Lung Tumors

**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 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.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepidic</td>
<td>Growing along the surface of alveolar walls (like AIS), non-invasive</td>
</tr>
<tr>
<td>Acinar</td>
<td>Round to oval glands with a central lumen space surrounded by tumor cells</td>
</tr>
<tr>
<td>Papillary</td>
<td>Glands growing along central fibrovascular cores</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>Cells growing in papillary tufts forming florets that lack fibrovascular cores (poorer prognosis)</td>
</tr>
<tr>
<td>Solid</td>
<td>Polygonal tumor cells growing in sheets (poorer prognosis)</td>
</tr>
</tbody>
</table>

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 Carcinoma

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

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

Frequently KRAS mutated. Often peripheral. Usually CK7+, TTF-1 negative with frequent CK20 expression.

Need to clinically exclude mucinous metastasis (e.g., pancreas).

### 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 intestinal markers CDX2, CK20 (+/-) TTF-1, CK7, and Napsin-A.

### Enteric Adenocarcinoma

Adenocarcinoma resembling colorectal-type adenocarcinoma.

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

Morphology and IHC identical to colon cancer: Eosinophilic, tall columnar cells with pseudostratified nuclei and abundant “dirty” necrosis.

### Fetal Adenocarcinoma

Adenocarcinoma resembling fetal lung.

Complex glandular structures composed of glycogen-rich, non-ciliated cells (resembling the developing epithelium of the lung).

Frequent morule formation. Variable atypia. Can be pure or combined with other types.

IHC: TTF-1(+). Frequent nuclear β-catenin, neuroendocrine marker, and germ cell marker expression.
**Atypical Adenomatous Hyperplasia**
A small (usually ≤ 0.5 cm) localized proliferation of mildly to moderately atypical type II pneumocytes and/or Clara cells lining alveolar walls (*lepidic growth*).

Often peripheral.
Benign—cured if resected.
(Glandular counterpart of squamous dysplasia)

**Minimally Invasive Adenocarcinoma**
Must fulfill *all* 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 **not** 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 **diffuse distribution** of adenocarcinoma throughout a region(s) of the lung as opposed to a well-defined lesion(s)
- These are typically mucinous, but can be non-mucinous
- Often **lepidic-predominant**, but can see any pattern
Squamous Lesions

Squamous Papilloma

Papillary proliferation covered by squamous epithelium.

HPV is involved in <½ of solitary lesions, but is involved in essentially all cases of laryngotracheal papillomatosis.

Often present with obstruction or hemoptysis.

Malignant transformation is rare.

Squamous Cell Carcinoma in situ

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

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

Strongly associated with smoking. Often central.

May be keratinizing or non-keratinizing

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

Basaloid Squamous Cell Carcinoma

Proliferation of small cells with high N:C ratios, distinct borders cells with lobular architecture and peripheral palisading. No nuclear molding. 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.

Worse prognosis than SCC otherwise
### Neuroendocrine Tumors

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

**Note:** Lung neuroendocrine neoplasms are graded based on mitoses and necrosis (counted in a hotspot). Ki67 may be helpful to confirm your morphologic impression, but is not currently used for grading.

<table>
<thead>
<tr>
<th></th>
<th>Typical carcinoid</th>
<th>Atypical carcinoid</th>
<th>Large cell neuroendocrine carcinoma</th>
<th>Small cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking association</td>
<td>No</td>
<td>Maybe</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mitoses/2mm²</td>
<td>0-1</td>
<td>2-10</td>
<td>&gt;10 (median 70!)</td>
<td>&gt;10 (median 80!)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>No</td>
<td>Focal, if any</td>
<td>Yes</td>
<td>Yes, extensive</td>
</tr>
<tr>
<td>Neuroendocrine morphology</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ki-67 Proliferation index</td>
<td>Up to 5%</td>
<td>Up to 20%</td>
<td>40-80%</td>
<td>Almost 100%</td>
</tr>
<tr>
<td>TTF1 expression</td>
<td>Usually not</td>
<td>Usually not</td>
<td>~50%</td>
<td>Usually, Yes (85%)</td>
</tr>
<tr>
<td>Combined with non-small cell component (e.g., squam)</td>
<td>No</td>
<td>No</td>
<td>Sometimes</td>
<td>Sometimes</td>
</tr>
</tbody>
</table>

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

### Typical Carcinoid

**Low-grade malignancy.**

Often arise near central airway. Can grow 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 mm², lacking necrosis, and >0.5 cm (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 mm² and/or necrosis (often punctate).

