Problemi aperti in Medicina Respiratoria: confronto con gli esperti
5-6 Giugno 2015 Catania

Diagnosi Differenziale IPF-UIP

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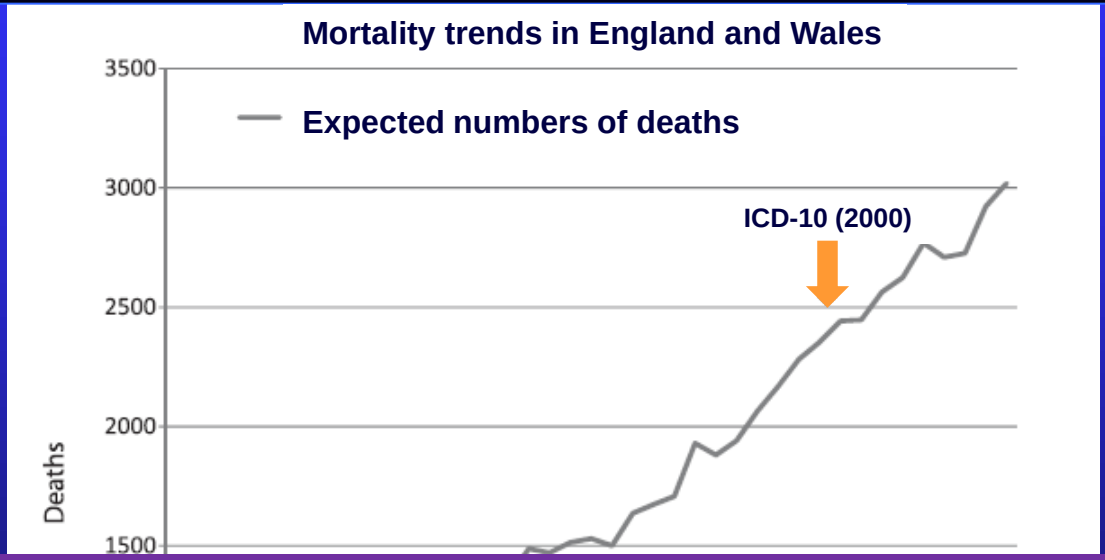
Diagnosis	Frequency	
Idiopathic Interstitial pneumonias		40%
Idiopathic pulmonary fibrosis	55%	
Non specific interstitial pneumonia	25%	
Respiratory bronchiolitis-ILD and desquamative interstitial pneumonia	15%	
Cryptogenic organizing pneumonia	3%	
Acute interstitial pneumonia	<1%	
Occupational and environmental		26%
Sarcoidosis		10%
Connective tissue diseases		9%
Drug and radiation		1%
Pulmonary hemorrhage		1%
Others		13%

The rising incidence of idiopathic pulmonary fibrosis in UK

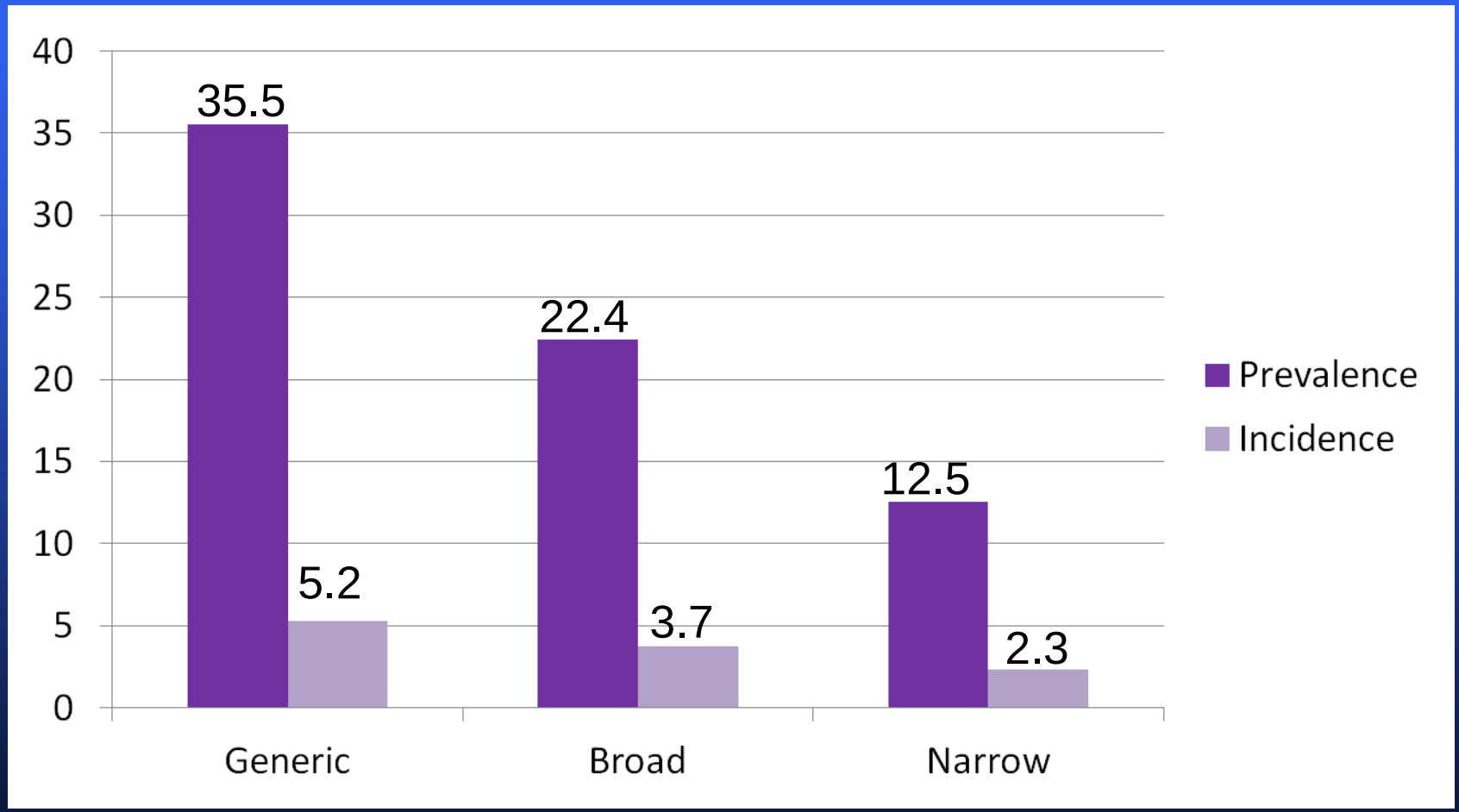
Navaratnam V et al. Thorax 2011;66:462

- 15000 people in the UK have a diagnosis of IPF-CS
- each year, 5000 new cases of IPF
- each year, 5000



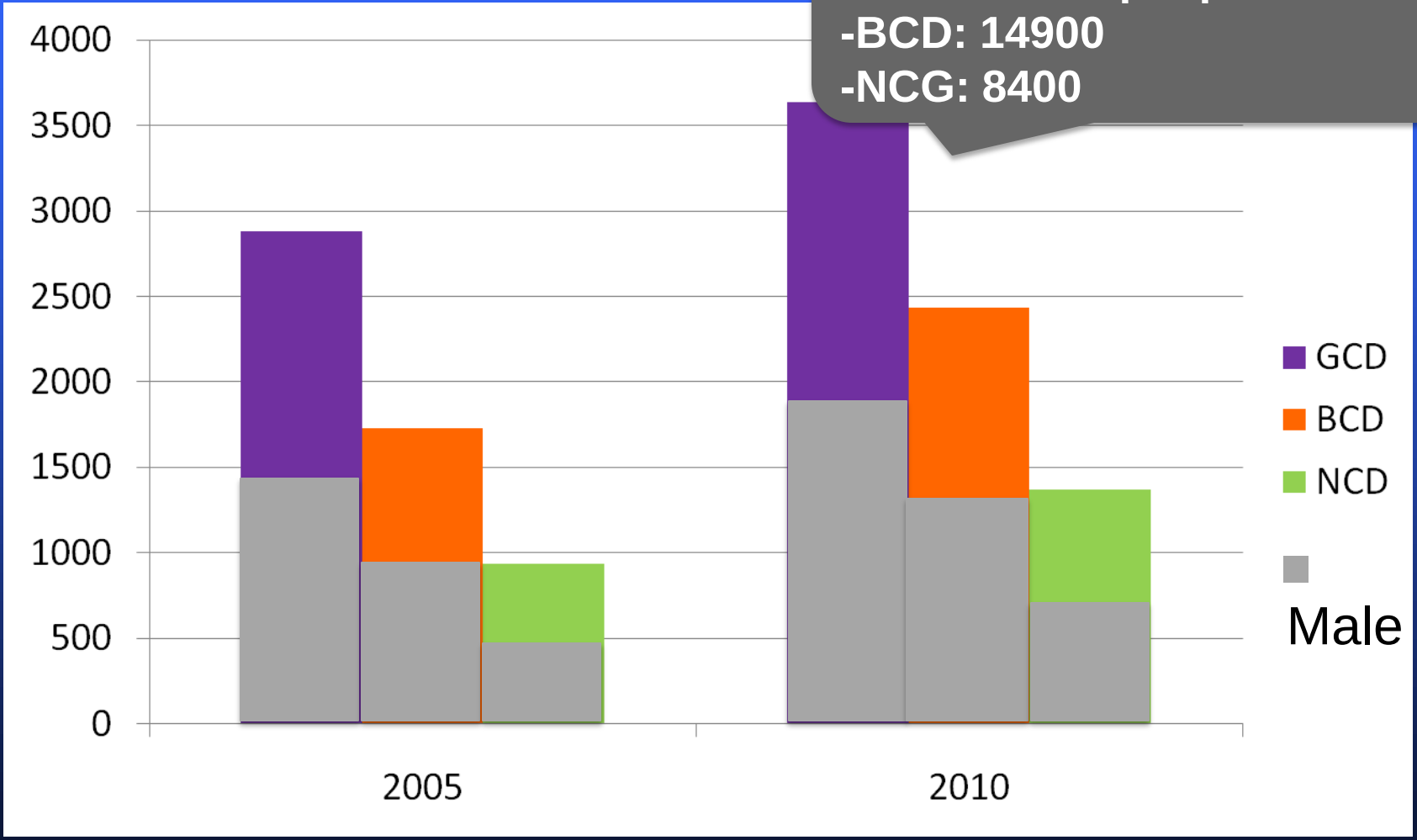
"This means that in the UK, more people will die each year from IPF-CS than from ovarian cancer, lymphoma, leukaemia, mesothelioma or kidney cancer"

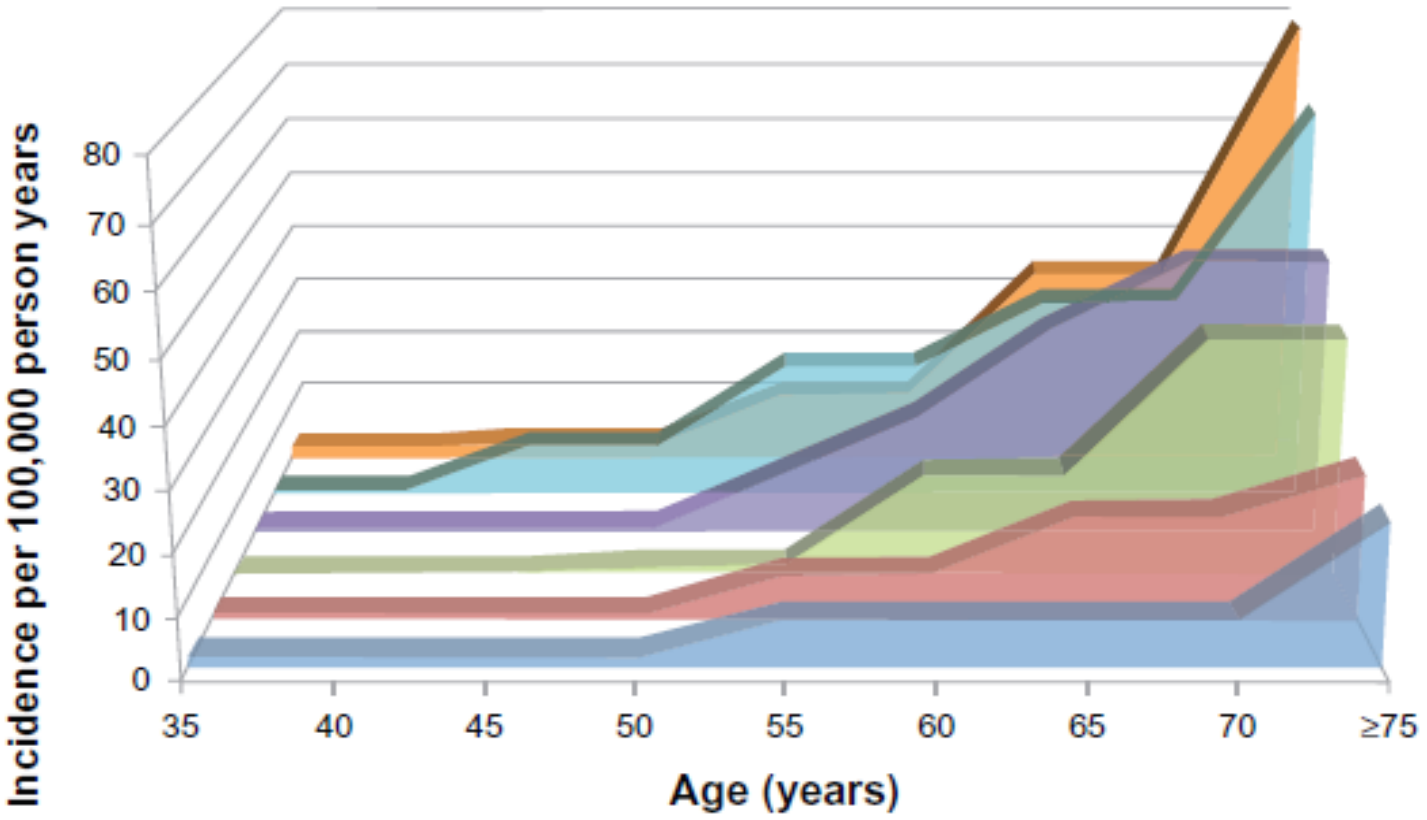
Prevalence and incidence rate *(x100,000 person-years) according to the three case definitions, during the period 2005-2010 in Lombardy*



Increase of prevalence - Lombardy

In Italy:
-GCD: 22300 people with IPF
-BCD: 14900
-NCG: 8400

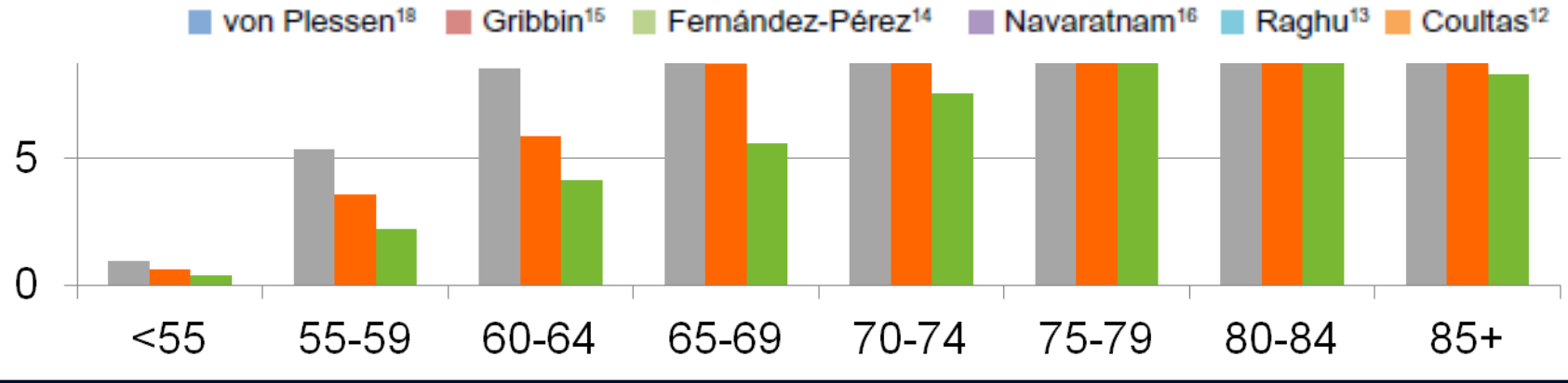



Incidence per 100,000 person years
80
70
60
50
40
30
20
10
0
35
40
45
50
55
60
65
70
≥75
Age (years)

