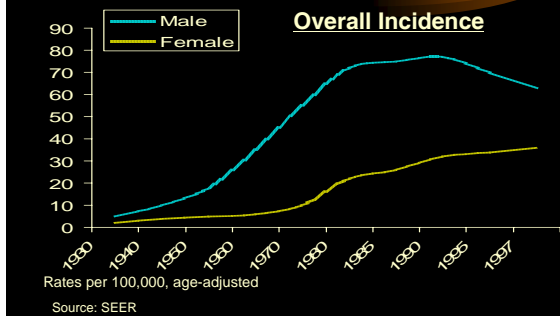


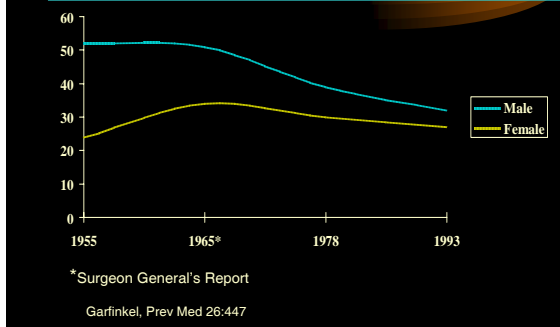
Lung Cancer Risks

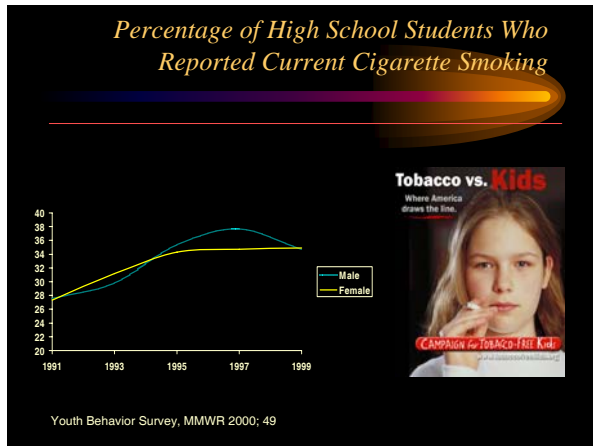
- Cigarette Smoking
 - Environmental Tobacco Smoke
- Other Carcinogens
 - Asbestos, Arsenic, Radon,
 - Bis(chloromethyl) ether, Chromium, Foundry fumes, nickel, mustard gas, coke oven emissions
- Air Pollution (foundries, diesel exhaust)
- Family History
- Diet (Vitamins A,C, E and selenium “protective”)

Cancer Death Rates, US 1973-1997

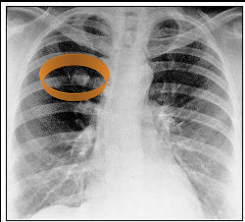


Smoking Prevalence Rates, US





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

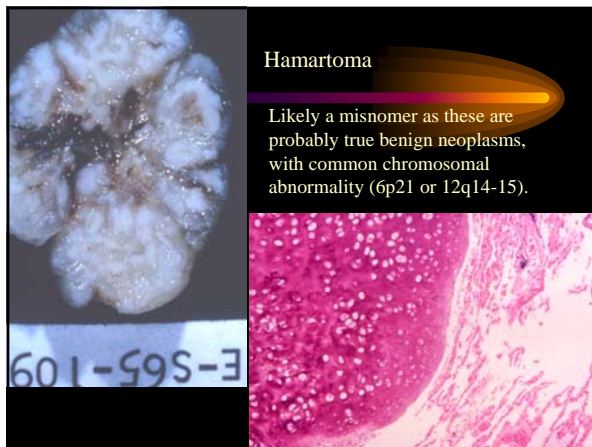
- ### Differential Diagnosis
- 
- Benign
 - Granuloma
 - Hamartoma
 - Malignant
 - Metastasis
 - Primary Lung Ca
 - Small Cell
 - Carcinoid
 - Non-small Cell
 - Adenocarcinoma
 - Squamous
 - Large Cell

