FINAL

Lecture 7&8

بسم الله الرحمن الرحيم

Pathology Mind Maps

Lung Cancer

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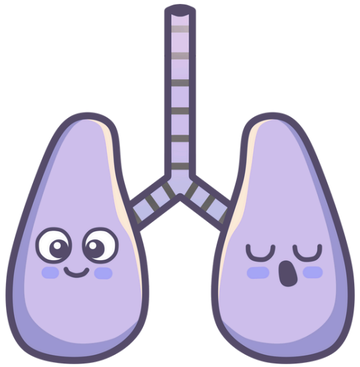


This file contains the lecture material presented through mind maps to make the information clearer, more organized, and easier to follow. It is designed to simplify studying and make revision more effective.

We truly hope you find it beneficial.
If it helps you in any way, please remember us in your prayers.

Best of luck in your studies💜!

LUNG TUMORS

رَبِّ اشْرَحْ لِي صَدْرِي وَيَسِّرْ لِي أَمْرِي وَاحْلُلْ عُقْدَةً مِّن لِّسَانِي يَفْقَهُوا قَوْلِي

General info

- metastasis to the lung are more common then primary neoplasm.
- 95% of primary lung tumors are carcinoma and 5% are others.
- lung carcinoma : associated with smoking , 1\3 of cancer related death in men , peak in 50s-60s , >50% have advanced disease at diagnosis , poor prognosis , Since 1987 leading cancer related deaths in women.

Pathogenesis

- **Carcinogenic exposure combined with genetic abnormalities** leads to a **stepwise** accumulation of driver mutations, mainly due to smoking and environmental carcinogens, producing neoplastic cells with the hallmarks of cancer.

Cigaratte smoking

- Epidemiology and Risk:
- About 90% of lung cancers occur in current smokers or recent quitters, yet only 11% of heavy smokers develop lung cancer. There is a linear correlation between lung cancer risk and pack-years.
- Intensity of Smoking:
- Heavy smoking (2 packs/day for 20 years) increases the risk 60-fold compared with non-smokers.
- **Women are more susceptible to tobacco carcinogens than men.**
- Additional Factors:
- Smoking cessation reduces the risk over time but never returns it to baseline. Pipe smoking, cigar smoking, and passive smoking also increase lung cancer risk.

Environmental Carcinogens

- Occupational Exposure:
- Includes exposure in uranium mines and to asbestos, arsenic, chromium, nickel, and vinyl chloride.
- Synergistic Effects:
- Asbestos exposure in non-smokers increases risk 5-fold, while asbestos combined with heavy smoking increases the risk up to 55-fold.

Molecular Pathogenesis

- Genetic Events:
- An **early event** is inactivation of tumor suppressor genes on chromosome 3p, followed by **late mutations** in TP53 and the KRAS oncogene.
- Special Subgroup and Therapy:
- A subset of adenocarcinomas in non-smoking women shows activating mutations of EGFR, allowing the use of targeted therapy against EGFR and KRAS.

Precursor Lesions

- **Adenocarcinoma Sequence:**
- Atypical adenomatous hyperplasia → adenocarcinoma in situ → invasive adenocarcinoma.
- **Squamous Cell Carcinoma Sequence:**
- Basal cell hyperplasia → squamous metaplasia → squamous dysplasia → carcinoma in situ → invasive squamous cell carcinoma.
- **small cell carcinoma** = no precursor lesions.

Main types

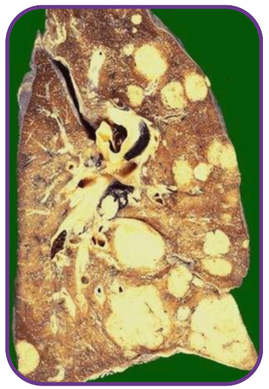
Small Cell Lung Carcinoma (SCLC):

Virtually all cases have metastasized by the time of diagnosis, therefore it is **not curable by surgery**. **The best treatment is chemotherapy** with or without radiation therapy.

