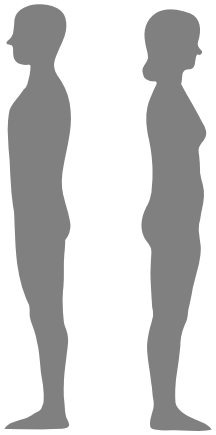
2007 Estimated US Cancer Cases*

Prostate	29%
Lung & bronchus	15%
Colon & rectum	10%
Urinary bladder	7%
Non-Hodgkin lymphoma	4%
Melanoma of skin	4%
Kidney	4%
Leukemia	3%
Oral cavity	3%
Pancreas	2%
All Other Sites	19%

Men 766,860 **Women 678,060**



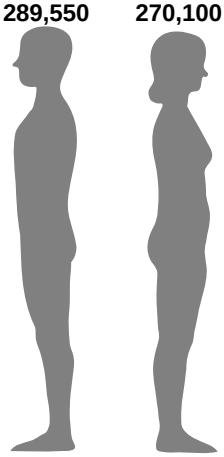
- •26% Breast
- •15% Lung & bronchus
- •11% Colon & rectum
- •6% Uterine corpus
- • 4% Non-Hodgkin lymphoma
- •4% Melanoma of skin
- • 4% Thyroid
- • 3% Ovary
- • 3% Kidney
- •3% Leukemia
- •21% All Other Sites

***Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.**
Source: American Cancer Society, 2007.

2007 Estimated US Cancer Deaths*

Lung & bronchus	31%
Prostate	9%
Colon & rectum	9%
Pancreas	6%
Leukemia	4%
Liver & intrahepatic bile duct	4%
Esophagus	4%
Urinary bladder	3%
Non-Hodgkin lymphoma	3%
Kidney	3%
All other sites	24%

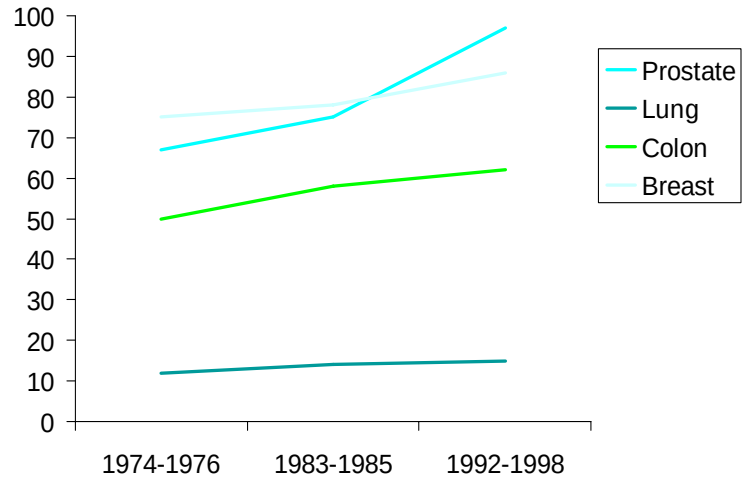
Men 289,550 **Women 270,100**



- •26% Lung & bronchus
- •15% Breast
- •10% Colon & rectum
- • 6% Pancreas
- • 6% Ovary
- • 4% Leukemia
- • 3% Non-Hodgkin lymphoma
- • 3% Uterine corpus
- • 2% Brain/ONS
- • 2% Liver & intrahepat bile duct
- •23% All other sites

ONS=Other nervous system.
Source: American Cancer Society, 2007.

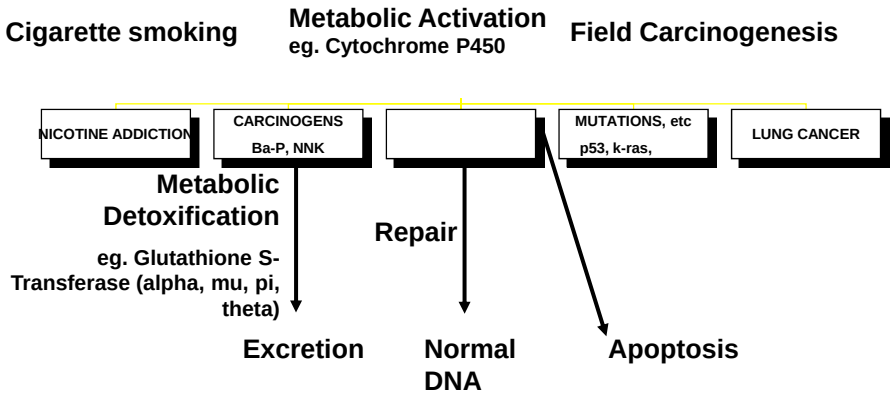
Five-year Cancer Survival Rates (%) US 1974-1998



Source: CA Cancer J Clin 2000;50:7-33

The Scheme:

From Nicotine Addiction to Lung Cancer



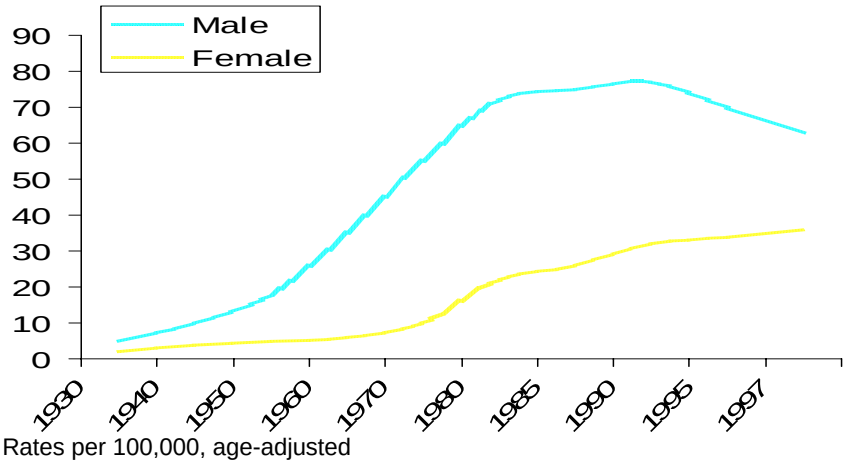
Modified from Hecht JNCI; 1999

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

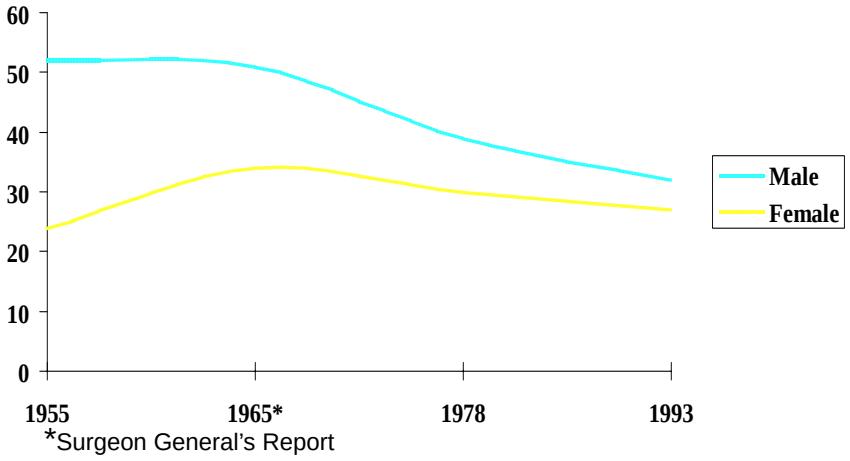
Overall Incidence



Rates per 100,000, age-adjusted

Source: SEER

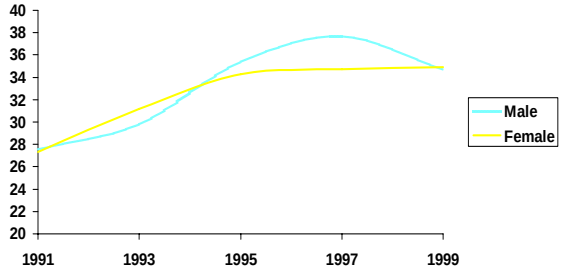
Smoking Prevalence Rates, US



*Surgeon General's Report

Garfinkel, Prev Med 26:447

Percentage of High School Students Who Reported Current Cigarette Smoking



Youth Behavior Survey, MMWR 2000; 49

Risk of lung cancer, men vs. women

Pack-years	MALES	FEMALES
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**

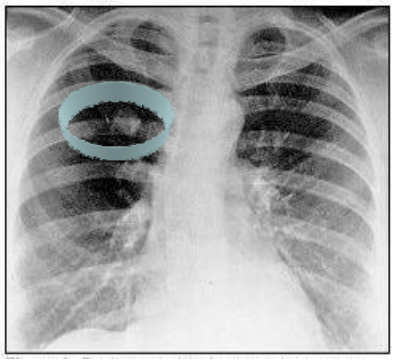
Presentation of Lung Cancer

- Local Symptoms
  - Cough
  - Dyspnea
  - Hemoptysis
  - Chest Pain
  - SVC Syndrome
  - Wheezing
- Systemic Symptoms
  - Constitutional
  - Skeletal
    - Clubbing
    - Hypertrophic Pulmonary Osteoarthropathy
  - Endocrine
    - SIADH (sclc)
    - Hypercalcemia (squamous)
    - Cushings Syndrome (sclc)
  - Neurologic
    - Horners Syndrome
    - Eaton-Lambert syndrome (sclc)

Vascular

Thrombophlebitis, DIC

Differential Diagnosis



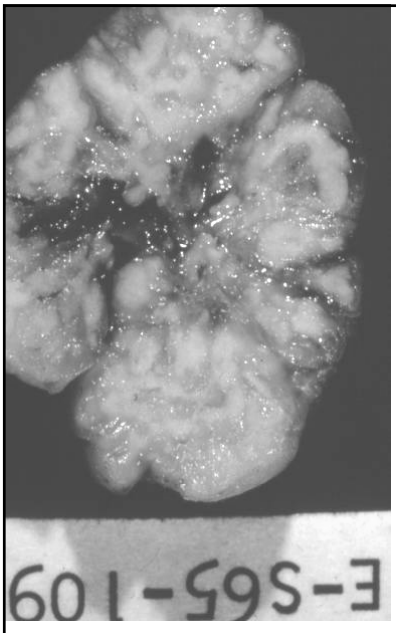
- Benign
  - Granuloma
  - Hamartoma
- Malignant
  - Metastasis
  - **Primary Lung Ca**
    - **Small Cell**
    - **Carcinoid**
    - **Non-small Cell**
      - » **Adenocarcinoma**
      - » **Squamous**
      - » **Large Cell**

Pathologic diagnosis: specimen types

- Transbronchial biopsy
- Transthoracic needle biopsy
- Cytology
  - Bronchial brushing
  - Lavage
  - Aspiration (transthoracic or transbronchial)
- Thoracotomy/VATS

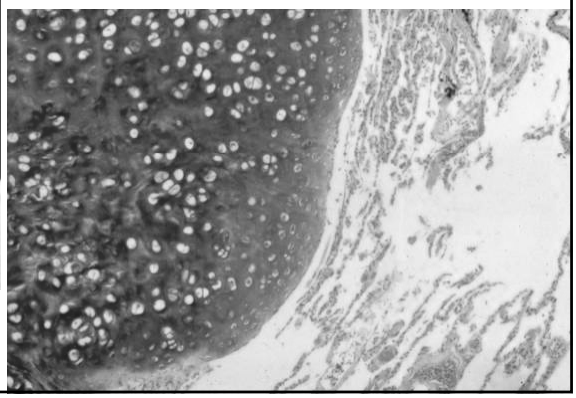
Lung tumors - Benign

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

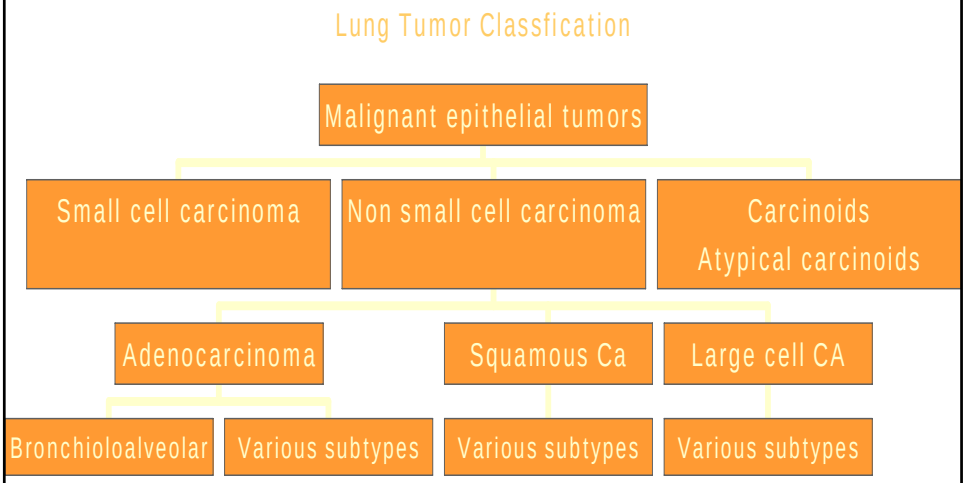


Hamartoma

Likely a misnomer as these are probably true benign neoplasms, with common chromosomal abnormality (6p21 or 12q14-15).



Malignant tumors - classification

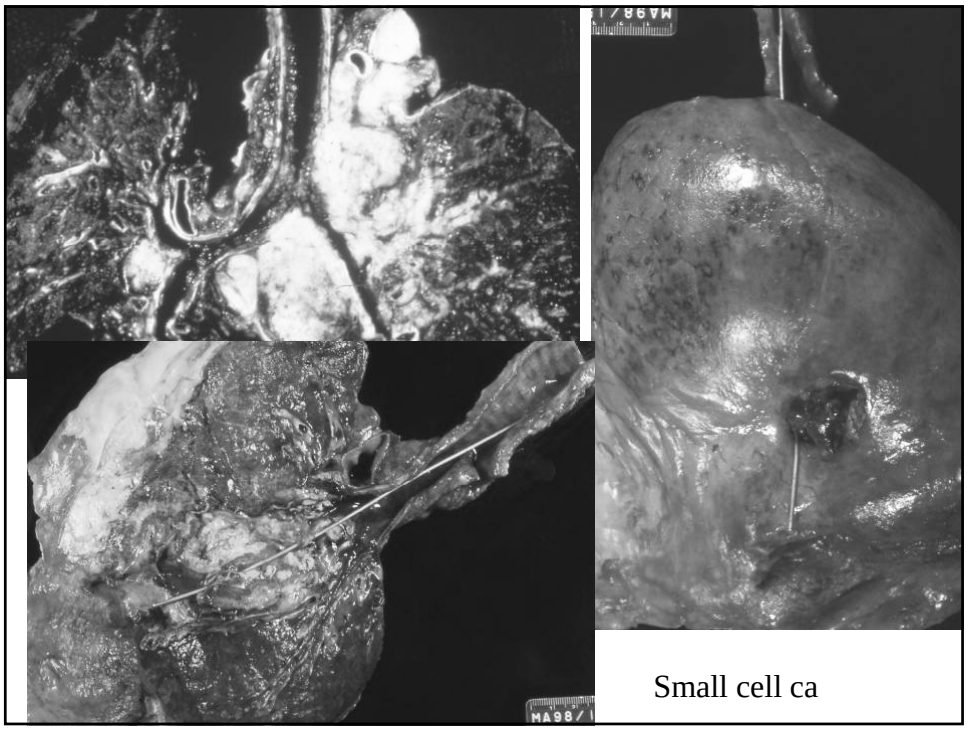


Small cell carcinoma

- 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.

