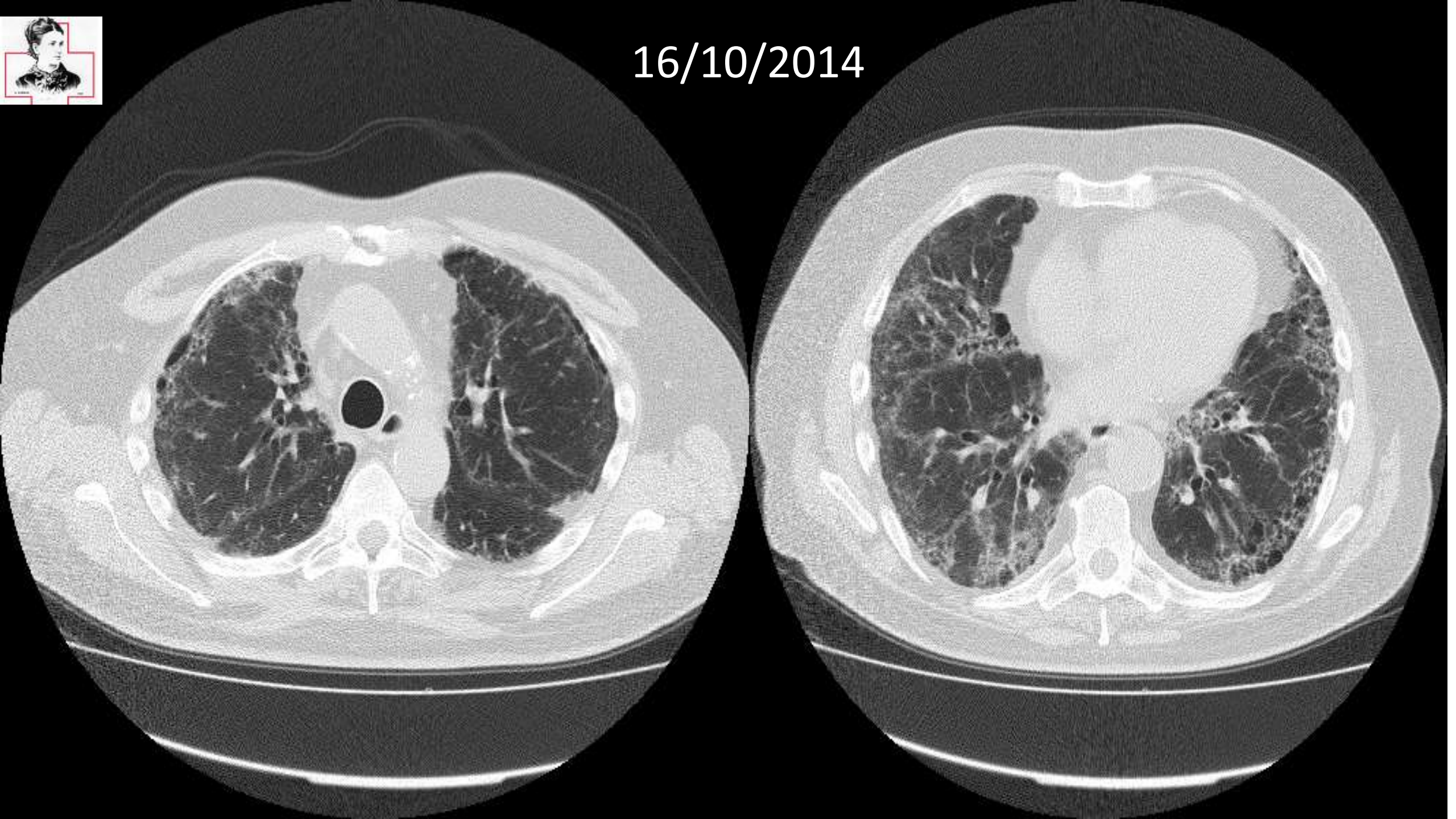
IPF AND LUNG CANCER

Distinct horns of the same devil

Αργύρης Τζουβελέκης
Πνευμονολόγος
argyrios.tzouvelekis@fleming.gr
First Respiratory Department, SOTIRIA Hospital

