KOPANA 2024 Virtual Spring Seminar

Interesting cases of

Pulmonary neoplasms

Hyo Sup Shim
Department of Pathology
Severance Hospital
Yonsei University College of Medicine, Seoul

Education:

- Medical School: Yonsei University College of Medicine, Seoul
- Residency: Severance Hospital, Seoul
- Fellowship: Severance Hospital, Seoul

Current Position & Institution:

- Professor, Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Seoul

Subspecialty area:

- Pulmonary pathology, Molecular pathology

Introduction

- **This is a case-based presentation on ‘Neoplastic lung diseases’.**

- **This talk will consist of 3 interesting case presentations, with each case followed by review and some key points.**

Contents

- **Pulmonary epithelial tumors with clinical implications**
  - **Malignant tumor- early stage**
  - **Malignant tumor- advanced stage**
  - **Benign tumor- genetic tumor syndrome**

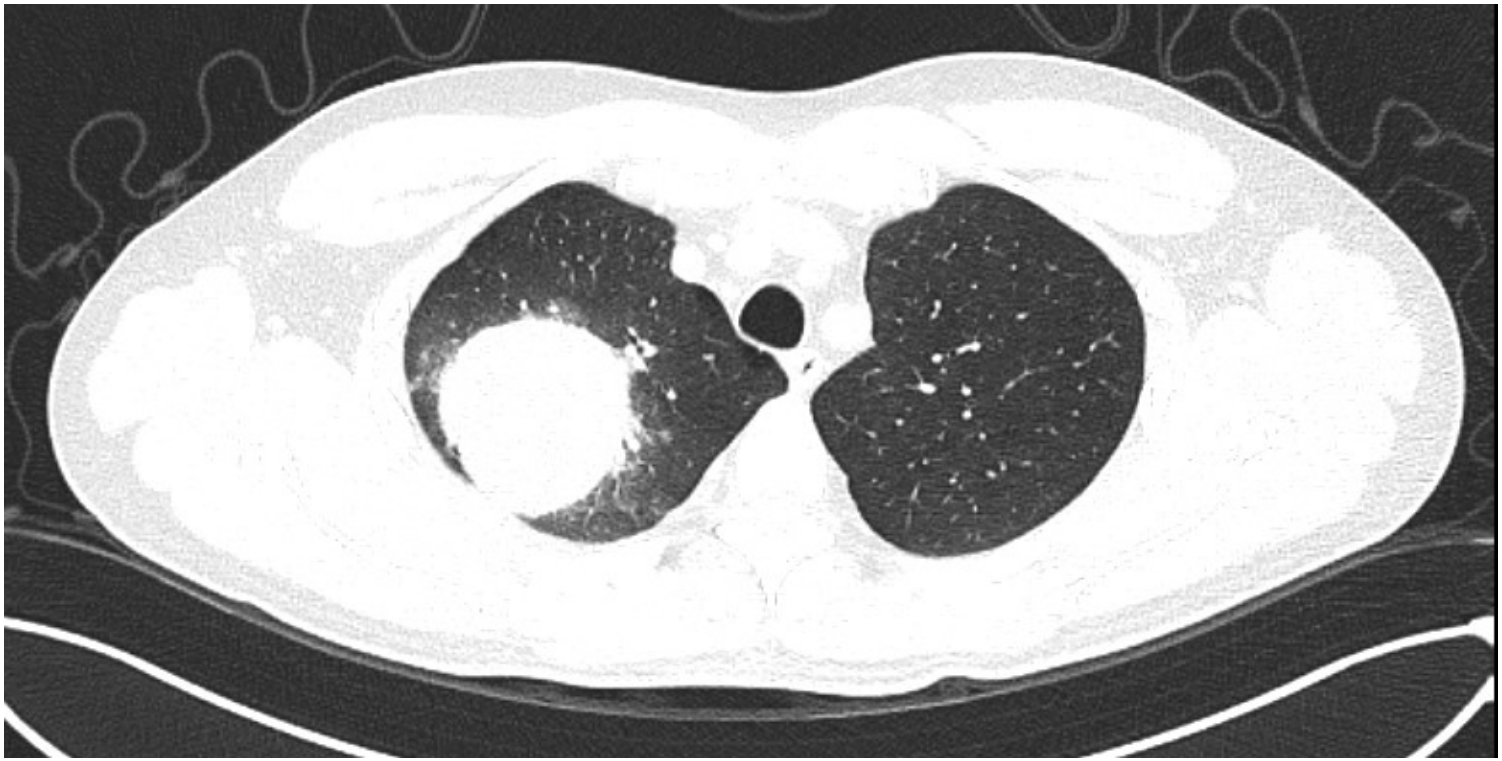
- **Including**
  - **Biopsy diagnosis**
  - **Immunohistochemistry interpretation**
  - **Diagnosis of surgical specimen**
  - **Genetics and biomarkers: Clinical and therapeutic implication**

Case 1.

Case presentation

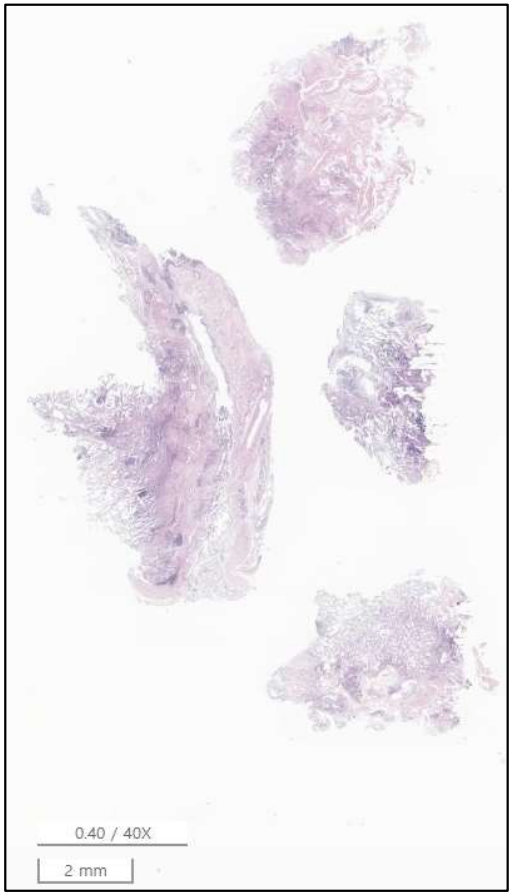
- **37/M**
- **Radiologic abnormality, lung, during health examination, at an outside hospital**
- **Current smoker (15PYS)**

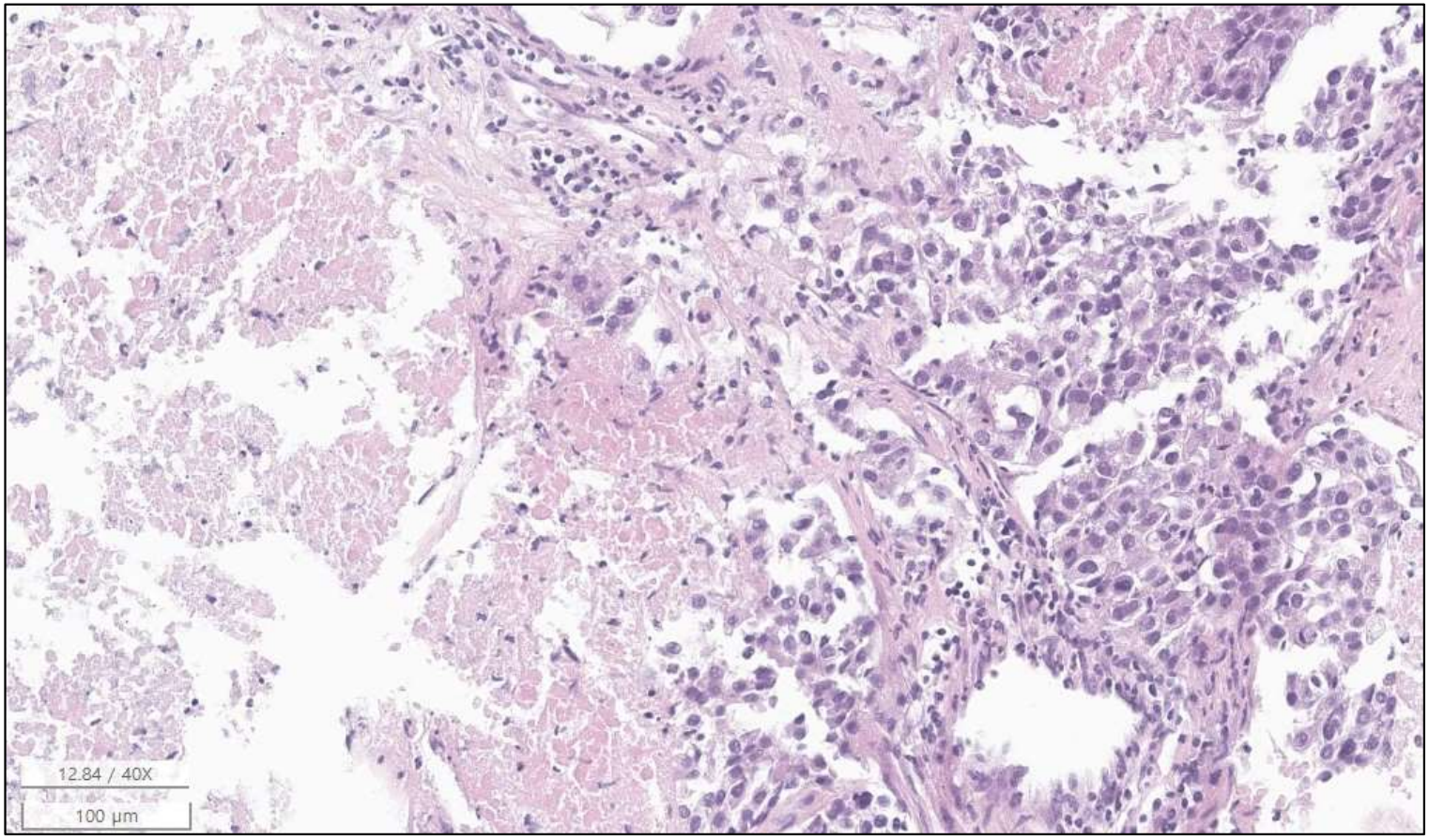
Chest CT



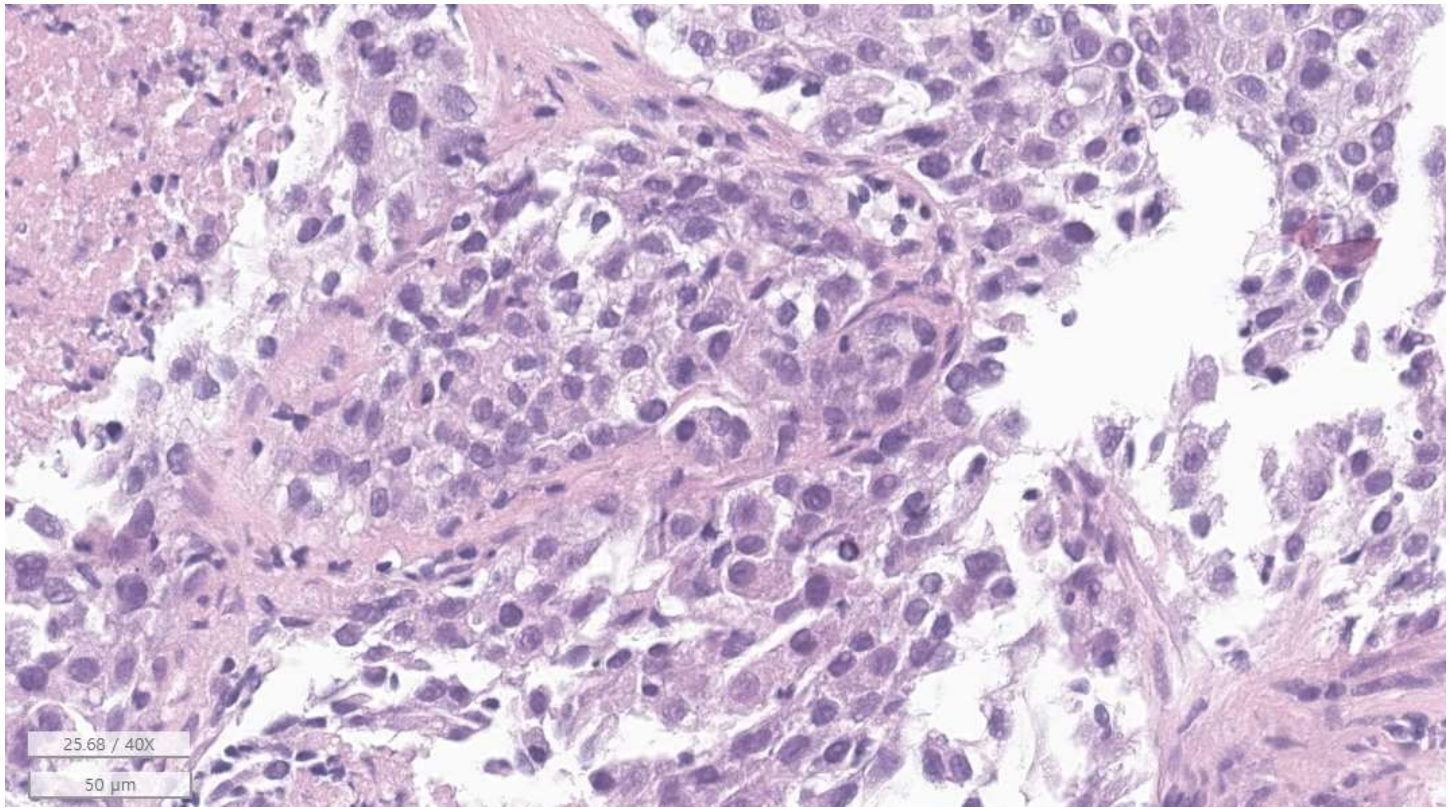
- **About 6cm-sized mass in the RUL**
- **IMP: Lung cancer T3N1**

TBLB (Lung, RUL)





Lung, RUL, TBLB



- **IHC**
  - **CK: +**
  - **TTF-1: -**
  - **P40: -**
  - **CD56: -**
  - **SYP: -**

Terminology in Small Biopsy

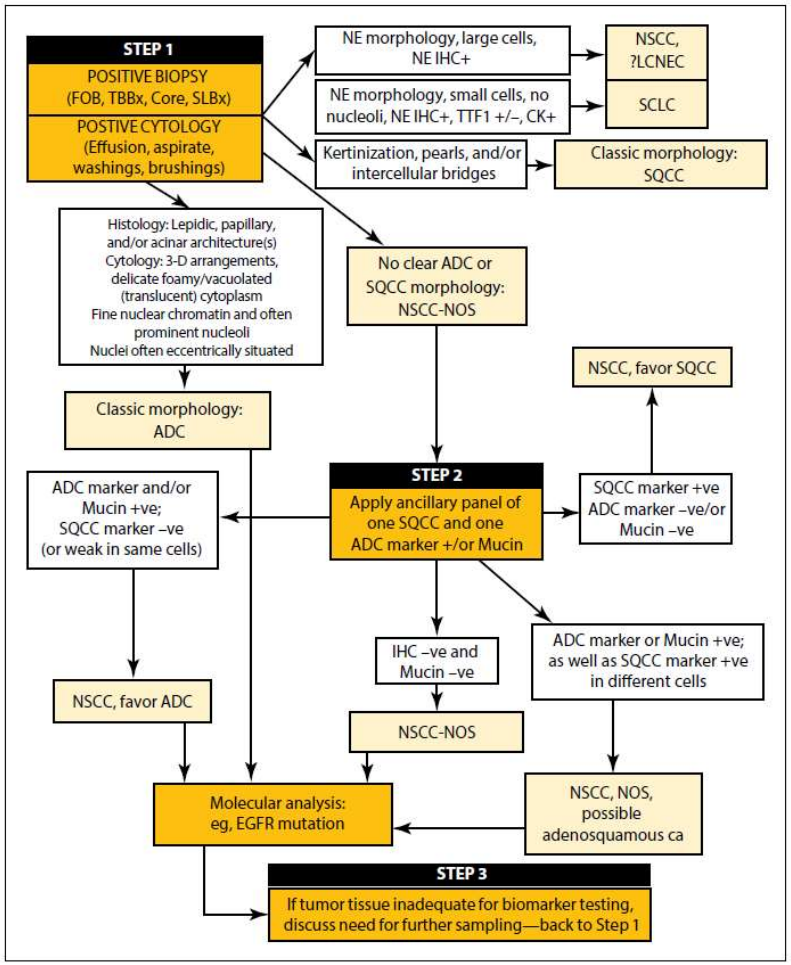


Table 3. Terminology in Small Biopsy and Cytology Versus Resection Specimens for Adenocarcinoma and Squamous Cell Carcinoma

Morphology/Stains	Terminology for Small Biopsies and Cytology Specimens	Terminology for Resection Specimens
Morphologic squamous cell patterns clearly present	Squamous cell carcinoma	Squamous cell carcinoma
Morphologic adenocarcinoma patterns clearly present		
	Adenocarcinoma (list the patterns in the diagnosis)	Adenocarcinoma Predominant pattern: Lepidic Acinar Papillary Solid Micropapillary
	Adenocarcinoma with lepidic pattern (if pure, list the differential diagnosis on the right and add a comment that an invasive component cannot be excluded)	Minimally invasive adenocarcinoma, adenocarcinoma in situ, or an invasive adenocarcinoma with a lepidic component
	Invasive mucinous adenocarcinoma (list the patterns; use the term "mucinous adenocarcinoma with lepidic pattern" if pure lepidic pattern and mention the differential diagnosis listed on the right)	Invasive mucinous adenocarcinoma
		Minimally invasive adenocarcinoma or adenocarcinoma in situ, mucinous type
	Adenocarcinoma with colloid features	Colloid adenocarcinoma
	Adenocarcinoma with fetal features	Fetal adenocarcinoma
	Adenocarcinoma with enteric features[a]	Enteric adenocarcinoma
Morphologic squamous cell patterns not present, but supported by stains (i.e., p40+)	Nonsmall cell carcinoma, favor squamous cell carcinoma[b]	Squamous cell carcinoma (nonkeratinizing pattern may be a component of the tumor)[b]
Morphologic adenocarcinoma patterns not present, but supported by special stains (i.e., TTF1+)	Nonsmall cell carcinoma, favor adenocarcinoma[b]	Adenocarcinoma (solid pattern may be just one component of the tumor)[b]
No clear adenocarcinoma, squamous, or neuroendocrine morphology or staining pattern	Nonsmall cell carcinoma NOS[a,c]	Large cell carcinoma

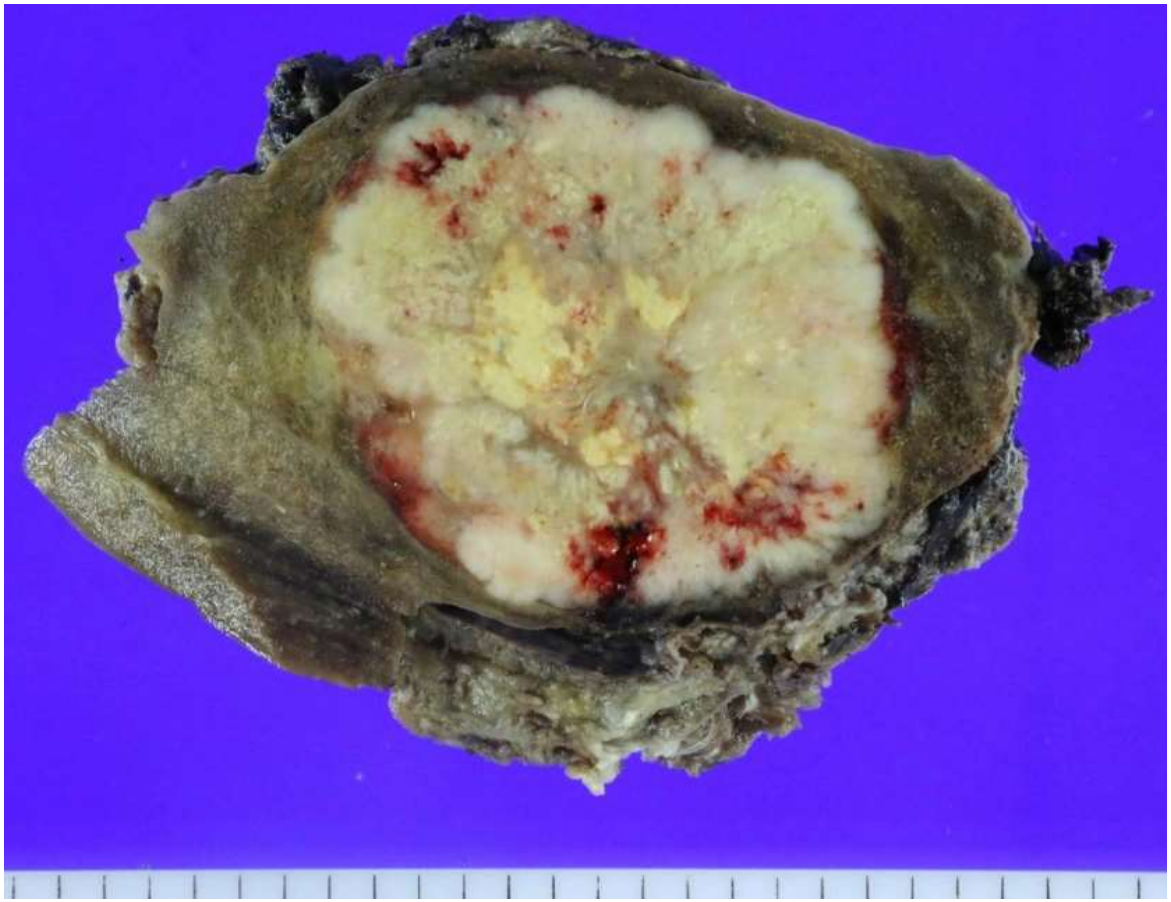
J Thorac Oncol 2022;17:362-87; IASLC ATLAS