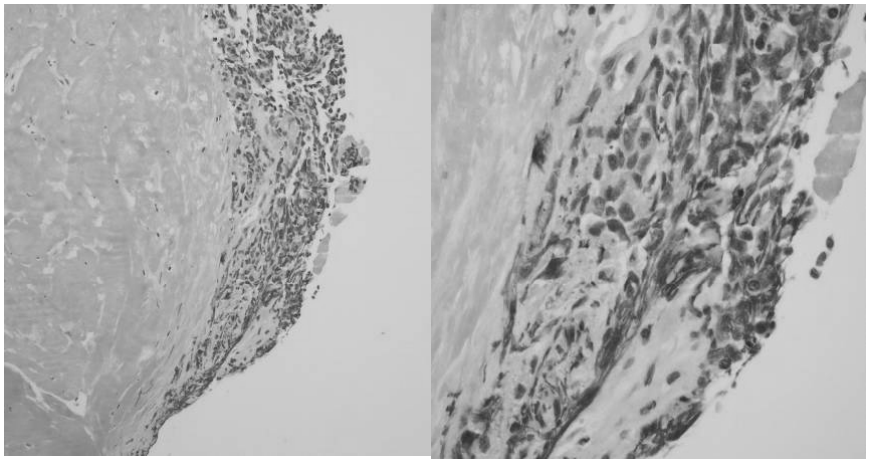
Small cell carcinoma

- 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 differentation)

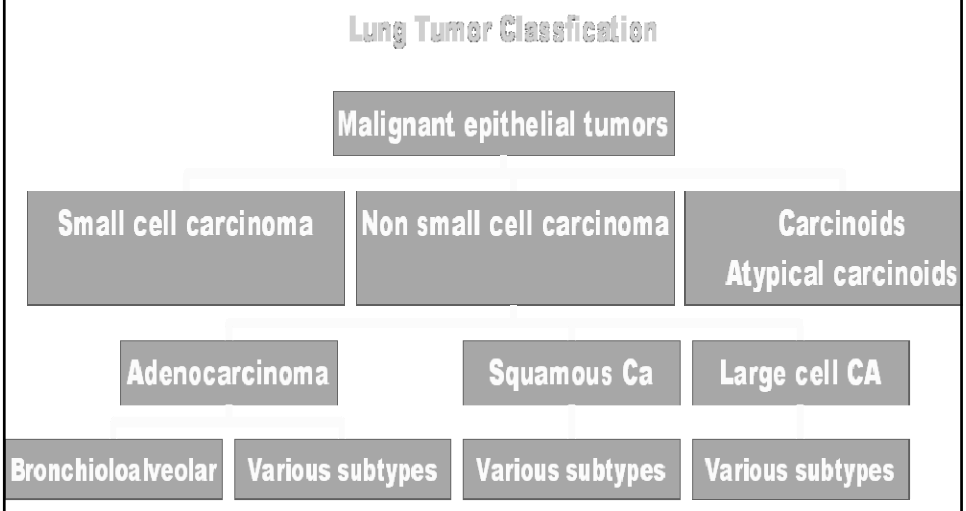


Small cell ca

Small Cell

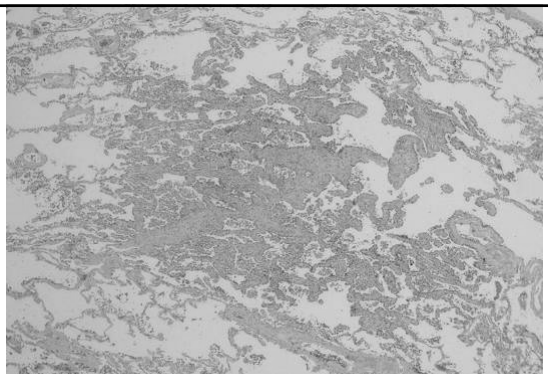


Malignant tumors - classification

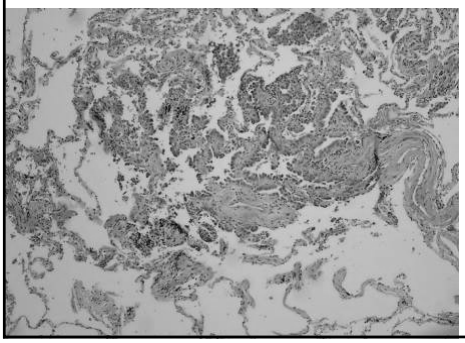


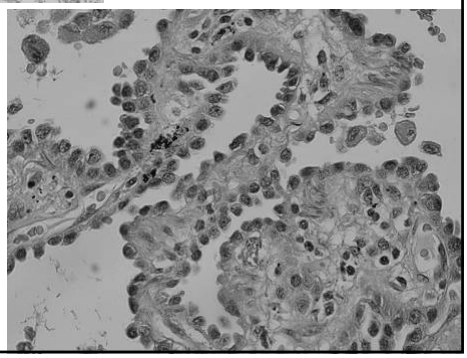
Atypical adenomatous hyperplasia-adenocarcinoma precursor

- 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)



