Lung Cancer and Paraneoplastic Syndromes

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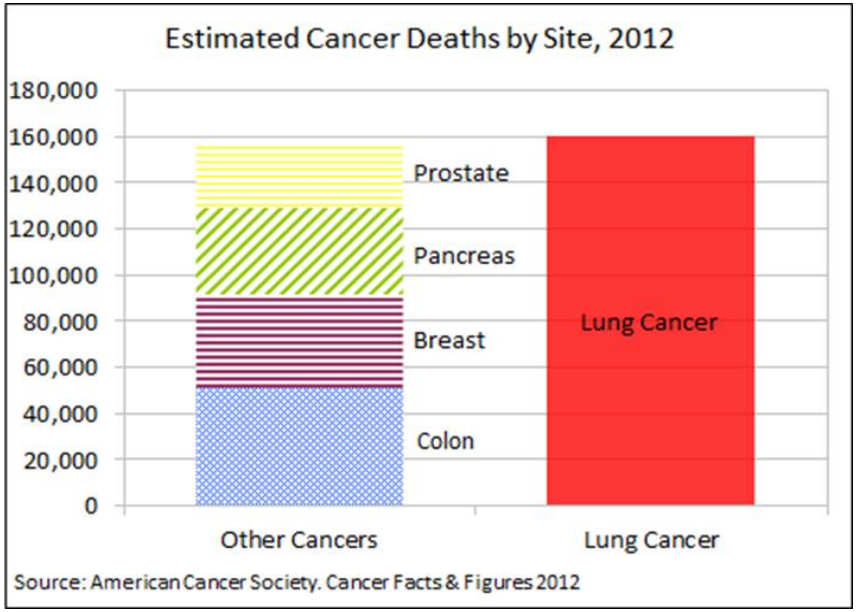
ACOI Board Review 2019

Disclosures

- None

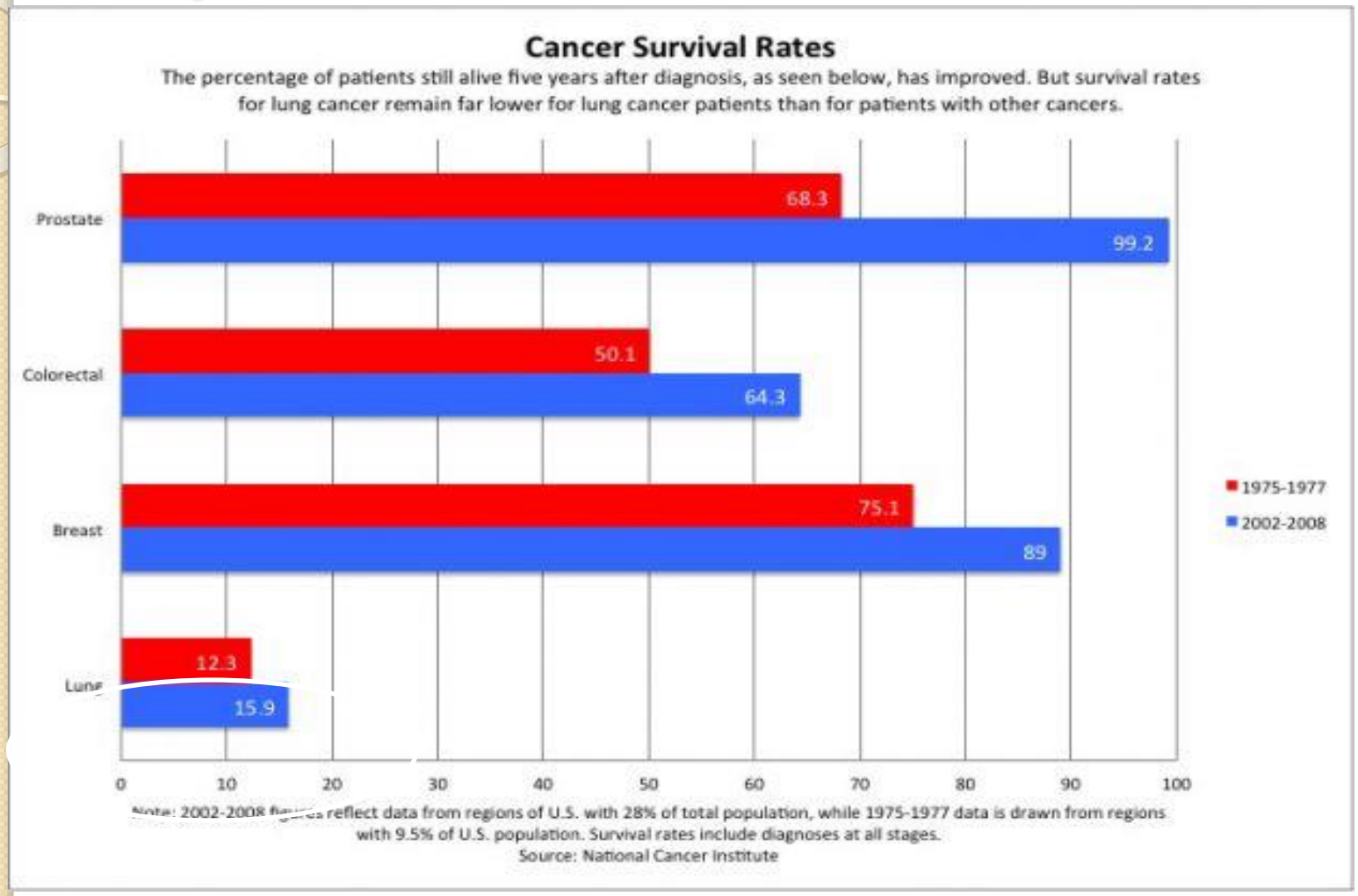
Introduction

- Lung cancer is the most common cause of mortality WORLDWIDE
- 1.3 million deaths per year
- In U.S. 2012: 226,000 new cases



American Cancer Society Facts & Figures 2012

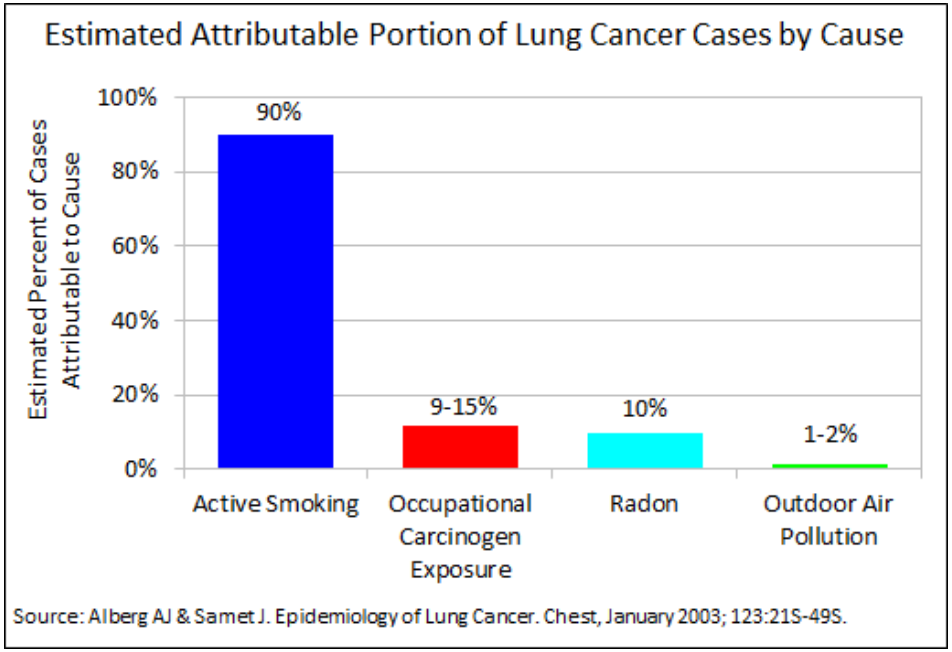
5 year Survival Rates



National Cancer Institute 2008

Risk Factors

- **SMOKING**
- Environmental
  - Radon
  - Air pollution
  - Metals
- Asbestos
- Genetics
- HIV
- Pulmonary Fibrosis
- Radiation therapy



Benign Lung Neoplasms

- Epithelial Derived
  - Papilloma (smoking, HPV)
    - Smoking, HPV
    - Squamous cell cancer
  - Micronodular Pneumocyte Hyperplasia
    - Tuberous sclerosis and/or LAM
- Nonepithelial Derived
  - Hamartoma
    - 50% of benign lung tumors
  - Solitary fibrous tumor

Malignant Lung Neoplasms

- Non-small cell lung cancer (NSCLC)-most common
  - Squamous cell
  - Adenocarcinoma-most common
    - "bronchoalveolar cell"
      - Atypical adenomatous hyperplasia, adenocarcinoma in-situ, minimally invasic adenocarcinoma
  - Large cell
  - Carcinoid
- Small cell lung cancer (SCLC)
  - Classic, large cell neuroendocrine, combined
  - Limited or Extensive
- Primary pulmonary lymphoma
  - Mucosa-associated lymphoid tissue type
  - Lymphomatoid granulomatosis

