Pathology of respiratory tract

Lung tumors

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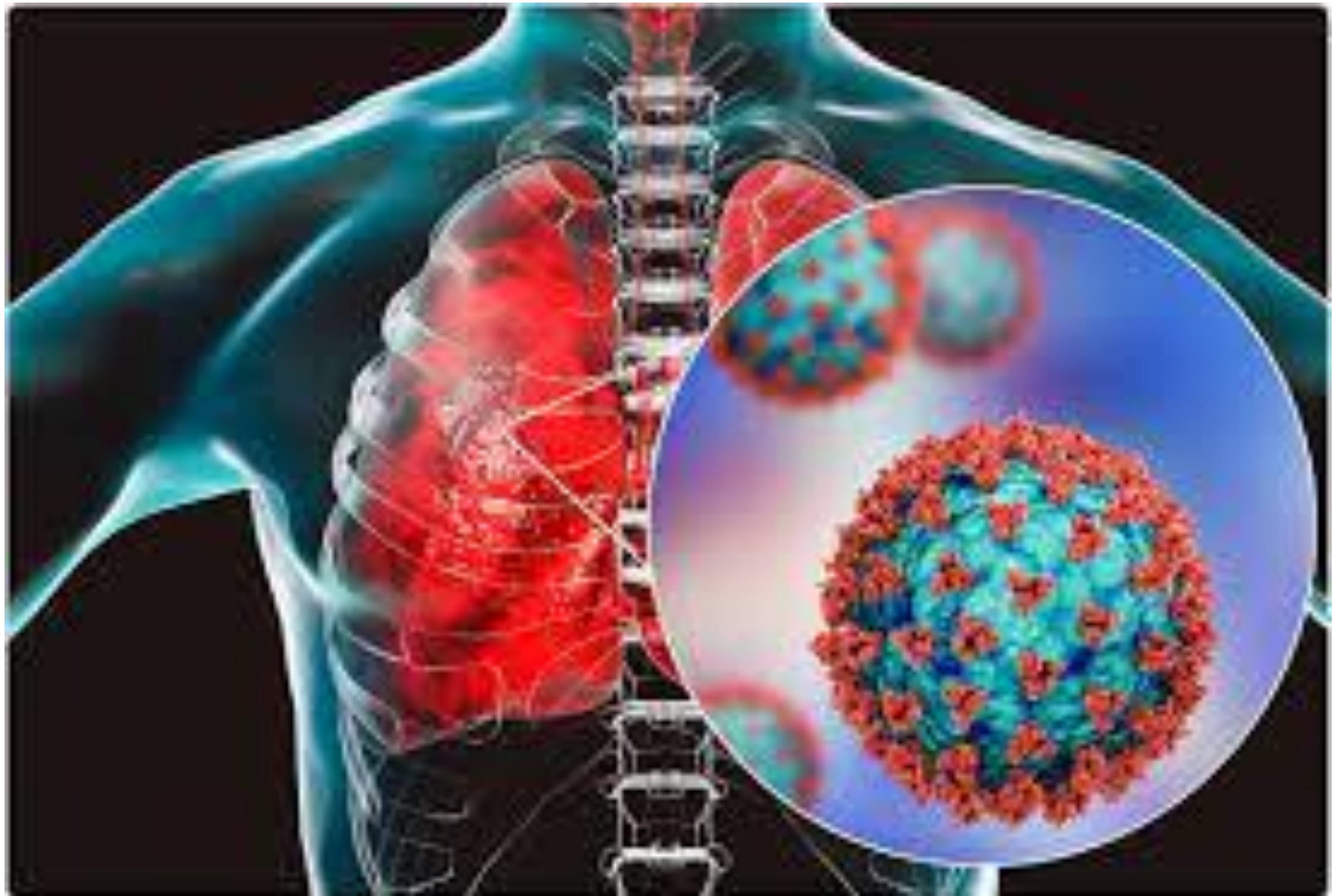
LEC 5



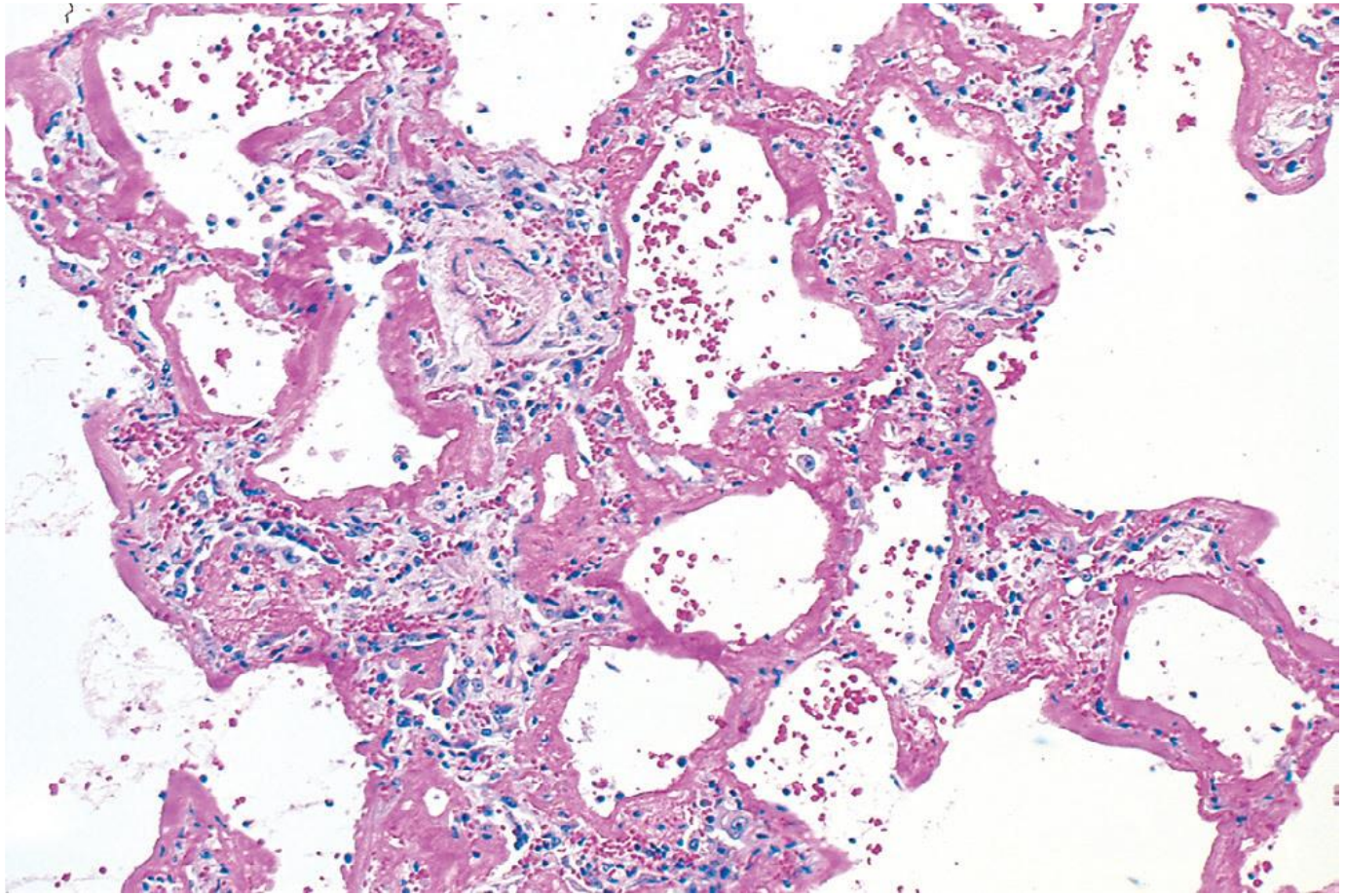
Human coronaviruses

- Coronaviruses are enveloped, RNA viruses that infect humans and animals
- **Weakly pathogenic coronaviruses** cause **mild cold-like upper respiratory tract** infections, while
- **highly pathogenic** ones may cause severe, often fatal pneumonia.
- An example of a highly pathogenic type is (**COVID-19**), a strain that emerged in late 2019 in China that is producing a still evolving pandemic.
- Highly pathogenic coronaviruses like (COVID-19)bind the **ACE2 protein** on the surface of pulmonary **alveolar epithelial cells**, explaining the tropism of these viruses for the lung.
- With **highly pathogenic forms** in **susceptible hosts**, typically **older individuals** with **comorbid conditions (DM, COPD, heart failure)**, the host immune response and locally released **cytokines** often produce **acute lung injury (ALI) and ARDS.**

