FIBROSING INTERSTITIAL LUNG DISEASES OF IDIOPATHIC AND EXOGENOUS ORIGIN. PHENOTYPE APPROACH.

Conference, Postgradual and Scientific Course

Pulmonary manifestations of CTDs
Diagnosis,
differential diagnosis and treatment

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ERS ILD Group Secretary

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Prague, June 2014

Outline of the presentation

- 1. Introduction
- 2. Main pulmonary manifestations in different CTDs
- 3. Scleroderma Lung (SSc- ILD)
- 4. Rheumatoid Lung (RA-UIP)
- 5. Role of smoking
- 6. Treatment issues

CONNECTIVE TISSUE DISEASE-ASSOCIATED DISORDERS

The connective tissue diseases (including rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, polymyositis/dermatomyositis, and their associated overlap syndromes) are associated with a wide variety of pulmonary complications.

While specific connective tissue diseases are typically associated with particular pulmonary complications, virtually all complications can occur with any of the connective tissue diseases and may even present prior to the diagnosis of the underlying connective tissue disease.

Eur Respir Mon, 2009

Types of pulmonary involvement

- ***When a patient with an underlying CTD presents with new signs or symptoms referable to the chest, a vast range of differential diagnostic possibilities exists:***

Eur Respir Mon, 2009

A.L. Olson*, K.K. Brown*,#

Types of pulmonary involvement

1. infection, drug toxicity, ***direct pulmonary complications (e.g. interstitial lung disease (ILD);***
2. indirect complications (e.g.hypoventilation secondary to myopathy);
3. cardiovascular complications (e.g. coronary artery disease or cardiomyopathy); and
4. unrelated disease

Eur Respir Mon, 2009

Interstitial lung disease in connective tissue disorders

Aryeh Fischer, Roland du Bois

	ILD	Airways	Pleural	Vascular	DAH
Systemic sclerosis	+++	–	–	+++	–
Rheumatoid arthritis	++	++	++	+	–
Primary Sjögren's syndrome	++	++	+	+	–
Mixed CTD	++	+	+	++	–
Polymyositis/ dermatomyositis	+++	–	–	+	–
Systemic lupus erythematosus	+	+	+++	+	++

The signs show prevalence of each manifestation (–=no prevalence; +=low prevalence; ++=medium prevalence; +++=high prevalence). ILD=interstitial lung disease. DAH=diffuse alveolar haemorrhage. CTD=connective tissue disease.

Table 1: **CTDs and common pulmonary manifestations**

Lancet

Vol 380 August 18, 2012

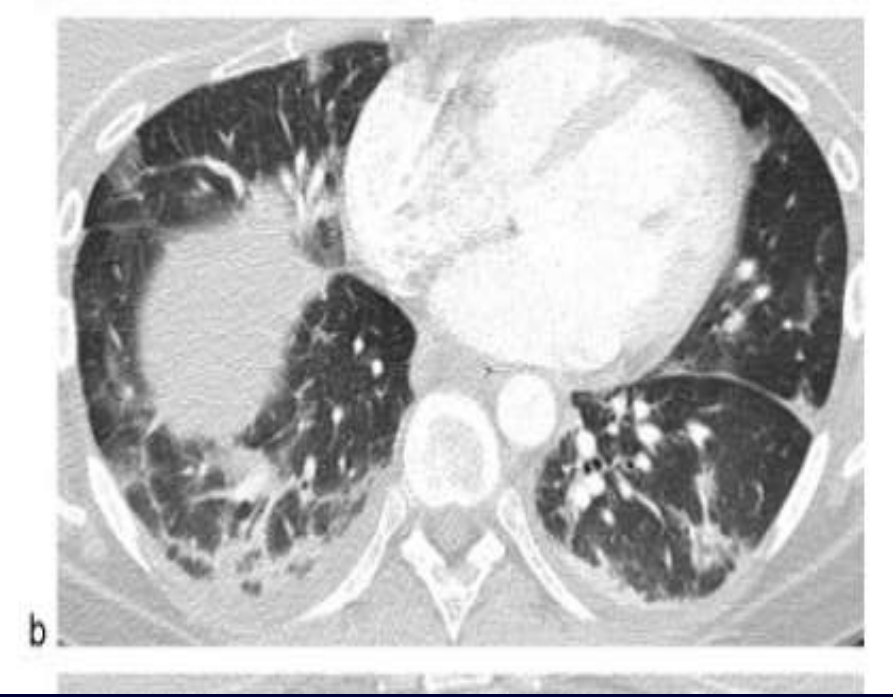
Radiology is cardinal in CTDs

- Imaging tests are central to the investigation of patients with CTDs in whom lung involvement is suspected.
- **Challenges:**
- ***Prevalence of individual ILDs varies between the CTDs.***
- ***Disease involvement may be multicompartmental***
- ***may also be iatrogenic; treatments used in CTD can be responsible for both pulmonary and cardiac damage***

Seminars in Respiratory and Critical Care Medicine Vol. 35 No. 2/2014

Table 3 Main HRCT findings in SLE

Interstitial and airspace disease	: DAD, lupus pneumonitis, pulmonary hemorrhage, opportunistic infection
Pulmonary vasculature	: Pulmonary infarction, pulmonary hypertension
Extrapulmonary involvement	: Pleural effusions, pericarditis, diaphragm dysfunction



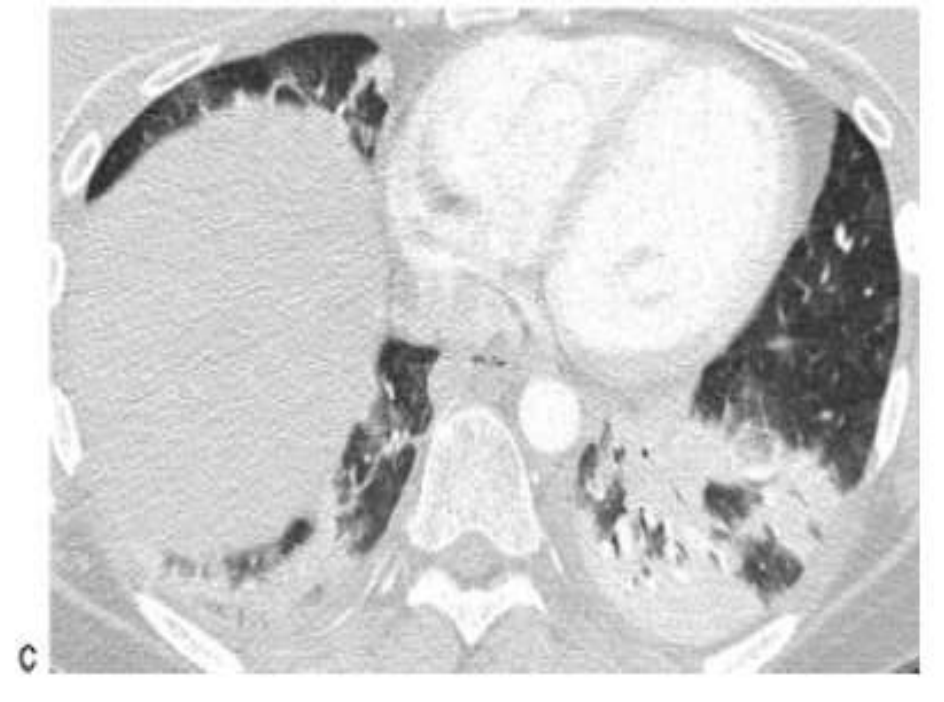
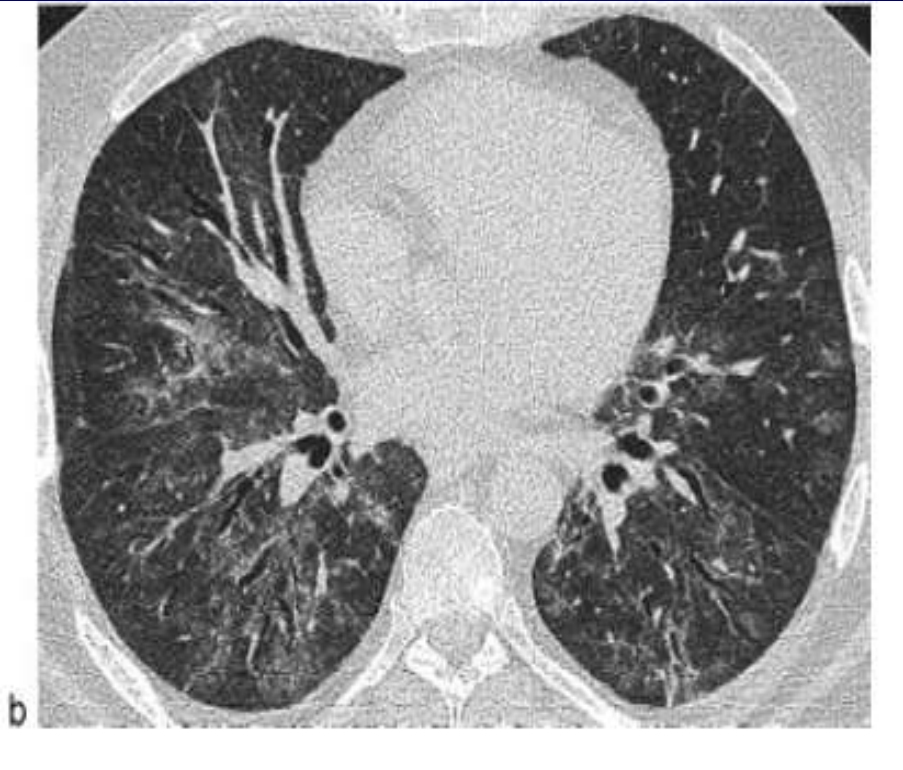


Table 4 Main HRCT findings in PM/DM

Interstitial disease	: OP, NSIP (often mixed), DAD
Extrapulmonary involvement	: Respiratory and esophageal/pharyngeal muscular weakness



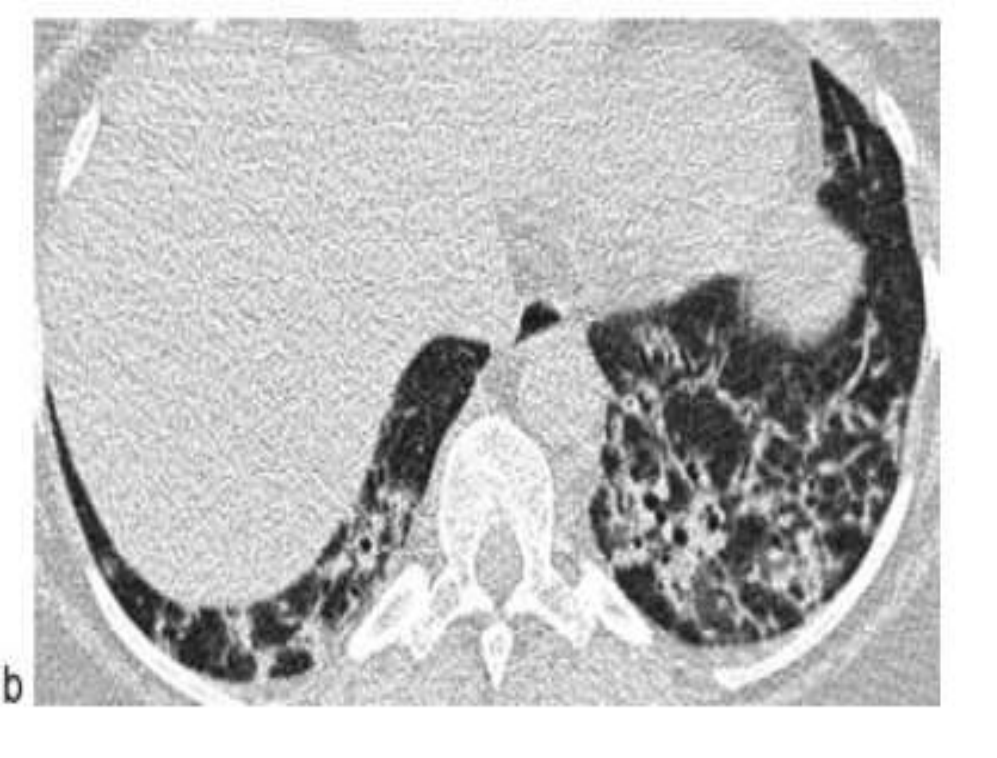


Table 6 Main HRCT findings in SS

Interstitial disease	: NSIP, LIP/amyloidosis, follicular bronchiolitis, lymphoma, OP
Airways disease	: Bronchitis, bronchiectasis, small airways disease

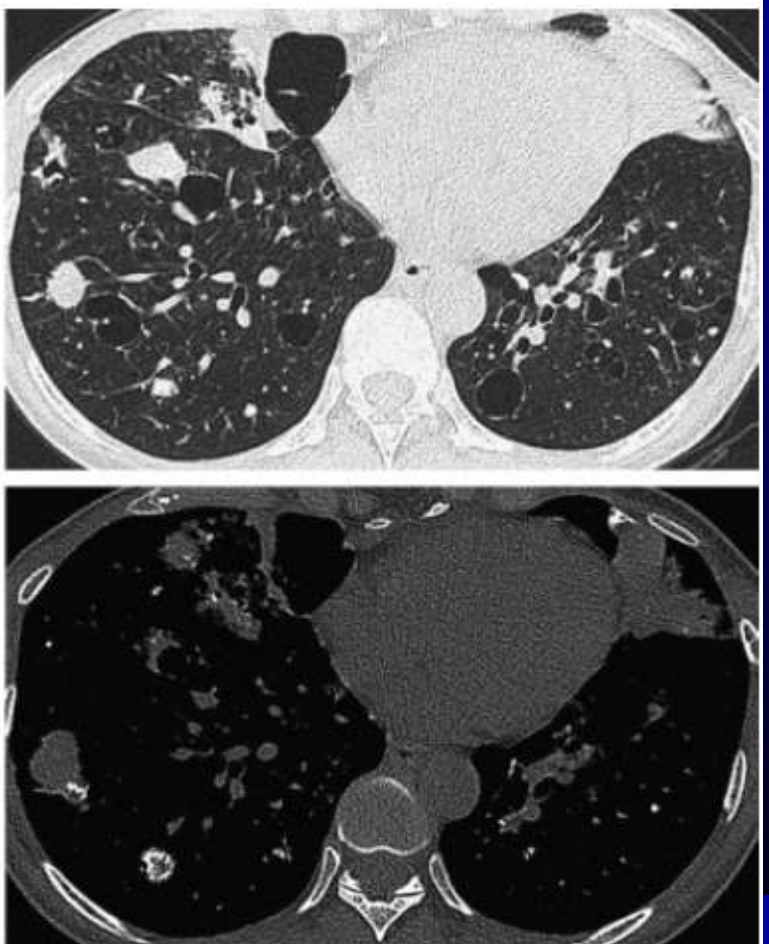


Fig. 11 A 55-year-old woman with Sjögren syndrome and biopsy-proven diagnosis of lymphoid interstitial pneumonia and amyloidosis. High-resolution computed tomography images on lung (a) and bone (b) window settings demonstrate that in addition to multiple cysts, multiple solid nodules and masses of varying sizes are present, many of which are calcified. Transbronchial biopsy confirmed the presence of a focally dense lymphocytic infiltrate, and positive Congo red staining for amyloid. No evidence of lymphoma was found.

