Doctor.021

no. 8

RS PATHOLOGY

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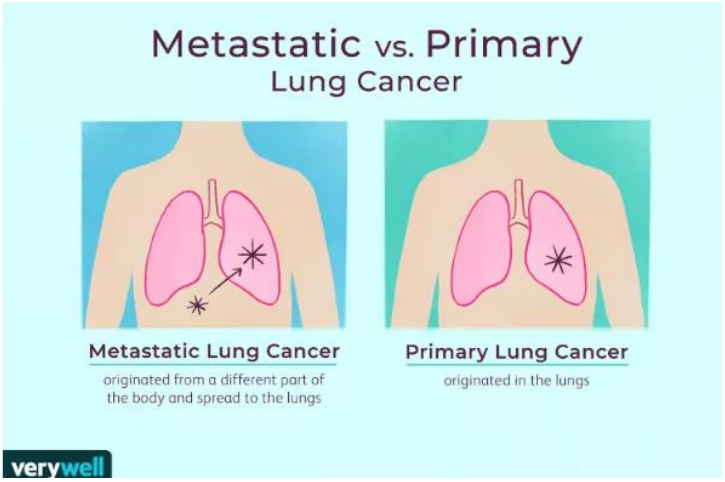
Lung as any organ can be a site of **a primary tumor** (originates from the lung parenchyma) or **metastatic tumors** (tumors spread to the lung from outside origins, examples for the most common extrapulmonary origins are as below;

Breast, gastrointestinal tract like colorectal, renal cancers.

In addition to head & neck tumors, testicular tumors, osteosarcoma, and others.



Today's lecture, we'll discuss the primary tumors only. And stay tuned to the recorded lecture to learn about the metastatic ones.

GOOD LUCK!

- **90- 95% of primary lung tumors are carcinomas.** Remember that carcinoma means a malignant tumor of epithelial origin.
- **5% are carcinoid tumors.** (slow-growing cancer arises in several places in the body).
- **2- 5% are mesenchymal and other neoplasms.** Like fibrosarcoma.

CARCINOMA OF THE LUNG

- **the most frequently diagnosed cancer in the world.**

- **the most common cause of cancer mortality worldwide.**
- **lung cancer is strongly linked to cigarette smoking:** How?
  - **Changes in smoking habits greatly influence lung cancer incidence, mortality & the prevalence of the various histologic types of lung cancer.**

- **The incidence of lung cancer among females is increasing, BECAUSE:**
  1. **The incidence of smoking in women increased markedly over the past half century.**
  2. Unfortunately ladies, new studies showed that your genes are more prone/susceptible for carcinogens inside the tobacco smoke than the males for unclear reasons. so if we looked at a male and a female with the same of lifestyle and have the same level of risk factors and the they start smoking in the same frequency, the female is more risky to develop lung cancer.
- **peak incidence: 65 and 74 years.**
  - **THE FOUR MAJOR HISTOLOGIC TYPES OF CARCINOMAS OF THE LUNG:**

1. Adenocarcinoma (50%)

2. Squamous Cell Carcinoma (20%)

3. Small Cell Carcinoma (a subtype of neuroendocrine carcinoma) (15%)

4. Large Cell Carcinoma (2%)

We will study all of them later.

But before that, keep in mind that lung carcinoma classification is not limited to what we have mentioned above, we still have more &

more subtypes according to WHO…. I will be grateful to you if you just look at the table below which shows these subtypes;

Table 15.9 Histologic Classification of Malignant Epithelial Lung Tumors

Tumor Classification
Adenocarcinoma
Lepidic, acinar, micropapillary, papillary, solid (according to predominant pattern)
Invasive mucinous adenocarcinoma
Minimally invasive adenocarcinoma (nonmucinous, mucinous)
Squamous cell carcinoma
Keratinizing, nonkeratinizing, basaloid
Neuroendocrine tumors
Small cell carcinoma
Combined small cell carcinoma
Large cell neuroendocrine carcinoma
Combined large-cell neuroendocrine carcinoma
Carcinoid tumor
Typical, atypical
Other uncommon types
Large cell carcinoma
Adenosquamous carcinoma
Sarcomatoid carcinoma
Pleomorphic, spindle cell, giant cell carcinoma, carcinosarcoma, pulmonary blastoma
Others such as lymphoepithelioma-like carcinoma and NUT carcinoma
Salivary gland–type tumors

- **Squamous cell & Small cell carcinomas have the strongest association with Smoking.**
- **Adenocarcinoma is the most common primary tumor arising in men & women, in never-smokers, and in individuals younger than 45 years of age.** (if these people developed lung carcinoma, most probably it is ADENOCARCINOMA).