GCD

BCD

NCD


von Plessen[18]
Gribbin[15]
Fernández-Pérez[14]
Navaratnam[16]
Raghu[13]
Coultas[12]
5
0
<55
55-59
60-64
65-69
70-74
75-79
80-84
85+

New definition of IPF

- IPF is a specific form of ***progressive*** fibrosing interstitial pneumonia
- Unknown cause
- Occurring in older adults
- Limited to the lungs
- Associated with a histological ***and/or radiological*** pattern of usual interstitial pneumonia (UIP)

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

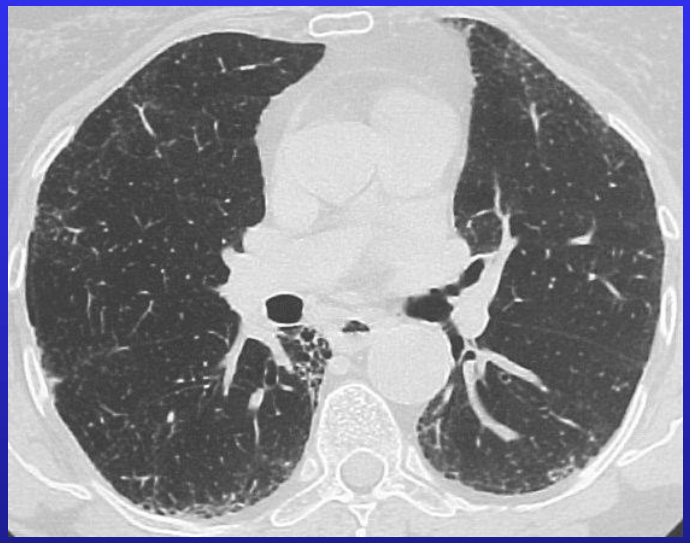
Importance of early diagnosis of IPF

- 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

UIP: progression of fibrosis on CT

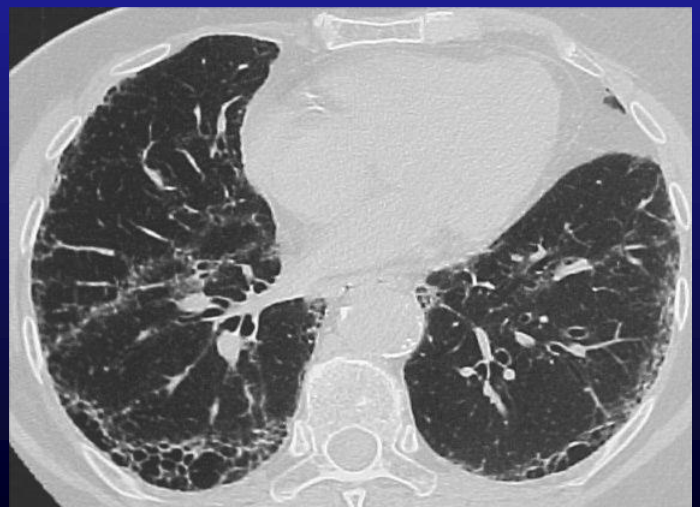
Early:

Reticular



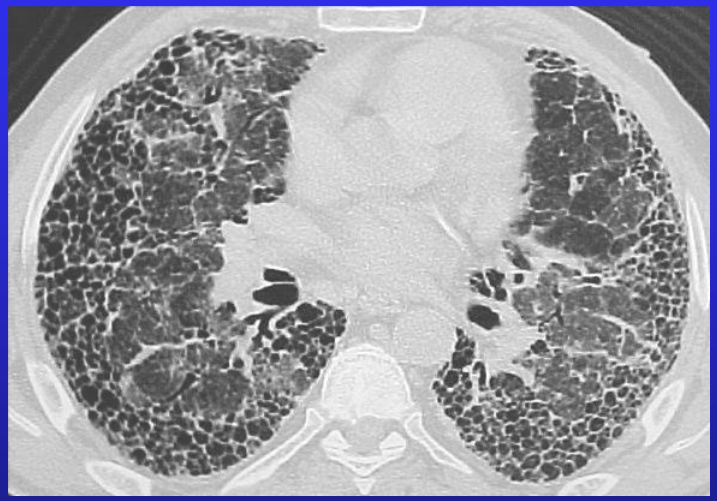
Midcourse:

Subpleural honeycombing



Late:

Diffuse honeycombing



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

American Thoracic Society Documents

An official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias

Travis TW et al. Am J Respir Crit Care Med 2013; 188: 733

Major IIPs are distinguished from rare IIPs and unclassifiable cases

Chronic fibrosing IIP

Smoking-related IIP

Acute/subacute IIP

NSIP is now accepted as a distinct clinical entity

rstitial pneumonias
Idiopathic pulmonary fibrosis
c interstitial pneumonia
litis-interstitial lung disease
itial pneumonia
ng pneumonia
Acute interstitial pneumonias
Rare idiopathic interstitial pneumonia
Idiopathic pleuro-parenchymal fibroelastosis
Idiopathic lymphoid interstitial pneumonia
Unclassifiable idiopathic interstitial pneumonias


Made in U.S.A.

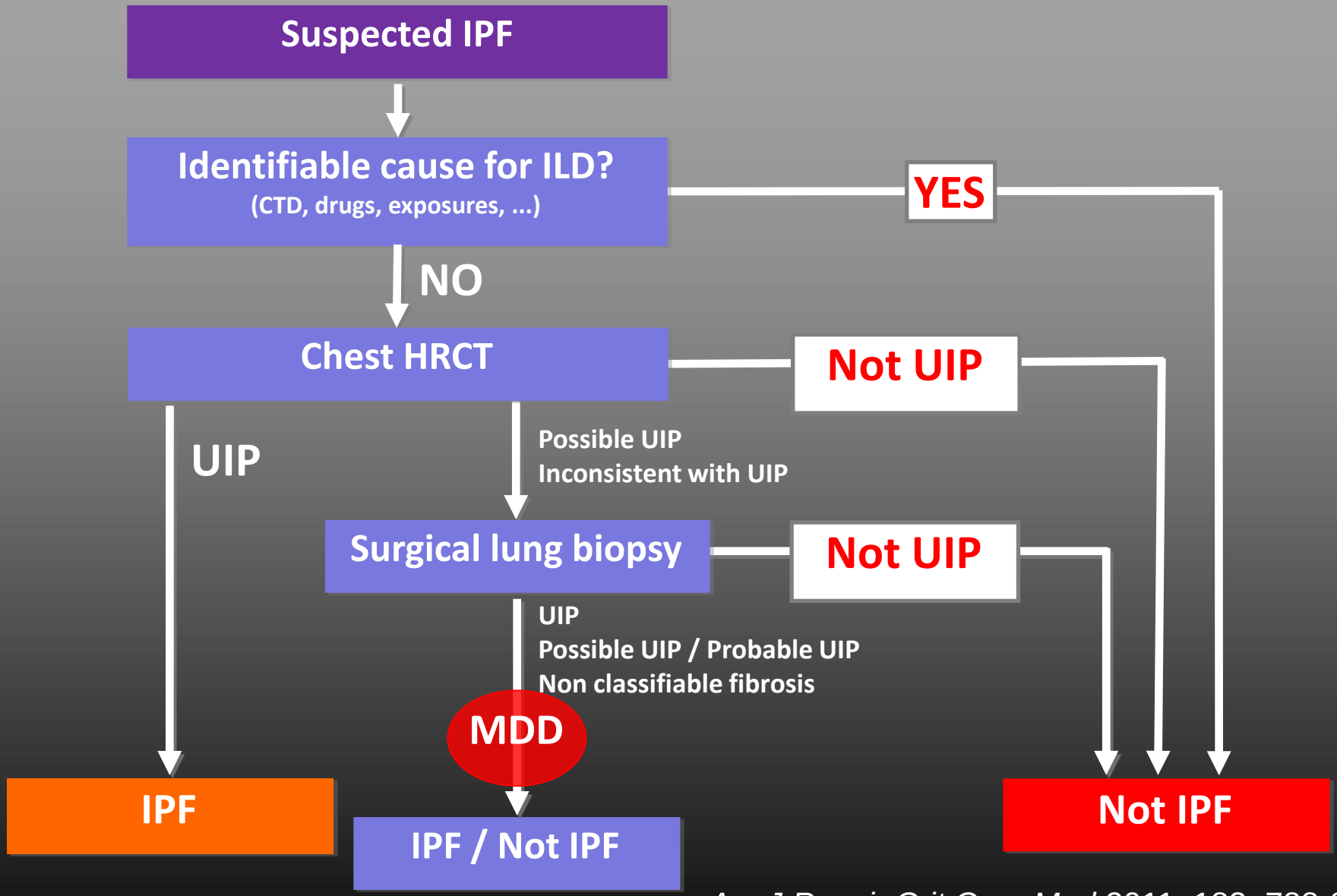
Typical exam is non-specific

Dry bi-basilar crackles most common finding

Inspiratory high-pitched squeaks can be seen with bronchiolitis

Skin, joint, or muscle findings should prompt evaluation for an underlying rheumatologic disorder

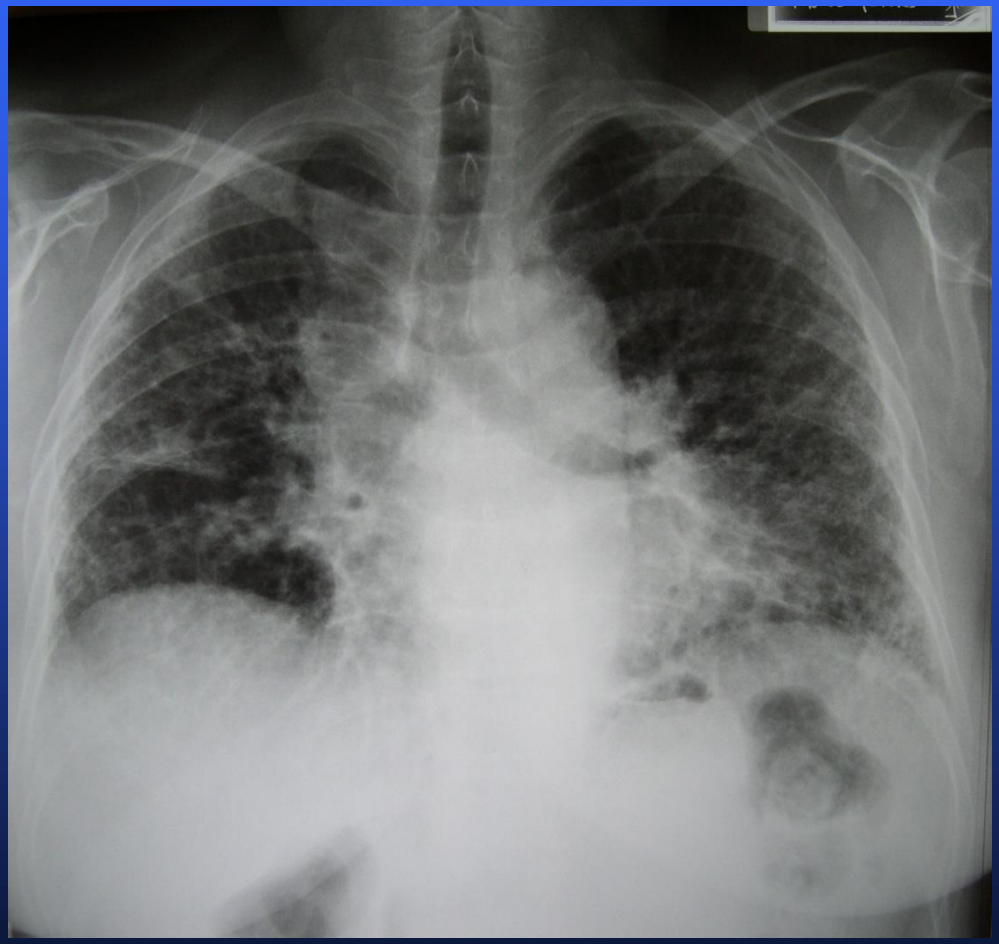
Diagnostic algorithm for IPF



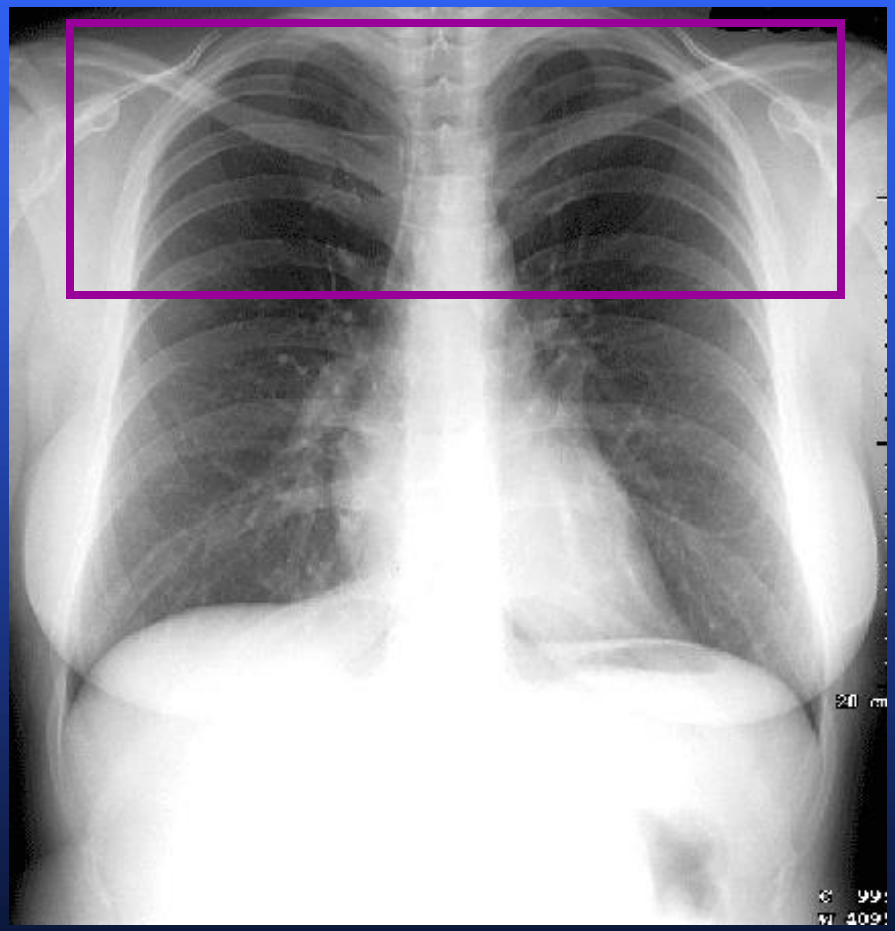
Am J Respir Crit Care Med 2011; 183: 788-824

