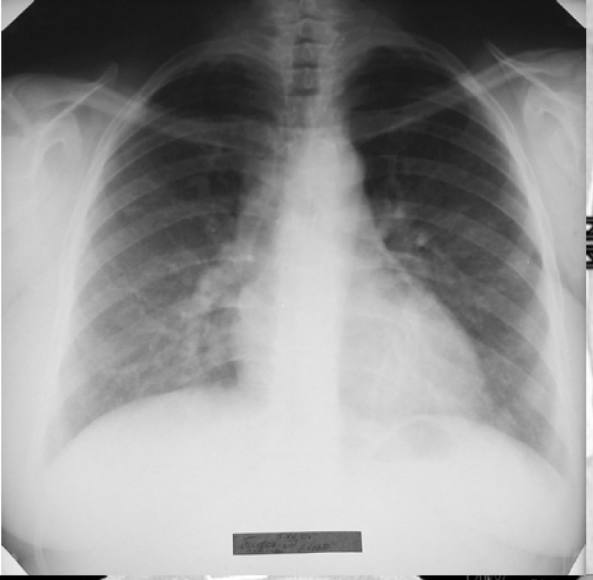
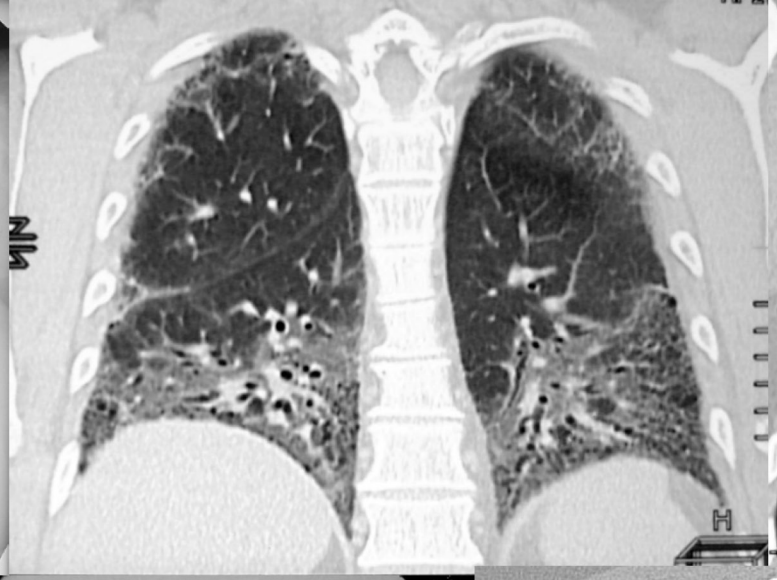
Interstitial Lung Diseases

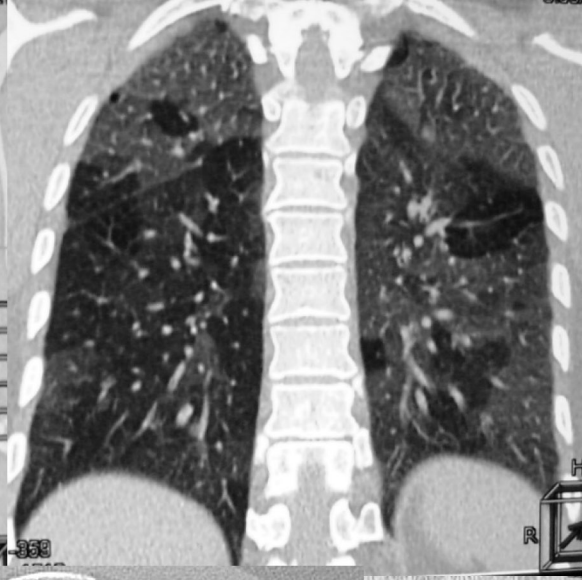
Oxana Munteanu

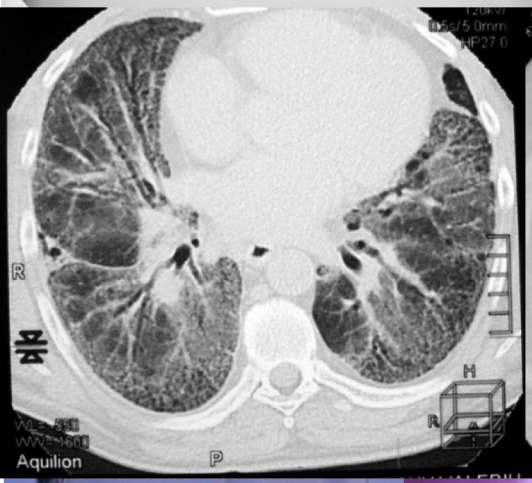
2017

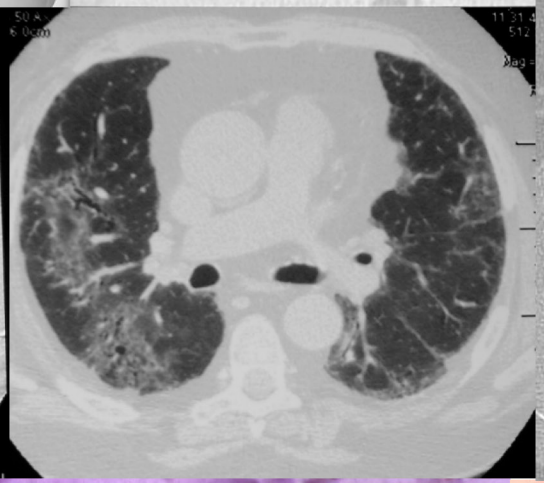

ILD

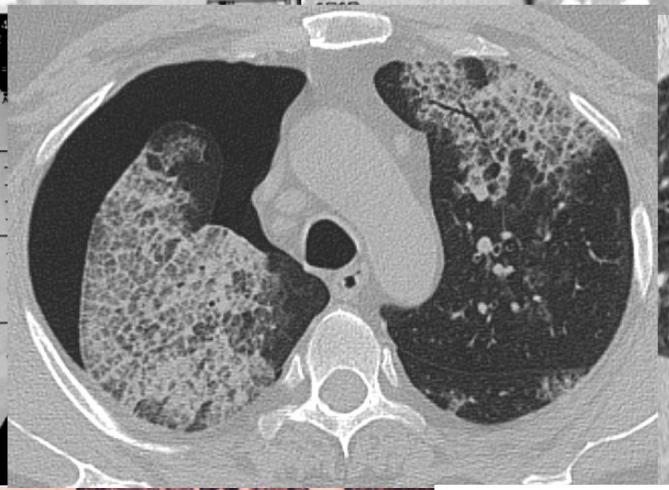


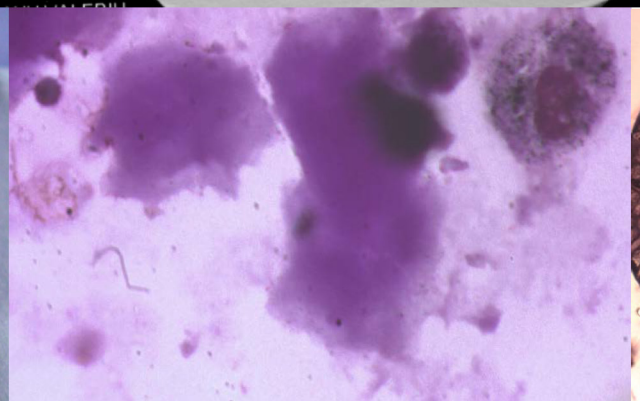


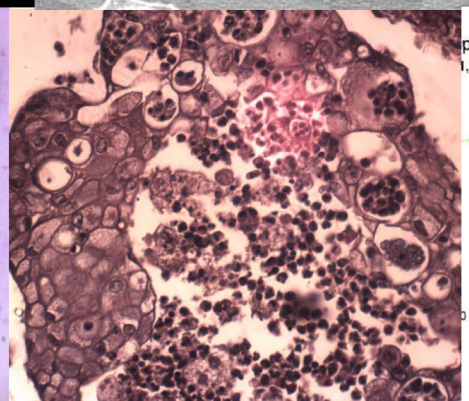










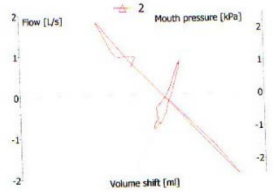


pneumologie "Ch. DRAGANIUC"
, str. C. Virnav nr.13

male
155,0 cm
75,0 kg

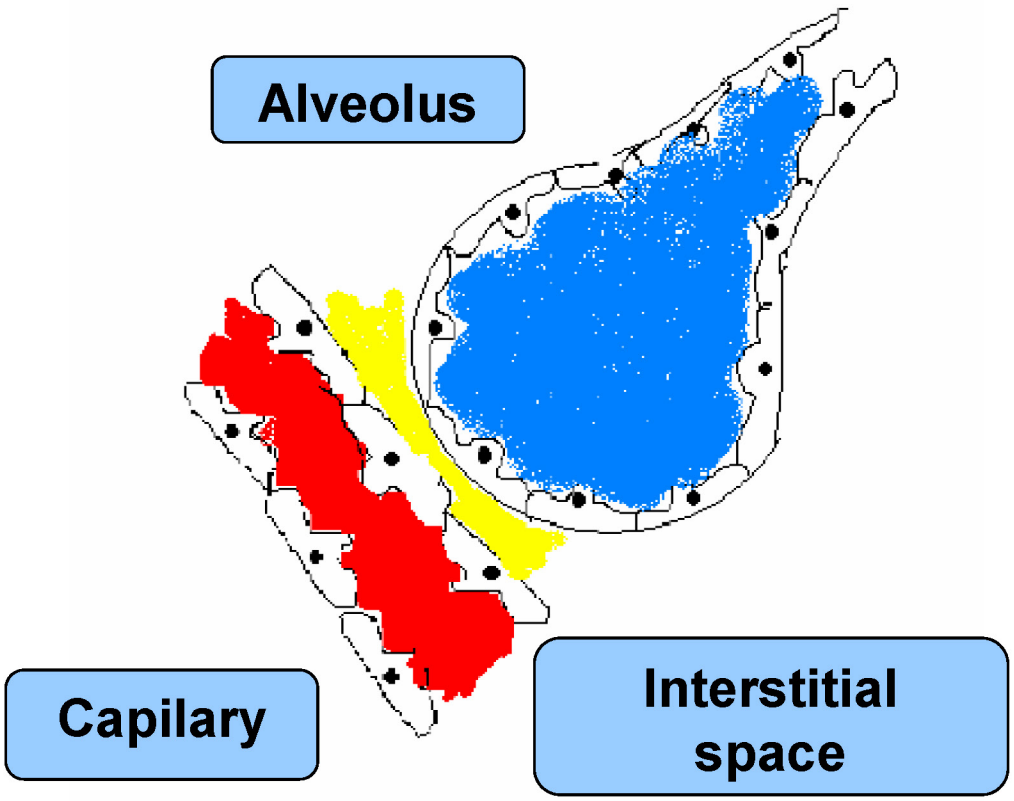
Hemoglobin: 14,6 g/100ml
Diagnosis:
Smoker:

Body-Plethysmography



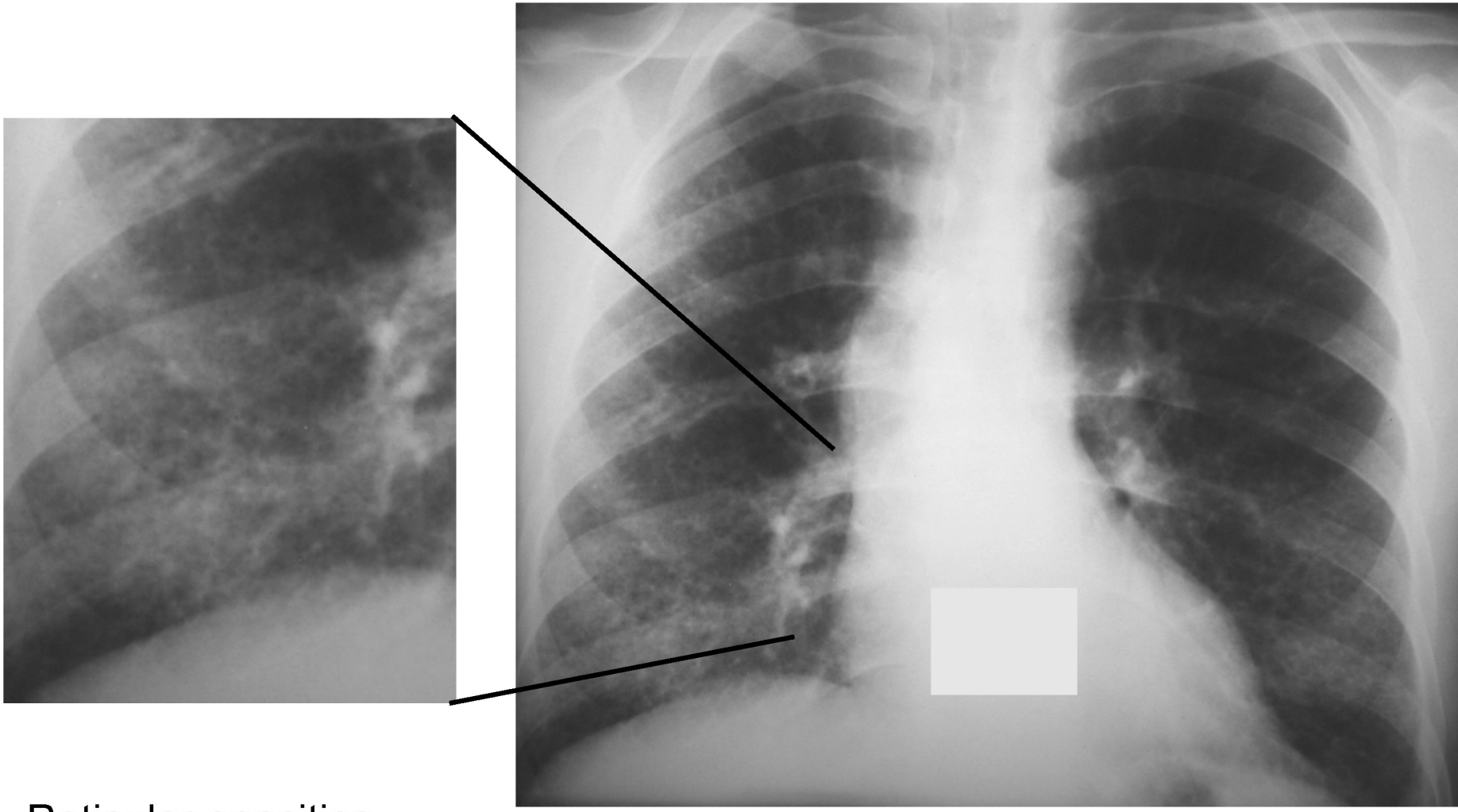
What is the Pulmonary Interstitium?

- Interstitial compartment is the portion of the lung sandwiched between the epithelial and endothelial basement membrane



The Lung Interstitium

- The interstitium of the lung is not normally visible radiographically
- It becomes visible only when disease (e.g., edema, fibrosis, tumor) increases its volume and attenuation

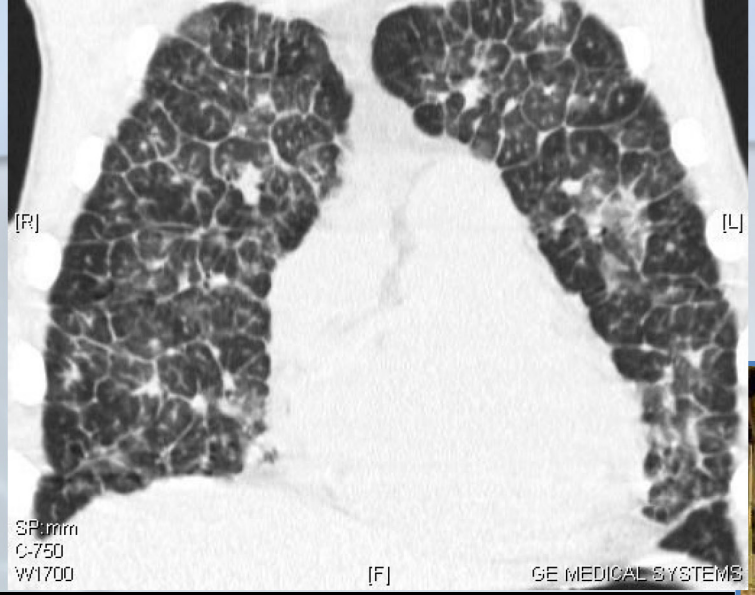


-Reticular opacities
-Nodular opacities
- “ground-glass” opacities

INTERSTITIAL SYNDROME

- linear
- reticular
- nodular
- reticulonodular
- “ground-glass”
- “honey-combing”

HRCT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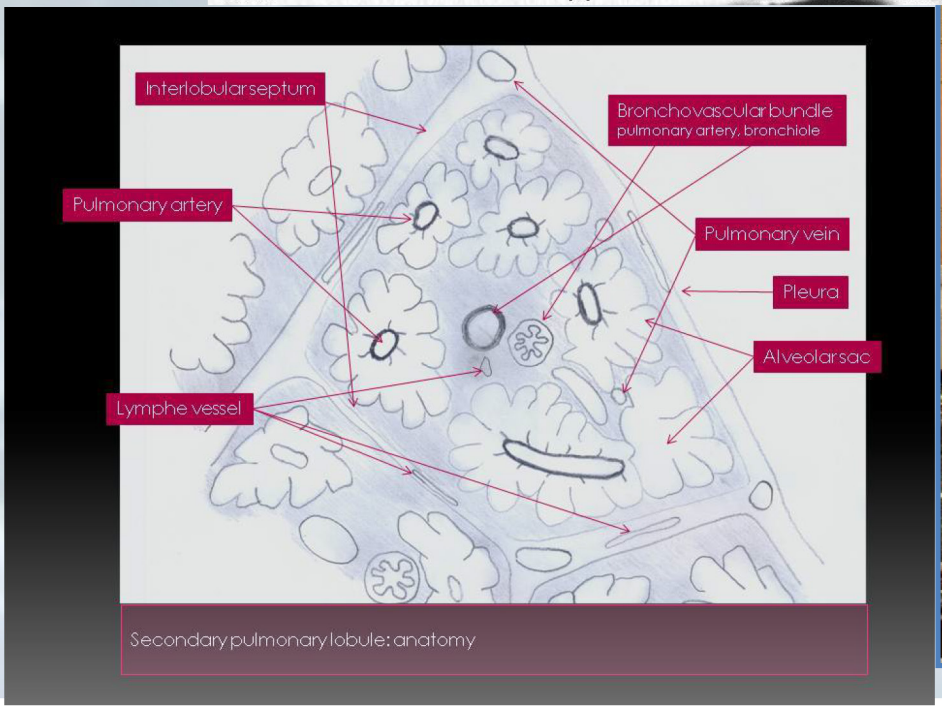
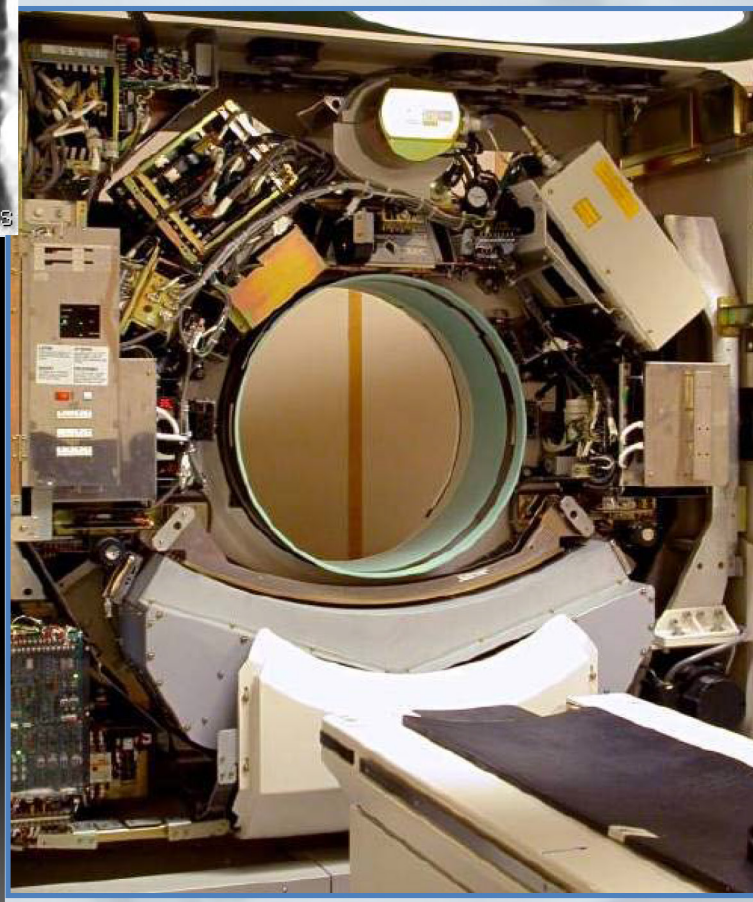
GE MEDICAL SYSTEMS

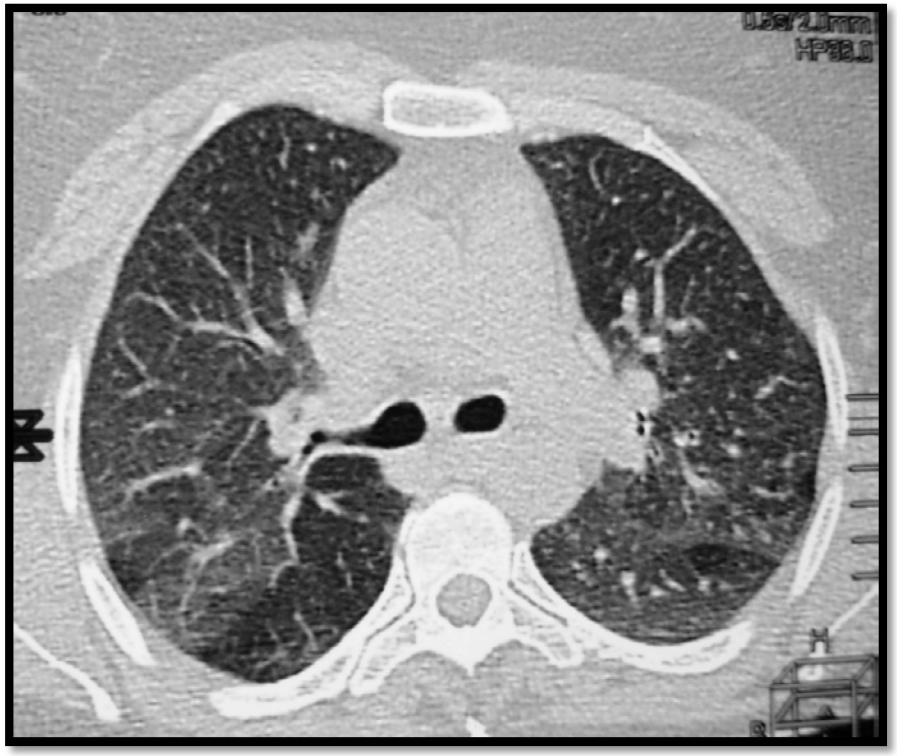

Interlobular septum
Bronchovascular bundle
pulmonary artery, bronchiole
Pulmonary artery
Pulmonary vein
Pleura
Alveolar sac
Lymphe vessel
Secondary pulmonary lobule: anatomy