Non-Small Cell Lung Carcinoma (NSCLC):

More likely to be **resectable**, but usually responds poorly to chemotherapy.
Currently, **targeted therapy is used for adenocarcinoma and squamous cell carcinoma.**

Metastatic Tumors to the Lung



SQUAMOUS CELL CARCINOMA and SMALL CELL CARCINOMA show STRONGEST association with SMOKING

Lung tumors types

Adenocarcinoma(most common)

Lung Adenocarcinoma Progression

Stage	Size	Growth Pattern / Architecture	Cellular Features	Key Points
Atypical Adenomatous Hyperplasia (AAH)	≤ 5 mm	Well-demarcated focus	Cuboidal to low-columnar cells with **nuclear hyperchromasia, pleomorphism, prominent nucleoli**	**KRAS mutation (monoclonal)**
Adenocarcinoma in Situ (AIS)	≤ 3 cm	**Lepidic pattern** (growth along pre-existing alveolar septa)	Mucinous or non-mucinous dysplastic cells	Old name: **Bronchioloalveolar carcinoma**
AIS – Definition	—	**Preserved alveolar architecture**	No stromal invasion	**No desmoplasia, no destruction**
Minimally Invasive Adenocarcinoma			Atypical epithelial cells	
Invasive Adenocarcinoma			Marked cytologic atypia	

- Epidemiology: The most frequent primary lung tumor. It is the most common type found in women and "never-smokers" , younger than 45 y .
- Location: Usually located **peripherally**.
- Characteristics: **Slowly growing** but tends to **metastasize widely at an early stage.**
- Histology: Features **gland formation** or mucin production. It is identified using the **TTF-1 stain.**
- Precursor Sequence: Atypical adenomatous hyperplasia (AAH) → Adenocarcinoma in situ (AIS) → Minimally invasive → Invasive adenocarcinoma.

Squamous cell carcinome

- Epidemiology: Strongly associated with a history of smoking and is more common in men.
- Location: Arises **centrally** in the major bronchi.
- Characteristics: Often shows **central necrosis leading to cavitation** (hollow spaces) in large lesions , Disseminate outside the thorax later.
- Preceded by squamous metaplasia >>> dysplasia >>> carcinoma in situ.
- Histology: Well-differentiated types show **keratin** pearls and intercellular bridges. Poorly differentiated SCC: only minimal residual squamous cell features.
- Atypical cells appear in sputum even in asymptomatic, undetectable lesions. Symptomatic stage: begins to obstruct the lumen of a major bronchus . +/- atelectasis and infection.

Mixed patterns:
Approximately 10% of all lung carcinomas have a combined histology, including two or more of the mentioned types.

Small cell lung carcinoma

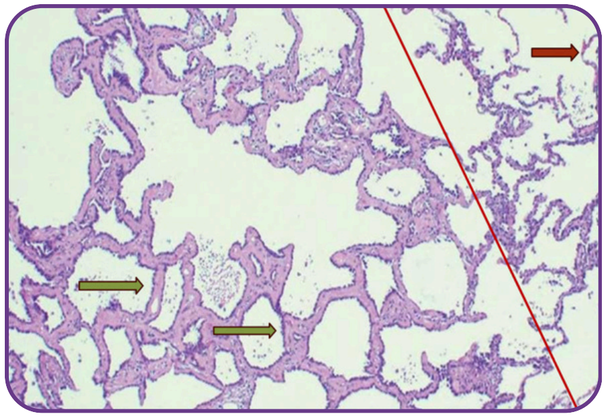
- Epidemiology: Extremely **aggressive** and strongly linked to smoking.
- Location: Centrally located.
- Characteristics: Almost all cases have metastasized to lymph nodes by the time of diagnosis, making them generally incurable by surgery.
- Histology: Fusiform cells are small with scant cytoplasm and "**salt and pepper**" (finely granular) chromatin -also seen in typical carcinoid -, Show Frequent mitotic figures
- Key Features: Shows the **Azzopardi** effect (blue staining of vessel walls from DNA of necrotic cells) and often causes **paraneoplastic syndromes** by secreting hormones.Express **neuroendocrine** markers (chromogranin, synaptophysin and CD56)

Large cell carinoma

- Definition: An **undifferentiated** malignant tumor that lacks the features of small cell, squamous, or glandular cancer.
- Characteristics: It is a diagnosis of exclusion.
- Histology: Features **large nuclei, prominent nucleoli, and a moderate amount of cytoplasm,** has a histologic variant called large cell neuroendocrine carcinoma. This variant has molecular and **neuroendocrine** features similar to small cell carcinoma, but the tumor cells are larger in size.