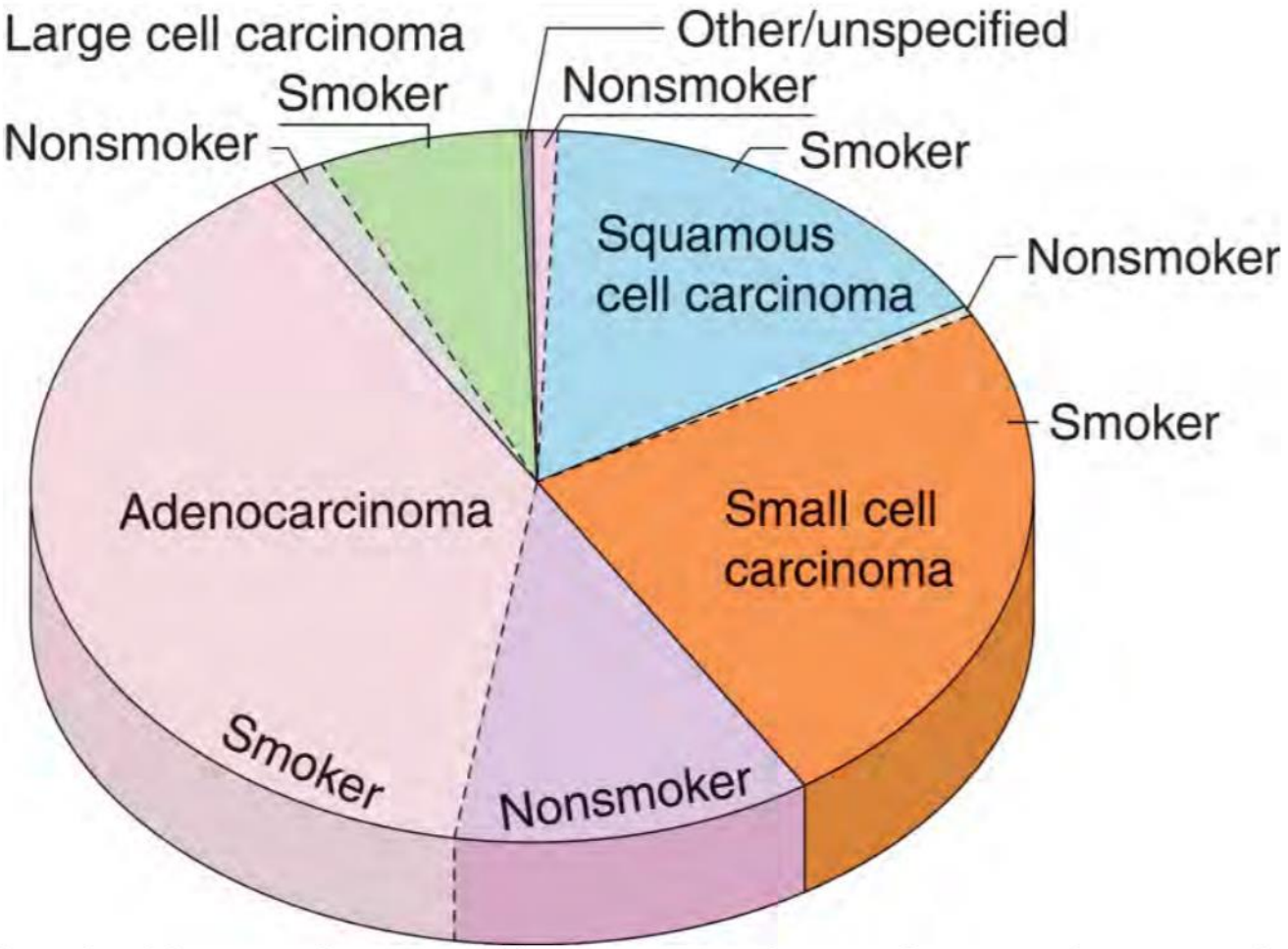


Figure 12-7. Incidence of types of lung cancer in smokers and nonsmokers.

Small Cell Lung Cancer

- Classic features:
  - Usually Central
    - 2/3 perihilar/hilar
    - 1/6 in main bronchus, 1/6 peripheral or apical
  - Most aggressive of all tumors with rapid doubling time
  - Early metastases (nearly 70% metastatic at presentation)
    - Liver 30-35%
    - Bone 40-50%
    - CNS 15%
  - Strongest association: Tobacco Use
  - Early response to therapy (chemo and radiation) but eventually becomes refractory

SCLC Staging

- **Limited Stage**
  - 30% of patients at presentation
  - Confined to one hemithorax
  - **Survival:**
    - Median survival is 15-20 months
    - 5 year ~ 10-15%
- **Extensive Stage**
  - 70 % of patients at presentation
  - Extends beyond one hemithorax
  - **Survival:**
    - Median survival is 8-13 months
    - 5 year ~ 1-2%

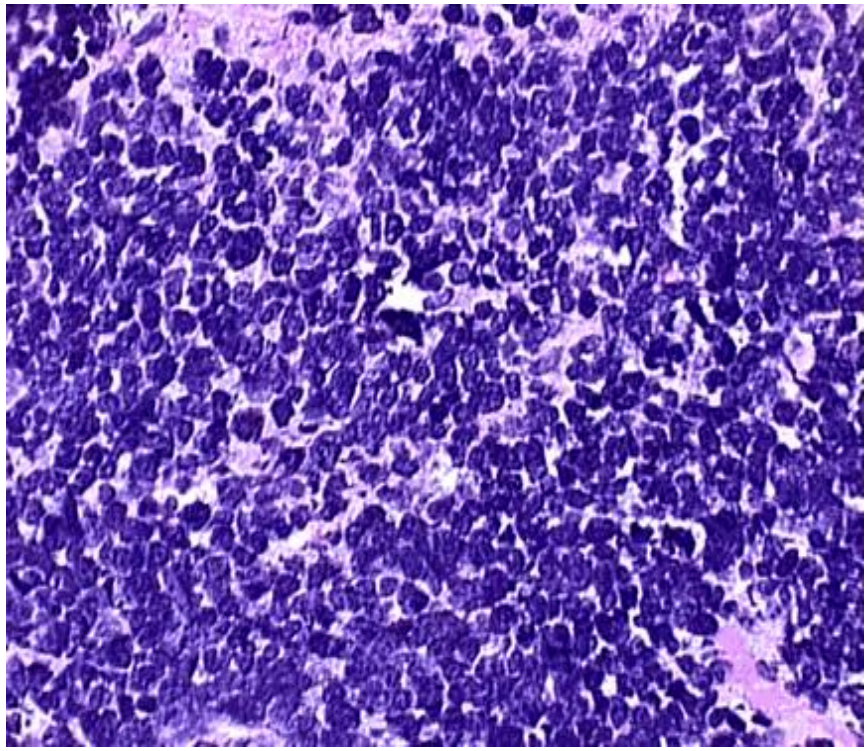
Median survival without treatment is 2-4 months

Small Cell Lung Cancer

- Paraneoplastic syndromes
  - Ectopic ADH, ACTH
  - Eaton Lambert
- Treatment
  - Chemotherapy, XRT
  - Prophylactic cranial irradiation if attain complete response with initial treatment
- Survival not related to stage

Small Cell Pathology

- Small blue cells
- Scant cytoplasm
- Nuclear “molding”
- Extensive necrosis
- Cells contain neurosecretory granules
- Stains positive for CD56, synaptophysin, chromogranin, TTF-1

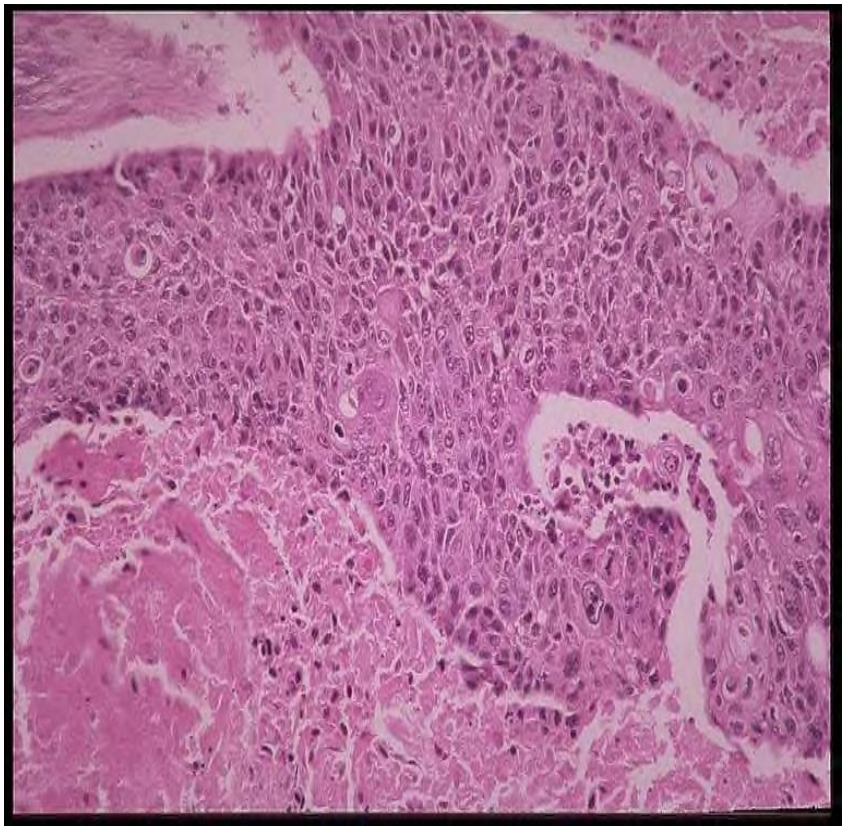


NSCLC: Squamous Cell

- Best prognosis of the major cell types
- Common Presentation:
  - Large central mass
  - Obstructive symptoms/signs,
  - May cavitate 10%
  - Locally invasive, but can metastasize widely
- Intermediate growth rate - late metastasis
- Associated with smoking
- Hypertrophic pulmonary osteoarthopathy (HPOA) is NOT most common with squamous anymore
- Hypercalcemia
- Pancoast syndrome

