Lung Tumors

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Adenocarcinoma

Malignant epithelial tumor with **glandular differentiation, mucin production, or pneumocyte marker expression**.

Lung Cancer (including other carcinoma types) is the **most common cause of cancer death world-wide**. Strong association with **tobacco smoking**. Other risk factors: Radon, air pollution, occupational exposure

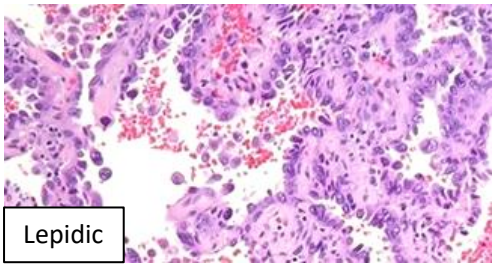
Symptoms vary depending on sites of involvement, and include cough, chest pain, and hemoptysis. However, most patients present late with advanced or metastatic disease that is inoperable.

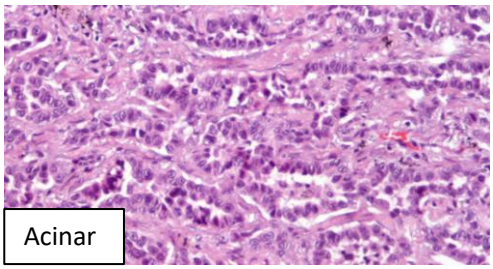
On CT, they are often **peripheral** with solid (invasive) areas and "ground-glass" (lepidic) areas.

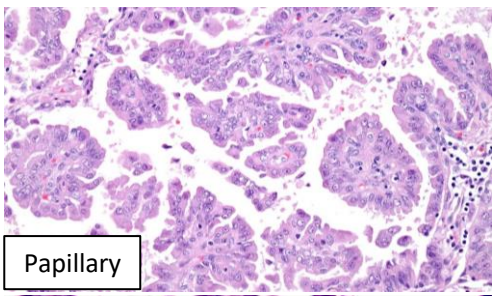
Histologic Patterns:

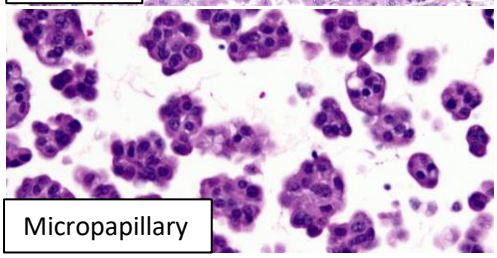
Use for non-mucinous adenocarcinomas. If an adenocarcinoma subtype/architectural pattern is identified on biopsy, it should be reported. Report in 5% increments and classify based on predominant pattern.

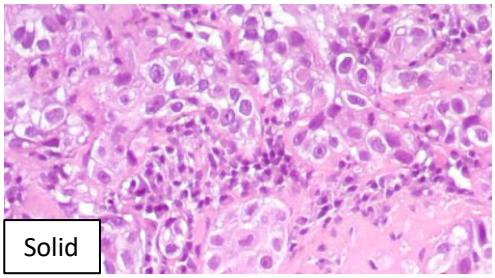
Subtype	Characteristics
Lepidic	Growing along the surface of pre-existing alveolar walls (like AIS), non-invasive
Acinar	Glands with a central lumen space surrounded by tumor cells. Often desmoplastic stroma. Includes cribriform, which has a worse prognosis.
Papillary	Glands growing along central fibrovascular cores
Micropapillary	Cells growing in papillary tufts forming florets that lack fibrovascular cores (poorer prognosis)
Solid	Polygonal tumor cells growing in sheets (poorer prognosis)


Lepidic


Acinar


Papillary


Micropapillary


Solid

If exclusively lepidic on biopsy, report as "Adenocarcinoma, lepidic pattern" (or something similar). On resection, this could represent Adenocarcinoma in situ (AIS), Minimally invasive adenocarcinoma (MIA), or simply a lepidic component of an invasive adenocarcinoma. Radiographic correlation is required pre-operatively.

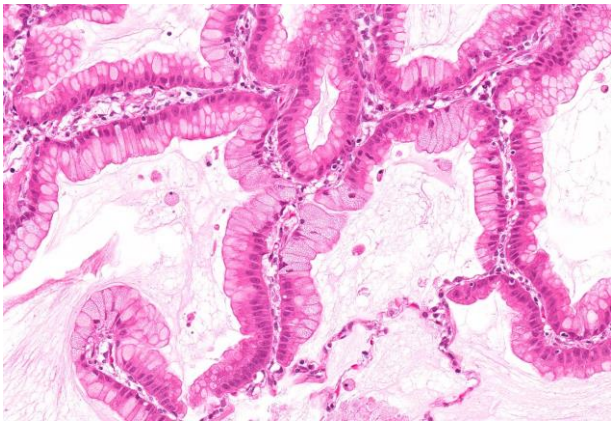
Criteria for invasion:

1) Histologic subtype other than lepidic (e.g., acinar),
2) Desmoplastic stroma associated with tumor,
3) Vascular or pleural invasion,
4) Spread through air spaces (STAS)

IHC: (+) TTF-1, Napsin-A, CK7

Variants of Adenocarcinoma:

Invasive Mucinous Adenocarcinoma



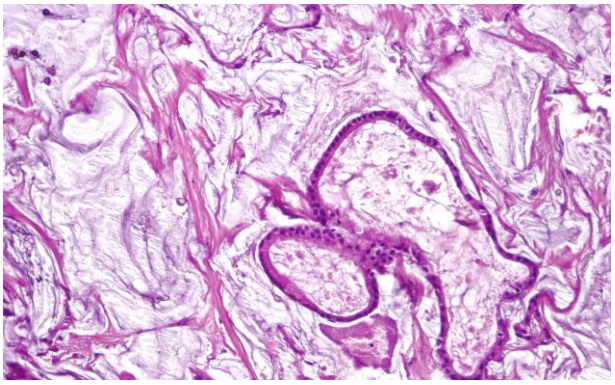
An adenocarcinoma with goblet or columnar cells with **abundant intracytoplasmic mucin**. Cytologically bland.

Any growth pattern may be seen. Even though often lepidic-predominant, usually areas of invasion.

Frequently KRAS mutated. Often peripheral, multifocal.
IHC: (+) CK7+, (-/+)TTF-1, (+/-)CK20 and CDX2.

Need to clinically exclude mucinous metastasis (e.g., pancreas). Poorer prognosis. Often multifocal/multilobar.

Colloid Adenocarcinoma



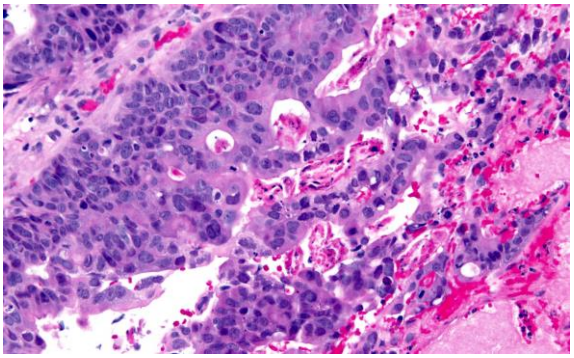
Adenocarcinoma where **pools of abundant mucin replace air spaces.**

Mucin distends alveolar spaces and destroy walls, with overtly invasive growth. Tumor cells often do not entirely line alveoli and may be relatively bland.

IHC: Often express CK7 and intestinal markers CDX2, CK20.

Must exclude a metastasis clinically.

Enteric Adenocarcinoma



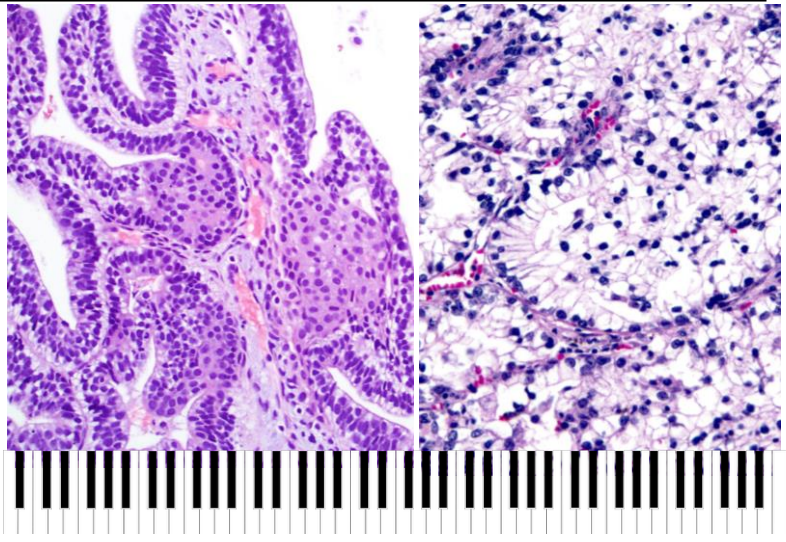
Adenocarcinoma **resembling colorectal-type adenocarcinoma.**

Requires careful clinical evaluation (e.g., colonoscopy and imaging) to exclude a metastasis from an occult GI primary.

Eosinophilic, tall columnar cells with pseudostratified nuclei and abundant "dirty" necrosis.

