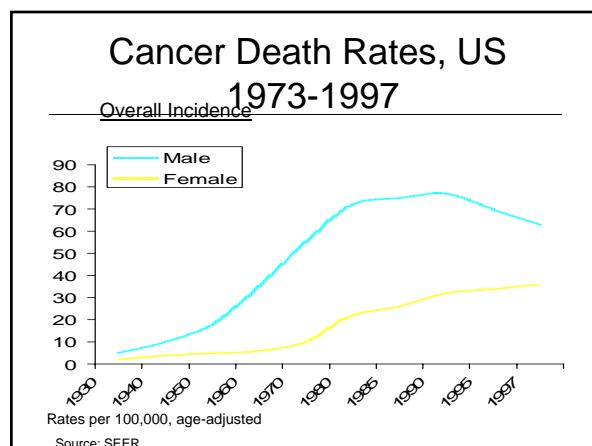
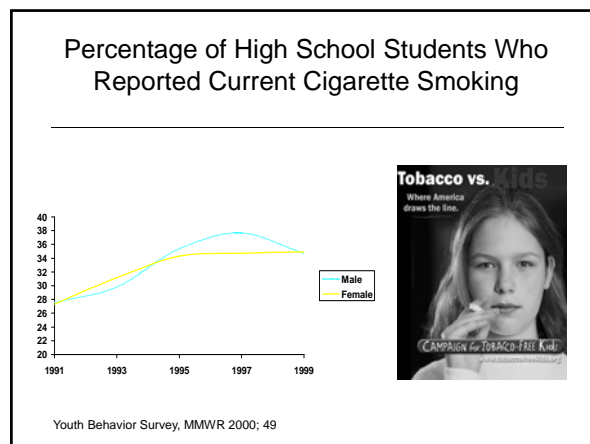
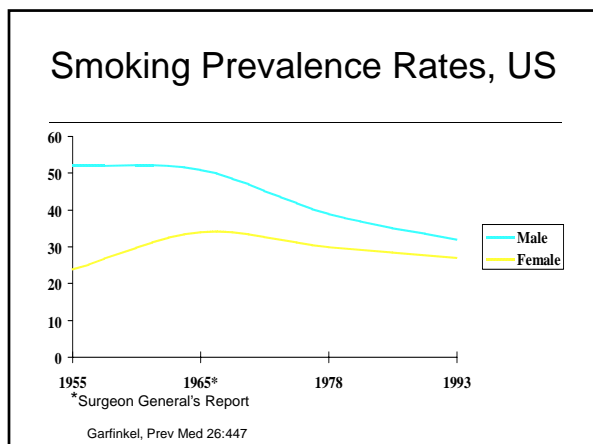


- ### Lung Cancer Risks
- Cigarette Smoking
 - Environmental Tobacco Smoke
 - Other Carcinogens
 - Asbestos, Arsenic, Radon,
 - Bis(chloromethyl) ether, Chromium, Foundry fumes, nickel, mustard gas, coke oven emissions
 - Air Pollution (foundries, diesel exhaust)
 - Family History
 - Diet (Vitamins A,C, E and selenium "protective")





Risk of lung cancer, men vs. women

<u>Pack-years</u>	<u>MALES</u>	<u>FEMALES</u>
0	1.0	1.0
1-19	2.4 (1.4-4.1)	6.8 (4.1-11.4)
20-39	5.6 (3.6-8.7)	11.2 (7.5-16.8)
40-49	11.6 (7.7-17.6)	21.4 (14.3-32.3)
>50	13.8 (9.2-20.9)	32.7 (19.0-56.2)

Relative risk for developing lung cancer is 1.25 for women for any "dose" of tobacco
Zang, JNCI 88:183, 1996

