

# LUNG CANCER: A CLINICIAN'S PERSPECTIVE

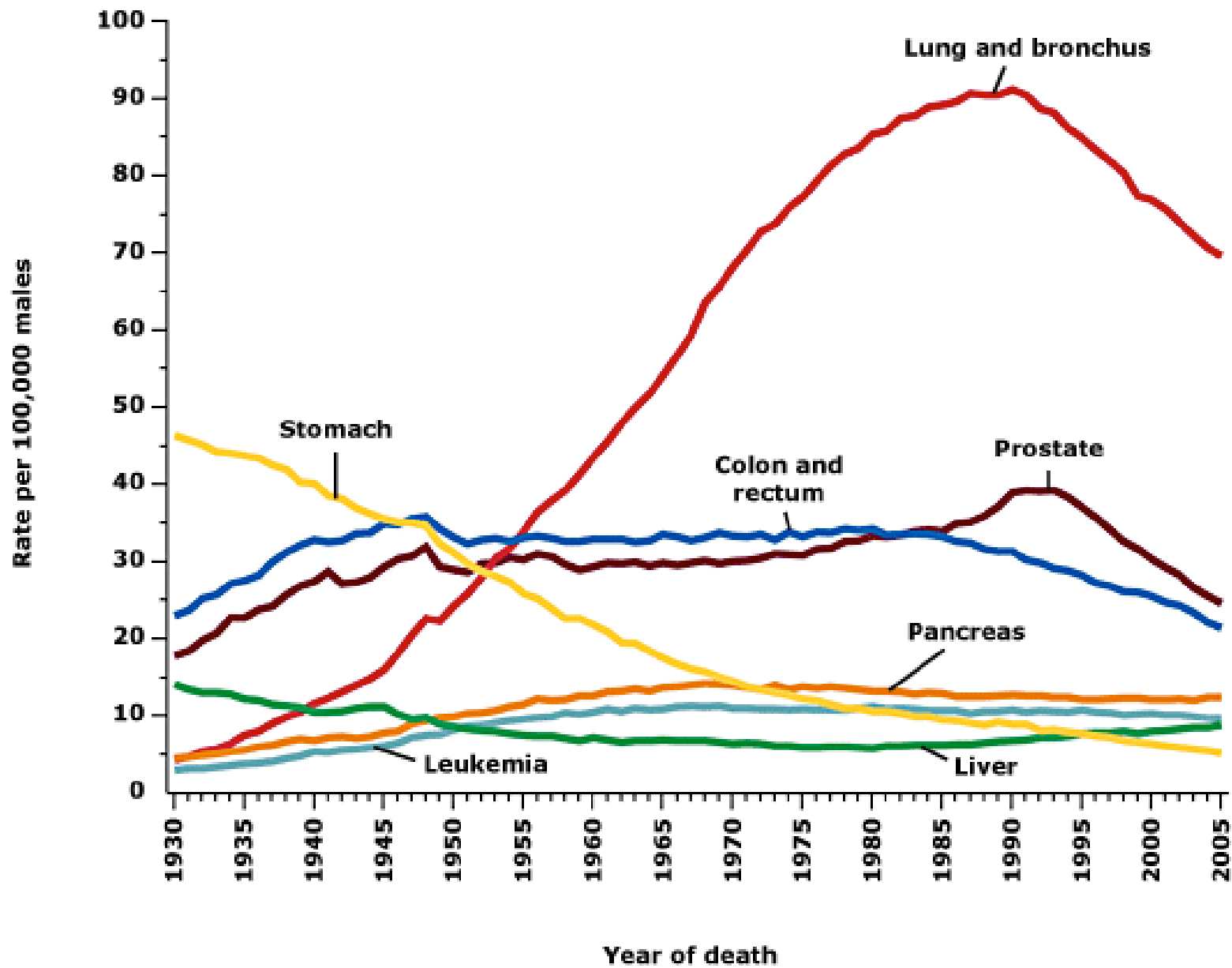
Michelle Wong  
Chris Hani Baragwanath Hospital

IAEA PET/CT Workshop: Improving Patient Care  
2 November 2010

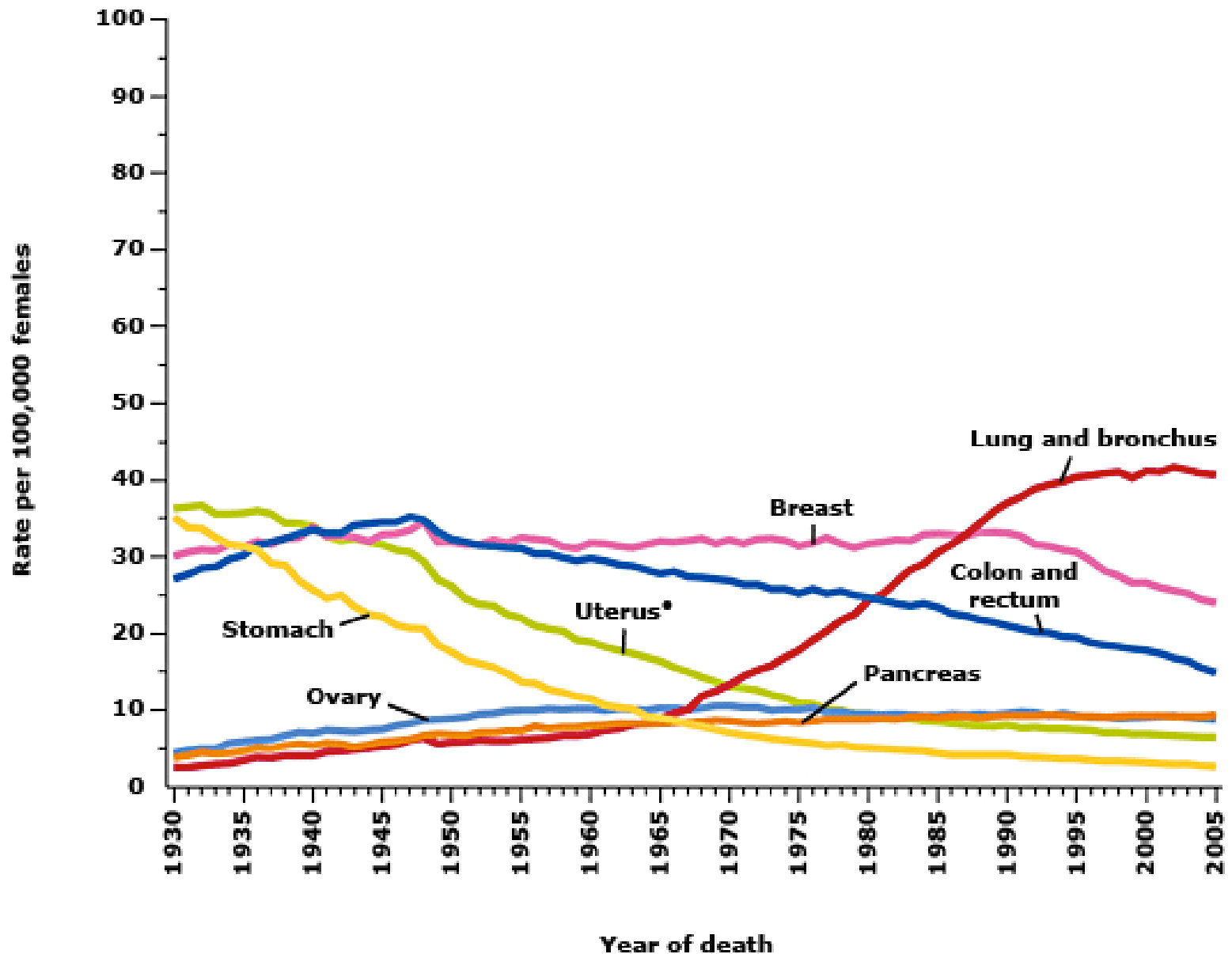


# EPIDEMIOLOGY OF LUNG CANCER

- ① Most common cause of cancer mortality worldwide in both men and women
- ① Causes more deaths than 4 next most common cancers combined (colon, breast, pancreas, prostate)



Annual age-adjusted cancer death rates among males for selected cancers, United States, 1930-2005