IHC: (+) CDX2; (+/-) CK20, CK7, (-/+)TTF1, SATB2

Fetal Adenocarcinoma



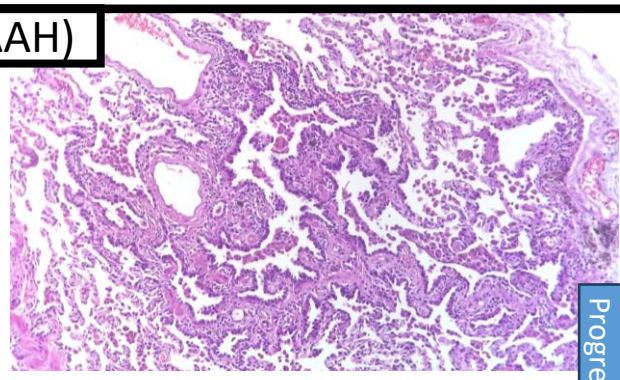
Adenocarcinoma **resembling fetal lung in pseudoglandular stage**.

Complex glandular structures composed of glycogen-rich, non-ciliated cells.
Frequent morule formation. *"Piano keys"*
Low-grade: Small, round, monotonous nuclei. Nuclear/cytoplasmic β-catenin,
High-grade: Diffuse atypia. Membranous β-catenin. Often combined with other types.

IHC: TTF-1(+/-). Frequent neuroendocrine marker, and germ cell marker expression.

Precursor/Early/Lepidic Lesions: Can only be definitively diagnosed **on <u>resection</u> specimens** (as there could be invasion elsewhere)

Atypical Adenomatous Hyperplasia (AAH)



A small (usually **≤ 0.5 cm**) localized proliferation of **mildly to moderately atypical type II pneumocytes** and/or club cells lining alveolar walls (**<u>lepidic growth</u>**) and sometimes respiratory bronchioles.

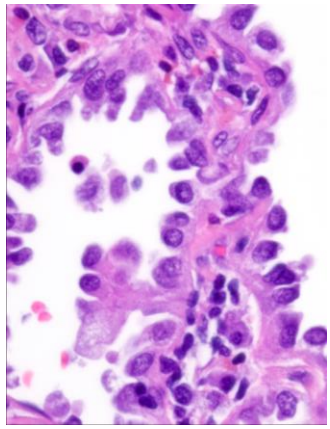
Putative **precursor to AIS** (below)
(Glandular counterpart of squamous dysplasia)

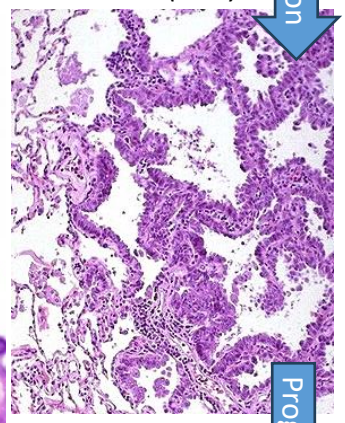
Often peripheral. Benign—cured if resected.

Progression

Adenocarcinoma in situ (AIS)

Formerly, "Bronchoalveolar Adenocarcinoma" (BAC)





A small (**≤ 3 cm**), **<u>solitary, localized adenocarcinoma with pure lepidic growth</u>** (no other patterns allowed).

<u>NO stromal, vascular, or pleural invasion. No STAS.</u>
Mostly non-mucinous. Usually peripheral.

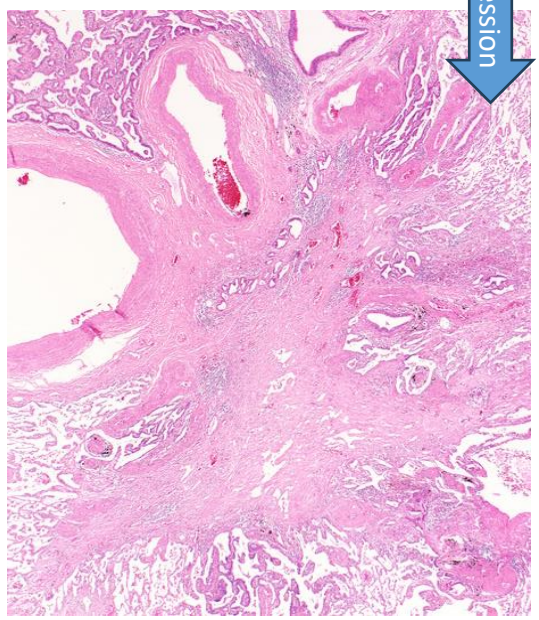
Septal widening with sclerosis/elastosis is common.
Minimal to moderate nuclear atypia.
Frequent intranuclear inclusions.

IHC: Express CK7, TTF-1, and Napsin-A.

Essentially Benign—100% survival if resected entirely.

Progression

Minimally Invasive Adenocarcinoma



Must fulfill *<u>all</u>* of the following criteria:

1) **Small tumor ≤3 cm**
2) **Solitary** adenocarcinoma
3) **Predominantly lepidic growth**
4) **Invasive component ≤ 0.5 cm in greatest dimension**
    - Includes any subtype other than lepidic and desmoplastic stroma
5) Does <u>not</u> contain:
    - Lymphovascular invasion
    - Pleural invasion
    - Spread through air spaces (STAS)
    - Tumor necrosis

Usually non-mucinous.
Essentially benign→ 100% disease-free survival if resected

Pneumonic-type Adenocarcinoma

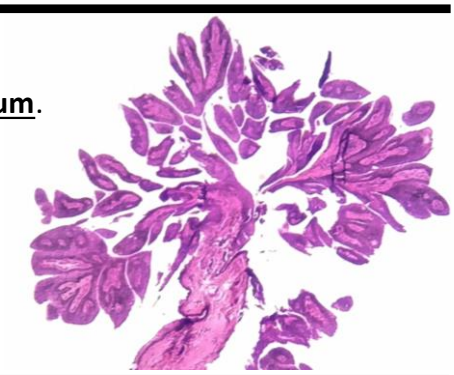
Tumors should be considered pneumonic-type adenocarcinoma if there is **<u>diffuse distribution</u>** of adenocarcinoma **<u>throughout a region(s)</u>** of the lung as <u>opposed to a well-defined lesion</u>(s)

- These are typically <u>mucinous</u>, but can be non-mucinous
- Often **<u>Lepidic-predominant</u>**, but can see any pattern

Squamous Lesions

Arise from **bronchial tree** squamous metaplasia→ usually more **central**

Squamous Papilloma



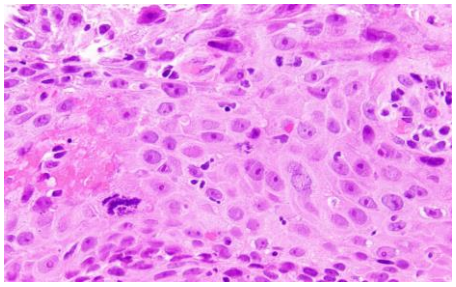
Papillary, arborizing fibrovascular cores covered by squamous epithelium.

Can be exophytic or inverted and/or mixed with glandular parts
HPV is involved in <½ of solitary lesions, but is involved in essentially all cases of laryngotracheal papillomatosis.

Usually **bronchial**: present with obstruction or hemoptysis.

Malignant transformation is rare.

Squamous Cell Carcinoma in situ *"SCCIS"*

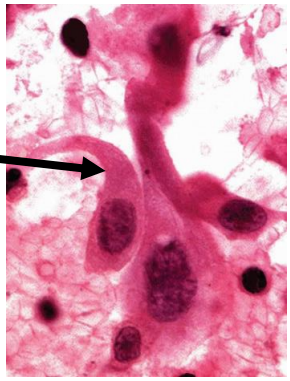


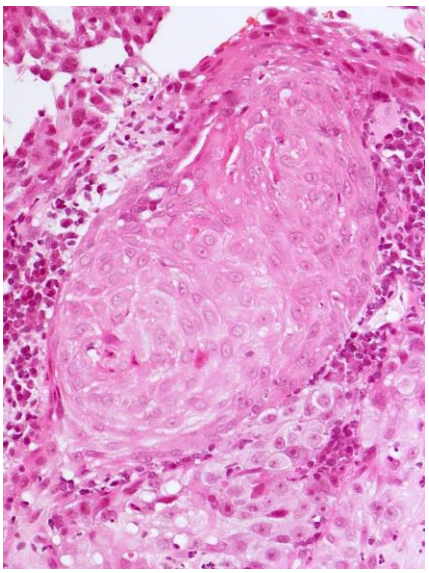
Squamous dysplasia precursor lesion arising in squamous metaplasia of the bronchial tree. Can be single or multifocal.

Part of a continuum with sequential molecular abnormalities and can morphologically graded from mild dysplasia to SCCIS using similar criteria to upper aerodigestive tract.