First case

- 78-yrs old, male, ex-smoker (70 p/yrs), DOE (mMRC II/IV)
- GERD symptoms
- No familial Hx/No exposure
- Medical Hx: Arterial hypertension
- No Raynaud, arthralgias or myalgias,
- + Velcro type crackles: + clubbing
- Negative immunologic profile
- FVC: 56%pred, TIF: 81, TLC: 52% pred, DLCO: 48% pred
- 6MWD: 440 m, 96% - 84%
- ECHO: RVSP: 28mmHg
- BAL: 88% ΜΦ, 8%L, 2% Eos, 2% Polys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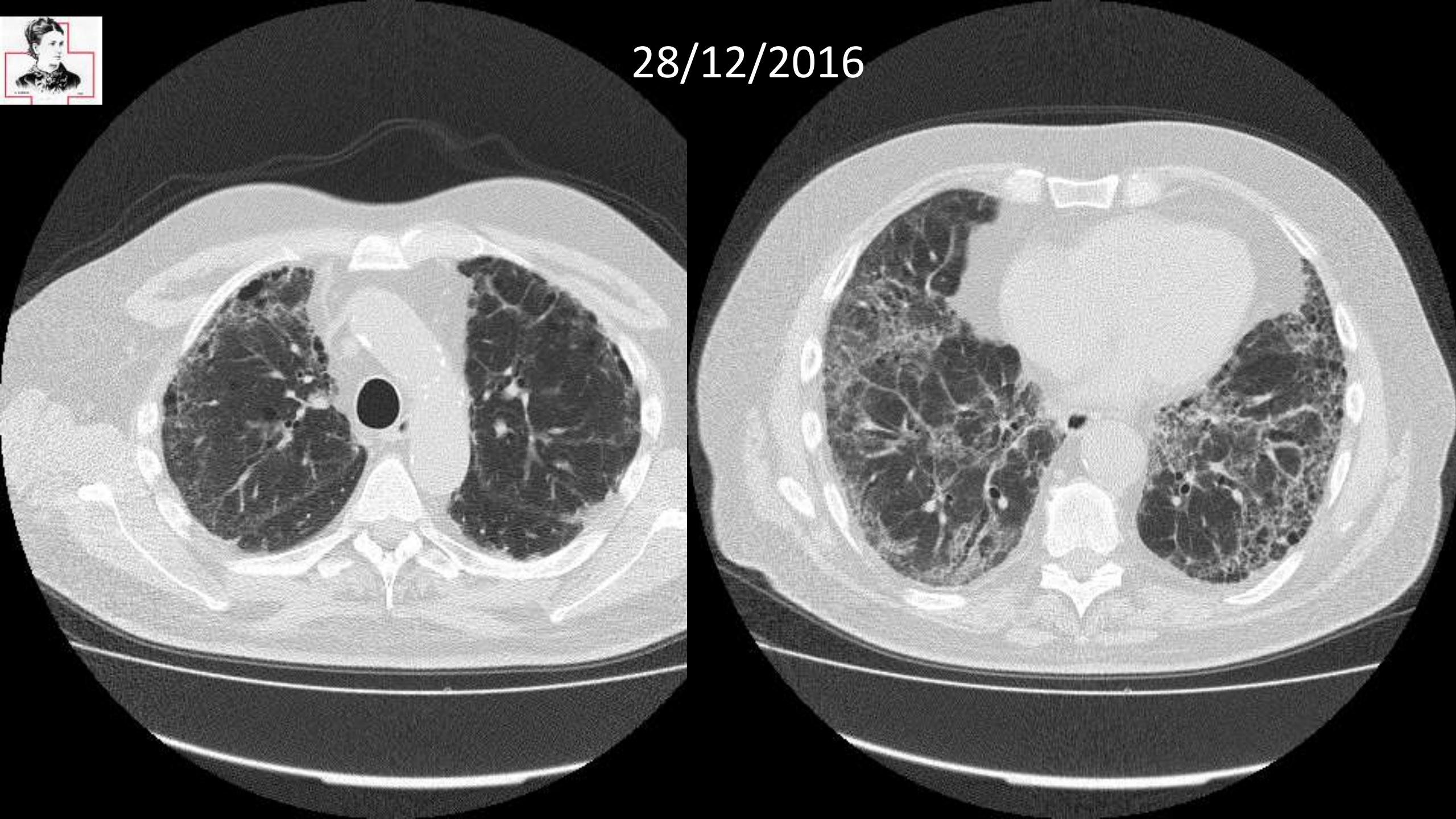
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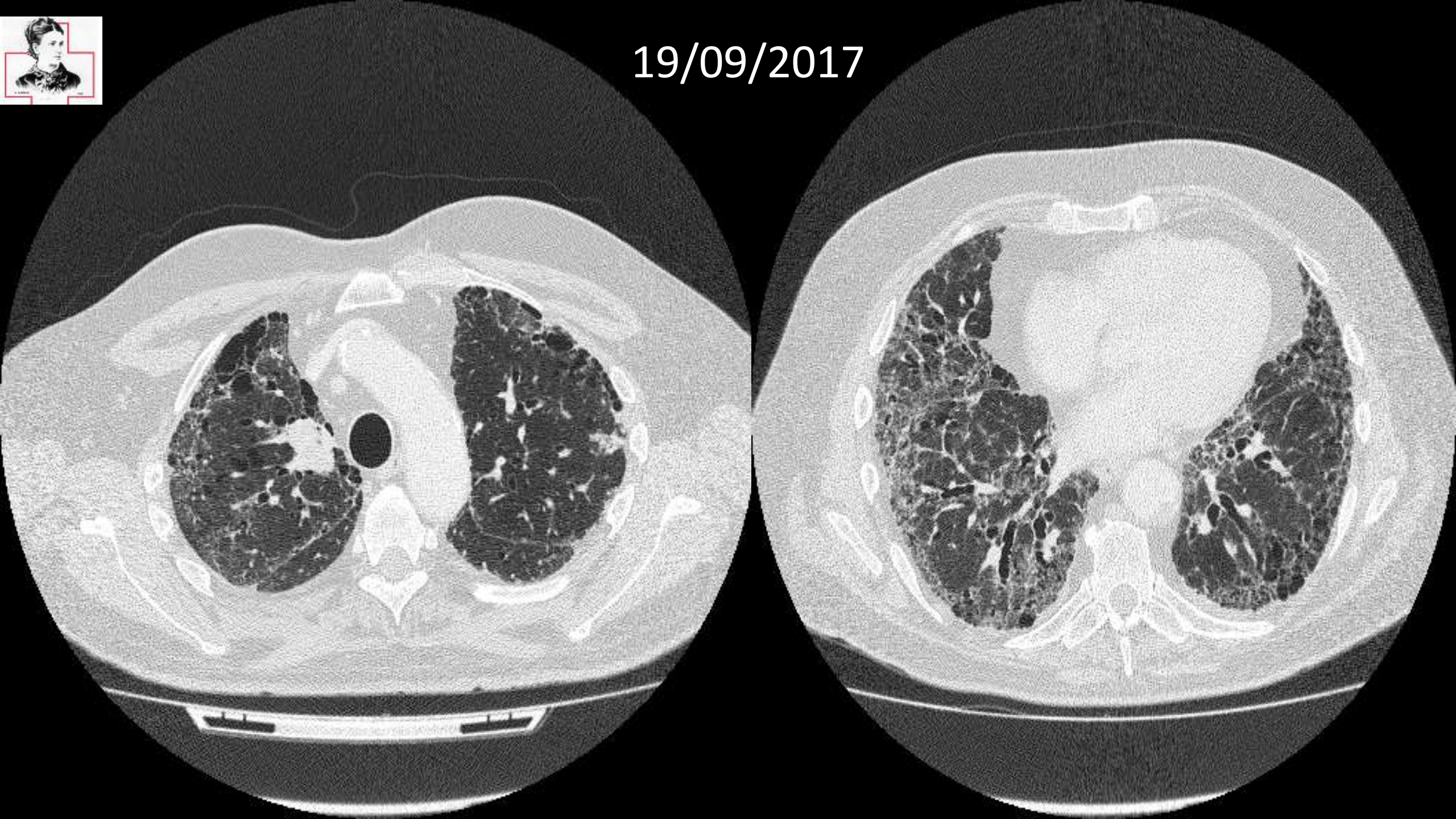
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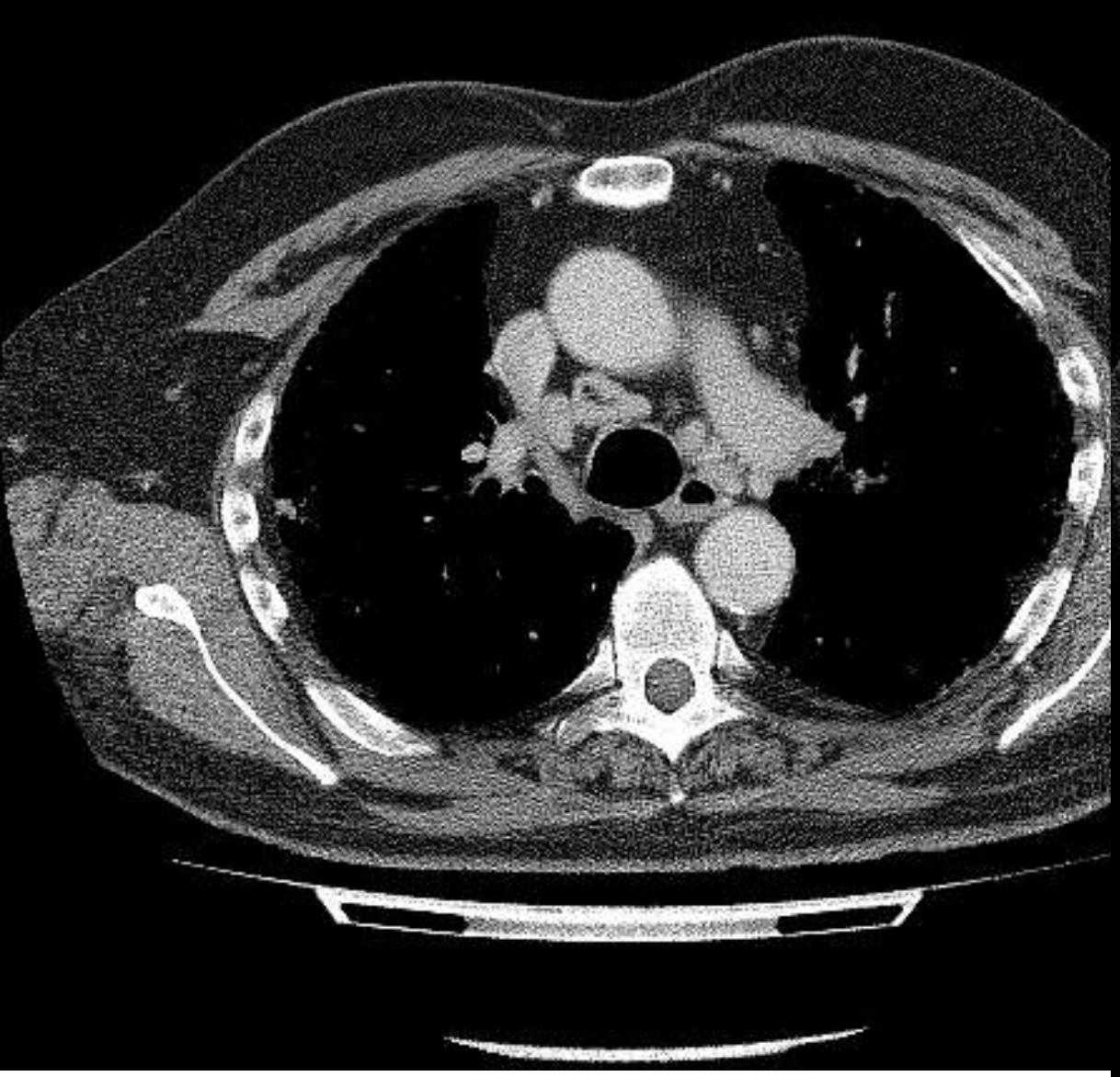
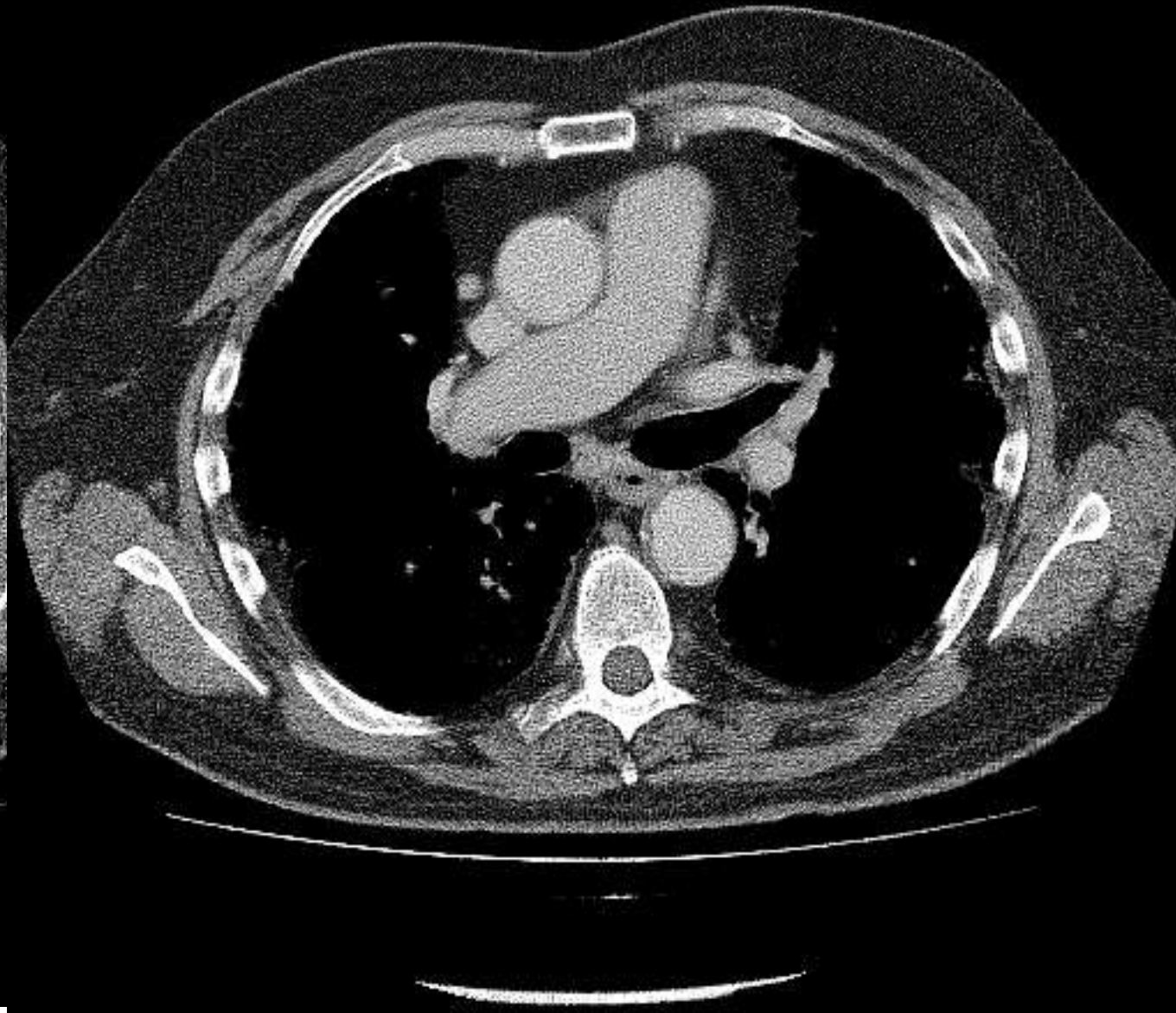
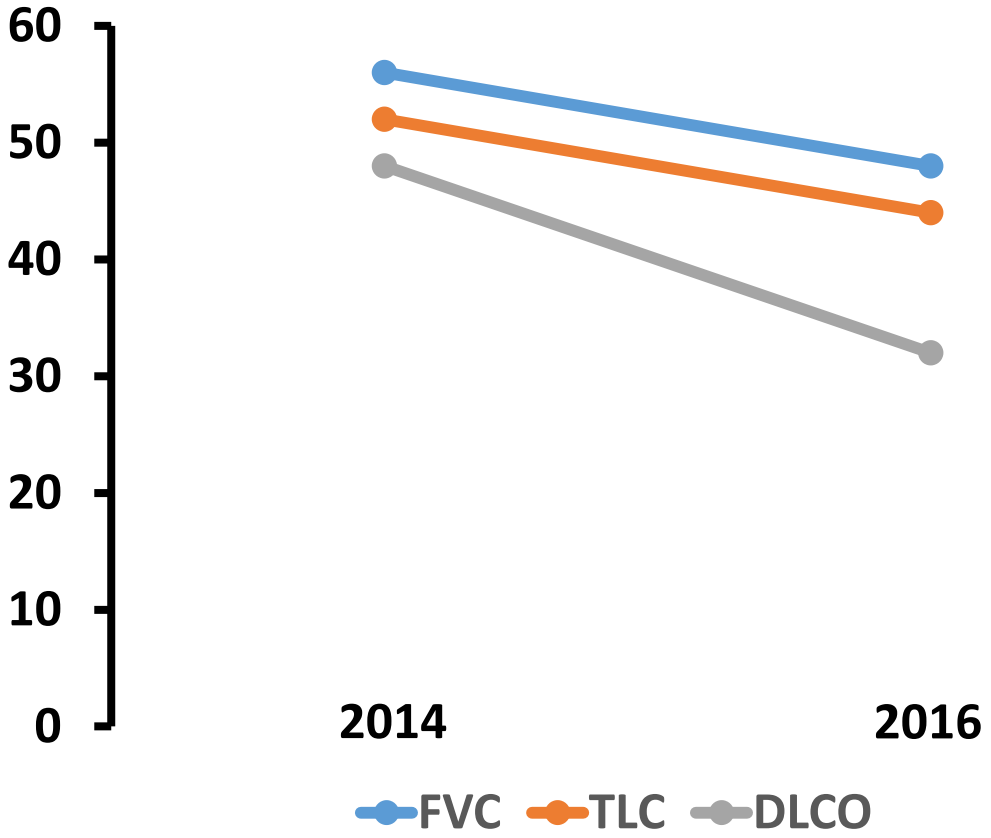
EBUS: Mass, 4R, 7 (+): SQUAMOUS – T2bN2M0-IIIA