Squamous Cell Carcinoma

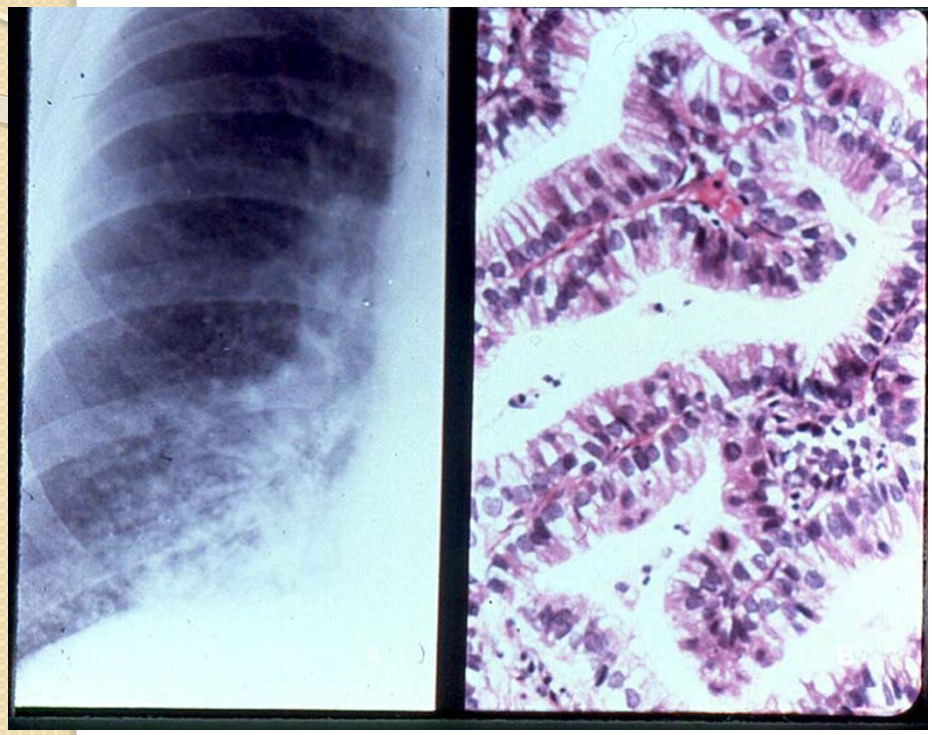
- Intercellular bridging
- Nesting formation
- Keratinization (well-differentiated type)
- “keratin pearls”

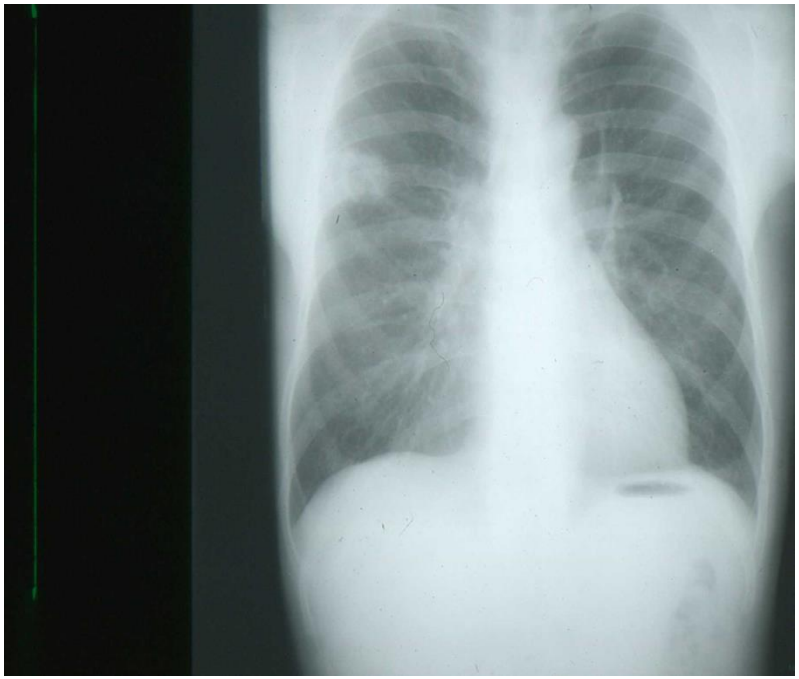


NSCLC: Adenocarcinoma

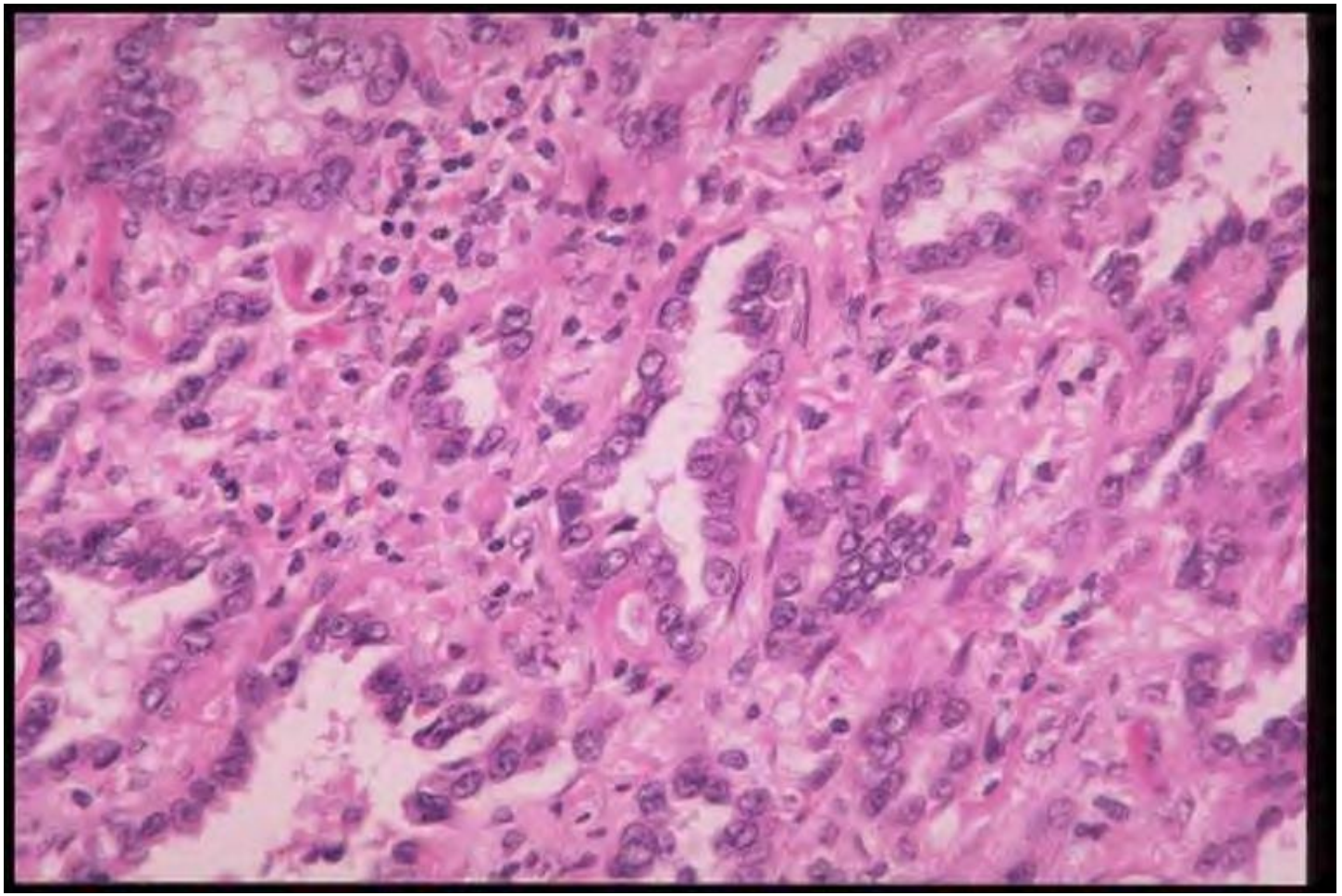
- Common Presentation
  - Peripheral in location
  - May metastasize widely before symptoms/signs develop
  - Not related to smoking
- Most common type of bronchogenic carcinoma in women NON-SMOKERS
- Slow growing but invades lymphatics and blood vessels
- May develop in or adjacent to fibrous lung "scar carcinoma"
- Many growth patterns exist: acinar, papillary, bronchioalveolar and solid w/ mucin formation, mixed subtype

