


Cancer in the United States, 2009

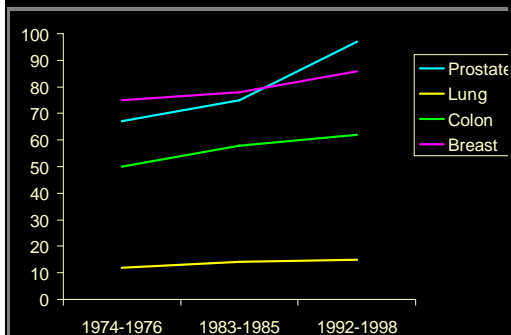
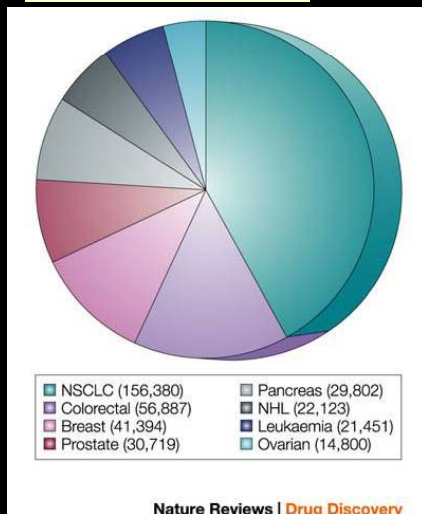
Estimated New Cases*

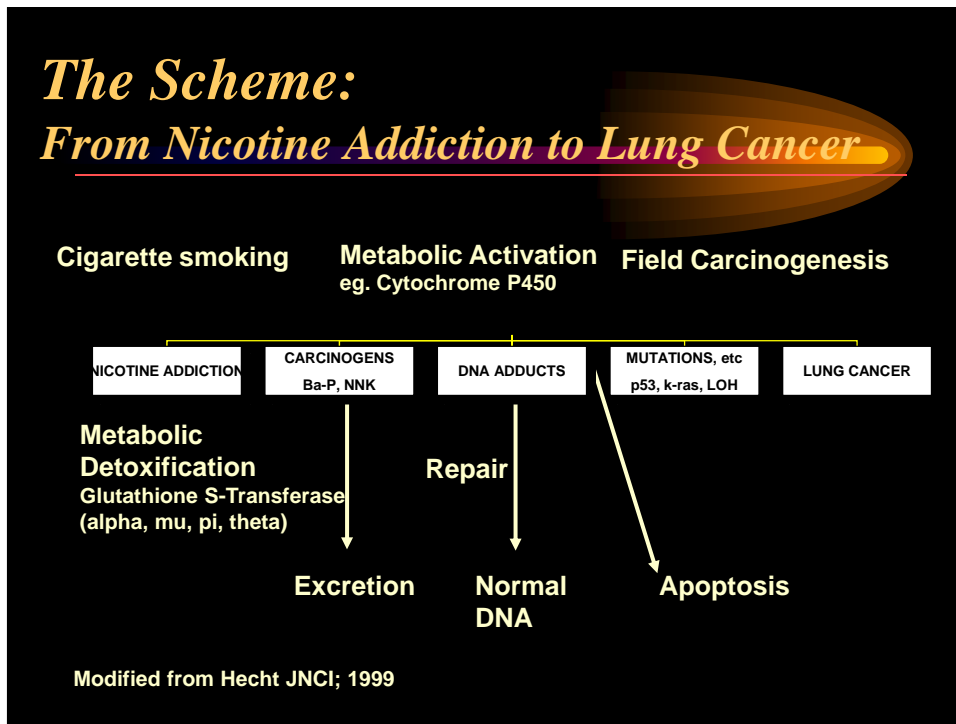
			Males	Females		
Prostate	218,890	29%			Breast	178,480
Lung & bronchus	114,760	15%			Lung & bronchus	98,620
Colon & rectum	79,130	10%			Colon & rectum	74,630
Urinary bladder	50,040	7%			Uterine corpus	39,080
Non-Hodgkin lymphoma	34,200	4%			Non-Hodgkin lymphoma	28,990
Melanoma of the skin	33,910	4%			Melanoma of the skin	26,030
Kidney & renal pelvis	31,590	4%			Thyroid	25,480
Leukemia	24,800	3%			Ovary	22,430
Oral cavity & pharynx	24,180	3%			Kidney & renal pelvis	19,600
Pancreas	18,830	2%			Leukemia	19,440
All Sites	766,860	100%	All Sites	678,060		

Estimated Deaths

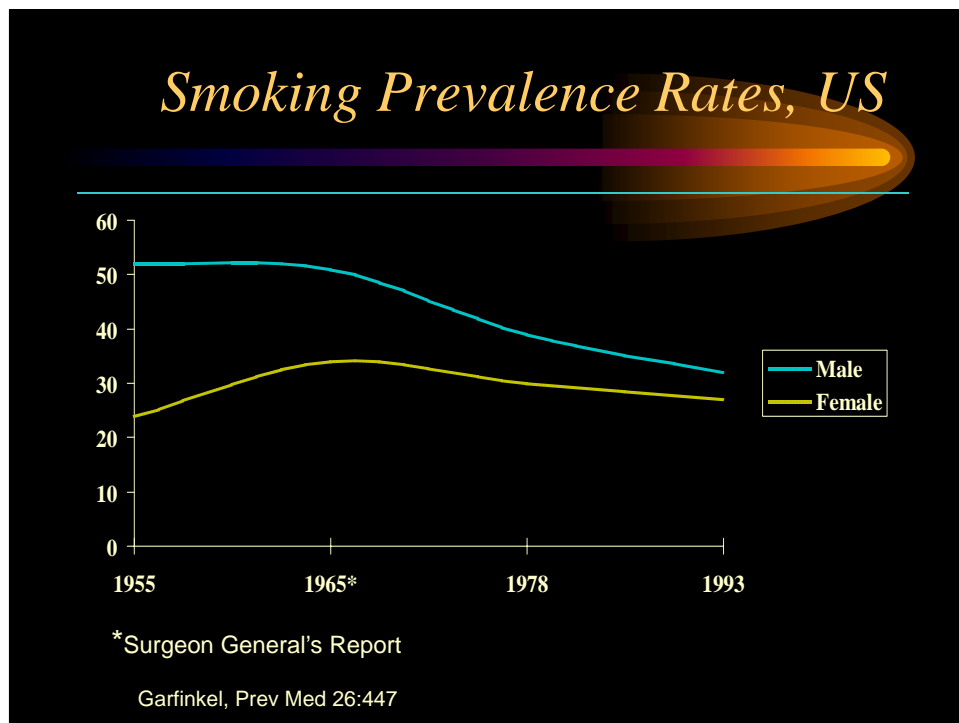
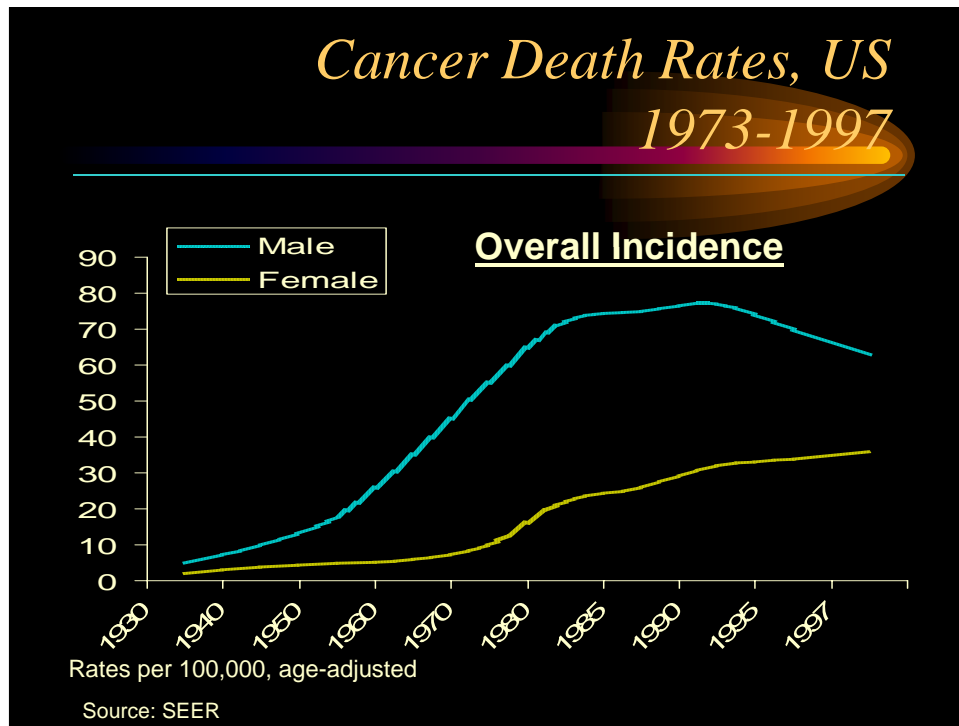
Lung Cancer in the United States

