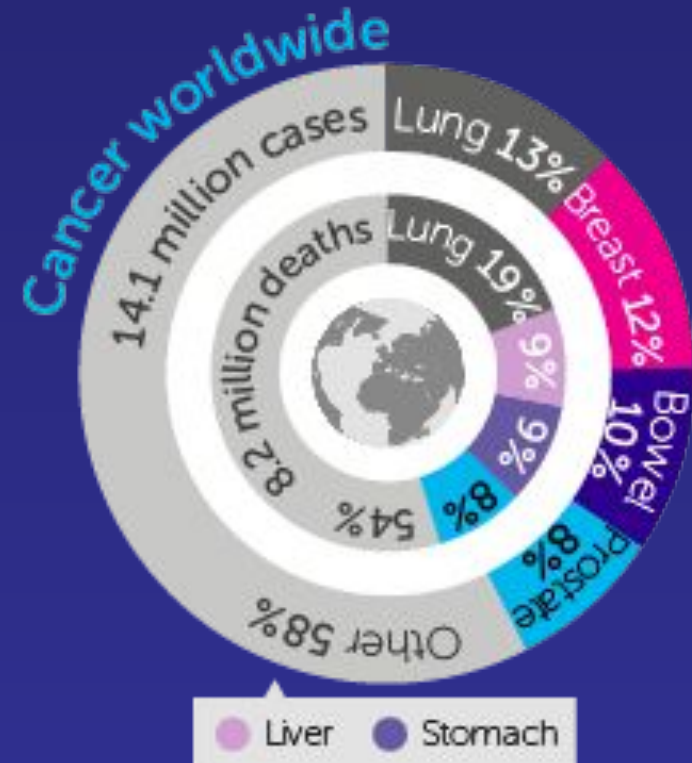


Lung Cancer

Epidemiology

- .
- Almost 9 in 10 lung cancer cases occur in people aged 60 and over.
- In 1975, for every 10 lung cancer cases diagnosed in women in the UK, there were around 39 in men. Now for every 4-10 cases in women there are around 12 in men.
- Lung cancer incidence rates in men peaked in the late 1970s and since then have decreased by around 48%. This reflects the decline in smoking rates in men since around the end of the 1940s.
- From the mid-1970s to late 1980s, lung cancer rates in women increased by around 45%, since then they have increased by around 19%. This reflects the increase in smoking rates in women between World War II and the 1970s.



Epidemiology

- Lung cancer is the most common cause of cancer death worldwide.
- The World Health Organization International Agency for Research on Cancer reported the global incidence of lung cancer at approximately 1.8 million new cases in 2012.
- The overall ratio of mortality to incidence is high, with the 5-year survival rate in the United States still only 17%.

Epidemiology

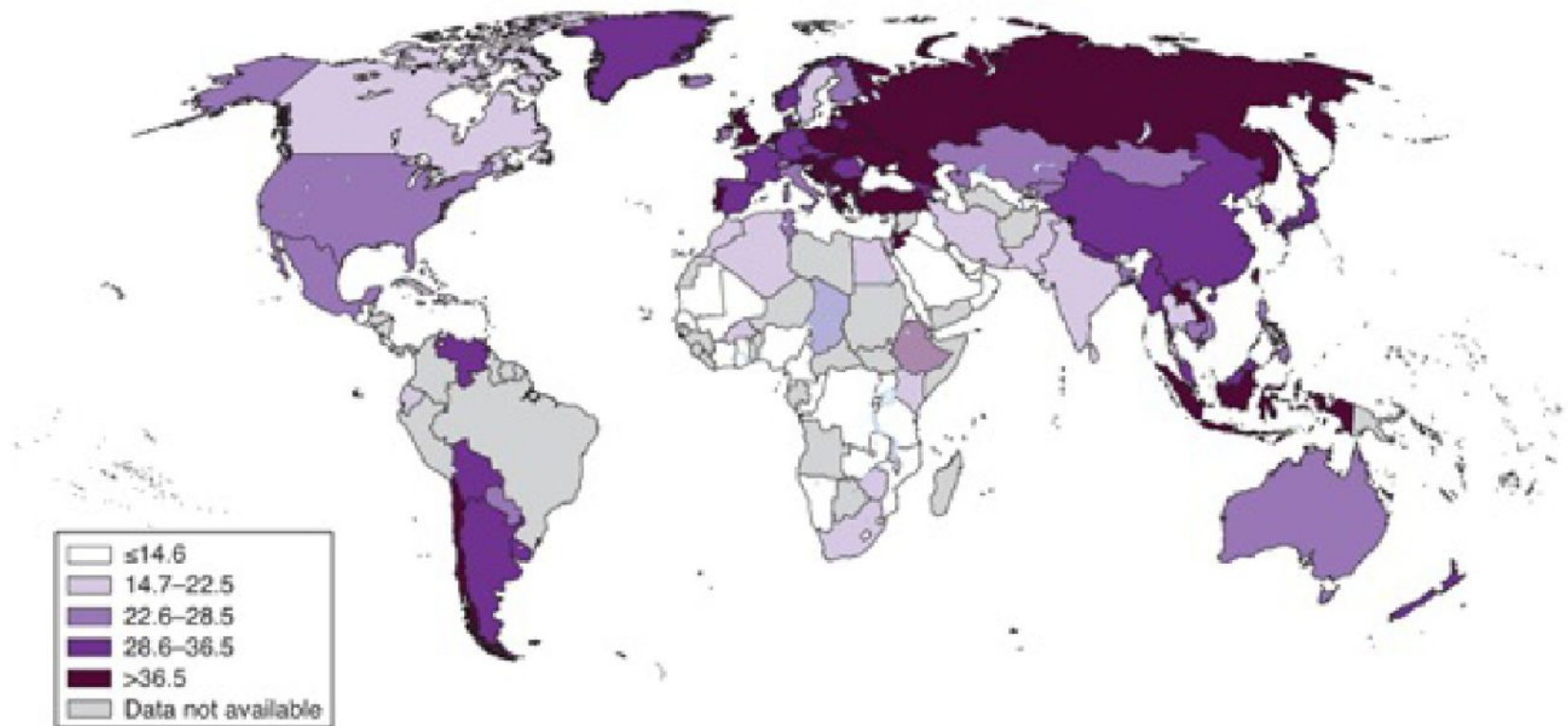
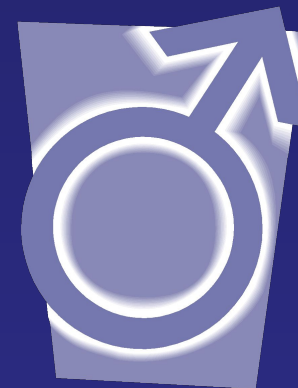
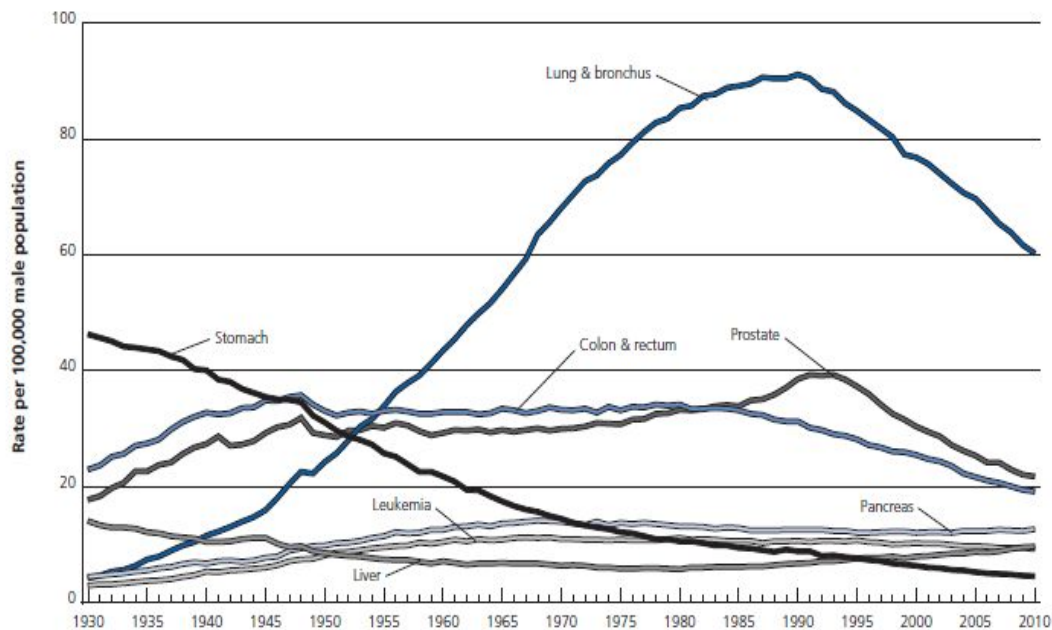
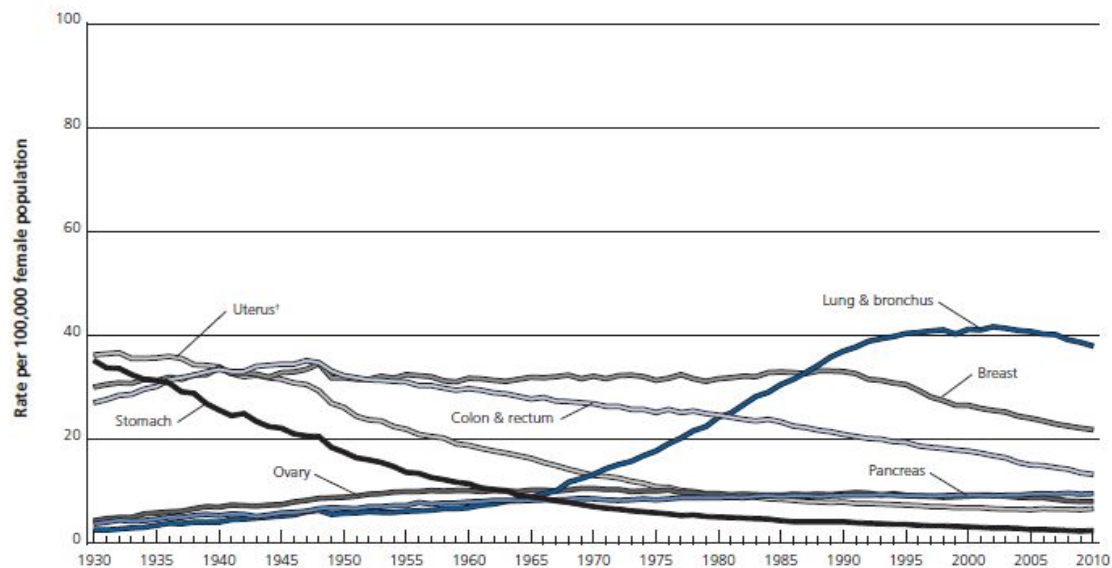