ERJ 2009

Pivotal clinical dilemmas in collagen vascular diseases associated with interstitial lung involvement

K.M. Antoniou, G. Margaritopoulos, F. Economidou and N.M. Siafakas

- When the lungs are affected, an increasing mortality and morbidity in CVDs occurs.

- Interstitial lung disease (ILD) is established as a clinical corollary across the spectrum of CTDs, with an overall incidence estimated at 15%.

Critical questions are:

- 1. The presence of fibrosis
- 2. Whether the disease is clinically significant.
- 3. Often admixed with other pulmonary pathology (non-ILD).
- *4. decide if treatment is warranted*
- *5. the best therapeutic approach.*

Antoniou KM, et al. ERJ 2009

CATEGORIZATION OF MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS, 2013,

All patterns may appear in patients with CTD-ILD

CATEGORY	CLINICAL-RADIOLOGIC- PATHOLOGIC DIAGNOSES	ASSOCIATED MORPHOLOGIC PATTERNS
Chronic Fibrosing IP	Idiopathic Pulmonary Fibrosis	**Usual Interstitial Pneumonia**
	Idiopathic Nonspecific Interstitial Pneumonia‡	**Nonspecific Interstitial Pneumonia**
Smoking-related IP †	Respiratory Bronchiolitis Interstitial Lung Disease	Respiratory Bronchiolitis
	Desquamative Interstitial Pneumonia	Desquamative Interstitial Pneumonia
Acute/subacute IP	Cryptogenic Organizing Pneumonia	Organizing Pneumonia
	Acute Interstitial Pneumonia	Diffuse Alveolar Damage

Histological patterns

- Same spectrum of histological patterns in CTD as in the IIPs
- However, there is NOT the same proportion of individual patterns as there is in idiopathic disease
- Patterns do NOT have the same prognostic significance

In CTD-ILD

- NSIP predominates in SSc
- NSIP predominates in PM/DM
- NSIP predominates in SS
- SLE: chronic ILD rare
- ***The exception seems to be RA, in which UIP is, on balance, the most prevalent pattern***

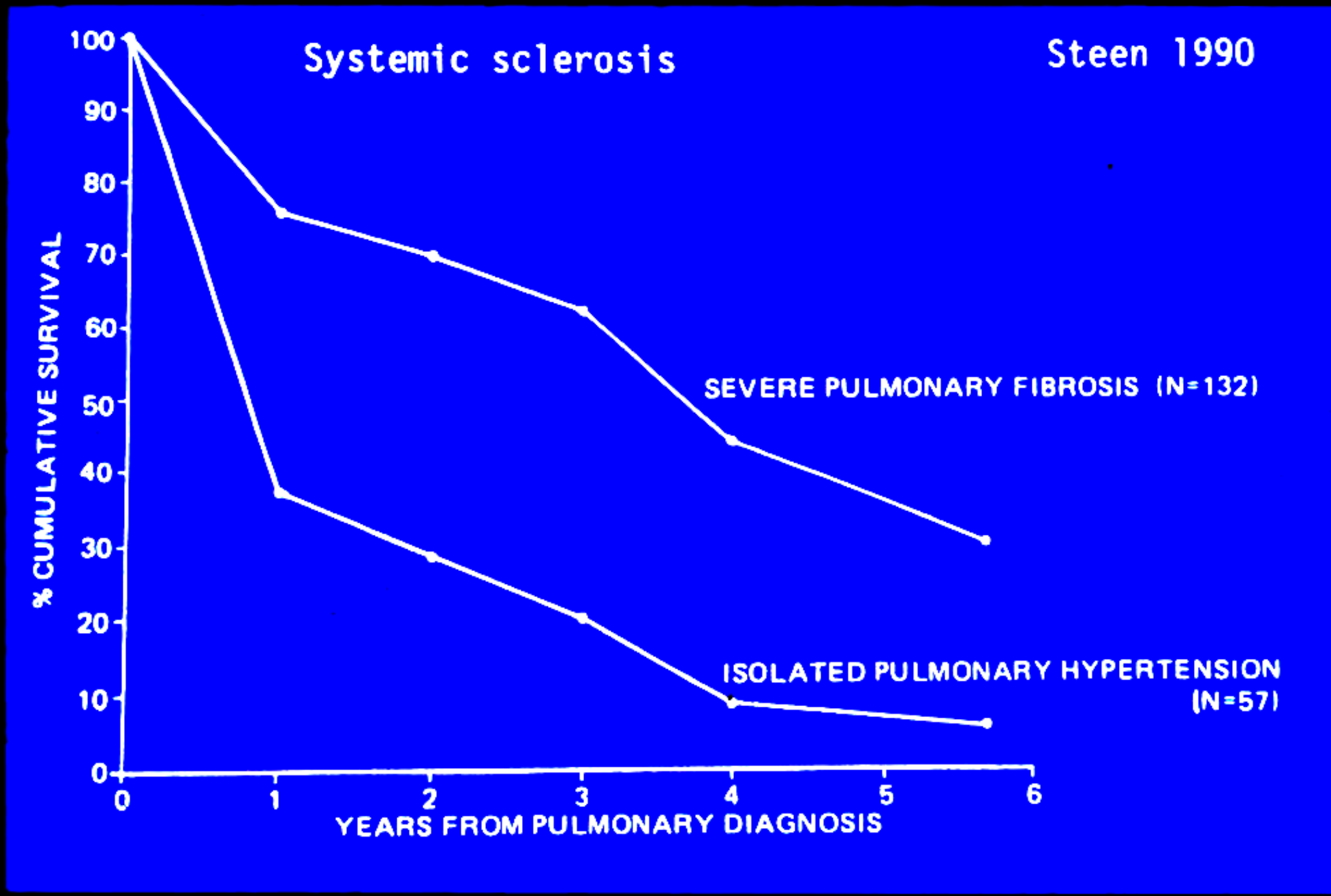
Bouros D et al. Am J Respir Crit Care Med 2002;165:1581-6

Douglas WW. Am J Respir Crit Care Med 2001; 164:1182-5

Ito I. Am J Respir Crit Care Med 2005;171:632-8

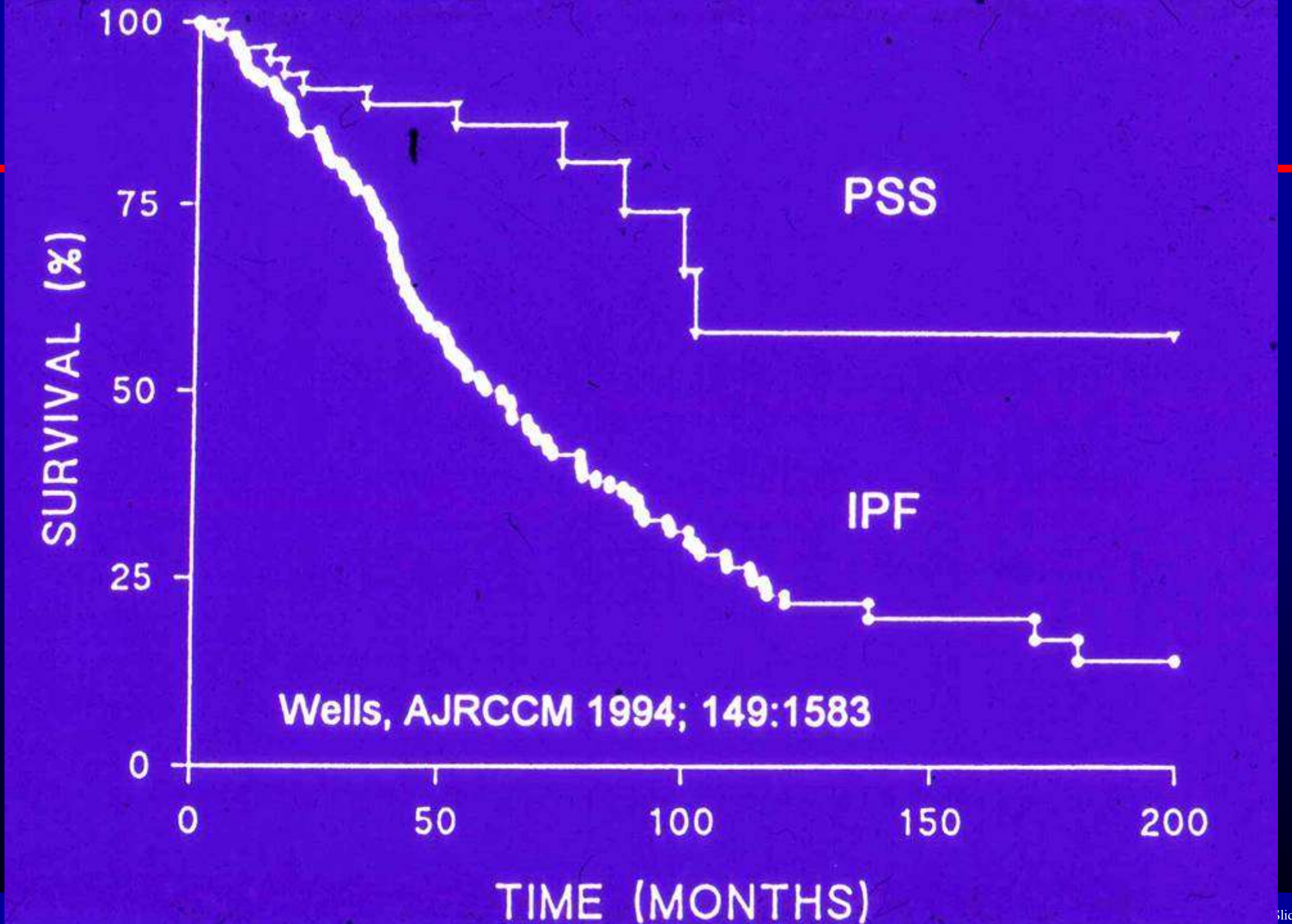
Systemic sclerosis (scleroderma)

- ***Systemic autoimmune disease, characterized:***
- *1. Widespread small-vessels vasculopathy*
- *2. Fibrosis of connective tissue*


Systemic sclerosis
Steen 1990
% CUMULATIVE SURVIVAL
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
YEARS FROM PULMONARY DIAGNOSIS
SEVERE PULMONARY FIBROSIS (N=132)
ISOLATED PULMONARY HYPERTENSION
(N=57)

Box 1
Manifestations of SSc in the respiratory system

1. ILD
   - Nonspecific interstitial pneumonia (NSIP)
   - Usual interstitial pneumonia (UIP)
   - Diffuse alveolar damage (DAD)
   - Cryptogenic organizing pneumonia (COP)
2. Pulmonary hypertension
3. Pleural involvement
4. Aspiration pneumonia
5. Alveolar hemorrhage
6. Small airways disease
7. Malignancy
8. Respiratory muscle weakness
9. Drug-induced toxicity
10. Spontaneous pneumothorax
11. Pneumoconiosis (silicosis)


100
75
50
25
0
SURVIVAL (%)
PSS
IPF
Wells, AJRCCM 1994; 149:1583
0
50
100
150
200
TIME (MONTHS)

Risk Factors for SSc-ILD

- Progression of ILD is associated with:
- *a shorter duration of systemic disease*
- *more severely impaired PFTs*
- *more extensive lung disease on HRCT*
- *Recent disease progression*

