UNIVERSITÀ DI PARMA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Piacenza

PNEUMOLOGIA 2018 - Milano, 14-16 giugno 2018

Ruolo dell’Imaging nella Dispnea

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Da un semplice prelievo di sangue la diagnosi di un tumore al polmone, identificato a uno stadio fino a due anni più precoce di quanto sia possibile utilizzando la Tac spirale, il più avanzato degli strumenti diagnostici oggi a disposizione.

Summary

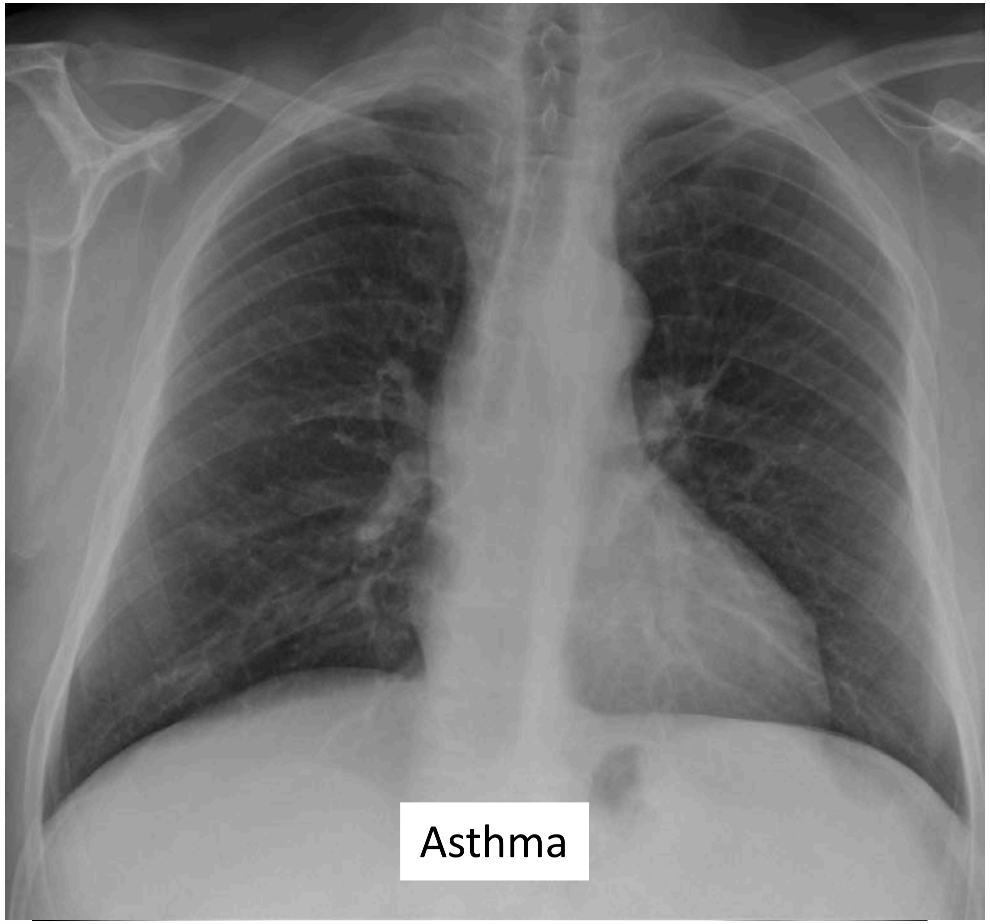
- **Acute dyspnea:**
  - Elderly (pneumonia, bronchitis, **acute pulmonary embolism**, myocardial infarction, liquid overload)
  - Oncologic
    - **Chemotherapy/target therapy/Immunotherapy** (drug-related pneumonia, organizing pneumonia, pneumonitis, bronchitis)
    - Not related to therapy (pleural effusion, acute pulmonary embolism, metastasis)
  - Youth (**severe asthma**, pneumothorax, pneumomediastinum, pneumonia, pericarditis-myocarditis, foreign body)
  - Diffuse alveolar damage (pulmonary or extrapulmonary cause)
  - Alveolar hemorrhage (vasculitidis, connective tissue disease, cocaine, toxic gas)
  - Foreign body/aspiration
  - Trauma (pneumothorax)

- **Chronic dyspnea:**
  - Elderly (chronic cardiac failure, **COPD, interstitial lung disease,** idiopathic or secondary pulmonary hypertension, anemia)
  - **Severe asthma**
  - Inhalational/professional exposure
  - Psychogenic
  - Iatrogenic tracheal stenosis
  - Pleural disease (effusion, etc.)

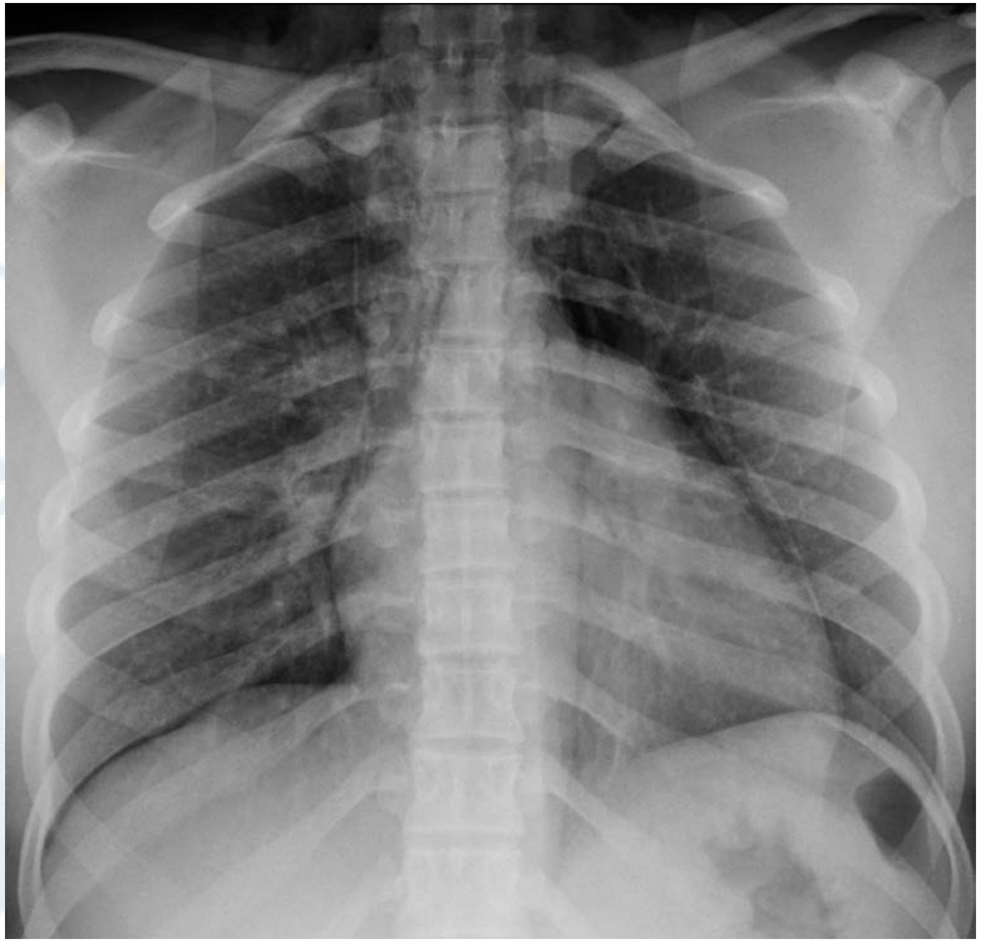
- **Acute onset in chronic dyspnea:**
  - **Acute exacerbation of idiopathic pulmonary fibrosis**
  - COPD exacerbation
  - Kidney/liver failure

Acute Dyspnea → Plain chest radiograph (CXR)

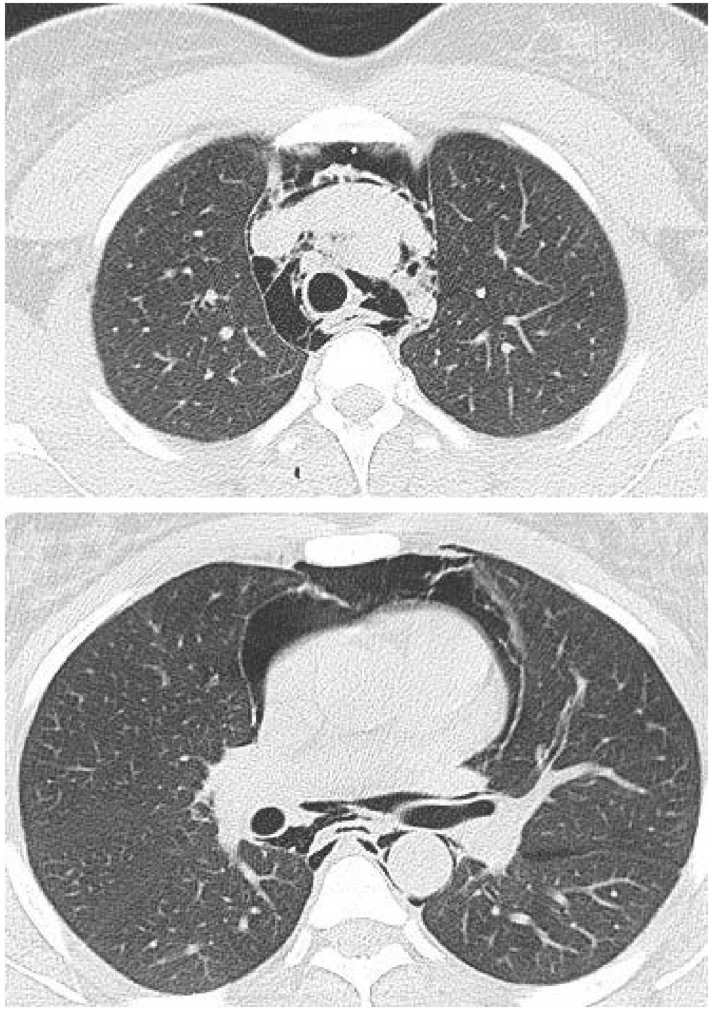
- Acute heart failure (20% non-diagnostic CXR)
- Pneumonia
- Oncologic: Pleural effusion/Metastasis
- Foreign body
- Pneumothorax / tension pneumothorax
- Asthma
- COPD



Acute Dyspnea → Plain chest radiograph (CXR)



Complication of severe asthma: pneumomediastinum



Acute dyspnea → Plain chest radiograph (CXR)

In severe asthma, chest imaging is most helpful for:

- Complications of severe asthma

- Alternative diagnoses:

  intrathoracic or extrathoracic airway obstruction,

  obliterative bronchiolitis,

  chronic obstructive pulmonary disease,

  hypersensitivity pneumonitis,

  hypereosinophilic syndromes,

  allergic bronchopulmonary aspergillosis,

  eosinophilic granulomatosis with polyangiitis

Acute dyspnea → CT pulmonary angiography

Pulmonary embolism:

CT pulmonary angiography

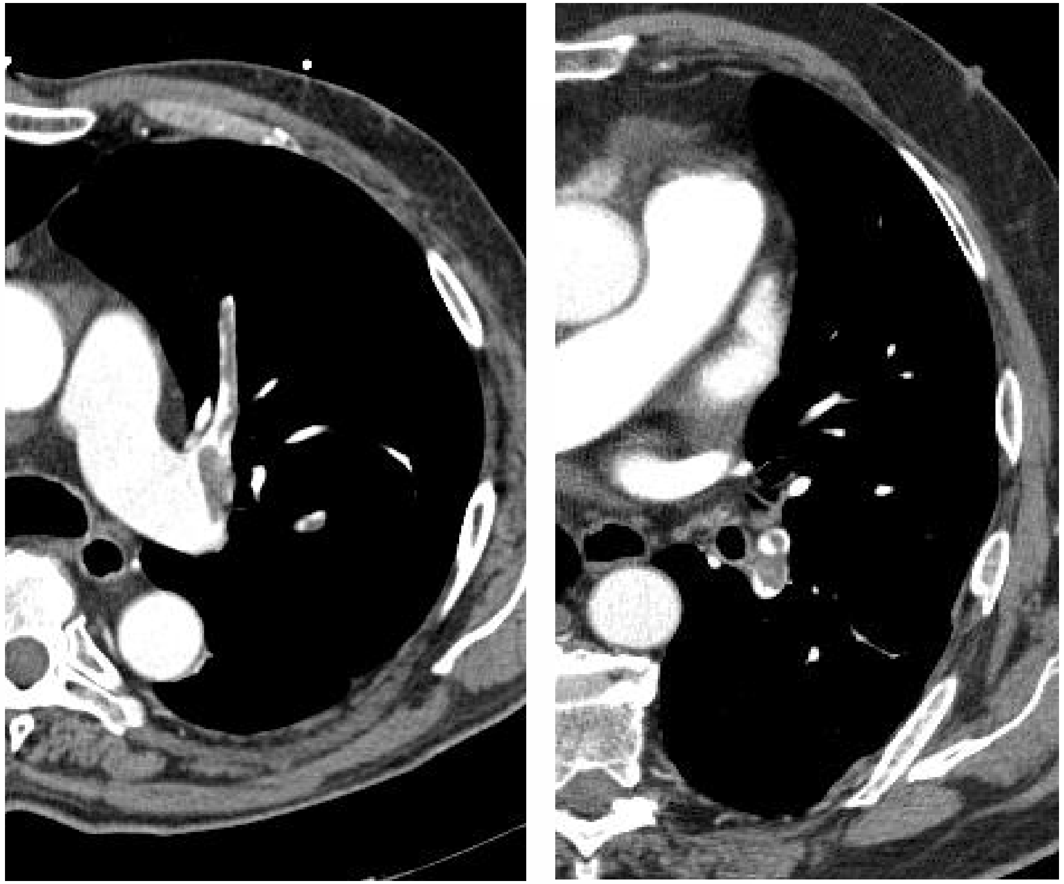
↓

Small vascular volume & Fast acquisition

↓

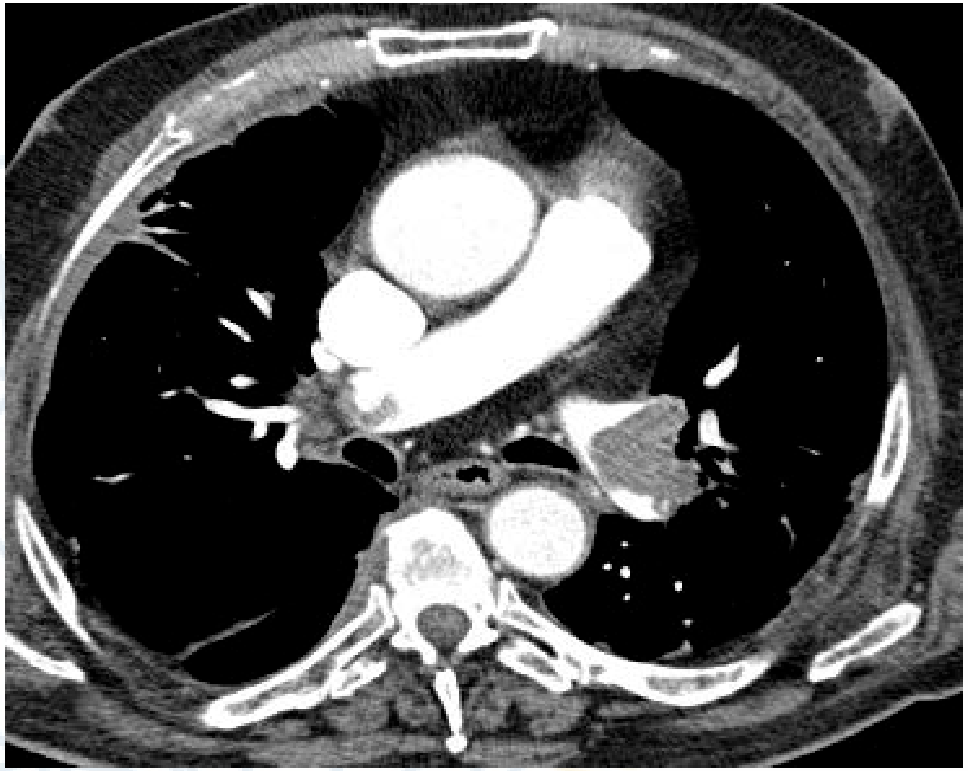
Contrast agent:

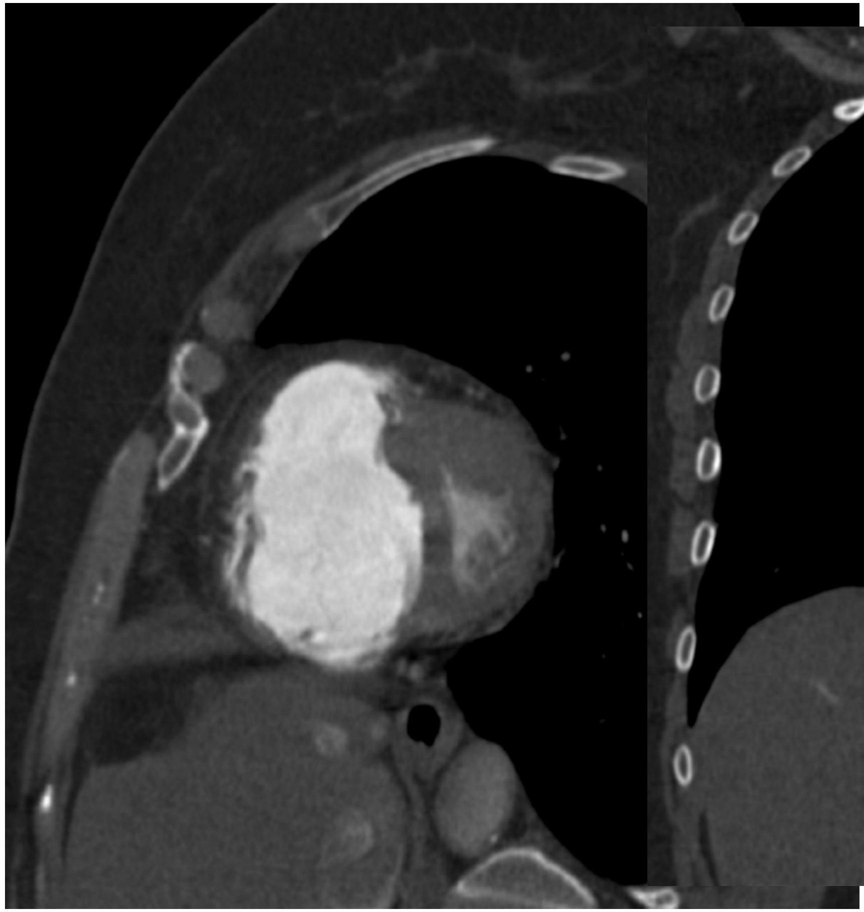
Low volume 40 ml (or less?)



Revel MP, Radiology 2007; 244(3):875-882.
Remy-Jardin M, Radiol Clin N Am 2014; 52:183–193

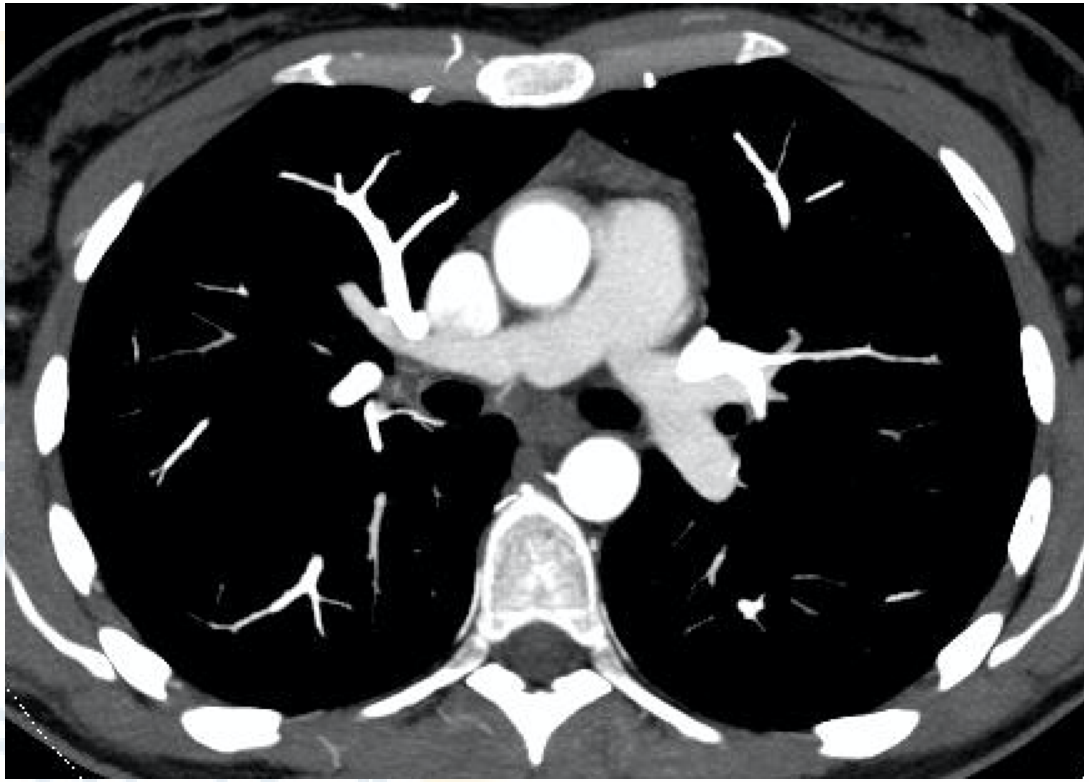
Acute dyspnea → Chest CT

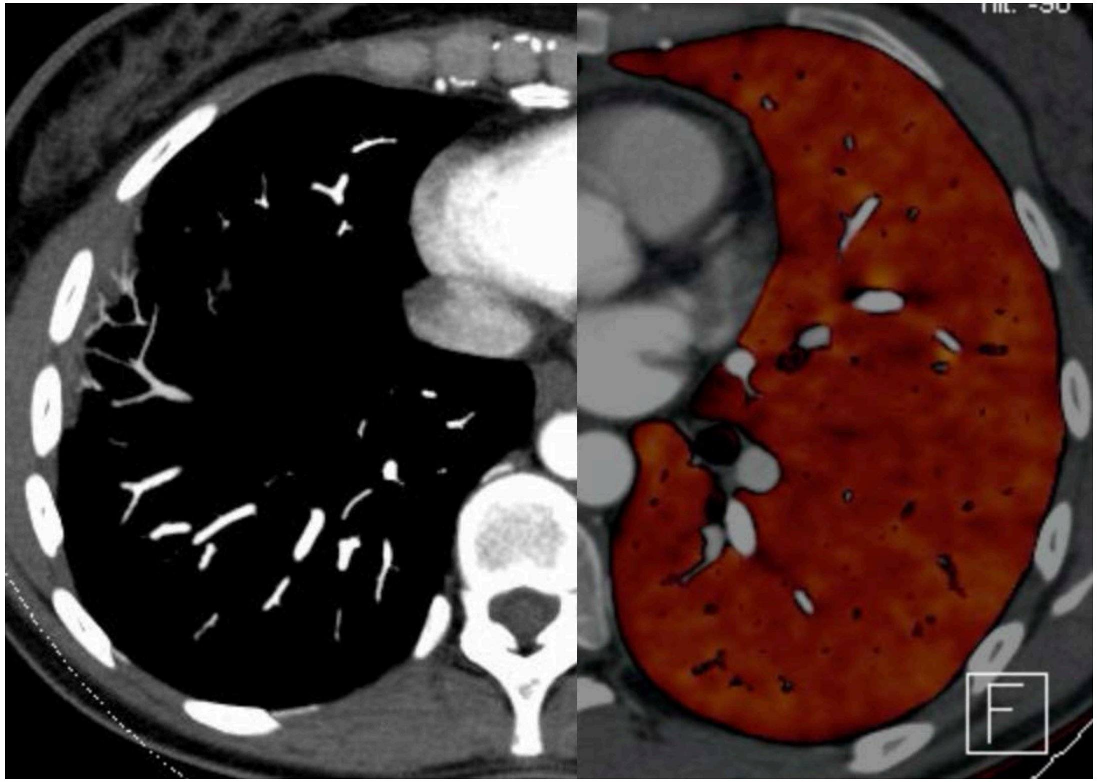




Galiè N, Eur Heart J 2016; 37(1):67-119

Acute dyspnea → Chest CT





Ameli-Renani S, Radiographics 2014; 34(7):1769-90
Hagspiel KD, Clinical Radiology 2012; 67:69-77

Acute dyspnea in the Oncologic patient

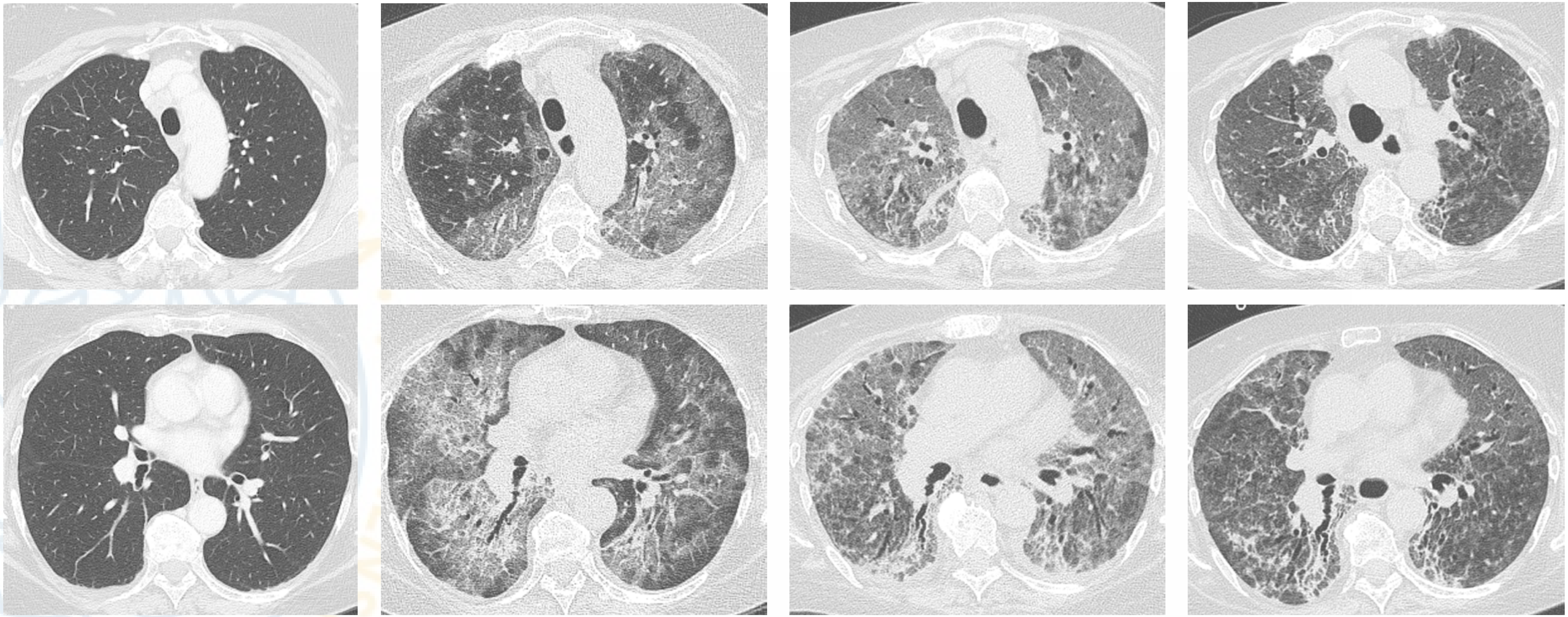
Drug toxicity:

differential with

- Infection
- Malignant disease progression

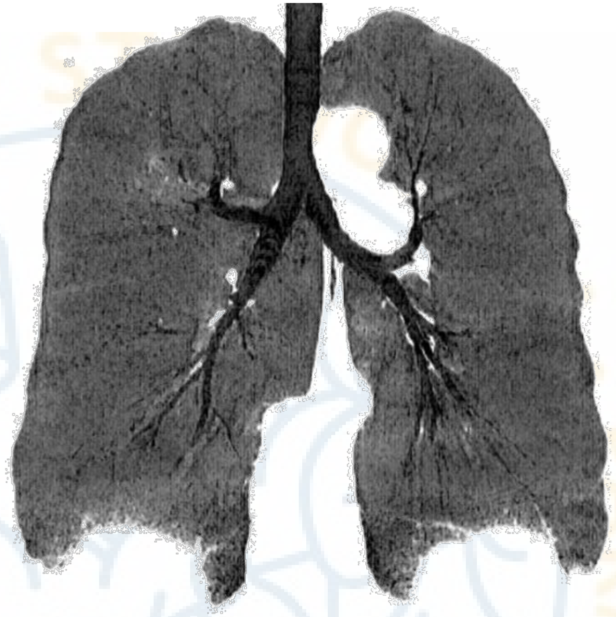
	Incidence	Onset	Disease
Platinum-based	+	Days	Broncospasm
Gemcitabine	++	Days	NSIP-like, DAD, haemorrage
Etoposid	+	Days	Broncospasm, NSIP-like, DAD
Pemetrexed	+	Days	NSIP-like
Bevacizumab	+	Months	Venous thrombosis, pulmonary haemorrage
Gefitinib Erlotinib	++	First 2 months	DAD
Crizotinib	++(+)	Months or later	DAD or haemorrage
Nivolumab	+ (?)	Months	DAD/OP