Respiratory epithelium→ irritant/carcinogen (e.g, smoking)→ hyperplasia→ squamous metaplasia → squamous dysplasia → squamous cell carcinoma in situ → invasive squamous cell carcinoma

Squamous Cell Carcinoma *"SCC"*





Malignant epithelial tumor that shows either **keratinization, intercellular bridges, or expresses immunohistochemical markers of squamous differentiation.**

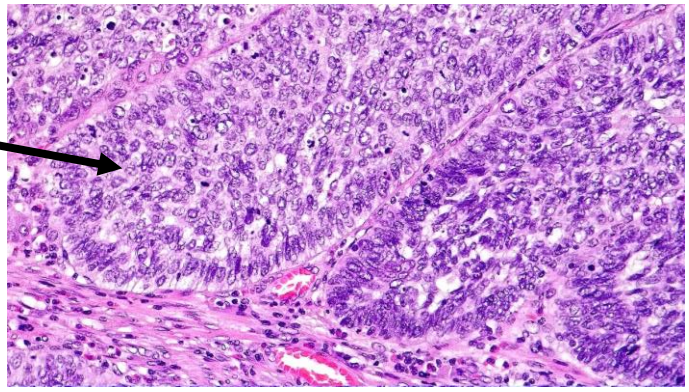
Strongly associated with **smoking**. Often **central**. Also, rarely, seen with interstitial lung disease. (Chronic inflammation is carcinogenic)

May be keratinizing or non-keratinizing

IHC: (+) p40, p63, CK5/6; (-) TTF-1, Napsin-A

Should consider/exclude SCC metastasis from other sites.

Basaloid Squamous Cell Carcinoma

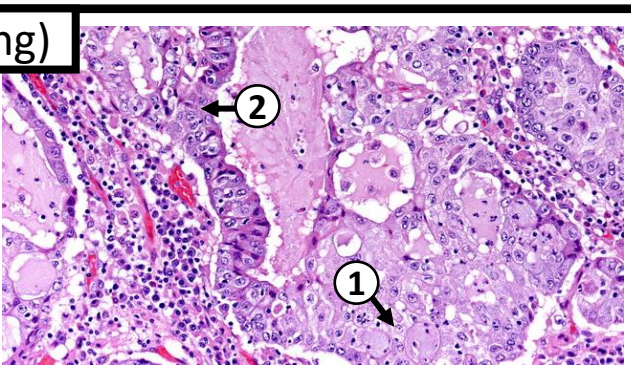


Proliferation of small cells with high N:C ratios, distinct borders cells with lobular architecture and peripheral palisading. Lack overt squamous morphology, but express squamous IHC markers. Lots of mitoses. Often hyaline or mucoid stroma. Most compose >50% of tumor.

IHC: Stain with same squamous markers. Ki67 often 50-80%. Only focal NE marker staining.

Other Carcinomas

Adenosquamous Carcinoma (of the lung)

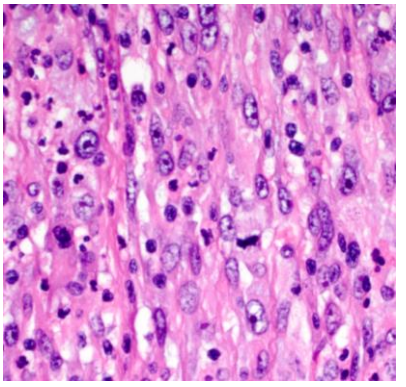


Carcinoma with both a **1) squamous cell carcinoma** and **2) an adenocarcinoma component**.

Each must constitute at least 10%.
Can only be definitively diagnosed on resection specimen (can suggest on Bx).

Consider/exclude mucoepidermoid carcinoma.

Large Cell Carcinoma (of the lung)



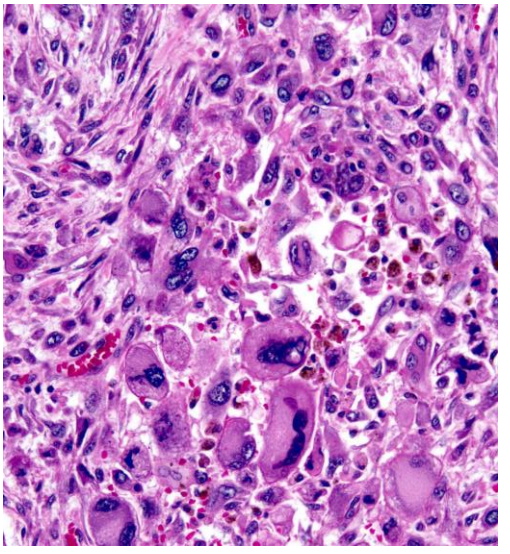
Undifferentiated non-small cell carcinoma that lacks cytologic, architectural, and IHC features of small cell carcinoma, adenocarcinoma, and SCC (etc…)

DX of exclusion! (Therefore, cannot be made on a Bx)
Prevalence is decreasing with increased IHC use.

Sheets or nests of large polygonal cells with vesicular nuclei and prominent nucleoli. IHC: CK(+), TTF1 (-), p40(- or focal), neuroendocrine marker (-)

Sarcomatoid Carcinomas

Diagnosis can only be definitively made on resection specimens.



Spindle Cell Carcinoma: a carcinoma consisting of almost entirely pure spindle cells

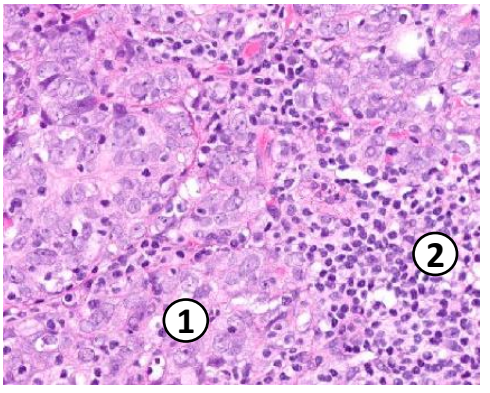
Giant Cell Carcinoma: a carcinoma consisting of almost entirely giant cells

Pleomorphic Carcinoma: contains at least 10% giant or spindle cell carcinoma admixed with better differentiated NSCC. This includes both of the above categories and is essentially the current term for sarcomatoid carcinoma in the lung.

IHC: Variable IHC

Carcinosarcoma: Mixture of NSCC *and* a sarcoma containing heterologous elements such as rhabdomyosarcoma, chondrosarcoma, or osteosarcoma. Poor prognosis.

Lymphoepithelial Carcinoma (of the lung)



1) Non-keratinizing squamous cell carcinoma with syncytial-appearing tumor cells, vesicular chromatin, and prominent nucleoli
2) Lymphoplasmacytic infiltrate between and within tumor islands.
Must exclude metastatic nasopharyngeal carcinoma clinically.

EBV infection (often, but not always) **(EBER +)**

IHC: (+) CK AE1/AE3, CK5/6, p40, p63.

Improved survival.

Salivary Gland Tumors

Relatively **rare**. Arise from salivary-like glands in **bronchi**.

Often endobronchial in central airway→ present with wheezing, cough, obstruction

Mucoepidermoid Carcinoma: 3 cell-type present: 1)Mucin-secreting cells, 2)Squamous cells, and 3)Intermediate cells. MAML2 rearrangements detectable by FISH. Low-grade has good prognosis.

Adenoid Cystic Carcinoma: Biphasic, basaloid carcinoma with epithelial and myoepithelial cells arranged in variable configurations including tubular, cribriform, and solid. Often myxoid or hyalinized material within tubules. Frequent MYB rearrangements. Consider/rule out a metastasis.

Epithelial-Myoepithelial Carcinoma: Low-grade malignancy with biphasic morphology consisting of ducts made up of epithelial cells with surrounding myoepithelial cells, often with clear to spindled morphology.

Pleomorphic Adenoma: Benign tumor with epithelial cells and myoepithelial cells intermingled with myxoid to chondroid stroma. PLAG1 rearrangements.

Myoepithelioma and Myoepithelial carcinoma: Tumors composed of purely myoepithelial cells (without ducts or tubules) arranged in sheets, nests, and variable stroma. Frequent EWSR1 rearrangements.

Hyalinizing Clear Cell Carcinoma: Low-grade malignant epithelial tumor with cords, trabeculae, and nests of clear and eosinophilic cell infiltrating within a background of myxohylaine and fibrous stroma. EWSR1-ATF1 fusions.

Adenomas

All relatively ***rare***.

Sclerosing Pneumocytoma

Old name: "Sclerosing hemangioma" (didn't know origin!)

Pneumocytic origin with **dual cell populations**:

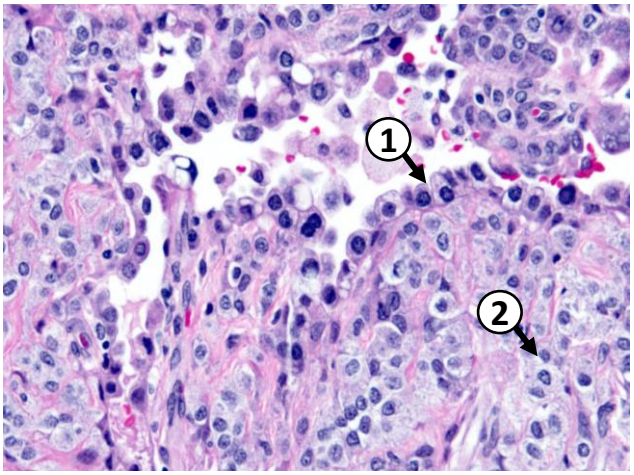
1) Surface cuboidal cells resembling type II pneumocytes
-Stain with Cytokeratins, TTF-1, Napsin-A, EMA

2) Round stromal cells
- Stain with TTF-1 and EMA; CK-negative

Growth patterns: Solid, Papillary, Sclerotic, Hemorrhagic.

AKT1 mutations

Benign (Very rare indolent mets). Often asymptomatic. More commonly women. Solitary, peripheral.



