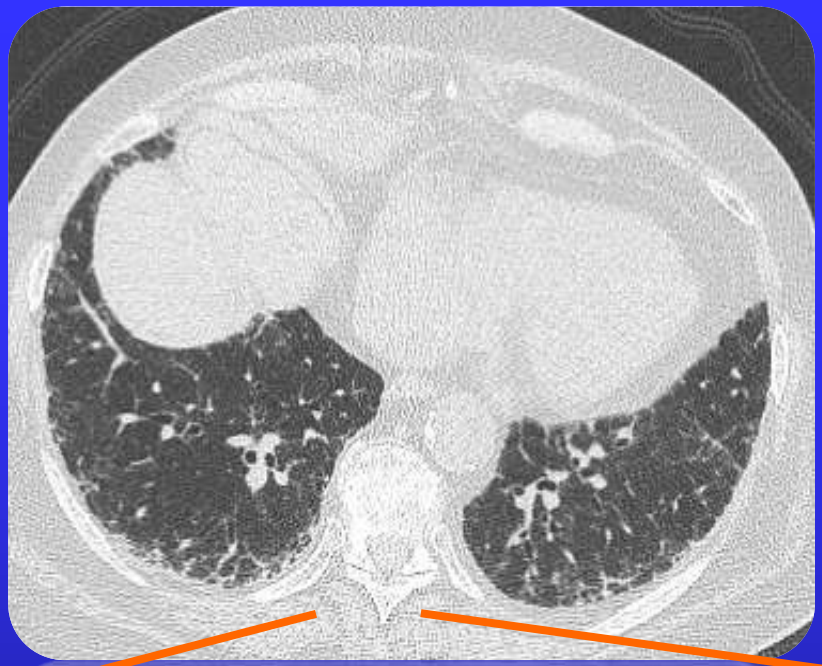
Subpleural, basal predominance

Reticular abnormality

Absence of features listen as inconsistent



Fell CD et al, AJRCCM 2010



Male gender
Current or former smoker
Older age (>70 yrs)
Low-inspiratory squeacks
Neutrophils on BAL

Very high likelihood of IPF (PPV 95%)

Female gender
Younger age
Non smoker

Mid-inspiratory squeaks
Positive serologies
Lymphocytosis on BAL
Skin findings

More likely idiopathic or secondary NSIP

The problems is….

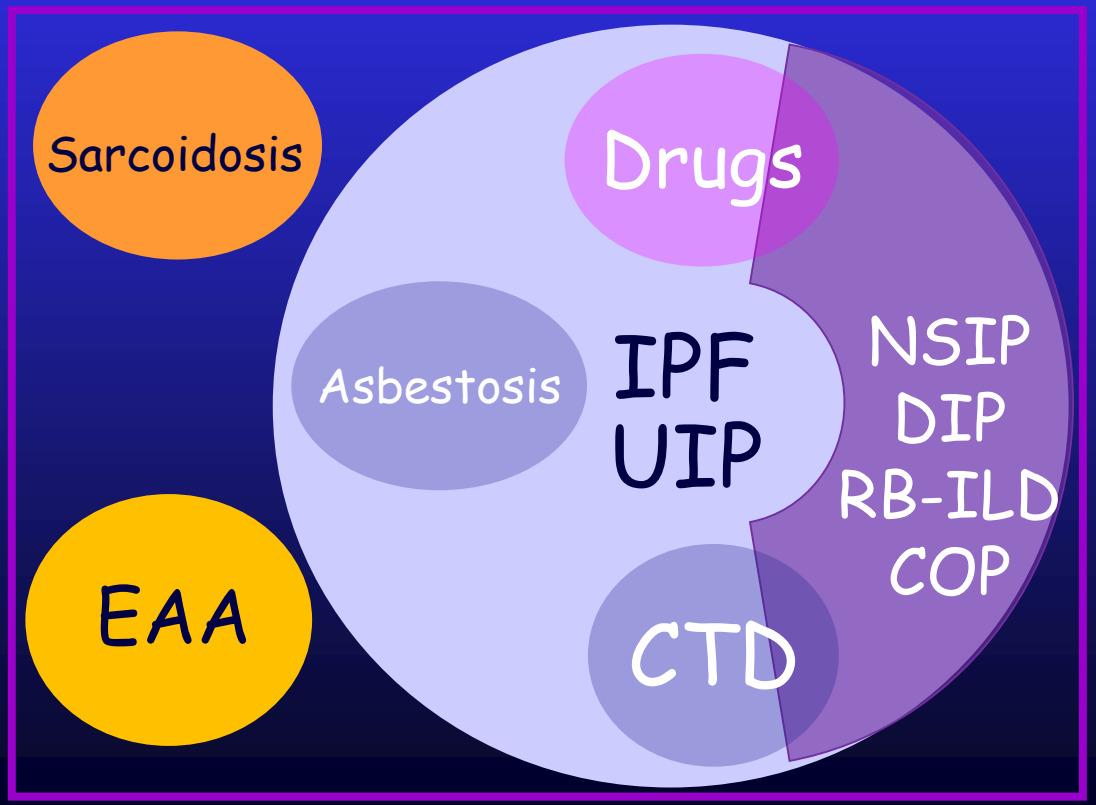
"Possible UIP" is the major current diagnostic problem in chronic fibrotic ILD:

- What's the treatment?
- What's the prognosis?
- What's the role of BAL evaluation?

If the distinction between IPF and alternative diagnoses remains in doubt after full evaluation, a period of treatment as for HP or NSIP is also a diagnostic test

Radiological differential diagnosis in 'IPF'

- An HRCT that predominantly shows bi-basal honeycombing is virtually 100% specific for UIP
- The HRCT pattern of UIP found in IPF can be indistinguishable from that seen in asbestosis, collagen vascular disease or as a response to drugs
- Patients with chronic hypersensitivity pneumonitis or with end-stage sarcoidosis can uncommonly develop a CT pattern similar to UIP



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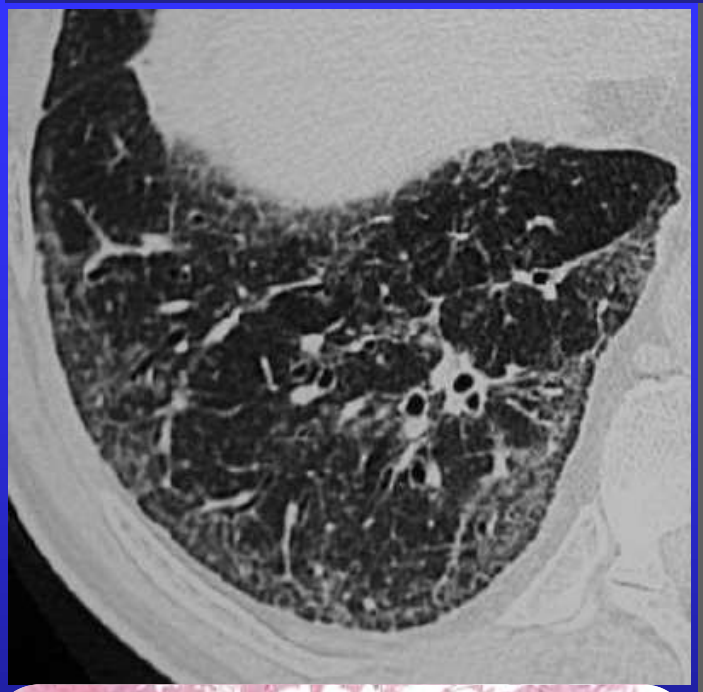
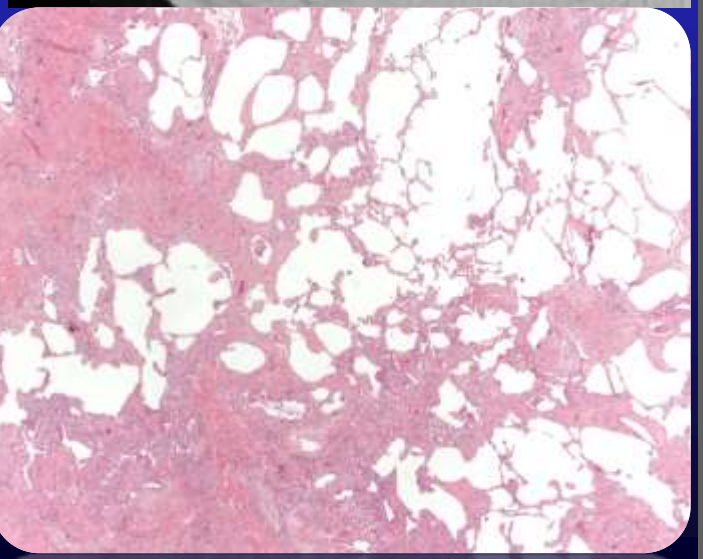