Annual Cancer Deaths

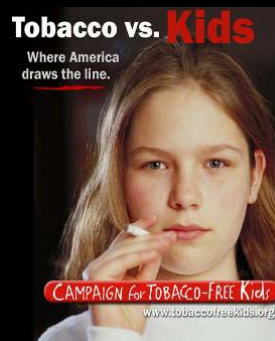
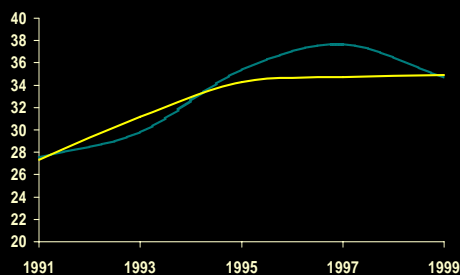




- ### *Lung Cancer Risks*
- Cigarette Smoking
 - Environmental Tobacco Smoke
 - Other Carcinogens
 - Asbestos, Arsenic, Radon,
 - Bis(chloromethyl) ether, Chromium, Foundry fumes, nickel, mustard gas, coke oven emissions
 - Air Pollution (foundries, diesel exhaust)
 - Family History
 - Diet (Vitamins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



Percentage of High School Students Who Reported Current Cigarette Smoking

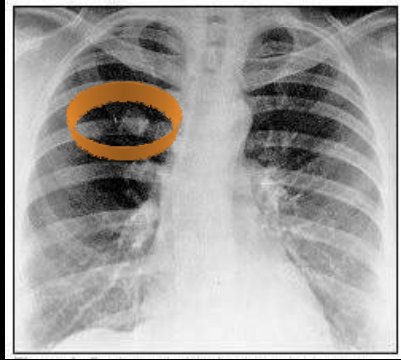


Youth Behavior Survey, MMWR 2000; 49

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

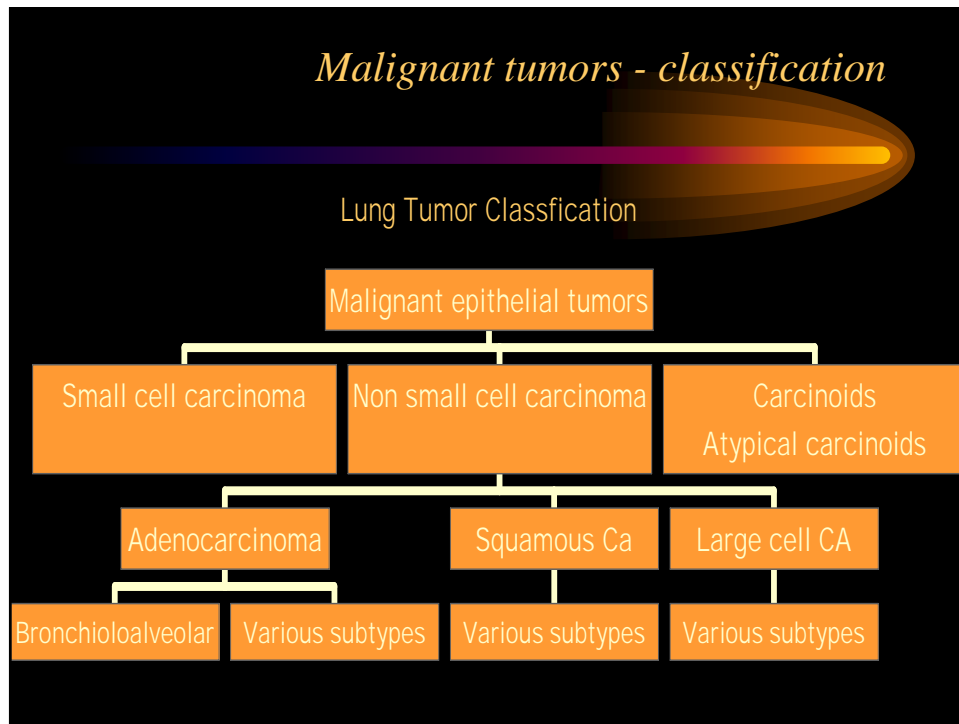
- The majority of pulmonary neoplasms are malignant
- Benign tumors/lesions
 - Hamartoma (most common)
 - Mesenchymal- leiomyoma, lipoma, chondroma (all unusual)
 - Alveolar adenoma (rare)



