Cancer in the United States, 2009

Estimated New Cases*

Males			Females		
Prostate	192,280	25%	Breast	192,370	27%
Lung & bronchus	116,090	15%	Lung & bronchus	103,350	14%
Colon & rectum	75,590	10%	Colon & rectum	71,380	10%
Urinary bladder	52,810	7%	Uterine corpus	42,160	6%
Melanoma of the skin	39,080	5%	Non-Hodgkin lymphoma	29,990	4%
Non-Hodgkin lymphoma	35,990	5%	Melanoma of the skin	29,640	4%
Kidney & renal pelvis	35,430	5%	Thyroid	27,200	4%
Leukemia	25,630	3%	Kidney & renal pelvis	22,330	3%
Oral cavity & pharynx	25,240	3%	Ovary	21,550	3%
Pancreas	21,050	3%	Pancreas	21,420	3%
All Sites	**766,130**	**100%**	**All Sites**	**713,220**	**100%**

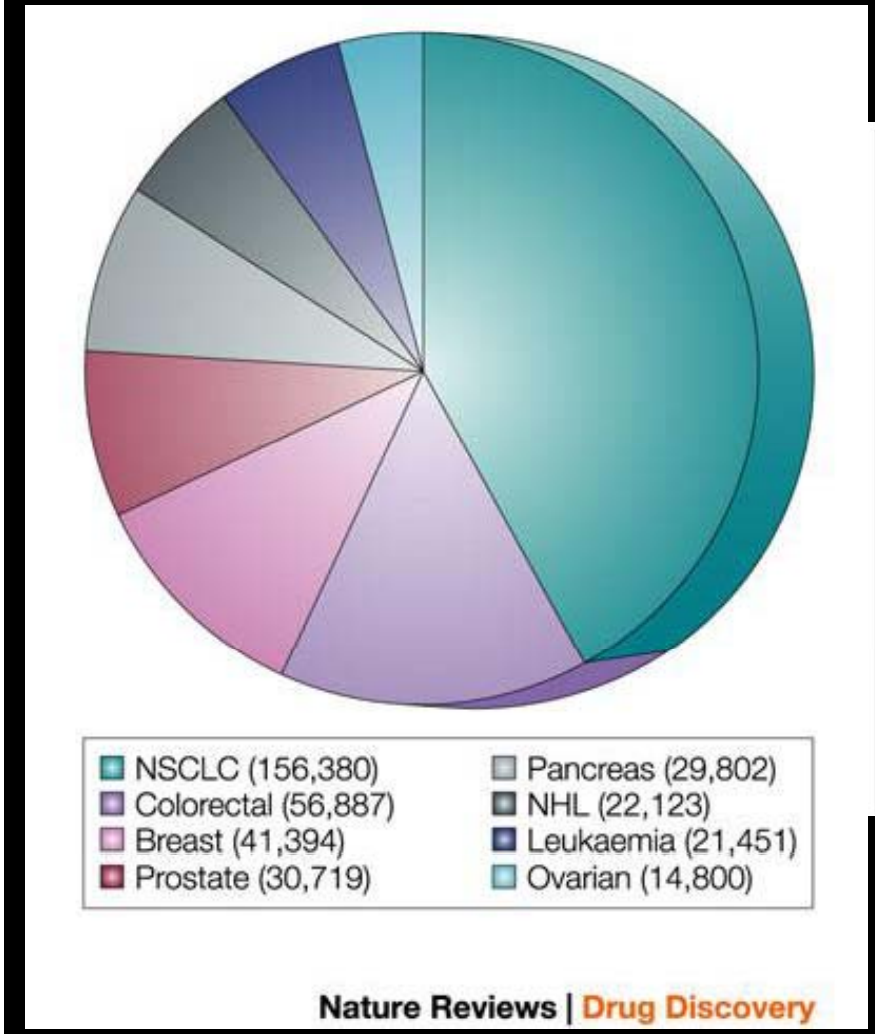
Estimated Deaths

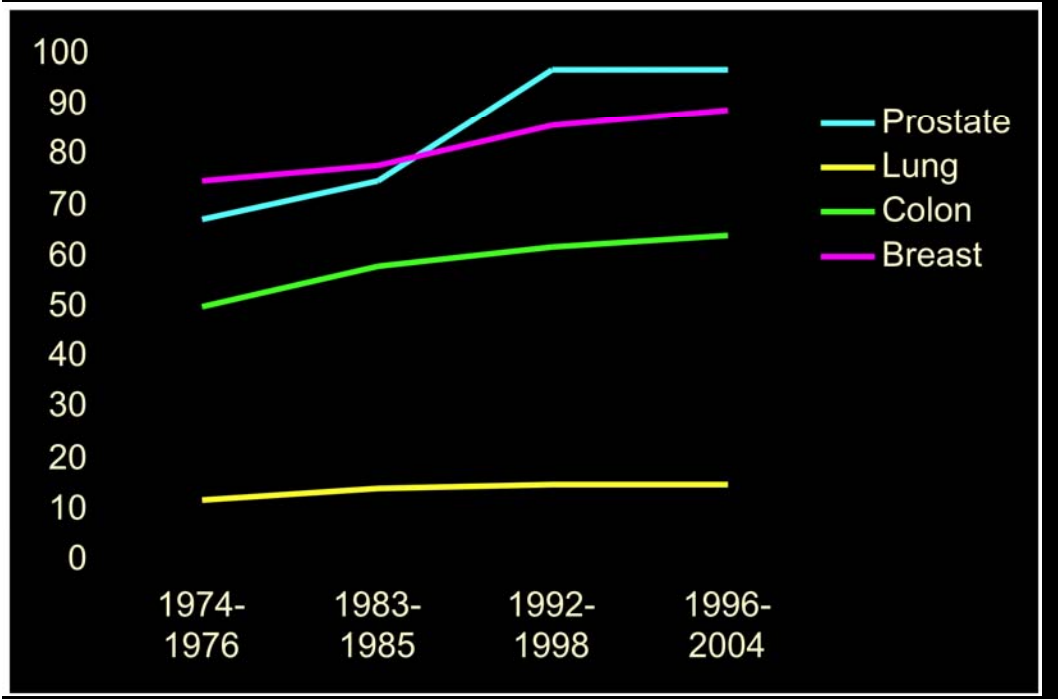
Males			Females		
Lung & bronchus	88,900	30%	Lung & bronchus	70,490	26%
Prostate	27,360	9%	Breast	40,170	15%
Colon & rectum	25,240	9%	Colon & rectum	24,680	9%
Pancreas	18,030	6%	Pancreas	17,210	6%
Leukemia	12,590	4%	Ovary	14,600	5%
Liver & intrahepatic bile duct	12,090	4%	Non-Hodgkin lymphoma	9,670	4%
Esophagus	11,490	4%	Leukemia	9,280	3%
Urinary bladder	10,180	3%	Uterine Corpus	7,780	3%
Non-Hodgkin lymphoma	9,830	3%	Liver & intrahepatic bile duct	6,070	2%
Kidney & renal pelvis	8,160	3%	Brain & other nervous system	5,590	2%
All Sites	**292,540**	**100%**	**All Sites**	**269,800**	**100%**

Jemal, A. et al. CA Cancer J Clin 2009;59:225-249

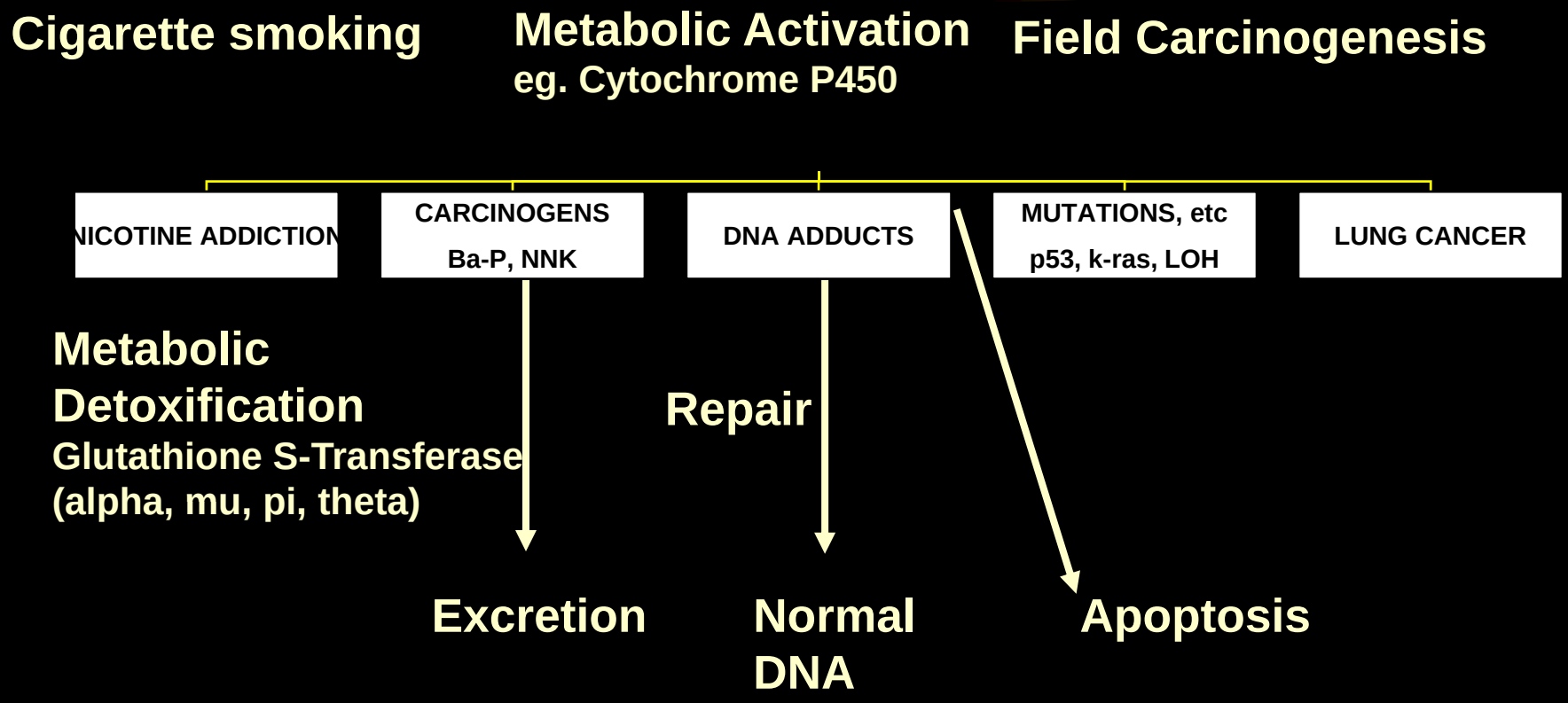
Lung Cancer in the United States

Annual Cancer Deaths





The Scheme:
From Nicotine Addiction to Lung Cancer

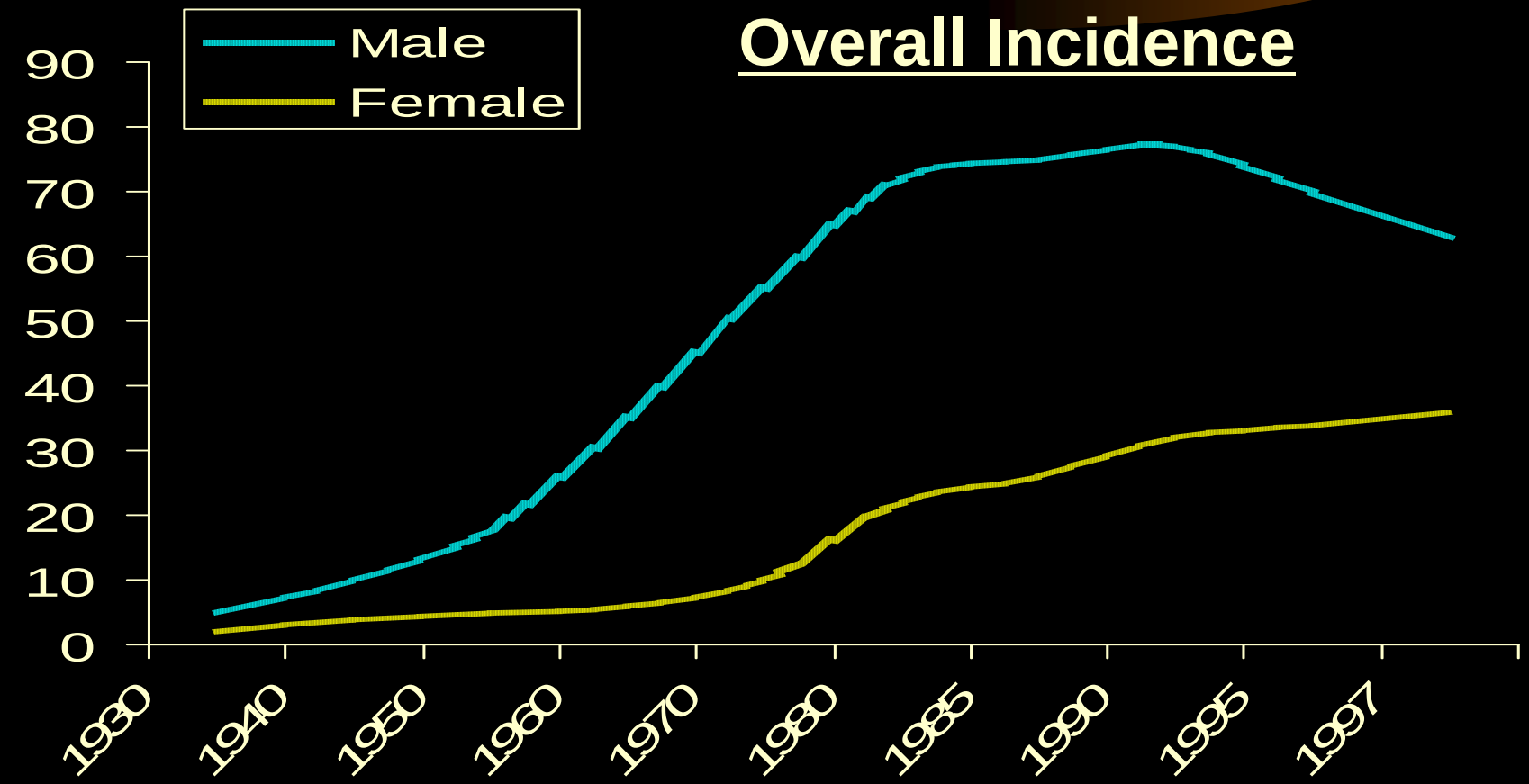


Modified from Hecht JNCI; 1999

Lung Cancer Risks

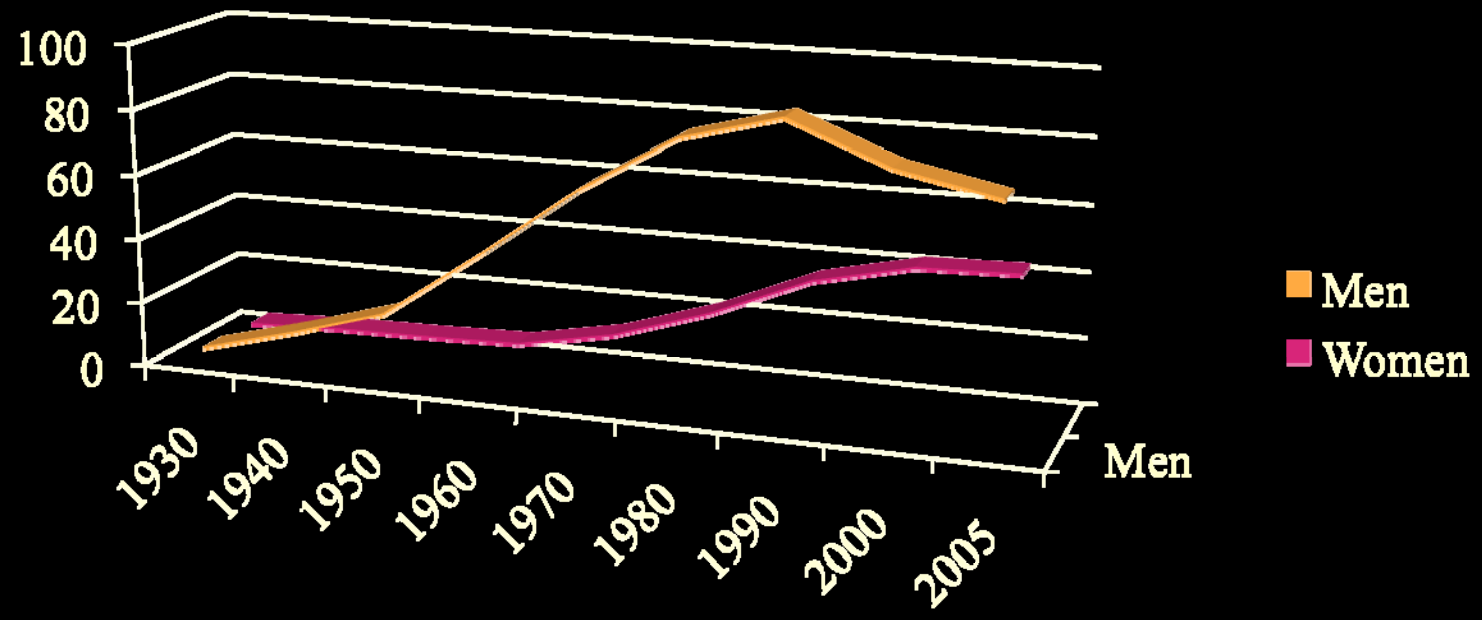
- Cigarette Smoking
  - Environmental Tobacco Smoke
- Other Carcinogens
  - Asbestos, Arsenic, Radon,
  - Bis(chloromethyl) ether, Chromium, Foundry fumes, nickel, mustard gas, coke oven emissions
- Air Pollution (foundries, diesel exhaust)
- Family History
- Diet (Vitamins A,C, E and selenium “protective”)