- **The pathological changes in respiratory system that produced in COVID19 infection:**
- All viral infections produce similar morphologic changes. Upper respiratory infections are marked by mucosal hyperemia and edema , infiltration of the submucosa by mononuclear cells (mainly lymphocytes and macrophages), and overproduction of mucus secretions(catarrhal inflammation).
- suppurative secondary bacterial infection may superimposed .
- Virus may induced **tonsillitis , sinusitis , otitis media, laryngitis, laryngotracheobronchitis and bronchiolitis.**
- there **Impairment of bronchociliary function** induce bacterial superinfection with more marked suppuration.
- Plugging of small airways may give rise to **focal lung atelectasis.**
- With more severe bronchiolar involvement, widespread plugging of terminal airways by **cell debris**, **fibrin**, and **inflammatory exudate** may, if prolonged, lead to **fibrosis,** resulting **in permanent lung damage**.

- **Lung involvement** :
- **Predominant** is an **interstitial inflammatory reaction** involving the walls of the alveoli.
- Other forms like **patchy (bronchopnemonea)** or if involve whole lobes(**lobar**) bilaterally or unilaterally may occur especially if **secondary bacterial infection** superimposed.
- **Pleuritis** or **pleural effusions** are **infrequent**.
- **The histologic pattern depends on the severity of the disease.**
- The alveolar septa are widened and **edematous** and usually contain a mononuclear inflammatory infiltrate of **lymphocytes, macrophages**, In **severe cases, neutrophils** may also be present.
- The **alveoli may be free of exudate**, but in many patients there is intra-alveolar proteinaceous material and a cellular exudate.
- When complicated by **ARDS, pink hyaline membranes line the alveolar walls** .Eradication of the infection is followed by reconstitution of the normal lung architecture.
- Superimposed bacterial infection modifies this picture by causing **ulcerative bronchitis**, **bronchiolitis**, and **bacterial pneumonia**.

Diffuse alveolar damage (acute respiratory distress syndrome ARDS). Some of the alveoli are collapsed, while others are distended. Many are lined by hyaline membranes .



- Clinical Features
- The clinical course is **extremely variable**.
- Many cases appear as **severe upper respiratory tract infections** .
- the major manifestations may consist only of **fever, headache, and myalgia** and Cough
- **Viral pneumonias** are usually mild and resolve spontaneously without any lasting sequelae.
- **interstitial viral pneumonias**
- The edema and exudation often cause ventilation-perfusion mismatch
- leading to **hypoxemia**

Respiratory Pathology Outline

- Congenital anomalies
- Atelectasis
- Obstructive lung diseases
- Restrictive lung diseases
- Infections(pneumonia)
- **Carcinoma**

LUNG TUMORS

- **Bronchogenic carcinomas constitute 95% of primary lung tumors;**
- **the remaining 5% includes :**
- **bronchial carcinoids,**
- **sarcomas,**
- **lymphomas,**
- **and a few benign lesions.**
- **Most common benign lung tumor is hamartoma**

Bronchogenic Carcinomas:

- Carcinoma of the lung is the commonest cause of cancer-related deaths in industrialized countries.
- The rate of increase among males is slowing down, but it continues to accelerate among females;
- this is related to the strong relationship of cigarette smoking and lung cancer.
- Most patients are in the age group of 50-60 years.
- The prognosis of lung cancer is very poor:
- the 5-year survival rate for all stages combined is about 15%.

- **Based on the WHO classification, there are four major histologic types of lung carcinomas :**

- **Adenocarcinoma (50%)**
- **Squamous cell carcinoma (20%)**
- **Small cell carcinoma (15%)**
- **Large cell carcinoma (2%)**
- **Other (13%)**

- ***For therapeutic purposes, carcinomas of the lung are divided into two groups:***

I. small-cell lung cancer (SCLC).

II. <u>non-small-cell lung cancer (NSCLC), includes:</u>

1. squamous cell
2. adenocarcinomas
3. large-cell carcinomas

- **The reason for this division is that virtually all SCLCs have metastasized by the time of diagnosis and therefore, are not curable by surgery.**
- **The best treatment by chemotherapy, with or without radiation.**
- **In contrast, NSCLCs usually respond poorly to chemotherapy and are better treated by surgery.**
- **In addition, these two groups show molecular genetic differences.**

Etiology and Pathogenesis

1- The role of Cigarette smoking:

- There is a great relation between lung carcinoma and the smoking,.
- **Statistical evidences**:
- ***The increased risk is 60 times greater in habitual heavy smokers (two packs a day for 20 years) than in nonsmokers***
- ***For unclear reasons, it appears that women are more susceptible to carcinogens in tobacco than men.***
- ***the carcinogenic effects of tobacco smoke extend to those who live and work with smokers*** Passive smoking increases the risk to twice that of nonsmokers.
- ***Squamous and small-cell carcinomas show the strongest association with tobacco smoking.***

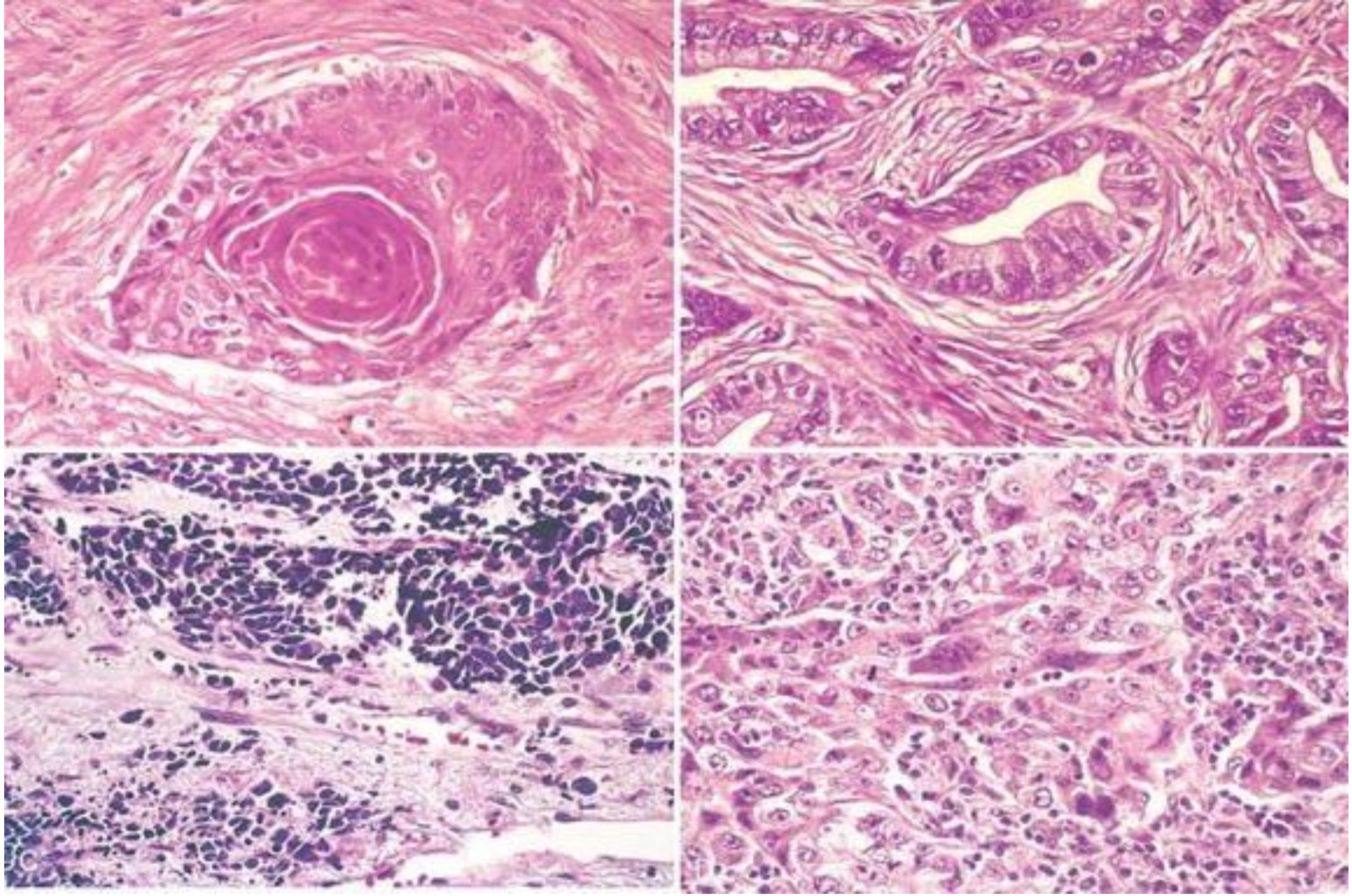
2-The role of occupation-related environmental agents:

- these may act alone or synergistically with smoking to be related to some lung cancers,
- for e.g. *radon*; *dusts containing arsenic, chromium, uranium, nickel, vinyl chloride, and mustard gas*.
- Exposure to *asbestos* increases the risk of lung cancer 5 times in nonsmokers.
- those who smoke have a 55-fold greater risk.

3- The role of hereditary (genetic) factors:

- **Not all persons exposed to tobacco smoke develop cancer.**
- **It seems that the effect of carcinogens is modulated by hereditary (genetic) factors.**
- **Squmous cell carcinoma: TP53 (tumor suppressor gene)in 60% to 90% of squamous cell carcinoma in situ**
- **Small cell carcinoma: inactivation of both TP53 and RB, amplification of genes of the MYC family**
- **Adenocarcinoma:**
- **KRAS gene (roughly 30% of tumors),**
- **EGFR, in 10% to 15% of tumors;**
- **ALK, in 3% to 5% of tumors**
- **these are important to recognize because they often can be targeted with specific inhibitors**

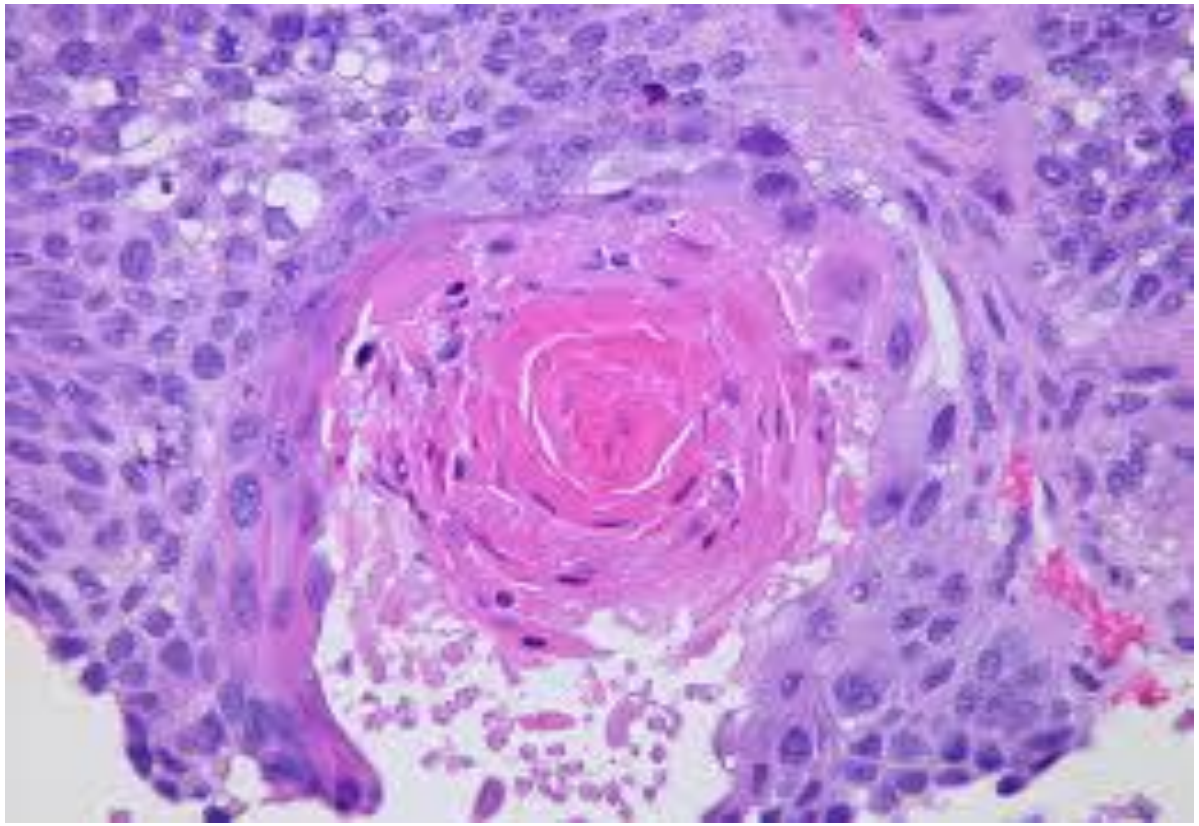
- **4- Air Pollution**. increases the risk of lung cancer, especially in smokers, through several different mechanisms.
- Chronic exposure to air particulates may cause
- lung irritation, inflammation, and repair, (any chronic inflammation and repair increases the risk of a variety of cancers).



Squamous cell carcinoma:

- **Common in *male.***
- **Related to *smoking***
- **arise *centrally* (hilar origin).**
- ***Areas of squamous metaplasia , dysplasia are seen in the adjacent mucosa.***