Hamartoma

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



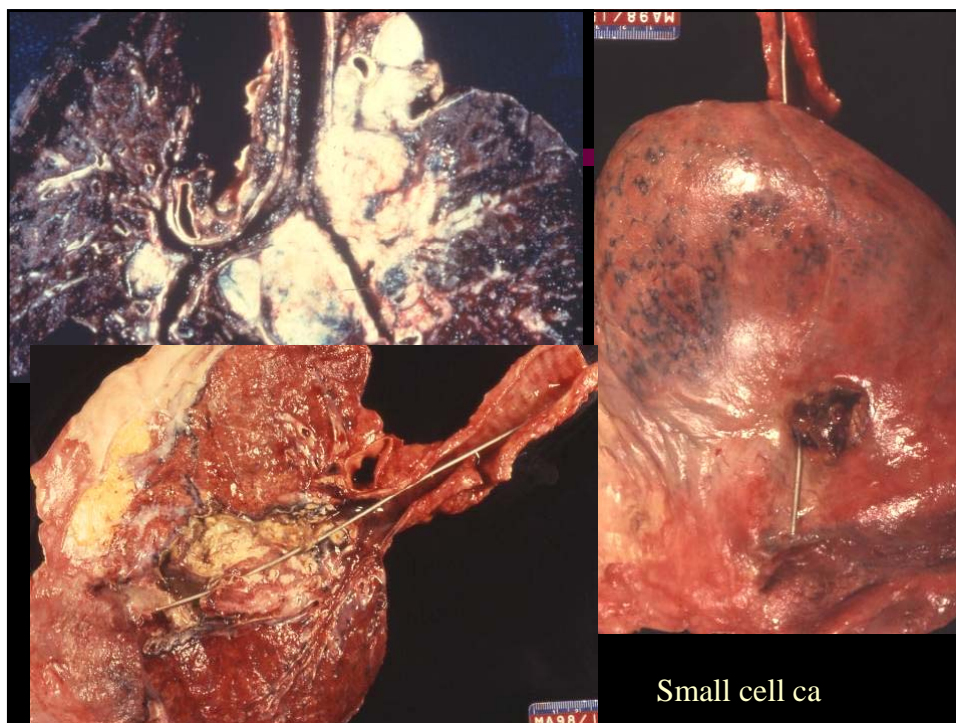


Small cell carcinoma

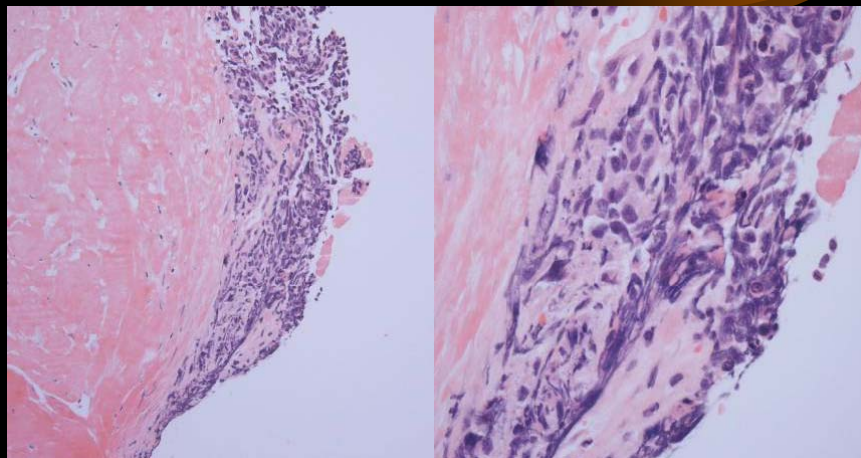
- Usually hilar/ central tumor
- The majority have extrapulmonary spread at time of presentation.
- Only 5% present as early stage disease.
- Critical divide between small cell and non-small cell carcinoma
 - Small cell carcinoma staged differently, treated with chemoradiation not surgery.

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)

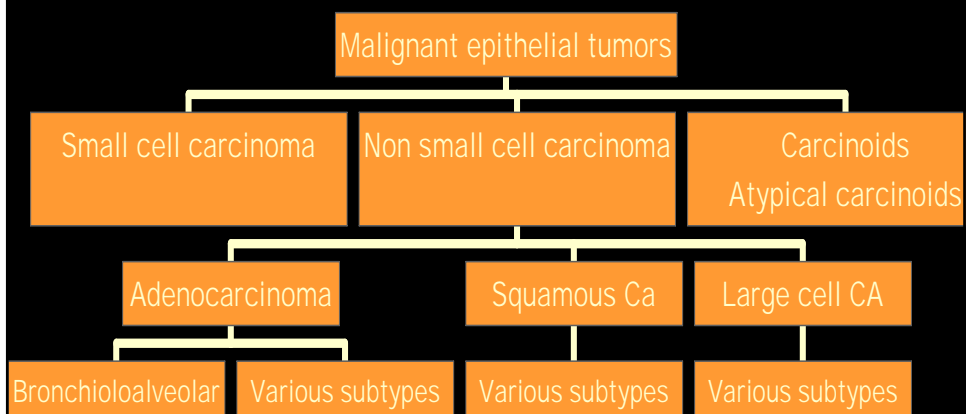


Small Cell



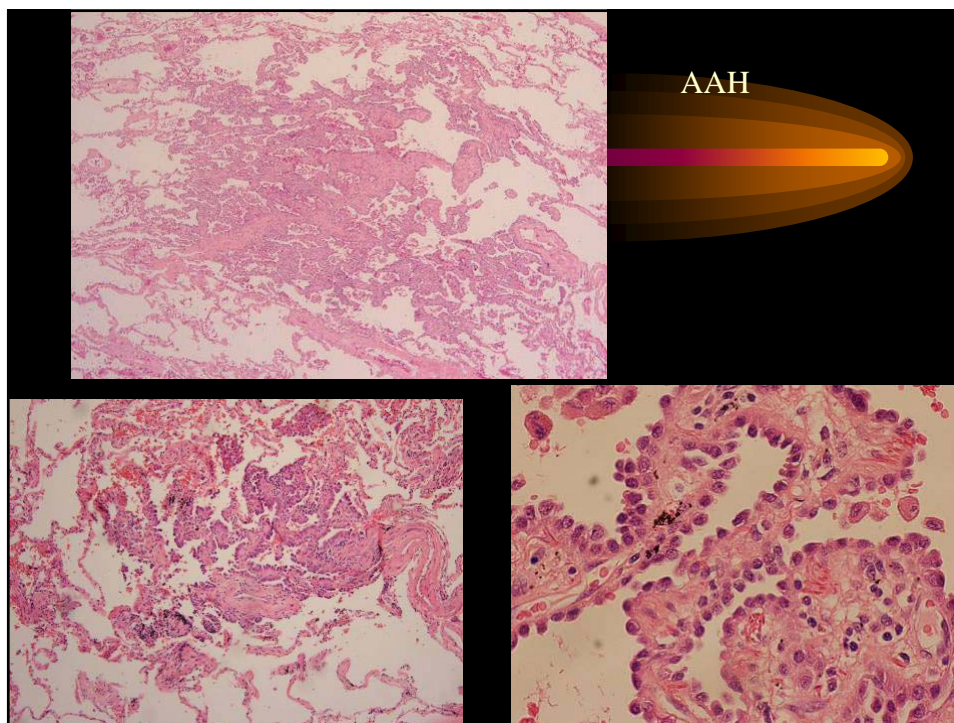
Malignant tumors - classification

Lung Tumor Classification



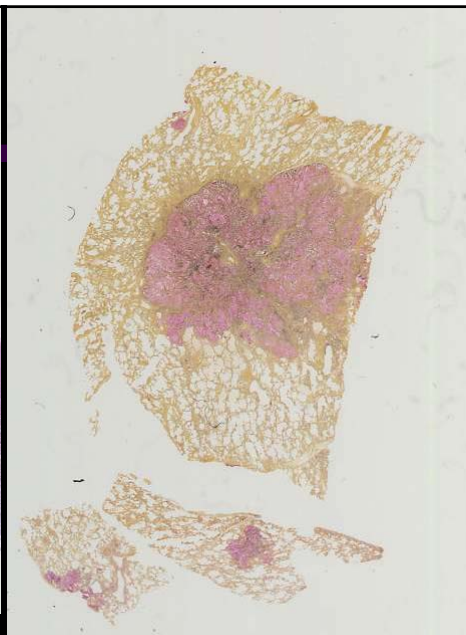
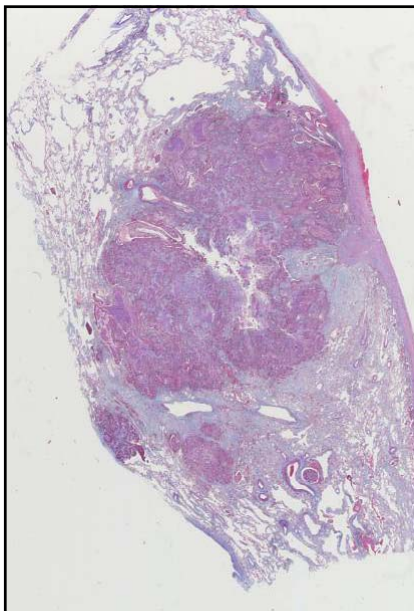
Atypical adenomatous hyperplasia- adenocarcinoma precursor