Radiografia standard del Torace

La radiografia standard del torace è un momento importante nella valutazione di un paziente con pneumopatia infiltrativa diffusa, tuttavia la sensibilità della metodica è bassa e la specificità scarsa



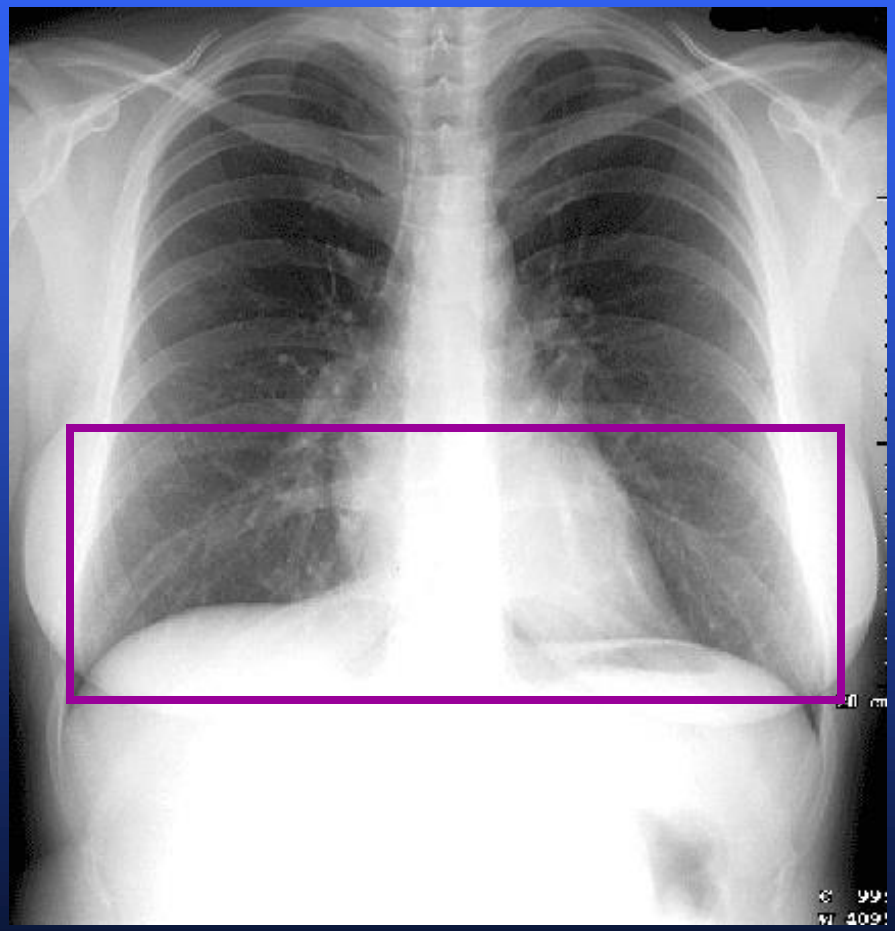
Radiografia standard del Torace



Predominanza Zone Superiori

- Sarcoidosi
- Istiocitosi X
- Silicosi
- Polmoniti da ipersensibilità
- Polmonite eosinofila cronica
- Farmaci

Radiografia standard del Torace

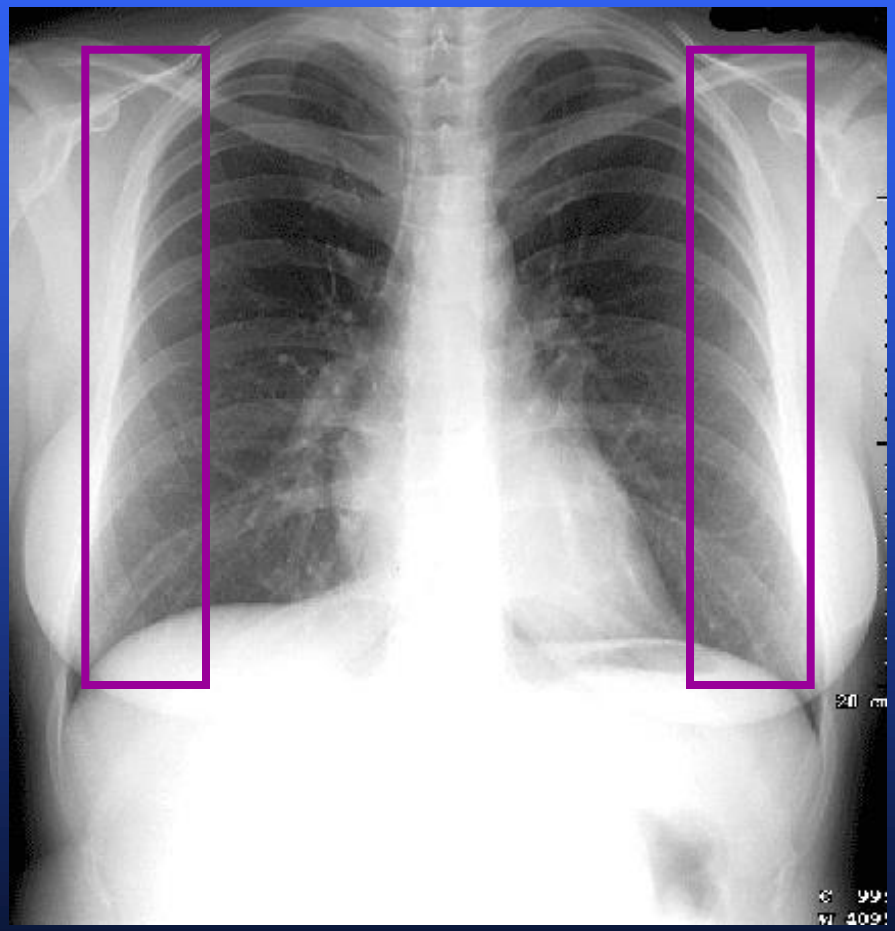


Predominanza Zone Inferiori

- Fibrosi Polmonare Idiopatica
- Asbestosi
- Connettiviti

Cortesia Prof. Pesci

Radiografia standard del Torace



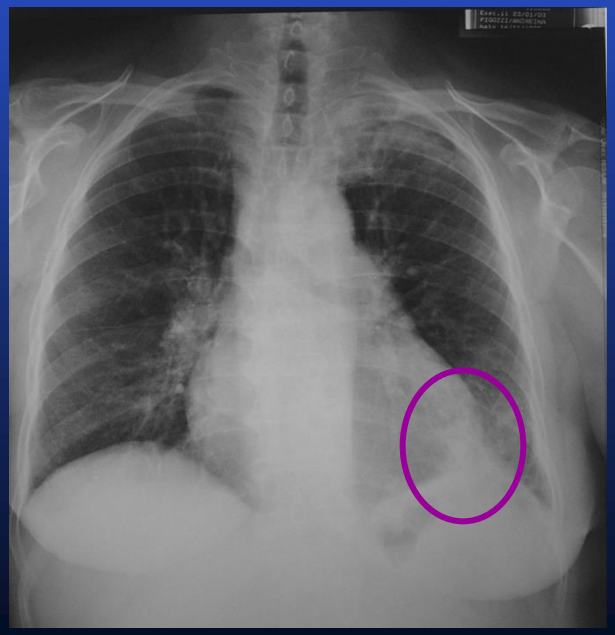
Predominanza Zone Periferiche

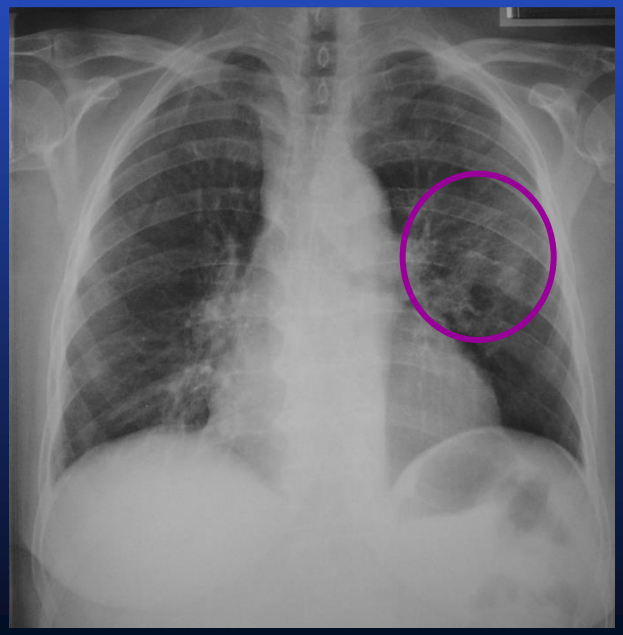
- Polmonite Eosinofila Cronica
- Polmonite Organizzativa Idiopatica

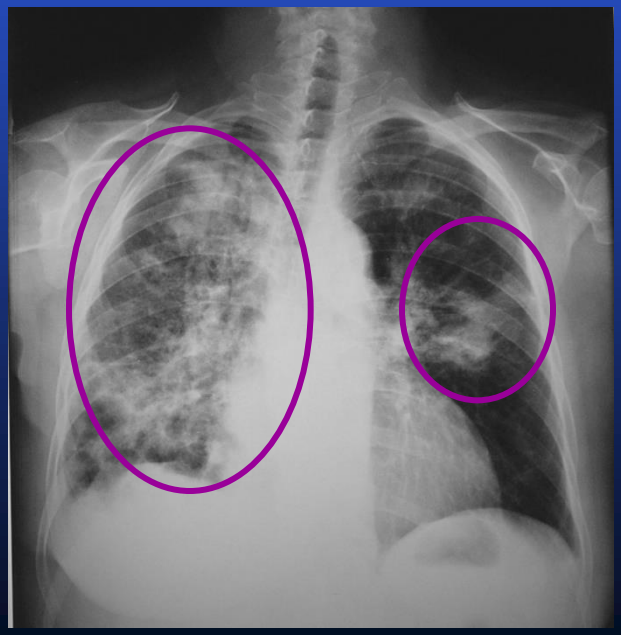
Radiografia standard del Torace

Infiltrati Migranti

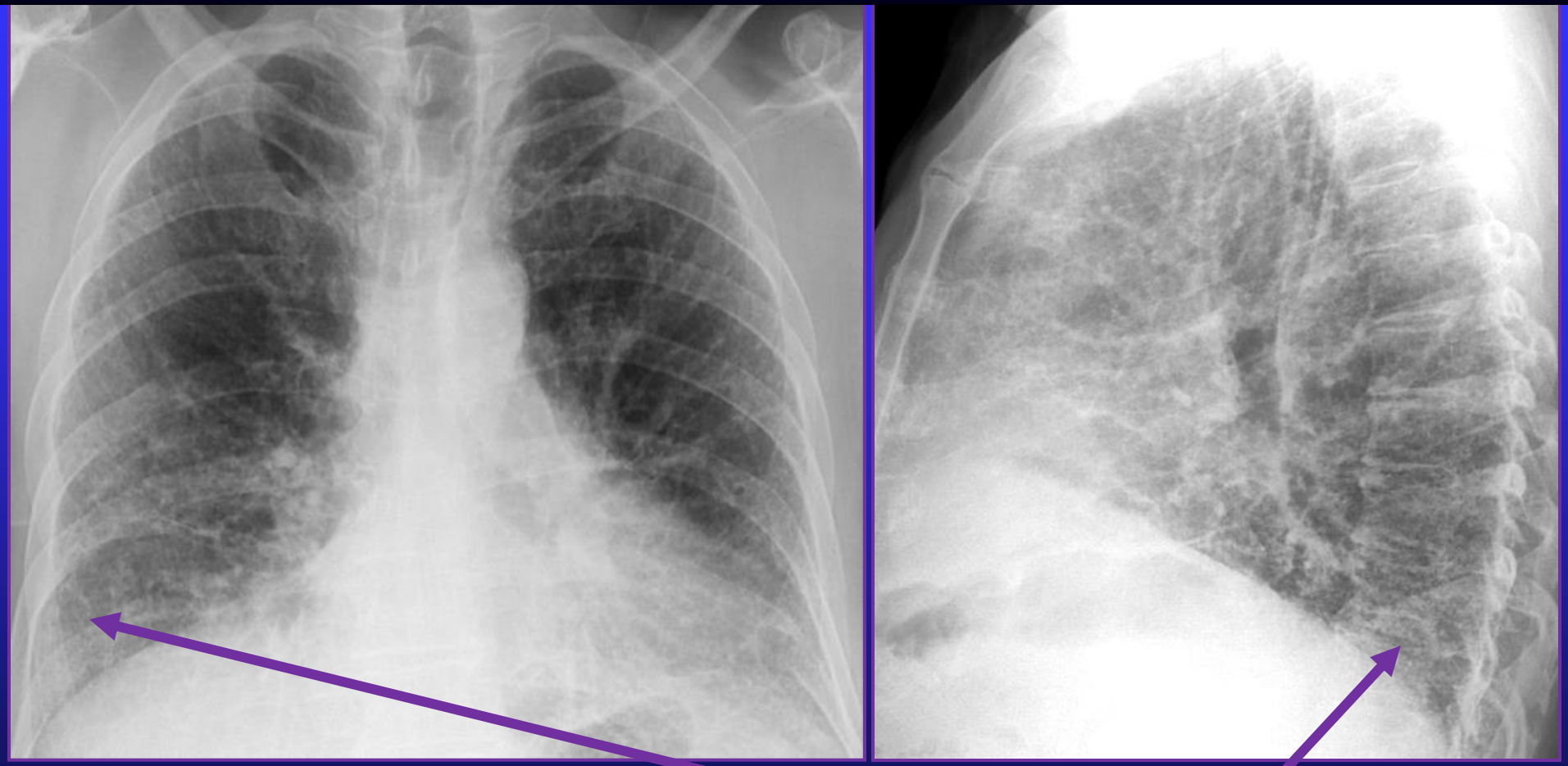
- Polmonite Eosinofila Cronica
- Polmonite Organizzativa Idiopatica
- Farmaci