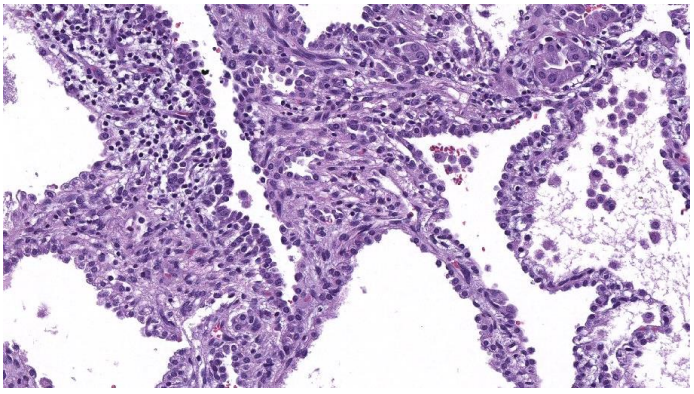
Alveolar Adenoma

Solitary, **well-circumscribed**, peripheral tumor.

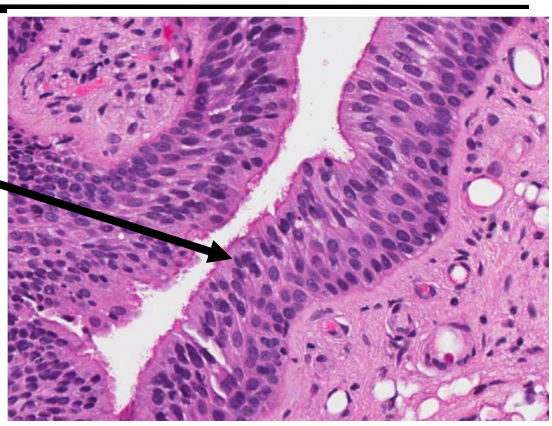
Network of cystic spaces (resembling alveoli) lined by a simple layer of type II pneumocytes overlying a spindle cell-rich stroma, sometimes with myxoid matrix.

IHC: Pneumocytes stain with TTF1

Benign. Very Rare. Often asymptomatic/incidental.



Other Adenomas

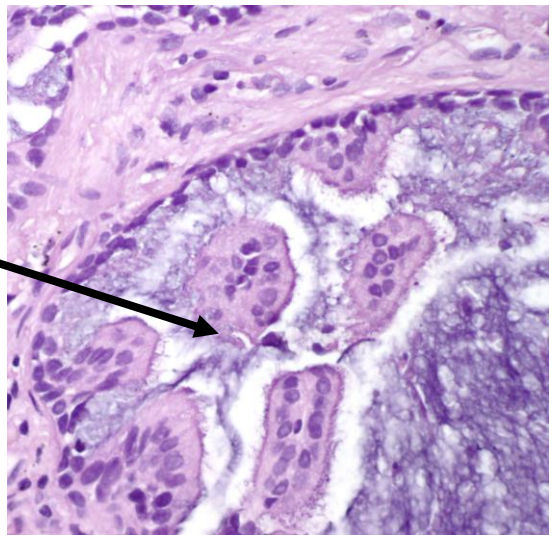


Glandular Papilloma: Benign papillary glandular tumor lined by ciliated or non-ciliated columnar cells with varying numbers of cuboidal and goblet cells. Broad fronds with inflamed stroma. Bronchial location. Can be mixed with squamous papillomas.

Papillary Adenoma: Benign circumscribed papillary neoplasm that consists of cytologically bland, cuboidal to columnar cells covering fibrovascular cores. (+)TTF1, Very low Ki67.

Mucinous Gland Adenoma: Exophytic, endobronchial, well-circumscribed tumor of the tracheobronchial seromucinous glands and ducts. Microacini, glands, and tubules of bland cells. No atypia.

Mucinous Cystadenoma of the Lung: Localized cystic mass filled with mucin and surrounded by columnar mucinous epithelium without significant cytologic atypia or invasive growth. Peripheral. Very rare.



Brochiolar adenoma/Ciliated Muconodular Papillary Tumor: Bilayer of bland bronchiolar-type (often ciliated) epithelium and mucinous epithelium with a continuous basal layer (highlighted by p40) with associated fibrous tissue. Peripheral location. Circumscribed. Peribronchial. No atypia/mitoses.
Pitfall Alert: Can appear infiltrative and be confused for adenocarcinoma on frozens!
On permanents, can support benign with p40 for basal cells and BRAF V600E IHC (highlights cilia)

Neuroendocrine Neoplasms

IHC Markers of Neuroendocrine Differentiation:
Synaptophysin, Chromogranin, INSM1. Less so CD56, NSE.
Cytokeratins often show perinuclear "dot-like" staining.

	Carcinoids (Neuroendocrine tumors, NET)	Neuroendocrine Carcinoma (NEC)
	Younger. Nonsmokers.	Older. Smokers.
Molecular	Low mutation rate. MEN1 mutations most common (lack TP53 and RB1 mutations).	Have mutations similar to smoking-related NSCC (molecular "smoking signature," high mutation rate). Often TP53 and RB1 inactivation.
Origin(s)	Arise from lung neuroendocrine cells, sometimes in the setting of DIPNECH. Not combined with other tumors.	Given that it's not uncommon to have combined NEC and NSCC, it's thought that these are often neuroendocrine de/trans-differentiation of conventional carcinomas.
Growth/ response	Slow growing. Treat primarily with surgery (not much response to chemo).	Grow very fast, often advanced stage→ not surgical candidates. Treated with platinum chemotherapy.
Prognosis	Often good long-term survival	Often temporarily respond, but then recur, and have very poor long-term survival.

	Typical carcinoid	Atypical carcinoid	Large cell neuroendocrine carcinoma	Small cell carcinoma
Smoking association	No	Maybe	Yes	Yes
Mitoses/2mm^2	0-1	2-10	>10 (median 70!)	>10 (median 80!)
Necrosis	No	Focal, if any	Yes	Yes, extensive
Neuroendocrine morphology	Yes	Yes	Yes	Yes
Ki-67 Proliferation index	Up to 5%	Up to 30%	40-80%	Often almost 100%
TTF1 expression	Usually No, sometimes in peripheral/spindled		Yes (70%)	Yes (85%)
Combined with NSCC component	No	No	Sometimes	Sometimes

Adapted from: WHO Classification of tumors of the lung, pleura, thymus, and heart. 2015 and 2021

Lung neuroendocrine neoplasms are graded based on mitoses and necrosis (counted in a hotspot). Ki67 may be helpful to confirm your morphologic impression (mostly to tell NET from NEC), but is not currently used for grading. Staining for NE markers should only be performed in cases with NE morphology.

The Ki67 can be notably higher in Carcinoid metastases. Also, no need to grade metastases, just diagnose as "metastatic carcinoid tumor NOS."

Typical Carcinoid

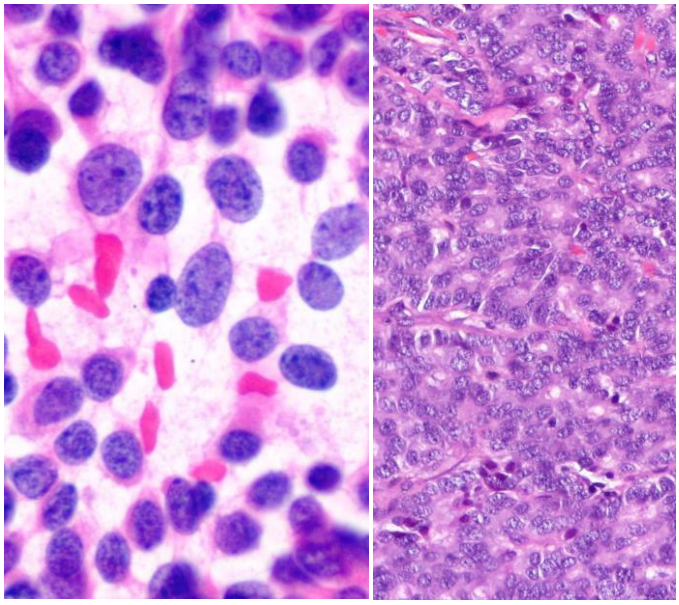
Low-grade malignancy.

Often arise near/in airway.
Occasionally peripheral (often spindled morphology).
Tumor syndromes are rare.

"**Carcinoid morphology**:" organoid or trabecular growth, uniform polygonal cells, finely granular "salt and pepper" chromatin, inconspicuous nucleoli, and abundant eosinophilic cytoplasm.

<2 mitoses per 2 mm^2, **lacking necrosis**, and **>0.5cm** (if less than 0.5 cm, it is designated as a "tumorlet").

On cytology, discohesive cells with stippled chromatin.

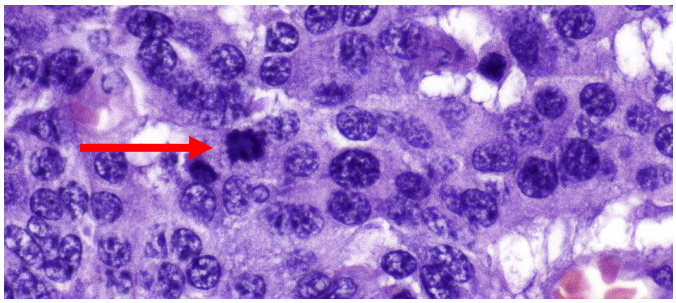


Atypical Carcinoid

Intermediate-grade malignancy

A tumor with "carcinoid morphology" **and 2-10 mitoses per 2 mm^2** and/or **necrosis** (often punctate).