- 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

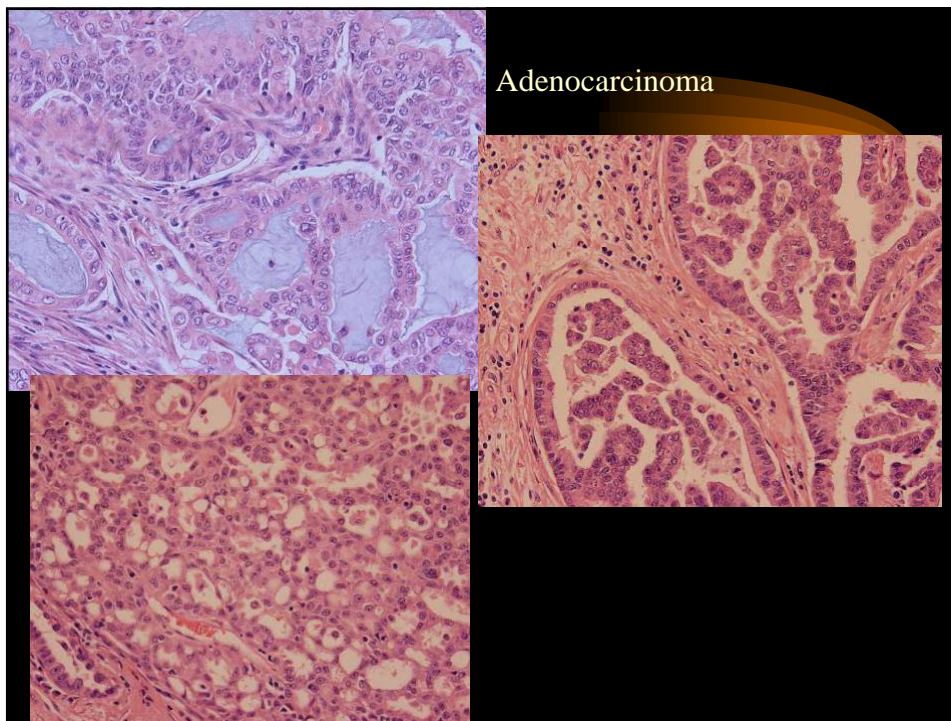
- Most often a peripheral tumor
- Many are near pleura and cause pleural puckering.
- Cut surface can be mucoid or firm, depending on degree of fibrosis and mucin production
- Small tumors can be associated with lymph node and distant metastasis.



Adenocarcinoma

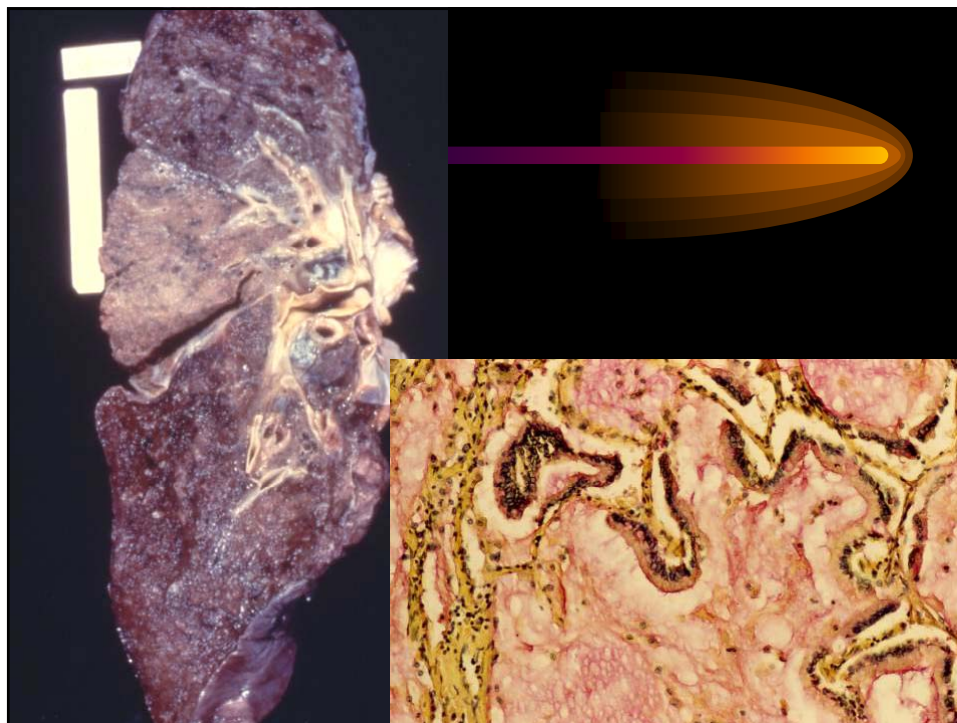
Adenocarcinoma

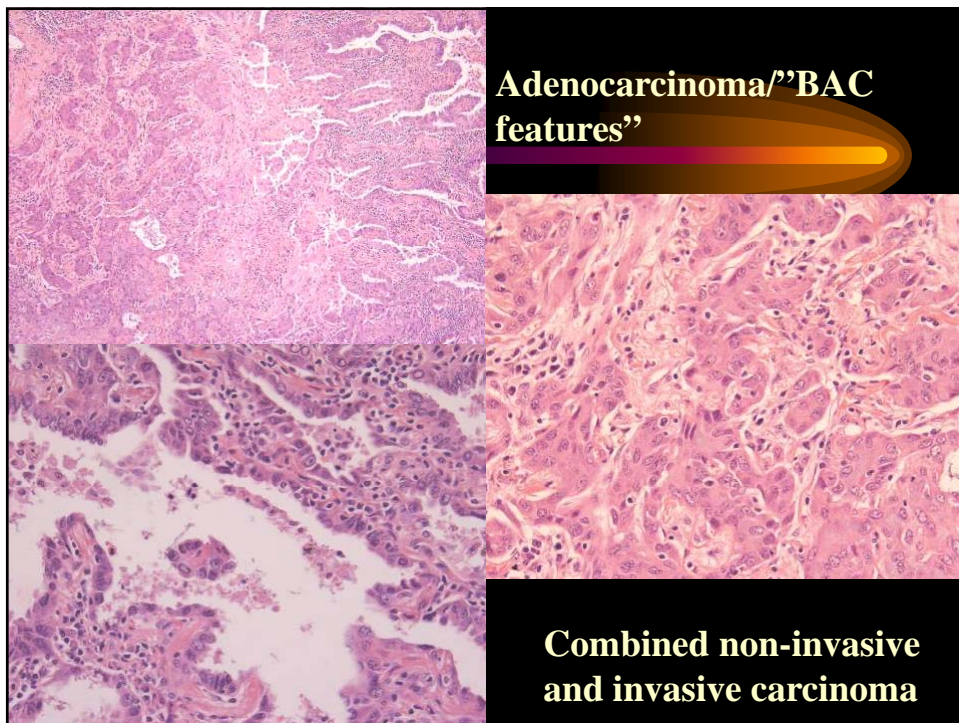
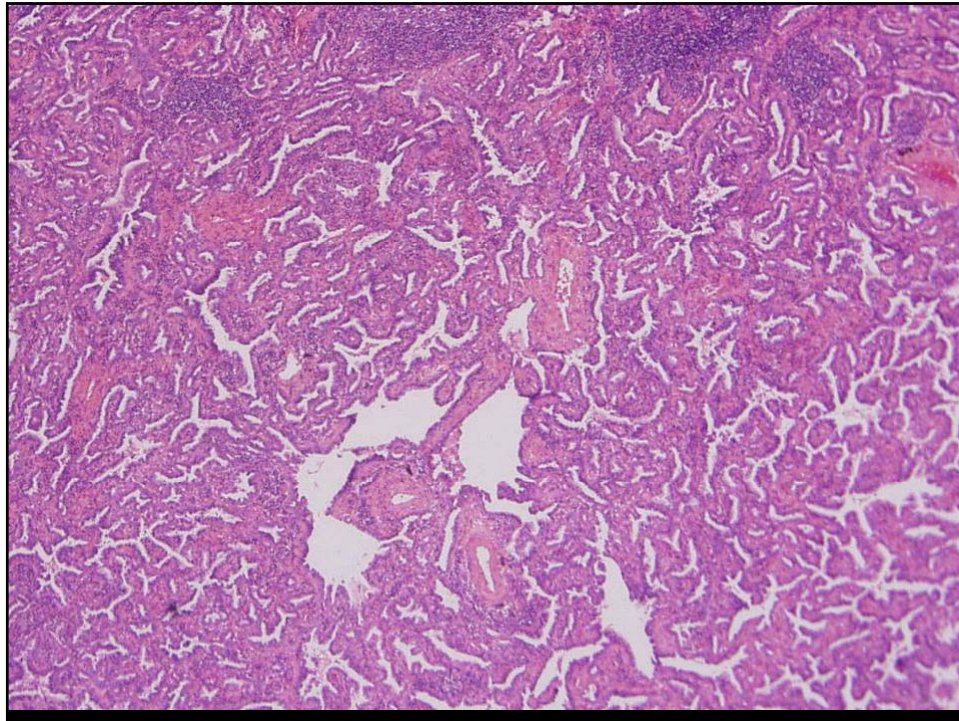
- Histologic varieties are multiple, including solid, acinar, papillary, mucinous types even within the same tumor
- Rarer types include signet ring morphology
- Differentiation can recapitulate goblet cell, Clara cell or type II pneumocyte differentiation
- Bronchial glands can produce a distinct subtype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