Drug toxicity – Diffuse alveolar damage

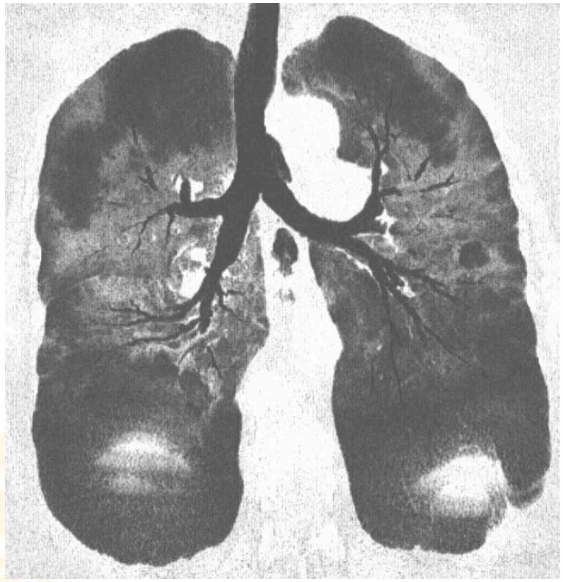


13 – 05 – 2016 | 25 – 07 – 2016 | 12 – 08 – 2016 | 02 – 09 – 2016

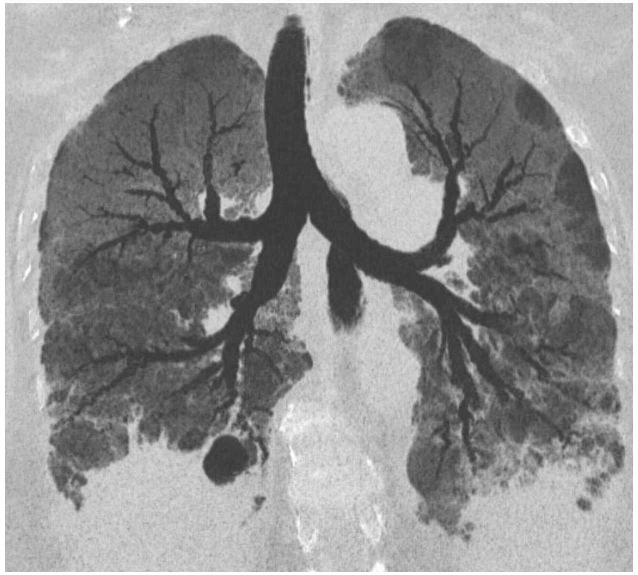
Drug toxicity – Diffuse alveolar damage



13 – 05 – 2016



25 – 07 – 2016



12 – 08 – 2016

02 – 09 – 2016

Immunotherapy – Lung toxicity

- Onset 2.5 months [range 2–24 months]
- Radiography may fail to identify ≈ 25%
- May appear **on CT before it becomes clinically evident**
- AIP/ARDS manifested as the highest grade of lung injury followed by COP, then NSIP and HP
- **Morphological subtypes of CIP**:
  - COP like
  - Ground-glass
  - Reticular
  - Hypersensitivity
  - Not otherwise specified
  - Sarcoid-like pulmonary changes (subpleural micronodular opacities and hilar lymphadenopathy; *elevated CD4:CD8 ratio*)

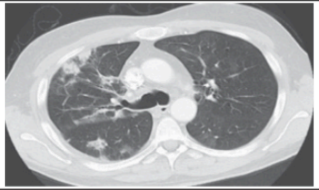
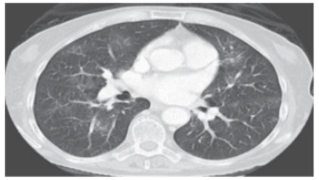
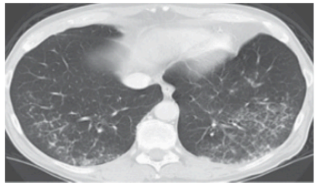
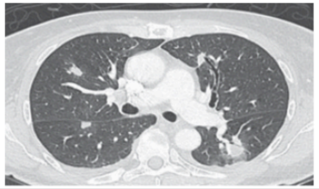
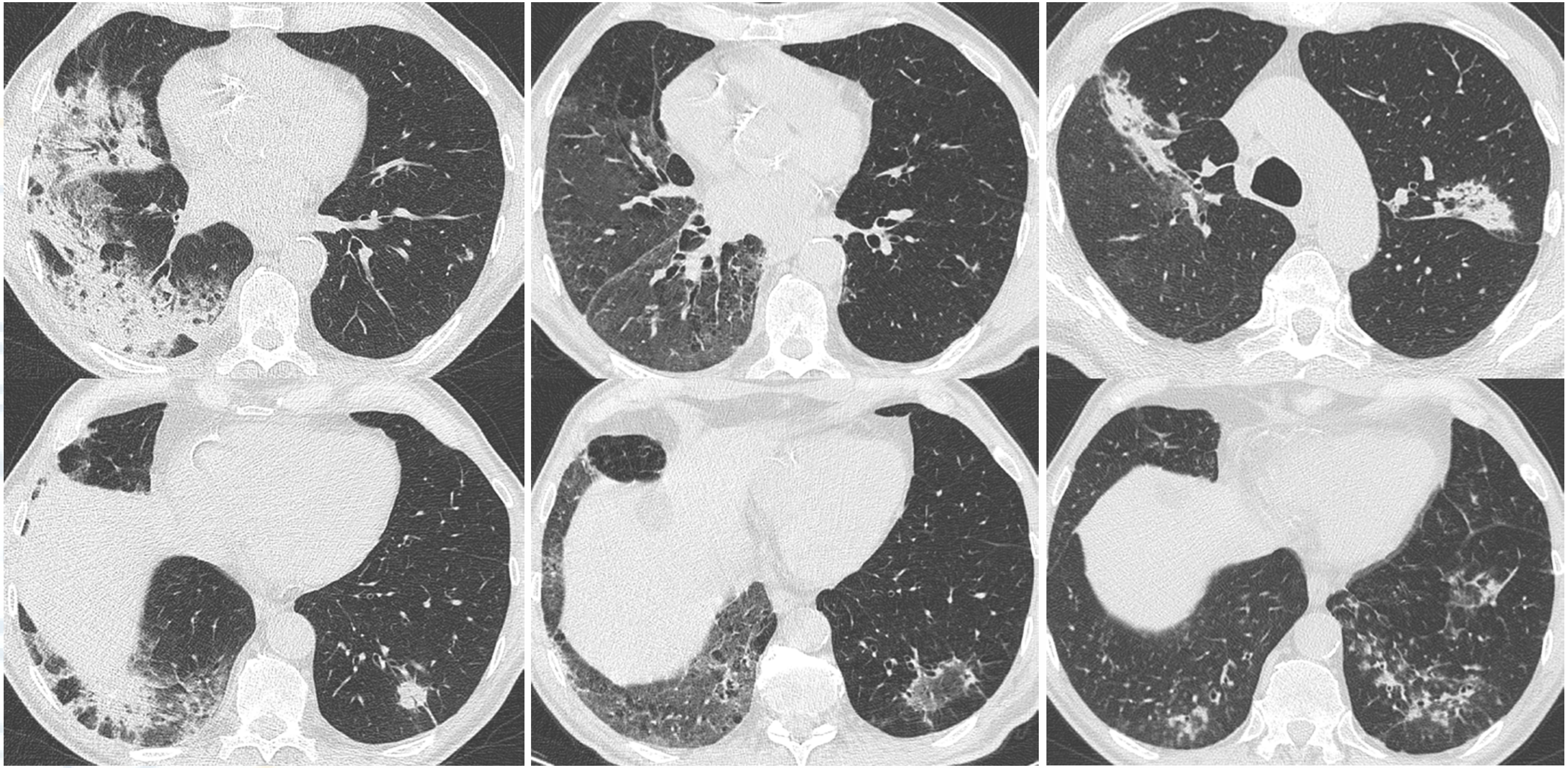
Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

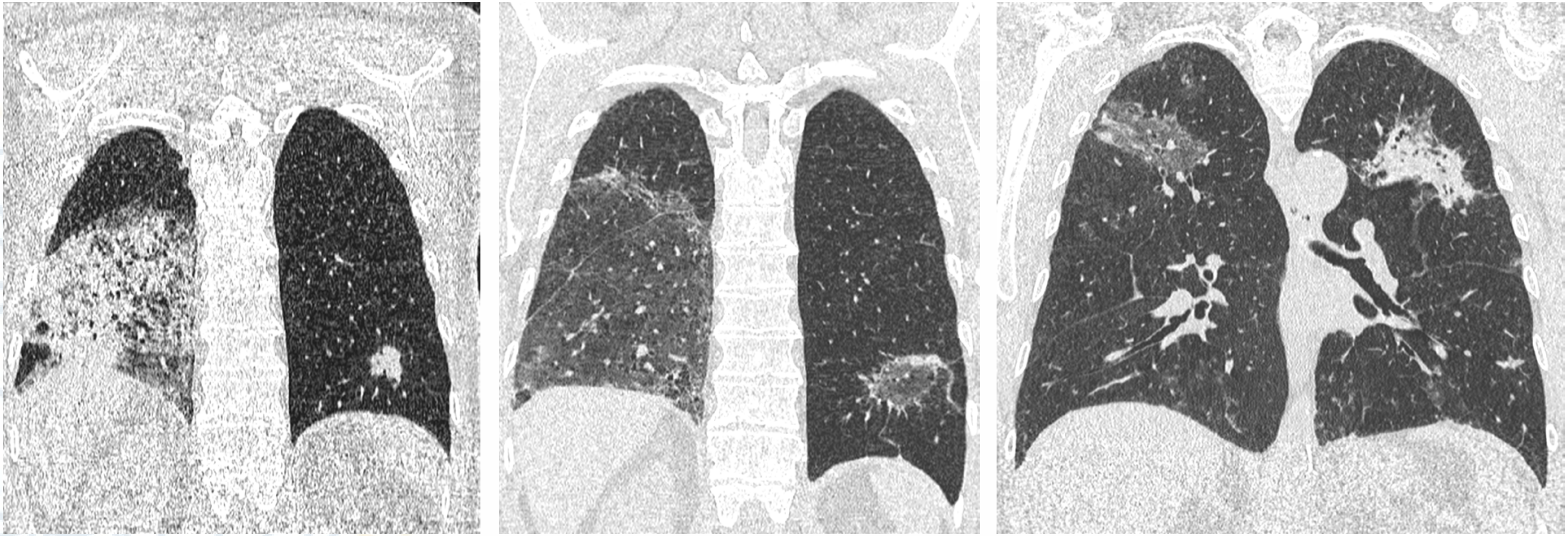
Table from Naidoo J, J Clin Oncol. 2017; 35(7):709–717

Immunotherapy – Lung toxicity – COP like

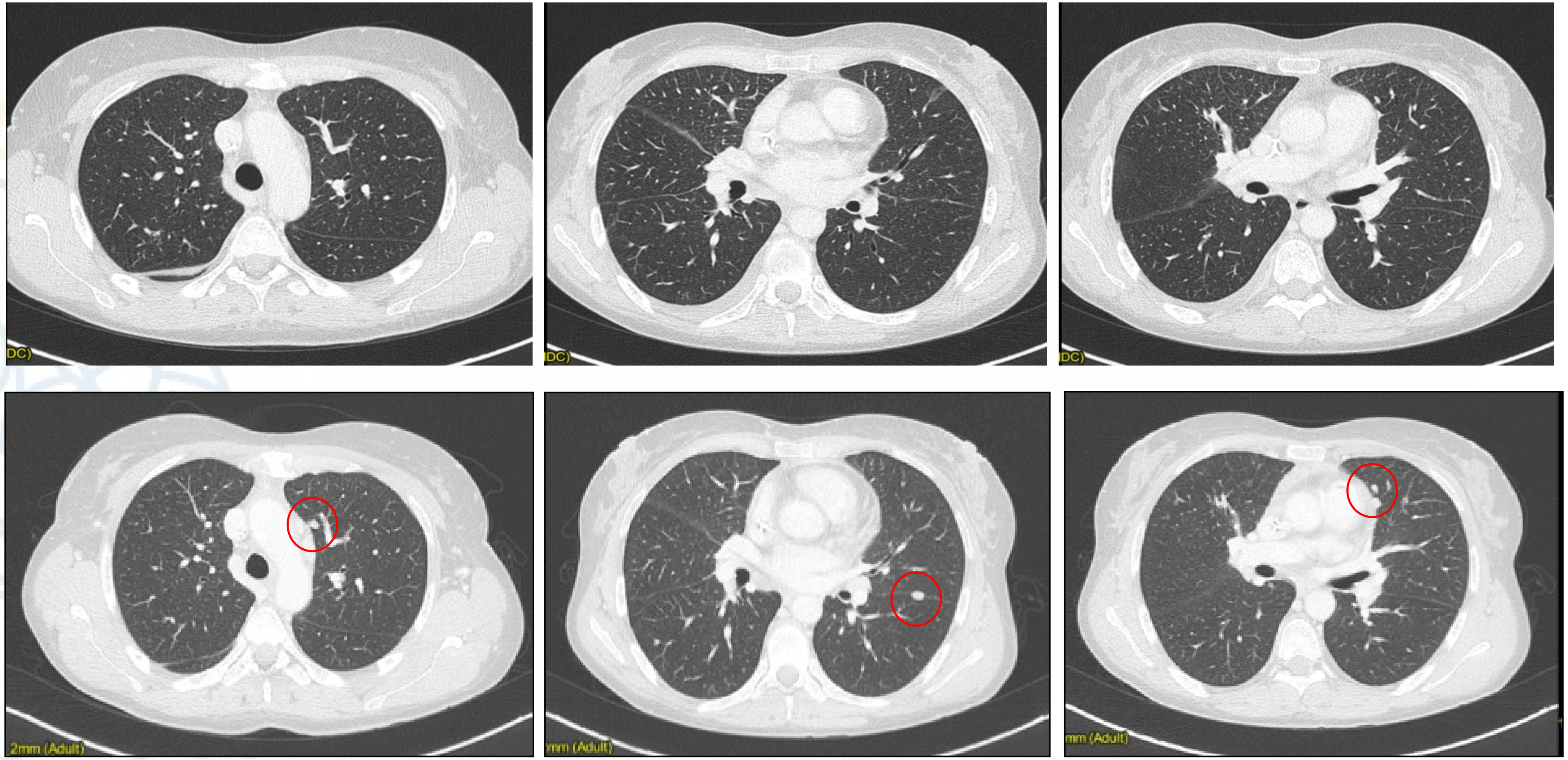


27-11-2015 11-01-2016 02-07-2016

Immunotherapy – Lung toxicity – COP like



Immunotherapy – Lung toxicity – Sarcoid like



Immunotherapy – Lung toxicity

- Interstitial lung disease:
  - anti-CTLA-4 treatment **< anti-PD-1 treatment**

    ≈ 1% PD-L1 inhibitors VS **≈ 4 % PD-1 inhibitors**

    ≈ 3% monotherapy VS **≈ 10% combination therapy**
  - **NSCLC is more associated with pneumonitis and/or treatment-related deaths** than melanoma and renal cell carcinoma
  - Hypotheses for risk prediction:
    - higher rates of **pre-existing adverse pulmonary conditions** (i.e., tobacco exposure, previous lung radiation)
    - previous exposure to **drugs associated with ILD** (taxanes, epidermal growth factor receptor tyrosine kinase inhibitors, and gemcitabine)