Figure 41.2 Percentage of tobacco use among adults by country in 2005. (Reproduced from GLOBOCAN 2012, International Agency for Research on Cancer, World Health Organization.)

Age-adjusted Cancer Death Rates*, Males by Site, US, 1930-2010



Age-adjusted Cancer Death Rates*, Females by Site, US, 1930-2010



Risk factors

- **SMOKING** More than 50 carcinogens in tobacco smoke have been identified, including N-nitrosoamines formed by nitrosation of nicotine during smoking, and polycyclic aromatic hydrocarbons.^{13–15} The N-nitrosoamine 4-(methylnitrosamino)-1(3-pyridyl)-1-butanone is associated with DNA adduct formation and DNA mutations that result in the activation of KRAS oncogenes.
- The cumulative lifetime risk for lifelong smokers in their eighth decade of life is approximately 16%.
- **OCCUPATION** 10% of lung cancer cases are at least in part related to occupational exposures
- African Americans have consistently been observed to have higher lung cancer rates as well as worse 5-year survival than Caucasian Americans
- COPD per se is an independent risk factor after controlling for smoking
- Furthermore, lung cancer occurring in never-smokers is relatively common, occurring in about 20,000 individuals in the United States

Screening

- CT.
 - At a median follow-up of 6.5 years, there was a 20% relative reduction in lung cancer mortality observed in the LDCT arm
 - Healthy smokers or former smokers (quit <15 years ago, ≥ 30 pack years of smoking) age 55 to 74 years or 80 years be considered for LDCT screening
- **X-ray. No influence on mortality**

Major Histological Types

Small Cell Lung Cancer (SCLC) ~15%

- Oat cell, intermediate and combined subtypes

Non-Small Cell Lung Cancer (NSCLC)

- Adenocarcinoma (includes bronchiolo-alveolar subtype) ~35-40%
- Squamous cell carcinoma ~25-30%
- Large cell carcinoma ~10-15%

Gene alteration / Treatment

Genetic Alteration	Frequency	Test	Targeted Agents ^a
Nonsquamous			
KRAS mutation	25%	Sequence	None
EGFR mutation	15%	Sequence	Gefitinib, erlotinib, afatinib
ALK rearrangement	5%–7%	FISH	Crizotinib, ceritinib
ROS1 rearrangement	1%–2%	FISH	Crizotinib
HER2 (mutation only)	2%–4%	Sequence	Traztuzumab, pertuzumab, lapatinib, afatinib
BRAF mutation	2%–3%	Sequence	Vemurafenib, dabrafenib
RET rearrangement	1%–2%	FISH	Carbozantinib
MET (mutation only)	1%–2%	Sequence	None
MEK1 mutation	<1%	Sequence	None
PIK3CA mutation	1%–2%	Sequence	None
Squamous			
FGFR1 amplification	20%–25%	FISH	None
FGFR1 mutation	5%	Sequence	None
PIK3CA mutation	5%–10%	Sequence	None
DDR2 mutation	3%–5%	Sequence	Dasatinib
PTEN mutation/deletion	15%–20%	Sequence	None

Pathology

Histological characteristics

Adenocarcinoma



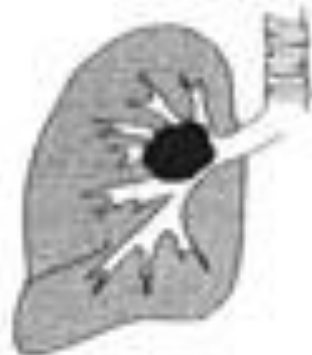
Peripheral coin-like lesion

Large Cell Carcinoma



Variable (peripheral or central)

Squamous Cell



Hilar region

Small Cell

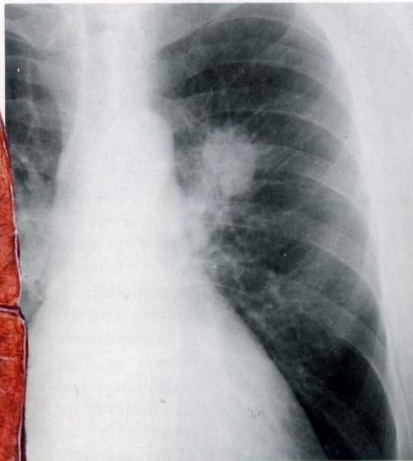


Central region, nodal metastasis

Bronchogenic Carcinoma; Adenocarcinoma

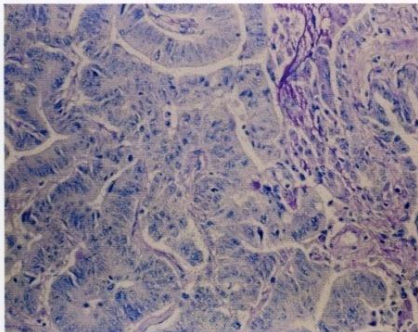
Although it is not possible to distinguish different histologic types of bronchogenic carcinoma from gross specimens or radiographs alone, a peripherally located tumor < 4 cm in diameter is most likely to be adenocarcinoma

Small peripherally placed tumor, l. upper lobe

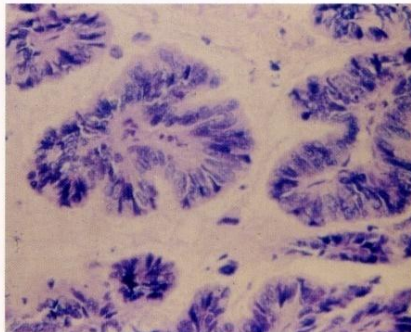


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Varied histology of adenocarcinoma