Treatment

- **Biopsy, Dx:**
  - **Favor non-small cell carcinoma, NOS**

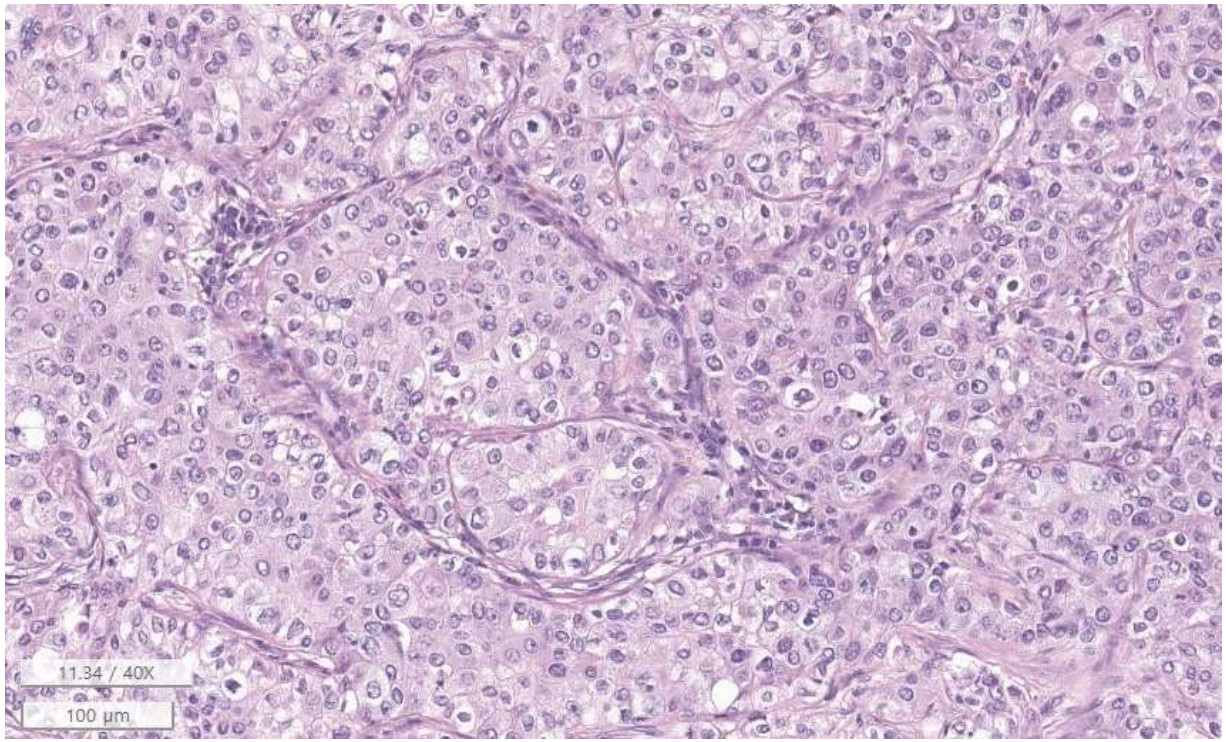
- **cT3N1M0**
- **Neoadjuvant chemo-immunotherapy, followed by surgery**

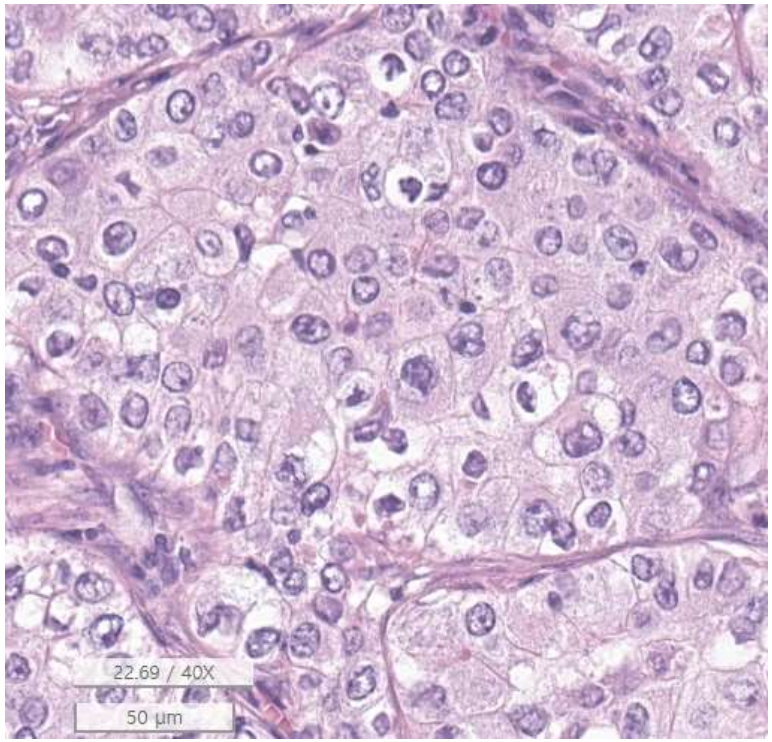
Lung, RUL, lobectomy



6.3x5.8cm

Lung, RUL, lobectomy





- **IHC: CK +/ TTF-1 - /P40 -/ CD56 - /SYP -**

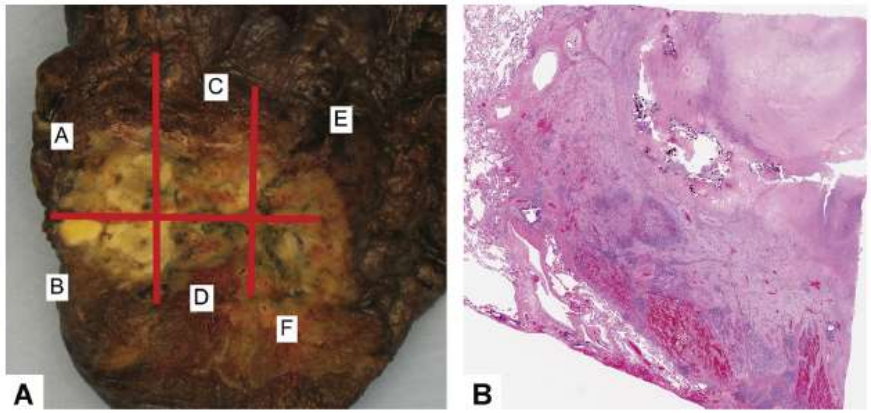
Pathologic response evaluation after neoadjuvant therapy

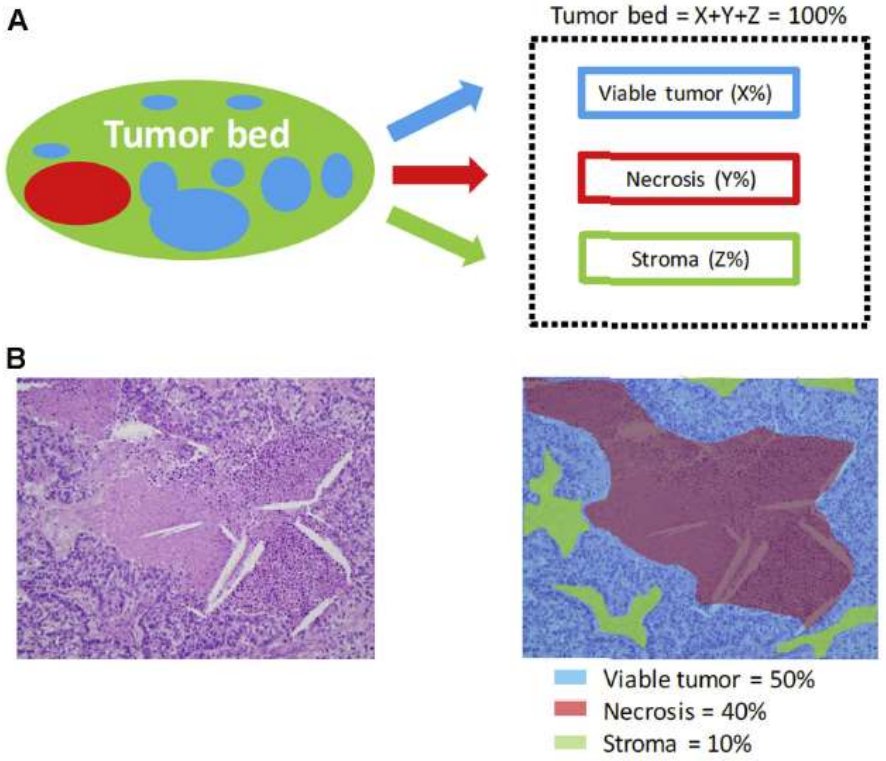
REVIEW ARTICLE

IASLC

IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy

William D. Travis, MD,[a,*] Sanja Dacic, MD,[b] Ignacio Wistuba, MD,[c] Lynette Sholl, MD,[d] Prasad Adusumilli, MD,[e] Lukas Bubendorf, MD,[f] Paul Bunn, MD,[g] Tina Cascone, MD, PhD,[h] Jamie Chaft, MD,[i] Gang Chen, MD,[j] Teh-Ying Chou, MD,[k] Wendy Cooper, MD,[l] Jeremy J. Erasmus, MD,[m] Carlos Gil Ferreira, MD,[n] Jin-Mo Goo, MD,[o] John Heymach, MD, PhD,[h] Fred R. Hirsch, MD,[p] Hidehito Horinouchi, MD,[q] Keith Kerr, MD,[r] Mark Kris, MD,[i] Deepali Jain, MD,[s] Young T. Kim, MD,[t] Fernando Lopez-Rios, MD,[u] Shun Lu, MD,[v]





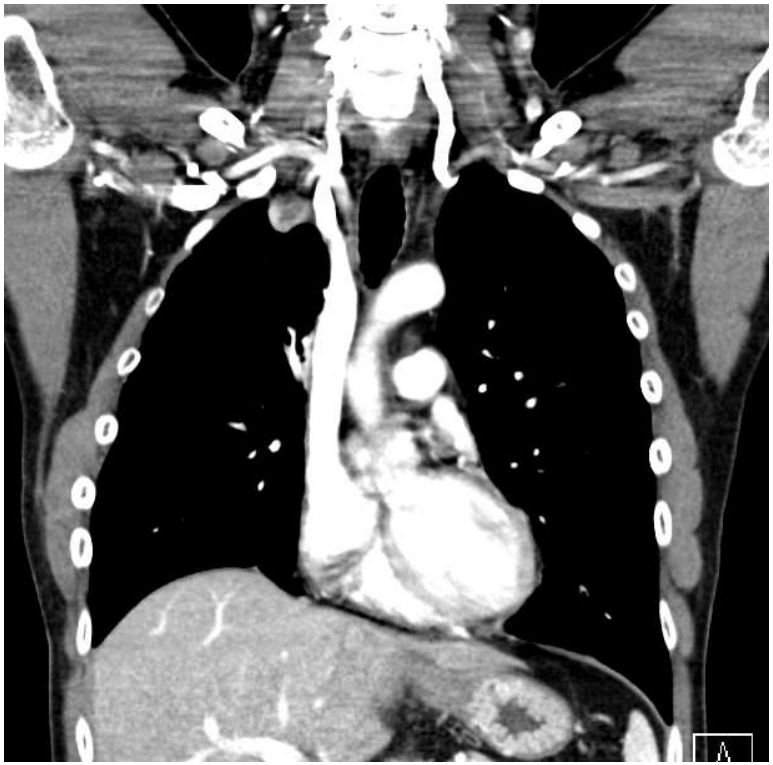
J Thorac Oncol 2020;15:709-40.

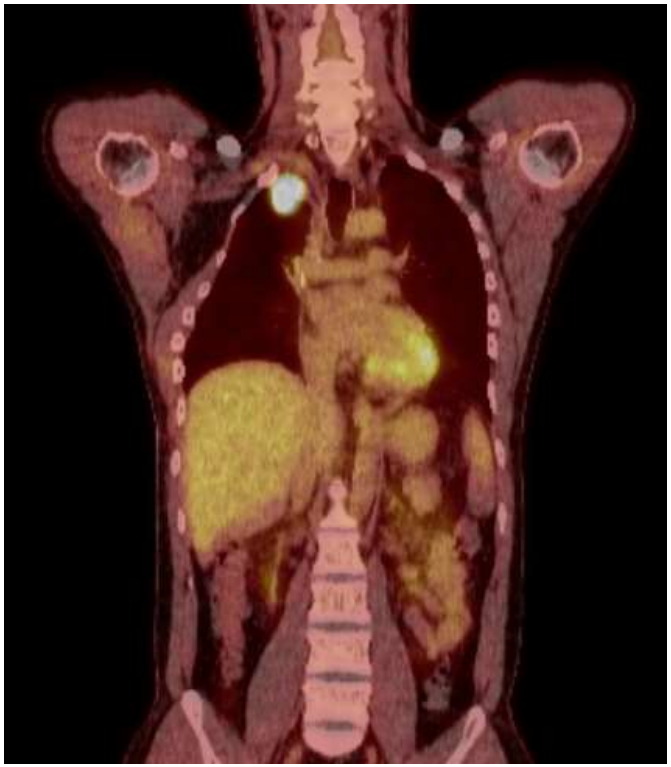
Diagnosis (surgical specimen)

- **Favor large cell carcinoma**

- **Viable tumor volume: 60% (No major pathological response)**
- **ypT3N0 (IIB)**

Chest CT & PET CT (8 months later)

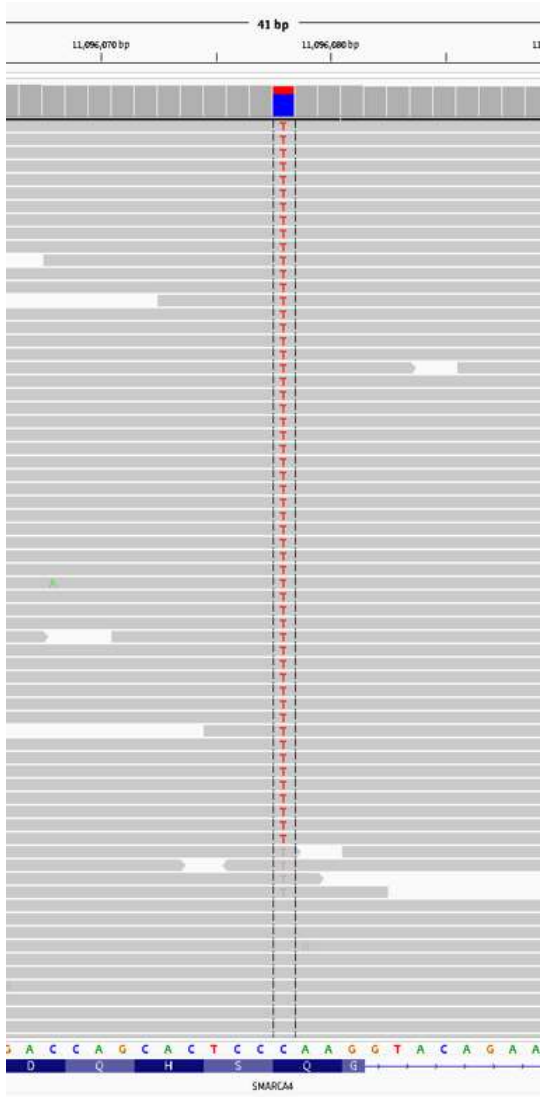




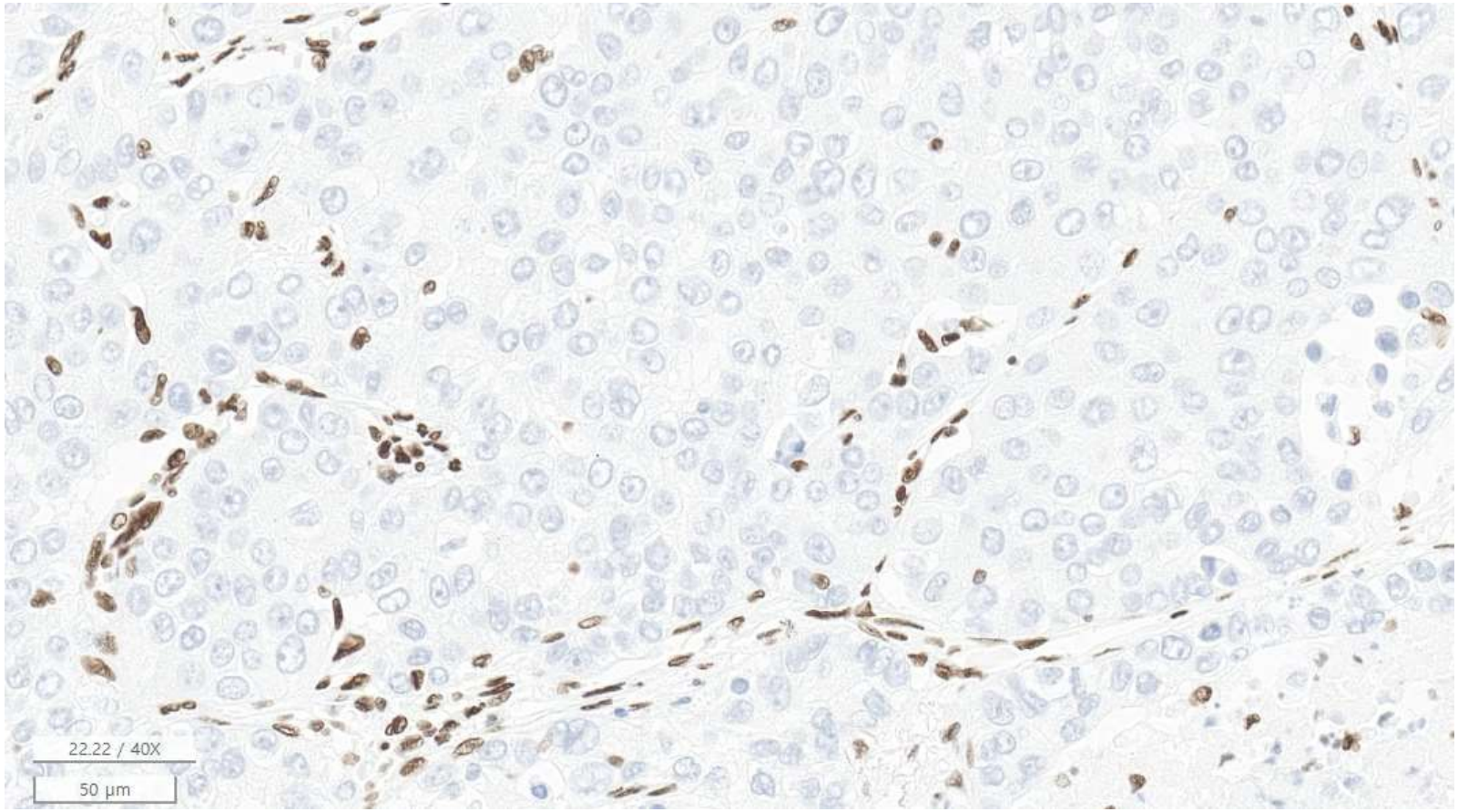
- **Newly appeared pleural nodule in Rt apical lung with apical pleural thickening**

NGS

- ***SMARCA4*** **Nonsense mutation p.Q118***
- ***TP53*** **Missense mutation p.R248L**
- ***KEAP1*** **Frameshift mutation p.A101Lfs*20**
- ***STK11*** **Frameshift mutation p.P281Rfs*6**



BRG1(SMARCA4) IHC



Points of Case 1.

