# Lung cancer

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# Histological classification of lung tumours

- **EPITHELIAL**
  - benign – papilloma, adenoma
  - preinvasive lesions –
    - Squamous cell dysplasia (Cis)
    - Atypical adenomatous hyperplasia,
    - Diffuse idiopathic hyperplasia of the lung neuroendocrine cells
  - malignant – **Lung cancer**
- SOFT TISSUE TUMOURS (benign - lipoma, fibroma, leiomyoma, etc)
  (malignant – sarcoma)
- MESOTHELIAL TUMOURS
- OTHER TUMOURS
- LYMPHOPROLIFERATIVE DISORDERS
- SECONDARY TUMOURS (metastases from breast, kidney, gut, thyroid, etc
- UNCLASSIFIED TUMOURS
- TUMOUR-LIKE LESIONS

# Lung cancer classification – ICD-10 (topographic)

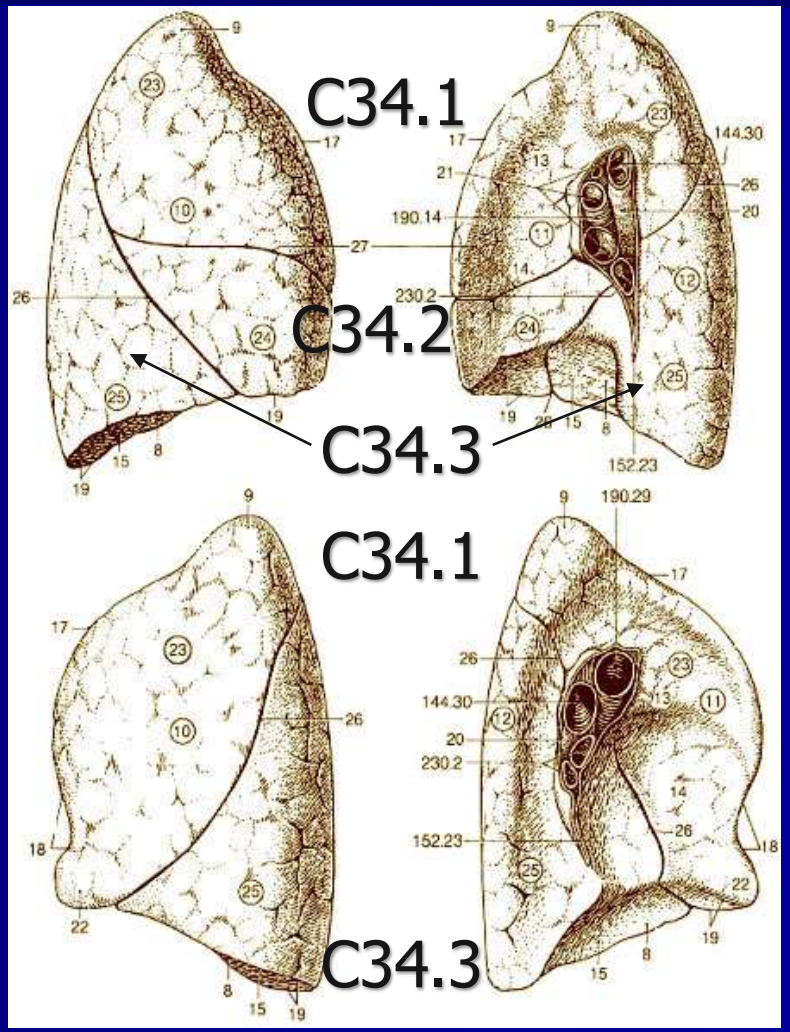
- C 33 – trachea
- C 34 – bronchus / lung

  C 34.1 – upper lobe

  C 34.2 – intermediate lobe

  C 34.3 – lower lobe

  C 34.9 – unspecified site



# Malignant epithelial tumours – histological classification

**SQUAMOUS CELL (EPIDERMOID) CARCINOMA**

- papillary
- clear cell
- basaloid cell

**ADENOCARCINOMA**

- acinar
- papillary
- bronchiolo-alveolar carcinoma
- solid AC with mucus formation
- AC with mixed subtypes

# Malignant epithelial tumours – histological classification

**SMALL CELL CARCINOMA**

variant - combined small cell carcinoma

**GIANT CELL CARCINOMA**

giant cell neuroendocrine carcinoma

non – neuroendocrine giant cell carcinoma variants (lymphoepithelioma-like, clear-cell, rhabdoid)

**ADENOSQUAMOUS CARCINOMA**

**SARCOMATOID CARCINOMA**

carcinosarcoma

pulmonary blastoma

# Malignant epithelial tumours – histological classification

**CARCINOID**

- typical
- atypical

**SALIVARY GLANDULAR-TYPE CARCINOMA**

- mucoepidermoid carcinoma
- adenoid cystic carcinoma
- myo-epithelial carcinomas