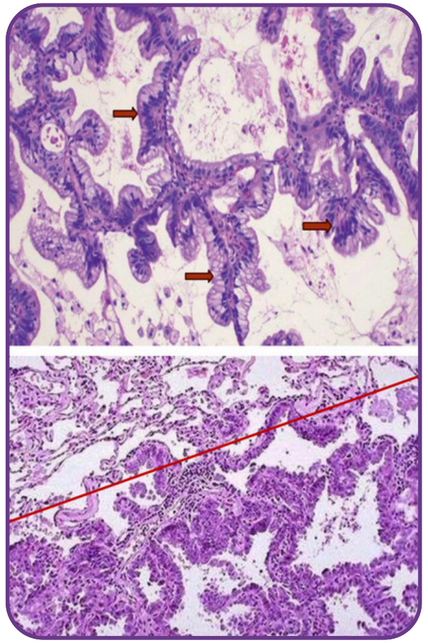
Adenocarcinoma

Atypical Adenomatous Hyperplasia (AAH)

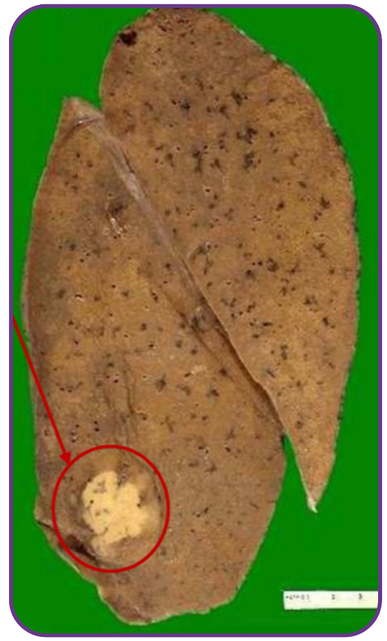


The histologic section demonstrates two distinct areas: one area with normal lung tissue (alveoli lined by type I pneumocytes and normal septal thickness), and another area showing AIS, characterized by cuboidal to columnar hyperchromatic cells and thickened interalveolar septa.
Adenocarcinoma is classified into minimally invasive and widely invasive (typical) adenocarcinoma

Adenocarcinoma In Situ (AIS)