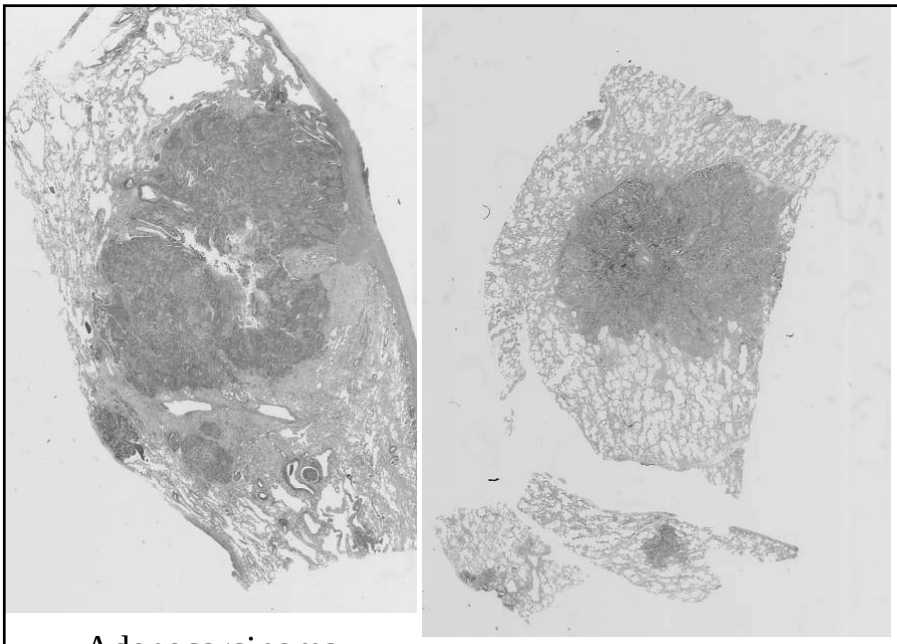
AAH





Adenocarcinoma

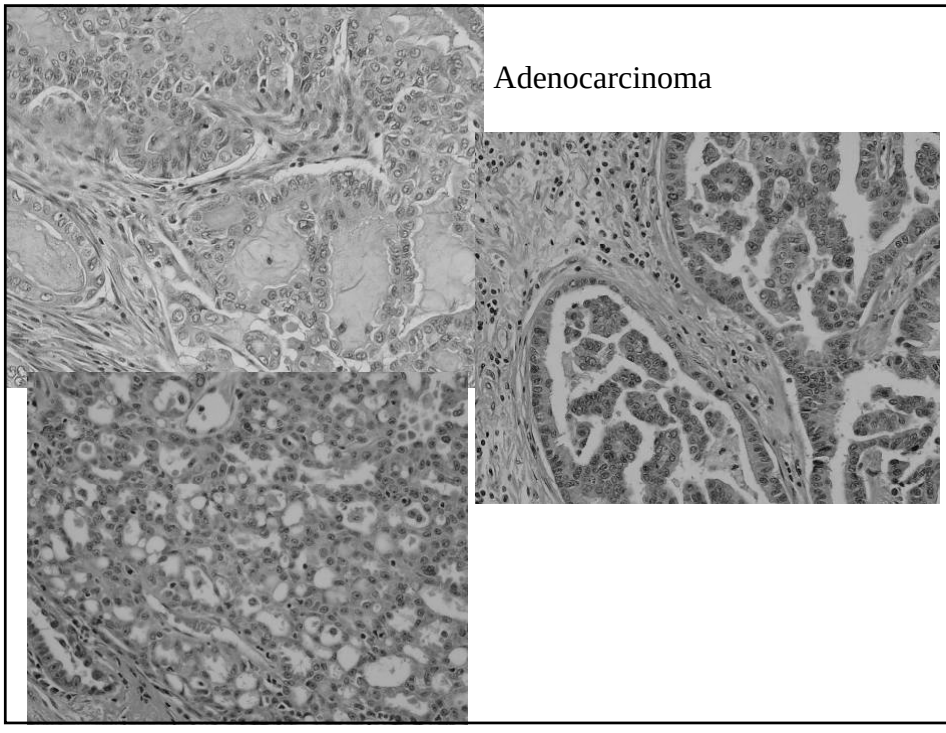
- Most often a peripheral tumor
- Many are near pleura and cause pleural puckering.
- Cut surface can be mucoid or firm, depending on degree of fibrosis and mucin production
- Small tumors can be associated with lymph node and distant metastasis.



Adenocarcinoma

Adenocarcinoma

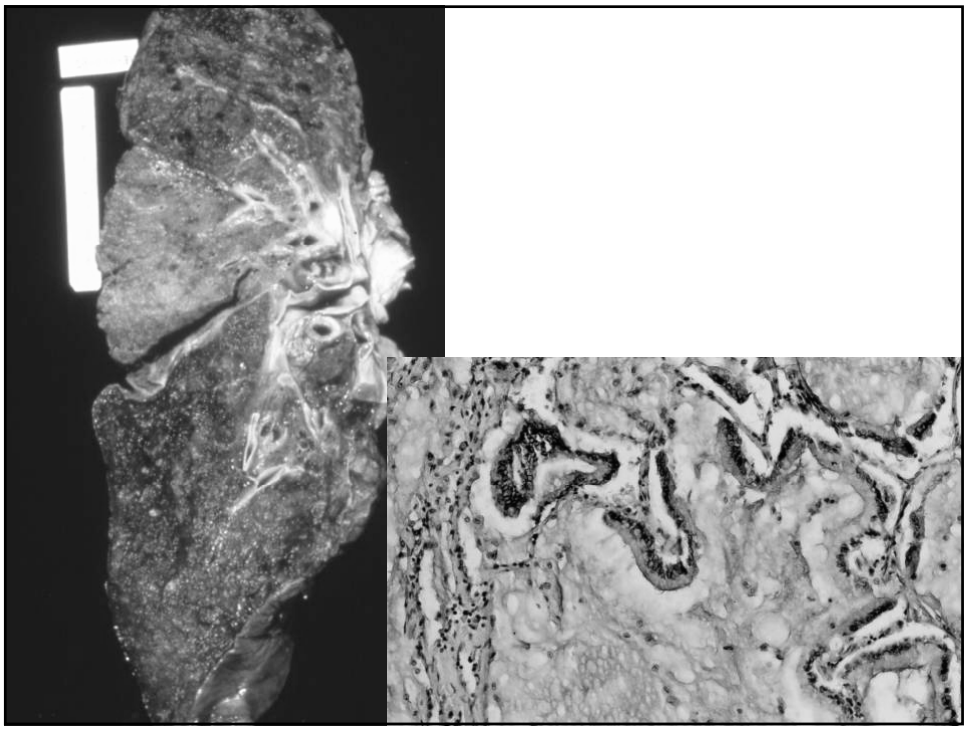
- Histologic varieties are multiple, including solid, acinar, papillary, mucinous types even within the same tumor
- Rarer types include signet ring morphology
- Differentiation can recapitulate goblet cell, Clara cell or type II pneumocyte differentiation
- Bronchial glands can produce a distinct subtype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