Lung Cancer Death Rates, US 1973-1997



Source: SEER

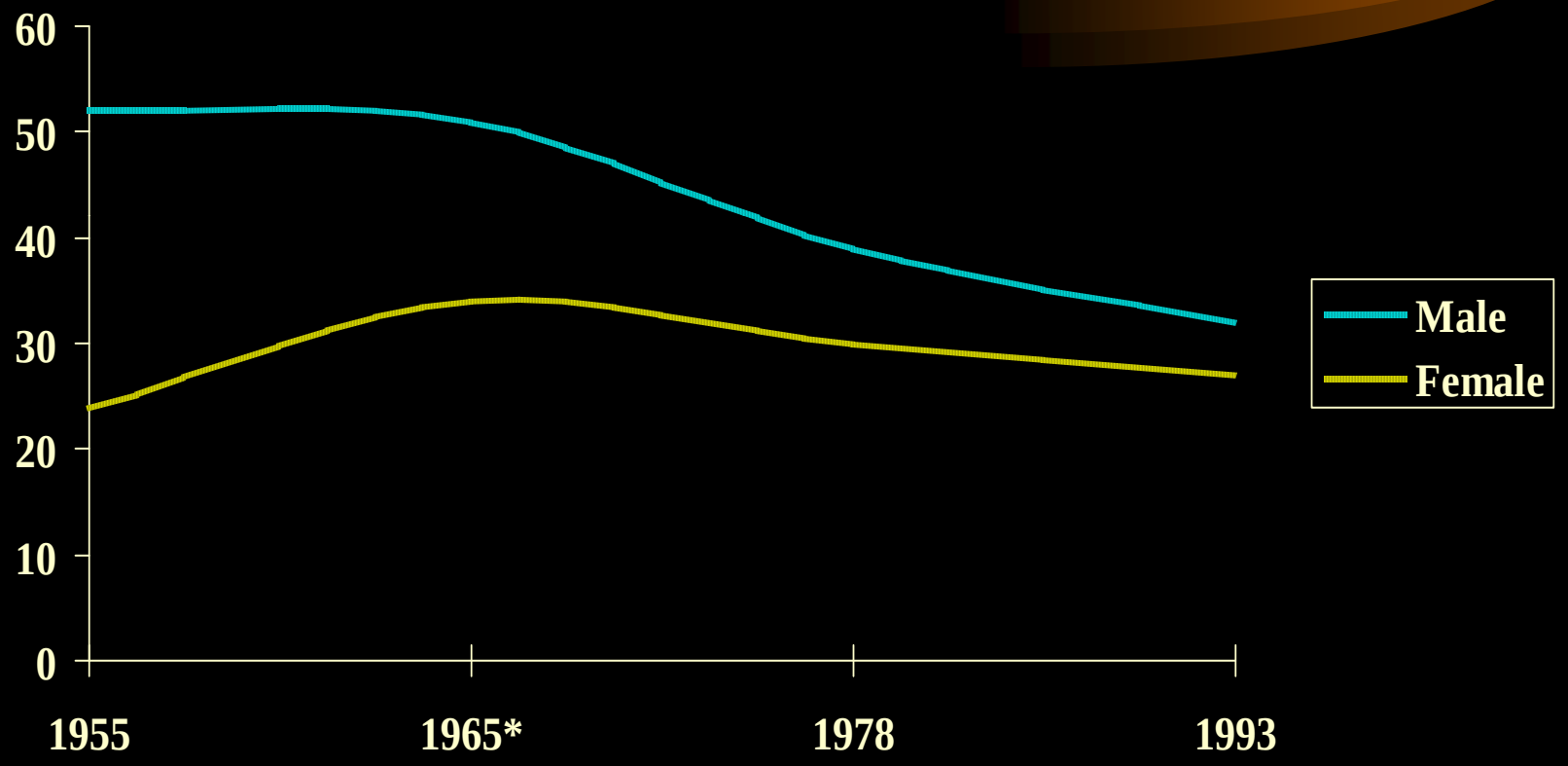
Lung Cancer Death Rates, US 1930-2005



Rates per 100,000, age-adjusted

Source: SEER

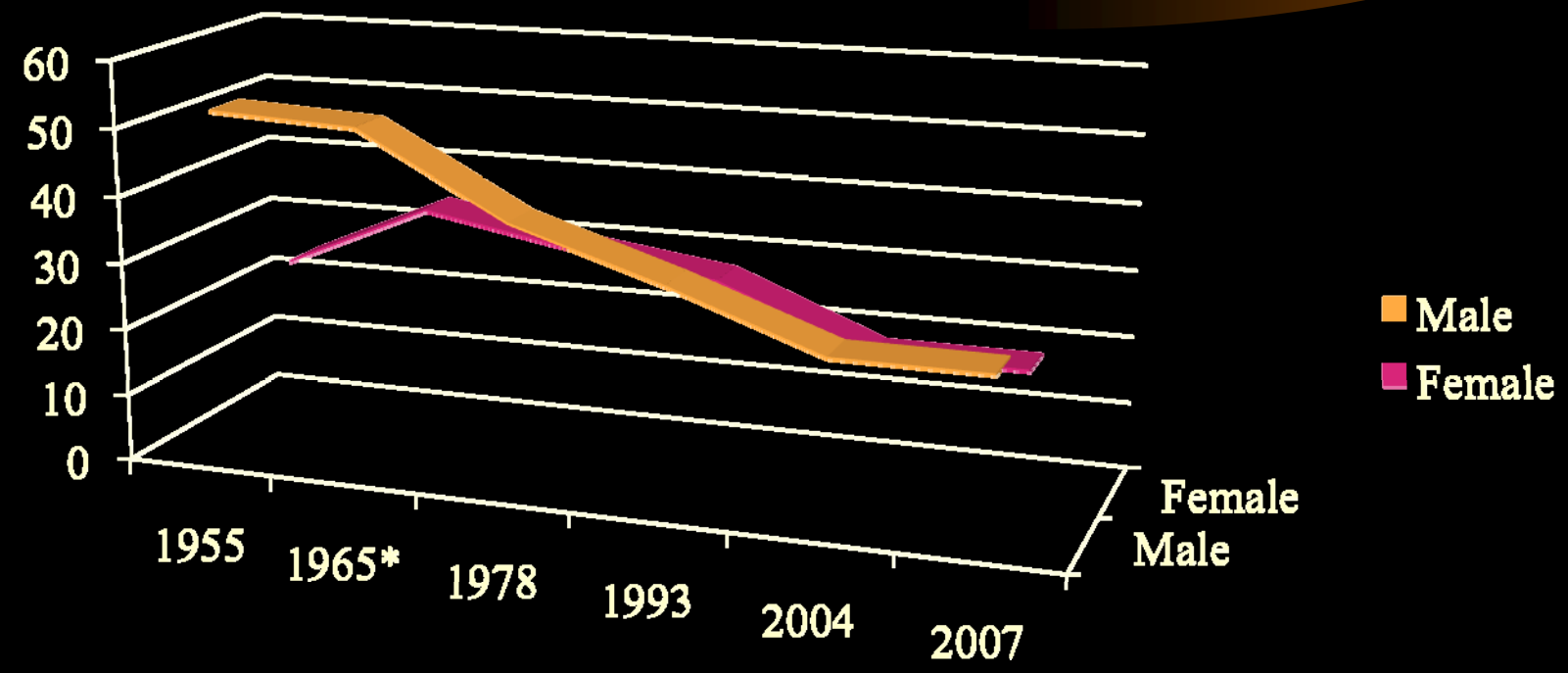
Smoking Prevalence Rates, US



*Surgeon General's Report

Garfinkel, Prev Med 26:447

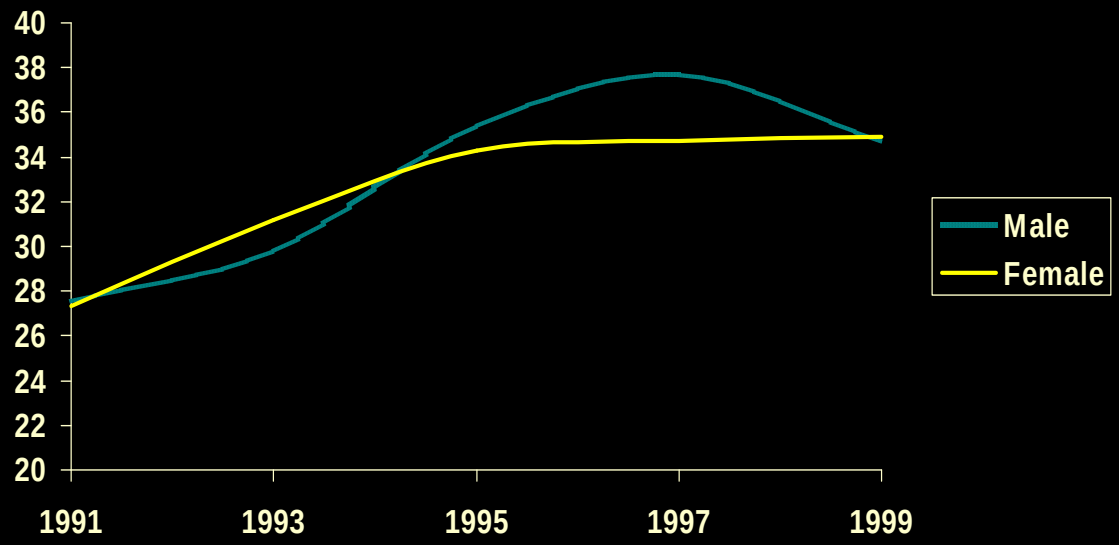
Smoking Prevalence Rates, US



*Surgeon General's Report

Garfinkel, Prev Med 26:447, CDC MMWR 56:1157

Percentage of High School Students Who Reported Current Cigarette Smoking



Youth Behavior Survey, MMWR 2000; 49

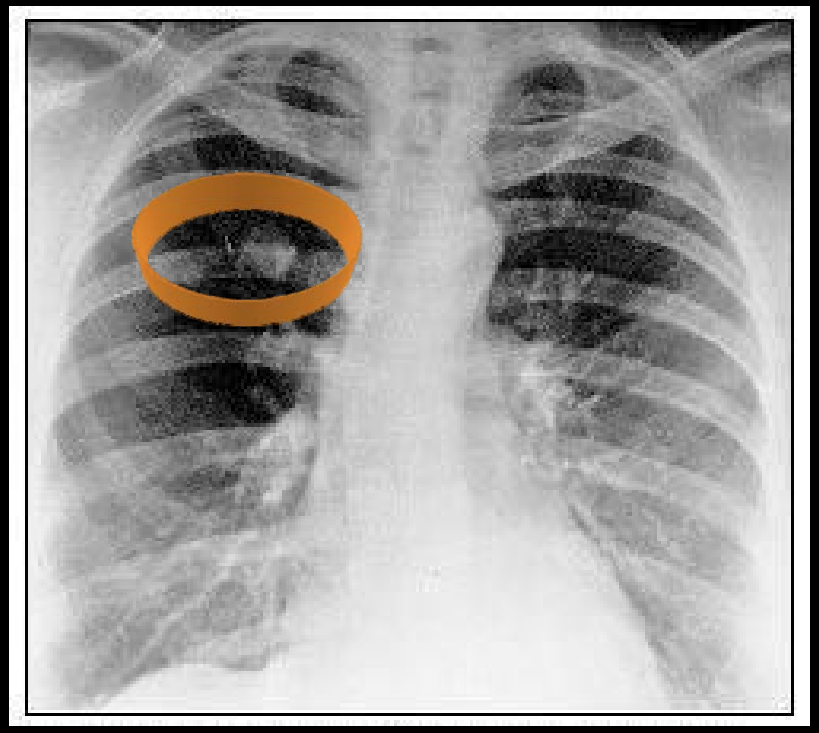
Presentation of Lung Cancer

- 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

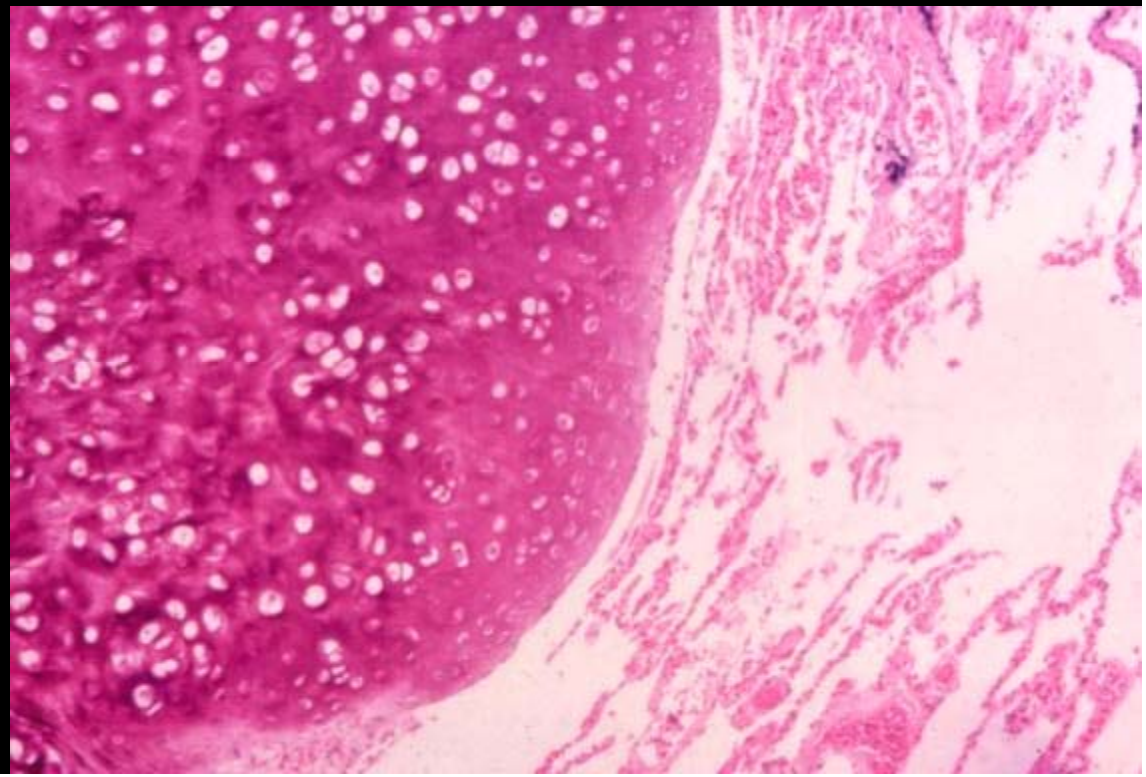
- Transbronchial biopsy
- Transthoracic needle biopsy
- Cytology
  - Bronchial brushing
  - Lavage
  - Aspiration (transthoracic or transbronchial)
- Surgical Resection-Thoracotomy/VATS

Lung tumors - Benign

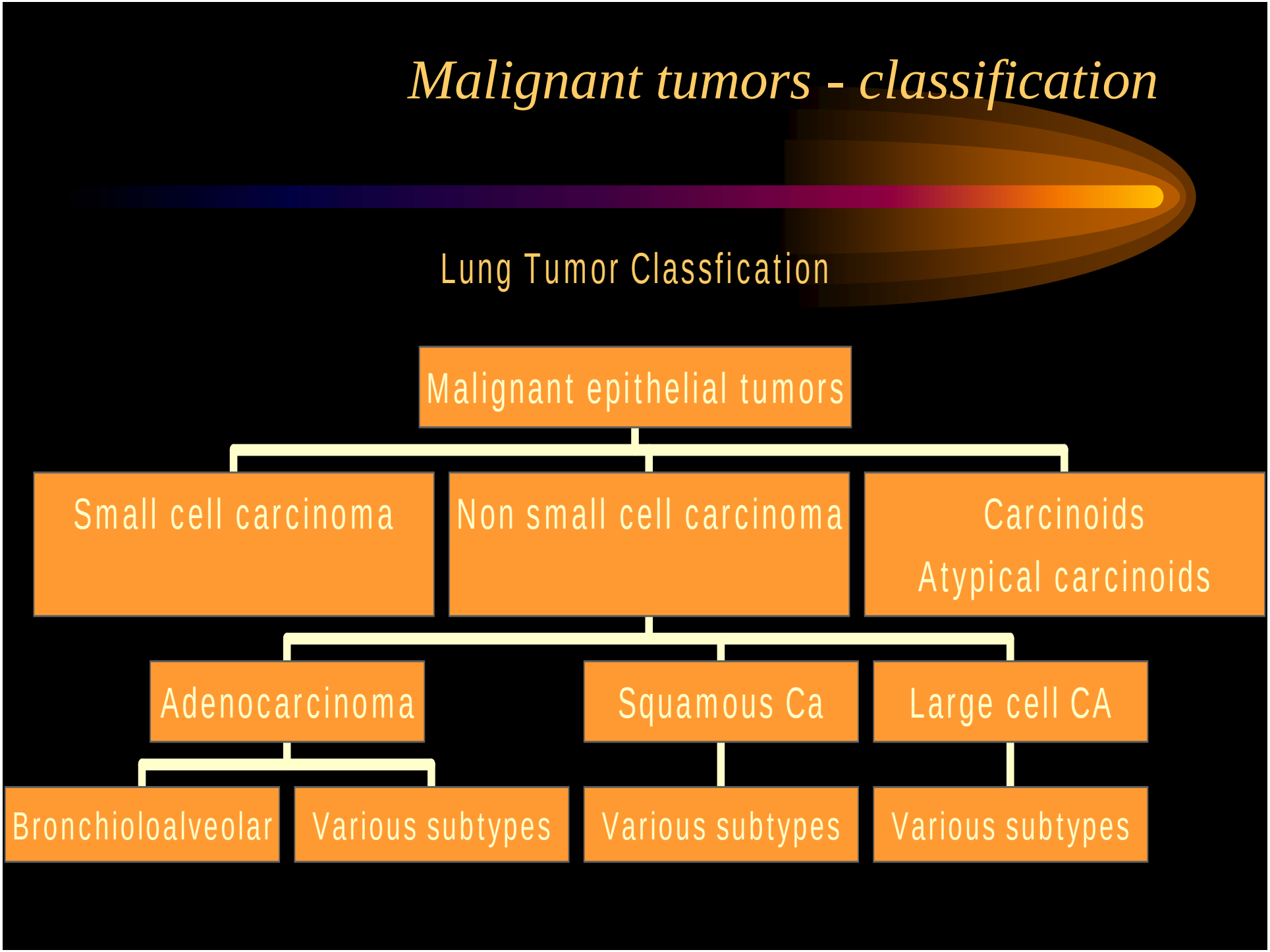
- The majority of pulmonary neoplasms are malignant
- Benign tumors/lesions
  - Hamartoma (most common)
  - Mesenchymal- leiomyoma, lipoma, chondroma (all unusual)
  - Alveolar adenoma (rare)