- ### Presentation of Lung Cancer
- Local Symptoms
 - Cough
 - Dyspnea
 - Hemoptysis
 - Chest Pain
 - SVC Syndrome
 - Wheezing
 - Systemic Symptoms
 - Constitutional
 - Skeletal
 - Clubbing
 - Hypertrophic Pulmonary Osteoarthropathy
 - Endocrine
 - SIADH (sclc)
 - Hypercalcemia (squamous)
 - Cushing's Syndrome (sclc)
 - Neurologic
 - Horner's Syndrome
 - Eaton-Lambert syndrome (sclc)
 - Vascular
 - Thrombophlebitis, DIC

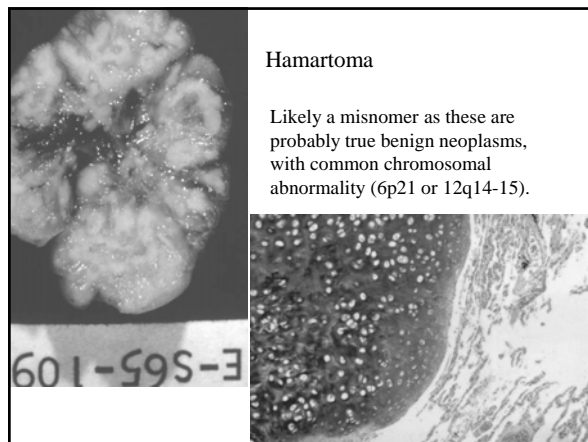
Differential Diagnosis

- Benign
 - Granuloma
 - Hamartoma
- Malignant
 - Metastasis
 - Primary Lung Ca
 - Small Cell
 - Carcinoid
 - Non-small Cell
 - » Adenocarcinoma
 - » Squamous
 - » Large Cell

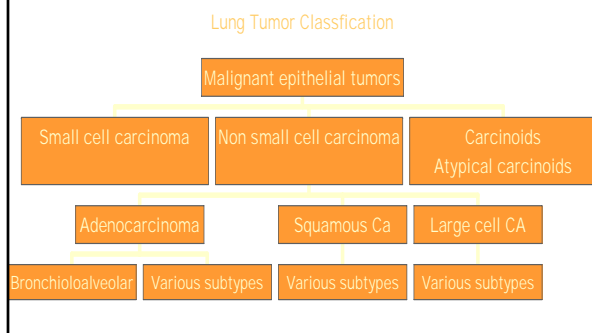
- ### Pathologic diagnosis: specimen types
- Transbronchial biopsy
 - Transthoracic needle biopsy
 - Cytology
 - Bronchial brushing
 - Lavage
 - Aspiration (transthoracic or transbronchial)
 - Thoracotomy/VATS

Lung tumors - Benign

- The majority of pulmonary neoplasms are malignant
- Benign tumors/lesions
 - Hamartoma (most common)
 - Mesenchymal- leiomyoma, lipoma, chondroma (all unusual)
 - Alveolar adenoma (rare)