Main HRCT findings in SSc

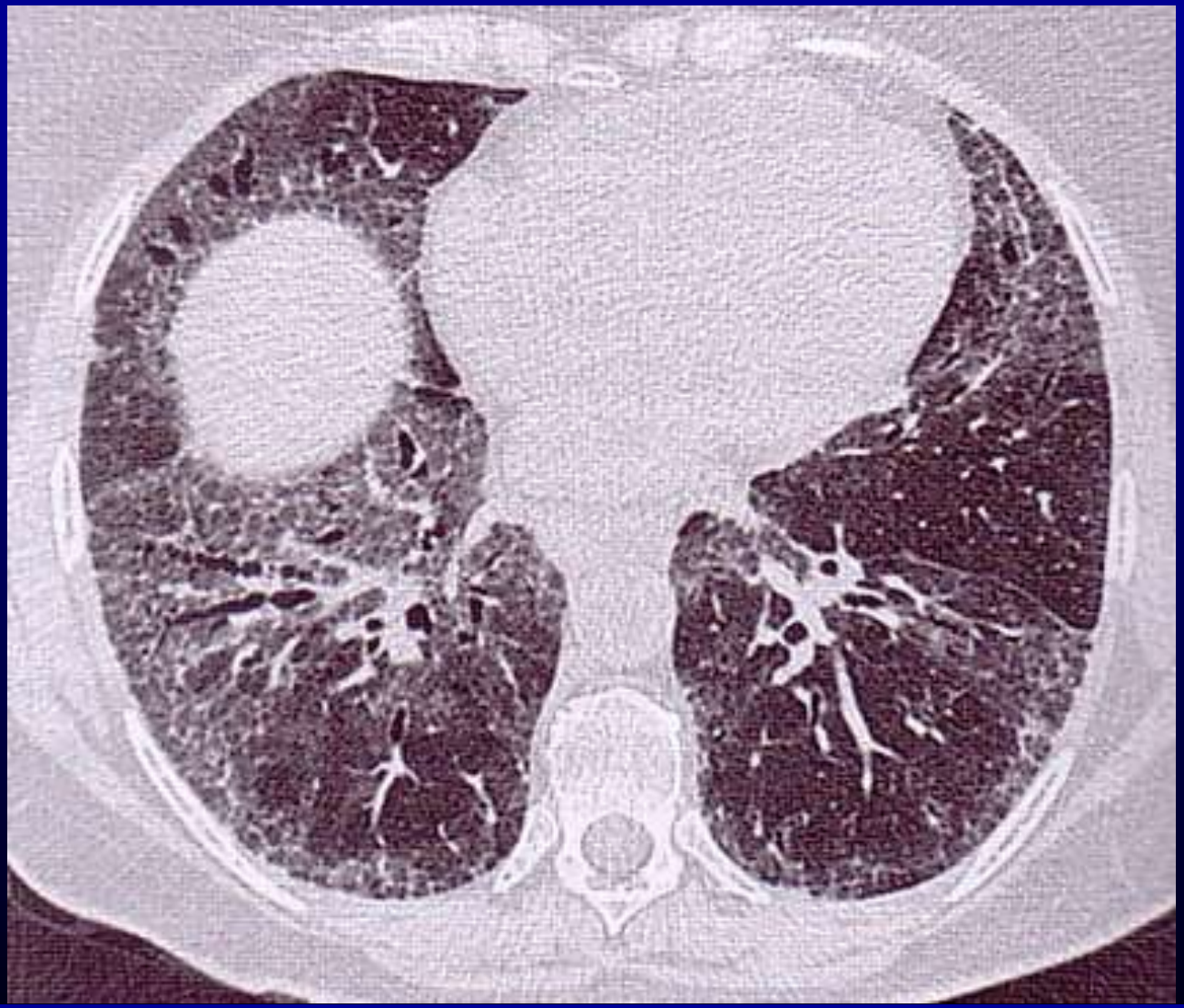
Table 2 Main HRCT findings in SSc

Interstitial disease	: Pulmonary fibrosis (majority NSIP type)
Airspace disease	: Lung cancer (usually peripheral adenocarcinoma)
Pulmonary vasculature	: Pulmonary hypertension
Extrapulmonary involvement	: Esophageal dilatation

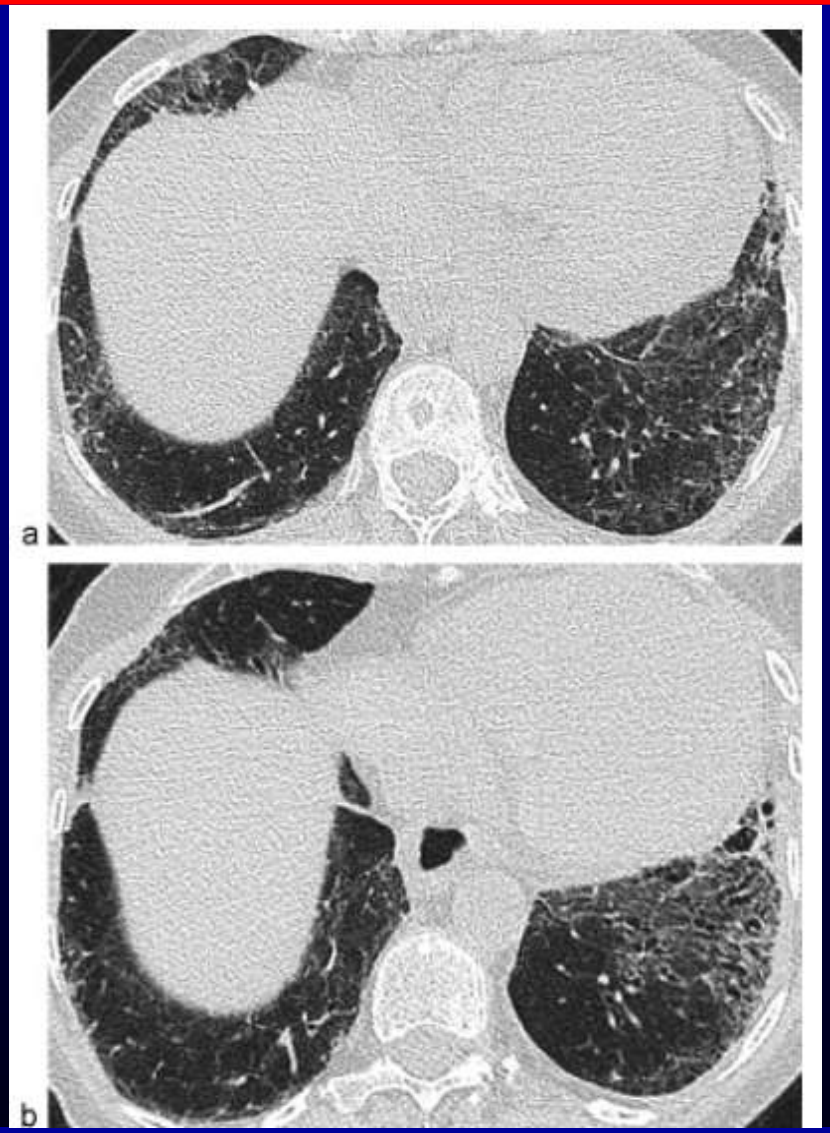
Pulmonary Manifestations of Connective Tissue Diseases Jacob et al.

Seminars in Respiratory and Critical Care Medicine Vol. 35 No. 2/2014

Scl-70-positive Systemic Sclerosis

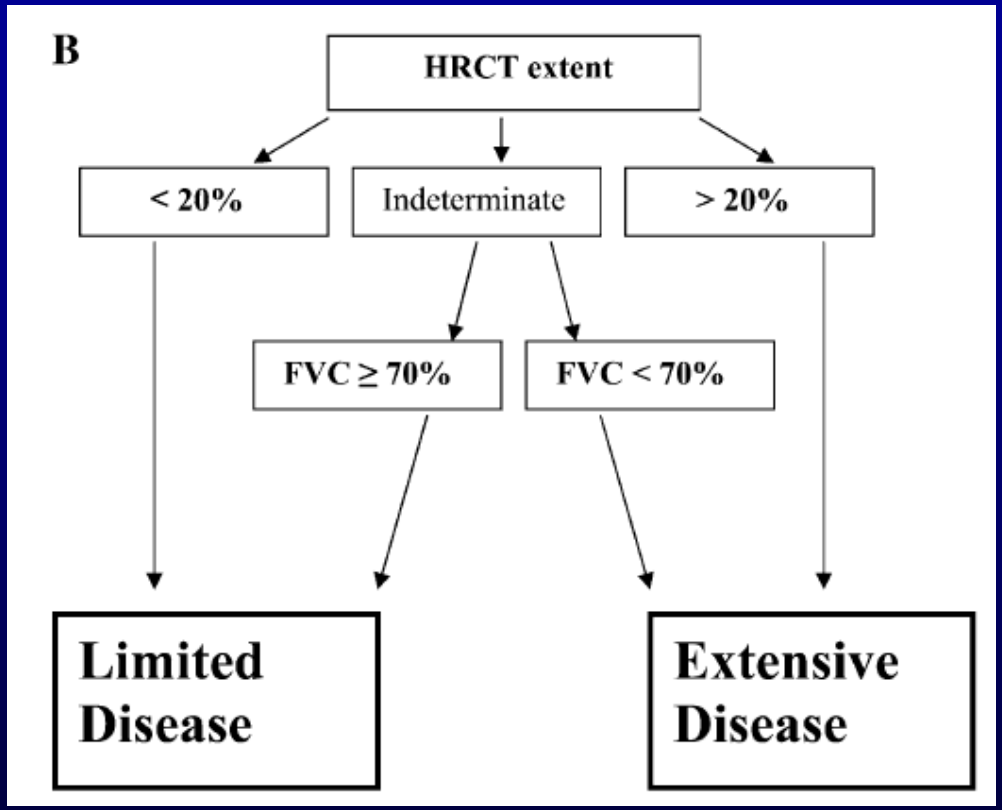


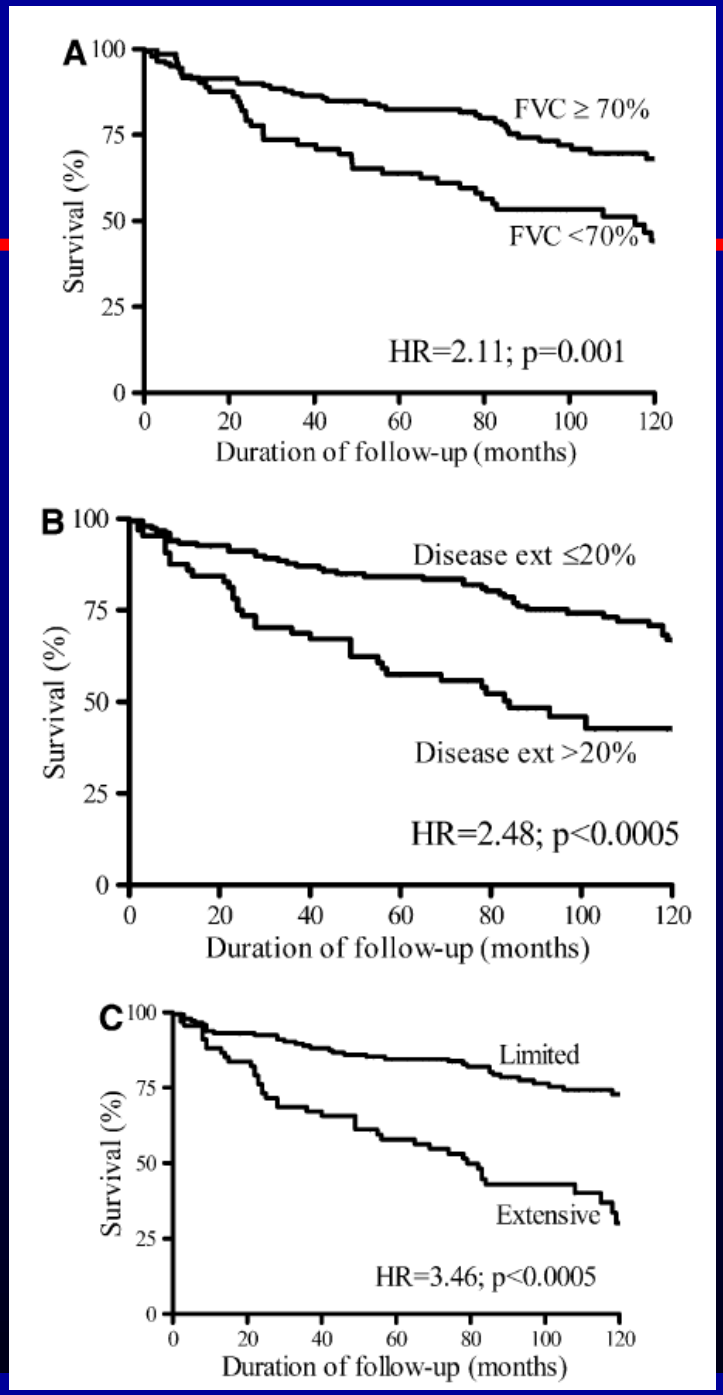
Alveolitis on CT? misleading terminology



- ***Only prominent GGO, in the absence of traction bronchiectasis: high likelihood of reversible inflammatory disease!***