Hamartoma

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



Malignant tumors - classification

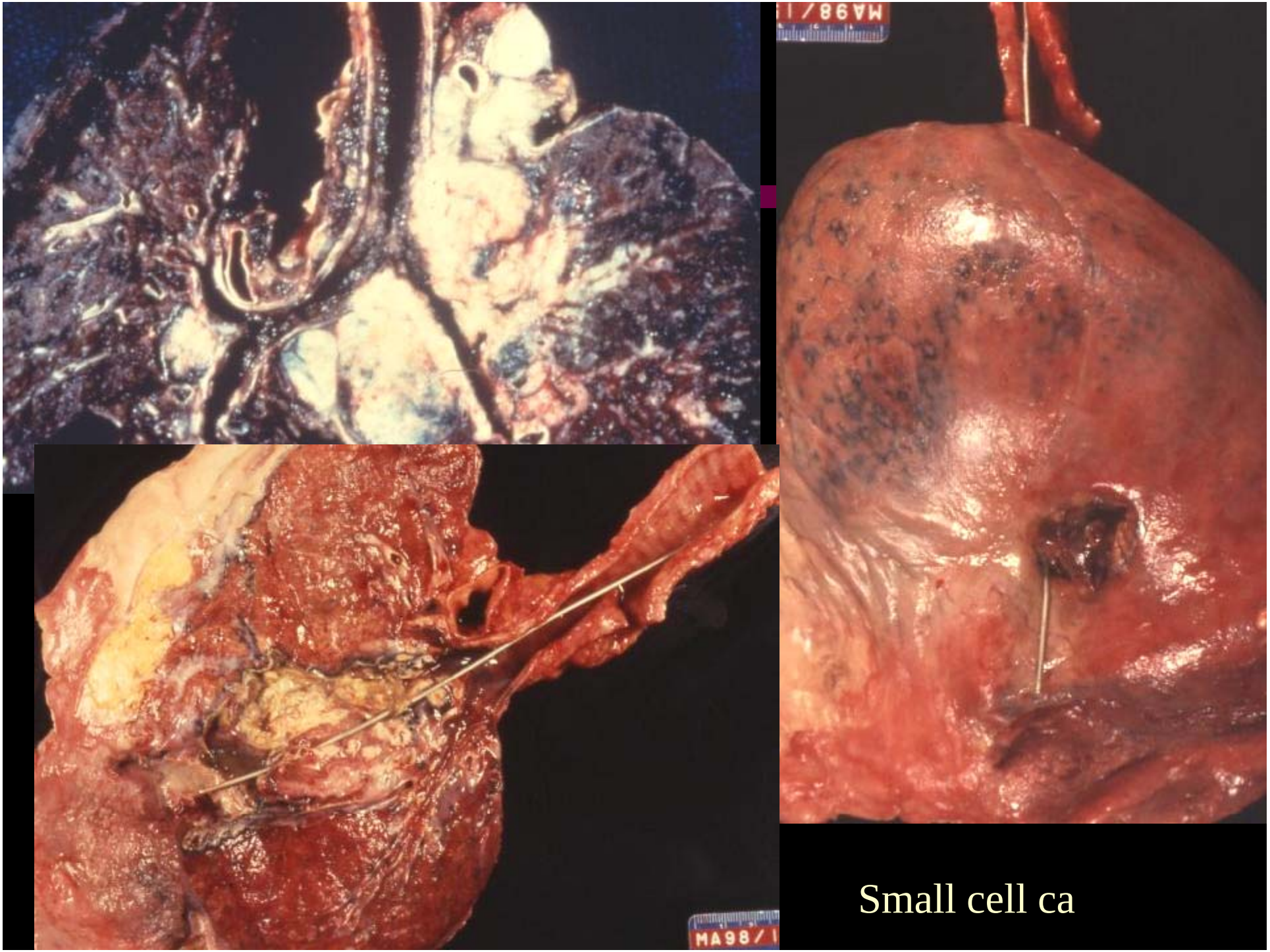


Small cell carcinoma

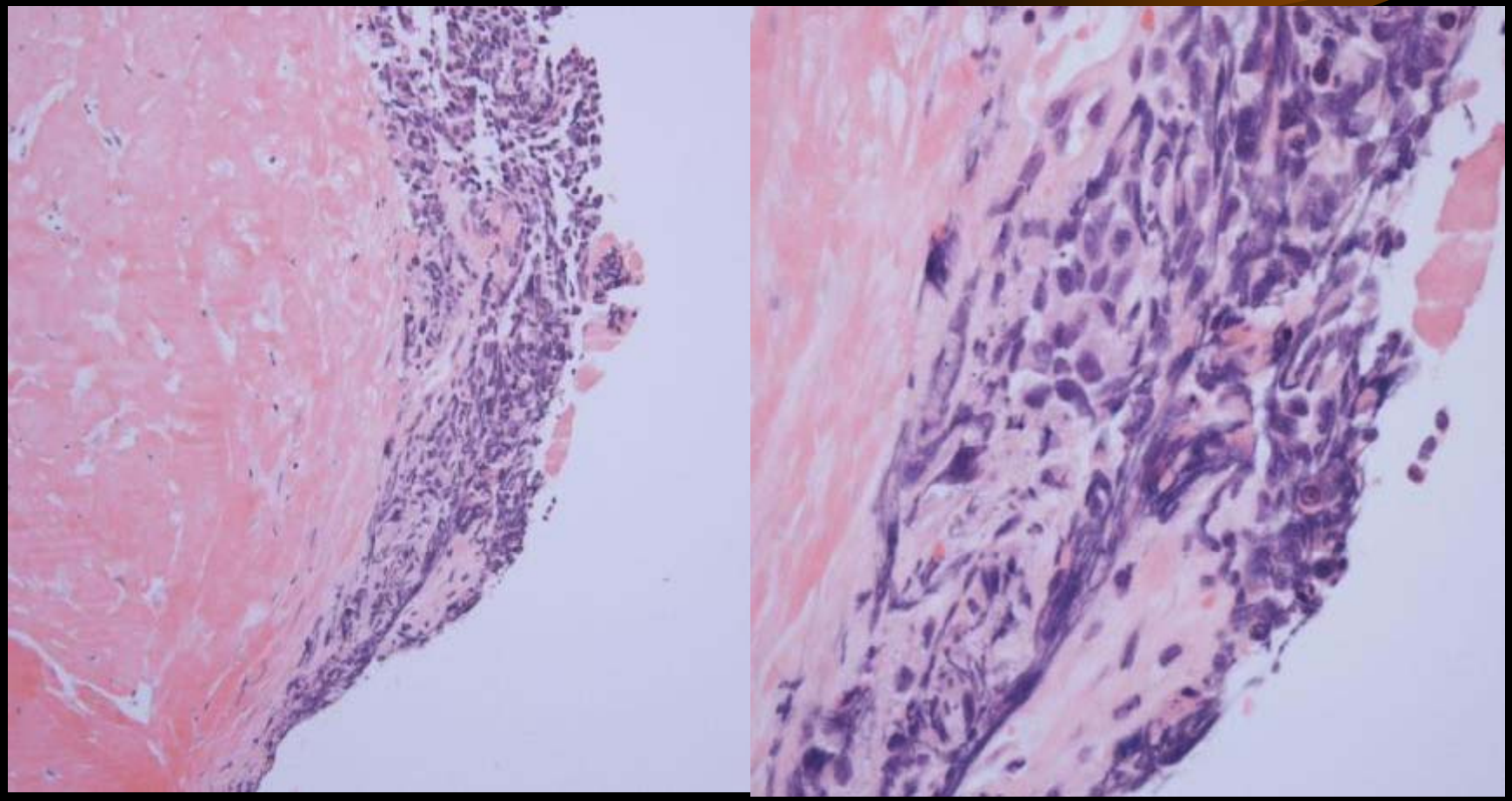
- Usually hilar/ central tumor
- The majority have extrapulmonary spread at time of presentation.
- Only 5% present as early stage disease.
- Critical divide between small cell and non-small cell carcinoma
  - Small cell carcinoma staged differently, treated with chemoradiation not surgery.

Small cell carcinoma

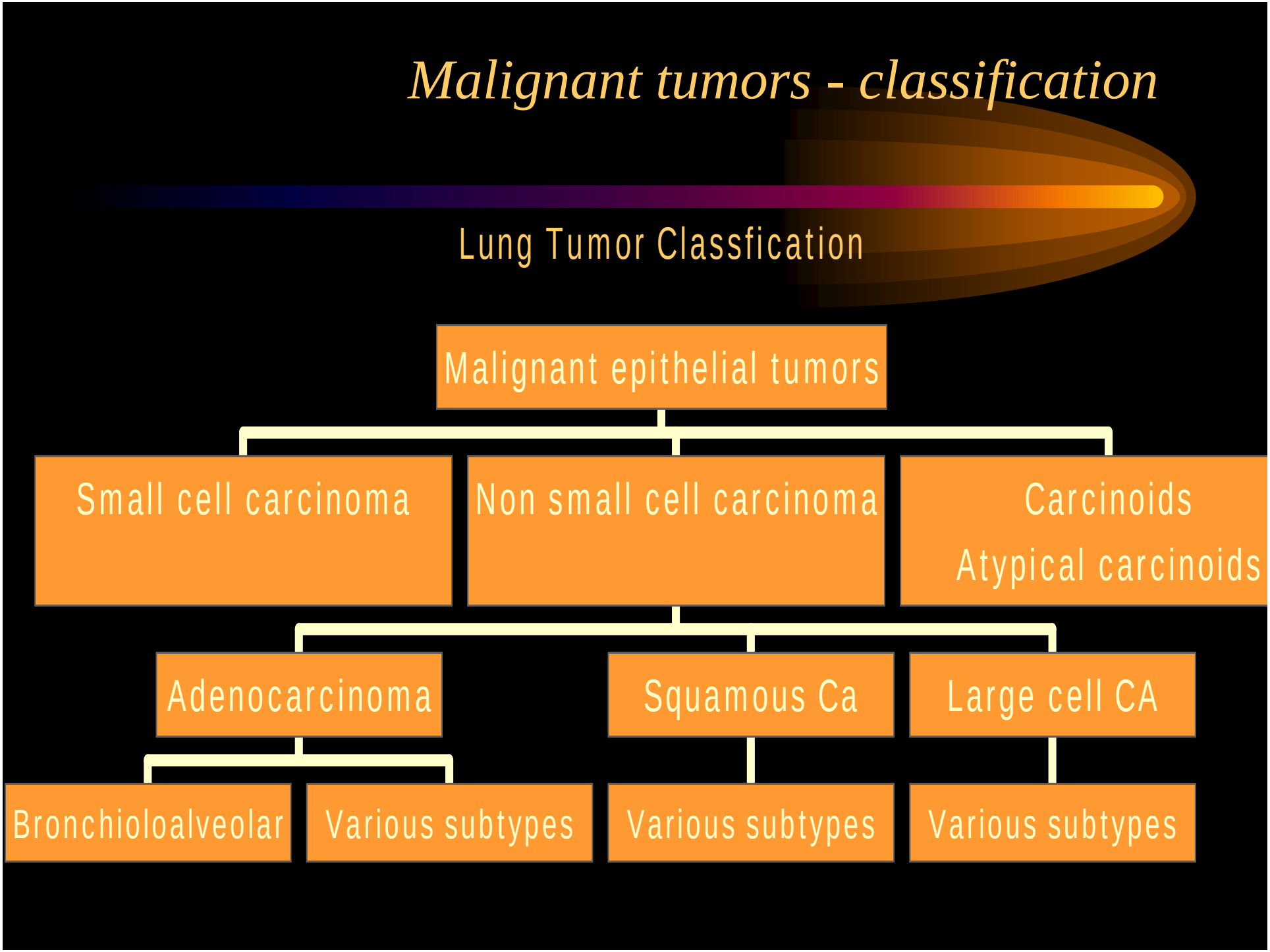
- High grade tumor
- Small cells with high nuclear to cytoplasmic ratio
- Nuclear molding with stippled, salt and pepper chromatin
- Frequent mitosis and apoptosis
- “Crush” artifact - very fragile cells
- Neuroendocrine differentiation can be demonstrated by electron microscopy and immunohistochemistry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


Small cell ca

Small Cell

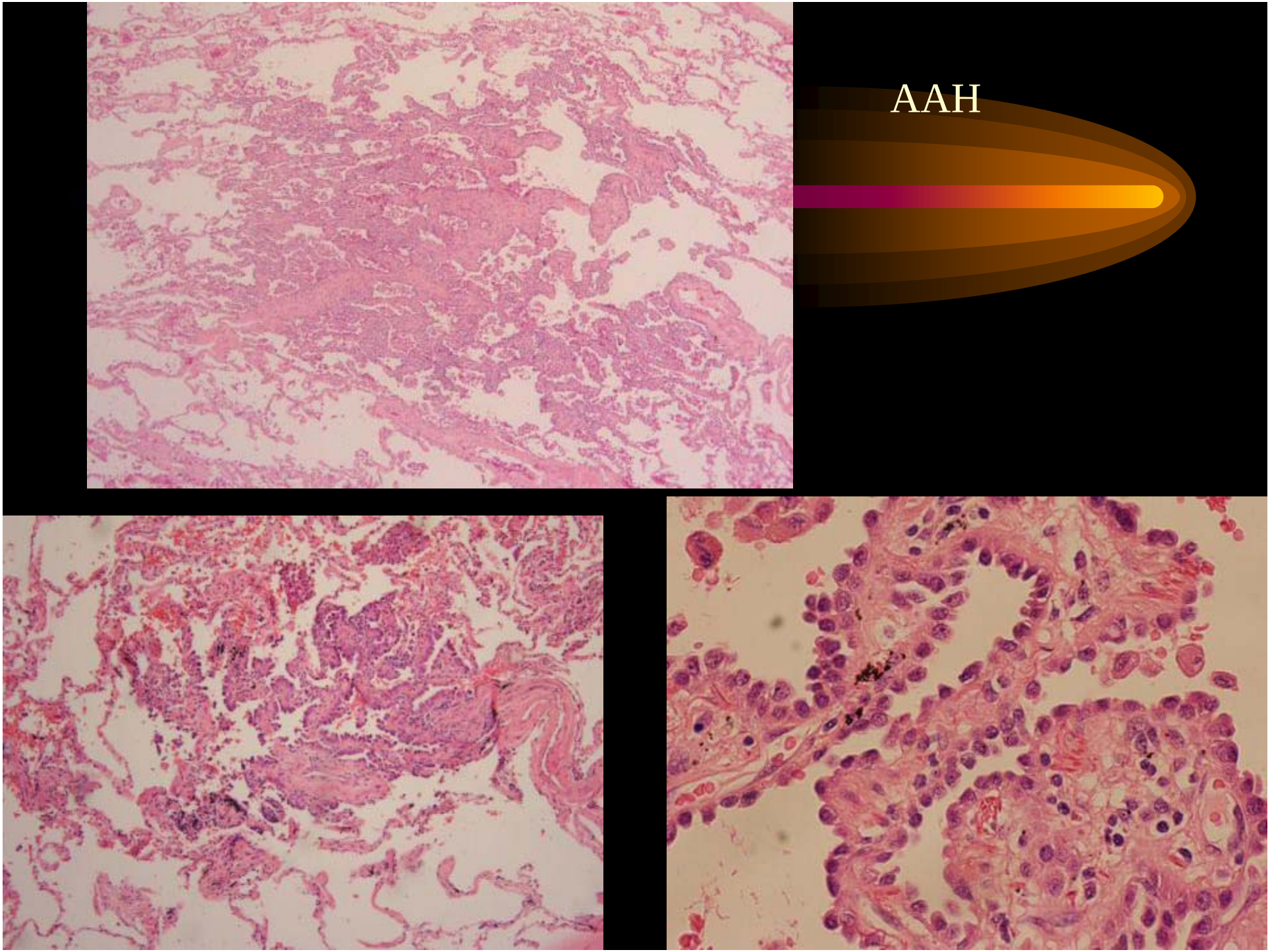


Malignant tumors - classification



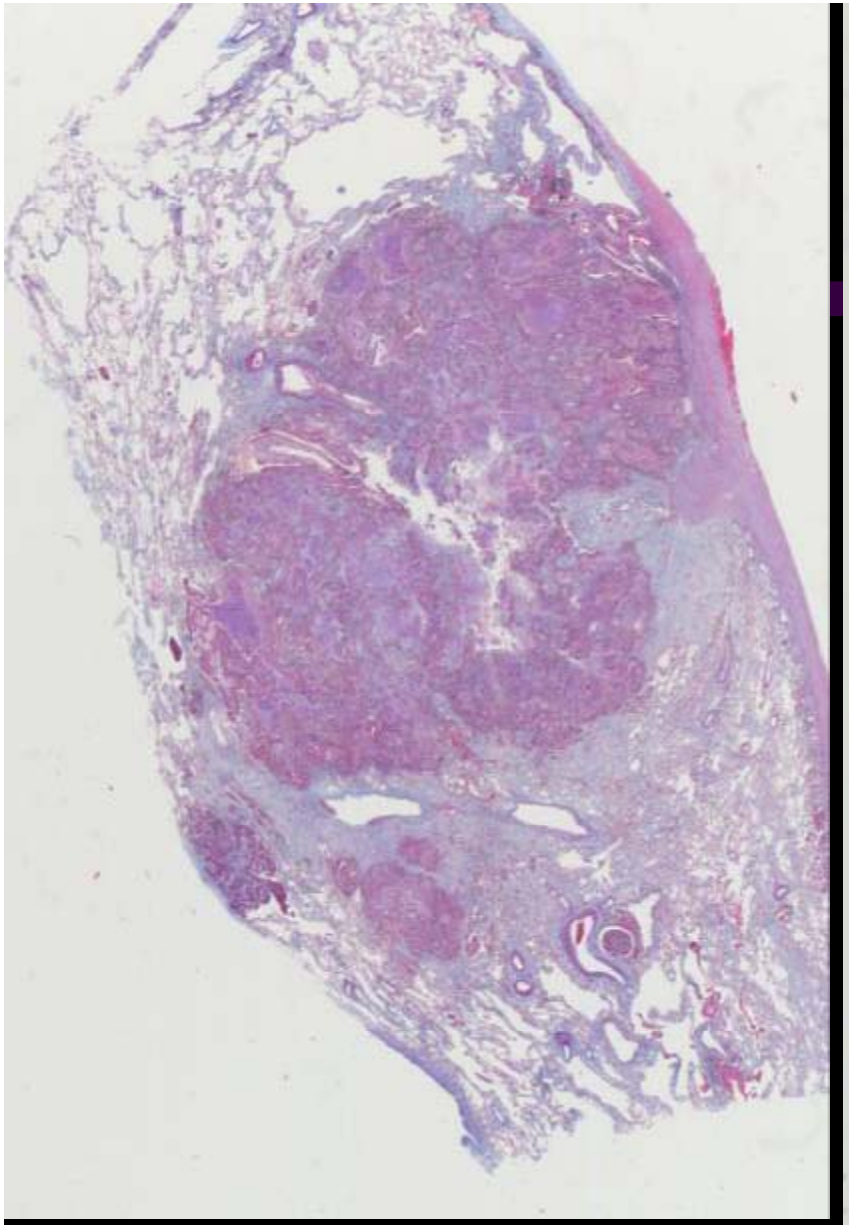
Atypical adenomatous hyperplasia-adenocarcinoma precursor