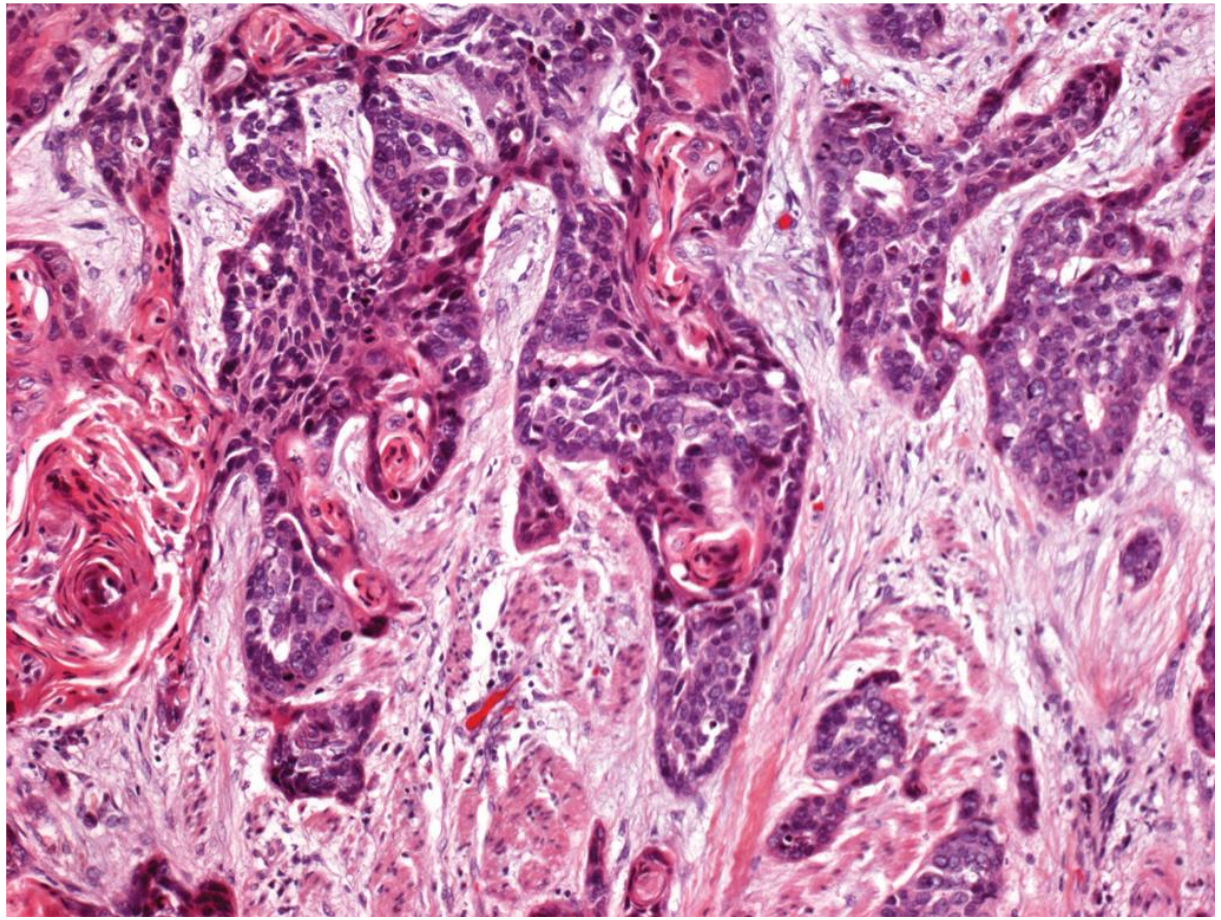
- MIC. squamous cell carcinoma is either well differentiated : characterized by the presence of **keratinization** (squamous pearls or markedly eosinophilic cytoplasm) and/or **intercellular bridges**.
- This features **are prominent and easily seen** in **well-differentiated tumors**
- **not extensive** in **moderately differentiated** tumors, and
- are **focally seen** in **poorly differentiated** tumors.



Squamous cell ca of the lung

Lung carcinoma. The gray-white tumor infiltrates the lung parenchyma. Histologic sections identified this tumor as a squamous cell carcinoma.

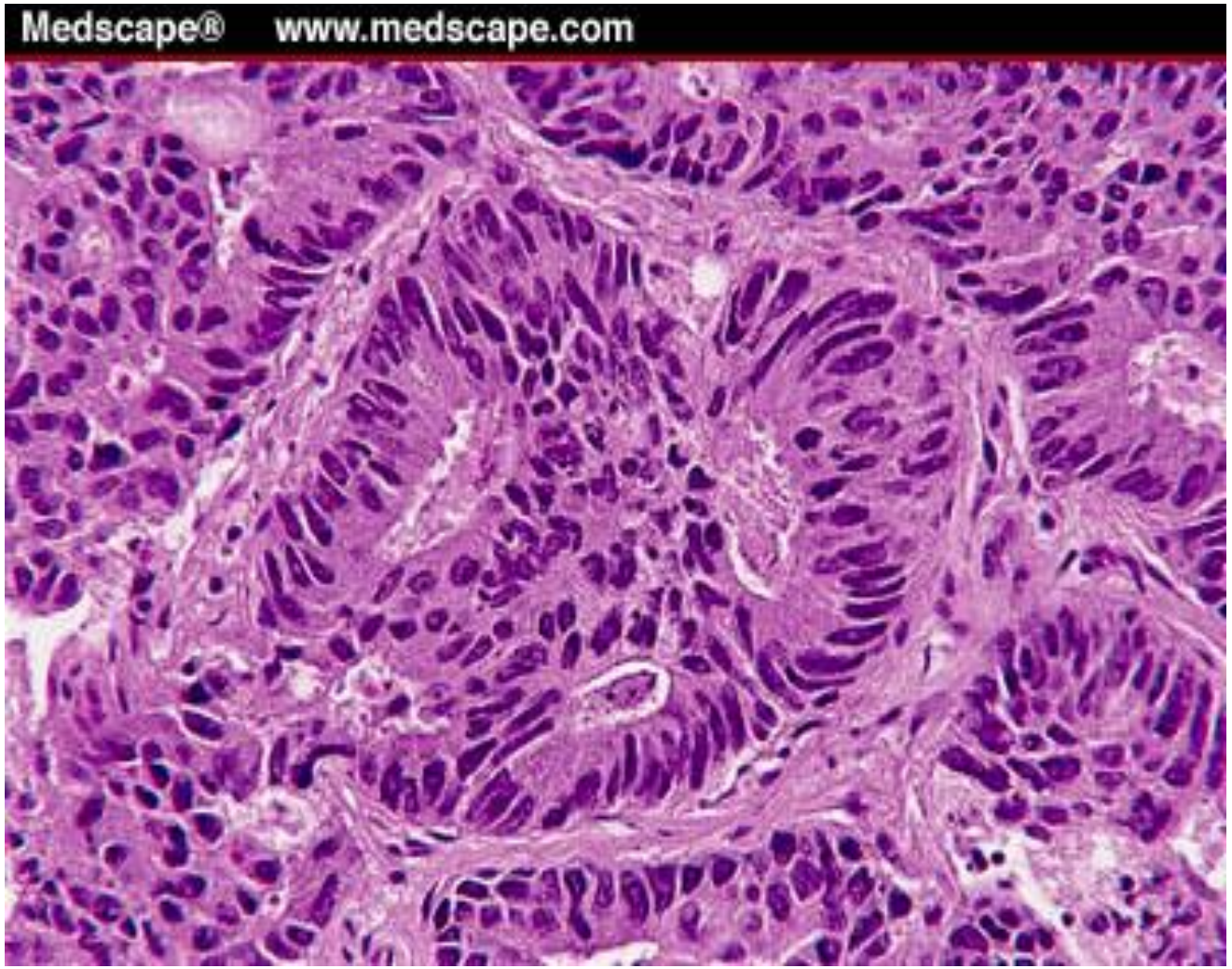
Well-differentiated squamous cell carcinoma showing keratinization



Adenocarcinoma :