**Annual age-adjusted cancer death rates among females for selected cancers, United States, 1930-2005**

# AETIOLOGY

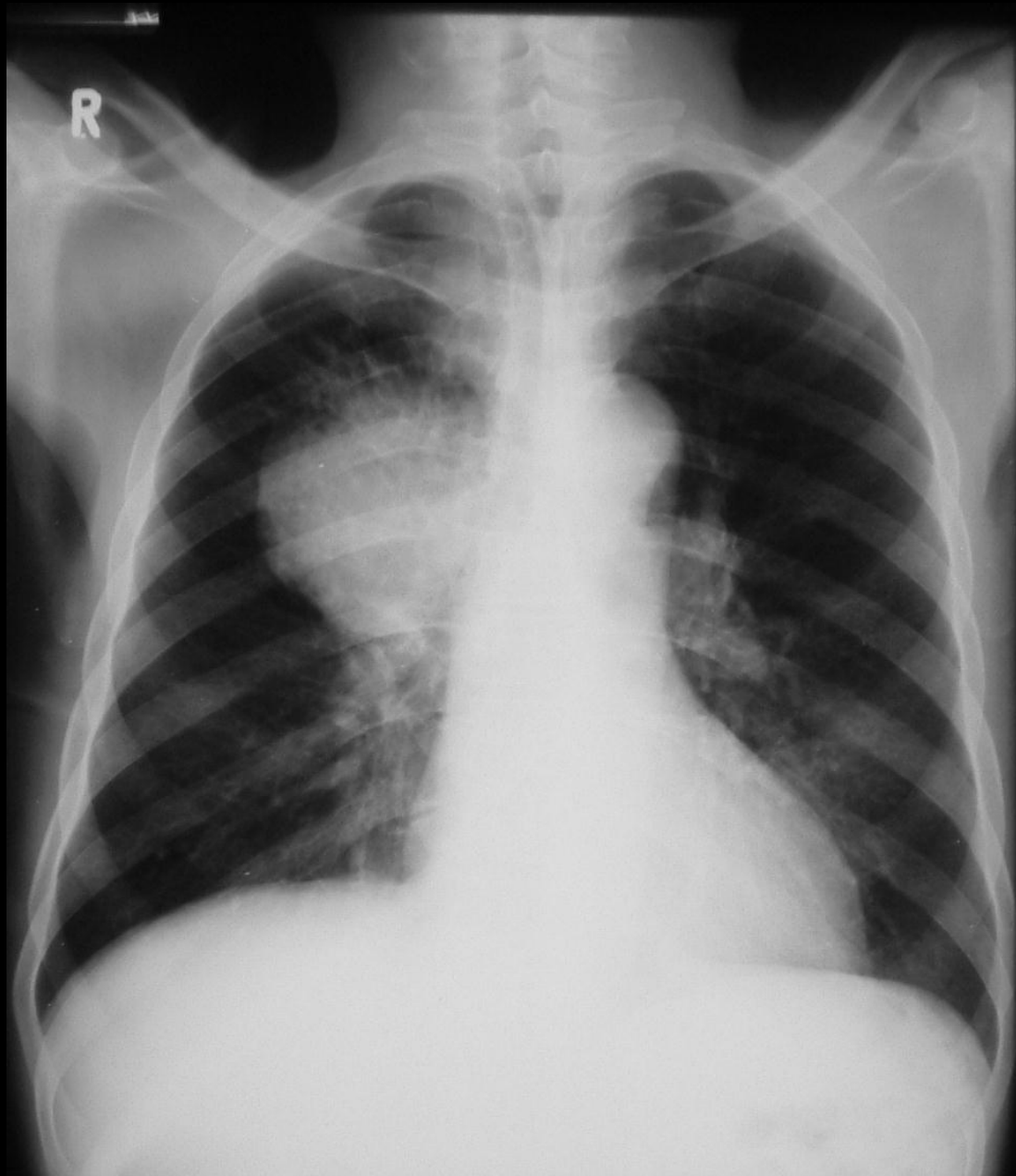
- ⊙ Smoking
  - ⊙ accounts for 90% of cases
  - ⊙  $\pm$  15% of lung cancer occurs in non-smokers
  - ⊙  $\pm$  5% due to passive smoking
- ⊙ Environmental and occupational exposures
  - ⊙ radon
  - ⊙ asbestos, chromates, nickel, arsenic, chloromethyl ethers, polycyclic aromatic hydrocarbons, radiation therapy
  - ⊙ air pollution, including exposure to fumes from cooking stoves and fires
- ⊙ Pulmonary fibrosis
- ⊙ HIV infection
- ⊙ Genetic predisposition

# PRESENTATION

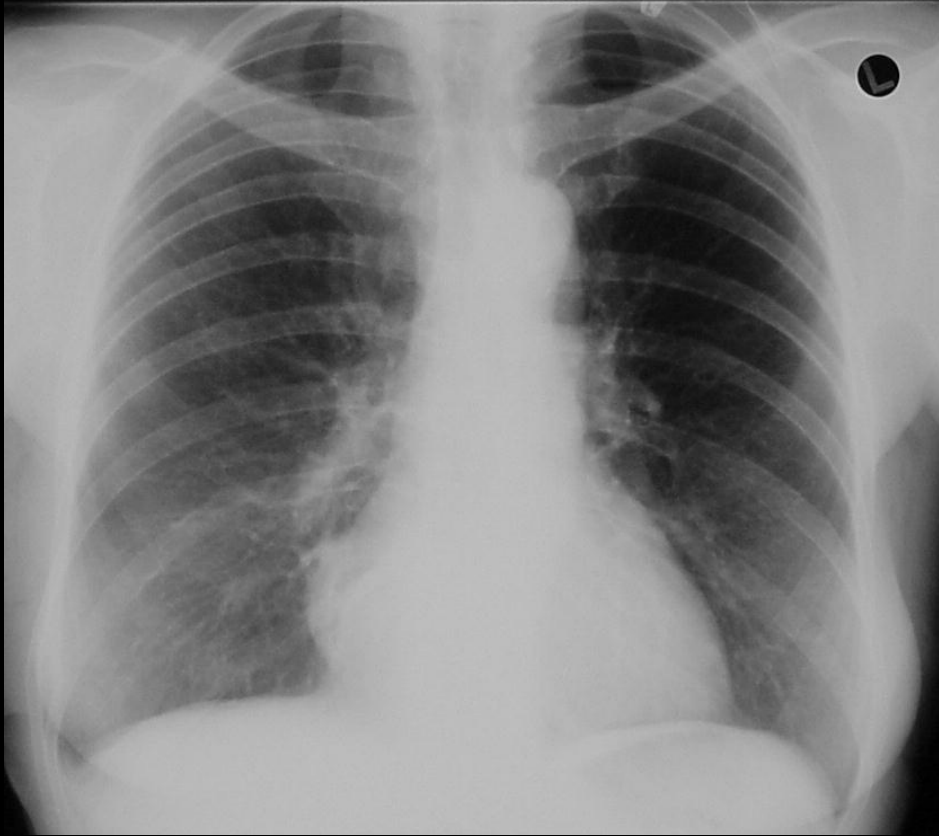
- ⊙ Symptoms due to local effects of tumour
  - ⊙ cough ± haemoptysis
  - ⊙ pneumonia due to obstructed bronchus
  - ⊙ local invasion, e.g. recurrent laryngeal nerve paralysis
- ⊙ Symptoms due to systemic effects of tumour
  - ⊙ metastatic disease
  - ⊙ constitutional symptoms
  - ⊙ paraneoplastic syndromes, e.g. hypercalcaemia, HPO
- ⊙ Incidental finding on CXR