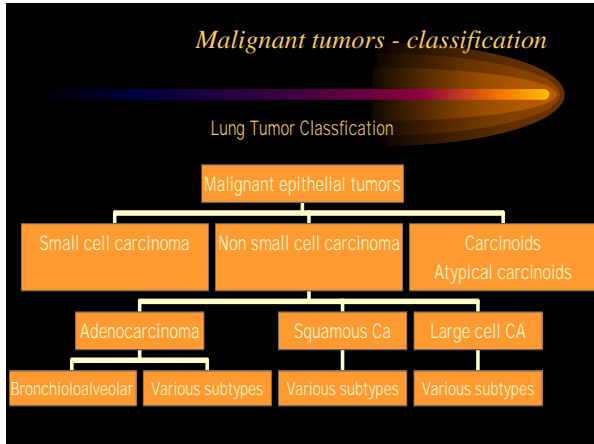
*Pathologic diagnosis:
specimen types*

- 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)



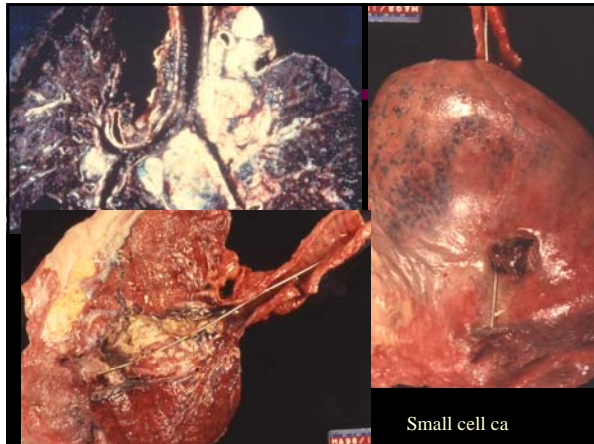


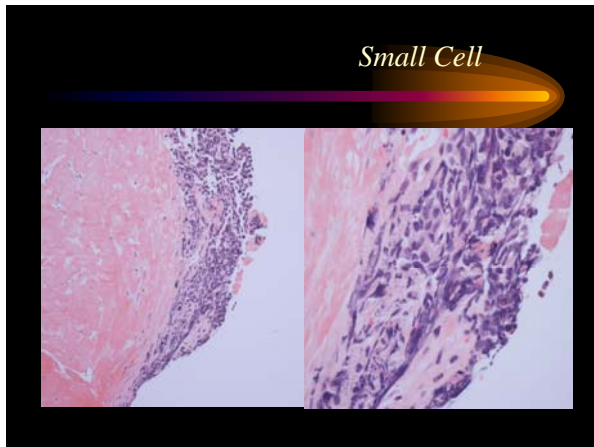
Small cell carcinoma

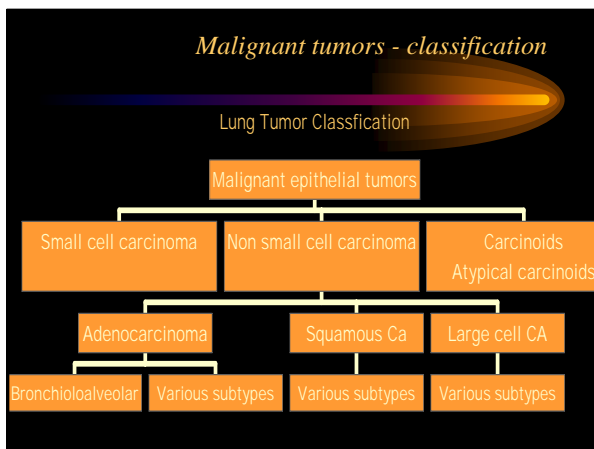
- Usually hilar/ central tumor
- The majority have extrapulmonary spread at time of presentation.
- Only 5% present as early stage disease.
- Critical divide between small cell and non-small cell carcinoma
 - Small cell carcinoma staged differently, treated with chemoradiation not surgery.