Postow MA, N Engl J Med 2015; 372(21):2006–2017
Naidoo J, J Clin Oncol 2017; 35(7):709–717
Nishino M, JAMA Oncol 2016; 2(12):1607-1616
Khunger M, CHEST 2017; 152(2):271-281

Immunotherapy- Hyperprogressive disease (HPD)

- Predict risk of HPD

NO association with

number of previous lines (P=0.69)

the occurrence of corticosteroids at baseline (P=0.16)

type of previous treatment line (conventional chemotherapy P=0.75, targeted therapy P=0.55, radiotherapy P=0.77, immunotherapy P=0.39)

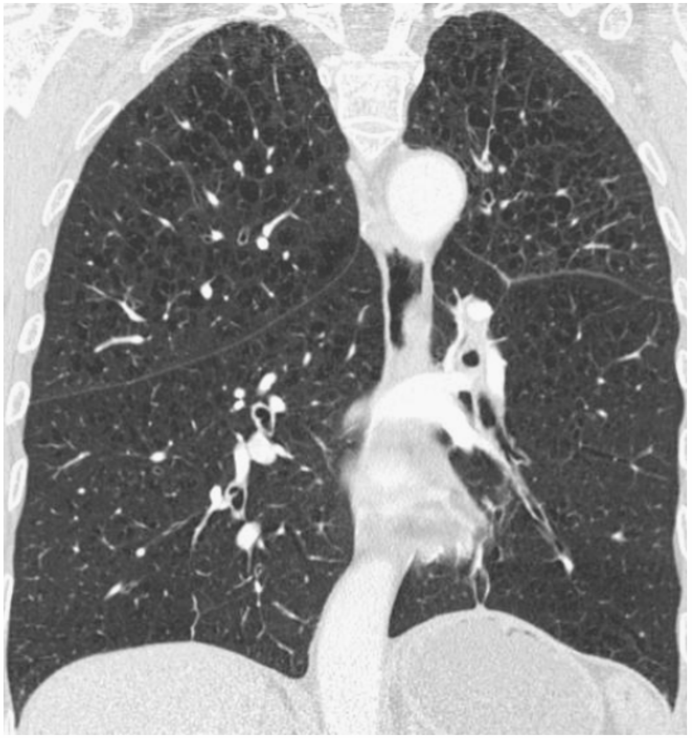
histology (P=0.29)

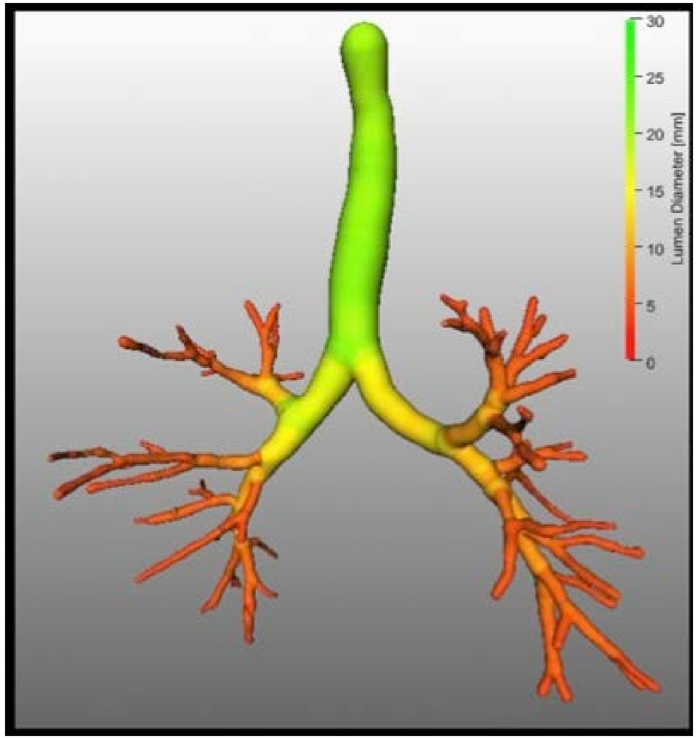
	All patients (N=131)	Non HPD (N=119)	HPD (N=12)	P value (Wilcoxon test)
Tumor burden (mm) (estimated by RECIST 1.1)	78 (12-364)	76 (12-364)	91.6 (12-167)	0.64
Age (y)	55 (22-82)	55 (22-82)	65.5 (32-82)	0.007
Leukocytes (1.e+9/l)	7.1 (2.4-41.7)	7.1 (2.4-41.7)	7.95 (3.5-21.0)	0.45
Lymphocytes (1e+9/l)	1.2 (0.1-3.5)	1.2 (0.1-3.5)	0.95 (0.6-2.9)	0.64
Neutrophils (1e+9/l)	5.1 (1.4-37.9)	5.1 (1.4-37.9)	5.0 (2.0-18.7)	0.69
CRP (mg/l)	21.1 (0.5-317.7)	21.1 (0.5-317.7)	21.7 (5.2-68)	0.97
Fibrinogen (g/l)	4.8 (2.8-9.6)	4.9 (2.8-9.6)	4.7 (3.2-7.1)	0.43
LDH (UI/l)	204 (9-1195)	198 (9-1195)	248 (132-547)	0.097
Albumine (g/l)	36 (20-61)	36 (20-61)	34.5 (30-39)	0.23

Table from Champiat S, Clin Cancer Res 2017; 23(8): 1920-1928

Chronic dyspnea in COPD

- COPD includes heterogeneous impairment of the lung
- Computed tomography grants detailed characterization of individual pulmonary abnormalities → Phenotypes



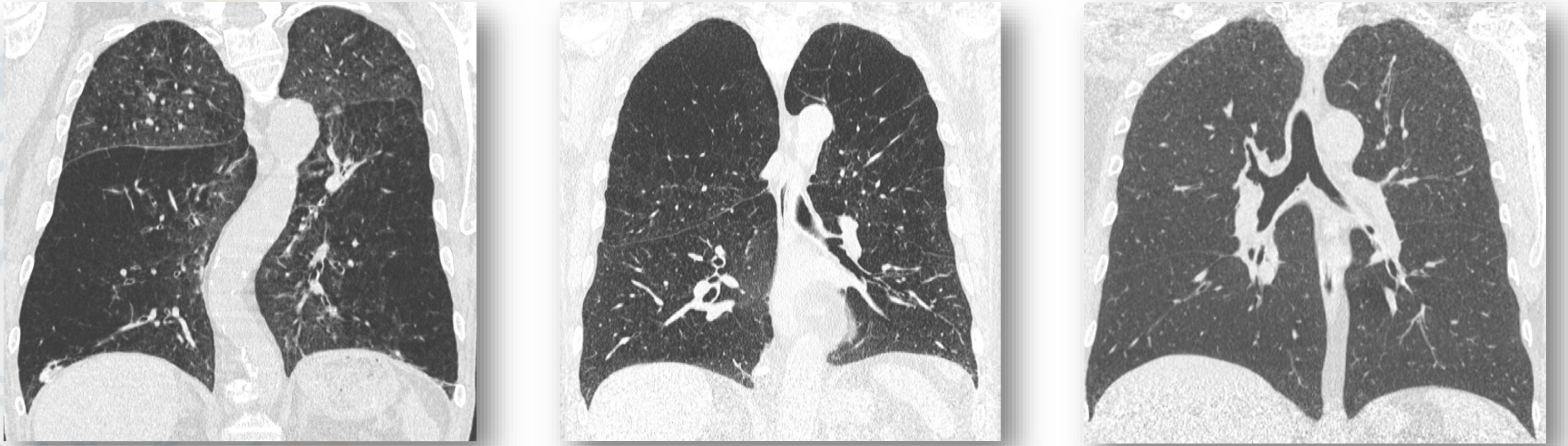


Crisafulli E, Respiratory Medicine 2016; 117:207-214

Treatment of Emphysema – Surgery

Lung volume reduction surgery

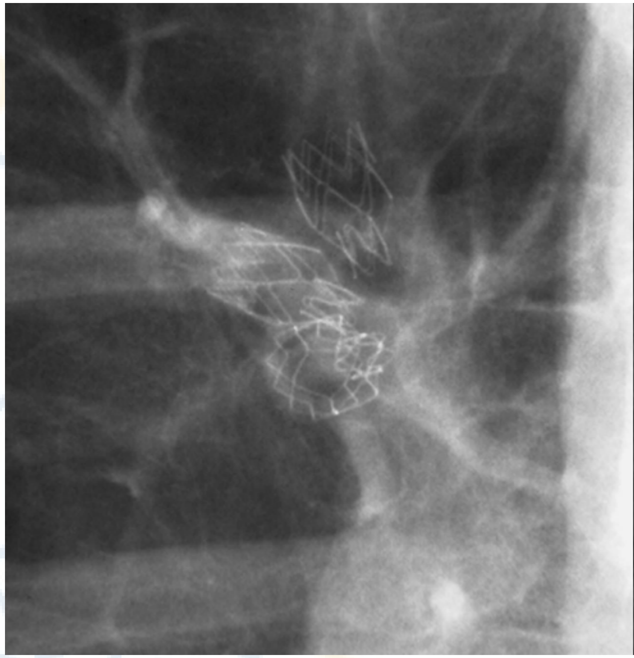
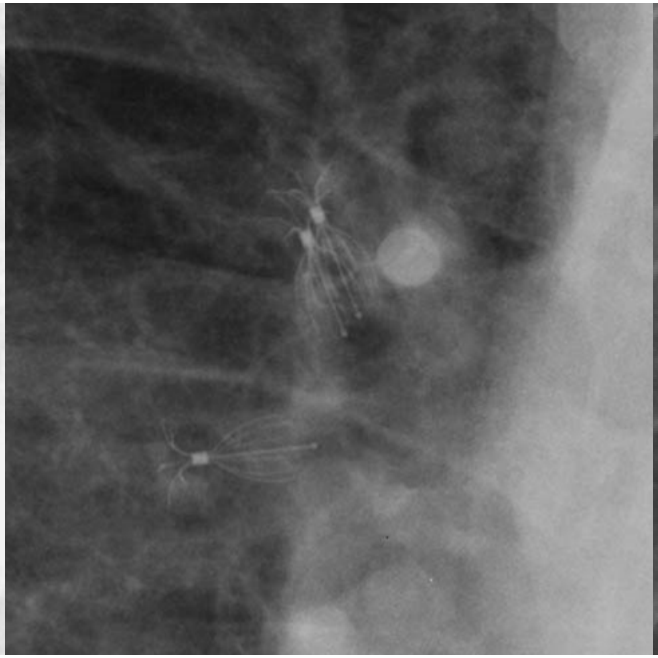
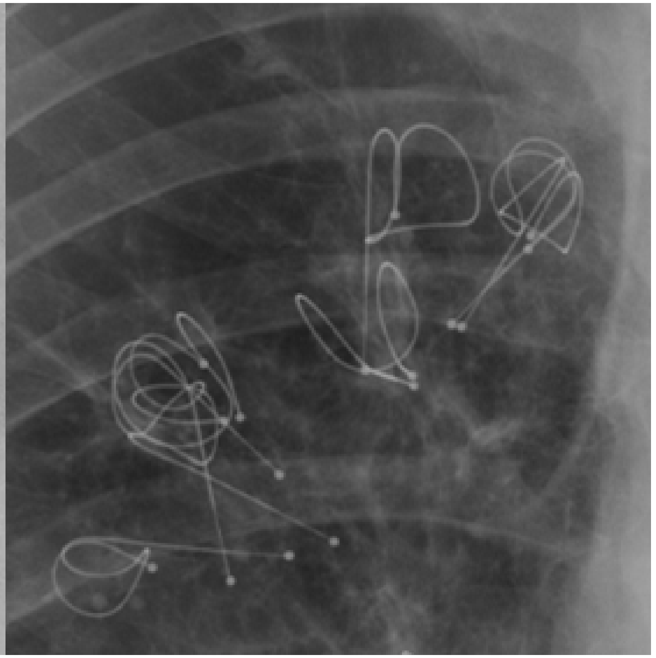
CT defines emphysema extent end distribution → Upper – Lower > 10%

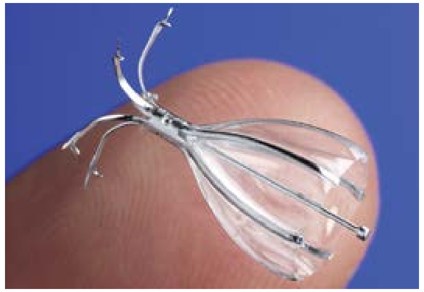
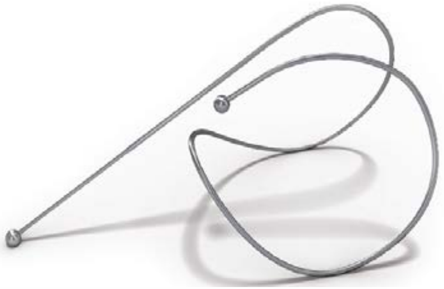


Fishman A et al., N Engl J Med 2003; 348:2059-73
Nakano Y et al., AJRCCM 2001; 164:2195-9
Flaherty KR et al., Chest 2001; 119:1337-46
Hunsaker A et al., AJR Am J Roentgenol 1998; 170:309-14