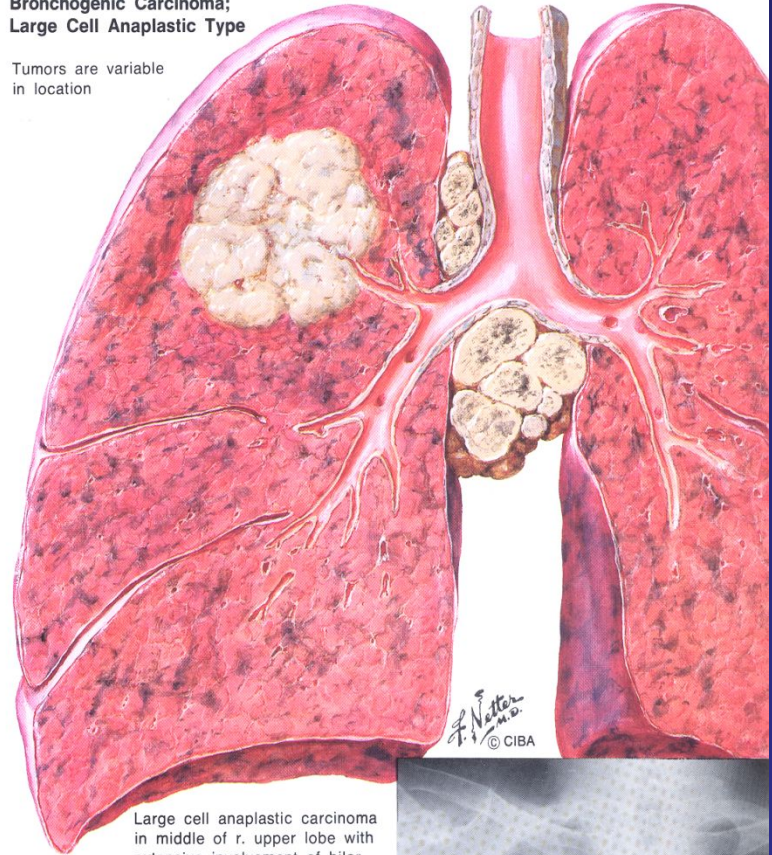
Tumor cells form glandlike structures with or without mucin secretion



Tumor cells may also form papillary structures

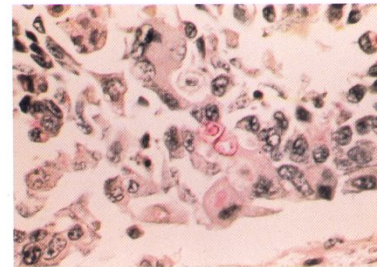
Bronchogenic Carcinoma; Large Cell Anaplastic Type

Tumors are variable in location

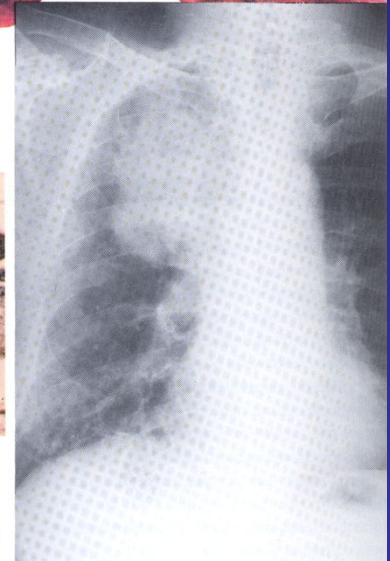


Large cell anaplastic carcinoma in middle of r. upper lobe with extensive involvement of hilar and carinal nodes. Distortion of trachea and widening of carina

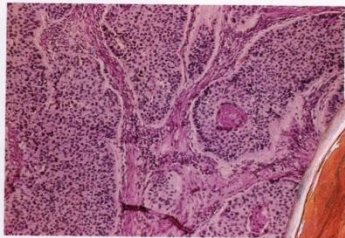
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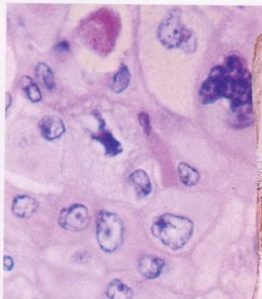
Tumor composed of large multinucleated cells without evidence of differentiation toward gland formation or squamous epithelium. These cells produce mucin (stained red). Some tumors may be composed of large clear cells containing glycogen



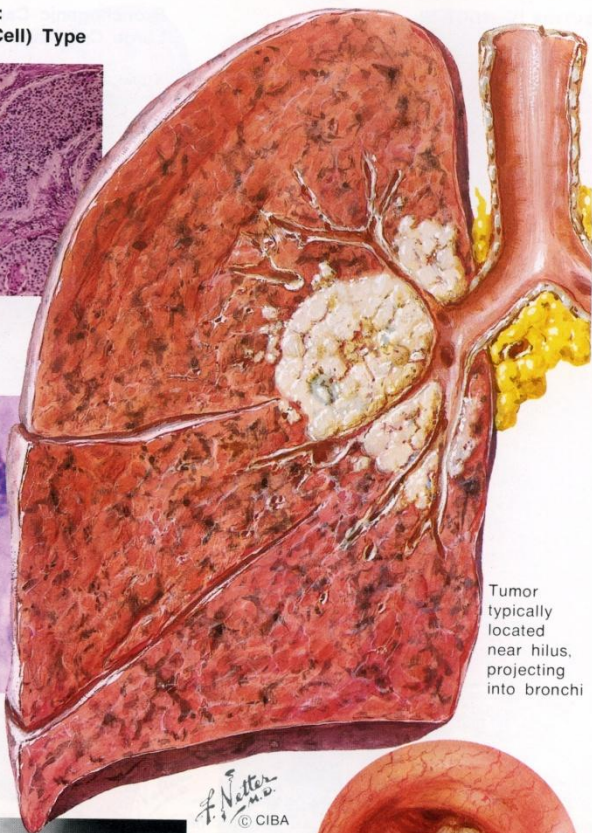
Bronchogenic Carcinoma: Epidermoid (Squamous Cell) Type



Low power (H and E); nests of tumor cells separated by fibrous bands. Keratin (horn) pearls present



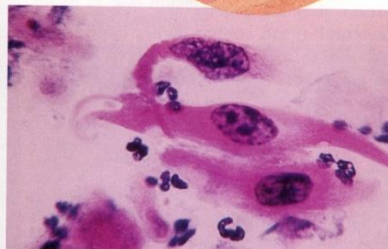
High power; nuclear pleomorphism and individual cell keratinization (pink)



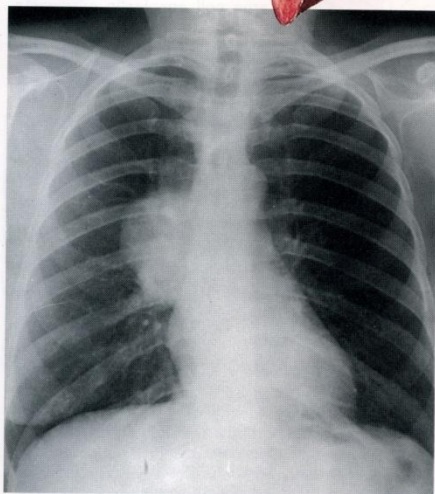
Tumor typically located near hilum, projecting into bronchi