NSCLC: Adenocarcinoma





Adenocarcinoma



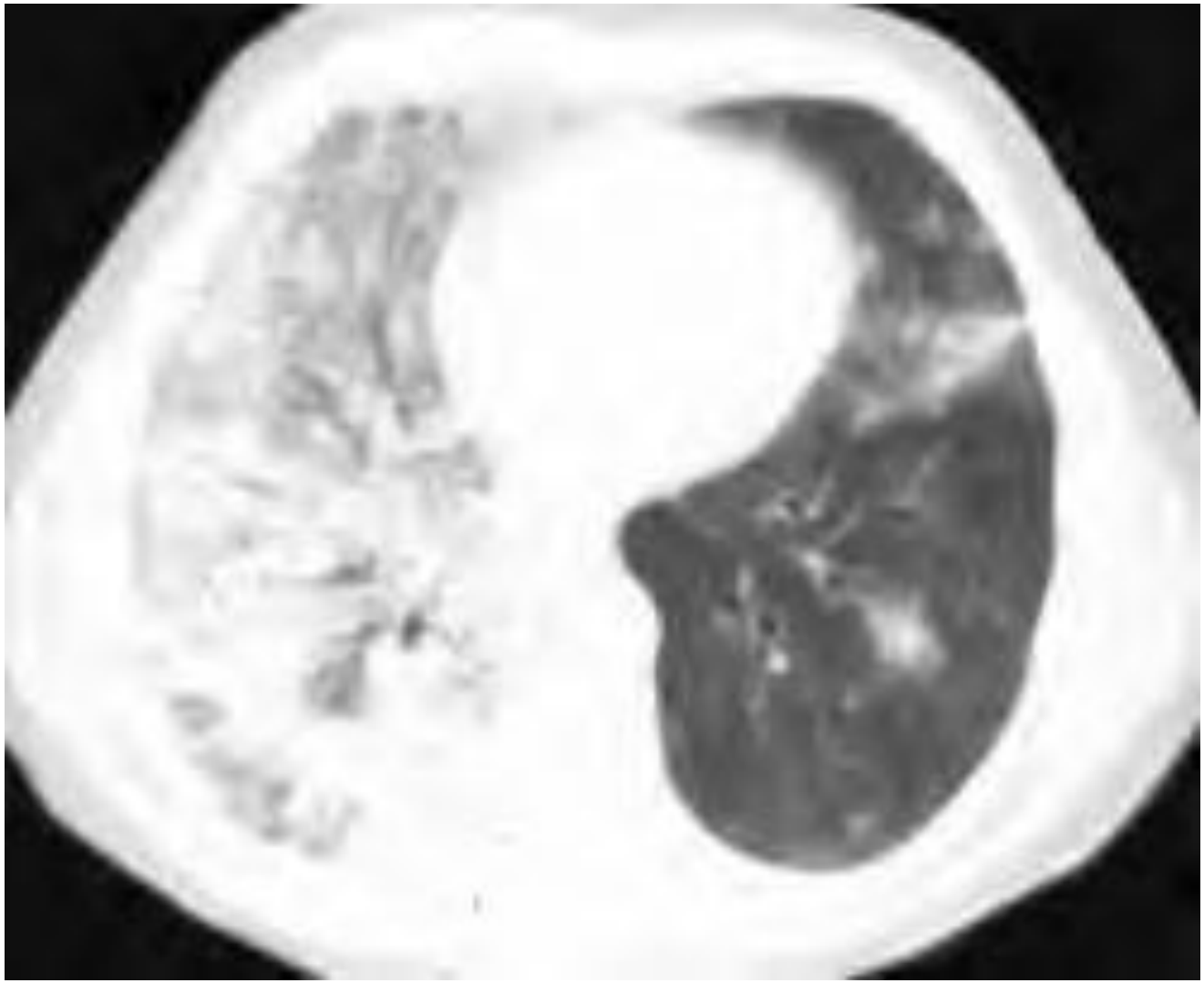
Tumor type	Immunoperoxidase staining
Carcinoma	Epithelial stains (eg, CK 7, 20 variable), EMA (+) CLA, S-100, vimentin (-)
Colorectal carcinoma	CK 7 (-); CK 20 (+)
Lung carcinoma	
Adenocarcinoma	TTF-1 (+), Surf-A and Surf-B (+)
Other non-small-cell carcinoma	CK 7 (+), CK 20 (-), TTF-1 (-)
Small-cell carcinoma	TTF-1 (+), chromogranin (+), NSE (+)
Neuroendocrine carcinoma	NSE, chromogranin, synaptophysin (+), epithelial stains (+)
Germ cell tumor	HCG, AFP (+)
	Oct4 transcription factor (+)
	Placental alkaline phosphatase (+)
	Epithelial stains (+)
Prostate carcinoma	PSA (+), rare false (-) and (+)
	Epithelial stains (+)
	CK 7 (-), CK 20 (-)
Pancreas carcinoma	Ca^{19-9} (+), CK 7 (+)
	Mesothelin (+), trifoil factor 1 (+)
Breast carcinoma	ER, PR (+)
	Her-2-neu (+)
	CK 7 (+), CK 20 (-)
	Gross cystic fluid protein 15 (+)

NSCLC: Adenocarcinoma In-Situ

- Presentation
  - Usually peripheral
  - Ground glass or infiltrative appearance
  - Can be diffuse, unifocal, or multicentric
  - +/- bronchorrhea
  - Slow growing
- Tumor may NOT invade stroma, pleura, or vasculature
- Lepidic growth
  - Tumor cells line alveolar walls

Invasive Adenocarcinoma

- Subtypes
  - Nonmucinous (lepidic predominant-LPA)
  - Mucinous (invasive mucinous adenocarcinoma)
  - Mixed/Indeterminate (rare)
- Increased risk with tobacco
  - However – 30-40% are non-smokers

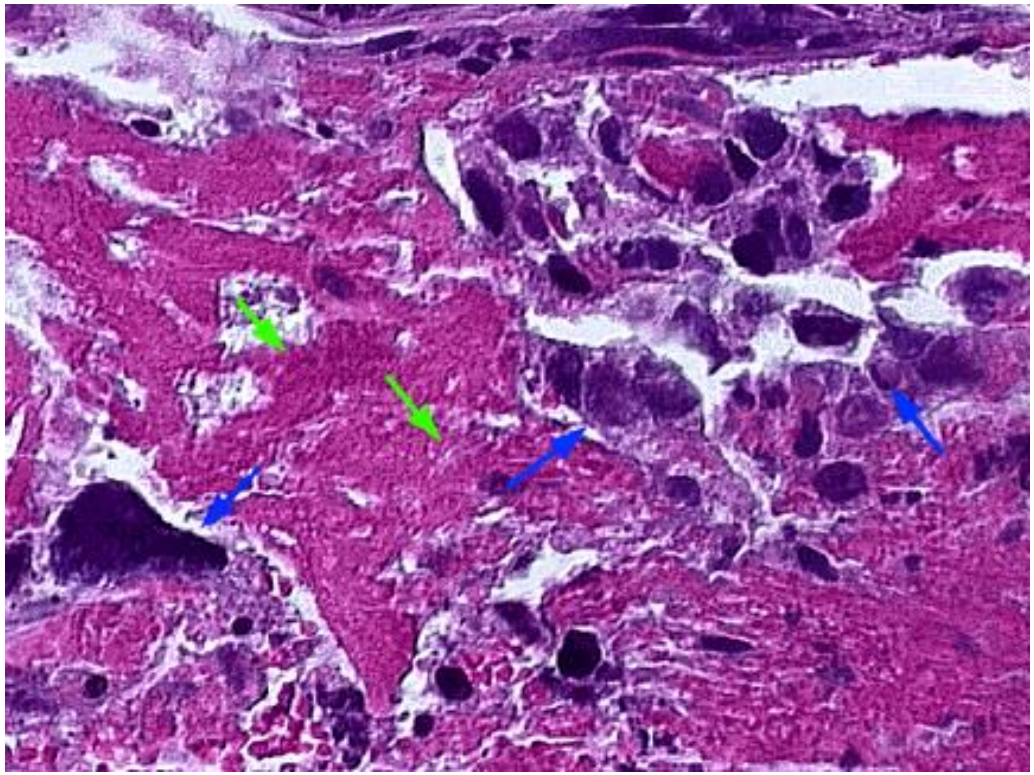


NCSLC: Large Cell

- 95% are undifferentiated
- Present as large masses (similar to squamous cell)
- Centrally located
- Fairly uncommon - 3% of all lung cancers
- Rapid Growth / Early metastasis
- Giant Cell variant - even more lethal with mean survival less than 6 months

Large Cell Carcinoma

- Large nuclei
- Moderate amt cytoplasm



Lung Cancer: Other types

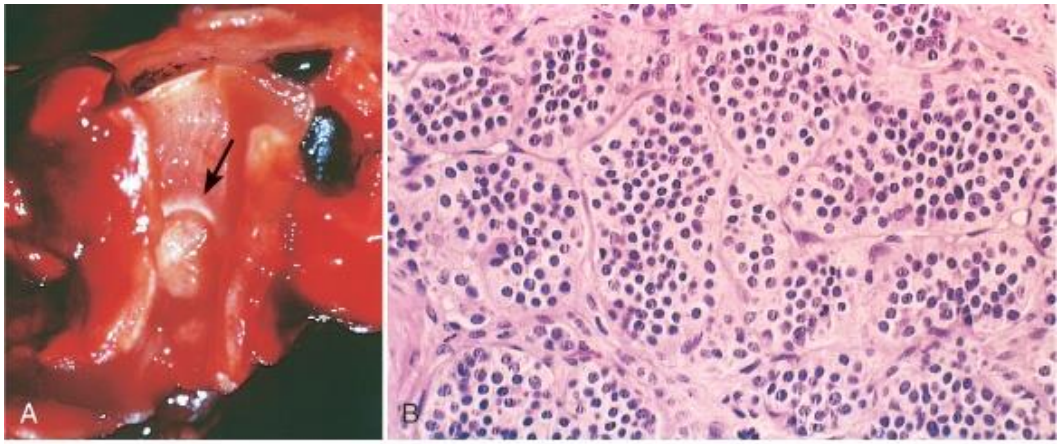
- Undifferentiated carcinoma
- Bronchial gland tumors
  - Adenoid cystic
  - Mucoepidermoid
- Other rare tumors
  - Sarcomatoid carcinoma
  - Carcinoid
    - Typical
    - Atypical