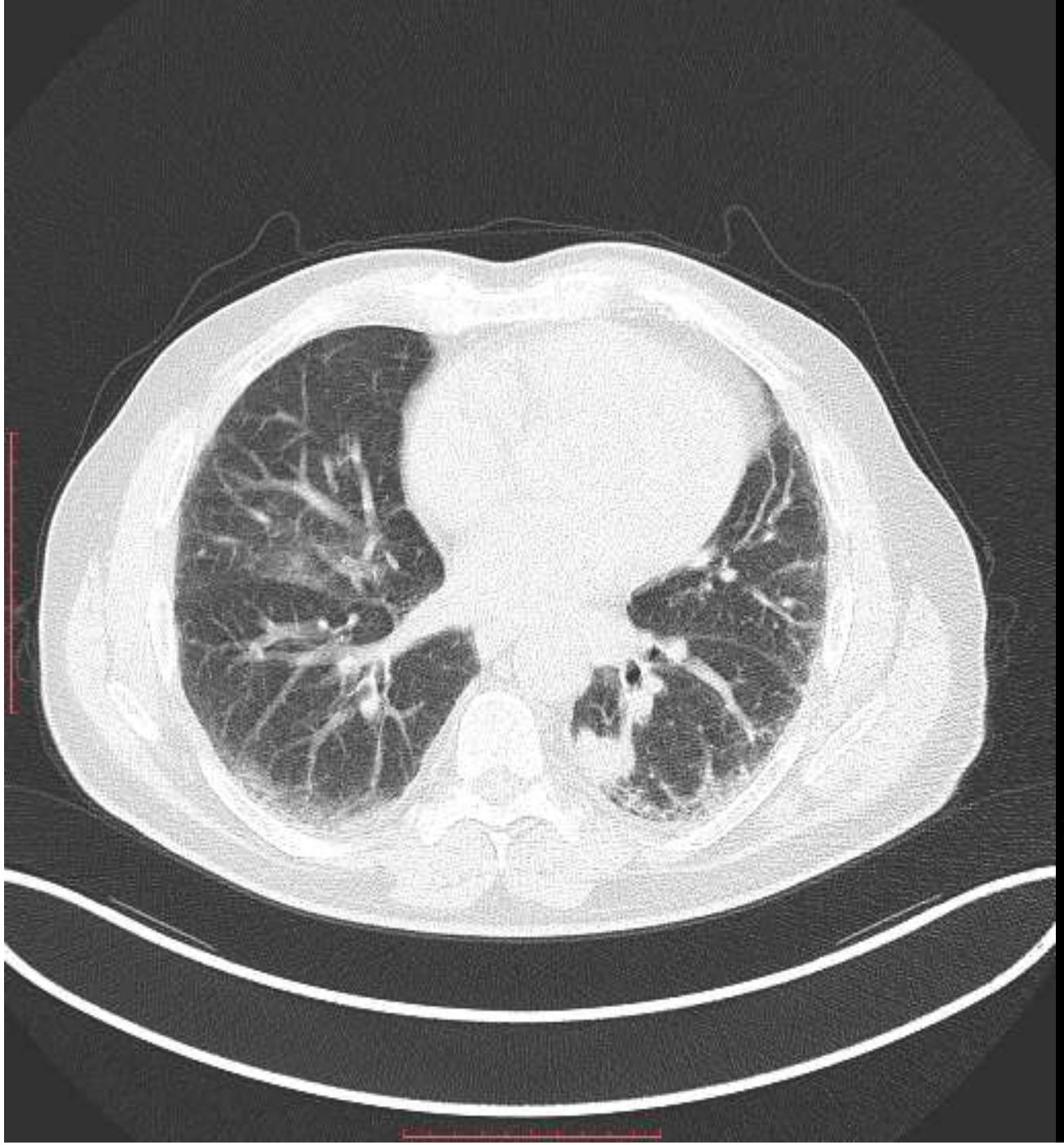
Management

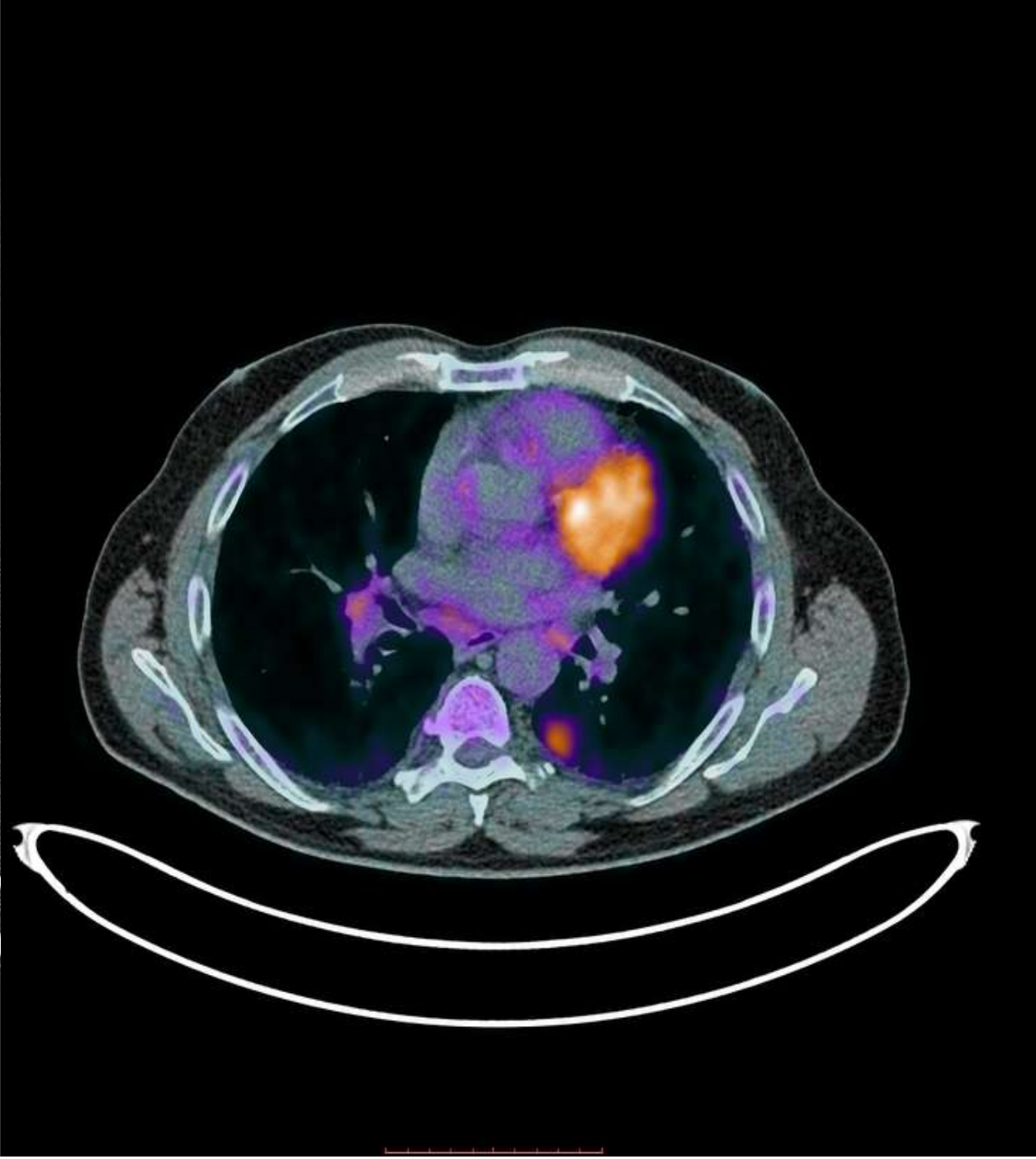


- Functional deterioration
- Severe disease status
- Male gender
- IIIA-borderline
- 80 yrs
- Nintedanib +CARBOPLATIN+ PACLITAXEL

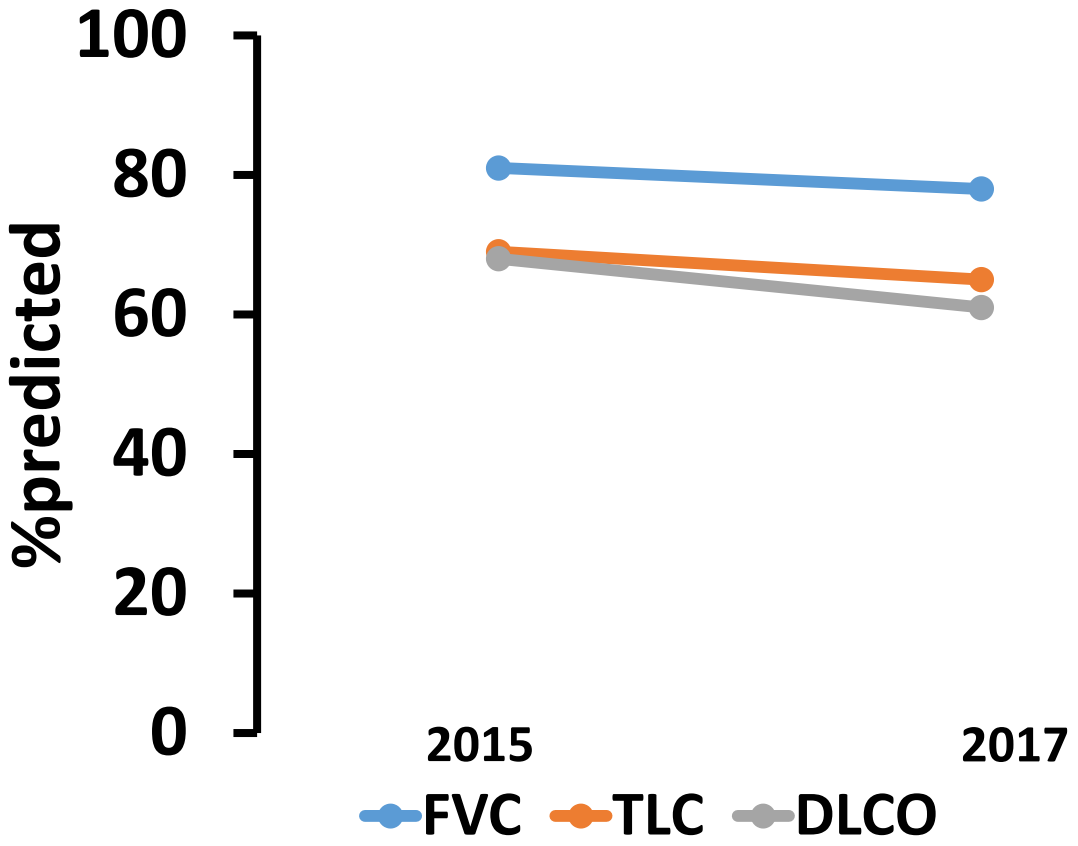
Second case

- 65 yrs –ex-50 p/yrs– IPF last 2.5 yrs – under OFEV last 2 yrs
- Negative immunologic profile
- FVC: 78%pred, TIF: 85, TLC: 65% pred, DLCO: 61% pred
- 6MWD: 480 m, 96% - 90%
- ECHO: RVSP: 24mmHg
- BAL: 85% ΜΦ, 10%L, 2% Eos, 3% Polys
- 6 mo- HRCT follow-up





Management



- FNB – Adenocarcinoma
- EBUS/TBNB – N0 - T2aN0M0-Ib
- Moderate (stable) disease
  Middle age – Male gender - Low TNM
- Lung surgery – Segmentectomy