# Paraneoplastic syndromes

<b>Systemic</b>	<b>Endocrine/metabolic</b>
Anorexia, cachexia, weight loss*	Cushing's syndrome
Fever	Hypercalcemia*
Orthostatic hypotension	Hyponatremia*
Nonbacterial thrombotic endocarditis	Hyperglycemia
Dermatomyositis/polymyositis	Hypertension
Systemic lupus erythematosus	Acromegaly
<b>Cutaneous</b>	Hyperthyroidism
Acquired hypertrichosis lanuginosa	Hypercalcitoninemia
Acrokeratosis (Bazex's syndrome)	Gynecomastia
Clubbing*	Galactorrhea
Dermatomyositis	Carcinoid syndrome
Erythema gyratum repens	Hypoglycemia
Exfoliative dermatitis	Hypophosphatemia
Hypertrophic pulmonary osteoarthropathy	Lactic acidosis
Deep venous thrombosis (Trousseau's syndrome)*	Hypouricemia
Tripe palms	Hyperamylasemia
Acanthosis nigricans	<b>Hematologic</b>
Acquired ichthyosis	Anemia*
Acquired palmoplantar keratoderma	Polycythemia
Erythema annulare centrifugum	Hypercoagulability
Florid cutaneous papillomatosis	Thrombocytopenic purpura
Pemphigus vulgaris	Dysproteinemia (including amyloidosis)
Pityriasis rotunda	Leukocytosis/Leukoerythroblastic reaction
Pruritus	Eosinophilia
Sign of Leser-Trelat	<b>Neurologic</b>
Sweet's syndrome	Peripheral neuropathy*
Vasculitis	Lambert-Eaton myasthenic syndrome*
<b>Renal</b>	Necrotizing myelopathy
Glomerulopathies	Cerebral encephalopathy
Tubulointerstitial disorders	Visual loss
	Visceral neuropathy













# CLASSIFICATION

- ① Non-small cell lung cancer (NSCLC)
- ① Small cell lung cancer (SCLC)

# MALIGNANT EPITHELIAL TUMOURS OF THE LUNG (WHO/IASLC CLASSIFICATION 1999)

## 1.3. Malignant

### 1.3.1. Squamous cell carcinoma

#### Variants

- 1.3.1.1. Papillary
- 1.3.1.2. Clear cell
- 1.3.1.3. Small cell
- 1.3.1.4. Basaloid

### 1.3.2. Small cell carcinoma

#### Variant

- 1.3.2.1. Combined small cell carcinoma

### 1.3.3. Adenocarcinoma

- 1.3.3.1. Acinar
- 1.3.3.2. Papillary
- 1.3.3.3. Bronchioloalveolar carcinoma
  - 1.3.3.3.1. Non-mucinous (Clara/pneumocyte type II)
  - 1.3.3.3.2. Mucinous
  - 1.3.3.3.3. Mixed mucinous and non-mucinous or intermediate cell type
- 1.3.3.4. Solid adenocarcinoma with mucin
- 1.3.3.5. Adenocarcinoma with mixed subtypes
- 1.3.3.6. Variants
  - 1.3.3.6.1. Well-differentiated fetal adenocarcinoma
  - 1.3.3.6.2. Mucinous ("colloid") adenocarcinoma
  - 1.3.3.6.3. Mucinous cystadenocarcinoma
  - 1.3.3.6.4. Signet-ring adenocarcinoma
  - 1.3.3.6.5. Clear cell adenocarcinoma



### 1.3.4. Large cell carcinoma

#### Variants

- 1.3.4.1. Large cell neuroendocrine carcinoma
  - 1.3.4.1.1. Combined large cell neuroendocrine carcinoma
- 1.3.4.2. Basaloid carcinoma
- 1.3.4.3. Lymphoepithelioma-like carcinoma
- 1.3.4.4. Clear cell carcinoma
- 1.3.4.5. Large cell carcinoma with rhabdoid phenotype

### 1.3.5. Adenosquamous carcinoma

### 1.3.6. Carcinomas with pleomorphic, sarcomatoid or sarcomatous elements

- 1.3.6.1. Carcinomas with spindle and/or giant cells
  - 1.3.6.1.1. Pleomorphic carcinoma
  - 1.3.6.1.2. Spindle cell carcinoma
  - 1.3.6.1.3. Giant cell carcinoma
- 1.3.6.2. Carcinosarcoma
- 1.3.6.3. Pulmonary blastoma
- 1.3.6.4. Others

### 1.3.7. Carcinoid tumour

- 1.3.7.1. Typical carcinoid
- 1.3.7.2. Atypical carcinoid

### 1.3.8. Carcinomas of salivary-gland type

- 1.3.8.1. Mucoepidermoid carcinoma
- 1.3.8.2. Adenoid cystic carcinoma
- 1.3.8.3. Others

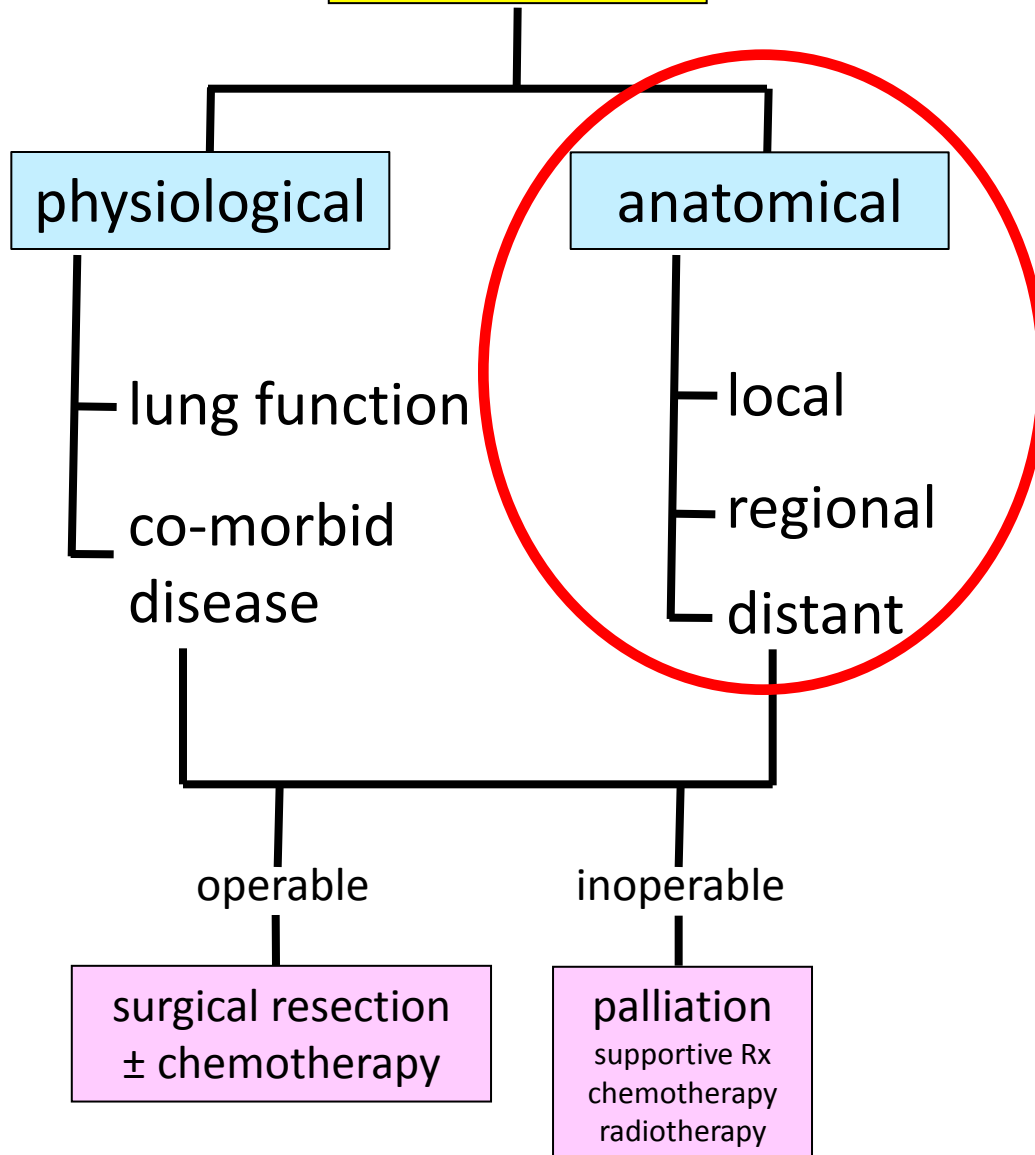
### 1.3.9. Unclassified carcinoma



# DIAGNOSIS

- ① Sputum cytology
- ① Flexible fiberoptic bronchoscopy and biopsy
- ① Transthoracic needle aspiration or core biopsy of primary tumour
- ① Diagnosis made from metastases (e.g. pleural effusions, lymph nodes)

# NSCLC



# STAGING OF NSCLC

- ⊙ Tests for staging
  - ⊙ based on clinical findings
  - ⊙ least invasive
  - ⊙ cost-effective
- ⊙ TNM staging classification – 7<sup>th</sup> edition (revised January 2010)
- ⊙ 3 types
  - ⊙ clinical staging
  - ⊙ pathological staging
  - ⊙ retreatment staging
  - ⊙ autopsy staging



## Primary tumor (T)

T1	Tumor $\leq 3$ cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus
T1a	Tumor $\leq 2$ cm in diameter
T1b	Tumor $> 2$ cm but $\leq 3$ cm in diameter
T2	Tumor $> 3$ cm but $\leq 7$ cm, or tumor with any of the following features: Involves main bronchus, $\geq 2$ cm distal to carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor $> 3$ cm but $\leq 5$ cm
T2b	Tumor $> 5$ cm but $\leq 7$ cm
T3	Tumor $> 7$ cm or any of the following: Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus $< 2$ cm from carina (without involvement of carina) Atelectasis or obstructive pneumonitis of the entire lung Separate tumor nodules in the same lobe
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe

## **Regional lymph nodes (N)**

N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar 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).