Inconsistent with UIP pattern (any of the seven features):

- Upper or mid-lung predominance
- Peribronchovascular predominance
- Extensive ground glass abnormality (extent > reticular abnormality)
- Profuse micronodules (bilateral, predominantly upper lobes)
- Discrete cysts (multiple, bilateral, away from areas of honeycombing)
- Diffuse mosaic attenuation/air-trapping (bilateral in three or more lobes)
- Consolidation in bronchopulmonary segment(s), lobe(s)

Key conclusion

- Typical HRCT features of IPF in association with a compatible clinical profile obviate surgical biopsy

BUT

- Atypical features on HRCT for IPF do NOT exclude the diagnosis

Computed Tomography Findings in Pathological Usual Interstitial Pneumonia

Relationship to Survival

Sumikawa A et al. Am J Respir Crit Care 2008; 177: 433

One of the most striking findings of this study is the variable HRCT appearance of UIP despite very rigid histo-pathologic criteria

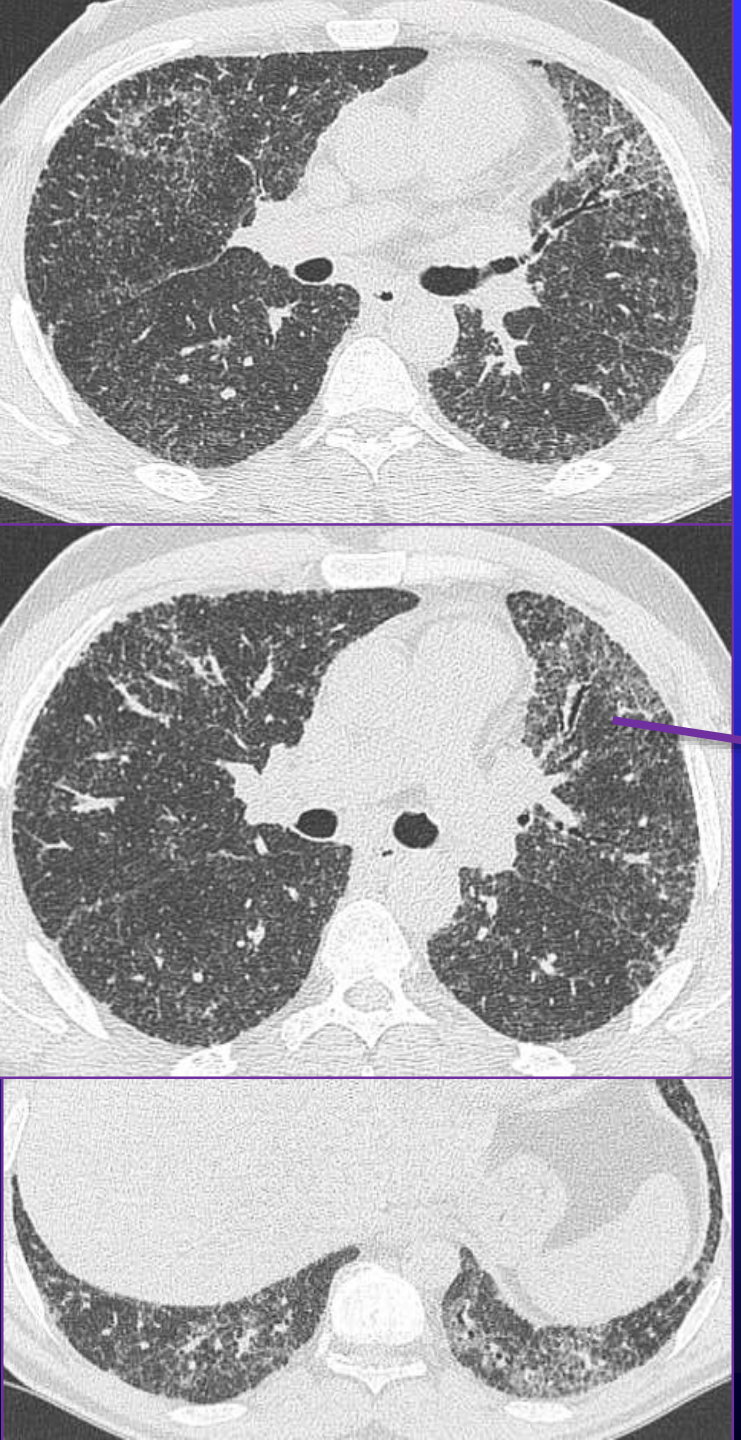
Interestingly, only approximately one-third of HRCTs showed definite IPF and approximately one-third suggested an alternative diagnosis, such as NSIP, or were unclassifiable!

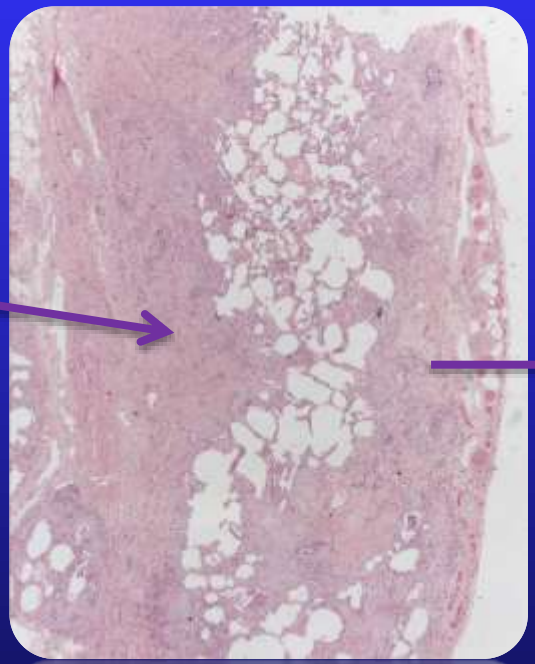
Spectrum of atypical radiologic appearances of biopsy proven UIP

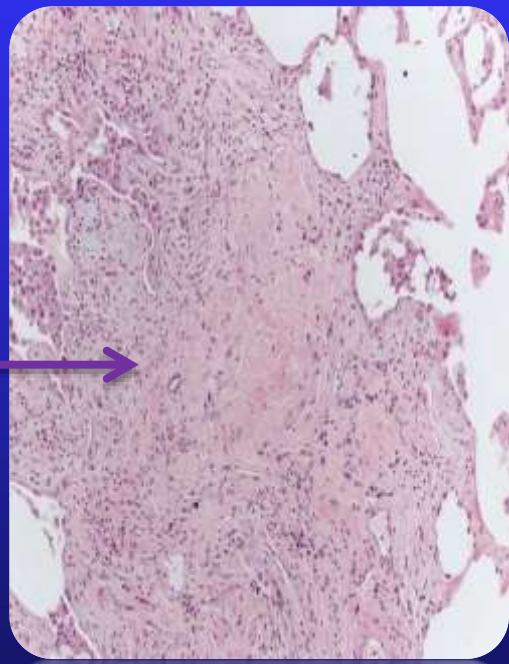
Most common radiologic diagnoses in 34 patients with biopsy proven UIP whose CT does not meet radiologic criteria for definite UIP (i.e. basal, subpleural honeycombing)……..