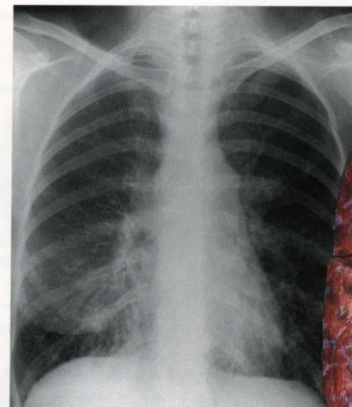
Bronchoscopic view



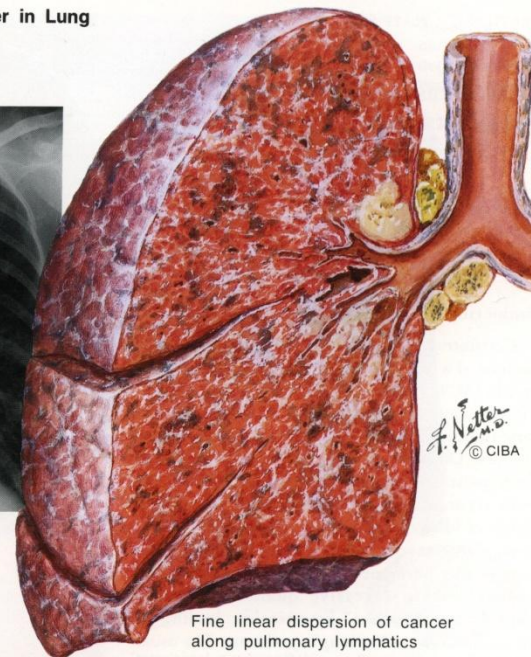
Cytologic smear from sputum or bronchoscopic scraping. Cells with dark nuclei and cytoplasm strongly pink because of keratin



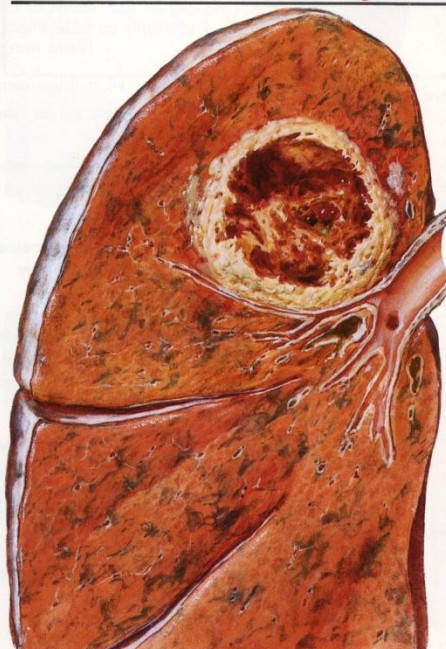
Lymphangitic Spread of Cancer in Lung



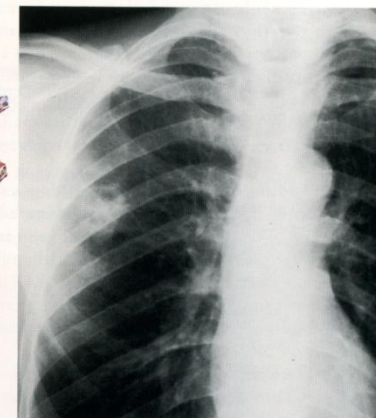
Bilateral lymphangitic cancerous permeation. One or both lungs may be involved, giving a weblike effect. Tumor may be primary or metastatic



Fine linear dispersion of cancer along pulmonary lymphatics



Cavitation of Lung Cancer



Carcinoma in peripheral zone of r. upper lobe with cavitation

Clinical presentation

Primary tumor

- Cough
- Hemoptysis
- Dyspnea
- Atelectasis, recurrent infections
- Solitary pulmonary nodule – incidental and rare

Locoregional spread

- Pleuritic chest pain, pleural effusion
- Hoarseness
- Superior Vena Cava Syndrome (SCVS)
- Pancoast's syndrome
- Dysphagia, tracheoesophageal fistula
- Diaphragm paralysis (phrenic nerve)
- Pericardial effusion

Distant metastases

- Bone pain
- Hypercalcemia
- Abdominal pain
- Elevated Liver Function Tests
- Headache
- Seizures

Clinical presentation

Constitutional signs and symptoms

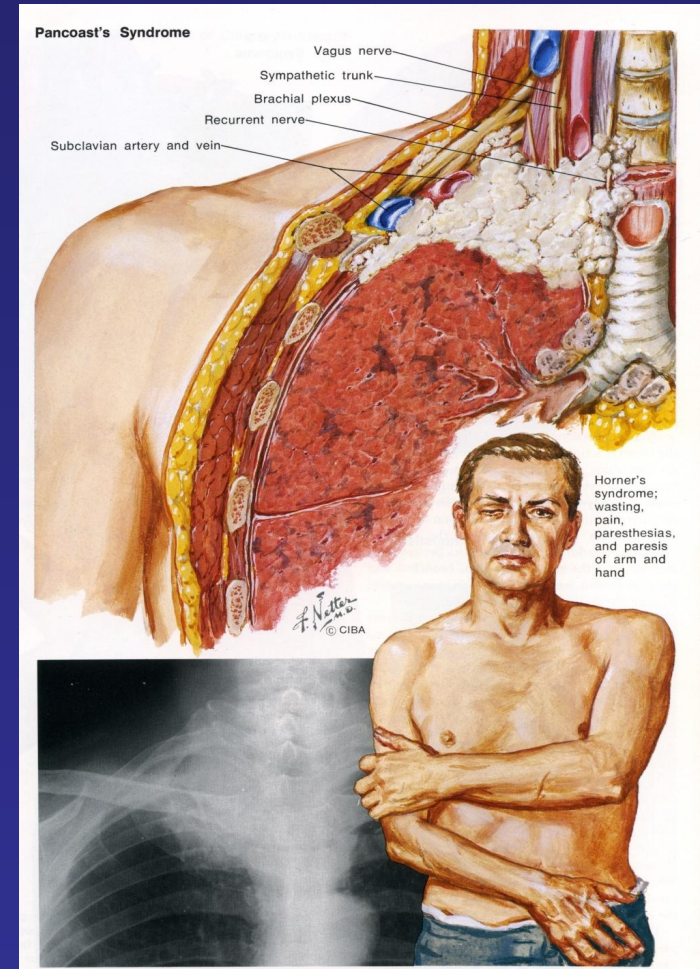
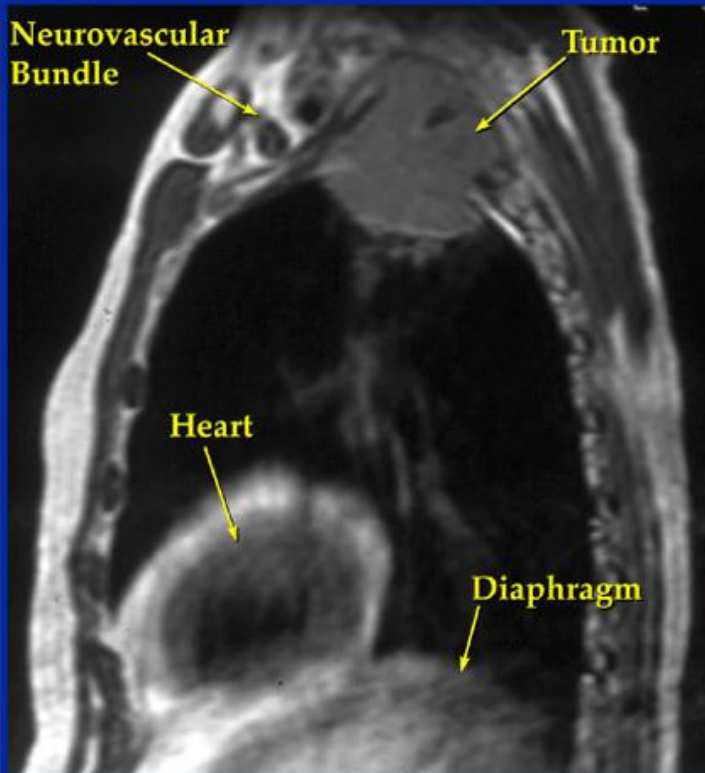
- Anorexia
- Weight loss
- Weakness
- Fever due to tumor



Paraneoplastic syndromes

- Hypertrophic pulmonary osteoarthropathy
- Clubbing
- Hypercoagulability (DVT, PE)
- Hypercalcemia (PTH-like)- Sq. cell ca
- SIADH (HypoNa, ↓ plasma osmolarity, ↑ urine osmolarity)-SCLC
- Ectopic ACTH (Cushing syndrome)-SCLC
- Neurological (Eaton-Lambert, SSN-EMN)-SCLC

Pancoast tumor (superior sulcus)