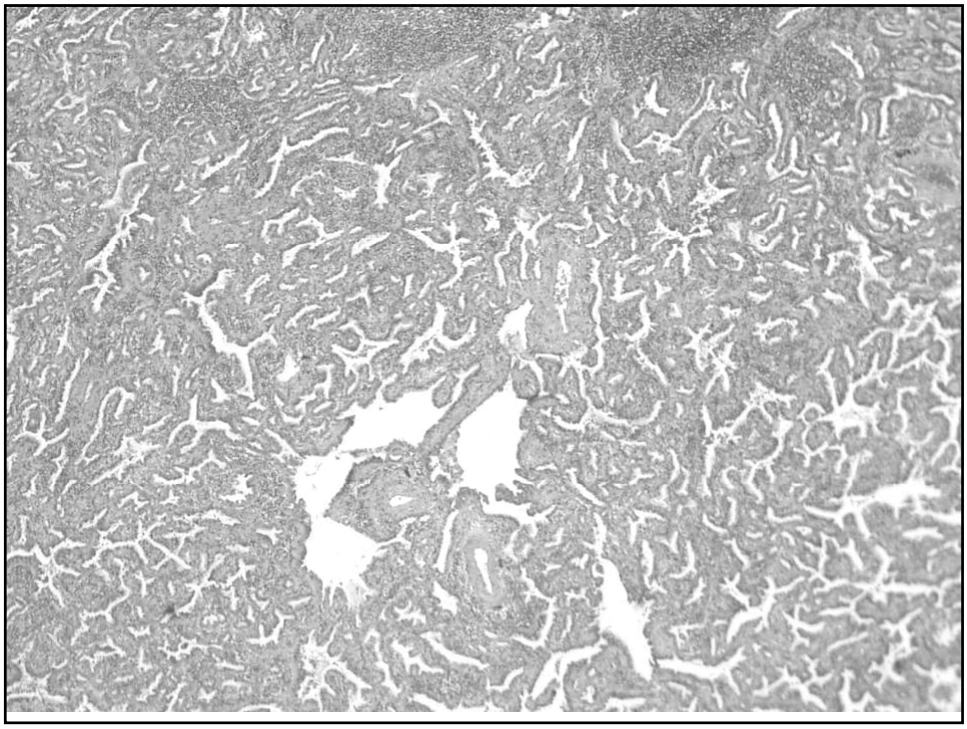


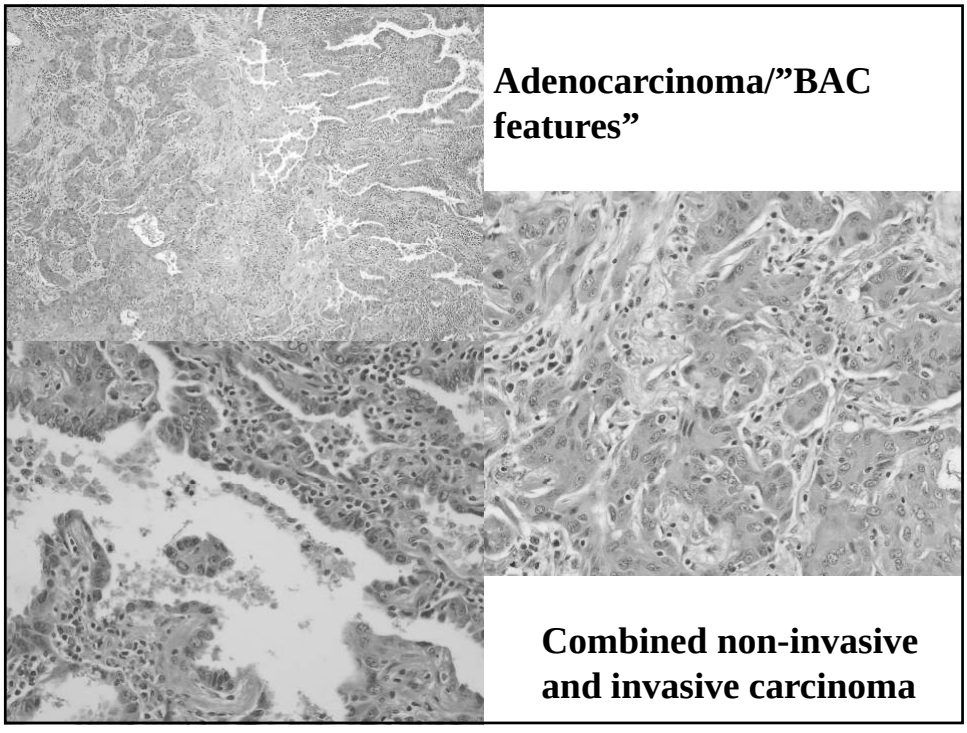
Adenocarcinoma

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





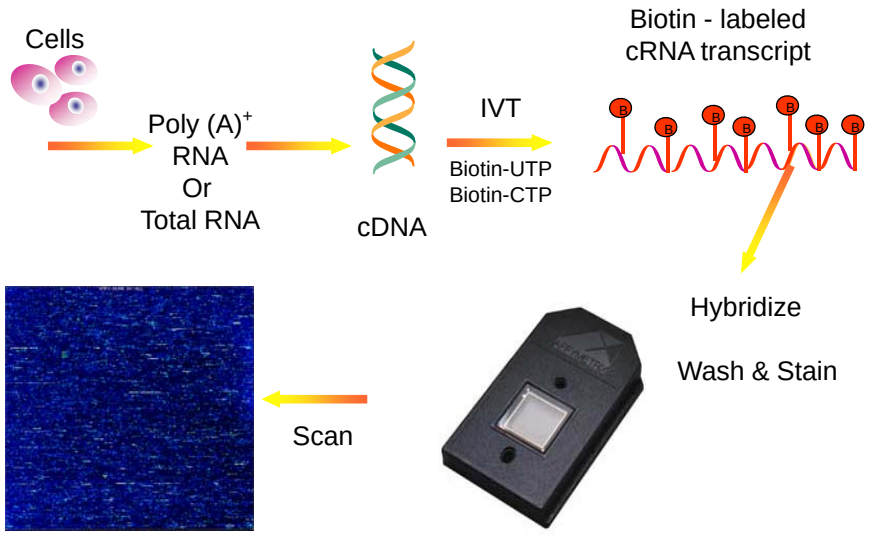


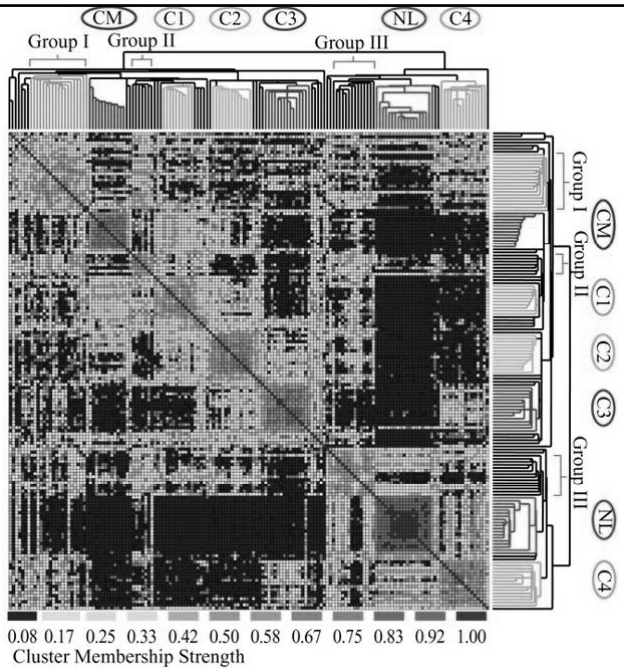
Adenocarcinoma/"BAC features"

Combined non-invasive and invasive carcinoma

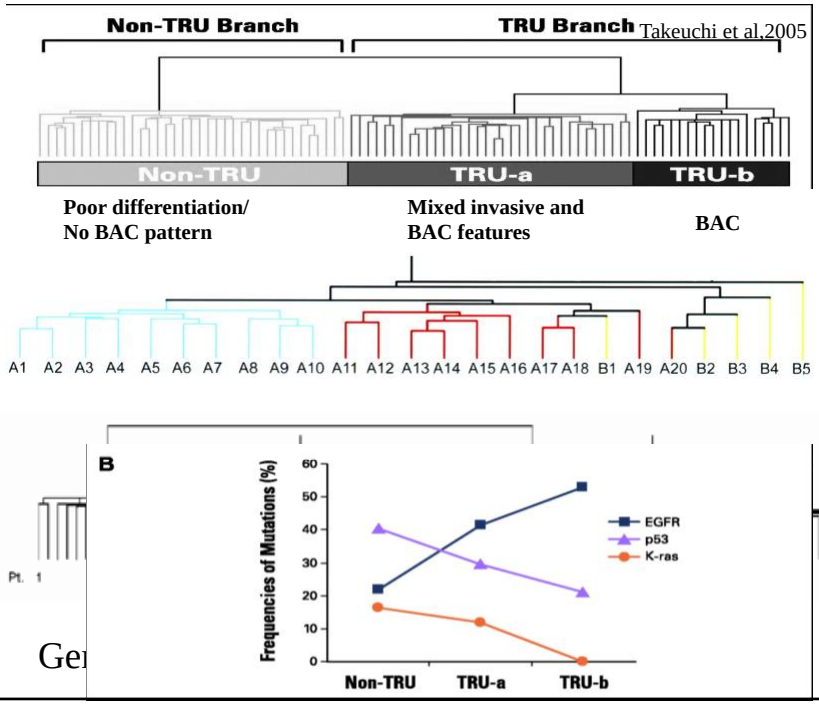
Is there a meaning to the histologic diversity of adenocarcinoma?