Malignant tumors - classification

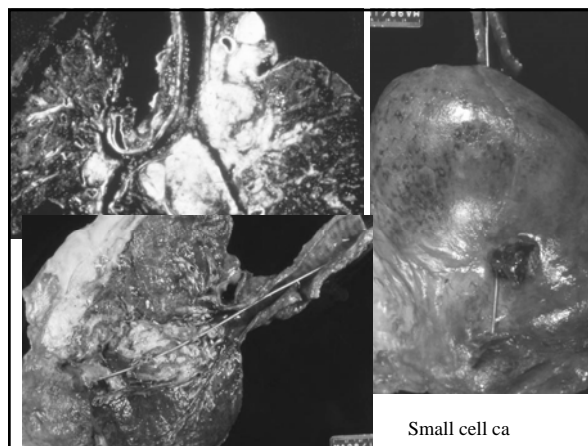


Small cell carcinoma

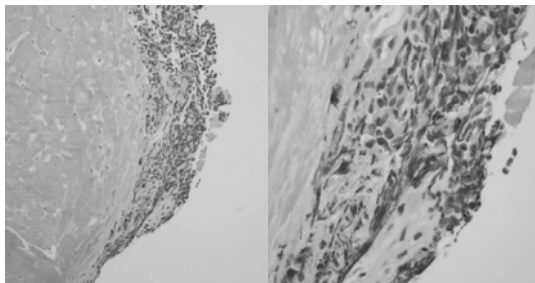
- Usually hilar/ central tumor
- The majority have extrapulmonary spread at time of presentation.
- Only 5% present as early stage disease.
- Critical divide between small cell and non-small cell carcinoma
 - Small cell carcinoma staged differently, treated with chemoradiation not surgery.

Small cell carcinoma

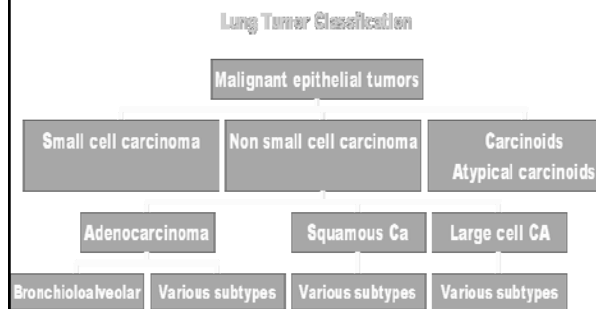
- High grade tumor
- Small cells with high nuclear to cytoplasmic ratio
- Nuclear molding with stippled, salt and pepper chromatin
- Frequent mitosis and apoptosis
- “Crush” artifact - very fragile cells
- Neuroendocrine differentiation can be demonstrated by electron microscopy and immunohistochemistry (few neurosecretory granules due to poor differentiation)



Small Cell

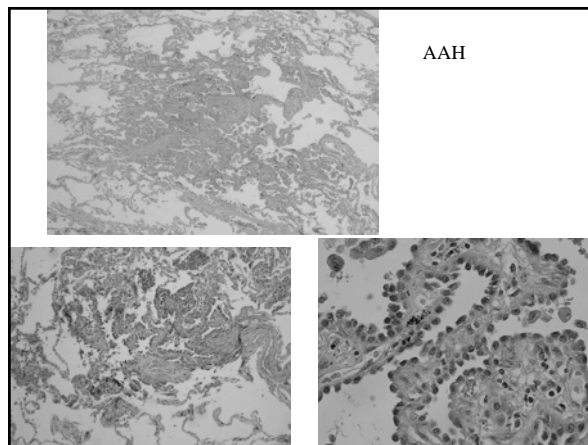


Malignant tumors - classification



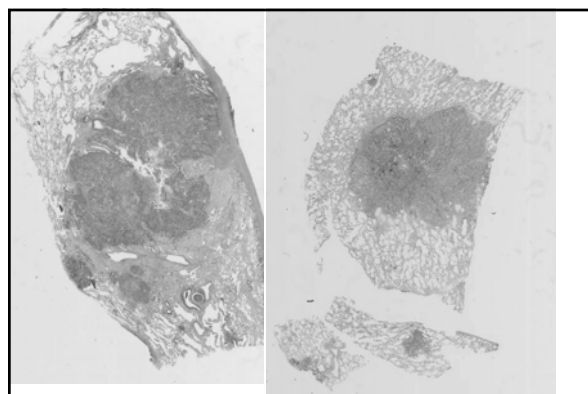
Atypical adenomatous hyperplasia-
adenocarcinoma precursor

- Focal, 5.0 mm or less, with defined borders
- Alveoli lined by cuboidal to low columnar cells with variable atypia
- Alveolar walls may be slightly thickened
- Non-mucinous
- Clinical significance unclear (?time to progression to carcinoma)