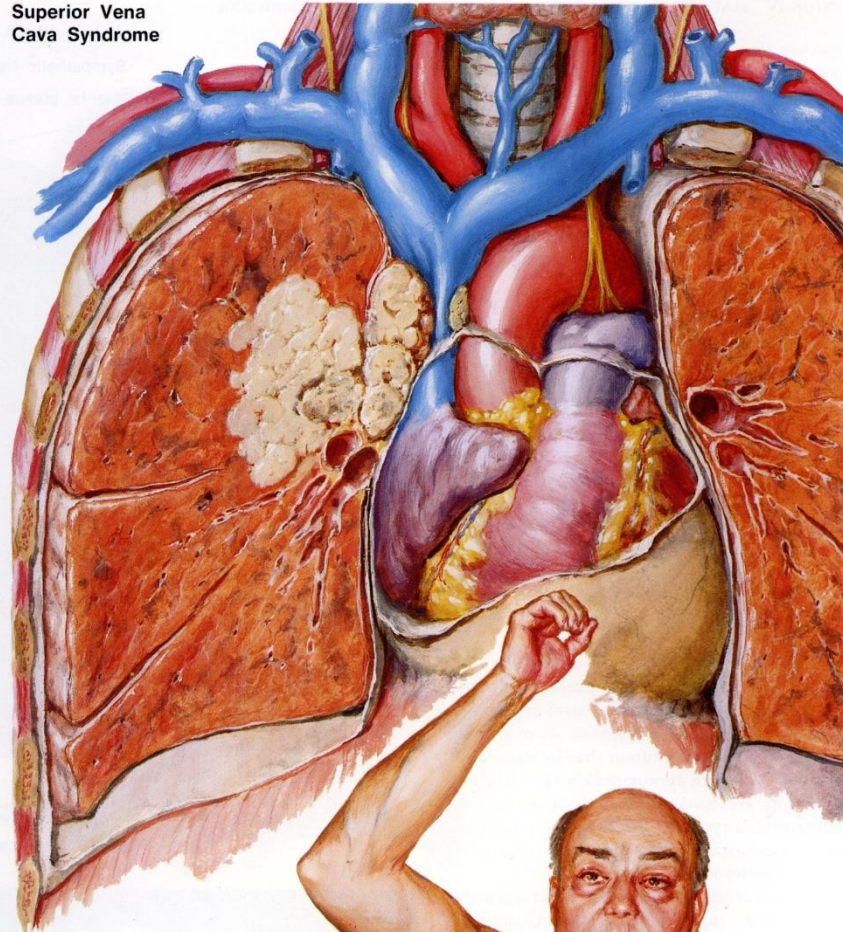
Involvement of:

- upper ribs (I-II)
- brachial plexus(shoulder and arm pain, atrophy of the hand muscles)
- stellate ganglion and paravertebral sympathetic chain

(Horner's syndrome; ptosis, myoclonic

Superior Vena Cava Syndrome(SCVS)

Superior Vena
Cava Syndrome



Obstruction of superior vena cava by cancerous invasion of mediastinal lymph nodes, with distention of brachiocephalic (innominate), jugular, and subclavian veins and tributaries

Edema and rubor of face, neck, and upper chest. Arm veins fail to

SYMPTOMS OF LUNG CANCER

- By Patient Reports (N = 121) -

	NON-SMALL CELL (n = 69)	SMALL CELL (n = 52)
FATIGUE	84%	79%
COUGH	71%	62%
DYSPNEA	59%	56%
ANOREXIA	57%	60%
PAIN	48%	54%
HEMOPTYSIS	25%	14%

Diagnosis

- Medical history
- Physical exam
- Labs
- Imaging studies
 - ✓ CXR
 - ✓ Chest/upper abdomen CT-scan
 - ✓ PET-CT scan
 - ✓ Chest MRI
 - ✓ Brain CT- scan/MRI
- A tissue diagnosis of malignancy
 - Sputum
 - Thoracentesis
 - Bronchoscopy (FOB)
 - ✓ Brushing
 - ✓ Washing
 - CT guided FNA
 - Mediastinoscopy
 - EUS+FNA/EBUS+TNBA
 - Anterior mediastinotomy
 - Thoracoscopy
 - Thoracotomy



TNM

TABLE 41.1

Stage Classification: T, N, M Descriptors

Category	Descriptor Definition	Subgroup ^a
T (Primary Tumor)		
T0	No primary tumor	
T1	Tumor ≤ 3 cm, ^b surrounded by lung or visceral pleura, not more proximal than the lobar bronchus	
T1a	Tumor ≤ 2 cm ^b	T1a
T1b	Tumor > 2 but ≤ 3 cm ^b	T1b
T2	Tumor > 3 but ≤ 7 cm ^b or tumor with any of the following ^c : Invades visceral pleura, involves main bronchus ≥ 2 cm distal to the carina, atelectasis/obstructive pneumonia extending to hilum but not involving the entire lung	
T2a	Tumor > 3 but ≤ 5 cm ^b	T2a
T2b	Tumor > 5 but ≤ 7 cm ^b	T2b
T3	Tumor > 7 cm ^d or directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, or tumor in the main bronchus < 2 cm distal to the carina, ^d or atelectasis/obstructive pneumonitis of entire lung, or separate tumor nodule(s) in the same lobe	T3 _{>7} T3 _{inv} T3 _{Cent} T3 _{Seel}
T4	Tumor of any size with invasion of heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; or separate tumor nodule(s) in a different ipsilateral lobe	T4 _{inv} T4 _{ipsi Nod}

TNM(2)

N (Regional Lymph Nodes)		
N0	No regional node metastasis	
N1	Metastasis in ipsilateral peribronchial and/or perihilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene or supraclavicular lymph node(s)	
M (Distant Metastasis)		
M0	No distant metastasis	
M1a	Separate tumor nodule(s) in a contralateral lobe; or tumor with pleural nodules or malignant pleural dissemination*	<i>M1a_{Con}</i> <i>M1a_{P.D}</i>
M1b	Distant metastasis	<i>M1b</i>
Special Situations		
TX, NX, MX	T, N, or M status not able to be assessed	
Tis	Focus of in situ cancer	<i>Tis</i>
T1 ^d	Superficial spreading tumor of any size but confined to the wall of the trachea or mainstem bronchus	<i>T1_{ss}</i>

Clinical stage

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	Ia	Ila	Illa	IIIb
	T1b	Ia	Ila	Illa	IIIb
T2	T2a	Ib	Ila	Illa	IIIb
	T2b	Ila	Ilb	Illa	IIIb
T3	T3 _{>7}	Ilb	Illa	Illa	IIIb
	T2 _{Inv}	Ilb	Illa	Illa	IIIb
	T3 _{Satell}	Ilb	Illa	Illa	IIIb
T4	T4 _{Inv}	Illa	Illa	IIIb	IIIb
	T4 _{Ipsi Nod}	Illa	Illa	IIIb	IIIb
M1	M1a _{Contra Nod}	IV	IV	IV	IV
	M1a _{PI Disem}	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

New, solid, indeterminate nodule on chest CT, 8 mm to 30 mm

Assess surgical risk

Low to moderate

Assess clinical probability of cancer

Very low
($<5\%$)

Low/moderate
(5–65%)

High
($>65\%$)

PET to assess
nodule

Negative
or mild
uptake

Moderate
or intense
uptake

Standard stage
evaluation (\pm PET)