- *NSIP 18*
- *CHP 4*
- *Sarcoidosis 3*
- *OP 1*
- *Other 8*

Sverzellati N et al, Radiology 2010





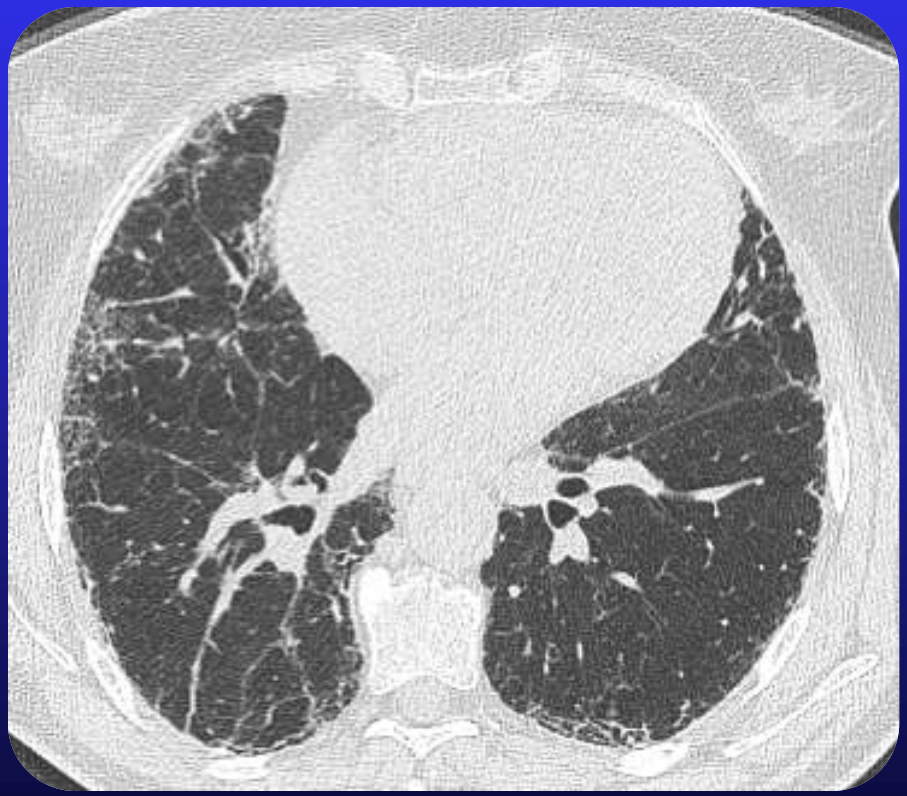


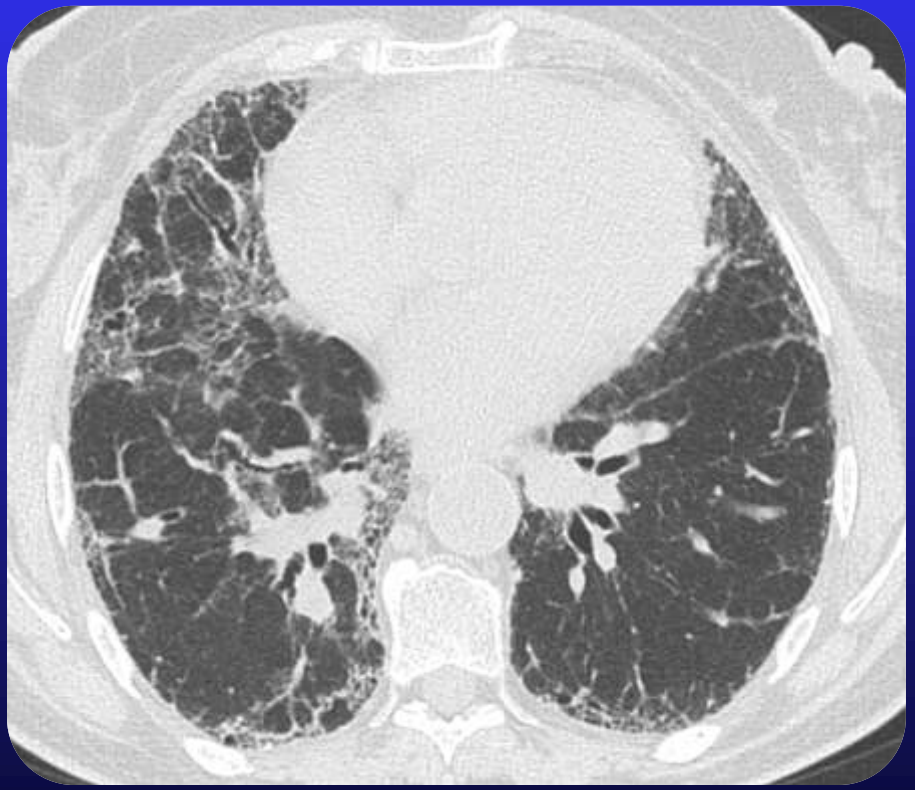
UIP pattern (All four features)	Possible UIP pattern (All three features)	Inconsistent with UIP pattern (Any of the seven Features)
• Subpleural , basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of features listed as inconsistent with UIP pattern	• Subpleural , basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern	•Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent > reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air-trapping (bilateral in three or more lobes) • Consolidation in bronchopulmonary segment(s), lobe(s)
UIP	**UIP or fibrotic NSIP**	**NSIP or chronic hypersensitivity pneumonitis**

- ✓ Do not downstage the «possible UIP» pattern
- ✓ Follow-up changes may be important, particularly when baseline CT is not diagnostic and surgical lung biopsy is not feasible

