Unusual Carcinoma of the Lung: "Usual" Suspects and New Kids on the Block

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Disclosures

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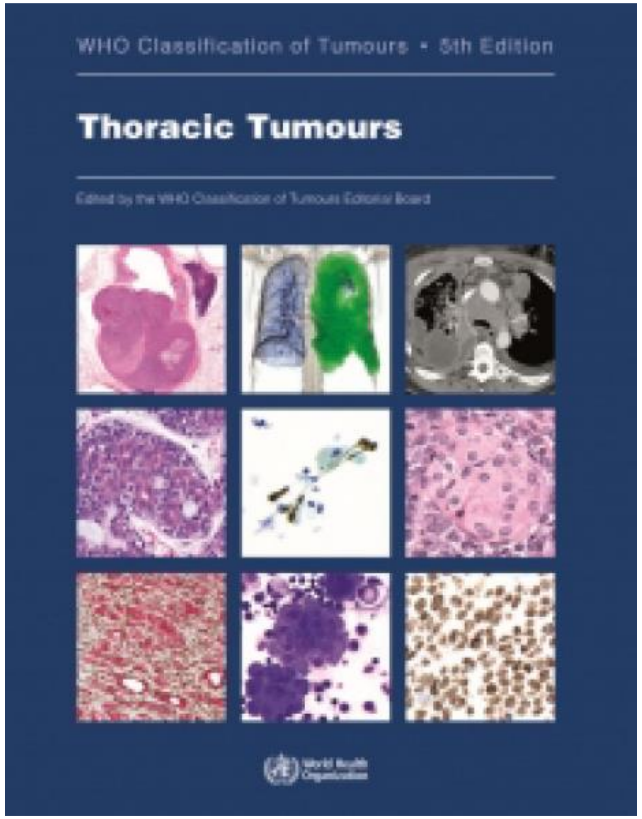


2. Tumours of the lung

Tumours of the lung: Introduction
Small diagnostic samples
Epithelial tumours
Papillomas
Bronchial papillomas
Adenomas
Sclerosing pneumocytoma
Alveolar adenoma
Papillary adenoma of the lung
Bronchiolar adenoma / ciliated muconodular papillary tumour
Mucinous cystadenoma of the lung
Mucous gland adenoma of the lung
Precursor glandular lesions
Atypical adenomatous hyperplasia of the lung
Adenocarcinoma in situ of the lung
Adenocarcinomas
Minimally invasive adenocarcinoma of the lung
Invasive non-mucinous adenocarcinoma of the lung
Invasive mucinous adenocarcinoma of the lung
Colloid adenocarcinoma of the lung
Fetal adenocarcinoma of the lung
Enteric-type adenocarcinoma of the lung
Squamous precursor lesions
Squamous dysplasia and carcinoma in situ of the lung
Squamous cell carcinomas
Squamous cell carcinoma of the lung
Lymphoepithelial carcinoma of the lung
Large cell carcinomas
Adenosquamous carcinomas
Adenosquamous carcinoma of the lung
Sarcomatoid carcinomas
Pleomorphic carcinoma of the lung
Pulmonary blastoma
Carcinosarcoma of the lung
Other epithelial tumours
NUT carcinoma of the lung (see NUT carcinoma of the thorax)
Thoracic SMARCA4-deficient undifferentiated tumour
Salivary gland-type tumours
Pleomorphic adenoma of the lung
Hyalinizing clear cell carcinoma of the lung
Myoepithelioma and myoepithelial carcinoma of the lung

Lung neuroendocrine neoplasms
Lung neuroendocrine neoplasms: Introduction
Precursor lesion
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
Neuroendocrine tumours
Carcinoid/neuroendocrine tumour of the lung
Neuroendocrine carcinomas
Small cell lung carcinoma
Large cell neuroendocrine carcinoma of the lung
Tumours of ectopic tissues
Melanoma of the lung
Meningioma of the lung
Mesenchymal tumours specific to the lung
Pulmonary hamartoma
Pulmonary chondroma
Diffuse pulmonary lymphangiomatosis
Pleuropulmonary blastoma
Pulmonary artery intimal sarcoma
Congenital peribronchial myofibroblastic tumour
Primary pulmonary myxoid sarcoma with EWSR1-CREB1 fusion
PEComatous tumours
Lymphangioleiomyomatosis of the lung
PEComa of the lung
Haematolymphoid tumours
Haematolymphoid tumours of the lung: Introduction
MALT lymphoma of the lung
Pulmonary diffuse large B-cell lymphoma
Intravascular large B-cell lymphoma of the lung
Pulmonary Langerhans cell histiocytosis
Pulmonary Erdheim-Chester disease

"Usual" suspect: Sarcomatoid carcinoma

New kids on the block: NUT carcinoma & Thoracic SMARCA4-deficient undifferentiated tumor

Sarcomatoid Carcinoma

- carcinoma with mesenchymal-like or sarcomatoid / sarcomatous component -

- Pleomorphic carcinoma of the lung
- Pulmonary blastoma
- Carcinosarcoma of the lung

✓ Carcinoma in transition: the mesenchymal-like or sarcomatoid / sarcomatous component derived from carcinoma cells through activation of a stable epithelial – mesenchymal transition program

Pelosi G, et al. Int J Surg Pathol 2000;18:103-20

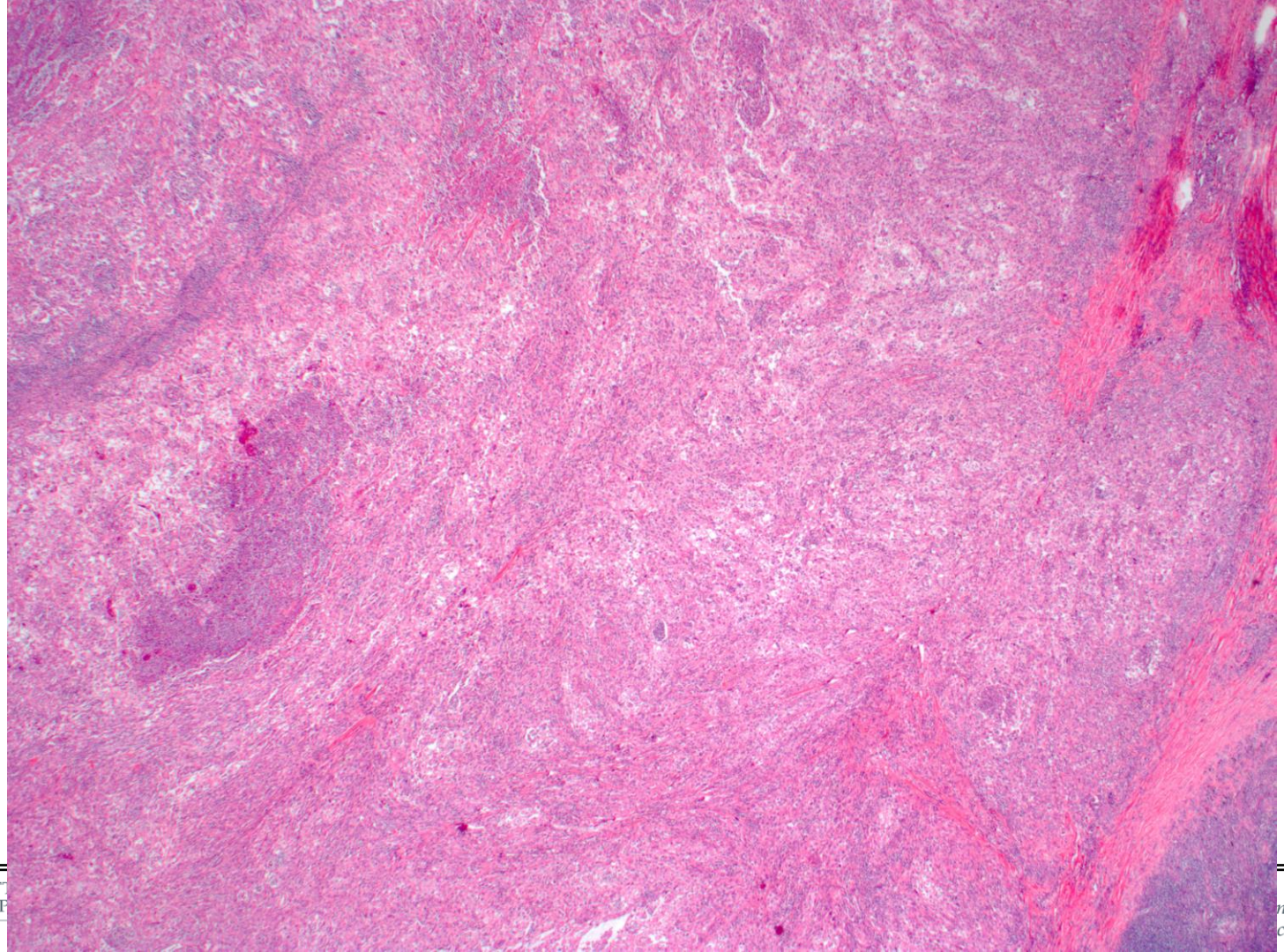
Pleomorphic Carcinoma of the Lung

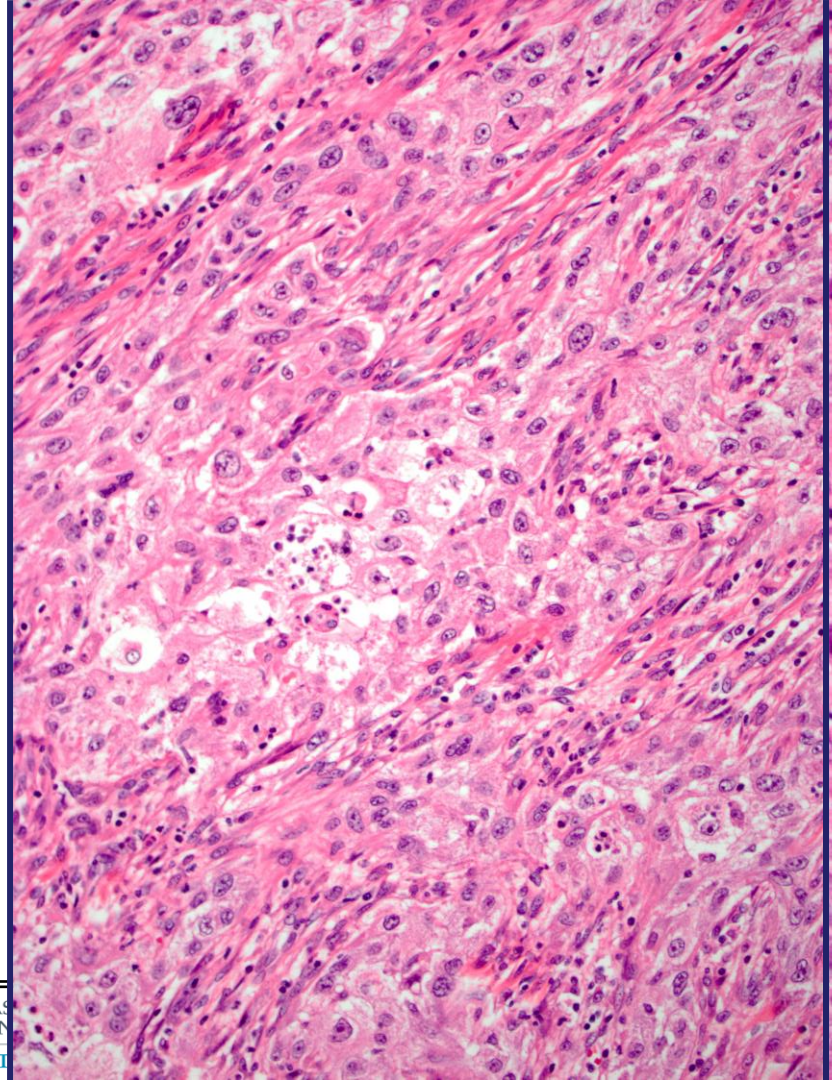
- Poorly differentiated NSCLC with at least 10% spindle cell and/or giant cells or a carcinoma consisting only of spindle and neoplastic giant cells
- 2-3% of all lung cancers in surgical series, but < 1% in the epidemiological studies
- Pure spindle cell and giant cell carcinomas are even rarer
- Peak incidence in the seventy decade with male predominance
- The majority occurs in tobacco smokers, although rare cases in never-smokers have been reported
- Aggressive tumors with distant metastases commonly found, and resistance to chemo- and radiotherapy

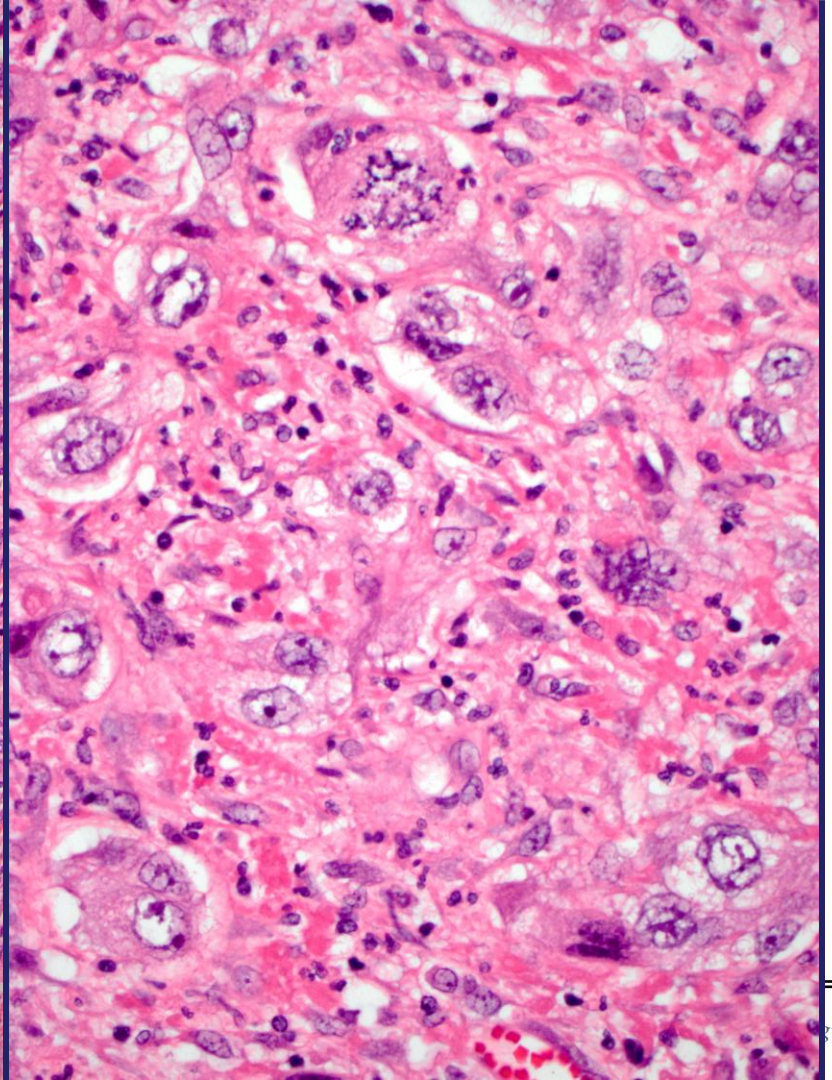
Fishback NF, et al. Cancer *1994;73:2936-45*, Mochizuki T, et al. Am J Surg Patho 2008;32:1727-35, Pelosi G, at al. In J Surg Pathol 2010;18:103-20, Rossi G, et al. Am J Surg Pathol 2002;27:311-24, Venissac N, et al. J Thorac Cardiovasc Surg 2007;134:619-23, Lin Y, et al. Am J Clin Oncol 2014

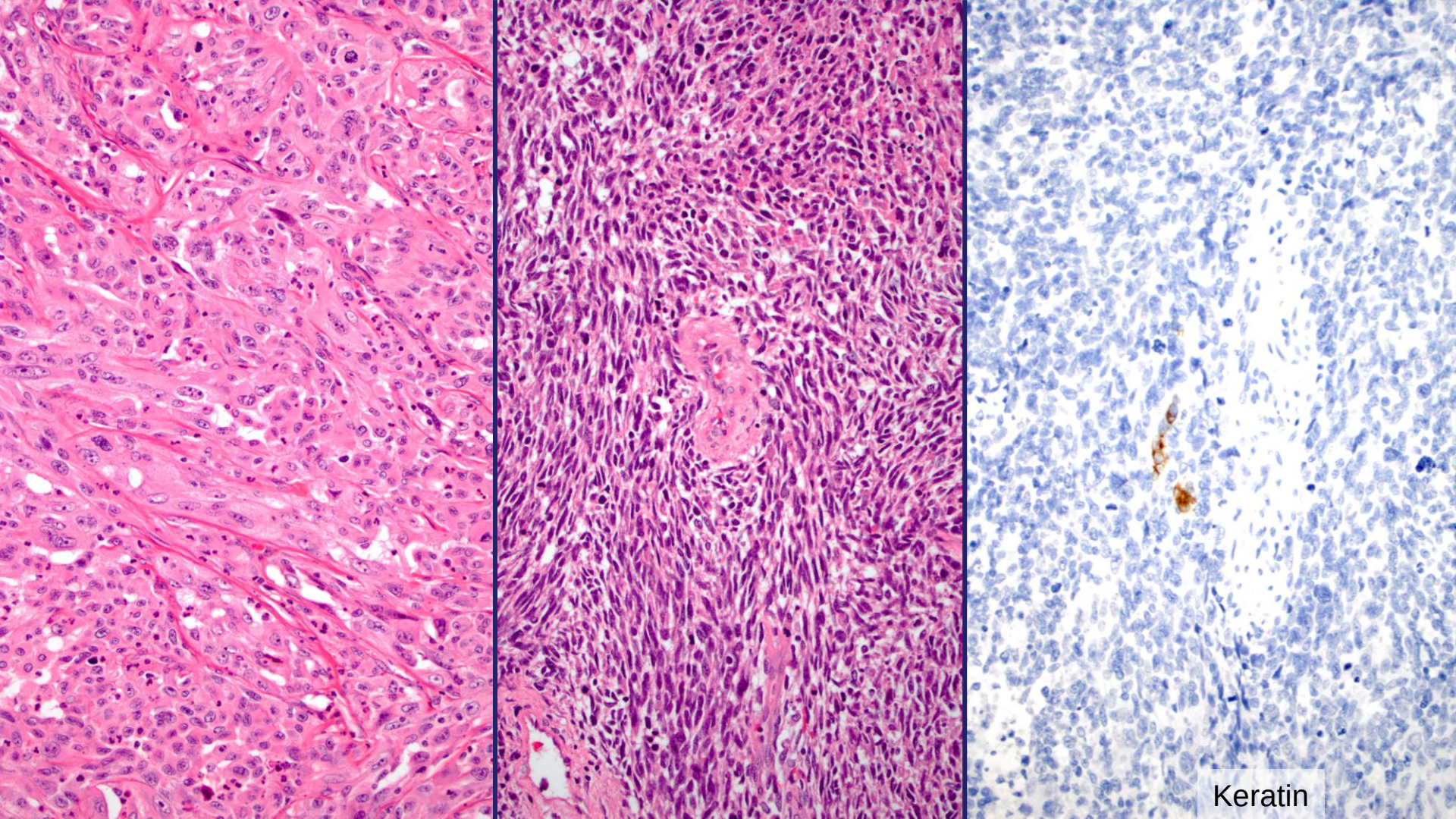
Pleomorphic Carcinoma of the Lung

- The NSCC component can be squamous cell carcinoma, adenocarcinoma and/or undifferentiated NSCC (“large cell carcinoma”)
- If high-grade neuroendocrine carcinoma is present, the tumor should be classified as combined small cell carcinoma or large cell neuroendocrine carcinoma
- The definite diagnosis may be rendered only on a resected tumor
- The specific histological components should be mentioned in the diagnosis