No
metastasis

High

or

Nonsurgical
biopsy*

CT
surveillance

Malignant

Non-
diagnostic

Specific
benign

CT
surveillance

Specific
treatment

CT
surveillance

Nonsurgical
biopsy

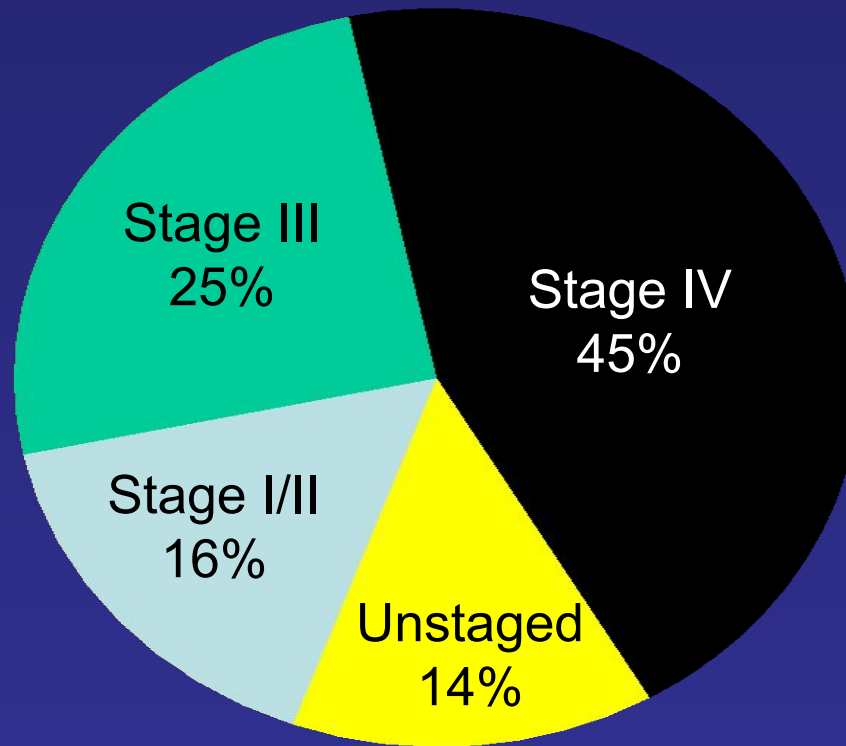
Surgical
resection

SBRT
or RFA

+ N2,3

Chemotherapy or
chemoradiation
(after biopsy)

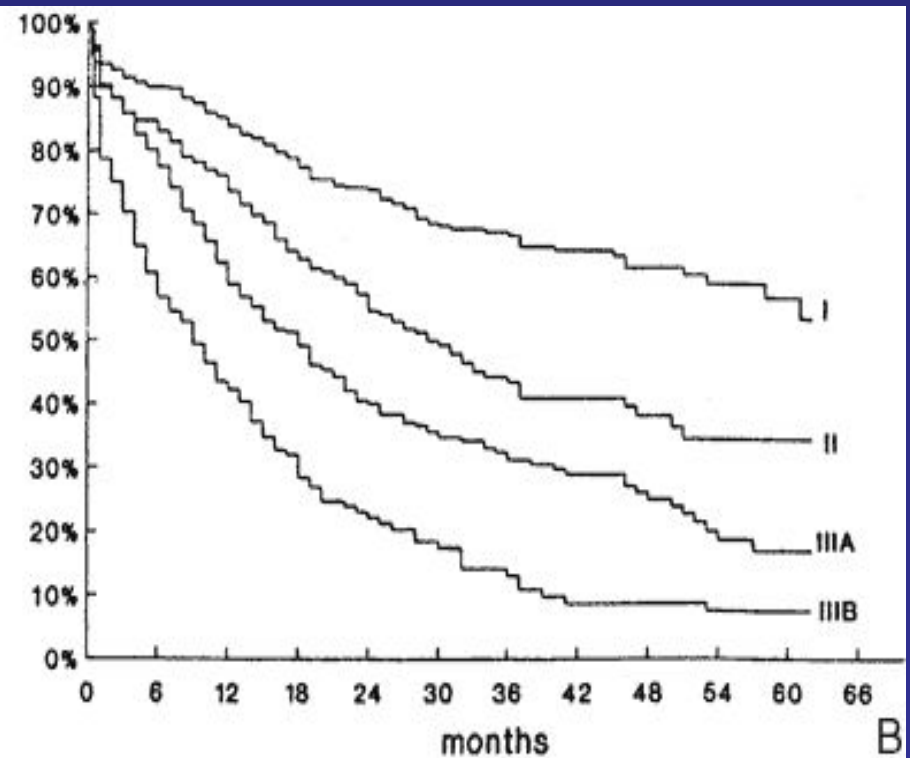
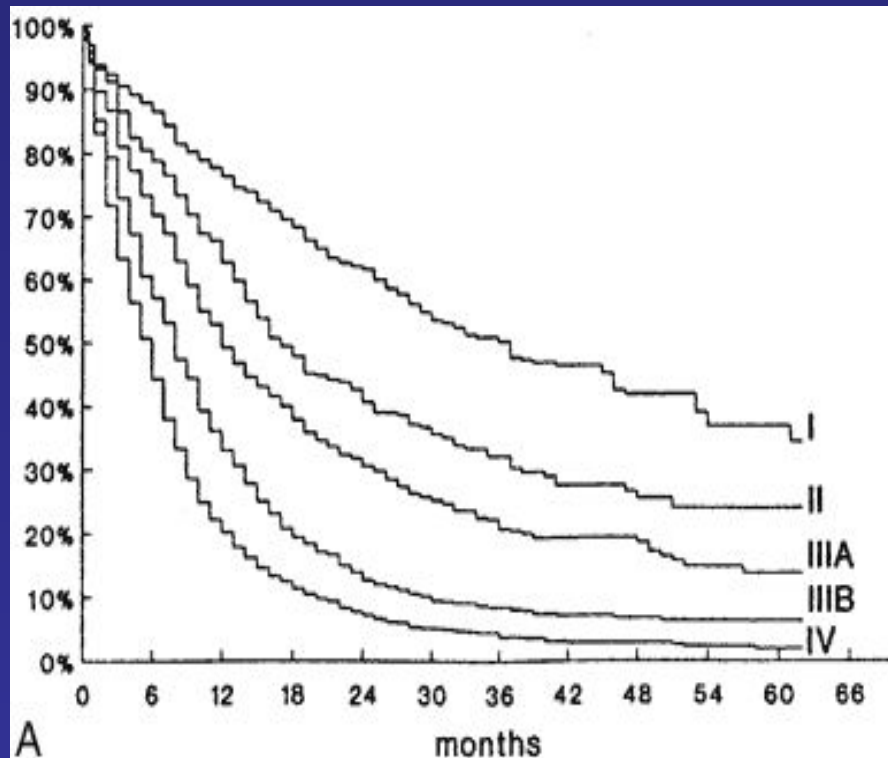
NSCLC: stage at diagnosis



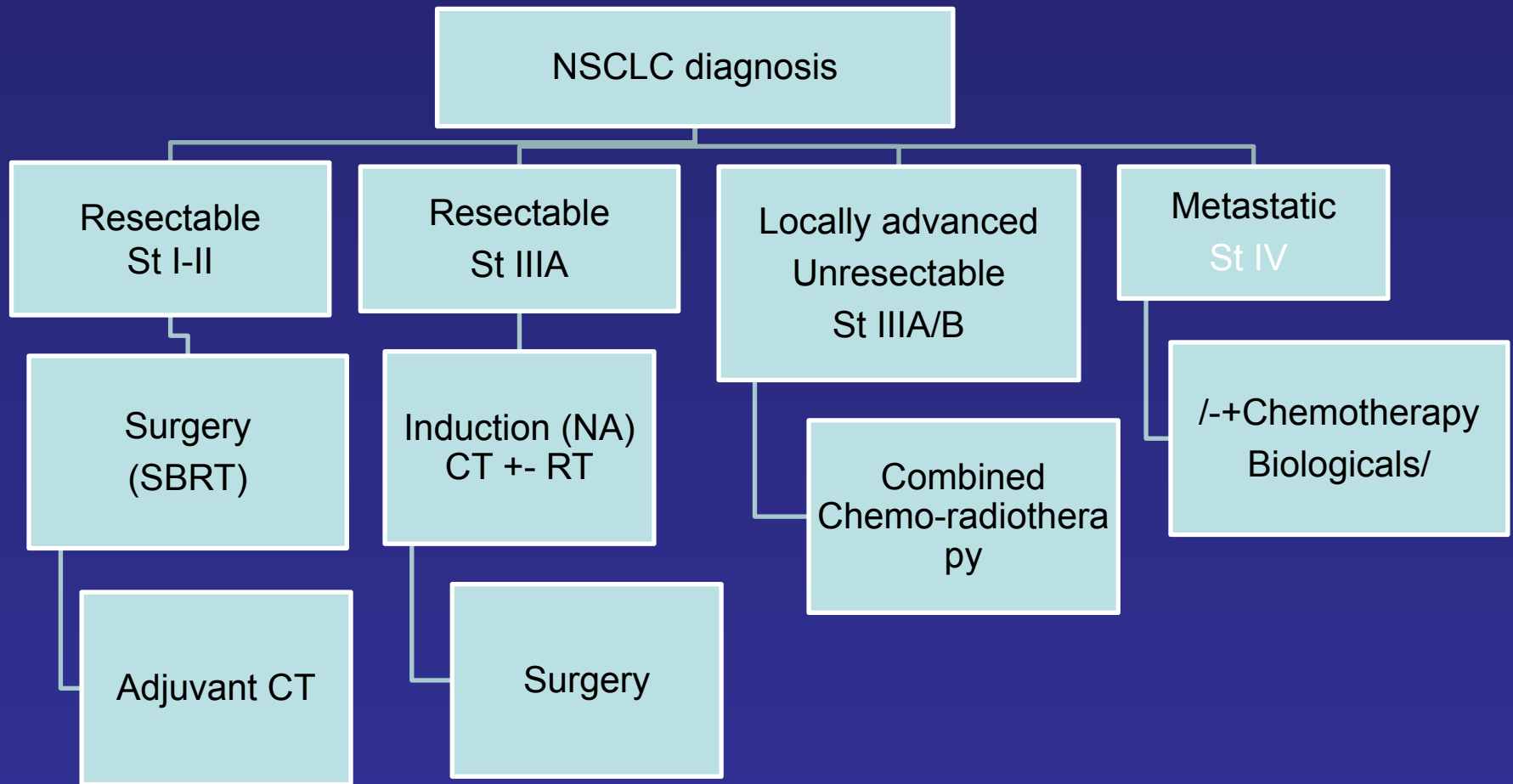
Survival curves according to different stages