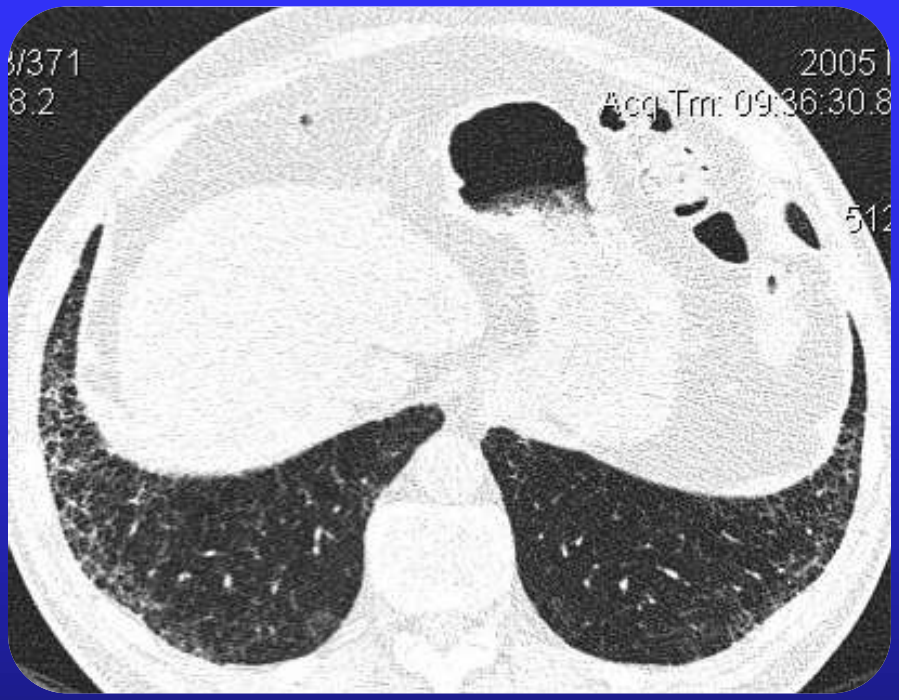
IPF: variazioni nel tempo all'HRCT

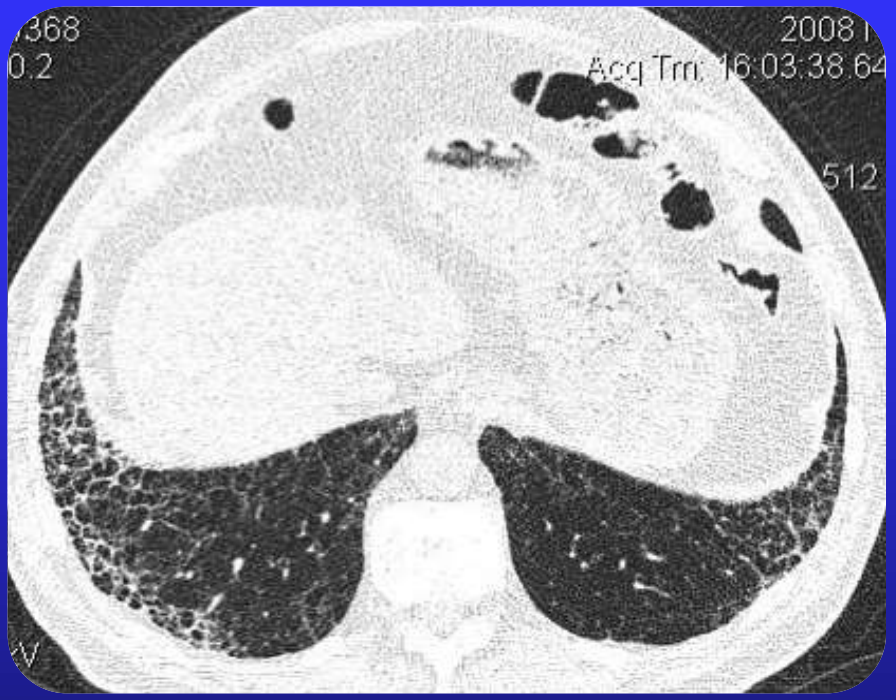
- Reticoli





1.5 anni dopo





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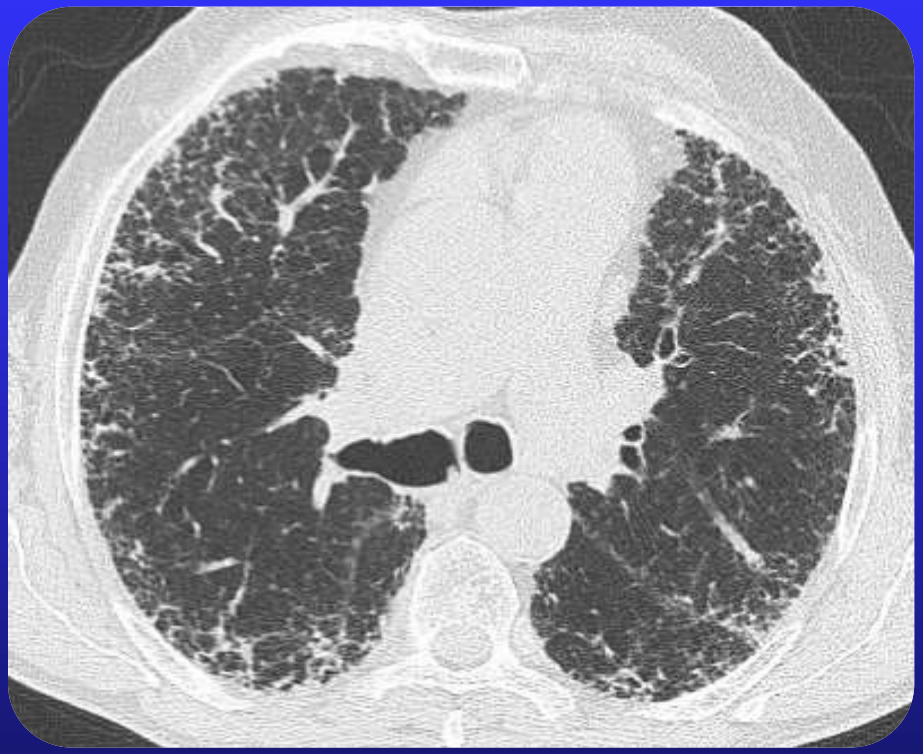
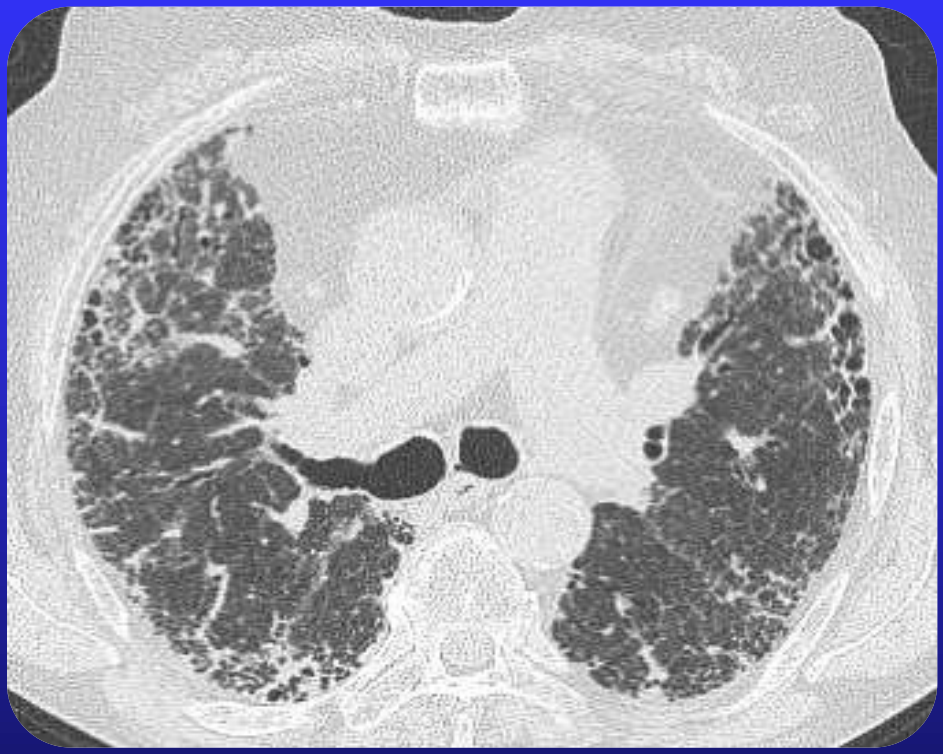
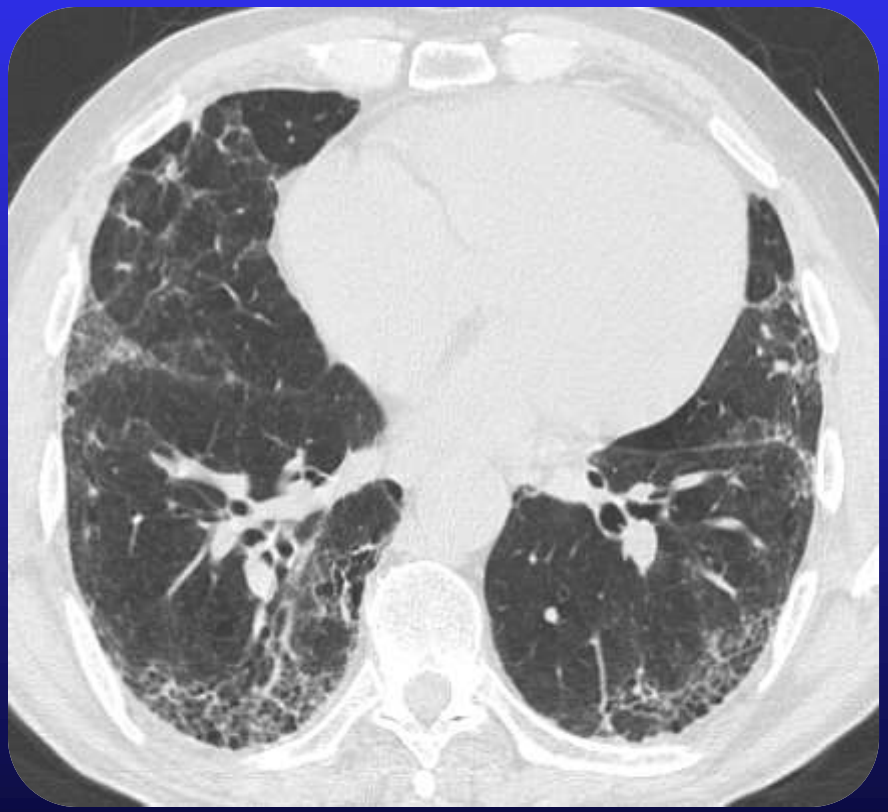