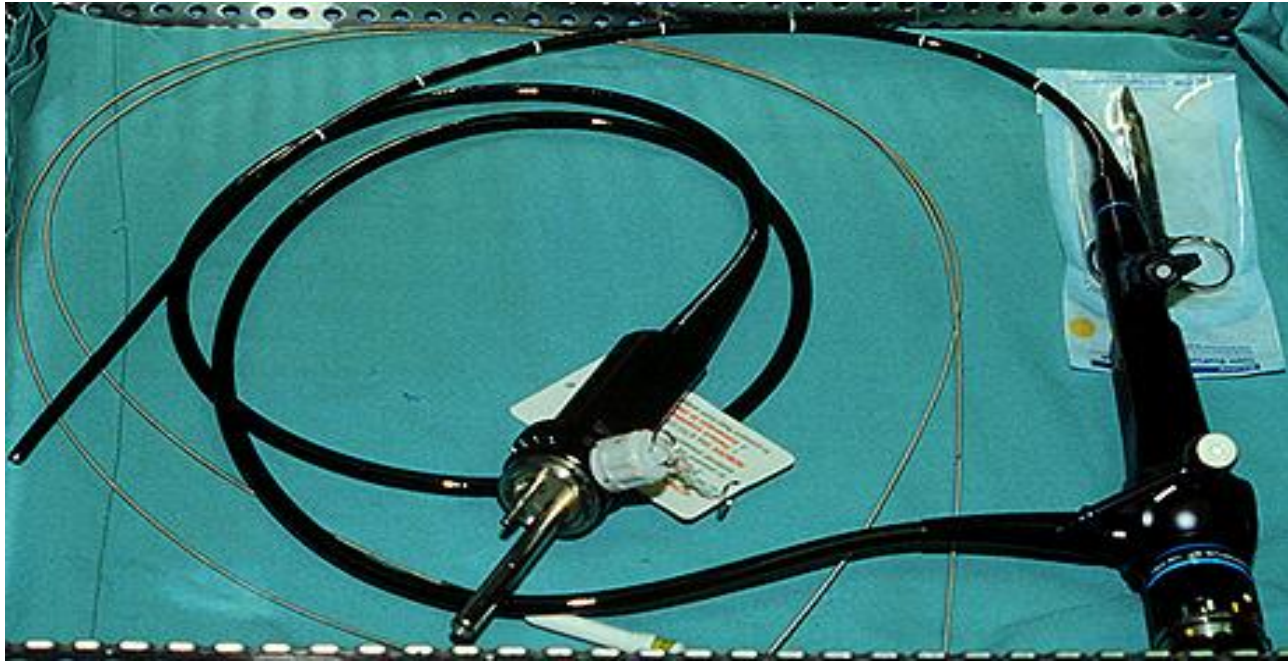
## **Distant metastasis (M)**

M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion
M1b	Distant metastasis

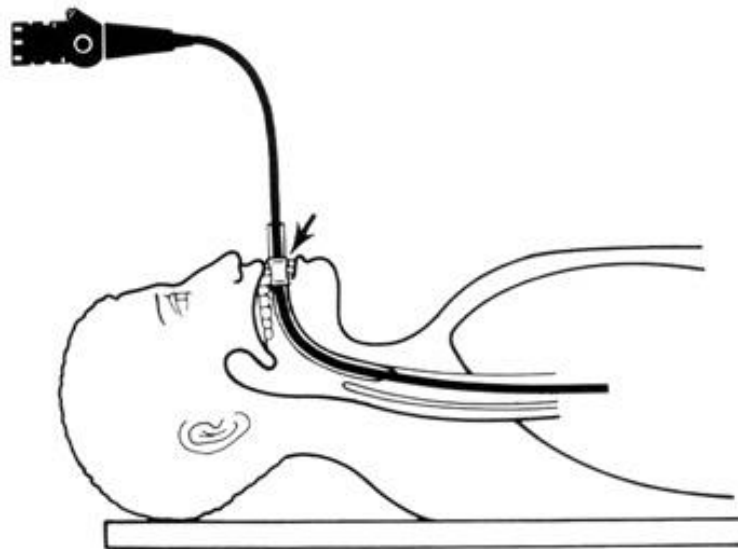
T/M	Subgroups	N0	N1	N2	N3
T1	T1a	IA	IIA	IIIA	IIIB
	T1b	IA	IIA	IIIA	IIIB
T2	T2a	IB	IIA	IIIA	IIIB
	T2b	IIA	IIIB	IIIA	IIIB
T3	T3 >7	IIIB	IIIA	IIIA	IIIB
	T3 <i>Inv</i>	IIIB	IIIA	IIIA	IIIB
	T3 <i>Satell</i>	IIIB	IIIA	IIIA	IIIB
T4	T4 <i>Inv</i>	IIIA	IIIA	IIIB	IIIB
	T4 <i>Ipsi Nod</i>	IIIA	IIIA	IIIB	IIIB
M1	M1a <i>Contr Nod</i>	IV	IV	IV	IV
	M1a <i>Pl Dissem</i>	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

# STAGING TECHNIQUES

- ⊙ Imaging
  - ⊙ CT scan
  - ⊙ PET scan
  - ⊙ bone scan
  - ⊙ ultrasound
- ⊙ Invasive techniques
  - ⊙ flexible bronchoscopy
    - ⊙ transbronchial needle aspiration (TBNA)
    - ⊙ endobronchial ultrasound needle aspiration (EBUS-NA)
  - ⊙ endoscopic transoesophageal ultrasound needle aspiration (EUS-NA)
  - ⊙ mediastinoscopy or mediastinotomy (Chamberlain procedure)
  - ⊙ fine needle aspiration or biopsy of distant metastases




FLEXIBLE FIBEROPTIC BRONCHOSCOPY





# CT SCANS

- ⊙ Advances in technology
  - ⊙ conventional CT
  - ⊙ spiral or helical CT
  - ⊙ multislice or multidetector CT
- ⊙ Useful in pre-operative staging
  - ⊙ localization, size and extent of tumour
  - ⊙ assessment of mediastinal involvement
  - ⊙ unsuspected distant metastases

- 
- ⊙ Surgical staging not infrequently disagrees with CT staging
  - ⊙ Difficult areas
    - ⊙ contiguous chest wall involvement without bone destruction
    - ⊙ vascular invasion
    - ⊙ lymph node metastases