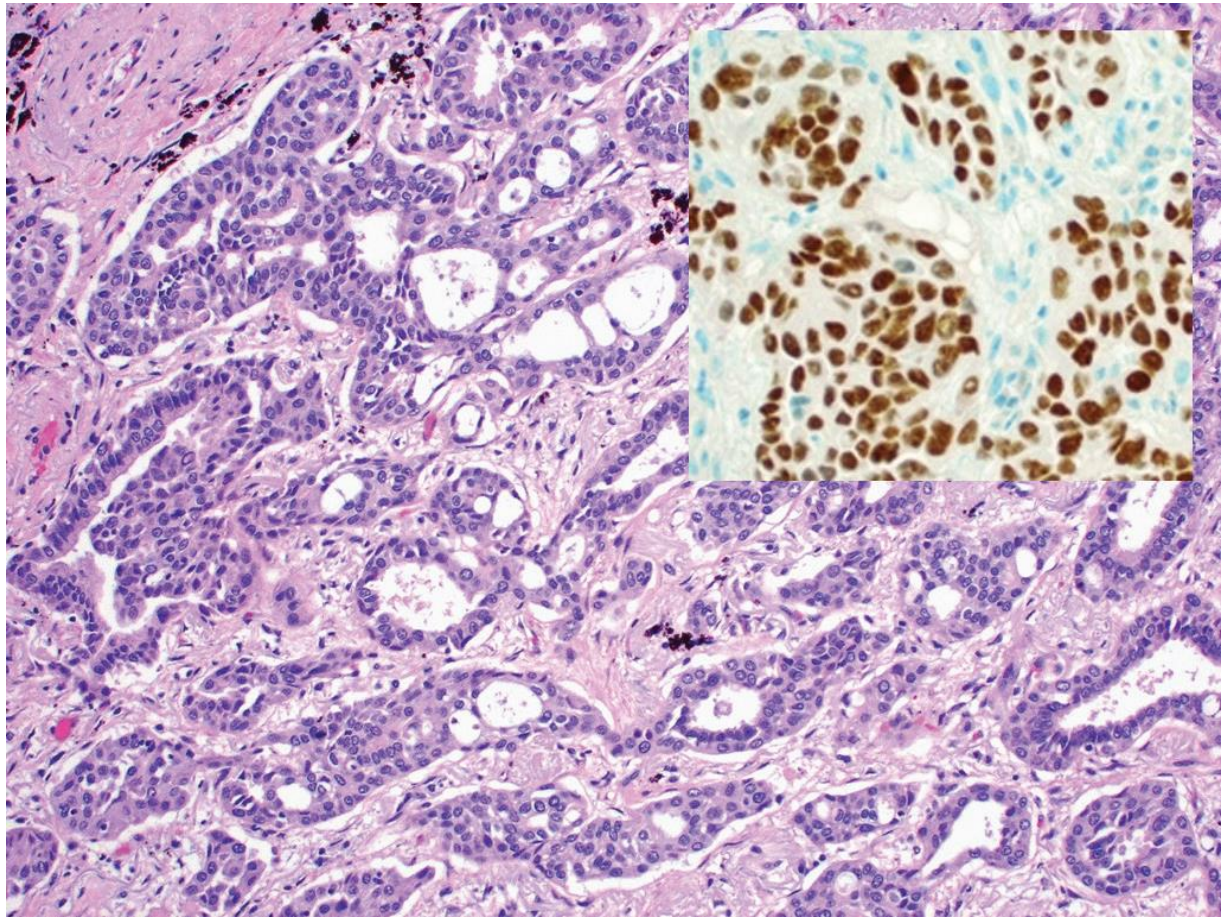
It is characterized by:

- **Seen commonly in *female.***
- **It is the common type seen in *non smokers*.**
- **It arises in more *peripheral locations*.**
- **It grows more *slowly.***
- **Sometimes it is *seen near areas of scarring***
- Mic. invasive malignant epithelial tumor with **glandular differentiation** or **mucin production** by the tumor cells.
- It grows in various patterns, including acinar, papillary, micropapillary, and solid.



peripheral adenocarcinoma of the lung

Gland-forming adenocarcinoma; inset shows thyroid transcription factor 1 (TTF-1) expression, as detected by immunohistochemistry

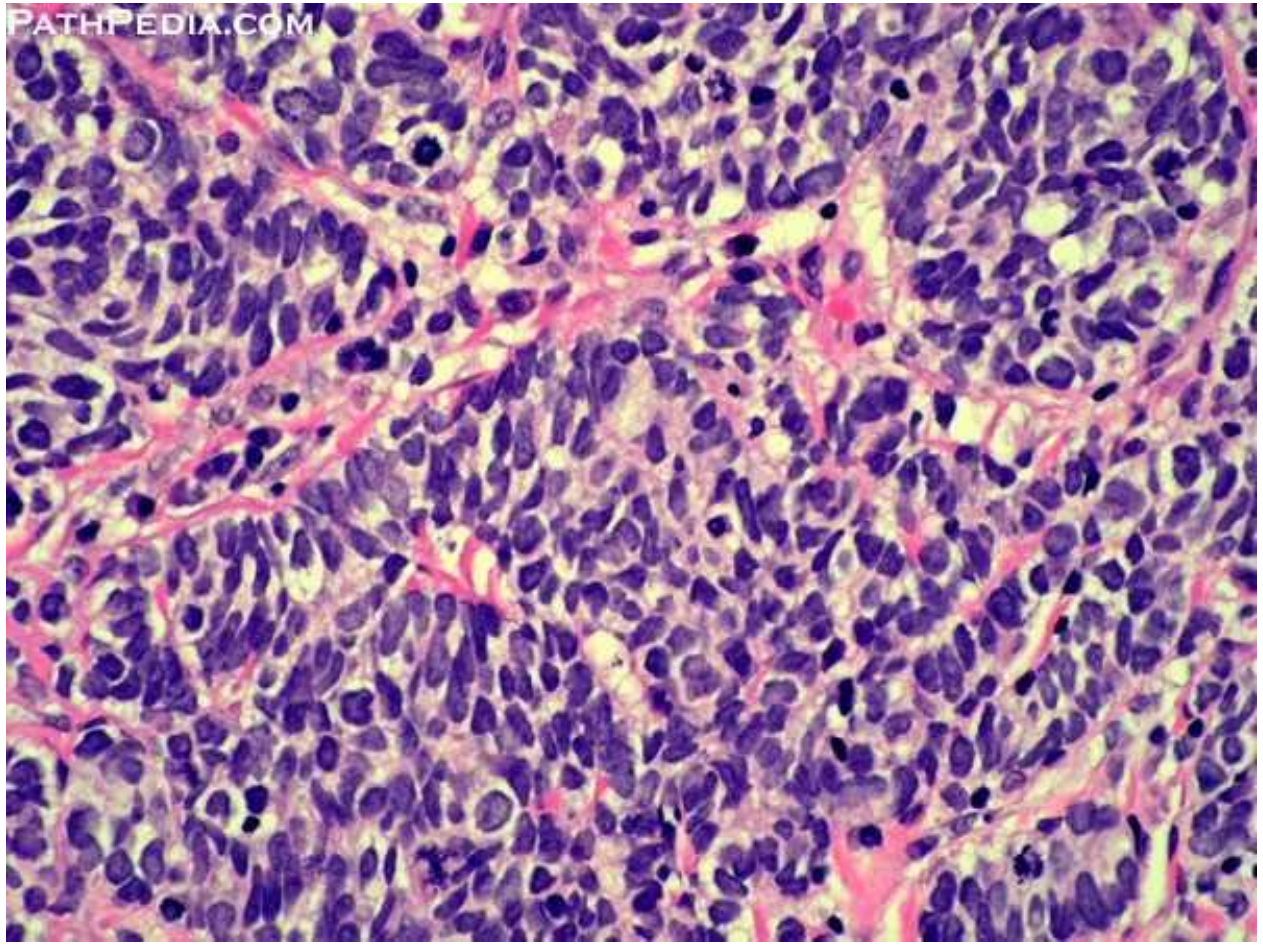


Small cell carcinoma:

- **Highly malignant, *most aggressive*.**
- ***Metastasize widely*.**
- ***Not* cured by surgery.**
- **Has *strong relation to smoking*.**
- **Arise *centrally* (hilar).**