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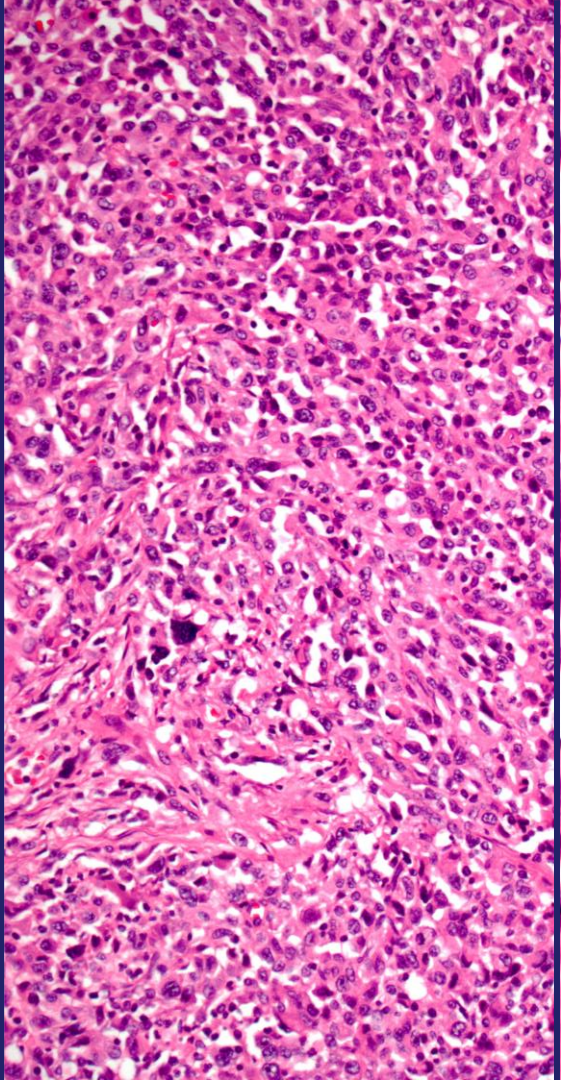

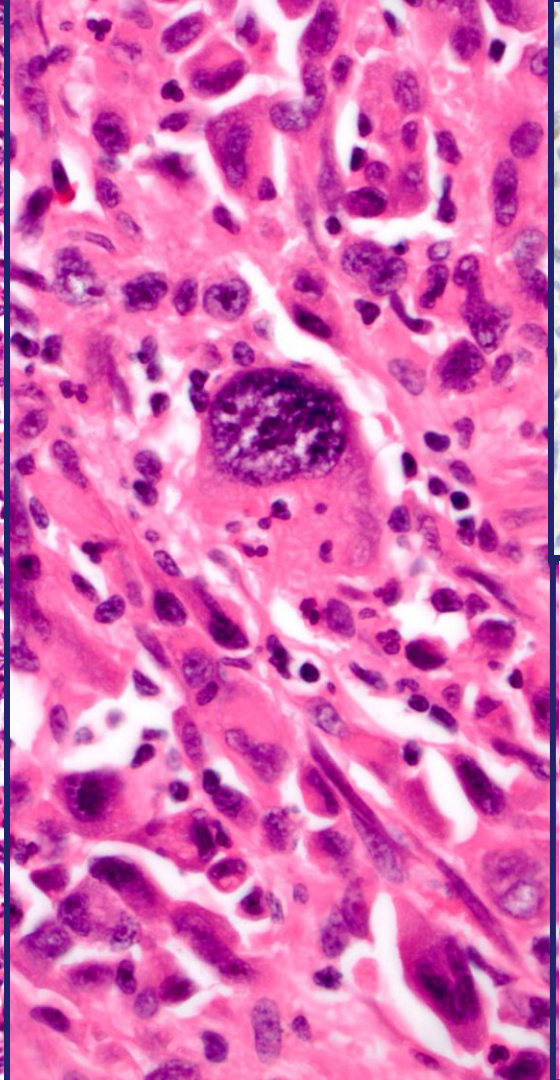

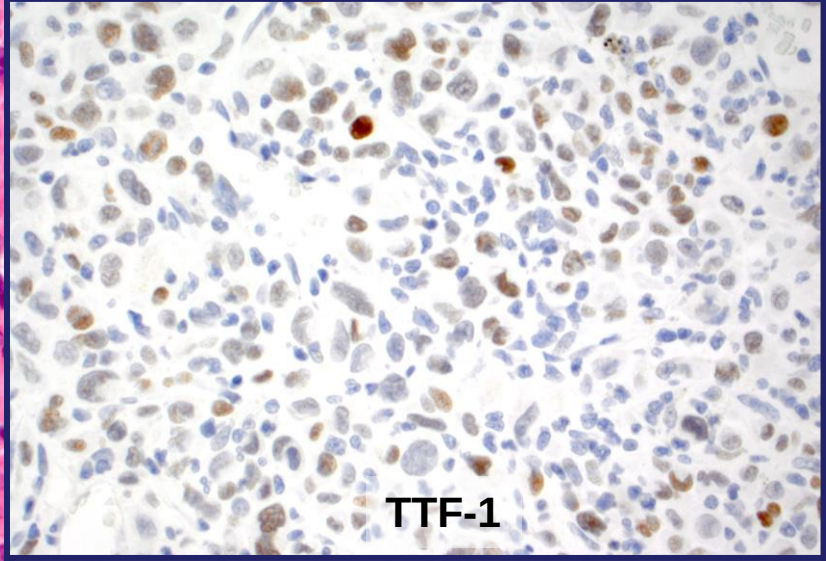
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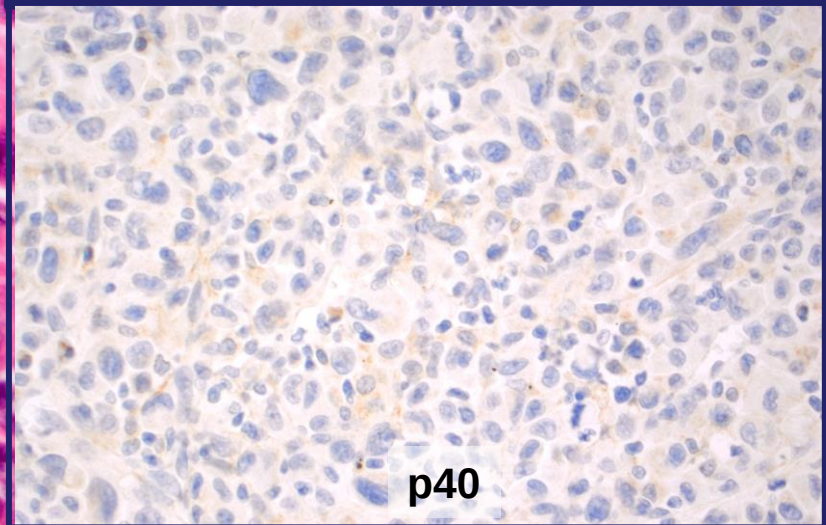
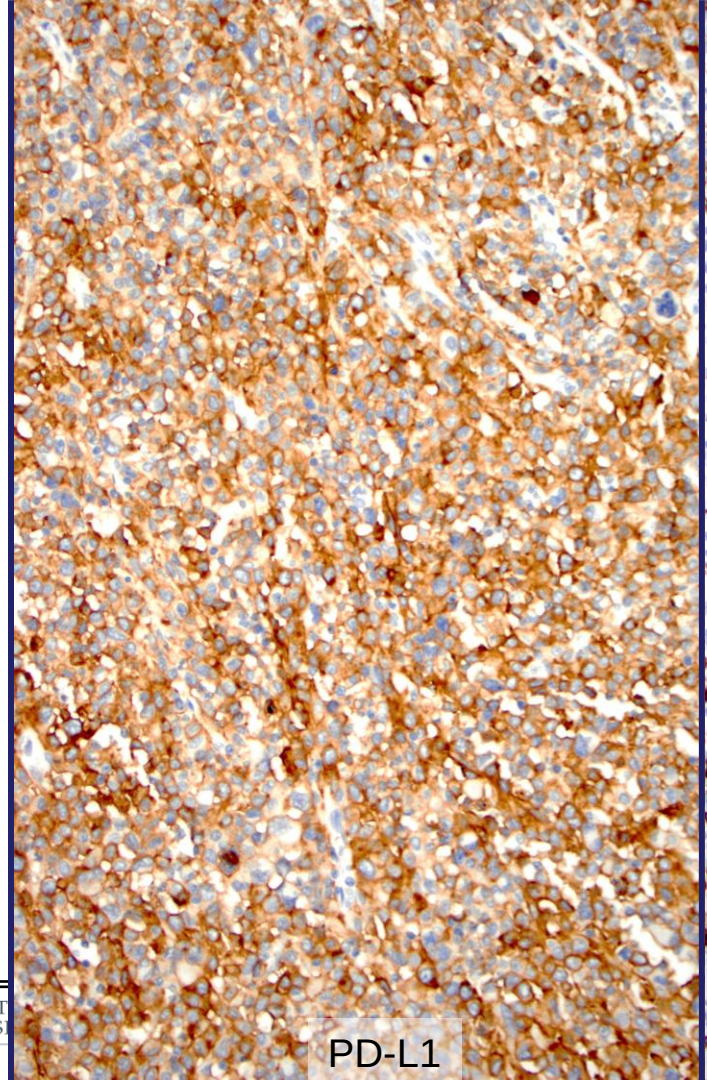

p40

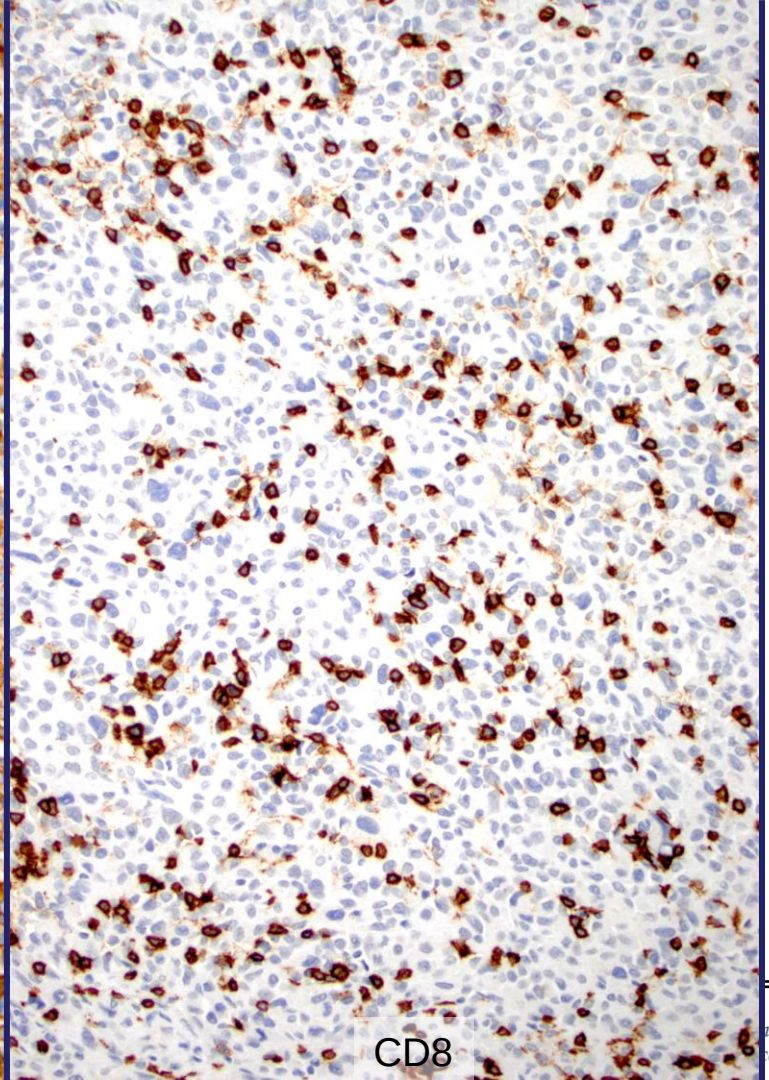
Molecular Alterations in Pleomorphic Carcinoma

- Similar to those found in other NSCLC, in particular lung adenocarcinoma
  - *KRAS* mutations (in up to 38% of cases)
  - *EGFR* mutations (in up to 25% of cases)
  - Frequent *TP53* mutations
- MET exon 14 skipping mutations in 12-22% of cases
- Frequent PD-L1 expression (60-90%) with more prominent expression in the sarcomatoid area

Schrock AB, et al. J Thoracic Oncol 2017, Liu X, et al. J Clin Oncol 2016, Nakanishi K, et al. Anticancer res 2019



PD-L1



CD8

Differential diagnosis

- Carcinosarcoma of the lung
- Pulmonary blastoma
- Metastatic sarcomatoid carcinoma
- Primary or metastatic sarcoma: synovial sarcoma, epithelioid hemangioendothelioma/angiosarcoma, follicular dendritic cell sarcoma, rhabdomyosarcoma, etc.
- Metastatic melanoma (spindle cell pattern)
- Pleural mesothelioma, biphasic or sarcomatoid
- Metastatic adrenocortical carcinoma
- Metastatic choriocarcinoma
- Inflammatory myofibroblastic tumor
- Reactive fibrotic and inflammatory processes

Pleomorphic Carcinoma vs. Sarcomatoid Mesothelioma

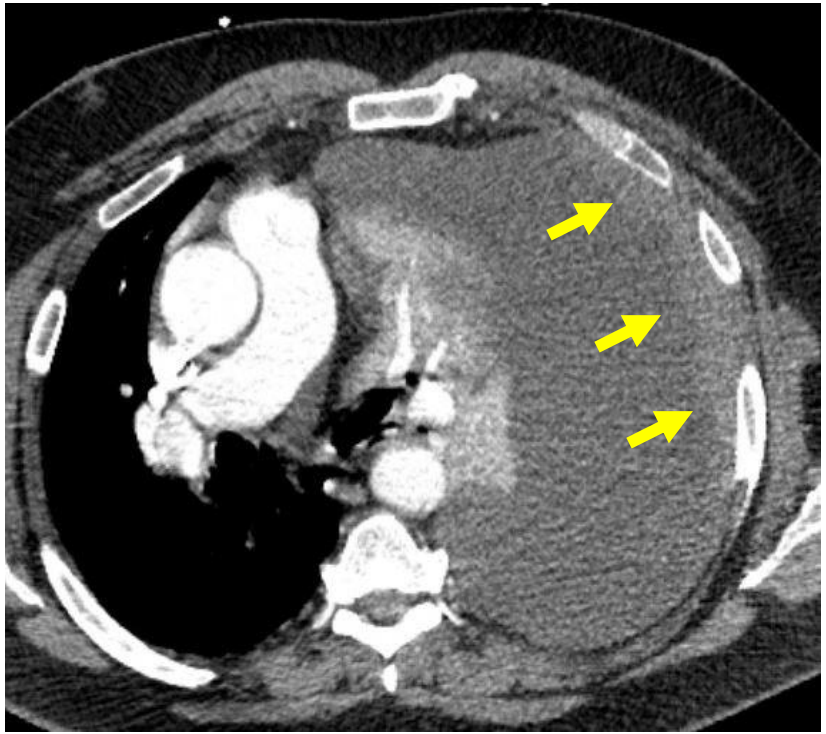
IHC marker	Pleomorphic carcinoma	Sarcomatoid mesothelioma
GATA 3	4%	100%
Claudin 4	36%	0%
EpCAM	23%	0%
HEG1	0%	44%
WT1	17%	49%
D2-40	15%	46%
Calretinin	33%	54%

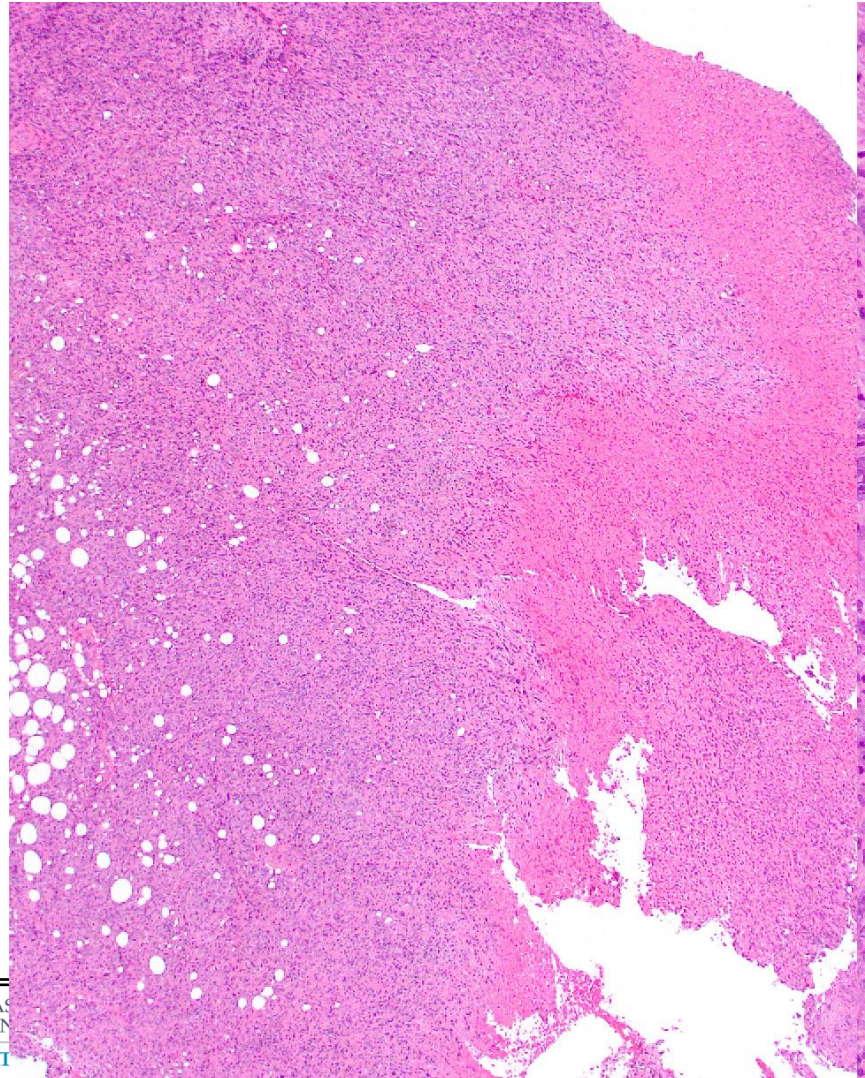
BAP1 loss: 34% of sarcomatoid mesothelioma; MTAP loss: 83% of sarcomatoid mesothelioma

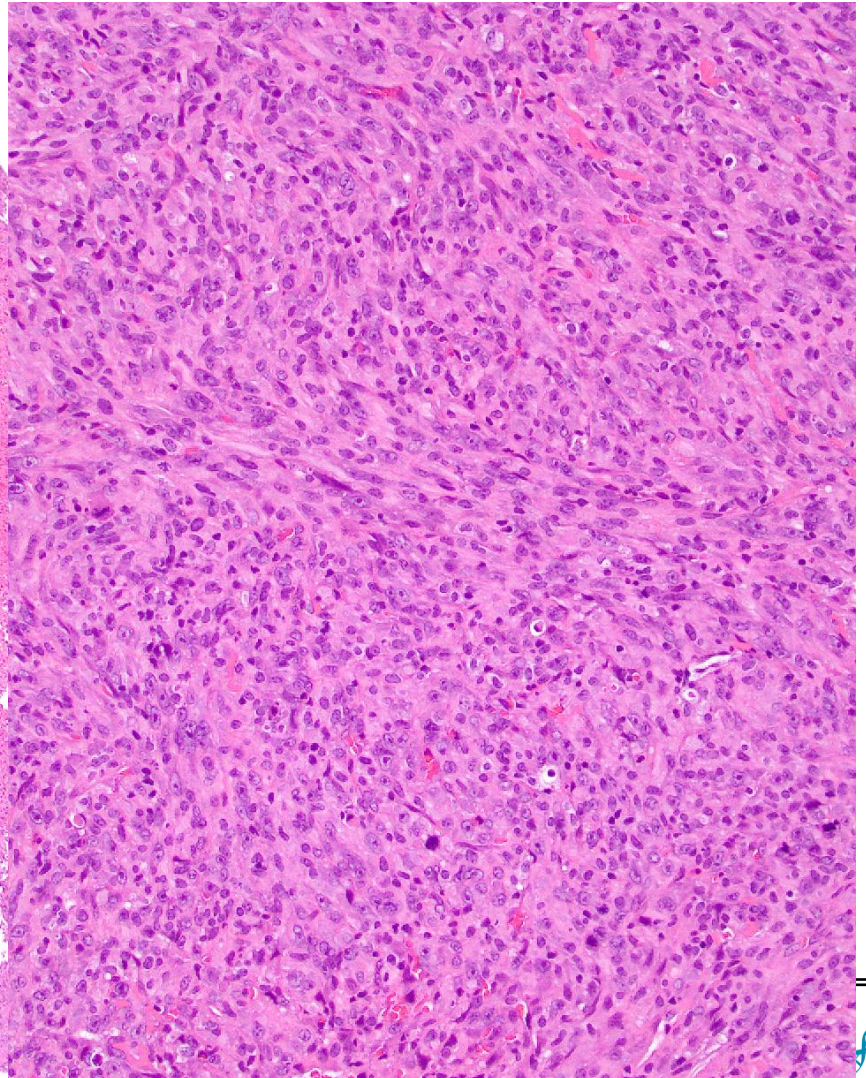
https://app.immunoquery.com/view/panel/dx?dxgroups=517,1040&sensitivity=1&minrefs=all&paneltype=comprehensive
(accessed on 9/13/2022)