Treatment of Emphysema – Bronchoscopic

Valves	Coils

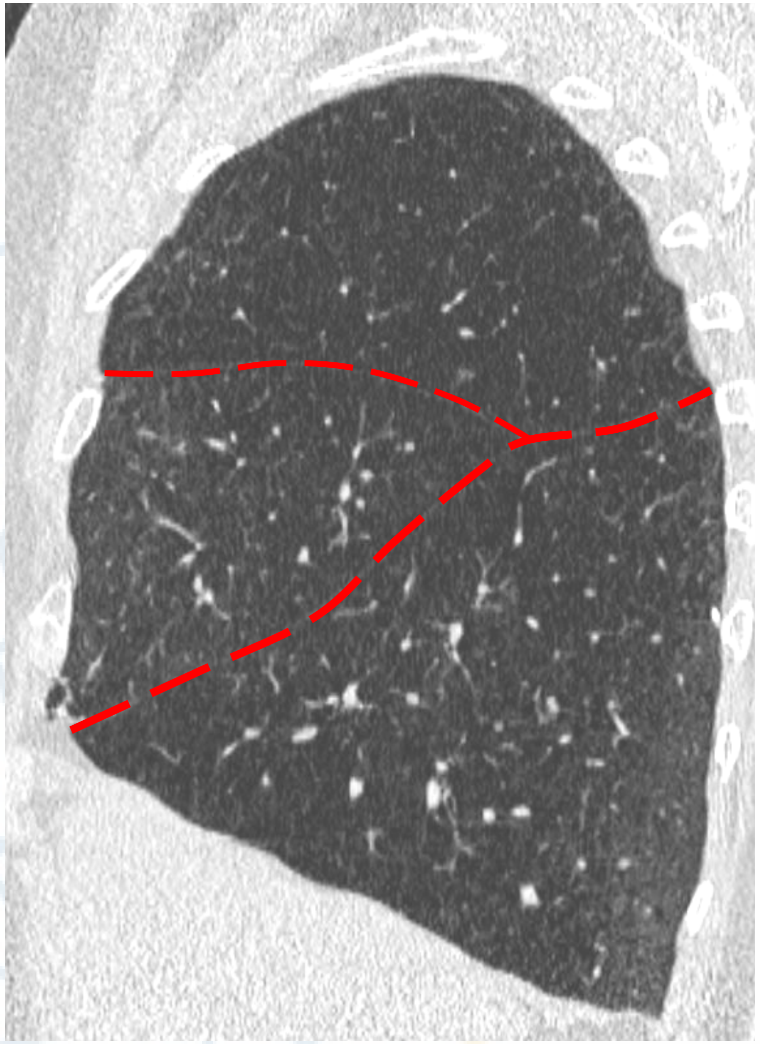
Treatment of Emphysema – Bronchoscopic

Computed tomography is mandatory to plan the most appropriate treatment, notably:

- Fissure integrity (>90%) has good correlation with Chartis
- Emphysema distribution (target lobe >10% compared to non-target)
- Bronchial anatomy

Milanese G, Curr Opin Pulm Med. 2016 Mar;22(2):179-86

Fissure integrity

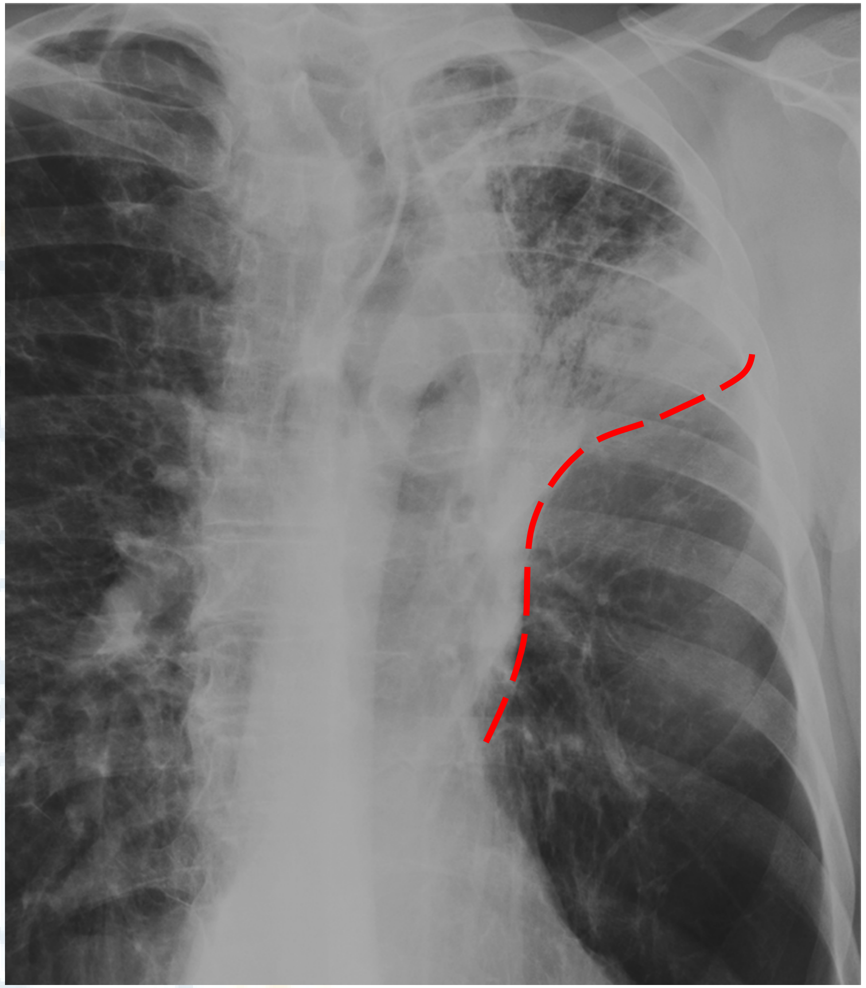


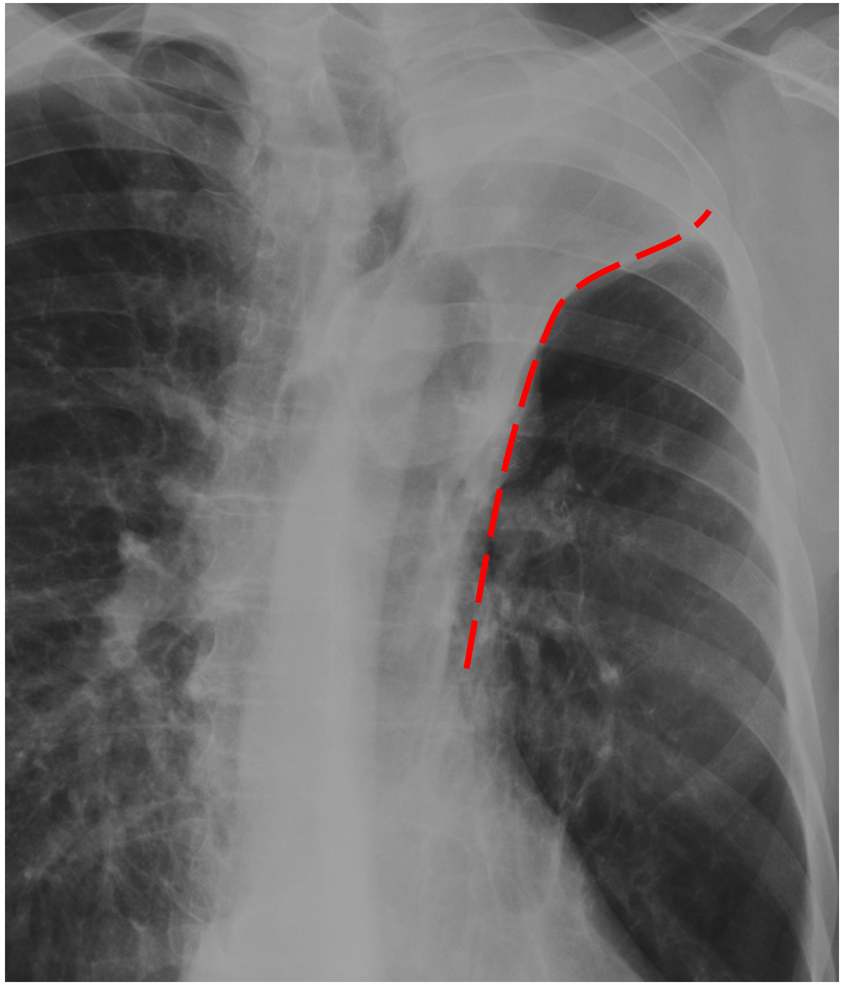
About **33%** of patients with severe emphysema have no collateral ventilation between the target and adjacent lobe and can thus potentially be treated using one-way valves

Shah PL, Herth FJ. Thorax 2014;69:280–6.

	Reymond *AJR 2013*	**Van Rikxoort** *Eur Radiol 12*	**Koenigkam-Santos** *Eur J Rad12*	**Cronin** *Eur J Rad 10*	**Ozmen** *Clin Anat 10*	**Hermanova** *Eur J Radi14*
Left Oblique	65.2%	33%	50%	25%	48%	24%
Right Oblique	84%	51%	81%	34%	70%	35%
Horizontal	92%	85%	89%	48%	87%	74%

Treatment of Emphysema – EBV Outcome





Sciurba FC et al, N Engl J Med 2010;363:1233-44

Treatment of Emphysema – Coil Outcome

Deslee G et al, Thorax 2014; 69:980-6.

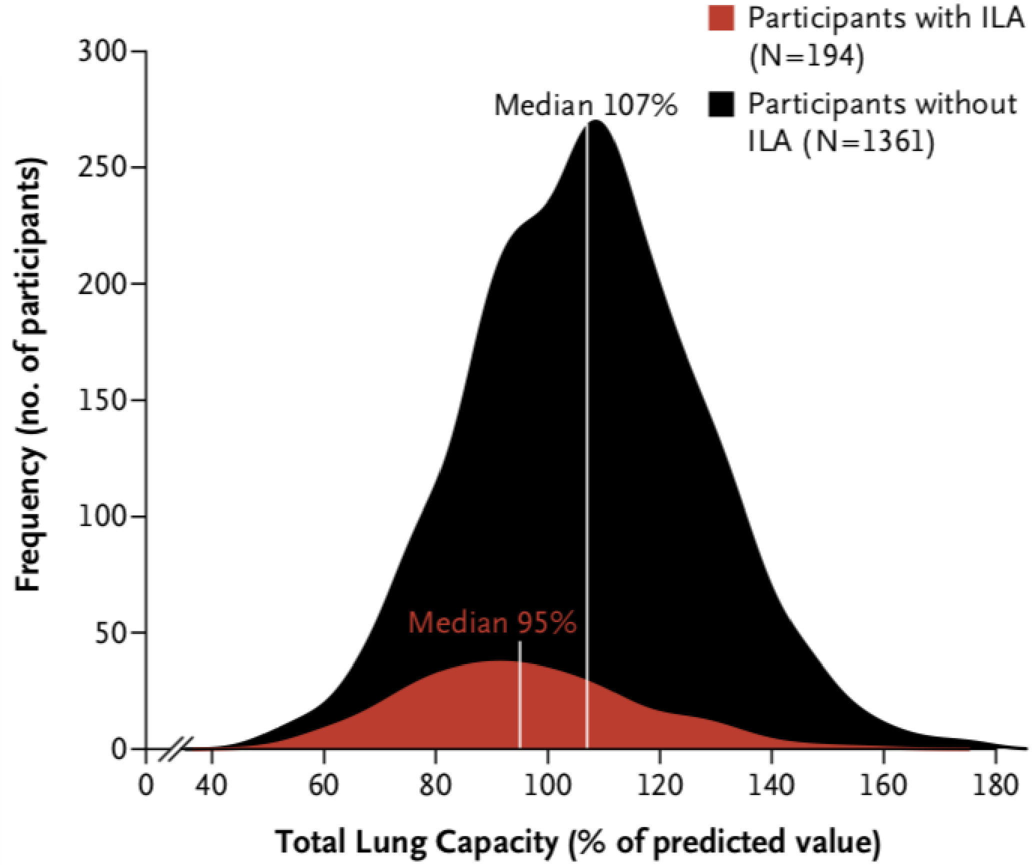
COPD: emphysema and interstitial lung abnormalities

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2011 VOL. 364 NO. 10

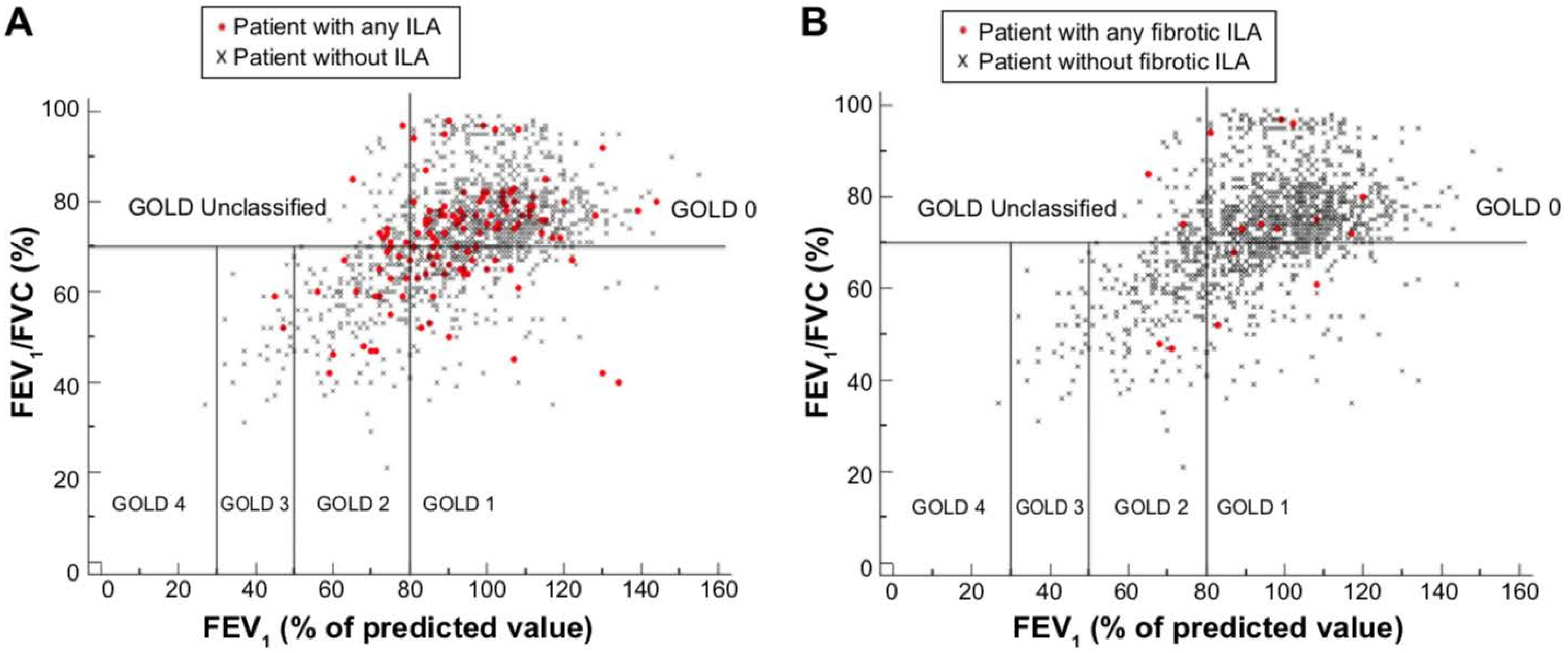
Lung Volumes and Emphysema in Smokers with Interstitial Lung Abnormalities