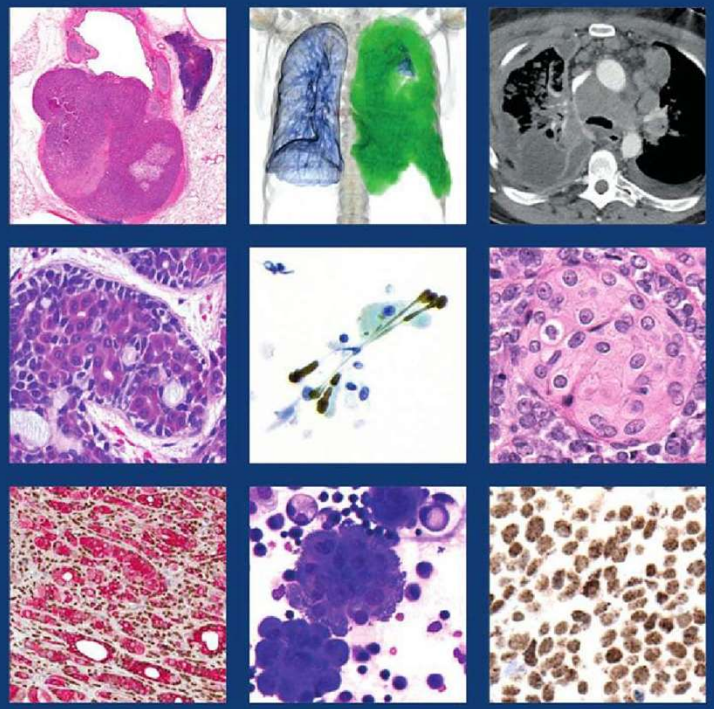
- **Thoracic SMARCA4-deficient undifferentiated tumor (according to 2021 WHO)**
- **Large cell carcinoma (with SMARCA4-deficiency)**

- **Clinical findings**
  - **Poor response to neo-adjuvant chemo-immunotherapy**
  - **Early recurrence**

WHO Classification of Tumours • 5th Edition

Thoracic Tumours

Edited by the WHO Classification of Tumours Editorial Board



World Health Organization

Contents

List of abbreviations xi

Foreword xii

ICD-O topographical coding 1

ICD-O morphological coding 1
Tumours of the lung 2
Tumours of the pleura and pericardium 4
Tumours of the heart 5
Mesenchymal tumours of the thorax 6
Tumours of the thymus 7
Germ cell tumours of the mediastinum 8
Haematolymphoid tumours of the mediastinum 8
Ectopic tumours of thyroid and parathyroid origin 9

TNM staging of lung, pleural, and thymic tumours 10
Carcinomas of the lung 11
Pleural mesothelioma 13
Epithelial tumours of the thymus 14

TNM staging of tumours of soft tissues 15

Staging of Hodgkin and non-Hodgkin lymphomas 17

1 Tumours of the lung 19
Introduction 20
Small diagnostic samples 29
Epithelial tumours
Papillomas
Bronchial papillomas 37
Adenomas
Sclerosing pneumocytoma 41
Alveolar adenoma 44
Papillary adenoma 46
Bronchiolar adenoma / ciliated muconodular papillary tumour 48
Mucinous cystadenoma 51
Mucous gland adenoma 53
Precursor glandular lesions
Atypical adenomatous hyperplasia 55
Adenocarcinoma in situ 57
Adenocarcinomas
Minimally invasive adenocarcinoma 60
Invasive non-mucinous adenocarcinoma 64
Invasive mucinous adenocarcinoma 75
Colloid adenocarcinoma 79
Fetal adenocarcinoma 81
Enteric-type adenocarcinoma 83
Squamous precursor lesions
Squamous dysplasia and carcinoma in situ 85
Squamous cell carcinomas
Squamous cell carcinoma 89
Lymphoepithelial carcinoma 94
Large cell carcinomas
Large cell carcinoma 97
Adenosquamous carcinoma
Adenosquamous carcinoma 100
Sarcomatoid carcinomas
Pleomorphic carcinoma 103
Pulmonary blastoma 106
Carcinosarcoma 109
Other epithelial tumours
NUT carcinoma of the lung (see Ch. 5)
Thoracic SMARCA4-deficient undifferentiated tumour 111
Salivary gland–type tumours
Pleomorphic adenoma 115
Adenoid cystic carcinoma 117
Epithelial-myoepithelial carcinoma 119
Mucoepidermoid carcinoma 121
Hyalinizing clear cell carcinoma 123
Myoepithelioma and myoepithelial carcinoma 125
Lung neuroendocrine neoplasms
Introduction 127
Precursor lesion
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia 130
Neuroendocrine tumours
Carcinoid/neuroendocrine tumour 133
Neuroendocrine carcinomas
Small cell lung carcinoma 139
Large cell neuroendocrine carcinoma 144
Tumours of ectopic tissues
Melanoma 150
Meningioma 152
Mesenchymal tumours specific to the lung
Pulmonary hamartoma 154
Pulmonary chondroma 156
Diffuse pulmonary lymphangiomatosis 158
Pleuropulmonary blastoma 160
Pulmonary artery intimal sarcoma 164
Congenital peribronchial myofibroblastic tumour 166
Primary pulmonary myxoid sarcoma with *EWSR1-CREB1* fusion 168
PEComatous tumours
Lymphangioleiomyomatosis 170
PEComa 172
Haematolymphoid tumours
Introduction 174
MALT lymphoma 175
Diffuse large B-cell lymphoma 178
Lymphomatoid granulomatosis 181
Intravascular large B-cell lymphoma 184
Pulmonary Langerhans cell histiocytosis 186
Erdheim–Chester disease 189

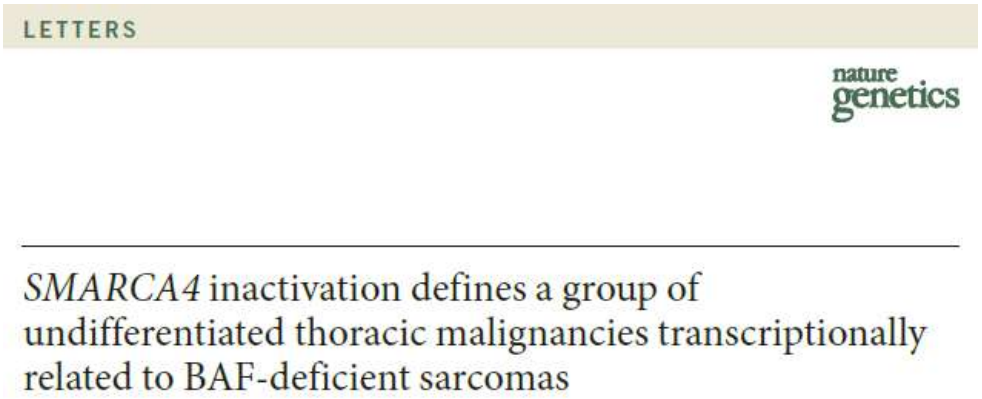
2 Tumours of the pleura and pericardium 193
Introduction 194
Mesothelial tumours
Benign and preinvasive mesothelial tumours
Adenomatoid tumour 196
Well-differentiated papillary mesothelial tumour 198
Mesothelioma in situ 200
Mesothelioma
Localized mesothelioma 202
Diffuse mesothelioma 204
Haematolymphoid tumours
Introduction 220
Primary effusion lymphoma 221
Diffuse large B-cell lymphoma associated with chronic inflammation 224

Differential diagnosis of thoracic SMARCA4-deficient undifferentiated tumor

- Conventional lung carcinoma with SMARCA4 loss
- SMARCA4-deficient undifferentiated tumor metastatic from extra-thoracic sites
- Germ cell tumor
- Proximal-type epithelioid sarcoma
- Malignant rhabdoid tumor
- Hematolymphoid neoplasm (lymphoma, myeloid sarcoma, etc.)
- Small round-cell sarcoma (Ewing sarcoma, CIC rearranged sarcoma, etc.)
- Malignant melanoma
- NUT carcinoma

SMARCA4-deficient undifferentiated tumor

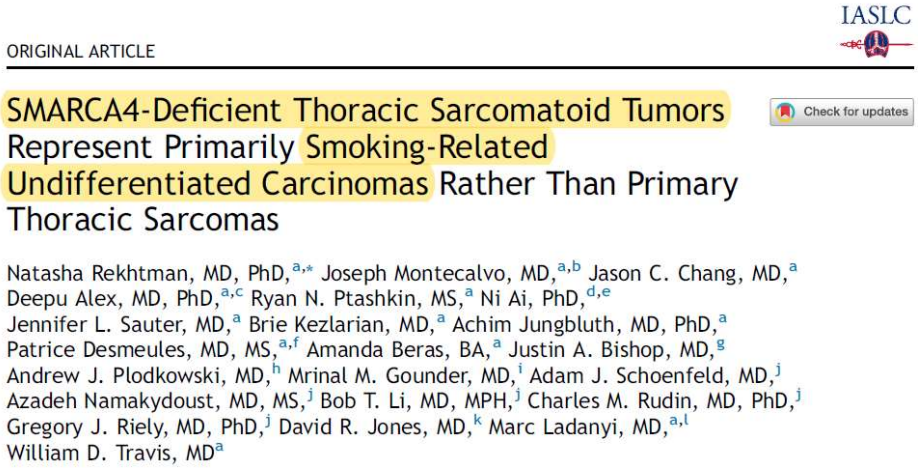
- **The question is…**
- **Sarcoma or carcinoma ?**



LETTERS

nature genetics

SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas



ORIGINAL ARTICLE

IASLC

SMARCA4-Deficient Thoracic Sarcomatoid Tumors Represent Primarily Smoking-Related Undifferentiated Carcinomas Rather Than Primary Thoracic Sarcomas

Check for updates

Natasha Rekhtman, MD, PhD,[a,*] Joseph Montecalvo, MD,[a,b] Jason C. Chang, MD,[a] Deepu Alex, MD, PhD,[a,c] Ryan N. Ptashkin, MS,[a] Ni Ai, PhD,[d,e] Jennifer L. Sauter, MD,[a] Brie Kezlarian, MD,[a] Achim Jungbluth, MD, PhD,[a] Patrice Desmeules, MD, MS,[a,f] Amanda Beras, BA,[a] Justin A. Bishop, MD,[g] Andrew J. Plodkowski, MD,[h] Mrinal M. Gounder, MD,[i] Adam J. Schoenfeld, MD,[j] Azadeh Namakydoust, MD, MS,[j] Bob T. Li, MD, MPH,[j] Charles M. Rudin, MD, PhD,[j] Gregory J. Riely, MD, PhD,[j] David R. Jones, MD,[k] Marc Ladanyi, MD,[a,l] William D. Travis, MD[a]

Nat Genet 2015;47:1200-5.
J Thorac Oncol 2020;15:231-47.

Thoracic SMARCA4-deficient undifferentiated tumor

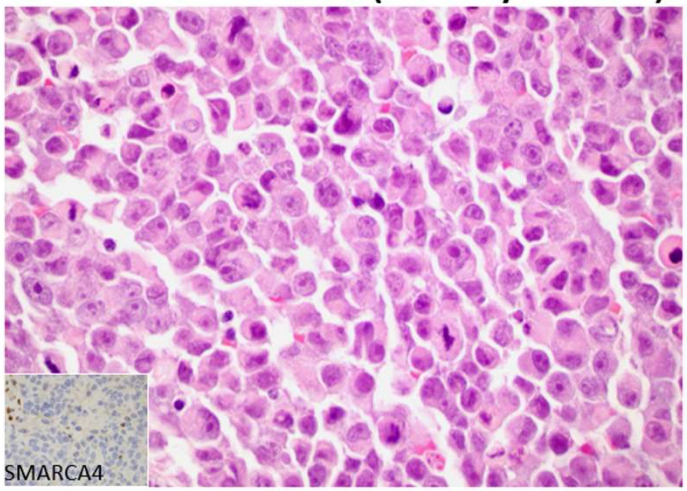
1) **A subset of cases harbored mutations characteristic of smoking related non-small-cell lung carcinoma (NSCLC)**
2) **Most examples tested harbored the smoking-related mutation signature, which is usually not seen in sarcoma**
3) **Many cases harbored high tumor mutation burden (TMB), which is also uncommon in sarcoma**
4) **SMARCA4 mutation and staining loss is known to occur in carcinoma de-differentiation process in other organs**
5) **SMARCA4-deficient undifferentiated histology was rarely juxtaposed to a conventional NSCLC**

☛**This is a carcinoma..**

J Thorac Oncol 2020;15:231-47.
Histopathology 2024;84:86-101.

Thoracic SMARCA4 undifferentiated tumor vs. Usual NSCLC with SMARCA4 loss

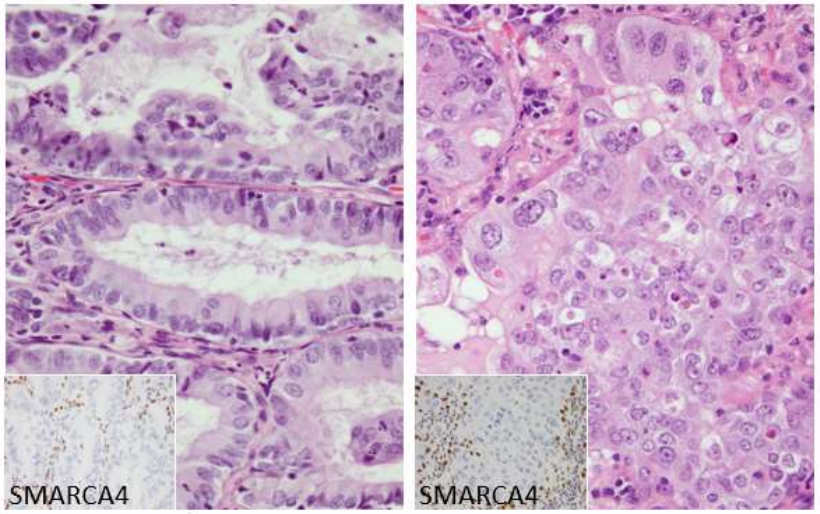
Thoracic SMARCA4-deficient undifferentiated tumor (formerly sarcoma)



Morphology	UNDIFFERENTIATED, round cell to rhabdoid, discohesive. By H&E, you do not know if this is a melanoma, lymphoma, some round cell sarcoma, etc
IHC	- Keratins negative or low (can be moderate in rare cases) - Claudin-4 consistently negative - SMARCA2 (BRM) almost always co-deficient - Stem cell markers commonly positive: SALL4, SOX2, CD34

@natasharekhtman

Usual NSCLC with SMARCA4 loss



Morphology	These are mostly adenocarcinomas but tend to be solid. Some are NSCLC without TTF-1 or p40. The difference from UT is that by H&E, you know these are carcinomas. **Strictly speaking there is no need to do SMARCA4 IHC in tumors like this.**
IHC	- Keratin and claudin-4 positive - BRM expressed - No or rare stem cell markers

@natasharekhtman

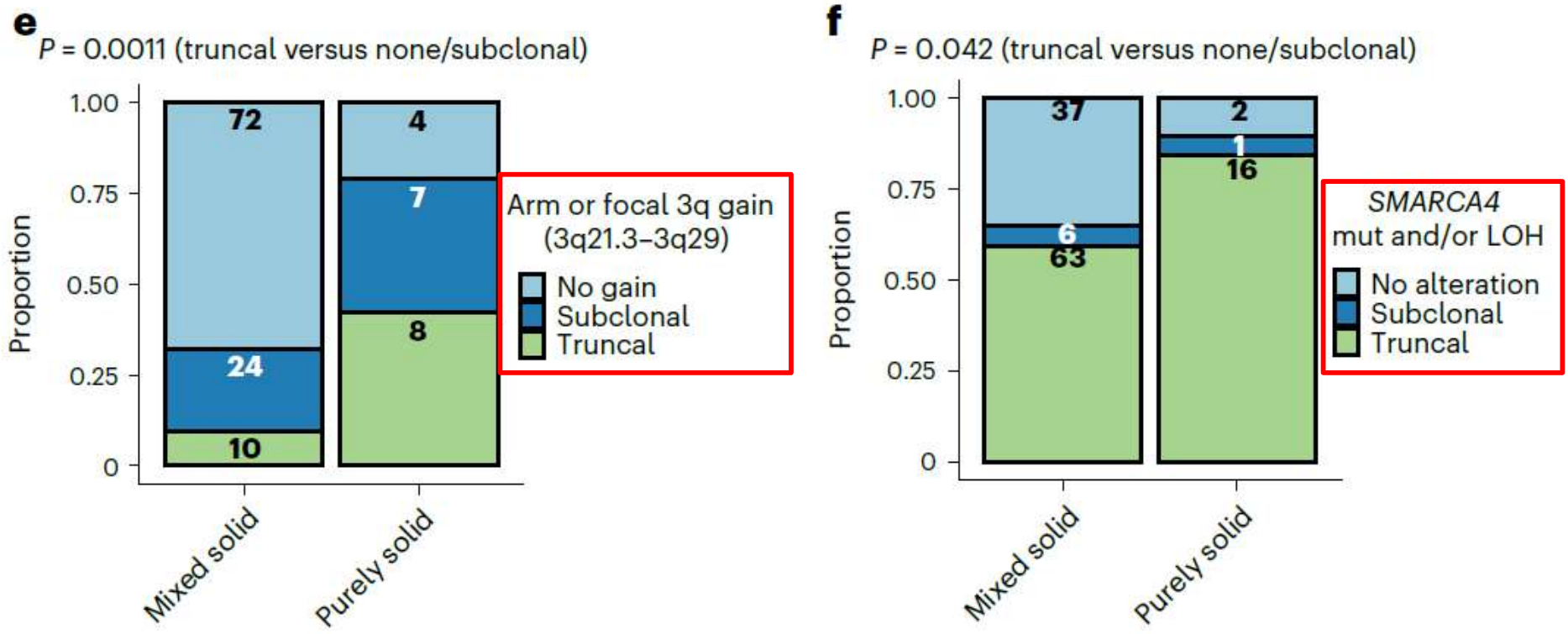
Courtesy of Dr. Natasha Rekhtman, MSKCC

Diagnostic tips

- **Routine SMARCA4 staining is not required in NSCLC, as it does not change diagnosis based on the current classification scheme.**
- **SMARCA4 staining is currently recommended only in cases where thoracic SMARCA4-UT is phenotypically suspected.**
- **NSCLC with SMARCA4 loss can be distinguished from thoracic SMARCA4-UT by epithelial architecture and unequivocal cellular cohesion.**

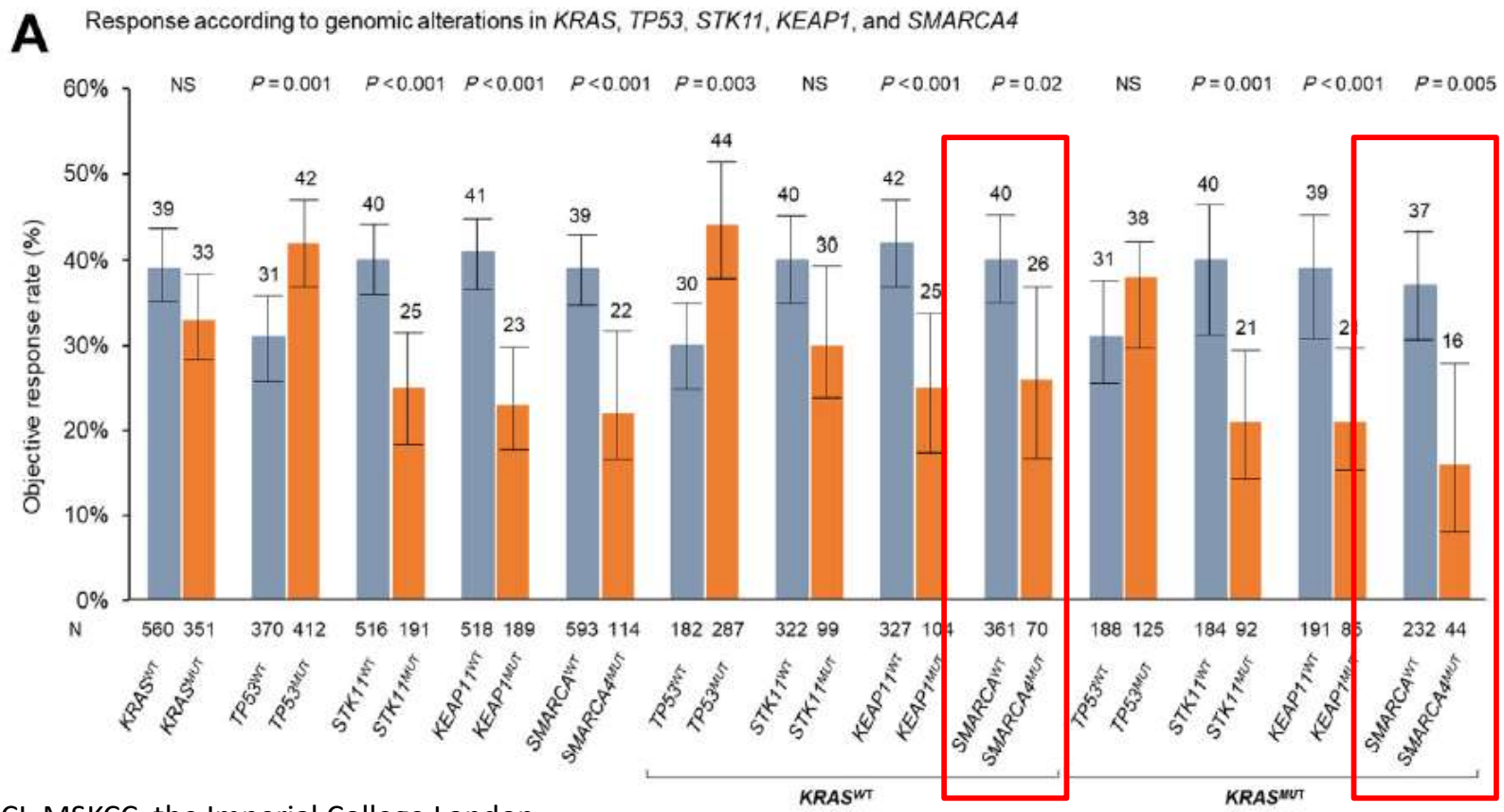
Histopathology 2024;84:86-101.

SMARCA4 mutation is associated with purely solid morphology in TRACERx cohort



Nat Med. 2023;29:833-45.

Genomic Factors Impacting Efficacy of Chemo-immunotherapy



DFCI, MSKCC, the Imperial College London, and MGH; n=1285

J Thorac Oncol. 2023;18:731-43.

Take home message of Case 1.