Chest radiograph in IPF

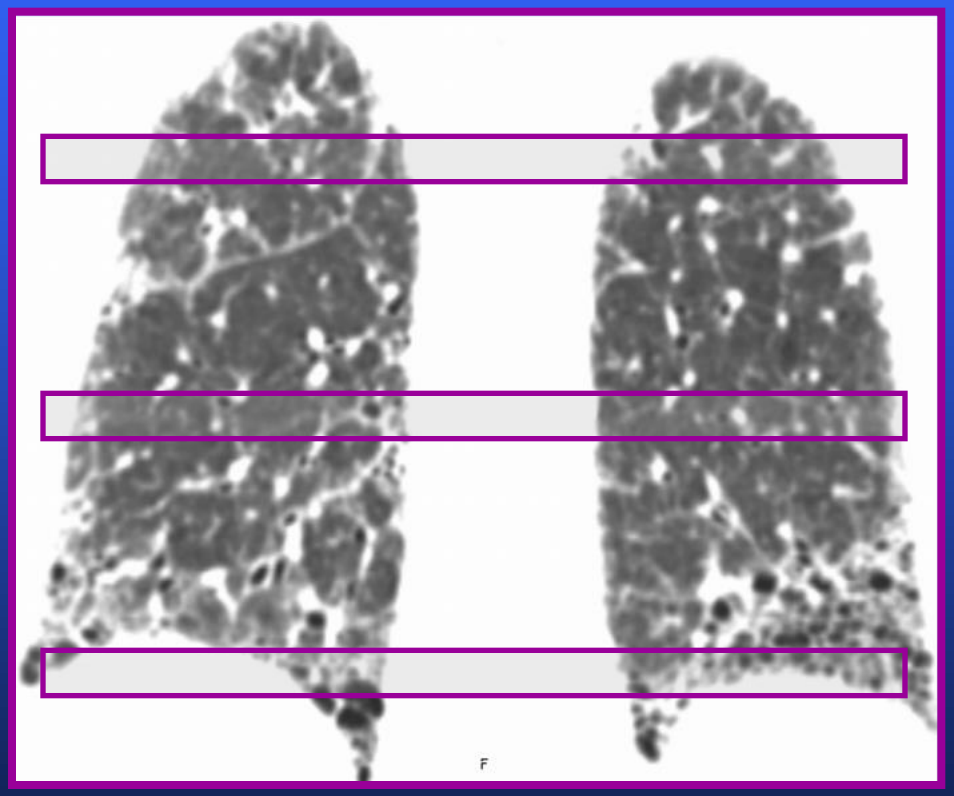


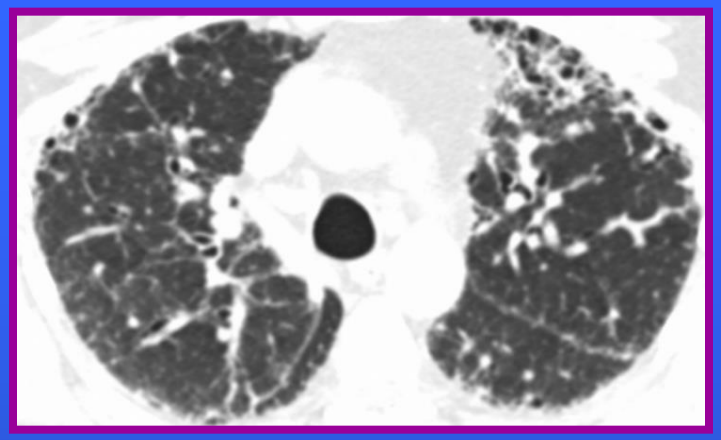
Reduced lung volume

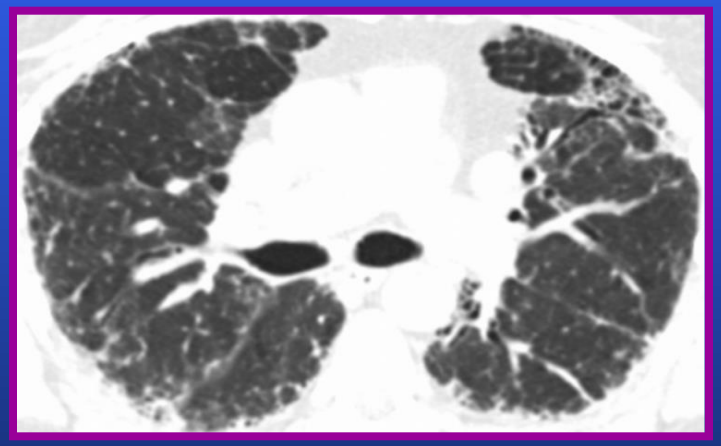
Basal and peripheral reticulation

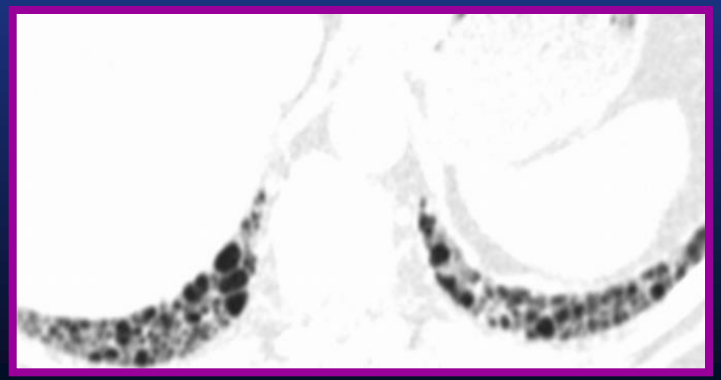
A normal chest x-ray does not exclude IPF

HRCT

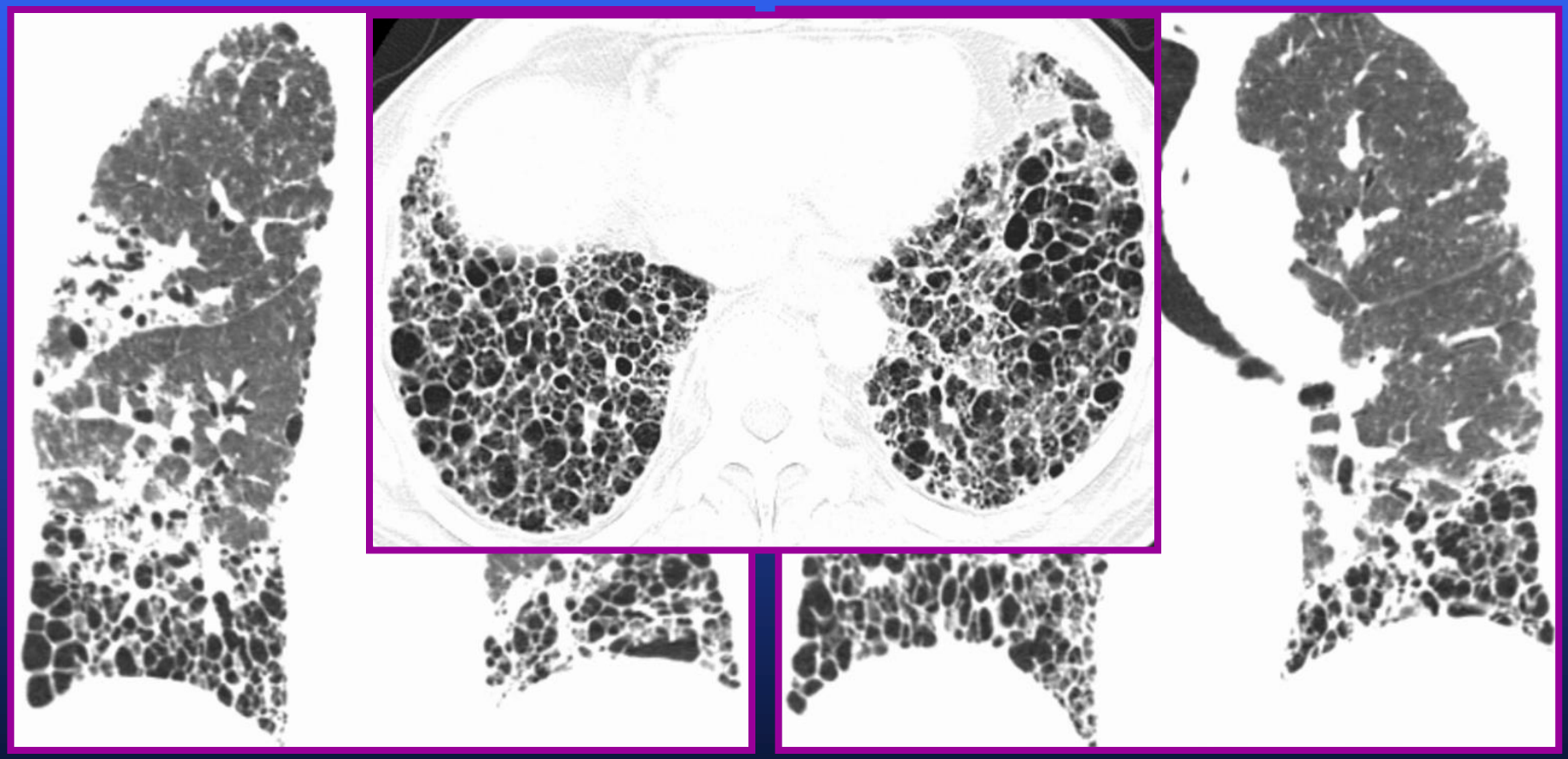




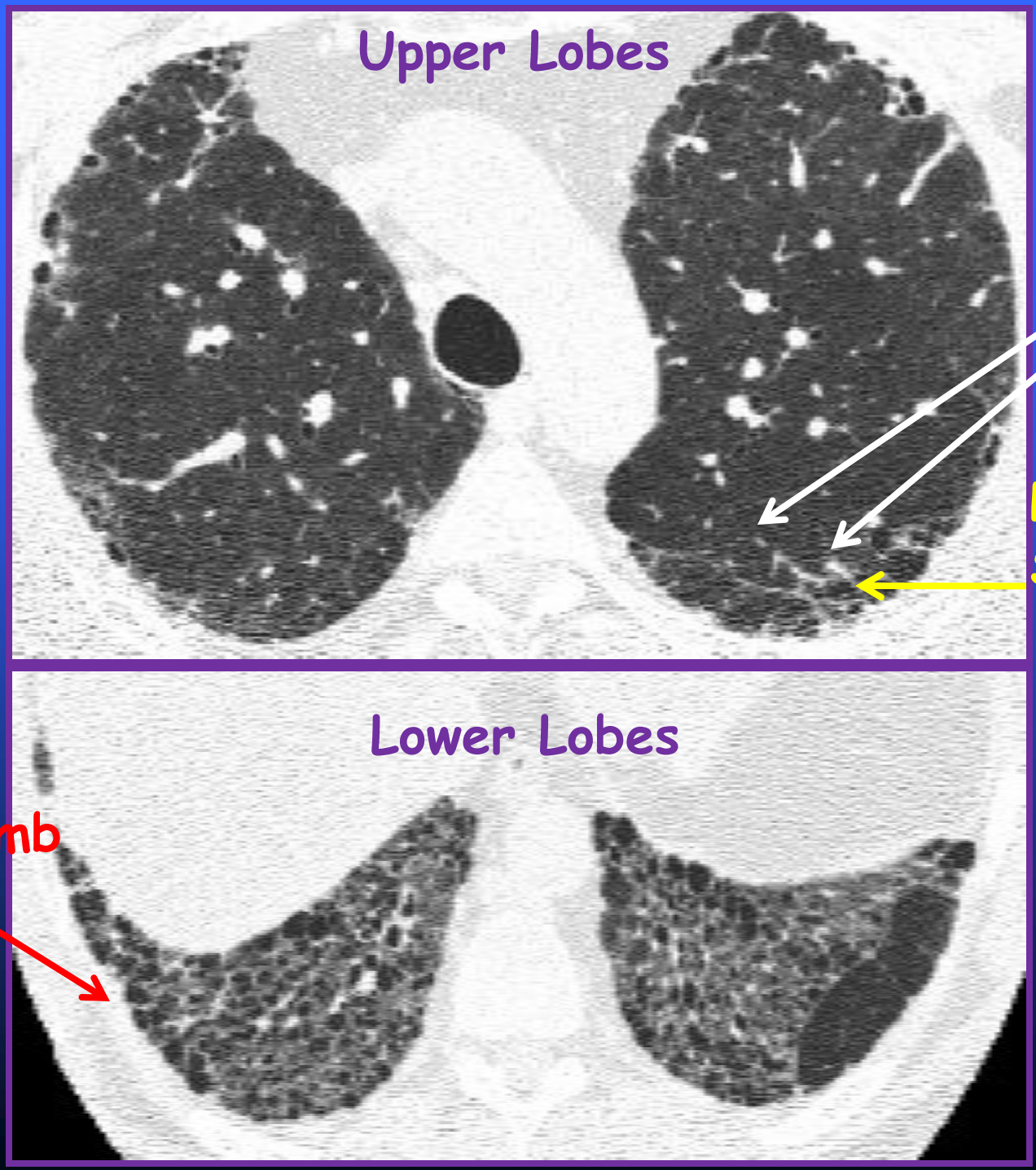




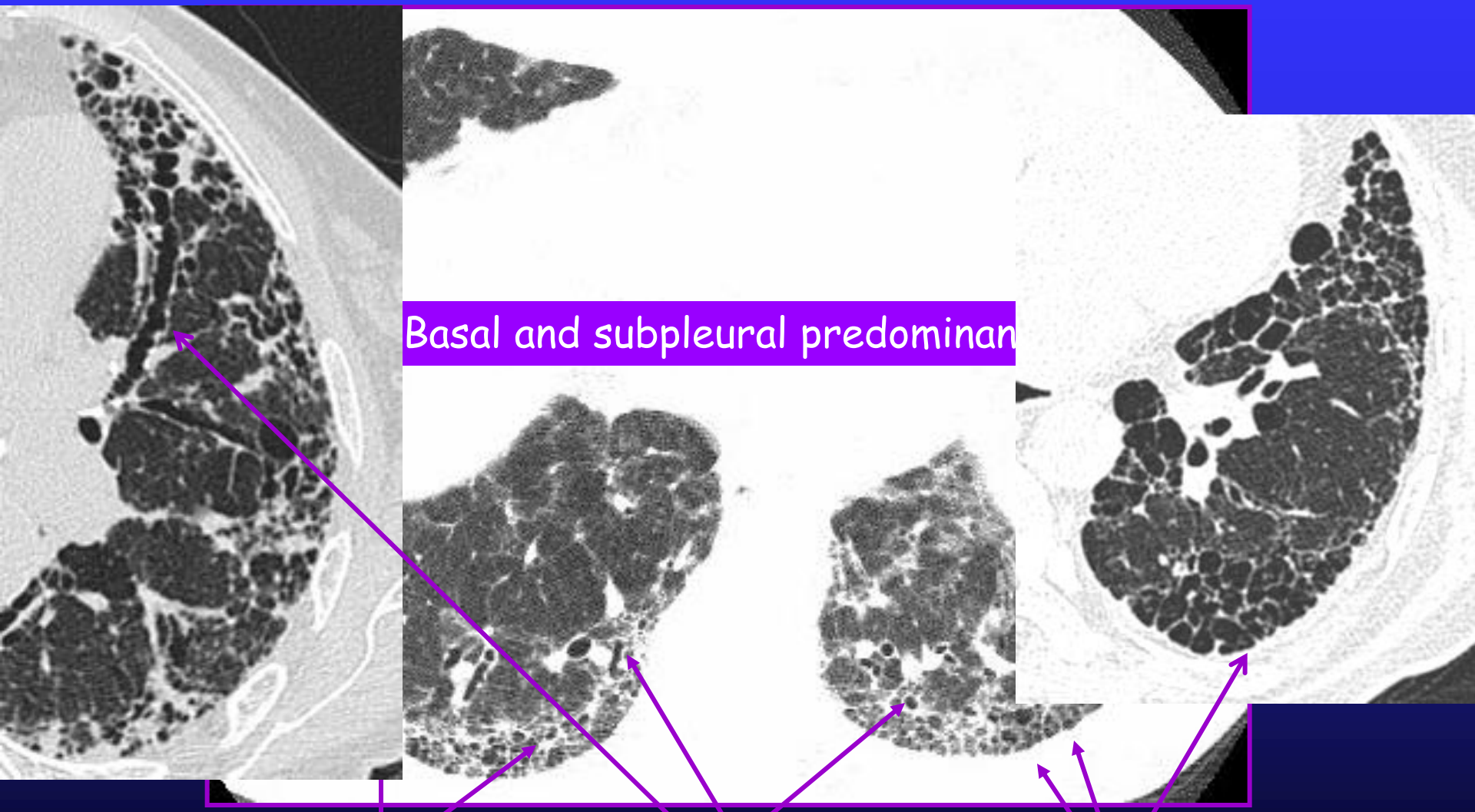
HRCT e Polmone
Honeycombing



UIP


Upper Lobes
Irregular lines
Peripheral/ Sub-pleural
Lower Lobes
Honeycomb
Lower Lobe Predominant