**UNCLASSIFIED CARCINOMA**

# Squamous cell cancer

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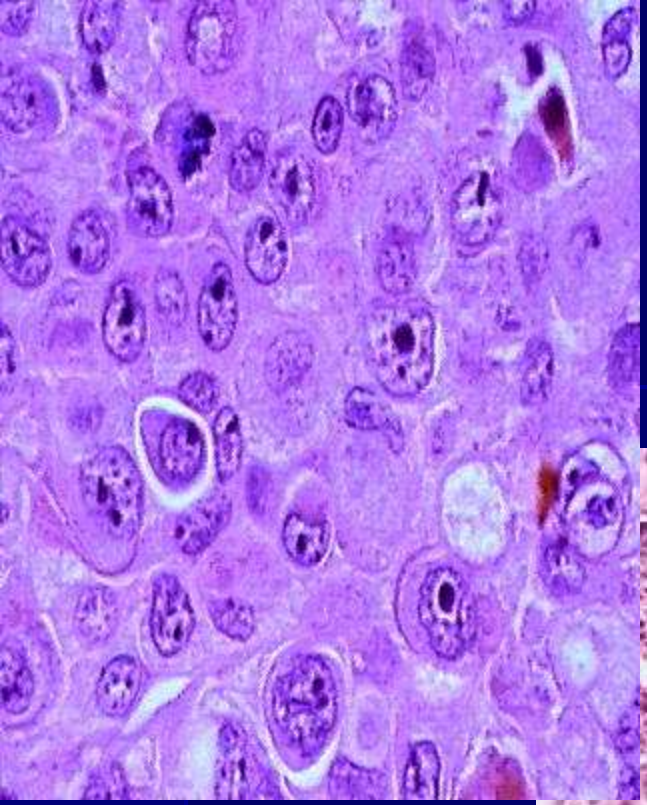
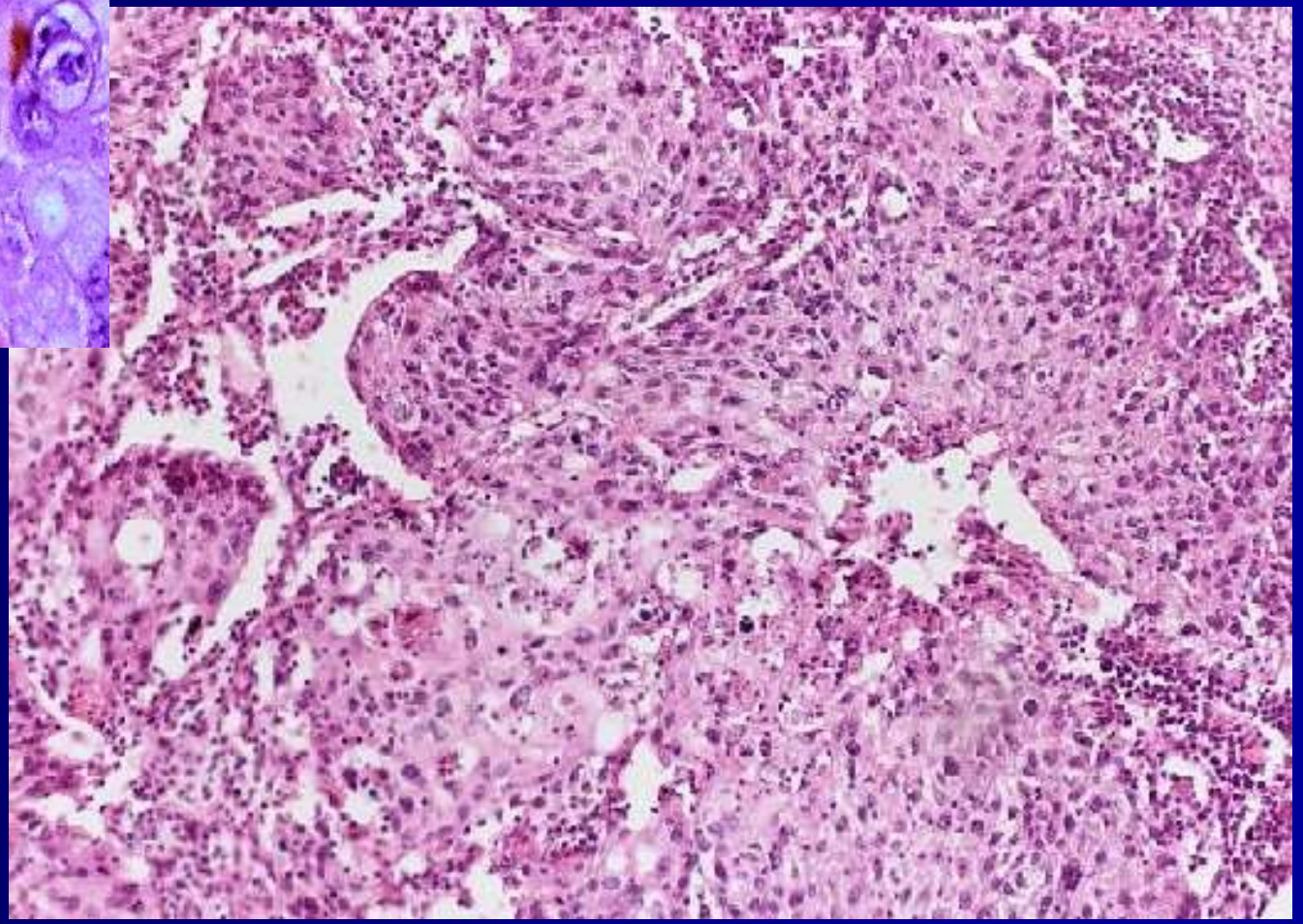
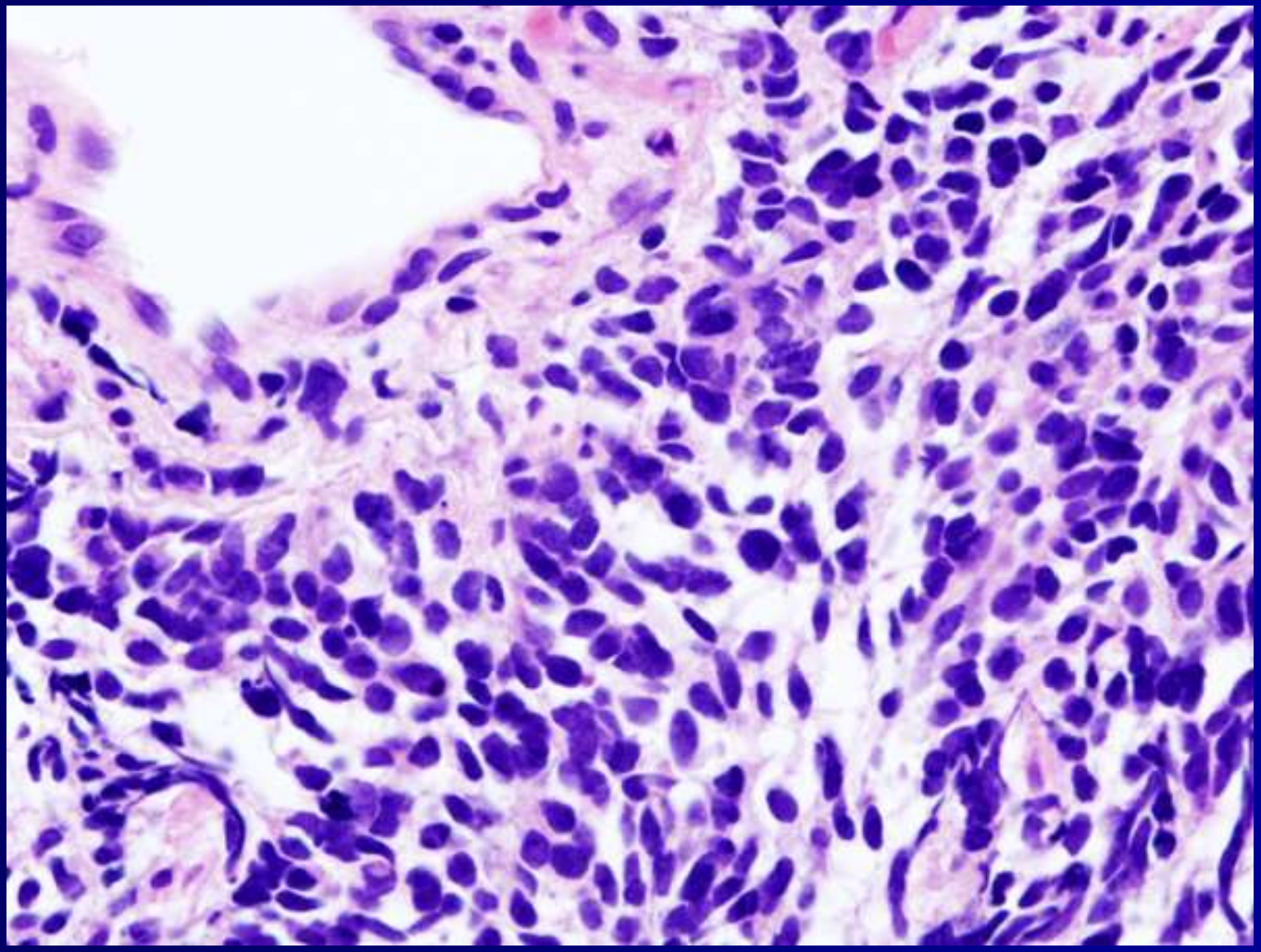