Third case

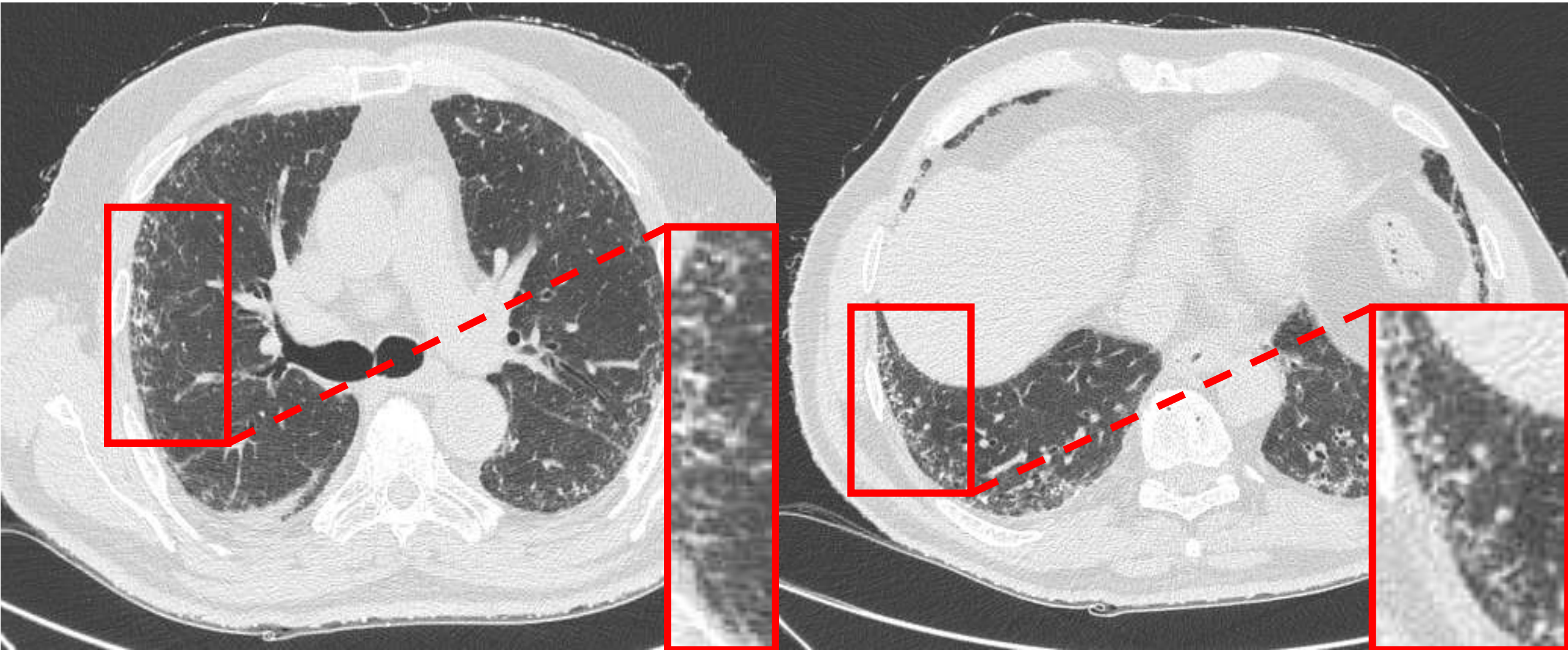
History

- 80-yrs old, male, ex-smoker (70 p/yrs), DOE (mMRC II/IV)+ GERD symptoms
- No familial Hx/No exposure
- Medical Hx: Arterial hypertension
- No Raynaud, arthralgias or myalgias,
- + Velcro type crackles: + clubbing
- Negative immunologic profile
- FVC: 62%pred, TIF: 82, TLC: 52% pred, DLCO: 29% pred
- 6MWD: 340 m, 96% - 84% - LTOT: 2lt/min
- ECHO: RVSP: 28mmHg
- BAL: 88% MΦ, 8%L, 2% Eos, 2% Polys
- Nintedanib Rx (2 years) – Gradual Progression
- FVC: 54%pred, TIF: 84, TLC: 48% pred, DLCO: 22% pred

HRCT

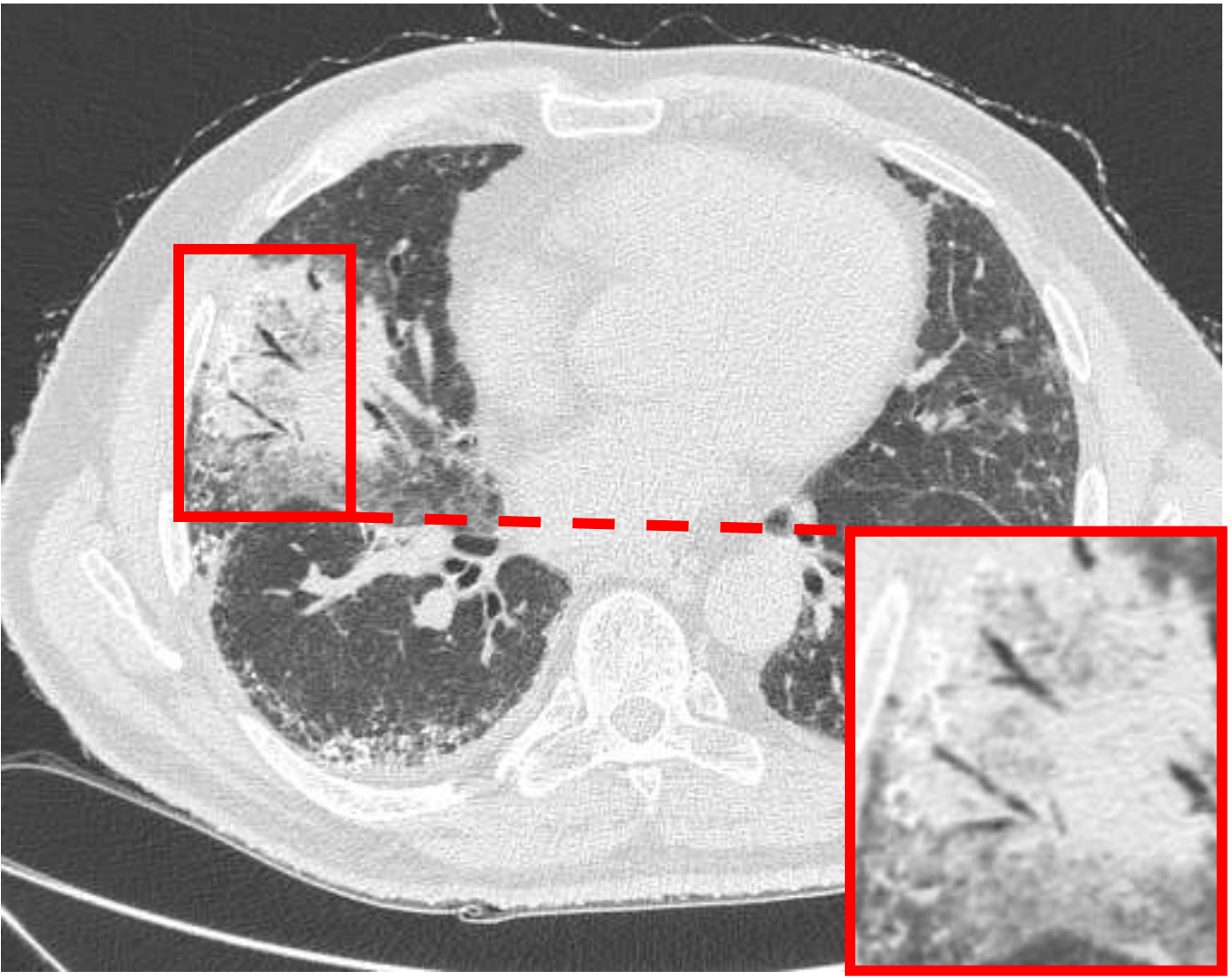
19/08/2016

19/08/2016



HRCT

19/08/2016



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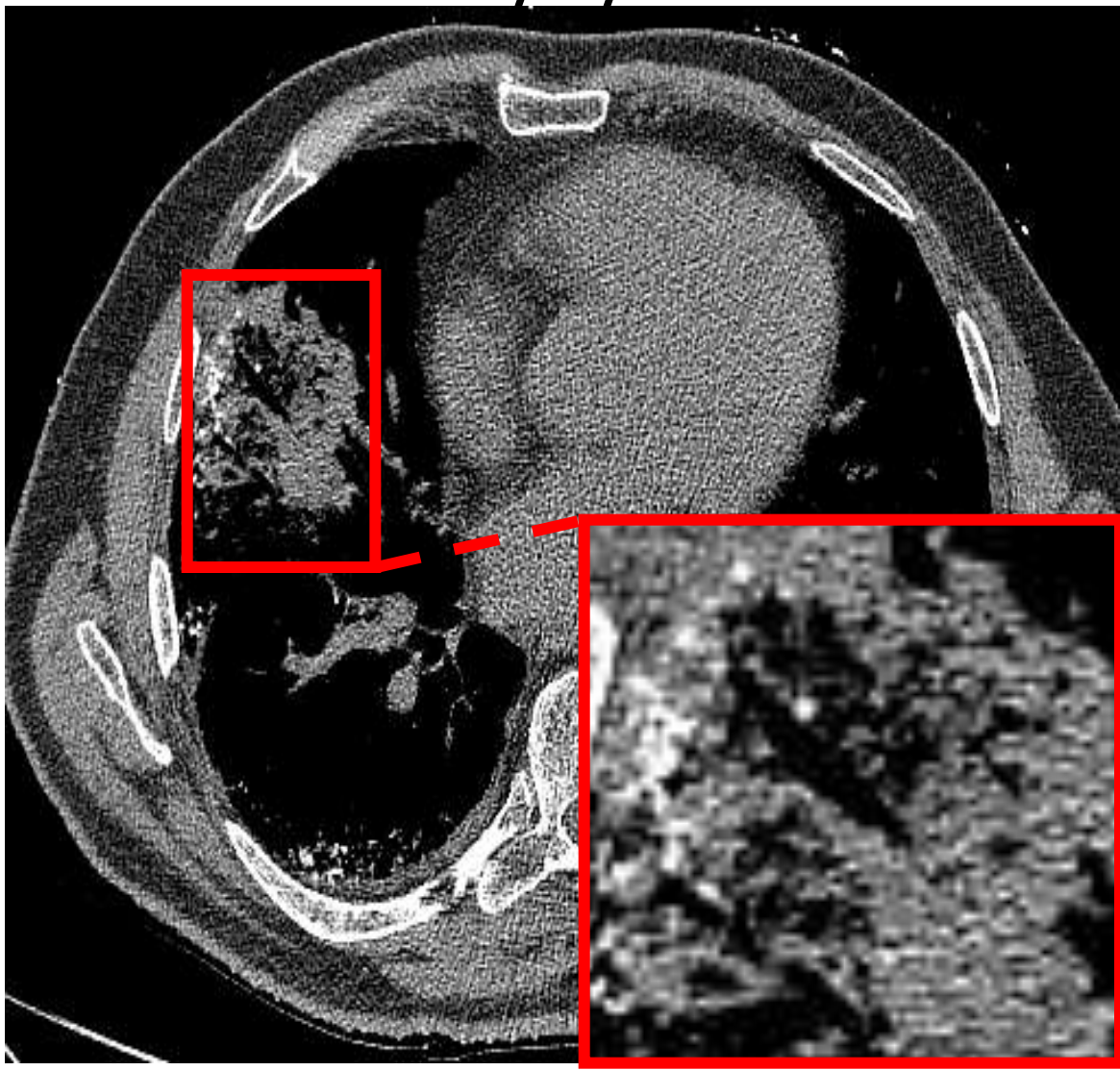
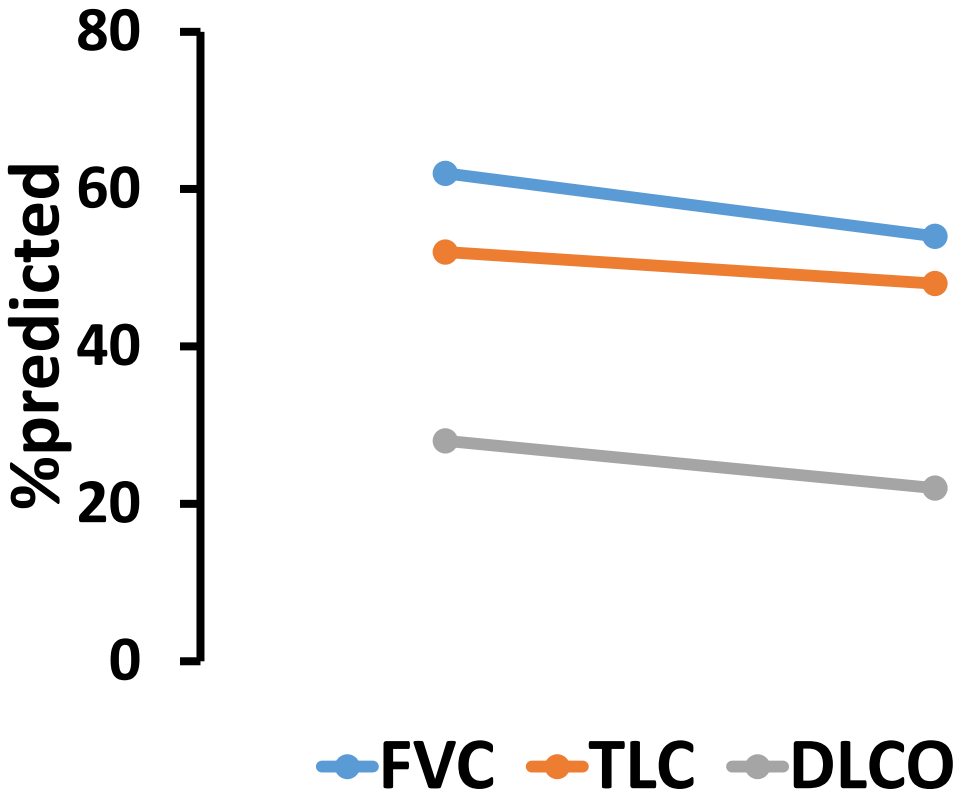