Worse prognosis than typical carcinoid.



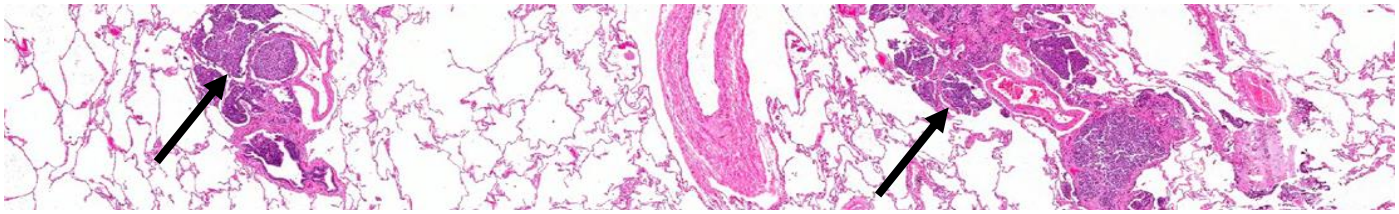
Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

aka "***DIPNECH***" **Requires clinical and radiographic correlation** (many things can cause NE hyperplasia!)

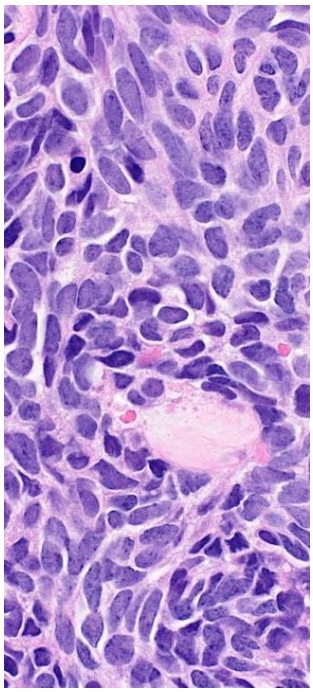
Multifocal proliferation of pulmonary neuroendocrine cells along airways→ Tumorlets

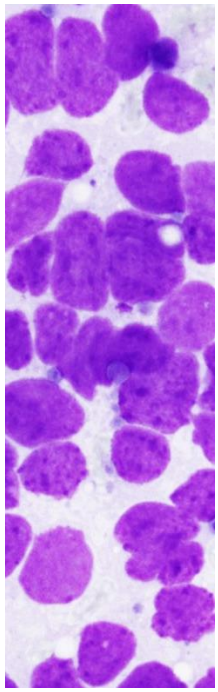
May invade locally and eventually grow into carcinoid tumors. Often older patients. Mostly female.

Patients often present with cough and wheezing misdiagnosed as asthma (or asymptomatic).
Chronic, slowly progressive disease with associated obliterative bronchiolitis.



Small Cell Carcinoma





Very poor prognosis. Often present with **rapid growth, metastases** (including bulky mediastinal lymphadenopathy), and paraneoplastic syndromes (e.g., hyponatremia, Cushing's, etc.)

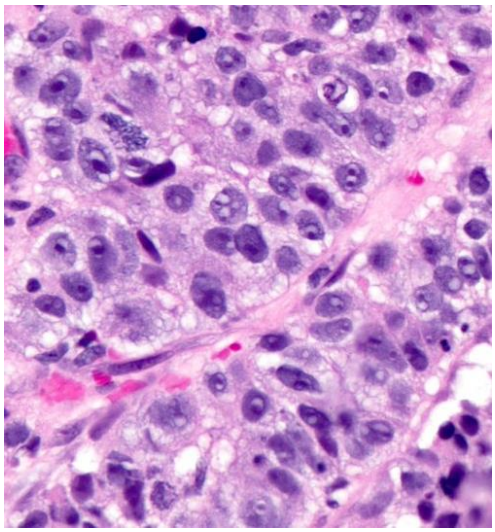
Strongest association with **heavy smoking** of all lung cancers.
Often **centrally** located in major airways/hilar.

Small cell size (usually smaller than 3 resting lymphocytes)
Scant cytoplasm. Unclear borders. Frequent nuclear molding.
Densely cellular sheet-like growth. Cells fusiform to round.
Finely granular chromatin (*no* nucleoli)
High mitotic rate: >10 mitoses per 2 mm^2 (median 80)
Frequent **necrosis** (often large zones) and apoptoses.
Ki67 often essentially 100% (if it's lower than 60% consider another Dx!)

Can be "combined" with other tumors, such as SCC.
Most common Neuroendocrine Neoplasm in the lung.

Technically an "H&E" diagnosis, but IHC is useful to exclude other diagnoses (lymphoma, SCC, sarcoma), and it's reassuring to have NE marker staining (up to 10% will be negative though!).

Large Cell Neuroendocrine Carcinoma



Smoking-related. Often peripheral. **Aggressive**.

"Neuroendocrine morphology" (***architecture***: **organoid nesting**, palisading, rosettes, trabeculae)

Cytological features of non-small cell carcinoma: **large cell size, vesicular, coarse,** or fine chromatin, frequent **prominent nucleoli**, and **abundant cytoplasm** (low N:C ratio)

High mitotic rate: >10 mitoses per 2 mm^2 (median 70)
Necrosis (often large zones)

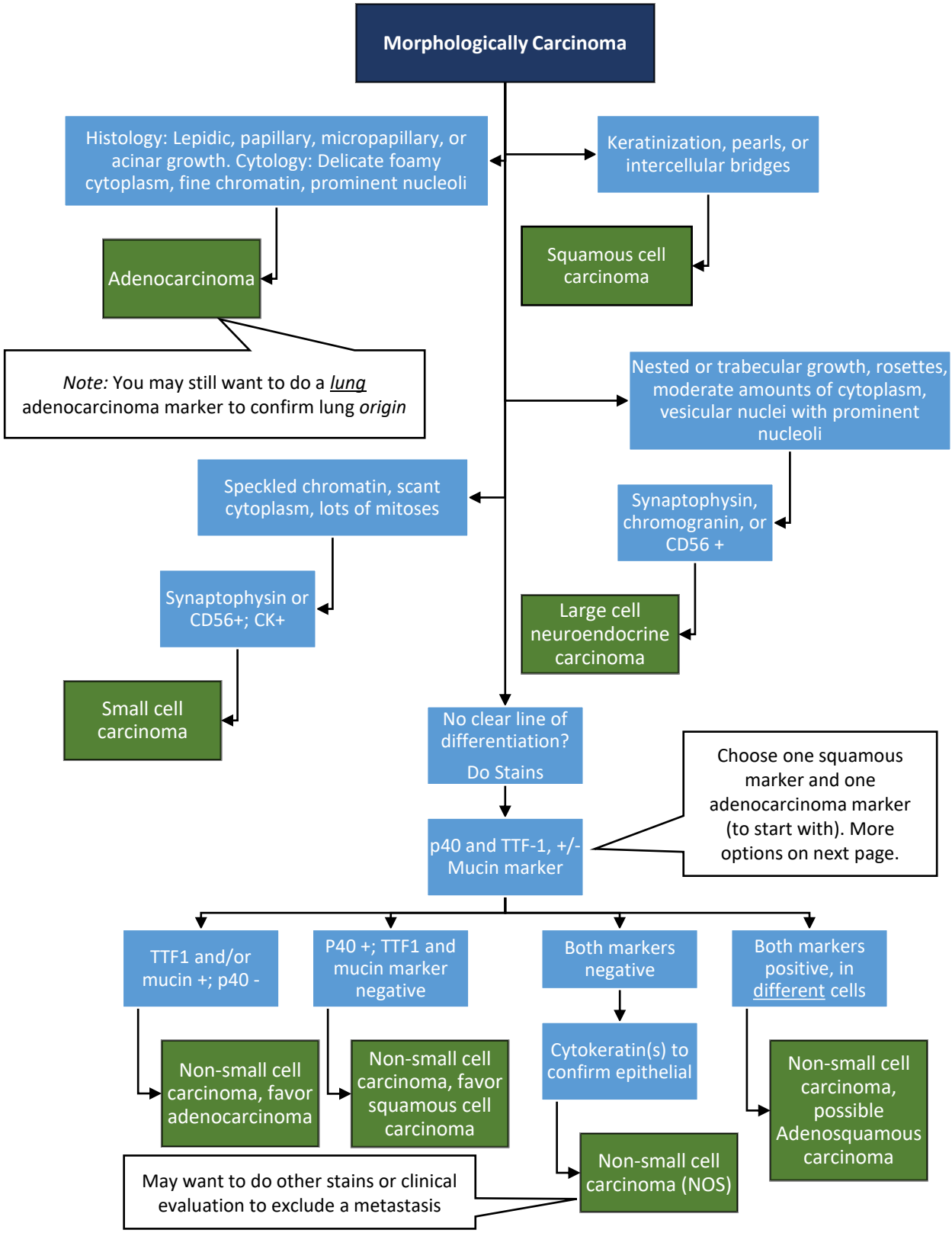
IHC: Should stain with *at least* 1 NE marker (other than NSE)

Can be combined with other types of lung carcinoma (e.g., SCC)

Classification of Lung Carcinomas with Limited Tissue

Diagnostic Algorithm

Try to be as *specific* as you can be, while also *sparing* as much tissue as you can for molecular testing (critical for lung cancer!)