64-year-old man

- Never – smoker
- Presented with dyspnea and cough
- A large left pleural effusion + pleural nodules depicted by imaging studies
- During VATS biopsy from left parietal pleura, studding noted throughout most of the parietal pleura

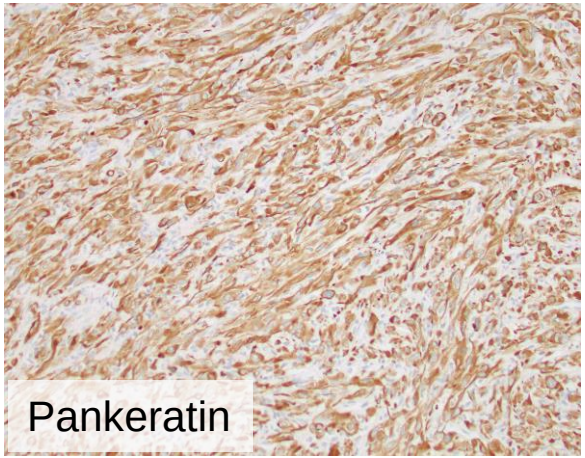


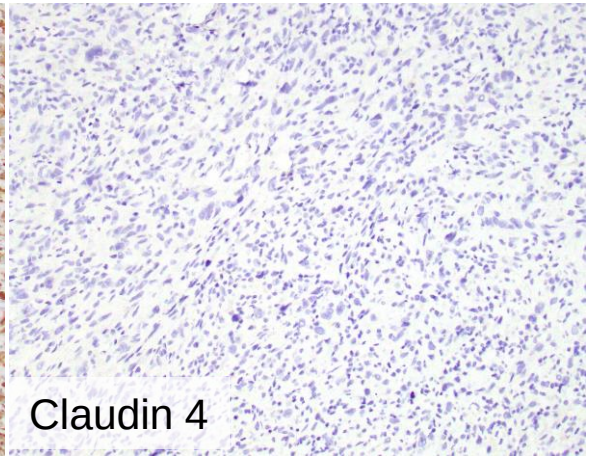


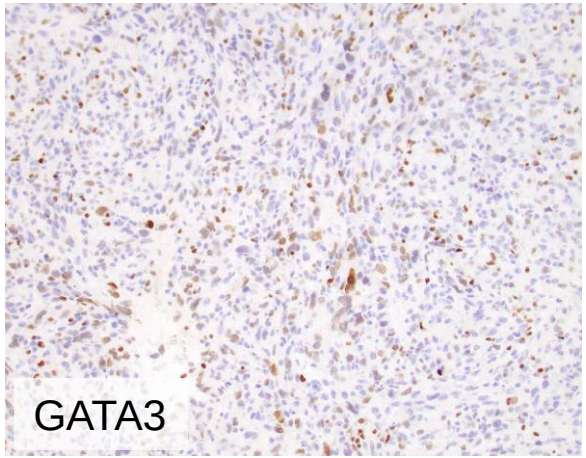


Mesothelioma

Positive	Negative
Pankeratin	Claudin 4
CK5/6 (focal)	MOC31
Calretinin (focal)	TTF-1/p40
D2-40 (focal)	CD31/CD34
GATA3 (weak & focal)	Desmin
	S100
	BAP1 (retained)

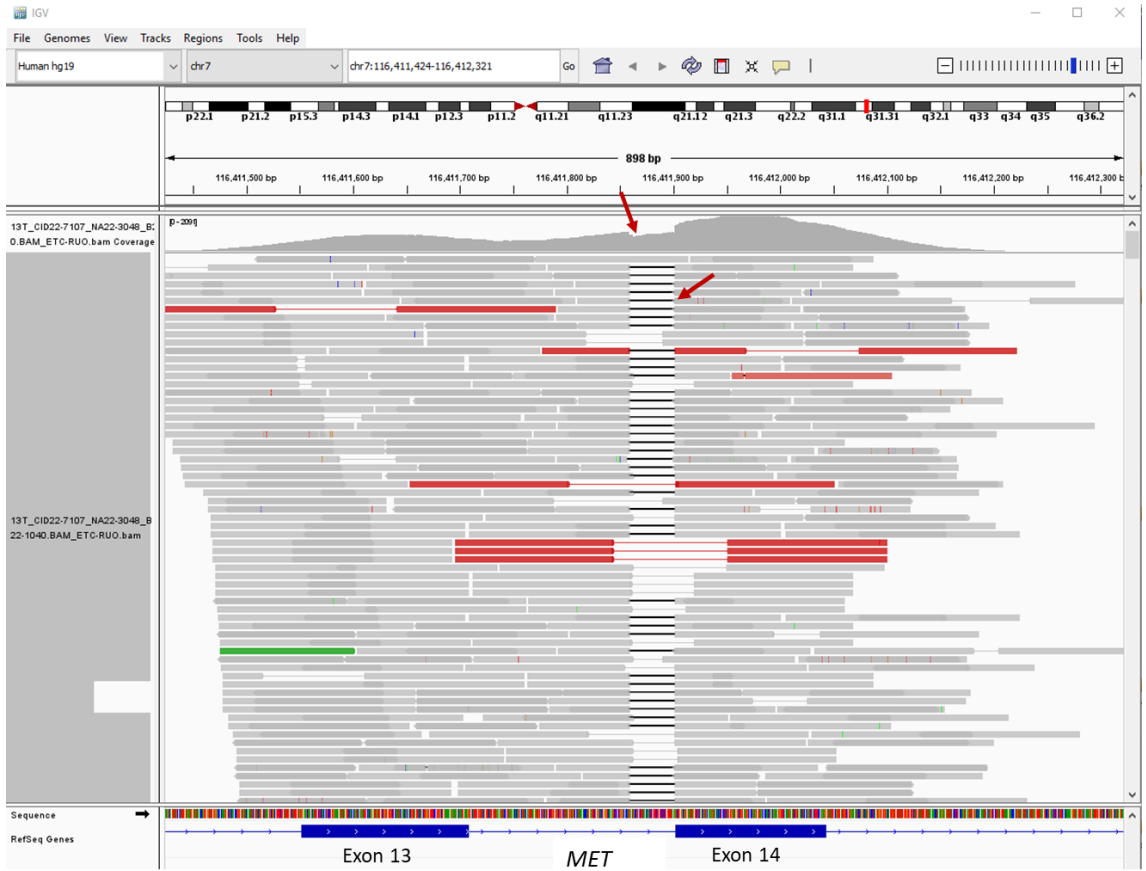






PD-L1 TPS 50%
-> Treated with Ipilimumab / nivolumab

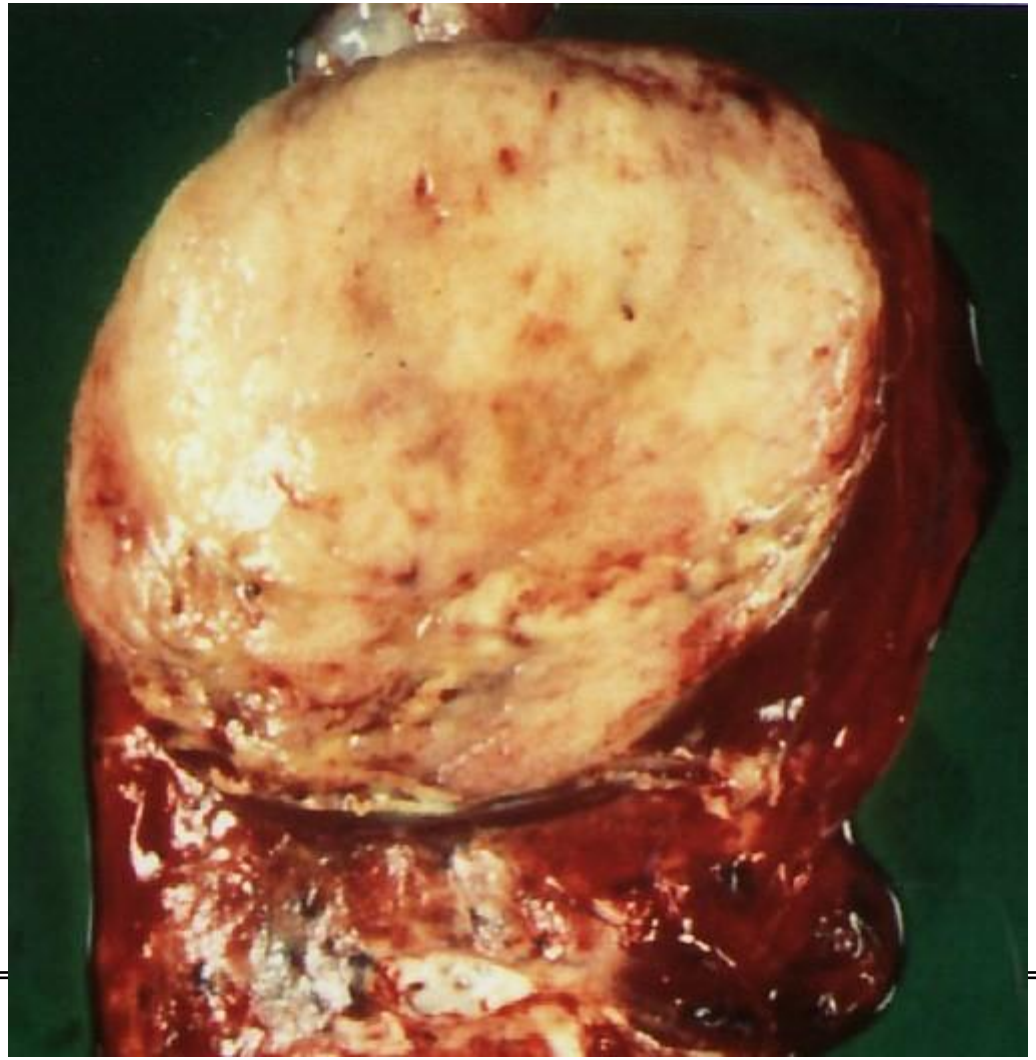
NGS



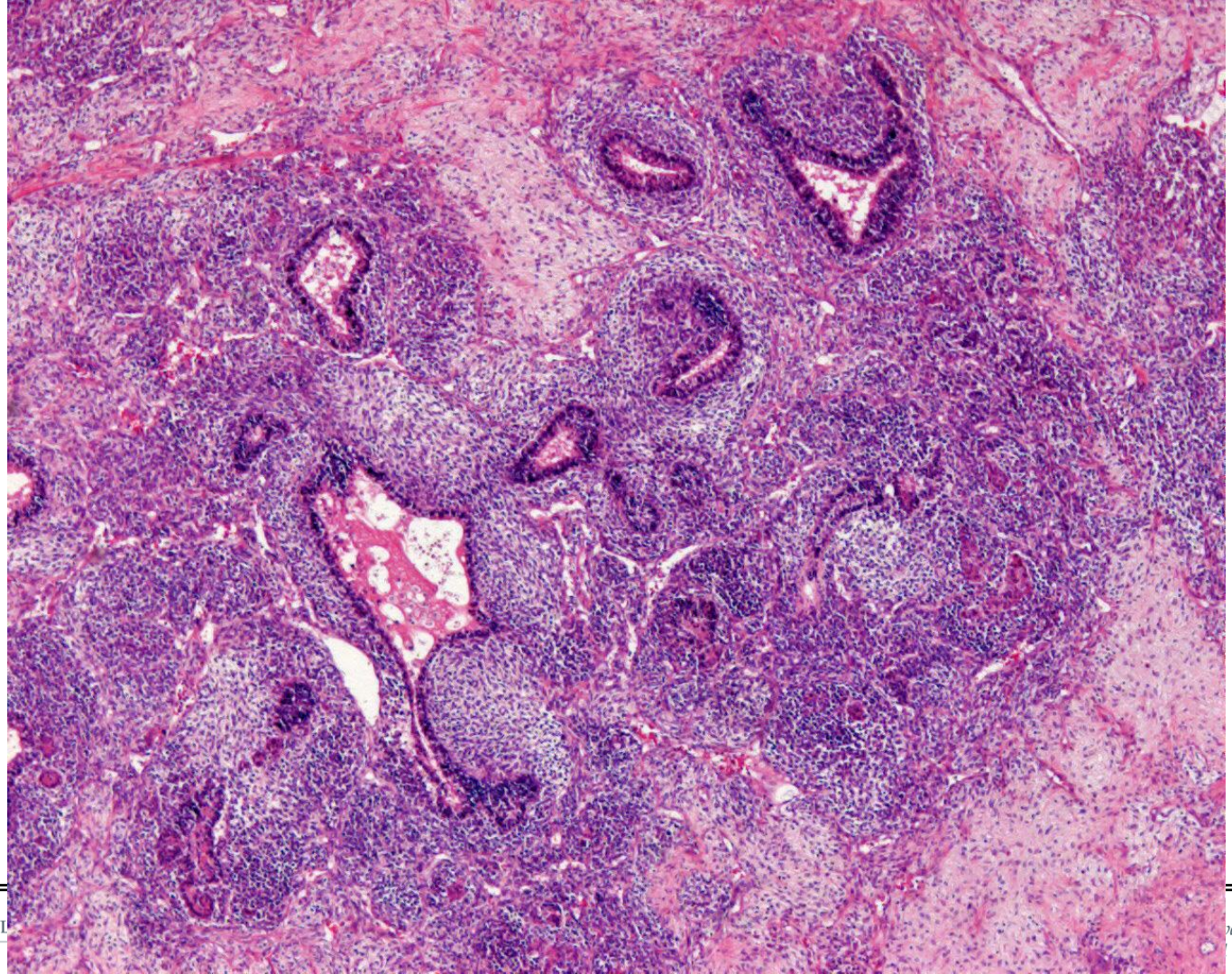
MET exon 14 skipping mutation supportive for the diagnosis of sarcomatoid carcinoma

Pulmonary Blastoma

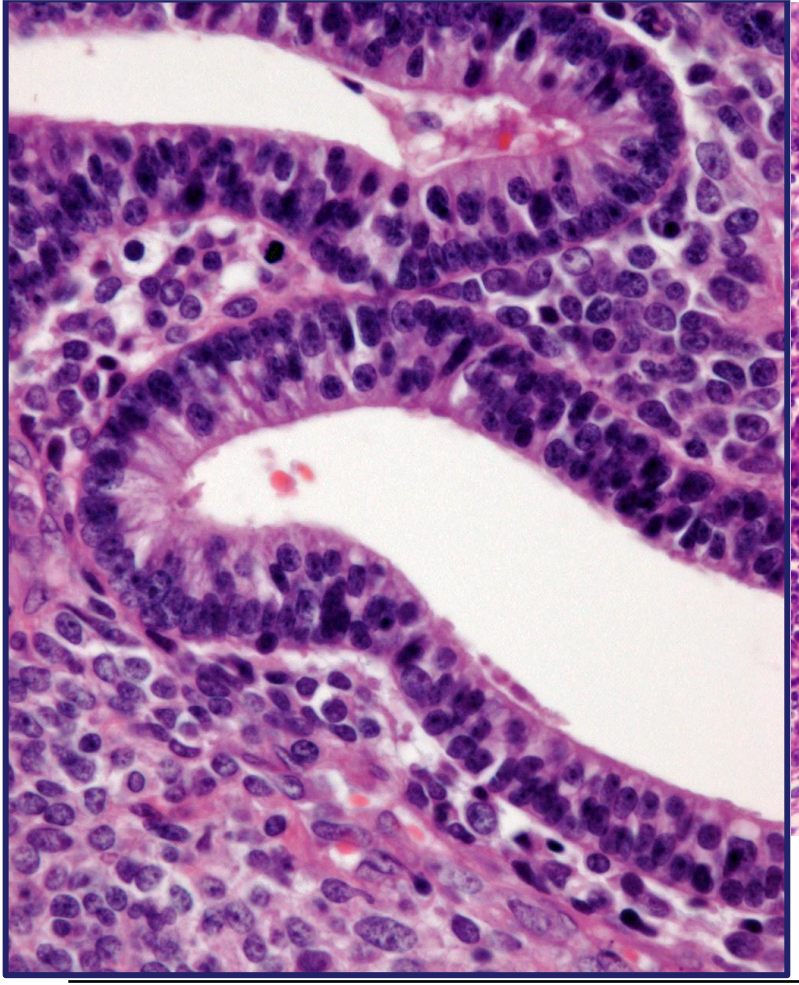
- A biphasic tumor consisting of low-grade fetal adenocarcinoma and primitive mesenchymal stroma; foci of specific mesenchymal differentiation may also be present, but not required for the diagnosis
- Completely different pleuropulmonary blastoma
- Very rare - <0.1% of all resected lung cancers
- Most common in the 5th decade with no gender predominance
- Distant metastases and tumor recurrence are common, and prognosis correlates is generally poor