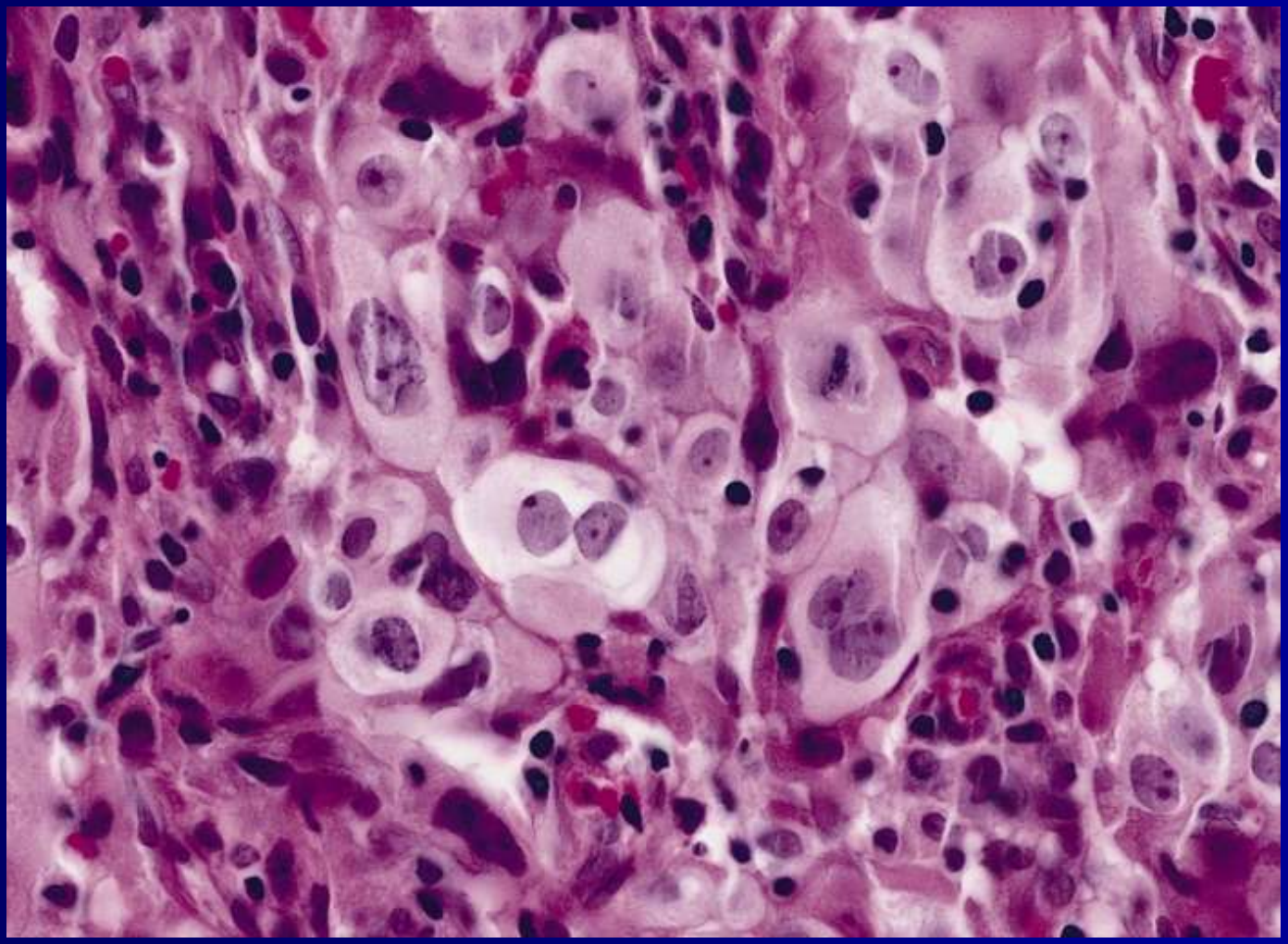
20x

# Small (oat) cell cancer



40x

# Giant cell cancer



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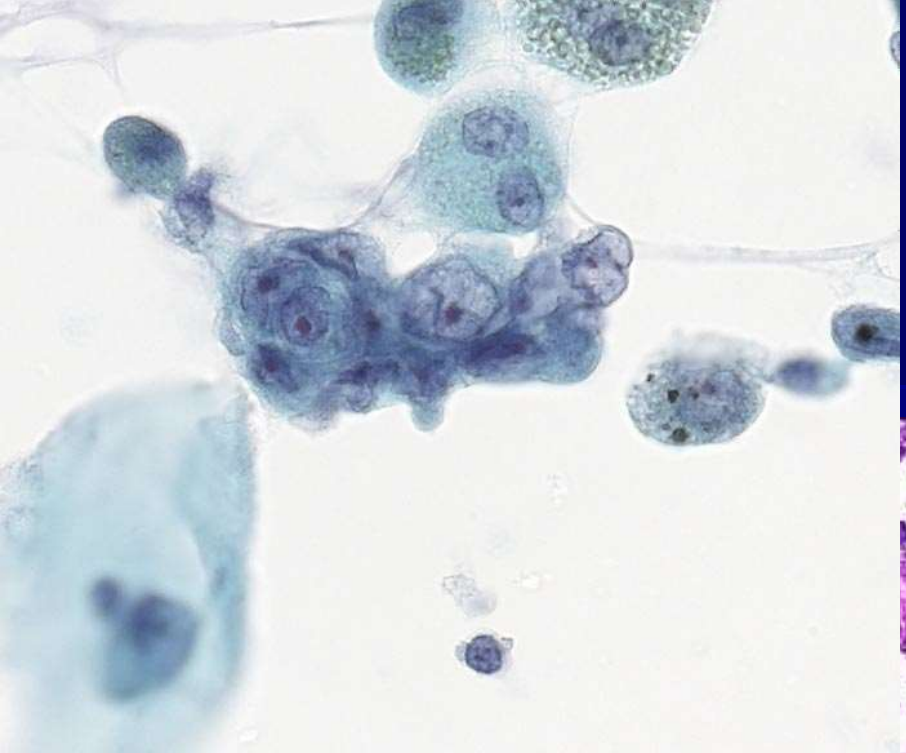
# Adenocarcinoma