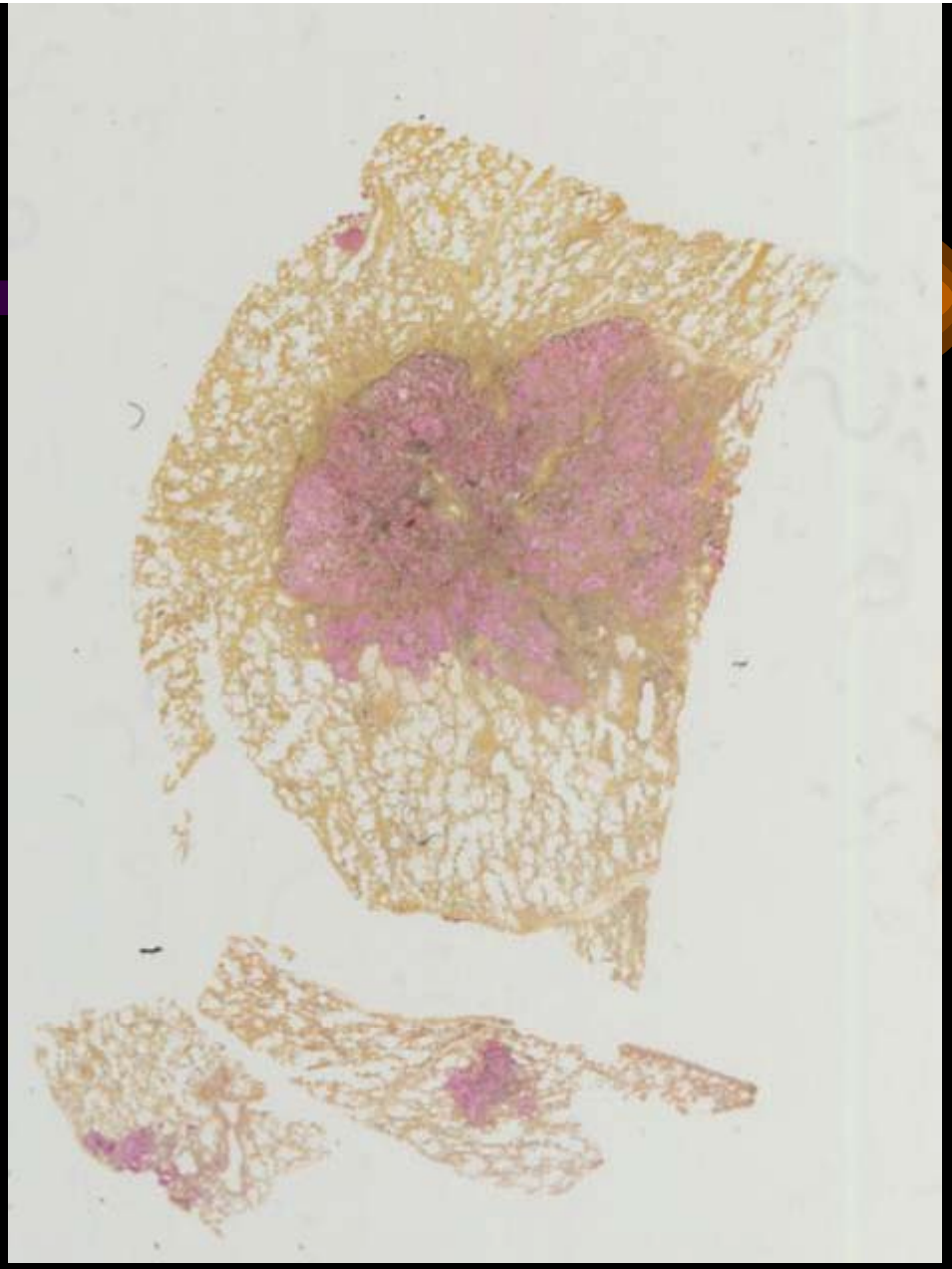
- Focal, 5.0 mm or less, with defined borders
- Alveoli lined by cuboidal to low columnar cells with variable atypia
- Alveolar walls may be slightly thickened
- Non-mucinous
- Clinical significance unclear (?time to progression to carcinoma)


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.