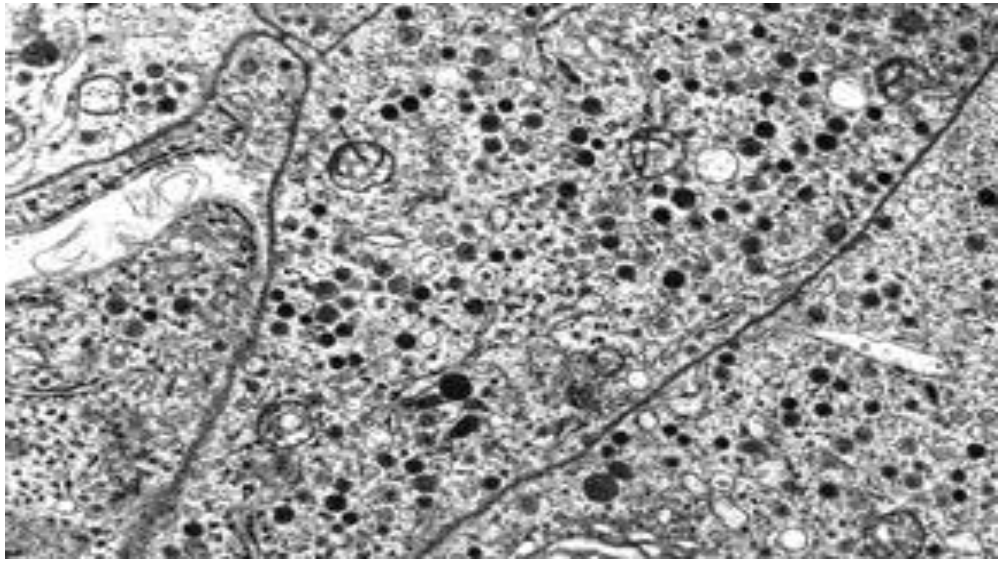
Carcinoid (Bronchial Neuroendocrine Tumors)

- Neuroendocrine differentiation with relatively indolent clinical behavior
  - GI is most common site, lung is 2nd
- Carcinoid tumors represent 1-5% of all lung tumors
- Patients are usually younger than 40 years of age, nonsmoker
- Central airways
- Fewer than 2% associated with carcinoid syndrome
- Subclassifications include typical and atypical
  - Typical carcinoid: no p53 mutations or BCL2/BAX imbalance
    - Low grade, well-differentiated, slowly growing tumors
    - Rarely metastasize
    - Often cause endobronchial obstruction
  - Atypical: can see p53 mutations or BCL2/BAX imbalance
    - Intermediate-grade tumors with a higher mitotic rate and or necrosis

Carcinoid

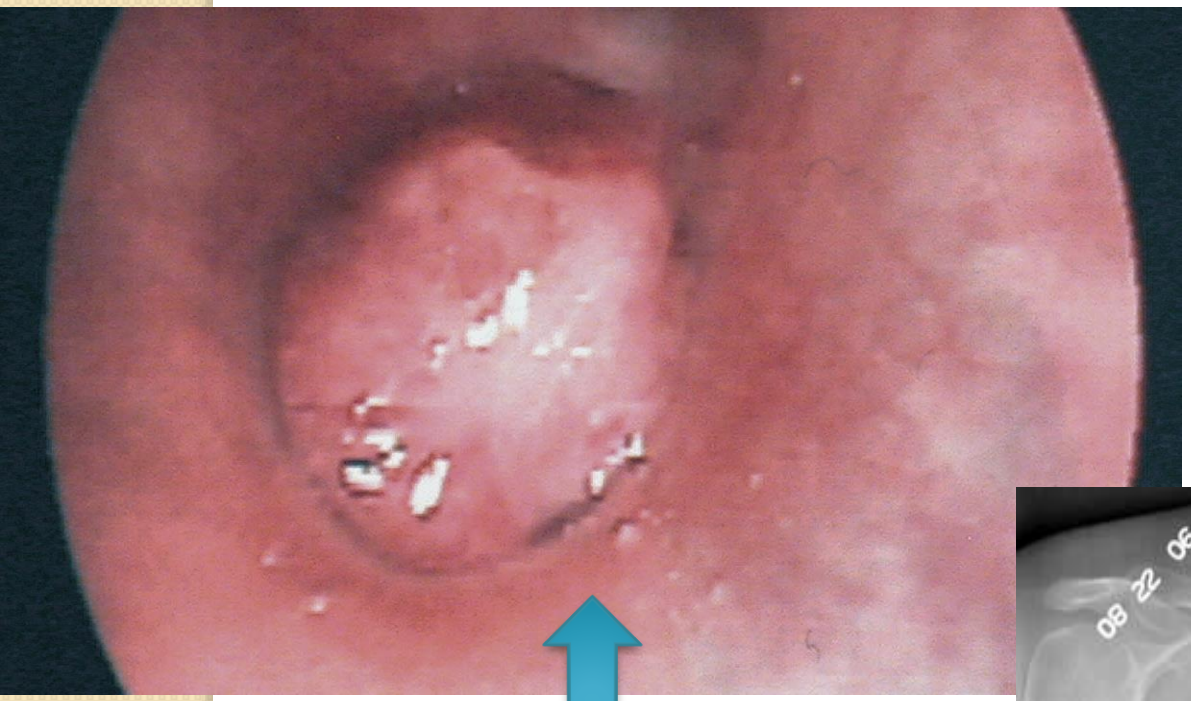
- Carcinoids may arise centrally or peripherally
- Rarely exceed 3-4 cm
- Histologically: organoid, trabecular, palisading, ribbon or rosette-like arrangement
- On electron microscopy, the cells exhibit the dene core granules characteristic of other neuroendocrine tumors

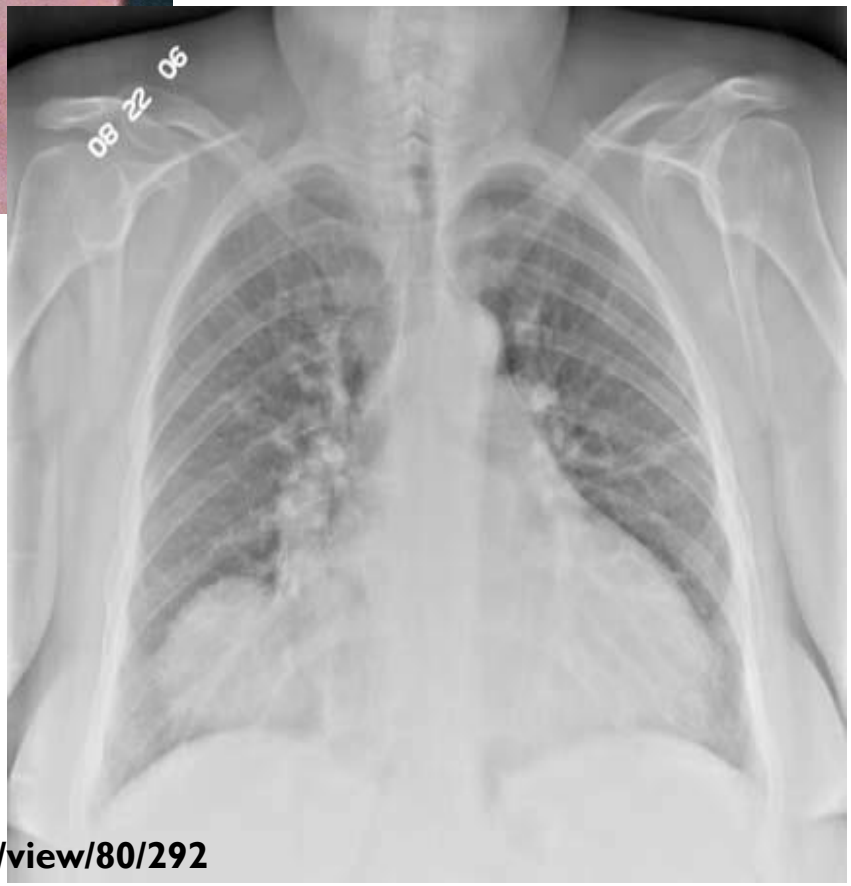




Carcinoid

- Clinical manifestations come from intraluminal growth, capacity to metastasize and the ability of some to elaborate vasoactive amines
- **Most** bronchial carcinoids are non-secretory and do not metastasize
- **Some** are rarely functioning and capable of producing the "carcinoid syndrome" (diarrhea, flushing and cyanosis)
- Patients can develop persistent cough, hemoptysis, secondary infections, bronchiectasis and atelectasis, especially with bronchial obstruction
- Usually amenable to complete resection