A: Survival after clinical staging.

B: Survival after final pathologic staging



Treatment algorithm



NSCLC treatment

Stage I/II/operated IIIA

□ Surgery

(Criteria: postoperative $FEV_1 + DLCO$
>40% of pred. value + $PCO_2 < 45\%$, w/o
PHT)

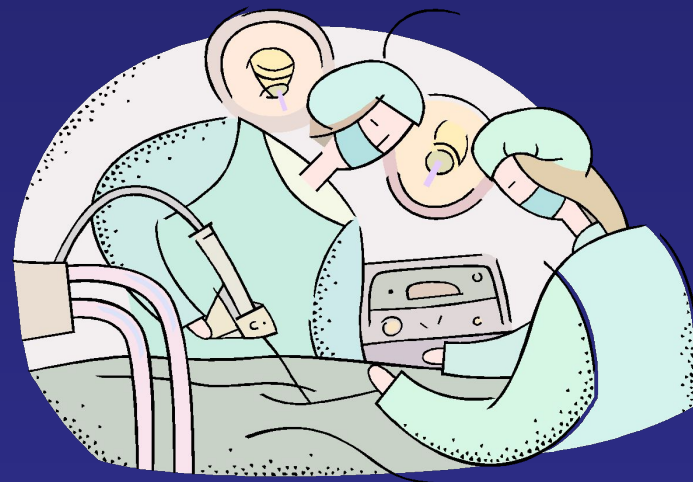
- ✓ Lobectomy
- ✓ Pneumonectomy
- ✓ En block resection

□ Non surgical candidate

- Segmentectomy
- Wedge resection
- SBRT

□ Adjuvant chemotherapy

□ Adjuvant XRT (suggested in N2)



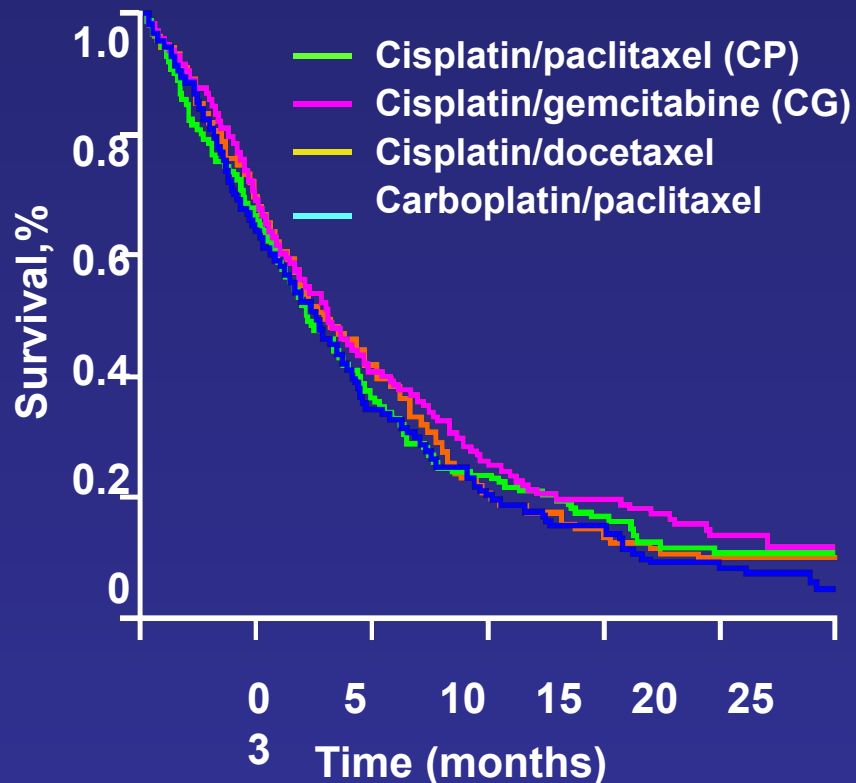
NSCLC Treatment

Chemotherapy active drugs

Agent	% Response
Cisplatin	25
Paclitaxel*	25
Docetaxel*^	25
Vinorelbine*	20
Gemcitabine*	25
Irinotecan	20
Topotecan	25
Alimta	20
Iressa#	10
Tarceva^#	10
ceritinib	
crizotinib	
afatinib	
avastin	
Pembrolizumab?	

The evolving standard of care for NSCLC

The past



“One size fits all”

The present and the future

- Tumours histological type
- Biomarkers
 - ✓ EGFR mutation status
 - ✓ K-ras status
- Pharmacogenomic parameters
- Non-genomic pt parameters
 - ✓ PS
 - ✓ Tempo of the disease
 - ✓ Co-morbidities status
- Pt priorities and preferences



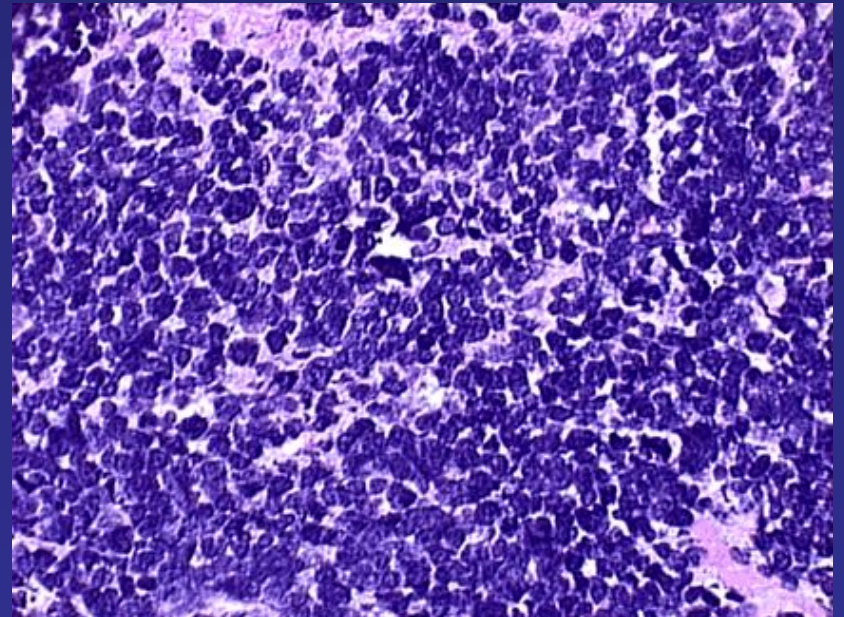
***Personalized,
“tailored” treatment***