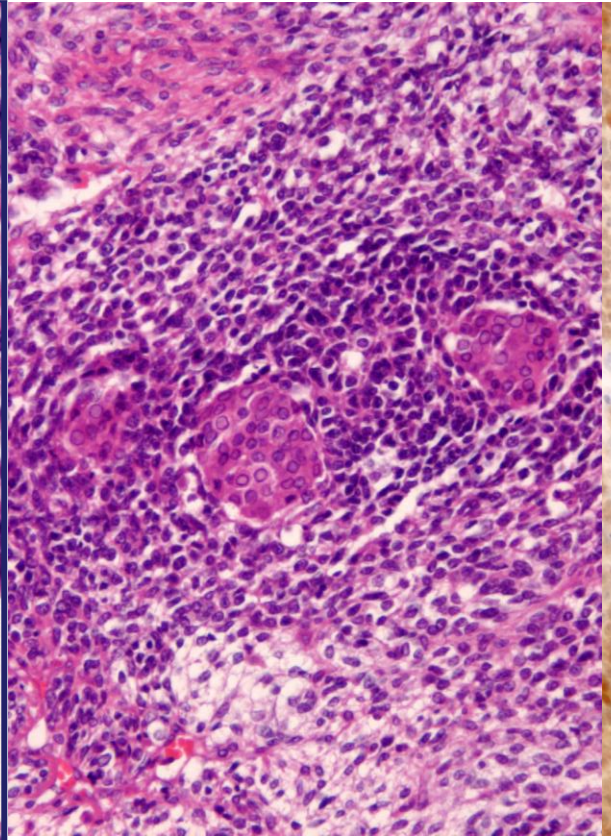


Courtesy of Dr. Yukio Nakatani

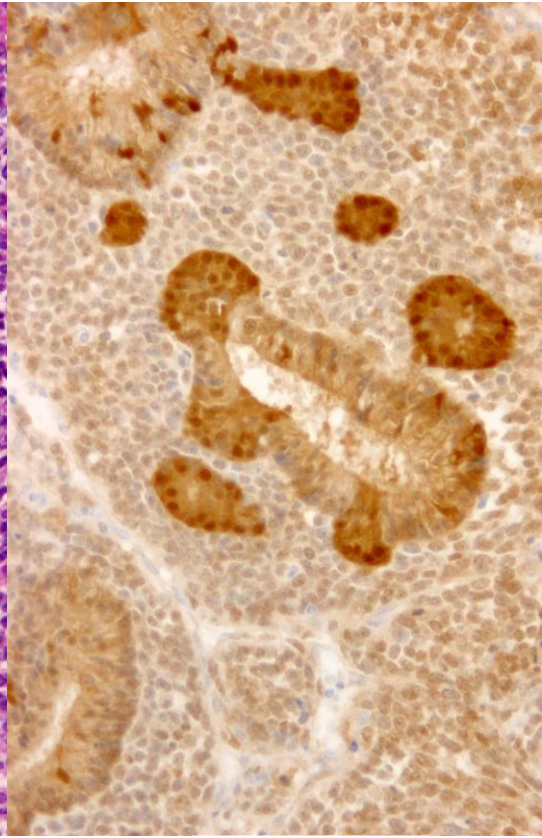


Courtesy of Dr. Yukio Nakatani



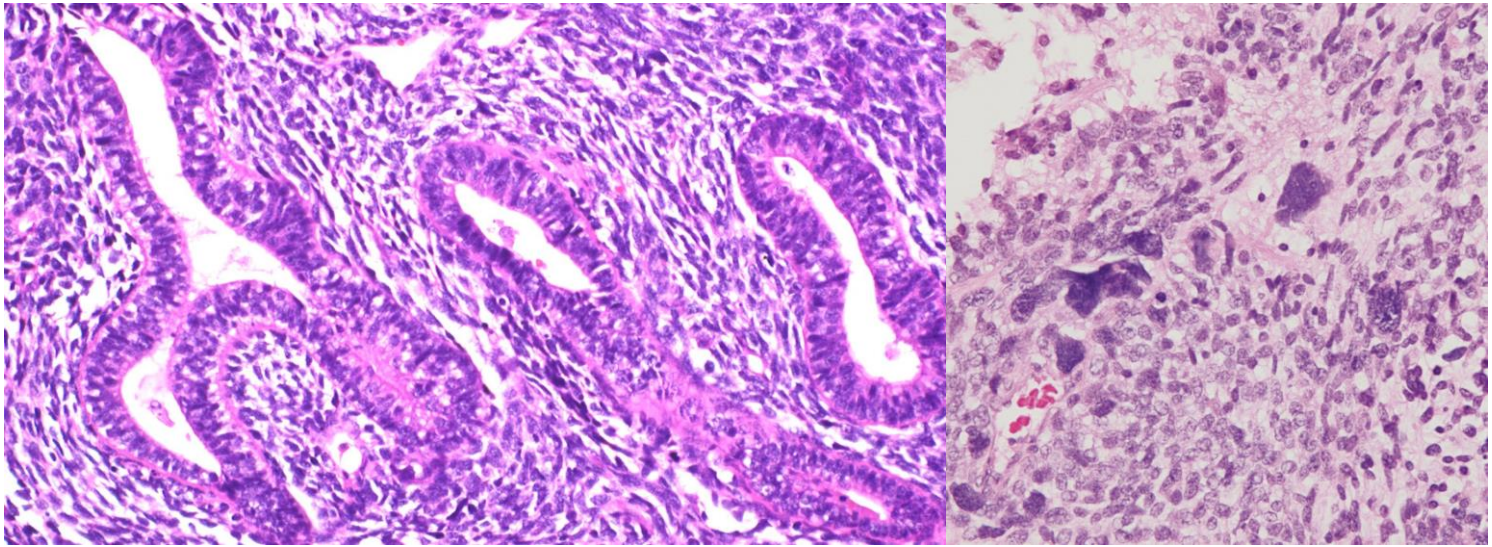


Morule formation



B-catenin

Mesenchymal Component

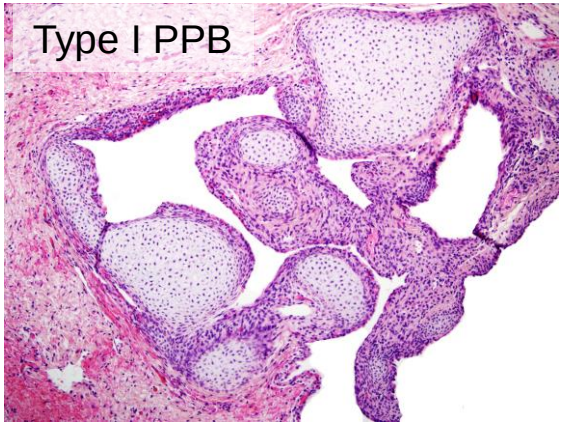


- Primitive mesenchymal stroma with a tendency to differentiate towards more mature fibroblast-like cells in the myxoid or fibrous background
- Occasional bizarre giant cells may be seen
- Heterologous elements reported in up to 25% of cases

Pulmonary Blastoma: Comparison with Low-grade Fetal Adenocarcinoma and Pleuropulmonary Blastoma

Feature	Fetal Adenocarcinoma	Biphasic Pulmonary Blastoma	Pleuropulmonary Blastoma
Clinical			
Younger than 10 years, %	0	0	>90
Smoker	Often	Often	No
Location	Lung	Lung	Lung, pleura, mediastinum
Average size, cm	4.5	10.1	NA, typically large
Asymptomatic	Often	Occasional	Rare
Prognosis	Good	Poor	Favorable for type I; poor for types II and III
Pathologic			
Malignant epithelium/stroma	Yes/no	Yes/yes	No/yes
Associated cystic change	No	No	In type I cases
Morules present, %	86	43	0
Chromogranin-positive cells	Frequent	Frequent	No

Abbreviation: NA, not available.



- Missense mutations in exon 3 of *CTNNB1* gene are frequently seen in pulmonary blastoma and shared with low-grade fetal adenocarcinoma

Travis WD Arch Pathol Lab Med 2010;134:1645-58, Sekine S, et al. J Pathol 2003;200:214-21

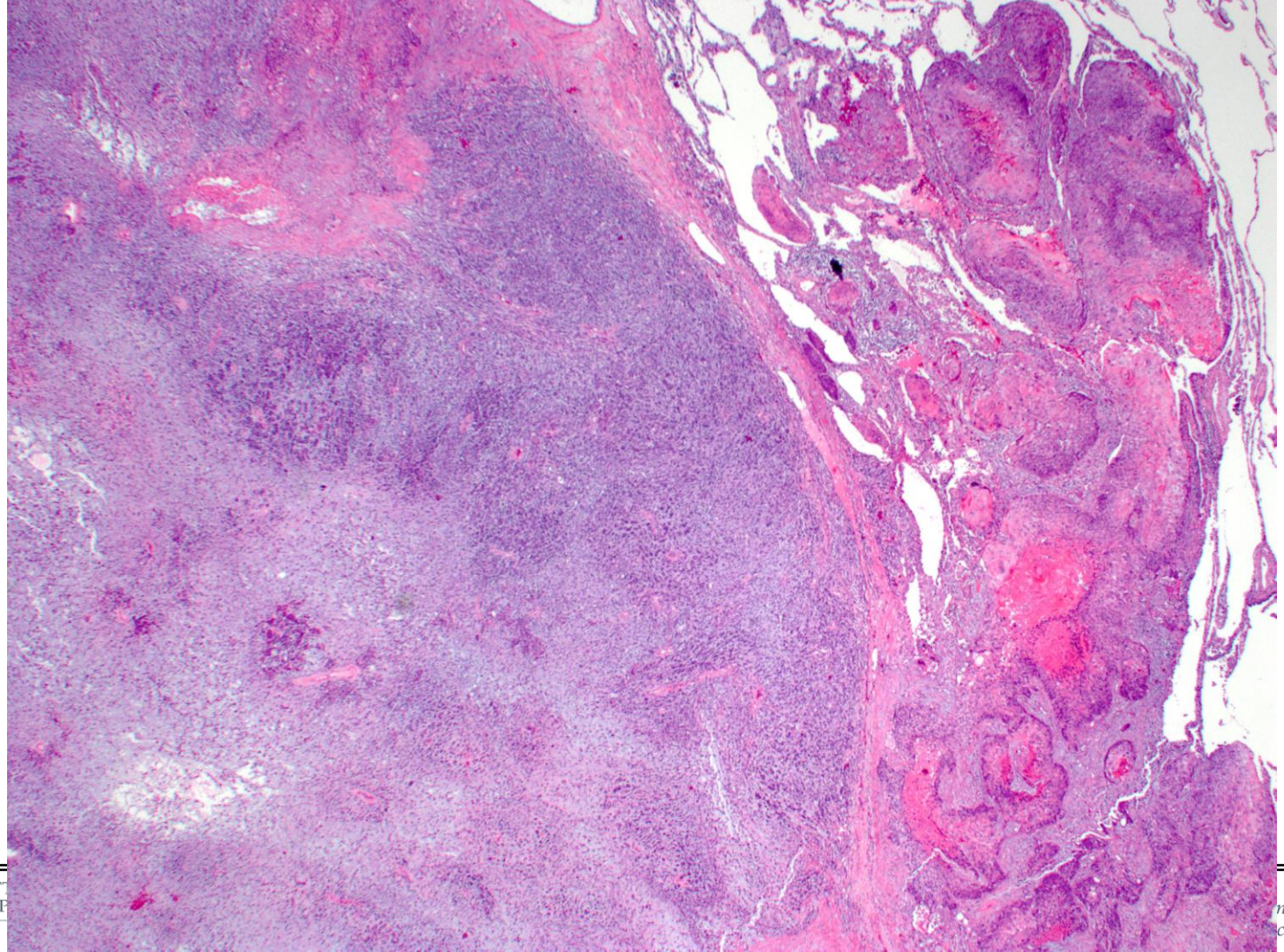
Carcinosarcoma of the Lung

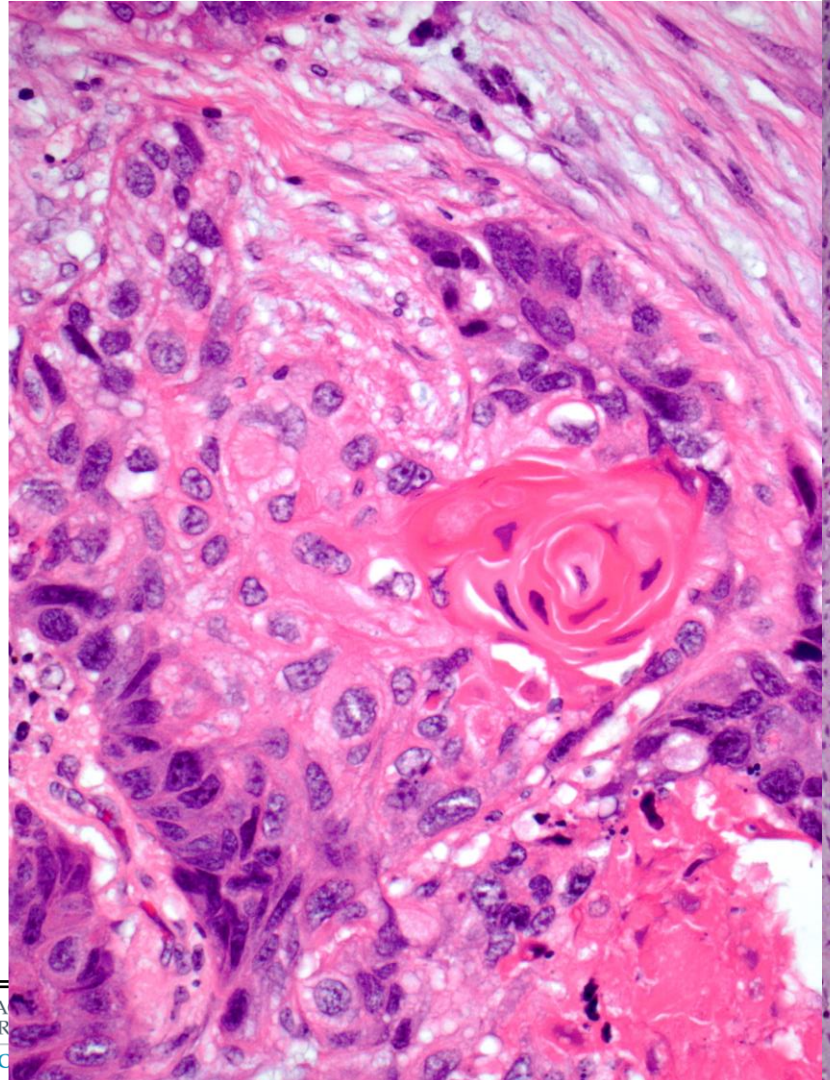
- A malignant tumor consisting of a mixture of NSCLC (typically squamous cell carcinoma > adenocarcinoma) and sarcoma with heterologous elements
- Very rare - < 0.2% of lung carcinomas
- The median age of 65 yeas with male predominance (M:F = 7-8:1)
- Prognosis is worse than those of other non-small cell carcinomas; Worse outcome has been associated with older age, comorbidities, higher T and N stages, vascular invasion, and spread through airspaces

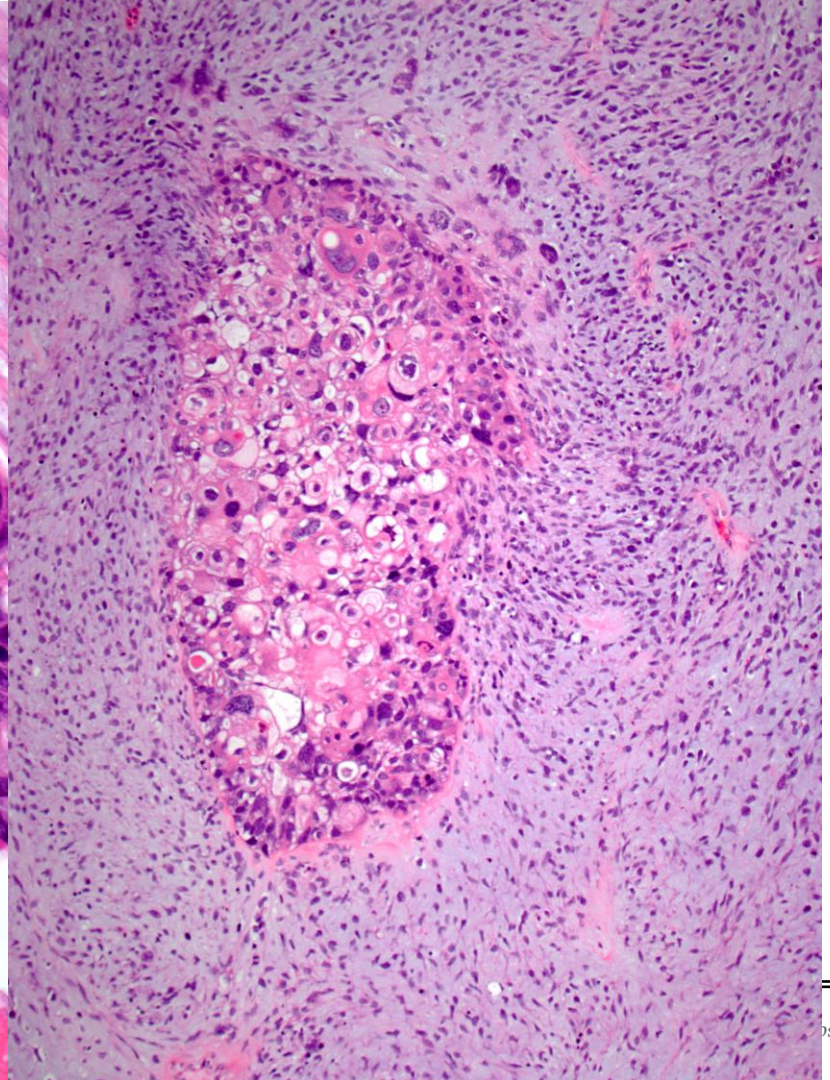
Carcinosarcoma of the Lung

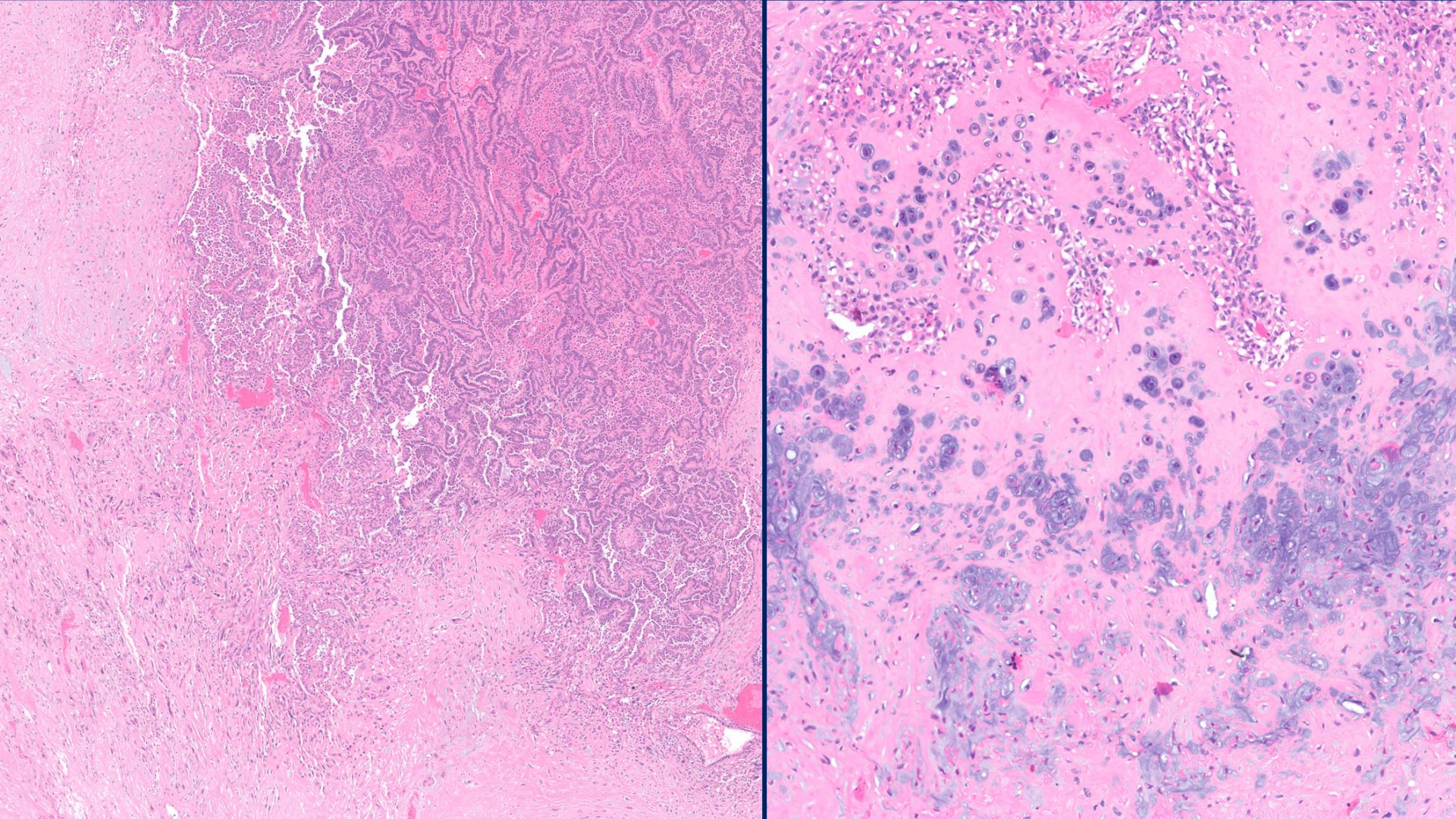
- High-grade neuroendocrine carcinoma are rare in tumors with heterologous elements and should be classified as combined small cell carcinoma or large cell neuroendocrine carcinoma
- Sarcomatous component - rhabdomyosarcoma, chondrosarcoma, and osteosarcoma; and combinations of these types are common; rarely liposarcoma or angiosarcoma
- Less differentiated area composed of malignant spindle cells
- High-grade fetal adenocarcinoma may be seen as a carcinoma element (“blastomatoid variant”) in up to 18% of cases