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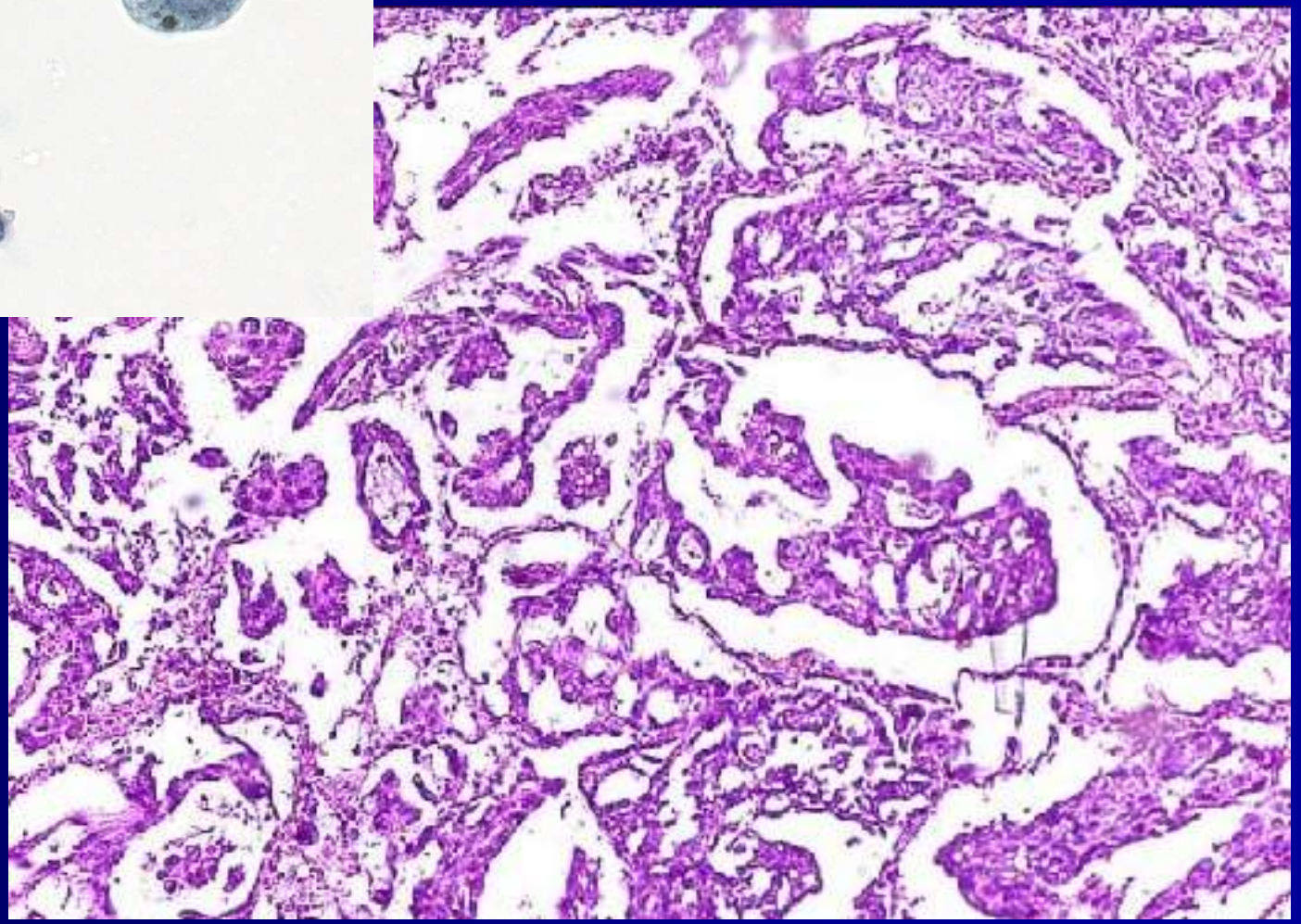

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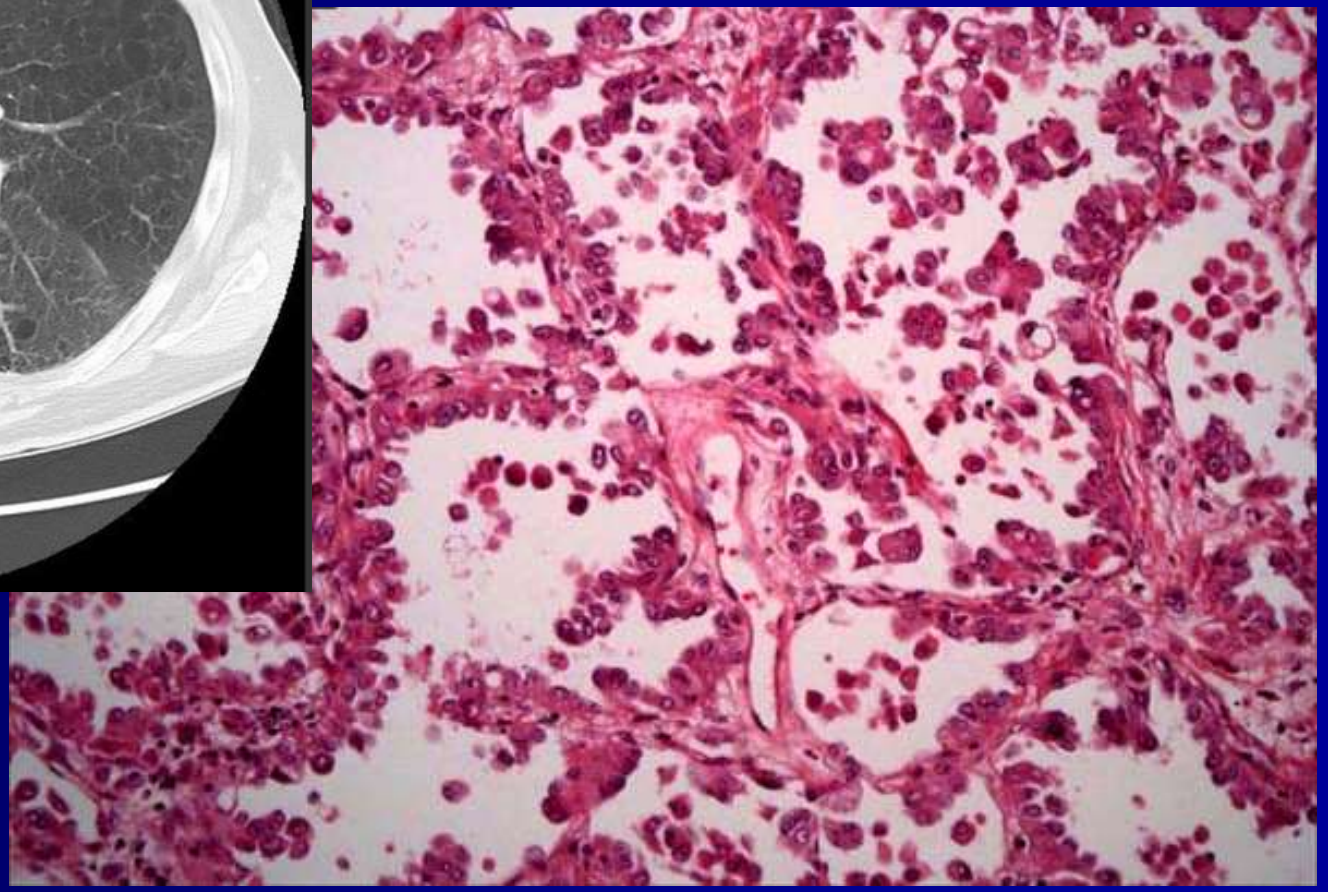
# Bronchiolo-alveolar carcinoma