Combined HRCT/LFT score-SSc





Goh, AJRCCM 2008

Rheumatoid arthritis

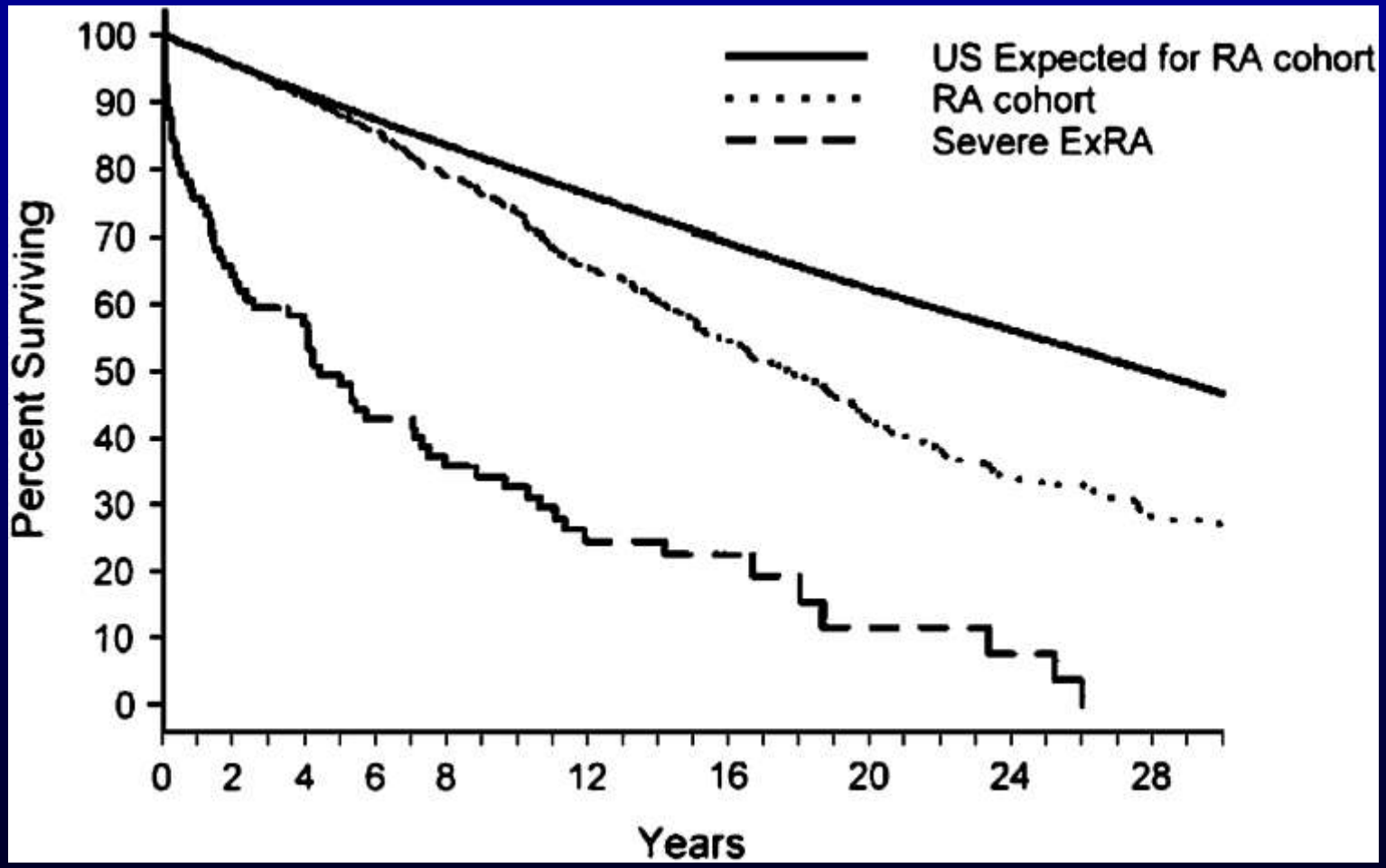
- most common CTD
- peak incidence is between the 4-6th decade
- Its extra-articular manifestations are frequent and may occur in virtually all organ systems.
- Pulmonary complications are common and account for between 10 and 20% of deaths.

TABLE 1. PRIMARY AND SECONDARY PLEUROPARENCHYMAL COMPLICATIONS OF RHEUMATOID ARTHRITIS

- Pleural disease
  - Pleural effusions
  - Pleural fibrosis
- Airway disease
  - Cricoarytenoid arthritis
  - Bronchiectasis
  - Follicular bronchiolitis
  - Bronchiolitis obliterans
  - Diffuse panbronchiolitis
- Interstitial lung disease
  - Usual interstitial pneumonia
  - Nonspecific interstitial pneumonia
  - Organizing pneumonia
  - Lymphocytic interstitial pneumonia
  - Diffuse alveolar damage
  - Acute eosinophilic pneumonia
  - Apical fibrobullous disease
  - Amyloid
  - Rheumatoid nodules
- Pulmonary vascular disease
  - Pulmonary hypertension
  - Vasculitis
  - Diffuse alveolar hemorrhage with capillaritis
- Secondary pulmonary complications
  - Opportunistic infections
    - Pulmonary tuberculosis
    - Atypical mycobacterial infections
    - Nocardiosis
    - Aspergillosis
    - *Pneumocystis jeroveci* pneumonia
    - Cytomegalovirus pneumonitis
- Drug toxicity
  - Methotrexate
  - Gold
  - D-penicillamine
  - Sulfasalazine

Brown KK, PATS 2007

Survival



Proc Am Thorac Soc Vol 4. pp 443–448, 2007

RA-ILD

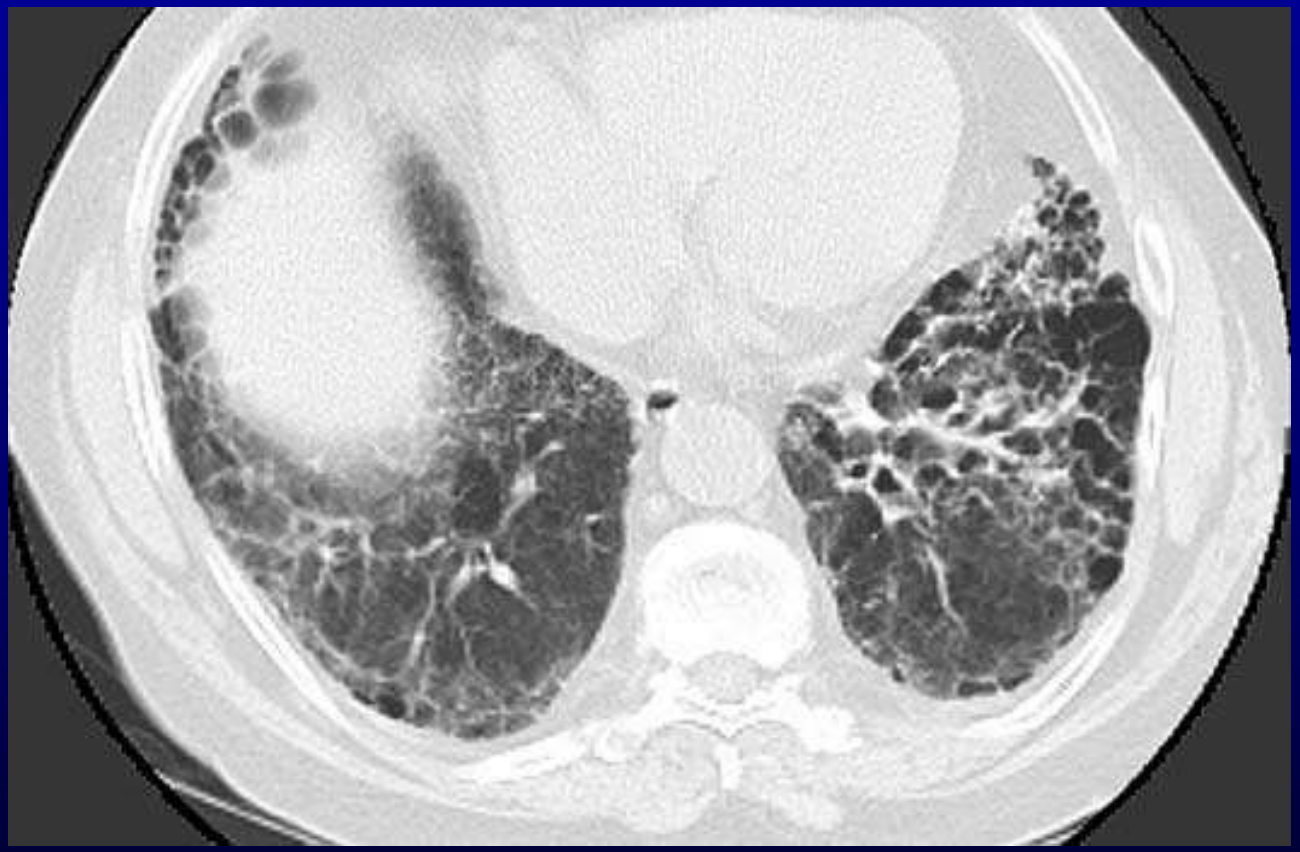
- The prevalence of ILD in unselected RA patients has been as high as 63% (HRCT).
- Clinically significant disease is less common and estimated to occur in 10% of patients.
- ***Unlike RA, which is more common in females, RA-ILD is more common in males.***

HRCT manifestations of RA

Table 1 Main HRCT findings in RA

Interstitial disease	: Signs of UIP, NSIP, LIP/follicular bronchiolitis, DAD, drug-induced disease
Airways disease	: Bronchitis, bronchiectasis, constrictive obliterative bronchiolitis
Airspace disease	: Organizing pneumonia
Pleural disease	: Pleural effusions/thickening

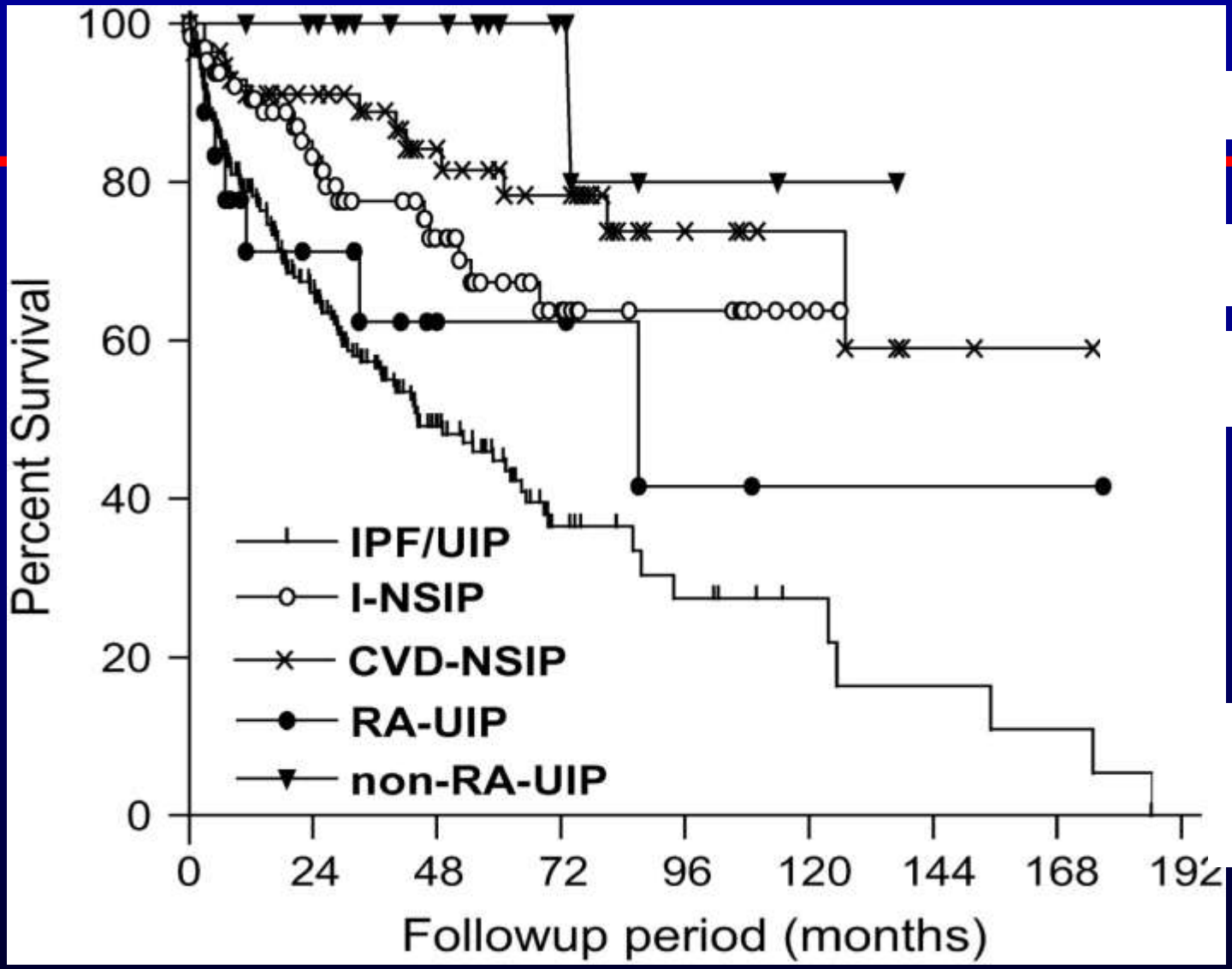
UIP is the most common pattern



63-yr-old-male with rheumatoid arthritis demonstrating a usual interstitial pneumonia pattern of disease with reticular abnormalities and honeycombing

There appear to be UIP subsets in CTD

- The majority of CTD-UIP patients has a better outcome than IPF and more prominent germinal centres. This includes patients with RA-UIP
- However, in RA, the subset of UIP patients with CT appearances similar to IPF have an IPF-like outcome. In RA, in particular, there may be two distinct UIP subsets
- Biopsy data not available in most CTD patients. HRCT data is what we usually have and so our "UIP" cases are this HRCT subset