Ground Glass Opacities (GGO)

Definition:

- Hazy increased lung opacity
- Preservation of bronchial and vascular margins
- Partial displacement of air
- No parenchymal displacement
- Can be homogenous or limited to lobules, segments or lobes

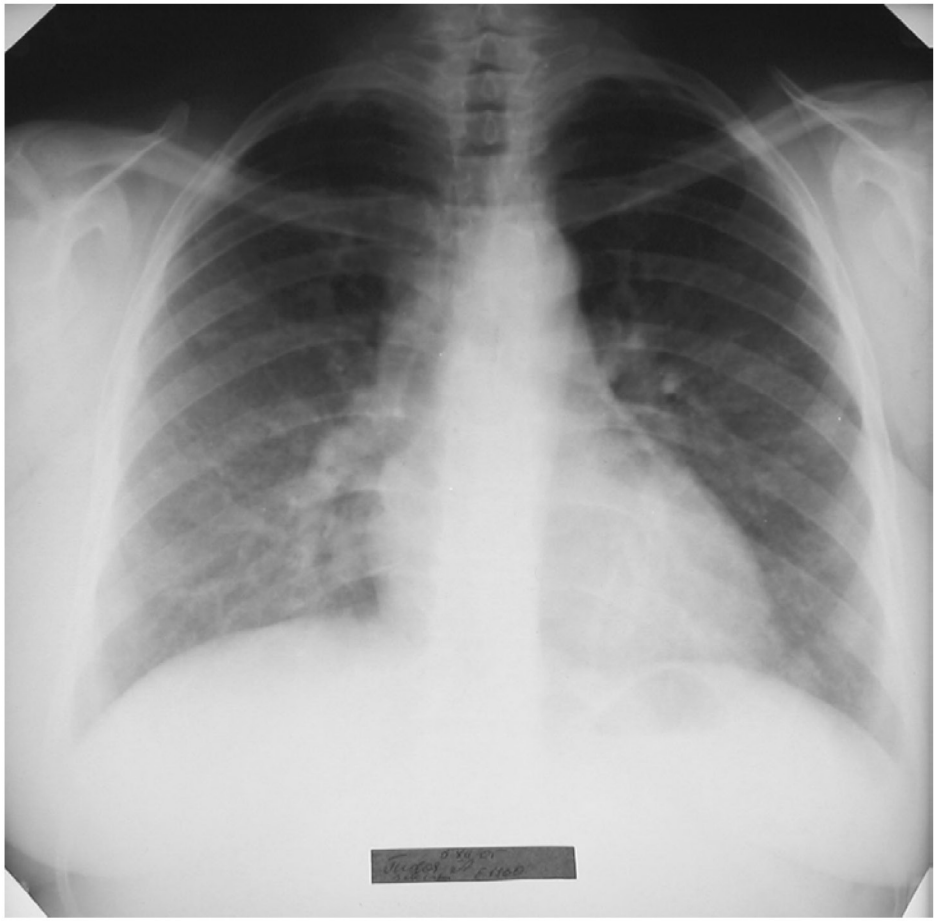


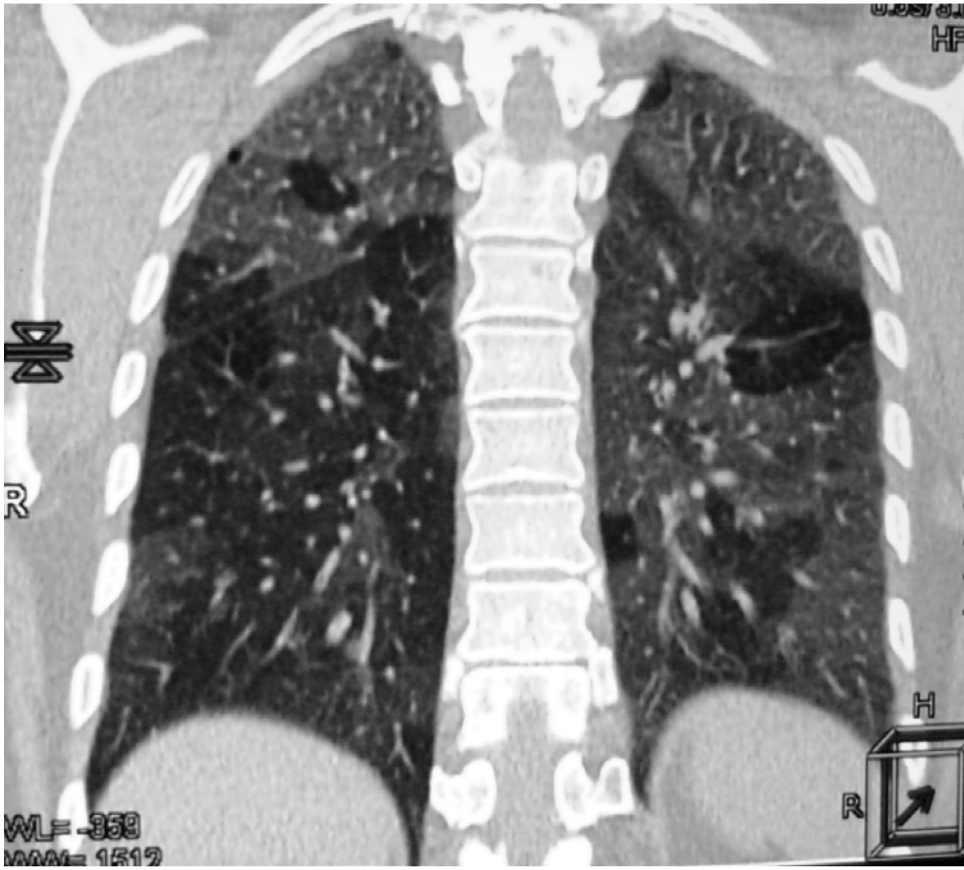
Ground Glass Opacities (GGO)

Interstitial / intra alveolar filling with:

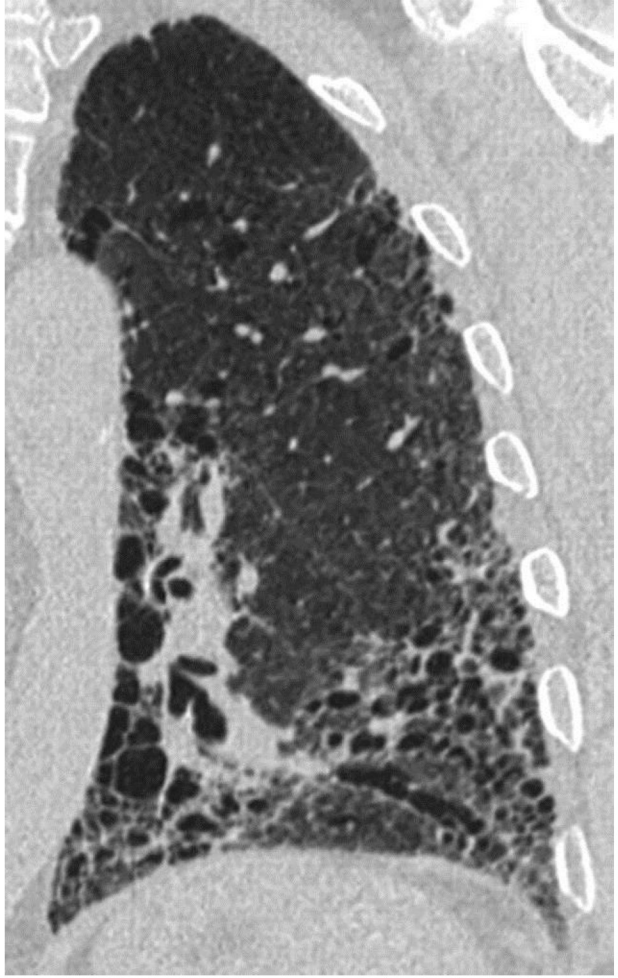
- Transsudate: pulmonary edema
- Blood: Hemorrhage
- Exsudate (Pneumonia / pneumonitis)
- Tumor cells (LAC; BAC)
- hyaline membrans (ARDS)
- faint fibrosis (!)

Ground Glass Opacities (GGO)

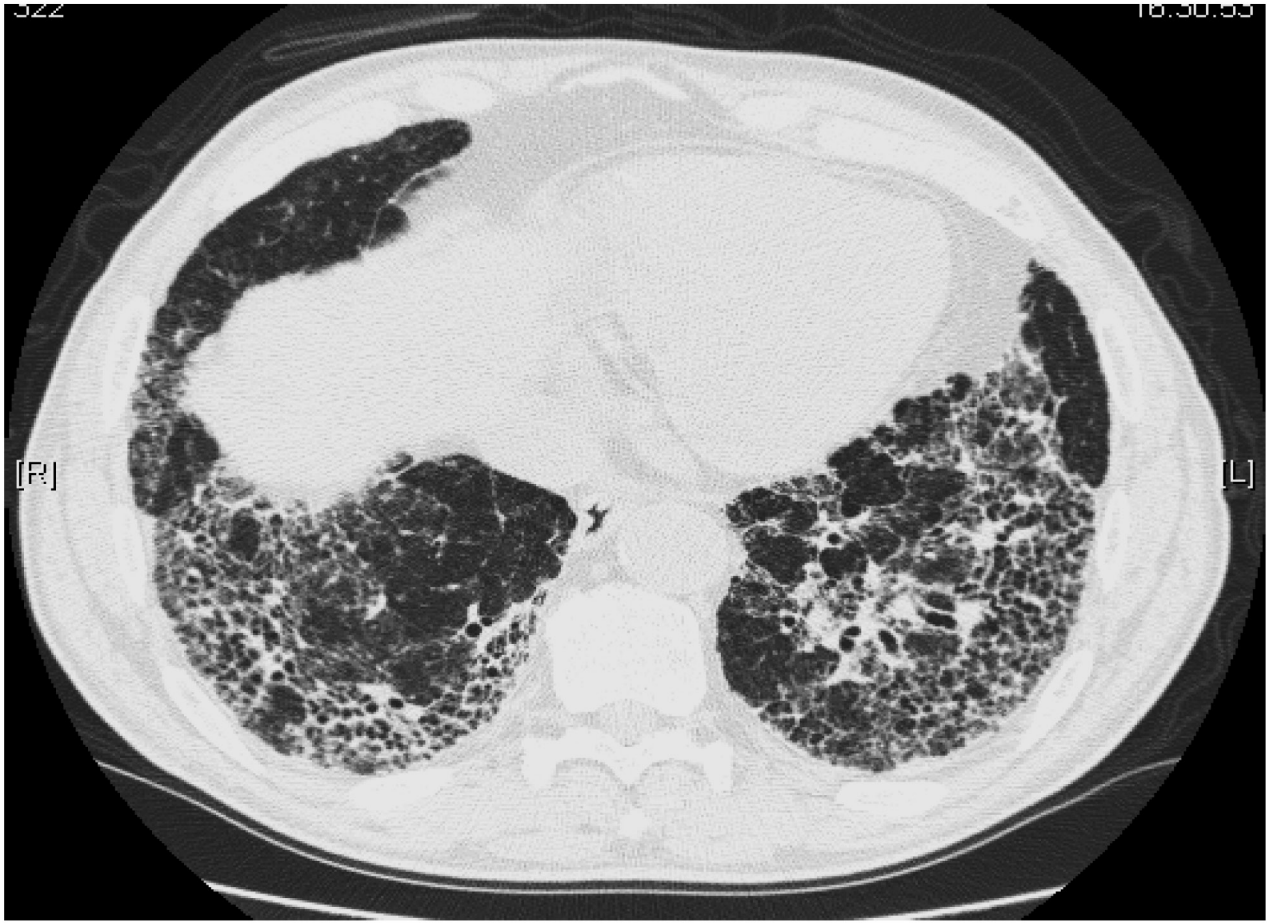




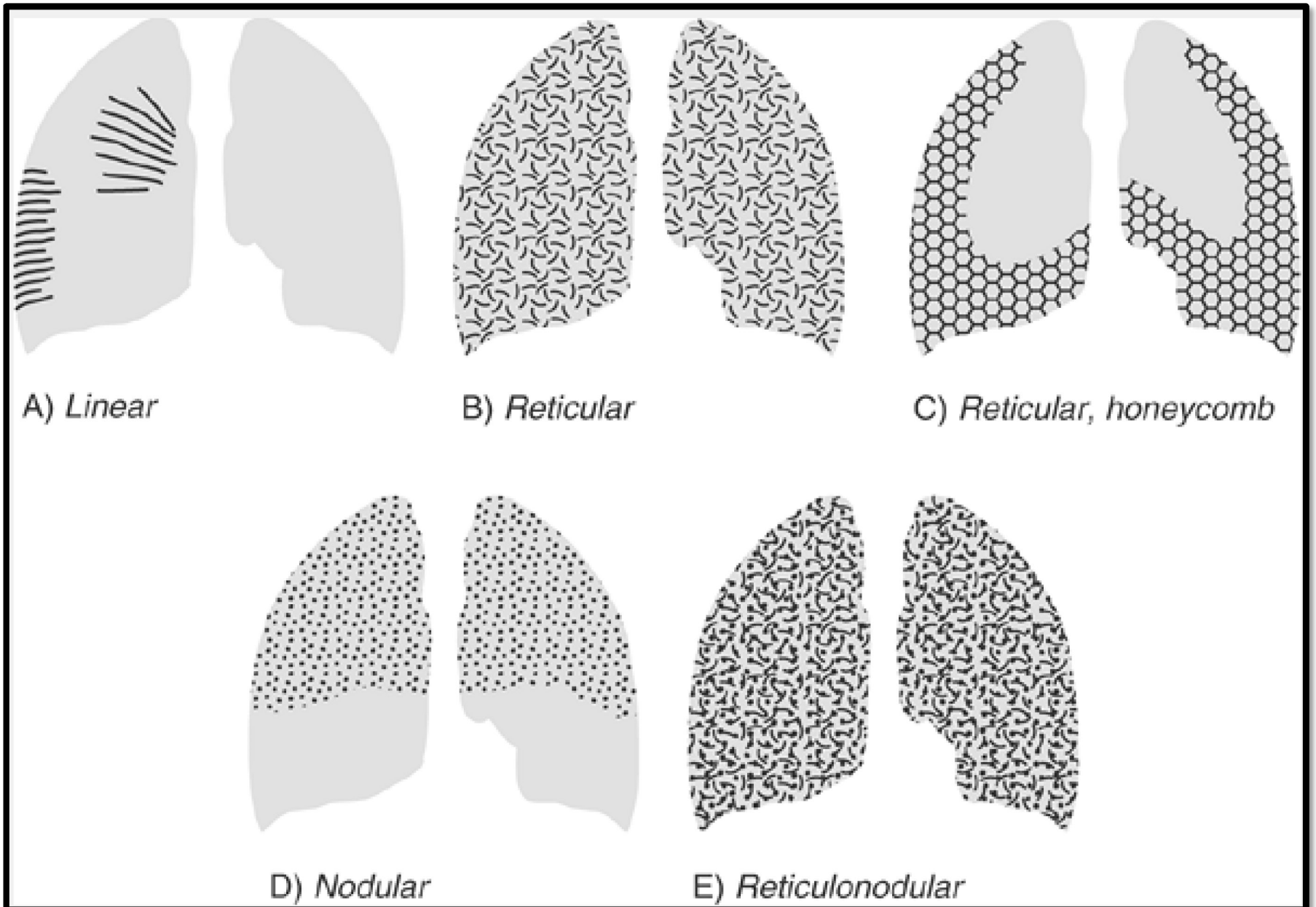
CT >>> X-Ray



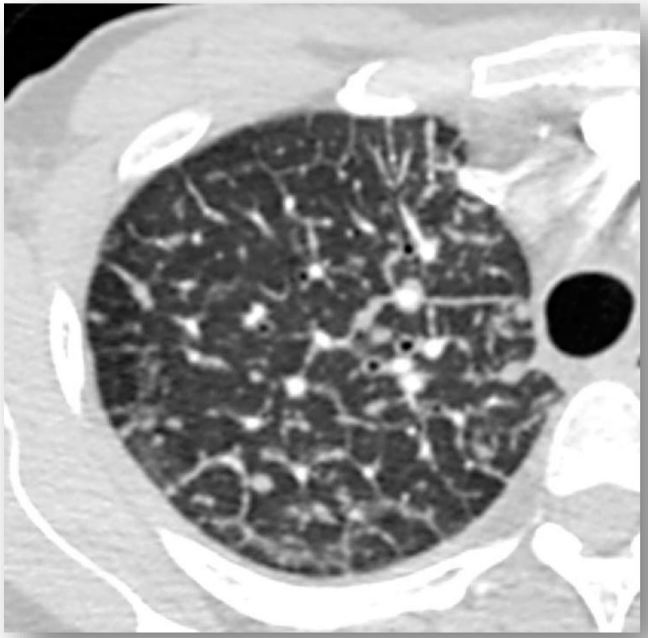
- **Honeycombing** consiste of multilayered thick-walled cysts