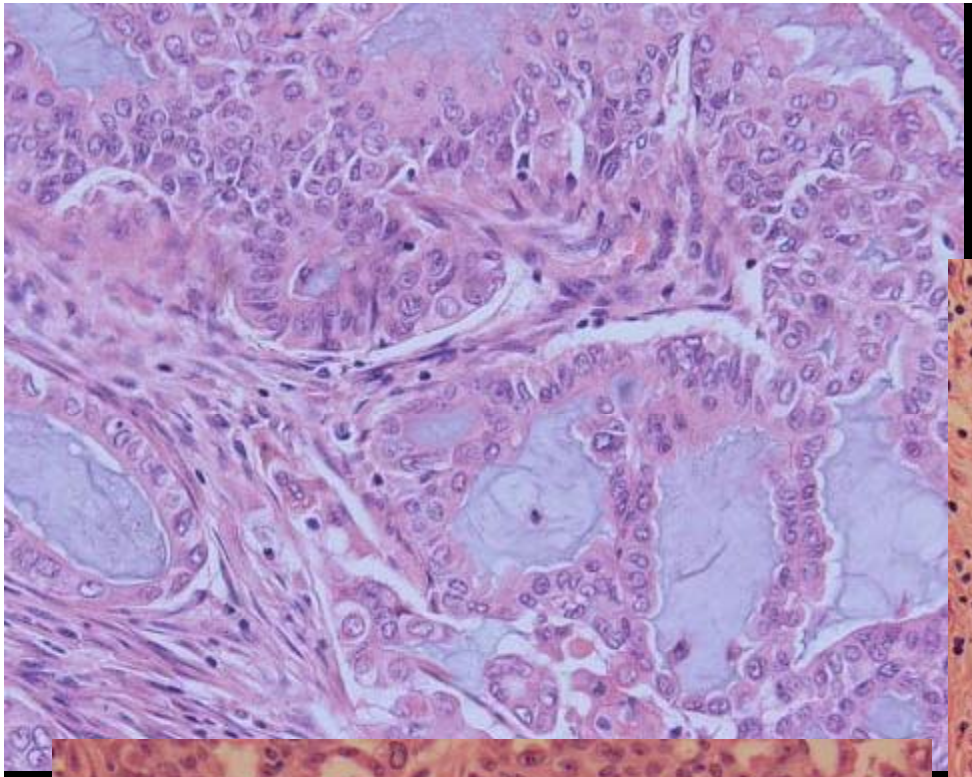


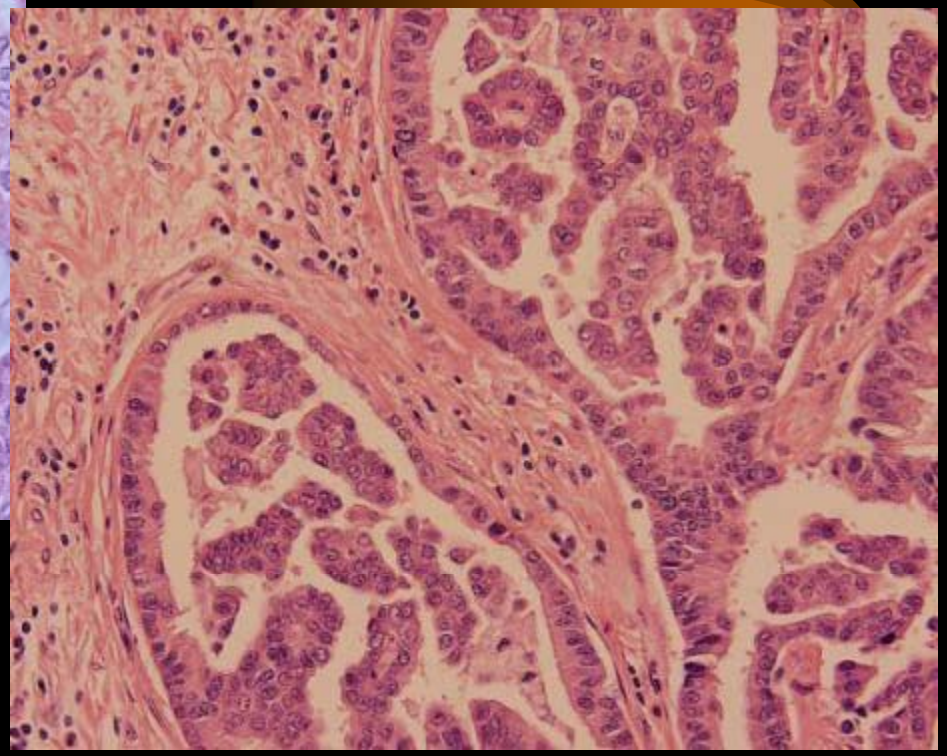
Adenocarcinoma

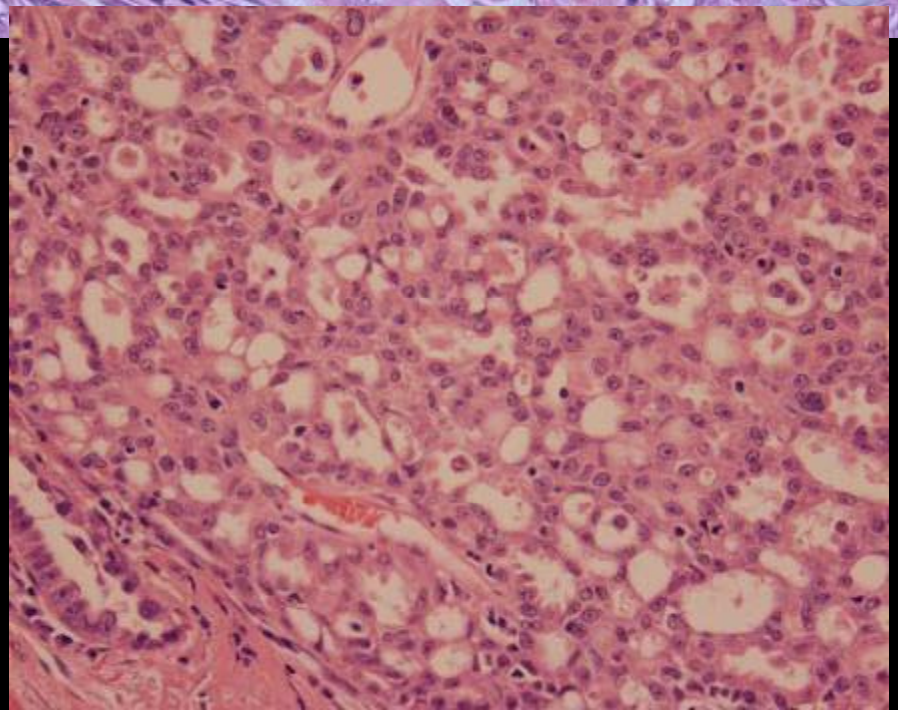
Adenocarcinoma

- 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

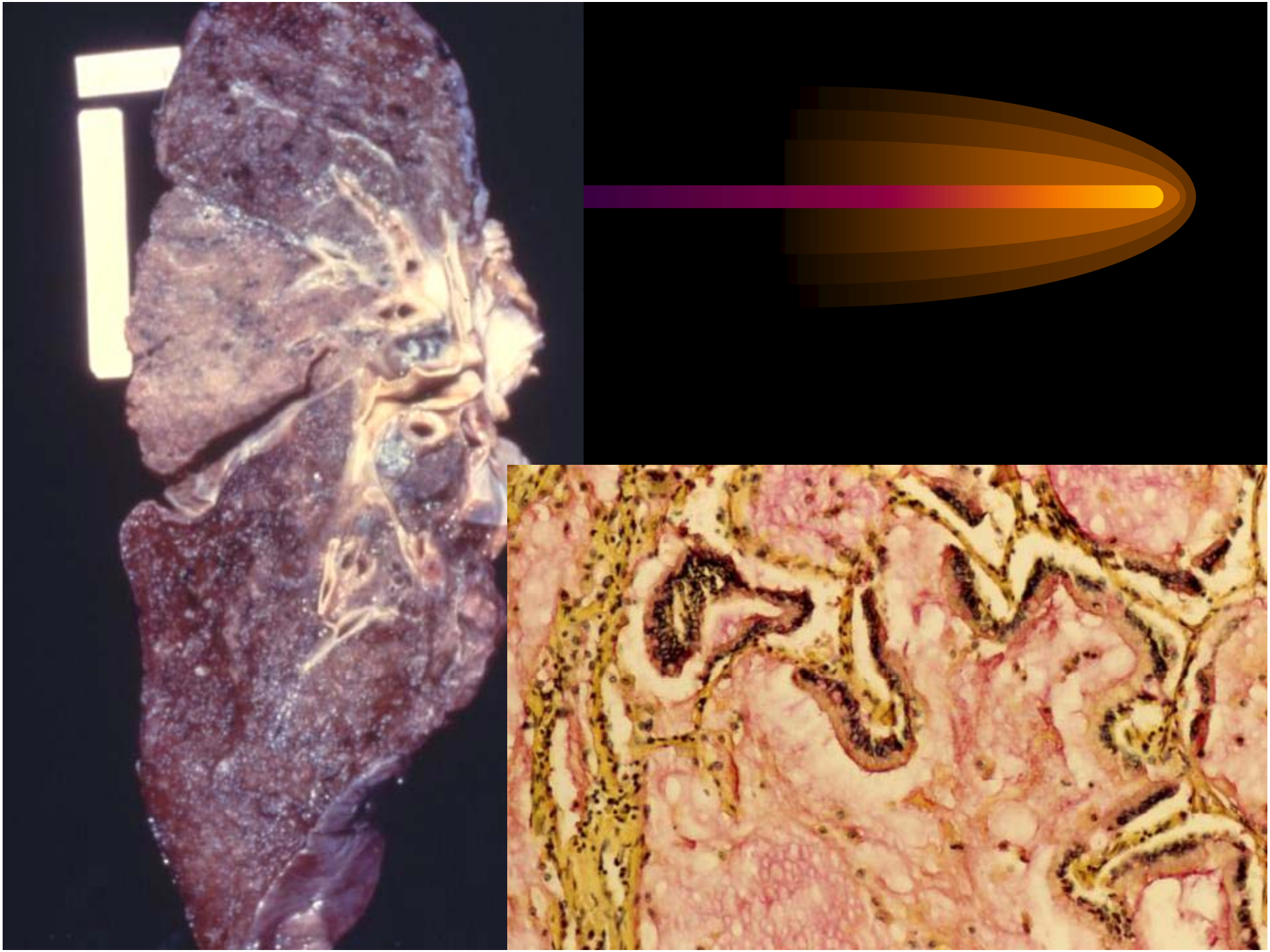


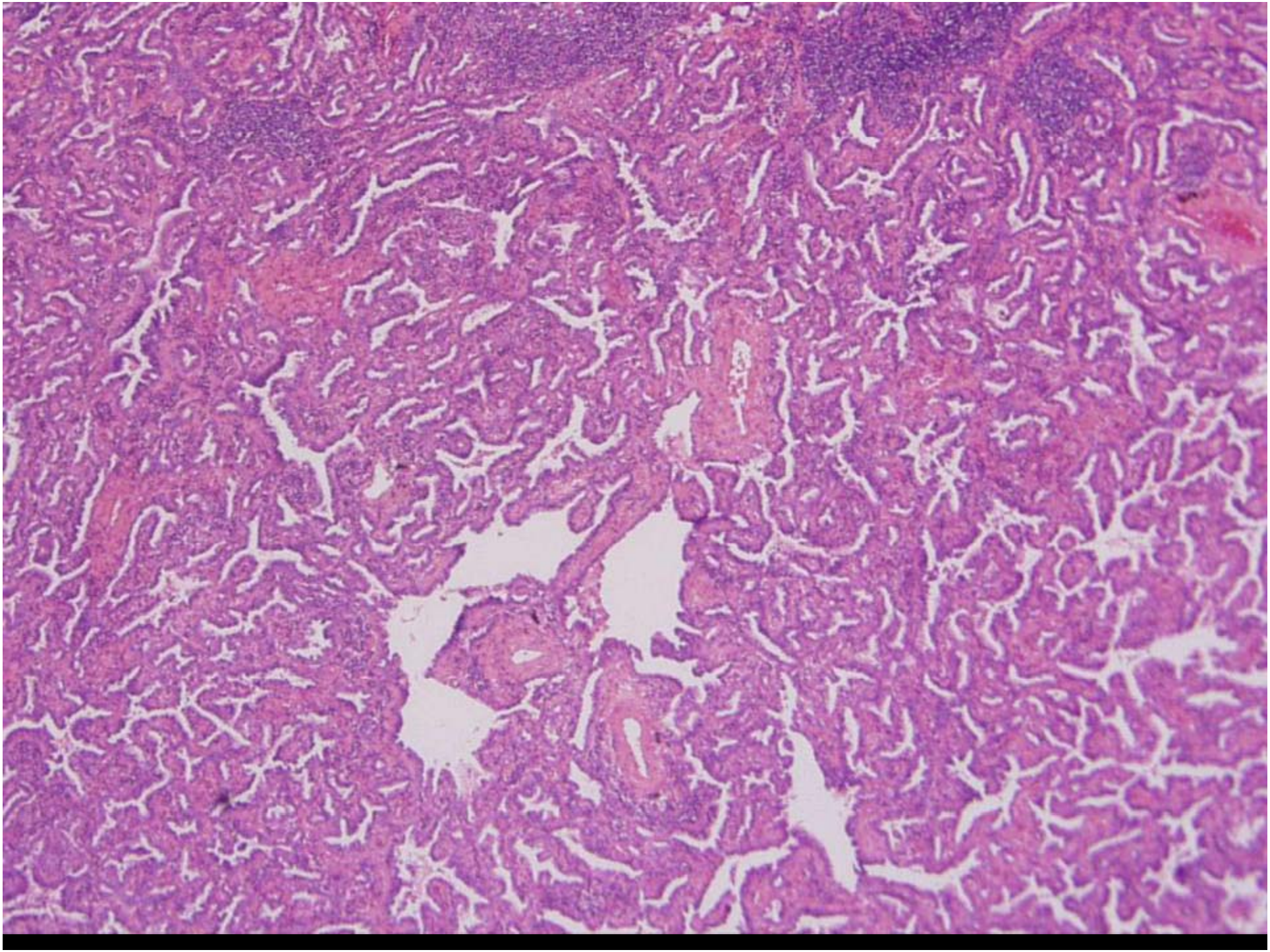


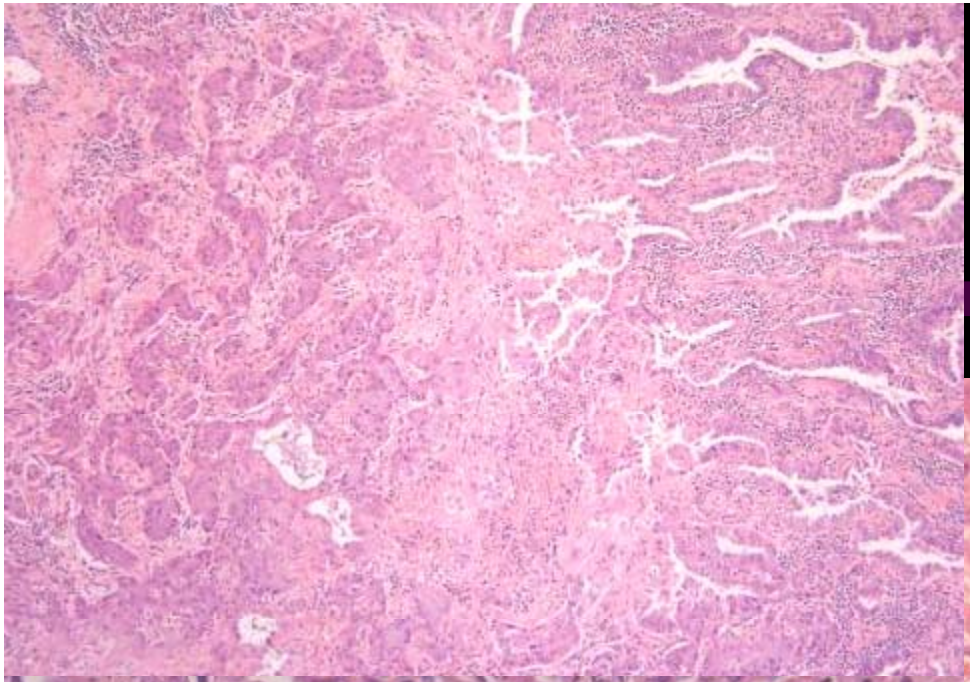


Adenocarcinoma - Bronchioloalveolar

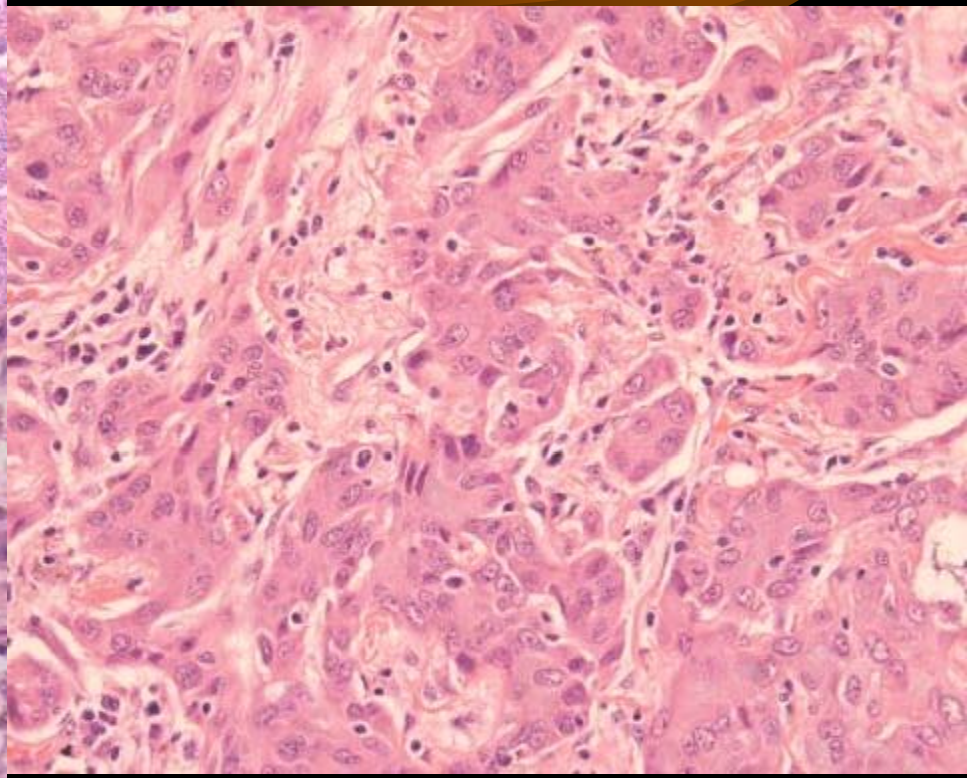
- Distinct morphologic and clinical variant
- Grows along pre-existing alveoli and terminal bronchioles without stromal invasion
- Grossly can form a nodule, but can also produce diffuse disease mimicking pneumonia
- Can be mucinous or non-mucinous.
- Often multifocal

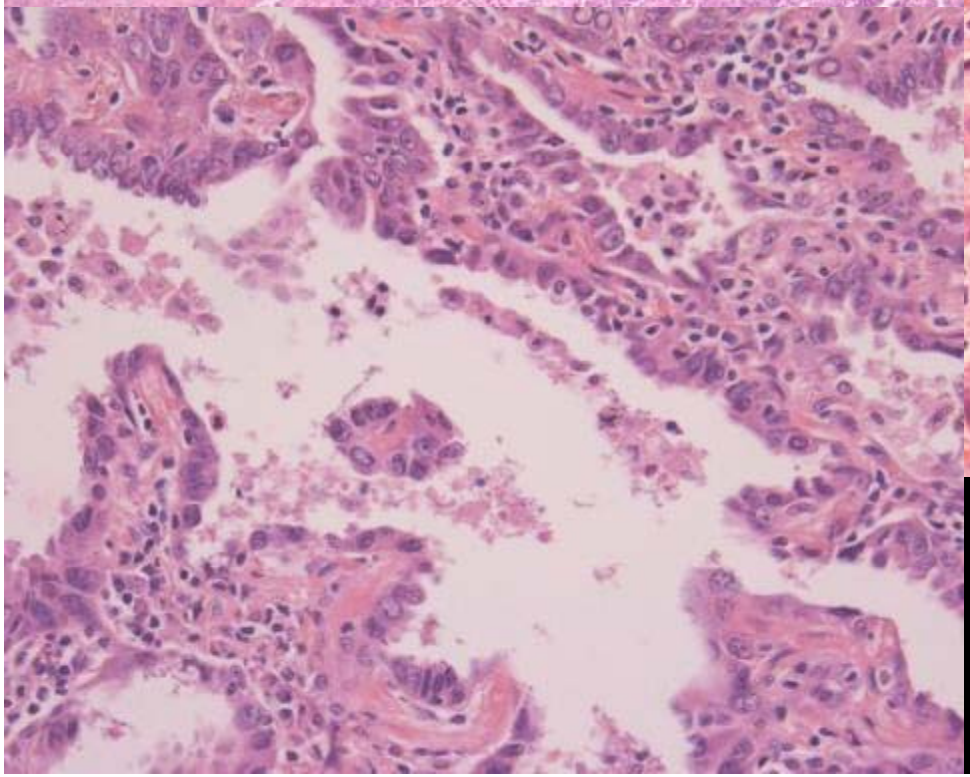






Adenocarcinoma/"BAC features"

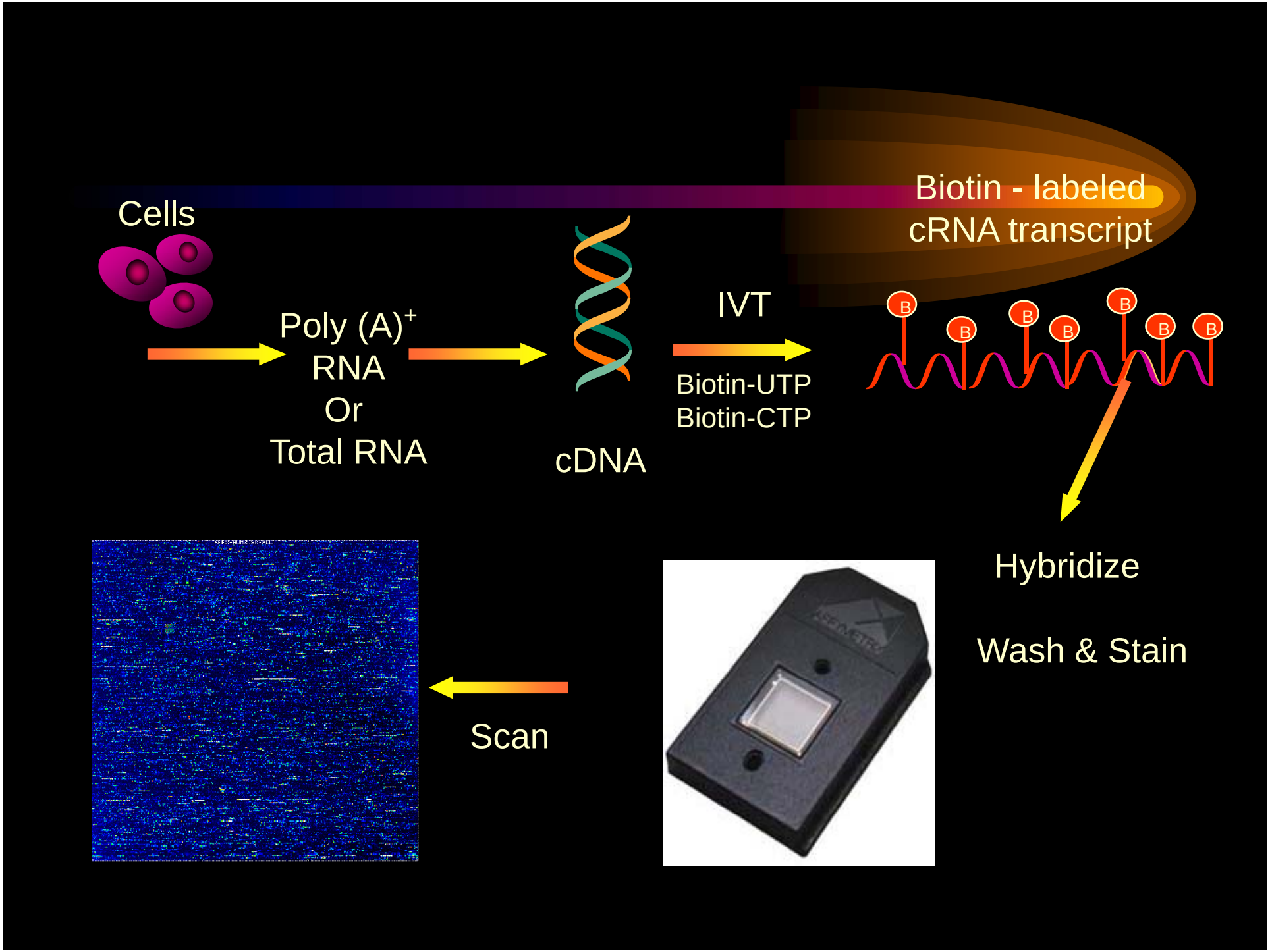


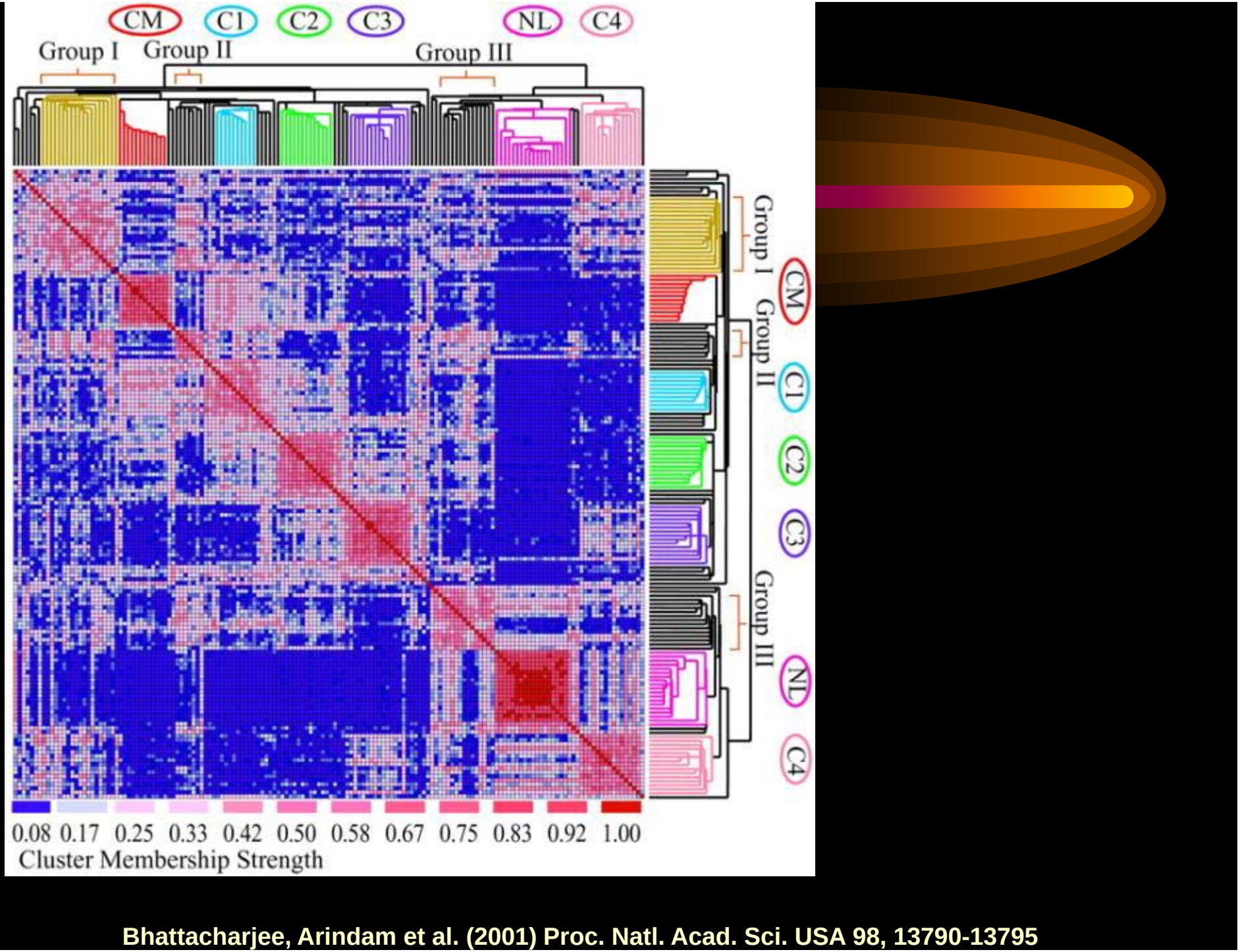


Combined non-invasive and invasive carcinoma

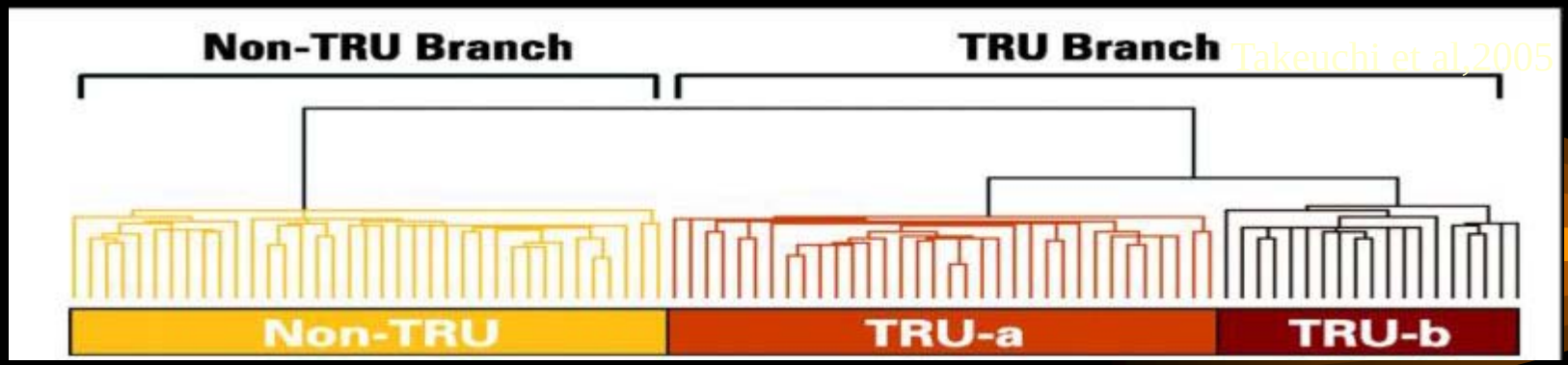
Is there a meaning to the histologic diversity of adenocarcinoma?

- 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.