01

120  
150



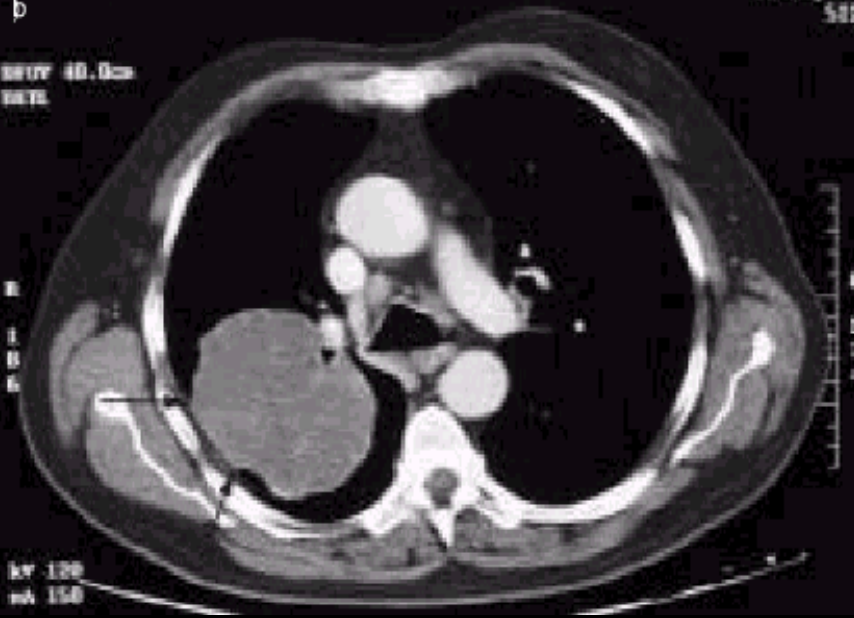
b

SWIV 40.0cm  
1075

120  
150

120  
150

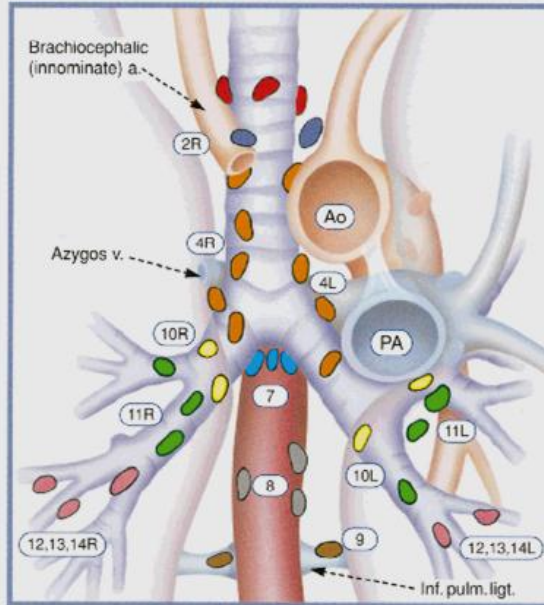
03 May 01  
5:02



# PET SCANS

- ① Useful
- ① Limitations

# MEDIASTINAL STAGING



## Superior Mediastinal Nodes

- 1 Highest Mediastinal
- 2 Upper Paratracheal
- 3 Pre-vascular and Retrotracheal
- 4 Lower Paratracheal (including Azygos Nodes)

N<sub>2</sub> = single digit, ipsilateral

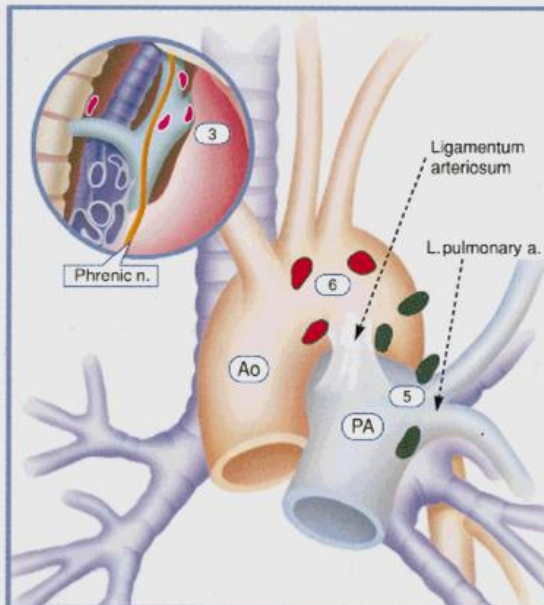
N<sub>3</sub> = single digit, contralateral or supraclavicular

## Aortic Nodes

- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)

## Inferior Mediastinal Nodes

- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary Ligament

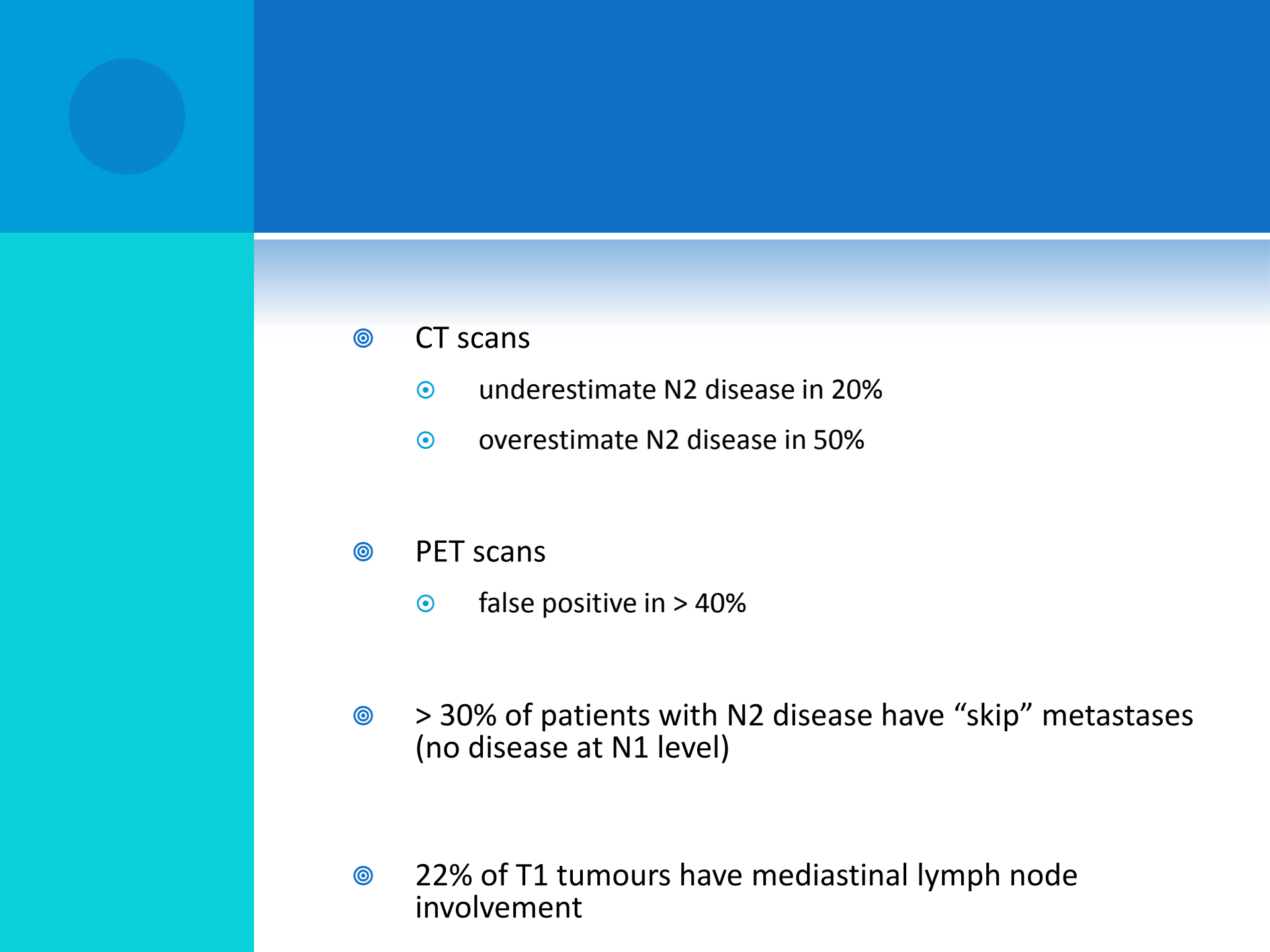


## N<sub>1</sub> Nodes

- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

# MEDIASTINAL STAGING

- ⊙ Methods
  - ⊙ mediastinoscopy (gold standard)
  - ⊙ needle techniques: EUS-NA, EBUS-NA, TBNA, TTNA
- ⊙ Evidence of mediastinal infiltration by CT scan
  - ⊙ no indication for invasive tests
- ⊙ Discrete mediastinal node enlargement
  - ⊙ invasive techniques to determine node status mandatory (staging by CT or PET scan not sufficiently accurate)