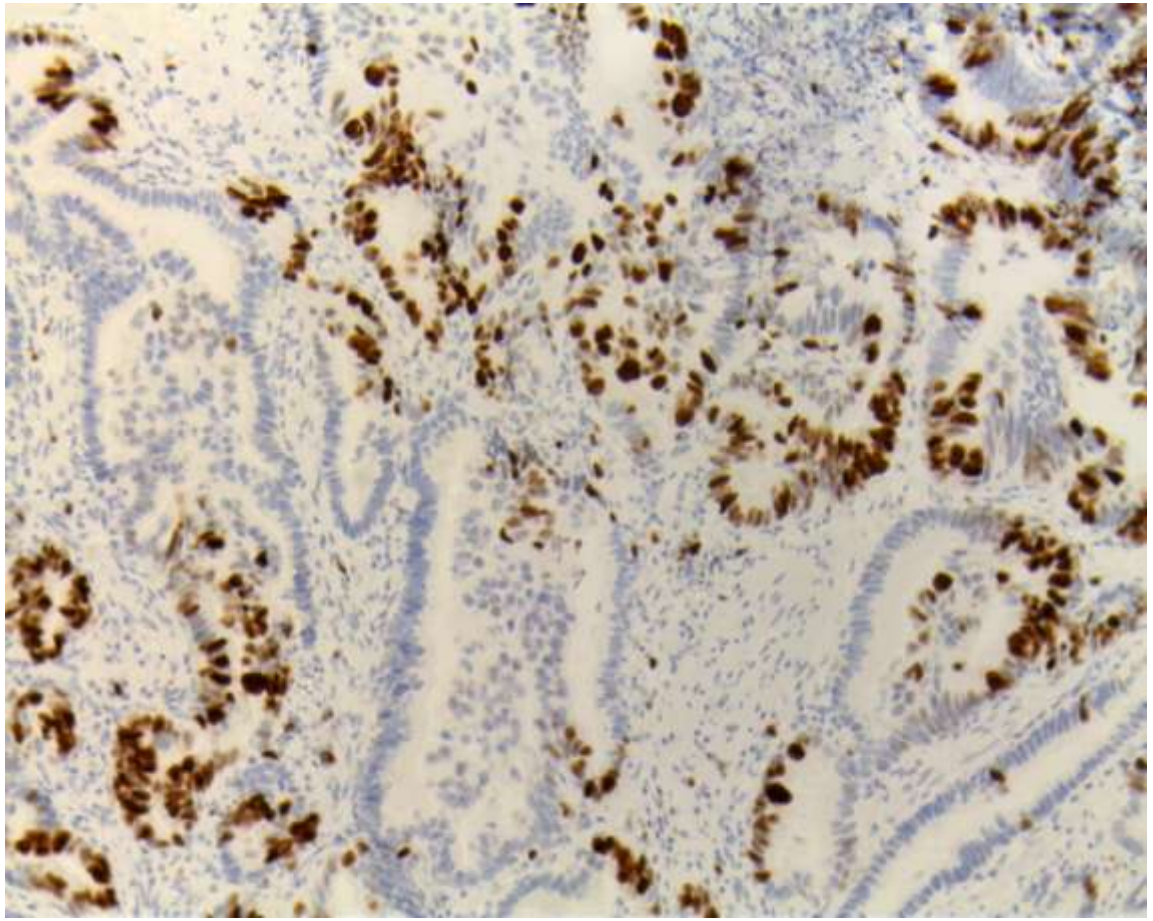
Management



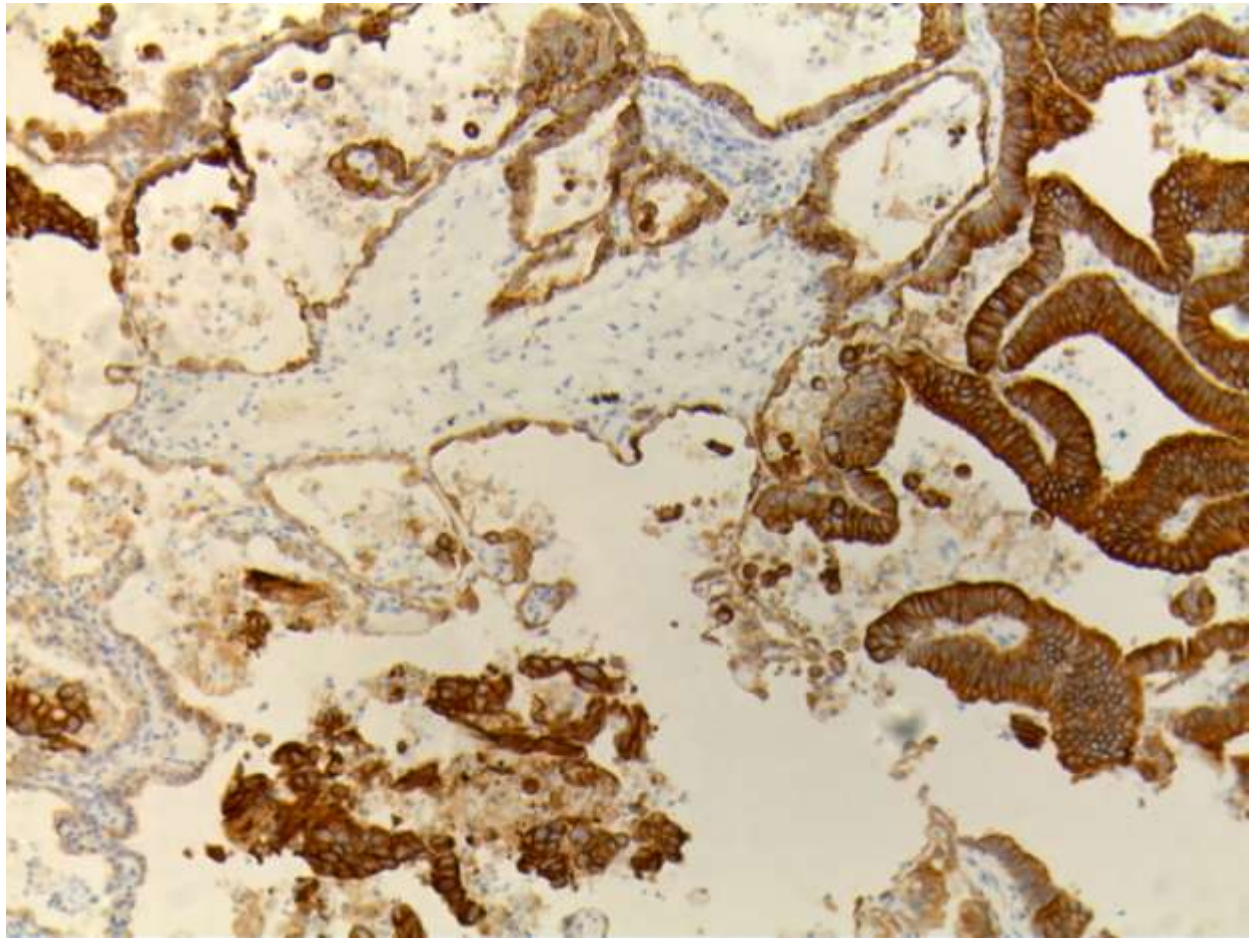
- FNB – Adenocarcinoma
- EBUS/TBNB – N1 – T4N1M0-IIIA
- Disease progression-Elderly pt – Male gender - IIIA
- MICO

Pathology

Hyper-proliferating – Ki67 + Epithelium



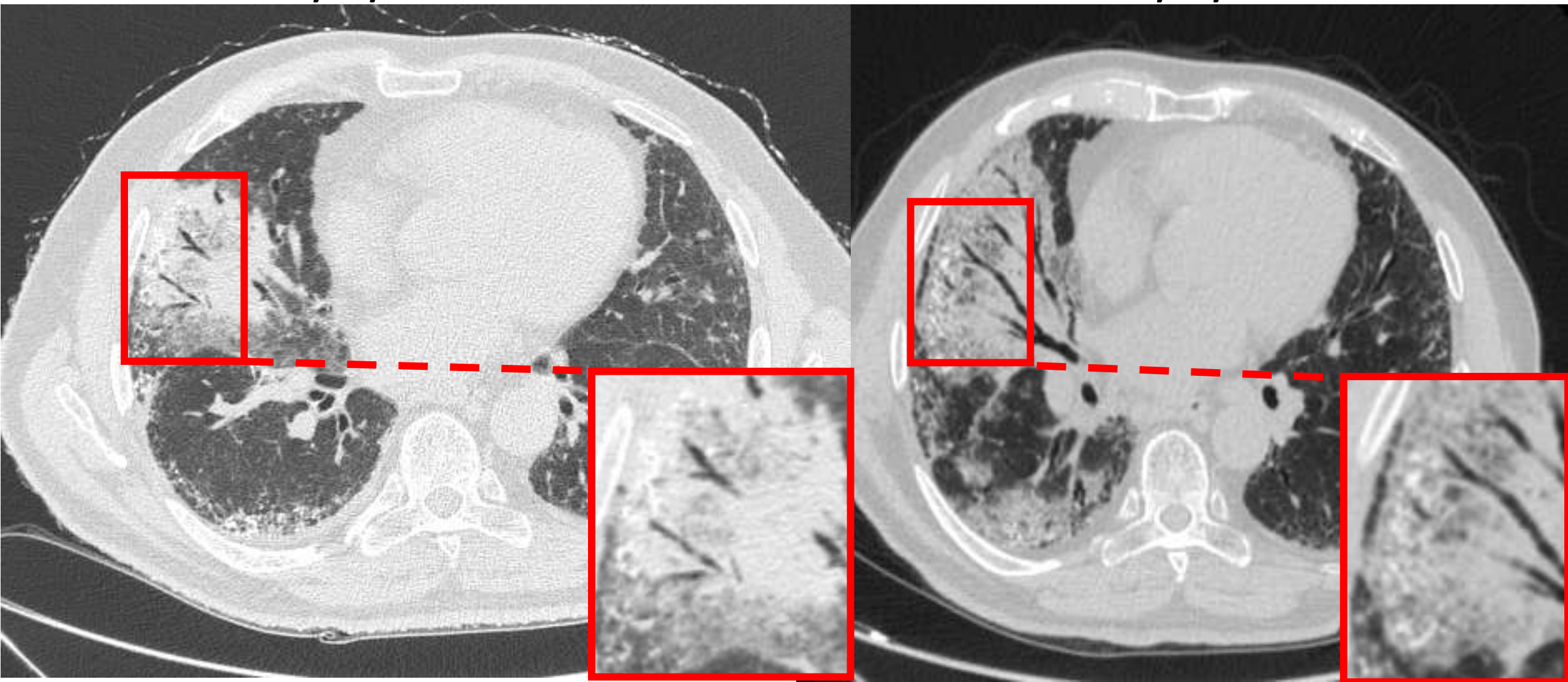
CK19 + AEC + Adenoid structures (ADC)



