

Lung Cancer

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 - ▶ Treatment
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Definitions

The term lung cancer, or bronchogenic carcinoma, refers to malignancies that originate in the airways or pulmonary parenchyma. Approximately 95 percent of all lung cancers are classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). This distinction is essential for staging, treatment, and prognosis. Other cell types comprise approximately 5 percent of malignancies arising in the lung.

Epidemiology

- ▶ Lung cancer is the leading cause of cancer deaths worldwide in both men and women. Around 1953, lung cancer became the most common cause of cancer deaths in men, and in 1985, it became the leading cause of cancer deaths in women.
- ▶ The relative incidence of adenocarcinoma has risen dramatically, and there has been a corresponding decrease in the incidence of other types of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).
- ▶ Non-small cell lung cancer (NSCLC) accounts for the majority (approximately 85 percent) of lung cancers with the remainder as mostly small cell lung cancer (SCLC).

Risk Factors

▶ Smoking


Account for approximately 90 percent of all lung cancers.

The risk of developing lung cancer for a current smoker of one pack per day for 40 years is approximately 20 times that of someone who has never smoked. Factors that increase the risk of developing lung cancer in smokers include the extent of smoking and exposure to other carcinogenic factors, such as asbestos.

In individuals who do quit smoking, the risk of developing lung cancer falls compared with those who continue to smoke; the benefit is greatest in those who stop by age 30. Despite stopping smoking, the risk for lung cancer continues to rise with age at a faster rate than those who never smoked.

▶ Radiation therapy can increase the risk of a second primary lung cancer in patients who have been treated for other malignancies.

▶ Environmental toxins: secondhand smoke, asbestos, radon, metals (arsenic, chromium, and nickel), ionizing radiation, and polycyclic aromatic hydrocarbons.

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- ▶ **Pulmonary fibrosis**: Sevenfold in patients with pulmonary fibrosis. This increased risk appears to be independent of smoking.
 - ▶ **HIV infection**
 - ▶ **Genetic factors** – Genetic factors can affect both the risk for and prognosis from lung cancer.
 - ▶ **Alcohol**
 - ▶ **Dietary factors**: Various dietary factors (antioxidants, cruciferous vegetables, phytoestrogens) may reduce the risk of lung cancer, but the role of these factors is not well established.

SCREENING

- ▶ Chest radiography and sputum cytology had NOT been shown to reduce mortality from lung cancer.

- ▶ CT scan:

National Lung Screening Trial that compared CT screening with chest radiograph. This trial demonstrated a **20 percent decrease in lung cancer mortality in heavy smokers** who were screened annually for three years. For age 55 to 77 who have no symptoms of lung cancer, have a 30 pack-year smoking history, and if they have quit, have done so within 15 years.

PATHOLOGY

- ▶ NSCLC and SCLC
- ▶ Separation of adenocarcinoma and squamous cell carcinoma is important in determining optimal therapy for stage IV disease. Subtype analysis of NSCLC epidermal growth factor receptors (EGFR), anaplastic lymphoma kinase (ALK), and c-ROS oncogene 1 (ROS1) mutations are not only identifiable but their targeted treatment results in responses better than that with standard chemotherapy

EGFR gene: 15 to 30 percent of non-Asian patients and 30 to 60 percent of Asian patients .

The ALK gene mutations present in 2 to 7 percent of patients with NSCLC.

- ▶ Checkpoint inhibitors promote recognition of cancer cells as foreign cells by the immune system and reverse the tumor-driven inhibition of the immune system that promotes tumor growth. Clinical trials using antibodies to programmed death receptor 1 and programmed death ligand 1 have shown significant survival benefit in advanced NSCLC

Tumor type	Changes from 2004 WHO classification	2015 variants (if applicable)
Adenocarcinoma	<ul style="list-style-type: none"> •Discontinuation of terms bronchioalveolar carcinoma, mixed subtype adenocarcinoma, clear cell and signet ring adenocarcinoma (these subtypes are descriptive features in the 2015 system), and mucinous cystadenocarcinoma (these tumors are reclassified as colloid adenocarcinomas). •Addition of adenocarcinoma in situ and minimally invasive adenocarcinoma. •Classification of invasive adenocarcinoma according to predominant subtype. •Introduction of the term lepidic for a noninvasive component of an invasive adenocarcinoma. 	<ul style="list-style-type: none"> •Lepidic •Acinar •Papillary •Micropapillary •Solid •Invasive mucinous (mixed invasive mucinous and non-mucinous) •Colloid •Fetal •Enteric •Minimally invasive •Preinvasive (atypical adenomatous hyperplasia, adenocarcinoma in situ [non-mucinous and mucinous])
Adenosquamous cell carcinoma	•No significant changes.	N/A
Squamous cell carcinoma	<ul style="list-style-type: none"> •Papillary, clear cell, small cell, and basaloid carcinoma have been replaced. •Clear cell change is now regarded as a cytologic feature. 	<ul style="list-style-type: none"> •Keratinizing •Non-keratinizing •Basaloid
Large cell carcinoma	<ul style="list-style-type: none"> •The following have been reclassified from "large cell carcinomas" to other subgroups: basaloid carcinoma is a subgroup of squamous cell carcinomas, large cell neuroendocrine carcinoma is a neuroendocrine carcinoma, and lymphoepithelioma-like carcinoma belongs to "other and unclassified carcinomas." •Clear cell and rhabdoid are now descriptive features rather than subtypes. 	N/A
Sarcomatoid carcinoma	•No significant changes, although molecular testing now recommended.	<ul style="list-style-type: none"> •Pleomorphic carcinoma •Spindle cell carcinoma •Giant cell carcinoma •Carcinosarcoma •Pulmonary blastoma
Neuroendocrine carcinoma	•Previously, small cell and large cell neuroendocrine tumors were in different categories and are now grouped together.	<ul style="list-style-type: none"> •Small cell carcinoma •Large cell neuroendocrine carcinoma •Carcinoid (typical and atypical)
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	•No significant changes.	N/A

CLINICAL MANIFESTATIONS

- ▶ Symptoms and signs from the tumor itself (both local and systemic symptoms and signs)
- ▶ Symptoms and signs from metastasis
- ▶ Symptoms and signs from paraneoplastic syndromes.

The majority of patients with lung cancer have advanced disease at clinical presentation non-specific symptoms → bcs there are no pain fibers inside the lungs

Symptom	Patients (percent)
* Cough <i>acute / chronic</i>	74-45
* Weight loss	68-46
* Dyspnea	58-37
Chest pain	49-27
Hemoptysis <i>قريب من الـ airways داخل على trachea</i>	29-27
Bone pain <i>if posterior & close to the vertebra (even no mets)</i>	21-20
* Hoarseness <i>حسب موقعه</i>	18-8

Clinical presentation from the tumor itself (both local and systemic)

- ▶ **Cough:** 50 to 75 percent of patients. Most in patients with central tumors (squamous and small)
- ▶ **Hemoptysis:** Hemoptysis is reported by 20 to 50 percent of patients.
- ▶ **Chest pain:** Chest pain is present in approximately 20 to 40 percent of patients. From mediastinal, pleural, or chest wall extension. Obstructive pneumonitis or a pulmonary embolus related to a hypercoagulable state may also cause chest pain.
- ▶ **Dyspnea:** 25 to 40 percent of cases. Dyspnea may be due to extrinsic or intraluminal airway obstruction, obstructive pneumonitis or atelectasis, lymphangitic tumor spread, tumor emboli, pneumothorax, pleural effusion, or pericardial effusion with tamponade.
- ▶ **Bronchorrhea** or cough productive of large volumes of thin, mucoid secretions may be a feature of mucinous adenocarcinoma and usually indicates advanced disease.

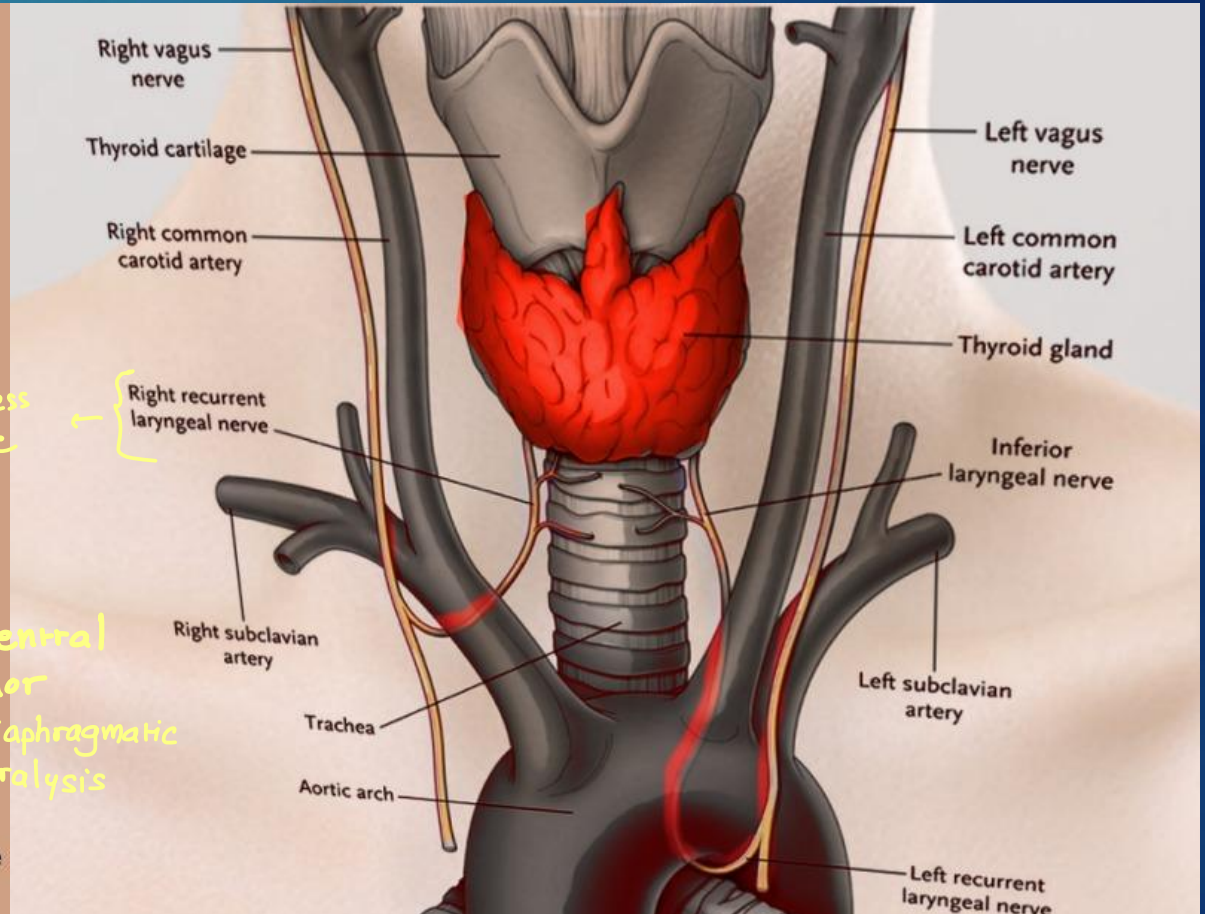
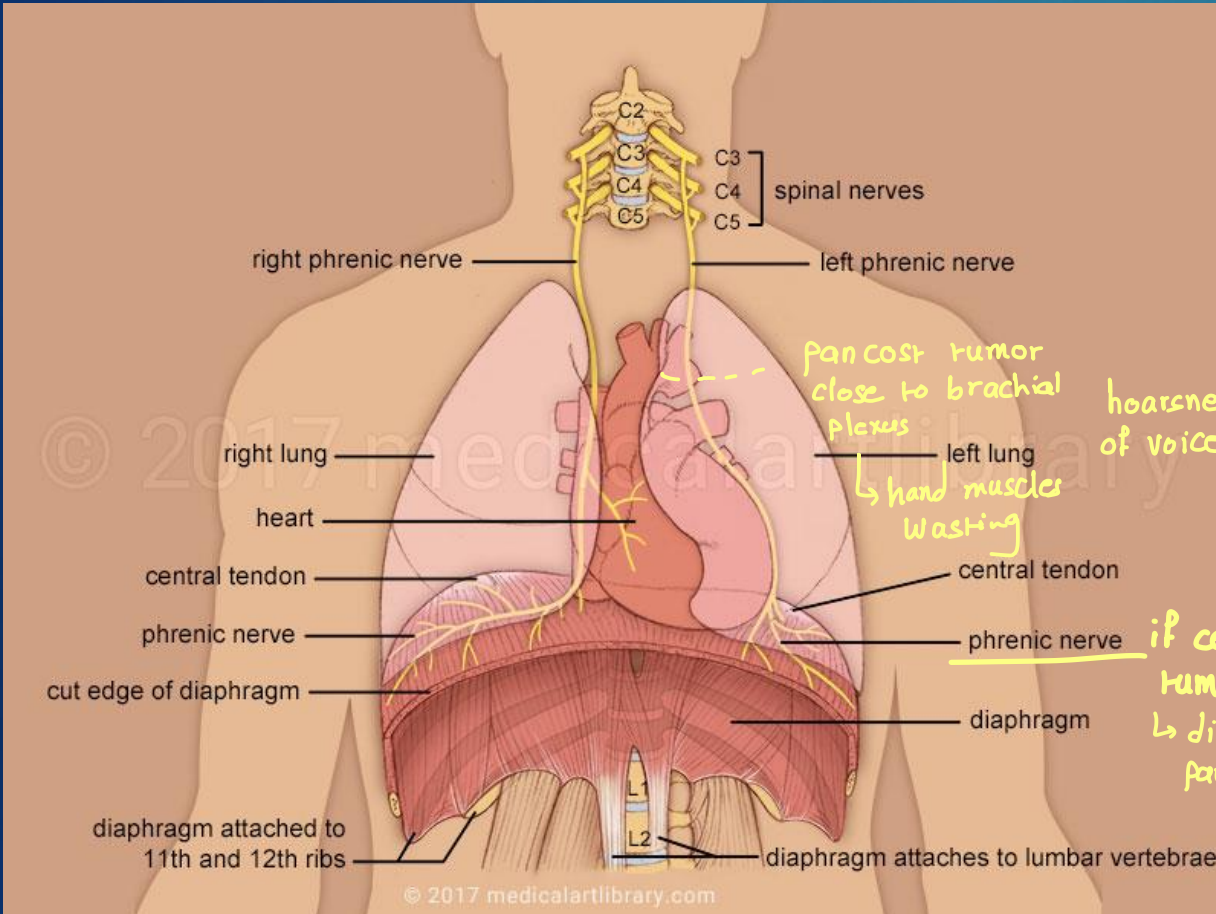
▶ Post-obstructive pneumonia.