Adenocarcinoma

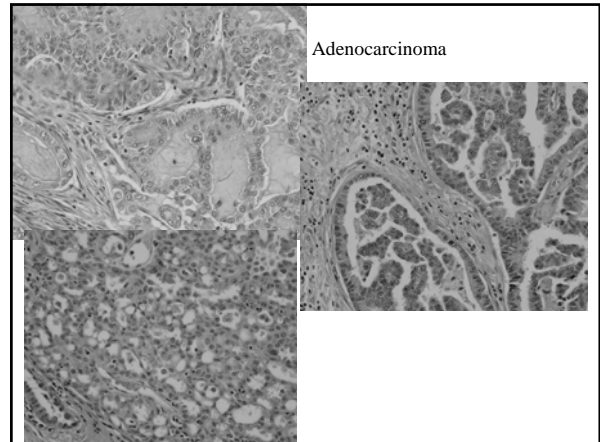
- Most often a peripheral tumor
- Many are near pleura and cause pleural puckering.
- Cut surface can be mucoid or firm, depending on degree of fibrosis and mucin production
- Small tumors can be associated with lymph node and distant metastasis.



Adenocarcinoma

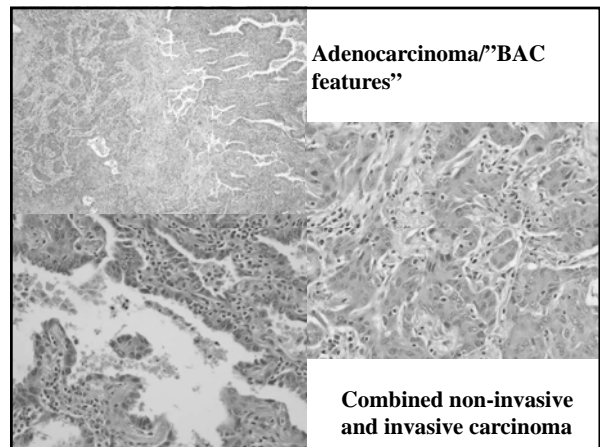
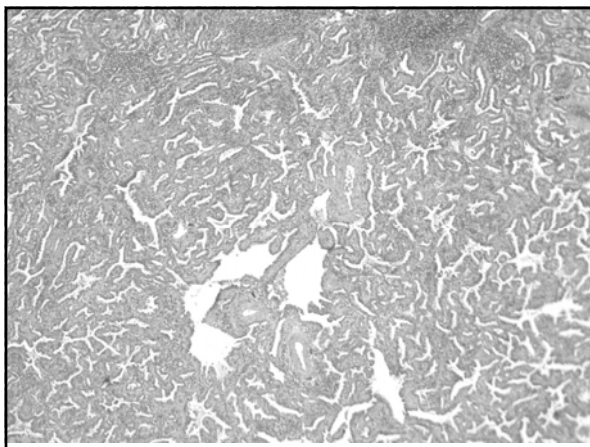
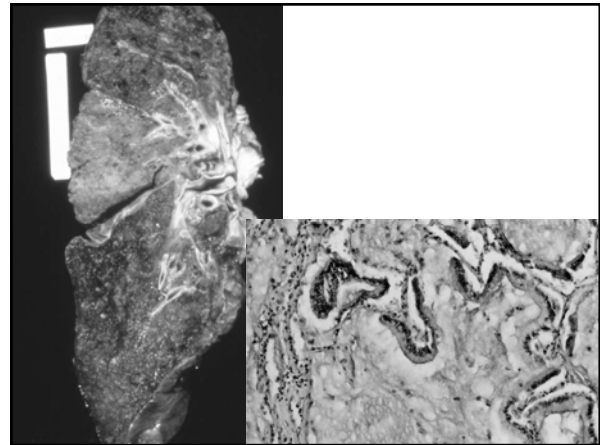
Adenocarcinoma