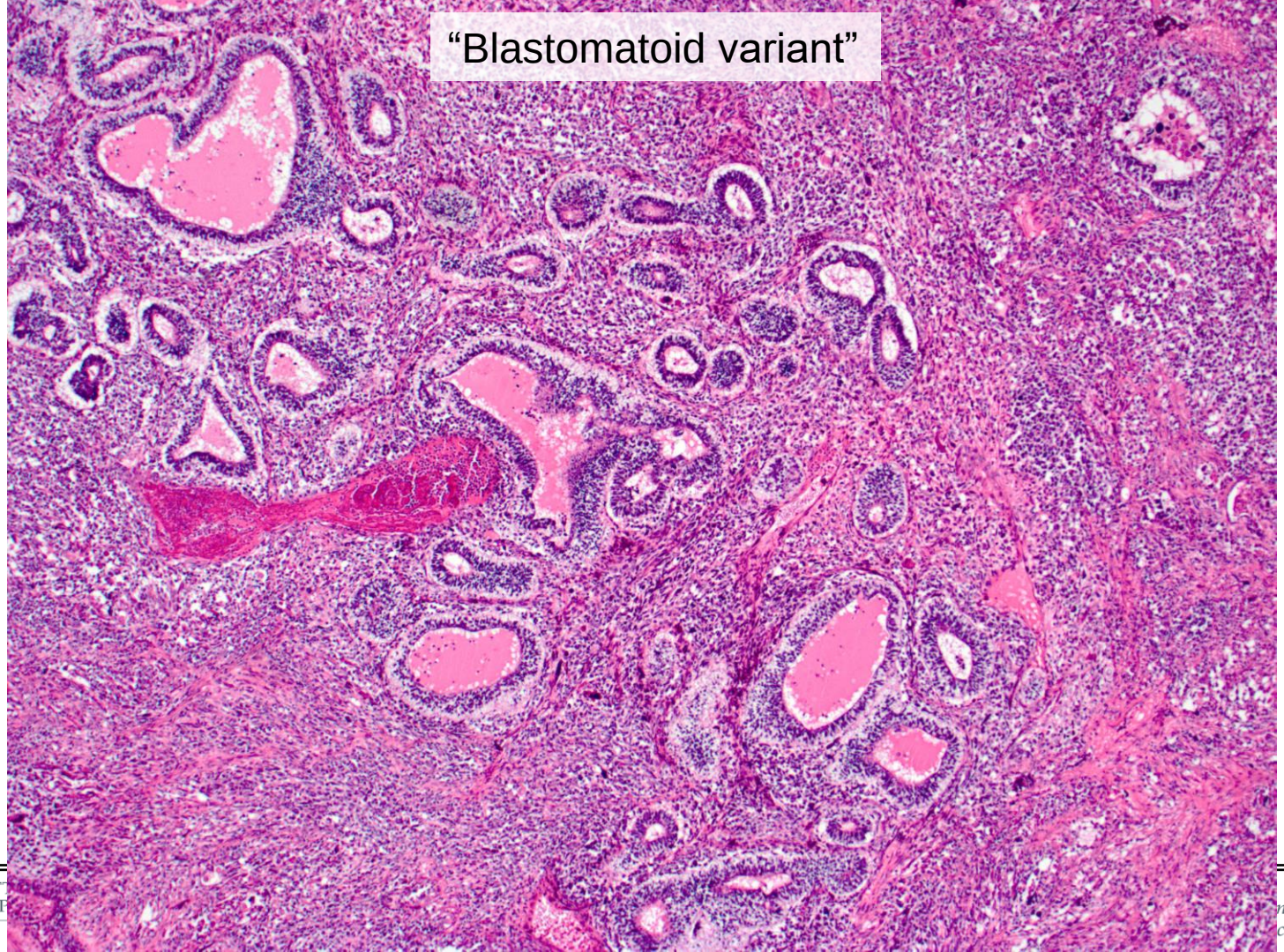
Konoplev S, et al. Am J Clin Pathol 2010;134:112-8, Nakatani Y, et al. Am J Surg Pathol 2004;28:921-7

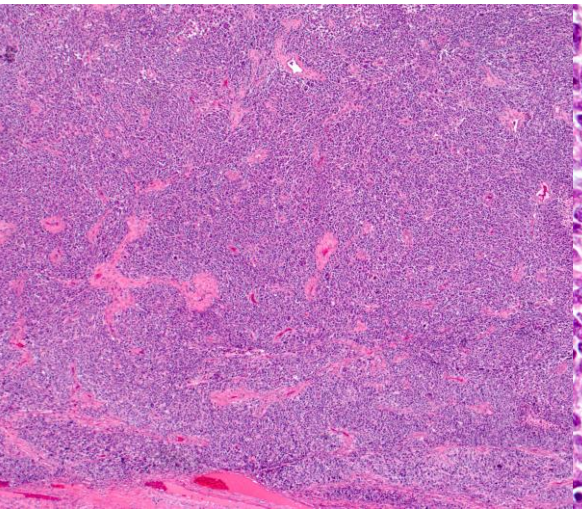


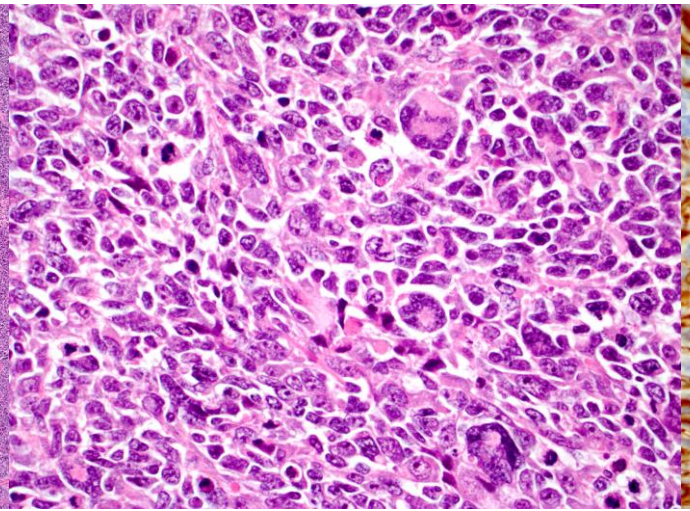


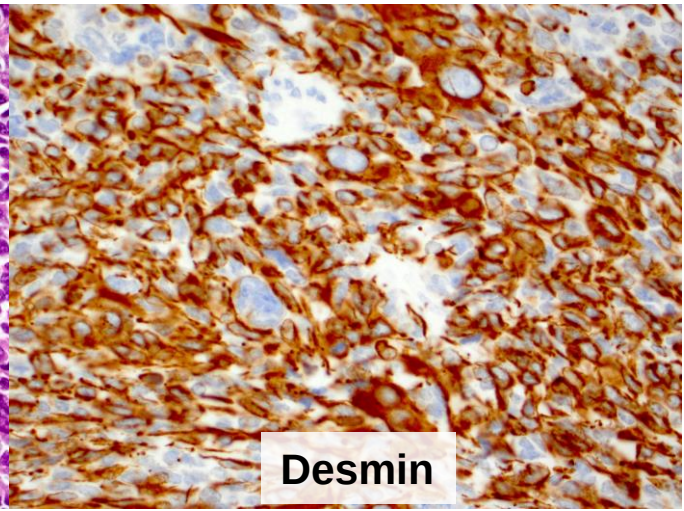





“Blastomatoid variant”



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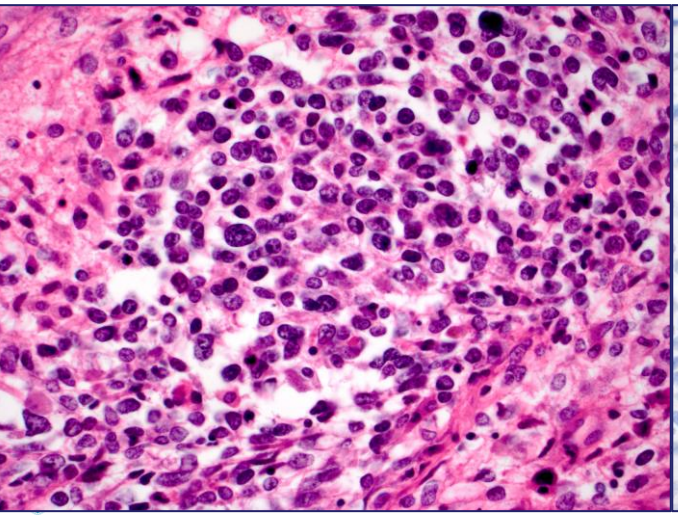
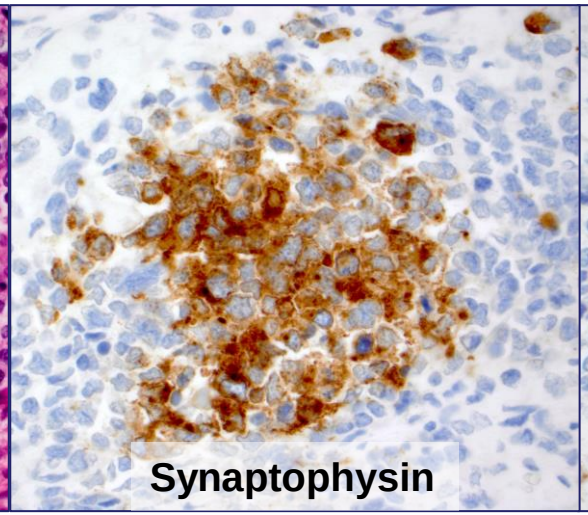
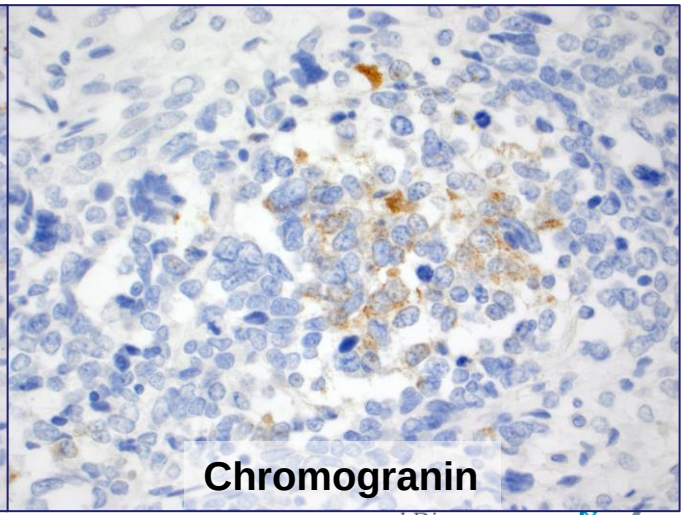
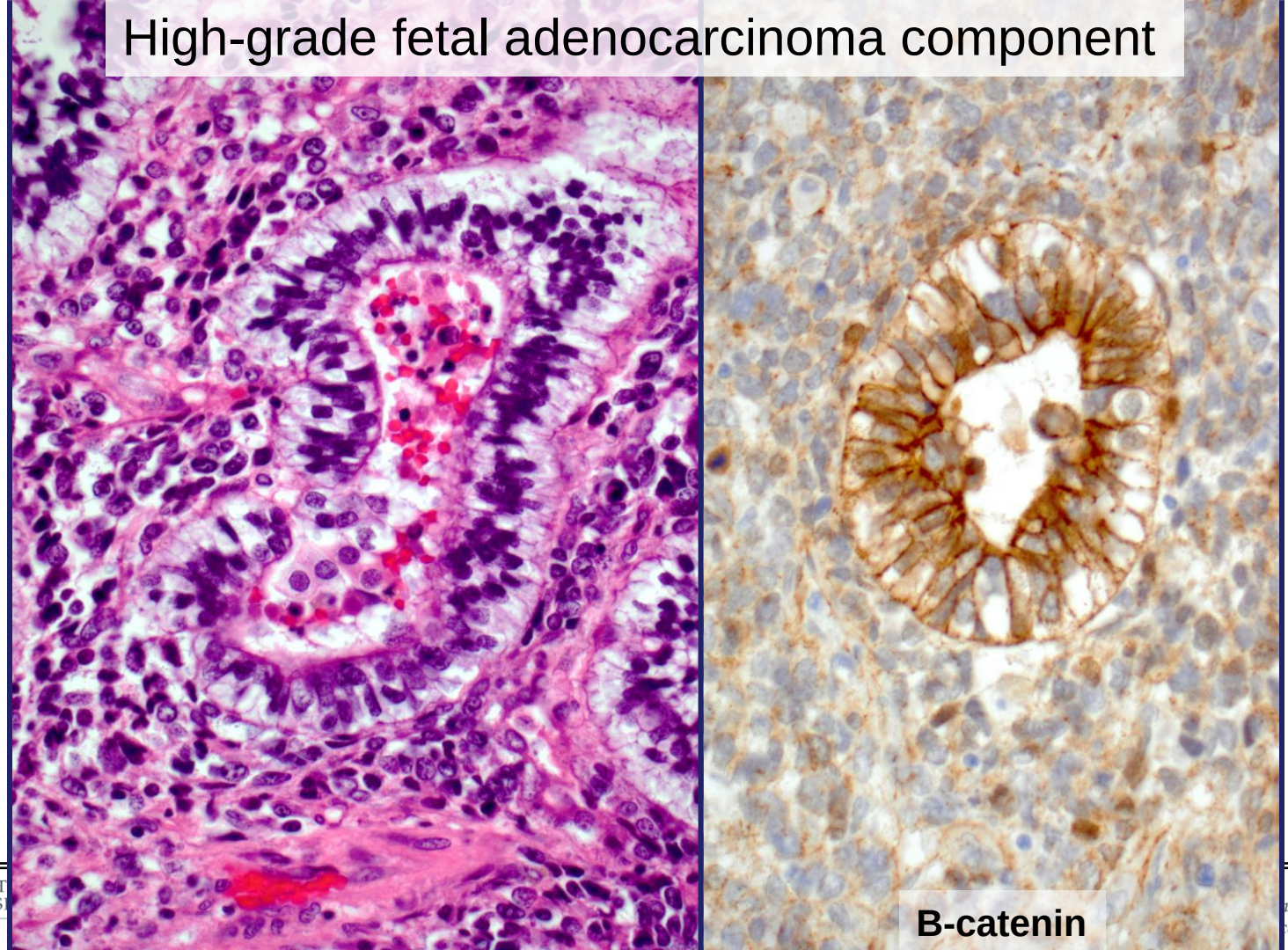



Synaptophysin


Chromogranin

High-grade fetal adenocarcinoma component



B-catenin

Differential diagnosis

- Pleomorphic carcinoma
- Pulmonary blastoma
- Primary or metastatic sarcoma
  - Entrapped reactive pneumocytes may mimic a carcinoma component
  - Synovial sarcoma, biphasic – lack of heterologous element
- Mesothelioma, biphasic

Sarcomatoid Carcinoma of the Lung

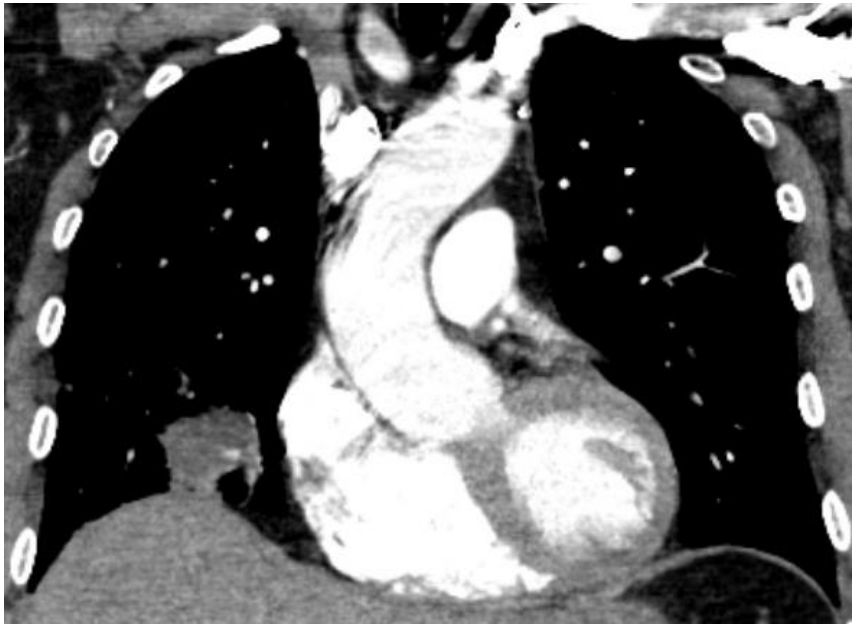
Components	Pleomorphic carcinoma	Pulmonary blastoma	Carcinosarcoma
Carcinoma	Non-small cell carcinoma except LCNEC*	Fetal adenocarcinoma	Typically squamous cell carcinoma or adenocarcinoma
Sarcomatoid / sarcomatous	Spindle and/or giant cells (≥10%) No heterologous element	Blastema-like area present	Heterologous element present