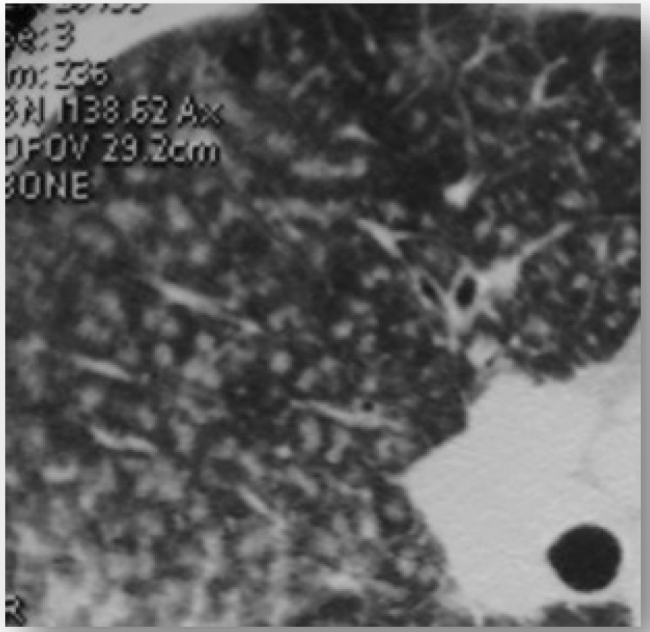


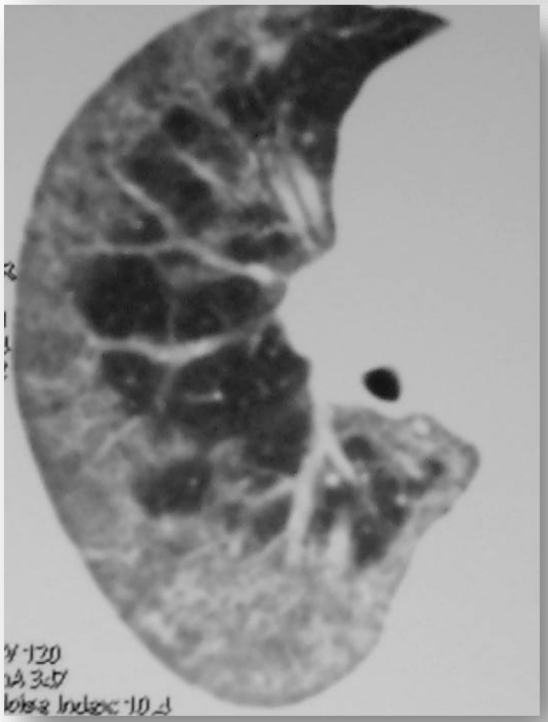
Patterns of Interstitial Lung Disease

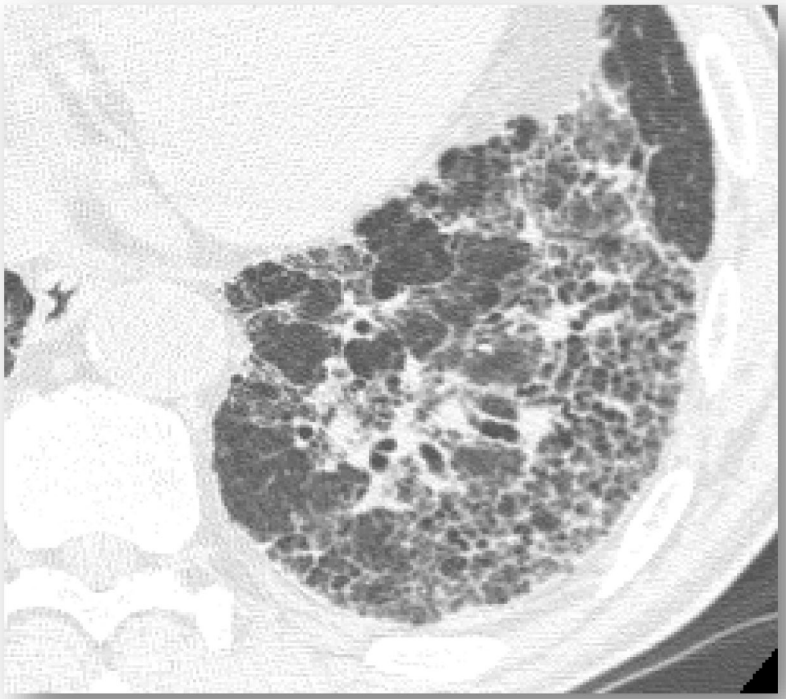


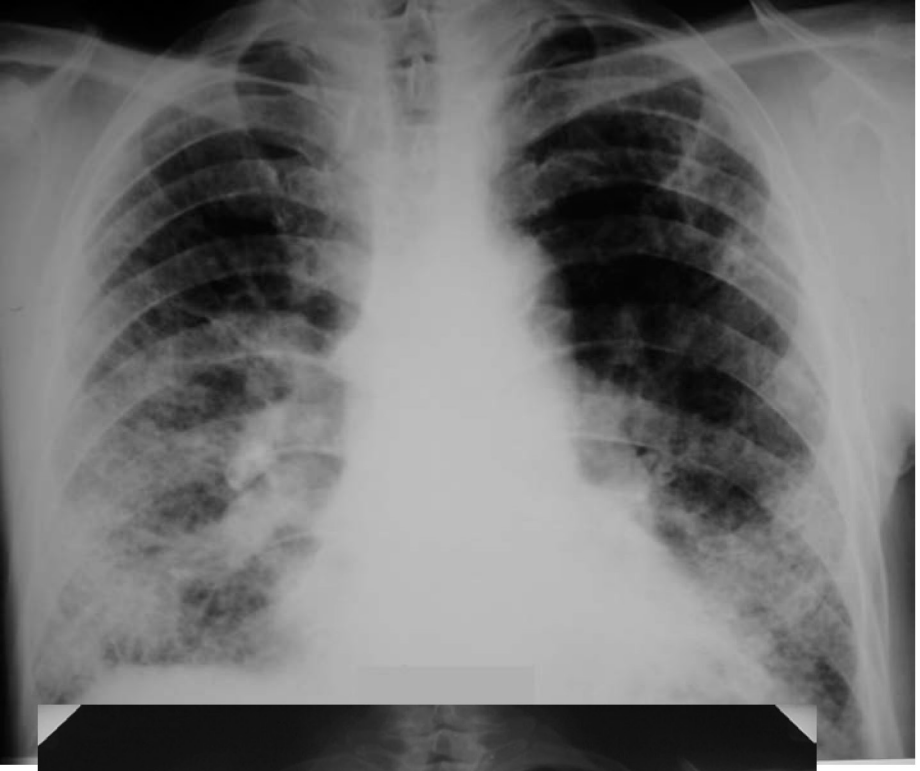
CT patterns

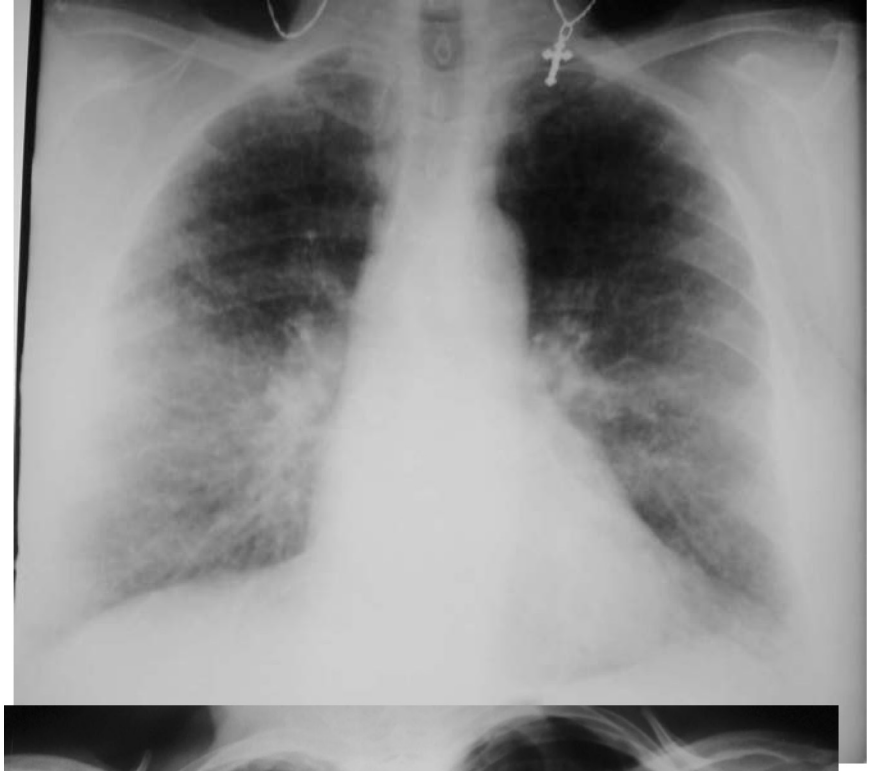


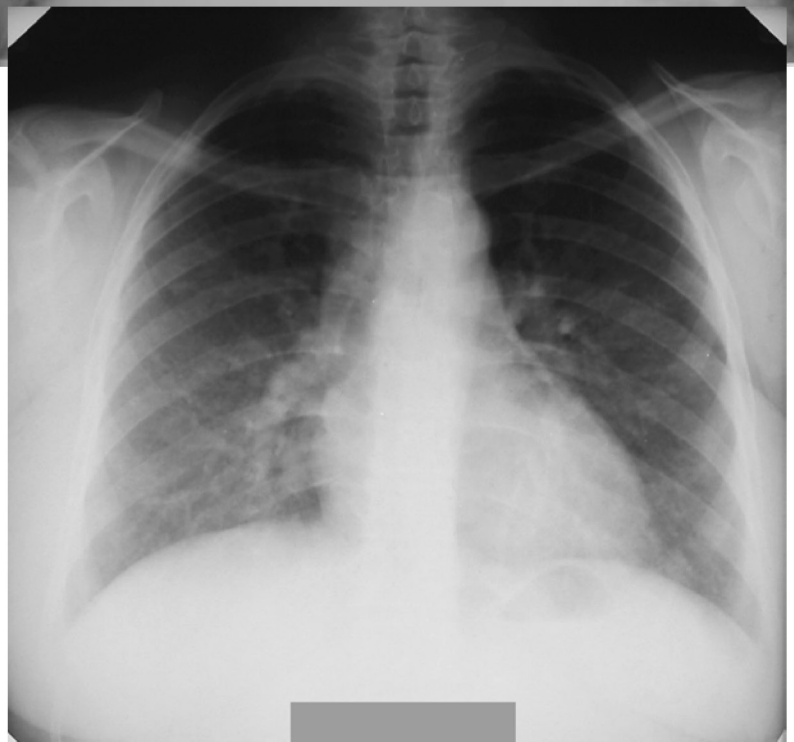


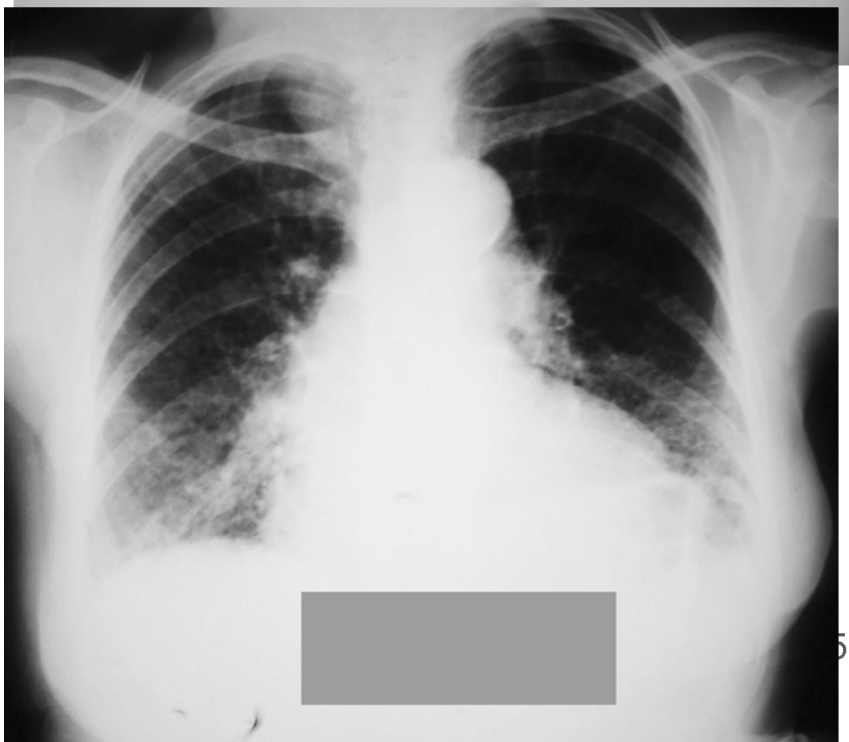






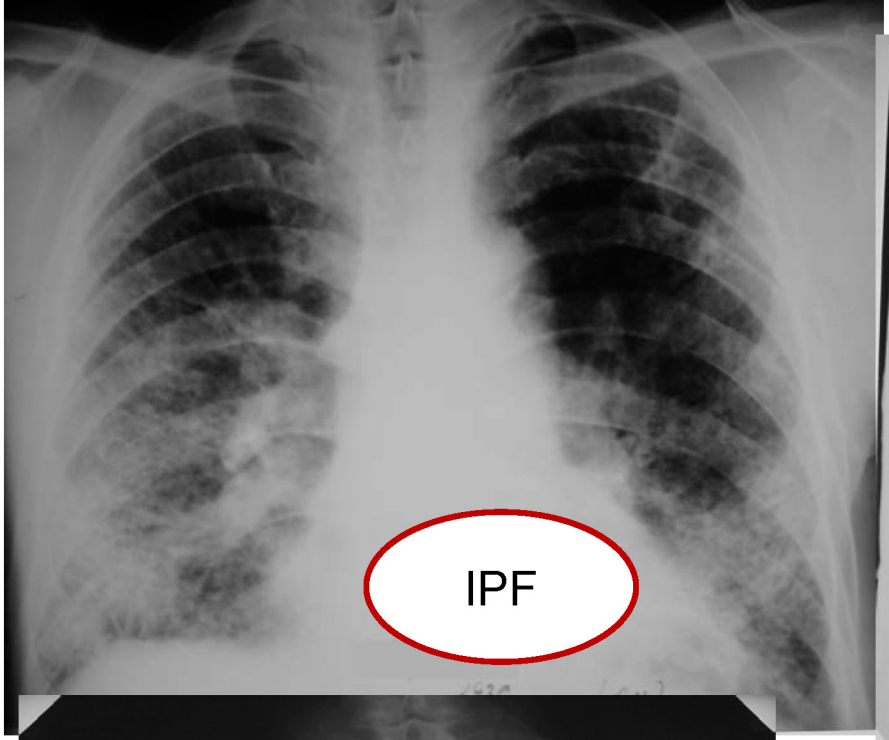


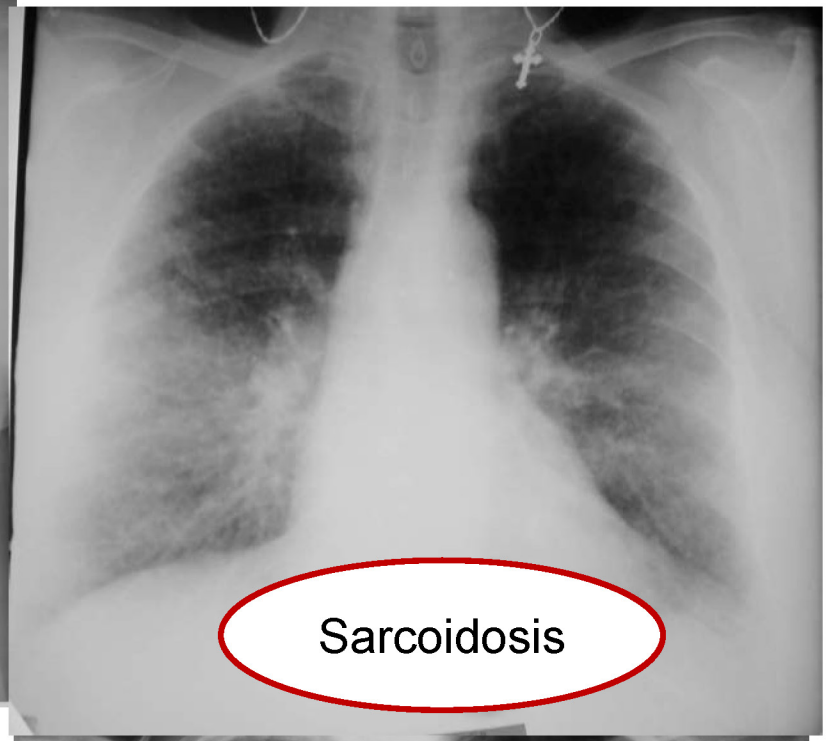


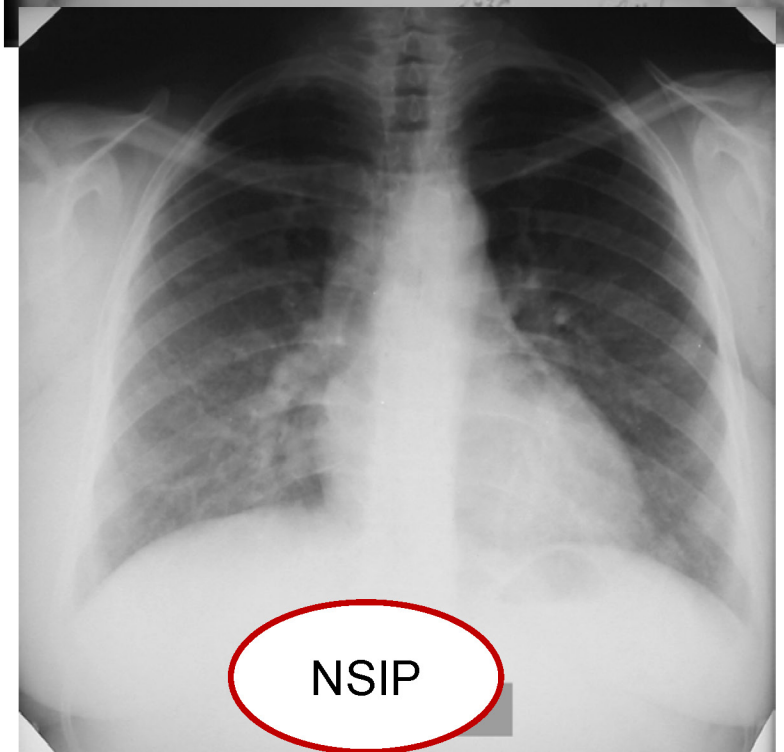


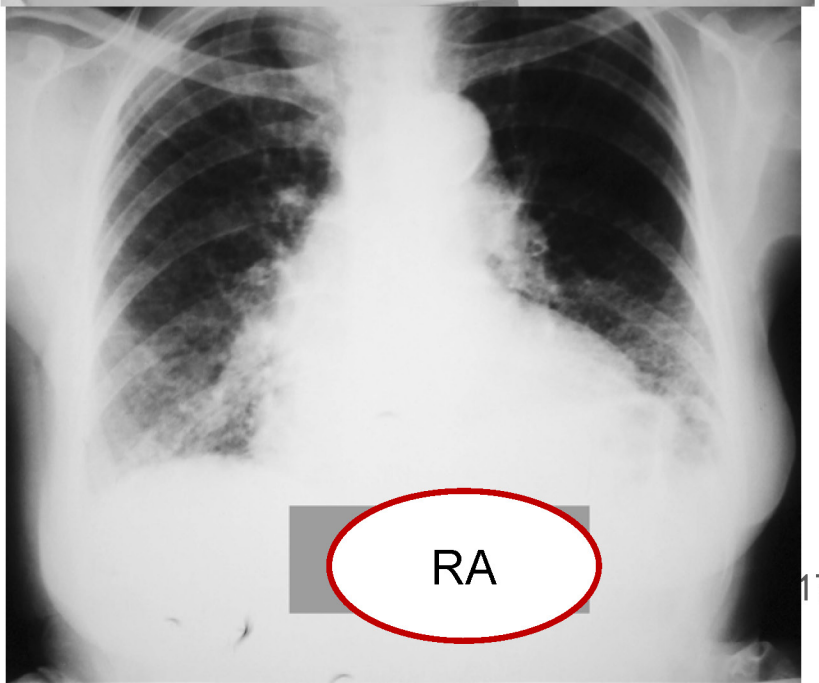
They have in common – interstitial syndrome

The difference between them - etiology


IPF


Sarcoidosis


NSIP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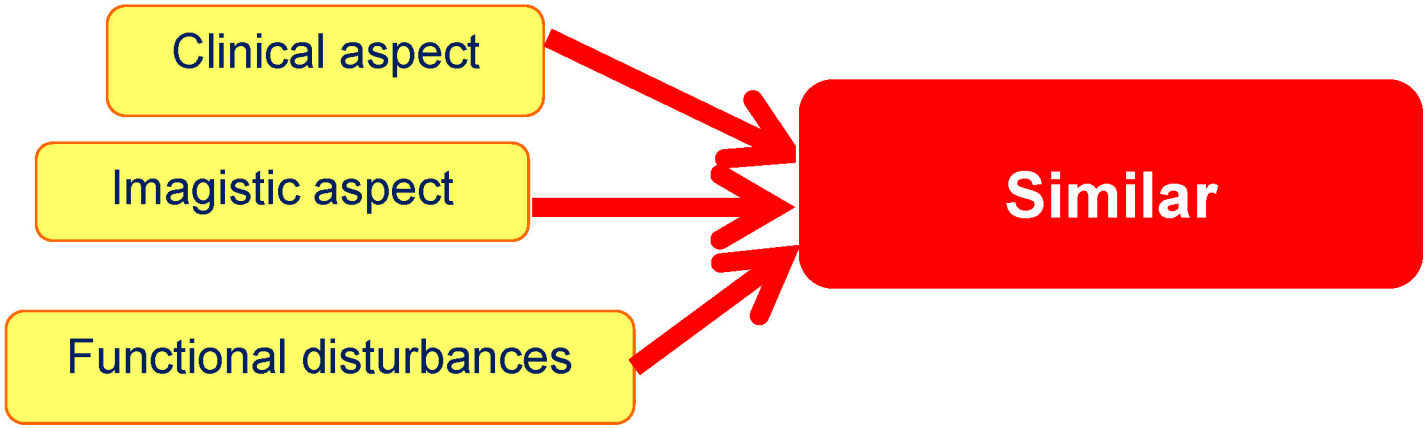
PATIENTS WITH INTERSTITIAL SYNDROME



The difference – etiology

Interstitial Lung Disease

Large and heterogeneous group of disorders characterized by diffuse thickening of alveolar walls

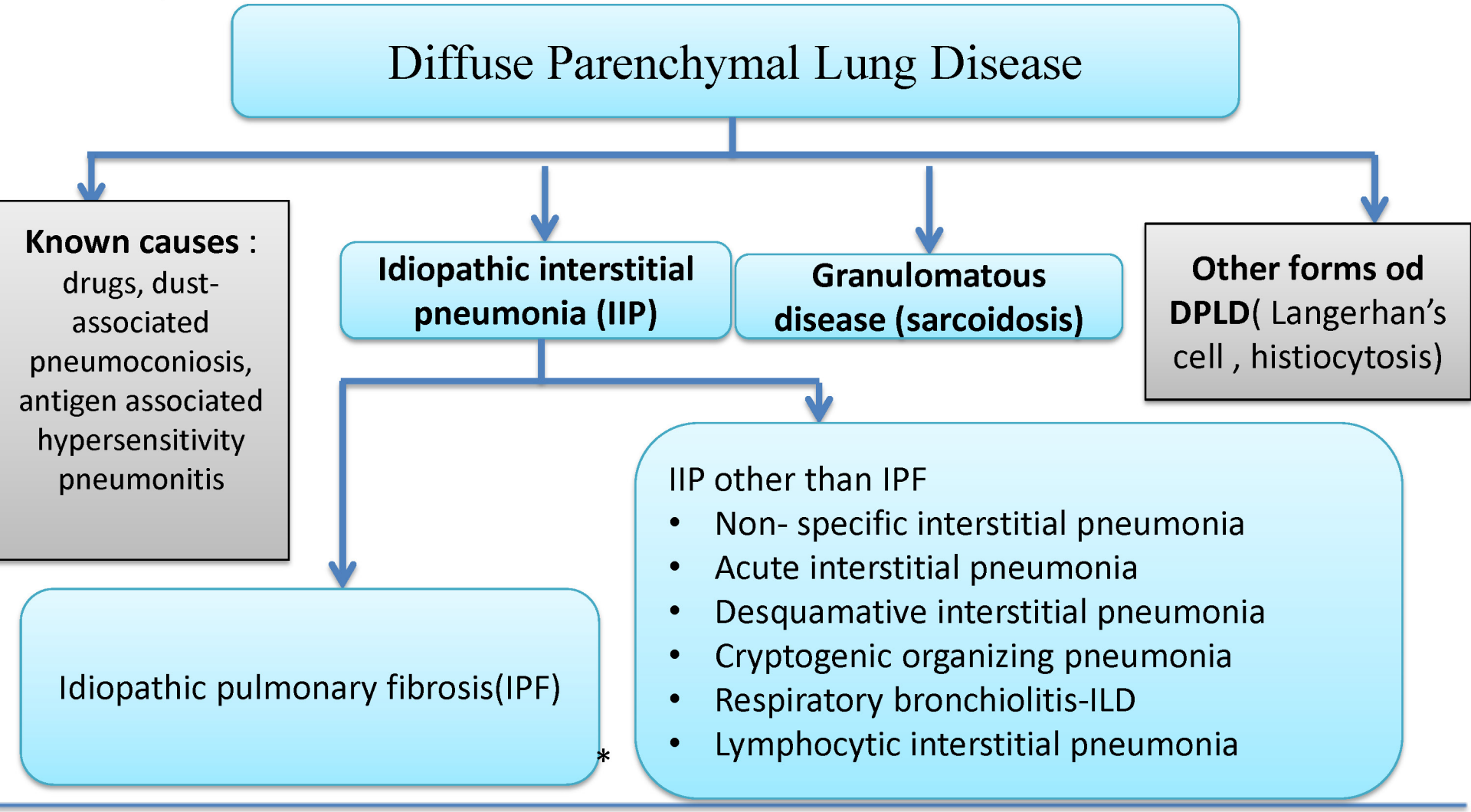
Interstitial Lung Disease

- Includes over 200 entities
- 10-15% of patients seen by the pulmonologist
- Prevalence: 80 /100.000 men, 65 /100.000 women
- Mortality: 3000 deaths / year
- 75% of ILD cases in internal medicine practice is one of three diagnoses:
    - Idiopathic pulmonary fibrosis
    - Sarcoidosis
    - Interstitial disease in collagen diseases

ATS/ERS Multidisciplinary Consensus Classification of IIPs. Am J Respir Crit Care Med 2002; 165: 277-304