- **Diagnosis of undifferentiated tumor (carcinoma) in lung & thorax**
- **SMARCA4-deficient undifferentiated tumor, newly added entity to 2021 WHO classification**
  - **Routine SMARCA4 staining is not required in NSCLC, currently recommended only in cases where thoracic SMARCA4-UT is phenotypically suspected.**
  - **Clinical findings**
    - **Young to middle aged male adults with heavy smoking history**
    - **Poor prognosis**
    - **Poor response to chemo-immunotherapy**

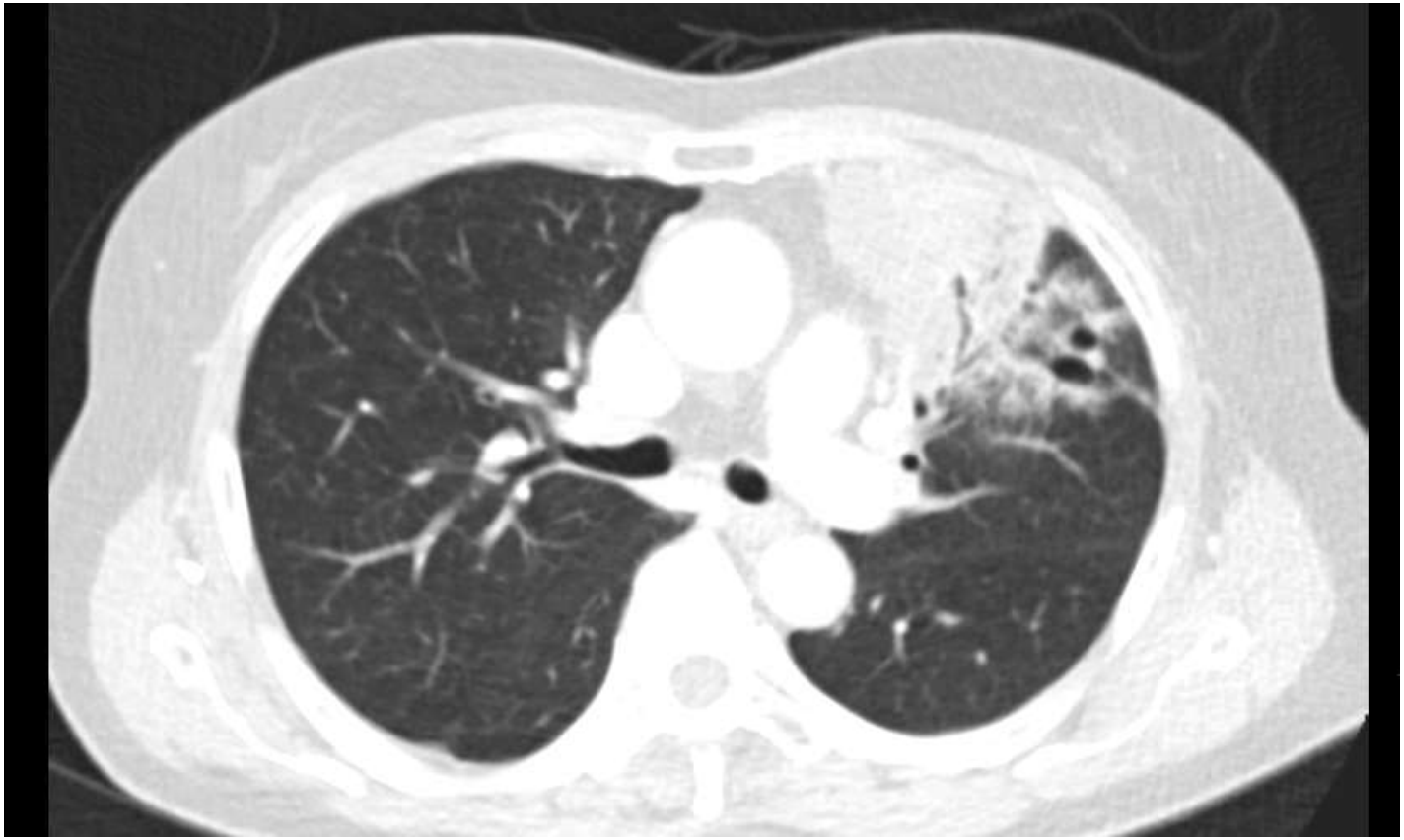
Case 2.

Case presentation

- **75/F**
- **Pneumonia lasting more than 2 months**
- **LUL lesion persists even after treatment for pneumonia**

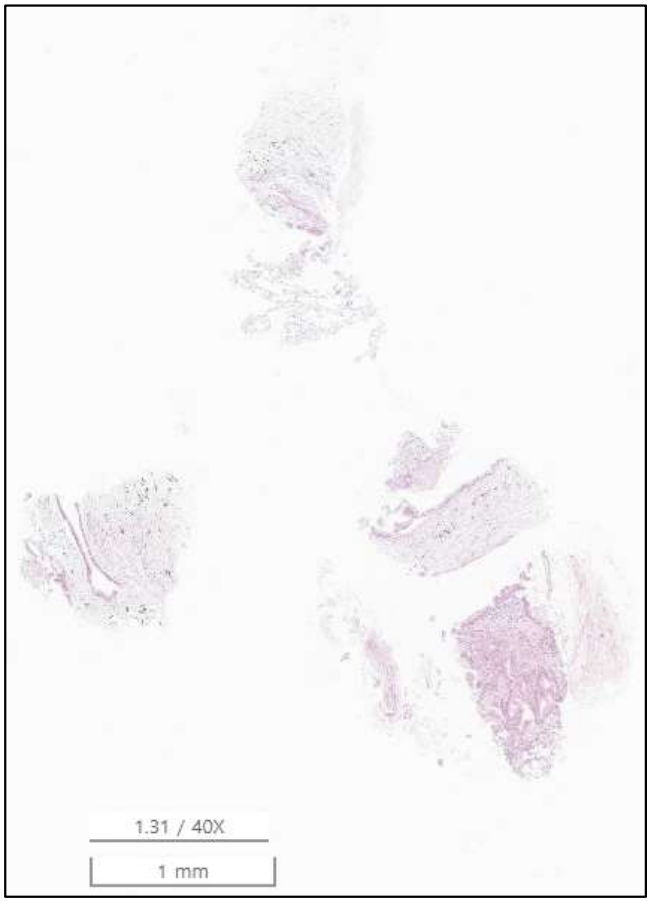
- **Never-smoker**

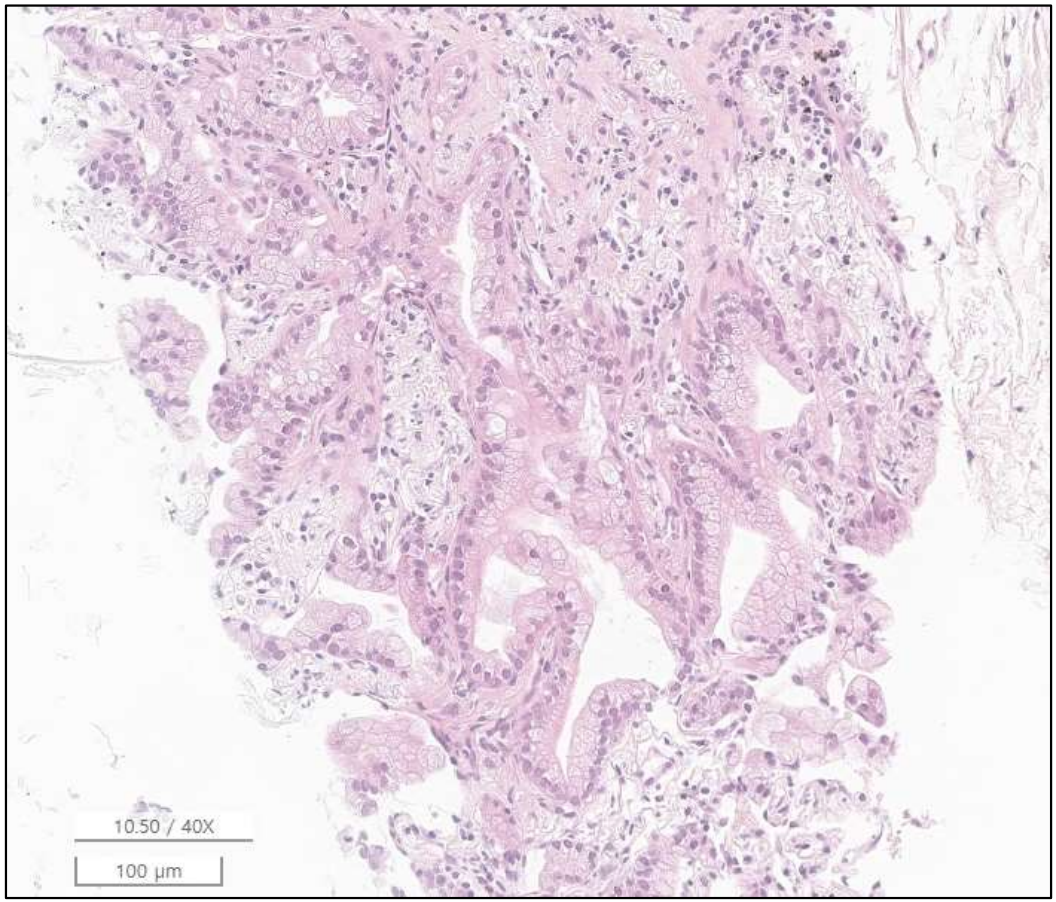
Chest CT



- **Segmental consolidation with GGO in LUL anterior segment, probable pneumonia**