▶ Bronchiectasis: Slow-growing neoplasms such as carcinoid tumor or hamartoma are more likely to present with bronchiectasis.

▶ Unilateral paralysis of the diaphragm may be due to damage of the phrenic nerve. Patients may be asymptomatic or report shortness of breath.

▶ Pancoast syndrome can present with ¹ pain in the shoulder, ² Horner syndrome, ³ bony destruction, and ⁴ atrophy of hand muscles.

▶ Hoarseness of voice from vocal cord paralysis. The differential diagnosis of persistent hoarseness in a smoker includes both laryngeal cancer and lung cancer. In patients with lung cancer, this is due to malignancy involving the recurrent laryngeal nerve along its course under the arch of the aorta and back to the larynx.



- ▶ **Pleural involvement:** subpleural tumor → can present as pleuritic chest pain

Can cause dyspnea and cough, approximately one-fourth of patients who have lung cancer and pleural metastases are asymptomatic. During the course of their disease, approximately 10 to 15 percent of patients who have lung cancer will have malignant pleural effusions.

- ▶ **Superior vena cava syndrome:**

Sensation of fullness in the head and dyspnea. Cough, pain, and dysphagia are less frequent. Physical findings include dilated neck veins, a prominent venous pattern on the chest, facial edema, and a plethoric appearance. The chest radiograph typically shows widening of the mediastinum or a right hilar mass. CT can often identify the cause, level of obstruction, and extent of collateral venous drainage. The SVC syndrome is more common in patients with SCLC than NSCLC.

- ▶ **Weight loss**

may be due to release of cytokines
in metastatic cancer mostly

Symptoms and signs from metastasis

▶ Liver:

Uncommon.

Asymptomatic liver metastases may be detected at presentation by liver enzyme abnormalities, CT, or positron emission tomography (PET).

*▶ Bone *with pain mostly*

Symptomatic.

Pain in the back, chest, or extremity, and elevated levels of serum alkaline phosphatase are usually present in patients who have bone metastasis.

The serum calcium may be elevated due to extensive bone disease. Approximately 20 percent of patients with NSCLC have bone metastases on presentation and more in SCLC.

An osteolytic radiographic appearance is more frequent than an osteoblastic one, and the most common sites of involvement are the vertebral bodies.

* Chest lymph nodes

*▶ Adrenal detected on imaging

The adrenal glands are a frequent site of metastasis but such metastases are only rarely symptomatic.

loss of more than 90% of adrenal to have symptoms which is unlikely

*▶ Brain

Neurologic manifestations of lung cancer include metastases and paraneoplastic syndromes.

Symptoms from central nervous system metastasis are similar to those with other tumors and include headache, vomiting, visual field loss, hemiparesis, cranial nerve deficit, and seizures.

↑ ICP

In patients with NSCLC, the frequency of brain metastasis is greatest with adenocarcinoma and least with squamous cell carcinoma.

In patients with SCLC, metastasis to brain is present in approximately 20 to 30 percent of patients at presentation.

Symptoms and signs from paraneoplastic syndromes.

mostly with small cell lung CA.

Paraneoplastic phenomena: Paraneoplastic effects of tumor are remote effects that are **not related** to the direct invasion, obstruction, or metastasis.

► **Hypercalcemia**:

Hypercalcemia in patients with lung cancer may arise from a **bony metastasis or less commonly tumor secretion of a parathyroid hormone-related protein (PTHrP), calcitriol or other cytokines, including osteoclast activating factors.**

More in **squamous cell carcinoma** but seen frequently with the other types.

Most patients with hypercalcemia have **advanced disease (stage III or IV) and a median survival of a few months.**

Symptoms: anorexia, nausea, vomiting, constipation, lethargy, polyuria, polydipsia, and dehydration. Confusion and coma are late manifestations as are renal failure and nephrocalcinosis.

Treatment: hydration, calcitonin and bisphosphonate.

► **SIADH secretion** → hyponatremia & its manifestations → nausea, vomiting

SIADH is frequently caused by SCLC. Approximately 10 percent of patients who have SCLC exhibit SIADH.

SCLC accounts for approximately 75 percent of all malignancy-related SIADH.

The severity of symptoms is related to the degree of hyponatremia and the rapidity of the fall in serum sodium.

Symptoms include anorexia, nausea, and vomiting. Cerebral edema can occur when the onset of hyponatremia is rapid. Symptoms caused by cerebral edema may include irritability, restlessness, personality changes, confusion, coma, seizures, and respiratory arrest.

The treatment of SIADH focuses on treating the malignancy. In the majority of patients with SCLC, the hyponatremia will resolve within weeks of starting chemotherapy.

↳ may not respond to treatment

► Neurologic

Lung cancer is the most common cancer associated with paraneoplastic neurologic syndromes, typically these are associated with SCLC.

Paraneoplastic neurologic syndromes are thought to be **immune-mediated**, and autoantibodies have been identified in a number of instances.

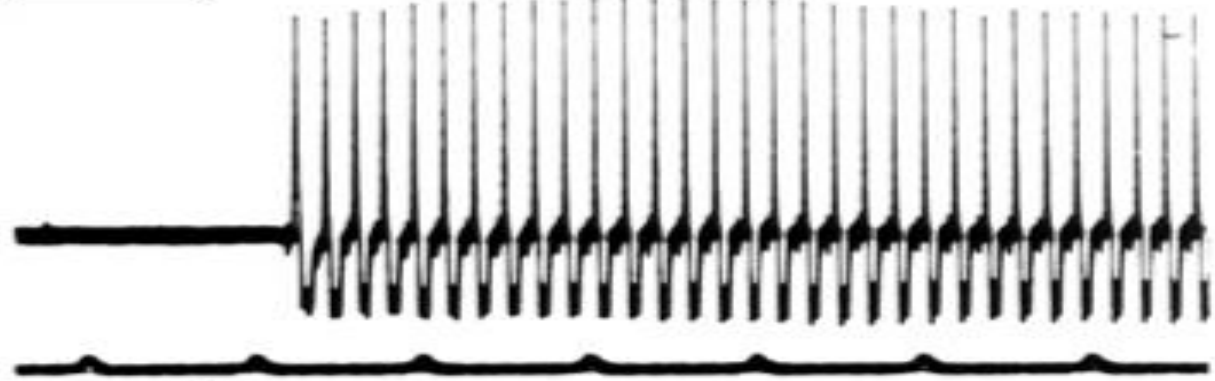
Lambert-Eaton myasthenic syndrome (LEMS), cerebellar ataxia, sensory neuropathy, limbic encephalitis, encephalomyelitis, autonomic neuropathy, retinopathy, and opsomyoclonus.

The most common of these is LEMS, which may be seen in approximately 3 percent of patients with SCLC.

As many as 70 percent of patients who have SCLC and an associated paraneoplastic neurologic syndrome have limited stage disease.

Paraneoplastic neurologic syndromes generally do not improve with immunosuppressive treatment. However, symptoms may stabilize with response of the underlying neoplasm to treatment.

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MG



بتقسه مع ال activity

بتقبه مع ال activity

► Hematologic manifestations

Anemia: Contribute to fatigue and dyspnea.

Leukocytosis: Thought to be due to overproduction of granulocyte-colony stimulating factor. Leukocytosis in association with lung cancer is associated with a poor prognosis and has also been associated with hypercalcemia.

Common

Thrombocytosis – Thrombocytosis is common and maybe present in as many as 14 percent of patients with lung cancer at presentation. Thrombocytosis at presentation has been identified as an independent predictor of shortened survival.

Eosinophilia: Eosinophilia in tissue or blood is rare but has been reported in patients with large cell carcinoma.