George R. Washko, M.D., M.M.Sc., Gary M. Hunninghake, M.D., M.P.H., Isis E. Fernandez, M.D., Mizuki Nishino, M.D., Yuka Okajima, M.D., Tsuneo Yamashiro, M.D., James C. Ross, M.S., Raúl San José Estépar, Ph.D., David A. Lynch, M.D., John M. Brehm, M.D., M.P.H., Katherine P. Andriole, Ph.D., Alejandro A. Diaz, M.D., Ramin Khorasani, Ph.D., Katherine D'Aco, M.S., Frank C. Sciurba, M.D., Edwin K. Silverman, M.D., Ph.D., Hiroto Hatabu, M.D., Ph.D., and Ivan O. Rosas, M.D., for the COPDGene Investigators*



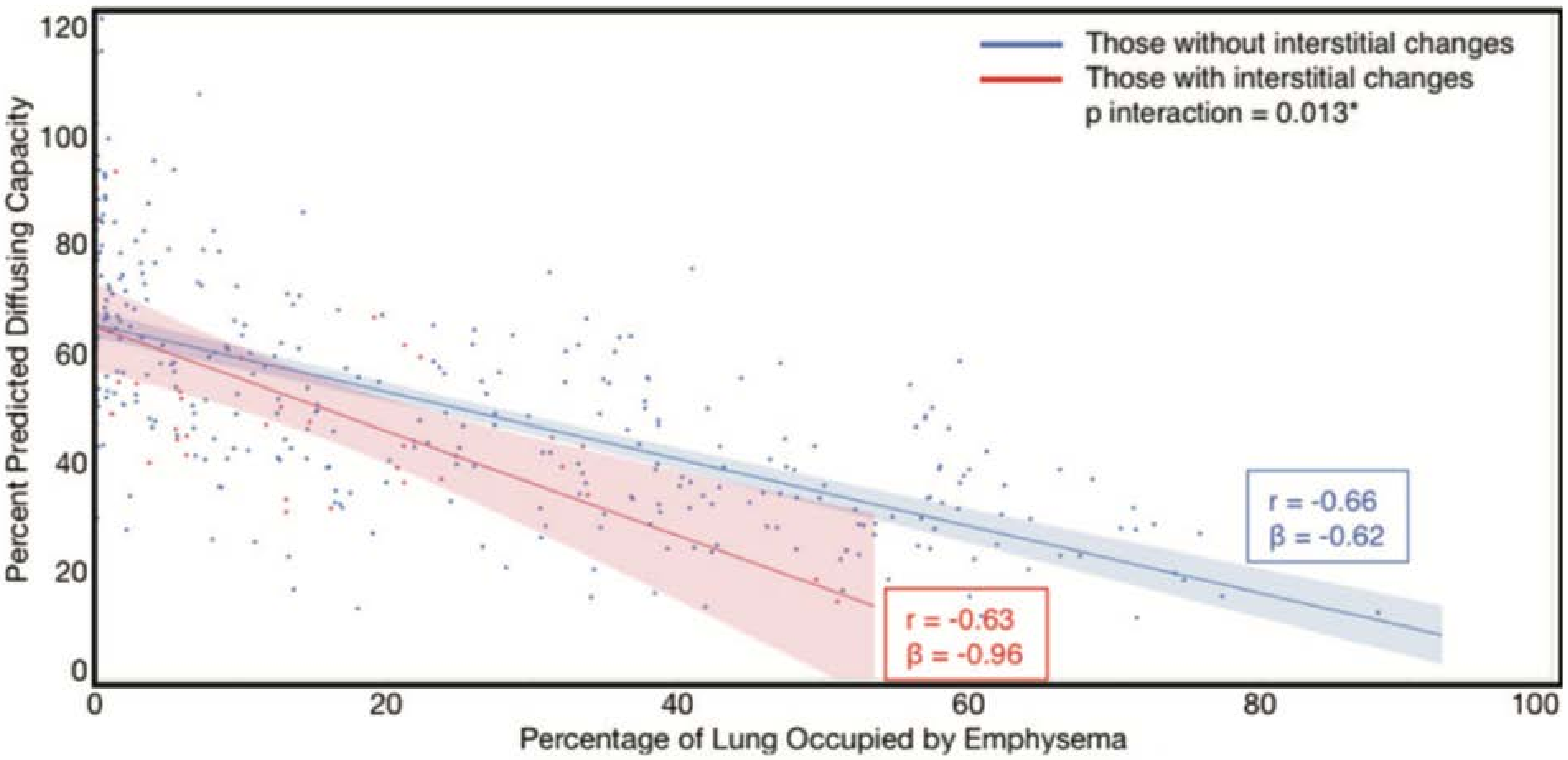
Washko GR et al, N Engl J Med 2011; 364(10):897–906

COPD: emphysema and interstitial lung abnormalities



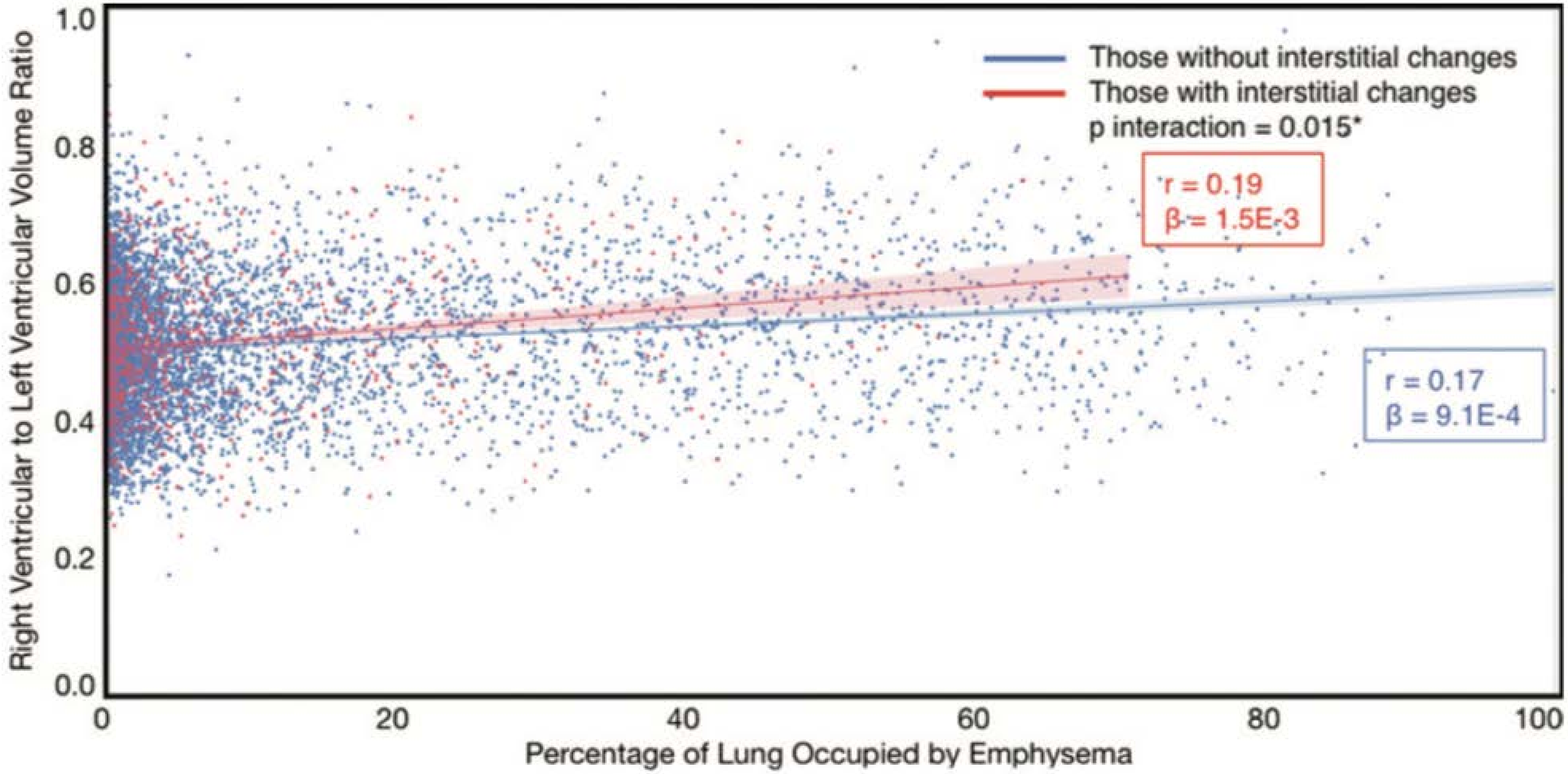
Bozzetti F et al., International Journal of COPD 2016; 11:1087–1096

COPD: emphysema and interstitial lung abnormalities



Ash SY, 2018, Radiology <u>in press</u>

COPD: emphysema and interstitial lung abnormalities

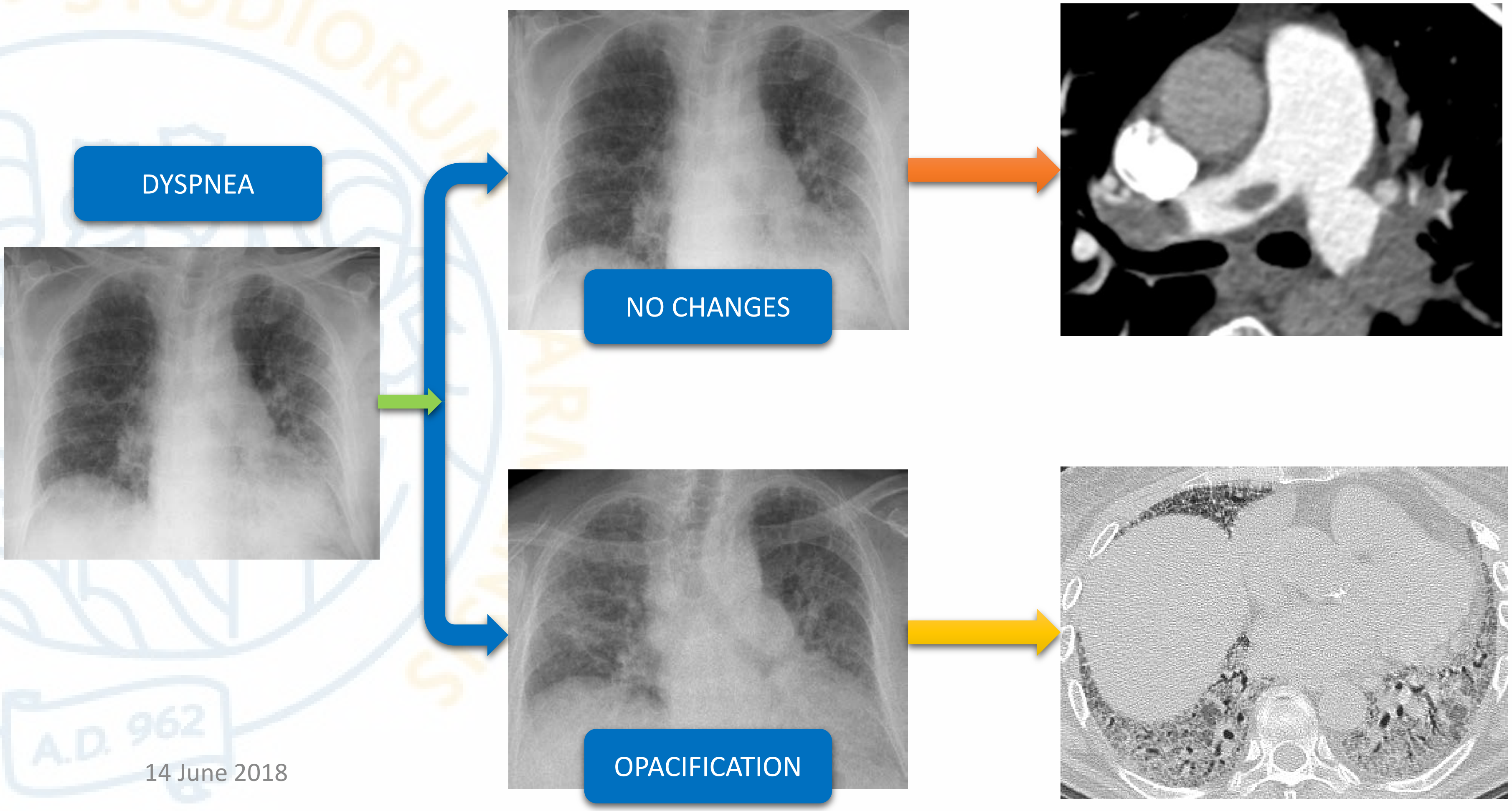


Ash SY, 2018, Radiology in press

Acute onset in Chronic dyspnea – IPF

Acute exacerbation of IPF: dyspnea

Exclusion criteria: left heart failure, pulmonary infection, pulmonary embolism



Collard HR, Am J Respir Crit Care Med. 2007; 176(7):636-43.

Juarez MM, J Thorac Dis 2015; 7(3):499-519.

Ryerson CJ, Eur Respir J 2015; 46(2):512-20.

Acute exacerbation of IPF

- Quite common: incidence 6-16%
- Poor prognosis: 3-month mortality 67%
- Association with surgical biopsy, infections, chemotherapy, radiation therapy
- HRCT does not allow differential between infection and diffuse alveolar damage → bronchoalveolar lavage

Collard HR, Am J Respir Crit Care Med 2007; 176(7):636-43
Juarez MM, J Thorac Dis 2015; 7(3):499-519
Luppi F, Intern Emerg Med 2015; 10(4):401-11
Agarwal R, Eur J Intern Med 2008; 19(4):227-35.