Cells
Poly (A)+
RNA
Or
Total RNA
cDNA
IVT
Biotin-UTP
Biotin-CTP
Biotin - labeled
cRNA transcript
B
Hybridize
Wash & Stain
Scan



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



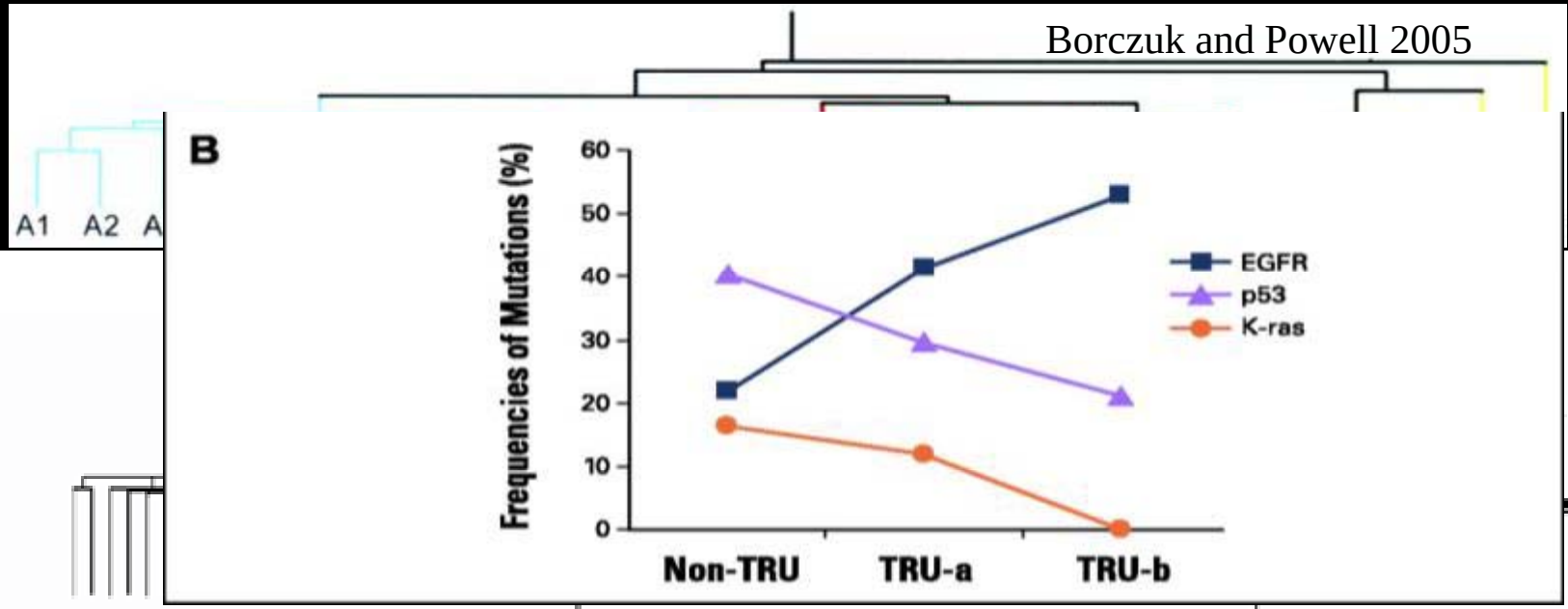
Takeuchi et al,2005

Poor differentiation/ No BAC pattern

Mixed invasive and BAC features

BAC

Borczuk and Powell 2005



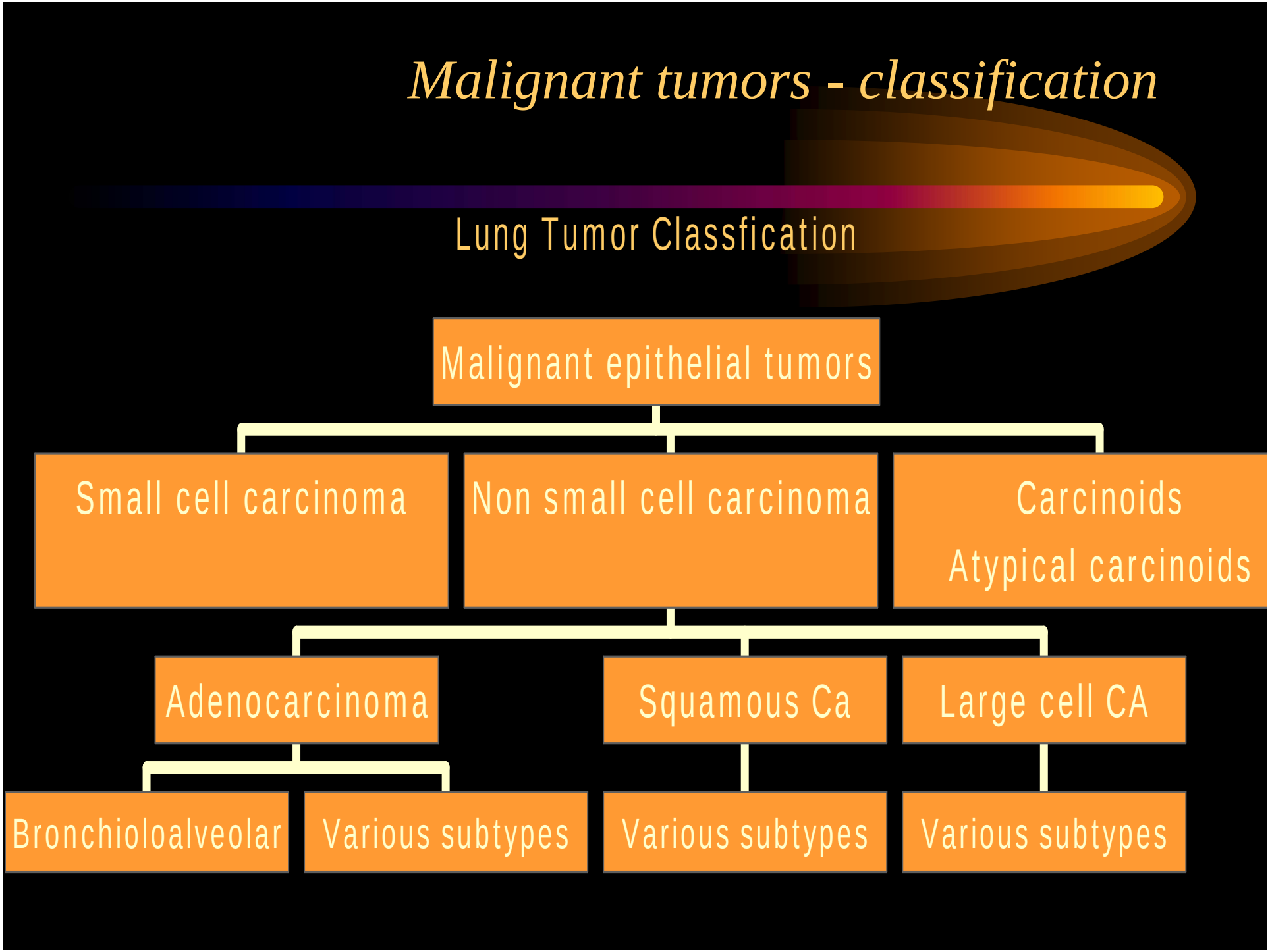
Beer et al,2002

Gene expression profiling in lung adenocarcinoma

Are these observations relevant?

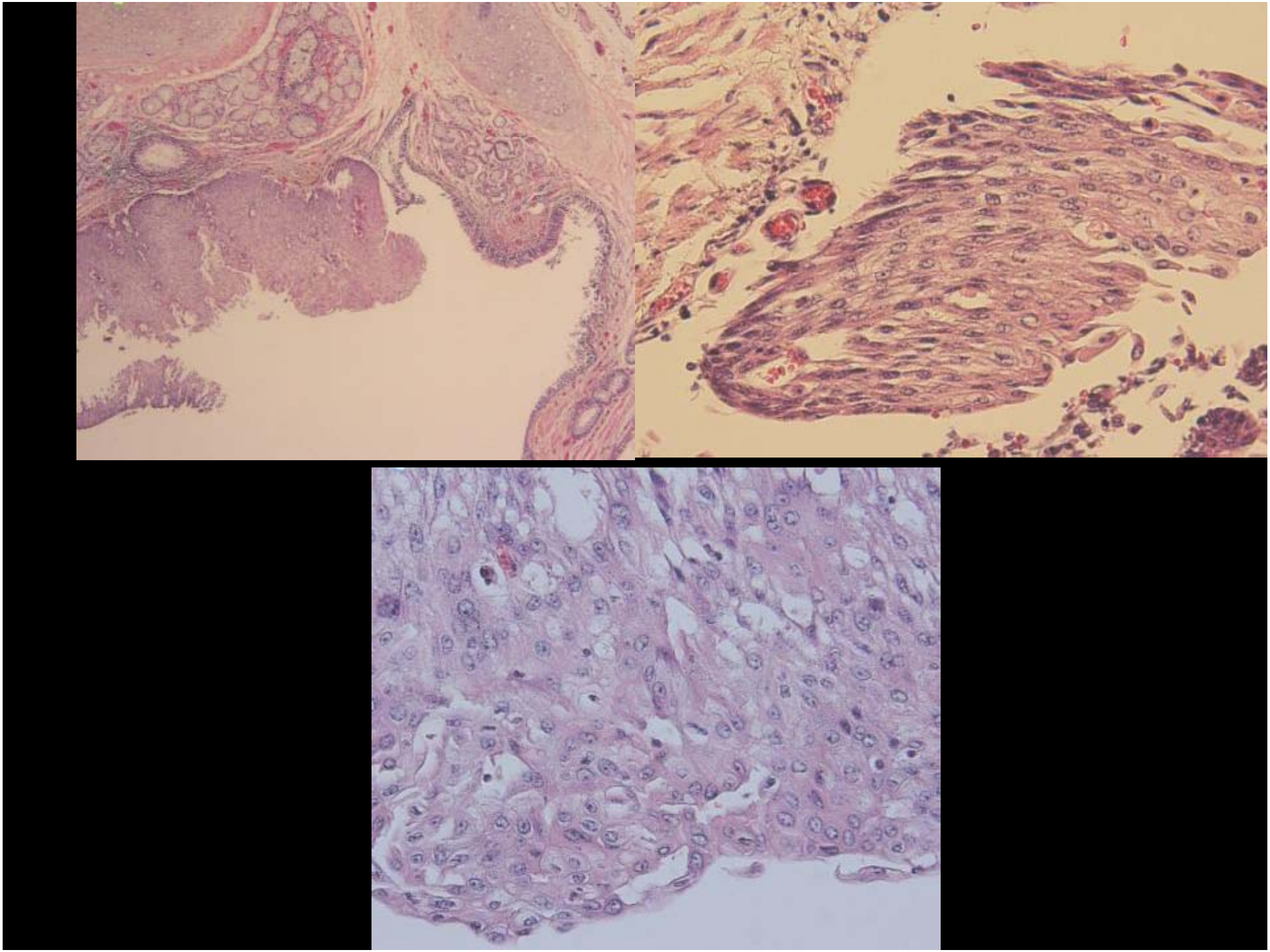
- EGFR mutation and amplification correlates with response to EGFR targeted agents (tyrosine kinase inhibitors gefitinib and erlotinib).
  - This subgroup of patients are also more likely to be women, non-smokers, and of Asian descent but not exclusively so.
- Activating K-ras mutations indicate resistance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



Squamous precursors

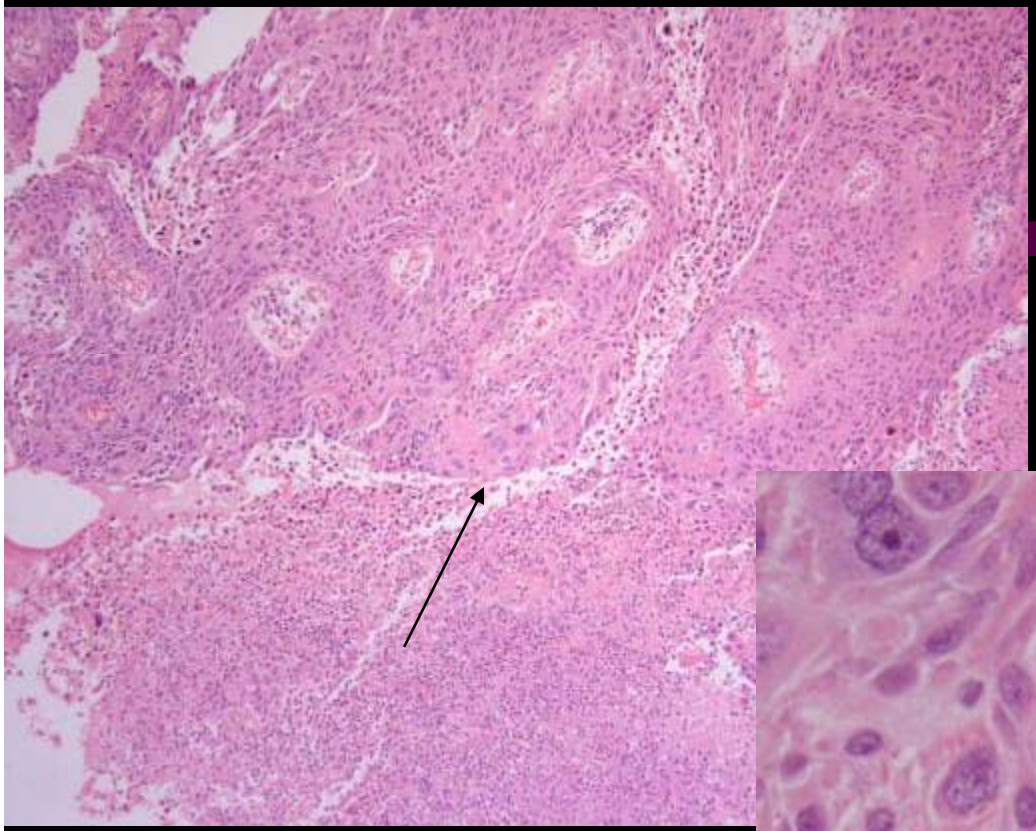
- Squamous metaplasia, dysplasia and carcinoma in situ in lung progresses in a sequence similar to the changes described in the head and neck and cervix.
- Koilocytosis is not common; this HPV viral cytopathic change is seen in papillomatosis of larynx and trachea (HPV 6/11)