Adapted from: WHO Classification of tumors of the lung, pleura, thymus, and heart. 2015.

Classification Guidelines

Some carcinomas can only be definitively diagnosed on ***resection*** (not on Bx): Adenocarcinoma in situ, Minimally invasive carcinoma, Adenosquamous carcinoma, Large cell carcinoma, Sarcomatoid carcinoma, Pleomorphic carcinoma, giant cell carcinoma, fetal adenocarcinoma, colloid adenocarcinoma, enteric adenocarcinoma.

If you can make the diagnosis morphologically → can call Adenocarcinoma or Squamous cell carcinoma

If can't tell *morphologically*, then do stains:
A simple panel of 2 stains (1 squamous and 1 adenocarcinoma) is usually adequate (e.g., p40 and TTF1)
A positive mucin stain (e.g., PAS-D, or mucicarmine) can also identify some adenocarcinomas.
→A mucin stain is supposed to highlight >5 intracytoplasmic mucin droplets in at least 2 HPFs
Report as "Non-small cell carcinoma, *favor*…." (either adenocarcinoma or squamous cell carcinoma)
Do not do neuroendocrine stains unless there are morphologic findings to suggest neuroendocrine differentiation (neuroendocrine differentiation in an SCC or Adeno doesn't impact treatment/prognosis).

Immunohistochemical Staining

Adenocarcinoma	Squamous cell carcinoma
TTF1	p40 (most specific)
Napsin A	CK5/6
CK7 (less specific)	p63 (less specific)

Note: Some primary lung adenocarcinomas, including Mucinous adenocarcinoma, Colloid carcinoma, and Enteric adenocarcinoma, can be TTF-1 negative. They can even stain with CK20 and CDX2. These cases require careful clinical correlation to exclude a metastasis from the GI tract.

IHC typing of a Cytokeratin-positive, morphologically undifferentiated non-small cell carcinoma (NSCC). Sarcomatoid carcinoma and neuroendocrine tumors should also be considered.

TTF1 Napsin-A	p63	p40	CK5/6	Resection Dx	Biopsy Dx
+	-	-	-	Adenocarcinoma	NSCC favor Adenocarcinoma
+	+	-	-	Adenocarcinoma	NSCC favor Adenocarcinoma
+	+	+ (focal)	-	Adenocarcinoma	NSCC favor Adenocarcinoma
+	-	-	+ (focal)	Adenocarcinoma	NSCC favor Adenocarcinoma
-	Any one of the above *diffusely* positive			Squamous cell carcinoma	NSCC favor SCC
-	Any one of the above *focally* positive			Large cell carcinoma	NSCC, NOS
-	-	-	-	Large cell carcinoma	NSCC, NOS

Adapted from: WHO Classification of tumors of the lung, pleura, thymus, and heart. 2015 & 2021.

Multiple Tumors

When more than 1 tumor nodule is identified in resection specimens, it is important to attempt distinction of synchronous primary tumors from a tumor with intrapulmonary metastasis.

Consider it a *second primary* if (and stage each separately):

- Tumors have different histologic types (e.g., 1 squamous and 1 adenocarcinoma)
- They are dramatically different morphologically after comprehensive review
- They are two squamous carcinomas with each having an in situ component

Consider it an *intrapulmonary metastasis* if:

- Identical genetic abnormalities are detected.

Relative arguments that favor a *second primary*:

- Different biomarker pattern
- Absence of nodal or systemic metastases

Relative arguments that favor an *intrapulmonary metastasis*:

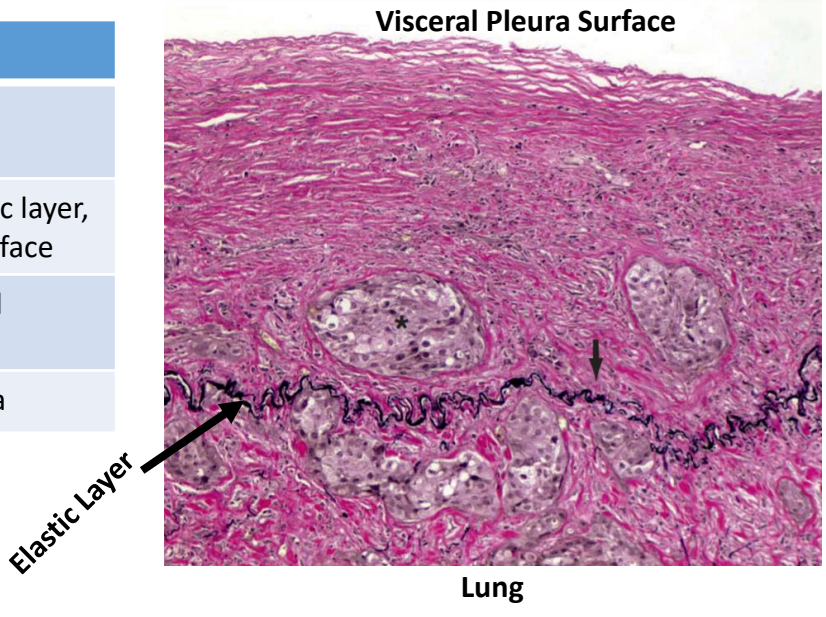
- Matching appearance after comprehensive review
- The same biomarker pattern
- Significant nodal or systemic metastases

Pleural Invasion

If tumor is approaching the visceral pleural surface, get an Elastin stain (e.g., EVG) to see if it crosses the elastic layer for staging purposes.

Stage	Depth of Invasion
PL0	Tumor does NOT completely traverse elastic layer
PL1	Tumor extends through elastic layer, but not to visceral pleural surface
PL2	Tumor extends to the visceral pleural surface
PL3	Tumor invades parietal pleura

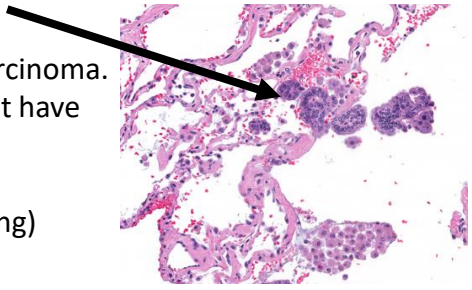
In this example, the tumor crosses the elastic layer, but doesn't go to the visceral pleural surface, so it is PL1.



Spread Through Air Spaces ("STAS")

Defined as **tumor within airspaces extending *beyond* the edge of the main tumor.**

- No strict distance cut-off.
- If present, cannot be considered AIS or minimally invasive adenocarcinoma.
- Associated with an increased incidence of recurrence in tumors that have undergone limited resection (e.g., wedge resection).
- Should not be incorporated into the measurement of tumor size.
- Try to exclude artifactual misplacement ("knife effect" during grossing)



Grading

This grading scheme is used for **resected** early-stage **non-mucinous** lung **adenocarcinoma**.

Grade	Differentiation	Pattern/Findings
G1	Well diff.	Lepidic-predominant (with <20% high-grade pattern)
G2	Moderately diff.	Acinar or papillary-predominant (with <20% high-grade pattern)
G3	Poorly diff.	Any tumor with ≥20% high-grade pattern (i.e., solid, micropapillary, cribriform, or complex glandular pattern)

Notes: "Complex glandular pattern" is defined as fused glands or single cells infiltrating in desmoplastic stroma.

There is NO established grading system for invasive mucinous adenocarcinoma or squamous cell carcinoma of the lung.

Is that Cancer?

Warning: *There are a variety of lesions that can mimic adenocarcinoma. Here are some tricks to identify them.*

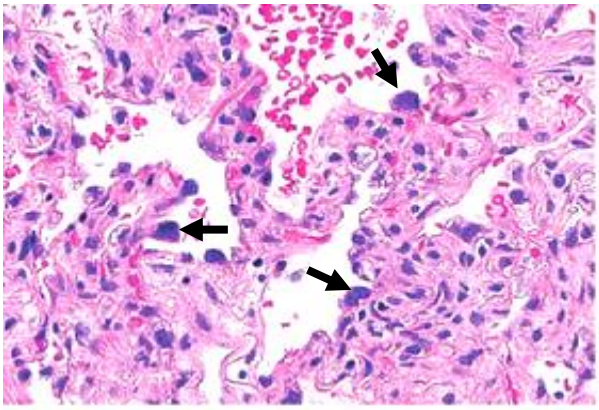
Mimic lesions to think of: Peribronchial metaplasia ("lambertosis," small airway remodeling), Type II pneumocyte hyperplasia, radiation atypia, Ciliated muconodular papillary tumor (CPMT),

Features of *benign* lesions:
- **Ciliated epithelium**
  (can highlight with BRAF V600E IHC stain)
- **Continuous basal layer** (in peribronchiolar metaplasia)
  (can highlight with p40 IHC)
- **NO significant atypia,** mitotic activity
- Gradual transitions

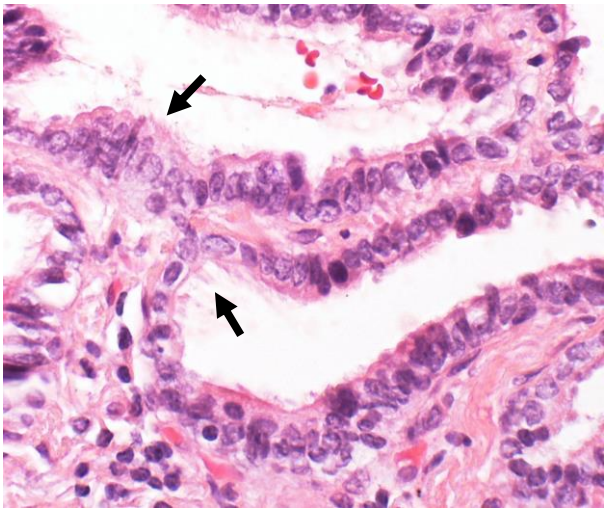
Features of *adenocarcinoma/neoplasia*:
- **Abrupt transition** from benign to abnormal
  (corresponding to clonal population)
- **Hyperchromasia, Nucleoli, Mitoses**
- "Piling up" and **crowding** in small clusters
- Rigid, "tombstoning" cells (vs reactive "windswept" cells)

Be extra *extra* careful if there is acute lung injury, inflammation, and/or interstitial fibrosis→ *reactive* lesions can look very atypical!! In this setting, "take a step back" and reconsider.