- Histologic varieties are multiple, including solid, acinar, papillary, mucinous types even within the same tumor
- Rarer types include signet ring morphology
- Differentiation can recapitulate goblet cell, Clara cell or type II pneumocyte differentiation
- Bronchial glands can produce a distinct subtype mimicking salivary gland type tumors
 - These unusual tumors are central and in younger patients



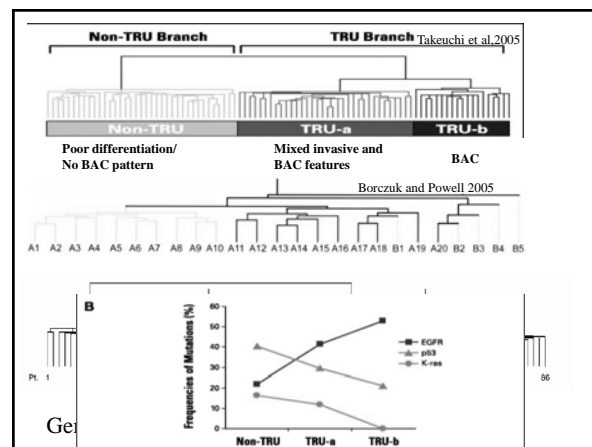
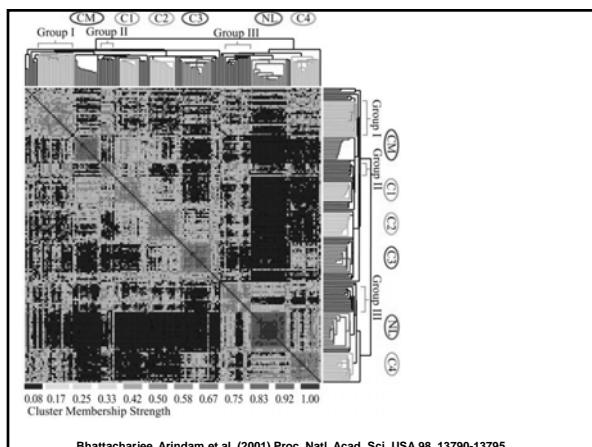
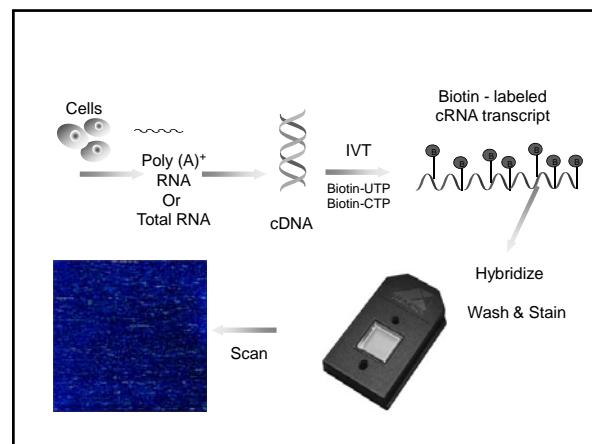
Adenocarcinoma - Bronchioloalveolar

- Distinct morphologic and clinical variant
- Grows along pre-existing alveoli and terminal bronchioles without stromal invasion
- Grossly can form a nodule, but can also produce diffuse disease mimicking pneumonia
- Can be mucinous or non-mucinous.
- Often multifocal



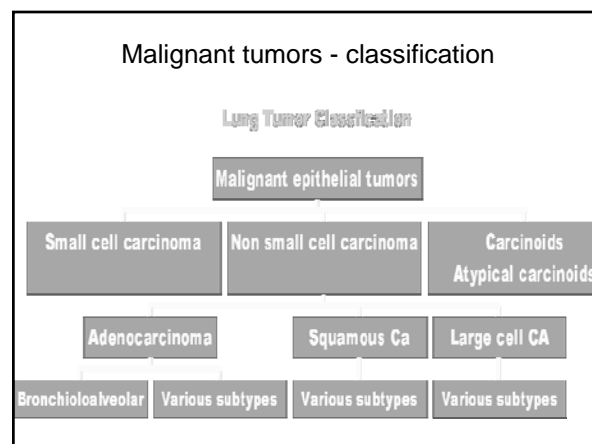
Is there a meaning to the histologic diversity of adenocarcinoma?