Acute exacerbation of IPF

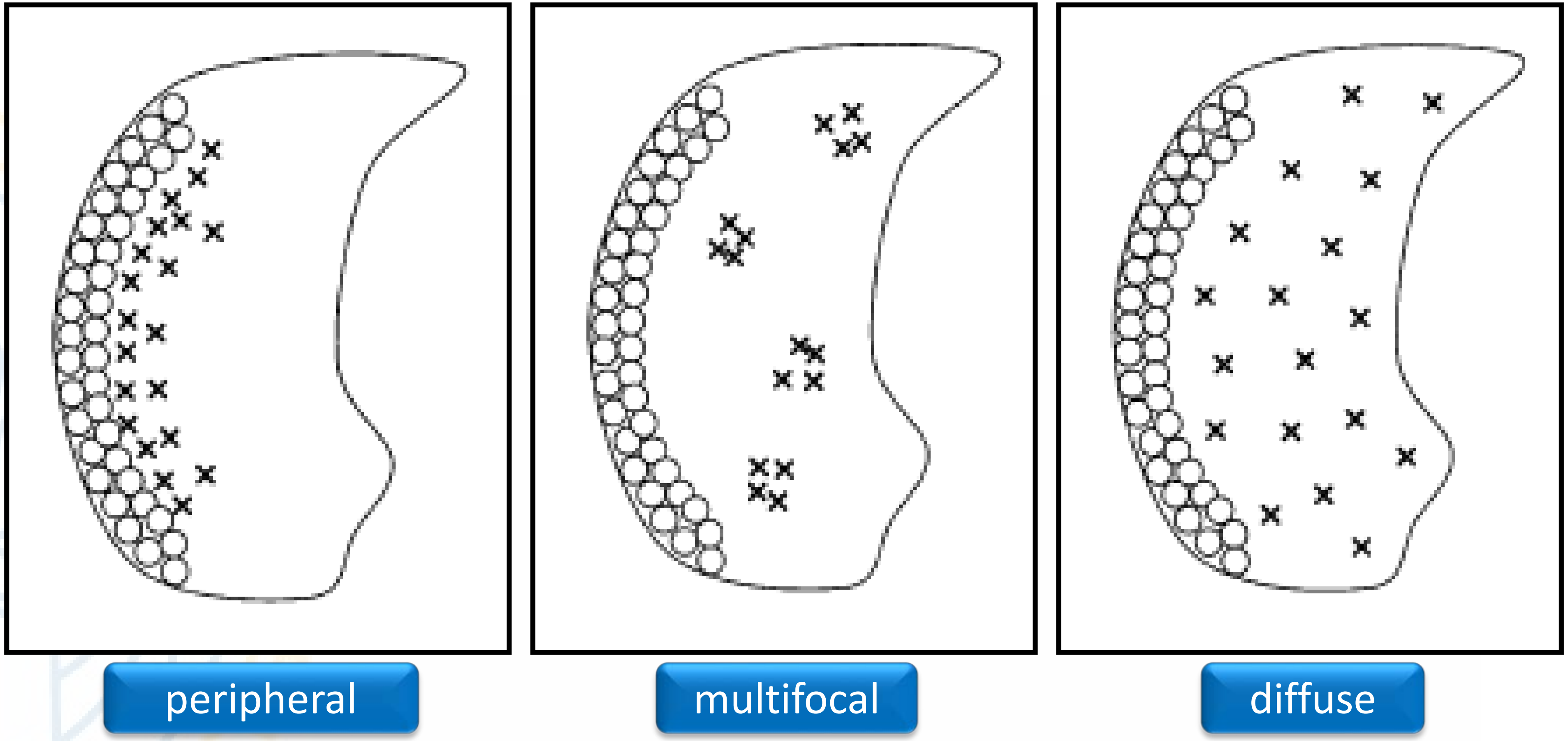
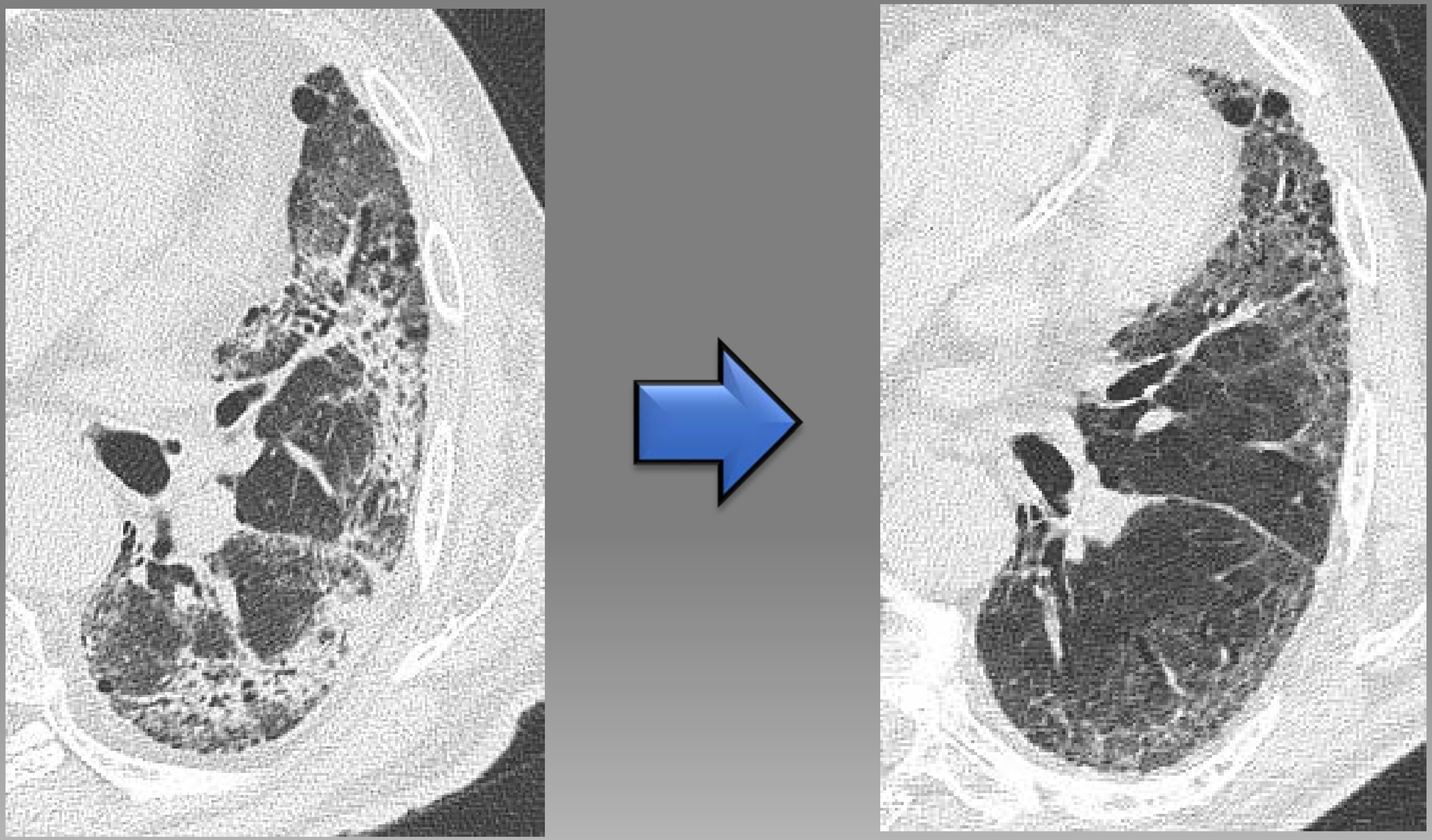
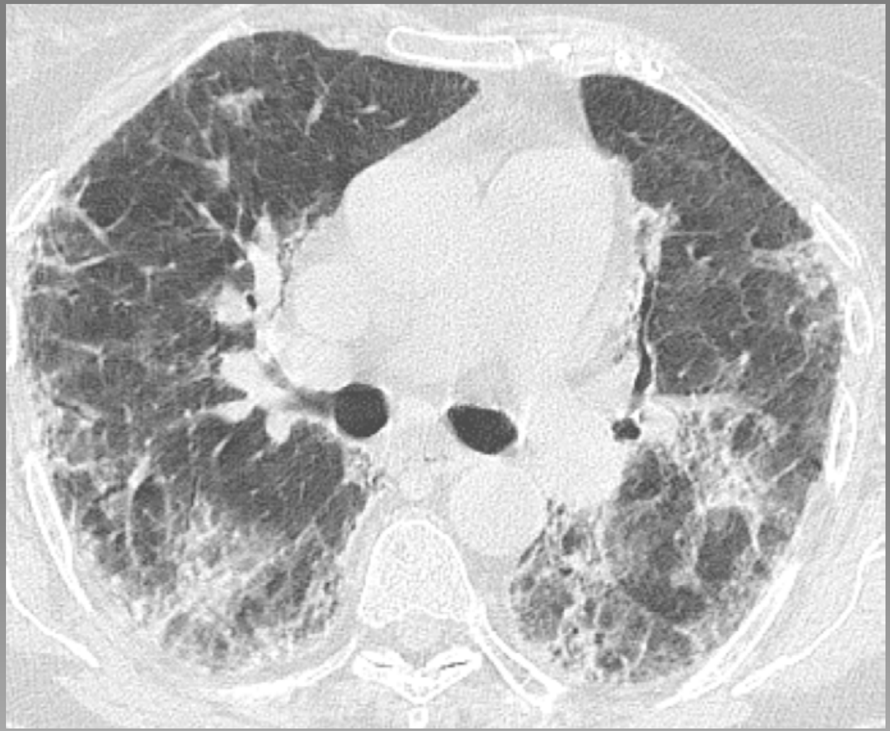


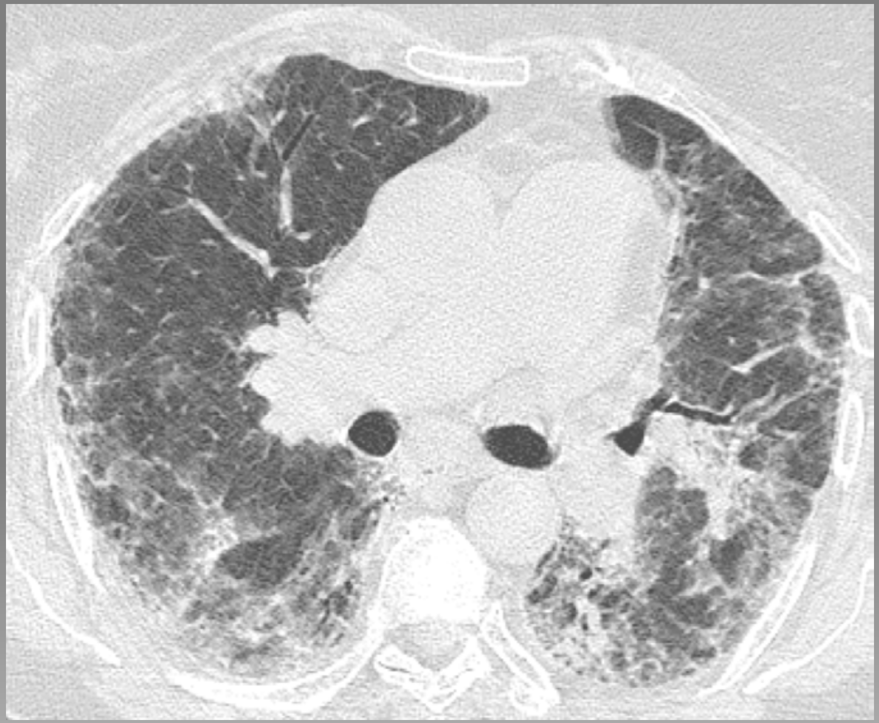
Image from Akira M et al. Computed tomography findings in acute exacerbation of IPF. AJRCCM 2008; 178(4):372-8.