CT-guided biopsy

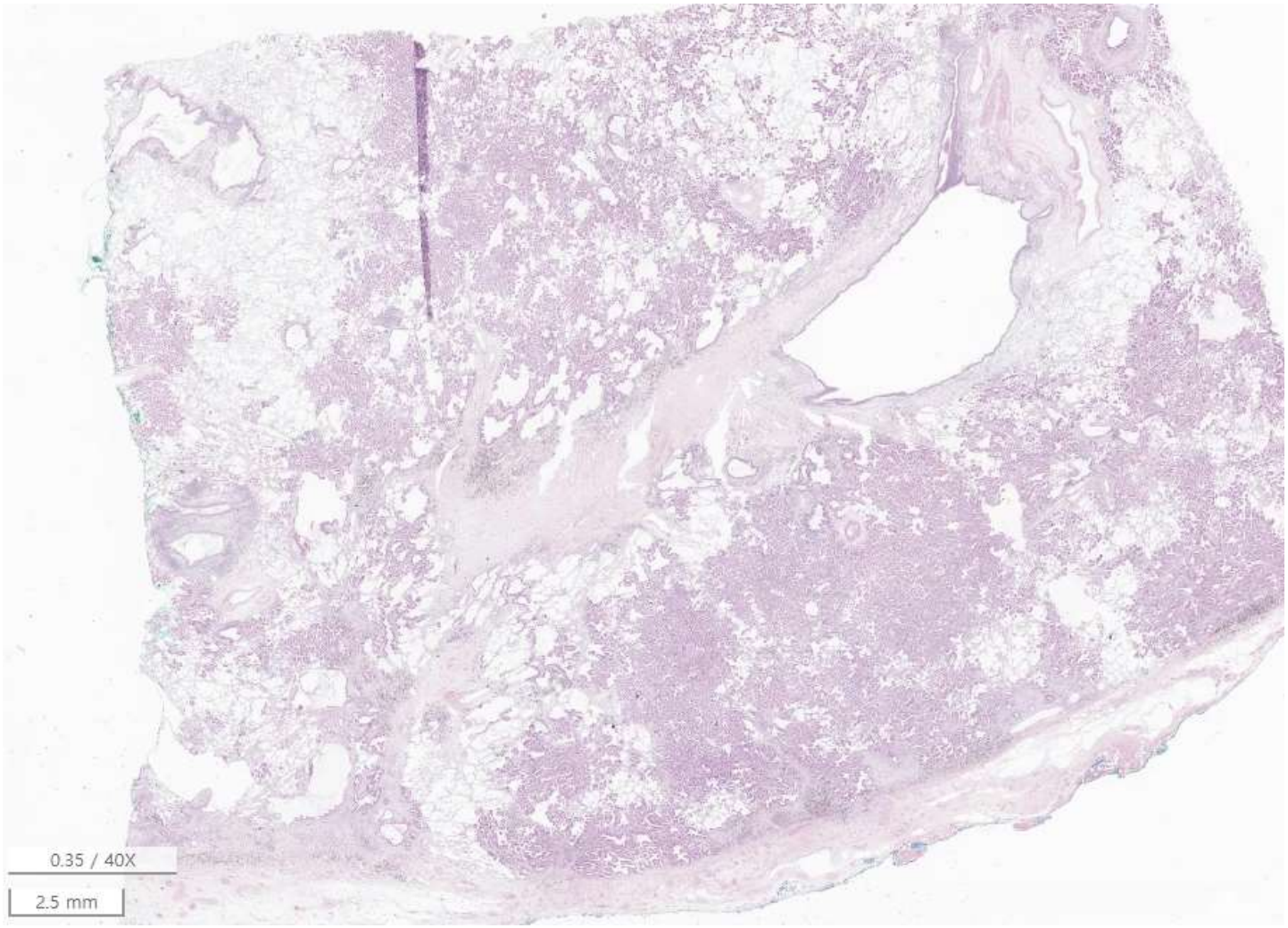




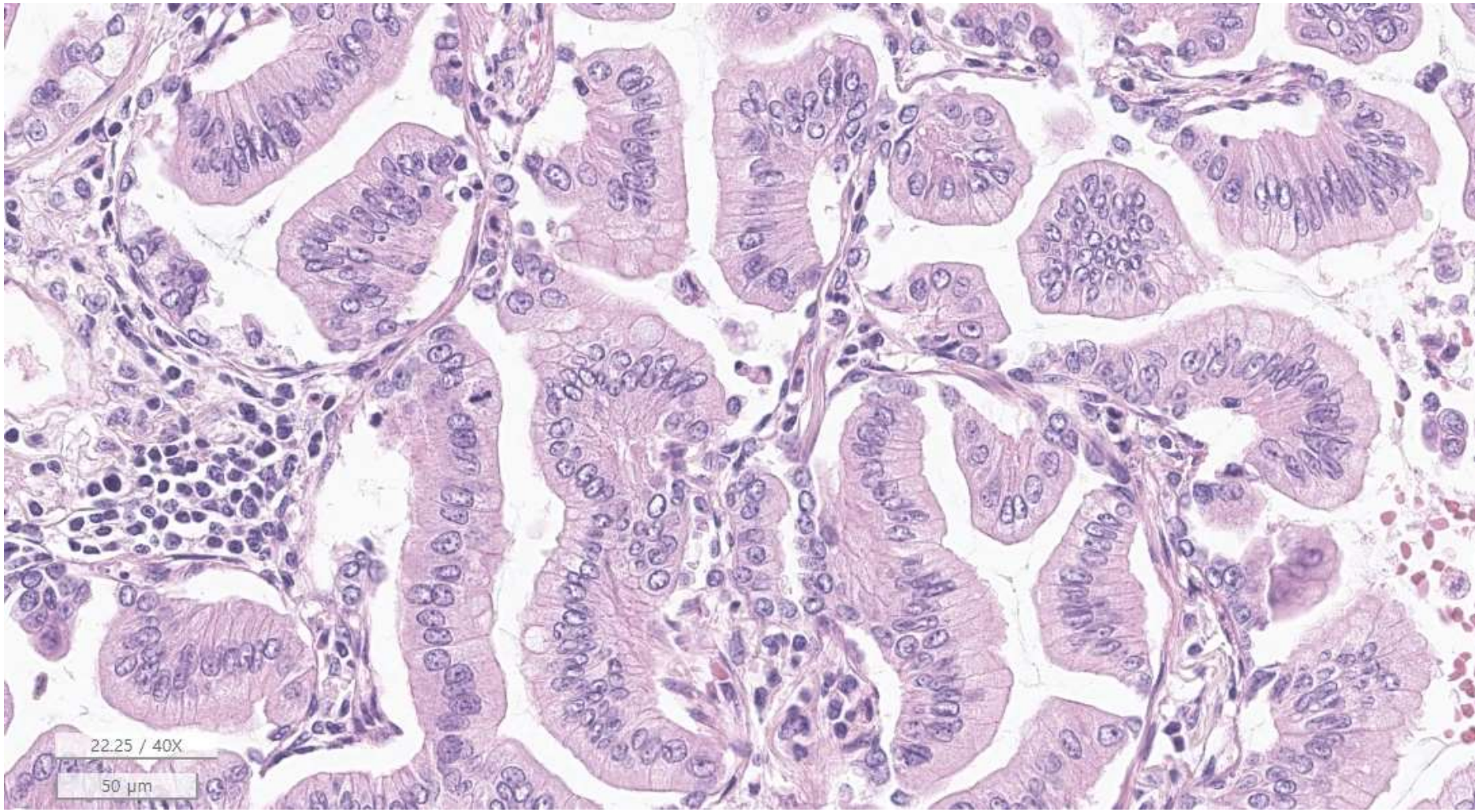
Lung, LUL, lobectomy

About 8x7cm

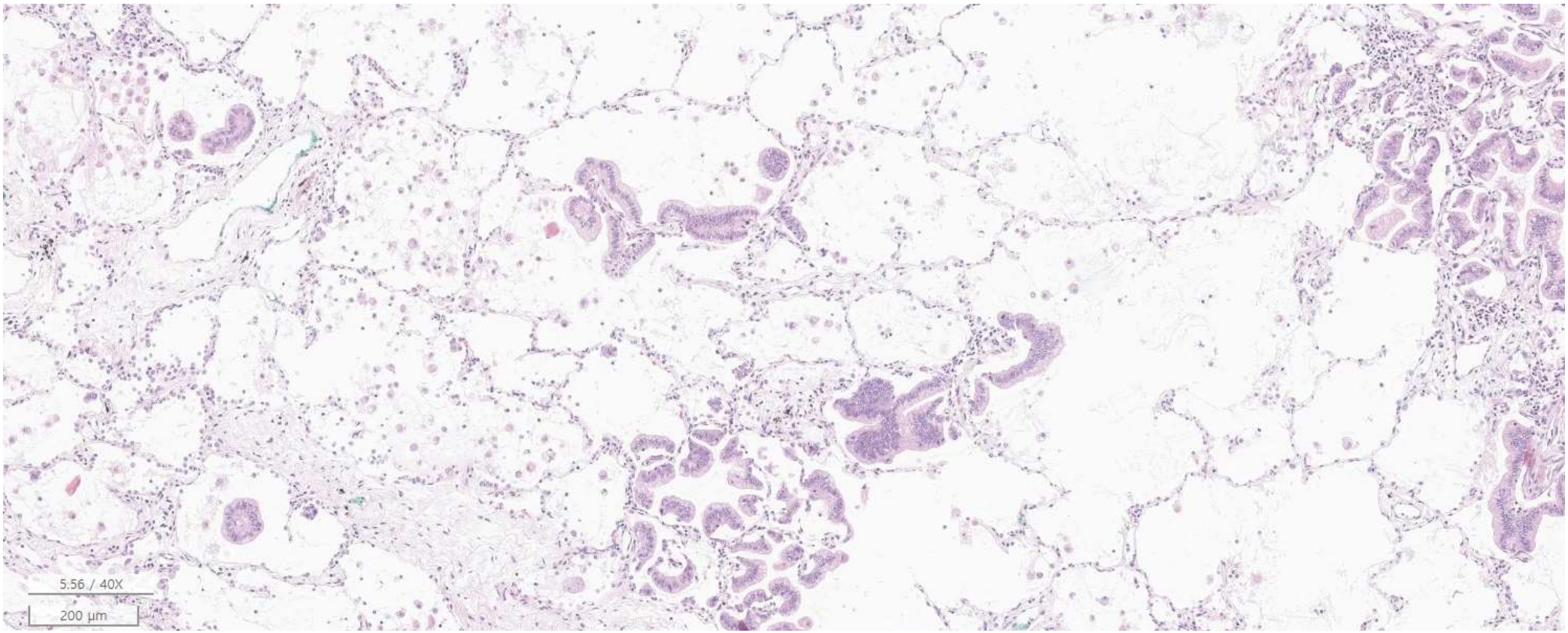
Lung, LUL, lobectomy



Microscopic finding



Microscopic finding



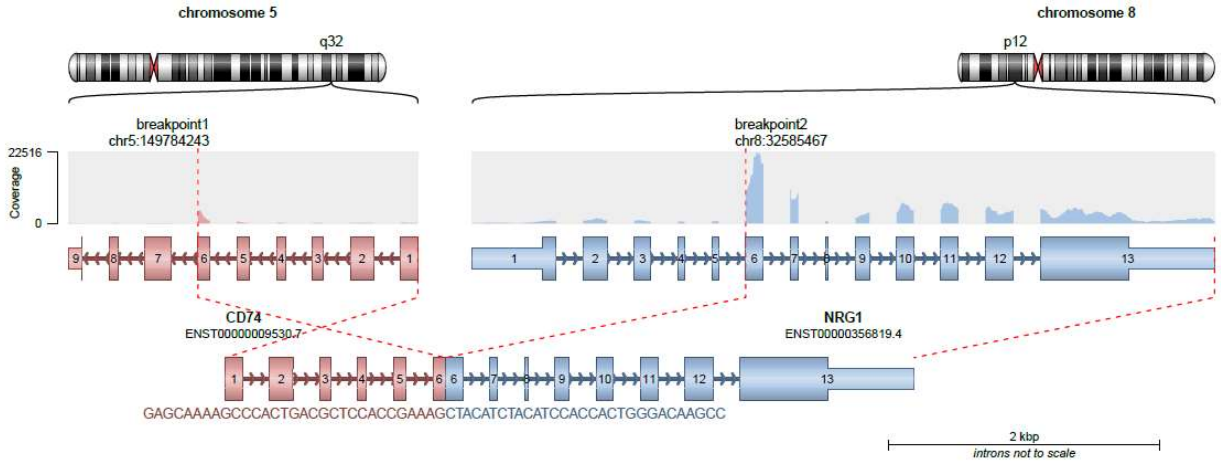
Diagnosis & Clinical follow-up

- **Invasive mucinous adenocarcinoma**
- **pT4N0**

- **s/p adjuvant CTx**
- **Recurrence: RUL mass**

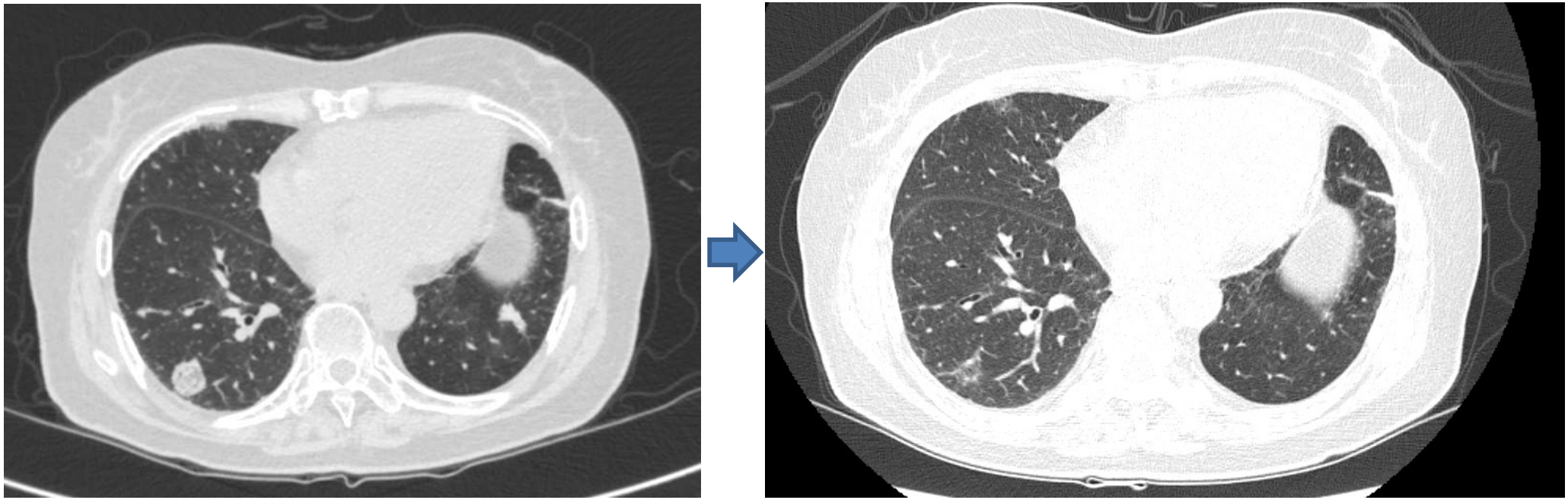
Molecular testing

- *EGFR/ALK/ROS1 -/-/-*
- **NGS**
  - *CD74::NRG1* **fusion**



- **Enrolled in a clinical trial with MCLA-128 (Zenocutuzumab)**

MCLA-128 clinical trial

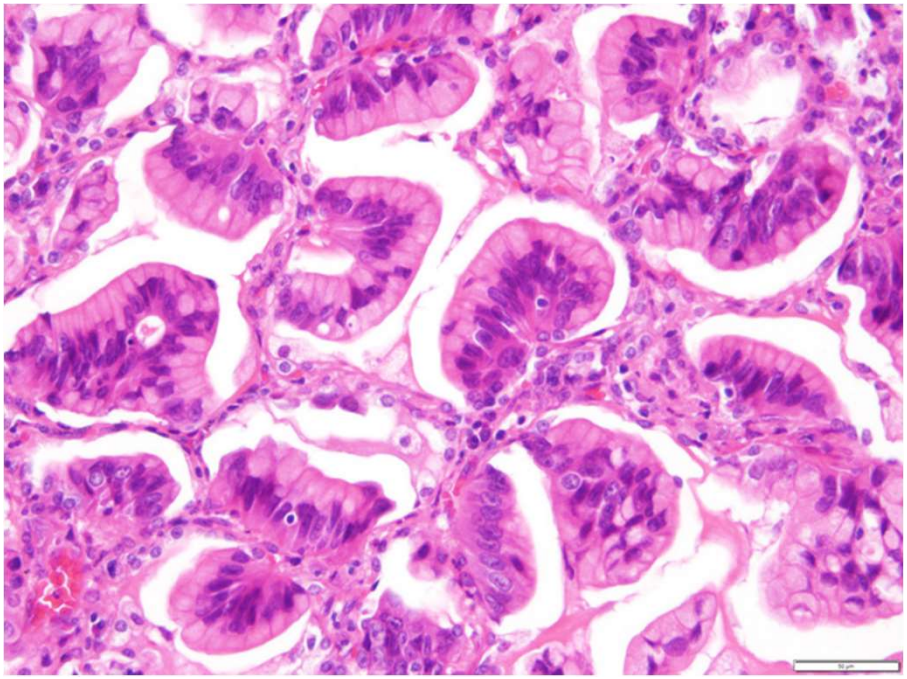


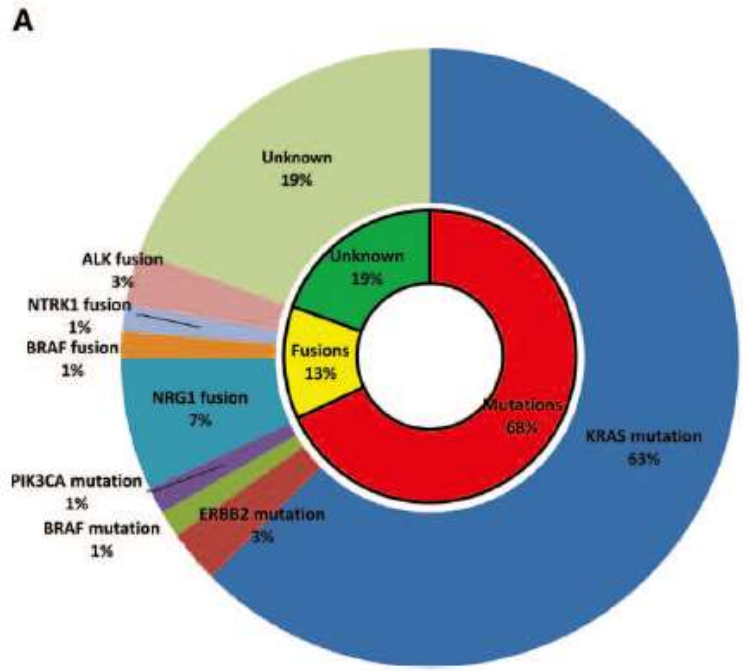
2 months later (decreased tumor burden)

Points of Case 2.

- **Presented as pneumonia**
- **Invasive mucinous adenocarcinoma**
- ***NRG1* fusion**
- **Response to HER2xHER3 inhibition**

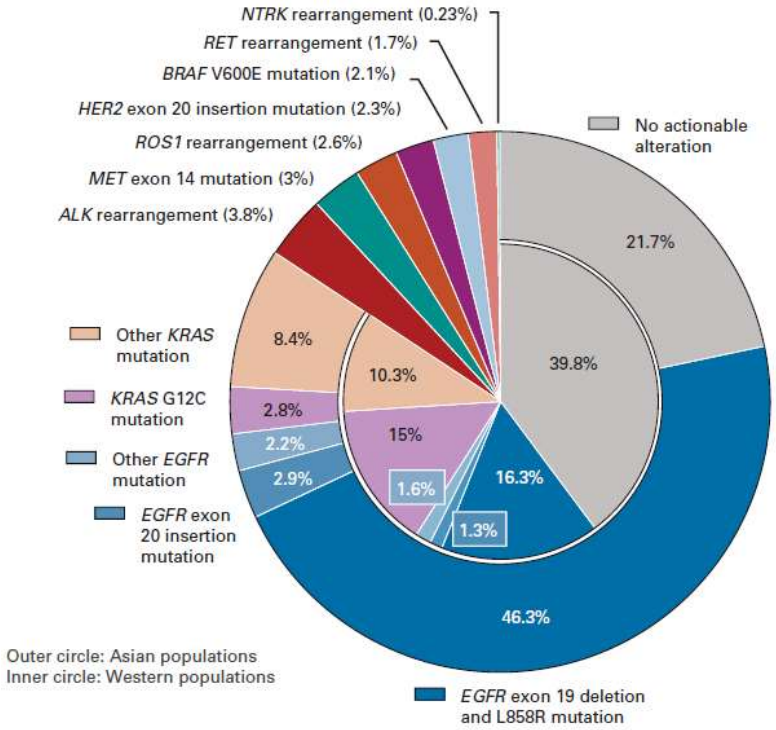
Invasive mucinous adenocarcinoma

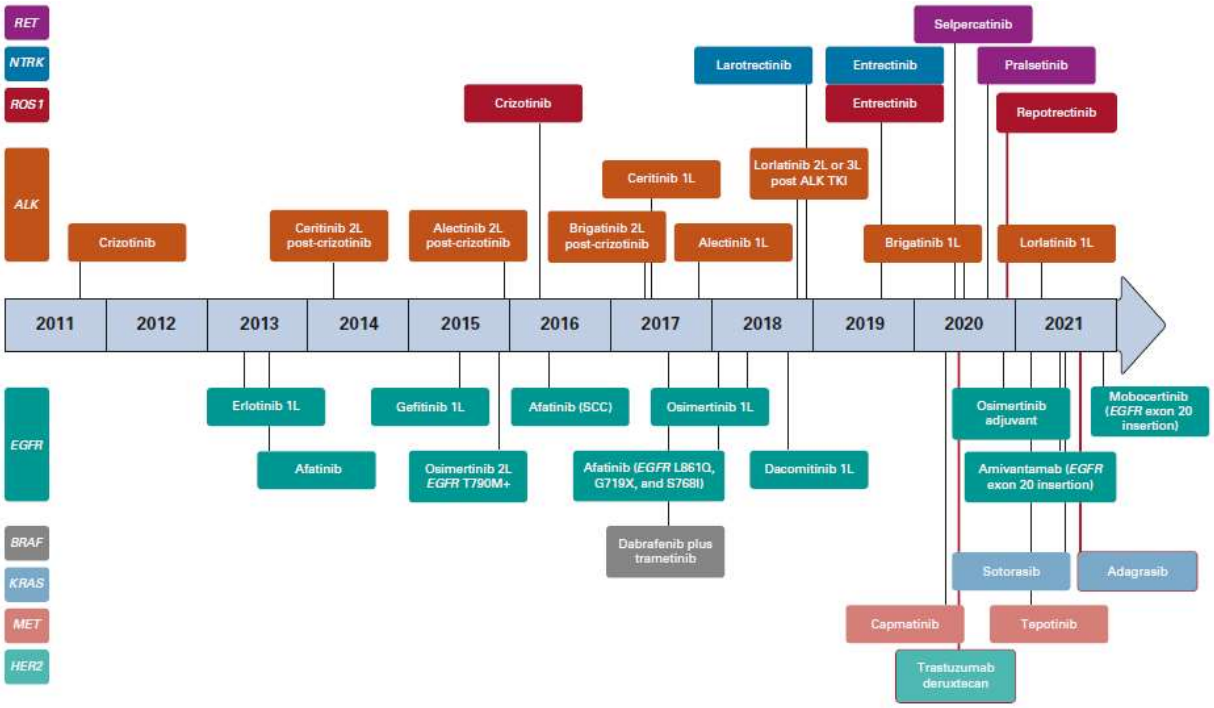




Shim HS, et al. J Thorac Oncol 2015;10:1156-62.
Cha YJ & Shim HS. Transl Lung Cancer Res 2017;6:508-12.

Cf. Targetable oncogenic driver molecular alterations in ADC





J Clin Oncol 2022;40:611-25.

NRG1 fusion & Targeted therapy

RESEARCH BRIEF

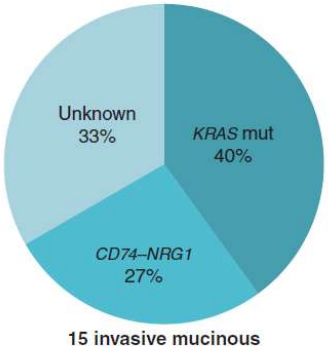
CD74–NRG1 Fusions in Lung Adenocarcinoma

A

Sample	Age	Sex	Stage	Smoking status	AD subtype
Index-case	64	Female	Ib	Never	Invasive mucinous
Case-A	73	Female	Ia	Never	Invasive mucinous
Case-B	72	Female	Ia	Never	Invasive mucinous
Case-C	66	Female	Ia	Never	Invasive mucinous
Case-D	31	Female	Ia	Never	Invasive mucinous

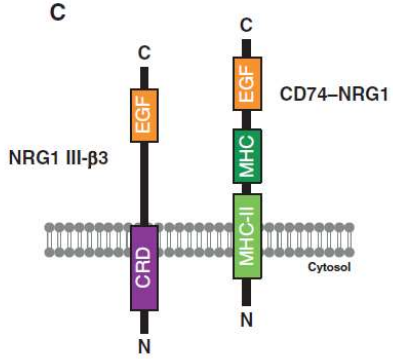
EGFR, KRAS, BRAF, HER2, ALK, ROS, RET negative

B

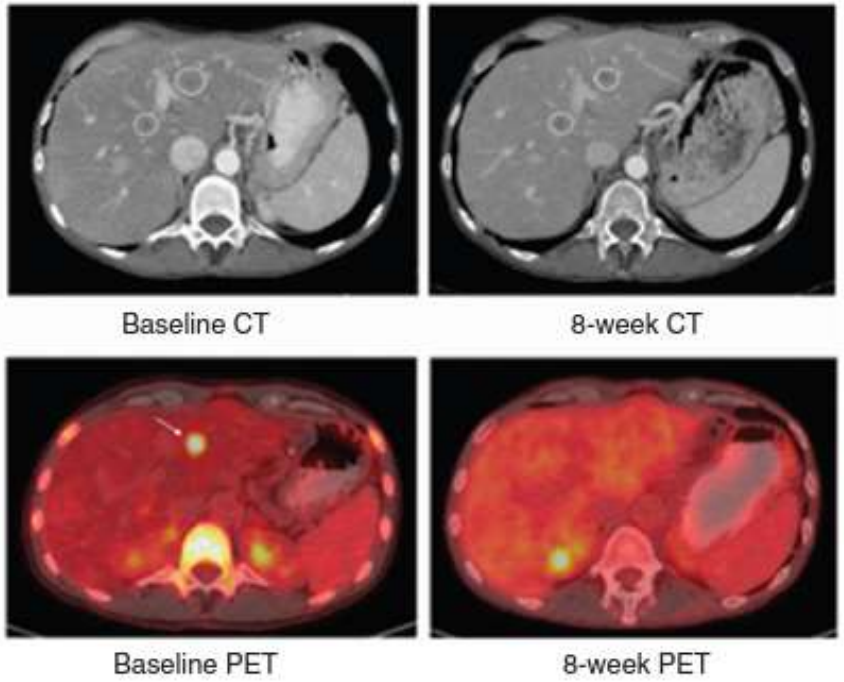


15 invasive mucinous adenocarcinomas

C



Zenocutuzumab, a HER2xHER3 Bispecific Antibody, Is Effective Therapy for Tumors Driven by *NRG1* Gene Rearrangements



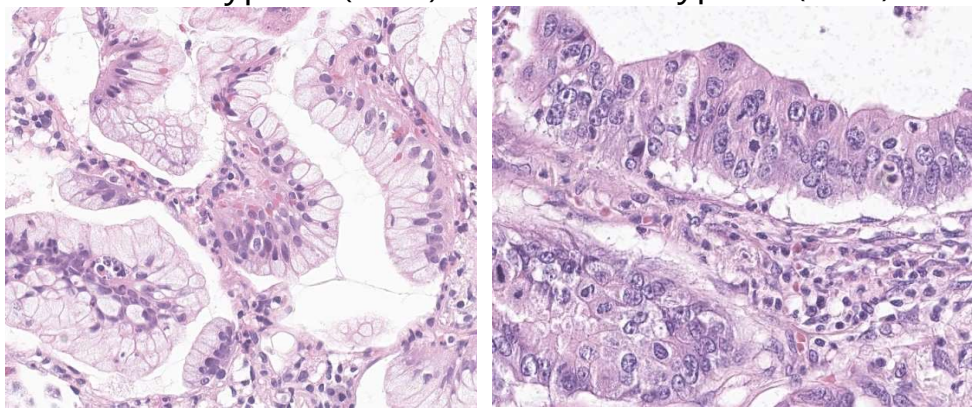
Cancer Discov 2014;4:415-22.
Cancer Discov, 2022. 12(5): p. 1233-1247.

NSCLCs with *NRG1* fusion at Severance Hospital (1)

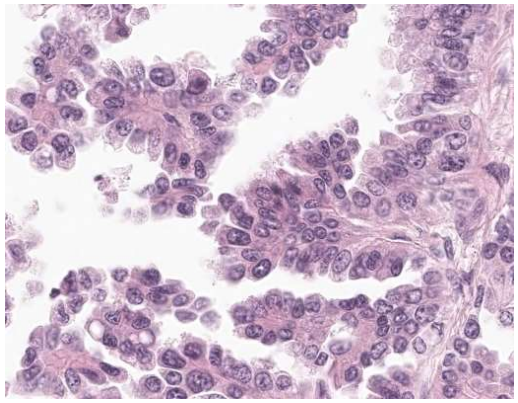
- **Frequency: 17 out of 1496 patients with Non-Squamous NSCLC (1.13%)**
- **Average age: 60 years (range: 32-78); Sex: Female (52.9%); Smoking history: Never-smoker (58.8%)**
- **Histology: Adenocarcinoma (100%); mucinous histology (58.8%)**

Mucinous (59%)

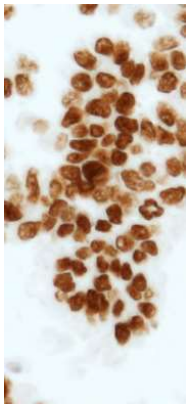
Typical (30%) Atypical (70%)



Non-mucinous (41%)



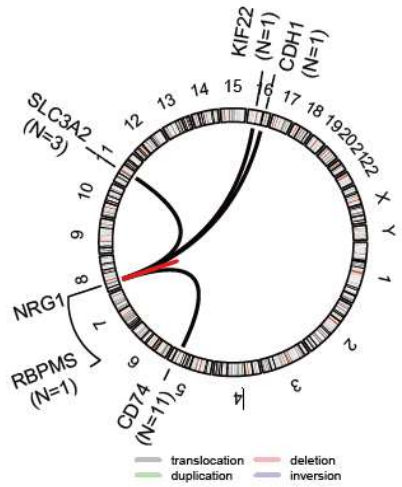
TTF-1 + (35.3%)



Shim HS, et al. Presented at 2023 WCLC

NSCLCs with *NRG1* fusion at Severance Hospital (2)

- **Partner genes: CD74 (64.7%), SLC3A2 (17.6%)**
- **Co-occurring genetic alterations: Less than 3 (88.2%), *TP53* mutation (47%)**
- **TMB: <10/Mb (84.6%); PD-L1 expression: TPS<1% (80%), 1~49% (20%), ≥50% (0%)**
- **Clinical feature: Combined extra- and intra-thoracic metastases (including lung-to-lung metastases) (58.8%); Poor response to conventional therapies.**



Order by *NRG1* partner

Clinical information	Patient ID	Lung15	Lung07	Lung09	Lung01	Lung04	Lung16	Lung06	Lung17	Lung03	Lung08	Lung11	Lung10	Lung13	Lung05	Lung02	Lung12	Lung14
Fusion	*NRG1* partner	*CD74*											*SLC3A2*			*KIF22*	*RBPMS*	*CDH1*
SNV/INDEL	*TP53*																	
	KRAS																	
	BRCA1																	
	BRCA2																	
	RBM10																	
	SMAD4																	
	NF2																	
	TSC2																	
	CDKN2A																	
	PAX3																	
CNV	*MDM2*																	
	CDK4																	
	MYC																	
	ERBB2																	
TMB (mut/Mb)		4.7	3.9	0.8	NA	NA	5.5	3.2	6.3	7.1	0.8	NA	5.5	<1	NA	51.2	22.8	4.7

*NA: Not available

Missense variant
Splice variant
Frameshift indel
Stop gain
Amplification
High-TMB

Shim HS, et al. Presented at 2023 WCLC

NRG1 fusion-positive solid tumors in Korean Patients

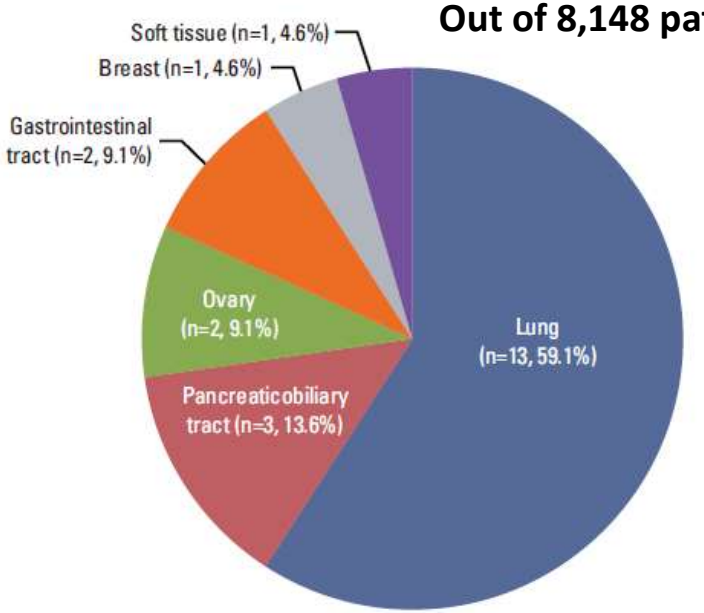
Original Article

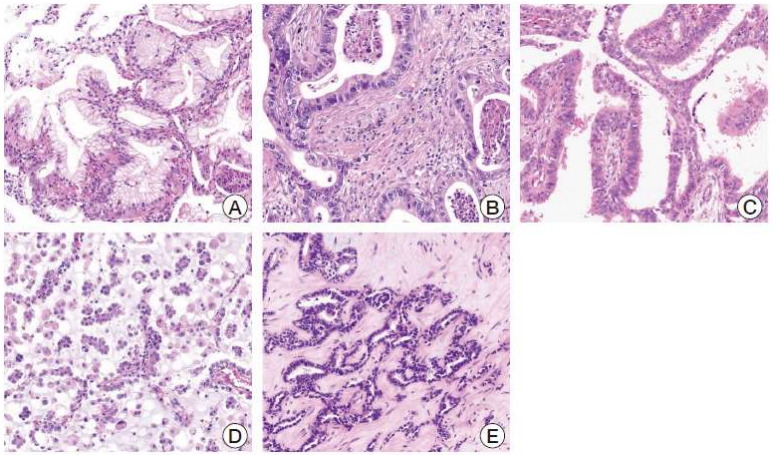
Clinicopathological Characteristics of *NRG1* Fusion–Positive Solid Tumors in Korean Patients

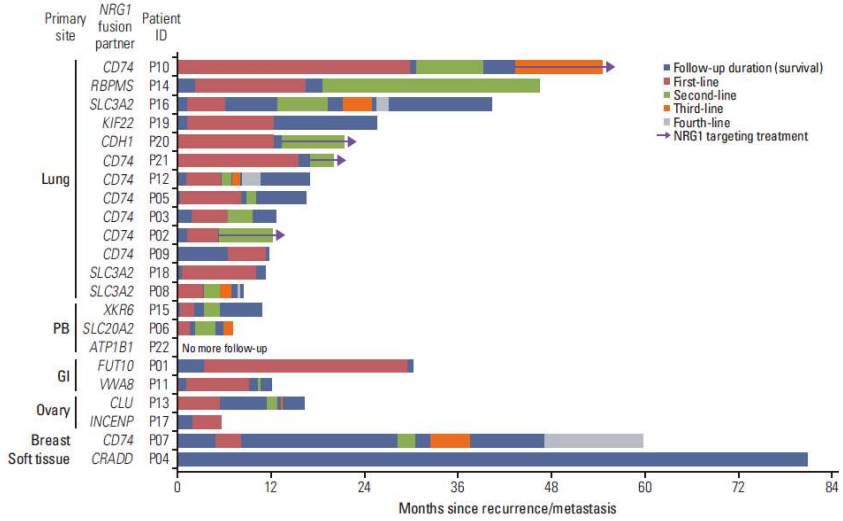
Yoon Jin Cha[1], Chung Lee[1], Bio Joo[2], Kyung A Kim[1], Choong-kun Lee[3], Hyo Sup Shim[1]

Departments of [1]Pathology and [2]Radiology, Yonsei University College of Medicine, Seoul, [3]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea

Out of 8,148 patients







Cancer Res Treat 2023;55:1087-95.