▶ Hypercoagulable disorders

Trousseau syndrome (migratory superficial thrombophlebitis)

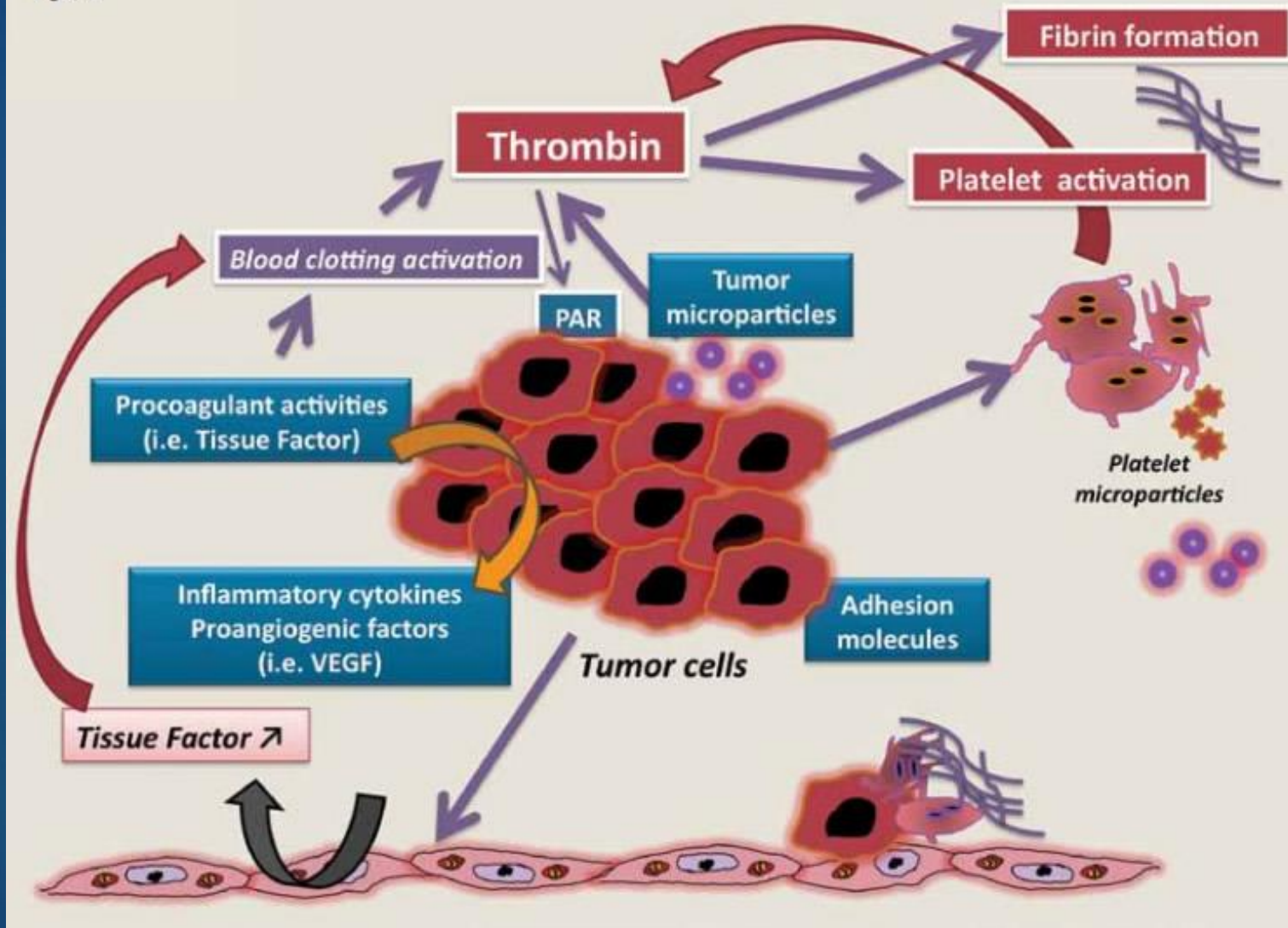
Deep venous thrombosis and thromboembolism

Disseminated intravascular coagulopathy

Thrombotic microangiopathy

Nonthrombotic microangiopathy

Figure



▶ Hypertrophic osteoarthropathy

Hypertrophic pulmonary osteoarthropathy (HPO) is defined by the presence of clubbing and periosteal proliferation of the tubular bones associated with lung cancer or other lung disease.

Clinically, HPO is characterized by a symmetrical, painful arthropathy that usually involves the ankles, knees, wrists, and elbows. The metacarpal, metatarsal, and phalangeal bones may also be involved.

A radiograph of the long bones (ie, tibia and fibula) shows characteristic periosteal new bone formation in patients with HPO.

The symptoms of HPO may resolve after tumor resection.

▶ Dermatomyositis and polymyositis

These inflammatory myopathies can be the presenting symptom in patients with lung cancer or can develop later in the course of disease. In addition to lung cancer, other frequent primary sites associated with these disorders include the ovary, cervix, pancreas, bladder, and stomach.

▶ Cushing syndrome with small cell lung cancer

Ectopic production of adrenal corticotropin (ACTH) can cause Cushing syndrome. Patients typically present with muscle weakness, weight loss, hypertension, hirsutism, and osteoporosis. Hypokalemic alkalosis and hyperglycemia are usually present.

Cushing syndrome is relatively common in patients with SCLC and with carcinoid tumors of the lung.

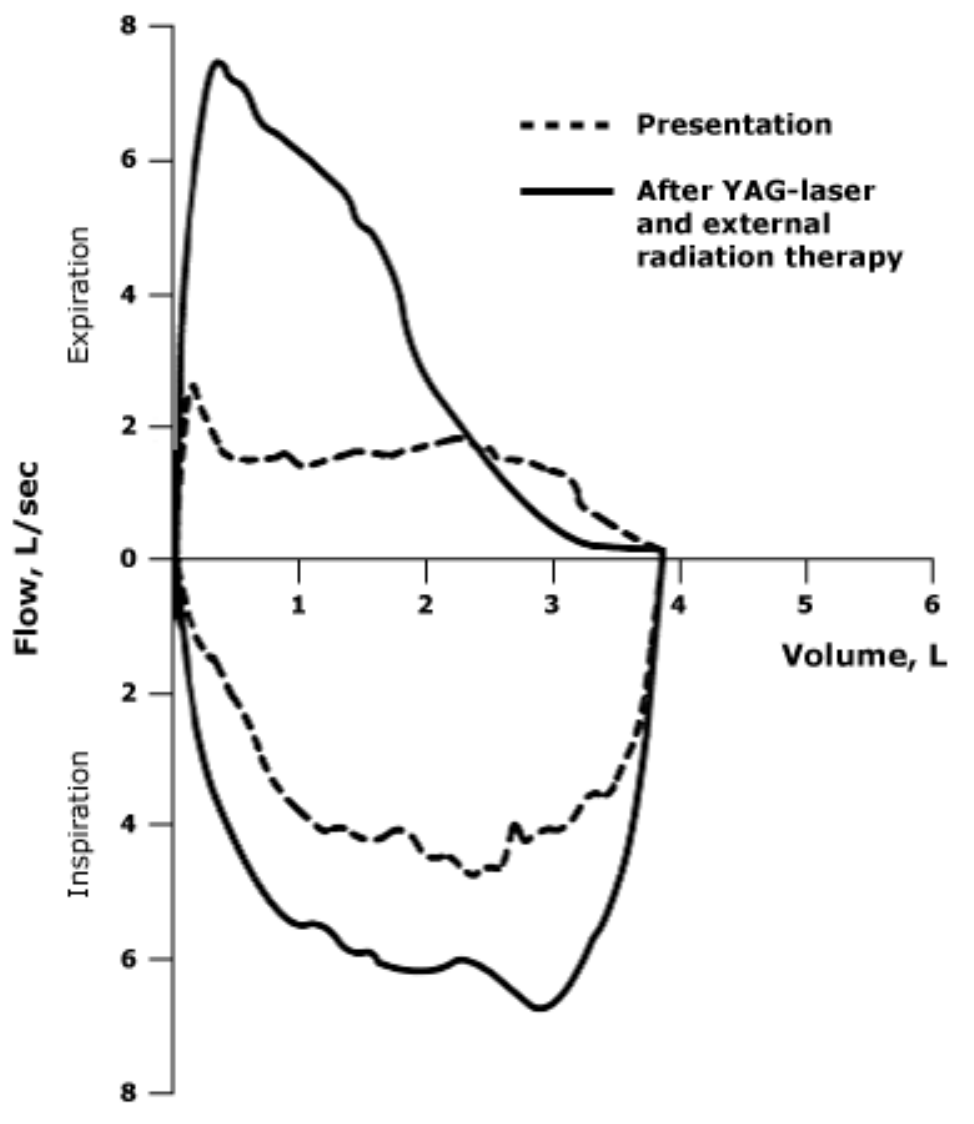
In Clubbing pts. → hypertrophic pulmonary osteoarthropathy



superior vena cava syndrome



Lung cancer → one of the causes of clubbing

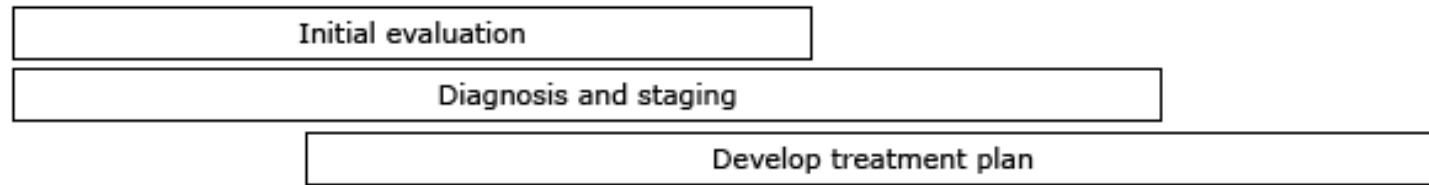


PFT

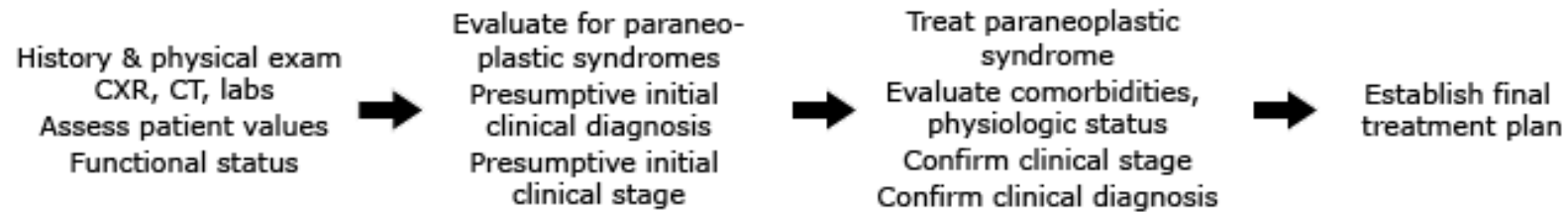
GENERAL GOALS AND TIMING OF EVALUATION

- ▶ Clinical extent and stage of disease
- ▶ Optimal target site and modality for the first tissue biopsy
- ▶ Specific histological subtype
- ▶ Presence of comorbidities, secondary complications, and paraneoplastic syndromes that influence treatment options and outcome

Cognitive processes



Clinical processes



Organizational and team processes



INITIAL EVALUATION

► Clinical:

Every patient with suspected lung cancer should undergo a thorough history and physical exam. Diagnostic tests should be directed to symptoms.

Examples:

Hip pain may prompt plain radiographs of the hip.

Horner's syndrome (ipsilateral ptosis, anhidrosis, and miosis) may prompt an MRI of the superior sulcus. tumor compressing the sympathetic chain

Neurologic symptoms may prompt imaging of the brain or spinal cord.

Hypotension with sinus tachycardia and pulsus paradoxus may prompt an echocardiogram to evaluate for malignant pericardial effusion.

► Laboratory

Complete blood count

Electrolytes *SIADH*

Calcium *hypercalcemia of malignancy*

Alkaline phosphatase *↑ with bone disease + liver mets*

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total bilirubin

Creatinine *base line before starting treatment*

Albumin and lactate dehydrogenase.