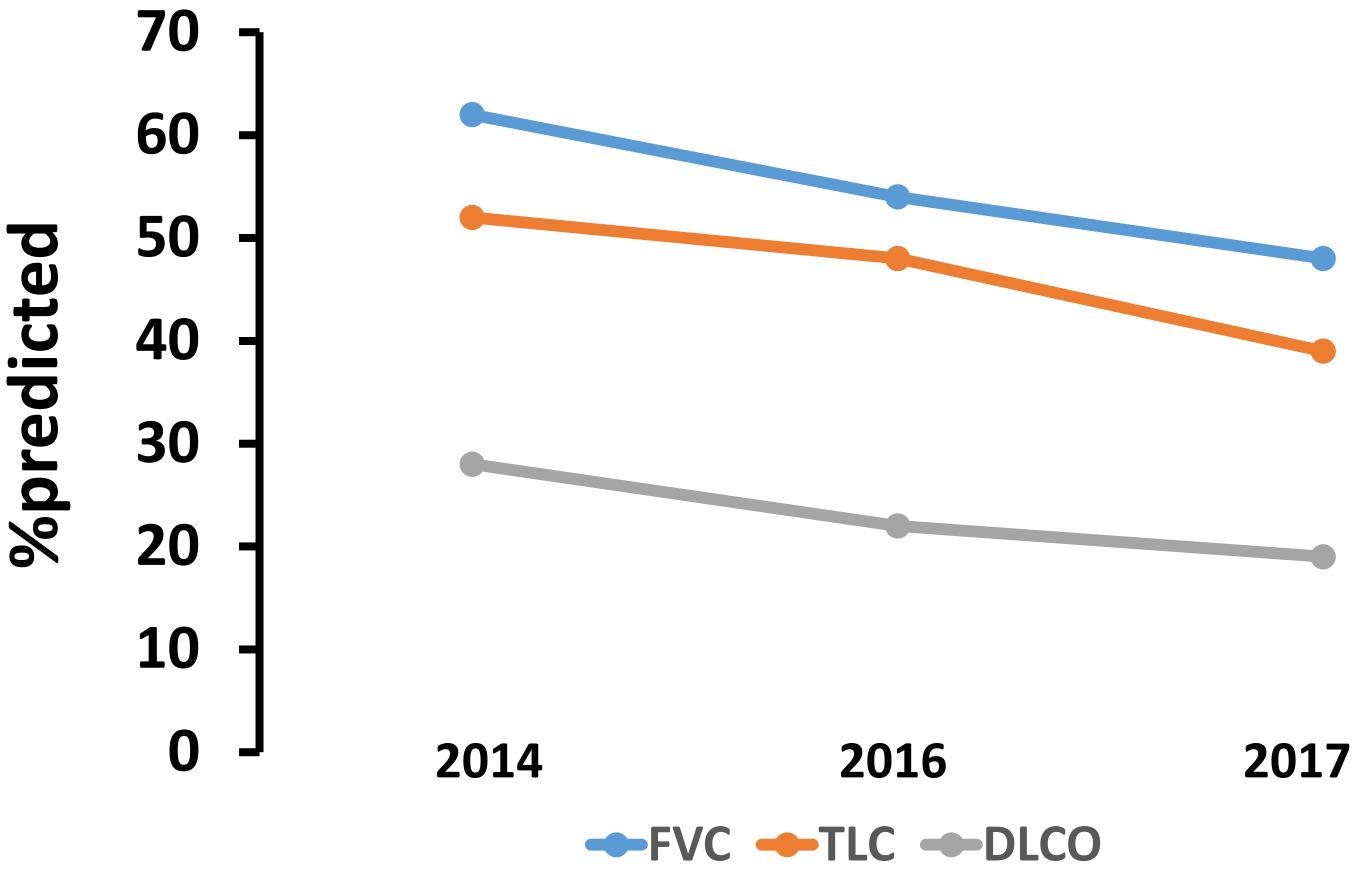
HRCT

19/08/2016

28/11/2017



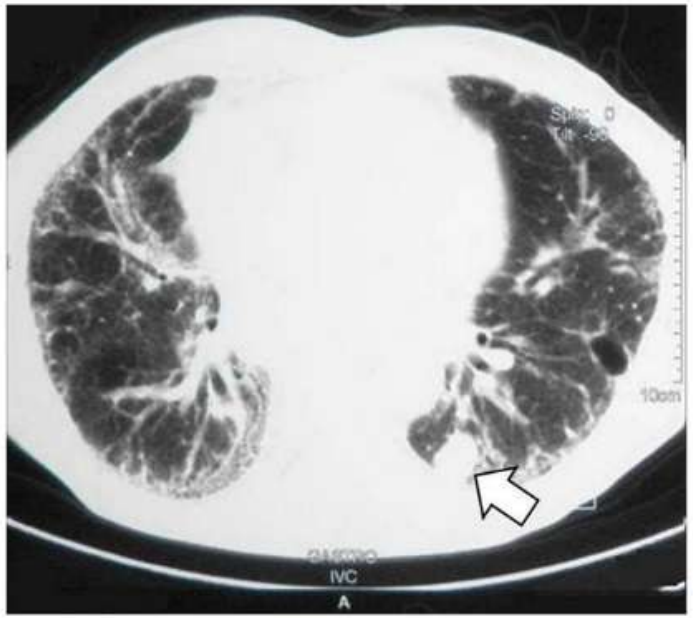
Functional course



INTRODUCTION

Factors that increased interest in patients with both IPF and lung cancer:

i. IPF risk factor for lung cancer development



ii. Patients with IPF and lung cancer have shorter survival

iii. Common pathogenetic pathways

Vancheri BMC Med. 2015

EPIDEMIOLOGY

PLOS ONE

RESEARCH ARTICLE

Lung cancer in idiopathic pulmonary fibrosis: A systematic review and meta-analysis

AliReza JafariNezhad[1]

PLOS ONE | https://doi.org/10.1371/journal.pone.0202360 August 16, 2018

- **35 (0.18% studies included)**
- **Prevalence of LC in IPF: 13.54% - x9 in men**
- **38% SQCC, 31% ADC, 20% SmCC, 5%LCC, 4% Adeno-squamous**
- **31% stage III, 13% stage II**
- **84% peripheral area, 16% central – RLL most common**

i. Prevalence of lung cancer in IPF 2.7 -31.3 %

Pulmonary Pharmacology & Therapeutics

Volume 45, August 2017, Pages 1–10

Lung cancer in patients with idiopathic pulmonary fibrosis

Theodoros Karampitsakos[a], Vasilios Tzilas[a], Rodoula Tringidou[b], Paschalis Steiropoulos[c], Vasilis Aidinis[d], Spyros A. Papiris[e], Demosthenes Bouros[a], Argyris Tzouvelekis[a, d]

[a] First Academic Department of Pneumonology, Hospital for Diseases of the Chest, "Sotiria", Medical School, National and Kapodistrian University of Athens, Athens, Greece

[b] Pathology Department, Hospital for Diseases of the Chest,"Sotiria", Messogion Avenue 152, Athens 11527, Greece

[c] Department of Pneumonology, Democritus University of Thrace, Greece

[d] Division of Immunology, Biomedical Sciences Research Center "Alexander Fleming", Athens, Greece

[e] 2nd Pulmonary Medicine Department, Attikon University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Received 22 December 2016, Revised 28 February 2017, Accepted 31 March 2017, Available online 1 April 2017

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http://doi.org/10.1016/j.pupt.2017.03.016

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Table 1: Studies reporting prevalence of lung cancer in patients with IPF

Study	Number of patients with IPF	Incidence of lung cancer	Year
Nagai	99	31 (31.3%)	1992
Park	281	63 (22.4%)	2001
Le Jeune	1064	29 (2.7%)	2007
Ozawa	103	21 (20.4%)	2009
Kreuter	265	42 (16%)	2014
Tomassetti	181	23(13%)	2015

ii. Squamous cell carcinoma (SCC) most frequent histologic type(35-46%)

Table 2: Studies reporting histologic predominance of lung cancer in patients with IPF

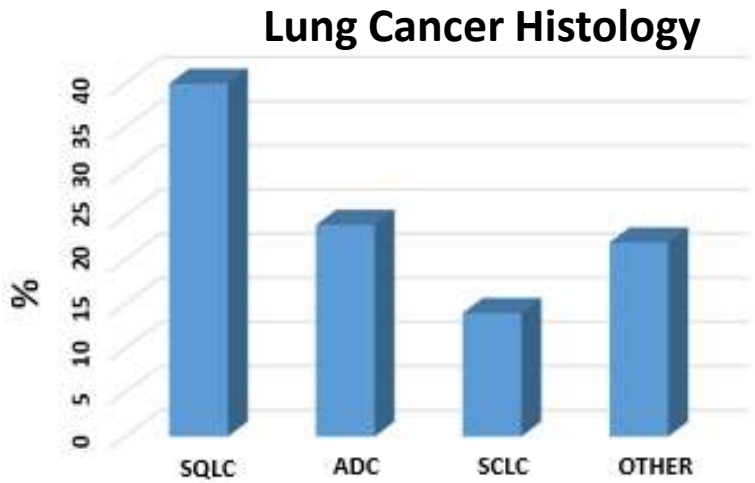
Study	Number of patients with IPF-lung cancer	SCC	ADC	Year
Nagai	31	45.2%	35.2%	1992
Park	63	35%	30%	2001
Kawasaki	53	46%	46%	2001
Ozawa	21	38%	29%	2009
Lee	70	40%	30%	2014
Kreuter	42	36%	31%	2014
Tomassetti	23	39%	35%	2015

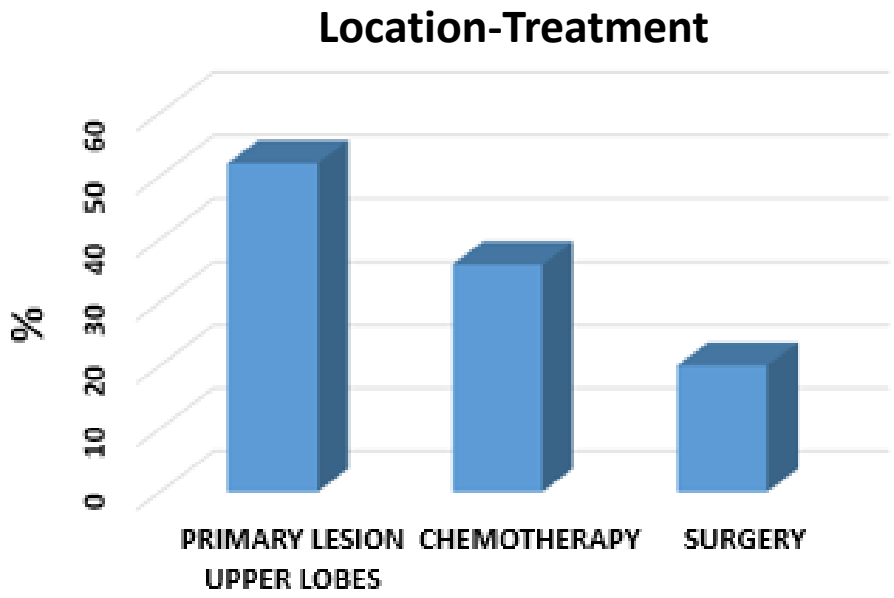
Abbreviations. IPF: Idiopathic pulmonary fibrosis, SCC: Squamous cell carcinoma, ADC: Adenocarcinoma

Otsuka MCO2016 Nagai TJEM 1992 Park ERJ 2001 Le Jeune Resp Med 2007 Ozawa Respirology 2009 Kreuter Sarc Vasc Dif Lung Dis 2014 Tomassetti Chest 2015

Greek cohort

CHARACTERISTICS	BASELINE DATA (N,%)
Total patients with IPF	**608**
Patients with IPF and cancer	63/608 (10.3%)
Males/ Females	57/6
Age (mean ± SD), years	72.8 ± 7.5
FVC %pred (mean ± SD)	75.9 ± 21.5
DLco %pred (mean ± SD)	47.2 ± 15.8
Patients with IPF and lung cancer	50/608 (8.2%)
Other types of cancer	16/608 (2.6%)
Both lung and other type of cancer	3/608 (0.5%)
Non-small cell lung cancer	37/50 (74 %)
Squamous cell carcinoma	20/50 (40 %)
Adenocarcinoma	12/50 (24 %)
Small cell lung cancer	7/50 (14 %)
Lung cancer post IPF diagnosis	23/36 (63%)
Median latency time (months) + SD	14.6 + 35.5
Lung cancer and IPF synchronously	11/36 (31%)
Lung cancer prior IPF diagnosis	2/36 (6%)
Median latency time (months) + SD	23.8 + 57.8
Missing data for time of lung cancer diagnosis	14/50 (28%)
Median survival (months)	24.0 (95% CI: 18.6 to 38.0)





PATHOGENETIC COMMONALITIES

SCARCINOMA

Is there a direct relationship between fibrotic areas and cancer development?