- 
- ⊙ CT scans
    - ⊙ underestimate N2 disease in 20%
    - ⊙ overestimate N2 disease in 50%
  
  - ⊙ PET scans
    - ⊙ false positive in > 40%
  
  - ⊙ > 30% of patients with N2 disease have “skip” metastases (no disease at N1 level)
  
  - ⊙ 22% of T1 tumours have mediastinal lymph node involvement



mediastinoscopy



# TRANSBRONCHIAL NEEDLE ASPIRATION (TBNA)

- ① 18-gauge Wang needle
- ① sensitivity 82%



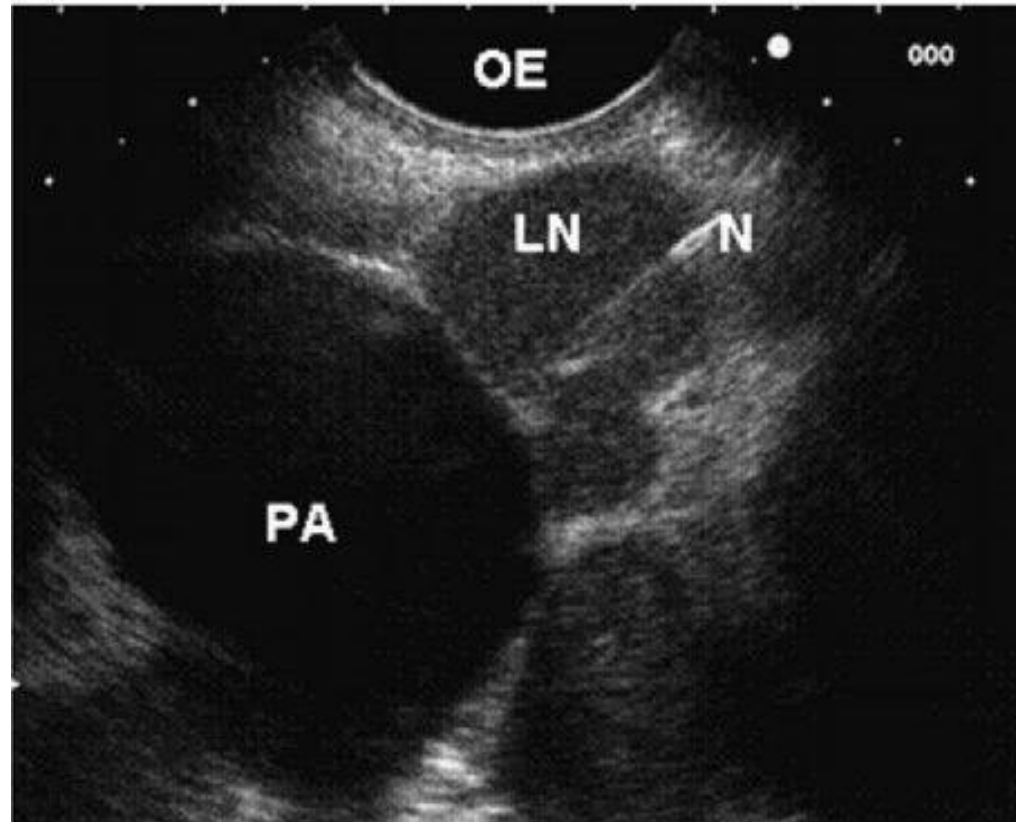
# ULTRASONOGRAPHY

- ⊙ Ultrasound probe may be passed
  - ⊙ into oesophagus (EUS)
  - ⊙ through fiberoptic bronchoscope (EBUS)
  
- ⊙ More sensitive in detecting mediastinal lymph nodes than CT (86% vs 49%)