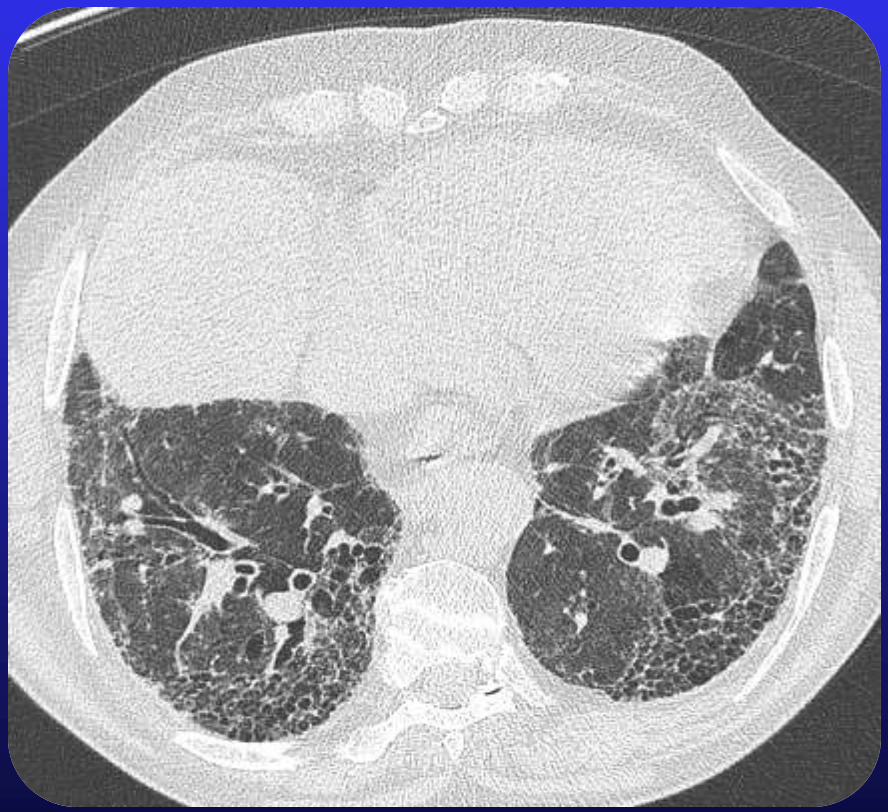


2 anni dopo

IPF: variazioni nel tempo all'HRCT

- Honeycombing

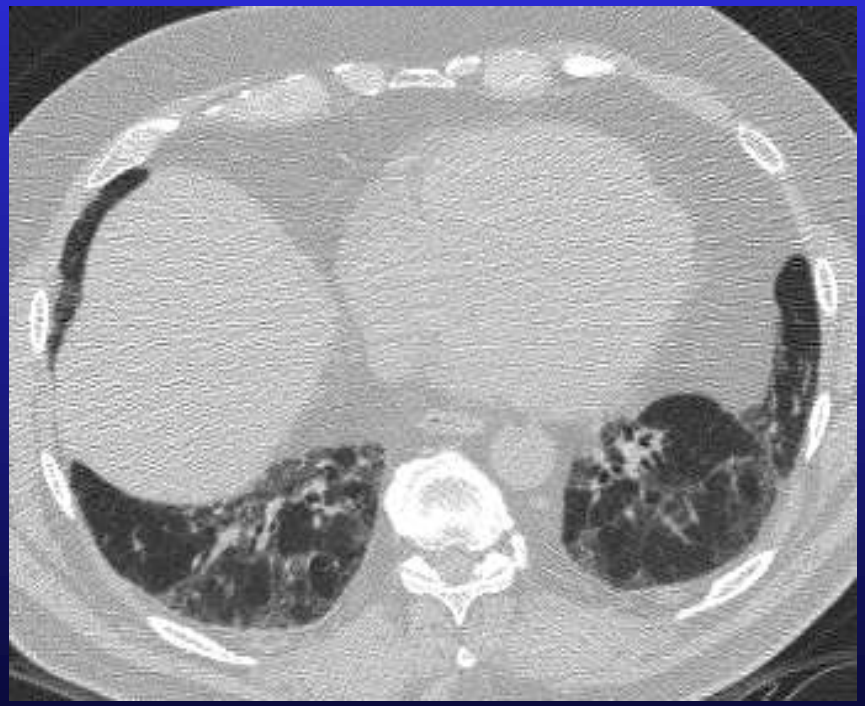


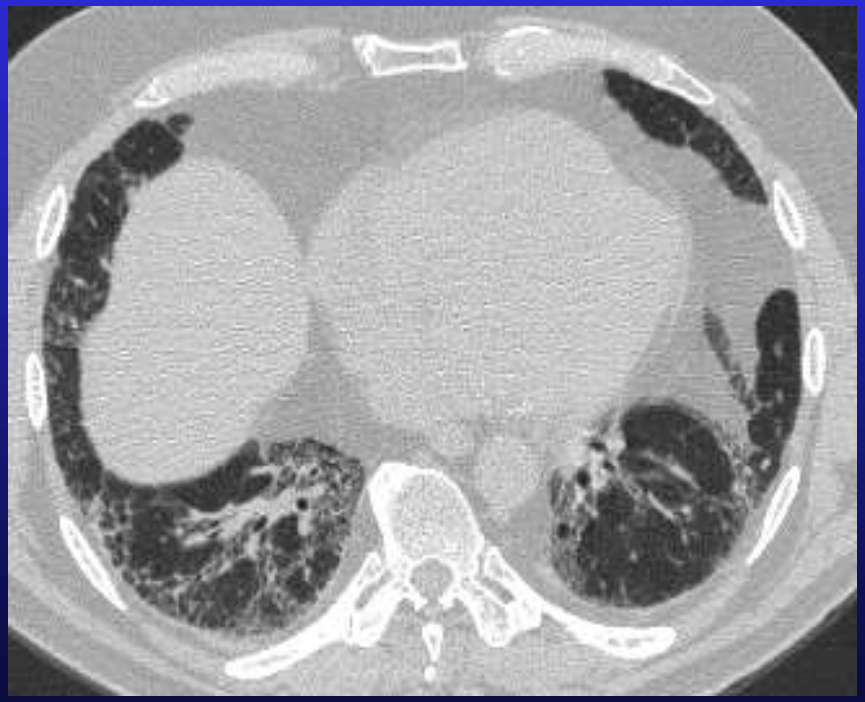


4 anni dopo

IPF: variazioni nel tempo all'HRCT

- Ground glass che migliora o sostituito dalle reticolazioni





10 mesi dopo

NSIP and UIP: changes in pattern and distribution of disease over time

CT Finding	NSIP (n= 23)	IPF (n= 25)	P value
Reticulation	21 (91)	24 (96)	NS
GGO	23 (100)	24 (96)	NS
Traction bronchiolectasis	21 (91)	23 (91)	NS
Relative subpleural sparing	10 (43)	2 (8)	<.005
Lower zone predominance of abnormalities	19 (83)	22 (88)	NS
peribronchovascular)			
Random	13 (57)	3 (12)	<.005

This study shows that a 3 years or longer follow-up, 28% of pts with initial CT findings suggestive of NSIP progress to findings suggestive of UIP