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)

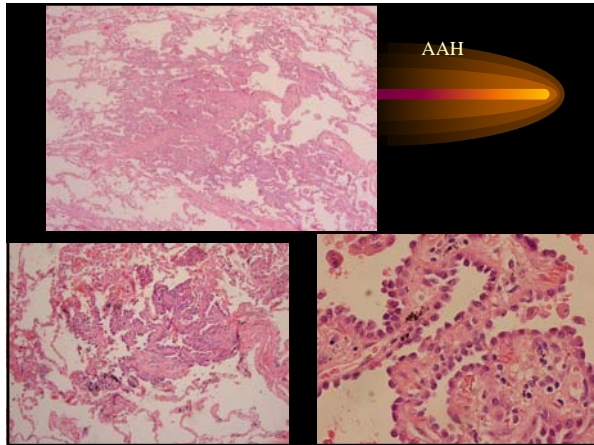






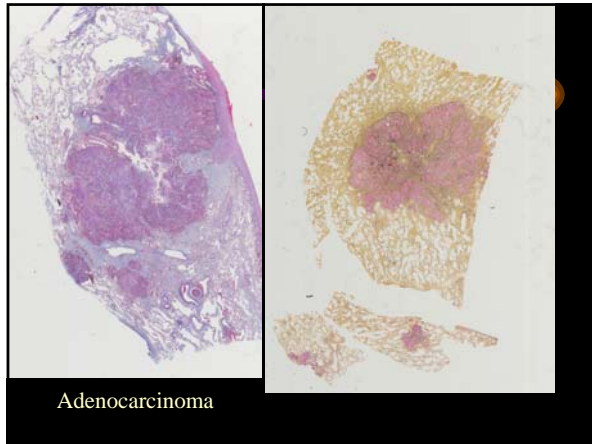
*Atypical adenomatous hyperplasia-
adenocarcinoma precursor*

- 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)



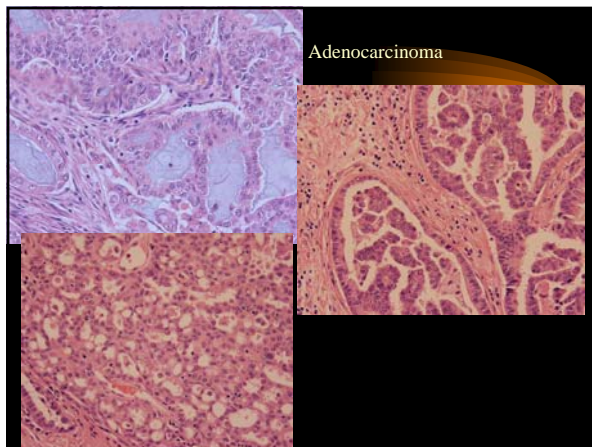
Adenocarcinoma

- 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.