Take home message of Case 2.

- **IMA is a unique subtype of lung cancer.**
- **About 7% of IMA is *NRG1* fusion-positive.**
- ***NRG1* fusion-positive lung cancers are molecularly, pathologically, and clinically heterogeneous.**
  - **41%: Non-mucinous adenocarcinoma.**
  - **Mucinous type: Frequently 'atypical' mucinous features**
  - **Clinical: Frequent involvement in extra-thoracic organs**
- **<u>Molecular identification of *NRG1* fusion in clinical practice can lead to new targeted therapies.</u>**

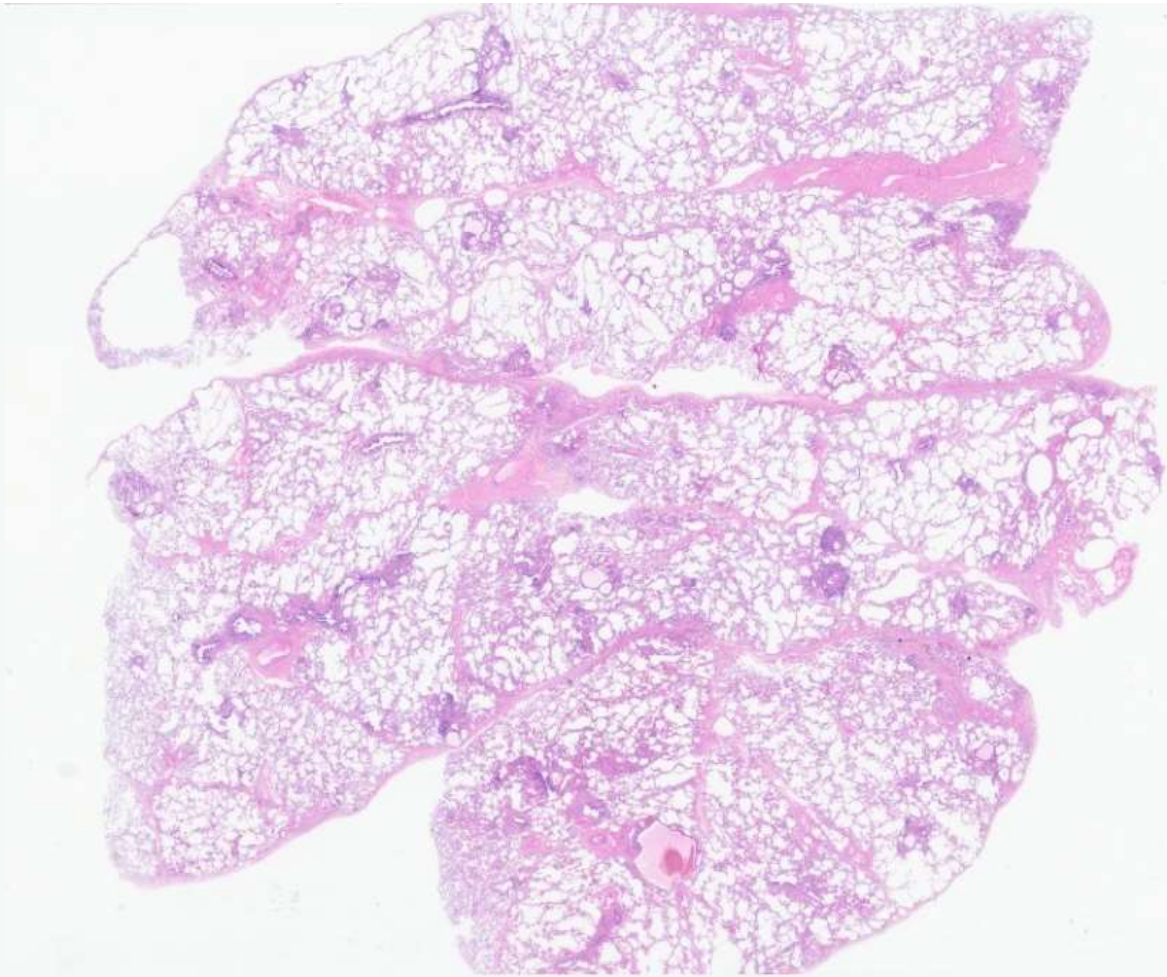
Case 3.

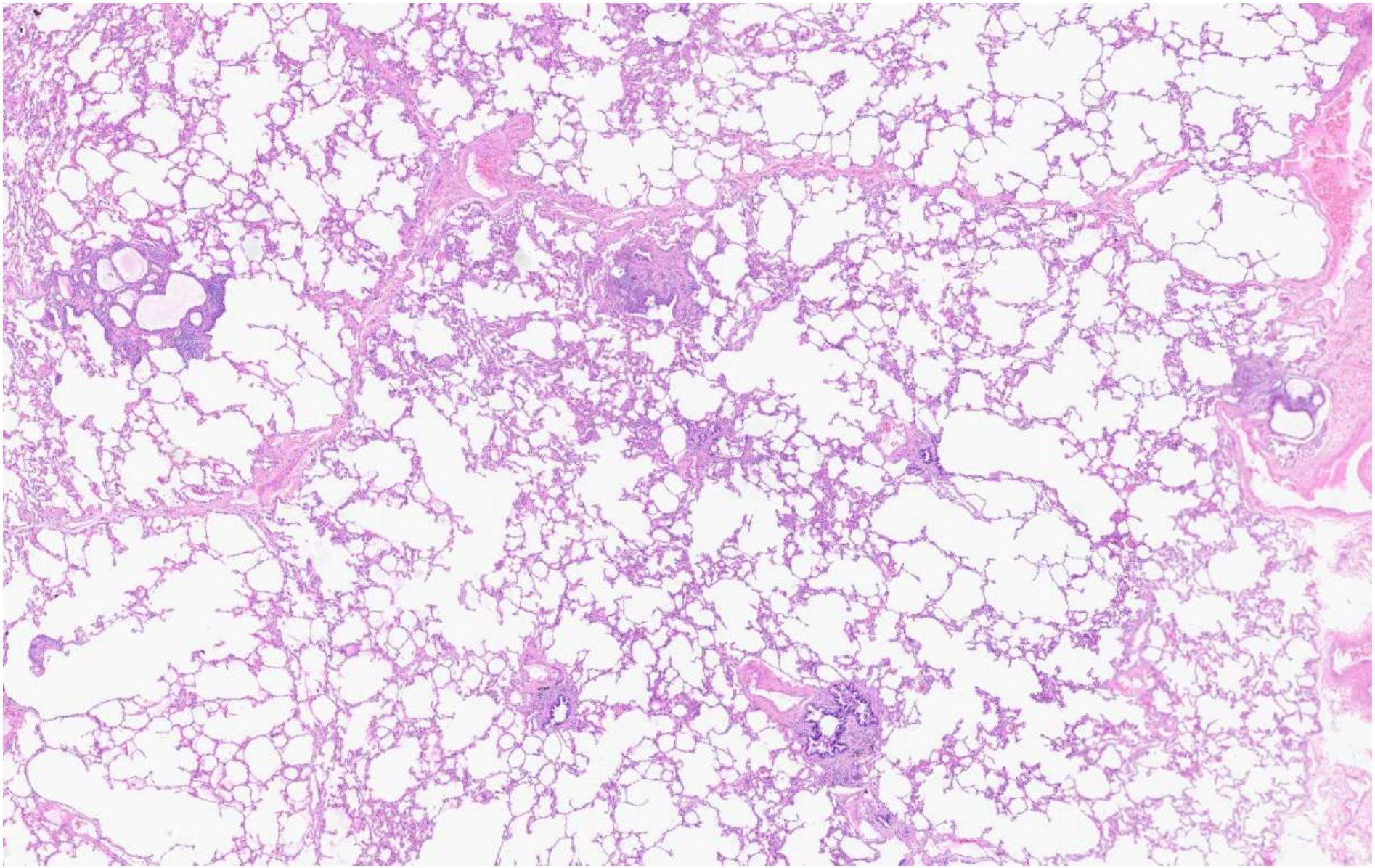
Case presentation

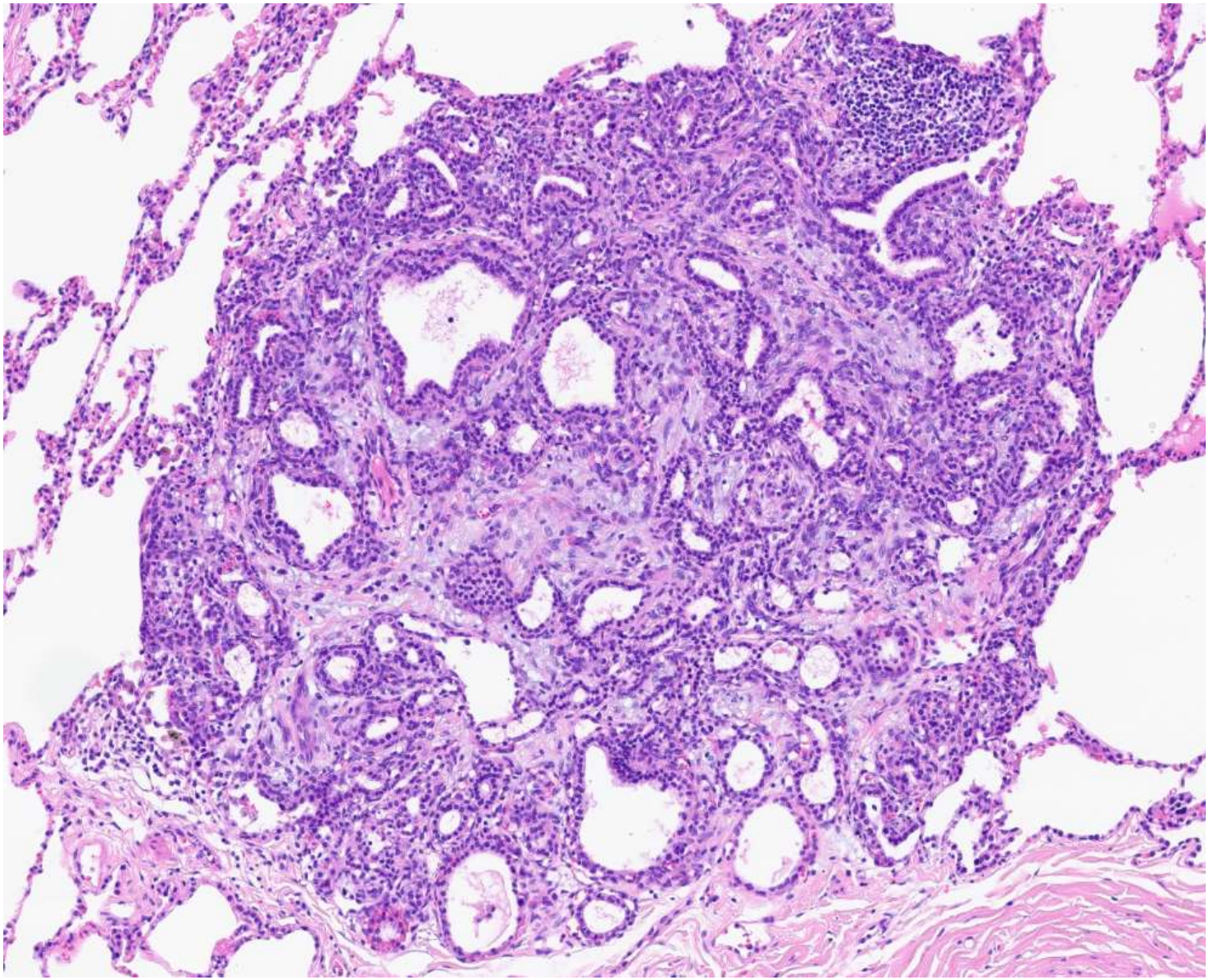
- **20/F**
- **Multiple variable sized noncalcified nodule, r/o lung metastasis, found on chest CT**

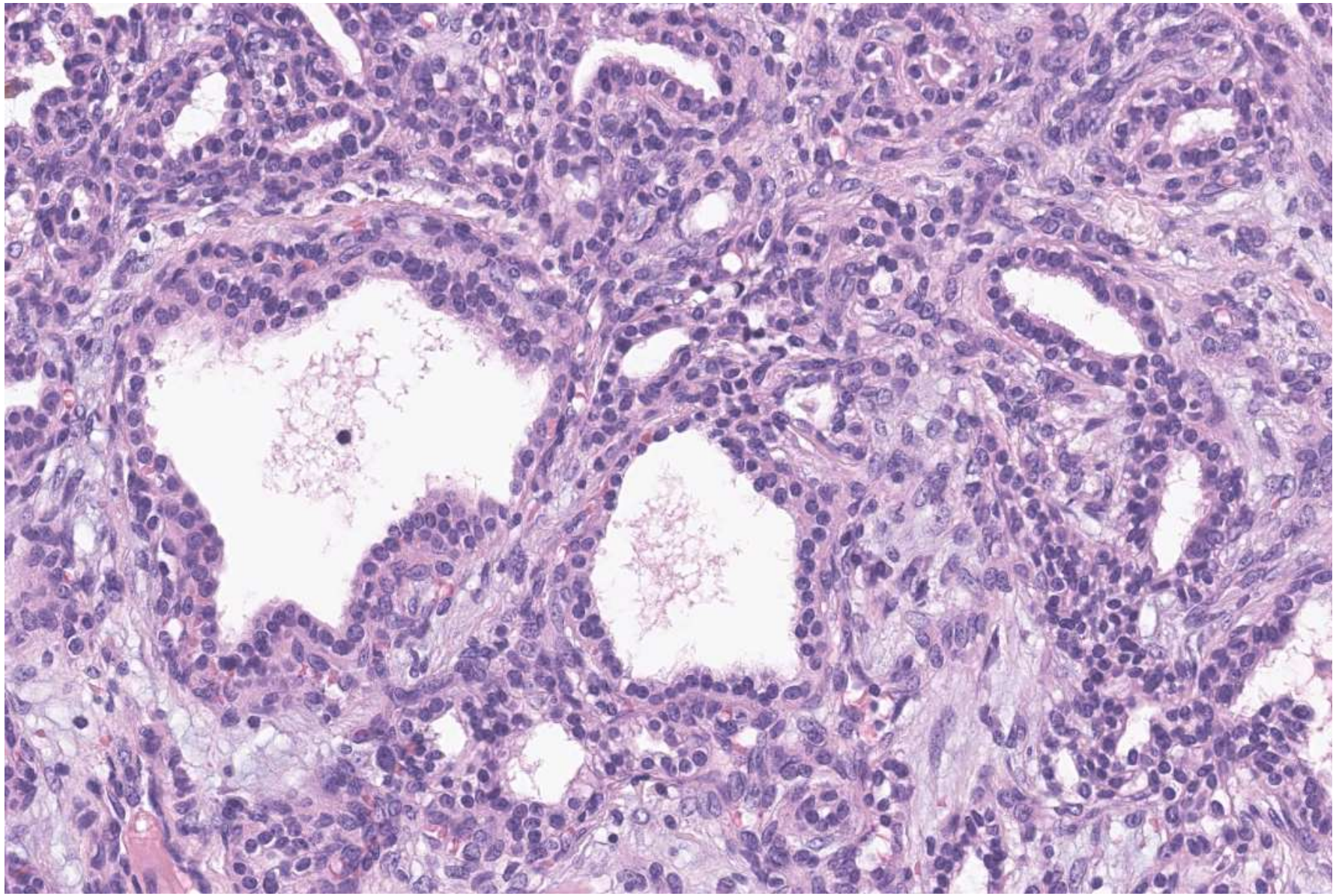
- **Lung, left upper lobe, wedge resection was done.**