Clinically, physicians tend to sort lung tumors into separate groups, why? To simplify their management and because all tumors in each group have the same prognosis and behaviour. So, we ended up with 2 groups for lung tumor: SCLC & NSCLC.

- **Old designation to small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC).**
- **NSCLC includes adenocarcinoma, squamous and large cell carcinoma, and large cell neuroendocrine carcinomas.**

SCLC is the most aggressive histologic type of lung tumors. **Why?** Look at the table below which shows a comparison between SCLC & NSCLC. It will answer you.

SCLC	NSCLC mainly adenocarcinoma and squamous cell carcinoma
virtually all cases have metastasized by the time of diagnosis. it means whatever the size of the tumor at the time of diagnosis; 1cm/2cm/10cm, it has already been metastasized.	more likely to be Resectable
not curable by surgery	Cured by surgery, Respond poorly to chemotherapy
best treated by chemotherapy, +/ - radiation therapy	targeted therapy nowadays for adenocarcinoma and SqCC

ETIOLOGY AND PATHOGENESIS

- **Accumulation of genetic abnormalities after exposure to carcinogens resulting in a stepwise accumulation of driver mutations >>> transformation of benign progenitor cells in the lung into neoplastic cells having all the hallmarks of cancer.** What are these hallmarks? ability to grow without signals, avoiding/escaping the apoptosis, forming its own blood vessel.
- Keep in your mind that the individuals genetics also play a role in determining if the patient who was exposed to carcinogens will develop genetic abnormalities or not. So not all who exposed to carcinogens will develop genetic abnormalities and then cancers. Again, it depends on the **genetic profile**.

GENETIC ABNORMALITIES: below are the most common abnormalities:

1. **Inactivation of tumor suppressor genes located on chromosome 3 (3p) as an early event.**
2. **mutations in TP53 tumor suppressor gene and KRAS oncogene as a late event.**
3. **mutations that activate the epidermal growth factor receptor (EGFR) >>> (adenocarcinomas arising in nonsmoking women).**

CARCINOGENS:

- **cigarette smoking**
- **environmental carcinogens**

Let's discuss them briefly:

CIGARETTE SMOKING:

- **80% in active smokers or those who stopped recently.**
- **linear correlation between the frequency of lung cancer and pack-years of cigarette smoking.** A person start smoking at age 16 isn't the same case of another person who start smoking at age 40.
- **Habitual heavy smokers (two packs a day for 20 years) have 60X more risk than nonsmokers.** So how much you smoke per day is also significant.
- **For unclear reasons, women are more susceptible to carcinogens in tobacco smoke than men**. Hope this point is clear to you.
- **Although smoking cessation decreases the risk over time, it never returns to baseline levels.** (if you stop smoking, your lungs are not the same as a person who never smoke, you may develop a silent genetic mutations that doesn't result in cancer due to your previous

smoking. But after you stop smoking, you'll decrease the risk of accumulation of these mutations that if accumulate will end up with cancer لا سمح الله

- **smoking of pipes, cigars and passive smoking increases the risk.**
- **The long-term effects of electronic cigarette "vaping" are still unknown,** you can do a research for that!
- **Chewing tobacco causes oral cancers and can lead to nicotine addiction.**
- **Secondhand smoke, or environmental tobacco smoke: increased the risk.**

- **lung cancer develops in only 10% to 15% of smokers>>>Because the mutagenic effect of carcinogens in smoke is modified by genetic variants.** we've discussed this point before, keep going!