Acute exacerbation of IPF

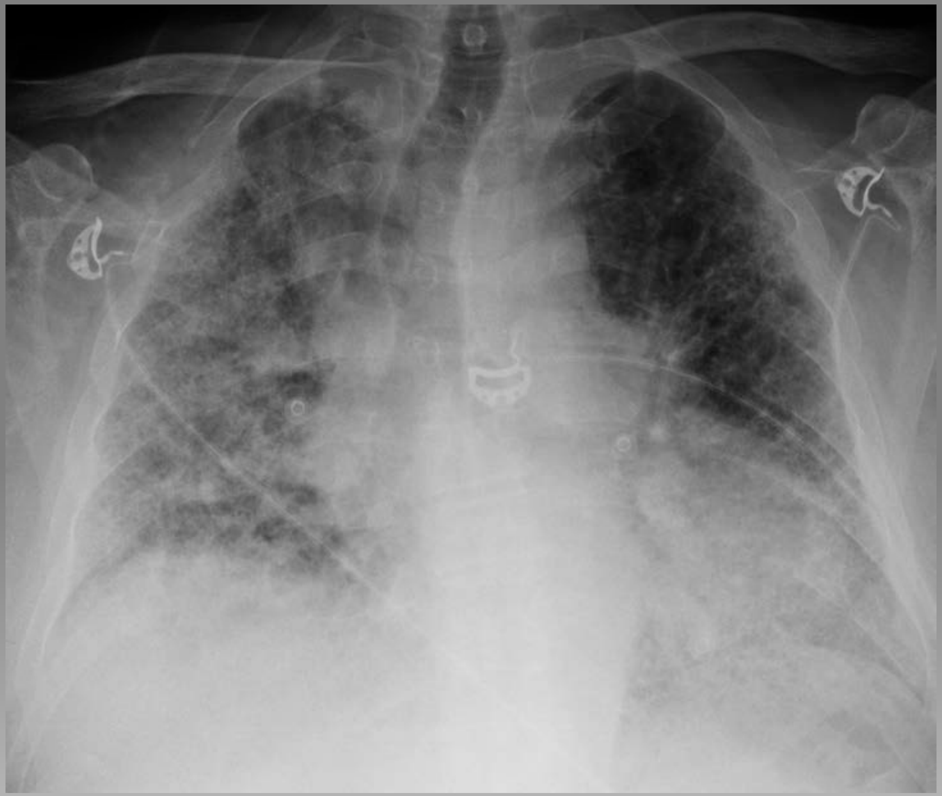


Acute exacerbation of IPF

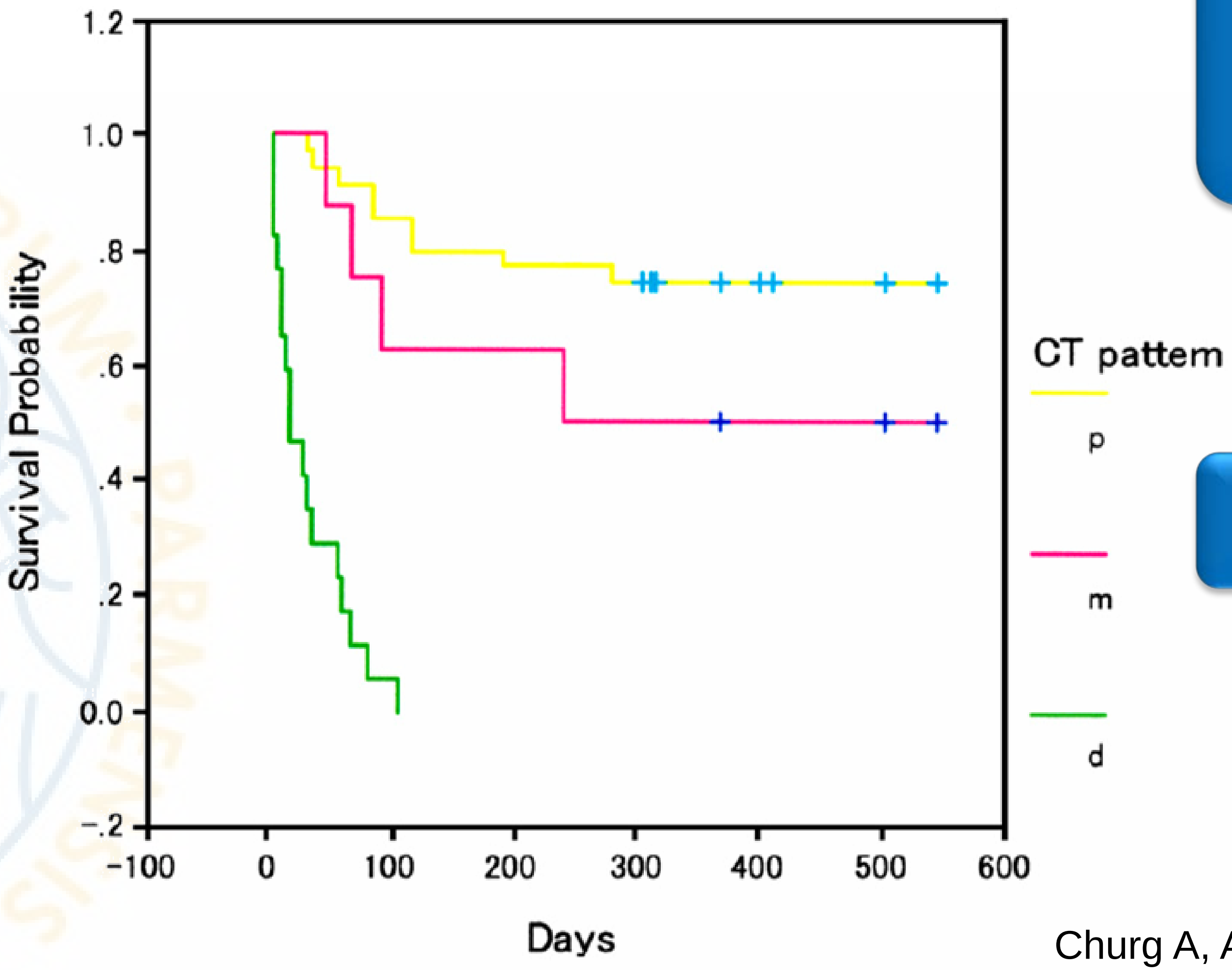




Acute exacerbation of IPF



Acute exacerbation of IPF

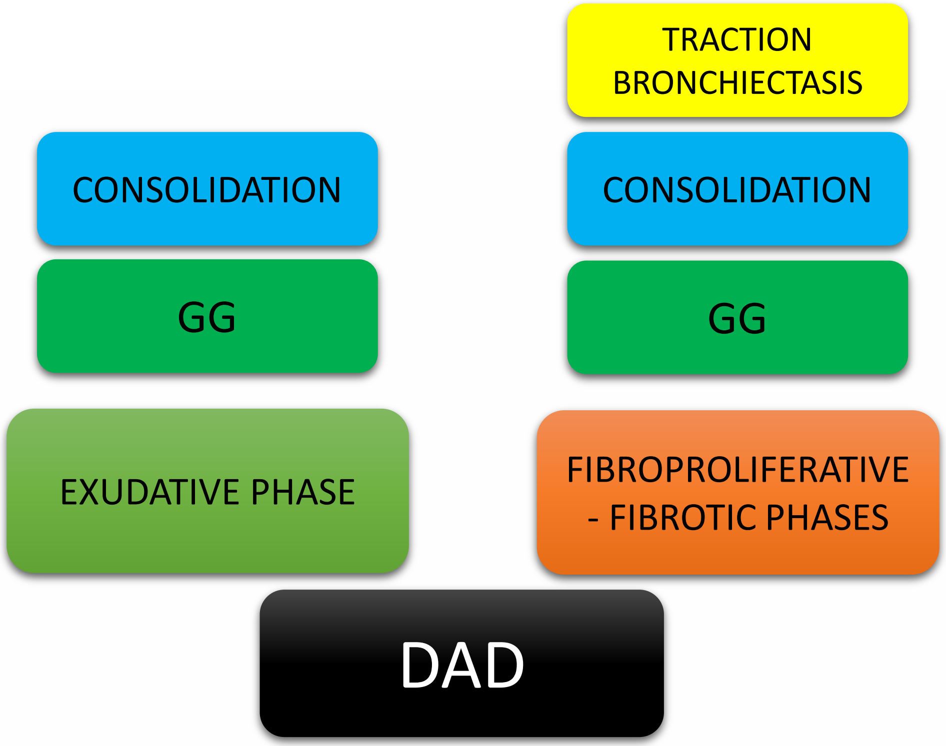


diffuse VS (multifocal & peripheral)
$p < 0.001$

multifocal VS peripheral
$p = 0.39$

Churg A, Am J Surg Pathol. 2007; 31(2):277-84

Acute exacerbation of IPF

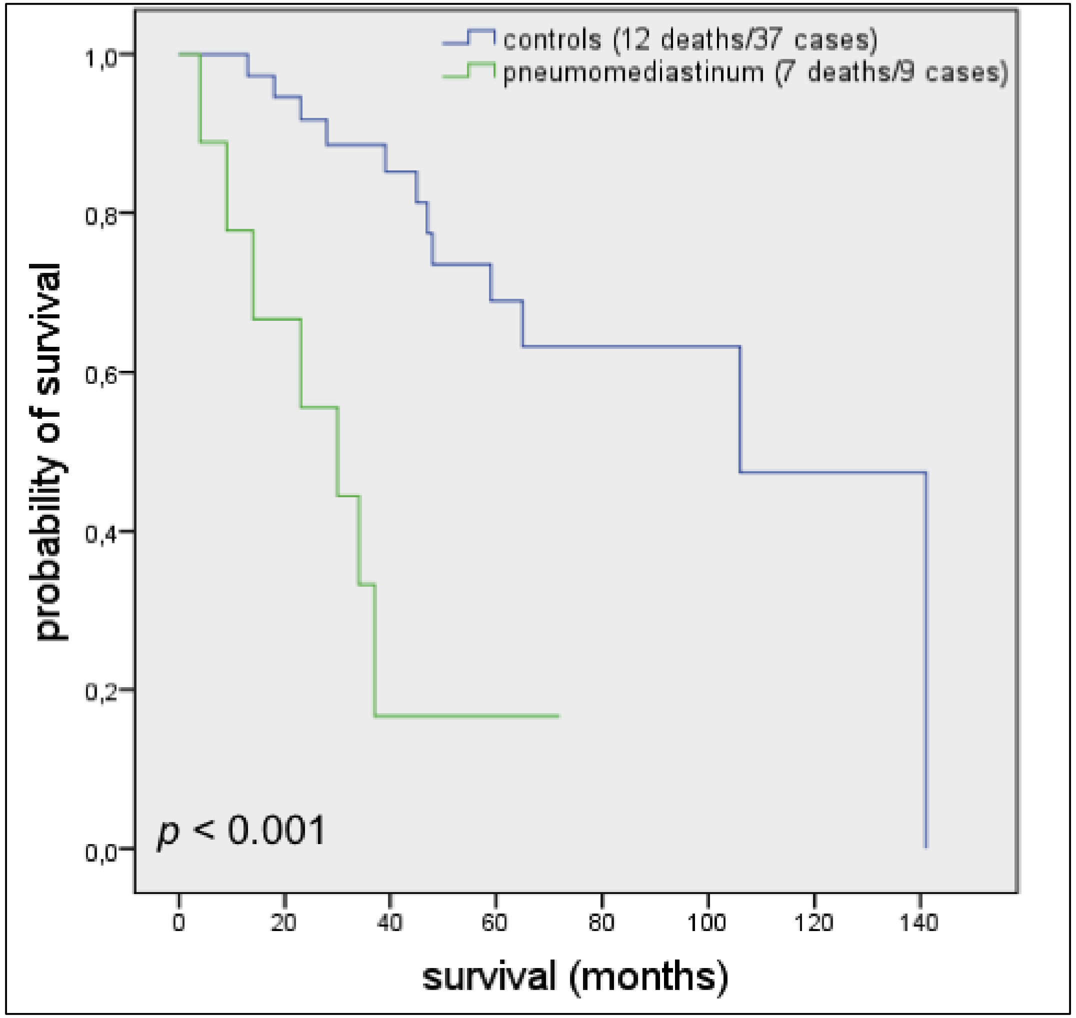


Fujimoto K, Eur Radiol 2012; 22(1):83-92.
Oda K, Respir Res 2014;15:109.

Ichikado K, Am J Respir Crit Care Med 2002;165(11):1551-6.

Pneumomediastinum in IPF

- Incidence, 5%
- New onset of dyspnea, 80%
- Potential predictor of mortality

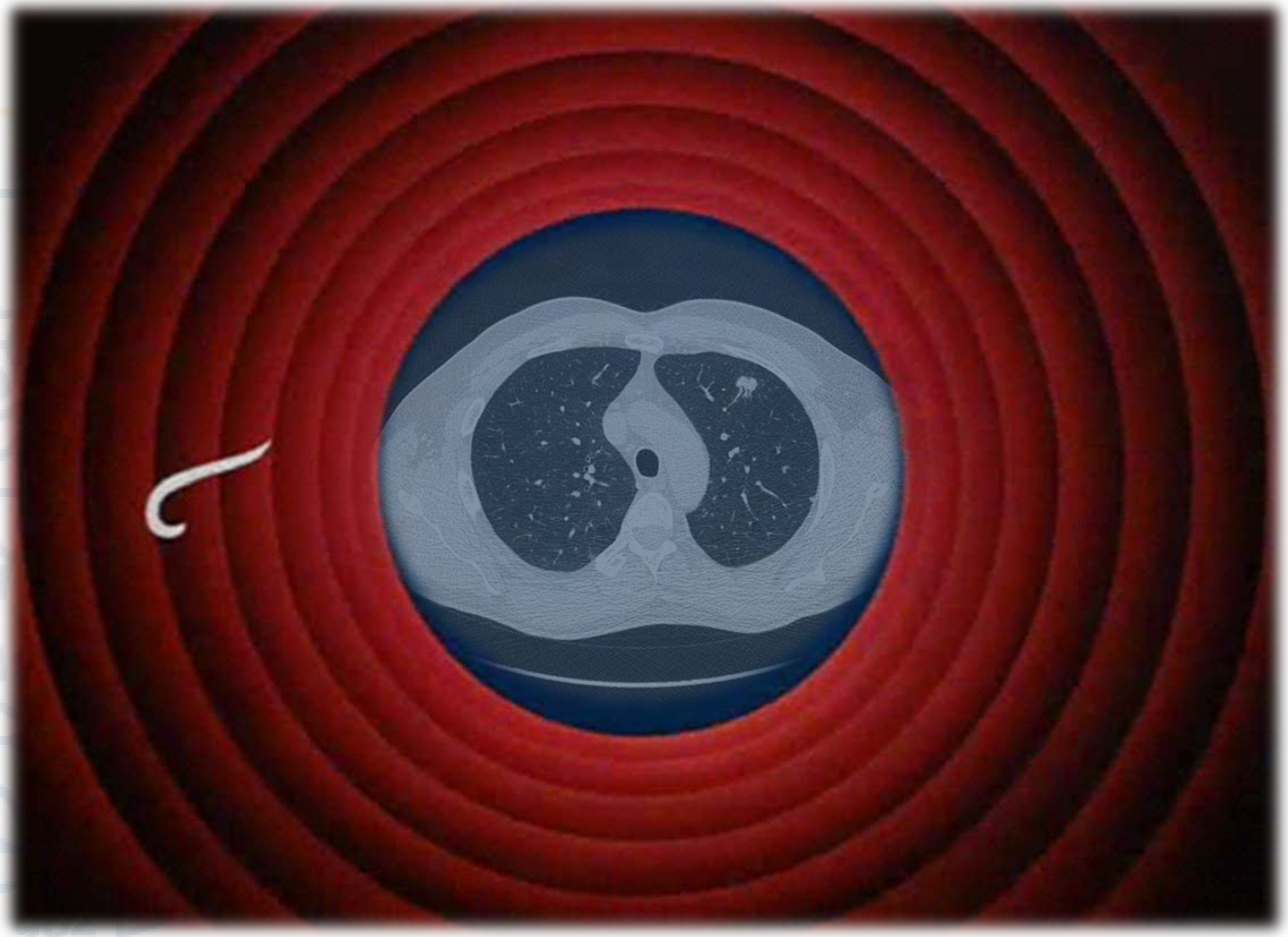


Colombi D et al., Respiration 2016; 92(1):25-33

Conclusions

- Chest imaging in dyspnea
  - is a main step for diagnosis of acute dyspnea causes (pulmonary embolism, asthma complications, drug toxicity)
  - can steer treatment in chronic dyspnea (COPD)
  - for acute onset in chronic dyspnea has diagnostic and prognostic significance (IPF acute exacerbations)

Ruolo dell’ Imaging nella Dispnea



Thanks to: Mario Silva, MD, PhD, Radiologist

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Da un semplice prelievo di sangue la diagnosi di un tumore al polmone, identificato a uno stadio fino a due anni più precoce di quanto sia possibile utilizzando la Tac spirale, il più avanzato degli strumenti diagnostici oggi a disposizione.