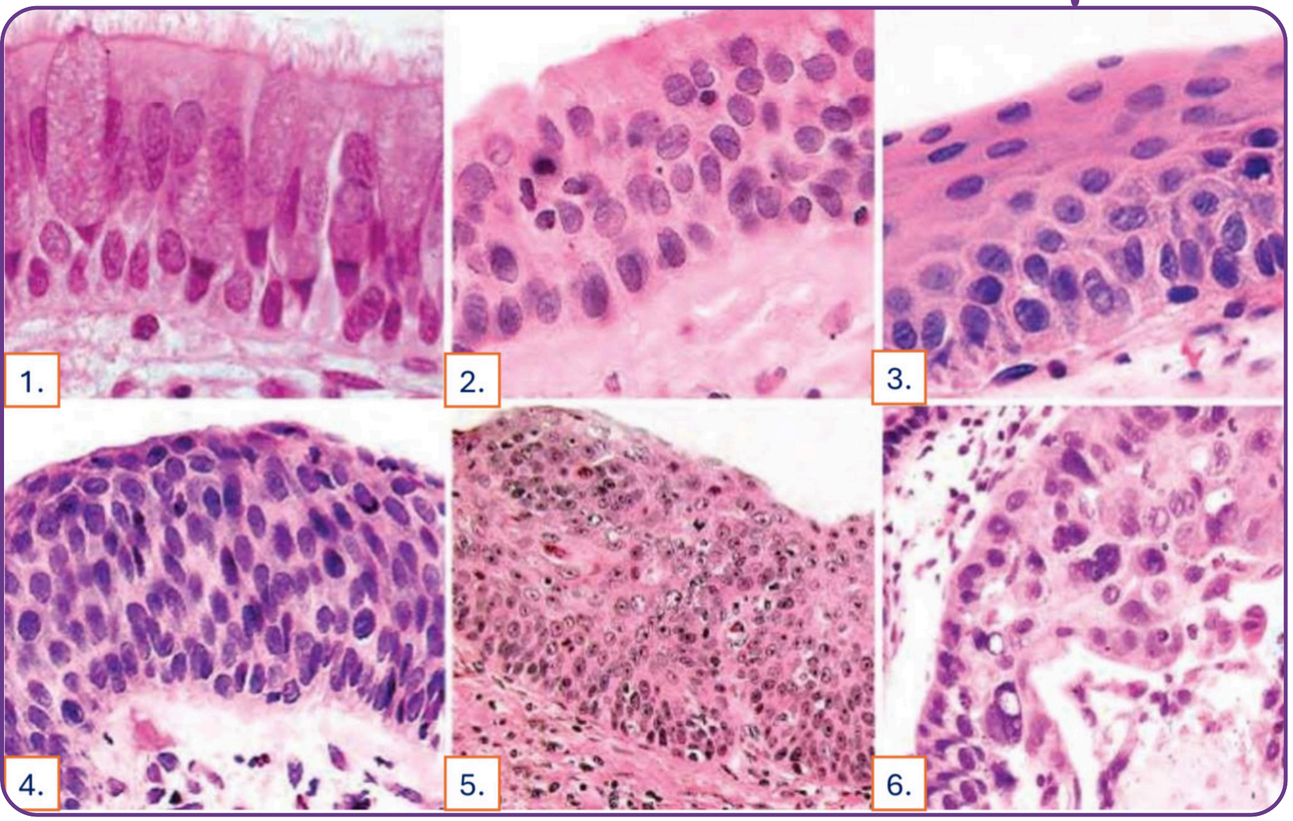


The AIS here exhibits preserved alveolar architecture, but it is lined by atypical cells. Mucin appears as pale/clear cytoplasmic vacuoles, and its amount varies between
Normal tissue is seen above, and AIS is present at the bottom.
There are two types of adenocarcinoma the minimally invasive and the widely invasive (typical) one.

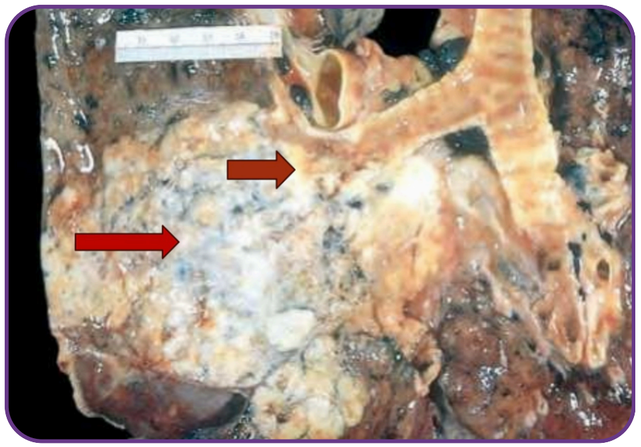


Peripheral, white circumscribed well-demarcated lesion, near the plural coverinig in Adenocarcinoma

Squamous Cell Carcinoma



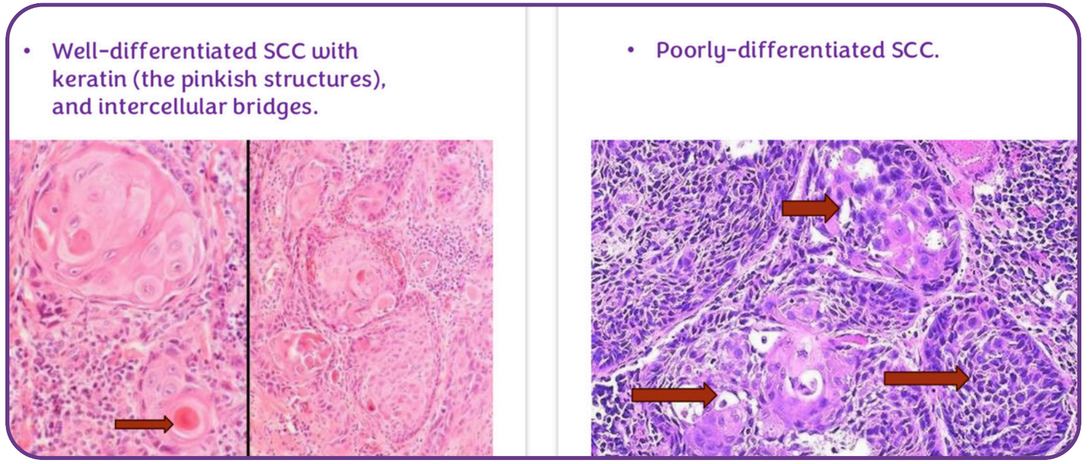
lesionis still a little well-demarcated, and infiltrating the lung parenchyma, in addition to a lumen obstruction.