- Liver function test abnormalities possibly due to liver metastasis should prompt evaluation of the liver with liver-directed imaging.
- Calcium elevation should prompt additional imaging for bone metastasis and/or a work up for a paraneoplastic manifestation of the primary tumor.
- Elevation of the alkaline phosphatase could be due to liver or bone metastases and should prompt measurement of gamma glutamyl transpeptidase (GGT). When GGT is normal an evaluation for bone metastasis is indicated; when abnormal, an evaluation for liver metastases is indicated.

 **Radiographic**

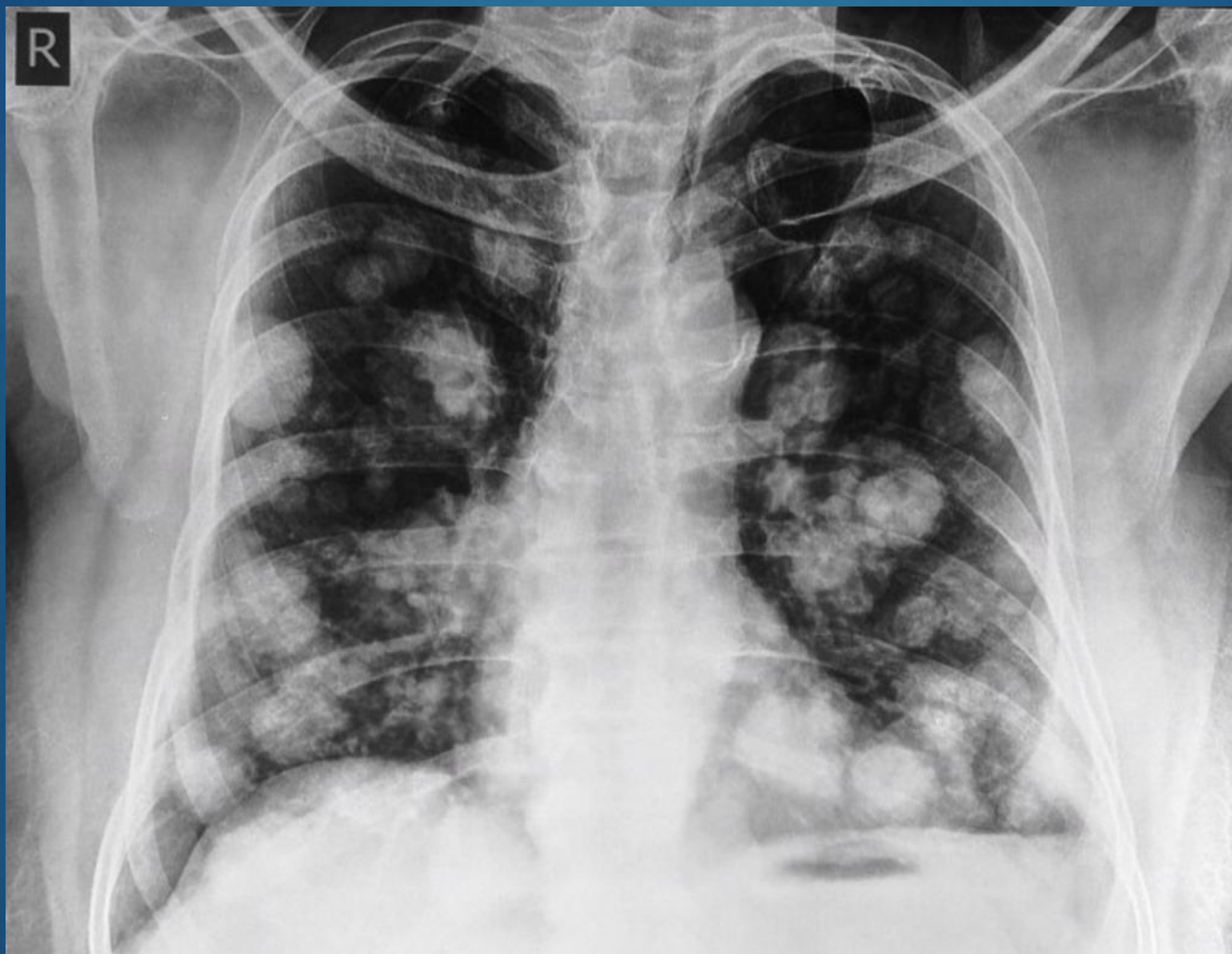
The clinical staging of patients with suspected lung cancer starts with radiographic imaging. Determining the highest radiographic stage prior to biopsy facilitates the selection of a modality that optimizes tissue sampling for diagnosis.

CXR

- ▶ Chest radiograph demonstrating a new or enlarging focal lesion, a pleural effusion, pleural nodularity, enlarged hilar or paratracheal nodes, endobronchial lesion, post-obstructive pneumonia or segmental or lobar atelectasis.
- ▶ Findings suggestive of cancer or cancer-related complications on chest radiograph should be further evaluated with CT chest.



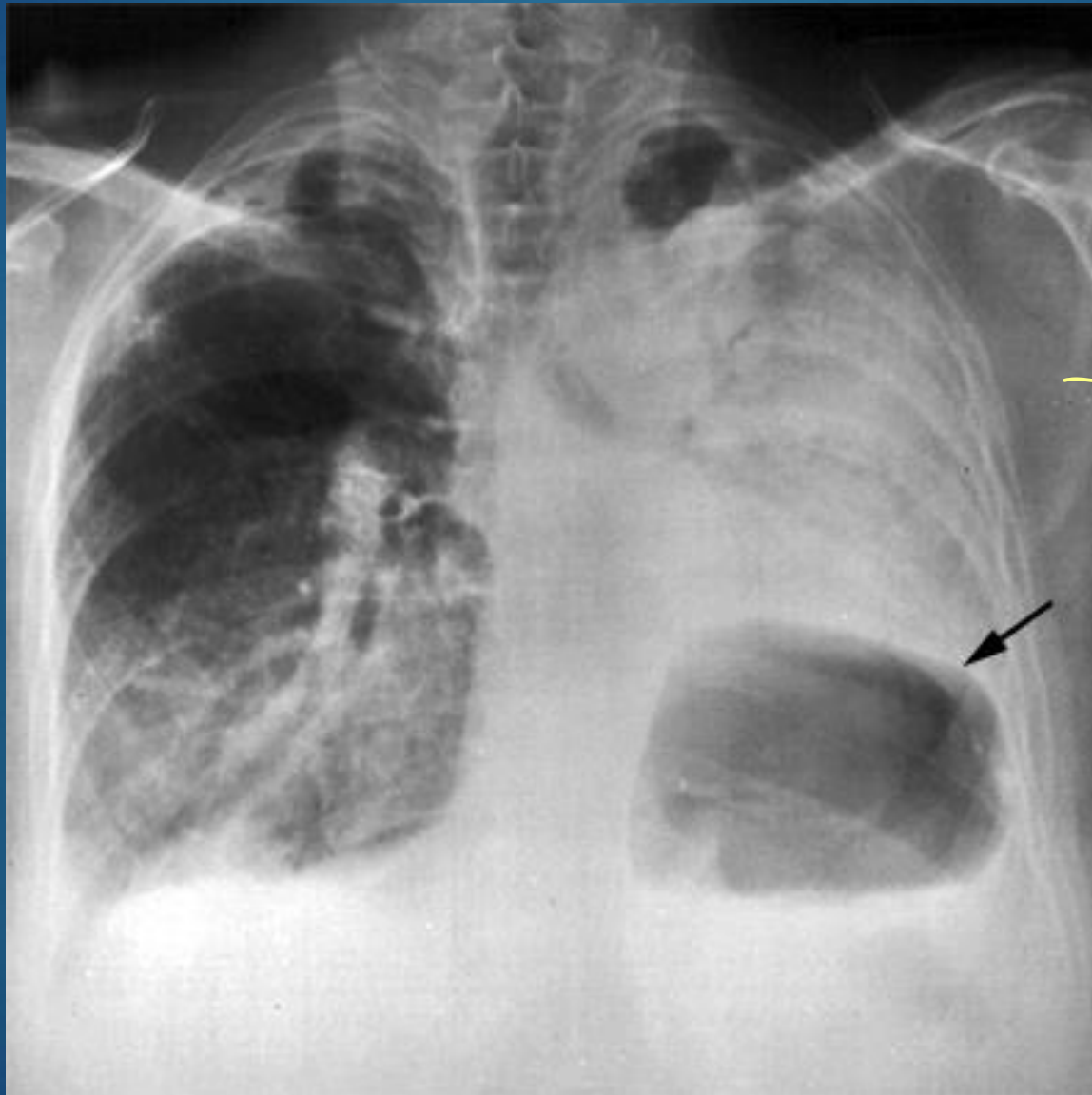
Central mass



cannon balls

↳ ① metastasis from outside the lung

② primary tumor in the lung with mets to the other lobes



→ consolidation or mass on the phrenic nerve → causes elevation of left hemi-diaphragm