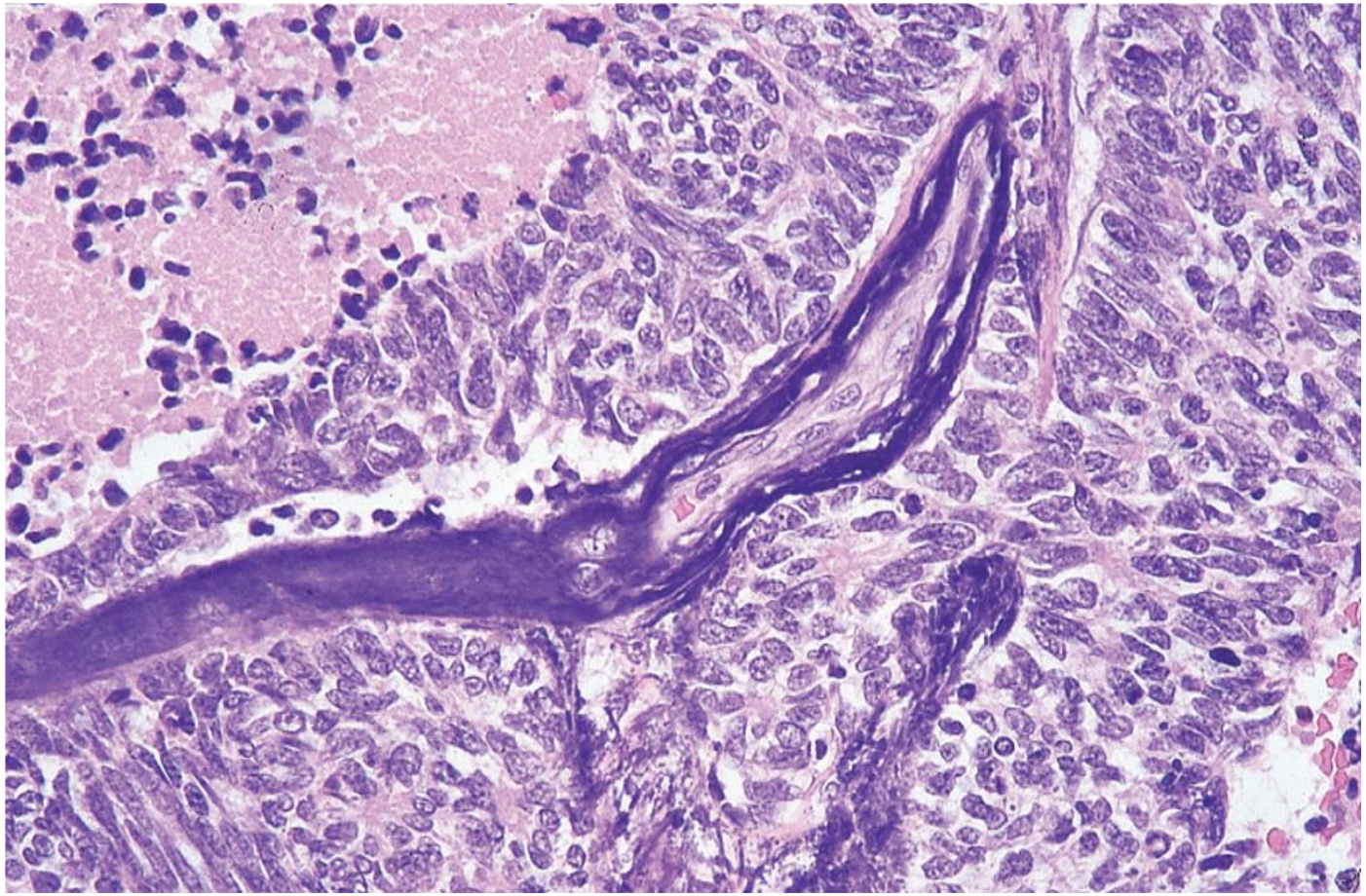
- **MIC.:** The cells appear **small** (2x the size of lymphocyte),
- dark nucleus,
- scant cytoplasm
- ill-defined cell borders,
- finely granular nuclear chromatin (salt and pepper pattern),
- and absent or inconspicuous nucleoli
- The cells are **round, oval, or spindle shaped**,
- and **nuclear molding** is prominent.
- The **mitotic count is high**. The cells grow in clusters that exhibit neither glandular nor squamous organization.
- **Necrosis** is common and often extensive**.**
- Small cell ca. are derived from **neuroendocrine cells** of the lung**,** and therefore, they express a variety of **neuroendocrine markers in** addition to many **polypeptide hormones** that may result in **paraneoplastic syndromes.**

This lung and spreading extensively in small cell carcinoma



The cells *appear small (2x the size of lymphocyte), dark nucleus, thin cytoplasme hence the name <u>OAT CELL CARCINOMA</u>.*

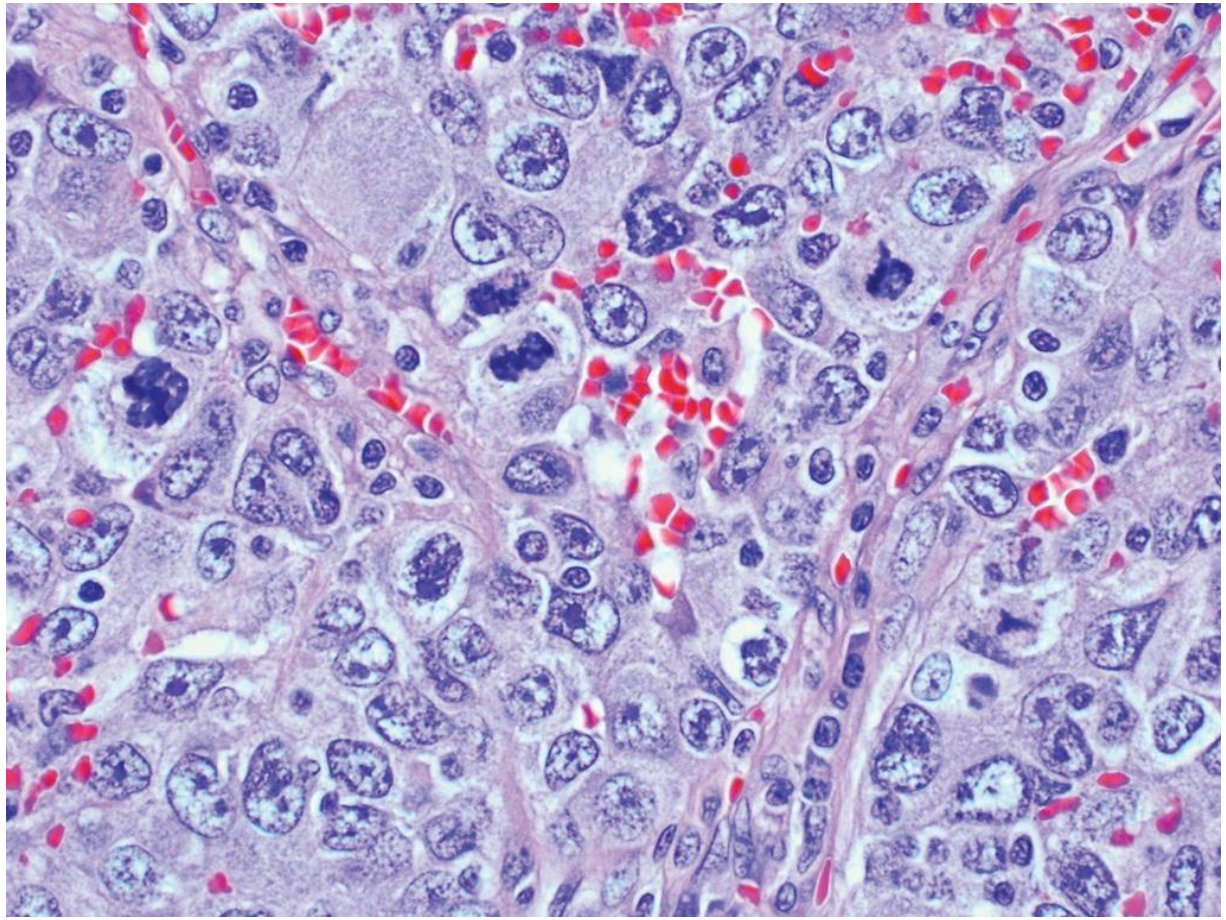
Small cell carcinoma. There are islands of small, deeply basophilic cells and areas of necrosis



Large cell carcinoma

- Highly anaplastic tumor.
- It may represent poorly differentiated squamous or adenocarcinoma.
- The cells appear so large, bizarre, and even giant cells could be seen.
- is an undifferentiated malignant epithelial tumor that lacks the cytologic features of other forms of lung cancer. The cells typically have large nuclei, prominent nucleoli, and a moderate amount of cytoplasm .