Classic IPF HRCT

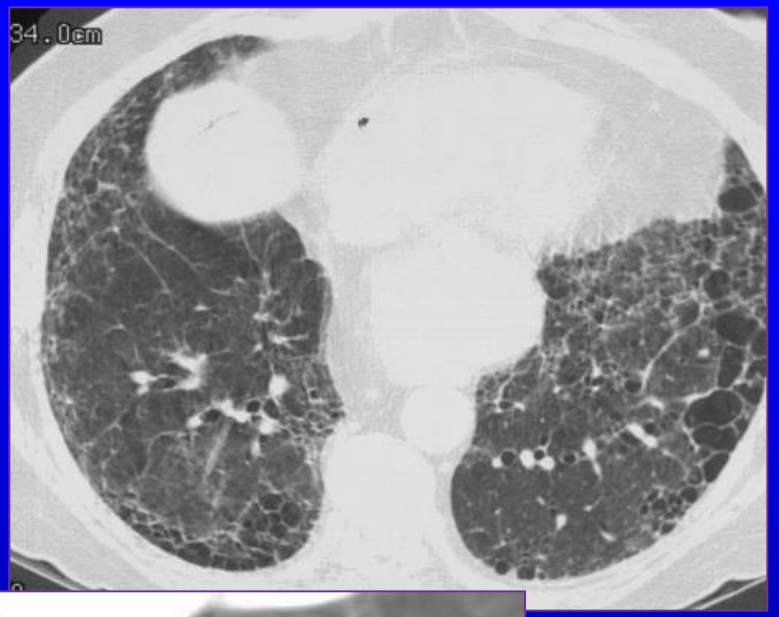


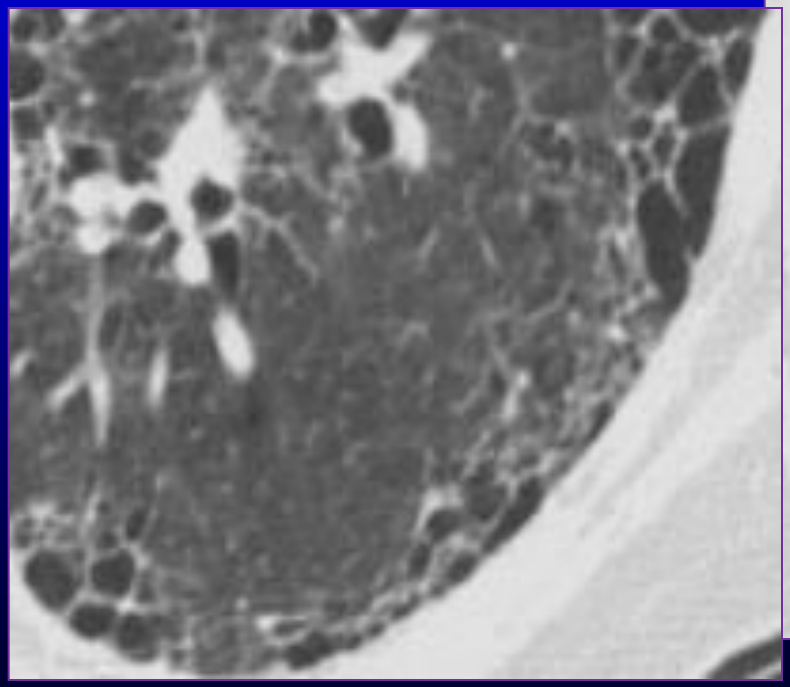
HRCT

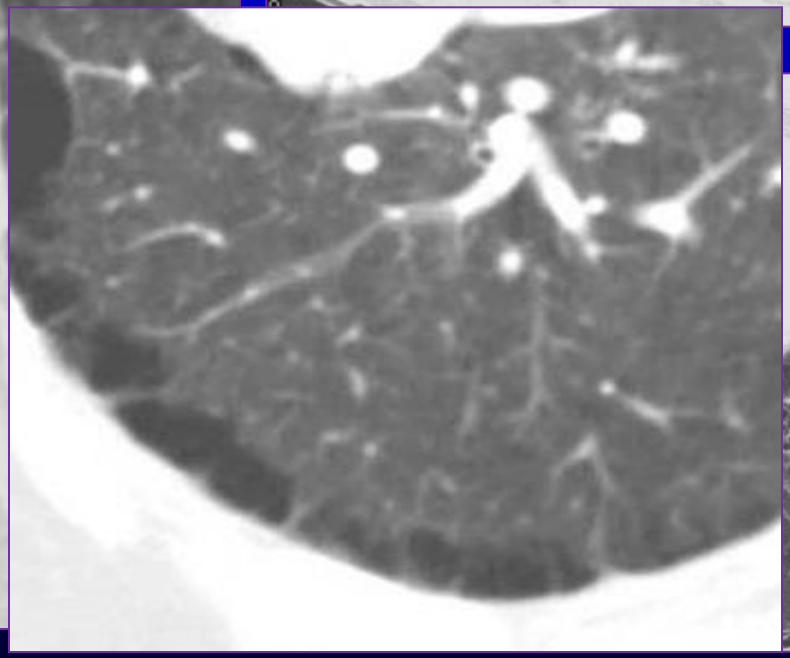
features of fibrosis,

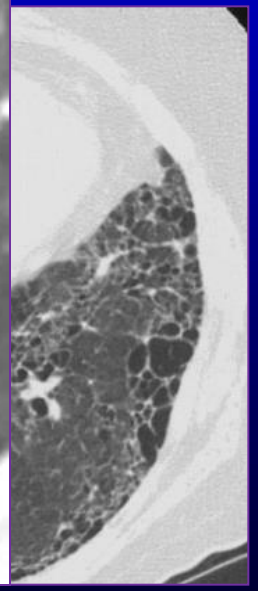
Intra-lobular and inter-lobular septal thickening, walled cysts representing honeycombing,

may be associated traction bronchiectasis







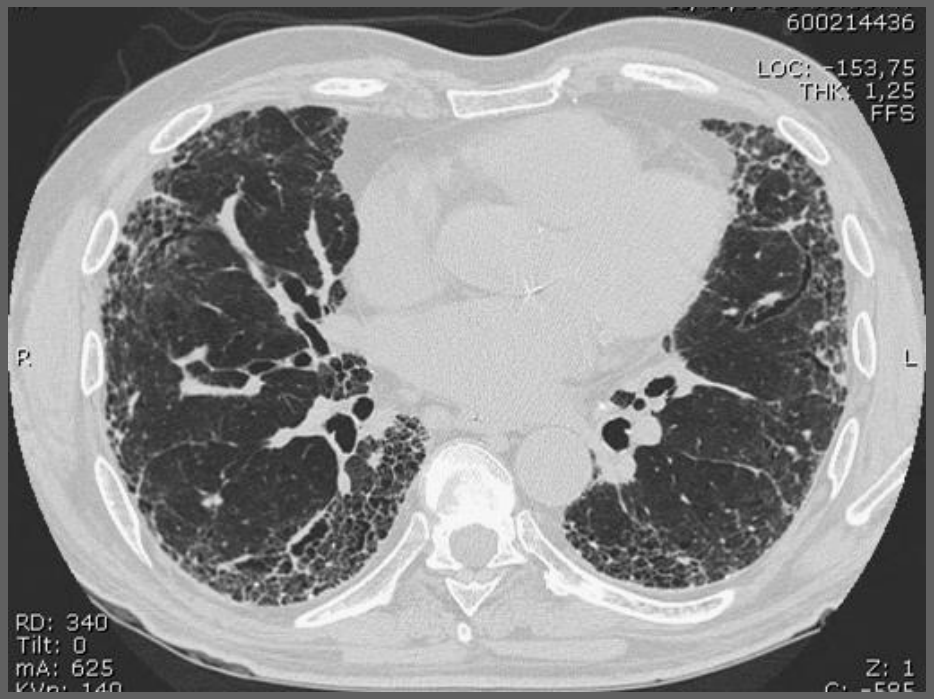


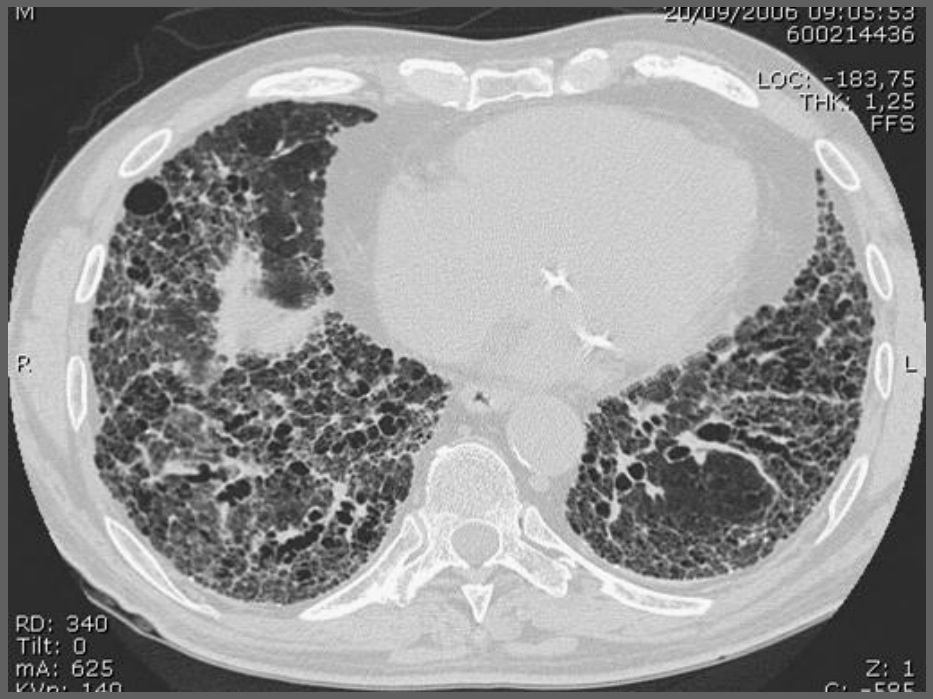
"The diagnosis of IPF *requires*:

a) exclusion of other known causes of interstitial lung disease

a) the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy

a) specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy"



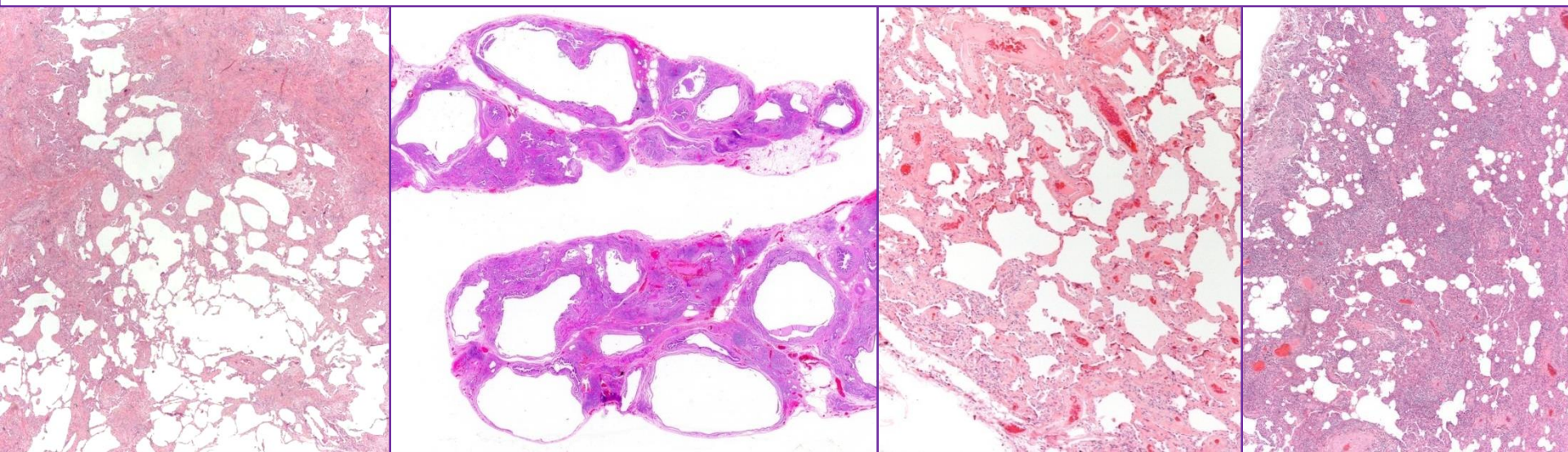


***Am J Respir Crit Care Med* 2011; 183: 788-824**

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



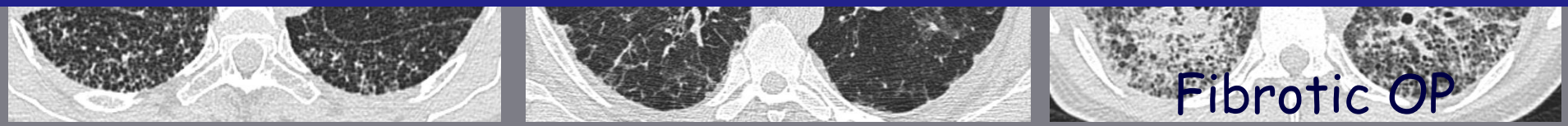
HRCT Pattern	Surgical Lung Biopsy Pattern *(when performed)*	Diagnosis of IPF?
UIP	**UIP** **Probable UIP** **Possible UIP** **Non-classifiable fibrosis**	**YES**
	Not UIP	**No**
Possible UIP	**UIP** **Probable UIP**	**YES**
	Possible UIP **Non-classifiable fibrosis**	***Probable***
	Not UIP	**No**
Inconsistent with UIP	**UIP**	***Possible***
	Probable UIP **Possible UIP** **Non-classifiable fibrosis** **Not UIP**	**No**

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

Inconsistent with UIP pattern (any of the seven):