ENVIRONMENTAL CARCINOGENS:

Occupational exposures to some environmental carcinogens may sometimes be responsible for lung cancer all by themselves, e.g:

- **uranium mines**
- **work with asbestos**
- **inhalation of dusts containing arsenic, chromium, nickel, or vinyl chloride.**

- **Some invasive adenocarcinomas of the lung arise through: an atypical adenomatous hyperplasia >>> adenocarcinoma in situ >>> invasive adenocarcinoma.** Explanation below

There is a sequence for developing mostly any cancer, starting with pre-invasive/precursor lesions which are: the **atypical adenomatous hyperplasia** that can transform to **adenocarcinoma in situ.**

These precursor lesions may or may not progress and develop **invasive adenocarcinoma.**

We have mentioned briefly that there are **FOUR MAJOR HISTOLOGIC TYPES OF CARCINOMAS OF THE LUNG:**

1. Adenocarcinoma (50%)

2. Squamous Cell Carcinoma (20%)

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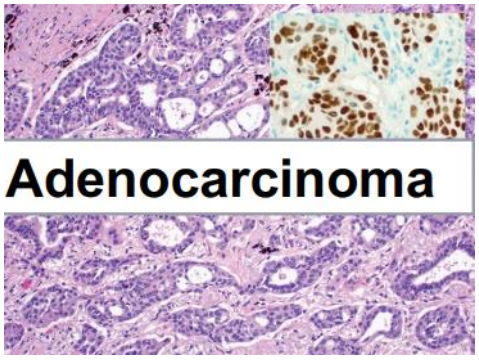
Let's focus on each one of them now:

1.ADENOCARCINOMA



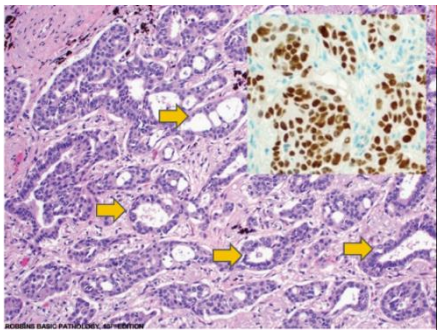
The most common type of lung cancer.

- **usually peripherally located,** near the pleura or on the periphery of the lung.
- **grow slowly**
- **form smaller masses**
- **tend to metastasize widely at an early stage.**

Morphology, microscopic:

- **Variety of growth patterns,** these patterns are as follows:
  - **Including acinar (gland-forming), papillary** (over fibrovascular cores)**, mucinous** (produce mucin)**, and solid types.**

The image below shows adeno/carcinoma, how you could know that?



Adeno=the microscopic image shows proliferating gland-like structures (Acini). look at the yellow arrows.

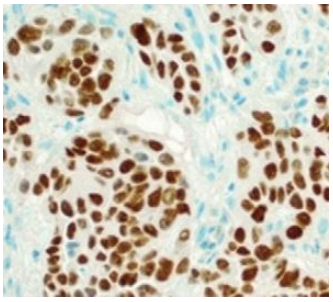
Carcinoma=malignant epithelial cells (dysplasia), characterized by being hyperchromatic, pleomorphic, they do not respect the boundaries between each other, invasive and surrounded by Desmoplastic reaction (a reaction that is done by our bodies in response to tumor invasion consists of fibrosis and lymphocytic infiltration), also as you can see the alveolar architecture is lost.

- Adenocarcinoma is graded into well-differentiated, moderate differentiated and poorly differentiated.

The well-differentiated tumor is similar to the cell of origin in term of morphology and function.

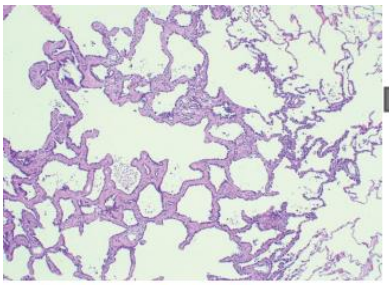
The poorly differentiated tumor has small areas of differentiation that are difficult to visualize.

In histopathology lab we use **TTF-1** immunostain, that detect a certain antigen on tumors of lung origin by highlighting their nucleus with brown color. look to the right.