Adenocarcinoma - Bronchioloalveolar

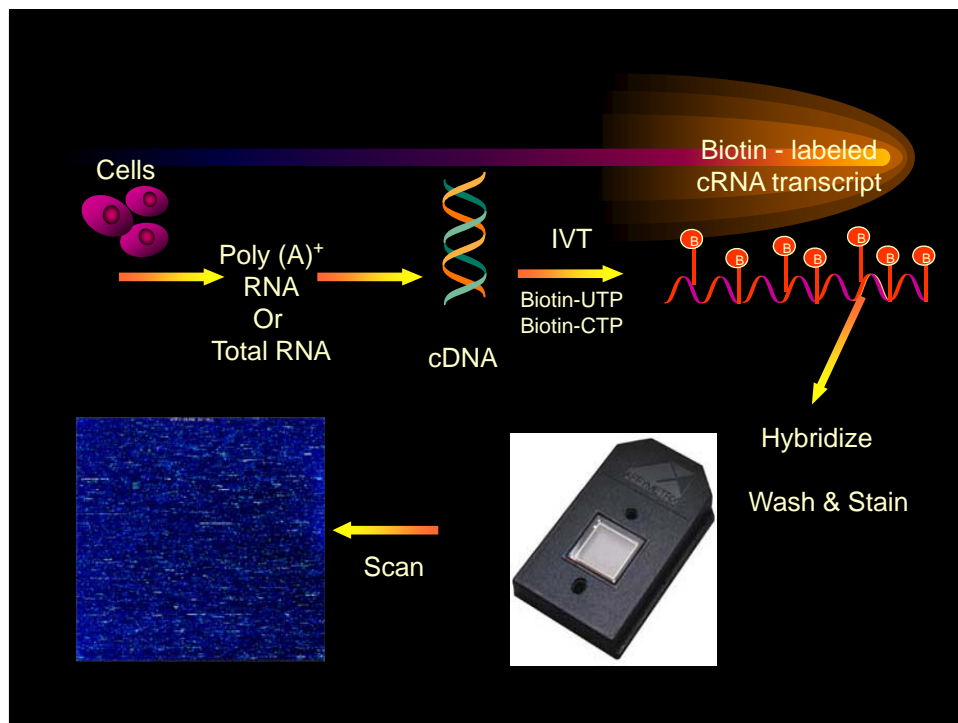
- Distinct morphologic and clinical variant
- Grows along pre-existing alveoli and terminal bronchioles without stromal invasion
- Grossly can form a nodule, but can also produce diffuse disease mimicking pneumonia
- Can be mucinous or non-mucinous.
- Often multifocal

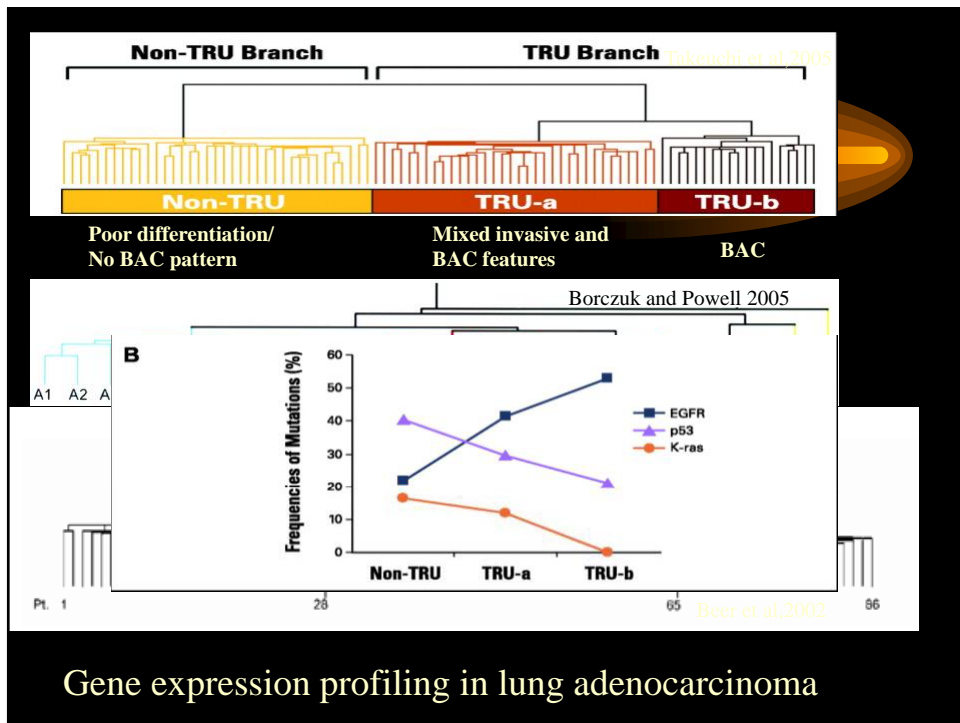
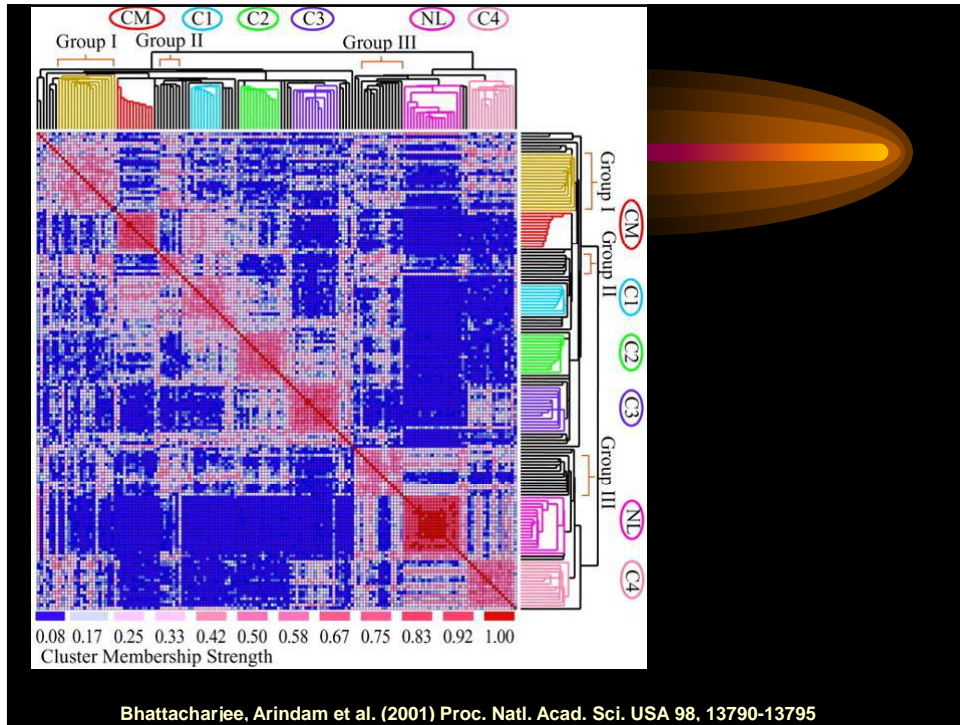




Is there a meaning to the histologic diversity of adenocarcinoma?

- 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.