Non-RA-UIP, n = 18

Idio. NSIP, n = 66

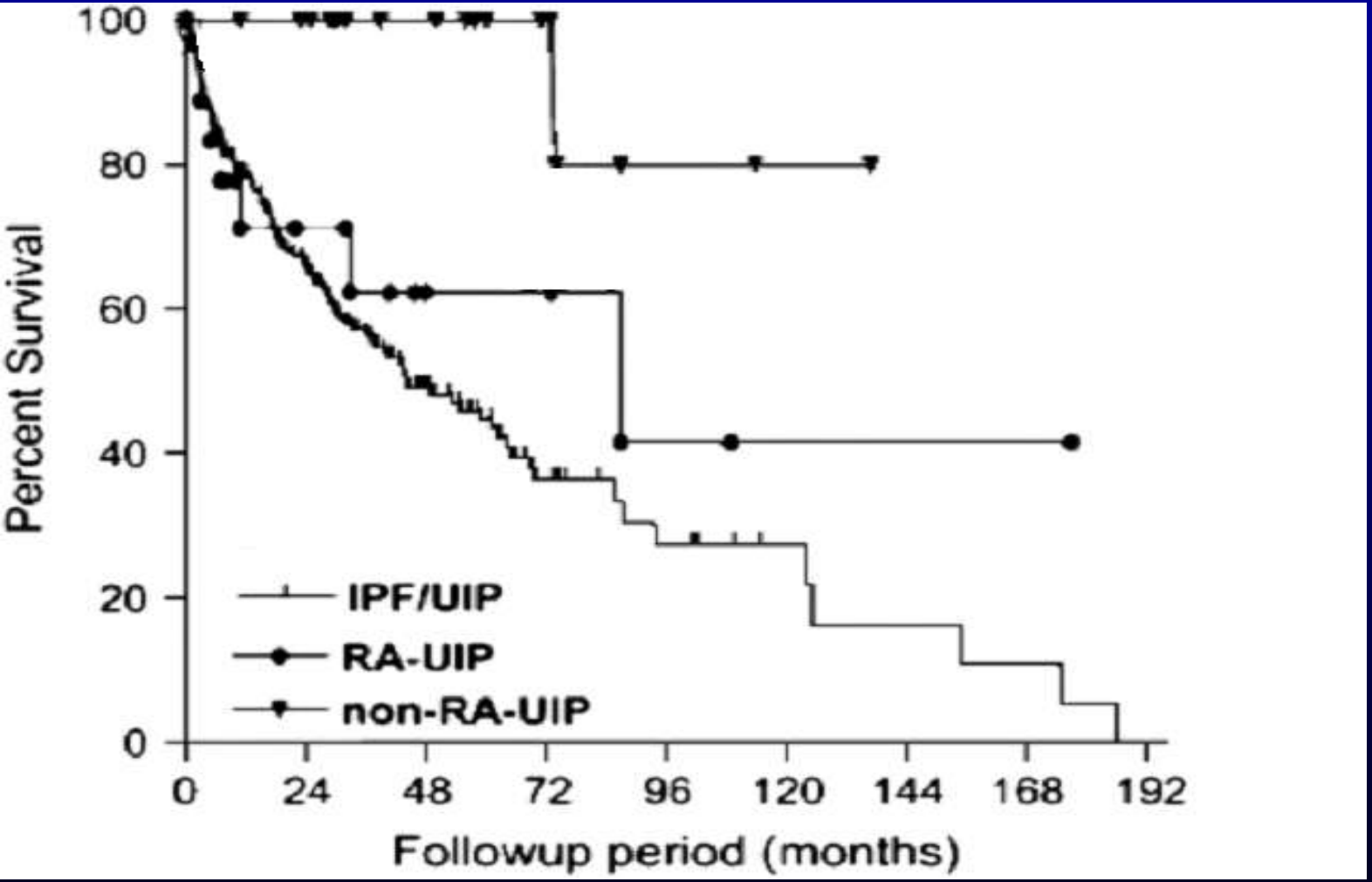
CTD-NSIP, n=57

RA-UIP, n=19

IPF-UIP, n=203

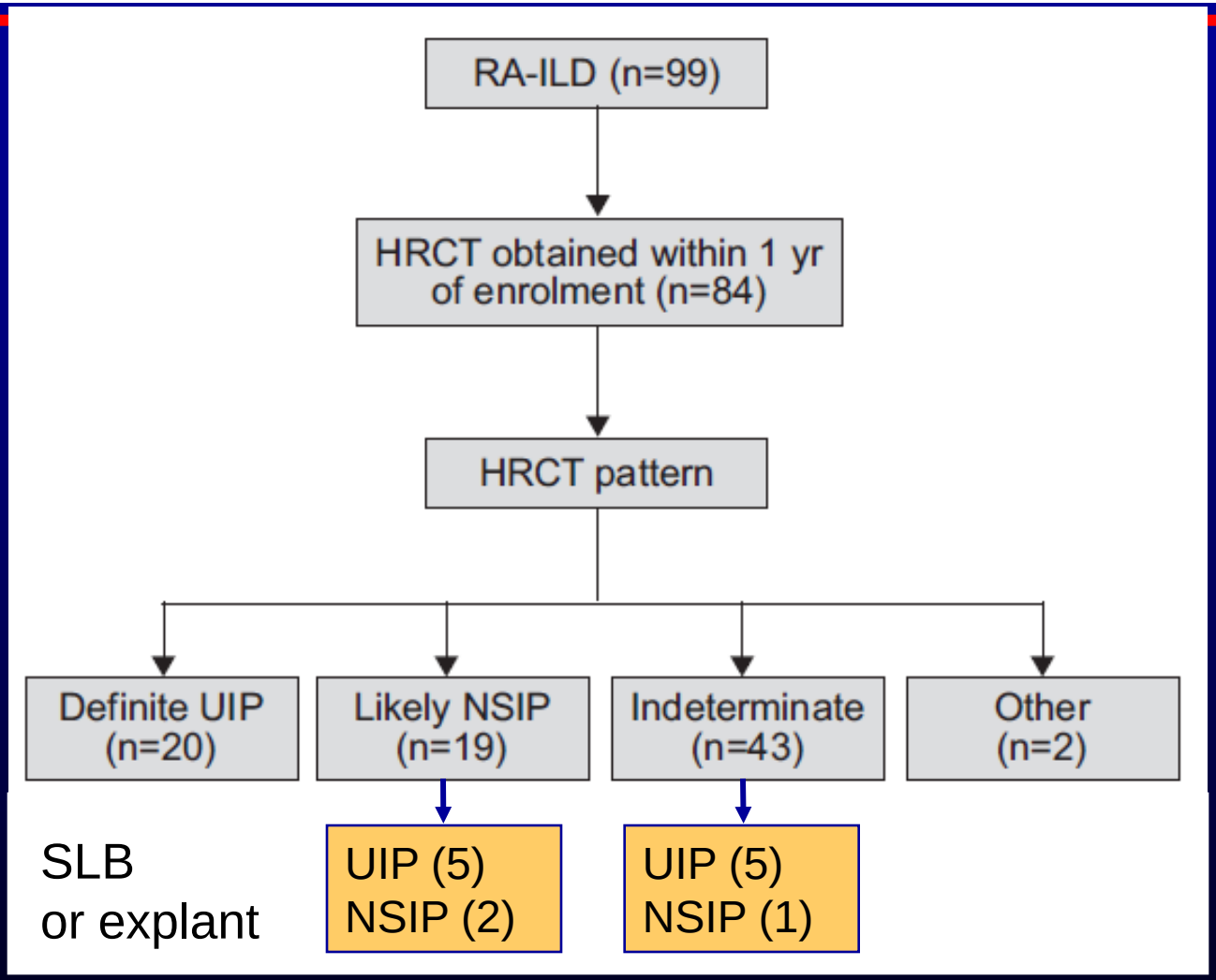
Park JH et al. Am J Respir Crit Care Med 2007; 175:705-711

Survival in RA –UIP



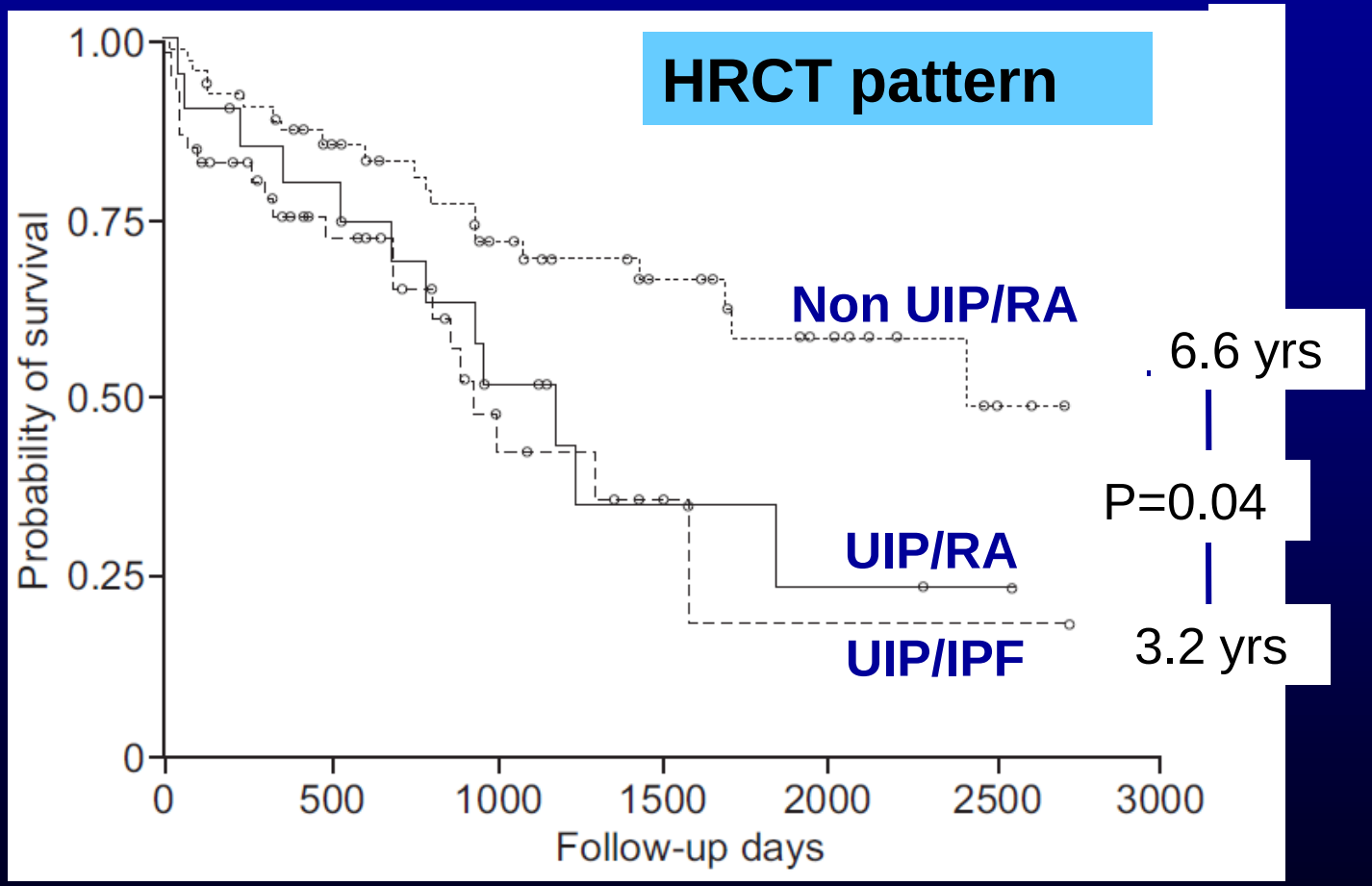
(Brown KK, PATS 2007)

Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease



(Kim, ERJ 2010; 35:1322-8)

Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease

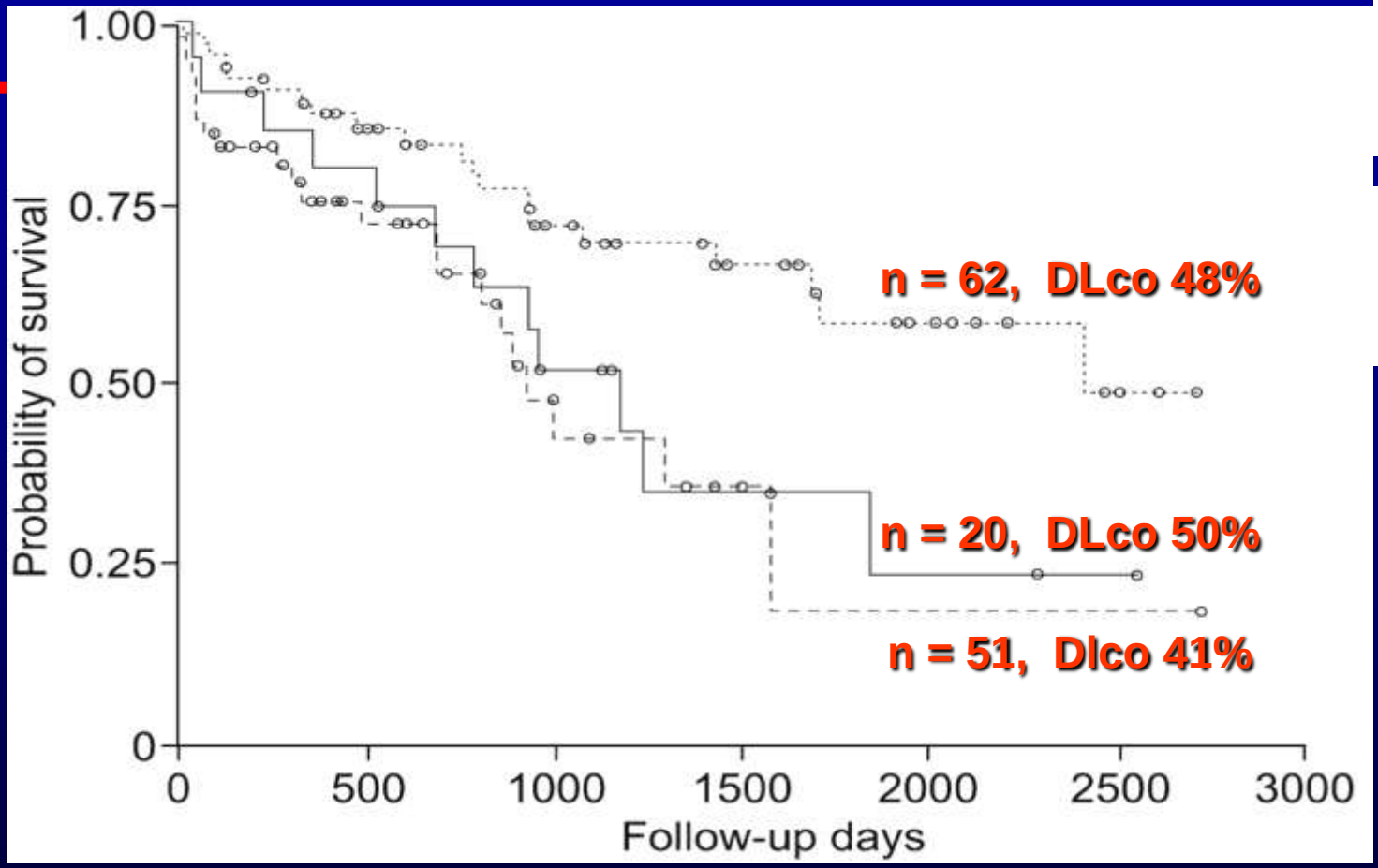


Survival	**HR**
Female	**0.3**
DLCO (%)	**0.96**
Definite UIP pattern	**2.3**

HRCT

Survival	**HR**
Honeycombing	**2.6**
Traction bronchiectasis	**2.1**

(Kim, ERJ 2010;35:1322-8)