Lepidic growth mimicking interstitial lung disease



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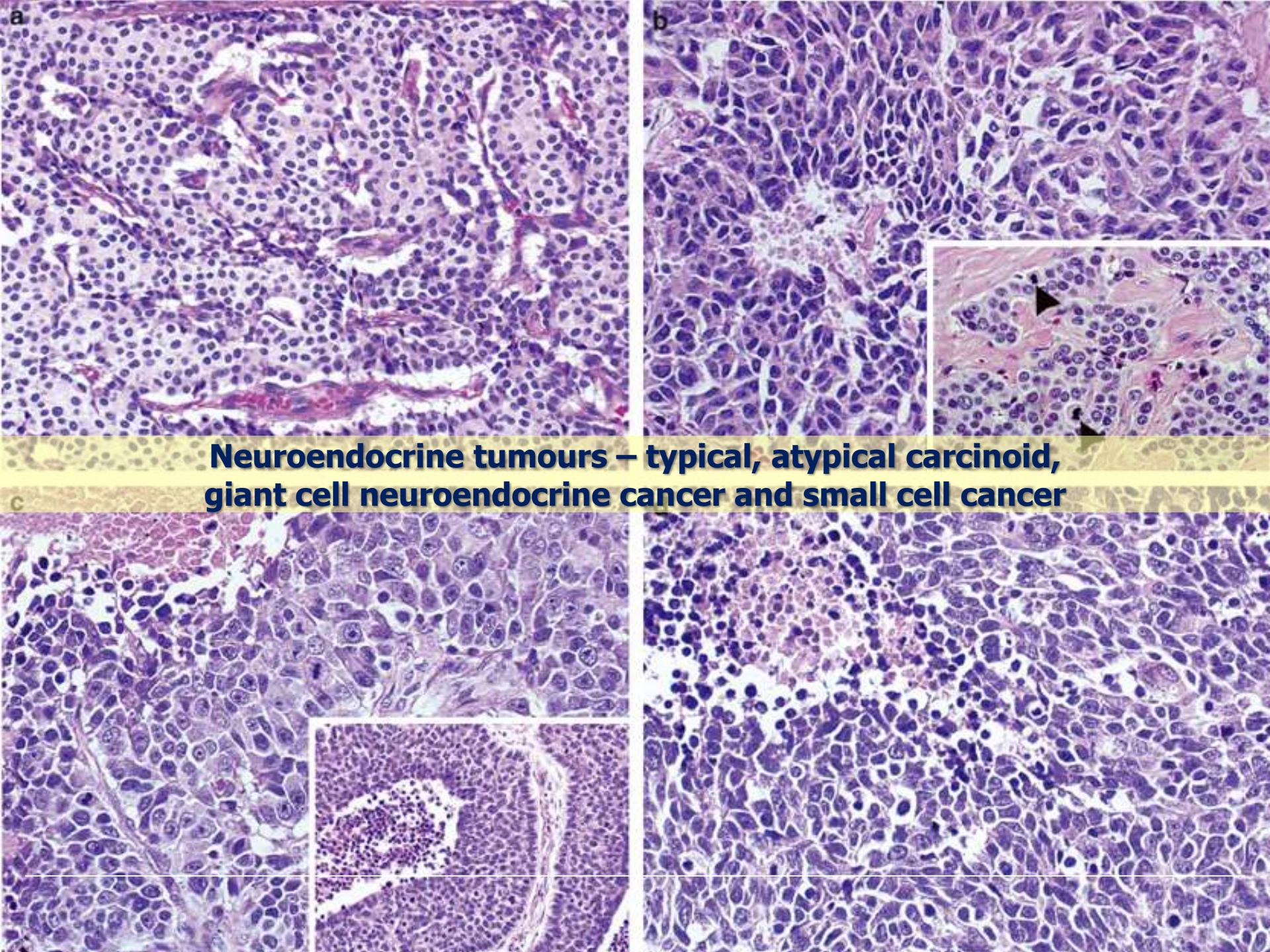
# Epithelial malignant tumours with neuroendocrine differentiation

Share common features in

- **conventional light microscopy** – neuroendocrine phenotype
- **immunohistochemistry** (chromogranin, synaptophysin, neural adhesive molecules NCAM)
- **electron microscopy** (dense neuroendocrine granules)

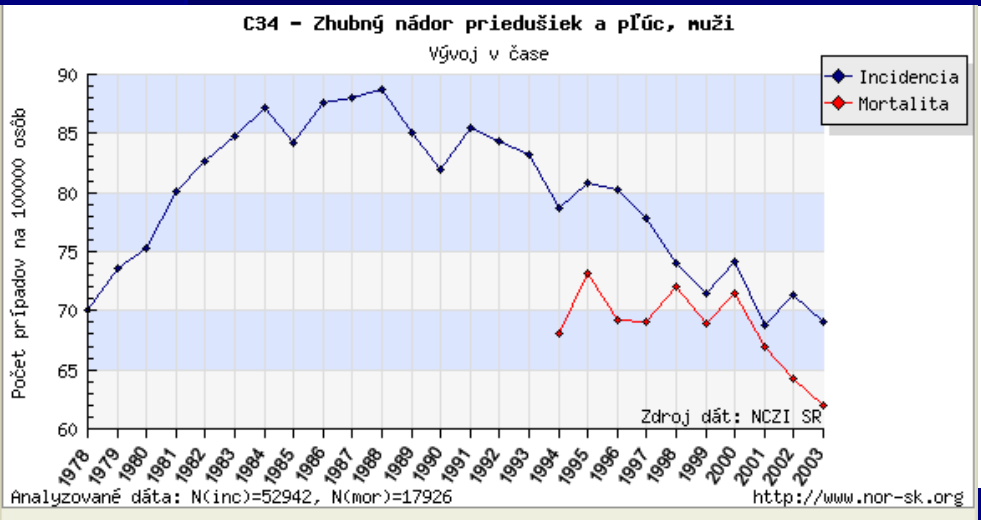
| | |
|---|---|
| **CARCINOID** | |
| typical | low-grade |
| atypical | intermediate-grade |
| **GIANT CELL N.E. CARCINOMA** | high-grade |
| **SMALL CELL CARCINOMA** | high-grade |