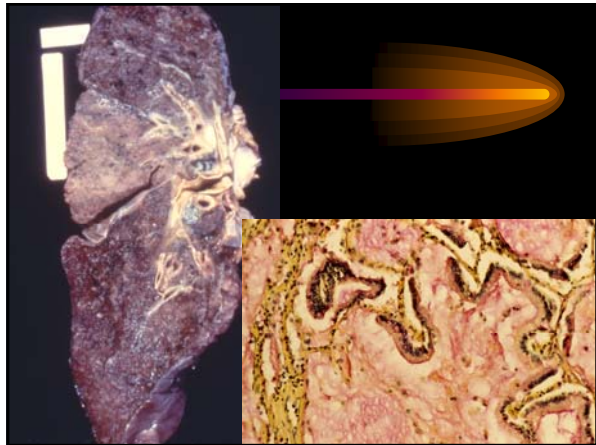
Adenocarcinoma

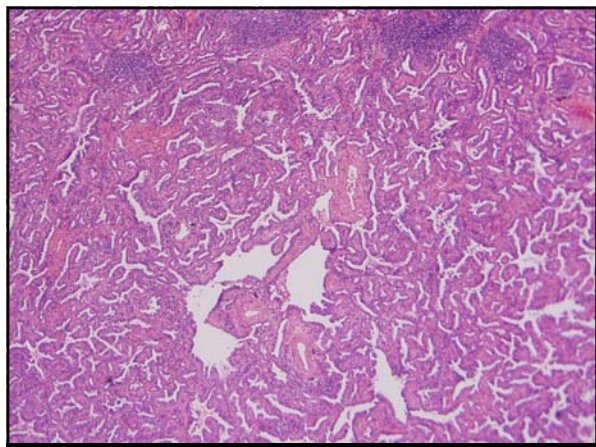
- Histologic varieties are multiple, including solid, acinar, papillary, mucinous types even within the same tumor
- Rarer types include signet ring morphology
- Differentiation can recapitulate goblet cell, Clara cell or type II pneumocyte differentiation
- Bronchial glands can produce a distinct subtype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