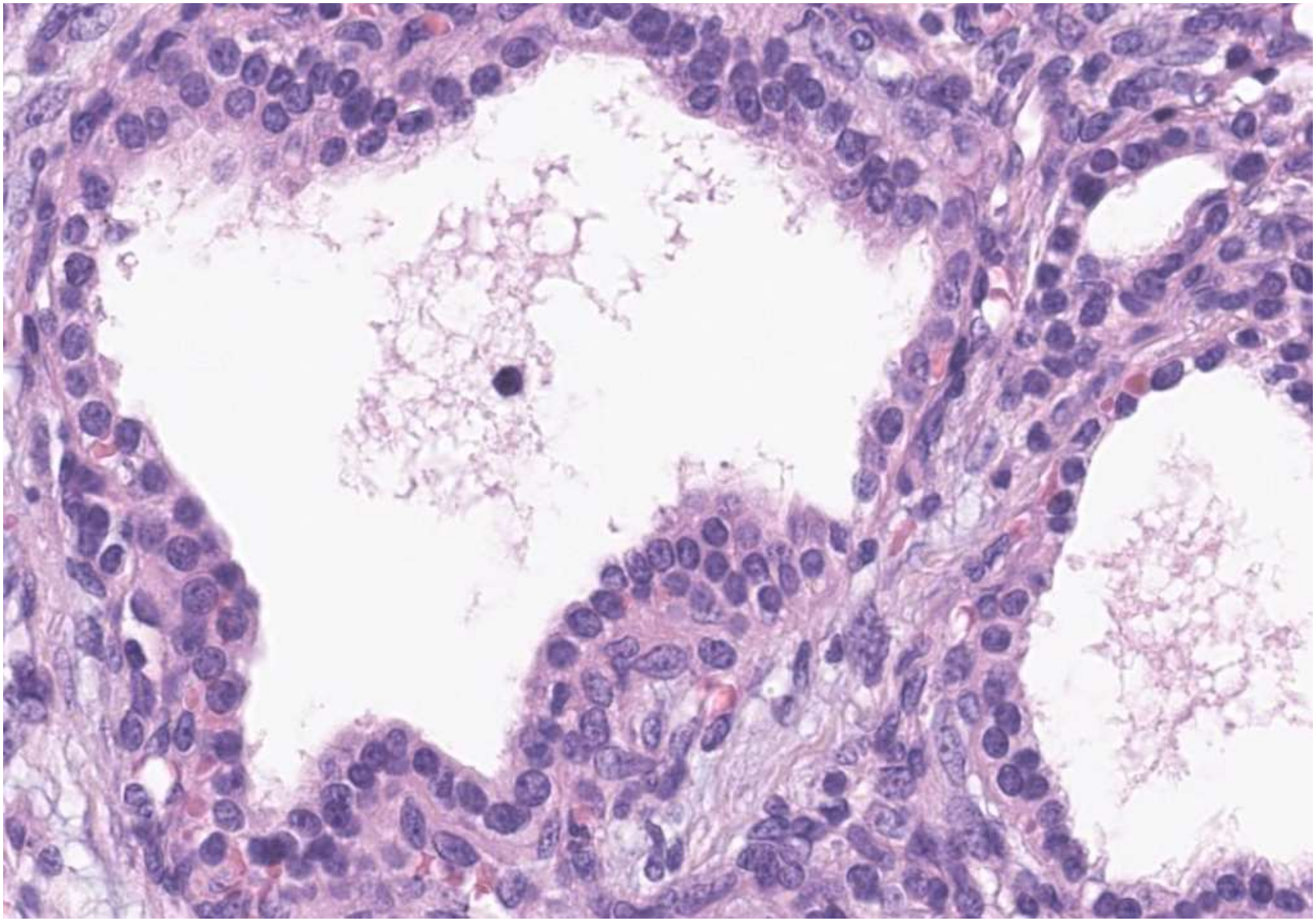
Microscopic finding

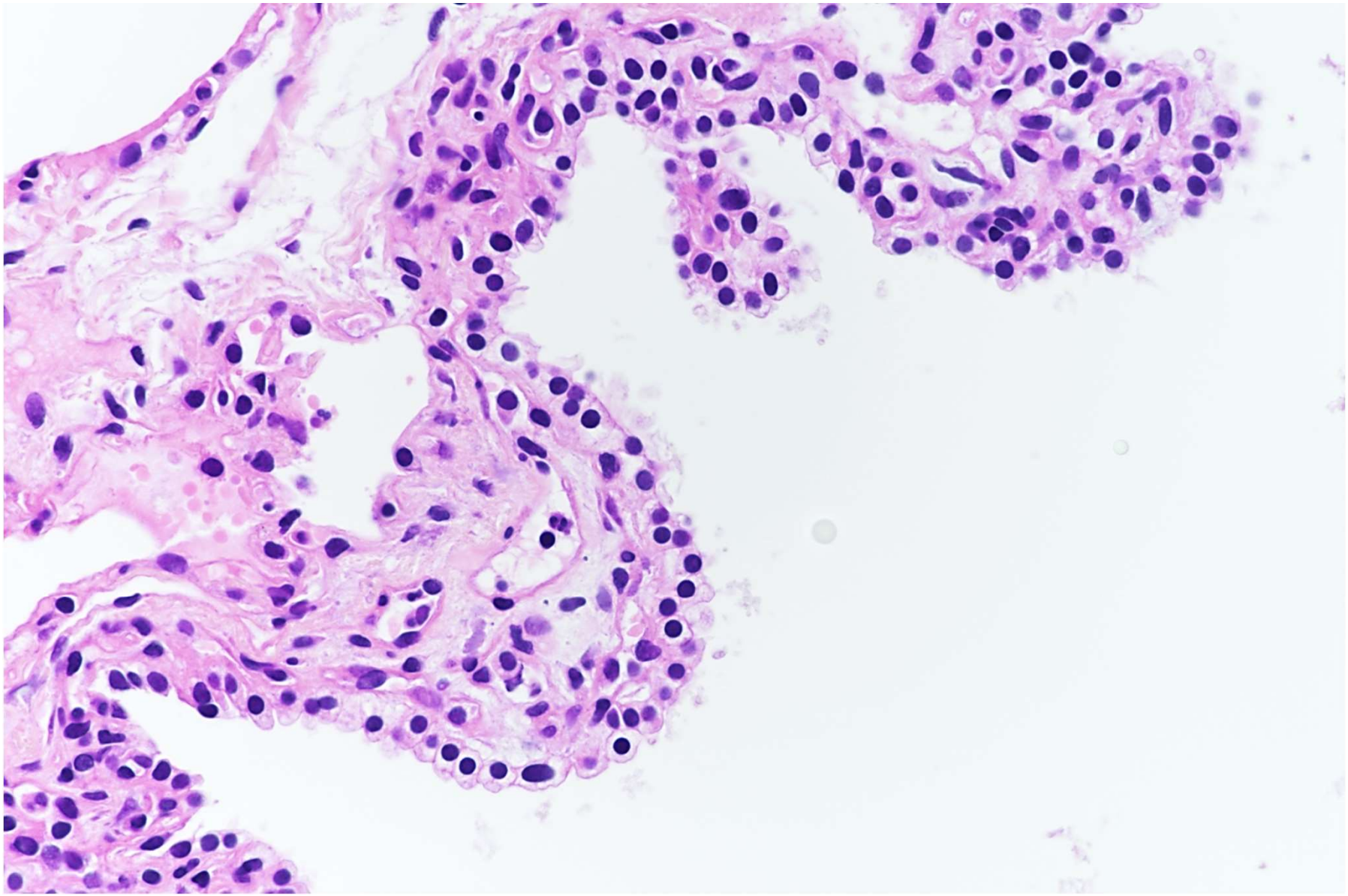


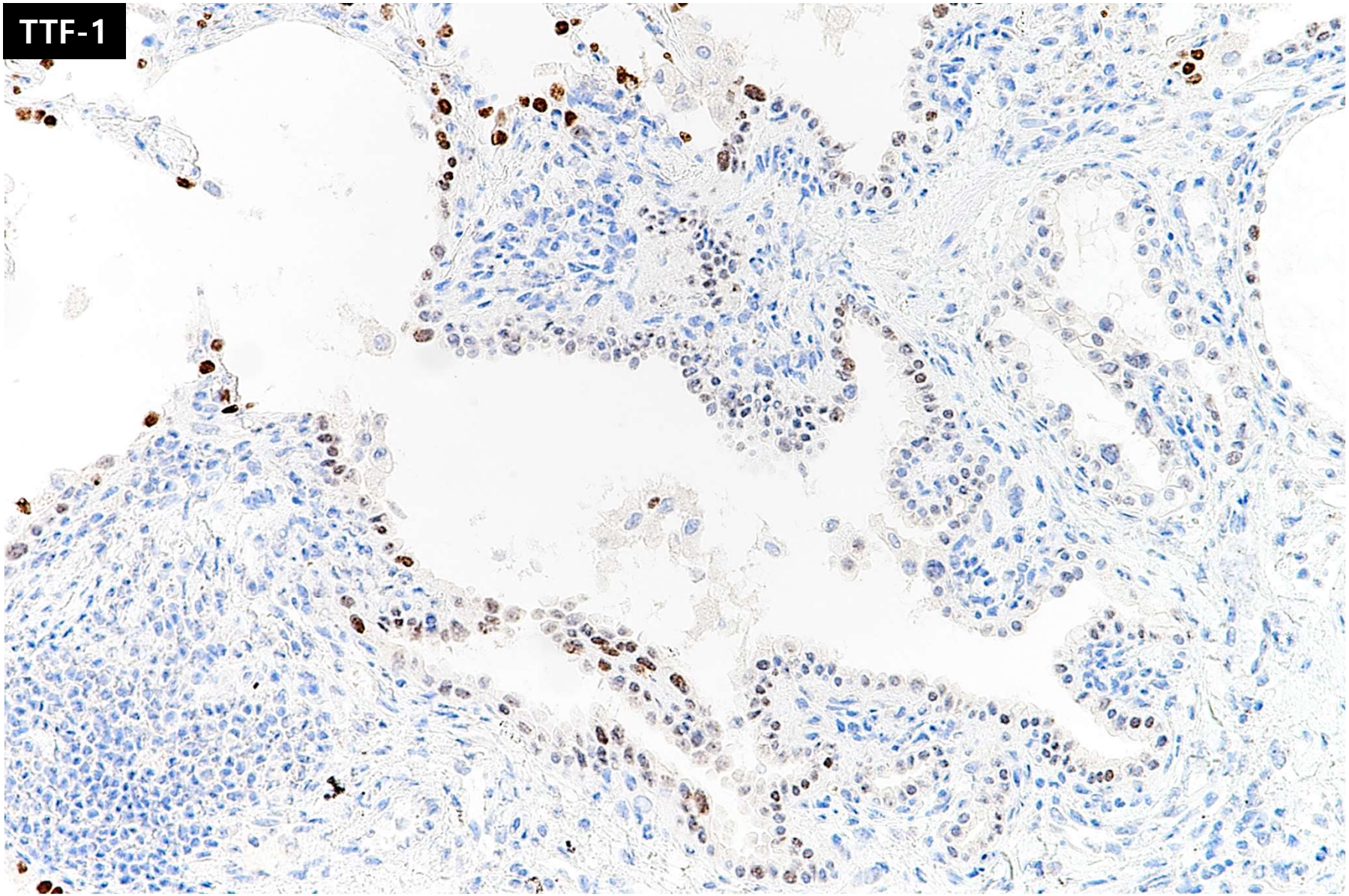




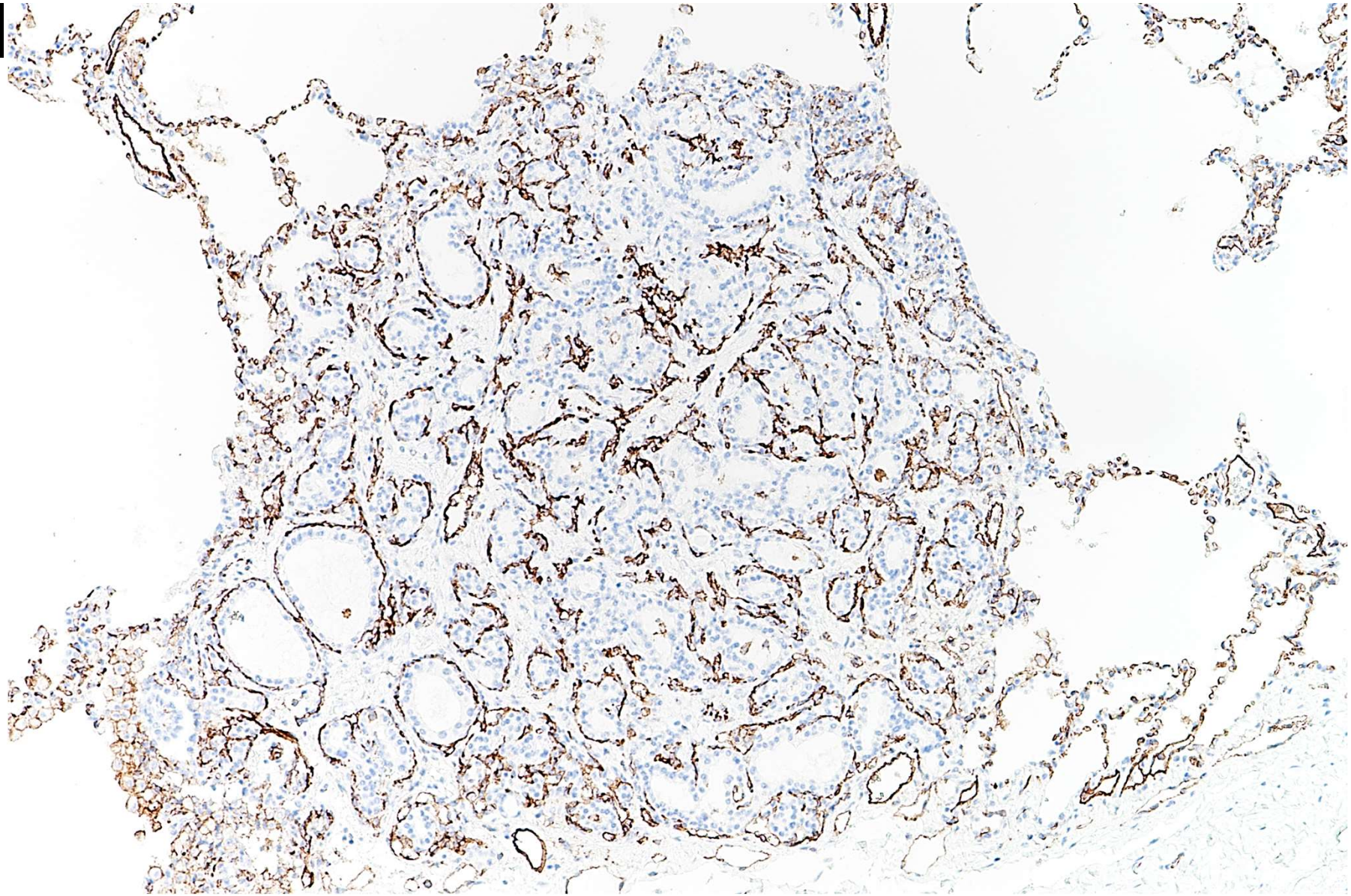







TTF-1

CD31



Microscopic findings

- **Multinodular small expansile mass-forming lesions, without connection to each other**
- **Multicystic lesion lined by non-ciliated cuboidal epithelium, some of which shows clear cytoplasm, without definite atypia**
- **Occasional minimal peritumoral lymphoid aggregates**

- **Hamartomatous lesion?**

*Clinical history

- **Abdominal pain in December 2017**
- **Suspected renal tumor (r/o RCC), pancreatic tumor (r/o NET)**
- **Germline NGS: *VHL* exon2 deletion; Diagnosis of von Hippel-Lindau syndrome**
- **Diagnosed with neuroendocrine tumor on pancreas biopsy and underwent embolization of pancreatic tumor and chemotherapy without surgery.**
- **GKS for cerebellum with cerebellum and spinal cord hemangioblastoma (no biopsy)**

Literature review

CASE REPORT

Multifocal Microcysts and Papillary Cystadenoma of the Lung in von Hippel-Lindau Disease

Julianne Klein, MD, Zhengping Zhuang, MD,† Irina Lubensky, MD,‡ Thomas V. Colby, MD,§ Felix Martinez, Jr, MD,¶ and Kevin O. Leslie, MD§*

Abstract: von Hippel-Lindau disease is an autosomal dominant inherited disorder characterized by a predisposition to multiple neoplasms. Renal cell carcinoma and hemangioblastomas of the retina and cerebellum are the most common of these, but other neoplasms and cysts also occur throughout the body. We report a distinctive, yet never described lung lesion in a 43-year-old woman with von Hippel-Lindau disease. Molecular genetic studies confirmed the presence of a VHL gene mutation in the cells of this lesion. We discuss the salient features of this novel lesion, and hypothesize on its origin and nature.

Key Words: von Hippel-Lindau, lung, cyst

(*Am J Surg Pathol* 2007;31:1292–1296)

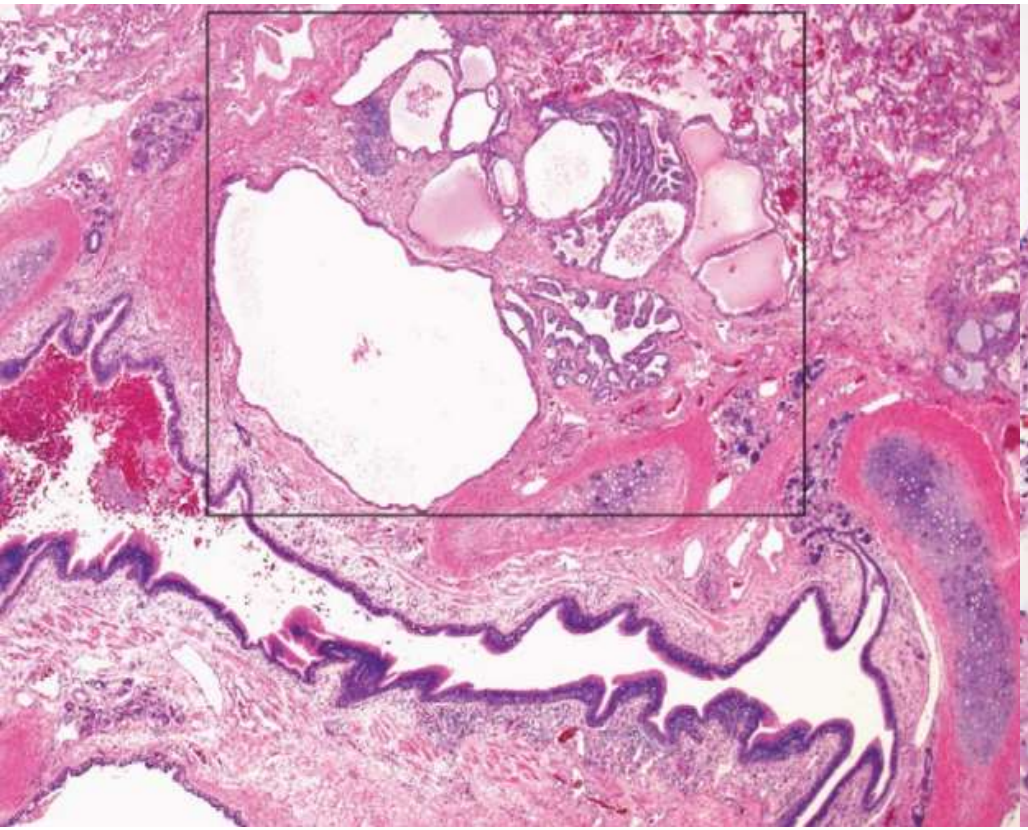
endolymphatic sac tumors,[3] clear cell carcinoid tumor of the gallbladder,[9] and clear cell papillary cystadenoma of the ovarian mesosalpinx.[1] Manifestations of VHLD are distinctly rare in the lung. Apart from a report of multiple hepatic and pulmonary hemangioblastomas,[7] primary lung lesions (hamartomas or neoplasms) related to VHL have never been reported.

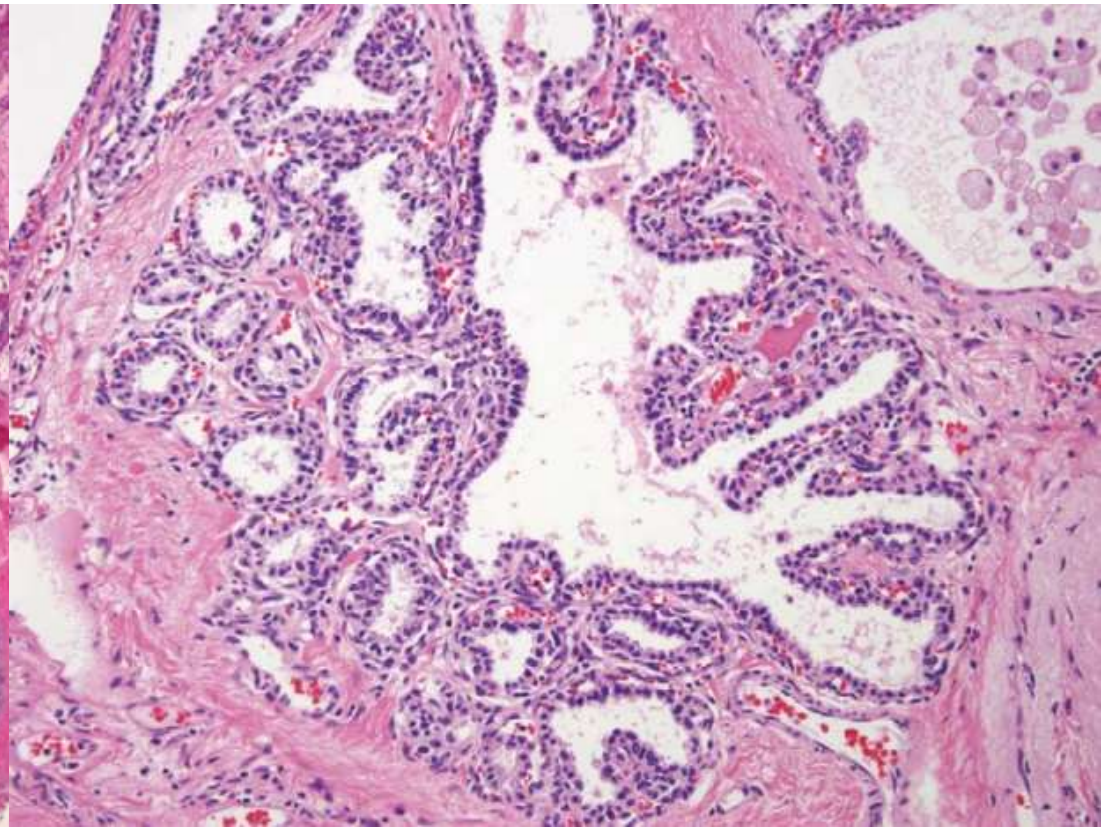
CASE REPORT

We present the case of a 43-year-old woman with VHLD. She inherited the condition from her mother, who had previously died of complications of a VHLD-related neoplasm. The patient initially presented with a pheochromocytoma and underwent adrenalectomy. She developed multiple hemangio-