Is there a round cell population?
- If so, consider sclerosing pneumocytoma.



Type II pneumocyte hyperplasia (in the setting of medication toxicity). A background of organizing alveolar damage should give you pause… scary right?!



Peribronchiolar metaplasia: The cilia and 2 cell layers (which can be supported with IHC) support a reactive process

Major Genetic Changes

~70% of lung cancers are inoperable
→ Dx and all testing done on core Bx or FNA

Must test **Adenocarcinoma** for: EGFR, ALK, ROS1 in all cases (molecular/FISH/IHC); **PD-L1** (IHC)
Usually though, most send for a large multiplexed sequencing assay including: BRAF, KRAS, HER2, RET, MET, NTRK, MEK, HER2, etc..
(Can consider some of these tests in non-adenocarcinomas if mixed histology or a when clinical features indicate a higher probability of an oncogenic driver.)

Alteration	Small cell carcinoma (%)	Adenocarcinoma (%)	Squamous cell carcinoma (%)
Mutation			
EGFR Caucasian	<1	10-20	<1
EGFR Asian	<5	35-45	<5
KRAS Caucasian	<1	15-35	<5
KRAS Asian	<1	5-10	<5
BRAF	0	<5	0
PIK3CA	<5	<5	5-15
RB	>90	5-15	5-15
P53	>90	30-40	50-80
Amplification			
EGFR	<1	5-10	10
FGFR1	<1	<5	15-25
MYC	20-30	5-10	5-10
Gene Rearrangement			
ALK	0	5	<1
ROS1	0	1-2	0
NTRK1	0	<1	0

Adapted from: WHO Classification of tumors of the lung, pleura, thymus, and heart. 2015.

Driver mutations are essential for tumor survival ("oncogene addiction"), so targeting them results in cancer cell death. These pathways are often mutually exclusive.

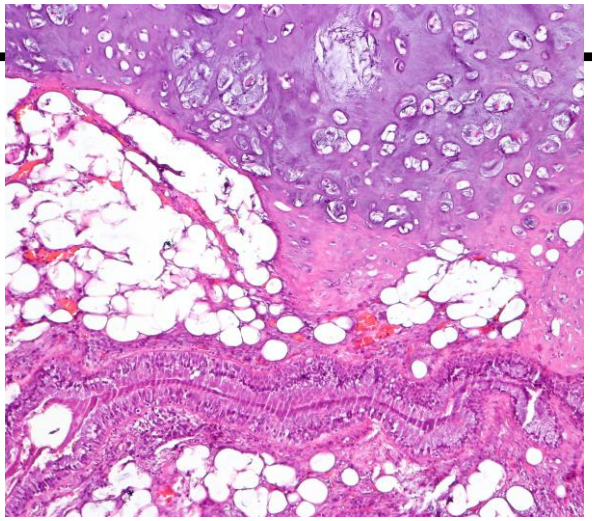
EGFR mutations→ can treat with receptor tyrosine kinase inhibitors: **E**rlotinib, gefitinib, afatinib, etc.
→ Eventually develop acquired resistance (usu. < 1 yr); Most commonly T790M mutation
KRAS mutations→ resistant to EGFR-targeted therapy (and no current specific treatments)
AL**K** and ROS1 rearrangement→ respond to **c**rizotinib

Associations

EGFR and ALK→ usually never smokers, Asian, non-mucinous adenocarcinoma, peripheral location
KRAS→ usually smokers, mucinous adeno, non-Asians, perihilar location (like small cell and SCC)
ALK fusions (usually with EML4)→ usu. Young, never smokers, associated with acinar/solid growth and signet-ring cells
Smoking → High tumor mutation burden (TMB) and "*Smoking signature*" (C > A and G>T transversions)

Mesenchymal Lesions

Pulmonary Hamartoma



Asymptomatic, solitary, well-circumscribed lesion.
Usually peripheral with "popcorn" calcifications on CT.

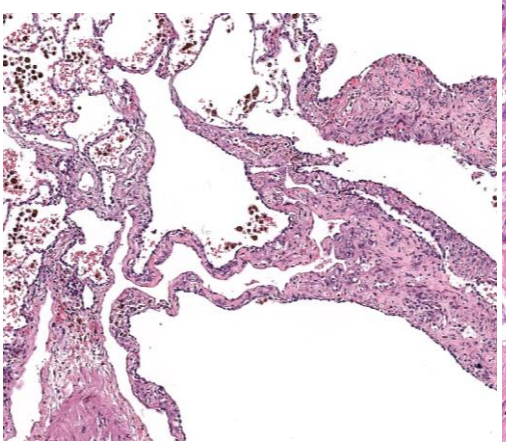
Varying amounts of **at least 2 mesenchymal elements** (e.g., **cartilage**, **fat**, or myxoid spindle cells) **combined with entrapped respiratory epithelium**.

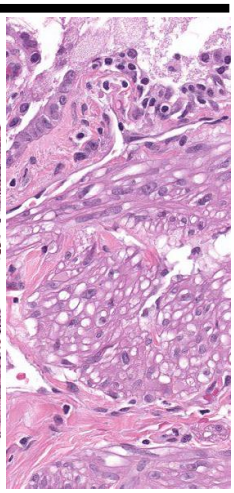
Benign. Neoplasms, with frequent HMGA2 fusions.
Relatively **common**.

Cartilage *only* benign neoplasm?→ Chondroma→ associated with Carney Triad (with GIST and paraganglioma)

Lymphangioleimyomatosis

aka "LAM"





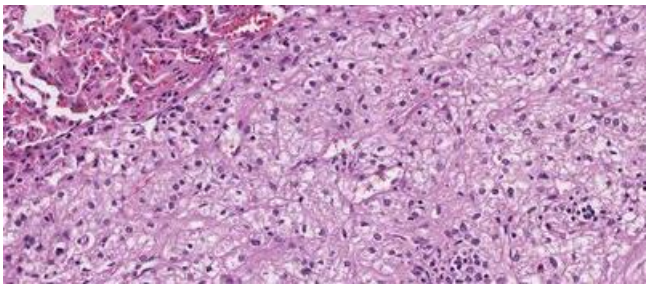
Diffuse, bilateral multicystic proliferation
Low-grade destructive, metastasizing.
Almost **exclusively young women**.
Associated with Tuberous sclerosis.
Slowly take over lungs→ SOB, Dyspnea

Abnormal smooth muscle proliferation along interstitial lymphatic routes→ Thin-walled cysts with plump spindled cells with pale eosinophilic to clear cytoplasm.

IHC: (+) **HMB45**, **SMA**, MelanA, CathepsinK, MiTF
Molecular: TSC2 mutations→ mTOR pathway

PEComa of the Lung

Perivascular **E**pithelioid **C**ell tumor *(Old name: Clear cell "sugar" tumor)*

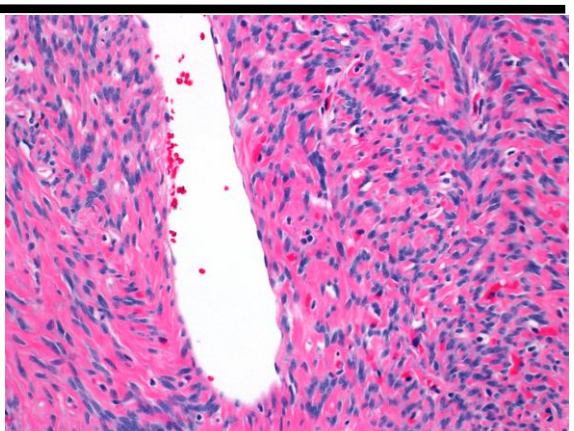


Benign. Very rare.
Solitary, well-circumscribed peripheral lesions.

Round to oval cells with **abundant clear or granular cytoplasm** in sheets and nests

IHC: (+) **HMB45**, **SMA**, MelanA, CathepsinK, MiTF, (myoid and melanocytic markers)
Molecular: TSC2 mutations often

Solitary Fibrous Tumor



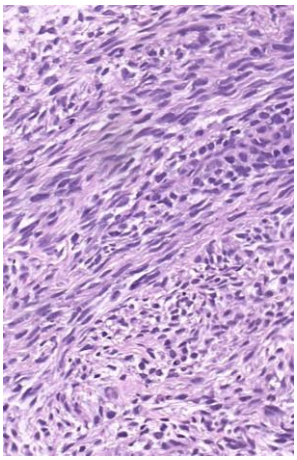
Usually benign.