Classification of ILDs

- ATS/ERS classification **2002**



This joint statement of the american thoracic society(ATS), and the european respiratory society (ERS) was adopted by the ats board of directors, june 2001 and by the ERS executive committee, june 2001

Revised ATS/ERS classification of ILDs (**2013**) **multidisciplinary diagnoses**

- **Major idiopathic interstitial pneumonias**

Idiopathic pulmonary fibrosis

Idiopathic nonspecific interstitial pneumonia

Respiratory bronchiolitis–interstitial lung disease

Desquamative interstitial pneumonia

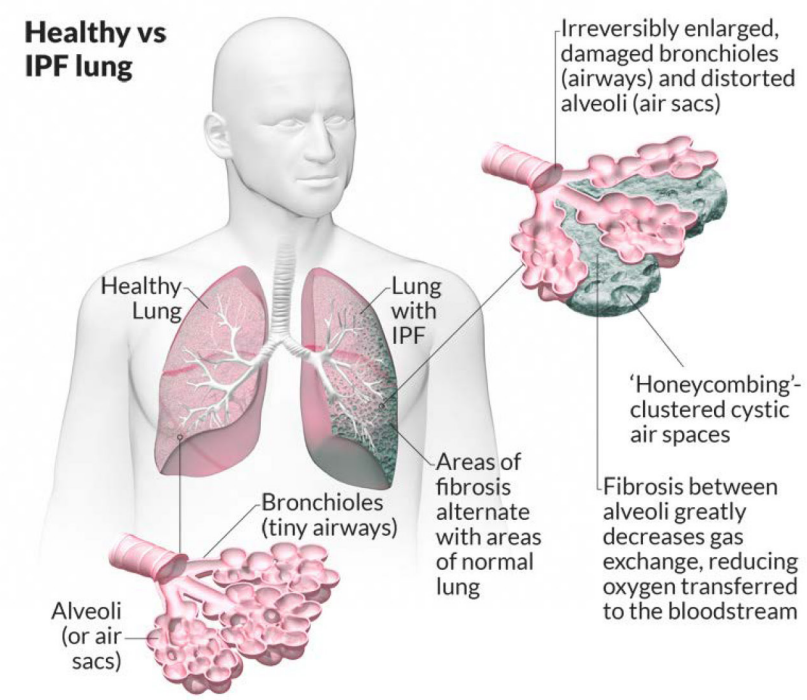
Cryptogenic organizing pneumonia

Acute interstitial pneumonia

- **Rare idiopathic interstitial pneumonias**

Idiopathic lymphoid interstitial pneumonia

Idiopathic pleuroparenchymal fibroelastosis



- **Unclassifiable idiopathic interstitial pneumonias***

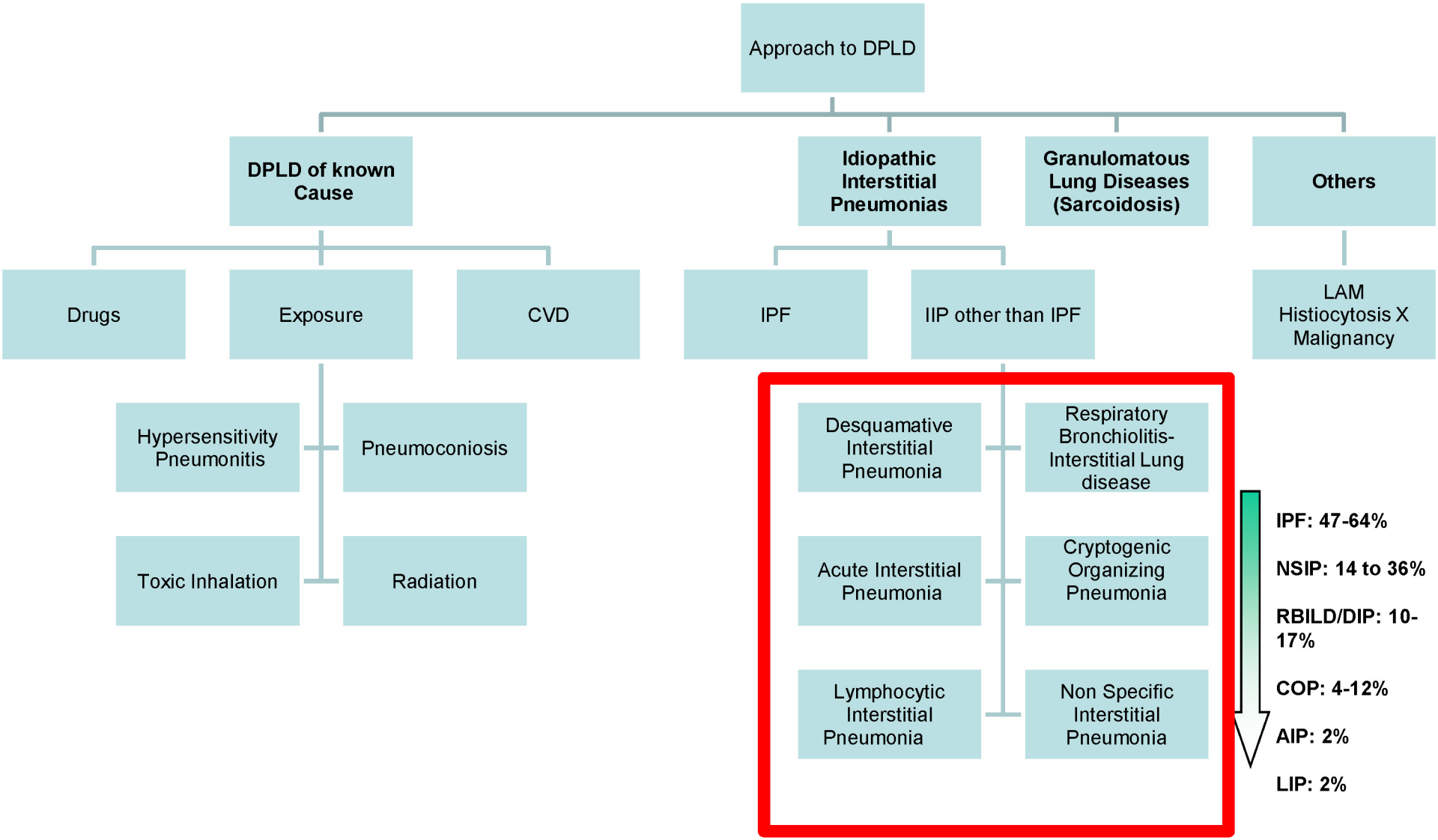
*Travis WD, Am J Respir Crit Care Med 2013;188:733-748

Categorization of major Idiopathic Interstitial Pneumonias

Category	Clinical–Radiologic–Pathologic Diagnoses	Associated Radiologic and/or Pathologic–Morphologic Patterns
Chronic fibrosing IP	• Idiopathic pulmonary fibrosis • Idiopathic nonspecific interstitial pneumoni	• Usual interstitial pneumonia • Nonspecific interstitial pneumonia
Smoking-related IP*	• Respiratory bronchiolitis-interstitial lung disease • Desquamative interstitial pneumonia	• Respiratory bronchiolitis • Desquamative interstitial pneumonia
Acute/subacute IP	• Cryptogenic organizing pneumonia • Acute interstitial pneumonia	• Organizing pneumonia • Diffuse alveolar damage

- **Definition of abbreviation: IP =interstitial pneumonia.**
  ***Desquamative interstitial pneumonia can occasionally occur in nonsmokers.**

*Travis WD, Am J Respir Crit Care Med 2013;188:733-748



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

IDIOPATHIC PULMONARY FIBROSIS

IDIOPATHIC PULMONARY FIBROSIS

ATS/ERS/JRS/ALAT definition: "IPF is defined as a specific form of **chronic**, **progressive** fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP**."**

- A distinct type of chronic **progressive** fibrosing interstitial pneumonia
- Unknown cause
- Limited to the lungs
- Associated with a histologic pattern of usual interstitial pneumonia (UIP)

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management, Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Risk factors associated with IPF

- Smoking
- Occupational factors (farmers, hairdressers, workers in stone quarries, the poultry industry, metallurgists, etc.)
- Air pollutants
- Chronic aspiration
- Drugs
- Viruses: Epstein-Barr virus, influenza A, parainfluenza 1 and 3, hepatitis C, HIV-1, herpes virus-6.

EPIDEMIOLOGY

- **Estimated to affect approx 5 million people worldwide**
- **The most common (and deadly) interstitial lung disease**
- **Most cases are sporadic, but rare cases of familial IPF have been described**

Raghu et. al., Am J of Resp Crit Care Med 2006

PATHOGENESIS

- Starting around 1998, studies began to demonstrate that **inflammation** is **NOT** a prominent finding in most cases of IPF/UIP.

- **Abnormal wound healing involving epithelial cells and fibroblasts**

- **Activated epithelial cells release potent fibrogenic molecules and cytokines, such as TNFα and TGFβ1**

PATHOGENESIS

IPF - original concept - as a latent inflammatory response that ultimately leads to chronic tissue damage and subsequent formation of lung fibrosis. Treatment focused only on stopping of chronic inflammation have been **unsuccessful.**

Contemporary approach suggests that IPF results from recurrent acute pulmonary injury. Healing response of these injuries lead to pulmonary fibrosis and inflammation as a less important mechanism. Fibrotic response intensity is influenced by genetic factors, by the inflammatory response (Th1 or Th2), environmental factors like smoking, viral infections, air pollutants.

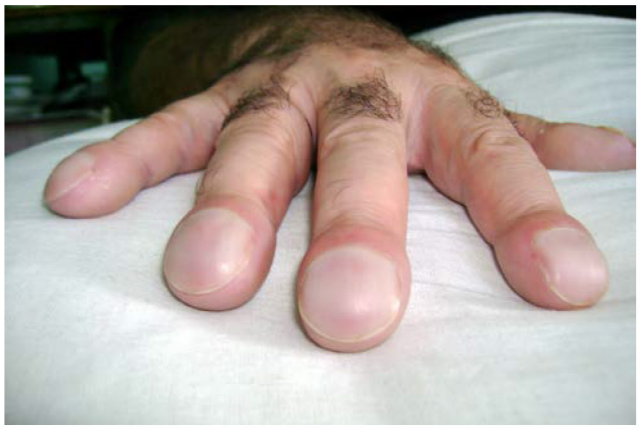
CLINICAL PRESENTATION

- Middle age 50-70s
- New onset of progressive exertional dyspnea
- non-productive cough
- Bibasilar crackles

PHYSICAL EXAM

- **Cyanosis**

- **Clubbing – 40-75% - late in disease course**



PARACLINICAL INVESTIGATIONS

- CBC
- CRP
- Pulse Oximetry
- DLCO
- 6MWT
- Spirometry
- BAL
- Chest Xray
- HRCT
- Pulmonary biopsy

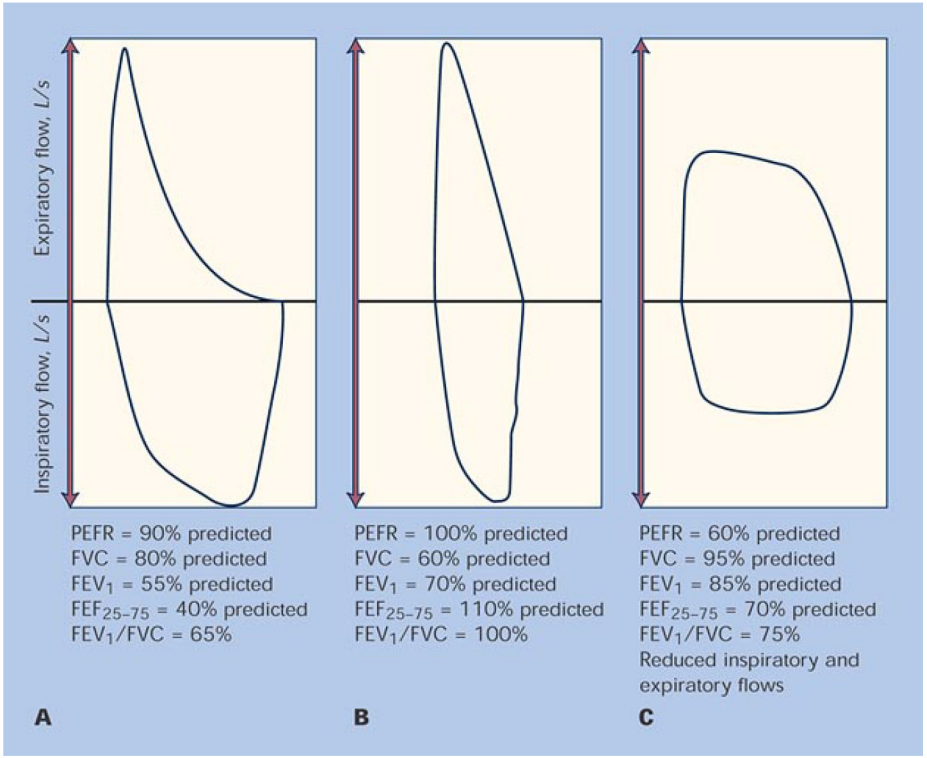
PFTs

PFT's = Restrictive pattern

Reduced TLC, VC, and/or RV (decreased compliance)

Normal or increased FEV_1/FVC

Decreased D_{LCO}



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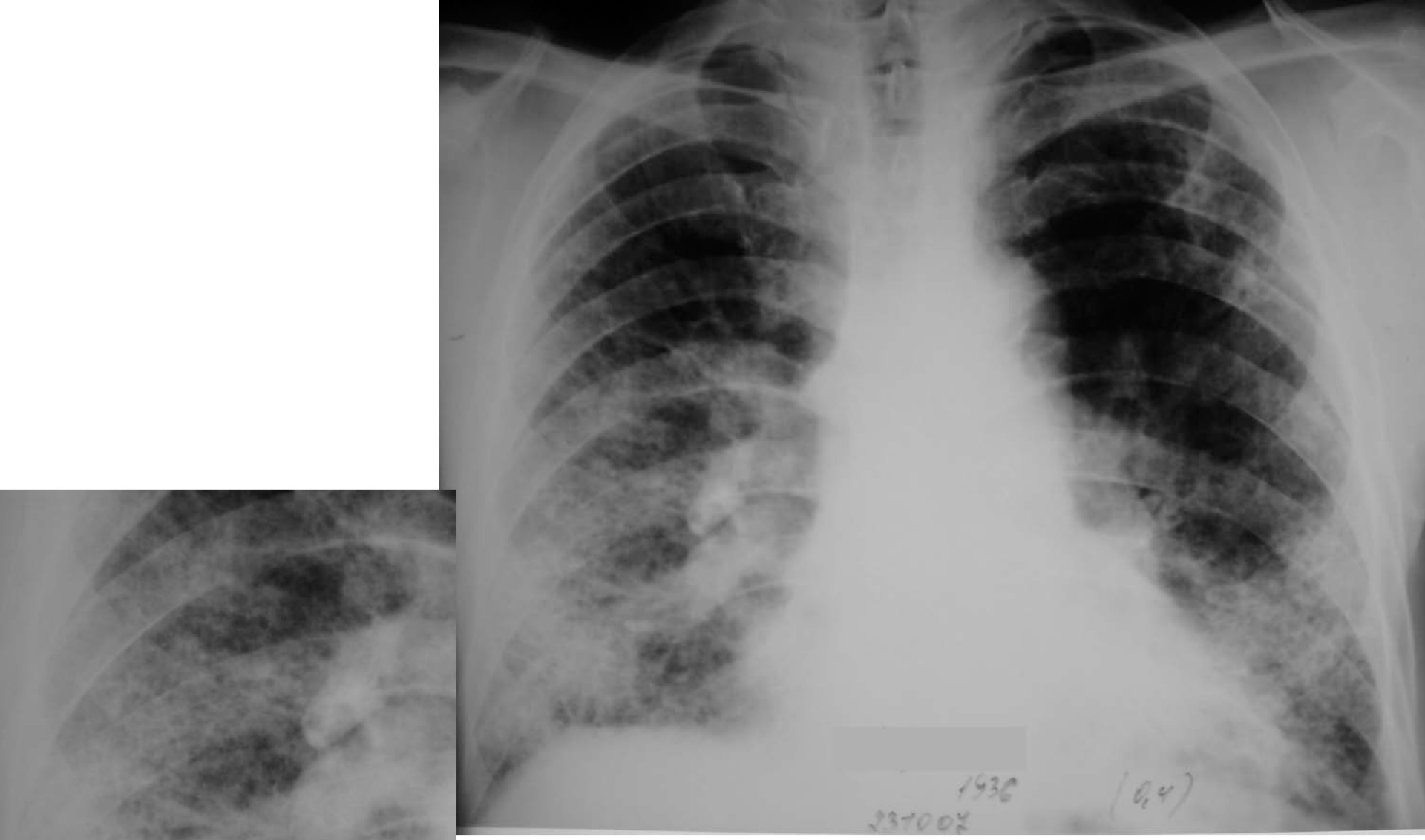
IMAGISTIC FEATURES

- Reticular opacities especially at bases and peripheral

- "honeycombing" - subpleural and lower areas, with lower lobe volume reduction

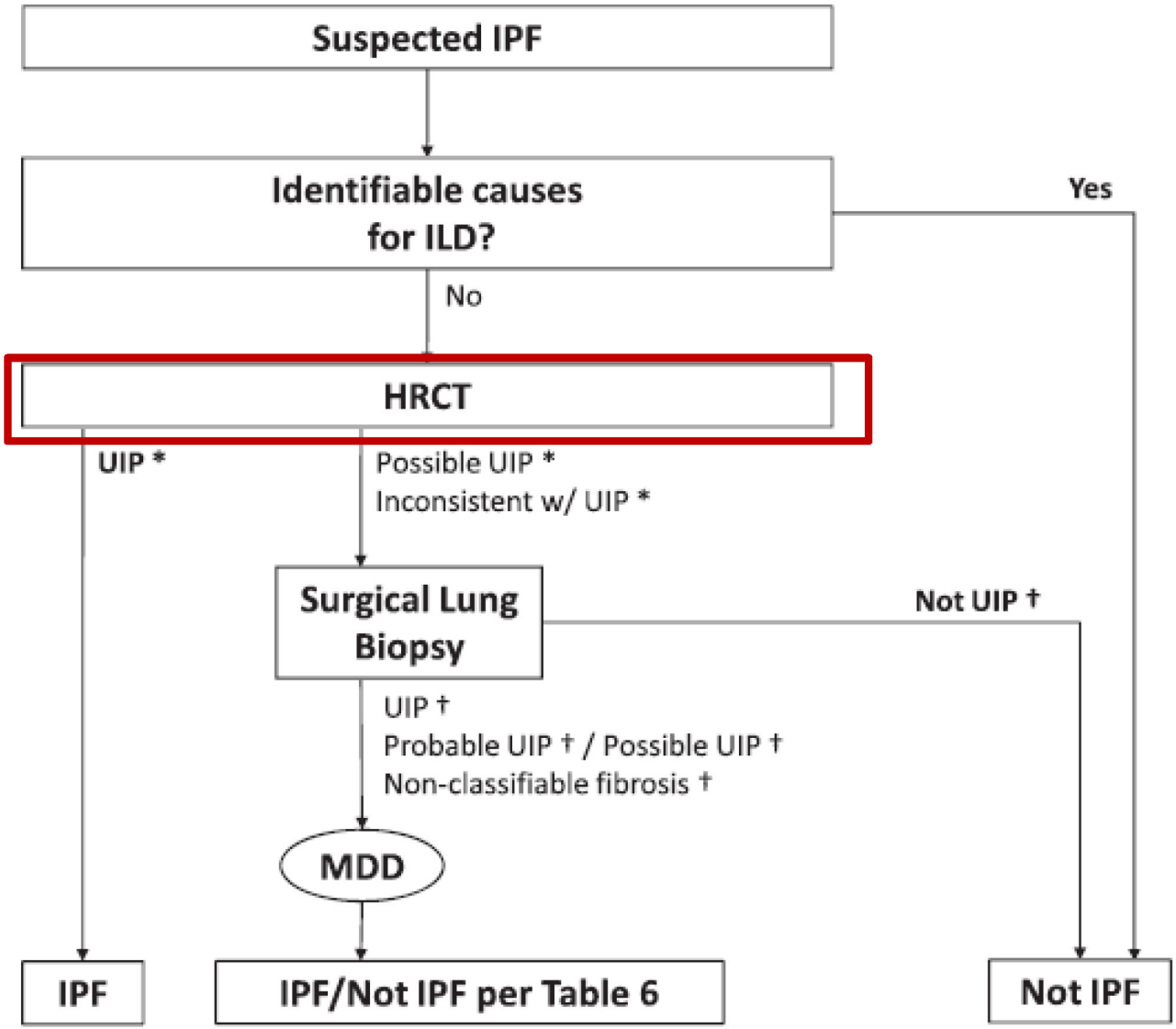


"honeycombing“ in lower areas,
lower lobe volume reduction
ill defined heart limit

- HRCT – big step foward in diagnostic approach of a patient with suspected ILD

- In over 80% of cases with IPF (confirmed by biopsy) the diagnosis could be established with based only on HRCT, without requiring lung biopsy

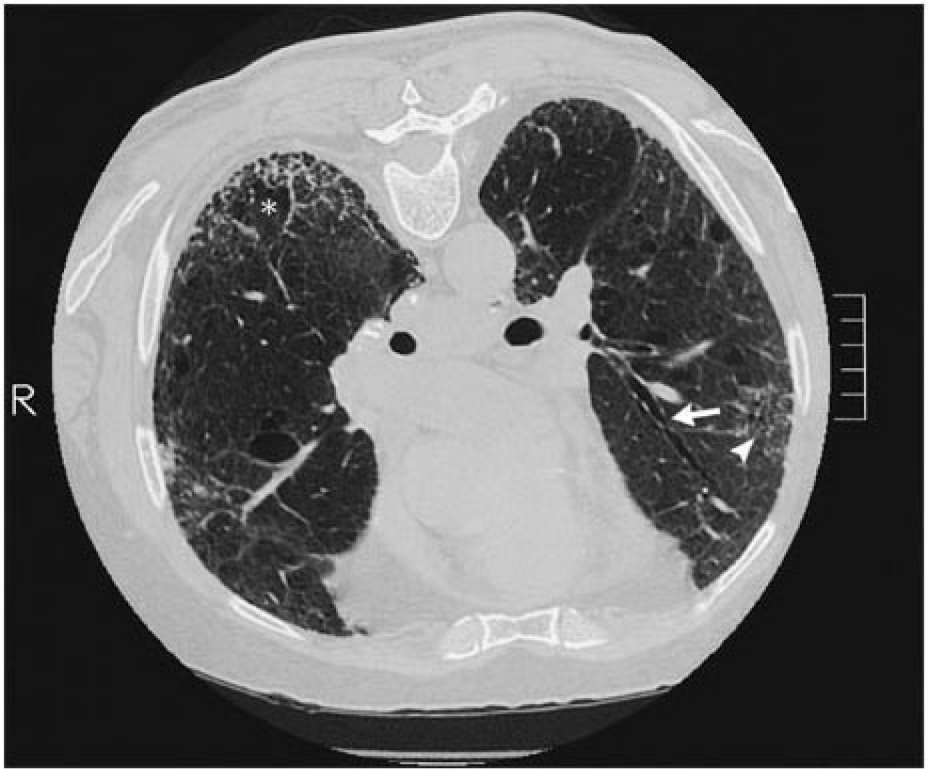
ATS/ERS Consensus Statement. *Am J Respir Crit Care Med*. 2000;161:646.