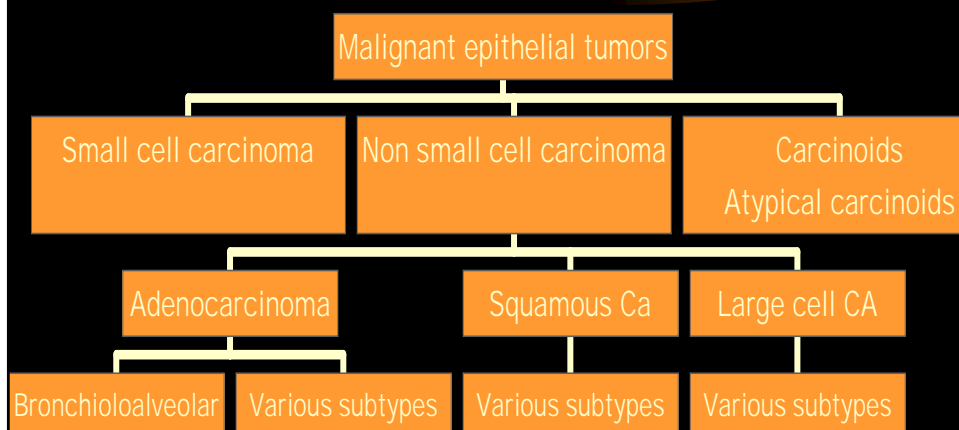


Are these observations relevant?

- 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.

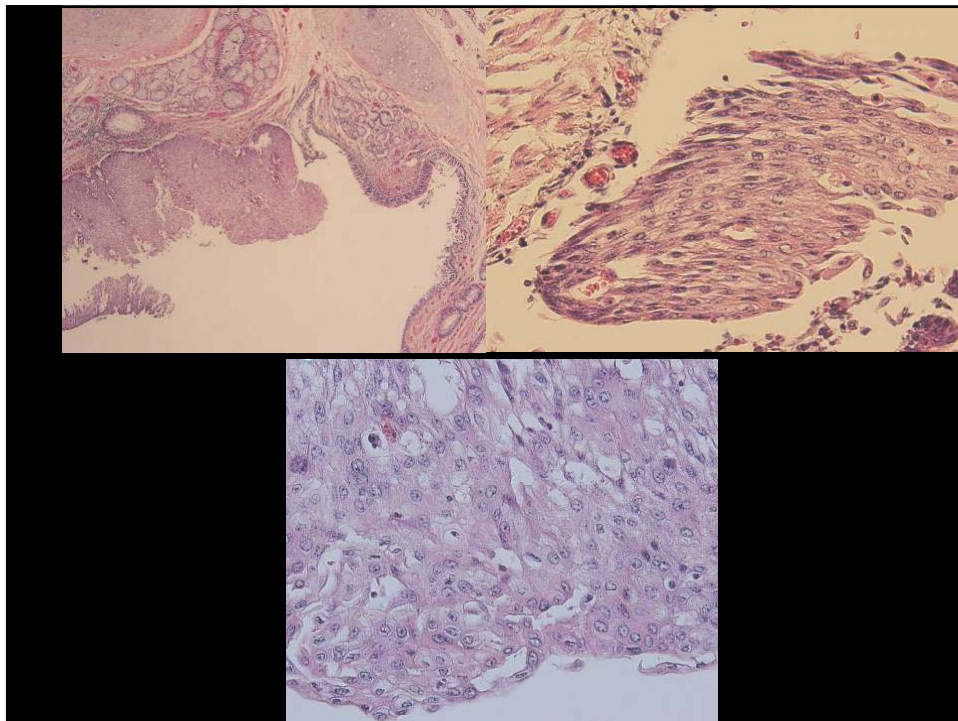
Malignant tumors - classification

Lung Tumor Classification



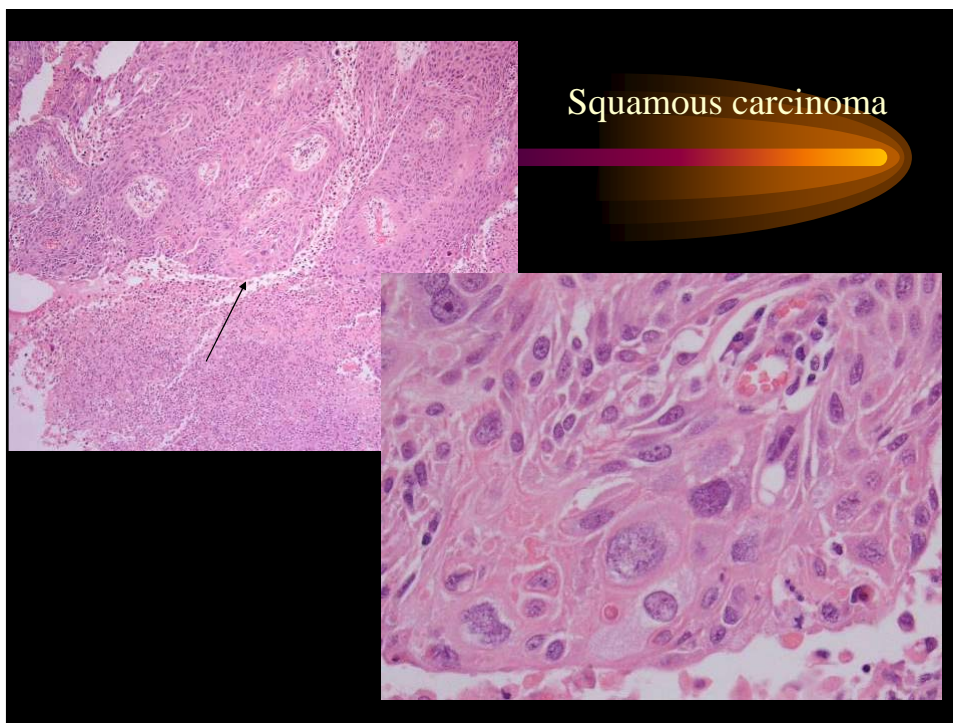
Squamous precursors

- 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)