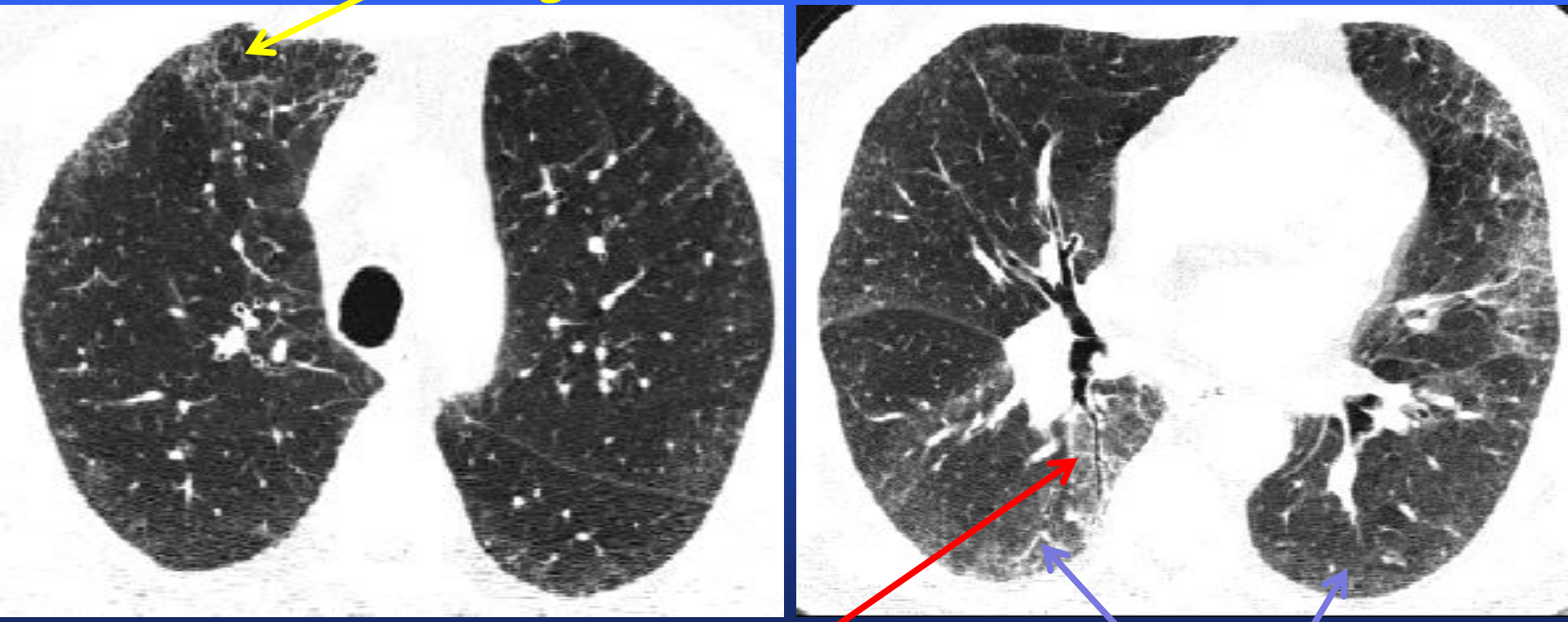
- Upper or mid-lung predominance
- Peribronchovascular predominance
- Extensive groud glass abnormality (extent > reticular abnormality)
- Profuse micronodules (bilateral, predominantly upper lobes)
- Discrete cysts (multiple, bilateral, away from areas of honeycombing)
- Diffuse mosaic attenuation/air-trapping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

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



HRCT e Polmone

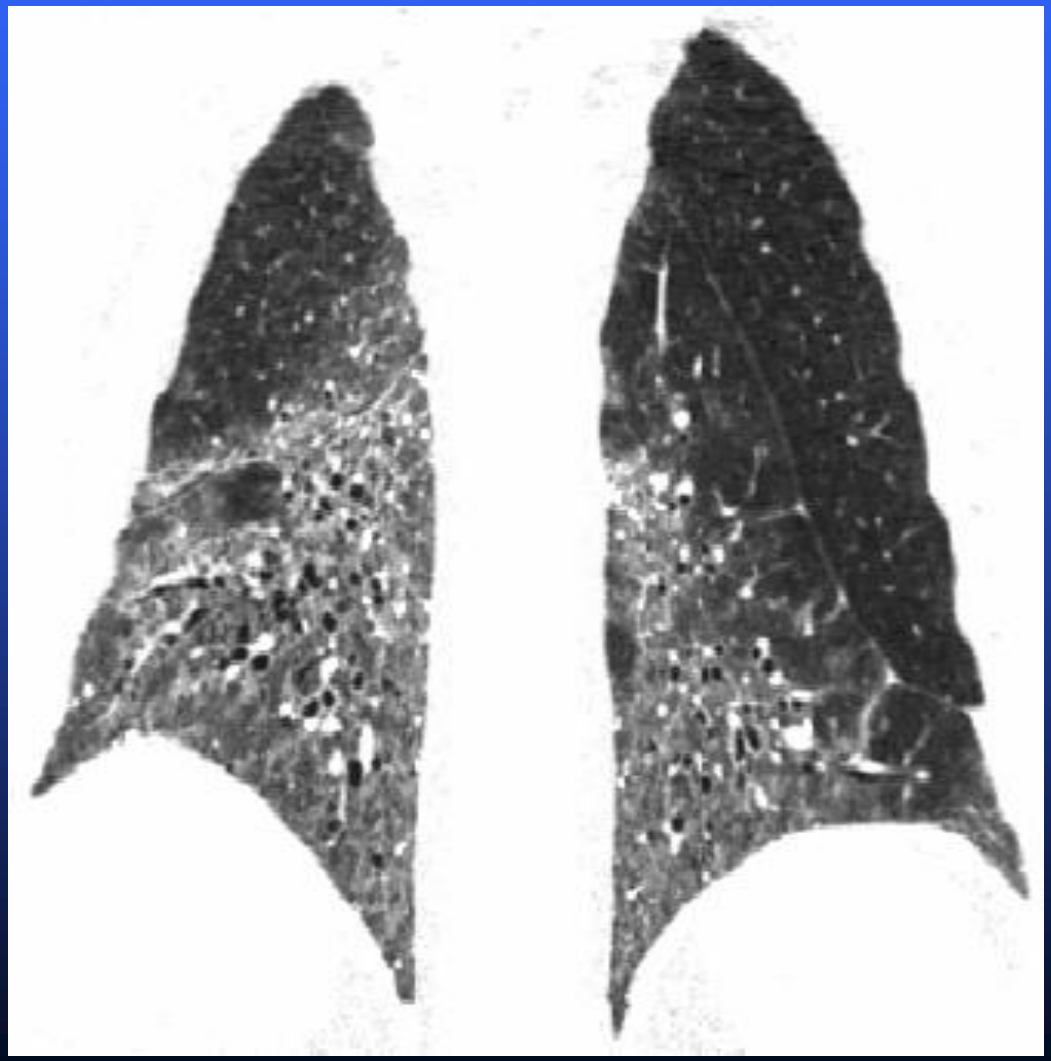
Non Specific Interstitial Pneumonia



Peripheral/
Lower Lobes
distribution

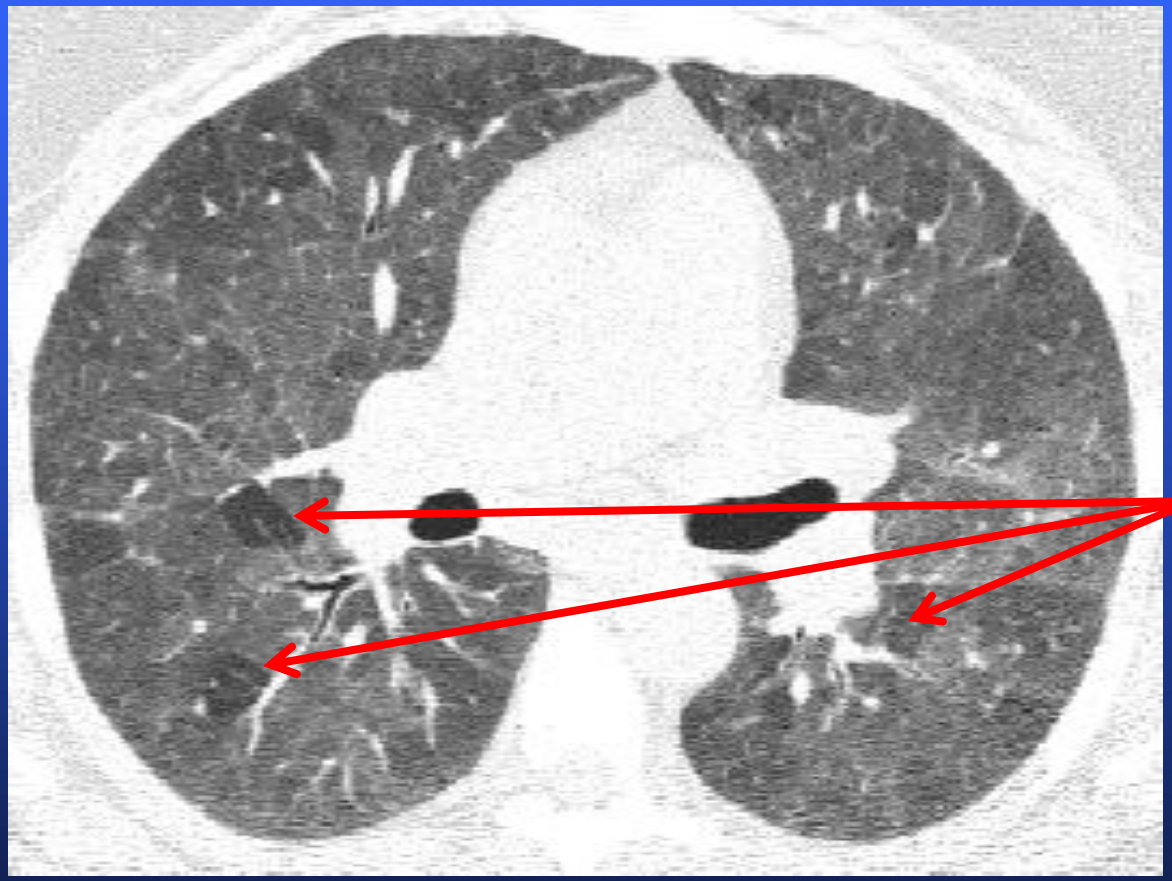
HRCT e Polmone

Non Specific Interstitial Pneumonia



HRCT e Polmone

Hypersensitivity Pneumonitis



Mosaic

- Ground glass
- air-trapping

**Note: if chronic, fibrosis can mimic UIP, but is usually patchy and less sub-pleural and lower lung in distribution

Chronic EAA

Churg A et al. Am J Surg Pathol 2006;30:201-8

- Traditionally divided on clinical grounds into acute, subacute, and chronic stages. Most biopsy specimens come from patients in the subacute stage.
- **Pathologic features in chronic, ie, fibrotic stage (n=13) showed 3 patterns:**
  1) **predominantly peripheral fibrosis in a patchy pattern with architectural distortion and fibroblast foci resembling, microscopically UIP;**
  2) relatively homogeneous linear fibrosis resembling fibrotic NSIP;
  3) irregular predominantly peribronchiolar fibrosis. In some instances, mixtures of the UIP-like and peribronchiolar patterns were found.

Chronic EAA

Churg A et al. Am J Surg Pathol 2006;30:201-8

- The presence of isolated giant cells, poorly formed granulomas, or Schaumann bodies is crucial to arriving at the correct diagnosis, and the finding of peribronchiolar fibrosis may be helpful.

- Despite the presence of extensive fibrosis, some patients responded to removal from exposure and steroid therapy

Chronic hypersensitivity pneumonitis: differentiation from UIP and NSIP using thin-section CT

Silva C. Radiology 2008; 246: 288

HRCT findings allow confident distinction of chronic HP from IPF and NSIP approximately 50% of the time

Diagnosis of HP at CT prompts a thorough clinical history to determine inciting antigens and removal of

IIPs are frequently confused with HP, and vice versa, except when the exposure is readily apparent
A detailed search for potential exposure in patients with these findings is essential, including consideration of specific circulating IgG antibodies, but up to 30% of subjects with histological HP have no identifiable exposure

The spectrum of atypical HRCT appearances in IPF

- Exploration of biopsy-proven IPF (n=55)
- As expected, a high prevalence of atypical HRCT findings (n=34, 62%), as judged by three observers
- Alternative HRCT diagnoses analysed

Sverzellati N et al. Radiology 2010; 254:957-64

Atypical HRCT appearances in IPF

- Alternative first choice diagnoses were NSIP (53%), chronic HP (12%), sarcoidosis (9%), “unclassifiable” (23%)

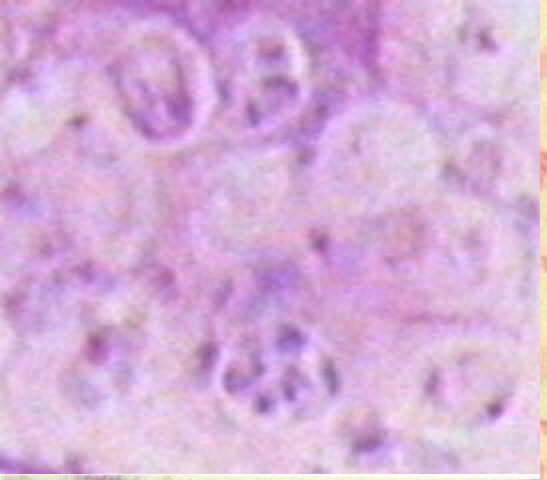
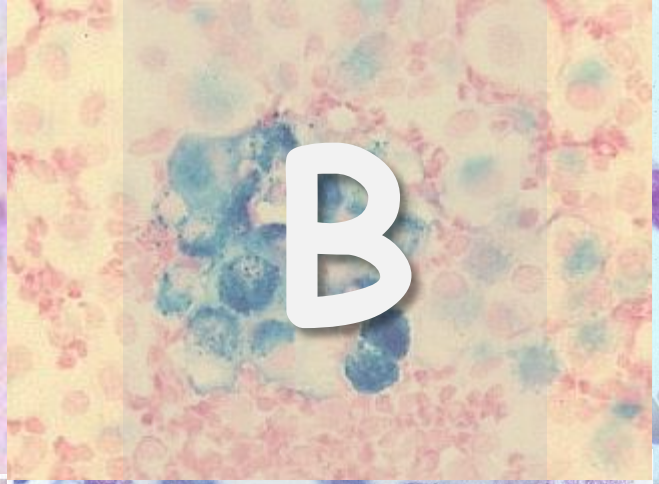
- Cases with atypical appearances had the same IPF-like outcome as those with typical HRCT appearances

Sverzellati N et al. Radiology 2010; 254:957-64

Reason for being unclassifiable

Reasons	•Examples
No biopsy performed or biopsy non-contributory (unclassifiable clinical/radiological condition)	• Biopsy non proposed (stable or mild disease with biopsy risk outweighing benefit) •Contraindication to biopsy •Biopsy suggested but refused by patient •Inadequate biopsy sample
Overlapping histological features (unclassifiable histology)	•NSIP/UIP overlap •HP/UIP overlap, etc.
Major discrepancy (unclassifiable clinical/radiological/ pathological condition)	•Stable disease, but UIP on histology