An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management, Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

HRCT

- Can be used to detect disease, especially in pts with no or minimal changes on CXR
- Can determine extent and severity of disease activity
- Can now be used to differentiate IPF from other ILD



Peripheral, subpleural fibrosis

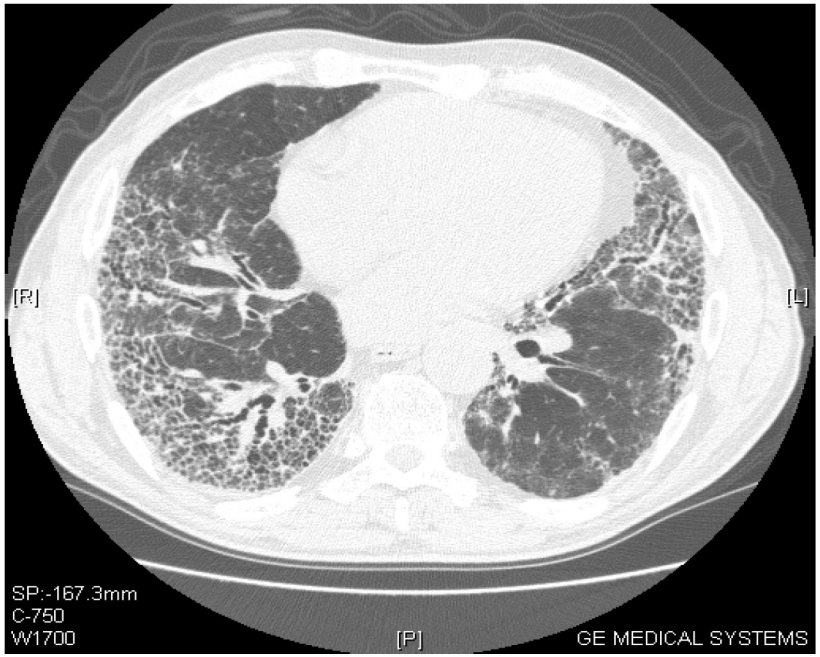
Alternating areas of normal tissue

Honeycombing

Traction bronchiectasis

Later stages - more diffuse reticular pattern prominent in lower lung zones associated with thickened interlobular septa

Idiopathic Pulmonary Fibrosis, Gross and Hunninghake, NEJM, 2001.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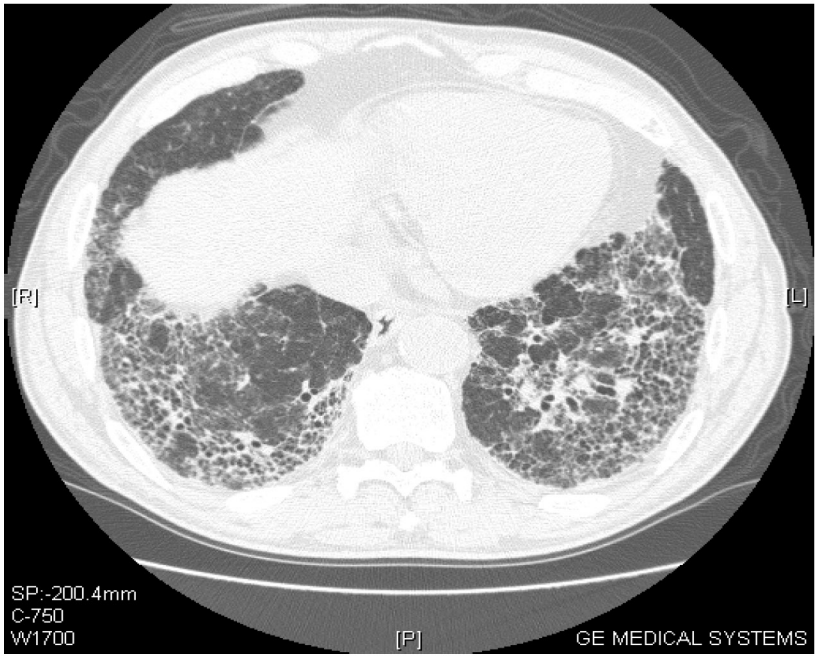
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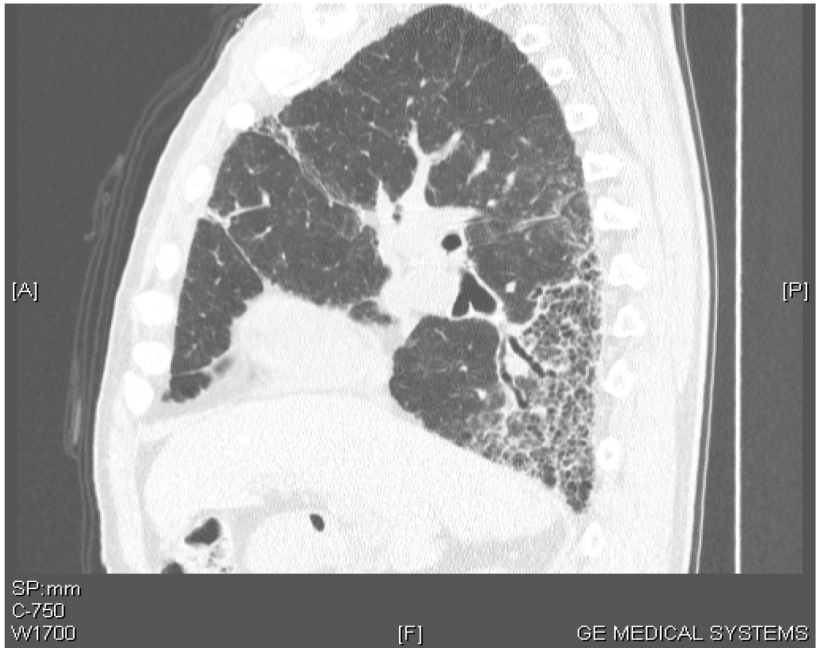
GE MEDICAL SYSTEMS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SP:mm
C-750
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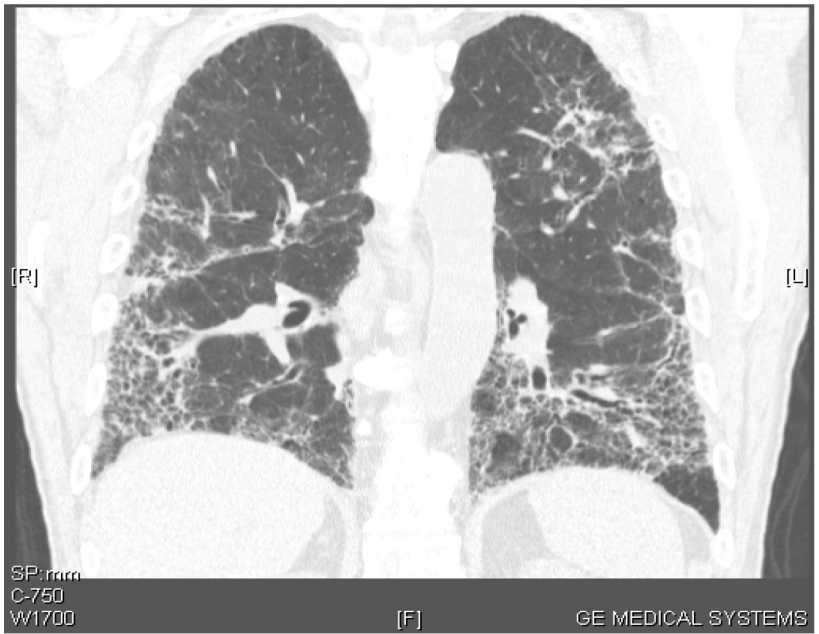
GE MEDICAL SYSTEMS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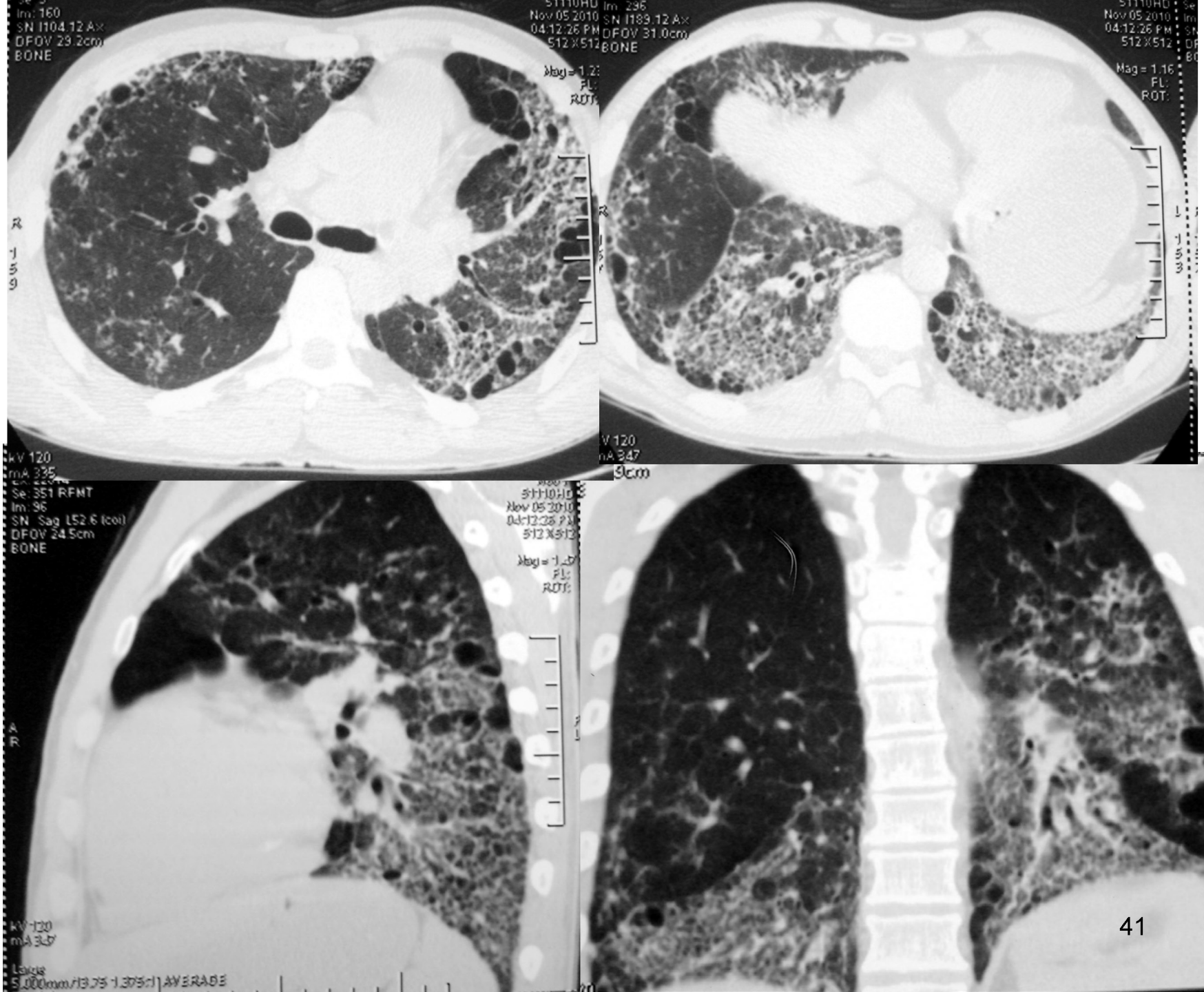
GE MEDICAL SYSTEMS


Im: 160
SN I104.12 Ax
DFOV 29.2cm
BONE
Nov 05 2010
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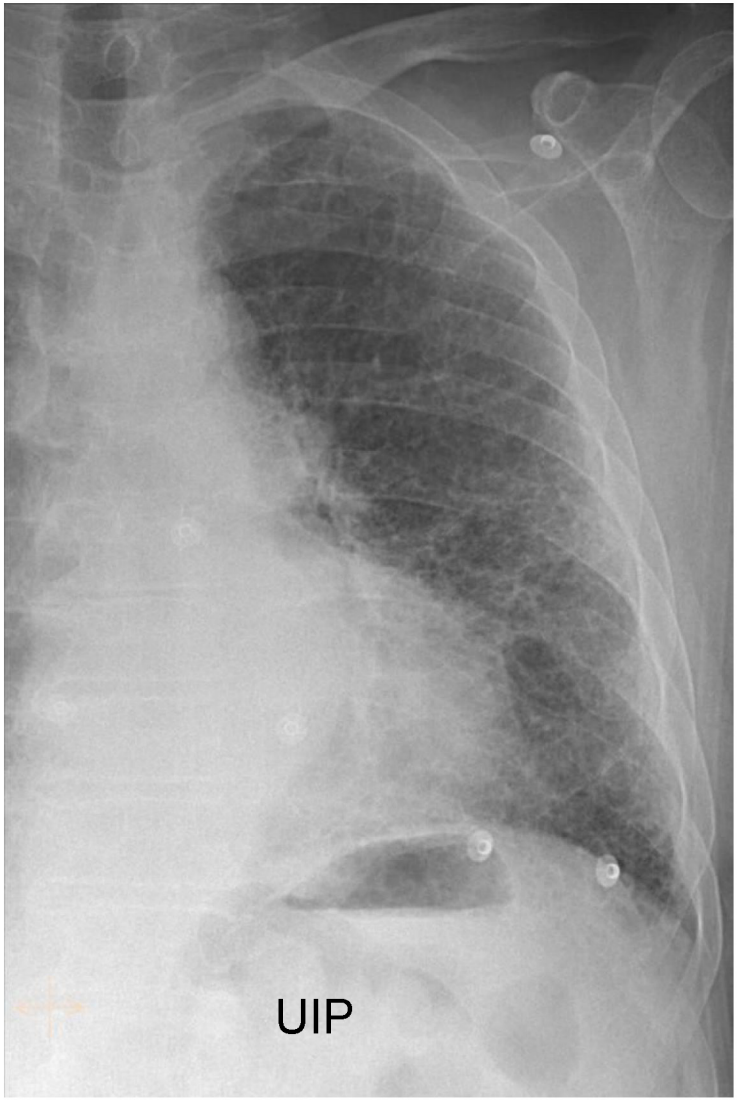
Mag = 1.16
FL:
ROT:
Im: 236
SN I189.12 Ax
DFOV 31.0cm
BONE
Se: 351 RFNT
Im: 96
SN Sag L52.6 (coil)
DFOV 24.5cm
BONE
kV 120
mA 335
AVERAGE

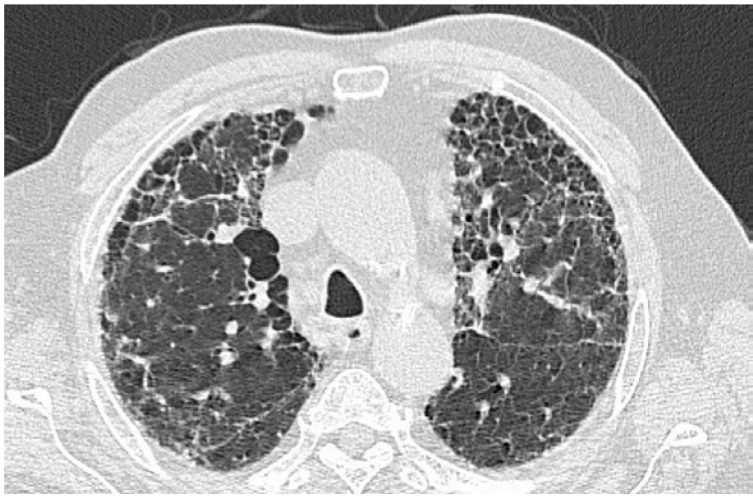
UIP / NSIP

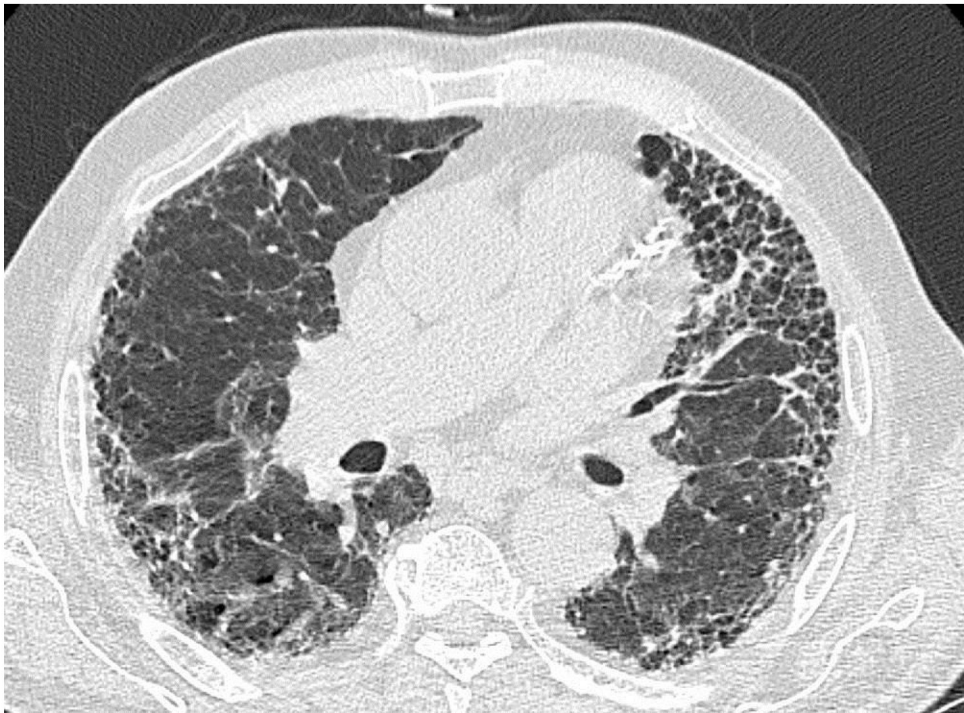
Definite UIP pattern (includes all 4 of):	**Possible UIP pattern** (no honeycombing, but includes all 3 of):	**Inconsistent with UIP pattern** (any 1 of):
-subpleural and basal predominance -reticular abnormalities -honeycombing with or without traction bronchiectasis -absence of inconsistent features (see category 3)	-subpleural and basal predominance -reticular abnormalities -absence of inconsistent features (see category 3)	-upper or mid-lung predominance -peri-bronchovascular predominance -Extensive ground glass abnormality (extent > reticular abnormality) -profuse micronodules (bilateral, predominantly in upper lobes) -discrete cysts (multiple, bilateral, away from areas of honeycomb) -diffuse mosaic attenuation / air-trapping (bilateral, in 3 or more lobes) -consolidation in bronchopulmonary segment(s) / lobe(s)

Raghu G et al. An Official ATS/ERS/JRS/ALAT Statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183: 788–824.