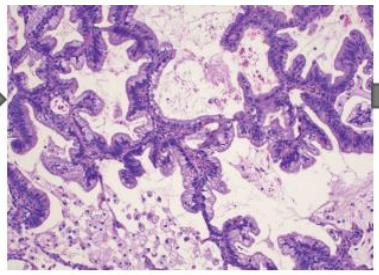


So, if the test of TTF-1 immunostain was positive, this indicates a primary pulmonary adenocarcinoma.

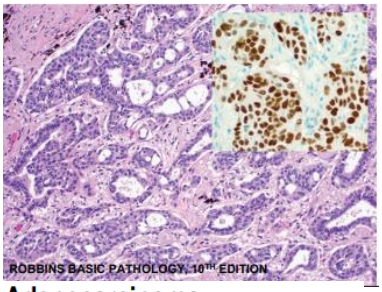
As we said, most tumors pass through a sequence of developing (2 precursor lesions & 1 invasive lesion), and that's what happens in adenocarcinoma:



atypical adenomatous hyperplasia (AAH)



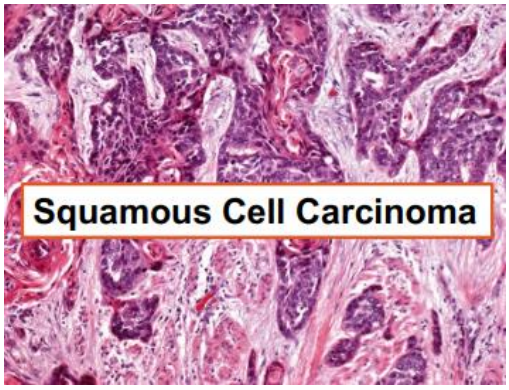
adenocarcinoma in situ (AIS)



Adenocarcinoma, minimally invasive or invasive

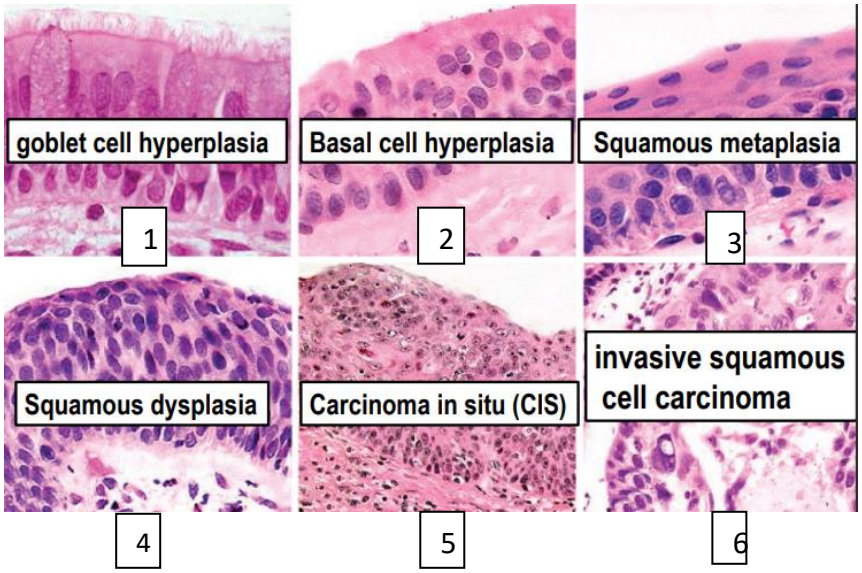
small precursor lesion **(≤5 mm)** characterized by dysplastic pneumocytes lining alveolar walls that are mildly fibrotic and show mild atypia.	diameter of **<3 cm**, composed entirely of dysplastic cells growing along pre-existing alveolar septa which serve as a scaffold.	**microinvasive adenocarcinoma:** Tumors **(≤3 cm)** with a small invasive component **(≤5 mm)**
demonstrating nuclear hyperchromasia, pleomorphism, and prominent nucleoli. Alveolar architecture is still preserved with no invasion.	growth along preexisting structures, and preservation of alveolar architecture. The basement membrane still well-respected.	**Invasive adenocarcinoma:** invasive malignant epithelial tumor with glandular differentiation or mucin production by the tumor cells. A tumor of any size with **an area of invasion >5 mm**
can be single or multiple	No destruction of alveolar architecture	
	No stromal invasion	
	No desmoplasia	