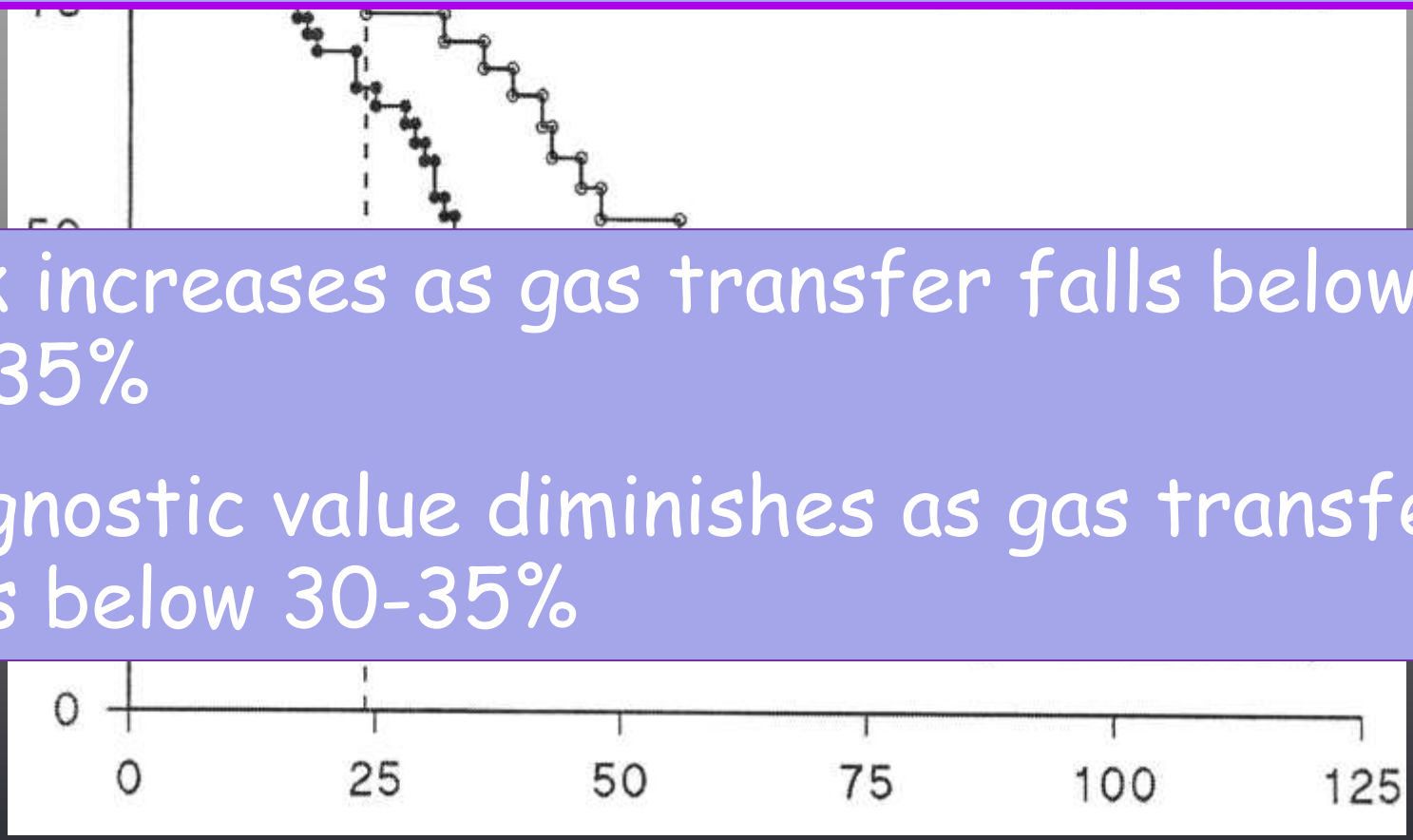
There are no CT features at presentation that allow distinction between pts with NSIP that maintain an NSIP pattern from those that progress to an IPF pattern at follow-up

Risks of biopsy

- Morbidity increases with age
- Co-morbidity a major constraint
- In many patients, disease severity does not allow biopsy
- In severe disease, a biopsy sometimes less useful

Only in ~15-25% of patients with suspected IPF is possible to perform a surgical lung biopsy

Early mortality was associated solely with the severity of lung function impairment at presentation, but mortality after 2 years of follow-up was primarily linked to the histopathologic diagnosis



- Risk increases as gas transfer falls below 30-35%
- Prognostic value diminishes as gas transfer falls below 30-35%

Latsi PI et al. *Am J Respir Crit Care Med* 2003; 168: 531

Radiologists' Observer Variation

HRCT diagnosis of diffuse parenchimal lung disease: inter-observer variation

Aziz et al. Thorax 2004;59:506

0 – 0.2 sligth 0.2 - 0.4 fair
0.4 – 0.6 moderate 0.6 – 0.8 substantial

Diagnostic category	Median (range) kw coefficient of agreement
Idiopathic pulmonary fibrosis	0.63 (0.48 – 0.78)
Non-specific interstitial pneumonia	0.51 (0.27 – 0.78)
Sarcoidosis	0.70 (0.58 – 0.84)
Extrinsic allergic alveolitis	0.60 (0.36 – 0.78)
Cryptogenic organizing pneumonia	0.49 (0.06 -0.76)
Smoking related interstitial lung disease	0.51 (0.20 – 0.73)

Inter-observer variation between pathologists in diffuse parenchymal lung disease

Nicholson et al. Thorax 2004; 59:500-505

Kappa coefficients (κ)

Diagnosis	Final diagnosis
UIP	0.49
NSIP	0.32
DIP	0.71
OP	0.67
Sarcoidosis	0.82

Intra-observer agreement varies from a kappa of 0.39 to 0.90 depending on the disease

What to expect from the pathologist?

- On a transbronchial biopsy?

  ~35% Dx rate in chronic diffuse disease

- On a surgical lung biopsy?

  ~90-95% diagnosis in diffuse disease

- On agreeing with his colleagues?

  Kappas from 0.4 - 0.8

- On agreeing with himself?

  Kappas from 0.4 - 0.9

Am J Respir Crit Care Med 2011; 183: 788-824

TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
• Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Evidence of marked fibrosis / architectural distortion, ± honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) OR • Honeycomb changes only‡	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (*see* UIP PATTERN column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	• Hyaline membranes* • Organizing pneumonia*† • Granulomas† • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis

Qual è il ruolo della TBB nella diagnosi di UIP?

- Specificità per UIP: 100%
  Tomassetti et al. Respir Med 2012;13:96
- Accordo interpersonale accettabile
  Tomassetti et al. Respir Med 2012;13:96
- Sensibilità per UIP:
  - 32% Berbescu et al. Chest 2006;129:1126-1131
  - 20% Tomassetti et al. Respir Med 2012;13:96
  - 0% Shim et al. Pathol Intern 2010;60:373-377