10-20% of ILD patients remain unclassified after multidisciplinary evaluation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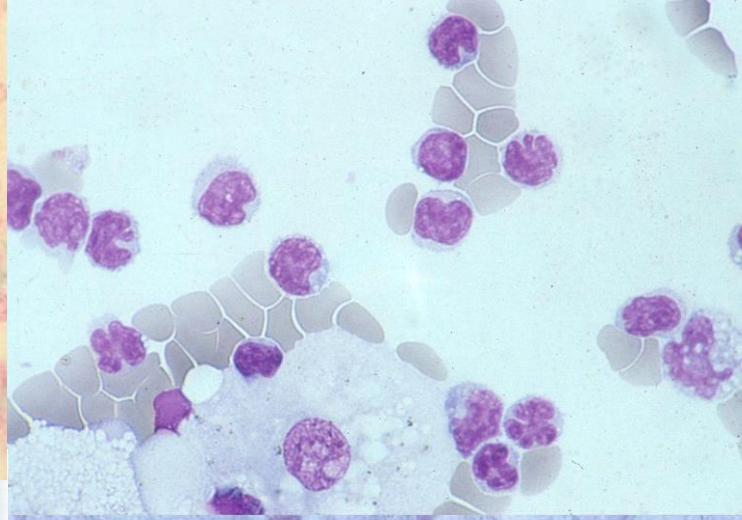
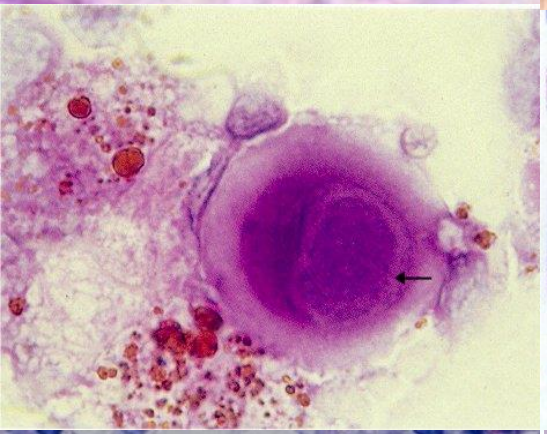
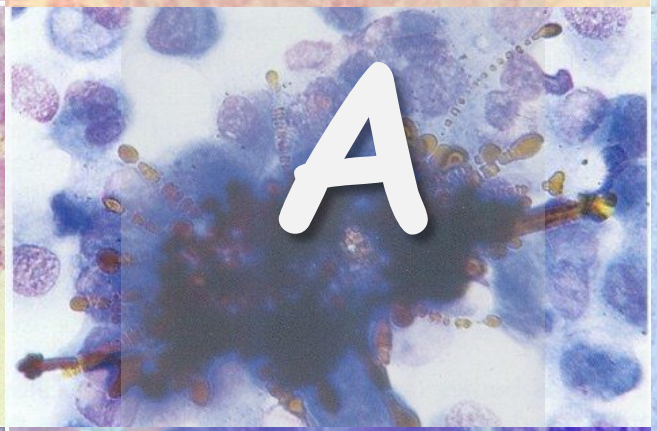
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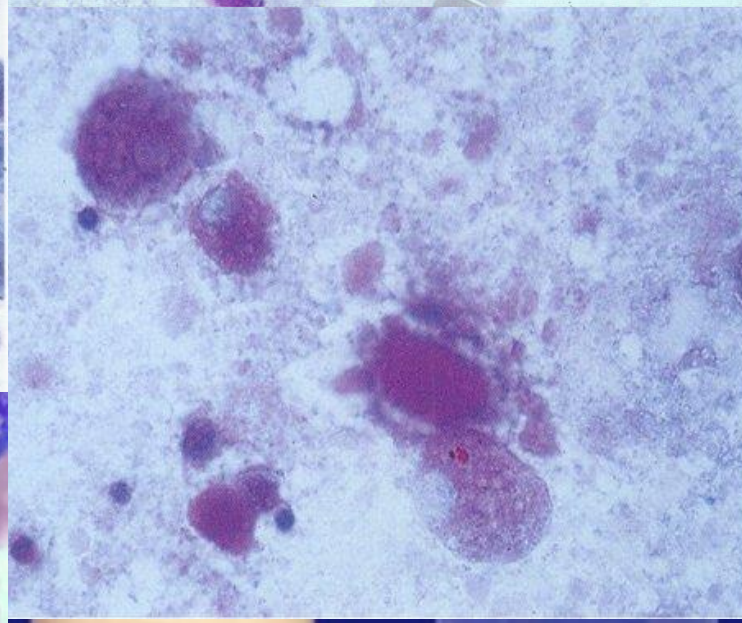
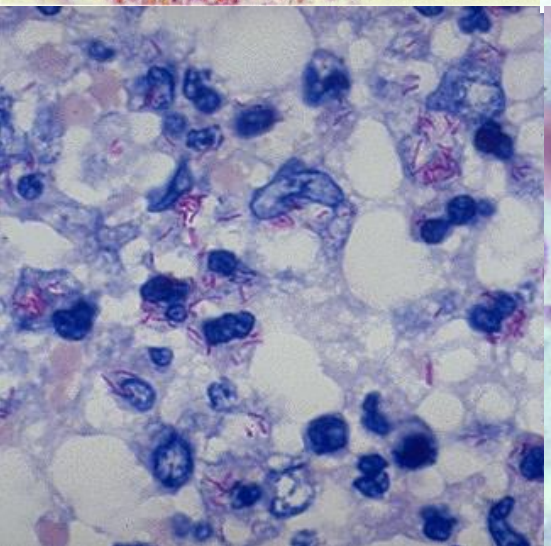
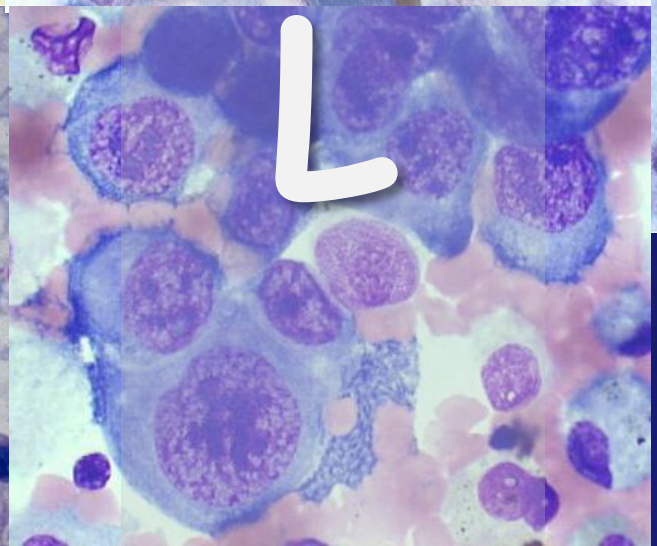



L


Usefulness of BAL in diagnosis of IPF: Conclusions

Should BAL cellular analysis be performed in the diagnostic evaluation of suspected IPF?

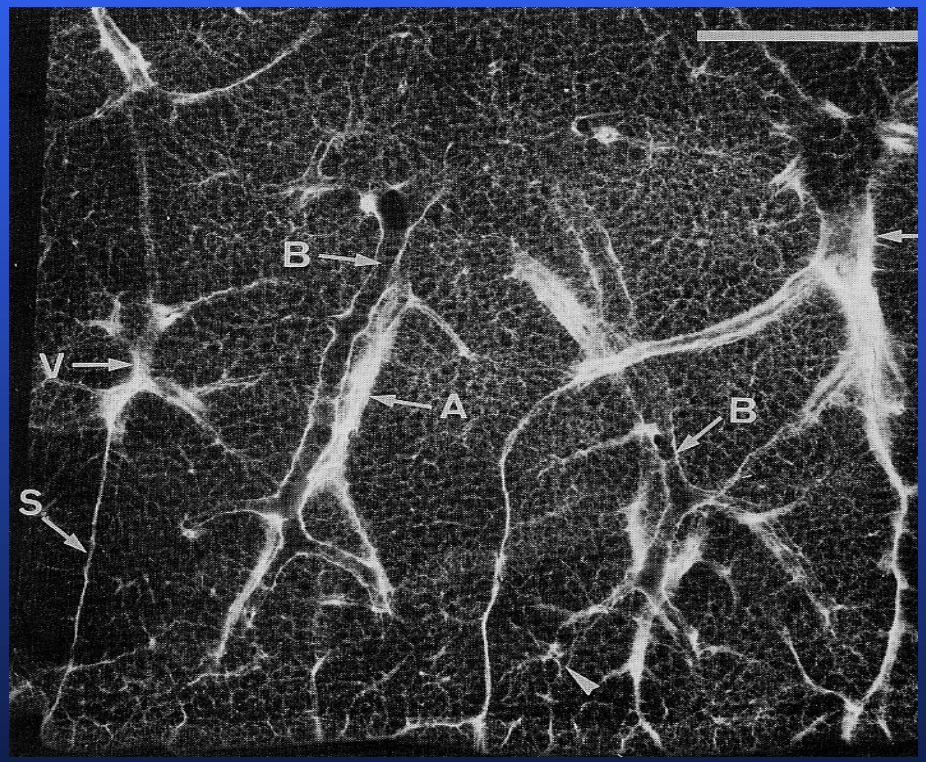
The most important application of BAL is in the exclusion of chonic HP; prominent lymphocitosis (>40%) should suggest the diagnosis

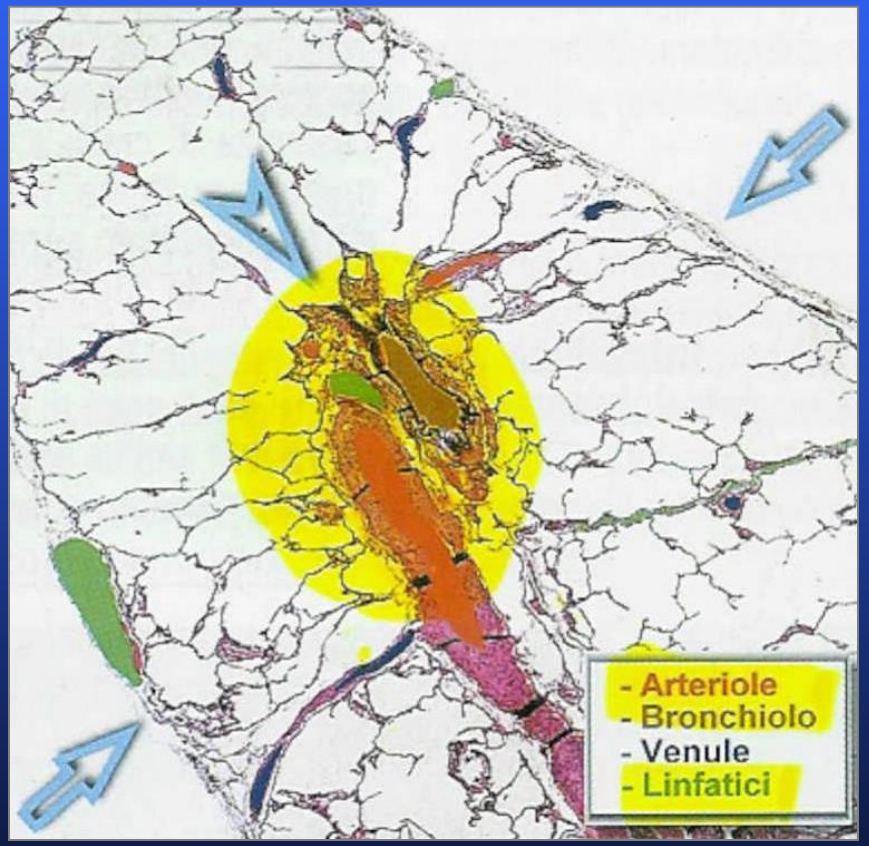
Recommendation: BAL cellular analysis should not be performed in the diagnostic evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation, low-quality evidence)

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

Biopsia Transbronchiale

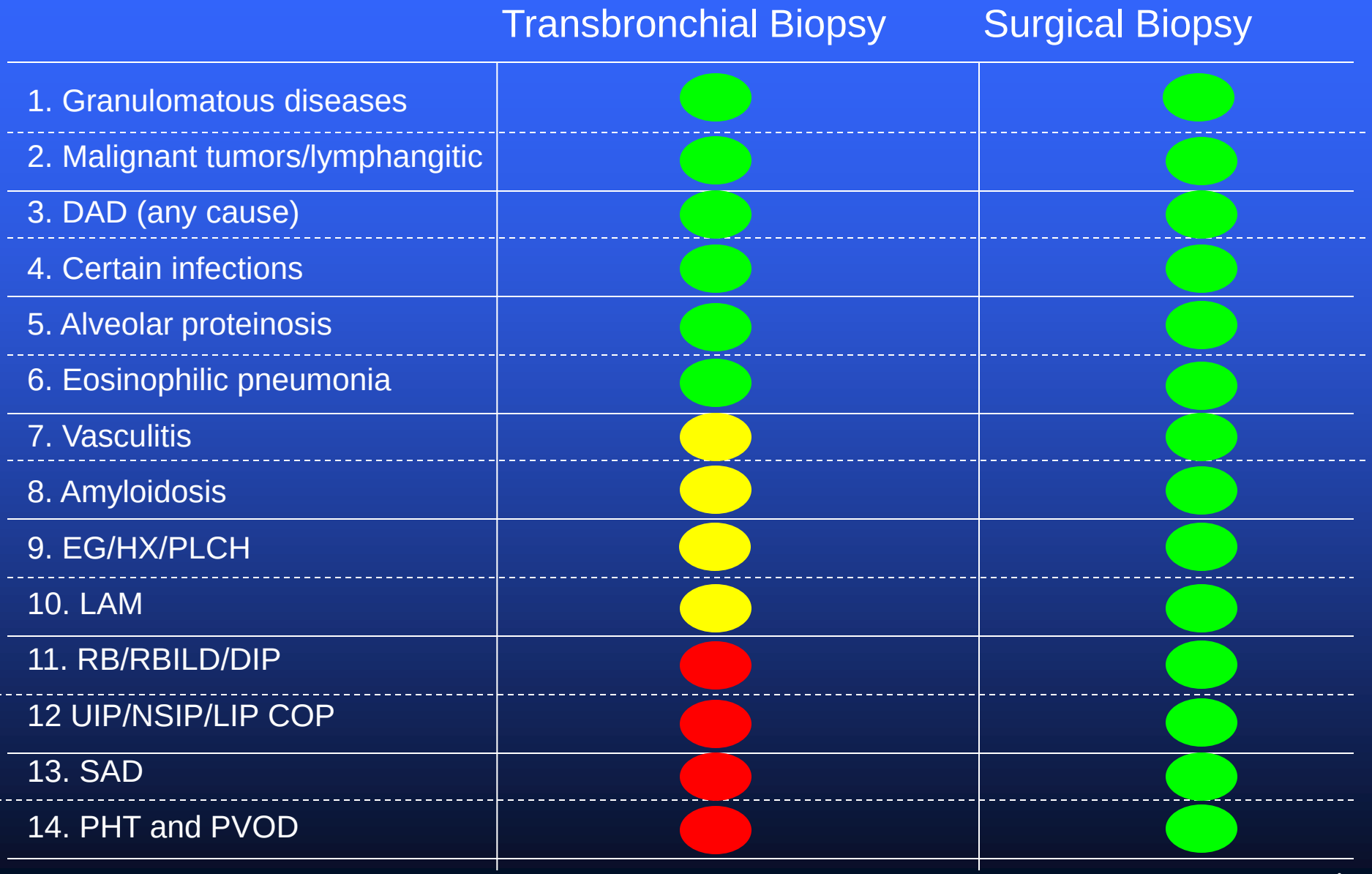
….distribuzione delle lesioni nel lobulo secondario