* LCNEC: large cell neuroendocrine carcinoma

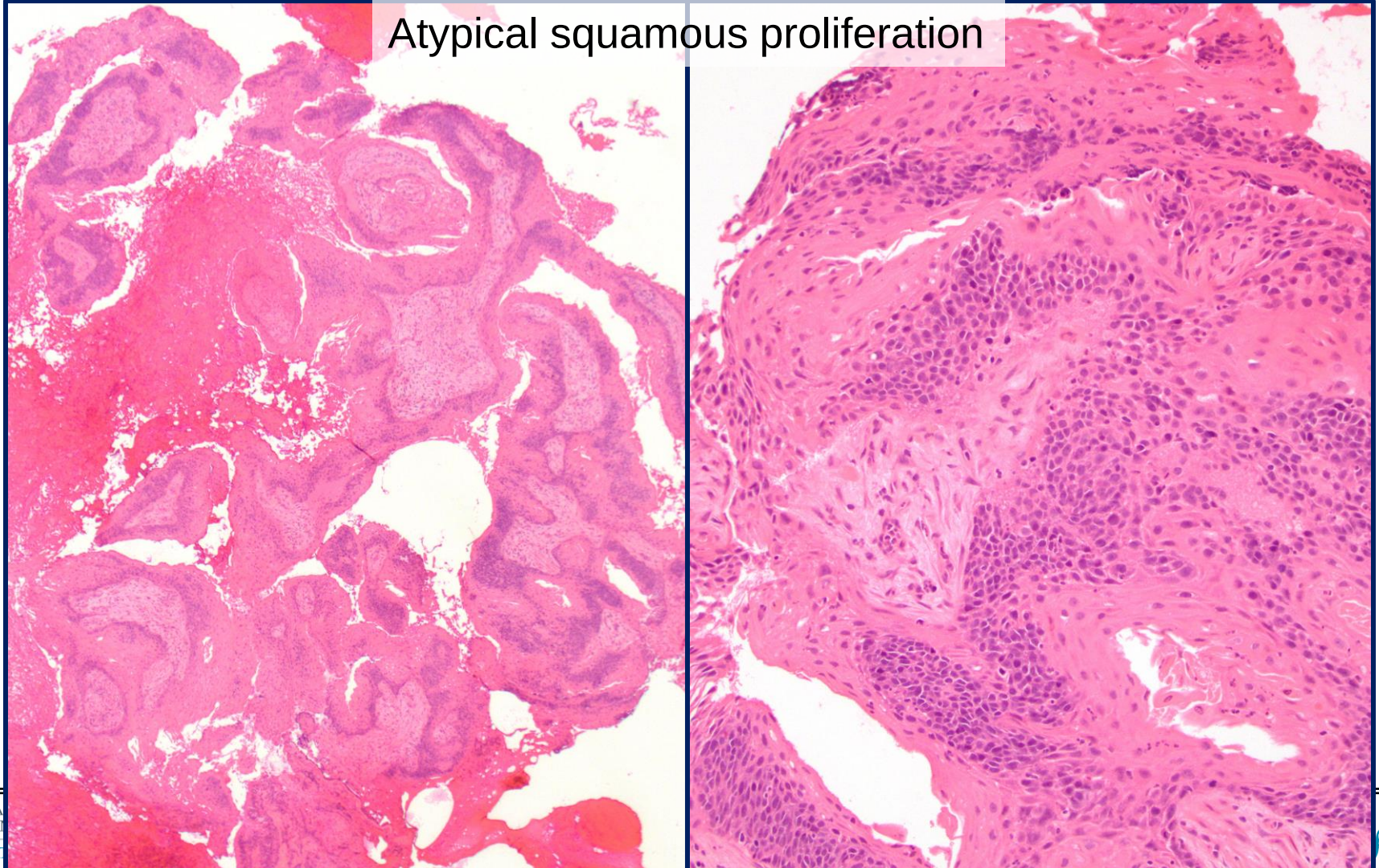
New Kids on the Block

53-year-old man

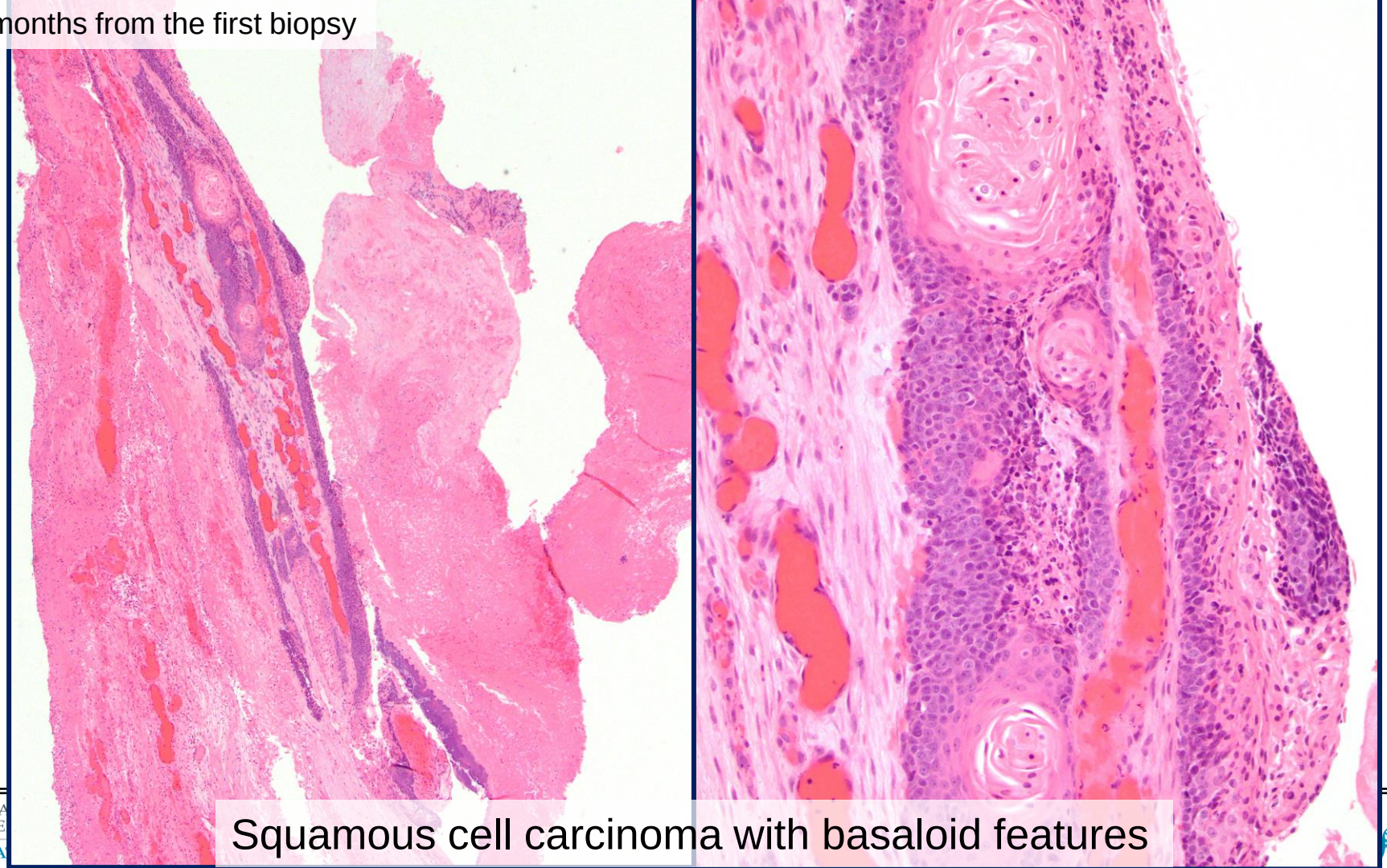
- Never smoker
- Presented with a 3.5 cm mass in the right middle lobe
- No distant metastasis found in the initial staging work-up, but the tumor rapidly grew within 1.5 months
- Neoadjuvant chemotherapy followed by curative operation was planned



Atypical squamous proliferation



1.5 months from the first biopsy



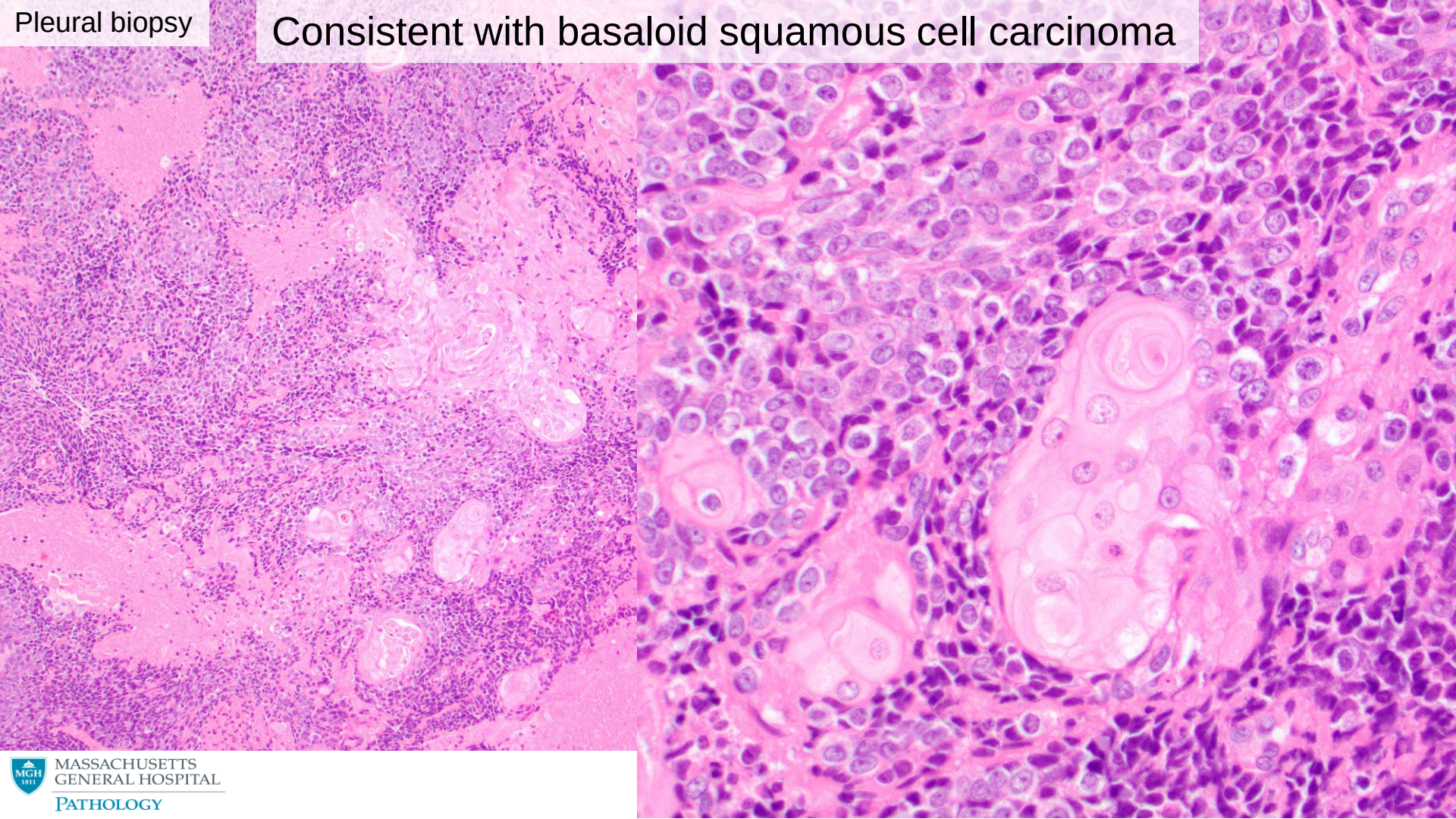
Squamous cell carcinoma with basaloid features

53-year-old never smoker

- Despite cisplatin + docetaxel chemotherapy and subsequent radiation therapy, the tumor grew to involve mediastinal and axillary lymph nodes and pleura

Pleural biopsy

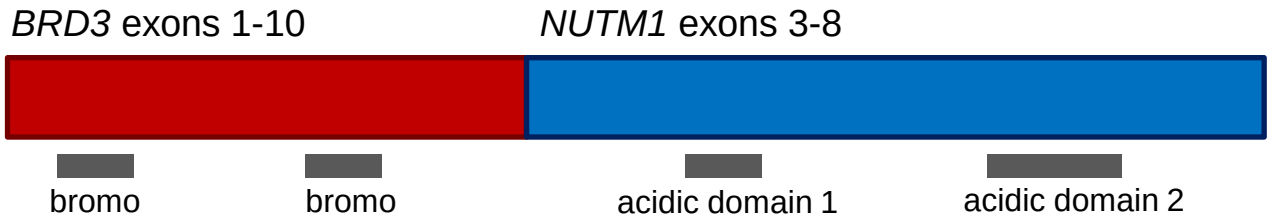
Consistent with basaloid squamous cell carcinoma



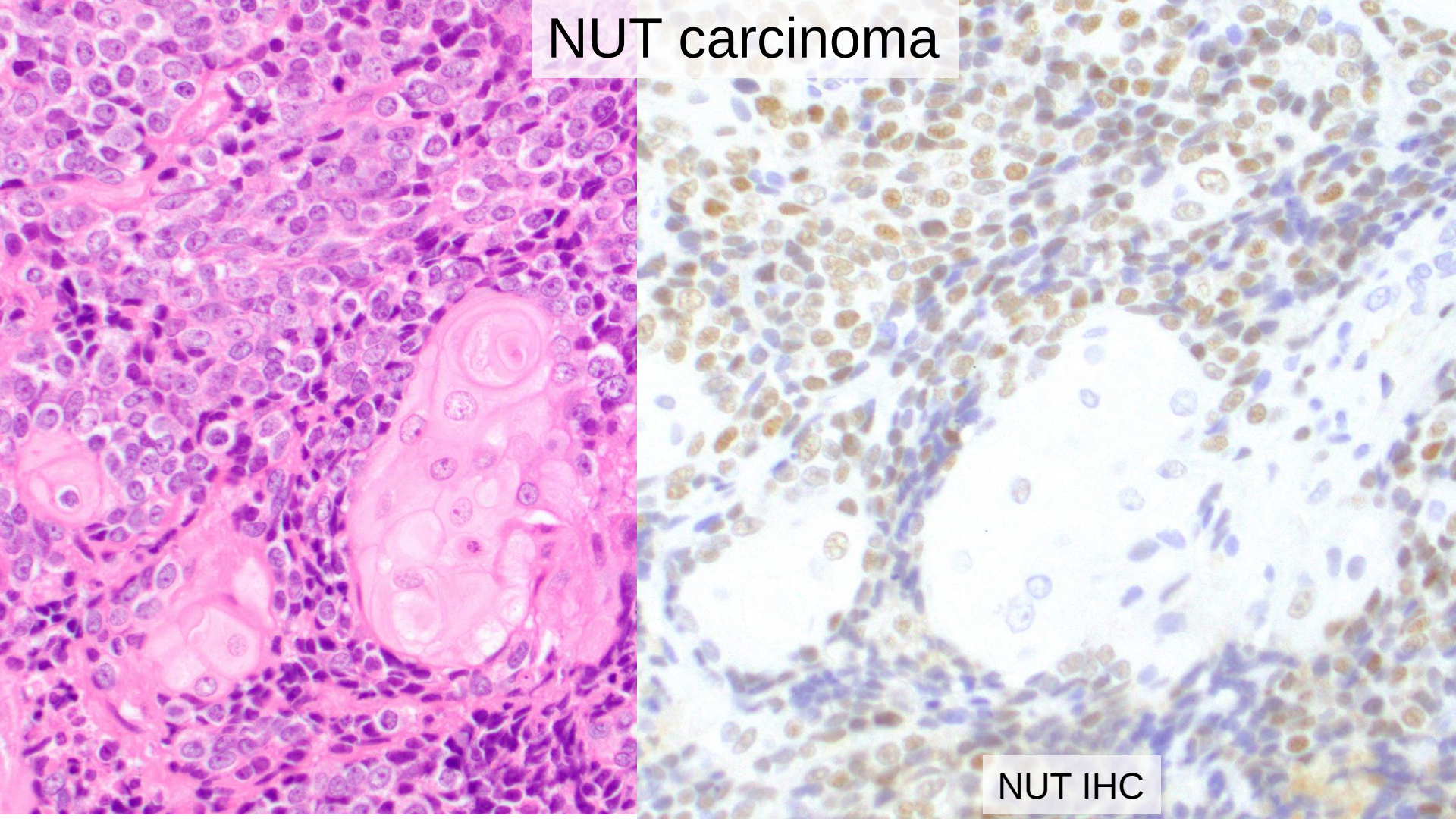
53-year-old never smoker

- Started treatment with nivolvumab 8 months after the initial presentation, but failed to respond to it
- NGS and fusion assay were performed as part of a search for alternative medical therapies

BRD3 Exon10 and *NUTM1* Exon3 (NM_175741)



NUT carcinoma



NUT Carcinoma

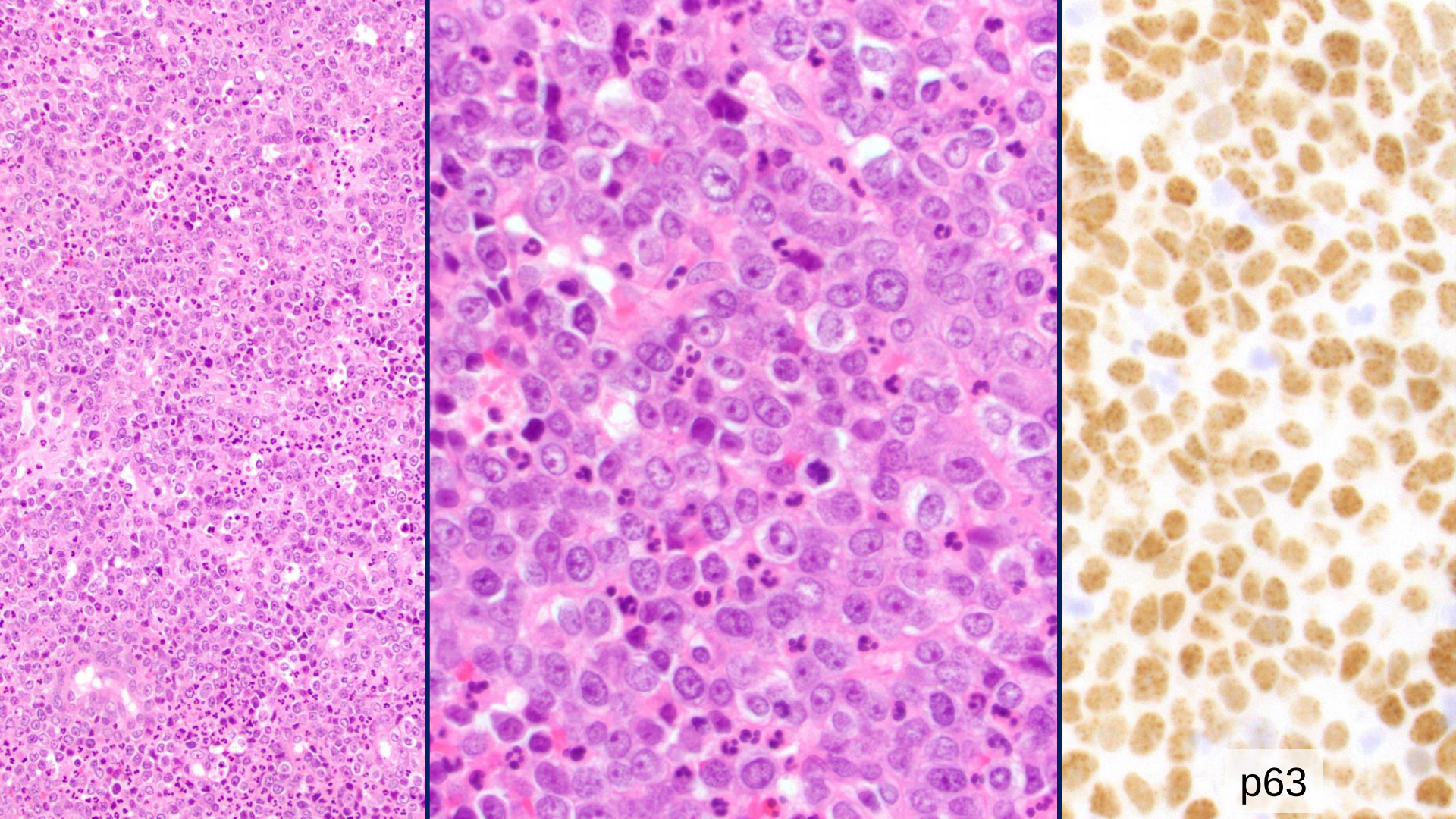
- A poorly differentiated carcinoma genetically defined by the presence of *NUTM1* gene rearrangement (*NUT-BRD4 >> NUTM1-BRD3 > NUTM1-NSD3* and others)
- Both lung and mediastinum are commonly involved at presentation
- Affect patients of any age (range: 0-80 years) and males and females equally
- 0.6% of lung carcinomas lacking glandular differentiation
- Extremely aggressive; median OS of 6.5 months for all and that of 4.4 months for thoracic *BRD4-NUTM1* carcinomas