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UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
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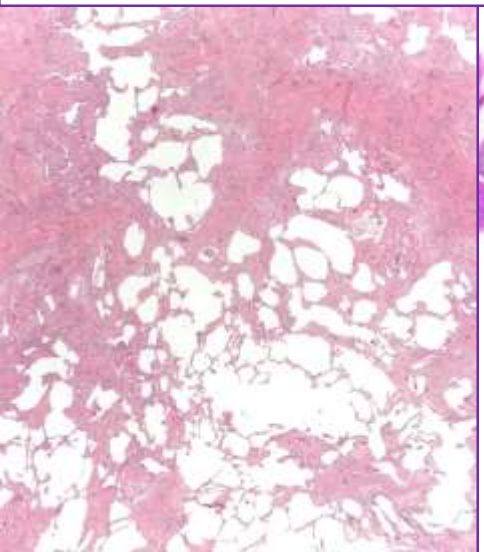
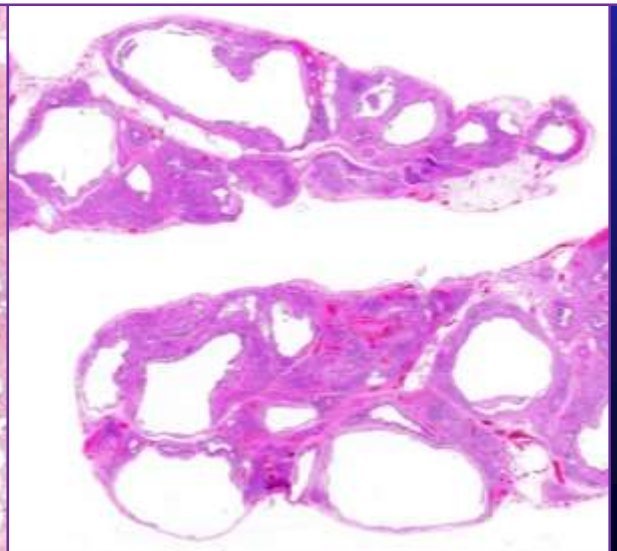
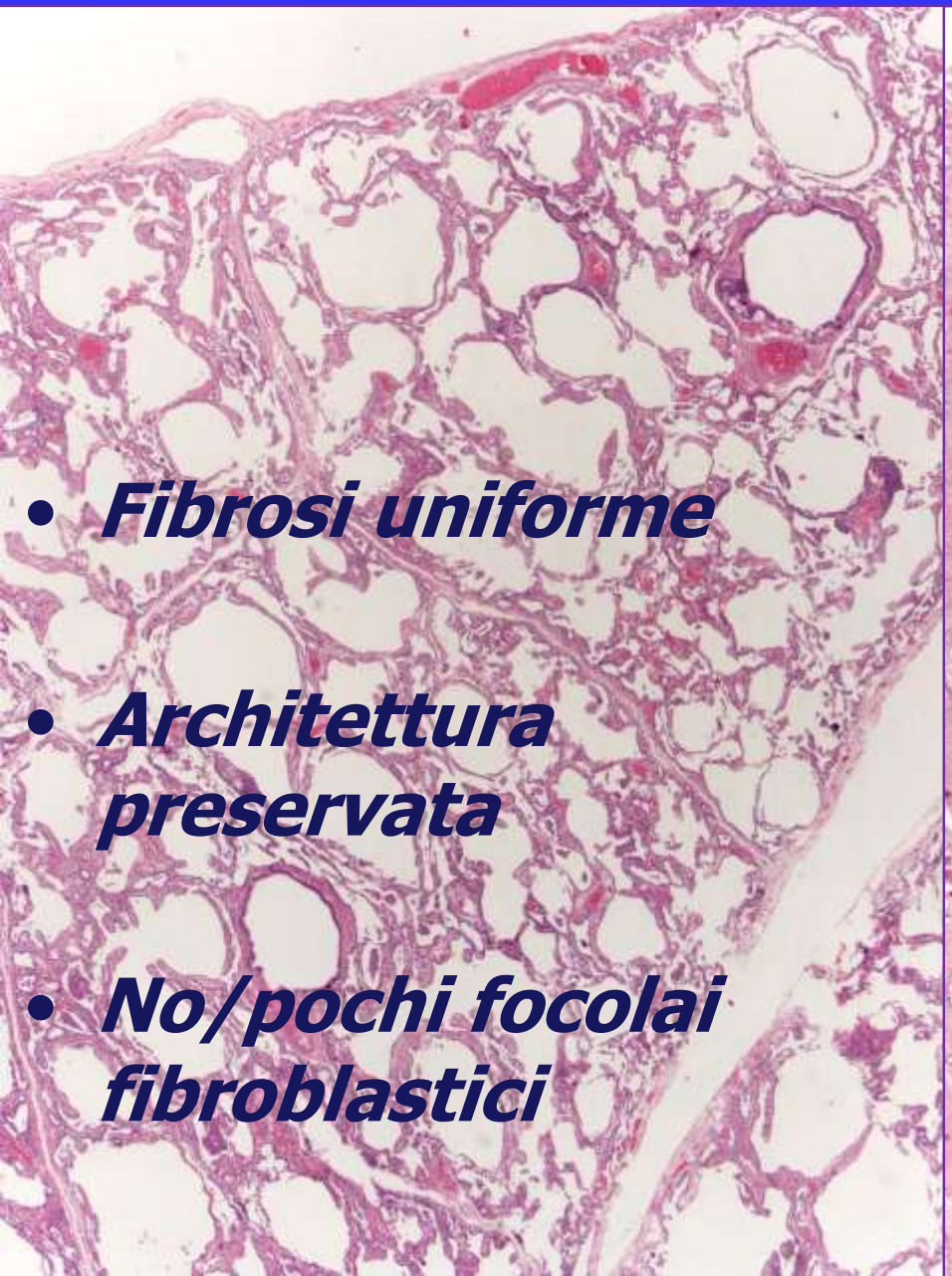




NSIP fibrosante

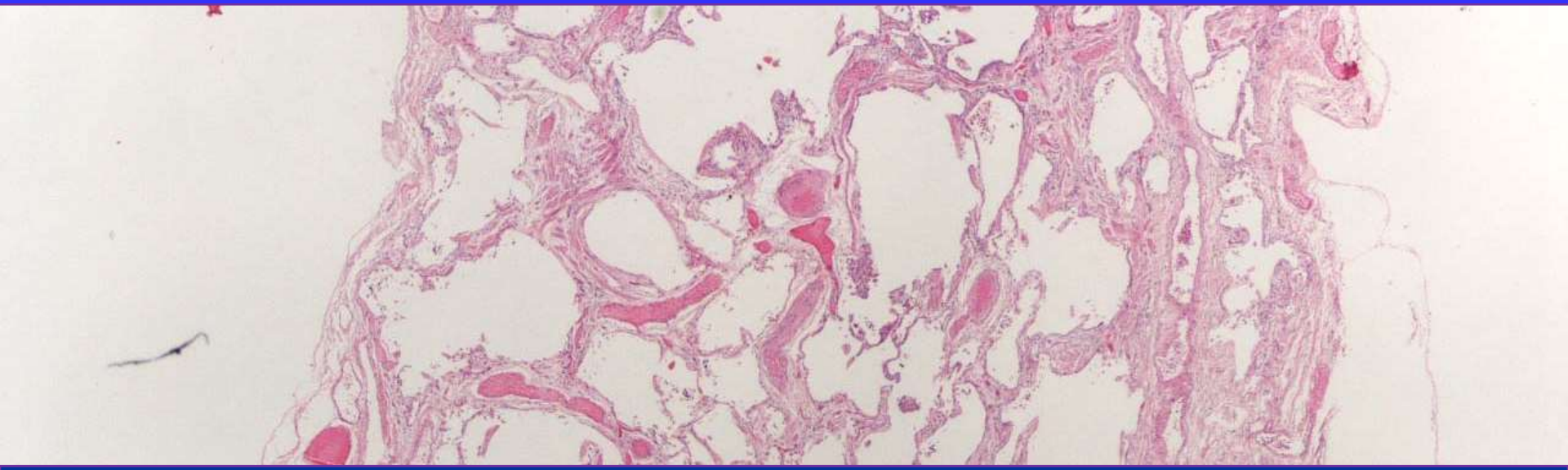


- ***Fibrosi uniforme***
- ***Architettura preservata***
- ***No/pochi focolai fibroblastici***

UIP

- ***Fibrosi "patchy"***
- ***Architettura alterata***
- ***Presenza di focolai fibroblastici***

NSIP fibrosante (forse!)



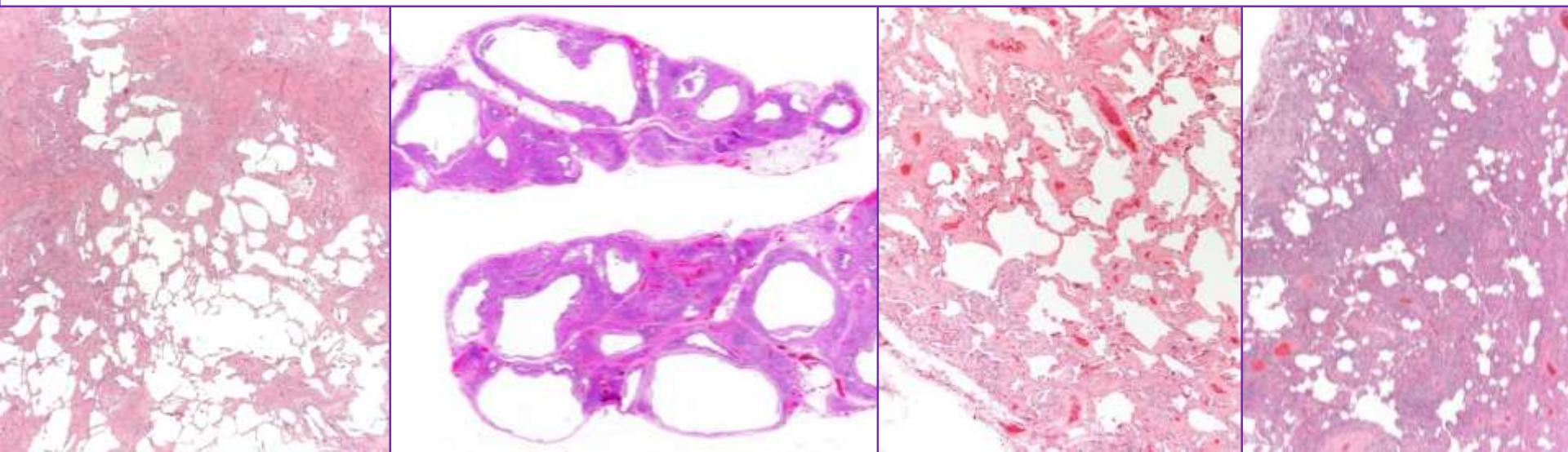
It is easy to be overcritical of the observer disagreement between histopathologists: in reality, histopathologic appearances may be intermediate between two entities in a significant proportion of cases, and observer variation may be an appropriate and accurate reflection of this fact