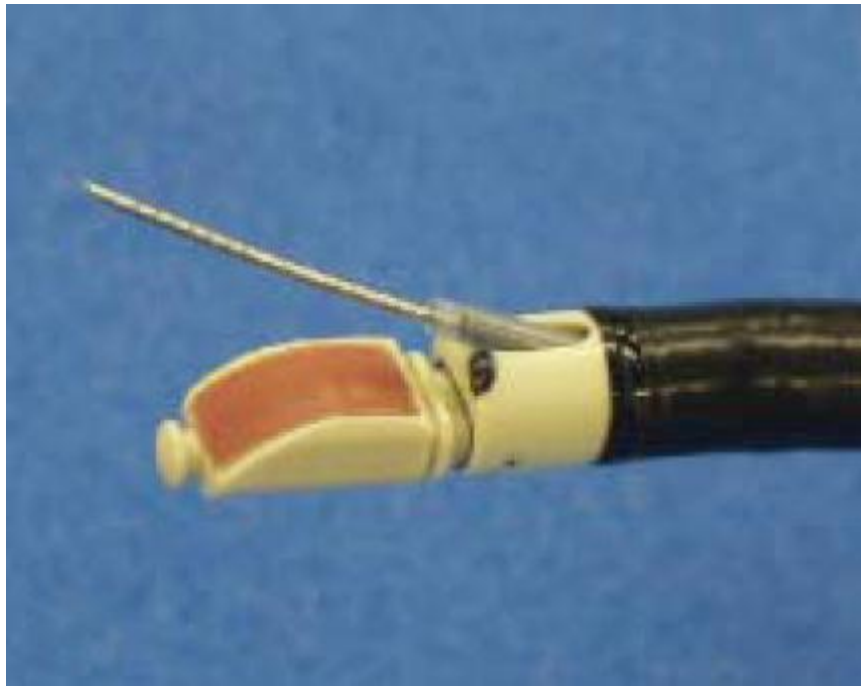
*Okamoto H et al. Chest 2002*



# OESOPHAGEAL ULTRASOUND-GUIDED NEEDLE ASPIRATION



# ENDOBONCHIAL ULTRASOUND-GUIDED NEEDLE ASPIRATION

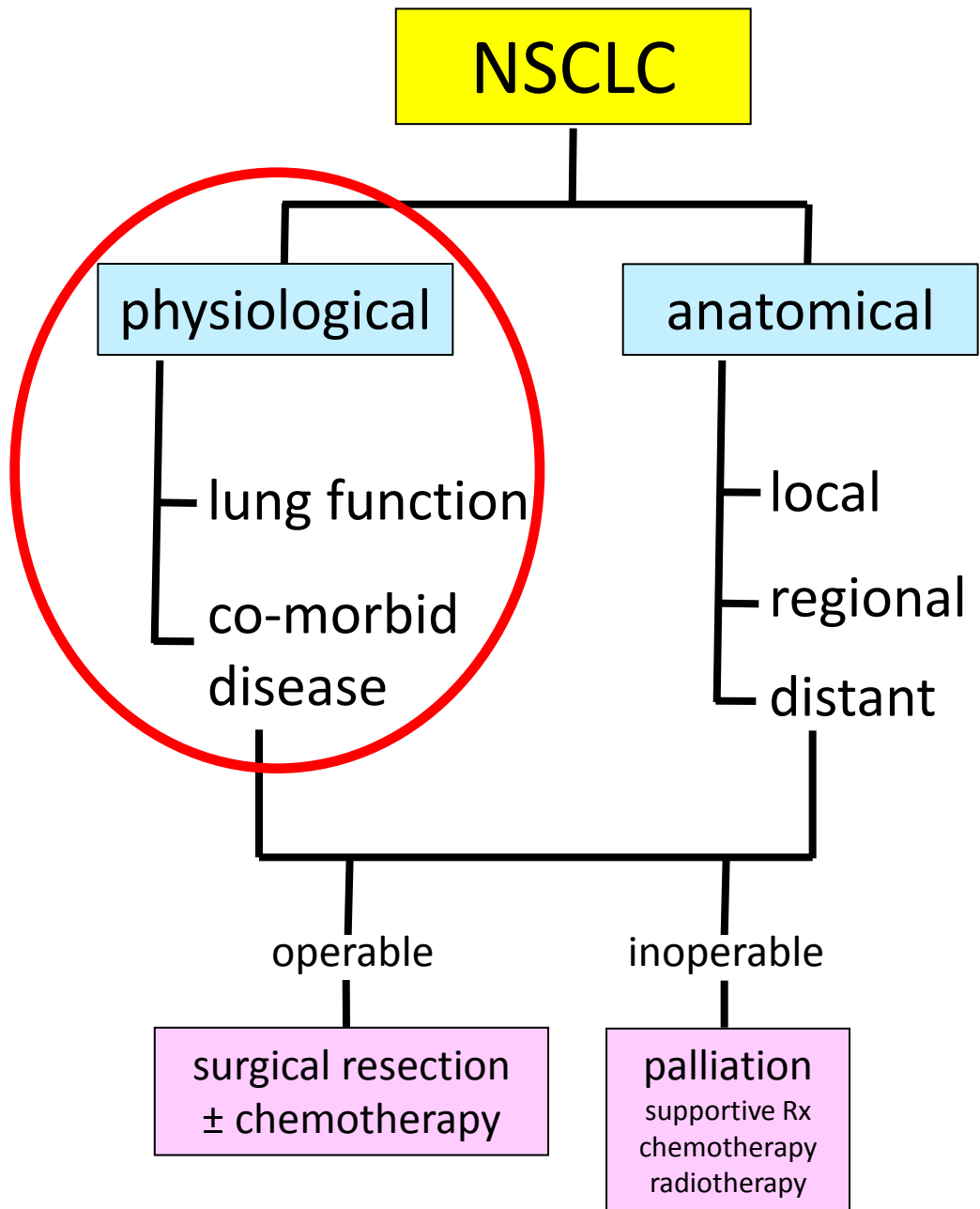




- ⊙ Combined EUS- and EBUS-guided needle aspiration in Stage IA – IIB NSCLC

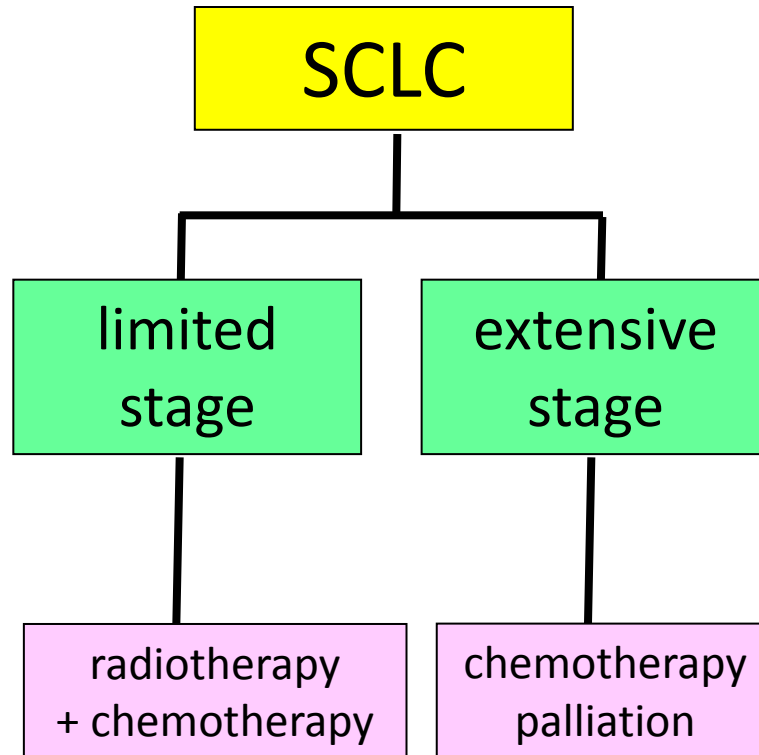
*Szlubowski A et al. Eur J Cardiothorac Surg 2010*

- ⊙ safe and effective
- ⊙ combined techniques had higher diagnostic yield than either technique alone
- ⊙ combined technique may allow surgical exploration of mediastinum to be omitted



# FITNESS FOR LUNG RESECTION SURGERY

- ⊙ Lung function tests
  - ⊙ fit for pneumonectomy
    - ⊙  $FEV_1 > 80\%$  predicted or  $> 2$  L
  - ⊙ fit for lobectomy
    - ⊙  $FEV_1 > 1.5$  L
  - ⊙ exercise testing pre-op
    - ⊙ PPO  $FEV_1 < 40\%$  pred OR PPO DLCO  $< 40\%$
  - ⊙ not fit for surgery
    - ⊙ PPO  $FEV_1$  % pred x PPO DLCO % pred  $< 1650$  OR PPO  $FEV_1 < 30\%$  OR unable to walk  $\geq 25$  shuttles OR unable to walk  $\geq 1$  flight of stairs
- ⊙ Split perfusion scan if contralateral lung diseased
- ⊙ Co-morbid disease



# STAGING FOR SCLC

- ◎ 95% have metastatic disease at diagnosis
- ◎ Limited stage
  - ◎ confined to one hemithorax and ipsilateral supraclavicular fossa
- ◎ Extensive stage
  - ◎ any disease beyond limited stage


# TREATMENT AND OUTCOMES: NSCLC

GROUP	STAGE	TREATMENT	5-YR SURVIVAL
Early stages	I	Surgical resection (adjuvant chemotherapy for large tumours) Radiotherapy if medically inoperable	58 – 73%
	II	Surgical resection + adjuvant chemotherapy Radiotherapy if medically inoperable	36 – 46%
Locally advanced stages	IIIA	Surgical or non-surgical combined modality treatment	24%
	IIIB	Non-surgical combined modality treatment	9%
Advanced stage	IV	Chemotherapy ± targeted agents	< 5%



# CHEMOTHERAPY FOR NSCLC

- ⊙ First-line treatment
  - ⊙ cisplatin or carboplatin PLUS
  - ⊙ pemetrexed for adenocarcinoma
  - ⊙ gemcitabine, vinorelbine, docitaxel or paclitaxel for squamous carcinoma
- ⊙ Adenocarcinomas with EGFR gene mutations
  - ⊙ EGFR tyrosine kinase inhibitor (e.g. gefitinib, erlotinib)
- ⊙ Second-line treatment
  - ⊙ docetaxel, pemetrexed, erlotinib

- 
- ④ ± 40% of NSCLC tumours do not respond to chemotherapy
  - ④ ± 20% have significant regression of their tumours



# TREATMENT AND OUTCOMES: SMALL CELL LUNG CANCER

- ⊙ Median survival
  - ⊙ limited stage: 15 – 20 months
  - ⊙ extensive stage: 8 – 13 months
  
- ⊙ 2-year survival
  - ⊙ limited stage: 20 – 40%
  - ⊙ extensive stage: < 5%

# TREATMENT OF SCLC

- ⊙ Limited stage:
  - ⊙ combined concurrent chemoradiotherapy
  - ⊙ Stage I who have undergone curative intent surgical resection: adjuvant platinum-based chemotherapy
- ⊙ Extensive stage:
  - ⊙ 4 – 6 cycles of cisplatin- or carboplatin-based combination chemotherapy
  - ⊙ cisplatin may be combined with etoposide or irinotecan
- ⊙ Prophylactic cranial irradiation (PCI) in all who achieve complete remission

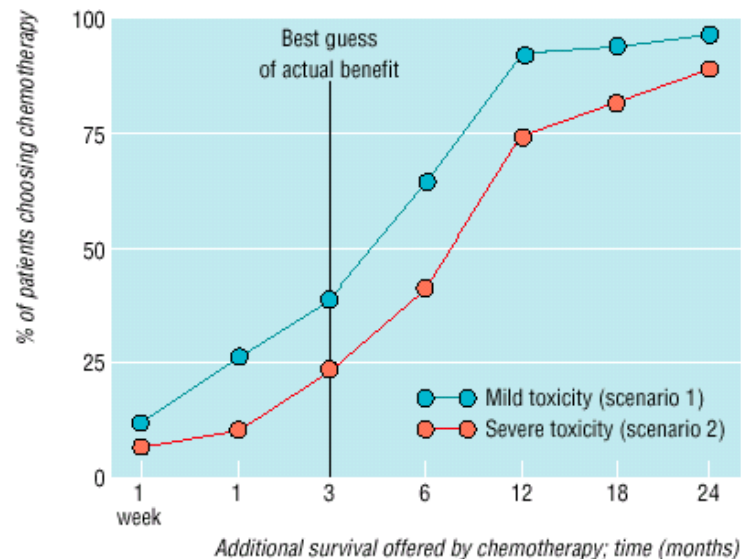


# CHEMOTHERAPY IN SCLC

- ⊙ Objective response and palliation in ~ 80%
- ⊙ Remissions short (mean < 1 year)
- ⊙ High-dose chemotherapy with blood stem-cell rescue disappointing
- ⊙ New drugs under investigation
  - ⊙ paclitaxel, docetaxel, topotecan, irinotecan, gemcitabine, vinorelbine