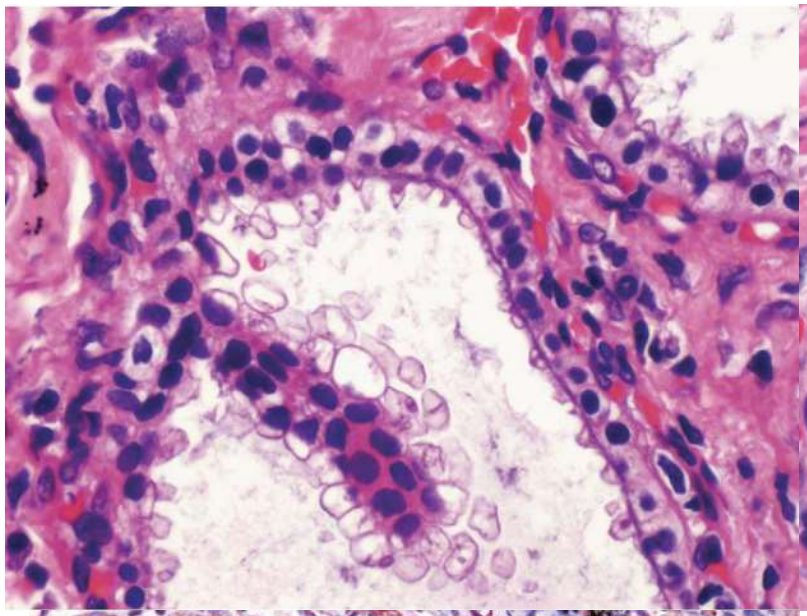
Am J Surg Pathol 2007;31:1292-6

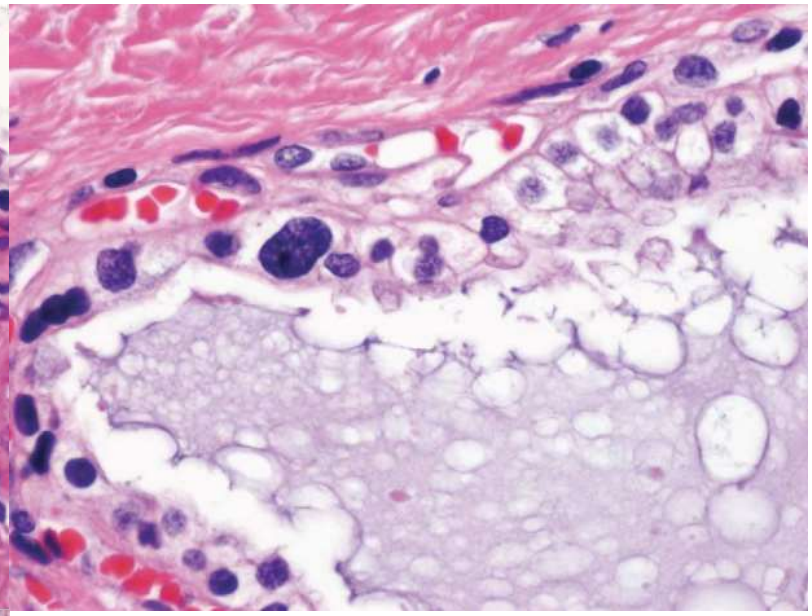
Microscopic cystic structures

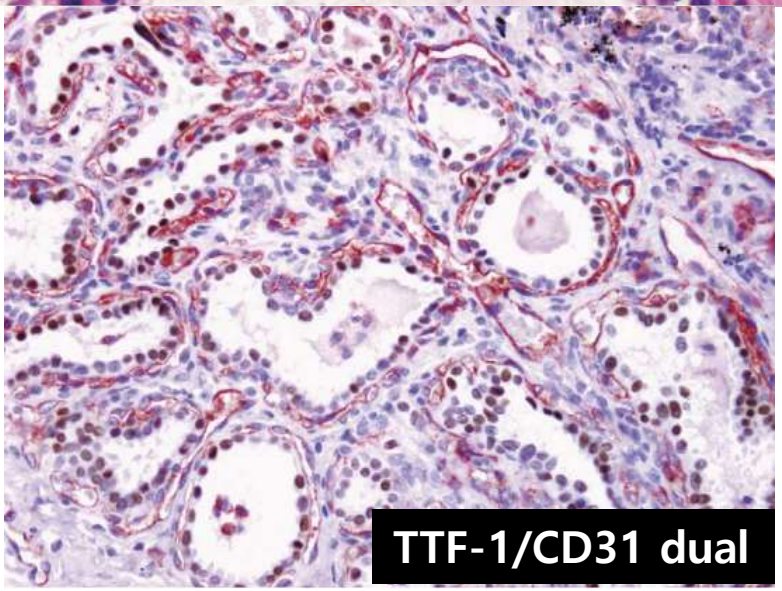




Am J Surg Pathol 2007;31:1292-6





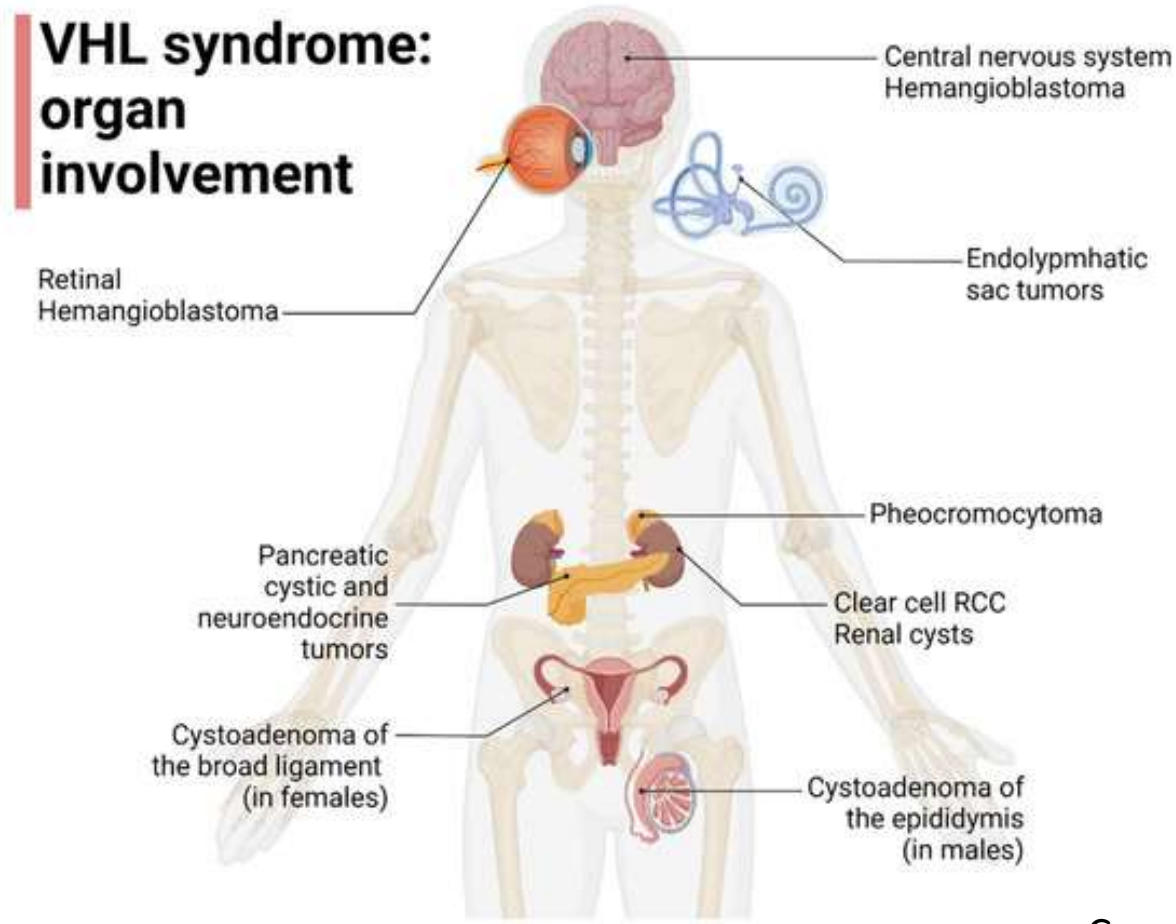


Am J Surg Pathol 2007;31:1292-6

Points of Case 3.

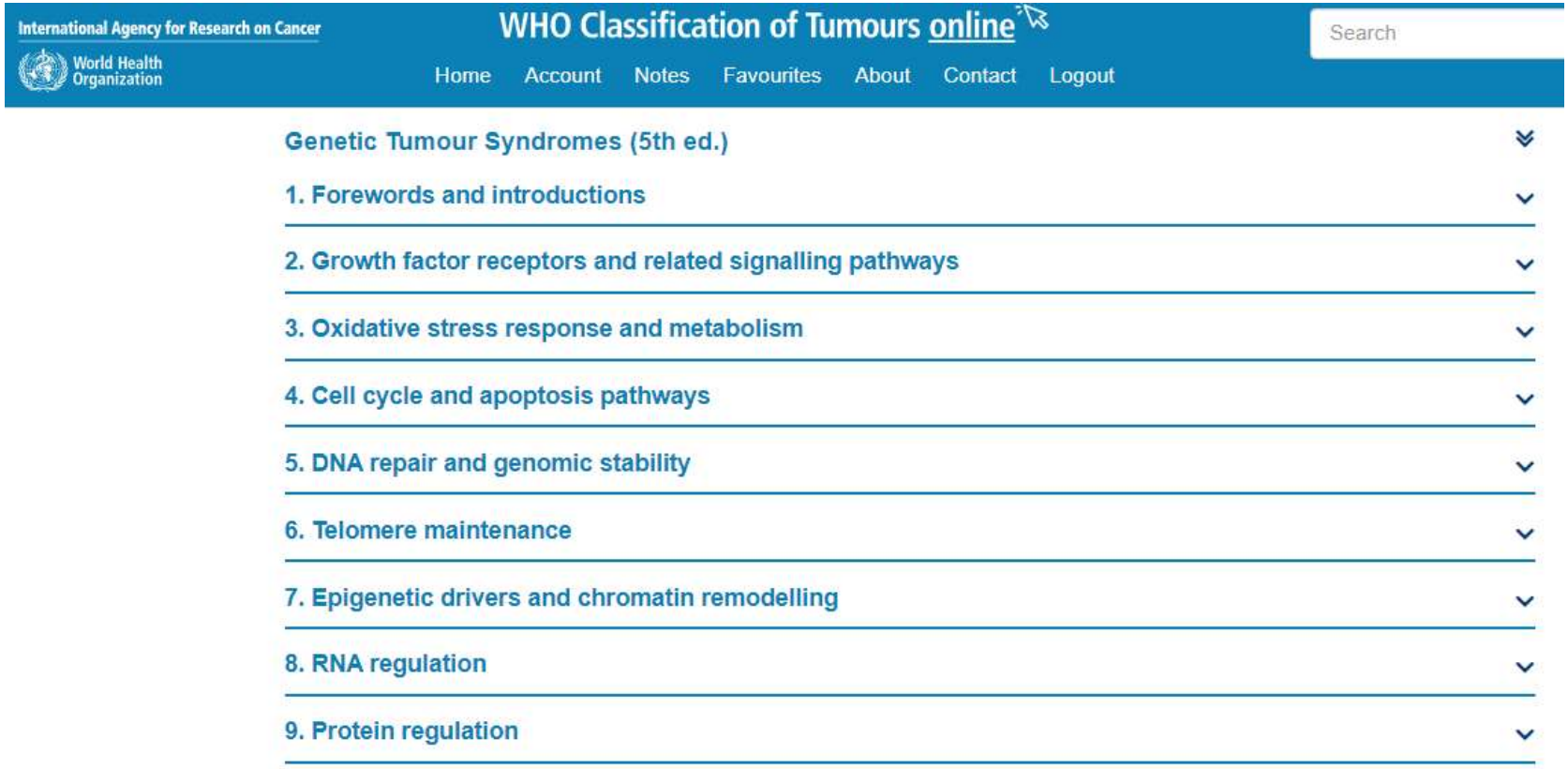
- **Lung involvement of VHL syndrome**
- **Pulmonary manifestations of genetic tumor syndrome**

Organ involvement in VHL disease



Cancers (Basel) 2022;14.

WHO classification: Genetic tumor syndrome



https://tumourclassification.iarc.who.int/

WHO classification: Genetic tumor syndrome

2. Growth factor receptors and related signalling pathways

WNT/TGFbeta pathway

- Familial adenomatous polyposis (*APC*)
- Gastric Adenocarcinoma and Proximal Polyposis of Stomach - GAPPS (*APC* promoter)
- *AXIN2*-associated polyposis (*AXIN2*)
- Serrated polyposis (*RNF43*)
- *WT1* related tumour predisposition syndrome (*WT1*)
- WAGR syndrome (*WT1*)
- Multiple endocrine neoplasia type 1 (*MEN1*)
- Peutz-Jeghers syndrome (*STK11*)
- Hereditary gastric and breast cancer syndrome (*CDH1*, *CTNNA1*)
- Hereditary mixed polyposis syndrome (*GREM1*)

Hedgehog signalling pathway

- Naevoid basal cell carcinoma syndrome - Gorlin syndrome (*PTCH1*, *SUFU*, *GPR161*)
- *SMO*-related Curry-Jones syndrome (*SMO*)
- *ELP1*-related medulloblastoma predisposition syndrome(*ELP1*)
- Osteochondromatosis (*EXT1*, *EXT2*)

NF-kB signalling pathway

- Brooke-Spiegler syndrome (*CYLD*)

MTOR and PI3K pathway

- Tuberous sclerosis (*TSC1*, *TSC1*)
- *PTEN* hamartoma tumour syndrome (*PTEN*)
- Activated Phosphatidylinositol-3-OH kinase δ Syndrome - APDS (*PIK3CD*)

3. Oxidative stress response and metabolism

Angiogenesis

- Von Hippel-Lindau syndrome (*VHL*)

Krebs cycle

- *SDH*-deficient tumour syndrome - Hereditary phaeochromocytoma-paraganglioma syndromes (*SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*)
- Hereditary leiomyomatosis and renal cell carcinoma syndrome (*FH*)

Toxic metabolite-mediated disorders

- Hereditary tyrosinaemia type 1 (*FAH*)

https://tumourclassification.iarc.who.int/

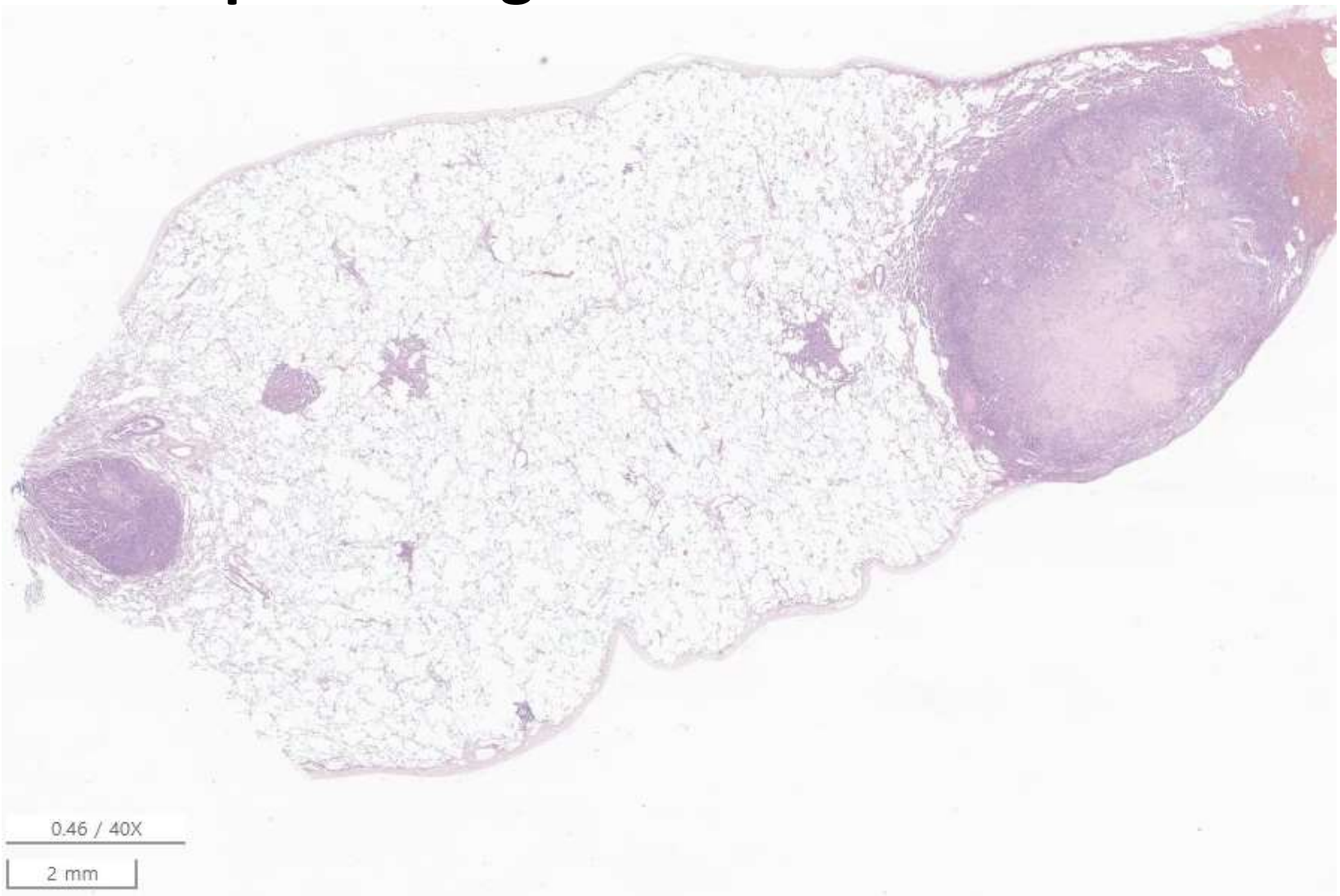
Lung involvement of genetic tumor syndrome

Genetic tumor syndrome	Lung involvement
Tuberous sclerosis	Lymphangioleiomyomatosis
Tuberous sclerosis	Multifocal micronodular pneumocyte hyperplasia
von Hippel-Lindau syndrome	Multifocal microcysts and papillary cystadenoma
PTEN hamartoma tumor syndrome	Sclerosing pneumocytoma
Multiple endocrine neoplasia type 1 (MEN1)	Bronchopulmonary neuroendocrine neoplasms
Birt-Hogg-Dube syndrome	Multiple cysts

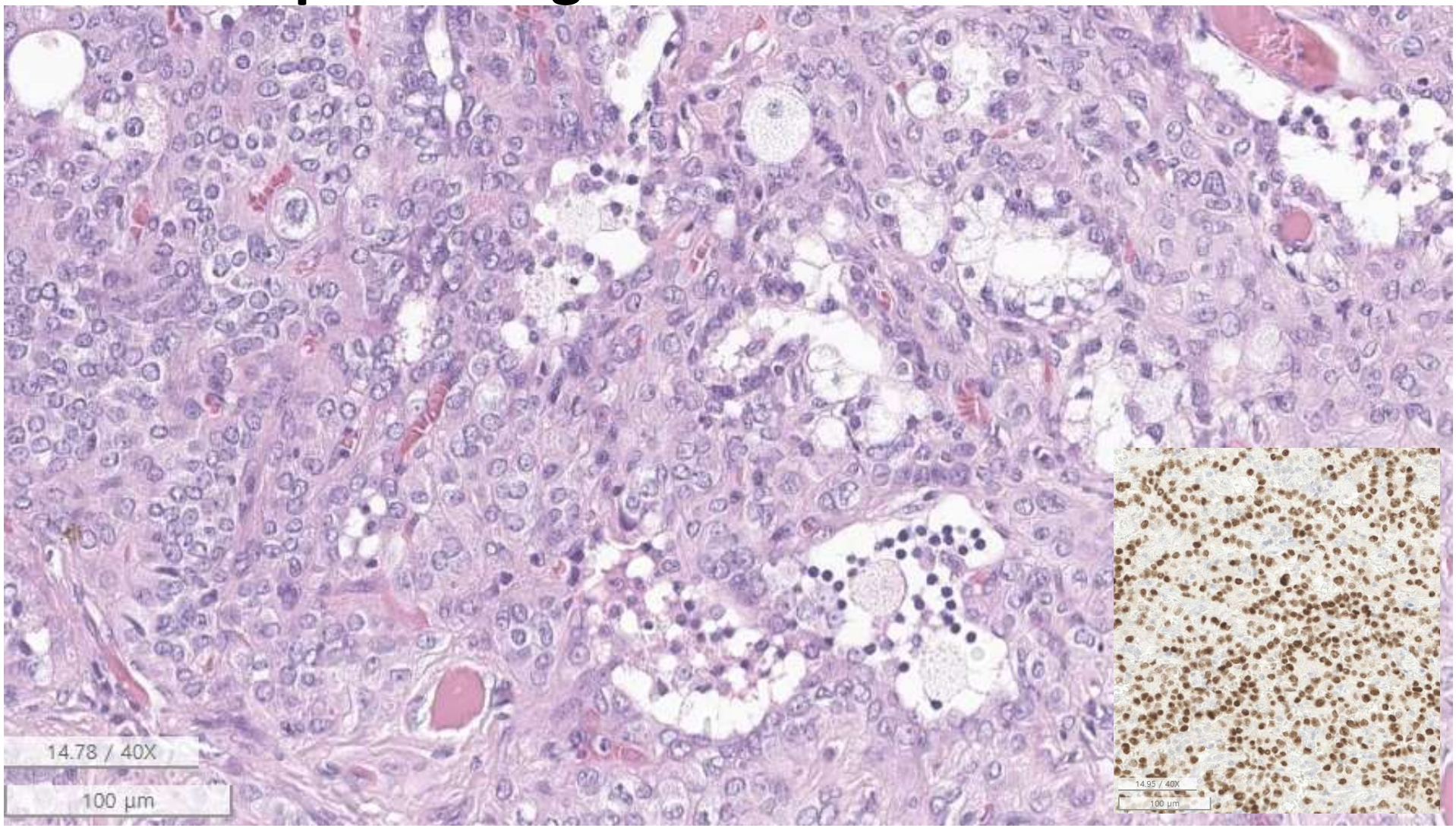
Cf. A patient with multiple lung nodules (case 3-2)

- 17/M

Microscopic finding



Microscopic finding



Diagnosis (case 3-2)

- **Pathology: Sclerosing pneumocytoma, multiple**
- **Germline mutation: PTEN Frameshift p.A333Gfs*10**

- **Lung involvement of PTEN hamartoma tumor syndrome**

Take home message of Case 3.

- **Lung involvement of genetic tumor syndrome is rare, but can be encountered.**
- **Multifocality with microscopic lesions or tumors can suggest a genetic tumor syndrome.**

Summary of Today's talk

- **Case 1: SMARCA4 deficient undifferentiated tumor**
  - **Distinct clinico-pathological entity**
- **Case 2: Invasive mucinous adenocarcinoma with *NRG1* fusion**
  - ***NRG1* fusion: Emerging target**
- **Case 3: Lung involvement of genetic tumor syndrome**
  - **Cases presented with multifocal benign tumors**