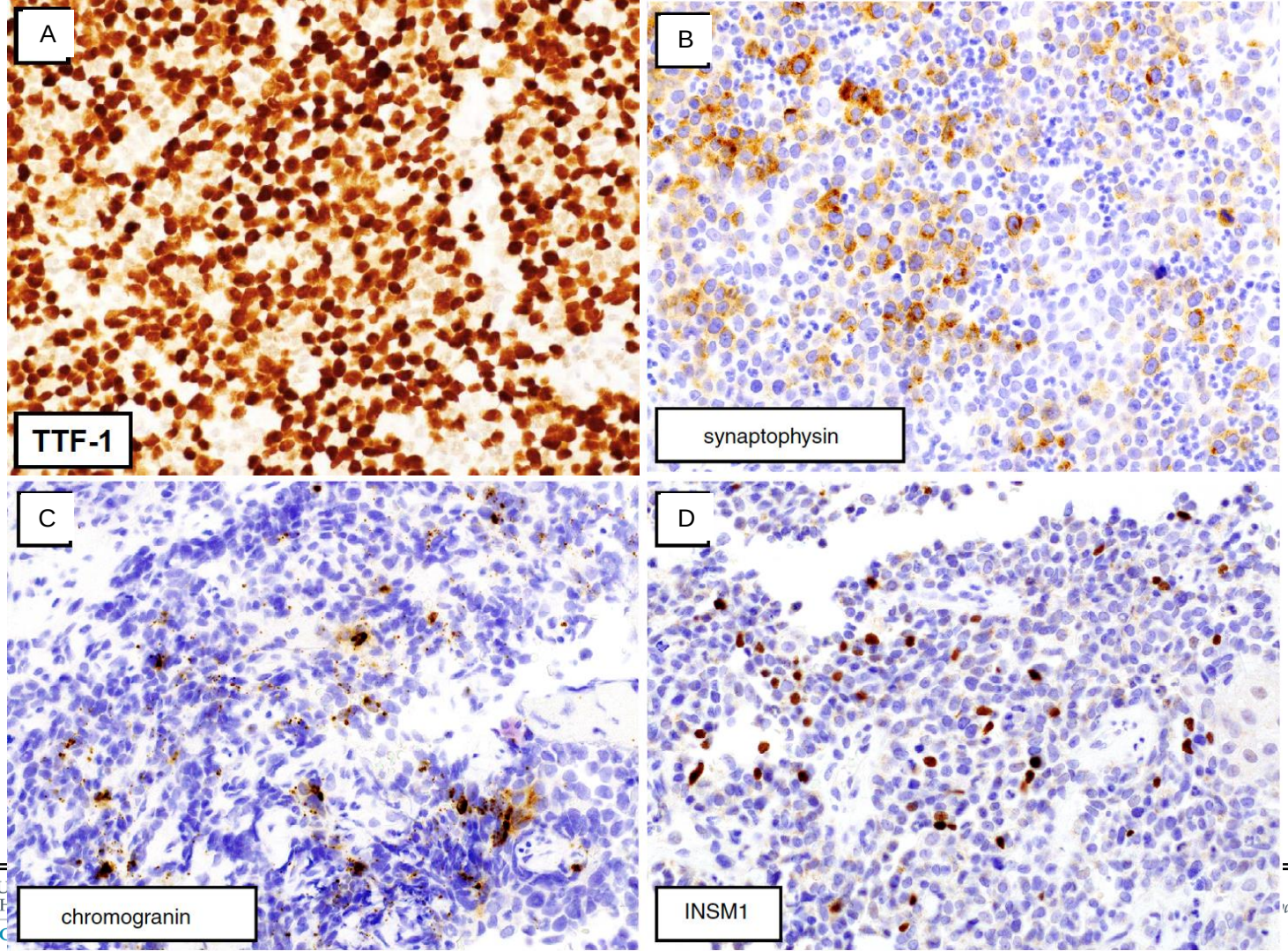
NUT Carcinoma: Histologic Features

- Sheets and nests of small to intermediate-sized undifferentiated cells with a monomorphic appearance
- Evenly sized nuclei with vesicular chromatin and prominent nucleoli
- Lack of nuclear moulding
- Abrupt foci of keratinization seen in 1/3
- No definitive glandular differentiation
- Prominent neutrophilic infiltrate w/ or w/o associated necrosis

NUT Carcinoma: Immunohistochemistry

- NUT protein expression in 87% (clone C52B1)
- Pancytokeratin expression in the majority; variable expressions of other epithelial markers (EMA, BerEP4, CEA, etc.)
- p63 /p40 nuclear expression in 90% and 2/3 of cases, respectively, indicative of squamous differentiation
- Chromogranin, synaptophysin and/or TTF-1 expressions can be seen in occasional cases
- CD34 (hematopoietic stem cell marker) is often expressed
- Very high KI-67 proliferative index


p63



Hing Y, at al. Histopahtology 2021;78:896-904

Differential Diagnosis

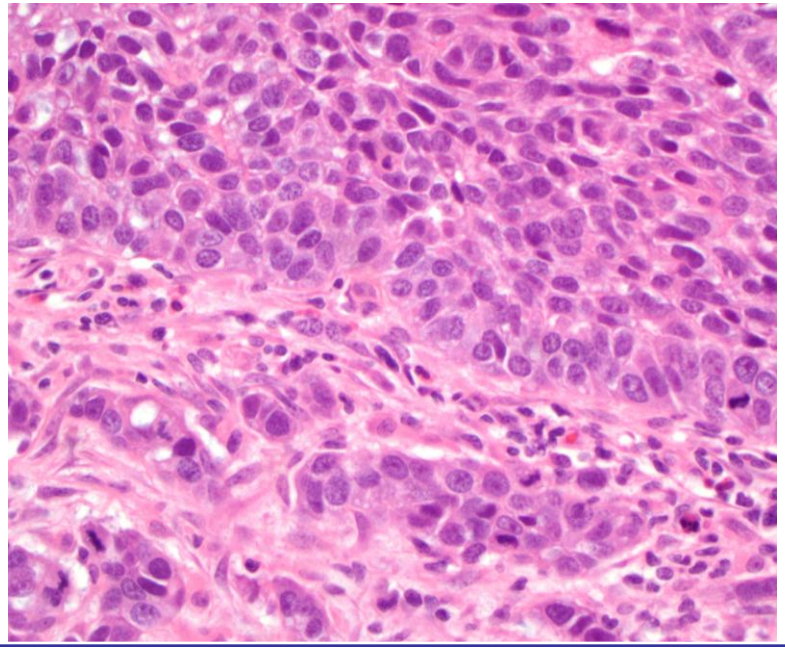
- Poorly differentiated / basaloid squamous cell carcinoma
- Small cell carcinoma

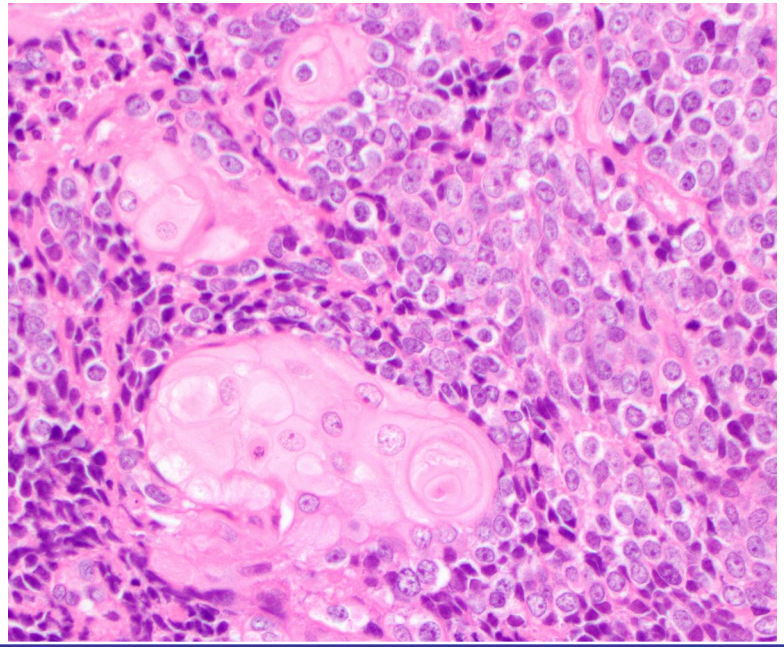
Caution: Neuroendocrine markers and/or TTF-1 can be expressed in a subset of NUT carcinomas

- Combined small cell and squamous cell carcinoma
- Undifferentiated carcinoma / SMARCA-4 deficient undifferentiated tumor
- Small round blue cell tumors including leukemia

✓ Significant fraction of patients are diagnosed by molecular testing

✓ NUT carcinoma needs to be ruled out in cases with histologic features suggestive of poorly differentiated / basaloid squamous cell carcinomas from never or light smokers

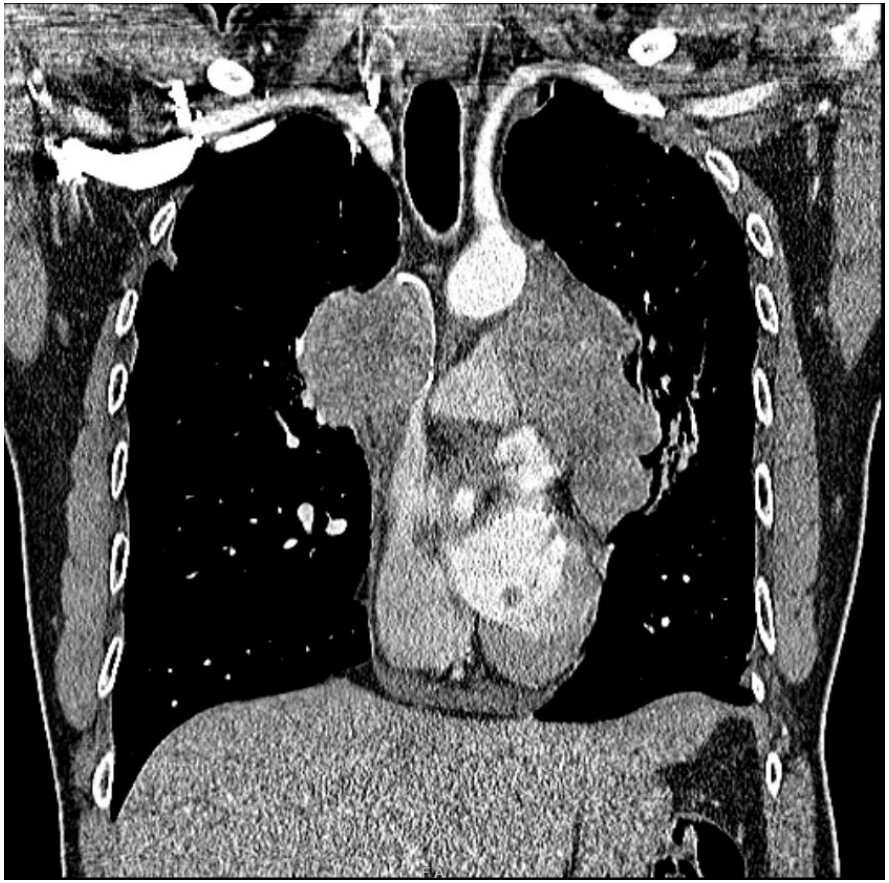


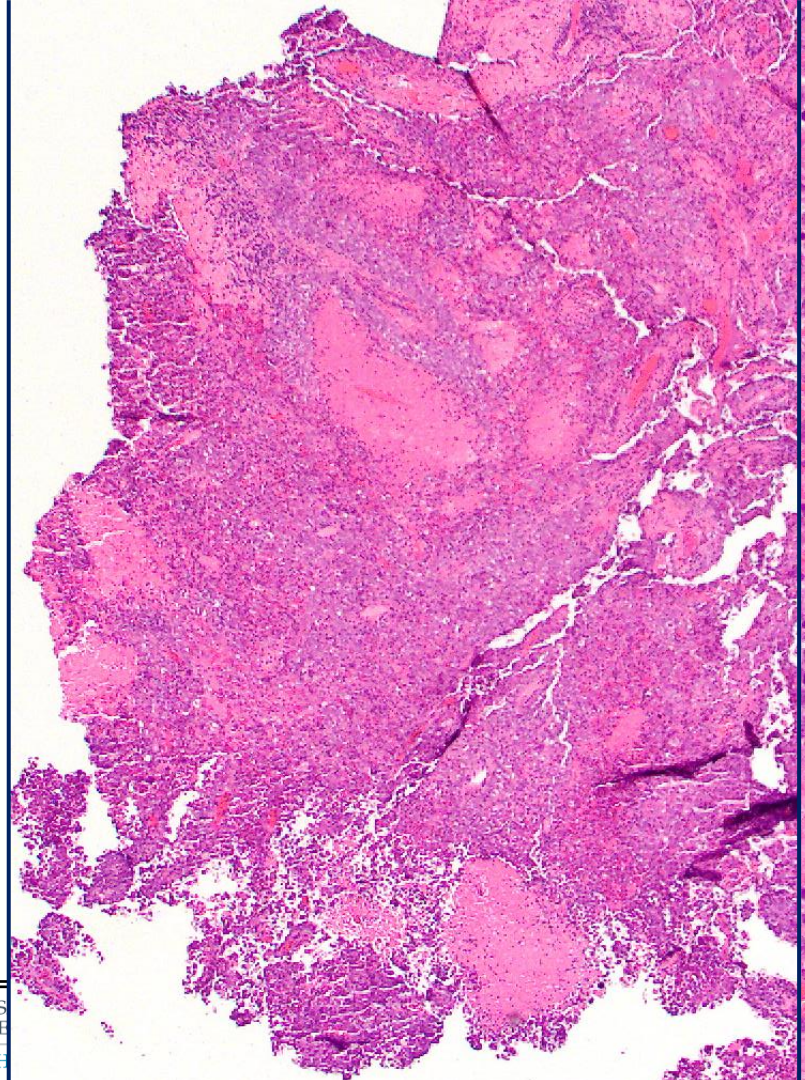


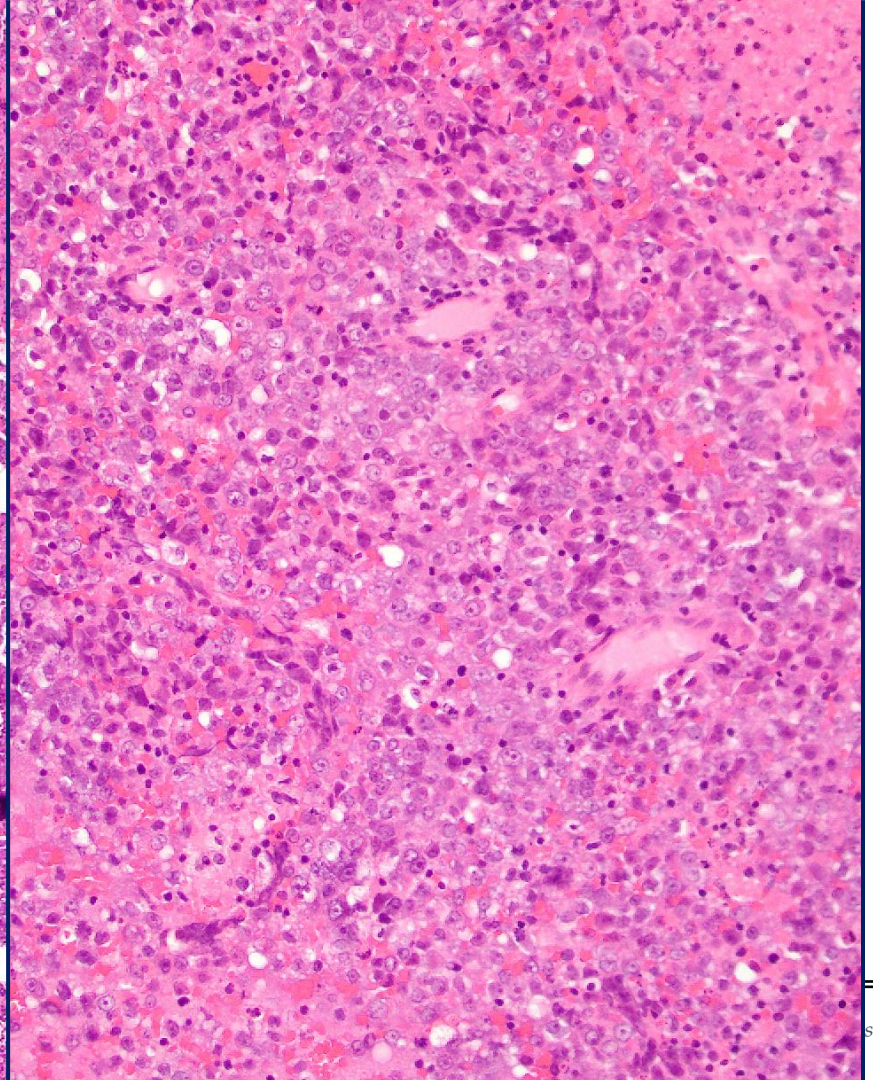
Basaloid squamous cell carcinoma	NUT carcinoma
Scant but well-defined cytoplasm	Pale eosinophilic to basophilic cytoplasm
Lobular architecture / peripheral palisading	Sheets / nests with even spacing of cells
Hyaline or mucoid stroma may be present	Prominent neutrophilic infiltrate
Squamous morphology may be seen in <50% of tumor cells	Abrupt foci of keratinization in 1/3

60-year-old man

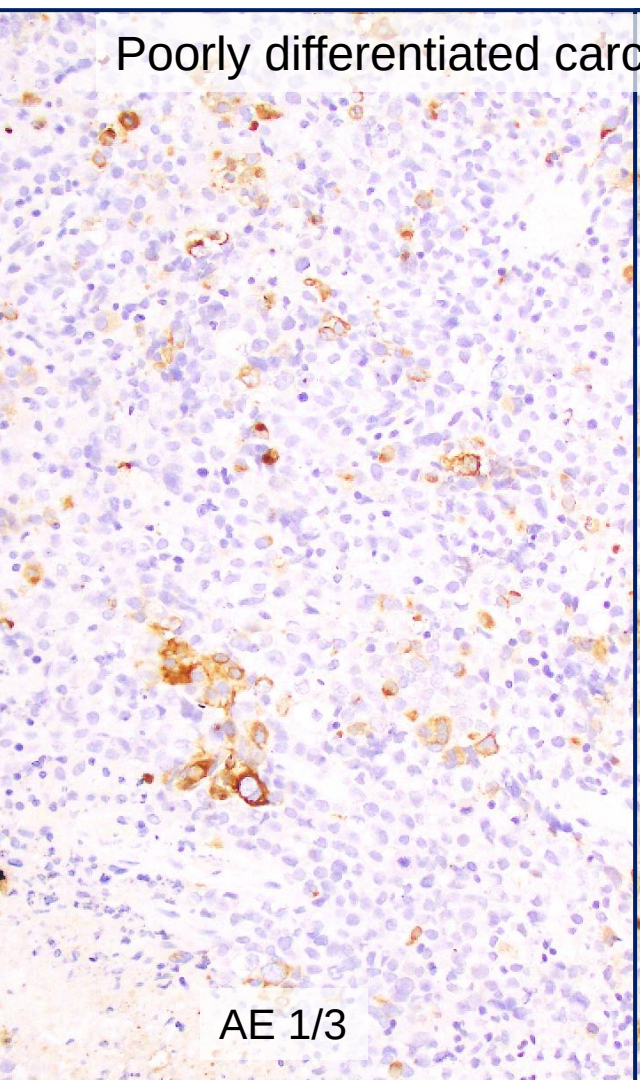
- 45 pack-year smoking history
- Emphysema
- Presented with chest pain and short of breath
- A bulky mediastinal tumor without a lung lesion on imaging studies