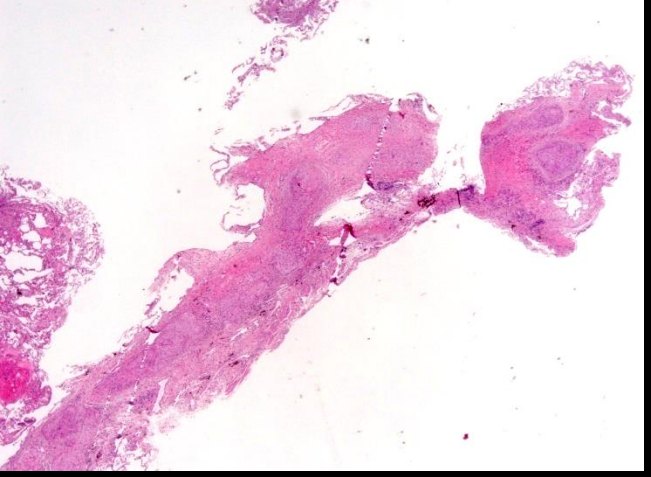


Maffessanti & Dalpiaz

Probability of Diagnosing Diffuse Diseases



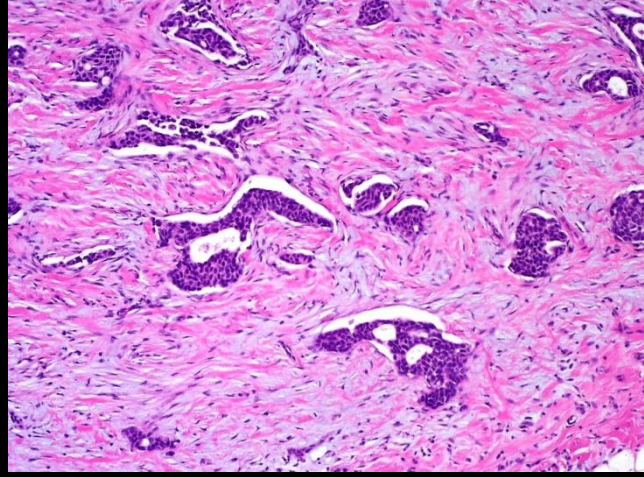
K.O. Lesly

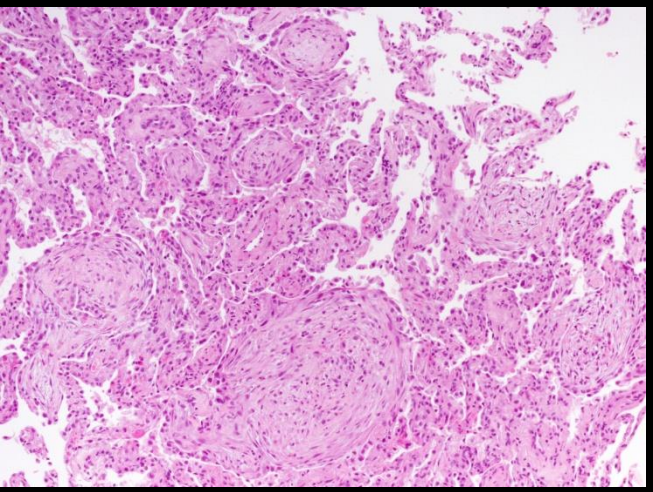


Sarcoidosi

T

Adenocarcinoma

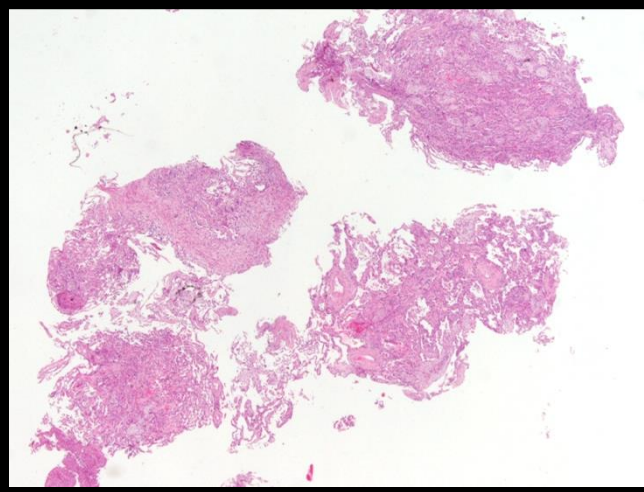


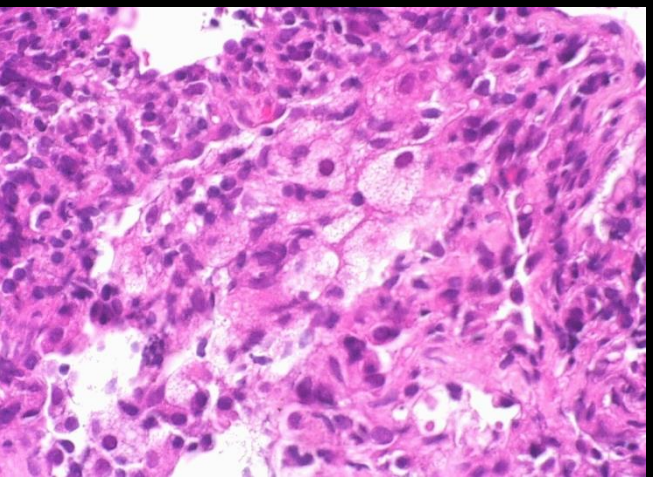


OP

B

Polmonite eosinofila

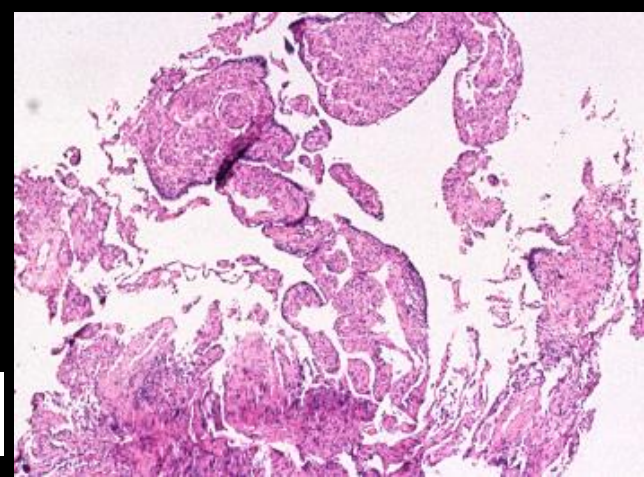




Polmonite da ipersensibilità

D

Linfangioleiomiomatosi



Transbronchial Lung Cryobiopsy in the Diagnosis of Fibrotic Interstitial Lung Diseases

Casoni GL et al. PlLOS One 2014

Conclusions: TBLC in the diagnosis of f-DPLD appears safe and feasible. TBLC has a good diagnostic yield in the clinical-radiological setting of f-DPLD without diagnostic HRCT features of usual interstitial pneumonia. Future studies should consider TBLC as a potential alternative to SLBx in f-DPLD.

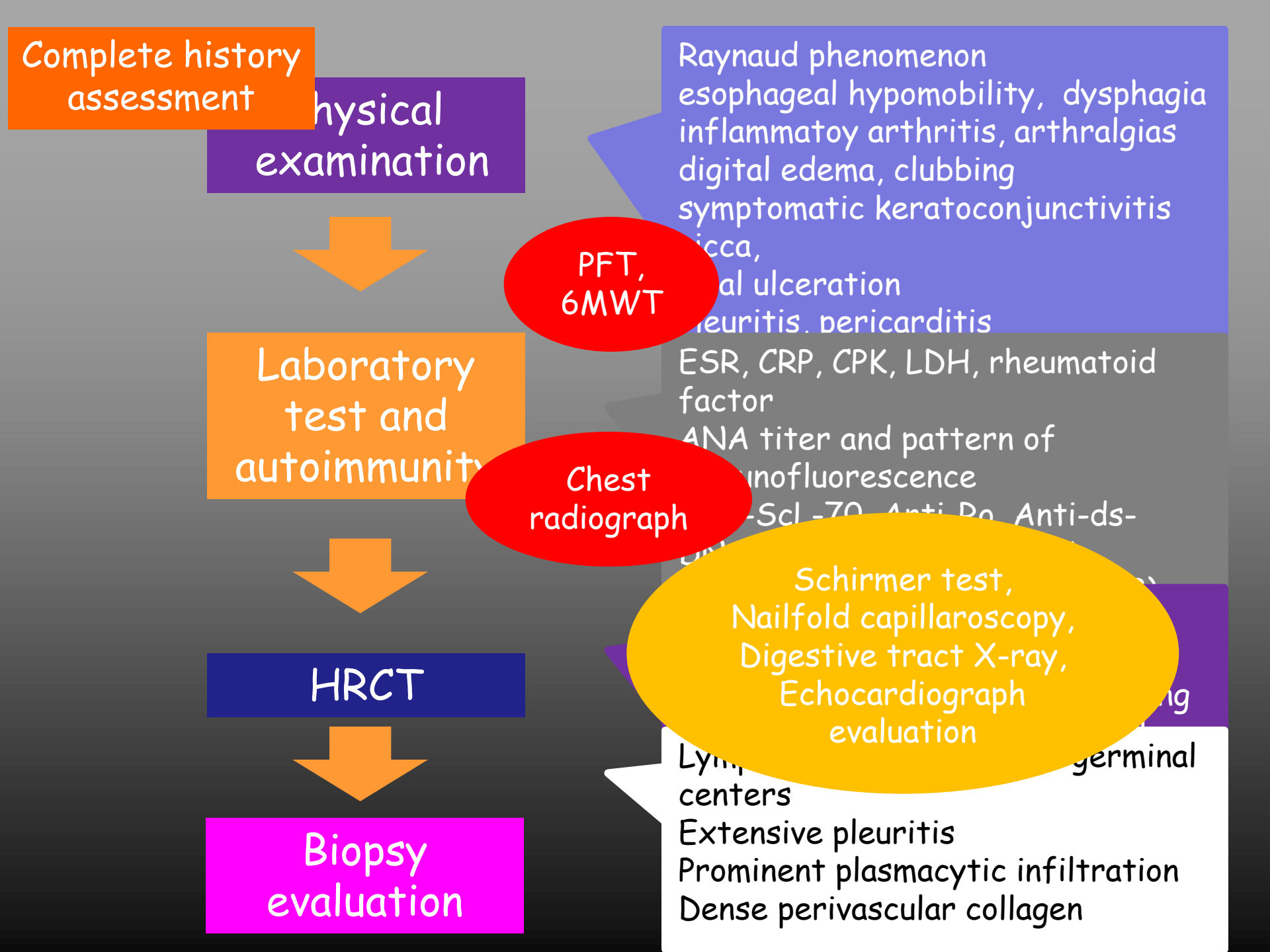
The big problem is the differential diagnosis between UIP and NSIP, HP and ILD in CVDs

What's the problem?

- It is not uncommon for pulmonologist to find patients with IP who are supposed to have a systemic autoimmune disease
- Within current classification schemes, many of these patients are labeled as idiopathic by default
- Despite the recognition that IP may be the *forme fruste* presentation of CTD, current classification criteria do not allow a CTD designation for ILD alone

Why is important to discover an occult CTD?

- For disease prognosis
- For appropriate therapeutic approach
- For a search of additional system involvement or underlying malignancy
- For specific complications
- Is lung biopsy indicated?


Complete history assessment
hysical examination
Laboratory test and autoimmunity
HRCT
Biopsy evaluation
PFT, 6MWT
Chest radiograph
Schirmer test, Nailfold capillaroscopy, Digestive tract X-ray, Echocardiograph evaluation
Raynaud phenomenon
esophageal hypomobility, dysphagia
inflammatoy arthritis, arthralgias
digital edema, clubbing
symptomatic keratoconjunctivitis
icca,
al ulceration
leuritis, pericarditis
ESR, CRP, CPK, LDH, rheumatoid factor
ANA titer and pattern of
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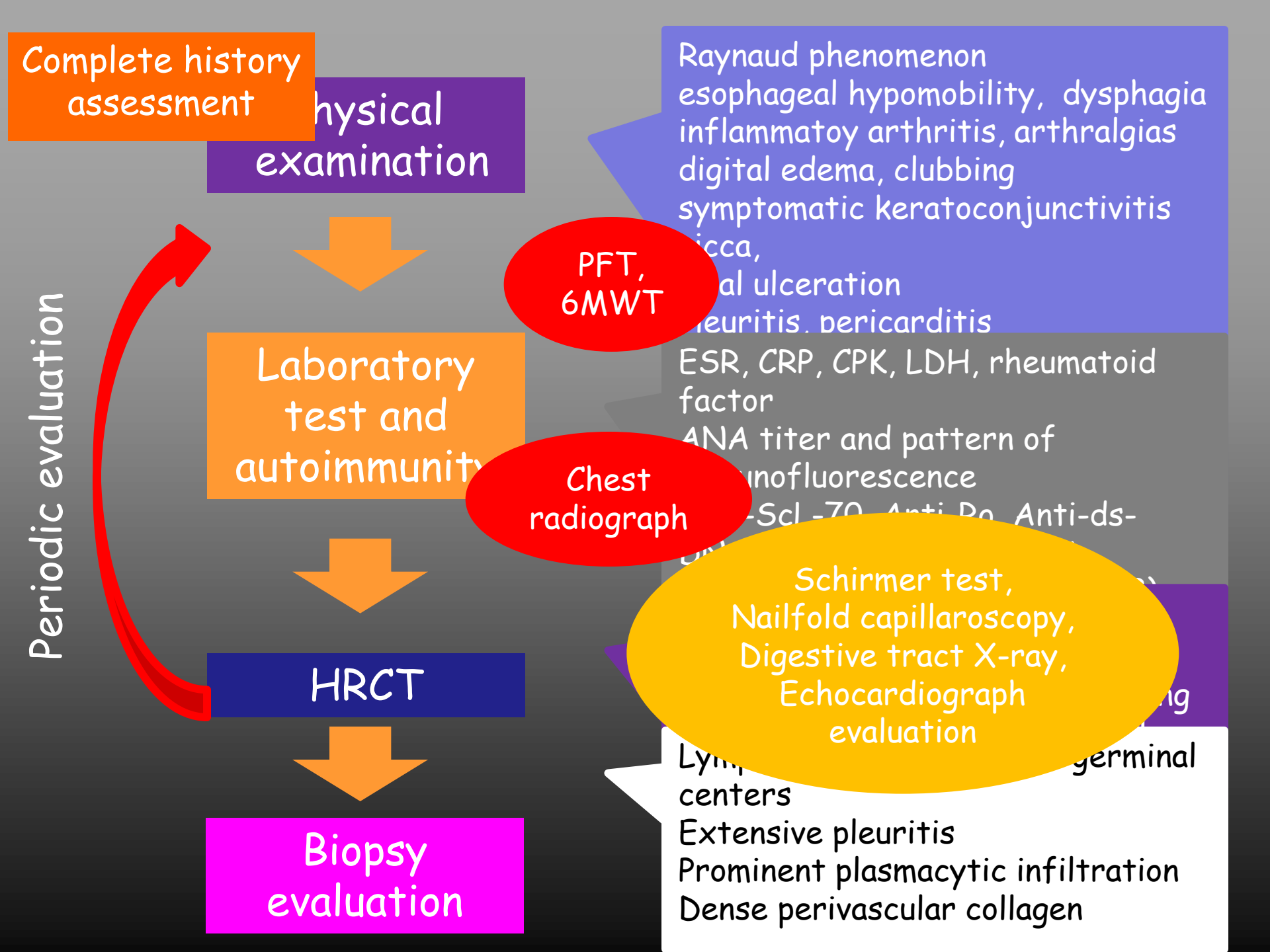
-Scl-70, Anti-Ro, Anti-ds-
germinal centers
Extensive pleuritis
Prominent plasmacytic infiltration
Dense perivascular collagen


Complete history assessment
hysical examination
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symptomatic keratoconjunctivitis
icca,
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leuritis, pericarditis
Laboratory test and autoimmunity
ESR, CRP, CPK, LDH, rheumatoid factor
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Chest radiograph
Periodic evaluation
Schirmer test,
Nailfold capillaroscopy,
Digestive tract X-ray,
Echocardiograph
evaluation
HRCT
germinal centers
Extensive pleuritis
Prominent plasmacytic infiltration
Dense perivascular collagen
Biopsy evaluation

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

- In some patients, lung involvement precedes other systemic manifestations, making the distinction between IIP and lung involvement of CTD impossible
- An association of IIP with CTD should be vigorously searched, not only at time of diagnosis but also during follow-up

Conclusions

- It is important to look for additional minor/minimal abnormalities (clinical, radiological, histological) that may help in diagnosis of occult CTD or chronic HP
- IPF can be diagnosed on HRCT in the majority of cases but a crucial sub-group have very atypical HRCT appearances
- Early diagnosis of IPF allows early treatment approaches and prompt referral for LTx