2.SQUAMOUS CELL CARCINOMAS



- **More common in men.**
- **Closely correlated with smoking history.**
- **Arise Centrally in major bronchi, near the hilum and eventually spread to local hilar nodes and outside the thorax.**
- **Large lesions may undergo central necrosis, giving rise to cavitation.**
- **Preneoplastic lesions,** that may precede the invasive squamous cell carcinoma:
  - **squamous metaplasia or dysplasia in the bronchial epithelium >>> carcinoma in situ >>> Squamous cell carcinoma.**
  - **the lesion is asymptomatic until reaches a symptomatic stage when it begins to obstruct the lumen of a major bronchus, +/- atelectasis and infection.**
- **Ranges from Well differentiated squamous cell neoplasms showing keratin pearls and intercellular bridges to Poorly differentiated neoplasms with only minimal residual squamous cell features.**

Upper 3 images show adaptive mechanisms of the airways due to exposure to injury in order to



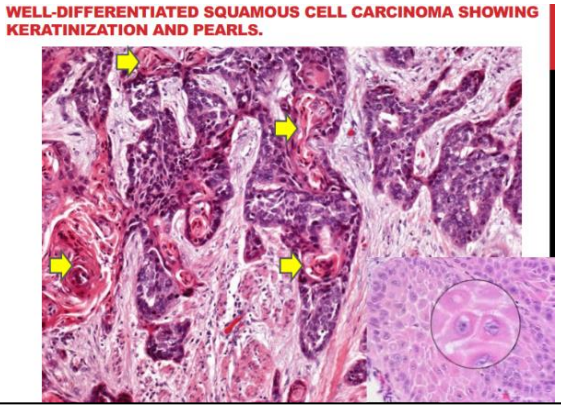
deal with the new environment, all these changes are reversible.

But when some cells start to show atypia, loss of polarity, pleomorphism, variations in nuclear & cellular size and shape, this is called >>> squamous dysplasia **image 4.** (This is the 1st precursor lesion)

Image 5 all the cells show the feature of malignancy but no invasion of the basement membrane>>Carcinoma in situ.(2nd precursor lesion)

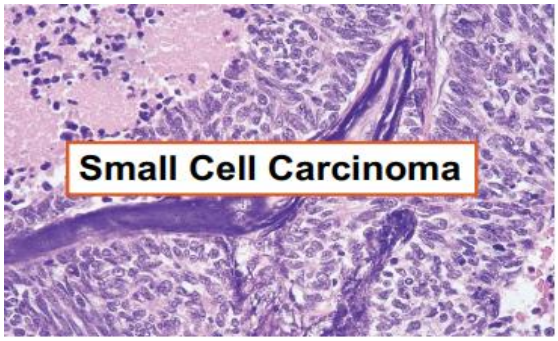
Image 6 the malignant cells infiltrate the basement membrane and the underlying structures. Invasive squamous cell carcinoma .

Squamous cell carcinoma, centrally located near the left main bronchus, shows some necrosis and obstruction of the bronchus.



Shows all features of malignancy, infiltration the underlying tissue surrounded by desmoplastic Rxn. Yellow arrows show keratin production called **keratin pearls**. And the image in the right-down corner shows **intercellular bridges** connects between cells. These 2 bolded signs indicate for well-differentiated squamous cell carcinoma. In poorly-differentiated it's difficult to see them.