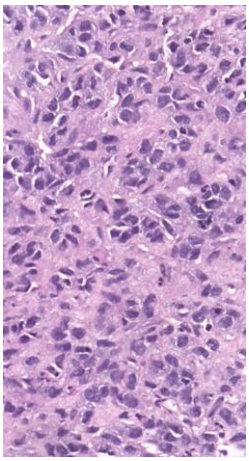
"**Patternless pattern**" of varying cellularity of bland spindled cells with varying amounts of collagenized stroma.
Prominent "**Staghorn vessels**" (dilated, thin-walled, branching vessels).
Can be hyalinized or myxoid.

IHC: **STAT6 (+).** Also, CD34, CD99 (+, but variable).

Molecular: **NAB2/STAT6 gene fusion**

Intimal Sarcoma





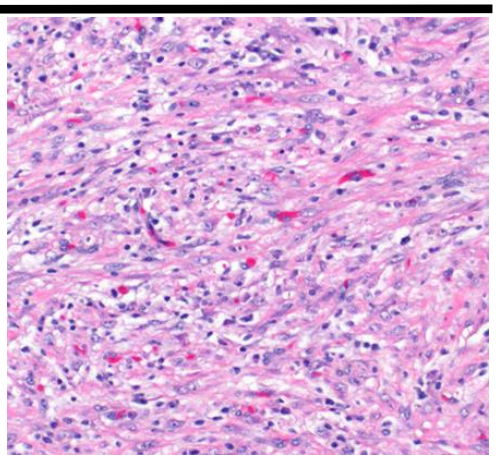
Malignant.
Arises in large blood vessels of systemic and pulmonary circulation. Characteristic **predominantly intraluminal growth** with obstruction of blood flow and seeding tumor emboli.

Mild to severely **pleomorphic spindled cells** with necrosis, nuclear pleomorphism, and mitoses. Can have myxoid or fascicular areas.

IHC: MDM2 (+)

Molecular: **Amplification of MDM2/CDK4** (like in ALT/WDL)

Inflammatory Myofibroblastic Tumor *"IMT"*



Relatively **indolent** (tend to recur, rarely metastasize).

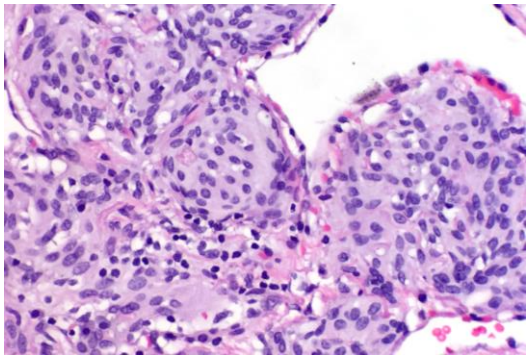
Any age. Usually solitary. Frequently asymptomatic.

Bland spindled to stellate cells in myxoid to hyalinize stroma. Can have loose, fascicular, or storiform growth.
Prominent lymphoplasmacytic infiltrate.
Most cells bland, but sometimes large cells with prominent nucleoli.

IHC: Variable staining with actin/desmin. **ALK (+) in ~50%**

Molecular: ~50% have ALK gene rearrangements.

Meningothelial-Like Nodule

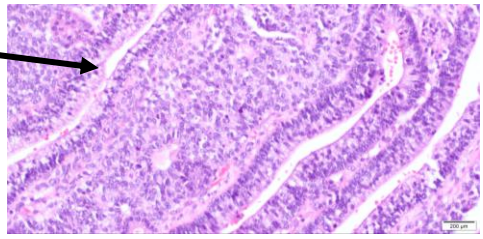


Old name: "*chemodectoma*"
Benign. Common, incidental, often multiple. Small (1-4mm); Monotonous, **bland, ovoid to spindle cells within septae**
Indistinct cell borders. Oval nuclei with occasional intranuclear **pseudoinclusions. Prominent whorled architecture**.
IHC: (+) SSTR2A, PR, EMA, CD56, Vimentin; (-)CK, S100, TTF1

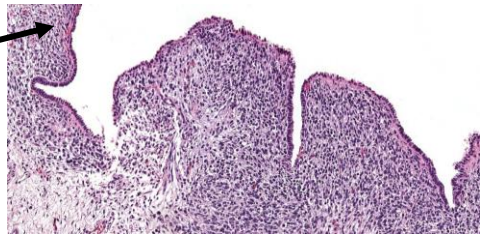
If larger (>4mm), solid, sharply circumscribed→ Meningioma

Pulmonary blastoma Vs. Pleuropulmonary blastoma

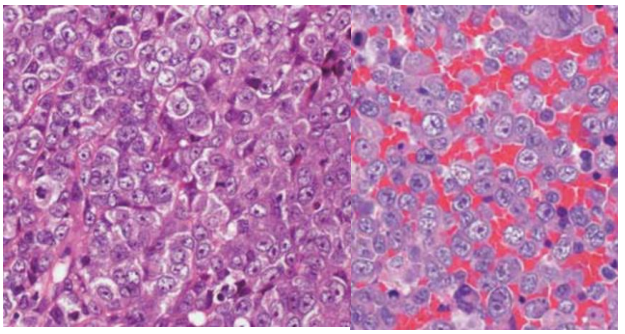
Pulmonary Blastoma: Biphasic tumor that consists of 1) low-grade fetal adenocarcinoma and 2) primitive mesenchymal stroma (may or may not show specific line of differentiation like muscle or bone). Uncommon carcinoma of *adulthood*. Poor prognosis. Considered a subtype of sarcomatoid carcinoma. Nuclear β-catenin.



Pleuropulmonary Blastoma: Sarcoma of the lung in infancy/ childhood. May be solid or cystic. Small round primitive cells with variable sarcomatous differentiation (e.g., rhabdomyosarcoma). DICER1 mutations. Can be seen in with germline DICER1 mutations.

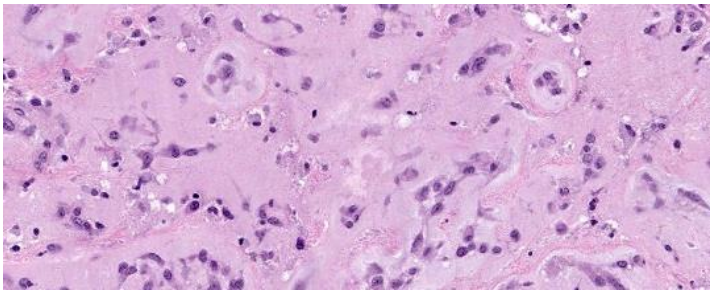


Thoracic SMARCA4-deficient Undifferentiated Tumor



Malignant, very aggressive. Centered in thorax.
Diffuse sheets of mildly discohesive, relatively monotonous, and rhabdoid to undifferentiated epithelioid cells with prominent nucleoli.
Have "smoking signature" so related/derived from NSCC.
IHC: **(+) CD34**, SALL4, (+/-)CK; (-)BRG1 (SMARCA4)
Molecular: **SMARCA4 mutations** (part of SWI/SNF chromatin remodeling complex, like INI-1)

Pulmonary Myxoid Sarcoma with EWSR1-CREB1 Fusion

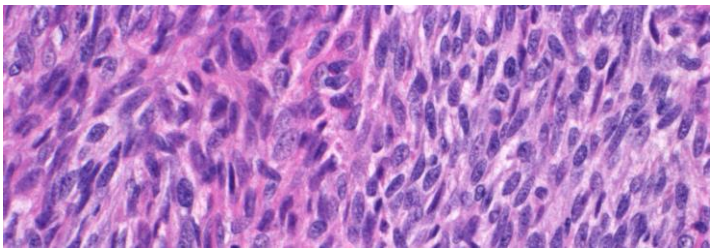


Malignant but indolent. Usually **arises in airways.**
Lobules of delicate, reticular, lace-like strands and cords of round to spindled cells within myxoid stroma.

IHC: Pretty much all negative except vimentin

EWSR1 rearrangements with FISH.
Need to exclude Myoepithelial and ESMC metastases.

Synovial Sarcoma



Malignant spindle cell neoplasm with characteristic SS18 translocation. Poor prognosis.

Like in soft tissue, monophasic or biphasic proliferation of spindled cells with stubby nuclei and frequent Stag-horn vessels

Other Mesenchymal tumors

Epithelioid hemangioendothelioma
Congenital peribronchial myofibroblastic tumor
Diffuse pulmonary lymphangiomatosis
Granular cell tumor

Other Lesions

Metastases!!! Always consider in the lung, especially if multiple/bilateral!

MALT Lymphoma—thought to arise secondary to inflammatory/autoimmune processes.

Lymphomatoid Granulomatosis—Pulmonary nodules composed of angiocentric/angiodestructive polymorphous lymphoid infiltrate containing EBV-positive B cells with reactive T cells.

Pulmonary Langerhans Cell Histiocytosis—Young smokers. Clonal (usually) proliferation of Langerhans cells with associated interstitial lung disease→ cellular, cystic, and fibrotic lesions. Frequent BRAF mutations (like elsewhere). Langerhans cells stain with S100, Langerin, CD1a.

Germ Cell Tumors—Mature teratomas most common

Intrapulmonary thymoma, Erdheim-Chester disease, Melanoma,