- 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.





Bhattacharjee, Arindam et al. (2001) Proc. Natl. Acad. Sci. USA 98, 13790-13795



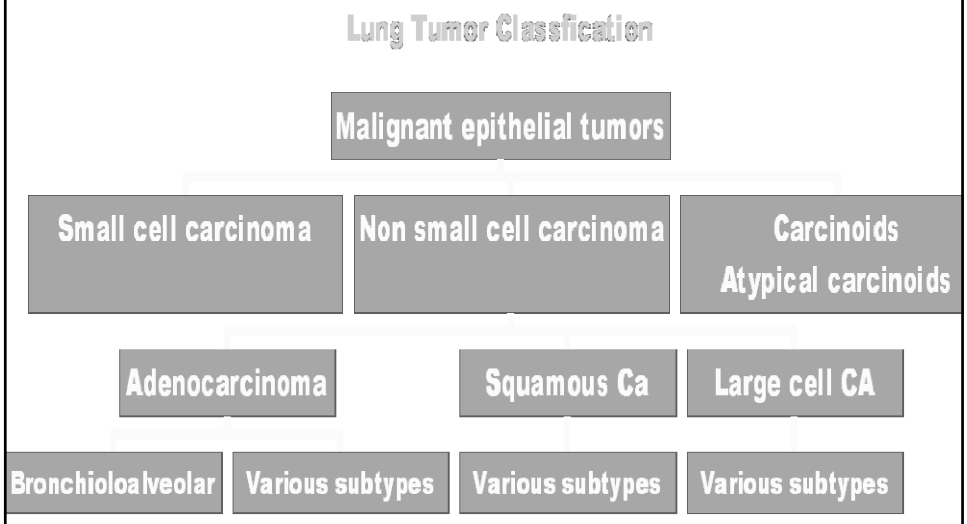
Takeuchi et al,2005

Ge

Are these observations relevant?

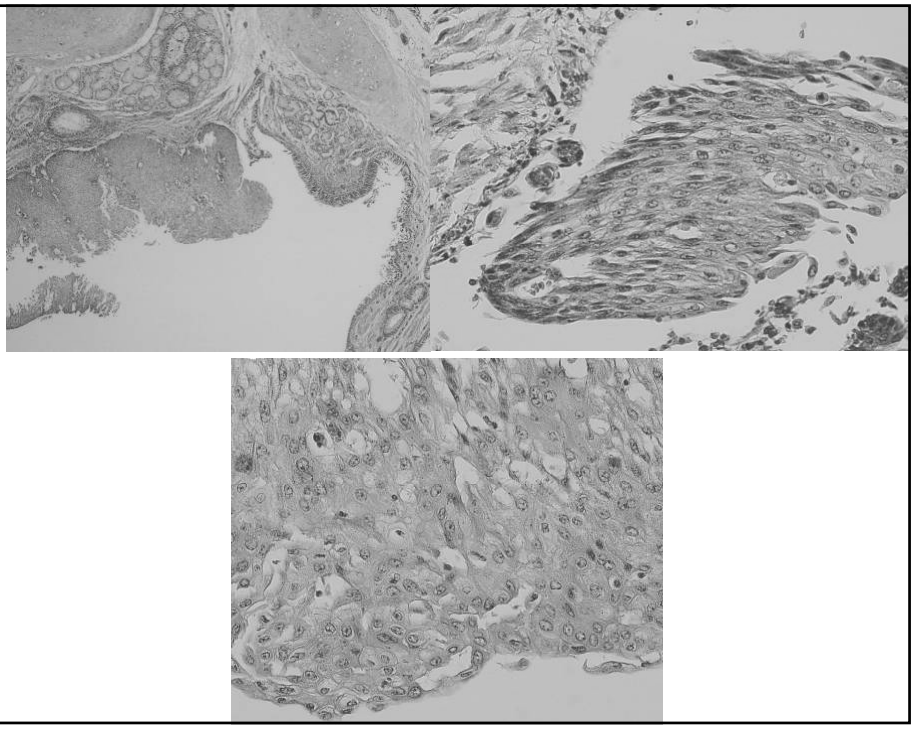
- EGFR mutation and amplification correlates with response to EGFR targeted agents (tyrosine kinase inhibitors gefitinib and erlotinib).
  - This subgroup of patients are also more likely to be women, non-smokers, and of Asian descent but not exclusively so.
- Activating K-ras mutations indicate resistance 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.

Malignant tumors - classification



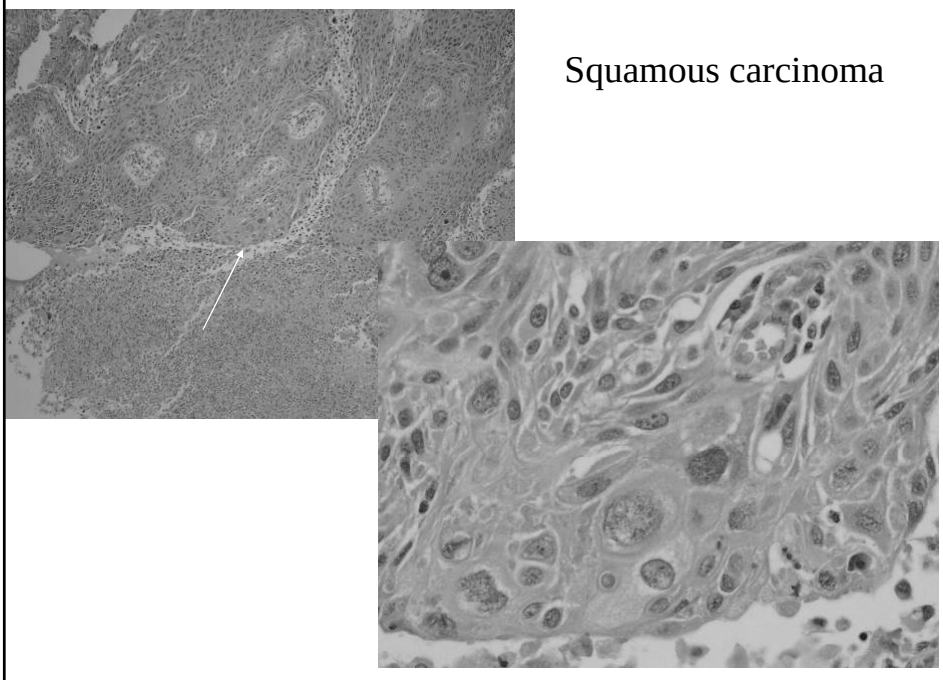
Squamous precursors

- 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

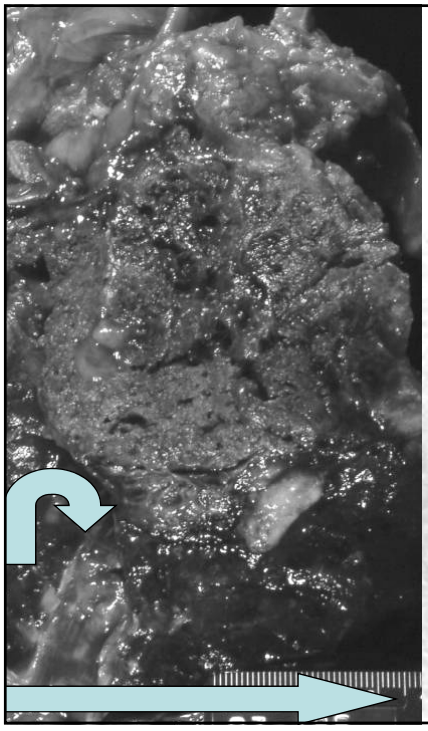
- Usually of bronchogenic origin; however can also arise from peripheral areas of squamous metaplasia
- Frequently have central necrosis
- Faster doubling time than adenocarcinoma; often larger at presentation
- Metastasis in relation to tumor size may occur later than adenocarcinoma