↳ more common to be malignant tumor

gastric bubble very high

↳ diaphragm is very high



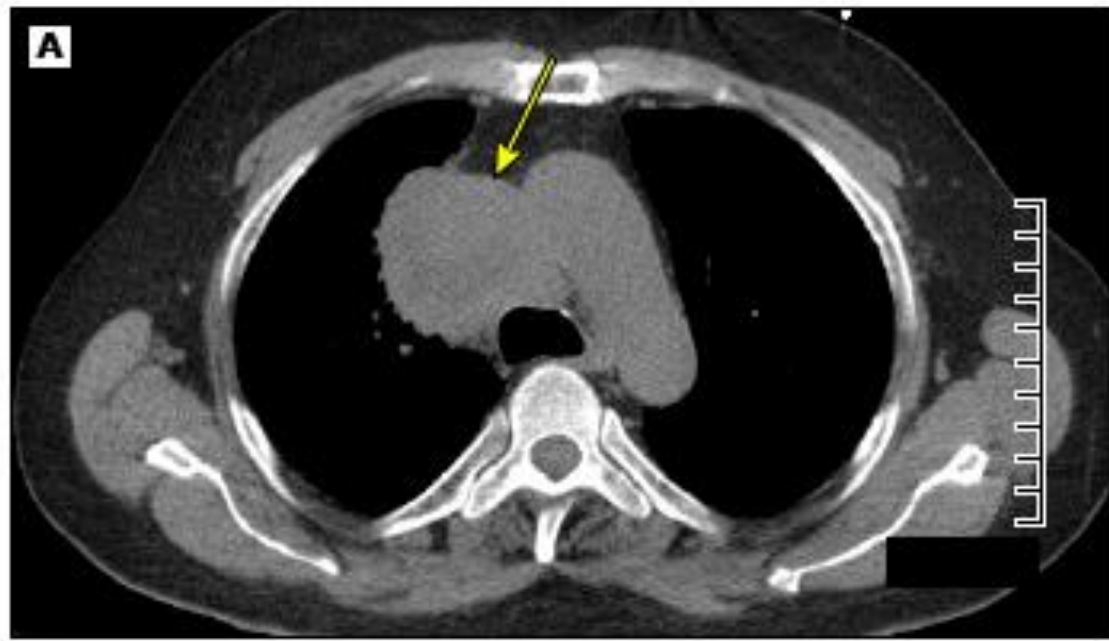
pleural effusion on right side

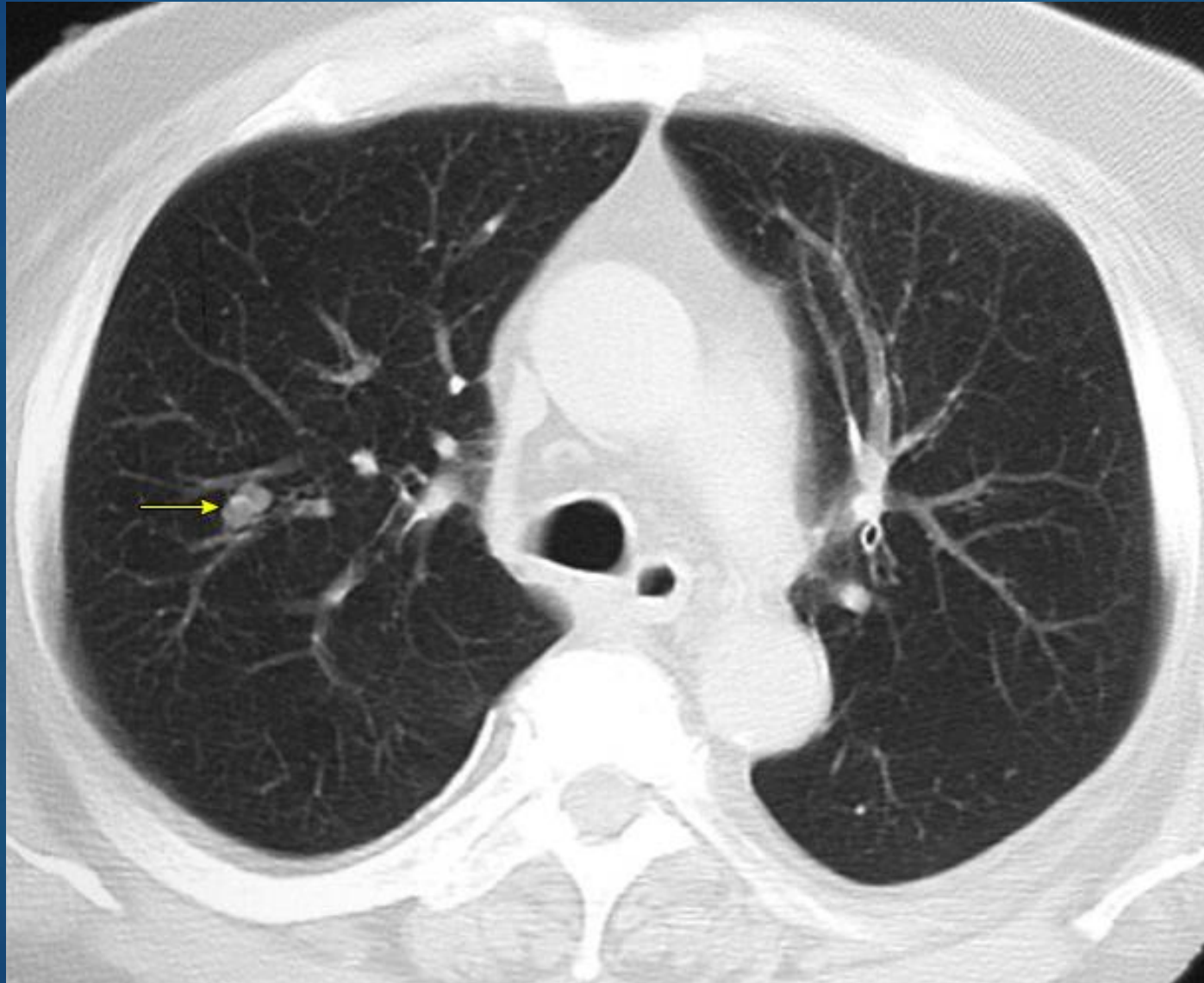
↳ if history is toward lung cancer
I would suspect this as malignant
pleural effusion either from direct
invasion or mets to pleura

↳ malignant cells in pleural fluid:
stage IV → very poor prognosis

CT

- ▶ Every patient with suspected lung cancer should undergo CT scan of the chest.
- ▶ CT findings: large lesion size (e.g., >15 mm), irregular or spiculated borders, upper lobe location, thick-walled cavitation, presence or development of a solid component within a ground glass lesion, and detection of growth by follow-up imaging. The finding of multiple nodules in a patient with a known or suspected extrathoracic malignancy strongly suggests pulmonary metastasis.







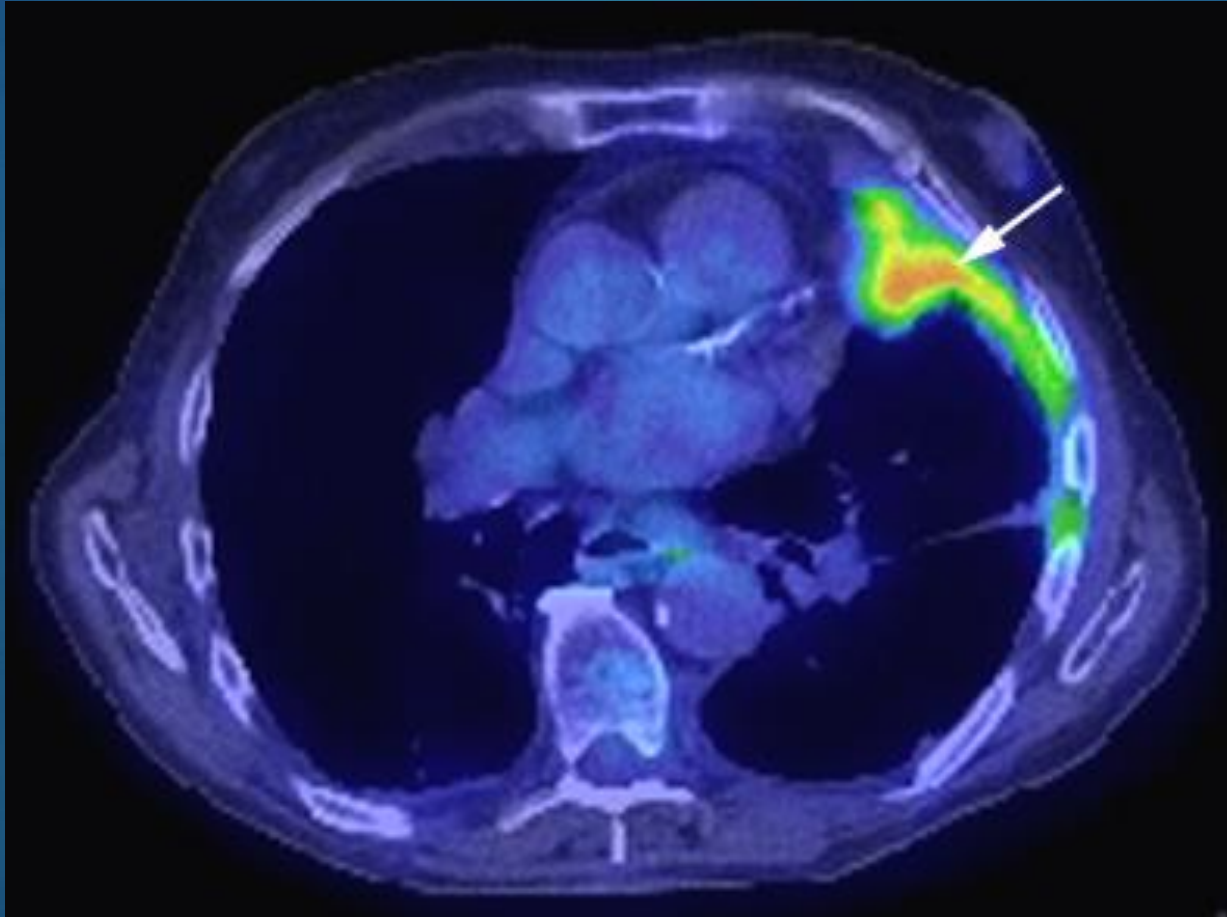
pleural effusion

CT:
more sensitive to detect
pleural effusions (very
minimal amount)



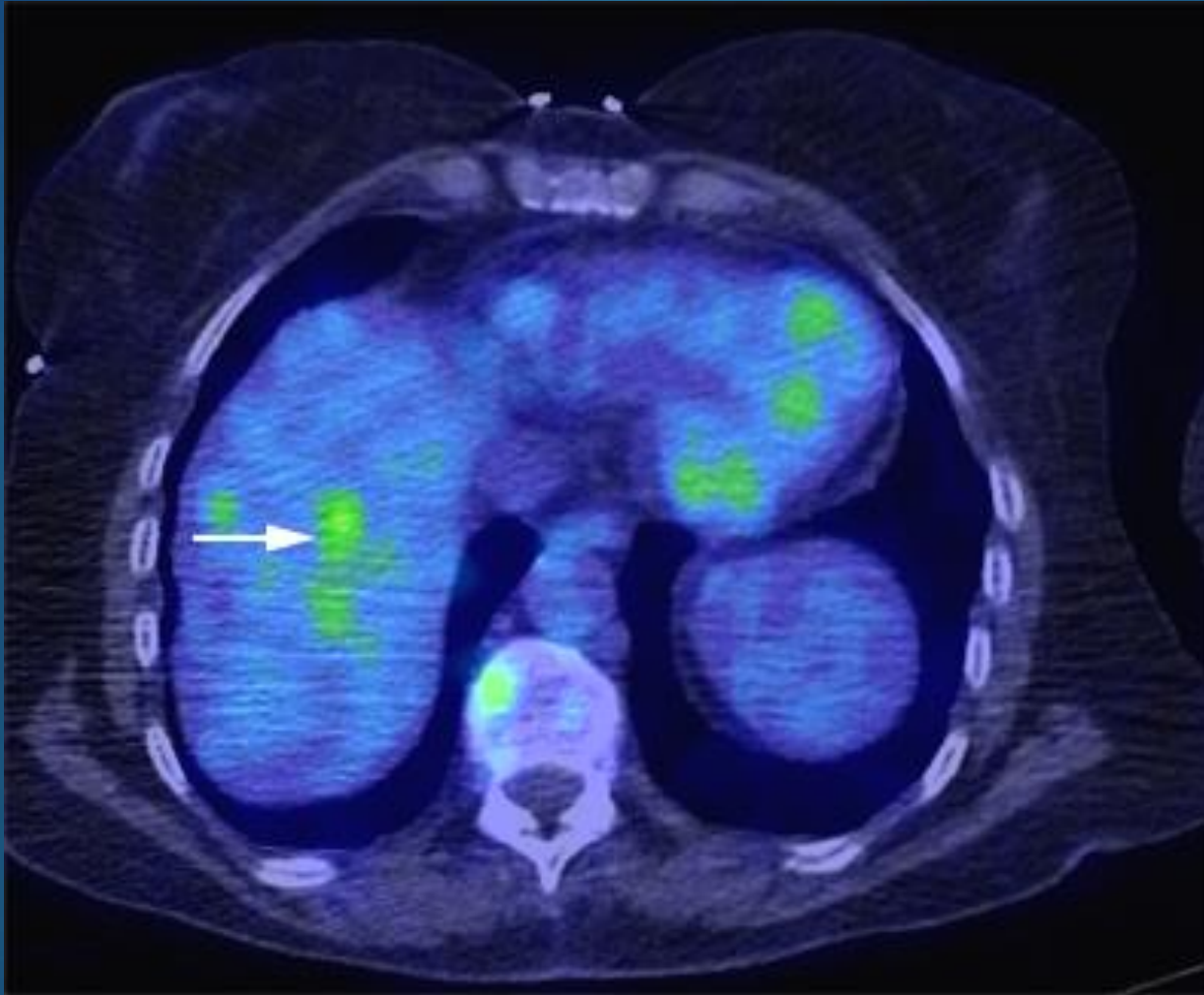
PET Scan

- ▶ Although whole-body PET is more accurate than CT in detecting occult disease, its use has not been shown to improve survival
- ▶ False positives can occur with benign FDG-avid lesions such as infections, inflammation, and granulomatous disease.
- ▶ False negatives typically occur when there are microscopic foci of metastasis, and in non-enlarged lymph nodes (<10 mm).