- Studies examining response to gefitinib (EGFR targeting tyrosine kinase inhibitor) found activating EGFR mutations in patients with favorable response.
- Gene profiling studies found distinct subclasses of adenocarcinoma.



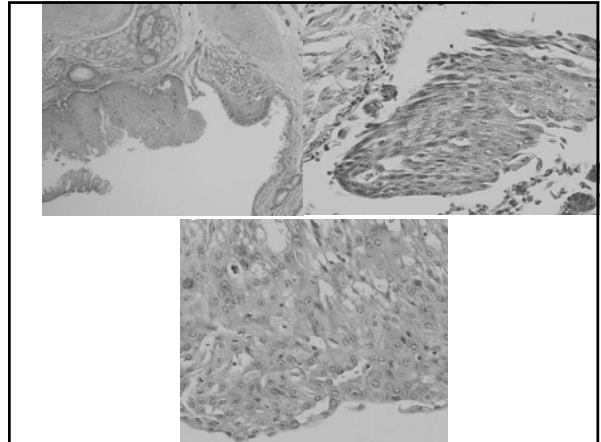
Are these observations relevant?

- EGFR mutation and amplification correlates with response to EGFR targeted agents (tyrosine kinase inhibitors gefitinib and erlotinib).
 - This subgroup of patients are also more likely to be women, non-smokers, and of Asian descent but not exclusively so.
- Activating K-ras mutations indicate resistance to these agents (about 30% of lung adenocarcinomas)
- Few, if any, lung adenocarcinomas have both activating K-ras and EGFR mutations in the same tumor.



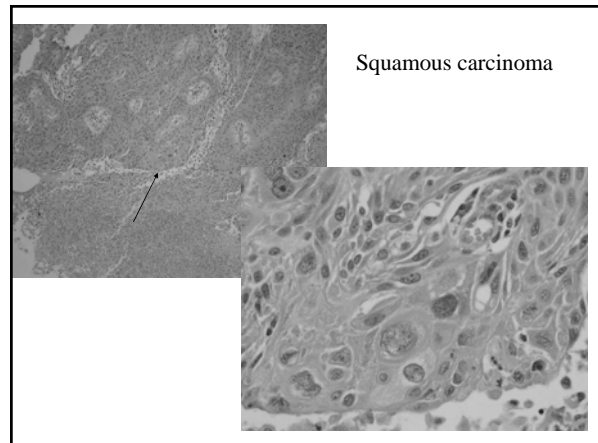
Squamous precursors

- Squamous metaplasia, dysplasia and carcinoma in situ in lung progresses in a sequence similar to the changes described in the head and neck and cervix.
- Koilocytosis is not common; this HPV viral cytopathic change is seen in papillomatosis of larynx and trachea (HPV 6/11)