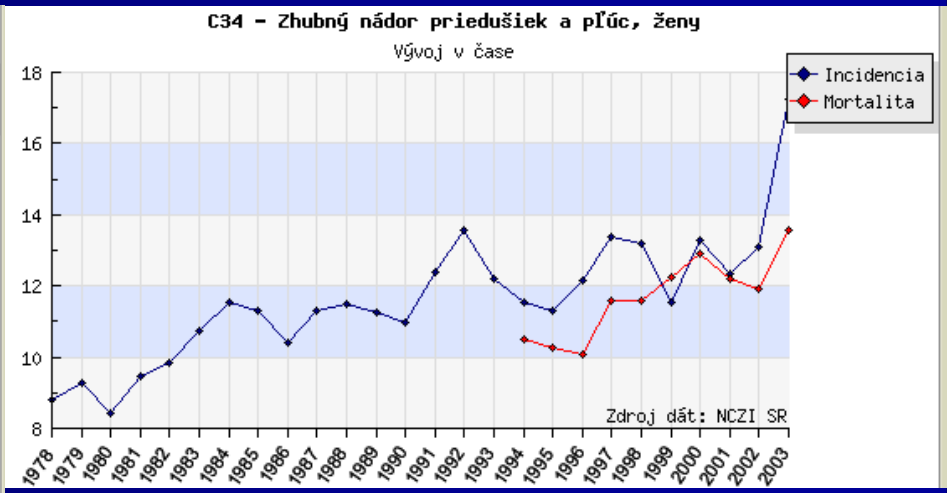



# Neuroendocrine tumours – typical, atypical carcinoid, giant cell neuroendocrine cancer and small cell cancer

# Epidemiology of the lung cancer

- 1st in mortality among malignancies in men, 2nd in women
- Incidence in men – slight decrease (51.1); women – lower in absolute count (10.6), steep increase



# Risk factors for the lung cancer

- Smoking

  Increased risk – heavy smokers 35 x ; ex-smokers 4.5 x ; passive smoking 16 %

- Radon

- Asbestos
- Other environmental exposures

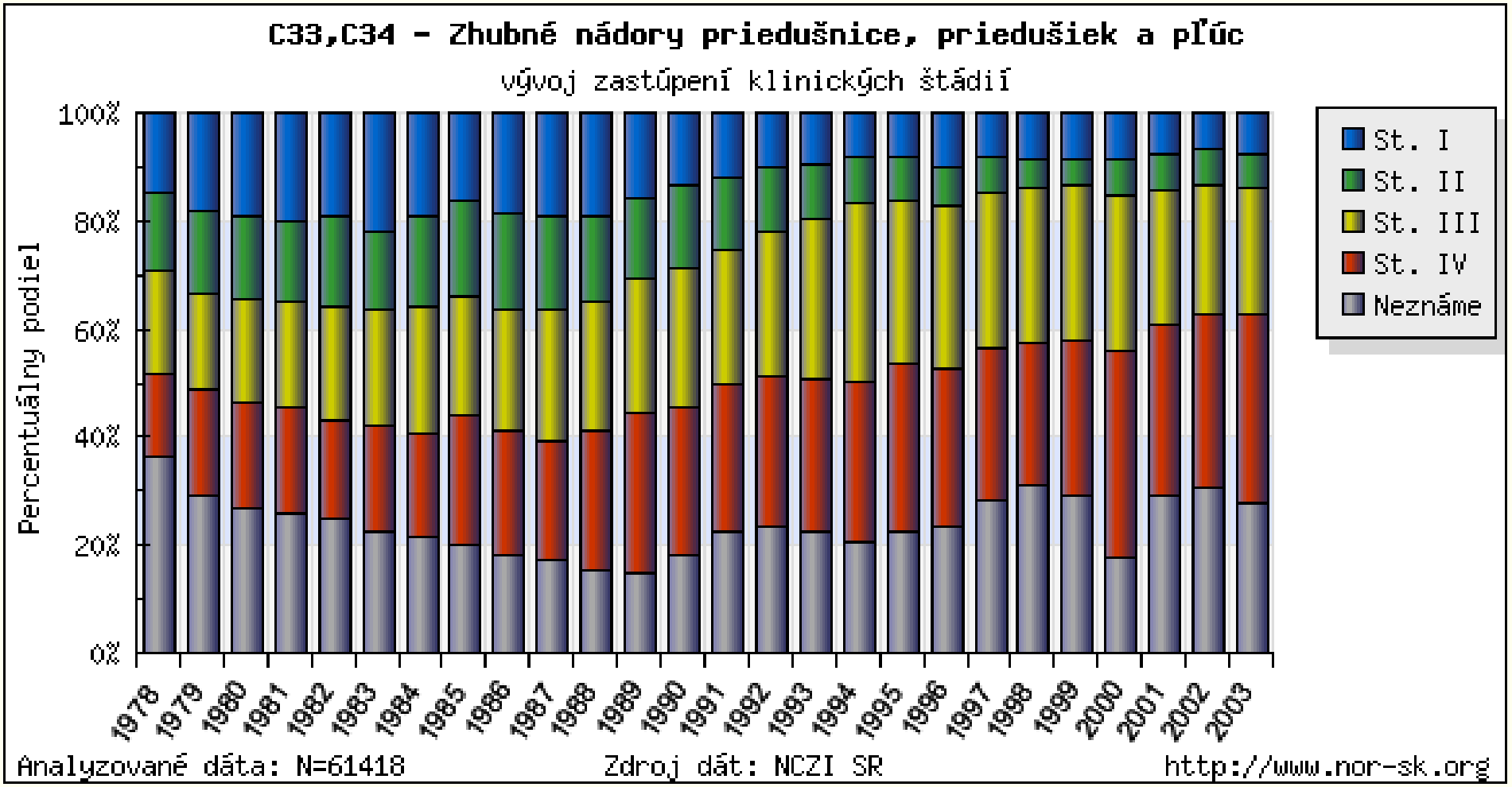
  Radioactivity, organic (PVC, di-chlorine-methylether) and inorganic (As, Ni, Cr) substances

- Genetic predisposition

  First-degree relative, young age occurence

  Genetic variants of detoxication enzymes (CYP450, glutathione transferase) and tumour-suppresor genes (p53).