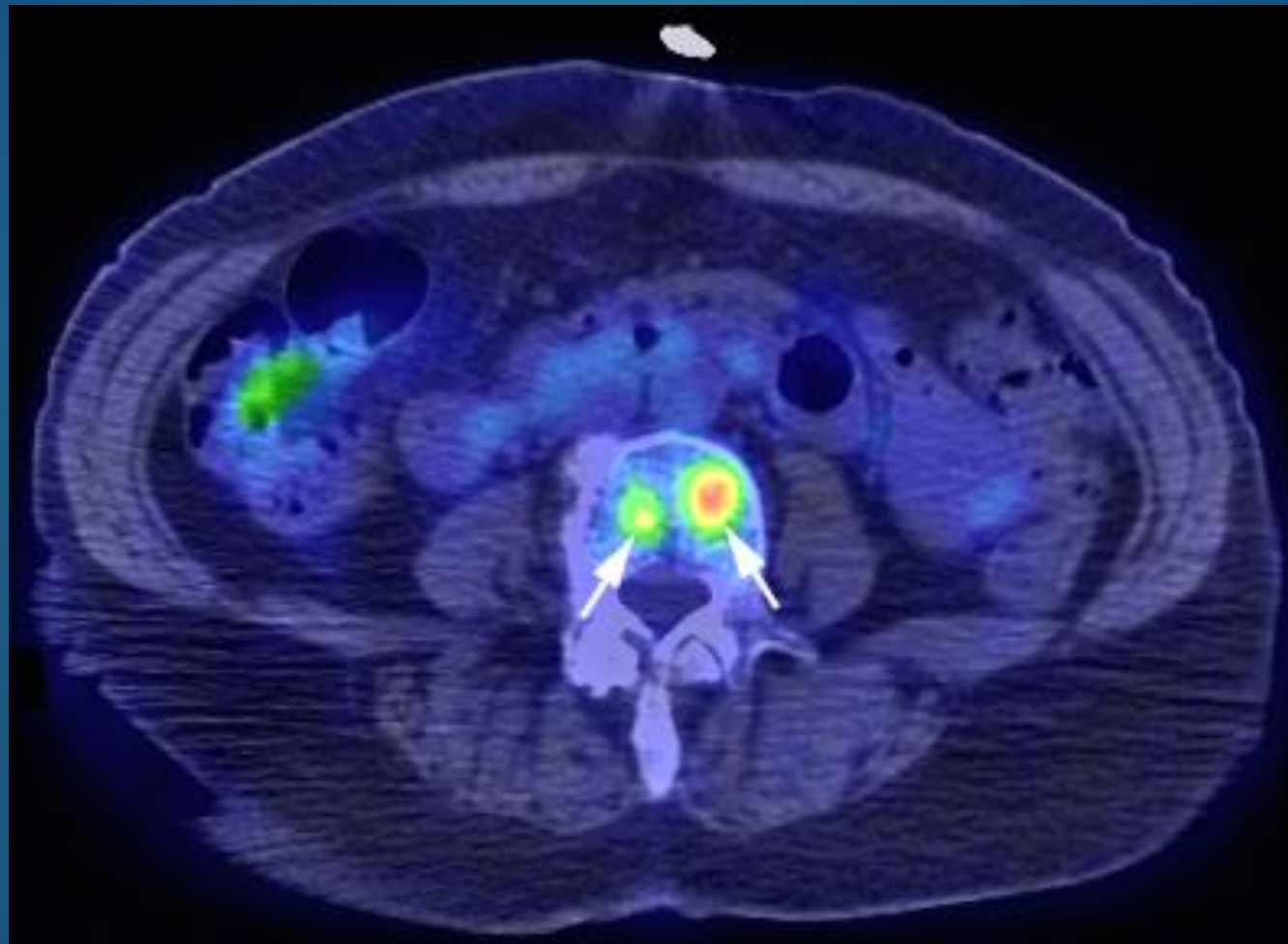


Tumor cells → active





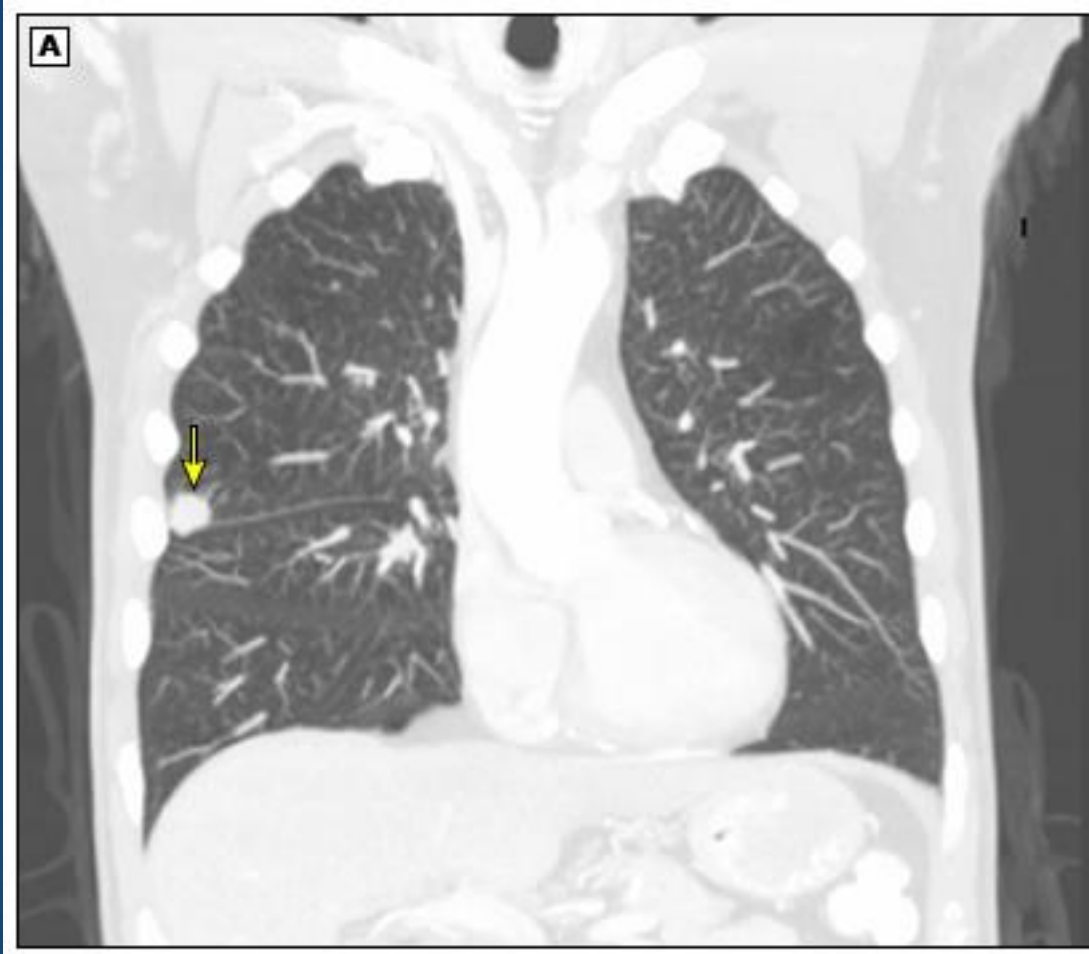
Liver lesions



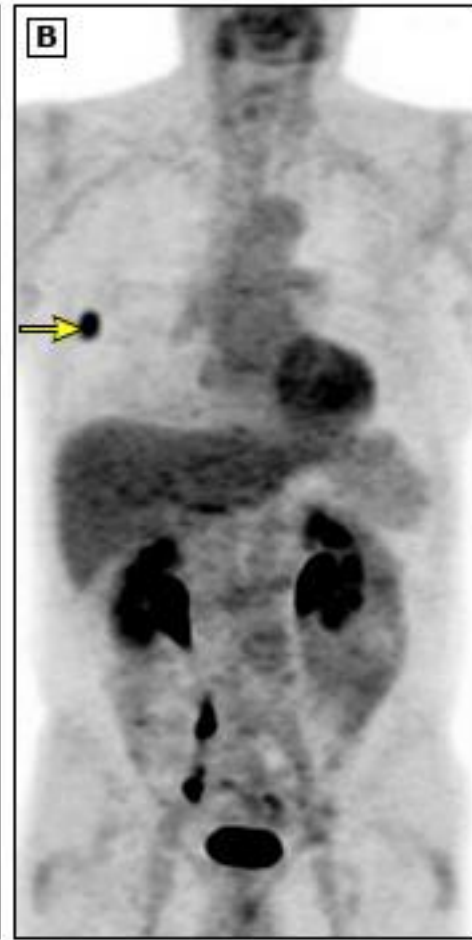
bone lesions

Integrated PET/CT

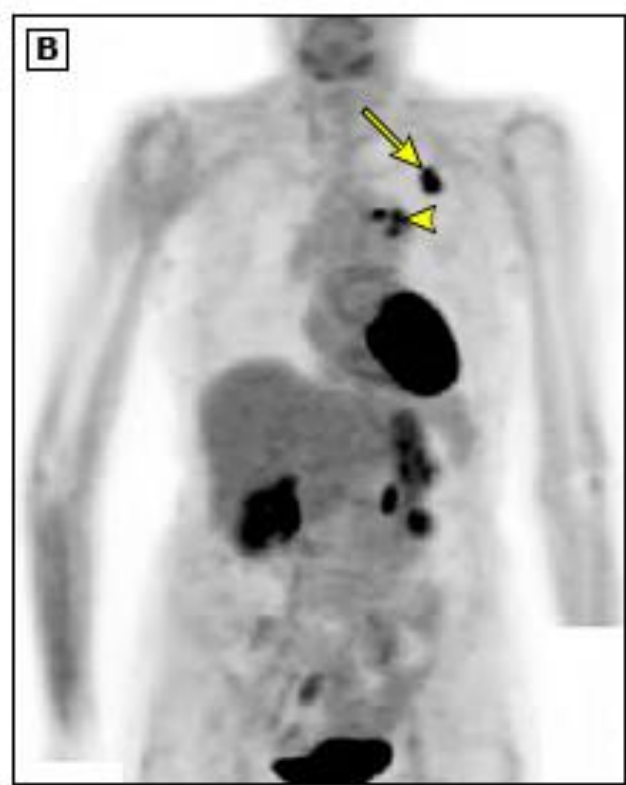
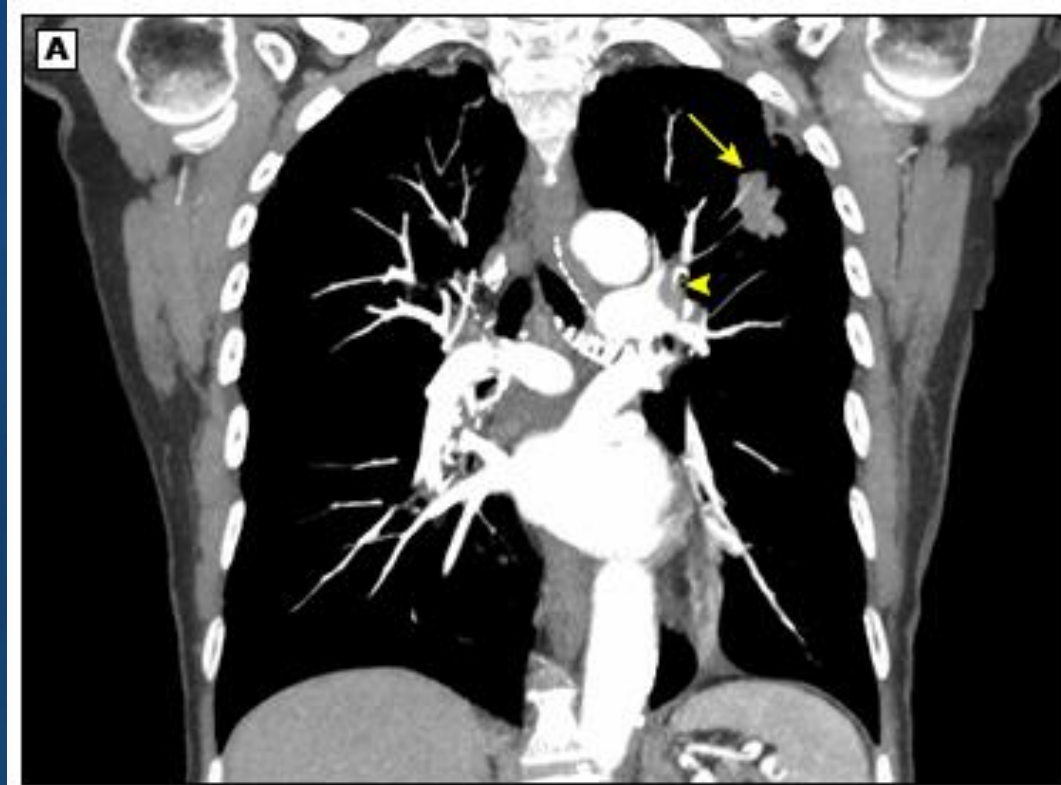
- ▶ Although randomized trials suggest that the use of integrated PET/CT reduced futile thoracotomies, and is probably superior to either modality alone, it has not been shown to improve survival.