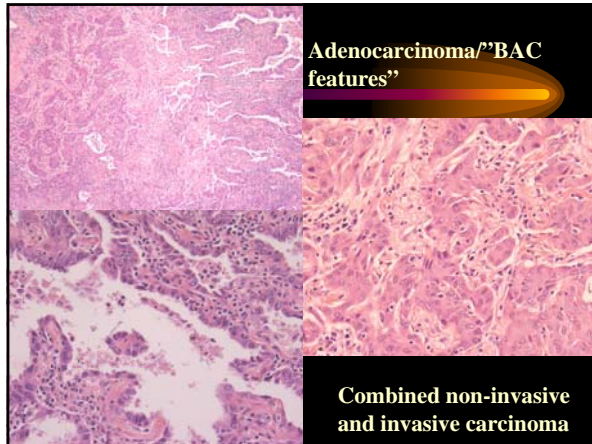


Adenocarcinoma - Bronchioloalveolar

- 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

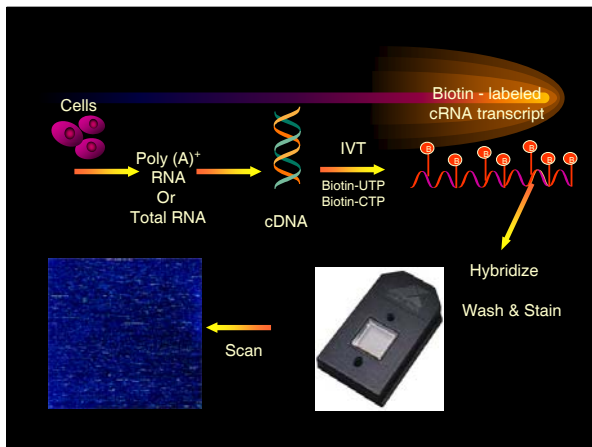


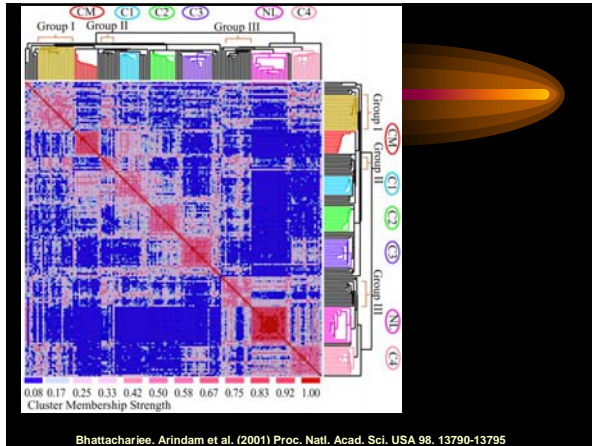


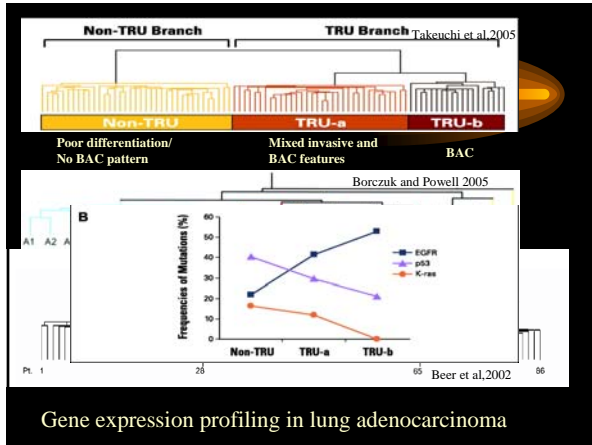


Is there a meaning to the histologic diversity of adenocarcinoma?

- 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.

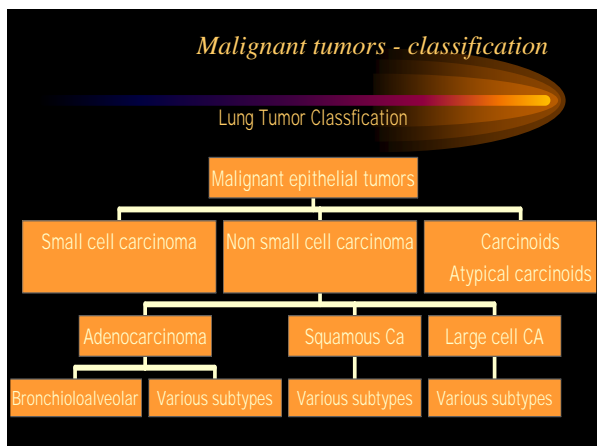






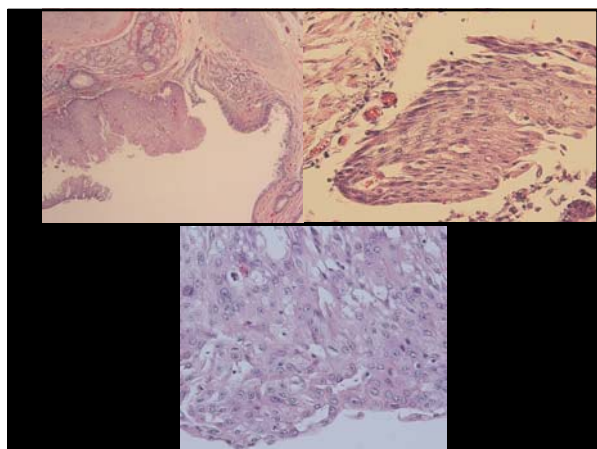
Are these observations relevant?

- 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.



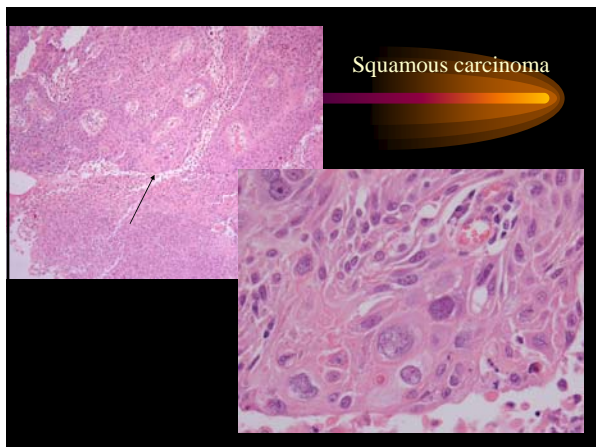
Squamous precursors

- 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)