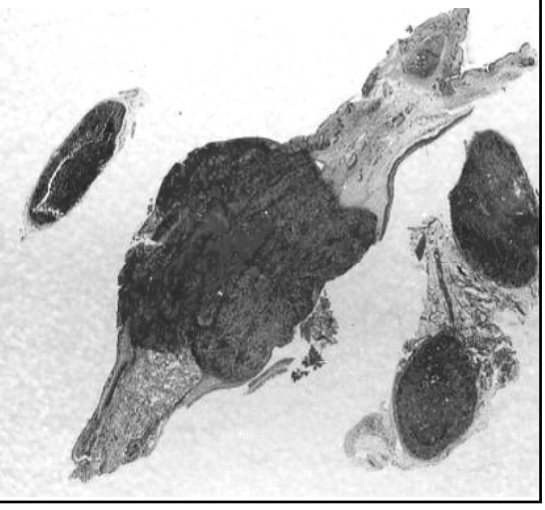
Squamous carcinoma

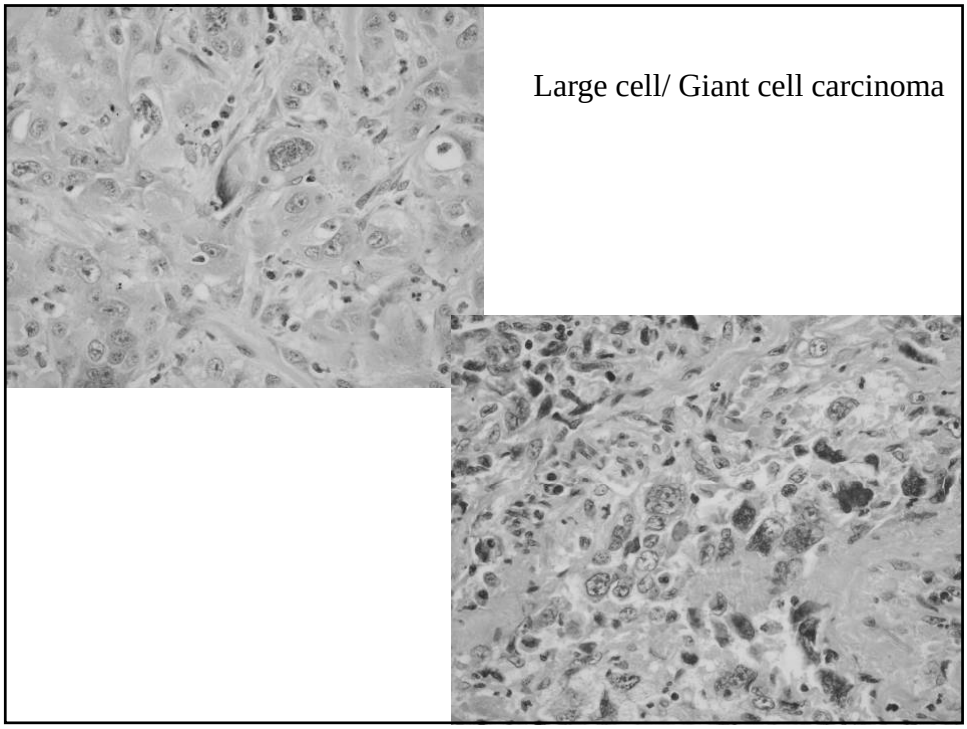
Large cell carcinoma

- 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



Large cell carcinoma

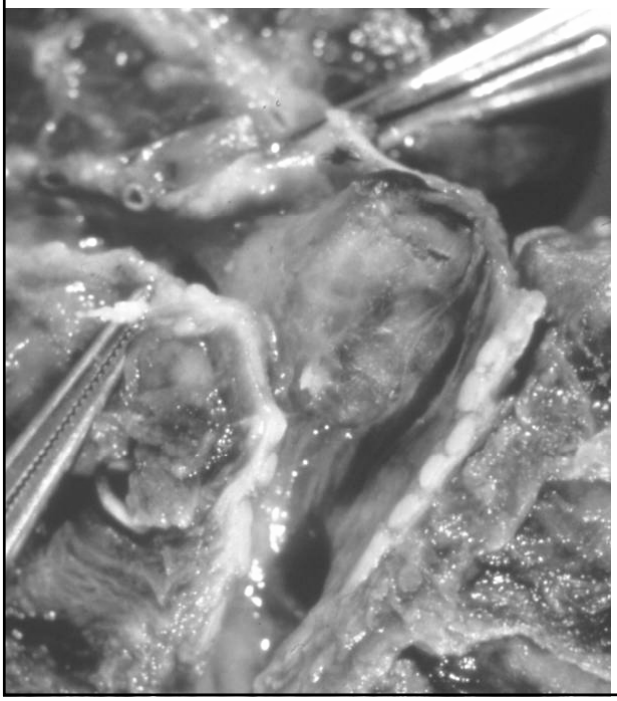




Large cell/ Giant cell carcinoma

Carcinoids

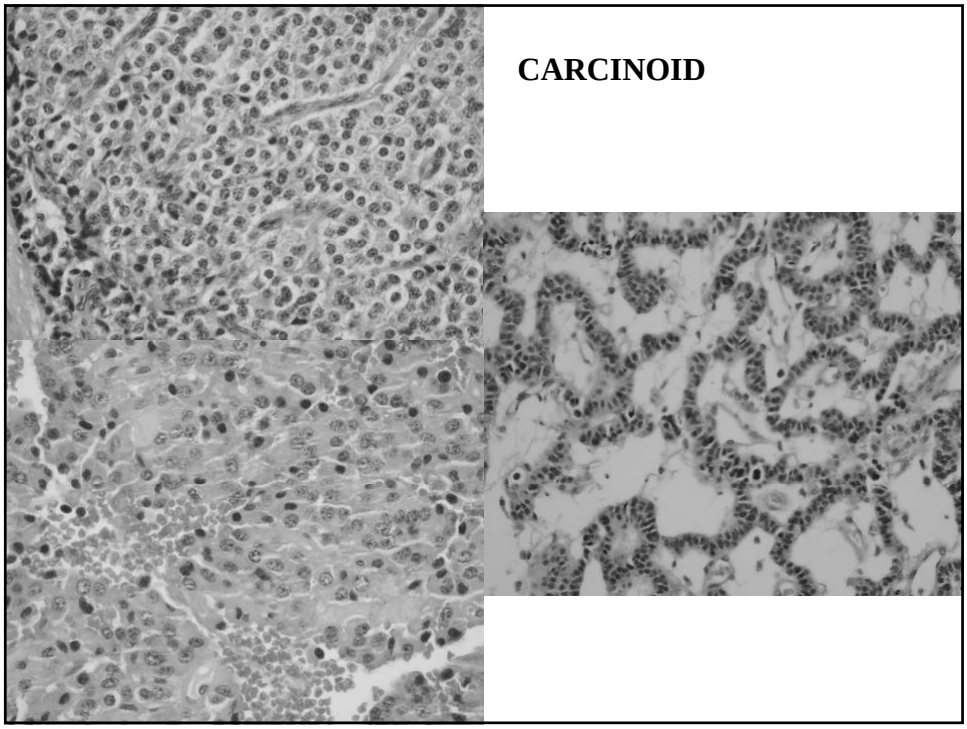
- Malignant neoplasm of neuroendocrine cell origin
- Can be central or peripheral; central lesions can cause bronchial obstruction
- Project into bronchial lumen but often have intact mucosa above them (grow under the mucosa)
- Typical carcinoids are low grade malignancies; atypical carcinoids (mitoses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