Large cell carcinoma. The tumor cells are pleomorphic and show no evidence of squamous or glandular differentiation



- Combined Carcinoma.

Approximately 4% to 5% of all lung carcinomas have a combined histology, including two or more of the aforementioned types

Clinical presentation of bronchogenic carcinoma:

- The age is *around* ***50 -60yrs****.*
- It is considered as the ***most aggressive neoplasm***.
- Presenting symptoms:
- cough, weight loss, chest pain, dyspnea, sputum production ,heamoptysis.
- *Most commonly it is discovered by its secondary spread*.

- **Course & prognosis**
- Carcinomas of the lung are silent lesions that more often than not have spread beyond curable resection at the time of diagnosis.
- Too often, the tumor presents with symptoms related to metastatic spread to the brain (mental or neurologic changes), liver (hepatomegaly), or bones (pain).
- Overall, **NSCLCs have a better prognosis than SCLCs**.
- When NSCLCs (squamous cell carcinomas or adenocarcinomas) are detected before metastasis or local spread, **surgery** is possible by lobectomy
- **SCLCs, on the other hand, is almost always have spread by the time of the diagnosis, even if the primary tumor appears small and localized. Thus, surgical resection is not a practical treatment.**
- They are very sensitive to chemotherapy but it may recur.
- Median survival even with treatment is 1 year.

Paraneoplastic syndromes

Up to10% of all patients with lung cancer develop *paraneoplastic syndromes.*

These include:

1. ***Hypercalcemia* caused by secretion of a parathyroid hormone-related peptide.**
2. ***Cushing syndrome* (from increased production of ACTH);**
3. ***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. ***Hematologic manifestations*, including migratory thrombophlebitis, nonbacterial endocarditis, and disseminated intravascular coagulation.**

- ***Hypercalcemia is most often encountered with squamous cell carcinomas, the hematologic syndromes with adenocarcinomas.***
- ***The remaining syndromes are much more common with small-cell neoplasms, but exceptions occur.***

Metastatic tumors:

- The lung is a frequent site of metastatic tumors from all over the body; it is more common than the primary.
- It reaches the lung by lymphatic, blood, or direct continuity as in esophageal carcinoma.

multiple nodules are characteristic for metastatic carcinoma to the lungs

• Carcinoid Tumors

- It represent 1% to 5% of all lung tumors.
- Most patients with these tumors are **younger than 60** years of age.
- The incidence is **equal for both sexes**.
- Approximately 20% to 40% of patients are **nonsmokers.**
- It is **a neuroendocrine tumor with low-grade malignant potential.**
- subclassified into ***typical*** and ***atypical carcinoids*.**
- **Morphology :**
- Carcinoids may arise centrally or may be peripheral.
- **Grossly :,** the central tumors grow as spherical polypoid masses that commonly project into the lumen of the bronchus and are usually covered by an intact mucosa. They rarely exceed 3 to 4 cm in diameter.
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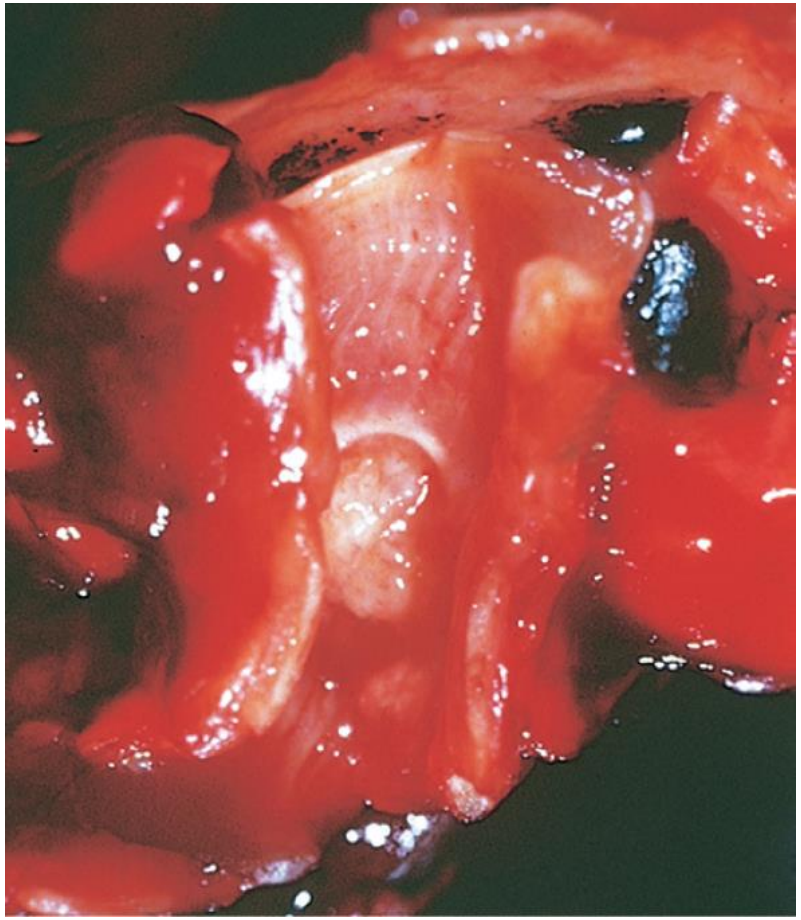
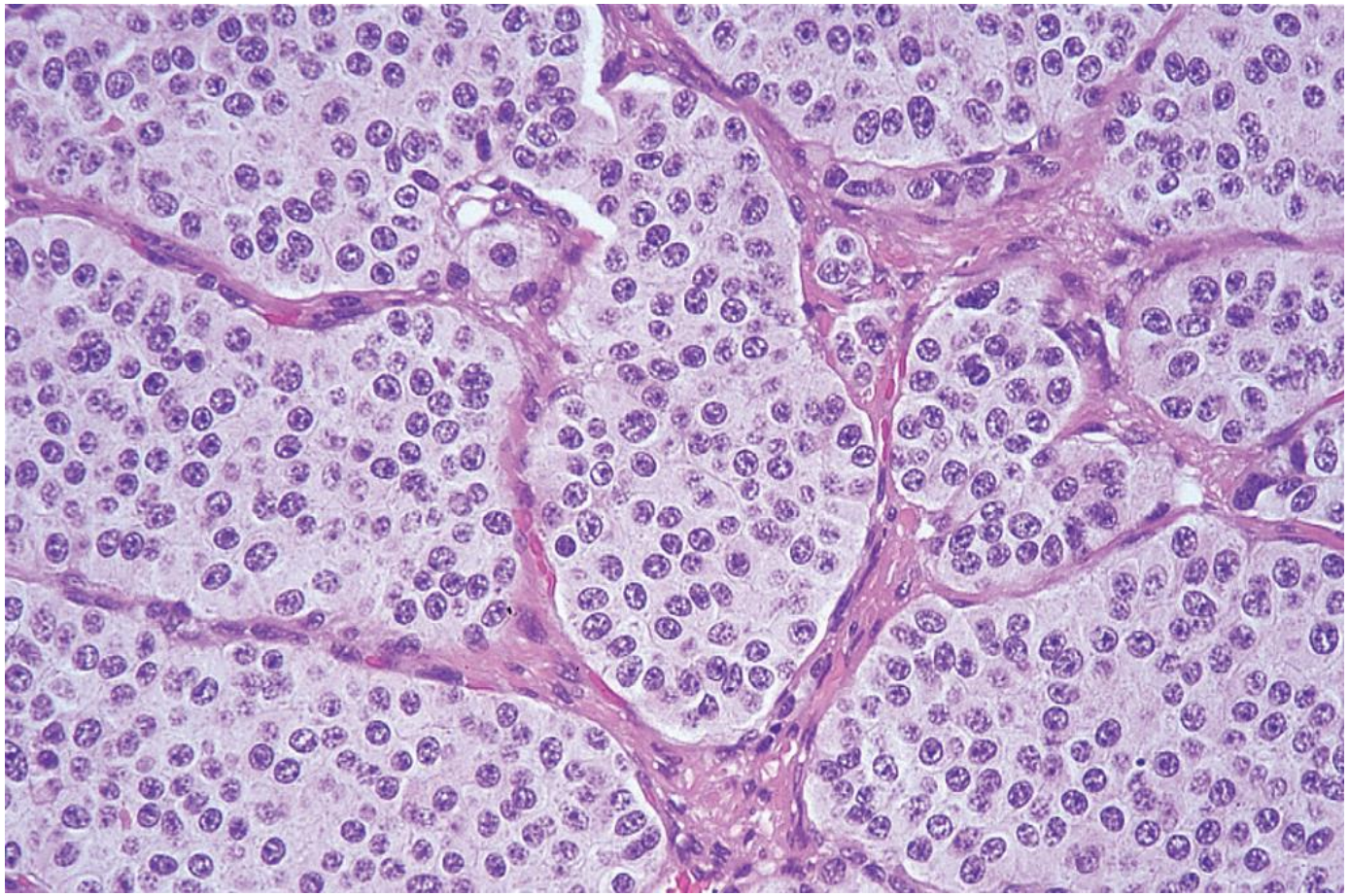
Carcinoid growing as a spherical mass protruding into the lumen of the bronchus.