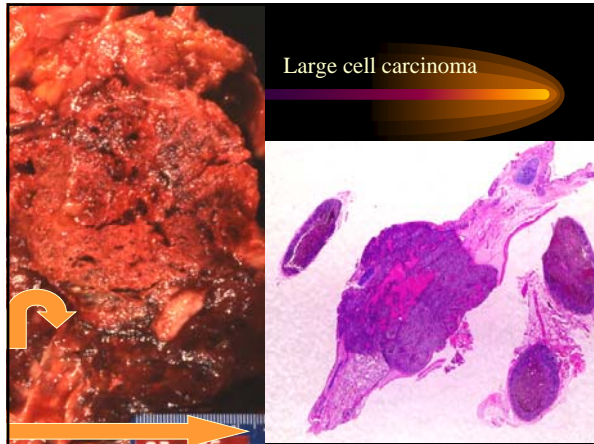
Squamous carcinoma

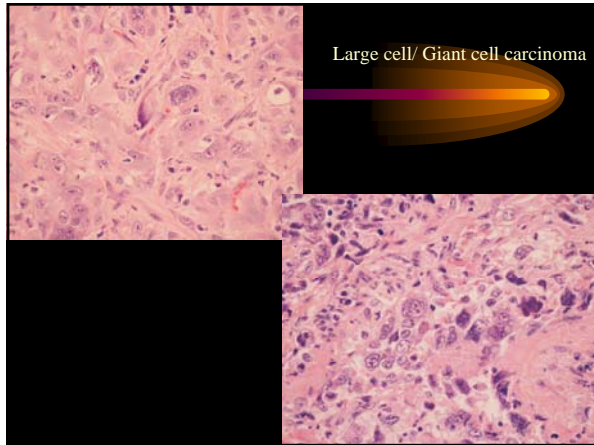
- Usually of bronchogenic origin; however can also arise from peripheral areas of squamous metaplasia
- Frequently have central necrosis
- Faster doubling time than adenocarcinoma; often larger at presentation
- Metastasis in relation to tumor size may occur later than adenocarcinoma



Large cell carcinoma

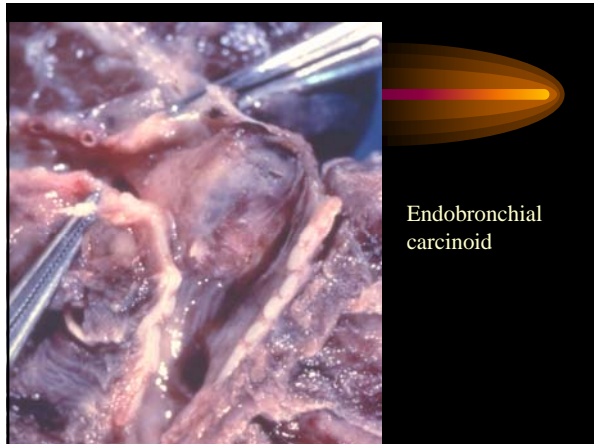
- This subtype shows no differentiation towards either squamous or adenocarcinoma
- Aggressive tumors with poor prognosis
- If subjected to ultrastructural examination, many of these tumors show either glandular or squamous differentiation.
- Nevertheless, these tumors are separated out because of their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