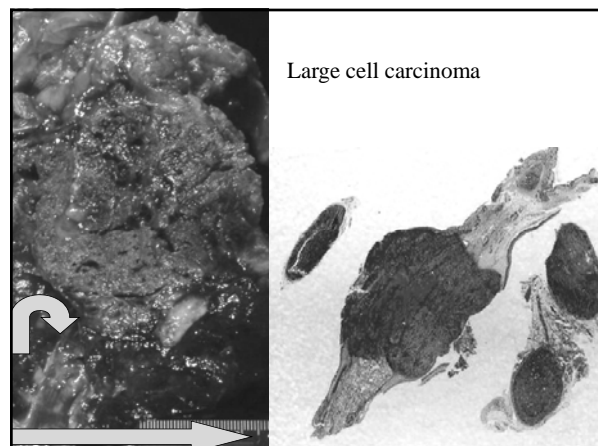
Squamous carcinoma

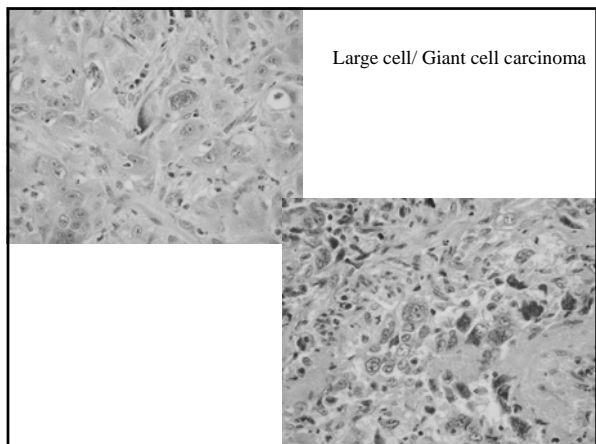
- Usually of bronchogenic origin; however can also arise from peripheral areas of squamous metaplasia
- Frequently have central necrosis
- Faster doubling time than adenocarcinoma; often larger at presentation
- Metastasis in relation to tumor size may occur later than adenocarcinoma



Large cell carcinoma

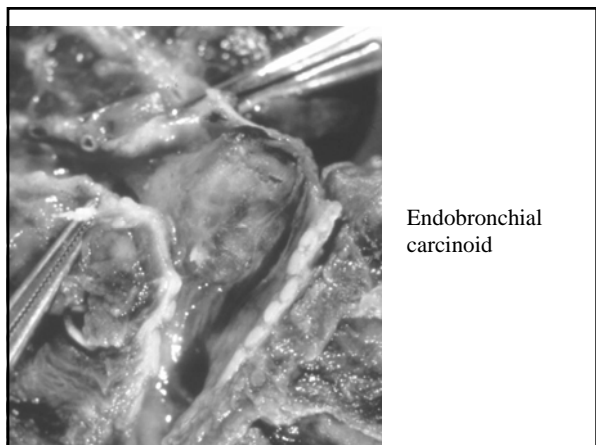
- This subtype shows no differentiation towards either squamous or adenocarcinoma
- Aggressive tumors with poor prognosis
- If subjected to ultrastructural examination, many of these tumors show either glandular or squamous differentiation.
- Nevertheless, these tumors are separated out because of their high grade and poor prognosis





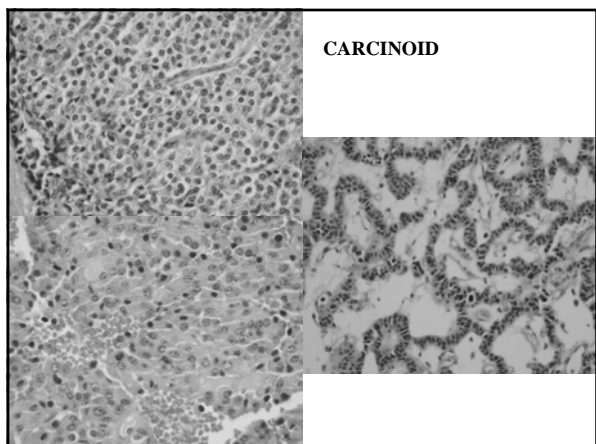
Carcinoids

- Malignant neoplasm of neuroendocrine cell origin
- Can be central or peripheral; central lesions can cause bronchial obstruction
- Project into bronchial lumen but often have intact mucosa above them (grow under the mucosa)
- Typical carcinoids are low grade malignancies; atypical carcinoids (mitoses and necrosis) are intermediate grade when compared to non-small cell carcinomas