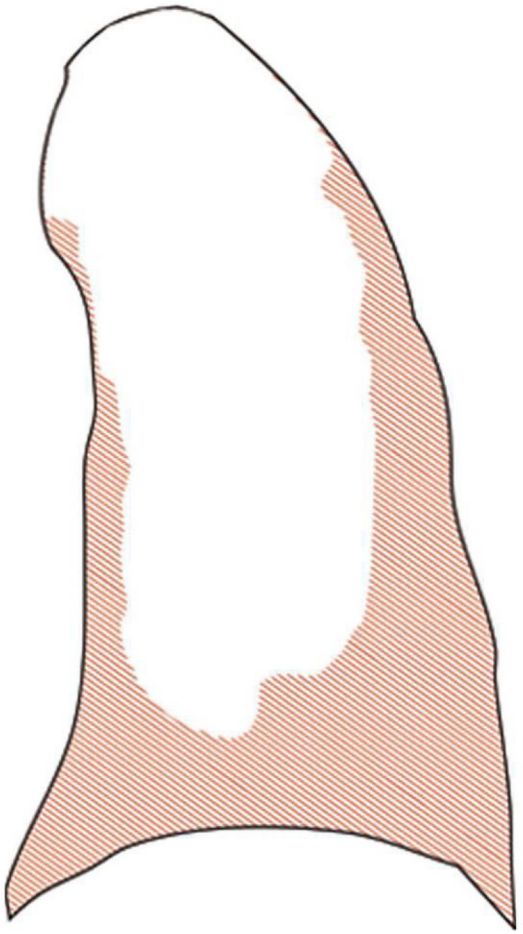
Lung: Interstitial diseases

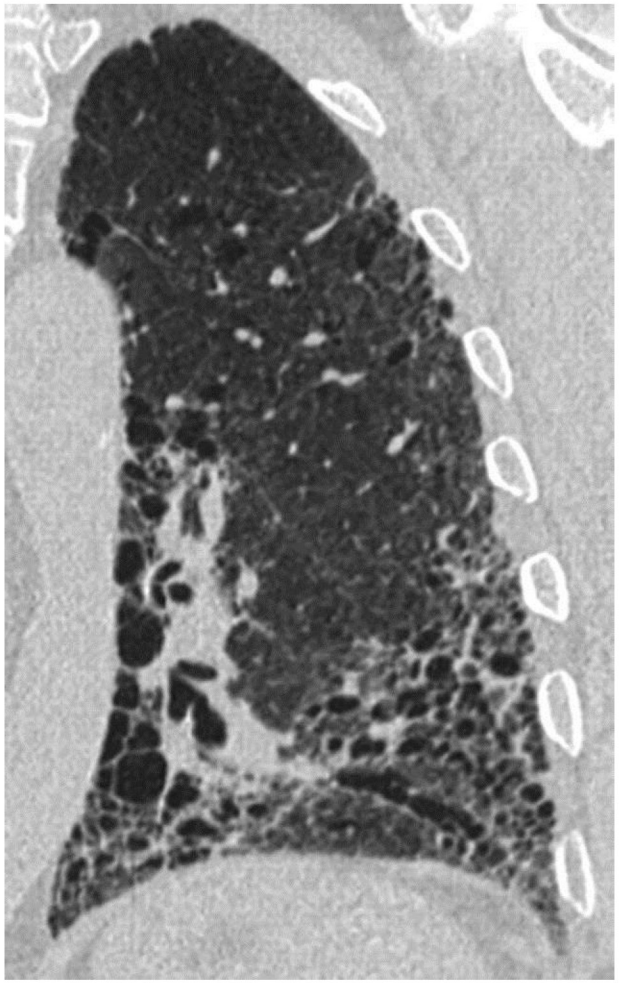


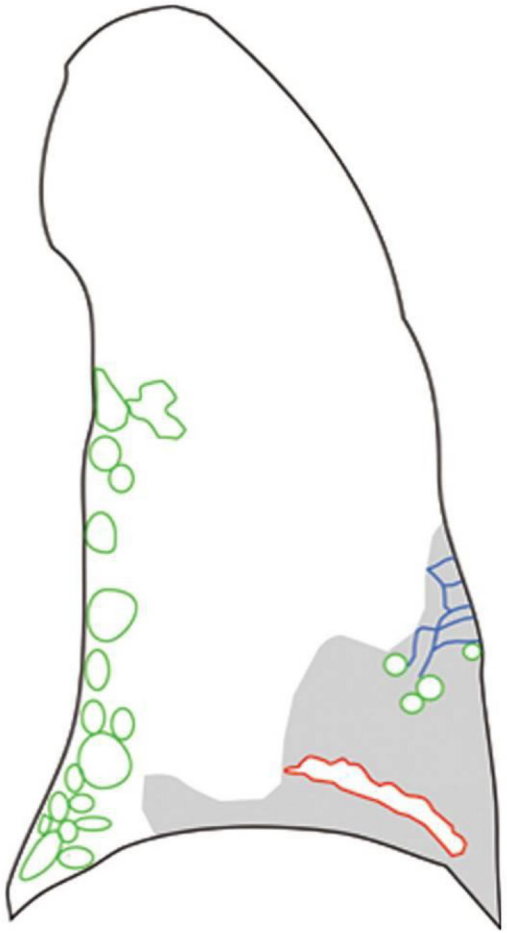




UIP: Distribution Pattern







Mueller-Mang C et al. Radiographics 2007;27:595

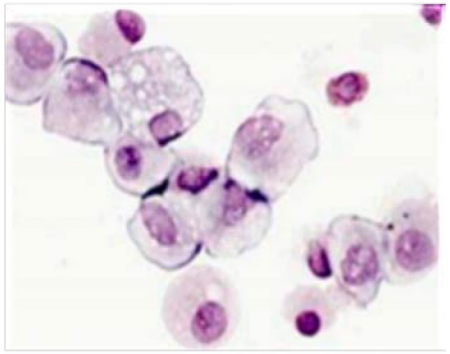
An Official American Thoracic Society Clinical Practice Guideline: The Clinical Utility of Bronchoalveolar Lavage Cellular Analysis in Interstitial Lung Disease

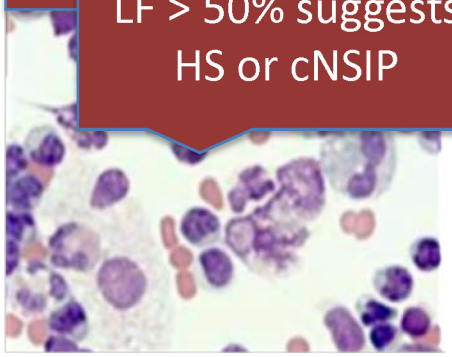
THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, JANUARY 2012

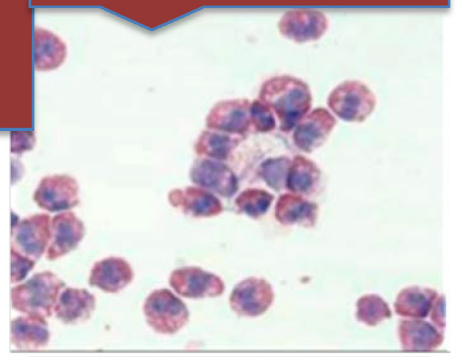
CD4+/CD8+>4 highly specific for

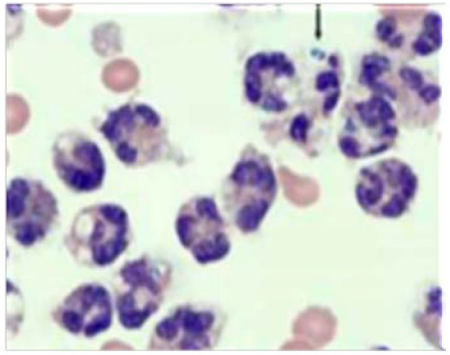
LF > 50% suggests HS or cNSIP

E >25% acute or chronic EP









Normal

- Alv macrof ≥ 85%
- Lf (CD4+/CD8+ = 0.9-2.5) 10-15%
- Neutr ≤ 3%
- Eos ≤ 1%

Lymphocytic

sarcoid, NSIP, HP, CVD, COP, drug-induced pneumonitis

Eosinophilic

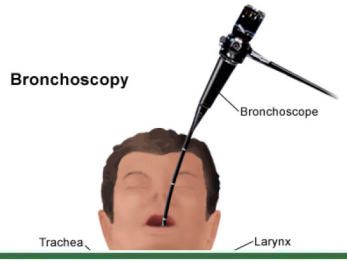
BA, bronchitis, ABPA, Pneumocystic inf, Hodgkin"s disease, EP

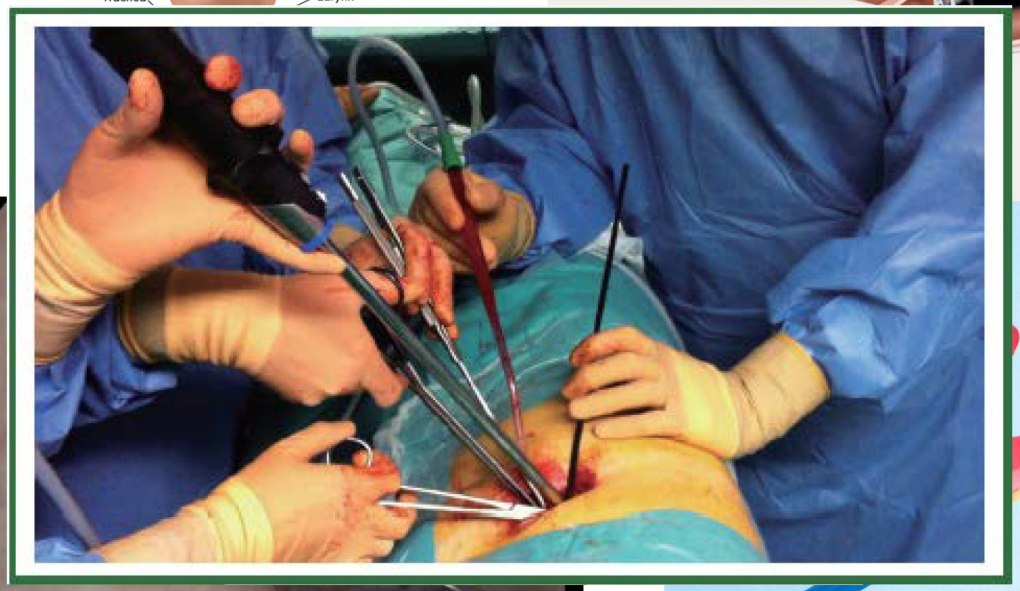
Neutophilic

CVD, IPF, bronchitis, asbestosis, ARDS, DAD

Lung biopsy

- **Transbronchial Biopsy**
- **Transbronchial Cryobiopsy**
- **Video-Assisted Thoracoscopic Surgery (VATS)**
- **Open lung biopsy (thoracotomy)**





LUNG BIOPSY

- ❑ Large piece of lung parenchyma is required, optimally from several sites
- ❑Transbronchial biopsy is only useful for ruling out other disorders
- ❑Can be performed by thoracotomy, thorascopy, or VATS

Pulmonary biopsy

Particularly for patients with idiopathic interstitial pneumopathies (20-30%)

VATS is the preferred approach

- Requires single lung ventilation
- Several disparate biopsies taken

Classical surgery : open lung biopsy (minithoracotomy)

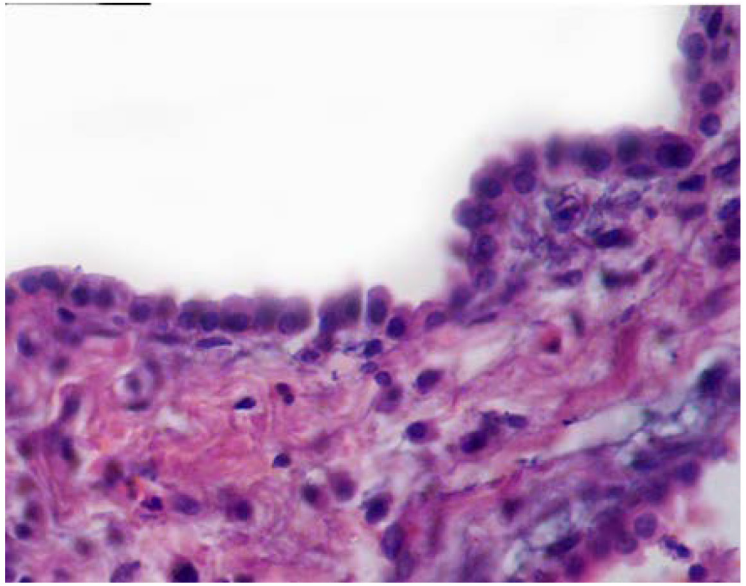
Contraindications of lung biopsy in ILD

- Age > 70 years old
- Morbid obesity
- Severe cardiac disease
- Coagulopathies
- Respiratory failure

ATS: Idiopathic pulmonary fibrosis: diagnosis and treatement, Am J Respir Crit Care Med 2000,
Lettiery, Shorr: Outcomes and safety of surgical lung biopsy for interstitial lung disease, Chest 2005

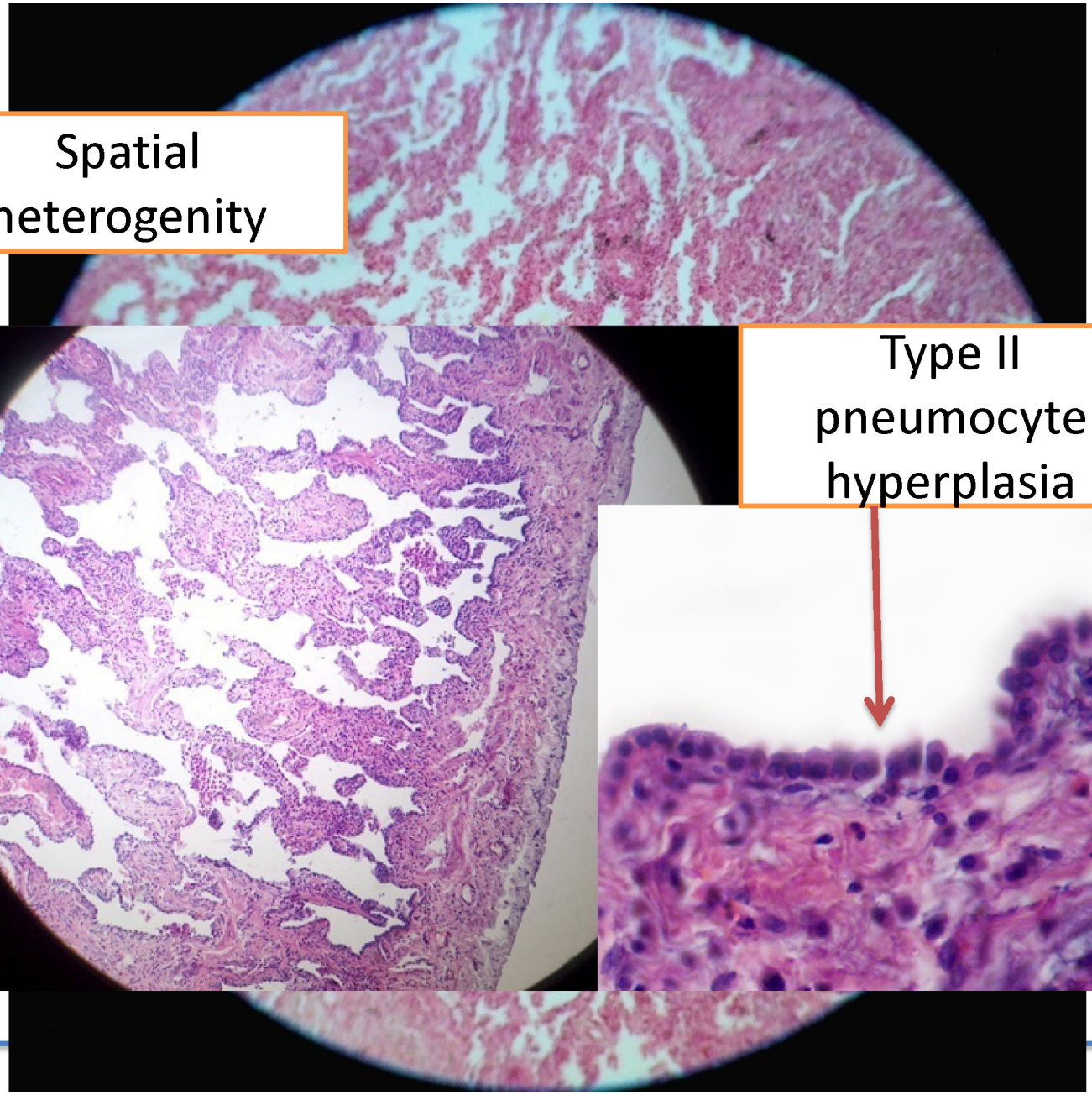
Histologic patterns

- Usual interstitial pneumonia
- Nonspecific interstitial pneumonia
- Diffuse alveolar damage
- Organizing pneumonia
- Respiratory bronchiolitis
- Desquamative interstitial pneumonia
- Lymphoid interstitial pneumonia



Spatial heterogenity

Type II pneumocyte hyperplasia



Clinical case

- Female, 59 y.o
- Smoking: No
- No history of exposure to environmental or occupational factors
- No pulmonary disease among family members

Complains in September 2007

- Dyspneea at minimal physical effort
- Cough
- pronounced fatigue
- periodically low grade fever

History

- Reports the presence of dyspnea and cough over the last three years, but worsening in time.

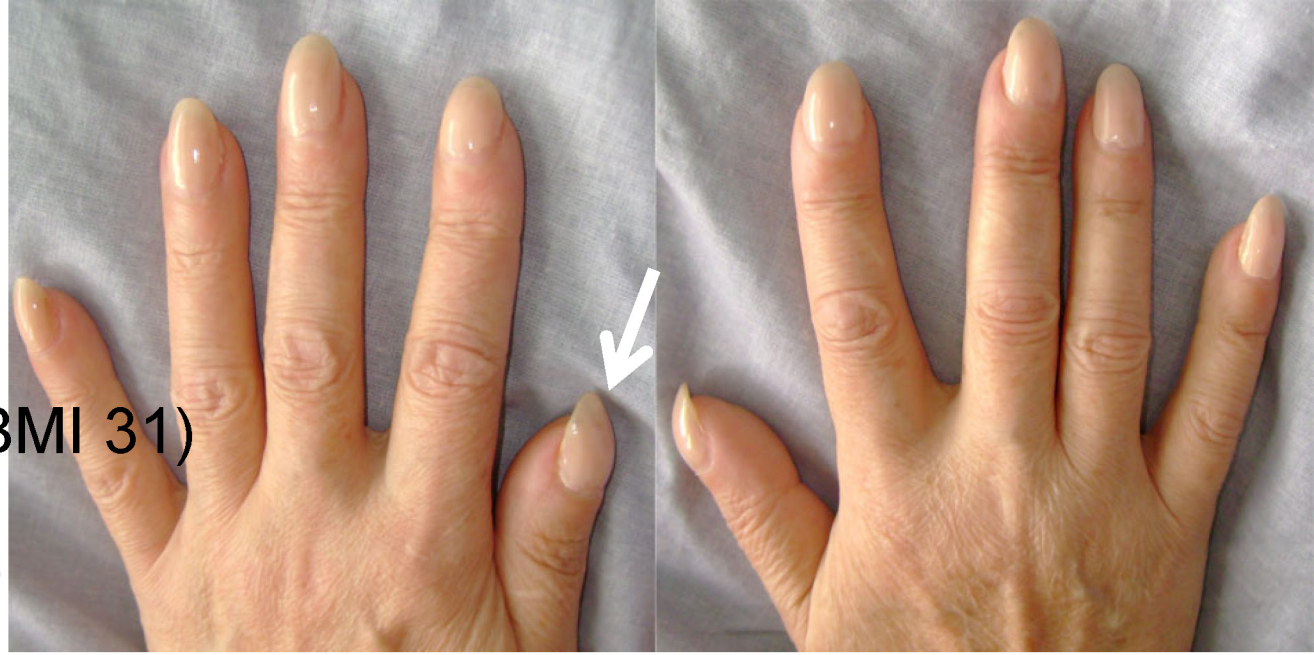
- Cough reported as the most disturbing symptom, usually with viscous sputum, with difficult expectoration.

- In 2005 received treatment for community acquired bilateral pneumonia, taking many courses of antibiotics during a year. Then she was diagnosed with COPD, no bronchodilato therapy

Pathological history

- Thyroidectomy for thyroid cancer in May 2007 ($T_3N_0M_x$)

Physical exam

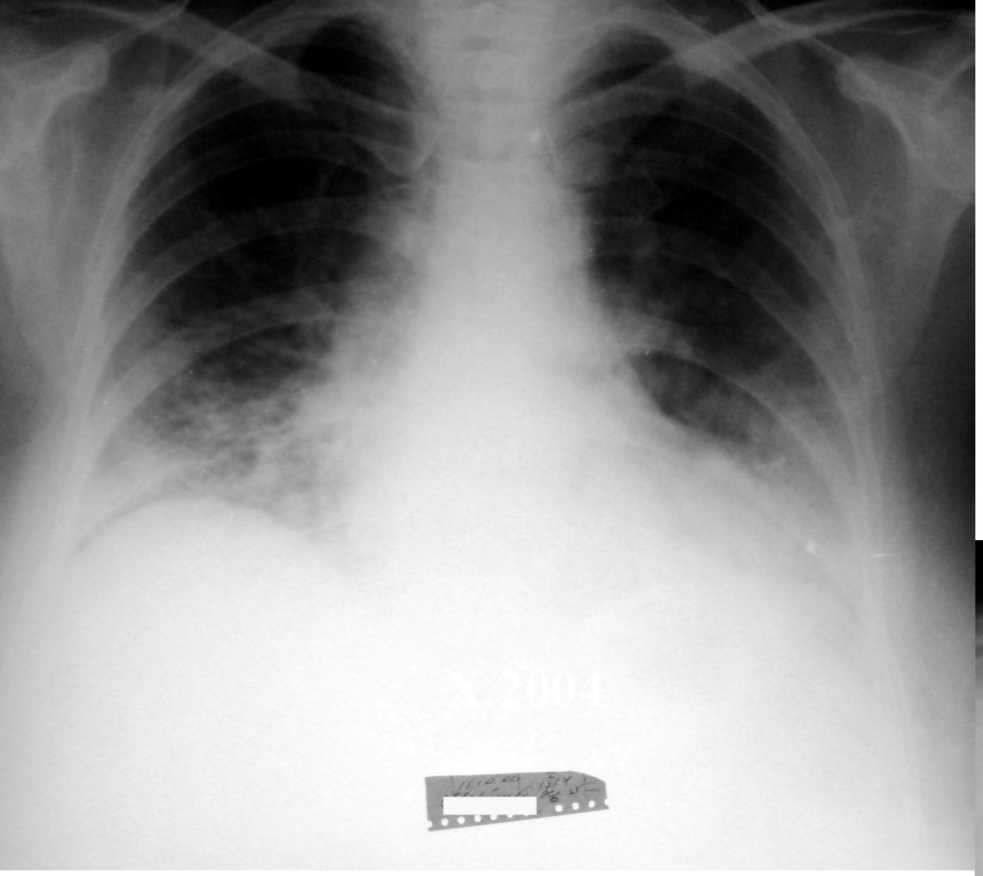


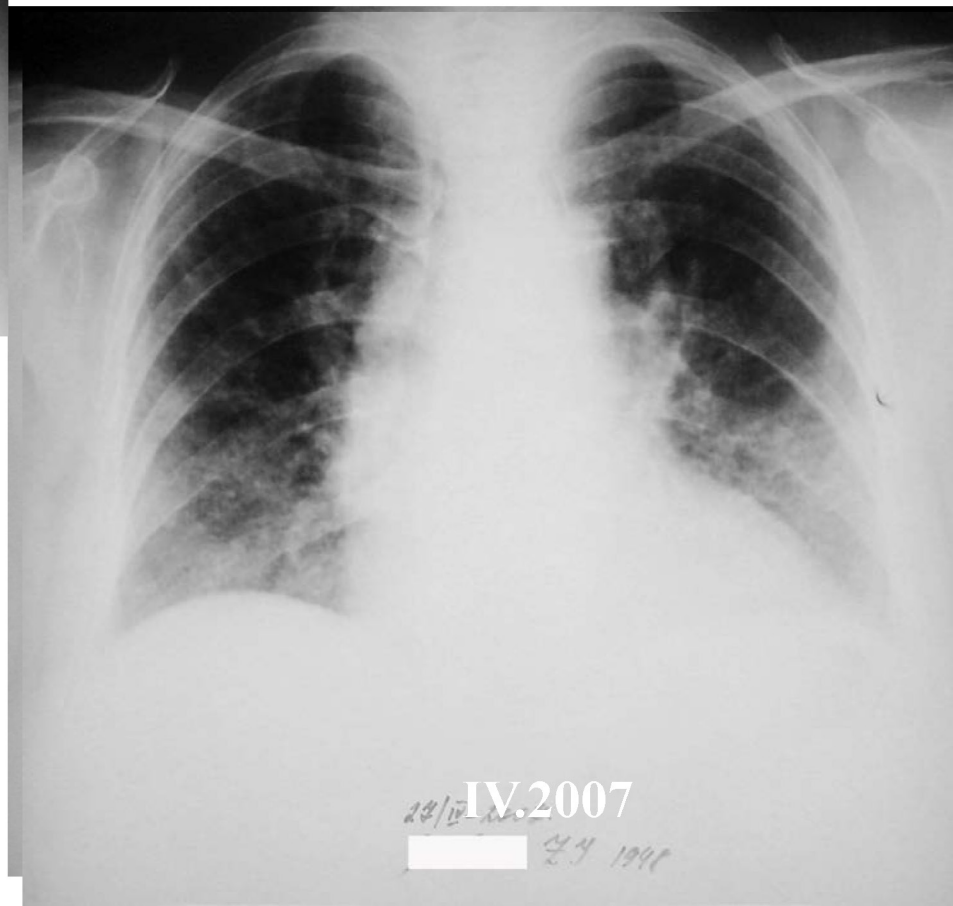
- overweight (BMI 31)
- Acrocyanosis
- tachypnea (24/min RR)
- clubbing
- auscultatory lungs – prolonged expiration, vezicular murmur decreased bilateral in lower fields, subscapular and axillary bilateral crepitation
- Heart auscultation - only tachycardia up to 110/min.