Worse prognosis than typical carcinoid.
Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia
aka “DIPNECH”

Generalized proliferation of pulmonary neuroendocrine cells along airways.
May invade locally and eventually grow to tumorlets or even carcinoid tumors. Often older patients. Tumor cells have neuroendocrine morphology (round to oval nuclei with salt and pepper chromatin) and start in respiratory mucosa.
Patients often present with cough and wheezing misdiagnosed as asthma (or asymptomatic). Chronic, slowly progressive disease

Small Cell Carcinoma
Often centrally located in major airways/hilar.
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.
Small cell size (usually smaller than 3 resting lymphocytes)
Scant cytoplasm. Unclear borders. Frequent nuclear molding.
Finely granular chromatin (no nucleoli)
High mitotic rate: >10 mitoses per 2 mm² (median 80)
Frequent necrosis (often large zones) and apoptoses.
Ki67 often essentially 100%
Can be “combined” with other tumors, such as SCC.
Very poor prognosis

Large Cell Neuroendocrine Carcinoma
Smoking-related. Often peripheral.
“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 mm² (median 70)
Necrosis (often large zones)
Can be combined with other types of lung carcinoma (e.g., SCC)
Aggressive.
Other Carcinomas

Adenosquamous Carcinoma
Carcinoma with both a 1) squamous cell carcinoma and 2) an adenocarcinoma component.
Each must constitute at least 10%.
Can only be diagnosed on resection specimen (can suggest though on Bx)

Large Cell Carcinoma
Undifferentiated non-small cell carcinoma that lacks cytologic, architectural, and IHC features of small cell carcinoma, adenocarcinoma, and SCC
**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. 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 NSCLC and a sarcoma containing heterologous elements such as rhabdomyosarcoma, chondrosarcoma, or osteosarcoma. Poor prognosis.

Lymphoepithelioma-like Carcinoma
Carcinoma with marked lymphoid infiltrate
**EBV infection** of neoplastic cells (EBER ish +)
Large cells with syncytial growth, large vesicular nuclei and prominent nucleoli.
IHC: (+) CK AE1/AE3, CK5/6, p40, p63.
Improved survival.
Classification of Lung Carcinomas with Limited Tissue

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!)

Morphologically Carcinoma

Histology: Lepidic, papillary, micropapillary, or acinar growth. Cytology: Delicate foamy cytoplasm, fine chromatin, prominent nucleoli

Keratinization, pearls, or intercellular bridges

Squamous cell carcinoma

Nested or trabecular growth, rosettes, moderate amounts of cytoplasm, vesicular nuclei with prominent nucleoli

Synaptophysin, chromogranin, or CD56 +

Large cell neuroendocrine carcinoma

No clear line of differentiation?

Do Stains

p40 and TTF-1, +/- Mucin marker

TTF1 and/or mucin +; p40 -

Non-small cell carcinoma, favor adenocarcinoma

P40 +; TTF1 and mucin marker negative

Non-small cell carcinoma, favor squamous cell carcinoma

Both markers negative

Cytokeratin(s) to confirm epithelial

Non-small cell carcinoma (NOS)

Both markers positive, in different cells

Non-small cell carcinoma, possible Adenosquamous carcinoma

Choose one squamous marker and one adenocarcinoma marker (to start with). More options on next page.

Adenocarcinoma

Note: You may still want to do a lung adenocarcinoma marker to confirm lung origin

Speckled chromatin, scant cytoplasm, lots of mitoses

Synaptophysin or CD56+; CK+

Small cell carcinoma

Choose one squamous marker and one adenocarcinoma marker (to start with). More options on next page.

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

May want to do other stains or clinical evaluation to exclude a metastasis.
Some carcinomas can only be diagnosed on resection (not on Bx): Adenocarcinoma in situ, Minimally invasive carcinoma, Adenosquamous carcinoma, Large cell carcinoma, Sarcomatoid carcinoma

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. 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

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
<th>Squamous cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTF1</td>
<td>p40 (most specific)</td>
</tr>
<tr>
<td>Napsin A</td>
<td>CK5/6</td>
</tr>
<tr>
<td>CK7 (less specific)</td>
<td>p63 (less specific)</td>
</tr>
</tbody>
</table>

**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 lung carcinoma (NSCLC). Mucin-negative. Sarcomatoid carcinoma and neuroendocrine tumors should also be considered.

<table>
<thead>
<tr>
<th>TTF1 Napsin-A</th>
<th>p63</th>
<th>p40</th>
<th>CK5/6</th>
<th>Resection Dx</th>
<th>Biopsy Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Adenocarcinoma</td>
<td>NSCLC favor Adenocarcinoma</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Adenocarcinoma</td>
<td>NSCLC favor Adenocarcinoma</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+ (focal)</td>
<td>-</td>
<td>Adenocarcinoma</td>
<td>NSCLC favor Adenocarcinoma</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+ (focal)</td>
<td>Adenocarcinoma</td>
<td>NSCLC favor Adenocarcinoma</td>
</tr>
<tr>
<td>-</td>
<td>Any one of the above <strong>diffusely</strong> positive</td>
<td></td>
<td>Squamous cell carcinoma</td>
<td>NSCLC favor SCC</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Any one of the above <strong>focally</strong> positive</td>
<td></td>
<td>Large cell carcinoma</td>
<td>NSCLC, NOS</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Large cell carcinoma</td>
<td>NSCLC, NOS</td>
</tr>
</tbody>
</table>