Median survival

RA nonUIP: 6.6 yrs

RAUIP: 3.2 yrs

IPF: 2.6 yrs

Kim EJ et al. Eur Respir J 2010; 35:1322-8

Other recent biopsy statements

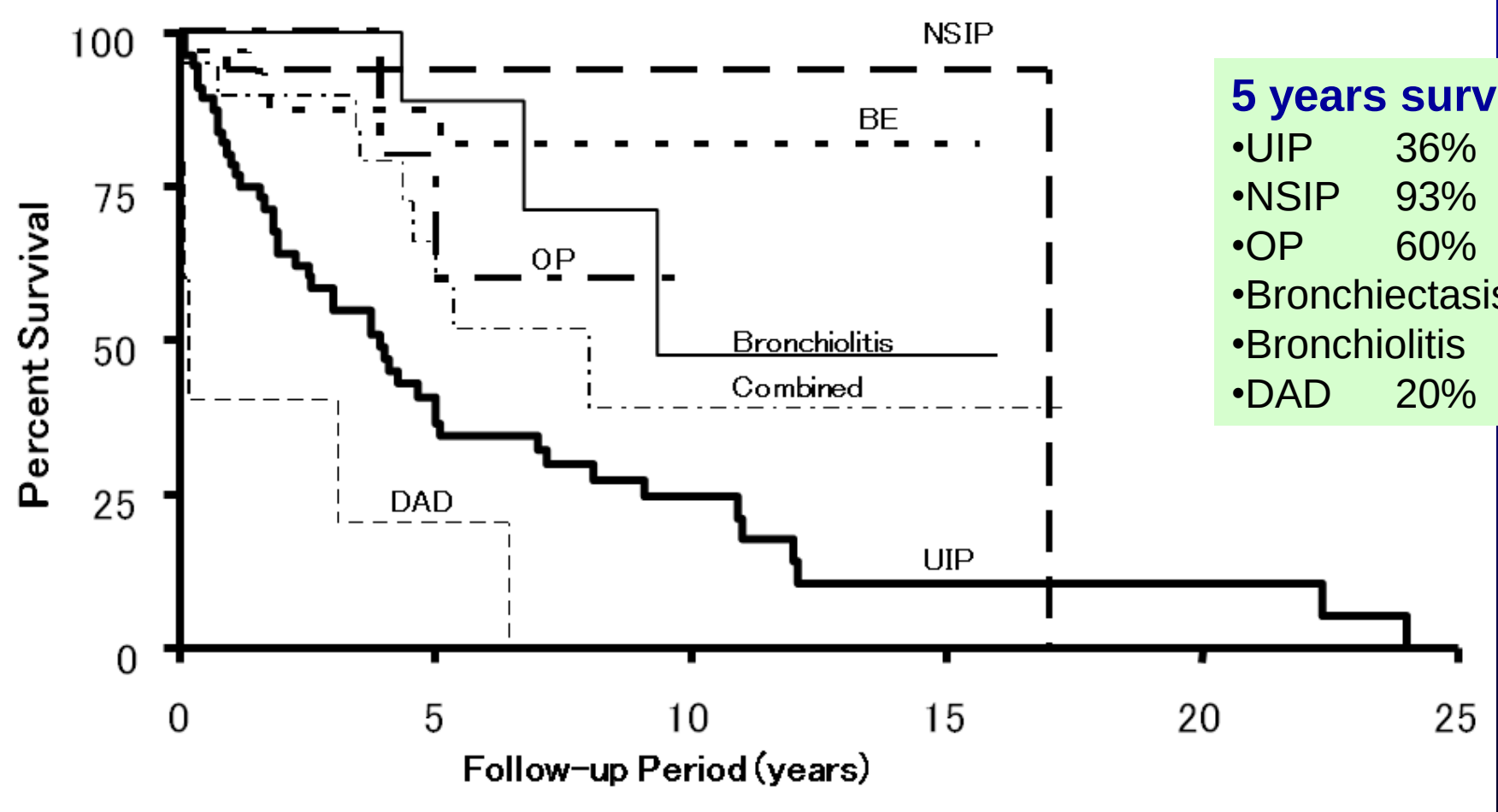
- RA cohort includes UIP (n=57), NSIP (n=16), diffuse alveolar damage (n=5)
- Worst outcome in DAD. Five year survival in UIP (37%) worse than in NSIP (94%)

Tsuchiva V et al. Eur Respir J 2011; 37:141-7

- UIP (n-15) survival worse than non-UIP (n-39)

Nakamura Y et al. Respir Med 2012

An UIP pattern on HRCT associates with a poor prognosis in RA



5 years survival

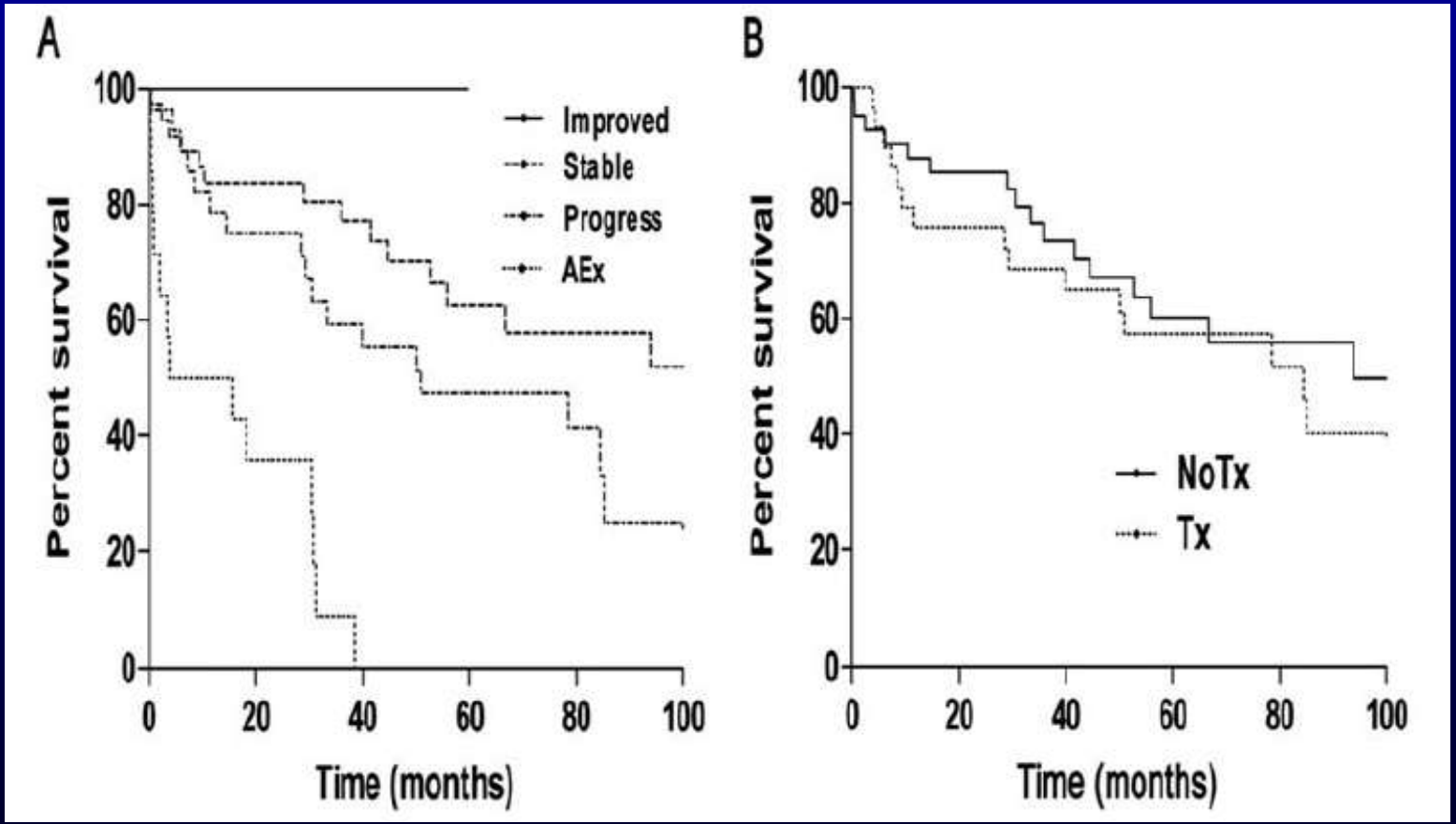
- UIP 36%
- NSIP 93%
- OP 60%
- Bronchiectasis 87%
- Bronchiolitis 89%
- DAD 20%

Tsuchiya, ERJ 2010

BE : bronchiectasis

Clinical course and outcome of rheumatoid arthritis-related usual interstitial pneumonia

J.W. Song[1], H.-K. Lee[2*], C.K. Lee[3], E.J. Chae[4], S.J. Jang[5], T.V. Colby[6], D.S. Kim[1]*



SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2013; 30; 103-112

Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD)

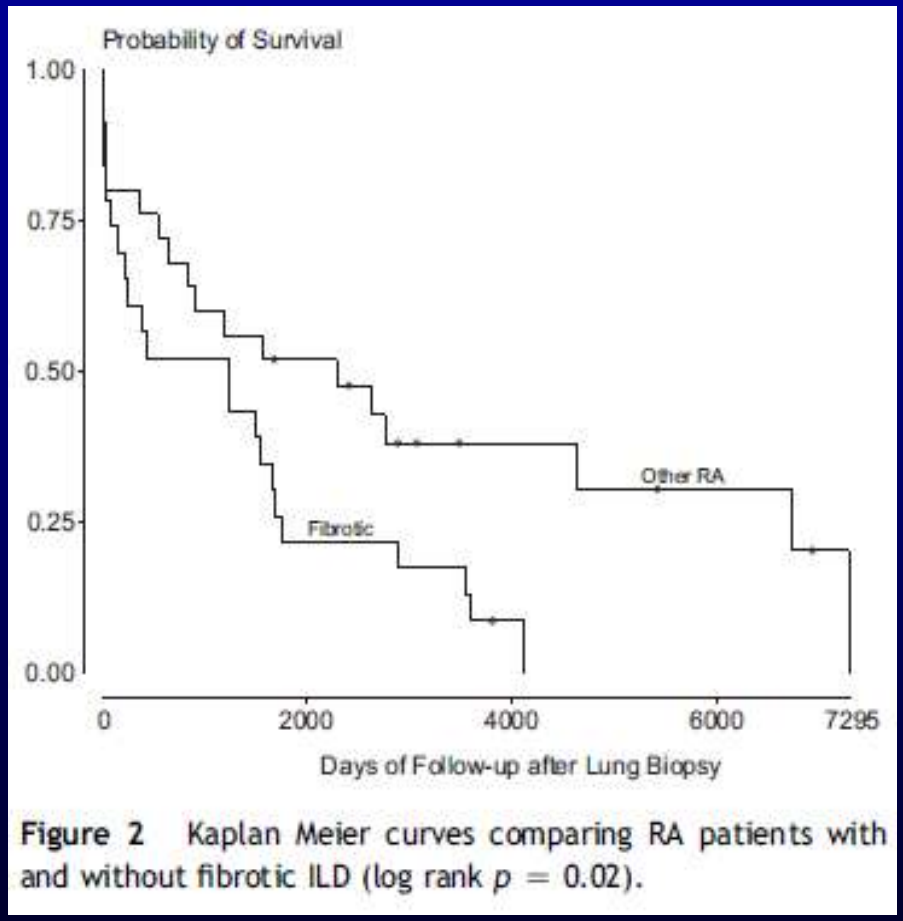


Figure 2 Kaplan Meier curves comparing RA patients with and without fibrotic ILD (log rank $p = 0.02$).