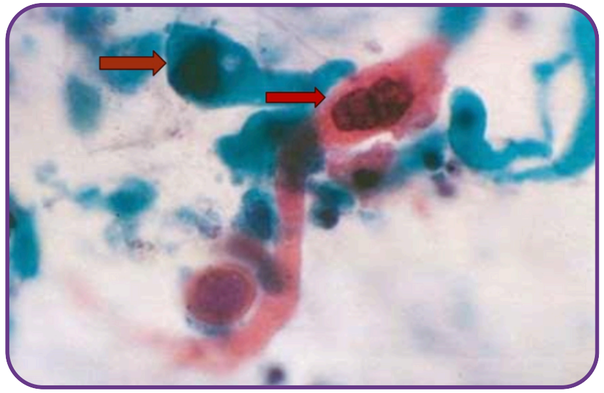


Central, not well demarcated (infiltrative), and destructive lesion.

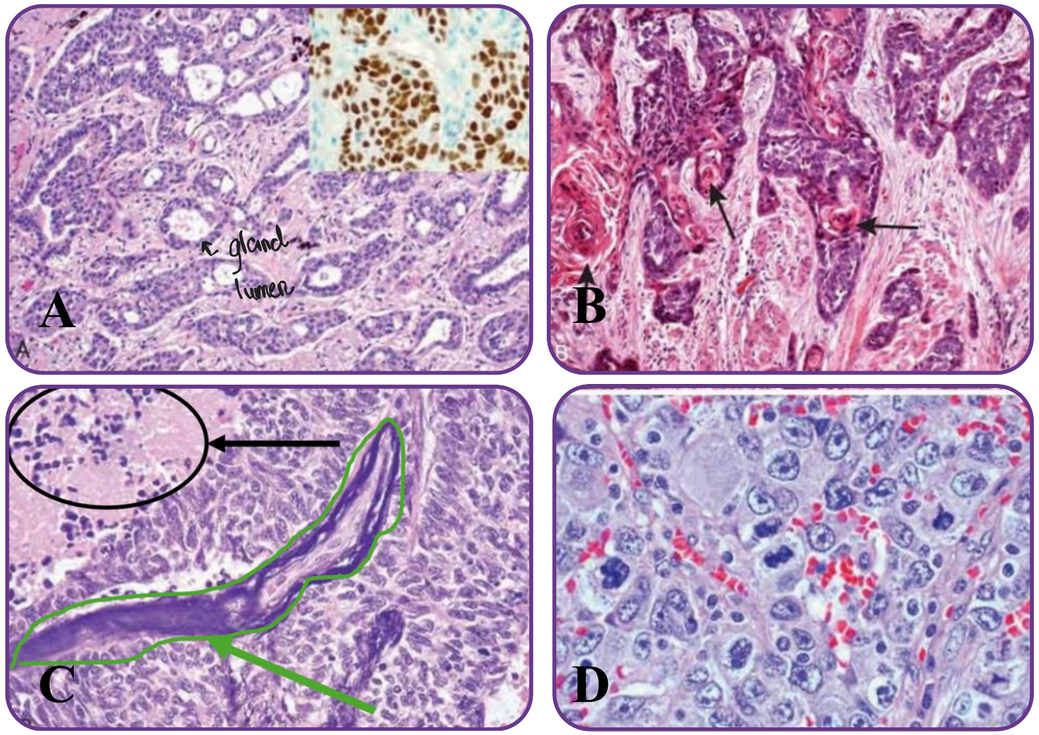
SCC stages

1. Goblet (mucous) cells hyperplasia appear first, explaining the high sputum in smokers.
2. Basal cell's hyperplasia.
3. Squamous metaplasia , with clear intercellular bridges.
4. Dysplasia.
5. SCCinsitu.
6. InvasiveSCC.