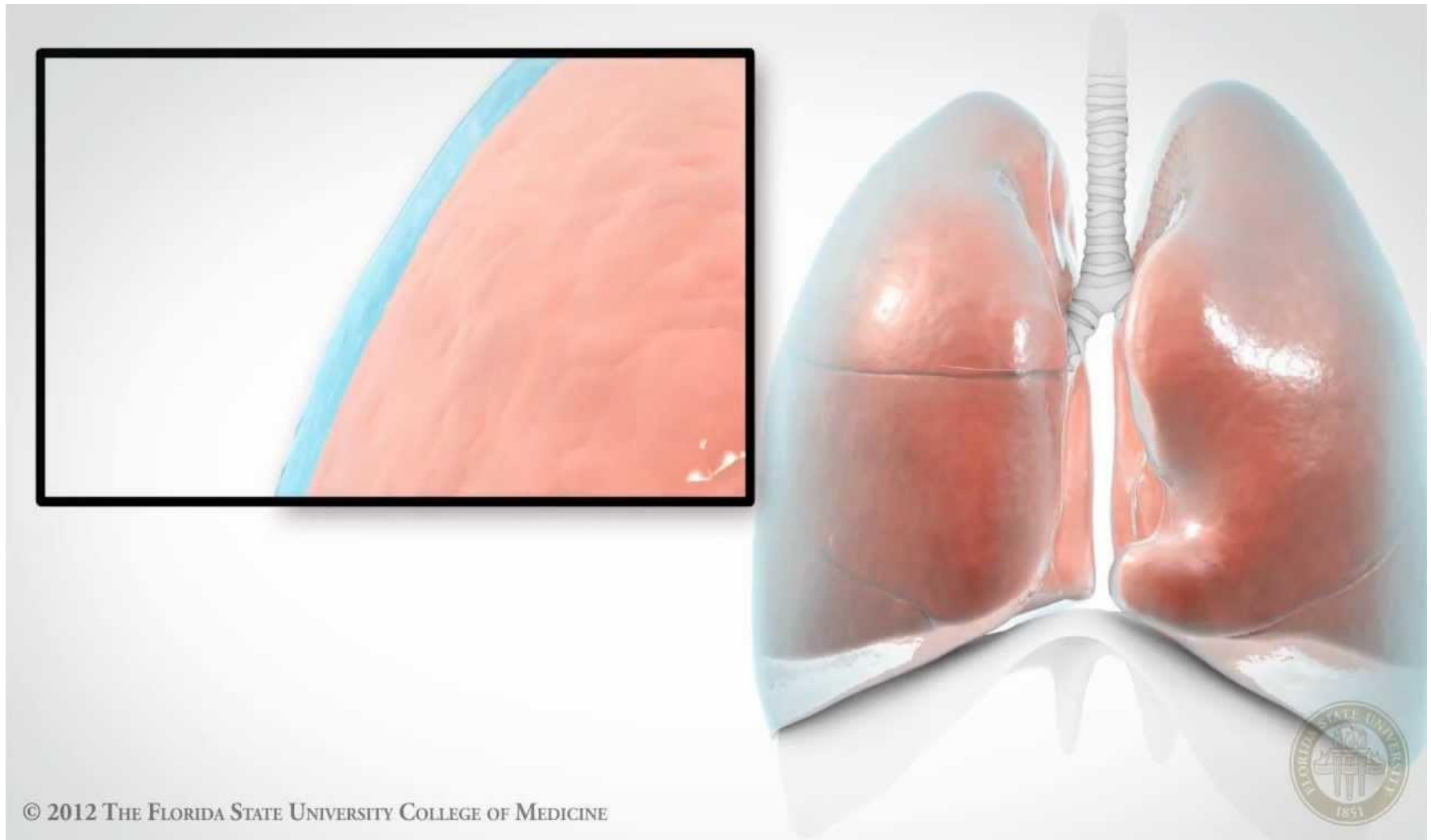


The tumor cells have small, rounded, uniform nuclei and moderate amounts of cytoplasm.



- **MIC.** the tumor is composed of organoid, trabecular, palisading, ribbon, or rosette-like arrangements of cells separated by a delicate fibrovascular stroma. the individual cells are regular and have uniform round nuclei and a moderate amount of eosinophilic cytoplasm .
- Typical carcinoids have few mitoses and lack necrosis, while
- **Atypical carcinoids** have :
- more mitoses and/or
- foci of necrosis.
- increased pleomorphism,
- have more prominent nucleoli, and
- are more likely to grow in a disorganized fashion and invade lymphatics.

- Behavior:
- Most carcinoid tumors DO NOT metastasize , DO NOT secrete hormones
- Some might show metastasize to the local L.N and some may secrete hormones.
- It follow a relatively benign course for long periods
- Treatment :
- Surgical resection.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- **THE PLEURA**
- May be involved by **primary or secondary tumors**.
- **The secondary involvement is more common**.
- The most common secondary comes **from the lung and breast carcinoma**.
- **Malignant mesothelioma:** is a rare cancer of mesothelial cells, usually arising in the parietal or visceral pleura , In the USA **approximately 50% of individuals with this cancer have a history of exposure to asbestos.**
- The latent period for developing malignant mesotheliomas is long (25 to 40 years) after initial asbestos exposure.

- **Grossly:** The lung is enclosed by a thick, soft, gelatinous, gray-white tumor.

The dense white encircling tumor mass is arising from the visceral pleura and is a mesothelioma.

Malignant mesothelioma. Note the **thick**, **firm**, **white** pleural tumor tissue that ensheathes the lung.

- Mic. one of three patterns:
- 1. **Epithelial,** in which cuboidal cells line tubular and microcystic spaces, into which small papillary buds project.
- 2. **Sarcomatoid,** in which spindled cells grow in sheets
- 3. **Biphasic**, having both sarcomatoid and epithelial areas.

- **Clinical feature**:
- chest pain,
- dyspnea,
- recurrent pleural effusions
- The lung is invaded directly, and there is often metastatic spread to the **hilar lymph nodes**
- and, then to the **liver** and **other distant organs**.
- 50% of patients die within 12 months of diagnosis, and few survive longer than 2 years.
- Aggressive therapy (surgery, chemotherapy and radiotherapy) seems to improve this poor prognosis in some patients.


Thank You!