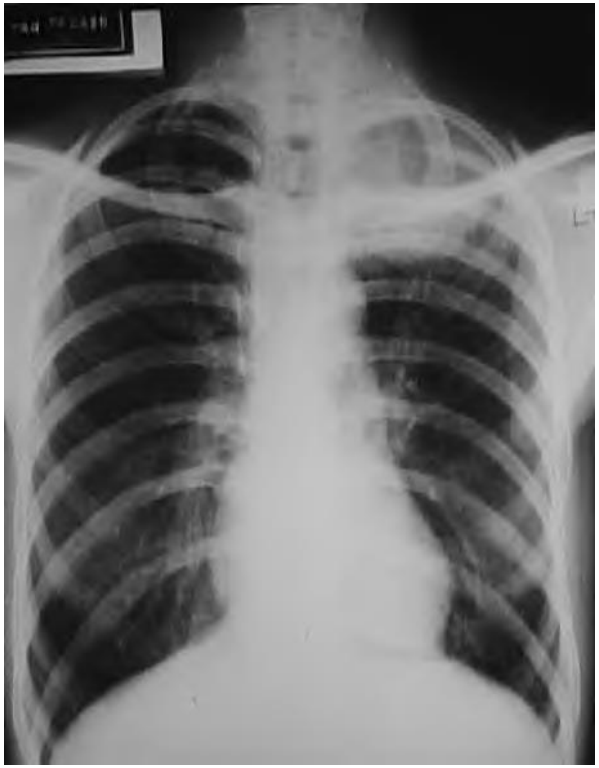
Carcinoid tumors are often endobronchial

http://najms.net/v02i01p017f01h/

http://radiology.casereports.net/index.php/rcr/article/view/80/292

Pancoast Syndrome

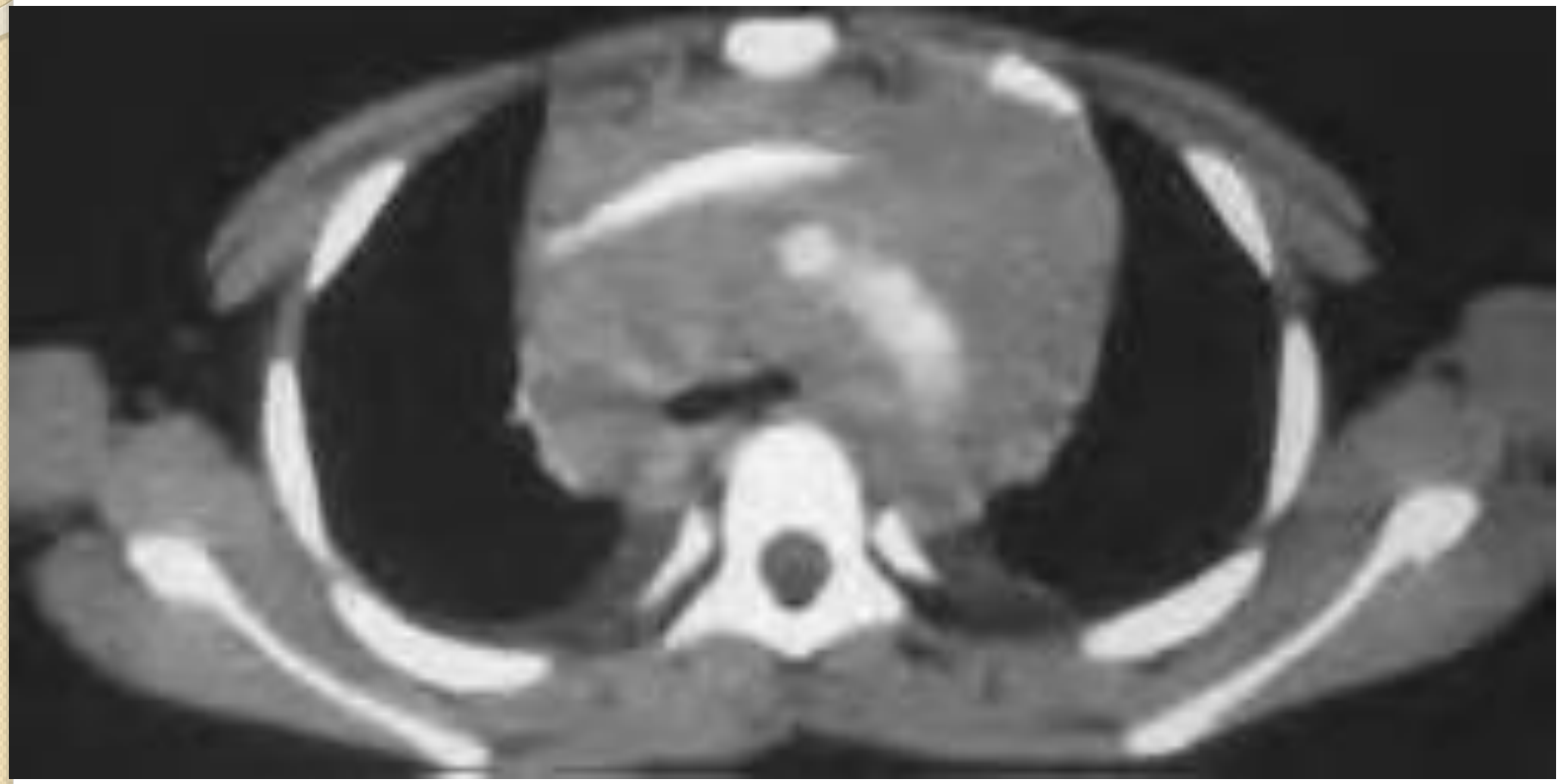
- Superior sulcus tumor
- Horner's syndrome
  - Ptosis
  - Miosis
  - Anhydrosis
- Brachial plexus
- Local erosion of vertebrae



Superior Vena Cava Syndrome

- Over 95% caused by malignancy
  - 5-10% lymphoma
- Histology: predominantly small cell or squamous
- May not be an "emergency" as previously thought
- Approach:
  - establish histologic diagnosis
  - institute therapy promptly (usually XRT)
  - steroids, diuretics, phlebotomy may help

Superior Vena Cava Syndrome



Metastasis

- Every organ system is susceptible to lung cancer metastasis
- Brain metastasis with deficits neurologically
- Bone metastasis with pain and fractures
- Spinal cord compression from bone or epidural metastasis
- Invasion of the marrow with cytopenias
- Liver metastasis causing biliary obstruction
- Lymph node metastasis in supraclavicular region
- Adrenal metastasis are common but rarely cause insufficiency

Clinical Evaluation

- Stage Patient: clinical stage and pathologic stage
- History and Physical
  - Cough, hemoptysis, exposures
  - Weight loss
- CT of chest and abdomen/pelvis with contrast,
- PET (sensitive for metastasis, recurrence)
- CT Brain/MRI Brain
- Bone Scan
- Review of any prior films very important
- Tissue diagnosis
  - Bronchoscopy (degree of obstruction/recurrence)
  - Mediastinoscopy
  - VATS/Thoracotomy

New Bronchoscopy Modalities

- EBUS
  - Endobronchial ultrasound→ will be able to get tissue samples from many more nodal stations without invasive surgical procedures
- Navigational Bronchoscopy
  - Via GPS mapping

PET Scans

- Whole Body Positron-emission Tomography
  - Nuclear medicine, functional imaging technique
  - 18F-fluorodeoxyglucose as a tracer (glucose analogue)
  - "Metabolic Imaging Technique"
    - Increased metabolism of glucose in all tumor cells
      - Carcinomas metabolize the tracer and "light-up" on the image
      - Concentrations of tracer imaged will indicate tissue metabolic activity by virtue of the regional glucose uptake
    - ~ 95% sensitivity for detecting primary bronchial tumors→ if lesion is greater than 1 cm!

Clinical Presentation

- 10% Asymptomatic at Time of Presentation!

Symptoms of lung cancer in over 3500 patients at presentation

Symptom	Patients (percent)
Cough	45-74
Weight loss	46-68
Dyspnea	37-58
Chest pain	27-49
Hemoptysis	27-29
Bone pain	20-21
Hoarseness	8-18

Modified from: Hyde, L, Hyde, CI. Chest 1974; 65:299-306 and Chute CG, et al. Cancer 1985; 56:2107-2111.

Associated Presentations

- Large Airway Obstruction
- Obstructive Pneumonitis
  - Obstructive pneumonia
- Atelectasis
  - Especially with endobronchial lesion
- Lymphangitic spread
- Pleural or Pericardial Effusion
- Hemopytsis

Lung Cancer Screening

Mayo Lung Project

- Randomized controlled trials have NOT demonstrated a reduction in mortality from screening with CXR or sputum cytology

Low Dose Spiral Chest CT Screening

- Radiation dose exposure is one third that of a standard CT scan
- NLST
  - Large randomized control trial of annual low-dose CT screening in patients with a 30+ pack year history of smoking (including those who quit in the last 15 years) demonstrated a decrease in lung cancer and all-cause mortality
  - *High rate of false + (non-cancer) findings causing additional testing and additional procedures
  - Yearly CXR has NOT been shown to be effective for lung cancer screening and should NOT be done (Grade 1A level of evidence)

NLST Criteria

- Age 55-74
- Current heavy (>30 pk-yr) or former smoker (quit within 15 yrs)
  - No CT within the last 18 months
  - Able to withstand lung cancer treatment
- Low dose helical CT scan
  - Single breath hold
  - 1.5 mSv (a standard CT is 8-12 mSv)
  - Read by thoracic radiologists

Solid Nodules		<6mm (<100mm³)	6 to 8mm (100mm³-250mm³)	>8mm (>250mm³)	Comments Volumes are approximate
Single	*Low risk**	No routine follow-up	6 to 12 months CT, then consider 18-24 months CT	Consider 3 months CT, PET-CT, or tissue sampling	<6mm do not require routine follow-up, but certain high risk cases with suspicious morphology and/or upper lobe location may warrant 12 month follow up. (Recommendation 1A)
	*High risk**	Optional 12 months CT	6 to 12 months CT then 18-24 months CT		
Multiple	*Low risk**	No routine follow-up	3 to 6 months CT, then consider 18 to 24 months CT		Use most suspicious nodule as guide to management. Follow-up intervals may vary according to size and risk (Recommendation 2A).
	*High risk**	Optional 12 months CT	3 to 6 months CT, then 18 to 24 months CT		

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Subsolid Nodules		<6mm (<100mm^3)	≥6mm (>100mm^3)	
Single	Groundglass	No routine follow-up	6 to12 months CT to confirm persistence, then CT every 2 years until 5 years	In certain suspicious nodules <6mm, consider follow-up in 2 and 4 years. If solid component(s) or growth develops, consider resection. (Recommendations 3A and 4A).
	Part-Solid	No routine follow-up	3-6 month CT to confirm persistence. If unchanged and solid component remains <6mm: annual CT for at least 5 years	In practice, part-solid nodules cannot be defined as such until ≥6mm, and nodules <6mm do not usually require follow-up. Persistent part solid nodules with solid components ≥ 6mm should be considered highly suspicious. (Recommendations 4A - 4C)
Multiple	3 -6 months CT. If stable consider 2 and 4 year CT		3 to 6 months CT Subsequent management based on the most suspicious nodule(s)	Multiple <6mm pure groundglass nodules are usually benign, but consider follow-up in selected high-risk cases at 2 and 4 years (Recommendation 5A).