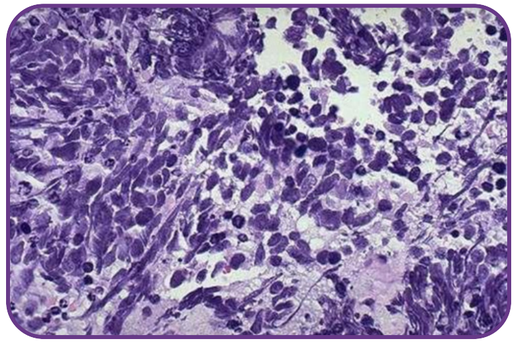




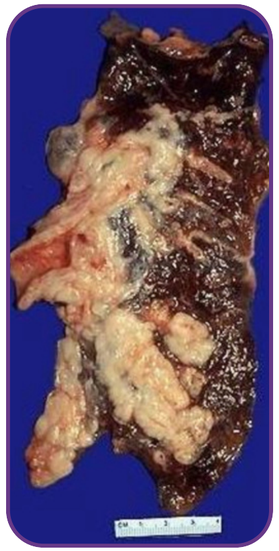
Sputum specimens:
Orange-staining, keratinized squamous cell carcinoma cells



Small Cell Lung Carcinomas (SCLC)



SCLC : Fragile tumor cells are easily crushed, releasing nuclear DNA that stains blue on biopsy (Azzopardi effect). The tumor cells appear small, smudged, crushed, with blue-staining nuclei and scant cytoplasm.



Small Cell Lung Carcinomas (SCLC)

A: **Adenocarcinoma** : These tumors show gland formation and mucin production. The nuclei stain positive for TTF-1, an immunohistochemical marker specific for lung and thyroid tissue. TTF-1 positivity supports adenocarcinoma, while TTF-1 negativity favors squamous cell carcinoma. The stain is also useful to confirm lung origin of the tumor.

B: **Squamous cell carcinoma** — these tumors produce keratin, and keratin production is a hallmark feature of squamous cell carcinoma.

C: **Small cell carcinoma** — these tumors commonly show areas of necrosis (**black arrow**).

The tumor cells are small, with a scant amount of cytoplasm, giving them the appearance of closely packed, clumped nuclei. They are highly fragile, which can result in a crush artifact during tissue processing or staining.

The **green arrow** highlights this crush artifact, where nuclear DNA is displaced from the crushed cells, staining blue and often seen around blood vessels—a characteristic feature of small cell carcinoma

D: **Large cell carcinoma** : The tumor shows large nuclei, prominent nucleoli, and moderate cytoplasm. It is a diagnosis of exclusion. TTF-1 negative .It must be distinguished from large cell neuroendocrine carcinoma, which has neuroendocrine markers and molecular features similar to small cell carcinoma, but with larger tumor cells.

LUNG TUMORS

Spread and metastasis

- Spreads to LNs around the carina, mediastinum, neck and clavicular regions.
- Left supraclavicular node (Virchow node) involvement is particularly characteristic.
- Extend into the pleural or pericardial space >>>>> inflammation and effusion.
- Compress or infiltrate the SVC to cause either venous congestion or the vena cava syndrome.

1.Pancoast tumors (Pancoast syndrome):

- Apical neoplasms.
- Destruction of the first and second ribs and sometimes thoracic vertebrae.
- Invade the brachial or cervical sympathetic plexus to cause:
- **Severe pain in the distribution of the ulnar nerve.**
- **Or Horner syndrome (ipsilateral enophthalmos, ptosis, miosis, and anhidrosis).**

Clinical features:

- Insidious lesions.
- Many cases unresectable by time of diagnosis.
- Localized lesions: Chronic cough and expectoration.
- Advanced lesions: Hoarseness, chest pain, SVC syndrome, pericardial or pleural effusion, or persistent segmental atelectasis or pneumonitis.
- Weight loss, dyspnea & chest pain.
- Symptoms of Mets:

1. Brain (mental or neurologic changes)
2. Liver (hepatomegaly),
3. Bones (pain).

Prognosis: **SCC and adenocarcinoma:**

- Carry more favorable Px than SCLC.
- Cure is possible by lobectomy or pneumonectomy if localized.
- Unresectable adenocarcinoma may respond to targeted Tx.

SCLCs:

- Invariably spread by the time of diagnosis.
- Surgical resection is not curable.
- Very sensitive to chemotherapy but invariably recur.
- Median survival even with treatment is 1 year

2.Paraneoplastic syndromes

(1) Hypercalcemia (secretion of a PTHrp)
(2) Cushing syndrome (production of ACTH);
(3) Syndrome of inappropriate secretion of ADH;
(4) Neuromuscular syndromes, including a myasthenic syndrome, peripheral neuropathy, and polymyositis;
(5) Clubbing of the fingers and hypertrophic pulmonary osteoarthropathy;
(6) Coagulation abnormalities, including migratory thrombophlebitis, nonbacterial endocarditis, and DIC.