Incidence of activating EGFR mutations in various subgroups of NSCLC

Characteristics of NSCLC Tumors	Positive for <i>EGFR</i> Mutation (%)
Smoking history	
<u>Never-smokers</u>	50.8
Smokers	9.0
Sex	
<u>Female</u>	37.5
Male	13
Histology	
<u>Adenocarcinomas</u>	31.3
Non-adenocarcinomas	2.3
Ethnicity	
<u>East Asian</u>	29.1
Non-East Asian	7.9
American (United States)	9.5
Total	19.6

Small Cell Lung Cancer (SCLC)

- Very aggressive cancer
- Responsive to CT and XRT
- High recurrence rate even in early stage



SCLC- VALSG Staging

□ *Limited disease (LD)*

- ✓ Tumor confined to one hemithorax and regional LN+
can be encompassed in a tolerable radiation field

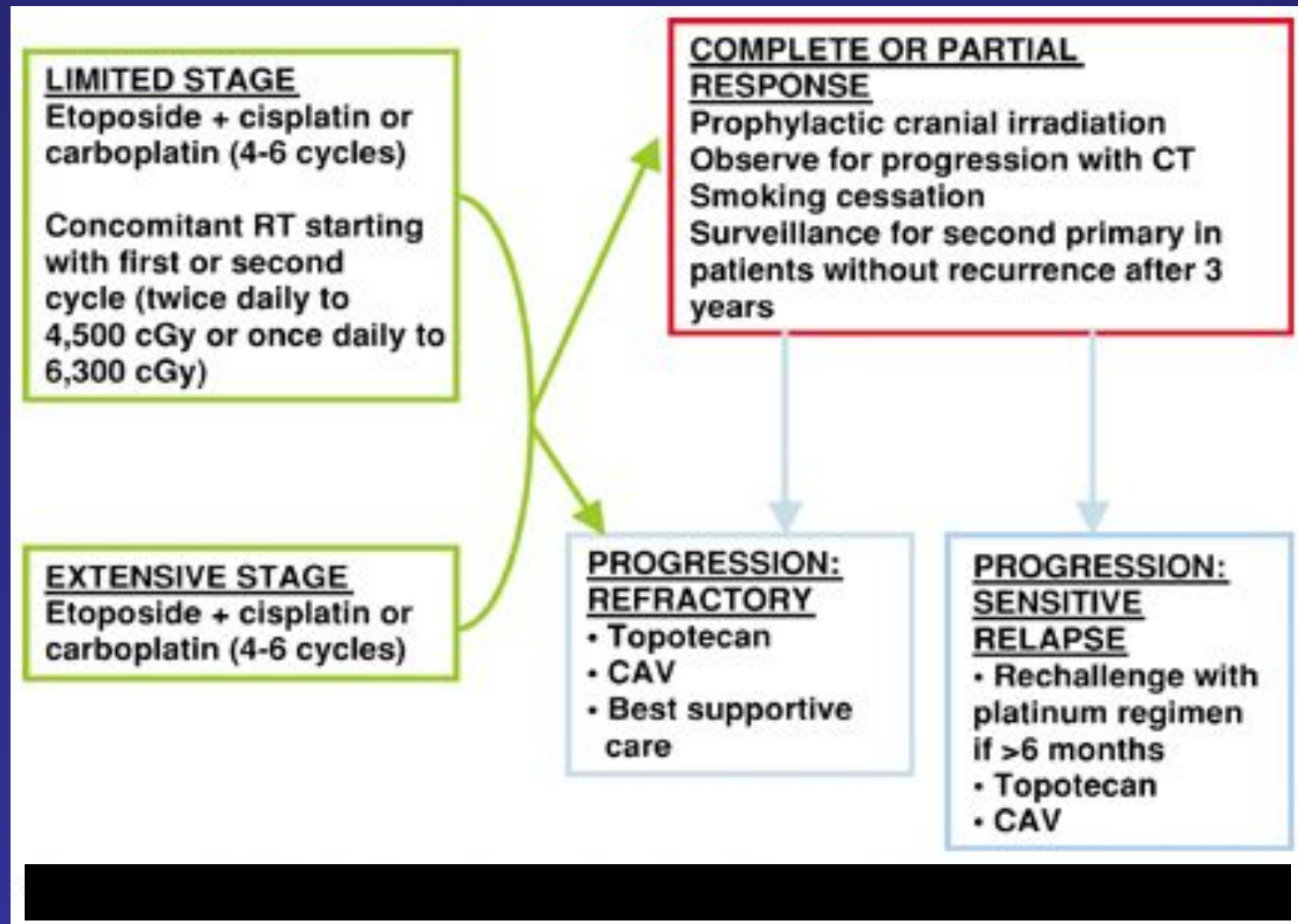
□ *Extensive disease (ED)*

- ✓ *cannot be encompassed in a tolerable radiation field*
- ✓ 2/3 of pts present with ED
- ✓ Common metastases sites are:
adrenals, bone, liver,
bone marrow, brain

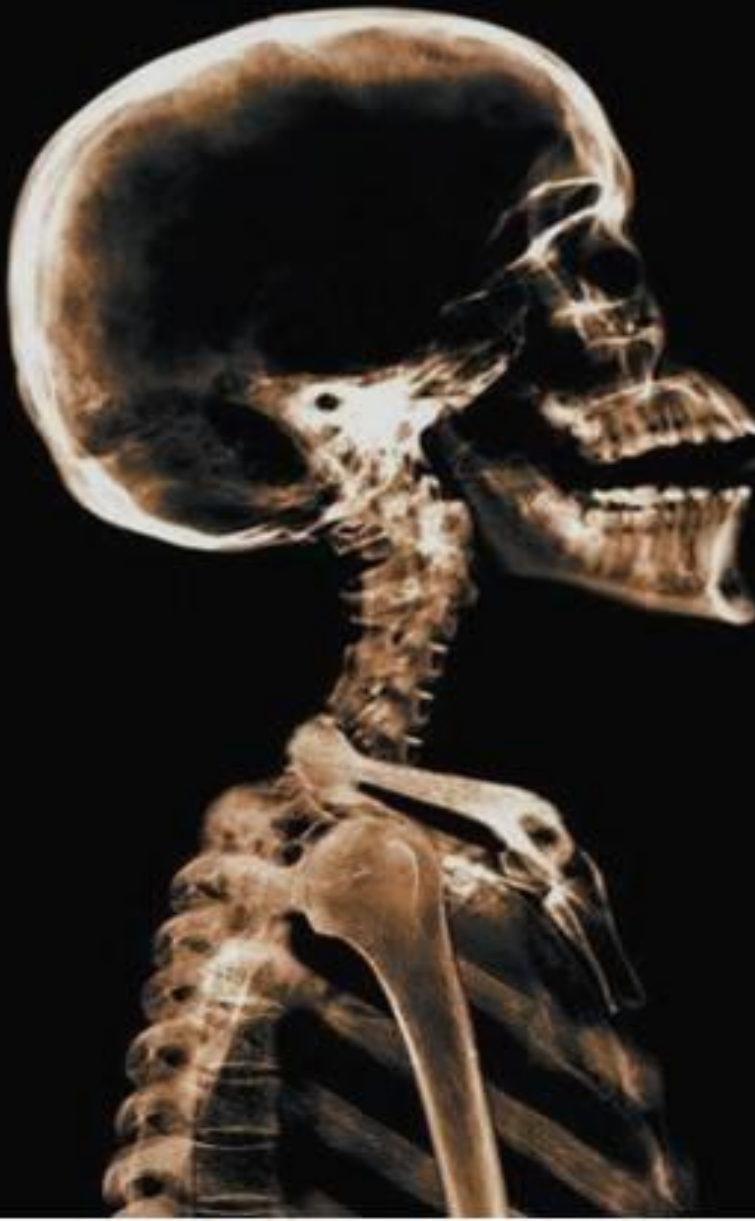
Staging procedures for SCLC:

- Chest + upper abdomen CT
scan + Bone scan or PET-CT
- Brain CT

SCLC treatment



Conclusions



- Smoking cessation is essential for prevention of lung cancer.
- New screening tools offer promise for detection of early lung tumors.
- Clinical trials are testing promising new treatments.
- New treatments offer improved efficacy and fewer side effects.
- Treatment can palliate symptoms and improve quality of life.