Vancheri *BMC Medicine* (2015) 13:220
DOI 10.1186/s12916-015-0478-1

BMC Medicine

Idiopathic pulmonary fibrosis: diagnosis, management and new therapies

OPINION Open Access

CrossMark

Idiopathic pulmonary fibrosis and cancer: do they really look similar?

Carlo Vancheri

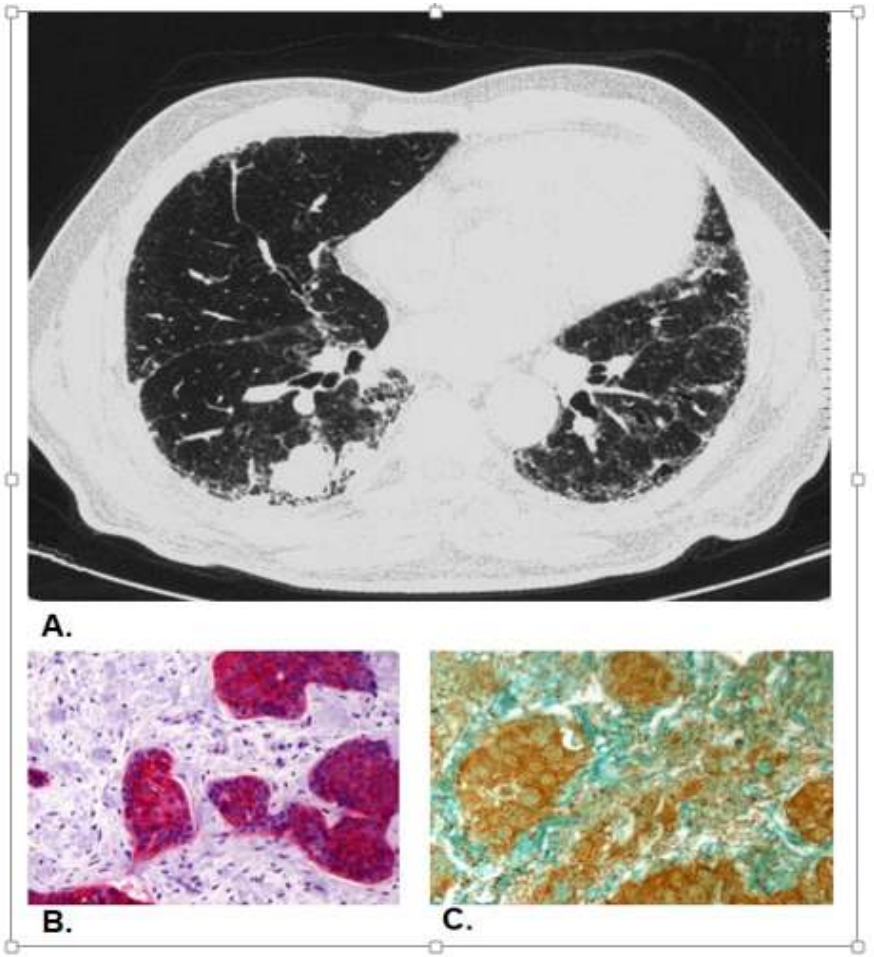


Figure 1: A) High Resolution Computed Tomography of a 78-years-old male with IPF and squamous cell carcinoma. B) CK-18 positive cancer cells in a fibrotic lung stroma. C) Masson stain positive for fibrosis in lung stroma surrounding solid nests of cancer cells.

This phenomenon has been coined out as ” scarcinoma”

PATHOGENETIC COMMONALITIES

CELL TO CELL COMMUNICATION AND SIGNALING PATHWAYS

IPF fibroblasts undergo glycolytic reprogramming towards myofibrolast differentiation (“Warburg effect”)

Cell-to-cell communication and signal transduction pathways

PI3K/AKT

(therapeutic target in both)

Wnt/β-catenin

(cancer development, fibrosis progression)

Tyrosine kinases/ phosphatases

(nintedanib, SHP2)

Vassilakis AJRCCM 2000 *Armanios Mutat Res 2012* *Rabinovich Plos one 2012* *Pandit AJRCCM 2010* *Staab-Weijnitz Thorax 2016* *Tzouvelekis AJRCCM 2016*

Epithelial biomarkers of cancer metaplasia predict survival in IPF

An epithelial biomarker signature for idiopathic pulmonary fibrosis: an analysis from the multicentre PROFILE cohort study

Toby M Maher, Eunice Oballa, Juliet K Simpson, Joanne Porte, Anthony Habgood, William A Fahy, Aiden Flynn, Philip L Molyneaux, Rebecca Braybrooke, Hrushikesh Divyateja, Helen Parfrey, Doris Rassl, Anne-Marie Russell, Gauri Saini, Elisabetta A Renzoni, Anne-Marie Duggan, Richard Hubbard, Athol U Wells, Pauline T Lukey, Richard P Marshall, R Gisli Jenkins

Lancet Respir Med 2017

Published Online
November 14, 2017

Findings In the discovery analysis, we identified four serum biomarkers (surfactant protein D, matrix metalloproteinase 7, CA19-9, and CA-125) that were suitable for replication. Histological assessment of CA19-9 and CA-125 suggested that these proteins were markers of epithelial damage. Replication analysis showed that baseline

Clinical Data

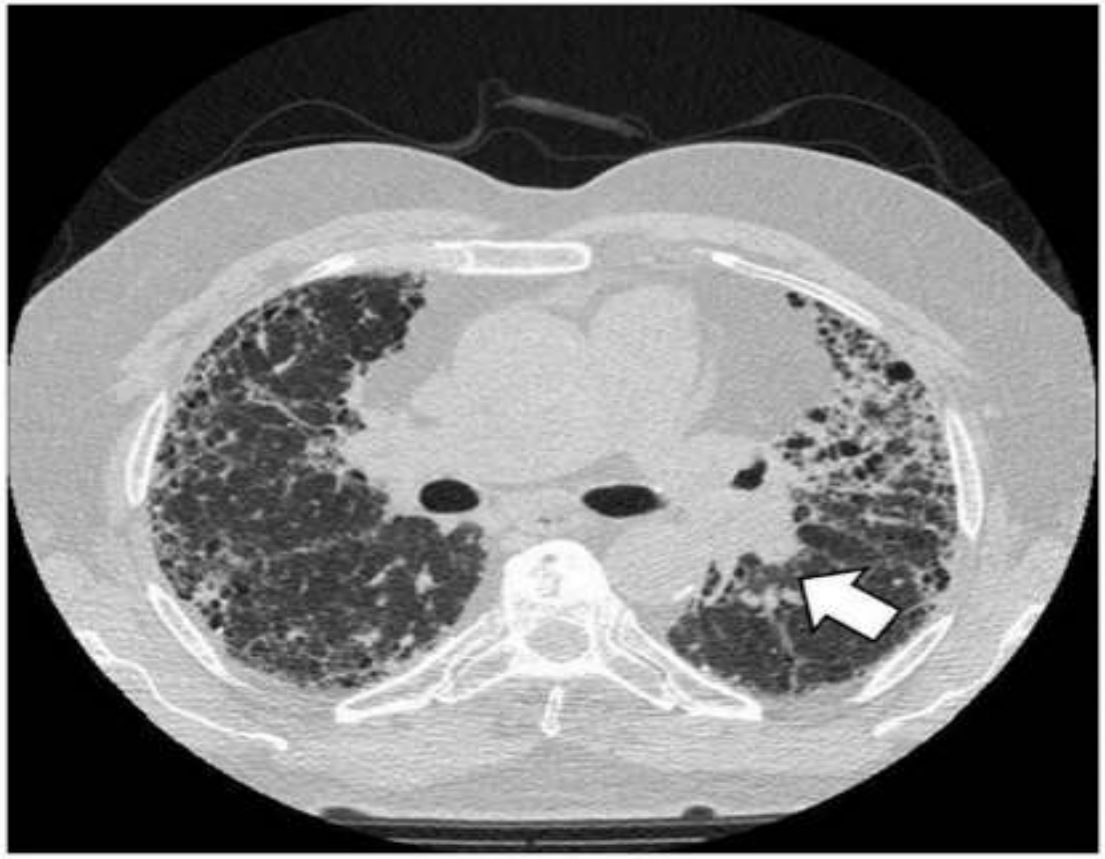
Patients with IPF and LC present with worse prognosis than IPF for the following reasons:

i.Increased perioperative mortality(7.1 % vs 1.9%)

ii.Increased likelihood for postoperative AEx(8.7% vs 1.8%)

iii.Relapse of malignancy (36%)

iv. Complications from aggressive therapeutic interventions (chemotherapy-infections, post-radiation pneumonitis/injury)



Negative prognostic factors for surgical interventions:

i.Increased levels of KL- 6, LDH

ii.Decreased FVC, DLCo

iii.Male gender, use of corticosteroids, history of AEx, definite UIP pattern

Sato J Thorac Cardiovasc Surg2015 Fujimoto Ann Thorac Surg 2003

How do we approach a patient with IPF and suspicious lung lesion (?)

Lancet Respir Med 2017
Published Online
December 11, 2017

Patients with IPF and lung cancer: diagnosis and management

*Argyris Tzouvelekis, Paolo Spagnolo, Francesco Bonella, Carlo Vancheri, Vasilios Tzilas, Bruno Crestani, Michael Kreuter, Demosthenes Bouros

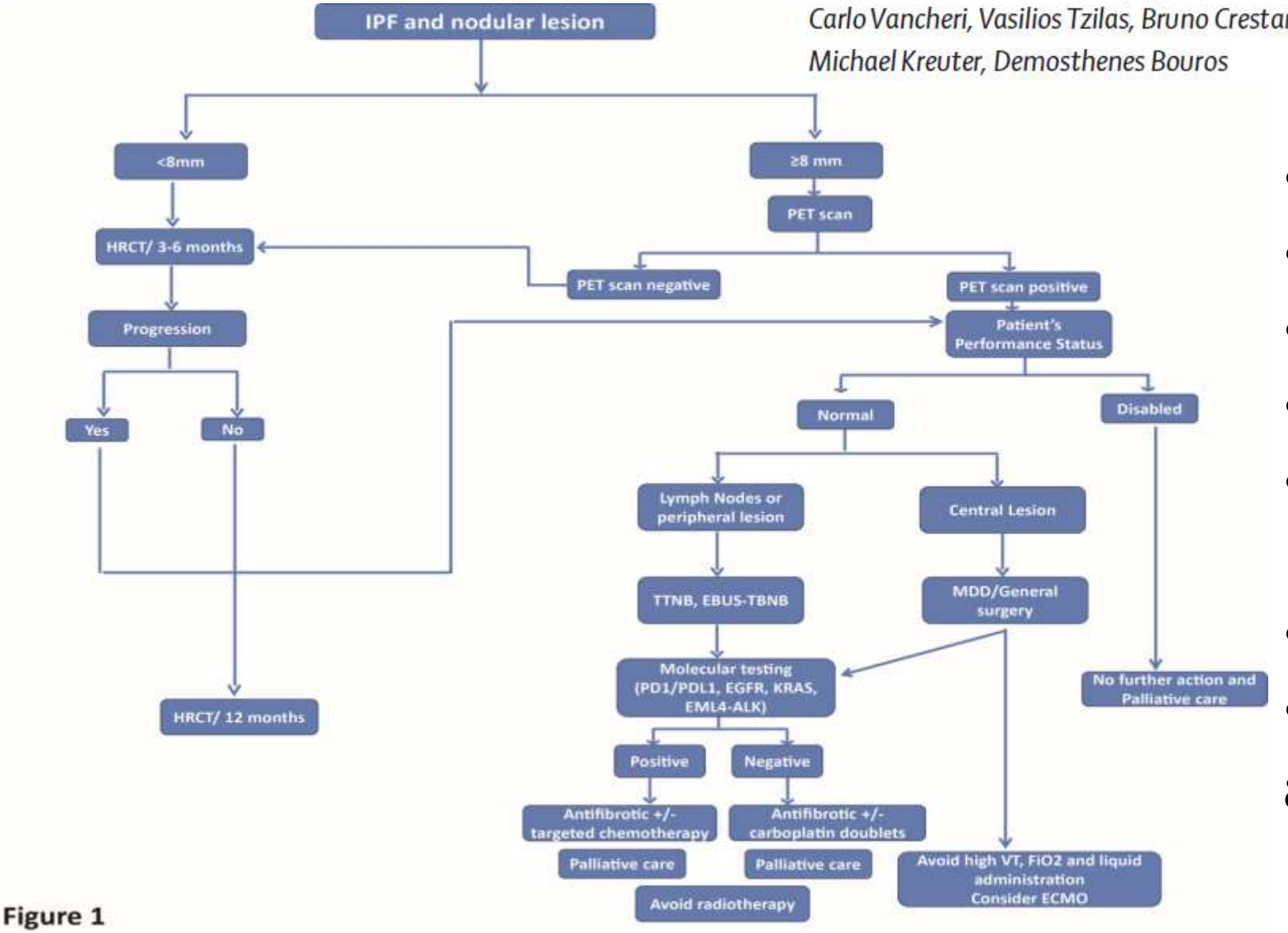


Figure 1

- **LDCT/PET scan**
- **PFS**
- **Location of the lesion**
- **Avoid irradiation**
- **Beware of surgical interventions**
- **Platin doublets/1st line**
- **Don't discontinue antifibrotics**