# PATIENT PREFERENCES

- 81 patients with Stage III or IV NSCLC
- At least one cycle of cisplatin-based chemotherapy
- Individual preferences highly variable
- Most would not choose chemotherapy for survival benefit of 3 months, except if it improved QoL





# RADIOTHERAPY

- ⊙ early medically inoperable NSCLC
- ⊙ locally advanced unresectable NSCLC
- ⊙ palliation of lung cancer, e.g. bone pain
- ⊙ adjuvant treatment of limited stage SCLC



# POST-OPERATIVE RADIOTHERAPY IN NSCLC

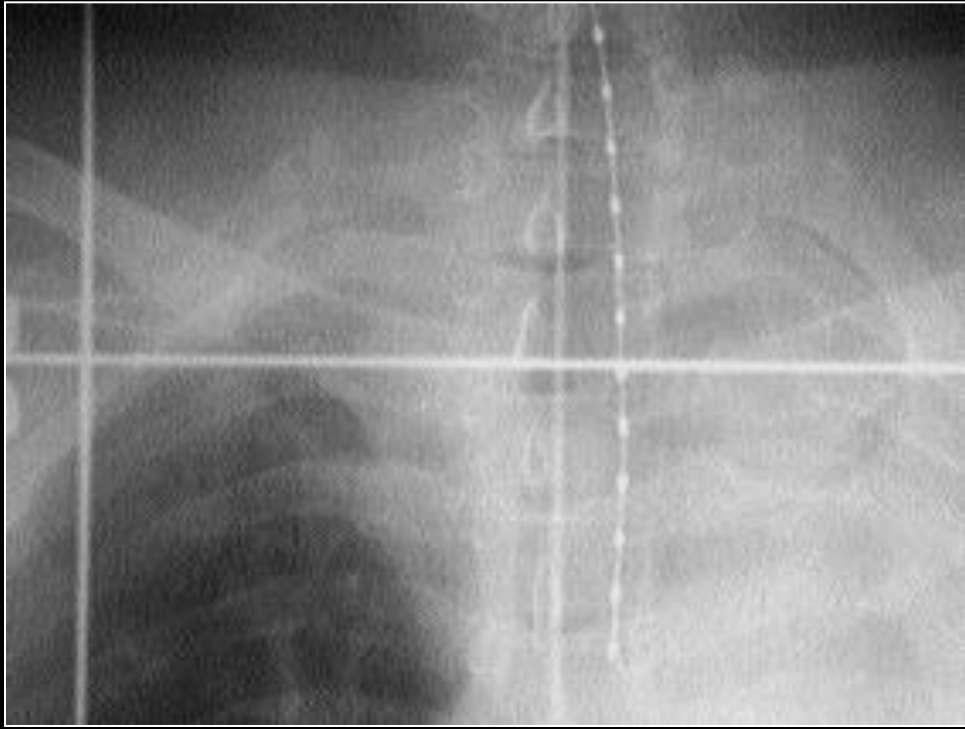
- ① produces improvement in local control, especially Stage III disease
- ① may reduce survival in Stage I and II disease






# ENDOBRONCHIAL BRACHYTHERAPY

- ⊙ alleviate symptoms related to endobronchial obstruction
  - ⊙ cough and haemoptysis
  - ⊙ post-obstructive atelectasis and infection
- ⊙ curative in medically inoperable patients with small strictly endobronchial tumours
- ⊙ endobronchial recurrence




- 
- ⊙ May be combined with external beam RT
  
  - ⊙ Complications
    - ⊙ radiation bronchitis
    - ⊙ haemoptysis
    - ⊙ bronchial stenosis
    - ⊙ fistula
    - ⊙ pneumothorax

# SCREENING FOR LUNG CANCER


# BIAS IN SCREENING STUDIES

- ⊙ Lead time bias
  - ⊙ earlier diagnosis with unchanged time of death
- ⊙ Length-time bias
  - ⊙ slow-growing tumours have longer potential screening period so that their detection causes apparent improvement in survival
- ⊙ Overdiagnosis
  - ⊙ detection of cancers which are so slow-growing that death is caused by disease other than lung cancer
- ⊙ Selection bias
  - ⊙ study population volunteers different to general population



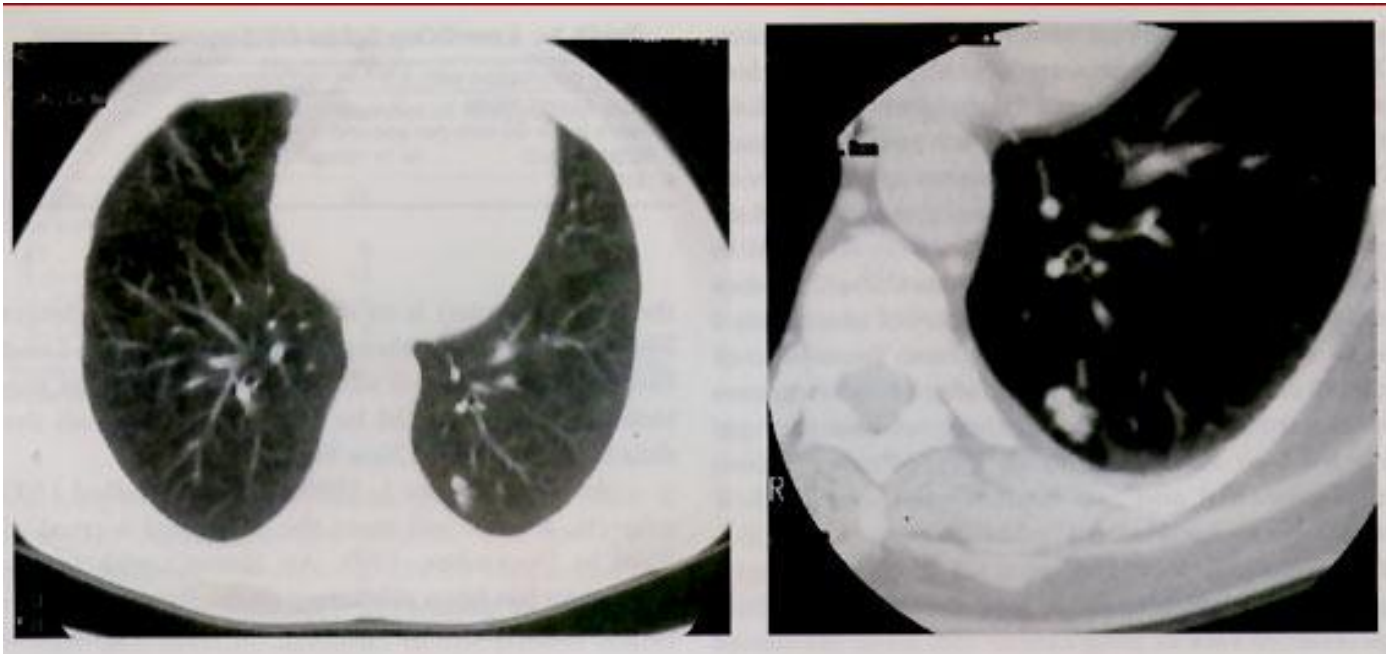
CELL TYPE	DOUBLING TIME (days)	TIME TO REACH 1 cm (years)
Squamous	88	7.2
Adenocarcinoma	161	13.2
Small cell	29	2.4

Average diameter at presentation 3 - 4 cm

- 
- ③ Screening by chest radiograph and sputum cytological analysis not shown to decrease lung cancer mortality
  - ③ Low-dose CT scanning still under evaluation
  - ③ ? Role of PET scans

- ⊙ Low dose spiral CT scan


- ⊙ can detect 80 - 85% of Stage I lung cancers



1 cm nodule LLL detected by spiral CT scan

(T1N1M0 at resection)



- 
- ⊙ Potential harms of screening
    - ⊙ benign nodules which require investigation
    - ⊙ unnecessary radiation exposure
    - ⊙ patient anxiety
    - ⊙ false negative results
    - ⊙ cost



*Thank you*