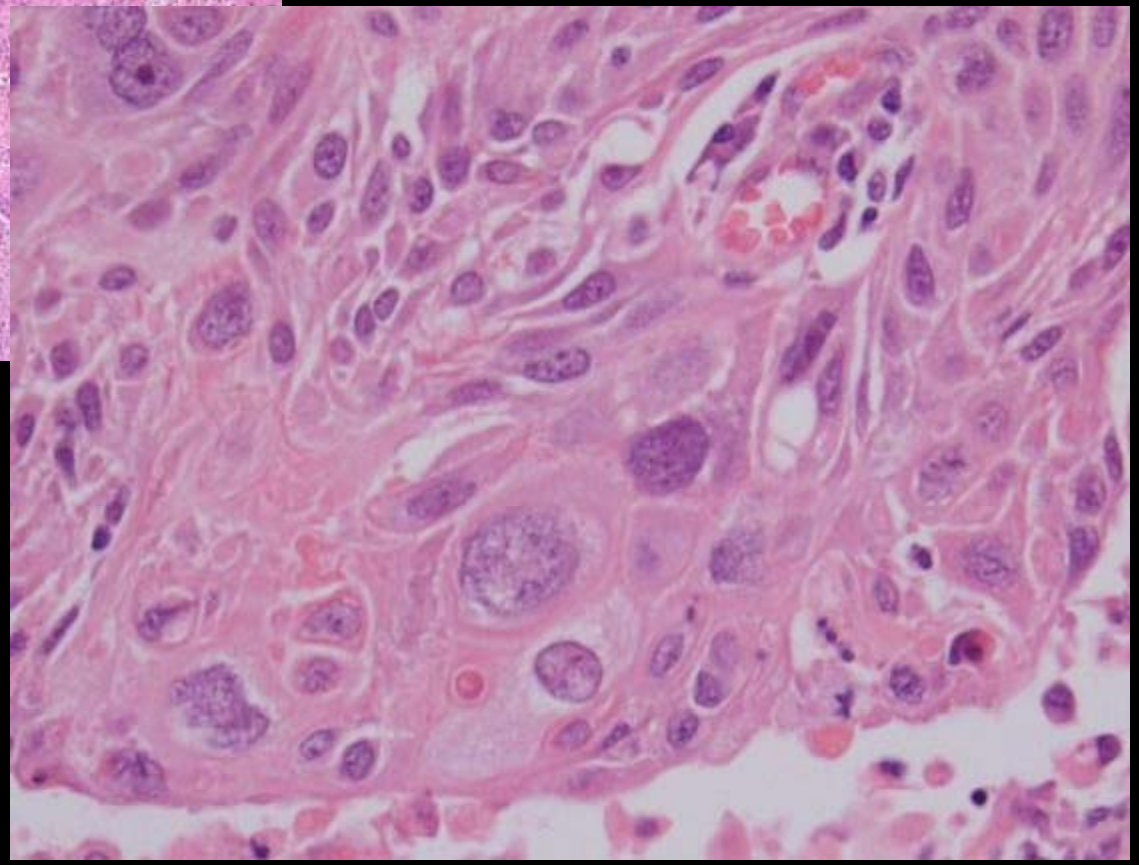


Squamous carcinoma

- 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

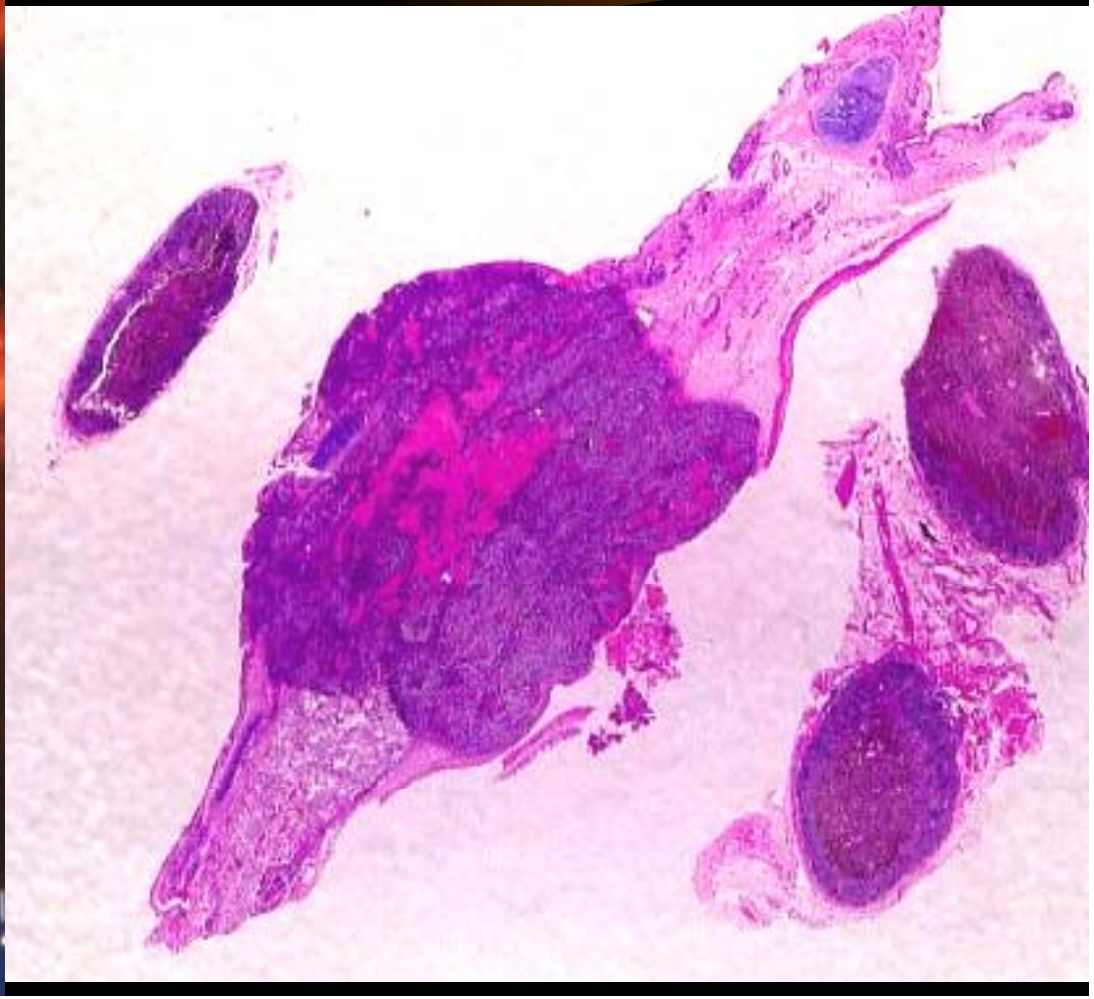




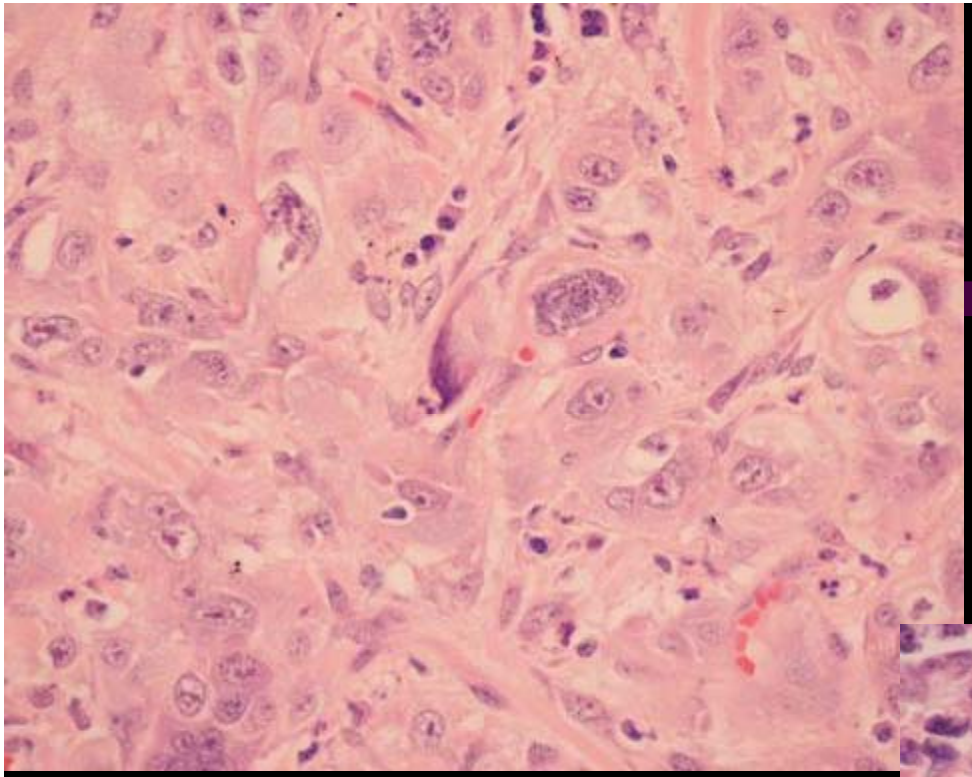
Large cell carcinoma

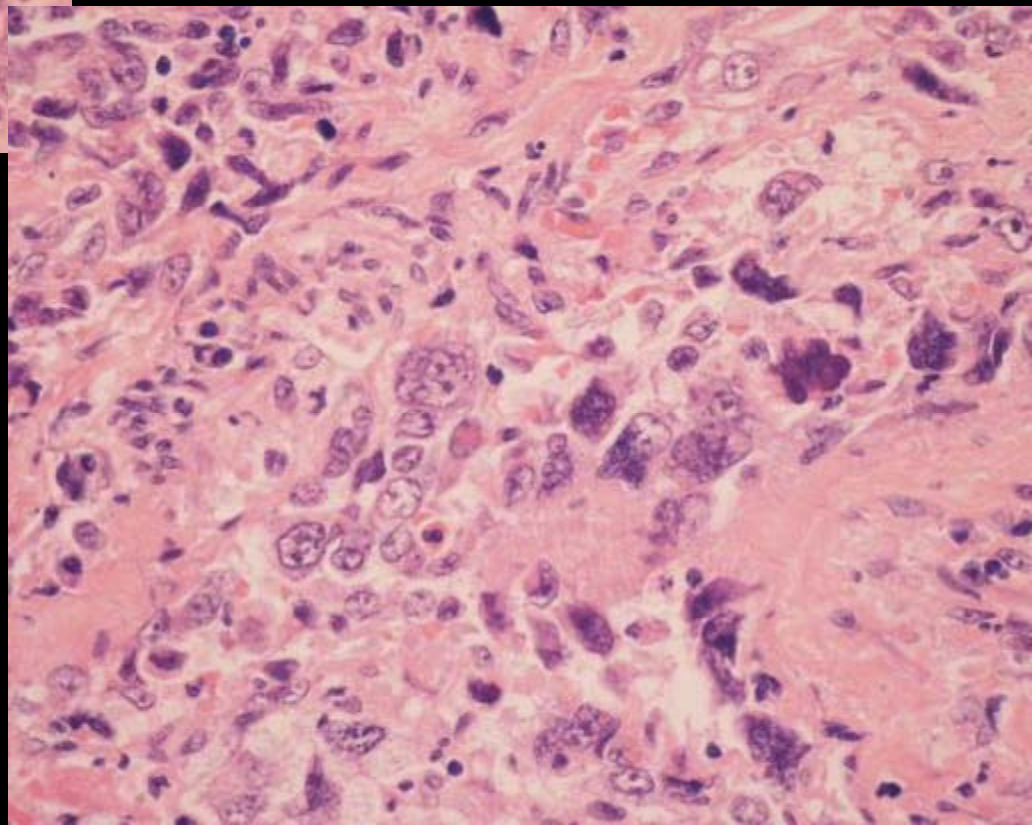
- This subtype shows no differentiation towards either squamous or adenocarcinoma
- Aggressive tumors with poor prognosis
- If subjected to ultrastructural examination, many of these tumors show either glandular or squamous differentiation.
- Nevertheless, these tumors are separated out because of their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

Large cell carcinoma



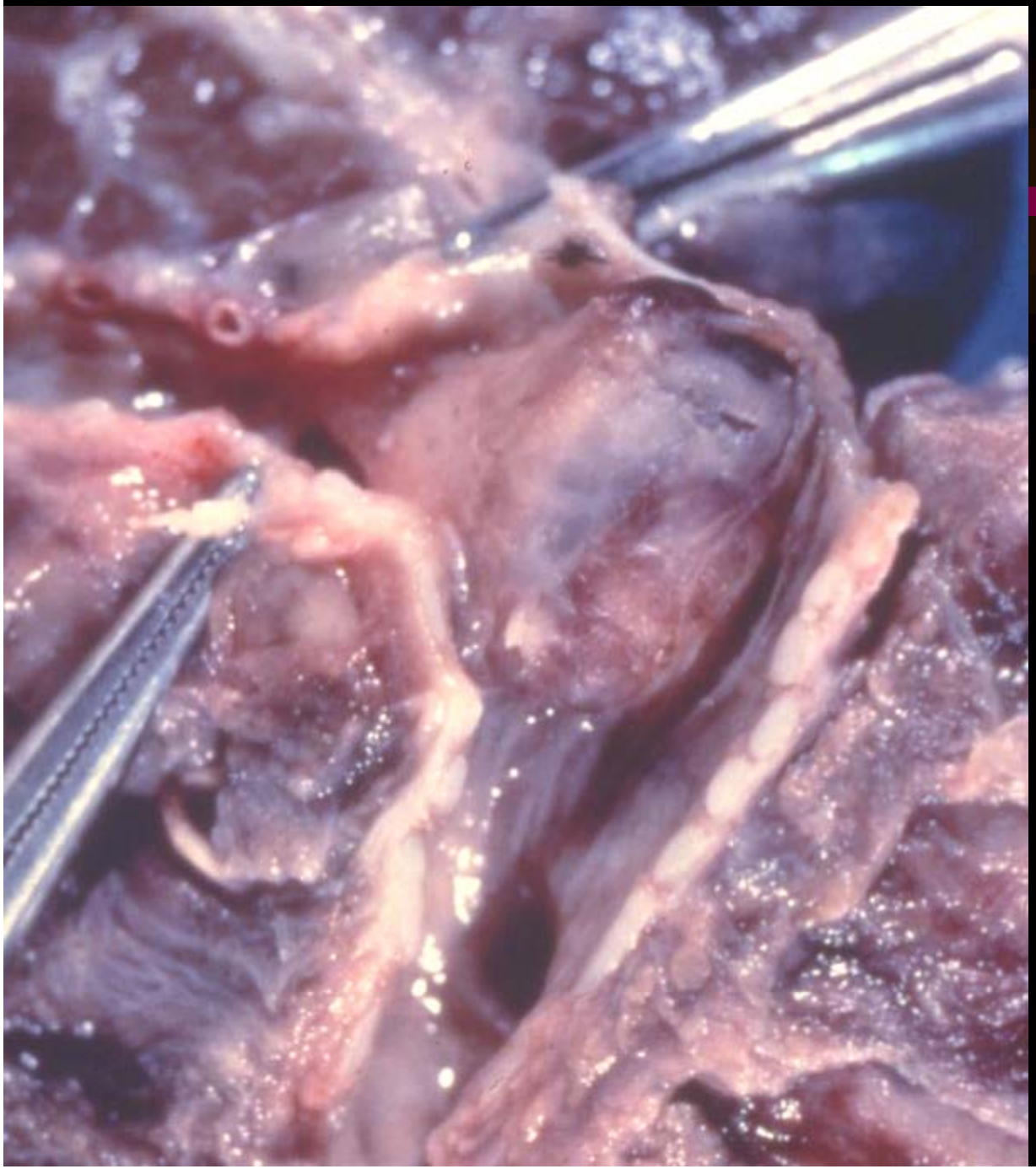
Large cell/ Giant cell carcinoma





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

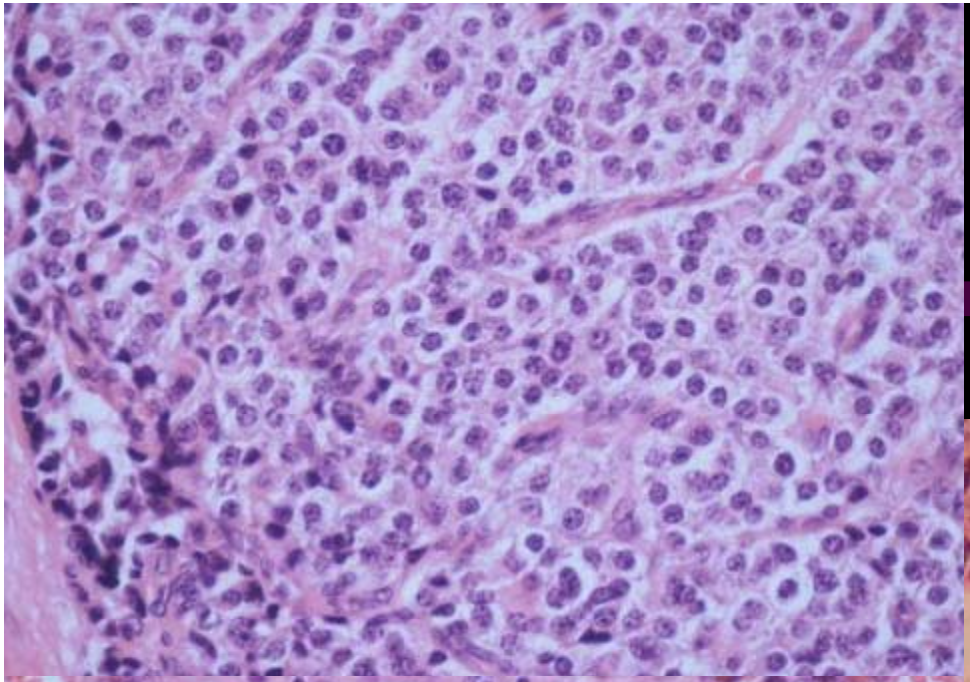


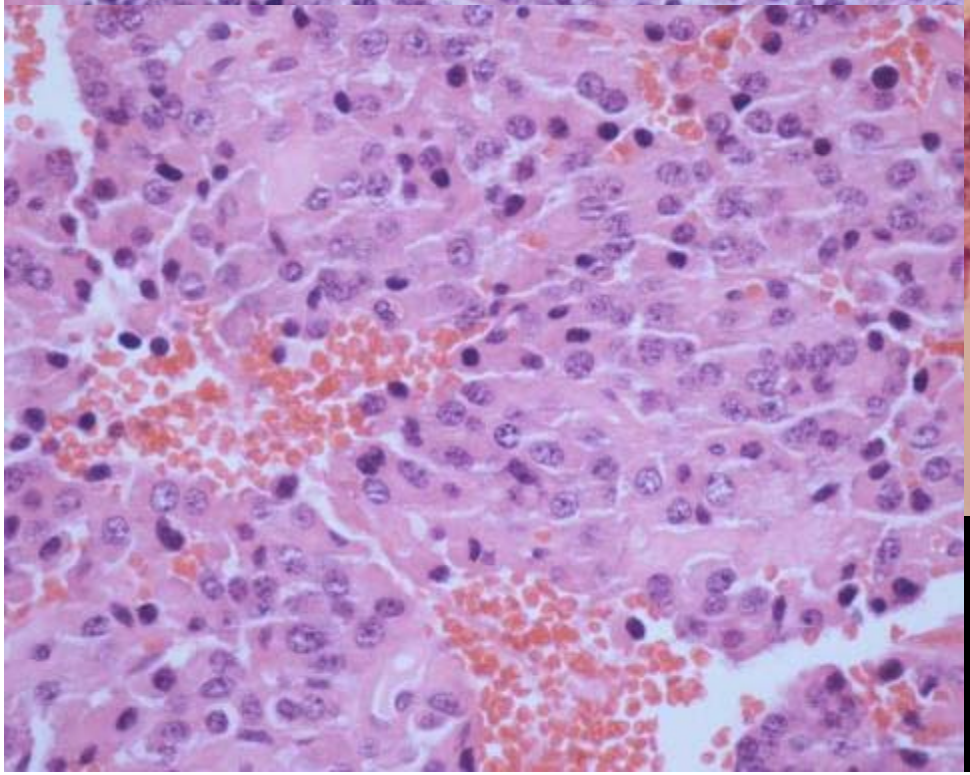
Endobronchial carcinoid

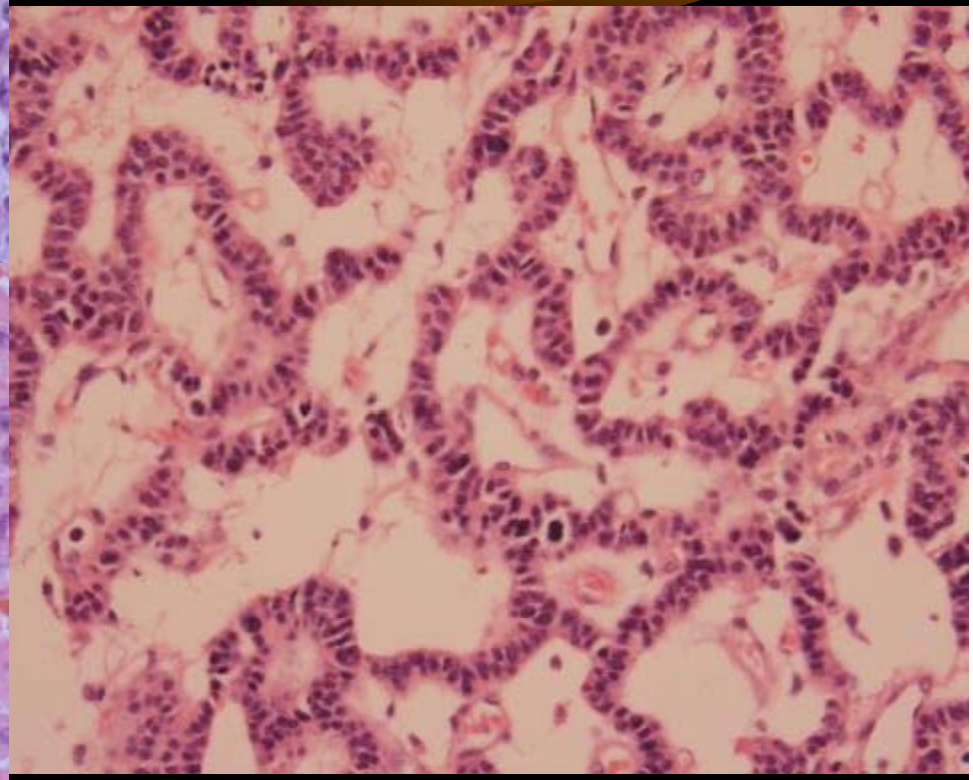
Carcinoids

- 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)