3.SMALL CELL LUNG CARCINOMAS (SCLC)

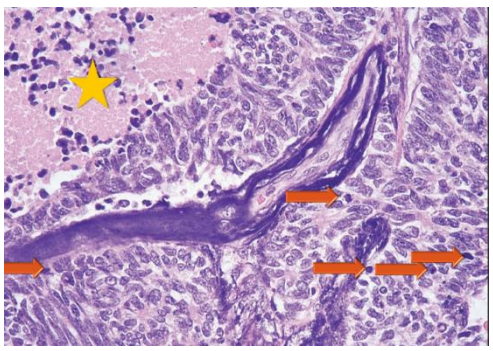


- **the most aggressive lung tumors, metastasizing widely; By the time of diagnosis, most will have metastasized to hilar and mediastinal lymph nodes.**
- **may arise in major bronchi or in the periphery of the lung.**
- **No known pre-invasive phase.**
- **In the 2015 WHO Classification, SCLC is grouped together with large cell neuroendocrine carcinoma.**

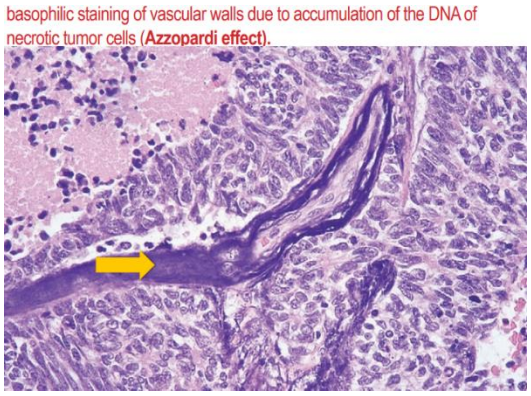
➢ **Morphology:**

- Grossly (macroscopically)**, it appears pale gray tumor.**

- Microscopically**, Small tumor cells: round to fusiform, scant cytoplasm** (rim of cytoplasm), **finely granular chromatin** (stipple chromatin) giving **a salt & pepper appearance.**
- **Cells are twice the size of resting lymphocytes.** This size is considered small in histology.
- **Frequent mitotic figures**
- **Necrosis invariably present, can be extensive.**



Nucleus is fusiform, little rim of cytoplasm, stipple chromatin (salt & pepper appearance), frequent mitosis orange arrows. Area of necrosis is shown by a yellow star.



yellow arrow shows basophilic staining of the blood vessels walls due to DNA accumulation of necrotic cells, **Azzopardi effect.**

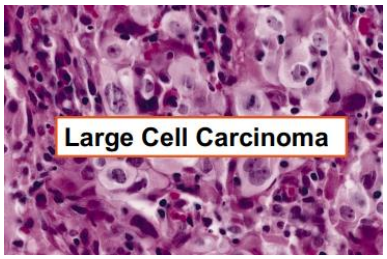
MORPHOLOGY:

• Fragile tumor cells with "crush artifact" in small biopsy specimens.

• Nuclear molding, due to close apposition of tumor cells that have scant cytoplasm so tend to appear fused with each other**.**

• Express neuroendocrine markers, We use these marker to highlight the tumor cells in the lab.

4.LARGE CELL CARCINOMAS

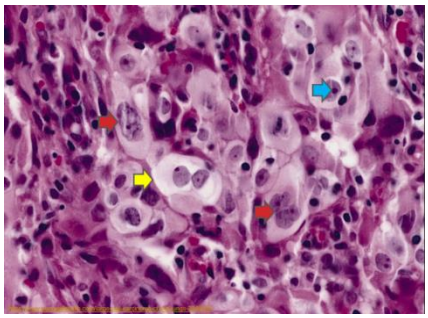


• Are undifferentiated malignant epithelial tumors.

• Lack cytologic features of small cell carcinoma and have no glandular or squamous differentiation.

• Large nuclei, prominent nucleoli, and a moderate amount of cytoplasm.

How to recognize this type? By excluding the other types.



The microscopic image shows no keratin, no glands, no papillae, no mucin, no signs of differentiation, it is just a sheet of pleomorphic cells, nuclei are large with irregular nuclear membrane (red arrows), bi-nucleated cells (yellow arrows).

Mixed patterns: (more than one of the 4 histologic types of lung carcinoma develop together)

- **Examples:**

Adenosquamous carcinoma (the most common one), mixed adenocarcinoma, and mixed **small cell carcinoma.**

- **4% to 5% of all lung carcinomas.**

Best Wishes