FUTURE PERSPECTIVES

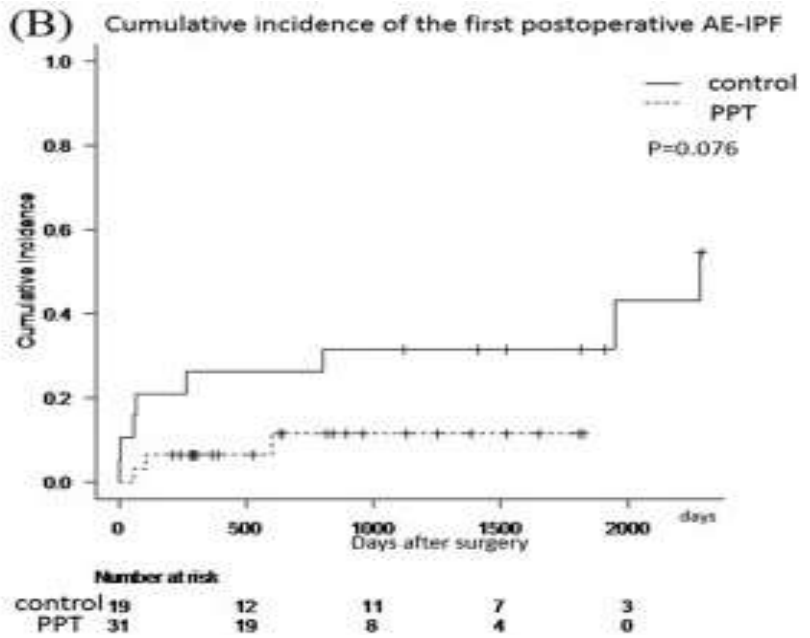
The approval of nintedanib and pirfenidone alters the scenario:

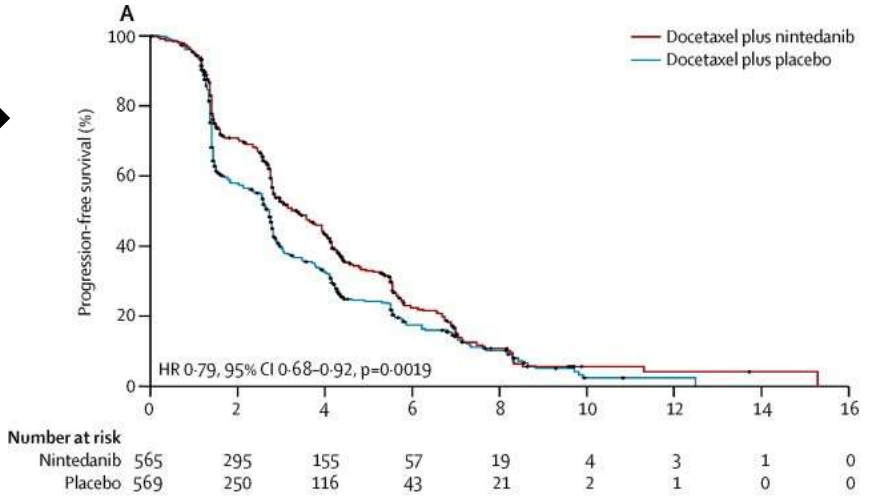
i. Pirfenidone **decreases** the incidence of lung cancer (**2.9% vs 20.3%**)

ii. **Prophylactic effect** of preoperative treatment with pirfenidone for postoperative acute exacerbations (**3.2% vs 21.1%** within 90 postoperative days)

iii. Nintedanib **improves** the outcome for docetaxel-based second-line therapy especially for patients with **adenocarcinoma**

iv. Drug **repositioning** like nintedanib (pan-class I **PI3K/mTOR** inhibitor ?)





Yazaki Chest 2016 *Iwata Ann Thorac Surg 2016* *Reck Lancet Oncol 2014* *Mercer Thorax 2016*

THE ROLE OF LIQUID BIOPSIES

- Similar concept to that of prenatal screening – circulating free DNA

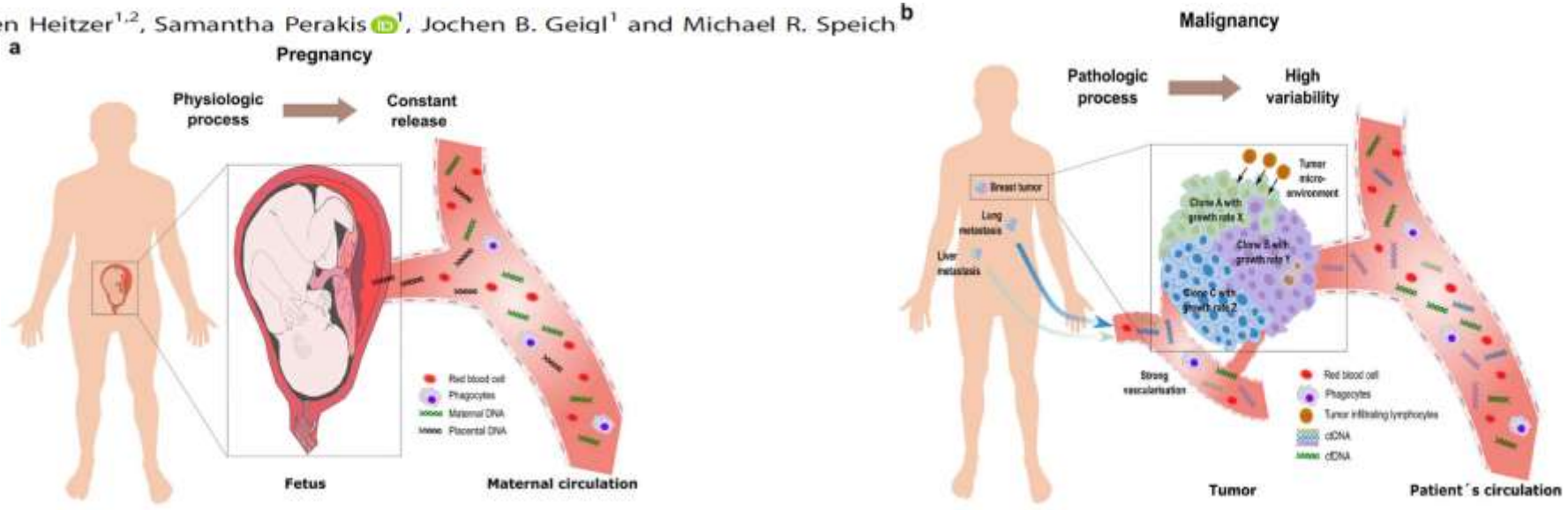
npj | Precision Oncology

www.nature.com/npjprecisiononcology

REVIEW ARTICLE OPEN

The potential of liquid biopsies for the early detection of cancer

Ellen Heitzer[1,2], Samantha Perakis[1], Jochen B. Geigl[1] and Michael R. Speich[b]



- Inability for molecular tumor profiling in 20% - Low PFS, small tissue
- First PCR-droplet biopsy test for BRAF (V600) and EGFR (T970M) in clinic

The role of liquid biopsy in early diagnosis of Lung Cancer in patients with Pulmonary Fibrosis

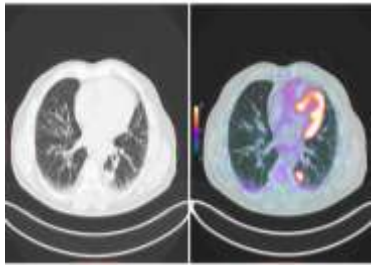
Argyrios Tzouvelekis,
Demosthenes Bouros

Editorial

- IPF risk of developing LC increases over time- 3.3% (1st yr) – 55% (10th yr)
- 70% of IPF pts have Mediastinal Lnpathy – Reactive or NOT?
- Amenable need for minimally invasive diagnostic/screening tools
- Low dose CT scan + EBUS/TBNB sampling = screening algorithm for early detection of high risk individuals

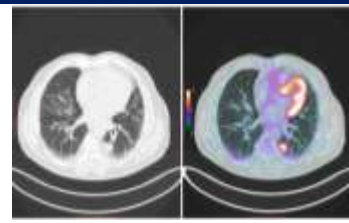
DIagnosis And Management Of lung canceR and FibrOSIS "DI-A-M-O-R-F-OSIS" survey

Aims



- To identify variations in diagnostic and management strategies across different hospitals and institutions
- To raise awareness on the association between the two conditions
- To provide rationale for a consensus statement (or position paper) for an improved, homogeneous and standardized approach

Design



- **Q & A- based survey – Approximately 40 Qs – 10-15 min**
- **General Knowledge Questions**: i.e. *What is your medical specialty?*
- **Prevalence-based Questions**: *i.e. What is the most common histologic subtype of lung cancer in your cohort of patients with IPF?*
- **Disease specific Questions (Diagnosis)**: i.e. *What diagnostic modality do you use to screen patients with IPF for lung cancer?*
- **Disease specific Questions (Treatment)**: i.e. *How would you treat a patient with severe IPF (DLCO<35%) and otherwise non-operable NSCLC ?*
- **Case report-based Questions**: i.e. *What would it be your next diagnostic step in a patient with severe IPF presenting with a nodular lesion of 9 mm*

TAKE HOME MESSAGE

i. IPF is an independent risk factor for lung cancer (10-15% prevalence)
ii. Pathogenetic similarities - scarcinoma
iii. Need for a consensus for the management of patients with IPF-LC
iv. Pirfenidone and nintedanib alter the scenario? PD-1 inhibitors?
v. Early diagnosis is the key – Role of Liquid biopsies- EBUS/TBNB – low dose CT

Ευχαριστίες

- Κος Παπίρης/Κα Μάναλη/Κος Τόμος – ΒΠΠ Νοσοκομείο «Αττικόν» -ΕΚΠΑ
- Κα Αντωνίου/Τραχαλάκη/Βαρσαμίδη – ΠΑΓΝΗ-Πανεπιστήμιο Κρήτης
- Κα Μαρκοπούλου – ΓΝ Παπανικολάου
- Κος Κολιλέκας – 7η Κλινική ΓΝΝΘΑ «ΣΩΤΗΡΙΑ»
- Κος Παπανικολάου – ΓΝ Κερκύρης
- Κα Παπακώστα- ΓΝ Παπανικολάου –ΑΠΘ
- Κα Δανιήλ/Μπαρδάκα – Πανεπιστημιακό Νοσοκομείο Λάρισας
- Κα Δημάκου – 5η Πνευμονολογική Κλινική – ΓΝΝΘΑ «ΣΩΤΗΡΙΑ»
- Κος Μπούρος/Καραμπιτσάκος/Τζίλας/Γομάτου/Μπούρος Ε/Ντάσιου/Μαρκοζάννες/Τριγγίδου-Α'ΠΠ ΓΝΝΘΑ «ΣΩΤΗΡΙΑ», ΕΚΠΑ