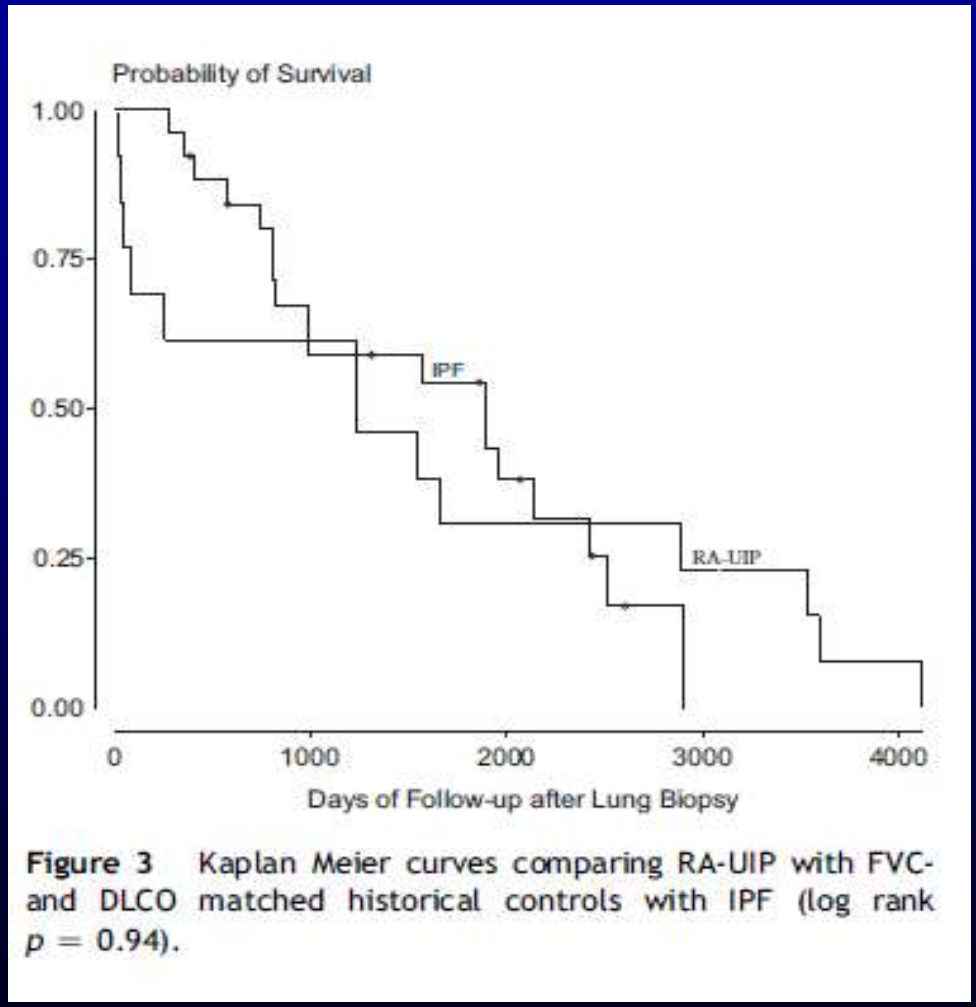
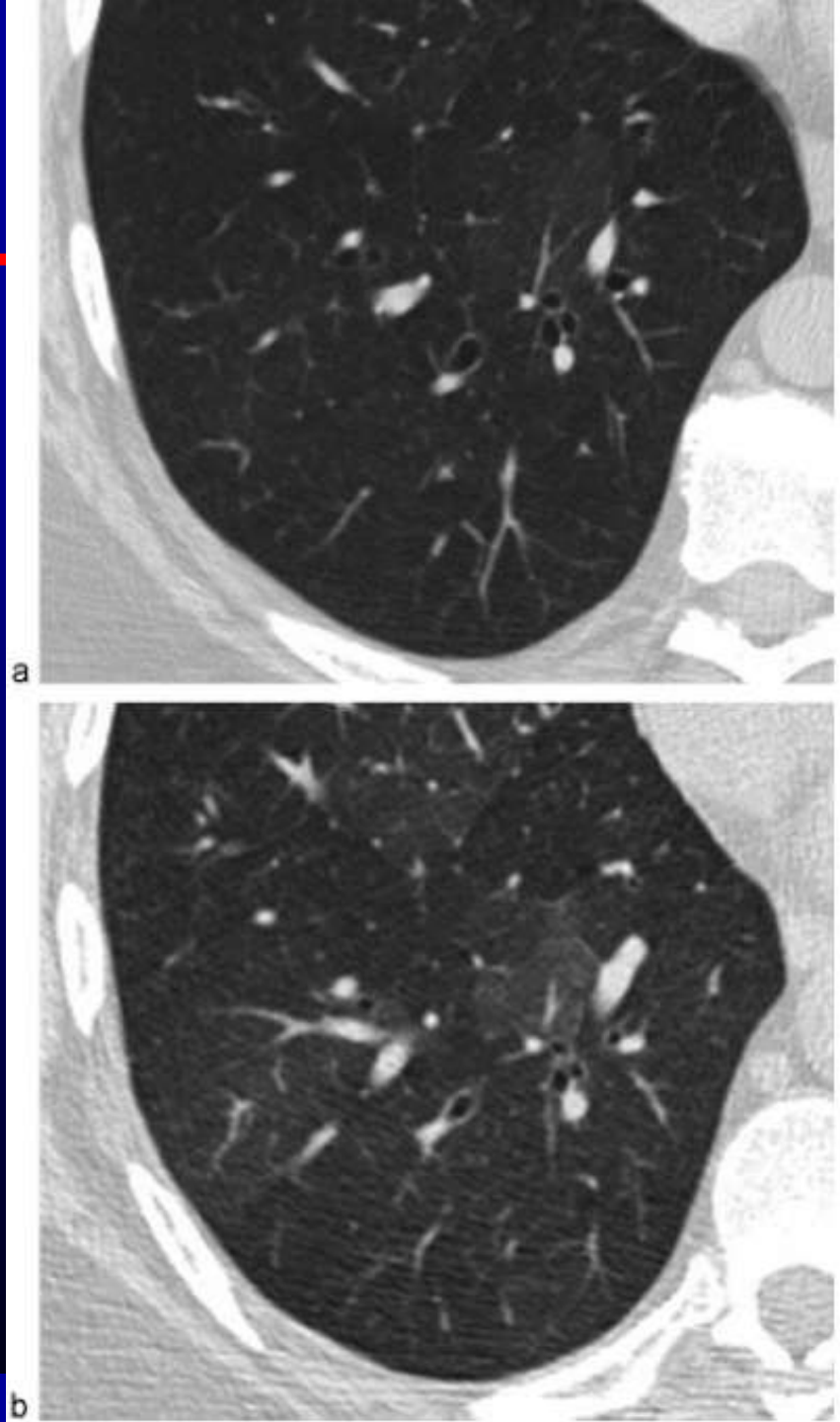


Figure 3 Kaplan Meier curves comparing RA-UIP with FVC- and DLCO matched historical controls with IPF (log rank $p = 0.94$).

Solomon JJ, et al. Respir Med 2013

Airway disease/bronchiectasis

- Prevalence: *varies*
- range: 8% in asymptomatic patients to 25% nonsmokers & 51% in symptomatic patients.
- Long-standing RA: increased extent of bronchiectasis & bronchial wall thickening



While most airways disease is ***subclinical*** in RA, obliterative bronchiolitis is an exception.

Rapid disease progression associated with a particularly poor prognosis .

ORIGINAL ARTICLE

Connective tissue disease related fibrotic lung disease: high resolution computed tomographic and pulmonary function indices as prognostic determinants

Simon L F Walsh,[1] Nicola Sverzellati,[2] Anand Devaraj,[1] Gregory J Keir,[3] Athol U Wells,[3] David M Hansell[1]

Walsh SLF, *et al. Thorax* 2014;**69**:216–222.

Severity of traction bronchiectasis, increasing extent of honeycombing and reduction in DLco were independently associated with increased mortality.

Table 5 Multivariable HRs for mortality according to HRCT and pulmonary indices in CTD-FLD (n=168)

Variable	HR	95% CI	p Value
Honeycombing	1.08	1.04 to 1.17	0.022
Traction bronchiectasis	1.10	1.02 to 1.13	0.001
DLco %predicted	0.96	0.94 to 0.98	0.001

CTD-FLD, connective tissue disease related fibrotic lung disease.

For patients with CTD and biopsy proven UIP, survival differences exist between those presenting with a UIP pattern of disease on HRCT, than those without typical features of UIP on HRCT.

Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke

Henrik Källberg,[1] Bo Ding,[1] Leonid Padyukov,[2] Camilla Bengtsson,[1] Johan Rönnelid,[3] Lars Klareskog,[2] Lars Alfredsson.[1,4] EIRA Study Group

- *Smoking and genetic risk factors interact in providing an increased risk of rheumatoid arthritis (RA).*

- *Less is known on how smoking contributes to RA in the context of genetic variability, and what proportion of RA may be caused by smoking.*

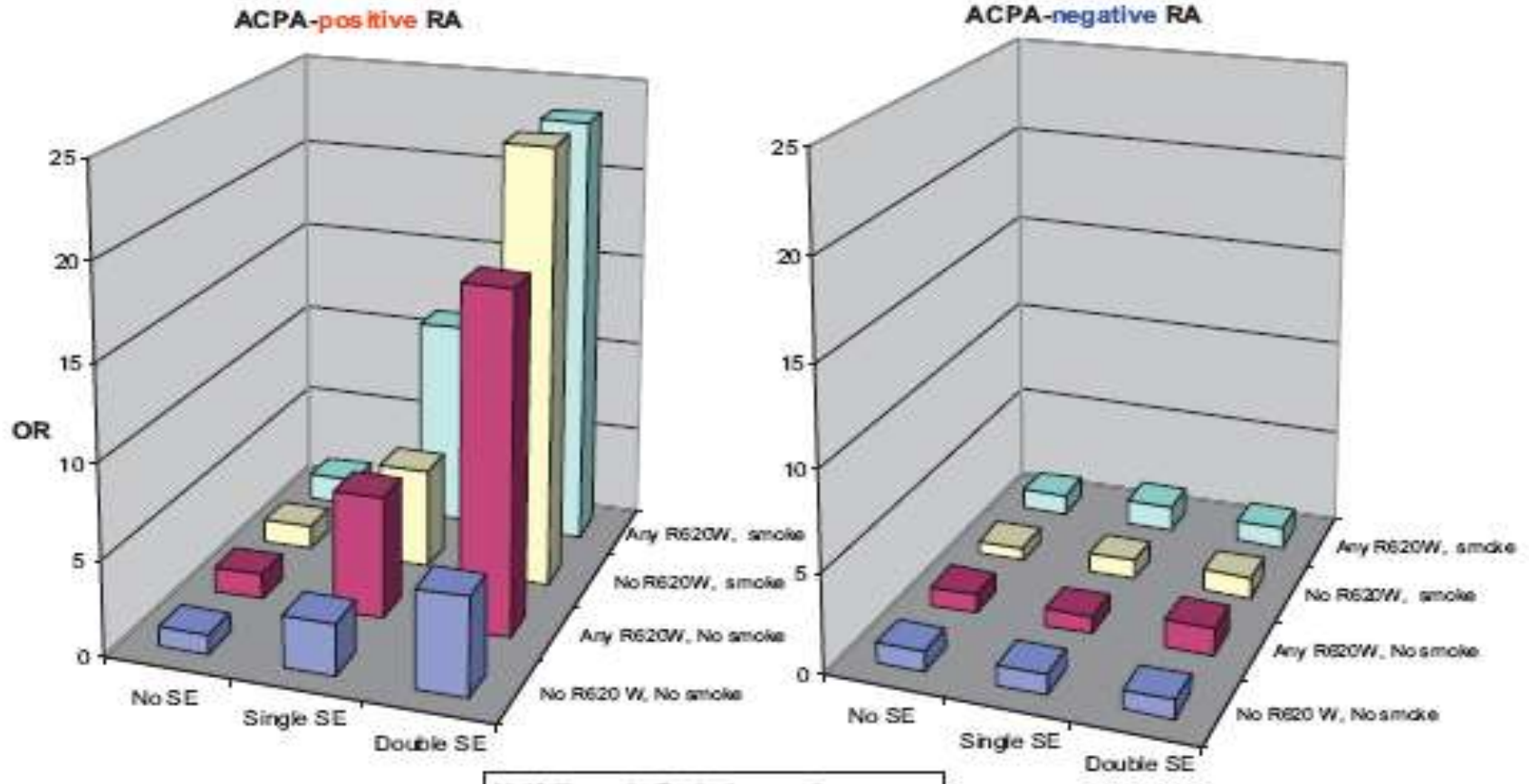
Ann Rheum Dis 2011

Review

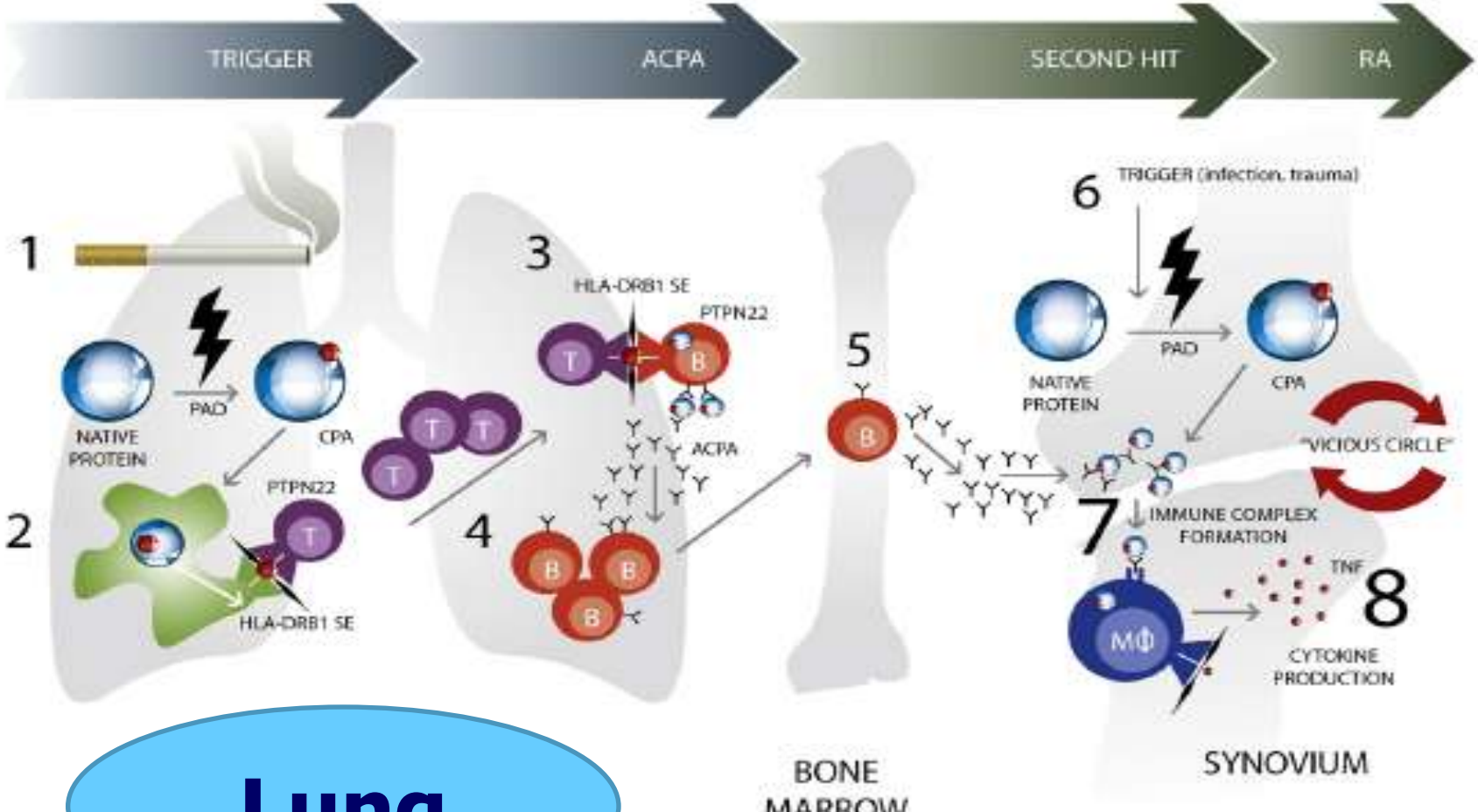
Smoking, citrullination and genetic variability in the immunopathogenesis of rheumatoid arthritis