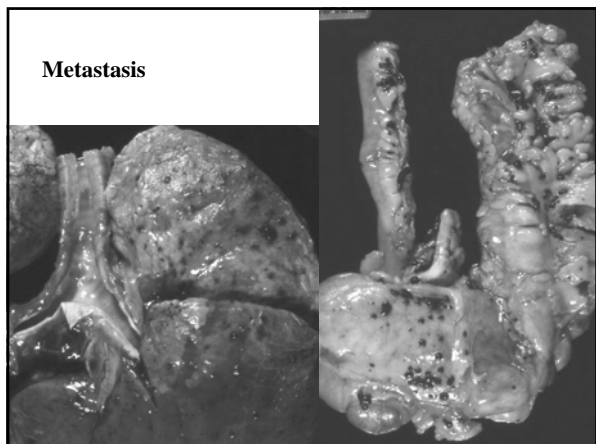
Carcinoids

- Histologic features
 - Nests and cords surrounded by delicate stroma
 - Uniform cells with salt and pepper chromatin
 - Neurosecretory granules are abundant and easily demonstrated by electron microscopy or immunohistochemistry (well differentiated tumors)



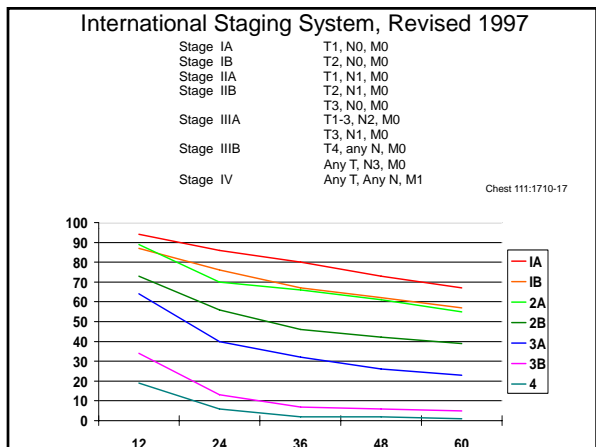
Metastatic Carcinoma

- The lung is a frequent site of metastatic tumor, both from extrapulmonary and intrapulmonary primaries.
- In autopsy series, between 20 and 50% of patients that expire from extra-pulmonary primaries have lung metastasis.
- Melanoma, sarcomas, renal cell carcinoma, germ cell tumors, breast carcinoma as well as carcinomas of bladder, larynx, thyroid and prostate



Lung Cancer Staging

- Small Cell Carcinoma
 - Limited- confined to hemithorax
 - Extensive
- Non-small Cell Carcinoma
 - T, N, M- Clinical Stage 1-4



Therapy- Non-small Cell Lung Cancer

- Stage I, II
 - Lobectomy + adjuvant chemotherapy
- Stage IIIa
 - Neoadjuvant chemotherapy, radiation, surgery
- Stage IIIb
 - Chemotherapy +/- radiation
- Stage IV
 - Chemotherapy

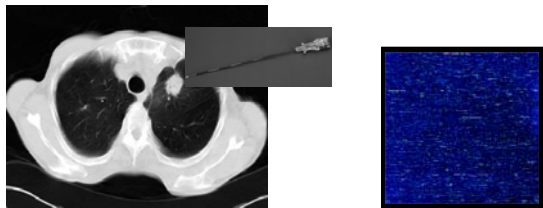
Therapy- small cell

- Limited
 - Chemotherapy + Radiation
- Extensive
 - Chemotherapy

CT Screening Assessment of Interval Growth

Benign or Malignant?

Gene Expression Signatures in Biopsy Specimens of Lung Cancer



Am J Respiratory and Critical Care Medicine 170: 167

Biopsy: Prognosis

High Risk for	Cancer Death	
	MYC	Gene transcription regulation
	TGFB1	Growth factor binding
	FHL2	Oncogenesis- β catenin
	CCNB1	G2/M transition
	LOXL2	Scavenger receptor
Low Risk		
	HLADPB1	Class II MHC
	SELENBP1	Selenium binding