- Rest SaO_2 94%
- 6MWT – 225m (50% of pred.), SaO2 -88%
- PFTs - restriction (FVC 53%, FEV1 67%, FEV1/FVC 87%)

CXR

(2004-2005-2006-April 2007-July 2007)





Negative evolution of lung lesions:

- decrease in bilateral lower lung fields
- "ground glass" opacities
- reticular opacities that in time extend to the to the upper areas of lung fields and involve mostly subpleurale zones

HRCT

September 2007

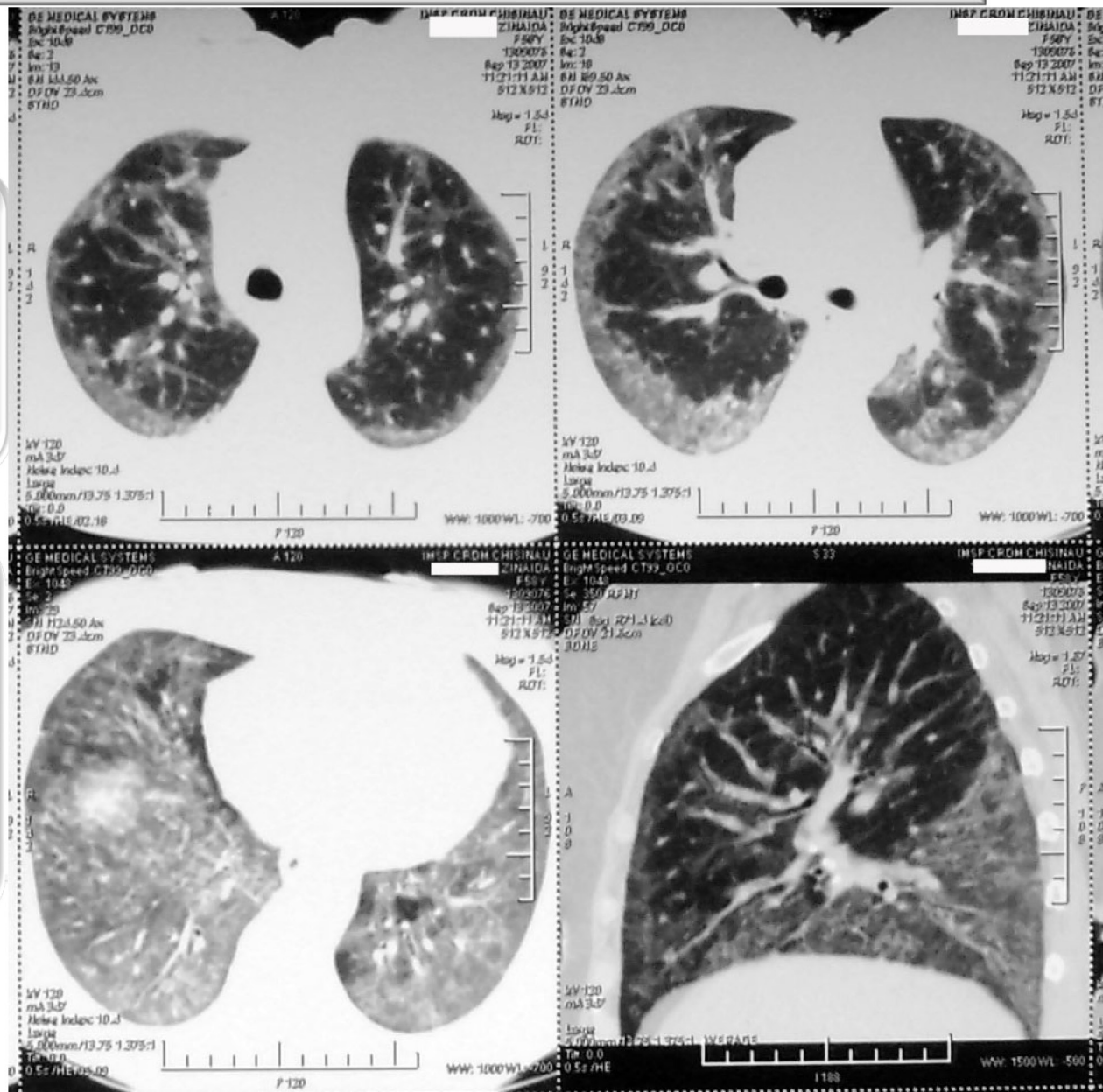
- “ground glass“ opacities
- reticular opacities
- Lower lobes bilaterl
- Subpleural zones

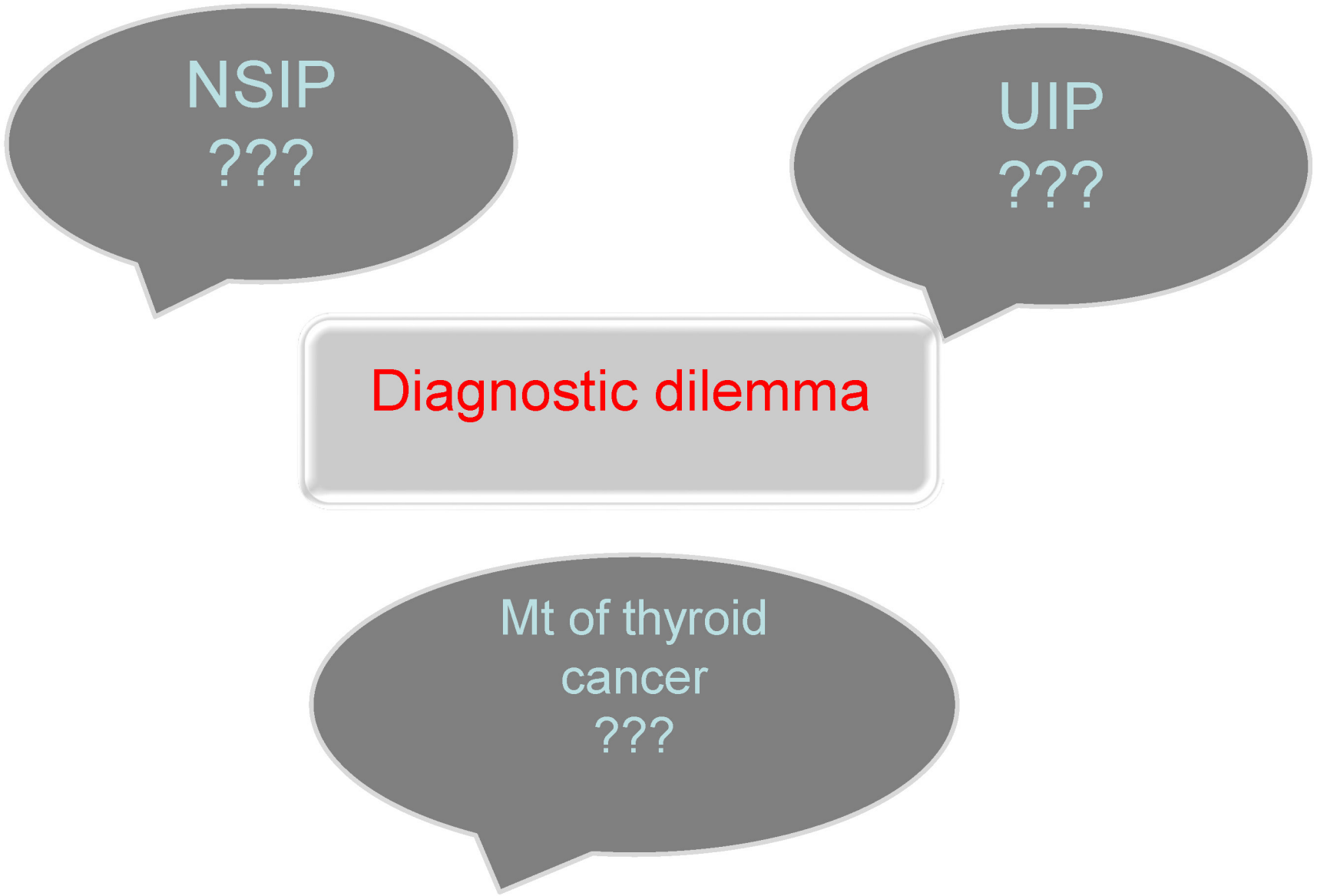
Fibrosis score

5 (25)

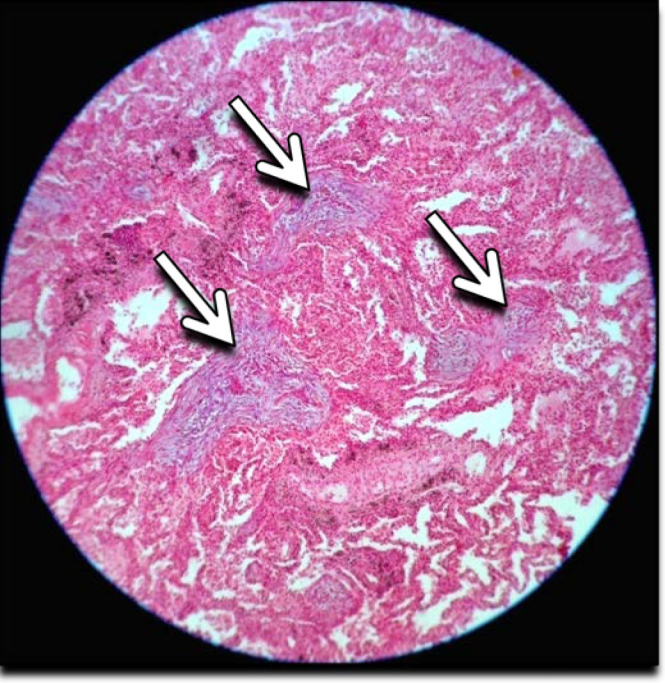
“ground glass“ score

20 (25)

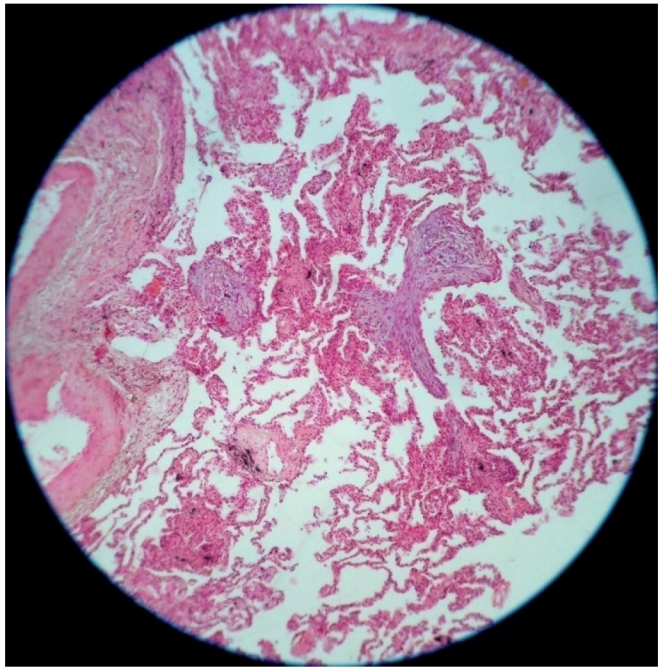



NSIP
???
UIP
???
Diagnostic dilemma
Mt of thyroid
cancer
???

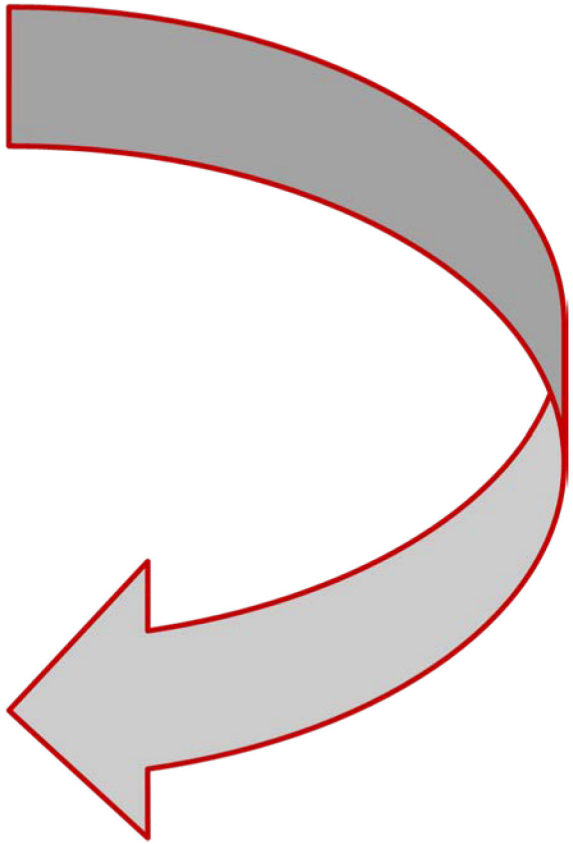
lung biopsy had a decisive role in the diagnosis



Multiple fibroblast foci



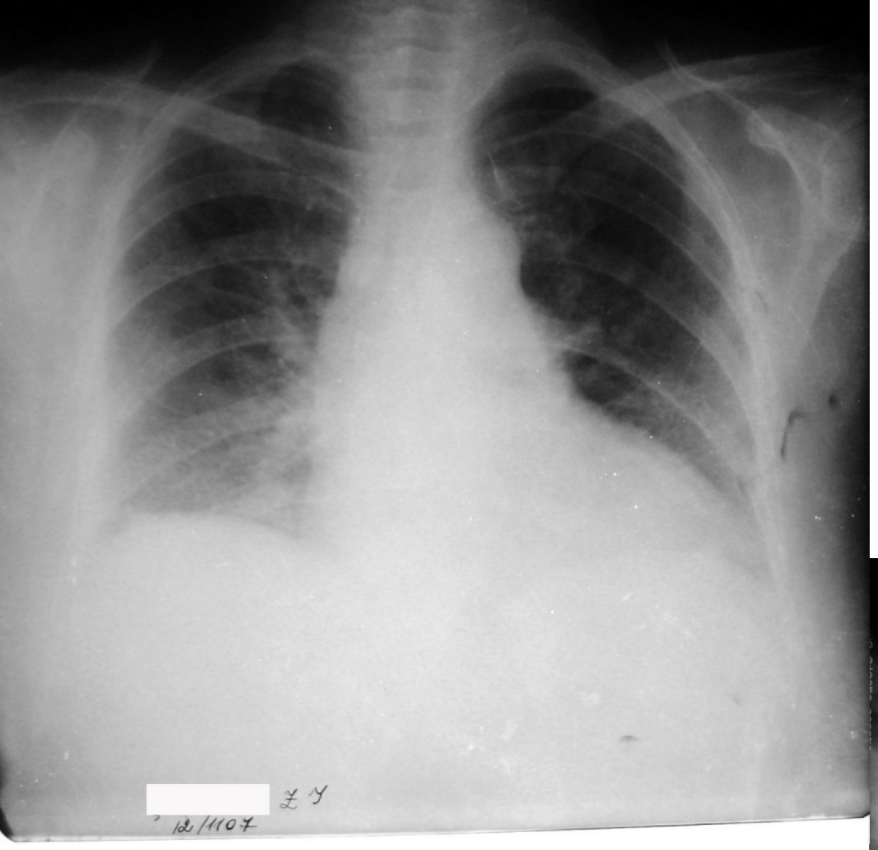
Morphologic *pattern* is UIP

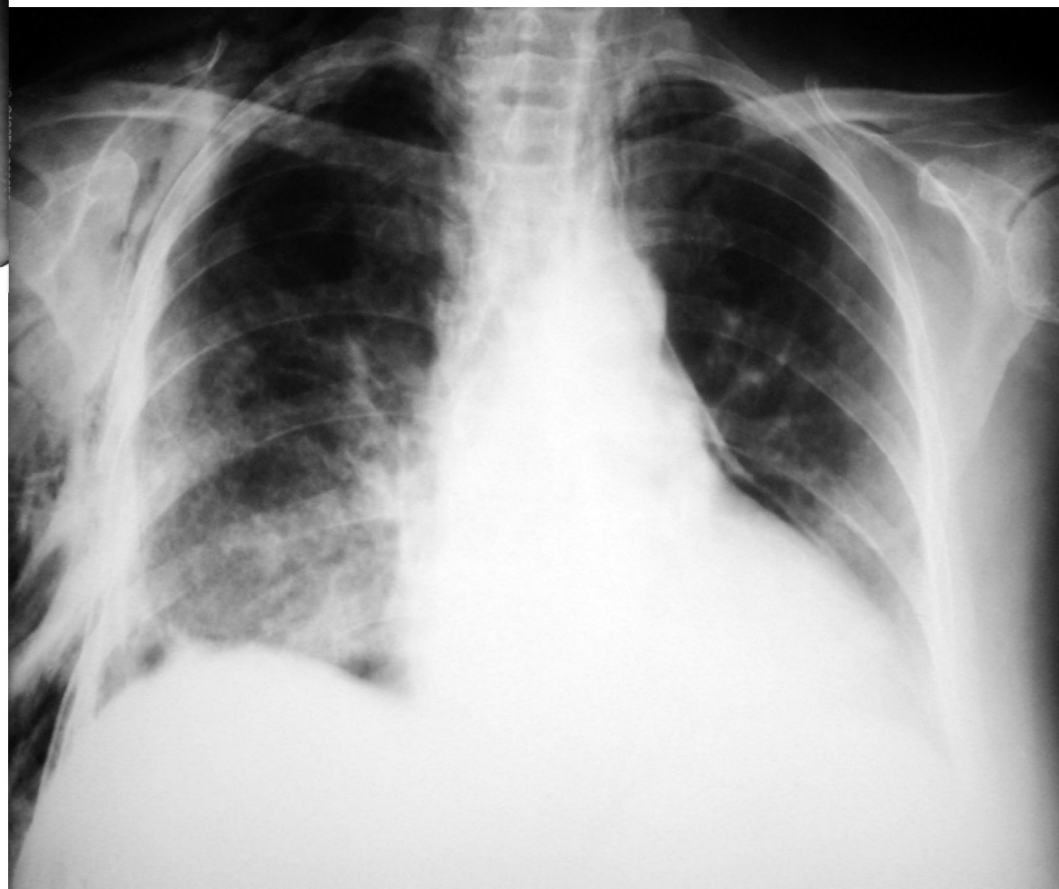


Diagnostic

IDIOPATHIC PULMONARY FIBROSIS

COMPLICATIONS





DIFFERENTIAL DIAGNOSIS

	IPF	NSIP	COP	AIP	RBILD	DIP	LIP
Epidemiology	50 – 70 y.o **M>F**	40 – 50 y.o B=F	All ages Average 50 y.o) B=F	All ages Average 50 y.o) B=F	30-50 y.o. Mostly smokers	40-50 y.o. Mostly smokers	30-50 y.o. Mostly females
Clinical signs	Chronic dyspnea, cough, crepitation, clubbing	Chronic dyspnea, cough, crepitation, digital clubbing occasionally	Acute, subacute dyspnoea, cough, fever crepitation, **NO** clubbing	Rapidly progressive dyspnea, cough, fever occasionally, crepitation, absent digital clubbing	Chronic dyspnea, cough, crepitation, NO clubbing	Chronic dyspnea, cough, crepitation, occasionally clubbing	Chronic dyspnea, cough, crepitation, NO clubbing, lymphadenopathy occasionally
Imaging	Reticular opacities in lower lobes bilaterally, subpleural, honeycombing, minimum ground glass opacities	Ground glass opacities bilateral in the lower lobes, subpleural, reticular opacities minimal	ground glass opacities in bilateral lower lobes, NO consolidations, reticular opacities and honeycombing	Difuse ground glass opacities, consolidations	Bilateral difuse ground glass opacities, Centolobular nodules, NO honeycombing	ground glass opacities bilateral in lower lobes, subpleural, Some cysts Reticular opacities rarely, NO honeycombing	inhomogeneous ground glass opacities bilaterally centrilobular nodules, thickening of the broncho-vascular bundles, cysts
Morphology	UIP pattern	NSIP pattern	OP pattern	DAD pattern	RB pattern	DIP pattern	LIP pattern
CS response	Poor (<10)	Good (50–90%)	Excellent (> 80%)	Unclear, probably bad	Excellent (> 90%)	Good (60%)	Neclar, mai probabil bun
Prognostic	Poor (20% 5-year survival)	Good (70% 5-year survival)	Excellent (> 90% 5-year survival)	Poor (< 50% short term survival)	Excellent > 90% 5-year survival	Good 70% 5-year survival	Good 60% 5-year survival

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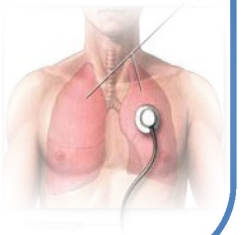
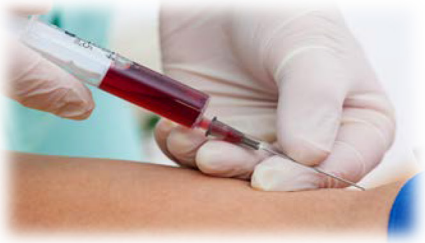
Summary of recommendations for ILD

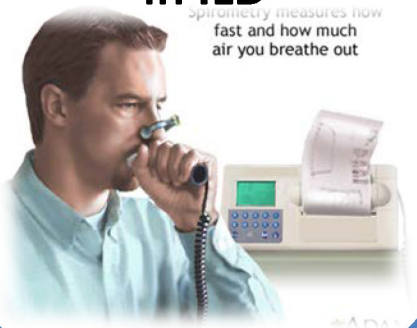
1. **History and clinical examination in ILD**