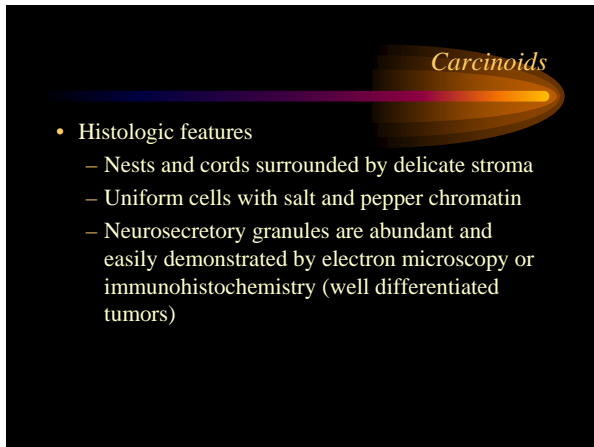


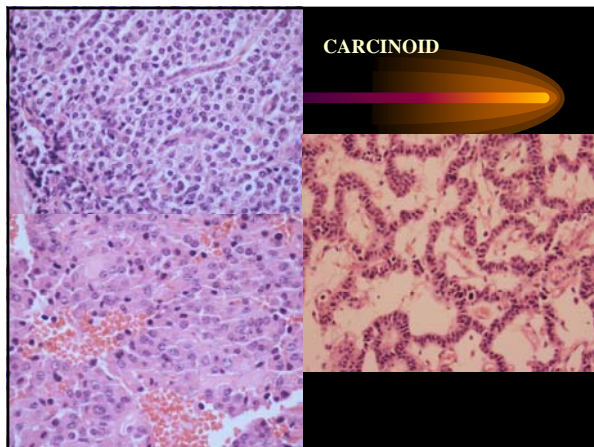


Carcinoids

- 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



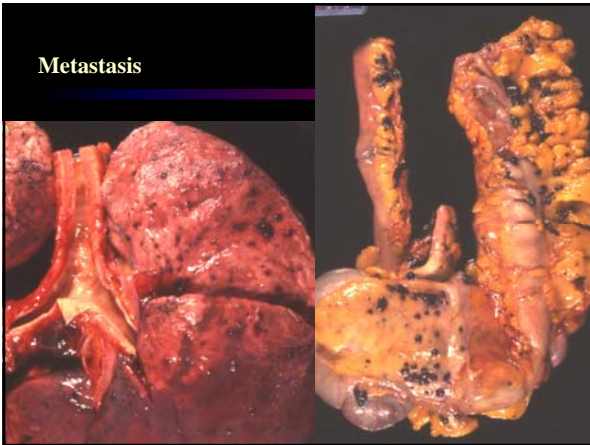




Metastatic Carcinoma

- 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

Metastasis



Lung Cancer Staging

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

Therapy- small cell

- Limited
 - Chemotherapy + Radiation
- Extensive
 - Chemotherapy

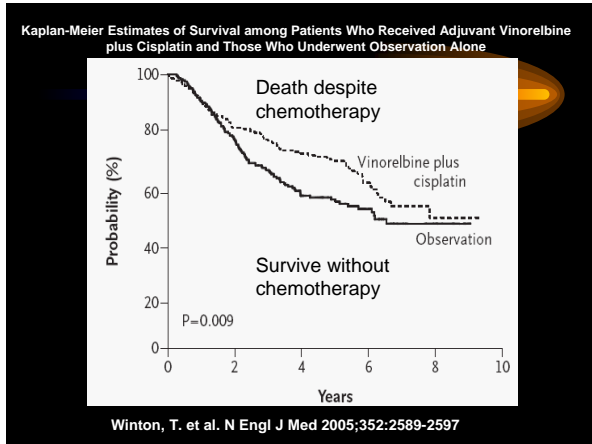
International Staging System, Revised 1997

Stage IA	T1, N0, M0
Stage IB	T2, N0, M0
Stage IIA	T1, N1, M0
Stage IIB	T2, N1, M0
Stage IIIA	T3, N0, M0 T1-3, N2, M0
Stage IIIB	T3, N1, M0 T4, any N, M0
Stage IV	Any T, N3, M0 Any T, Any N, M1

Chest 111:1710-17

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



Tumor Biology

- Morphology
 - Small cell Non-small cell
 - Squamous Adeno (BAC, Invasive) Large cell
- Progression
 - Clinical Stage: Size Local invasion Metastasis
- Response to therapy- ERCCI
- Recurrence propensity

ERCCI Negative Tumors benefit from Cisplatin Adjuvant Therapy

Figure 1. An ERCCI-Positive Squamous Cell Carcinoma (Panel A) and an ERCCI-Negative Squamous Cell Carcinoma (Panel B).

1 ERCCI-Negative Tumors

2 ERCCI-Positive Tumors

NEJM 355:983