**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

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**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.*

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**Spread Through Air Spaces (“STAS”)**

Defined as **micropapillary clusters, solid nests or single cells of tumor extending beyond the edge of the tumor into the air spaces of the surrounding lung parenchyma.**

- 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.
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)

Consider testing for: BRAF, KRAS, HER2, RET,

*(Can consider some of these tests in non-adenocarcinomas if mixed histology or small biopsy)*

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Small cell carcinoma (%)</th>
<th>Adenocarcinoma (%)</th>
<th>Squamous cell carcinoma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mutation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR Caucasian</td>
<td>&lt;1</td>
<td>10-20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>EGFR Asian</td>
<td>&lt;5</td>
<td>35-45</td>
<td>&lt;5</td>
</tr>
<tr>
<td>KRAS Caucasian</td>
<td>&lt;1</td>
<td>15-35</td>
<td>&lt;5</td>
</tr>
<tr>
<td>KRAS Asian</td>
<td>&lt;1</td>
<td>5-10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>BRAF</td>
<td>0</td>
<td>&lt;5</td>
<td>0</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>5-15</td>
</tr>
<tr>
<td>RB</td>
<td>&gt;90</td>
<td>5-15</td>
<td>5-15</td>
</tr>
<tr>
<td>P53</td>
<td>&gt;90</td>
<td>30-40</td>
<td>50-80</td>
</tr>
<tr>
<td><strong>Amplification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR</td>
<td>&lt;1</td>
<td>5-10</td>
<td>10</td>
</tr>
<tr>
<td>FGFR1</td>
<td>&lt;1</td>
<td>&lt;5</td>
<td>15-25</td>
</tr>
<tr>
<td>MYC</td>
<td>20-30</td>
<td>5-10</td>
<td>5-10</td>
</tr>
<tr>
<td><strong>Gene Rearrangement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK</td>
<td>0</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>ROS1</td>
<td>0</td>
<td>1-2</td>
<td>0</td>
</tr>
<tr>
<td>NTRK1</td>
<td>0</td>
<td>&lt;1</td>
<td>0</td>
</tr>
</tbody>
</table>

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**Driver mutations** are essential for tumor survival (“oncogene addiction”), so targeting them results in cancer cell death.

**EGFR mutations** can treat with receptor tyrosine kinase inhibitors: Erlotinib, 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)

**ALK** and **ROS1 rearrangement** respond to crizotinib

**Adenocarcinomas:**

EGFR and ALK→ usually never smokers, Asian, non-mucinous, peripheral location

KRAS→ usually smokers, mucinous, non-Asians, perihilar location (like small cell and SCC)

ALK rearrangements→ usu. Young, never smokers, associated with cribriform morphology
Salivary Gland Tumors

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**: 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.

**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.

## Adenomas

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

**Four growth patterns**: 1)Solid, 2)Papillary, 3)Sclerotic, 4)Hemorrhagic.

**Benign**. Often asymptomatic. More commonly women.

### Alveolar Adenoma

Solitary, well-circumscribed, peripheral tumor.

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

**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.

**Papillary Adenoma**: Benign circumscribed papillary neoplasm that consists of cytologically bland, cuboidal to columnar cells covering fibrovascular cores.

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, smooth muscle, or fibrous tissue)combined with entrapped epithelium.

Benign. Neoplasms, with frequent HMGA2 fusions. Relatively common.
Cartilage only benign neoplasm? → Chondroma→ associated with Carney Triad.

Lymphangioleiomyomatosis aka “LAM”


Thin-walled cysts with plump spindled cells with pale eosinophilic to clear cytoplasm (glycogen)

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

Clear Cell “Sugar” Tumor


IHC: (+) HMB45, MelanA, CathepsinK, MiTF,

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)

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Inflammatory myofibroblastic Tumor

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; (-)CK, S100, TTF1

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Pulmonary blastoma Vs. Pleuropulmonary blastoma

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

**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, increasing risk of other malignancies too.
SMARCA4-deficient Thoracic Sarcomas


IHC: (+) CD34, SALL4, (+/-)CK

Molecular: SMARCA4 mutations (part of SWI/SNF chromatin remodeling complex, like INI-1)

Pulmonary Myxoid Sarcoma with EWSR1-CREB1 translocation

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

IHC: Pretty much all negative except vimentin EWSR1 rearrangements with FISH.

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

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Other Mesenchymal tumors

Epithelioid hemangioendothelioma
Congenital peribronchial myofibroblastic tumor
Diffuse pulmonary lymphangiomatosis

Myoepithelial tumors
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—Strongly associated with smoking and in the lung is classified as an interstitial lung disease in most cases (not a neoplasm)

Germ Cell Tumors—Mature teratomas most common

Intrapulmonary thymoma

Melanoma