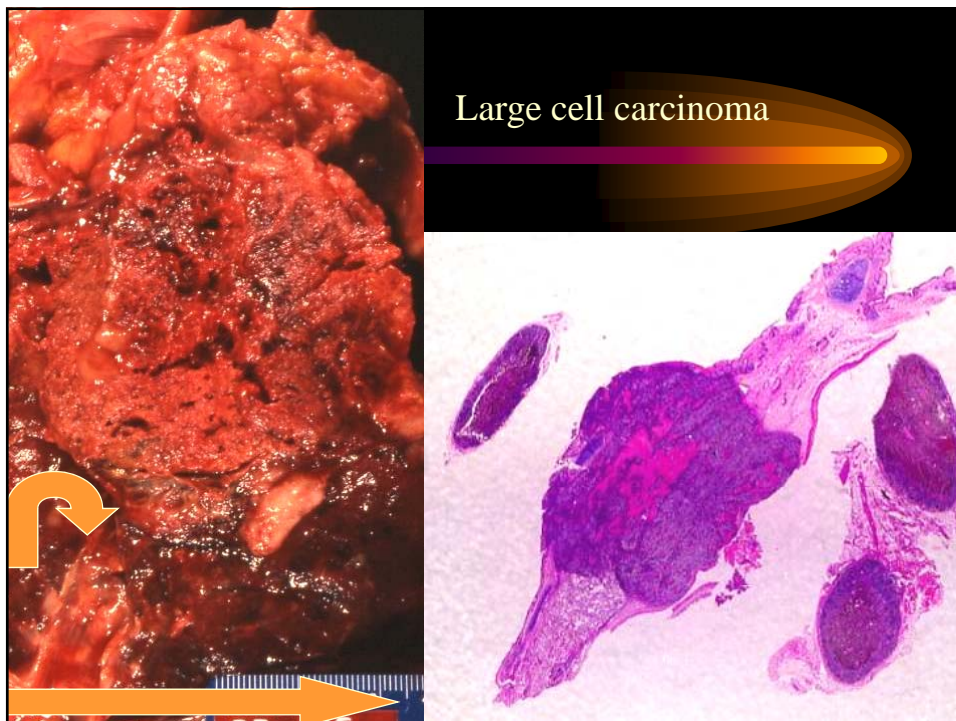
Squamous carcinoma

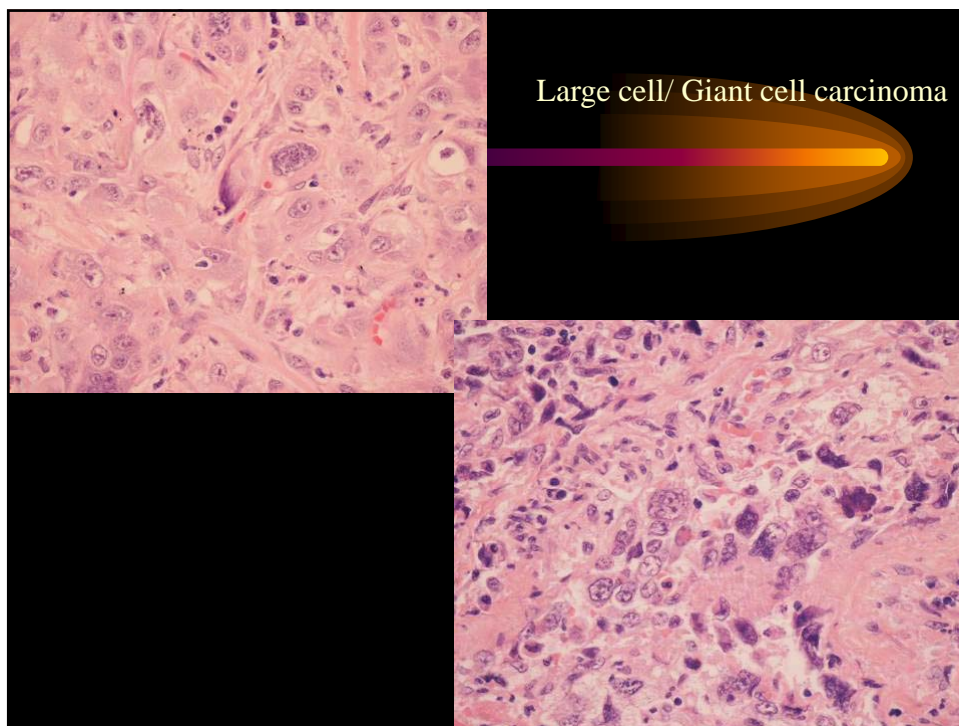
- Usually of bronchogenic origin; however can also arise from peripheral areas of squamous metaplasia
- Frequently have central necrosis
- Faster doubling time than adenocarcinoma; often larger at presentation
- Metastasis in relation to tumor size may occur later than adenocarcinoma



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

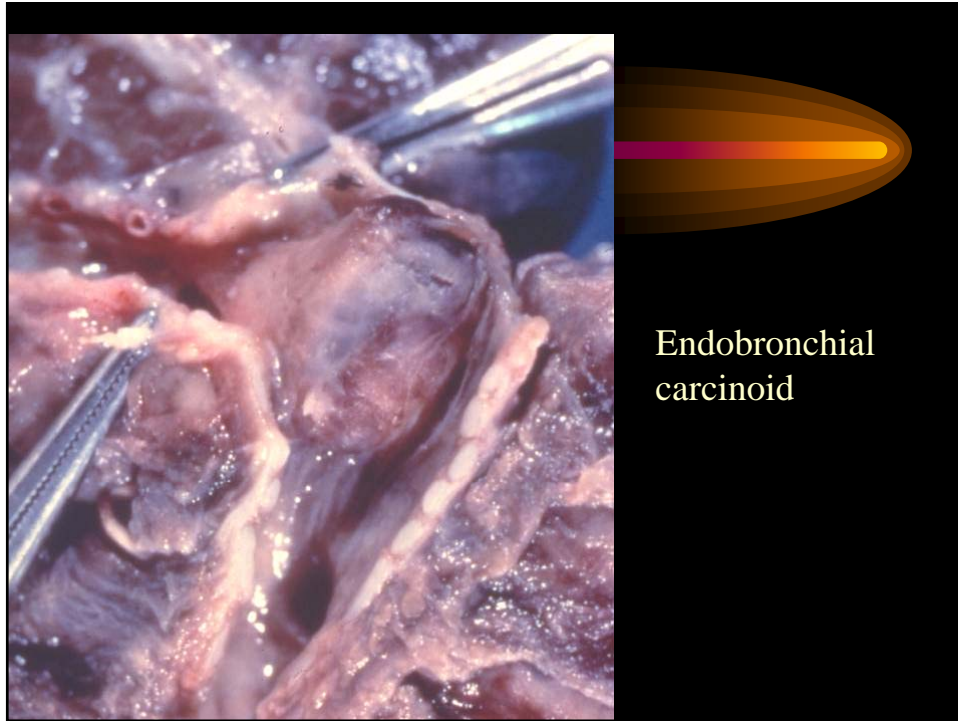




Carcinoids

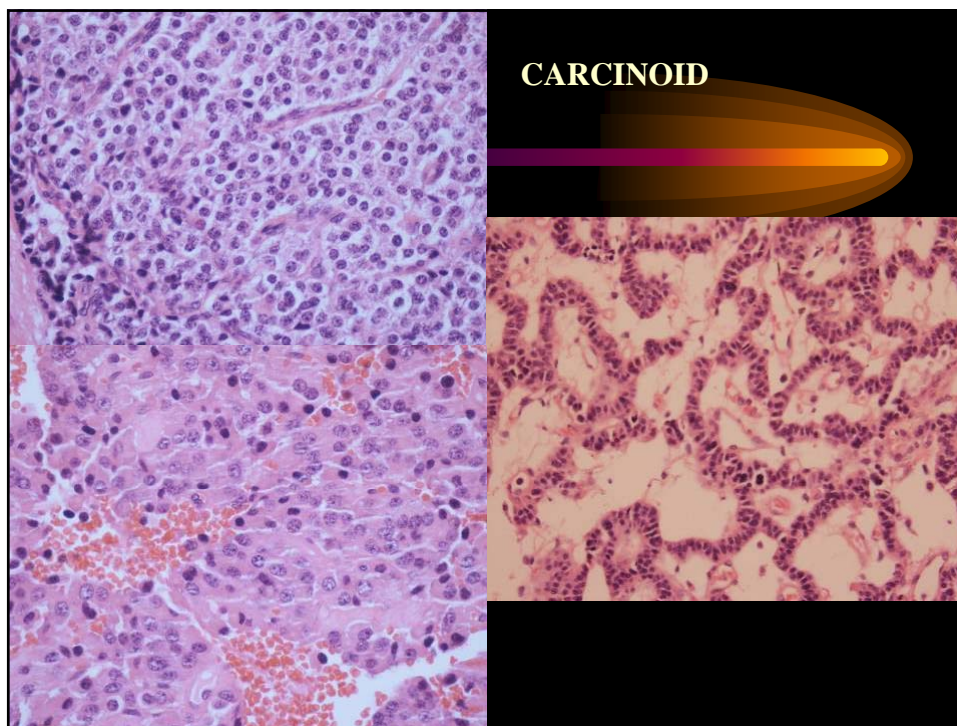
- Malignant neoplasm of neuroendocrine cell origin
- Can be central or peripheral; central lesions can cause bronchial obstruction
- Project into bronchial lumen but often have intact mucosa above them (grow under the mucosa)
- Typical carcinoids are low grade malignancies; atypical carcinoids (mitoses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

The slide features a decorative graphic at the top consisting of a horizontal bar with a gradient from purple to yellow and a teardrop shape at the end, with the word 'Carcinoids' written in a stylized font above it.