# Diagnosis by disease stage



# Clinical presentation – I.

- Up to 5% of patients **asymptomatic** – picked up by routine CXR
- **Early symptoms**

  - respiratory: chronic cough, cough worsening / change, haemoptysis

  - general: weight loss, anorexia, fatigue
- **Local (chest) presentations of advanced cancer growth:**

  - pneumonia distal to a (partial) obstruction of the bronchus

  - atelectasis
  - chest pain
  - stridor
  - superior vena cava sy.
  - pleural effusion
  - dysfagia
  - dysphonia (laryngeus recurrens nerve)
  - Pancoast tumour

  - dyspnoea (consider lymphangiopathia carcinomatosa)

# Clinical presentation – II.

- **Extrapulmonary manifestations – paraneoplastic syndromes**

  - endocrine (SIADH, hypercalcemia – PTH-rP, ectopic ACTH production)
  - polymyositis / dermatomyositis
  - myasthenia-like syndrome (Eaton-Lambert) , peripheral neuropathy
  - migratory thrombophlebitis
  - skin rashes (acanthosis nigricans)
  - hypertrophic pulmonary osteoartropathy (finger clubbing, joint swelling)

- **Extrapulmonary manifestations – due to metastases**

  - bone – pain, fractures, brain – headache, hemiplegia, liver – jaundice

    ...

# Investigations

- Chest radiograph – PA and lateral view
- Fiberoptic **bronchoscopy** (cytology / histology sample)
- Cytology – pleural aspiration (if applicable), sputum
- Basic laboratory investigations , onco-markers

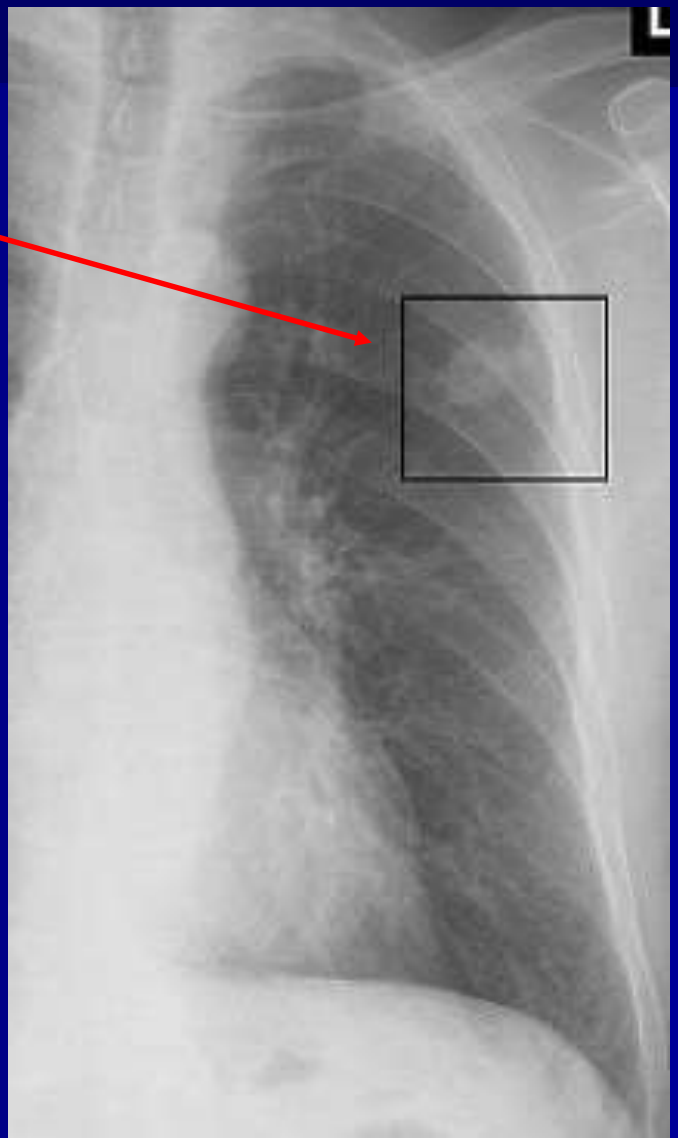
  (CYFRA 21-1, NSE, CEA, CA 72-4, CA 125, TPSA)