CT



PET






Imaging metastatic disease

Based on symptoms:

- ▶ Brain, spine, and nerves: MRI // pet scan not beneficial for brain. always active

Patients with clinical stage III or IV disease have an increased risk of occult intracranial metastasis and may benefit from routine imaging of the brain with magnetic resonance imaging (MRI) or CT if MRI is not available.

Gadolinium-enhanced MRI detects spinal bone lesions and brain lesions and differentiates metastases from other central nervous system lesions with greater sensitivity than non-enhanced MRI.

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- ▶ **Other mets:** With the exception of brain metastases, whole body PET or PET/CT scanning is more accurate than conventional scanning (abdominal CT, bone scan) for the detection of unsuspected pleural and extrathoracic metastases.

When PET, PET/CT or MRI is not available, conventional staging with abdominal CT, bone scintigraphy, and CT scan of the brain should be performed when indicated.

Sometimes US, Body MRI, Bone scan...etc

Suggestive of metastasis

Symptoms elicited in history

Constitutional - weight loss >10 pounds

Musculoskeletal - focal skeletal pain

Neurologic - headaches, syncope, seizures, extremity weakness, recent change in mental status

Signs found on physical exam

Lymphadenopathy (>1 cm)

Hoarseness, superior vena cava syndrome

Bone tenderness

Hepatomegaly (>13 cm span)

Focal neurologic signs, papilledema

Soft tissue mass

Routine laboratory tests

Hematocrit, <40% in males

Hematocrit, <35% in females

Elevated alkaline phosphatase, GGT, SGOT



bone mets





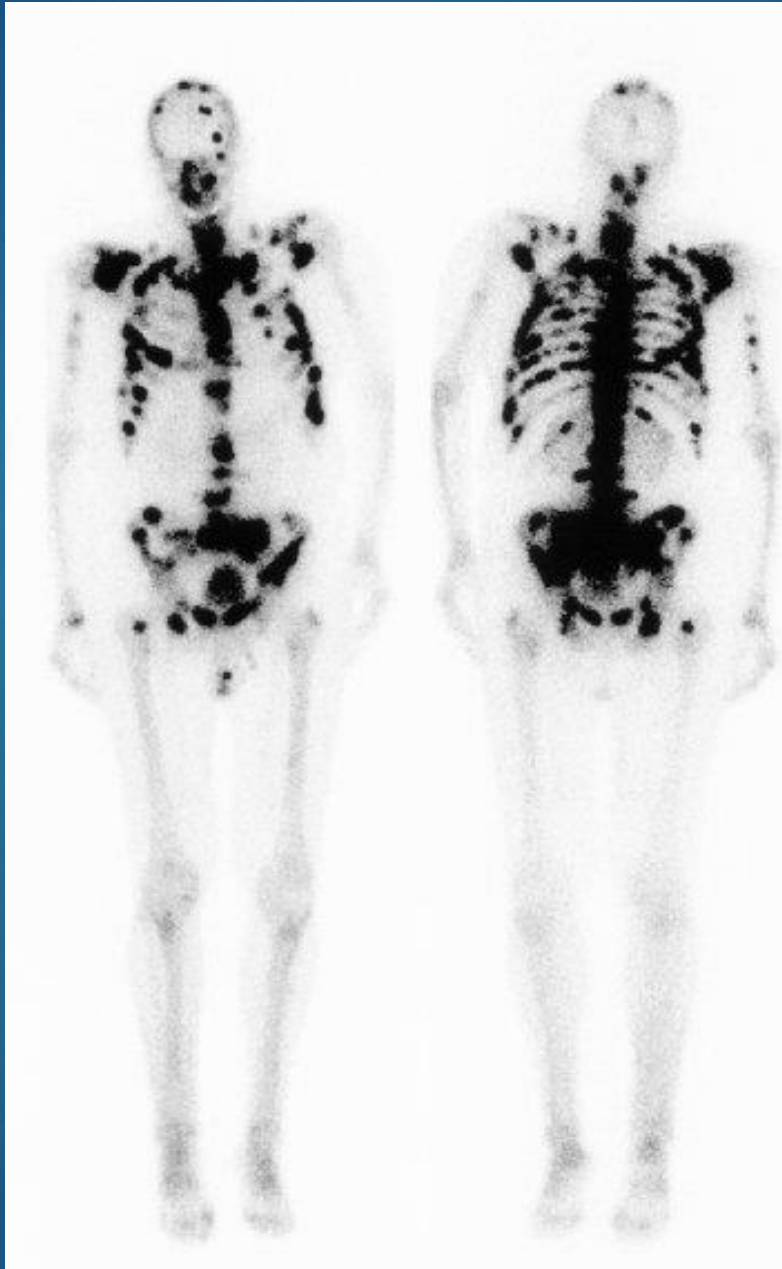
brain met-s

S



I





diffused bone mets



Pathologic diagnosis

- ▶ **Diagnosis of lung cancer should not be made without definitive pathology**. At a minimum, this involves selecting a biopsy site and obtaining an adequate sample for microscopic examination. Additional consideration needs to be given to obtaining a large enough sample for supplemental immunohistochemical and genetic analysis.

- ▶ **Modality** *easiest biopsy / biopsy with high stage*

Cytologic specimens can be obtained from the following sites:

Lung: Sputum, transthoracic needle aspirates, and bronchoscopic washings, brushings, or needle aspirates

Lymph node: Transthoracic, transbronchial, and transesophageal aspirates

Distant metastasis: Pleural fluid, needle aspirates of metastatic tissue (eg, liver)

Core or biopsy tissue can be obtained from the following:

Lung: Endobronchial biopsy (forceps), transbronchial biopsy (forceps or needle), transthoracic (needle) biopsy, surgical biopsy

Lymph node: Bronchoscopic and transthoracic needle core biopsy, surgical biopsy

Distant metastasis: Core needle aspirates of metastatic tissue (eg liver, bone, adrenal)

Immunohistochemical and histochemical stains useful in the differential diagnosis of various carcinomas

مو حفظا

Tumor type	Immunohistochemical staining
Carcinoma	Positive: Pankeratin, AE 1/3, CAM 5.2, OSCAR, EMA Negative: CD 45 Variable: CK 7, CK 20, S-100, vimentin
Colorectal carcinoma	Positive: CK 20, CDX-2 Negative: CK 7
Lung carcinoma	
Adenocarcinoma	Positive: TTF-1, napsin A, CK 7, mucicarmine, PAS-D
Squamous cell carcinoma	Positive: p 40, p 63, CK 5/6, desmoglein Negative: CK 7 (usually)
Small-cell carcinoma	Positive: TTF-1, high proliferative rate (Ki-67, MIB-1) Variable: Chromogranin, synaptophysin
Neuroendocrine carcinoma	Positive: Chromogranin, synaptophysin, epithelial stains
Germ cell tumor	Positive: HCG, AFP, Oct4 transcription factor, placental alkaline phosphatase, epithelial stains
Hepatocellular carcinoma	Positive: Hep par 1, CEA, AFP, glypican 3 Negative: CK 7, CK 20
Renal cell carcinoma	Positive: Pan keratin, CAM 5.2, Pax-8, CK 7, vimentin, RCC, CD 10 Negative: CK 20, CEA
Prostate carcinoma	Positive: PSA, prostatic acid phosphatase Negative: CK 7, 20
Pancreas carcinoma	Positive: CA 19-9, CK 7, CDX-2, CK 17 Variable: CK 20
Breast carcinoma	Positive: ER, PR, Her-2-neu, CK 7, gross cystic fluid protein 15, epithelial stains, GATA 3, mammaglobin Negative: CK 20
Ovarian carcinoma	Positive: CK 7, WT-1, Pax-8, ER Negative: CK 20, CDX-2

STAGING

- ▶ The 8th edition for staging non-small cell lung cancer (NSCLC) is in use. Staging NSCLC determines the appropriate therapy and, when combined with the patient's unique features, provides valuable prognostic information. adeno
squamous
- ▶ The TNM system for staging NSCLC
- ▶ The staging for small cell lung cancer (limited versus extensive) and TNM) ↳ I can put the whole tumor with single radiation port
- ▶ The clinical-diagnostic stage and the surgical-pathologic stage

Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)*
T1a(mi)	Minimally invasive adenocarcinoma[¶]
T1a	Tumor ≤ 1 cm in greatest dimension*
T1b	Tumor >1 cm but ≤ 2 cm in greatest dimension*
T1c	Tumor >2 cm but ≤ 3 cm in greatest dimension*
T2	Tumor >3 cm but ≤ 5 cm or tumor with any of the following features: ^Δ Involves main bronchus regardless of distance from the carina but without involvement of the carina <ul style="list-style-type: none"> •Invades visceral pleura •Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
T2a	Tumor >3 cm but ≤ 4 cm in greatest dimension
T2b	Tumor >4 cm but ≤ 5 cm in greatest dimension
T3	Tumor >5 cm but ≤ 7 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	Tumor >7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm , mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina


N: Regional lymph node involvement

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M: Distant metastasis

M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion [◇]
M1b	Single extrathoracic metastasis[§]
M1c	Multiple extrathoracic metastases in one or more organs

Stage groupings			
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1a(mi)	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a to c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a to c	N2	M0
	T2a to b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a to c	N3	M0
	T2a to b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	AnyT	AnyN	M1a
	AnyT	AnyN	M1b
Stage IVB	AnyT	AnyN	M1c

- 
- ▶ **Limited disease** – Tumor confined to the ipsilateral hemithorax and regional nodes able to be included in a single tolerable radiotherapy port (corresponding to Tumor, Node, Metastasis [TNM] stages I through IIIB).
 - ▶ **Extensive disease** – Tumor beyond the boundaries of limited disease including distant metastases, malignant pericardial, or pleural effusions, and contralateral supraclavicular and contralateral hilar involvement.