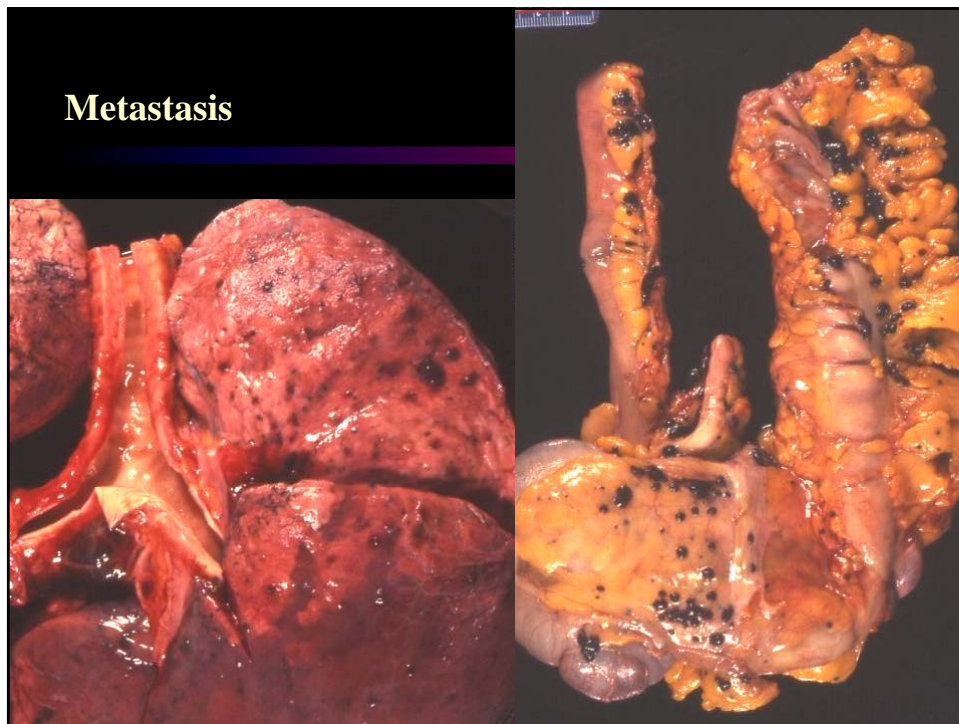
Carcinoids

- 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

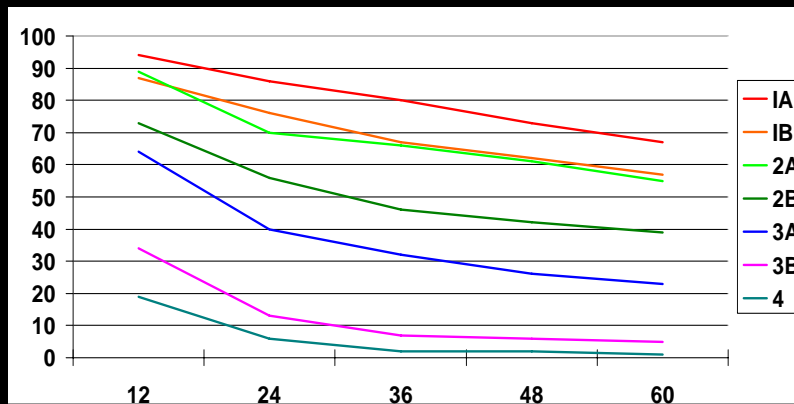
Therapy- small cell

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

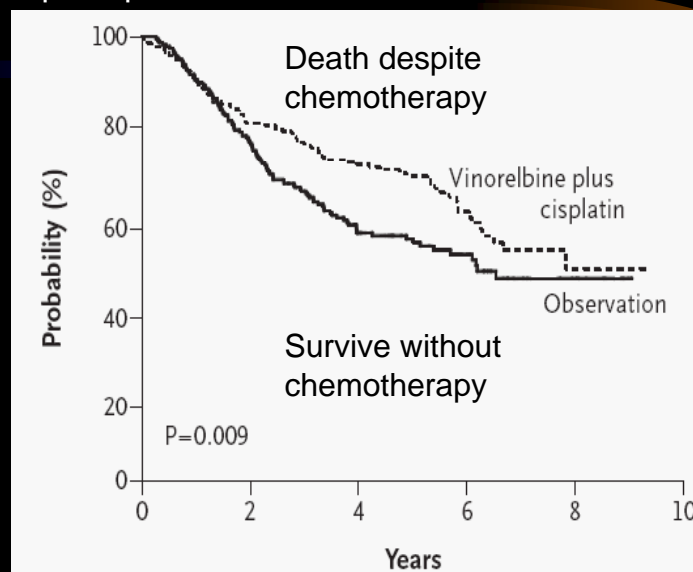
Chest 111:1710-17



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

Kaplan-Meier Estimates of Survival among Patients Who Received Adjuvant Vinorelbine plus Cisplatin and Those Who Underwent Observation Alone

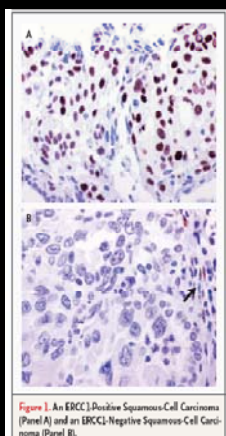


Winton, T. et al. N Engl J Med 2005;352:2589-2597

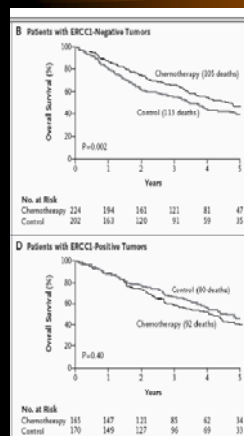
Tumor Biology

- 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

ERCC1 Negative Tumors benefit from Cisplatin Adjuvant Therapy



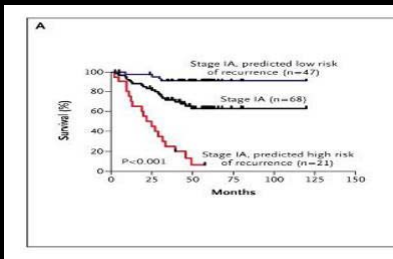
NEJM 355:983



Genomic Signatures of Resected Tumors Predict Outcome

A Genomic Strategy to Refine Prognosis in Early-Stage Non-Small-Cell Lung Cancer

Anil Potti, M.D., Sayan Mukherjee, Ph.D., Rebecca Petersen, M.D., Holly K. Dressman, Ph.D., Andrea Bild, Ph.D., Jason Koonitz, M.D., Robert Kratzke, M.D., Mark A. Watson, M.D., Ph.D., Michael Kelley, M.D., Geoffrey S. Ginsburg, M.D., Ph.D., Miles West, Ph.D., David H. Harpole, Jr., M.D., and Joseph R. Nevins, Ph.D.



Potti A, et al. N Engl J Med. 2009;361:570-580

Columbia Pilot

Shared Decision Making

Name: _____ (Lung Cancer)
 Age: 60 Sex: Female

Pathologic T Stage: T2
 Pathologic N Stage: N0
 Stage: 1B

Decision: No Additional Therapy

50 out of 100 persons are alive in 5 years.
 40 out of 100 persons die because of cancer.
 4 out of 100 persons die of other causes.

Decision: Chemotherapy

50 out of 100 persons are alive in 5 years. Plus...
 7 out of 100 persons are alive because of therapy.
 33 out of 100 persons die because of cancer.
 4 out of 100 persons die of other causes.

- Pathology Assessment
 - Invasion
 - Immunostaining
 - IRS1, CCNB1, LOX
 - Kras, EGFR
- Gene Expression Profiling
 - Comparison with Prognosis GeneSets.

Adjuvant Lung!
<https://www.adjuvantonline.com/lungstandar>

CUMC Approach

- Screen High Risk Individuals
 - Algorithm for Nodule Management
- Stage Diagnosed Tumors with PET/CT
- Resect with Minimally Invasive Techniques
- Individualize Decisions regarding Adjuvant Chemotherapy
 - Pathology Panel
 - Research assays
 - Gene Profiling