CARCINOID



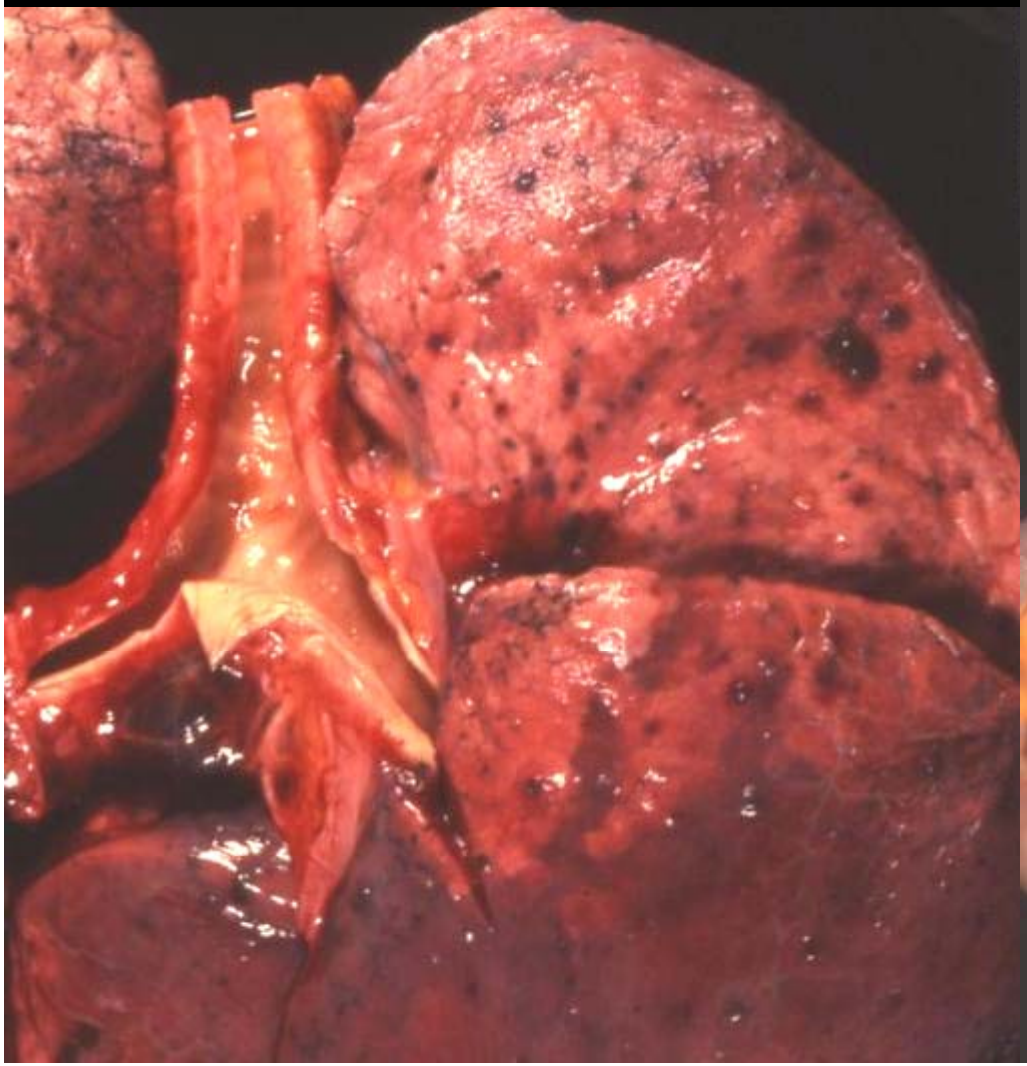


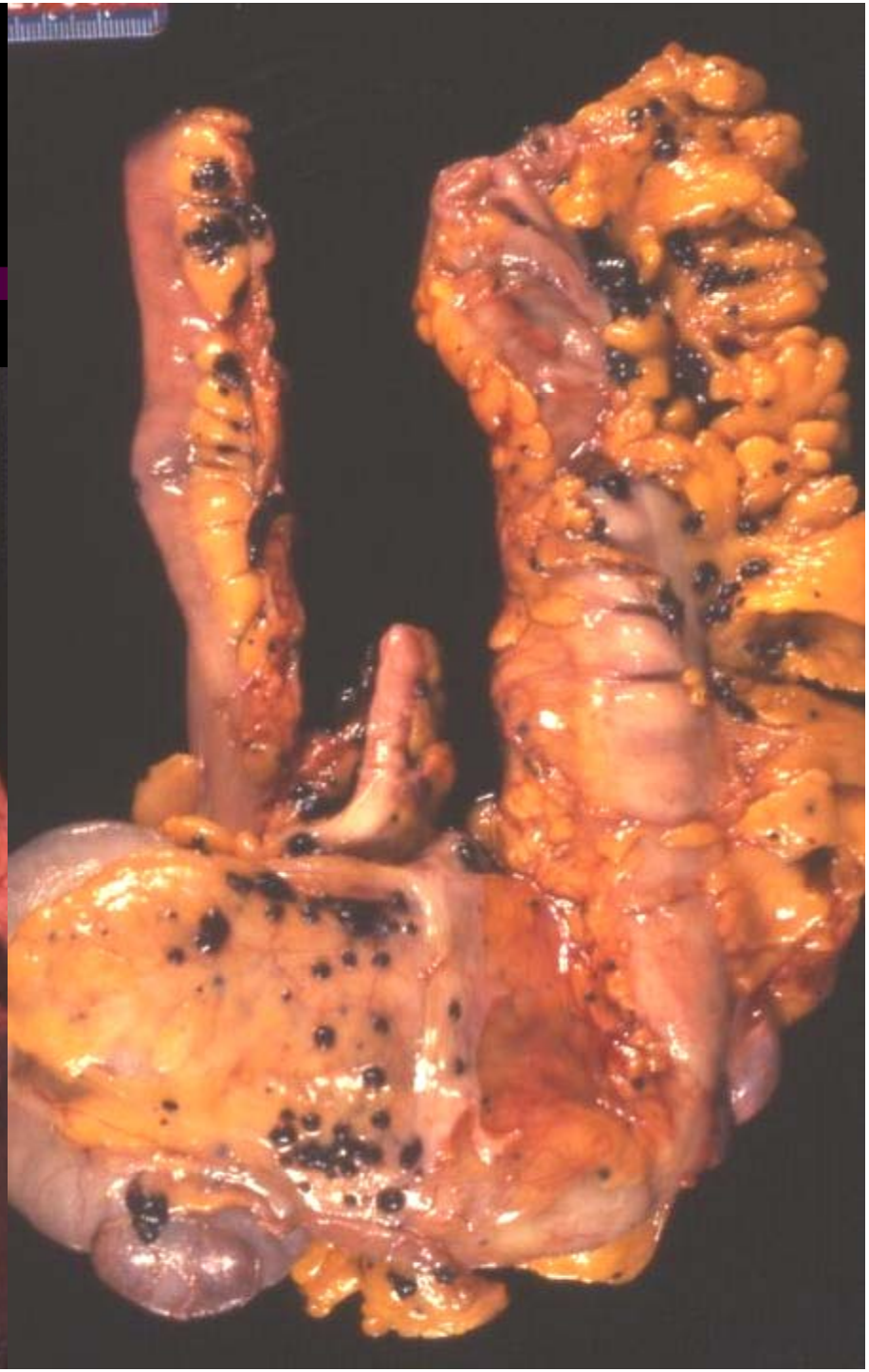


Metastatic Carcinoma

- 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

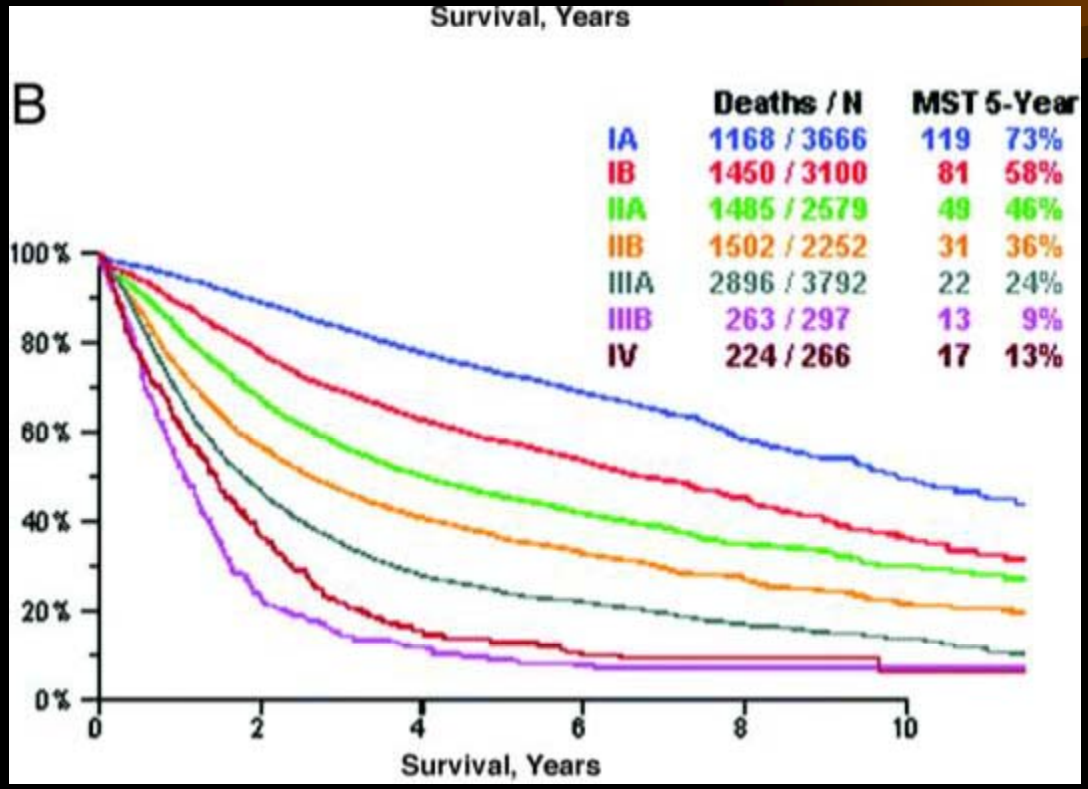
Therapy- small cell

- Limited
  - Chemotherapy + Radiation
- Extensive
  - Chemotherapy

International Staging System, Revised 2009

T/M 6th ed.	T/M 7th ed.	N0	N1	N2	M3
T1 (≤ 2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (> 2-3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (> 2-3 cm)	T2a	IB	IIA	IIIA	IIIB
T2 (≤ 5 cm)	T2b	IB	**IIA**	IIIA	IIIB
T2 (5-7 cm)	T2b	**IIA**	IIB	IIIA	IIIB
T2 (> 7cm)	T3	**IIB**	**IIIA**	IIIA	IIIB
T3 invasion	T3	IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)	T3	**IIB**	**IIIA**	**IIIA**	IIIB
T4 (extension)	T4	**IIIA**	**IIIA**	IIIB	IIIB
M1 (ipsilateral lung nodules)	T4	**IIIA**	**IIIA**	**IIIB**	**IIIB**
T4 (pleural effusion)	M1a	**IV**	**IV**	**IV**	**IV**
M1 (contralateral lung)	M1a	IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

SURVIVAL BY PATHOLOGICAL STAGE

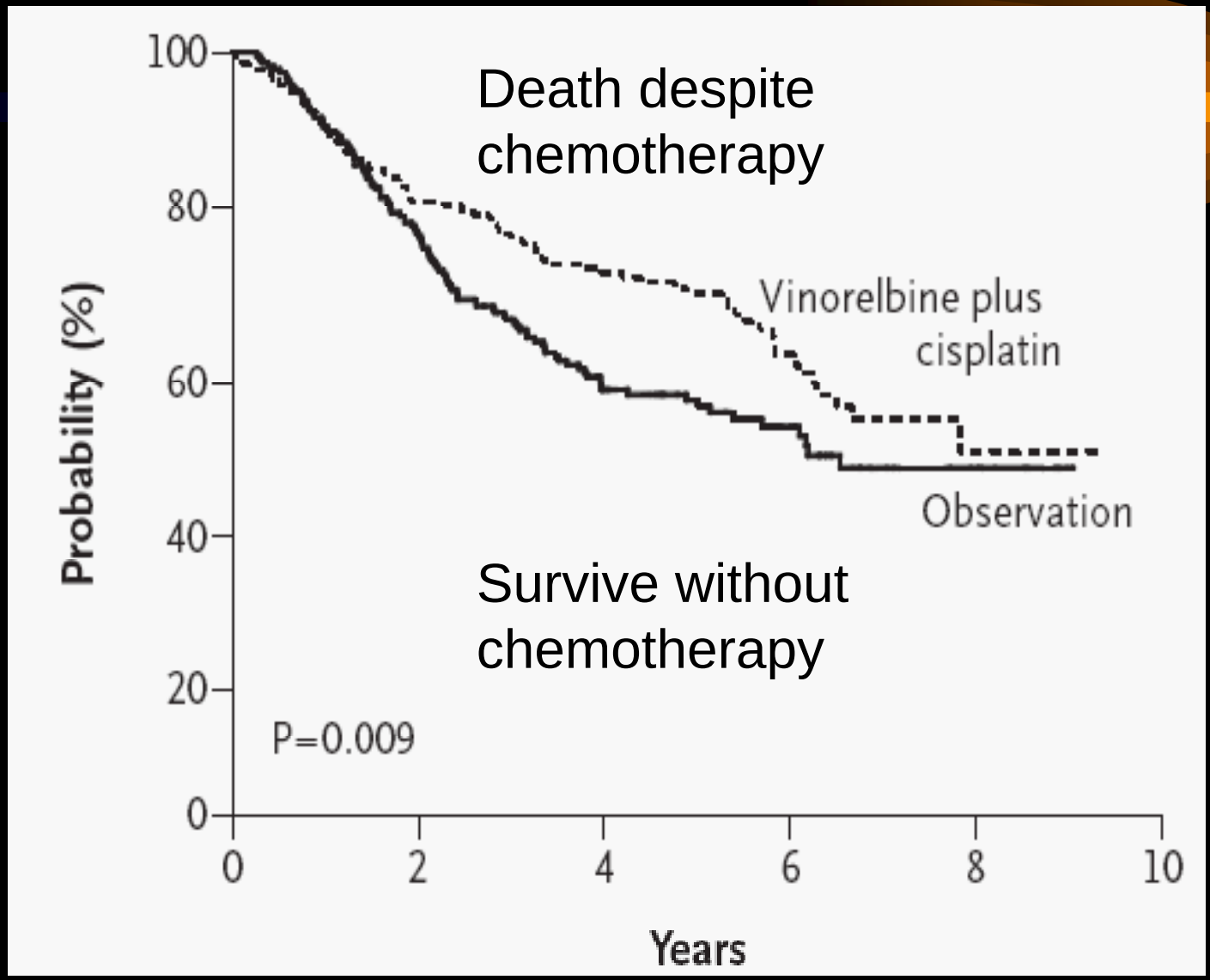


Detterbeck F C et al. Chest 2009;136:260-271

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

PERSONALIZED THERAPY

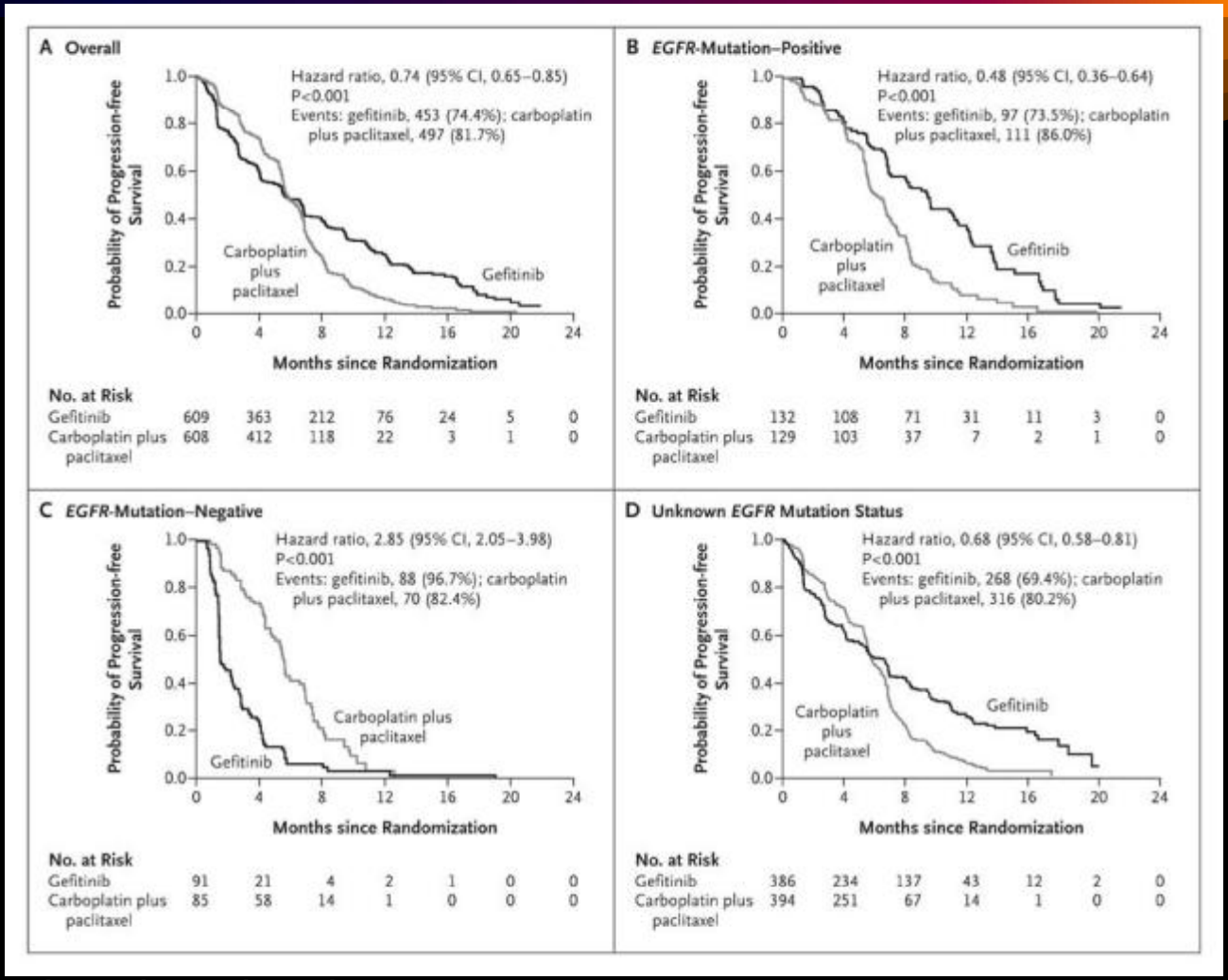
- Morphology

  Small cell Non-small cell

  Squamous Adeno (BAC, Invasive) Large cell

- Prediction: Response to therapy- EGFR mutation
- Prognosis: Recurrence propensity- Gene expression

EGFR MUTATION STATUS PREDICTS RESPONSE TO TYROSINE KINASE INHIBITOR THERAPY

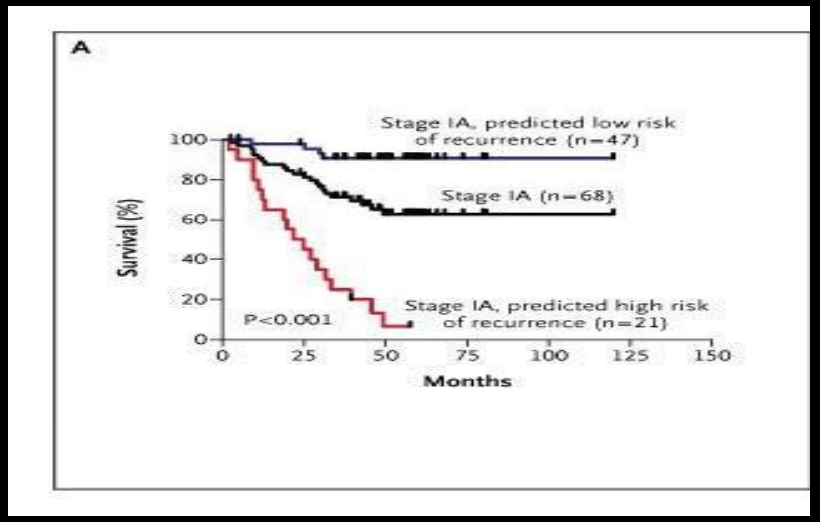


Mok T et al. N Engl J Med 2009

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 Koontz, M.D., Robert Kratzke, M.D., Mark A. Watson, M.D., Ph.D., Michael Kelley, M.D., Geoffrey S. Ginsburg, M.D., Ph.D., Mike West, Ph.D., David H. Harpole, Jr., M.D., and Joseph R. Nevins, Ph.D.



Potti A et al. N Engl J Med 2006;355:570-580