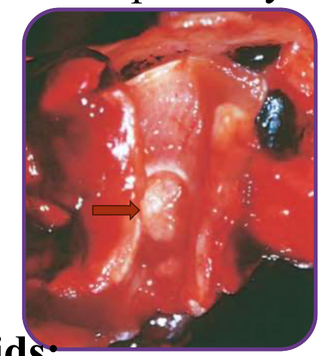
- **Hypercalcemia most often with SCC.**
- **Hematologic syndromes with adenocarcinomas.**
- **Neurologic syndromes: much more with SCLCs.**
- **ACTH & ADH: much more with SCLCs.**

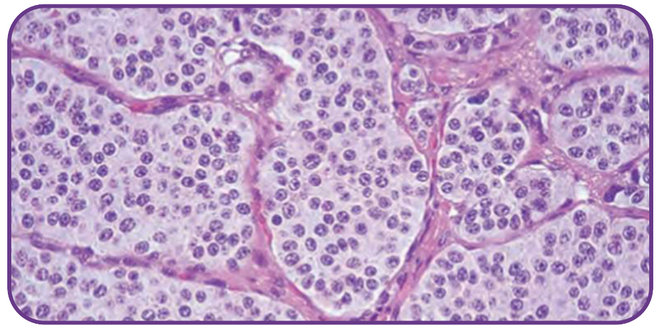
Staging:

- Tumor-Node-Metastasis(TNM) staging system is used to indicate the size and spread of the primary neoplasm.

3.Carcinoid tumors :

- 5% of all lung tumors.
- Composed of cells containing dense-core neurosecretory granules in their cytoplasm and, rarely, may secrete hormonally active polypeptides.
- Young adults (mean 40 years)
- Best regarded as malignant, low-grade neuroendocrine carcinomas.
- Subclassified as typical or atypical carcinoids; both are often resectable and curable.
- May occur as part of the multiple endocrine neoplasia syndrome (MEN syndrome).





Morphology:

Macroscopically:

- In main bronchus, well demarcated.
- 5-15% Mets to LNs at presentation.
- Distant Mets is rare.
- **Two growth patterns:**

1-Polypoid intraluminal mass.

2-Mucosal plaque penetrating the wall to fan out in the peribronchial tissue (collar button lesion)

Microscopic:

- **Typical carcinoids:**

Nests of regular uniform cells with round nuclei, salt and pepper chromatin, separated by a delicate fibrovascular stroma.
Few mitoses and lack atypia and necrosis.

- **Atypical carcinoids:**

Higher mitosis and/or foci of necrosis + pleomorphism.
High incidence of LN and distant Mets.
TP53 mutations in 20-40% of cases.

Clinical Features:

- Peripheral tumors: asymptomatic, incidental finding.
- Central tumors: cough, hemoptysis and recurrent infections due to obstruction.
- Carcinoid syndrome (rare): intermittent attacks of diarrhea, flushing, and cyanosis.
- **Typical carcinoids have better prognosis than atypical.**

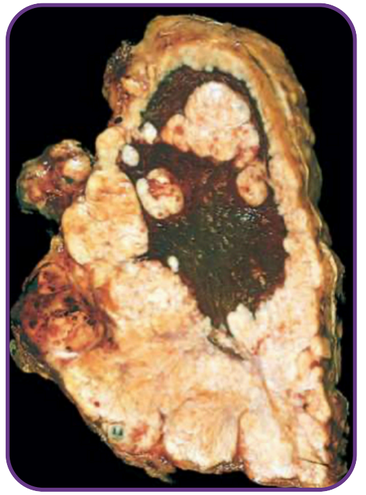
4.Malignant Mesothelioma

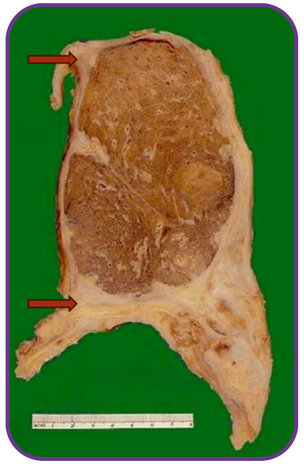
- Rare cancer of mesothelial cells in the parietal or visceral pleura.
- Less commonly in peritoneum and pericardium.
- Occupational exposure to airborne asbestos in 80-90% of cases.
- **Once inhaled, asbestos fibers remain in the body for life.**
- **The lifetime risk after exposure DOES NOT diminish over time (unlike with smoking cessation)**
- Risk in people living in proximity to an asbestos factory or being a relative of an asbestos worker
- Long latent period: occur after 25 to 40 years from initial asbestos exposure.
- The combination of cigarette smoking and asbestos exposure DOES NOT increase the risk of malignant mesothelioma.
- **In asbestos workers (esp. smokers), the risk of dying of lung carcinoma exceeds that of developing mesothelioma.**