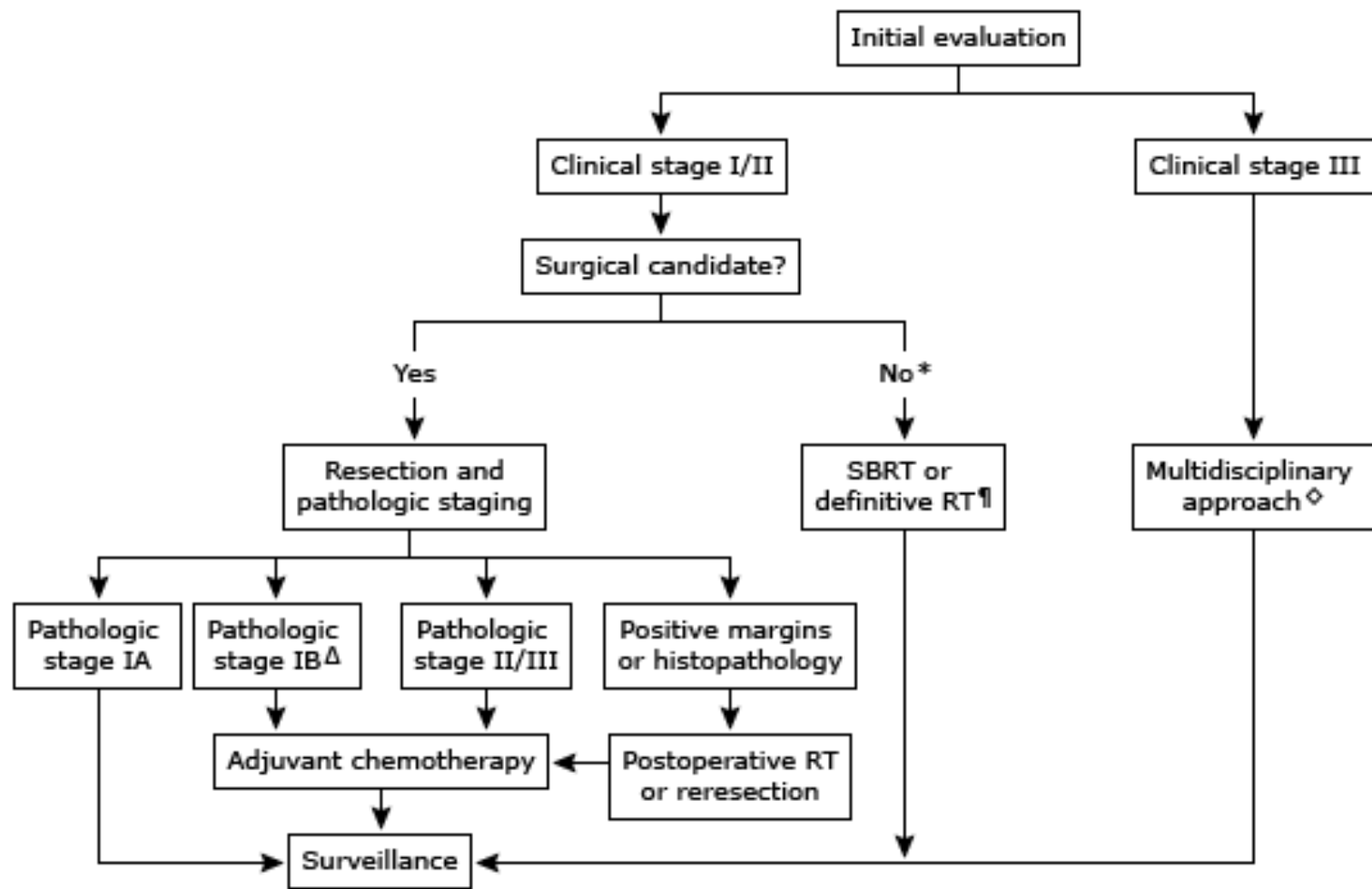
Treatment

- ▶ Surgical for early stages
- ▶ Chemotherapy
- ▶ Radiotherapy
- ▶ Molecularly targeted therapy EGFR mutations pts.
- ▶ Immunotherapy staining positive for PDL1... pts.

systemic therapy

Treatment of NSCLC

- ▶ Stage I or II NSCLC should be treated with complete surgical resection whenever possible. Postoperative adjuvant chemotherapy improves survival in patients with pathologic stage II disease and may have a role for patients with stage IB disease.
- ▶ Concurrent chemoradiotherapy is preferred for those with more extensive intrathoracic disease.
- ▶ Patients with advanced disease are managed palliatively with systemic therapy and/or local palliative modalities.
- ▶ Patients with stage IV disease are generally treated with systemic therapy or a symptom-based palliative approach. In appropriately selected patients, chemotherapy, molecularly targeted therapy, and/or immunotherapy may prolong survival without sacrificing quality of life.
- ▶ Patients with stage IV disease based upon the presence of an isolated metastasis (eg, brain, adrenal) may benefit from resection of the metastasis as well as aggressive treatment of the primary tumor



Treatment of SCLC

- ▶ SCLC is a disseminated disease in most patients at presentation and is **very responsive to chemotherapy**. Thus systemic chemotherapy is an integral part of the initial treatment.
- ▶ Patients with **limited-stage disease** are primarily treated with a **combination of chemotherapy and radiation therapy**
- ▶ Surgery is not used except in the rare patient who presents with a solitary pulmonary nodule without distant metastases or regional lymph node involvement
- ▶ Prophylactic cranial irradiation decreases the incidence of brain metastases and prolongs survival in patients with limited-stage SCLC who respond to their initial treatment.
- ▶ For patients with **extensive-stage SCLC**, **chemotherapy** is used as the initial therapy, with or without immunotherapy. Radiation therapy, including both prophylactic cranial irradiation and thoracic RT, may be beneficial in patients with a complete or partial response to their initial chemotherapy.

Prognosis

Prognosis of NSCLC (Some of them)

- ▶ **Stage of disease:** The TNM stage at presentation in patients with NSCLC is the factor that has the greatest impact on prognosis.
- ▶ **Performance status:** Poor performance status and weight loss have been associated with shortened survival. Reduced appetite, a precursor of weight loss, also has negative prognostic implications.
- ▶ **Histopathology:** The degree of differentiation, lymphatic invasion, occult lymph node metastases and intense tumor lymphocytic infiltration

- ▶ **Molecular characterization:**

Activating mutations in *EGFR* have a significantly better prognosis than those without *EGFR* mutations

The presence of the *ROS1* or *EML4-ALK* fusion oncogene are highly responsive to inhibitors of ALK.

Expression of tumor PD-L1 predicts response to certain immunotherapies

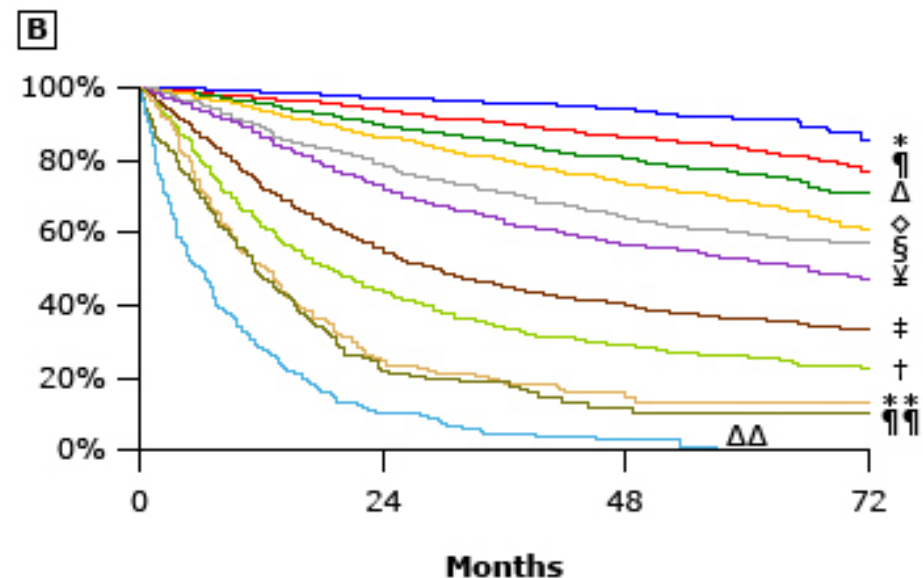
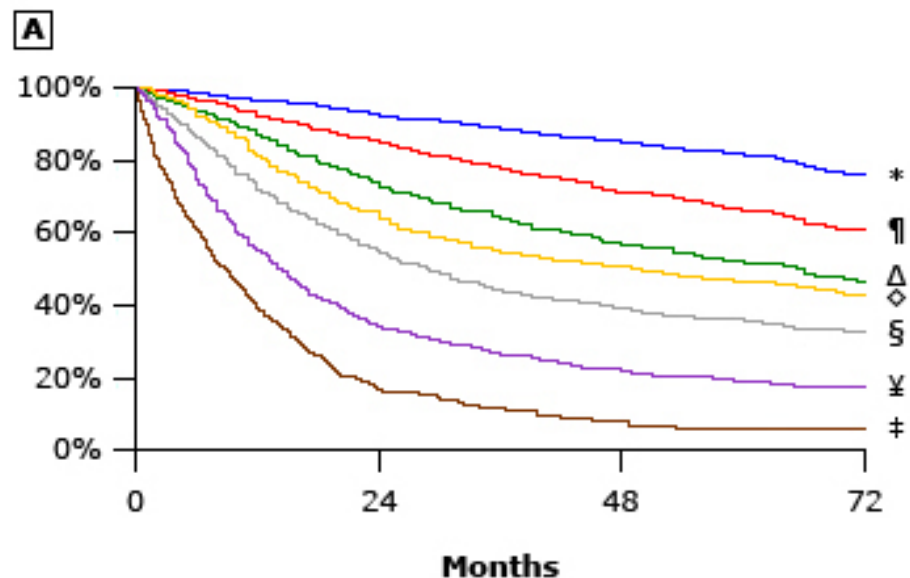
- ▶ **Recurrence after complete resection**



Prognosis of SCLC

The most important prognostic factor in patients with SCLC is the extent of disease (stage) at presentation. For patients with limited-stage disease, median survivals range from 15 to 20 months, and the reported five-year survival rate is 10 to 13 percent. By contrast, for patients with extensive-stage disease, the median survival is 8 to 13 months, and the five-year survival rate is 1 to 2 percent.

Clinical parameters also have prognostic importance in patients with SCLC. Poor performance status and/or weight loss have been associated with shortened survival.



7 th edition	Events / N	MST	24 month	60 month
* IA	1119 / 6303	NR	93%	82%
† IB	768 / 2492	NR	85%	66%
Δ IIA	424 / 1008	66.0	74%	52%
◇ IIB	382 / 824	49.0	64%	47%
§ IIIA	2139 / 3344	29.0	55%	36%
¥ IIIB	2101 / 2624	14.1	34%	19%
‡ IV	664 / 882	8.8	17%	6%

8 th edition	Events / N	MST	24 month	60 month
* IA1	68 / 781	NR	97%	92%
† IA2	505 / 3105	NR	94%	83%
Δ IA3	546 / 2417	NR	90%	77%
◇ IB	560 / 1928	NR	87%	68%
§ IIA	215 / 585	NR	79%	60%
¥ IIB	605 / 1453	66.0	72%	53%
‡ IIIA	2052 / 3200	29.3	55%	36%
† IIIB	1551 / 2140	19.0	44%	26%
** IIIC	831 / 986	12.6	24%	13%
†† IVA	336 / 484	11.5	23%	10%
ΔΔ IVB	328 / 398	6.0	10%	0%

Questions??