Lars Klareskog[a,*], Vivianne Malmström[a], Karin Lundberg[a], Leonid Padyukov[a], Lars Alfredsson[b]

Interplay between two genes (HLA-DR-SE, PTPN22)
and one environmental factor (smoking) in two subsets of RA



H. Källberg, L. Padyukov et al.,
Am J Hum Genet, 2007, 80 (5): 867-875



Lung

Klareskog L, et al. Seminars in Immunology 2011

Smoking-related emphysema is associated with idiopathic pulmonary fibrosis and rheumatoid lung

KATERINA M. ANTONIOU,[1] SIMON L. WALSH,[2] DAVID M. HANSELL,[2] MICHAEL R. RUBENS,[2] KATHARINA MARTEN,[6] RACHEL TENNANT,[3] TREVOR HANSEL,[3] SUJAL R. DESAI,[4] NIKOLAOS M. SIAFAKAS,[7] ROLAND M du BOIS[5] AND ATHOL U. WELLS[1]

- *A CPFE syndrome has been proposed, but the basis for this syndrome is currently uncertain.*

- The aim was to evaluate:
- the prevalence of emphysema in IPF and RA-ILD
- *to compare the morphological features of lung fibrosis between smokers and non-smokers.*

Respirology (2013) 18, 1191–1196

Emphysema in IPF and rheumatoid lung

	Non-COPD controls ($n = 103$)	COPD controls ($n = 34$)	Smokers with RA-ILD ($n = 46$)	Smokers with IPF ($n = 186$)	*P*-value
Age (years)	53.6 ± 8.8	59.8 ± 10.2	61.6 ± 8.9	63.4 ± 9.3	<0.0005
Male/female (% male)	47/56 (46%)	17/17 (50%)	30/16 (65%)	156/30 (84%)	<0.0005†
Pack-year smoking history (median/range)	44.0 (10–195)	60.0 (25–180)	20.0 (2–100)	22.5 (2–120)	<0.0005
Prevalence of emphysema, *n* (%)	16 (15%)	22 (65%)	22 (48%)	66 (35%)	<0.0005†
Prevalence of emphysema at the main carina, *n* (%)	12 (12%)	20 (59%)	18 (40%)	57 (31%)	<0.0005†

Fibrotic abnormalities on HRCT are coarser in smokers with both disorders. These observations raise the possibility of shared mechanisms between fibrogenesis and smoking-related damage.

Respirology (2013) **18**, 1191–1196

CPFE in Scleroderma Lung

- **336 patients with SSc-ILD**

- ***Emphysema (HRCT) in 26/132 smokers and in 15/201 non-smokers***

- After adjustment for the extent of ILD, emphysema:
  1) reduced DLco by over 10%
  2) had no effect on FVC
  3) increased the FVC/DLco by over 40%

In smokers and non-smokers

Antoniou KM, Margaritopoulos G, et al.

CPFE in Scleroderma Lung

- Predilection of SSC-ILD to develop emphysema despite the smoking status
- The presence of emphysema confounds the use of the FVC/DLco ratio as a non-invasive screening test for PH in Scleroderma lung.

Antoniou KM, Margaritopoulos G, et al.

Key determinants of management

- **Consider a wide differential**
  - Primary diffuse lung disease: large variety of processes: inflammation vs DAD
  - Vasculitis/alveolar haemorrhage
  - Cardiac disease
  - Opportunistic or typical infection
  - Drug induced lung disease
- **Treat the treatable**

Treatment issues

- *Disease severity and intrinsic progressiveness crucial both in determining current management and in evaluating future treatments*
- First do no harm
- The worst crime is to miss an opportunity

The key clinical dilemma

- **We need to treat major pulmonary inflammation and progressive fibrosis.**
- **But we need to avoid unnecessary treatment in inherently stable disease.**
- **How to decide? A trend towards routine screening for pulmonary fibrosis in SSc has made this a frequent issue.**

Clinical trials in ILD of PSS

- Placebo-controlled oral cyclophosphamide (USA): positive
- Placebo-controlled i.v. cyclophosphamide (UK)
- Bosentan (endothelin-receptor antagonist) for antifibrotic efficacy (BUILD 2 trial): negative

Tashkin DP,et al. N Engl J Med 2006

Hoyles RK,et al. Arthritis Rheum 2006

Seibold JR,et al. Arthritis Rheum 2006

Kowal-Bielecka O,et al. Ann Rheum Dis 2009

Management

- The average FVC treatment effects in both trials was small (less than 5% of baseline values).
- SLS trial: the benefits came at the price of a significant prevalence of adverse effects.

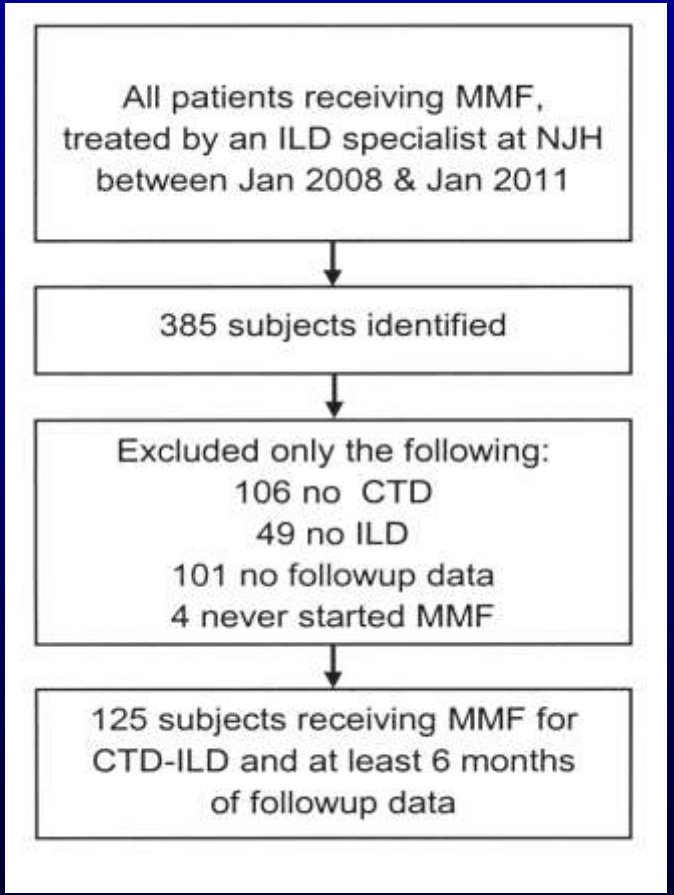
- ***The crucial conclusion, to be drawn from the SLS trial, is that in more typical lung disease, stabilisation of pulmonary fibrosis should be regarded as the primary treatment goal.***

Wells AU,et al.

Seminars in Respiratory and Critical Care Medicine Vol. 35 No. 2/2014

MMF in CTD-ILD

- Experience of MMF
- Well tolerated
- 10% of patients discontinued
- 2.5 years median follow-up



Fischer A et al. J Rheumatol 2013; 40:640-6

Main Results

- MMF was discontinued in 13 subjects
- MMF was associated with significant improvements in estimated percentage of predicted (FVC%) from MMF initiation to 52, 104, and 156 weeks.); and
- in estimated percentage predicted DLCO% from MMF initiation to 52 and 104 weeks (6.3% ± 2.8%, p = 0.02; 7.1% ± 2.8%, p = 0.01).

Eur Respir J 2012; 40: 641–648
DOI: 10.1183/09031936.00163911

Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy

Gregory J. Keir*, Toby M. Maher*, David M. Hansell#, Christopher P. Denton¶, Voon H. Ong¶, Suveer Singh+, Athol U. Wells* and Elisabetta A. Renzoni*

33 pts with CTD-ILD

FVC: 44.0% (24.0-99.0%) and diffusing capacity of carbon monoxide (DL_{CO}) of 24.5%

median improvement in FVC of 6.7% ($P < 0.01$) and stability of DL_{CO} (0% change; $P < 0.01$) in the 6-12 months following rituximab treatment

Keir JG. Respirology 2013

RHEUMATOLOGY

Rheumatology 2011;50:2297–2305
doi:10.1093/rheumatology/ker289
Advance Access publication 22 October 2011

Concise report

Non-infectious pulmonary complications of newer biological agents for rheumatic diseases—a systematic literature review

Andreas V. Hadjinicolaou[1,*], Muhammad K. Nisar[1,*], Shweta Bhagat[1], Helen Parfrey[2], Edwin R. Chilvers[2] and Andrew J. K. Östör[1]

7 cases of RTX-induced ILD:

5 cases resolved on discontinuing drug and high dose steroids

2 cases fatal:

-RA+lymphoma treated with weekly 375 mg RTX>12 weeks (ILD 3 weeks after last dose)

-SLE nephritis treated with RTX 1 gr x2 (ILD on day 58)

DRUG POINTS

Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab

Andrew J K Ostor, Adrian J Crisp, Margaret F Somerville, David G I Scott

BMJ VOLUME 329 27 NOVEMBER 2004 bmj.com

(3 patients)

Fatal exacerbation of fibrosing alveolitis associated with systemic sclerosis in a patient treated with adalimumab

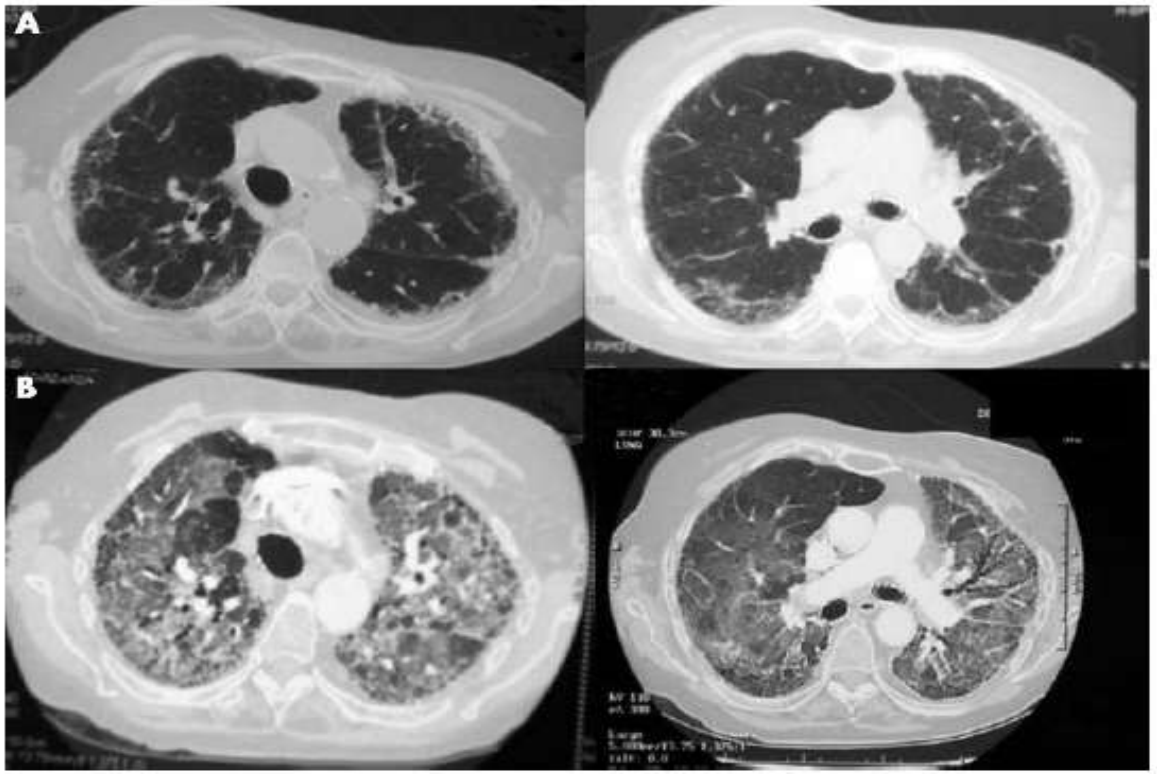
Y Allanore,

Ann Rheum Dis 2006;65;834-835

Lung Injury Linked to Etanercept Therapy*

Laura Peno-Green, Geronomo Lluberas, Thomas Kingsley and Steven Brantley

Chest 2002;122;1858-1860



Conclusion

While specific connective tissue diseases are typically associated with particular pulmonary complications, virtually all complications can occur with any of the connective tissue diseases and may even present prior to the diagnosis of the underlying connective tissue disease.

Due to the resultant morbidity and mortality from these processes, pulmonary involvement needs to be recognized early, diagnosed accurately and treated aggressively. This requires all practitioners involved in the care of these patients to have a broad knowledge of these potential complications, including infection, drug toxicity, direct and indirect pulmonary complications of disease, and cardiovascular complications, for optimal care.

Eur Respir Mon, 2009