Morphology:

Macroscopic:

- Preceded by extensive pleural fibrosis and plaque formation.
- Begin in a localized area and spread widely, either by contiguous growth or by diffusely seeding the pleural surfaces.
- Lung is ensheathed by a firm gelatinous tumor.
- May invade thoracic wall or lung tissue.
- Distant metastases are rare.





Microscopic:

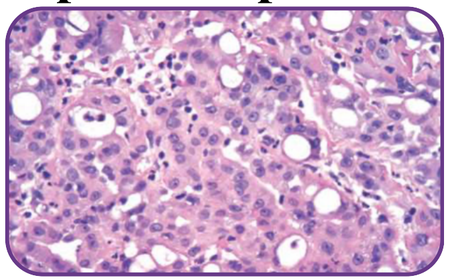
Three patterns:

(1) Epithelial: cuboidal cells line tubular and microcystic spaces (the most common & confused with a pulmonary adenocarcinoma)

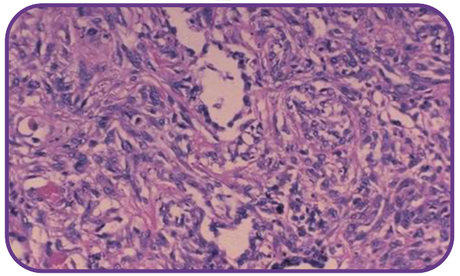
(2) Sarcomatous: spindled fibroblast-like cells grow in sheets.

(3) Biphasic: both sarcomatous and epithelial areas.

Epithelial pattern:



Mixed pattern:



Clinical features:

- Gradually worsening respiratory symptoms: cough & dyspnea.
- Thickening of pleura and pleural effusion on CXR.
- Shift of mediastinum
- 50% die after 12 months of diagnosis.

اللهمّ لک الحمد حتّی ترضی، ولک الحمد إذا رضیت، ولک الحمد بعد الرّضا.

اللهم اجعل أجر هذا العمل صدقة جارية عن روح **عمر عطيه عوده المرابي**

- اللَّهُمَّ اغْفِرْ له وَارْحَمْهُ، وَاعْفُ عنْه وَعَافِهِ، وَأَكْرِمْ نُزُلَهُ، وَوَسِّعْ مُدْخَلَهُ، وَ اغْسِلْهُ بمَاءٍ وَثَلْجٍ وَبَرَدٍ، وَنَقِهِ مِنَ الخَطَايَا كما يُنَقّى الثَّوْبُ الأبْيَضُ مِنَ الدَّنَسِ.
- اللَّهُمَّ أبدله داراً خيراً من داره، وأهلاً خيراً من أهله، وأدخله الجنّة، وأعذه من عذاب القبر ومن عذاب النّار.
- اللهمّ يمّن كتابه، ويسّر حسابه، وثقل بالحسنات ميزانه، وثبّت على الصراط أقدامه، وأسكنه في أعلى الجنات، بجوار حبيبك محمد صلّى الله عليه وسلم.
- اللهم اغفر لحينا وميتنا وشاهدنا وغائبنا وصغيرنا وكبيرنا وذكرِنا وأنثانا اللهم من أحييته منا فأحيِه على الإسلام ومن توفيته منا فتوفه على الإيمان اللهم لا تحرمنا أجره ولا تضلنا بعده.
- اللهم اغفر له وارفع درجته في المهديين، واخلفه في عقبه في الغابرين، واغفر لنا وله يا رب العالمين، وافسح له في قبره، ونوّر له فيه.
- اللَّهُمَّ أنزل على أهله الصّبر والسلوان وارضهم بقضائك.

اللهم لا تفجعنا بأنفسنا ولا أهلنا ولا أحبتنا، اللهم أعوذ بك من فواجع الأقدار ومن مصائب الدنيا وتقلب حوادثها، اللهم إنا نخاف الفقد فلا تحملنا ما لا طاقة لنا به.