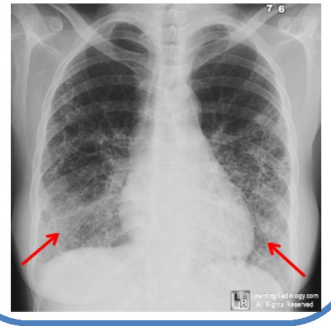
2.a.Initial blood and other tests



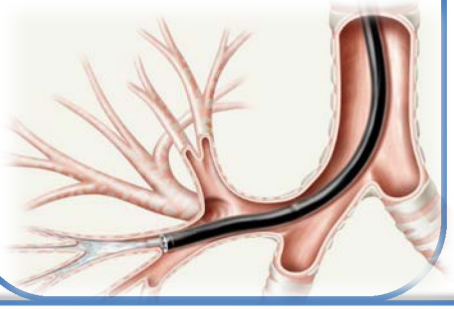
2.b. Lung function testing in ILD



2.c.Chest radiography and HRCT



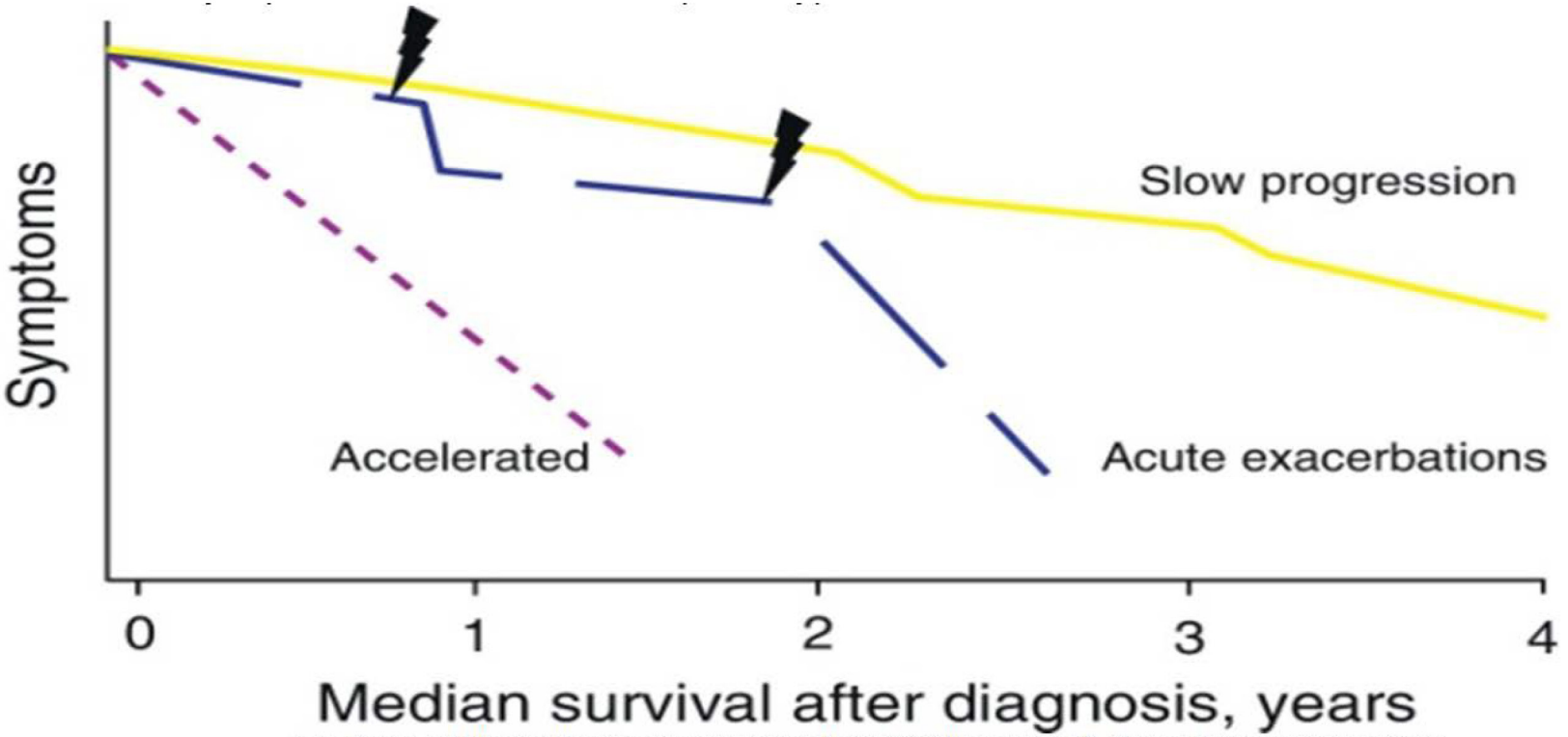
3.Bronchoalveolar lavage (BAL) and transbronchial lung biopsy



4.Surgical lung biopsy in ILD

! The multidisciplinary approach
is now considered the
"gold standard"

IPF

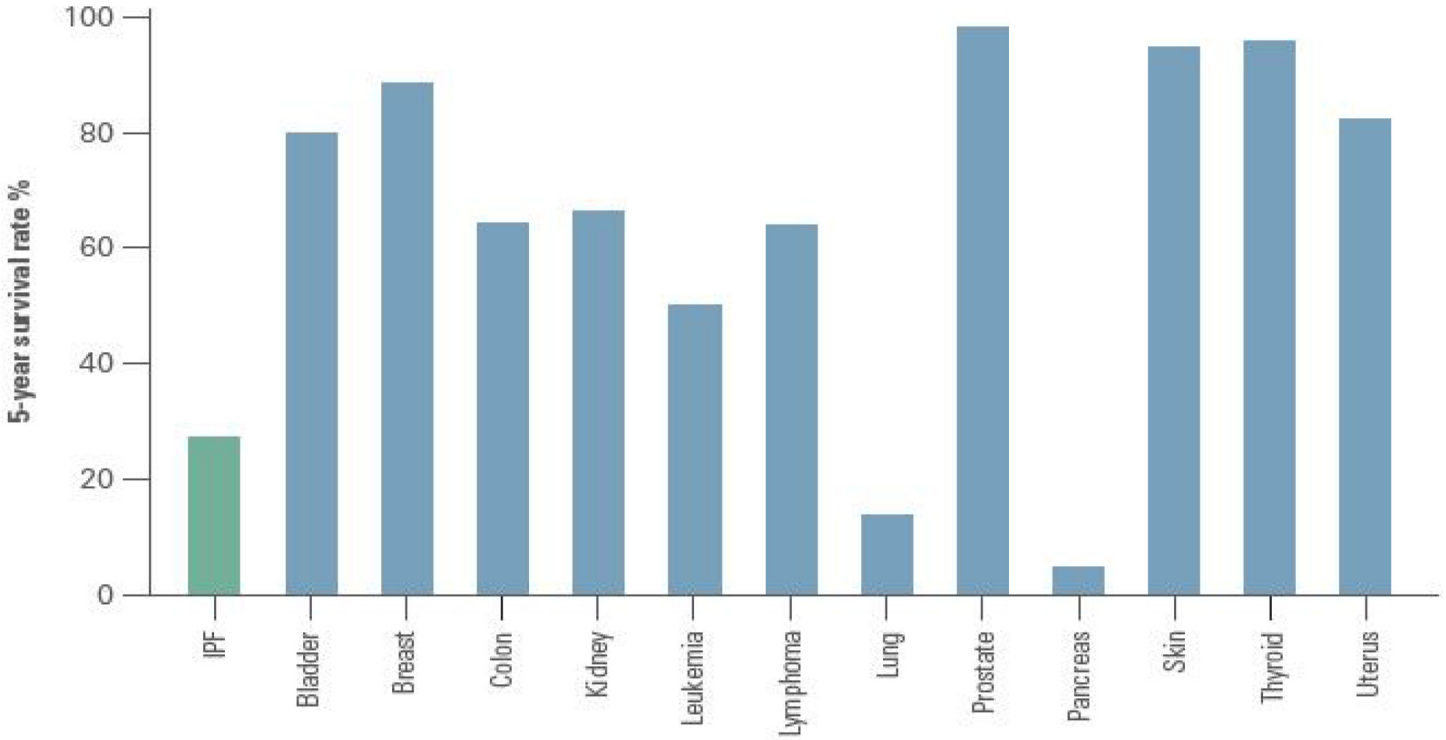


Antoni Xaubet. Guidelines for the Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis. Archivos de Bronconeumologia. Spain

IPF PROGNOSIS

Very bad prognosis, median survival time 3-4 years

IPF has a worse prognosis than many types of cancer



Jürgen Behr. The Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis. Deutsches Ärzteblatt International. 2013

Treatment

QUIT SMOKING!!!

Oxygen Therapy

Pirfenidone

Treatment of GERD - PPI

Pulmonary rehabilitation

Nintedanib

Lung Transplantation

IPF treatment

Panel: **Therapies identified in clinical trials as harmful, ineffective, or effective in the treatment of idiopathic pulmonary fibrosis**

Potentially harmful therapies

- Ambrisentan[81]
- Everolimus[82]
- Prednisolone, azathioprine, acetylcysteine[9]
- Warfarin[83]

Potentially ineffective therapies

- Bosentan[84]
- Imatinib[85]
- Macitentan[86]
- Acetylcysteine[87]
- Sildenafil[88]

Effective disease-modifying therapies

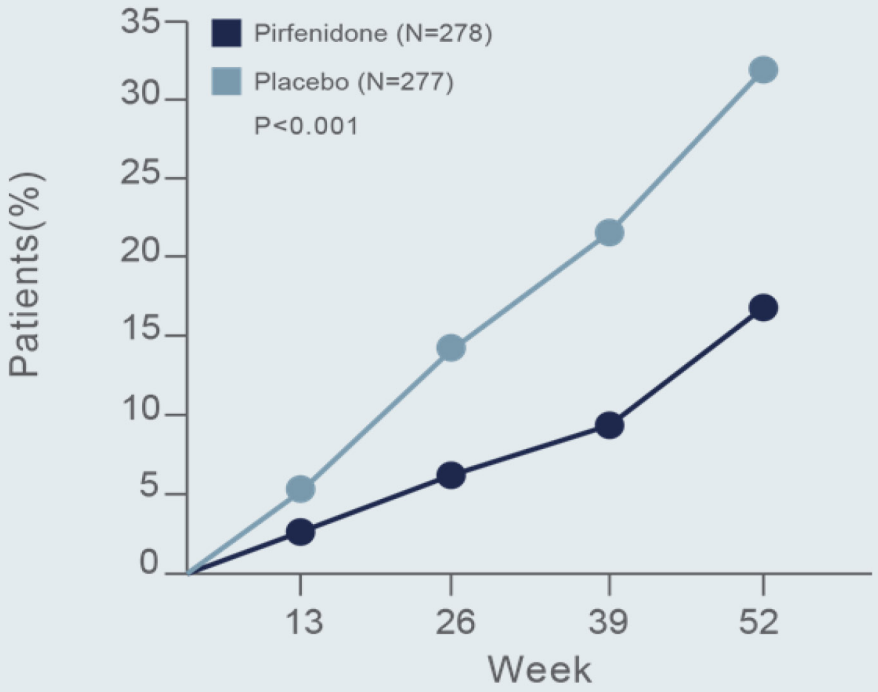
- Nintedanib[89]
- Pirfenidone[90,91]

Pneumo Update Europe 2017

Richeldi L et al, *Lancet* 2017; 389: 1941-1952

Pirfenidone

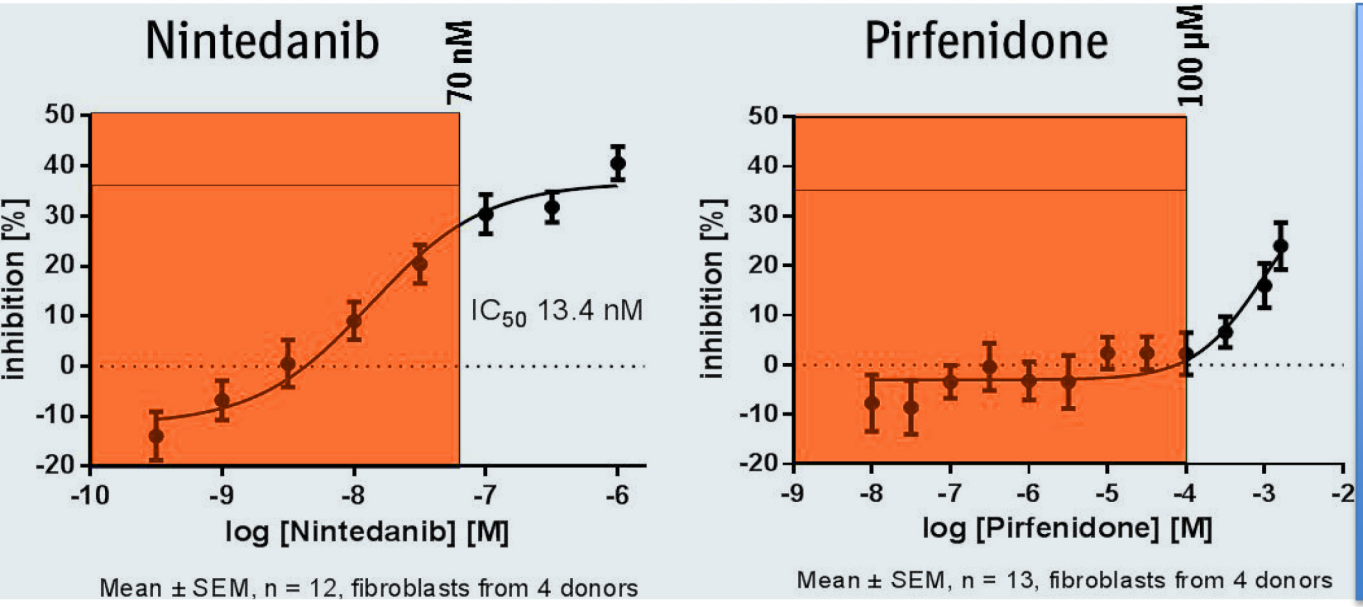
- Antiinflammatory, antifibrotic , antioxidant properties, TGF-β antagonism. It inhibits fibroblastic proliferation and the synthesis of pro-fibrogenic proteins and cytokines.



- First week: one 267mg capsule/8 h
- Second week: 2 capsules/8 h
- From the third week onwards: 3 capsules/8 h
- Take with food
- The recommended treatment duration is at least 12 months.

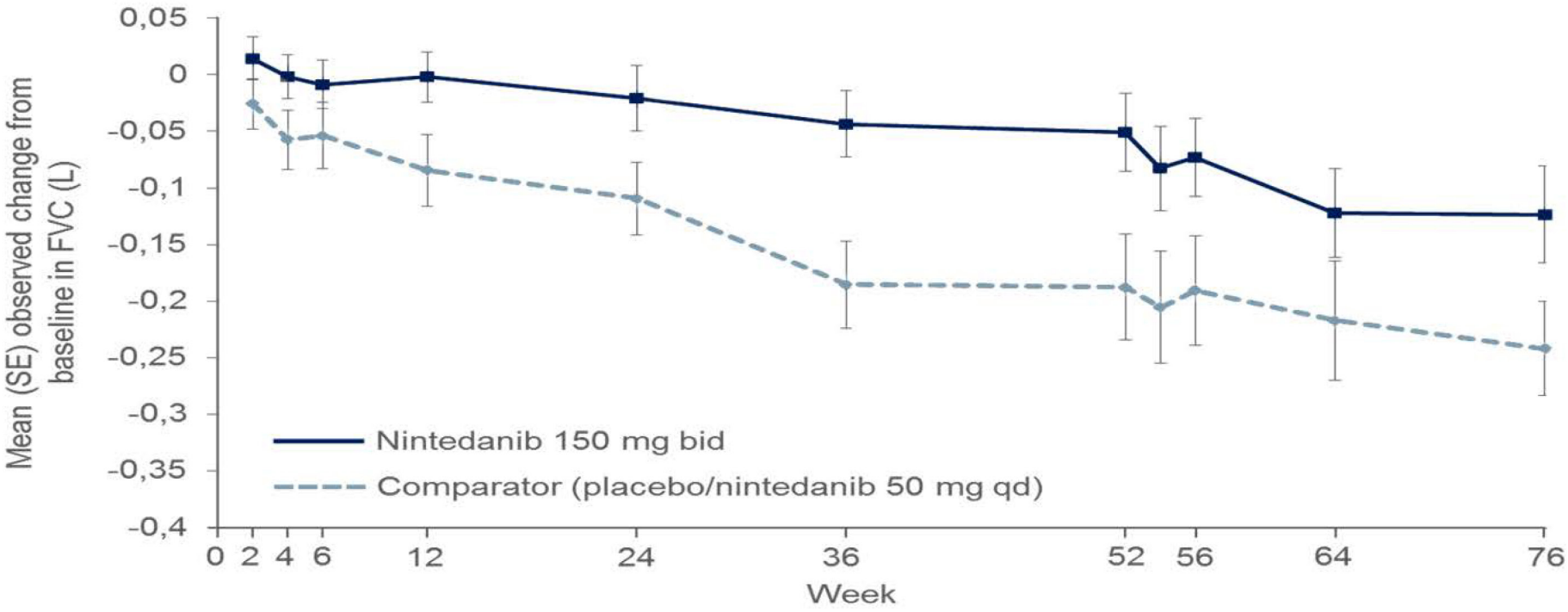
NINTEDANIB

- reduces spontaneous TNFα and IL-1β release from lung fibroblasts => anti-inflammatory and anti-fibrotic activity
- inhibits DGFR, FGFR and VEGFR receptors, that are involved in fibroblast differentiation => inhibition of fibroblast differentiation.



150 mg twice daily administered approximately 12 hours apart taken with food

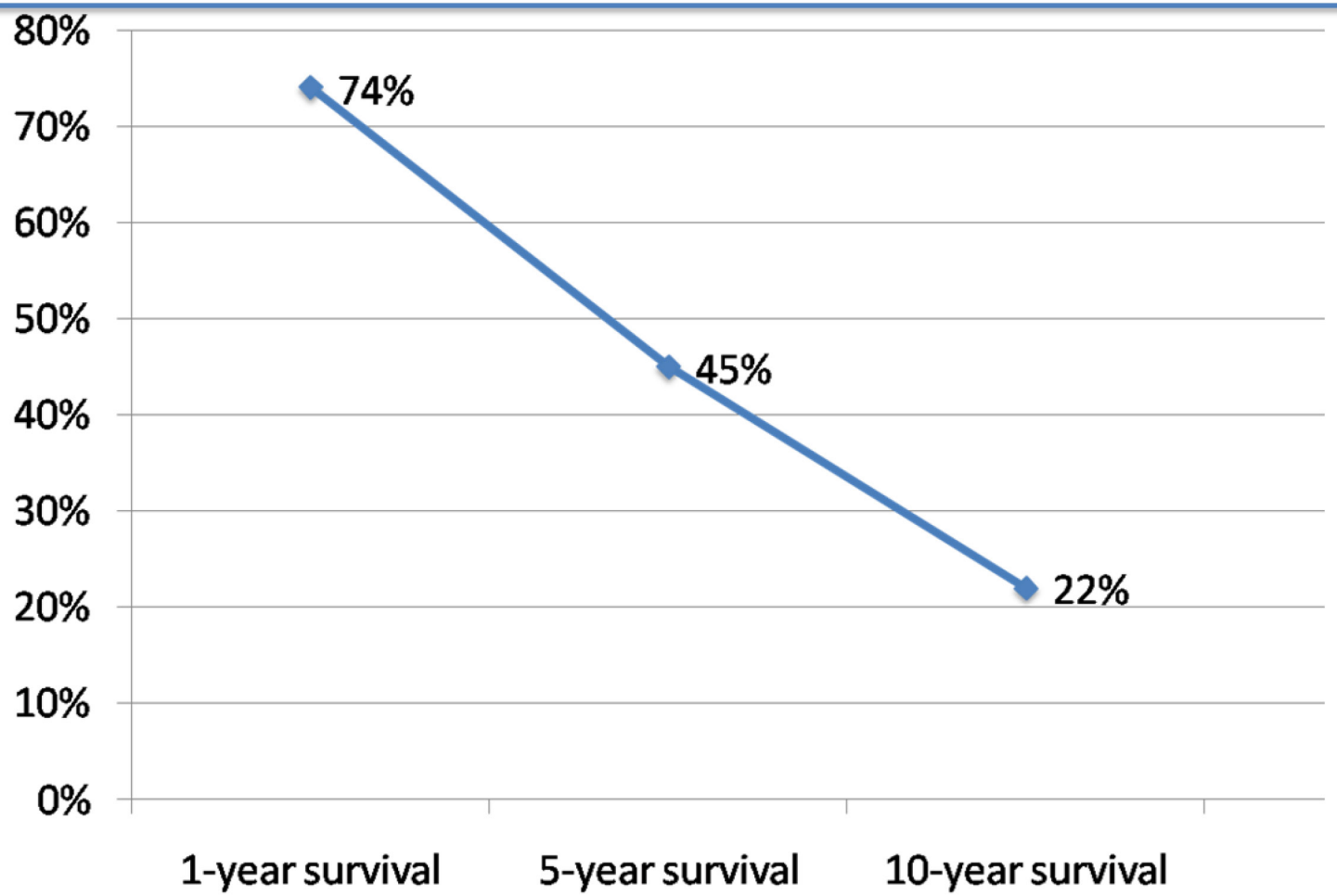
Nintedanib


Mean (SE) observed change from baseline in FVC (L)
0,05
0
-0,05
-0,1
-0,15
-0,2
-0,25
-0,3
-0,35
-0,4
Nintedanib 150 mg bid
Comparator (placebo/nintedanib 50 mg qd)
0 2 4 6 12 24 36 52 56 64 76
Week

Treatment

- Currently more evidence prove that corticosteroid treatment, even in high doses or in combination with immunosuppressors, **don't improve** the condition of patients with IPF.
- While other types of IIP (NSIP, DIP, COP, RB-ILD) often **respond positively**, especially in the initial stage.
- Two drugs approuved for IPF treatment: **pirfenidone and nintedanib**
- Lung transplantation seems to improve the quality of life and survival

Survival after lung transplant in IPF



Antoni Xaubet, Guidelines for the Diagnosis and Treatment of IPF. Archivos de Bronconeumologia. Spain


2015.07.14
120kV
0.5s/5.0mm
HP27.0
Thank you!