Wells. Am J Respir Crit Care Med 2004;170:828-829

Am J Respir Crit Care Med 2011; 183: 788-824

TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
• Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Evidence of marked fibrosis / architectural distortion, ± honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) OR • Honeycomb changes only‡	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (*see* UIP PATTERN column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	• Hyaline membranes* • Organizing pneumonia*† • Granulomas† • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis



Am J Respir Crit Care Med 2011; 183: 788-824

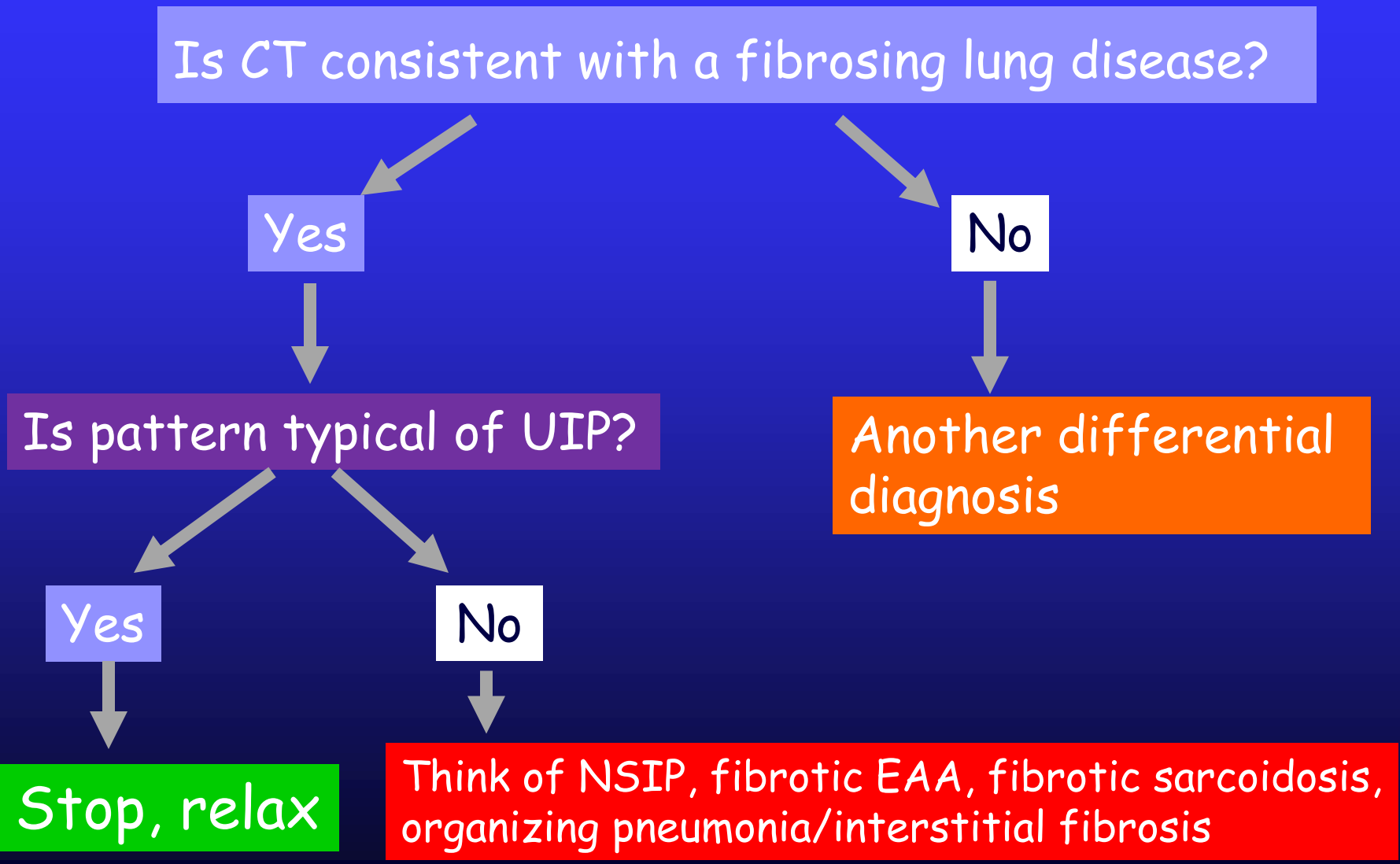
Combination Of HRCT and surgical lung biopsy for the diagnosis of IPF (requires multidisciplinary discussion)

HRCT pattern	Surgical lung biopsy pattern (when performed)	Diagnosis of IPF
UIP	UIP Probable UIP Possible UIP Non classifiable UIP	YES
Possible UIP	Not UIP	NO
	UIP	YES

"Not something for routine pathological reports… This scheme is not really workable except in the setting of selecting patients for clinical trials…"

T.V. Colby, comunicazione personale (Trento 2012, Roma 2013)
e Update for pathologists on idiopathic interstitial pneumonias
Larsen, Colby. Arch Pathol Lab Med 2012;136:1234-1241

A CT approach to "chronic fibrosing lung disease"



Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study

Morell et al. Lancet Respir Med 2013; 1: 684

20 of the 46 (43%, 95% CI 29-58) patients with IPF according to 2011 guidelines had a subsequent diagnosis of chronic hypersensitivity pneumonitis

Almost half of patients diagnosed with IPF on the basis of 2011 criteria were subsequently diagnosed with chronic hypersensitivity pneumonitis, and most of these cases were attributed to exposure of occult avian antigens from commonly used feather bedding.

ASCEND Study Design
Eligibility

- Age: 40–80 years
- HRCT: Confident diagnosis of IPF
  - Definite UIP, or
  - Possible UIP, with confirmation on SLB
- FVC: ≥50% and ≤90% percent of predicted
- DL_{CO}: ≥30% and ≤90% percent of predicted
- FEV_1/FVC ratio: ≥0.80
- Centralized review: spirometry, HRCT, SLB, deaths

King TE et al. *N Engl J Med* 2014 May 18. doi:10.1056/NEJMoa1402582

This article was published on May 18, 2014, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

- Age ≥40 years
- Diagnosis of IPF within 5 years of randomization
- Chest HRCT performed within 12 months of screening
- HRCT pattern, and, if available, surgical lung biopsy pattern, consistent with diagnosis of IPF, as assessed centrally by one expert radiologist and one expert pathologist
- FVC ≥50% of predicted value
- DL_{CO} 30–79% of predicted value

Primary endpoint

- Annual rate of decline in FVC (mL/year)

Key secondary endpoints

- Time to first acute exacerbation (investigator-reported) over 52 weeks
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over 52 weeks

Ascend study and HRCT

In the Ascend study 1007 out of 1562 patients assessed for eligibility by expert centres were excluded, with 445 not meeting the diagnostic criteria after central review.

Conclusions

- The early recognition of IPF starts with a high level of clinical suspicion
- The approach to the diagnosis of IPF requires a multi-disciplinary effort (pulmonologist, radiologist, and pathologist)
- Differentiating IPF from other ILDs can direct the management and predict the prognosis of these patients

Conclusions

- IPF can be diagnosed on HRCT in the majority of cases but a crucial sub-group have very atypical HRCT appearances
- Perform an accurate diagnosis of ILD and IPF is very difficult and complex!