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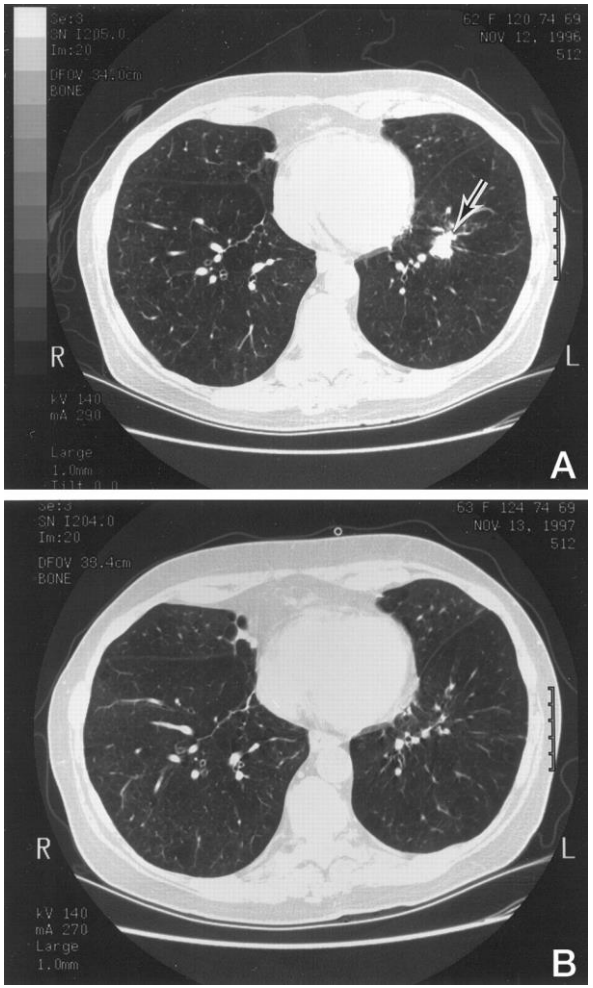
Treatment of SCLC

- LIMITED
  - Radiation and Chemotherapy
  - PCI for complete responders
  - Occasionally surgery
- EXTENSIVE
  - Chemotherapy
  - PCI for complete responders
  - Radiation therapy for symptomatic metastasis (bone, epidural, brain)

Surgical treatment is rarely possible

NSCLC: Stage I and II Treatment

- Complete surgical resection
- Postoperative adjuvant chemotherapy for Stage II and possibly Stage Ib
- Patients who refuse chemotherapy or are not candidates may try radiation therapy



NSCLC: Stage III Treatment

- Locoregionally advanced disease due to primary tumor extension into extrapulmonary structures (T3 or T4) or mediastinal lymph node involvement (N2 or N3) without evidence of distant metastases (M0)
- Stage IIIA
  - Combined modality approach
    - Chemotherapy followed by surgery and postoperative chemo or radiation
    - 5yr Survival 10-30% with surgery alone
    - Multimodality treatments improve survival
- Stage IIIB
  - Surgery NOT an option
  - Combination chemo & XRT→ 5yr survival 10%

NSCLC: Stage IV Treatment

- Chemotherapy or Palliative treatment only options
  - Palliative Therapy:
    - Brachytherapy
    - Laser Therapy
    - Airway stents and/or photodynamic therapy for airway obstruction
      - Radiotherapy→ Palliative Treatment of bronchial obstruction, painful bone metastases, or CNS metastases

Treatment

- The following are major contraindications to curative surgery or radiotherapy alone in patients with non-small cell lung cancer:
  - Extrathoracic metastasis
  - SVC, vocal cord/phrenic nerve paralysis
  - Malignant pleural effusion
  - Cardiac tamponade
  - Tumor within 2cm of carina
  - Contralateral lung metastasis
  - Bilateral endobronchial tumor
  - Metastasis to supraclavicular lymph nodes
  - Contralateral mediastinal node metastasis
  - Main pulmonary artery involvement

Treatment

- Chemotherapy: clearly effective for small cell, but relatively poor results for non-small cell carcinomas
- Laser Therapy: Nd-YAG laser for palliation of obstructing endobronchial lesions

Treatment:
Tyrosine Kinase Inhibitors

- Beyond histologic features, the status of molecular targets, such as the epidermal growth factor receptor (EGFR) gene, has been shown to correlate with response to treatment with EGFR tyrosine kinase inhibitors in patients with relapsed or refractory disease and in the first-line therapy setting.

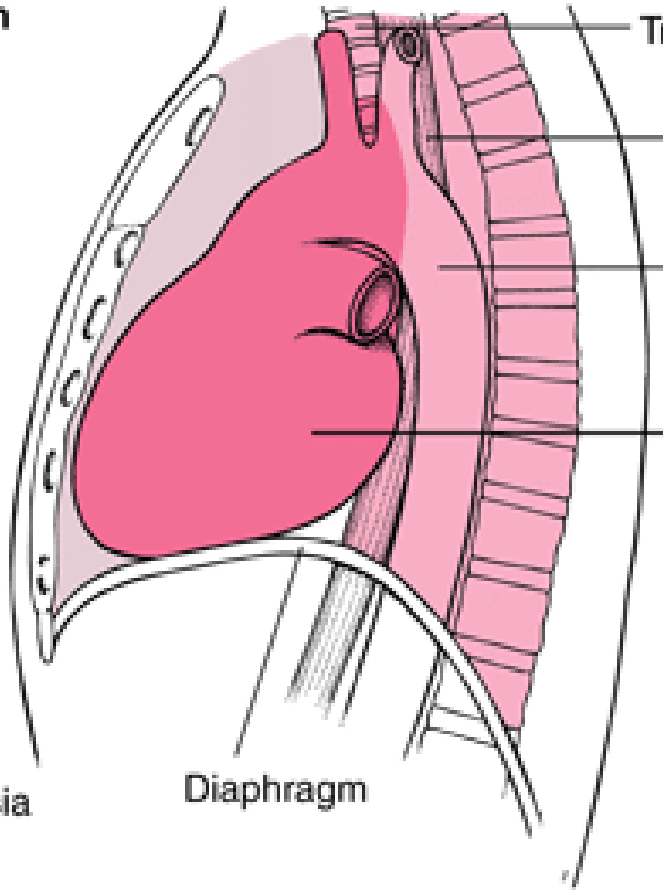
Treatment: SPN

- Xray density that is surrounded by normal aerated lung, with circumscribed margins > 5cm
- 35% of such lesions are malignant (primary)
- "To resect or not to resect?" that is the question
- The following favors resection:
  - Young, large lesion, lack of calcification, chest symptoms, atelectasis, pneumonitis, adenopathy, growth revealed via x-rays
- Lack of growth over a > 2 year period and calcification would indicate a benign nature
- Dense central nidus, multiple punctate foci, "bull's eye" (granuloma) and "popcorn ball" (hamartoma) calcifications suggest benign lesion

Mediastinal Mass

Anterior mediastinum
- Aneurysm
- Angiomatous tumor
- Goiter
- Lipoma
- Lymphoma
- Morgagni hernia
- Parathyroid tumor
- Pericardial cyst
- Teratoma
- Thymoma
- Thyroid tumor

Middle mediastinum
- Bronchogenic cyst
- Bronchogenic tumor
- Lymph node hyperplasia
- Lymphoma
- Pleuropericardial cyst
- Vascular masses



Posterior mediastinum
- Aneurysm
- Bronchogenic tumor
- Enteric cyst
- Esophageal diverticula
- Esophageal tumor
- Neurogenic tumor