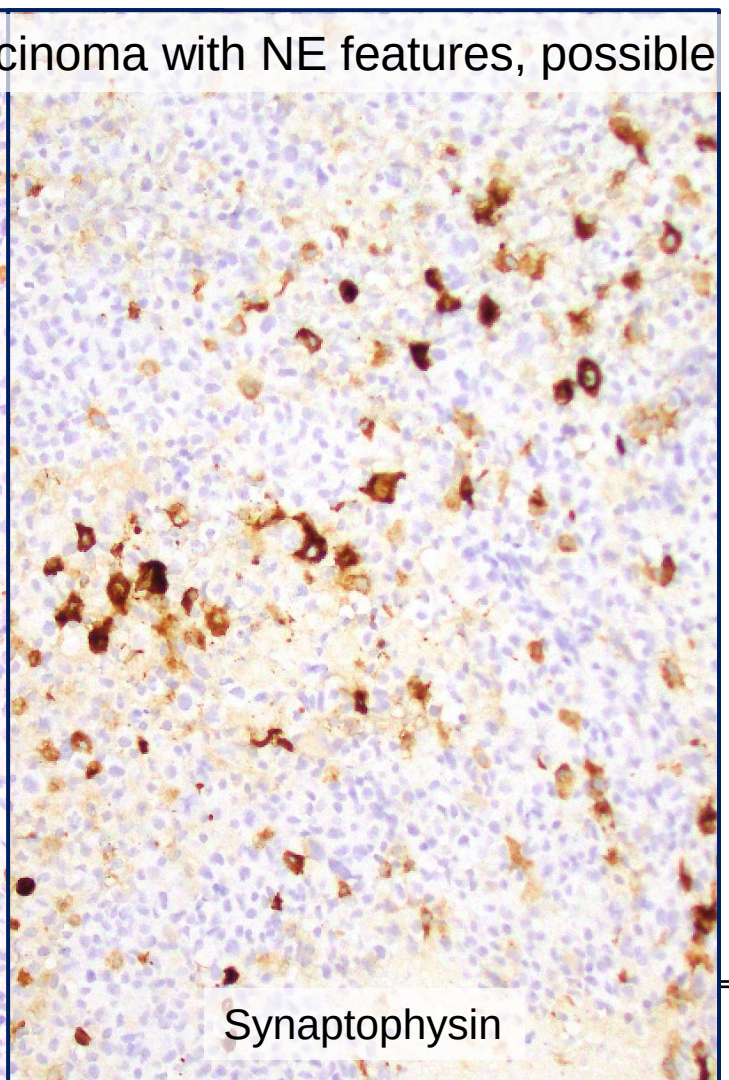




Poorly differentiated carcinoma with NE features, possible LCNEC



AE 1/3



Synaptophysin

IHC Results

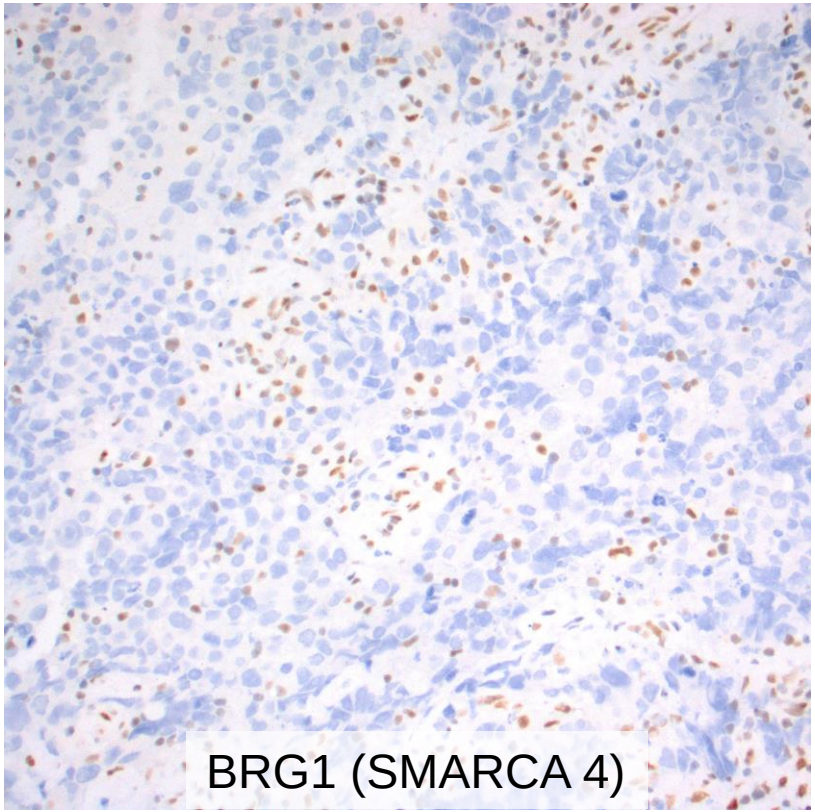
Positive:
- AE1/3 (patchy)
- CAM 5.2 (patchy)
- Synaptophysin (10%)
- TTF-1 (rare)

Negative:
- p40
- Chromogranin
- Napsin A
- NUT

Thoracic SMARCA4-Deficient Undifferentiated Tumor

NGS Results

- *KEAP1*
- *SMARCA4*
- *CDKN2A*
- *CSF1R*
- *TP53*
- *NF1*

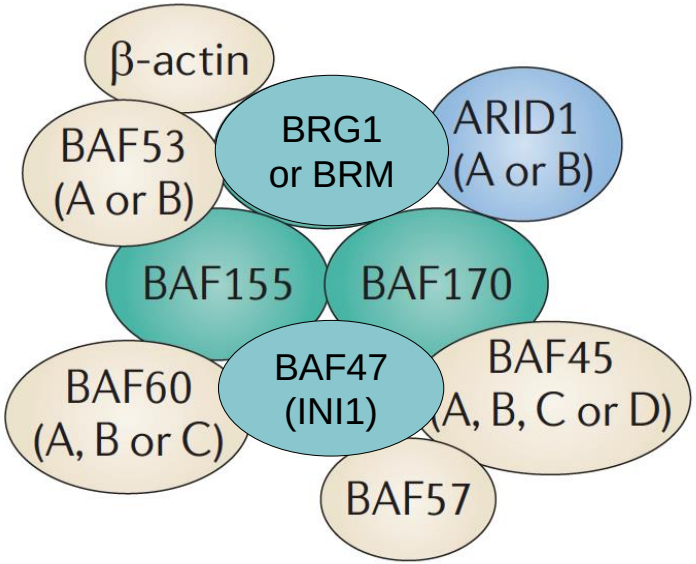


BRG1 (SMARCA 4)

What does SMARCA4 deficiency mean?

SWI/SNF complexes (ATP-dependent chromatin remodeling complexes)

- Critical tumor suppressor
- Multiple protein complex (>20 proteins)
- Responsible for epigenetic programing
- Regulate transcription by modifying DNA and histones to promote cell differentiation from stem cell to terminal states
- 20% of human cancers harbor mutations of its subunits



Protein	BRG1	BRM	INI1
Gene	*SMARCA4*	*SMARCA2*	*SMARCB1*

Wilson BG, et al. Nat Rev Cancer 2011;11:481-92, modified

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

Francois Le Loarer[1–3], Sarah Watson[4,5], Gaelle Pierron[6], Vincent Thomas de Montpreville[7], Stelly Ballet[6], Nelly Firmin[8], Aurelie Auguste[9], Daniel Pissaloux[2], Sandrine Boyault[10], Sandrine Paindavoine[2], Pierre Joseph Dechelotte[11], Benjamin Besse[12,13], Jean Michel Vignaud[14], Marie Brevet[3,15], Elie Fadel[13,16], Wilfrid Richer[4,17], Isabelle Treilleux[2], Julien Masliah-Planchon[5,6], Mojgan Devouassoux-Shisheboran[18], Gerard Zalcman[19,20], Yves Allory[21–23], Franck Bourdeaut[6,24], Francoise Thivolet-Beju[3,15], Dominique Ranchere-Vince[2], Nicolas Girard[3,25], Sylvie Lantuejoul[26,27], Francoise Galateau-Sallé[28,29], Jean Michel Coindre[30,31], Alexandra Leary[9,12], Olivier Delattre[4–6], Jean Yves Blay[1,3,32,33] & Franck Tirode[4,5,33]

Nat Genet 2015;47:1200-5

Modern Pathol 2017;30:797-809

Clinicopathological and molecular characterization of SMARCA4-deficient thoracic sarcomas with comparison to potentially related entities

Akihiko Yoshida[1,2], Eisuke Kobayashi[2,3], Takashi Kubo[4], Makoto Kodaira[2,5,12], Toru Motoi[6], Noriko Motoi[1], Kan Yonemori[2,5], Yuichiro Ohe[7], Shun-ichi Watanabe[8], Akira Kawai[2,3], Takashi Kohno[9], Hiroshi Kishimoto[10], Hitoshi Ichikawa[4,11] and Nobuyoshi Hiraoka[1]

Modern Pathol 2017;30:1422-32

SMARCA4-deficient thoracic sarcoma: a distinctive clinicopathological entity with undifferentiated rhabdoid morphology and aggressive behavior

Jennifer L Sauter[1,4], Rondell P Graham[1], Brandon T Larsen[2], Sarah M Jenkins[3], Anja C Roden[1] and Jennifer M Boland[1]

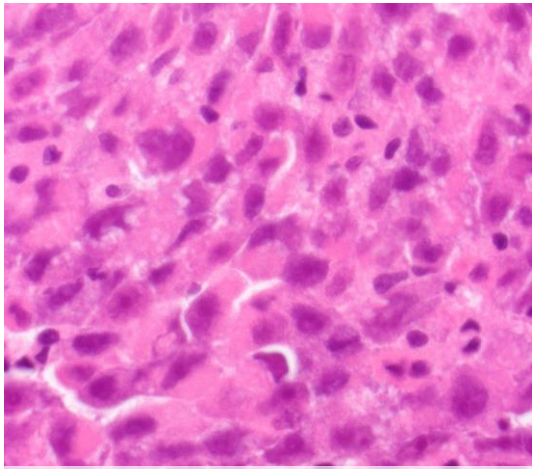
Thoracic SMARCA4-Deficient Undifferentiated Tumor (SMARCA4-UT)

- SMARCA-UT is a high-grade malignant neoplasm that significantly involves the thorax of adults and shows undifferentiated or rhabdoid phenotype and deficiency of SMARCA4, a key member of the BAF chromatin-remodeling complex

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

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]

Rekhtman N, et al. J Thorac Oncol 2020;15:231-47



Rhabdoid cytomorphology

Thoracic SMARCA4-Deficient Undifferentiated Tumor

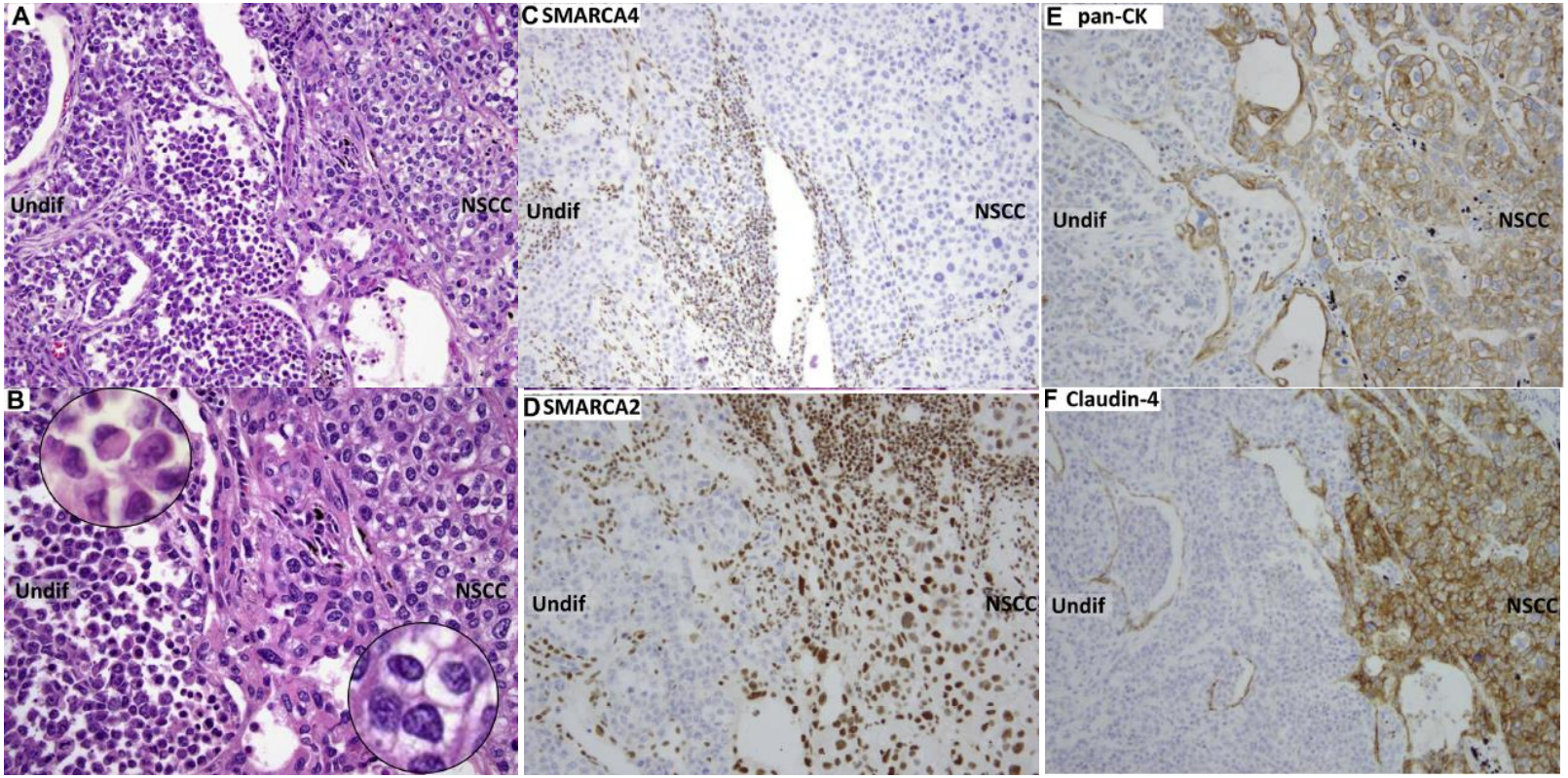
- Primarily present at younger age (30 – 50 year)
- Heavy smoking history
- Bullous emphysema in >50% of cases
- Larger primary tumor size
- Present in all clinical stages including stage I, but the majority (80-90%) present at stage IV
- No consensus guidelines or definitive therapies currently exist
- Overall survival of 4-7 months; worse prognosis compared to conventional NSCLC

Dagogo-Jack I, et ai. J Thorac Oncol 2020;15:766-76
Rekhtman N, at al. J Thorac Oncol 2020;15:221-47

Thoracic SMARCA4-Deficient Undifferentiated Tumor

- Undifferentiated round cells or rhabdoid morphology
- Prominent nucleoli
- Increased mitotic activity +/- atypical mitoses
- Often focal or weak, or negative expression of cytokeratins
- Lack or limited expression of adhesion molecule claudin-4
- SMARCA2 (BRM) codeficiency
- Frequent expression of stem cell markers
- Commonly exhibit synaptophysin immunoreactivity (up to 70%)

Dagogo-Jack I, et ai. J Thorac Oncol 2020;15:766-76
Rekhtman N, at al. J Thorac Oncol 2020;15:221-47


A
Undif
NSCC
B
Undif
NSCC
C SMARCA4
Undif
NSCC
D SMARCA2
Undif
NSCC
E pan-CK
Undif
NSCC
F Claudin-4
Undif
NSCC

Thoracic SMARCA4-Deficient Undifferentiated Tumor (SMARCA4-UT)

Essential:

- Tumor in adults, with significant thoracic involvement
- Diffuse sheets of variably discohesive, round to epithelioid, relatively monotonous cells with vesicular nuclei and prominent nucleoli
- No clear evidence of epithelial differentiation (except juxtaposed carcinoma in combined cases)
- SMARCA4 (BRG1) deficiency by immunohistochemistry

Desirable:

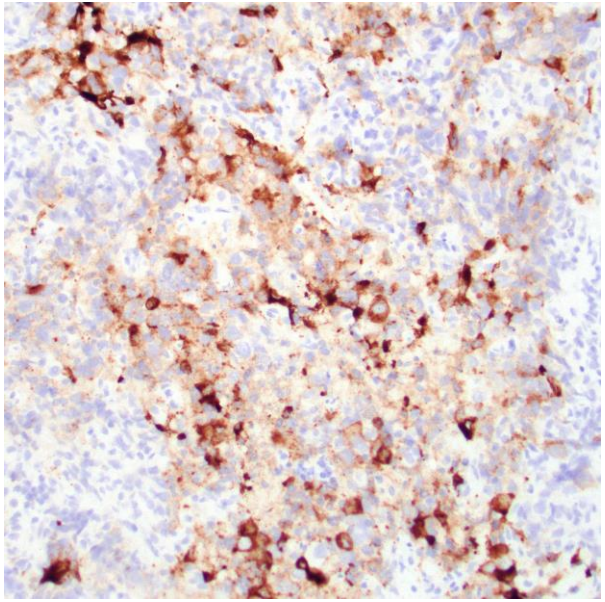
- SMARCA2 (BRM) deficiency by immunohistochemistry
- Expression of CD34, SOX2, and/or SALL4
- Absent or focal claudin-4 expression

Differential Diagnosis

- Large cell lymphoma
- NUT carcinoma
- Germ cell tumor
- High-grade neuroendocrine carcinoma (LCMEC)
- Melanoma
- Various type of sarcomas
  - CIC-rearranged sarcoma, malignant rhabdoid tumor, epithelioid sarcoma, etc.
- Conventional NSCLC with SMARCA4 loss

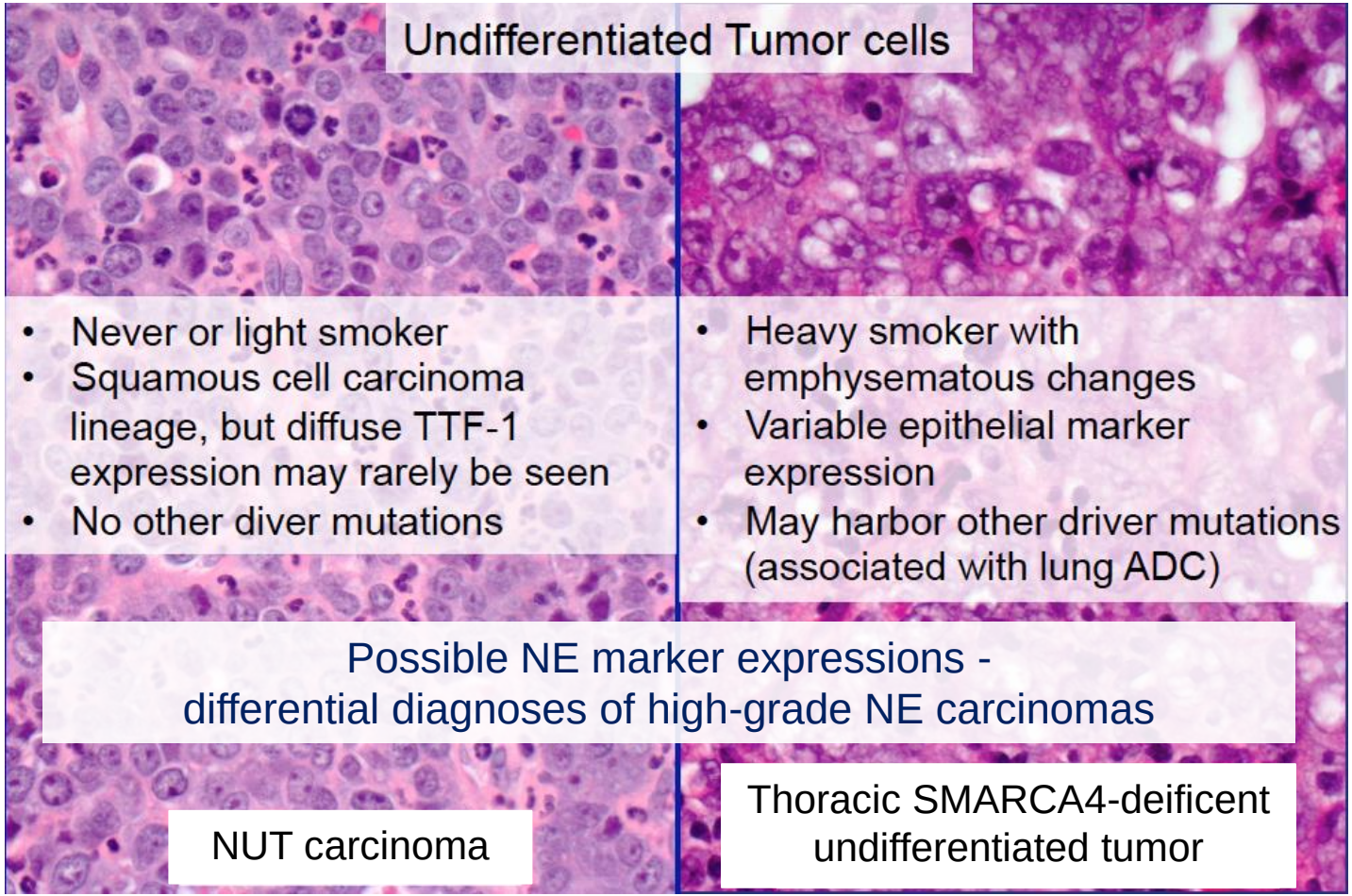
Lack of NE morphology excludes LCNEC diagnosis

Caution: up to 70% of SMARCA4-UTs are immunoreactive to synaptophysin



Synaptophysin

Dagogo-Jack I, et ai. J Thorac Oncol 2020;15:766-76
Rekhtman N, at al. J Thorac Oncol 2020;15:221-47


Undifferentiated Tumor cells
• Never or light smoker
• Squamous cell carcinoma lineage, but diffuse TTF-1 expression may rarely be seen
• No other diver mutations
• Heavy smoker with emphysematous changes
• Variable epithelial marker expression
• May harbor other driver mutations (associated with lung ADC)
Possible NE marker expressions - differential diagnoses of high-grade NE carcinomas
NUT carcinoma
Thoracic SMARCA4-deificent undifferentiated tumor

Thank You!