Endobronchial carcinoid

Carcinoids

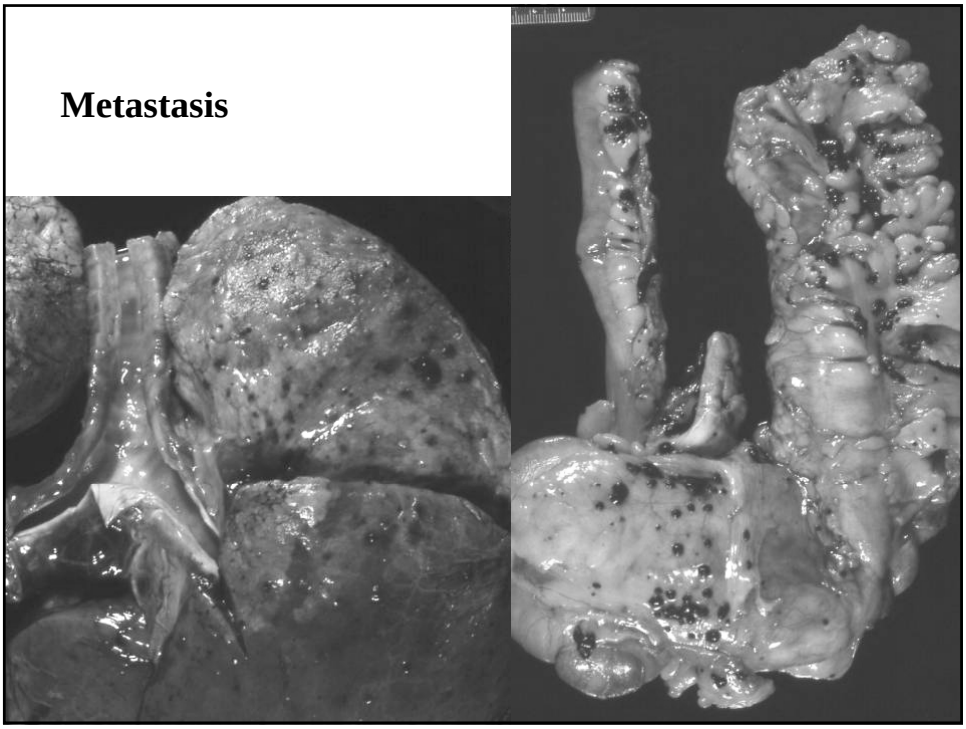
- Histologic features
  - Nests and cords surrounded by delicate stroma
  - Uniform cells with salt and pepper chromatin
  - Neurosecretory granules are abundant and easily demonstrated by electron microscopy or immunohistochemistry (well differentiated tumors)



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

Metastasis



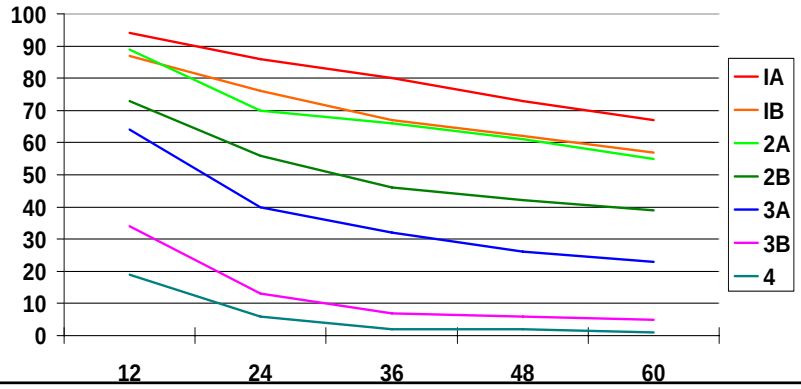
Lung Cancer Staging

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

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

Chest 111:1710-17



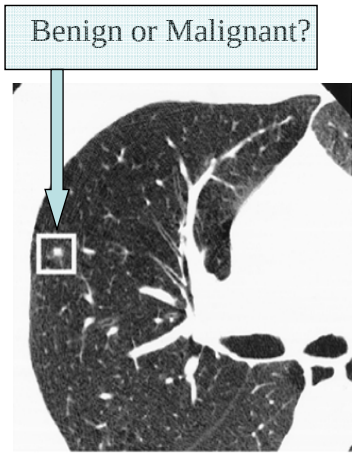
Therapy- Non-small Cell Lung Cancer

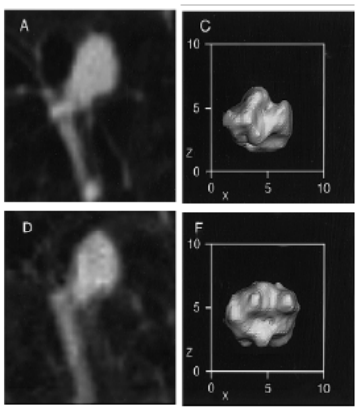
- Stage I, II
  - Lobectomy + adjuvant chemotherapy
- Stage IIIa
  - Neoadjuvant chemotherapy, radiation, surgery
- Stage IIIb
  - Chemotherapy +\- radiation
- Stage IV
  - Chemotherapy

Therapy- small cell

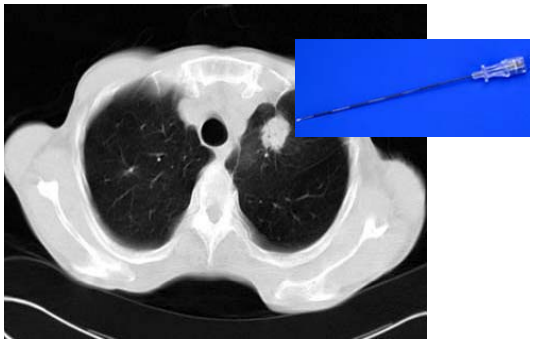
- Limited
  - Chemotherapy + Radiation
- Extensive
  - Chemotherapy

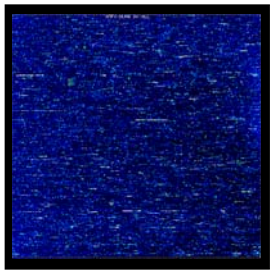
CT Screening
Assessment of Interval Growth





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- βcatenin
	CCNB1	G2/M transition
	LOXL2	Scavenger receptor
Low Risk		
	HLADPB1	Class II MHC
	SELENBP1	Selenium binding