Benign Lung Neoplasms

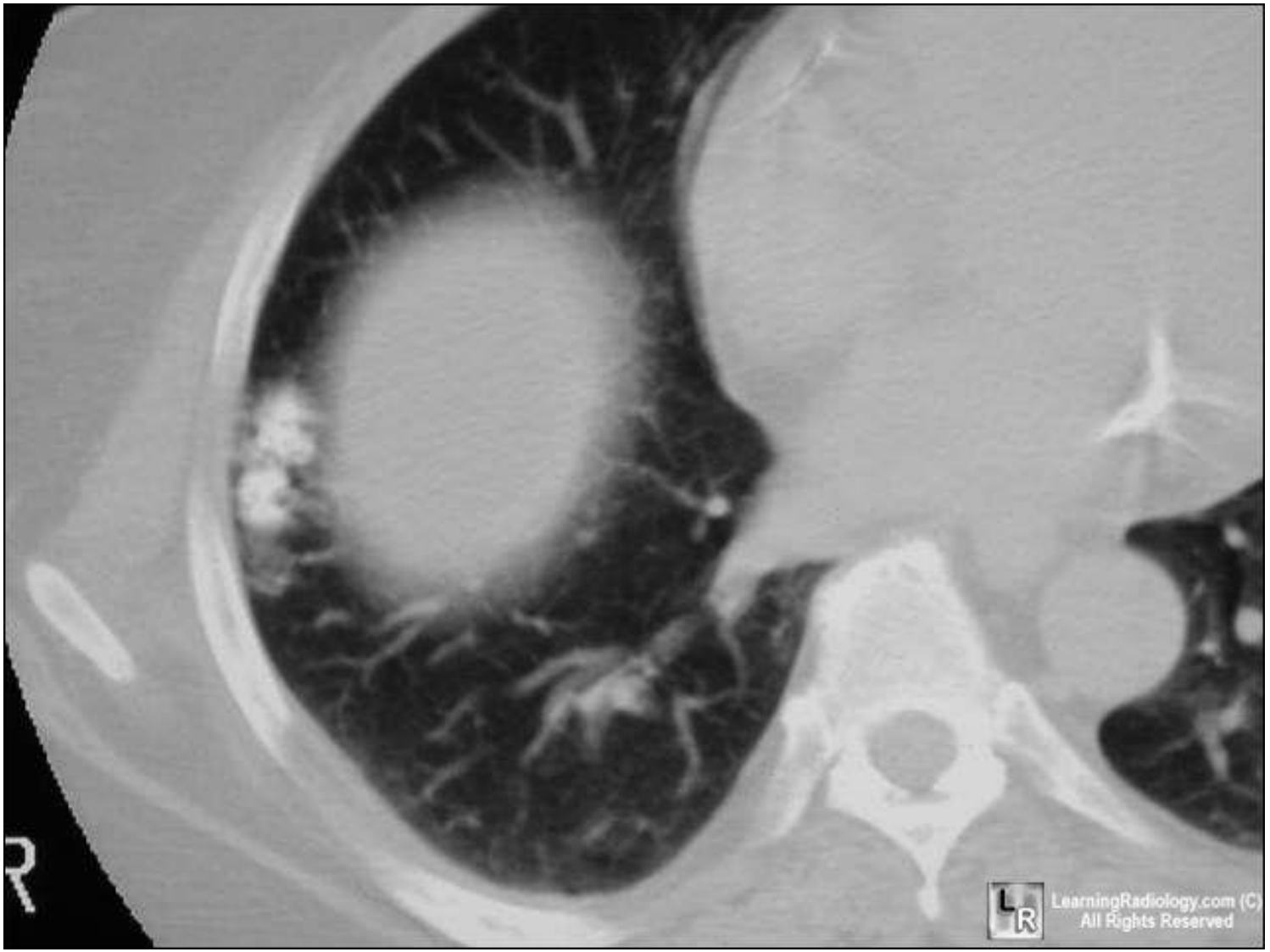
- Represents < 5% of all primary tumors including:
  - Bronchial adenomas
  - Hamartomas (popcorn calcification)
  - Uncommon neoplasms
    - Chondromas, Fibromas, Lipomas, Hemangiomas, Leiomyomas, Teratomas, Pseudolymphomas

Bronchial Adenomas

- 80% are central
- Slow growing, endobronchial lesions
- Represent 50% of all benign pulmonary lesions
- 80-90% are carcinoids
- 10-15% are adenoid cystic tumors (cylindromas)
- 2-3% are mucoepidermoid tumors

Hamartomas

- Peak incidence age 60 with a preponderance in males
- Histologically they contain normal pulmonary tissue components in a disorganized fashion
- Peripheral, clinically silent and benign in behavior
- Radiological findings are "popcorn" calcification
- The lesions usually have to be resected if patient is a smoker – VATS can be used to minimize problems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Paraneoplastic Syndromes

- Clinical syndromes caused by underlying malignancy
- Mediated by humoral factors secreted by tumor cells or by responses to tumor antigen
- Associated with many types of lung cancer
- Can be the first manifestation of disease or disease recurrence
- 10% lung cancer patients present with a paraneoplastic syndrome

Paraneoplastic Syndromes

- Adenocarcinoma
  - Hypertrophic pulmonary osteoarthropathy
- Small Cell Lung Cancer
  - SIADH (Hyponatremia)
  - Cushing syndrome (ACTH producing)
  - Carcinoid syndrome
  - Neurogenic syndromes
    - Eaton-Lambert (proximal muscle)
    - Peripheral neuropathy
- Squamous cell cancer
  - Hypercalcemia (PTH related peptide)
- Bronchial Carcinoid
  - Cushing syndrome

Hypercalcemia

- Tumor secretion of PTH related peptide, increased active metabolite of vitamin D, and/or localized osteolytic hypercalcemia
- Occurs in 10-25% lung cancer patients
- Squamous Cell
- Median survival lung ca plus hypercalemia: one month
- s/sx: polydipsia, GI sx-nausea, abd pain, mental status changes, dysrhythmia, hypotension, dehydration, renal dysfunction

SIADH

- Unregulated ADH production by tumor
- Leads to water retention by reabsorption in renal tubules
- Euvolemic hypo-osmolar hyponatremia
- s/sx: weakness, headache, nausea, altered mental status, coma, seizure

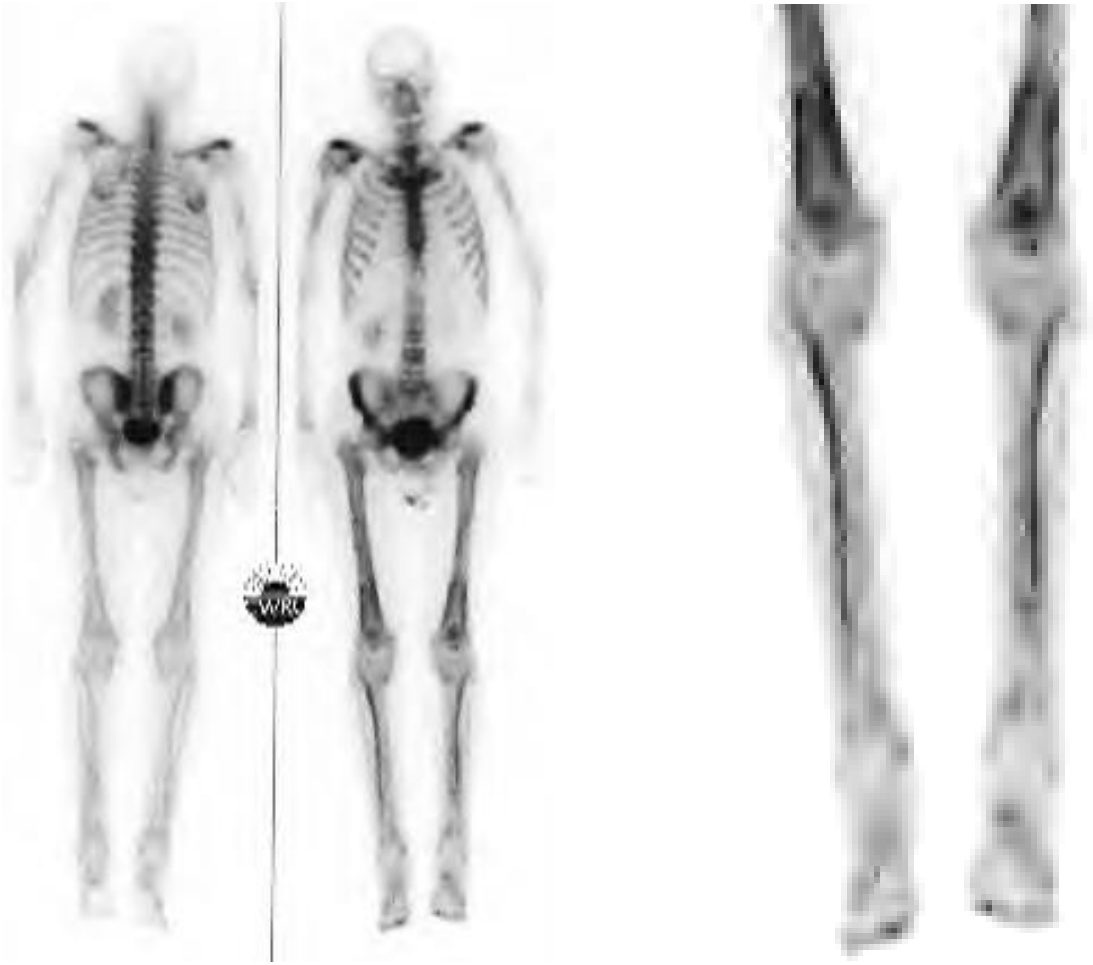
Cushing Syndrome

- Ectopic secretion of ACTH
- SCLC, bronchial carcinoid
- s/sx: weight gain, moon facies, acne, purple striae, proximal muscle weakness, peripheral edema, skin hyperpigmentation

Hypertrophic Pulmonary Osteoarthropathy

- Digital clubbing
- Painful symmetrical arthropathy (wrists, elbows, ankles, knees)
- Periosteal new bone formation (distal long bones)
- Adenocarcinoma
- Overexpression of vascular endothelial growth factor

Hypertrophic Pulmonary Osteoarthropthy



"Lose some weight, quit smoking, move around more, and eat the carrot."