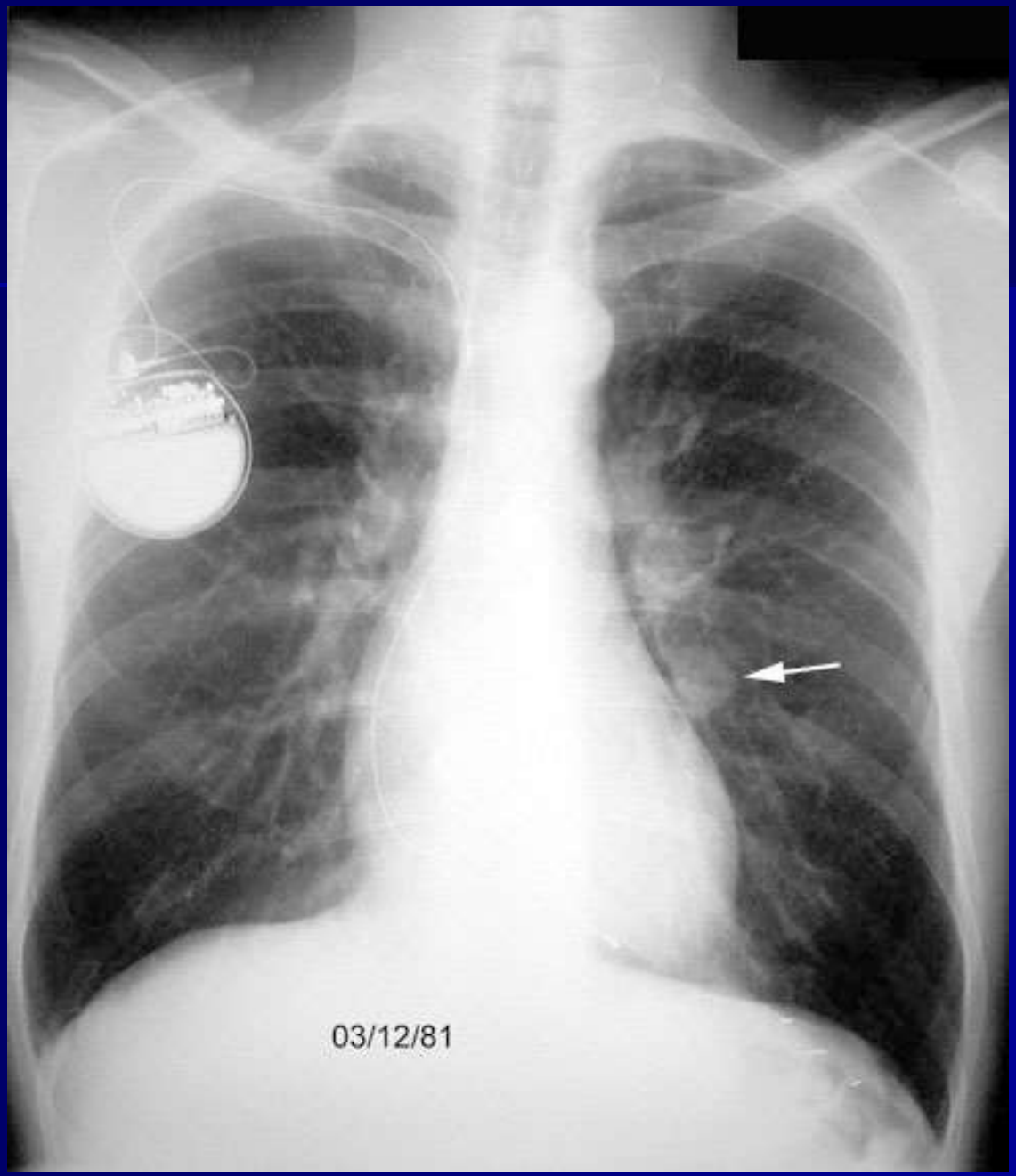
# Investigations – staging, operability

- **CT** scanning - chest (lungs and mediastinum) and upper abdomen (extension to liver and adrenal glands)
- CT – brain (routinely at SCLC; NSCLC in symptom presence), MRI
- Bone scintigraphy scanning
- PET (staging of mediastinal LN), location of metastases
- Ultrasound – chest wall, abdominal
- Pulmonary function testing and arterial blood gases, exercise test
- Invasive (open chest surgery) biopsy and staging
- Percutaneous needle biopsy, cervical lymph node biopsy, mediastinoscopy (respectively, if applicable)

# CXR – posteroanterior and lateral view possible presentations of lung cancer:

- Solitary nodule, "coin lesion"
- Opacity with irregular margin adjacent to the pulmonary hilum
- Cavitating lesions
- Pneumonia (infiltrate distal to a relatively smaller tumour)
- Atelectasis
- Pleural effusion
- Phrenic nerve paralysis (diaphragm elevation)
- Reticulonodular shadows (lymphangiopathia carcinomatosa)

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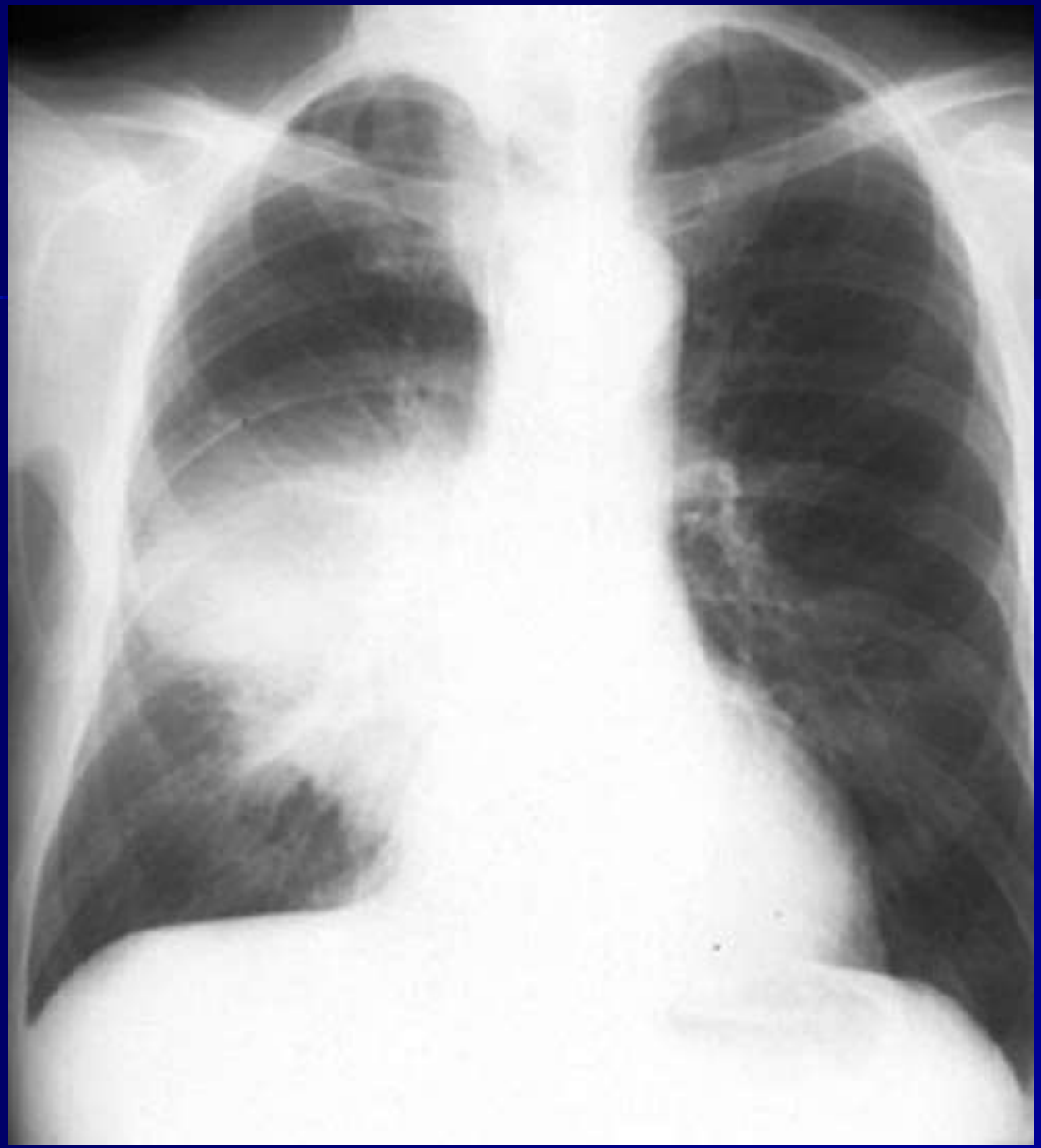


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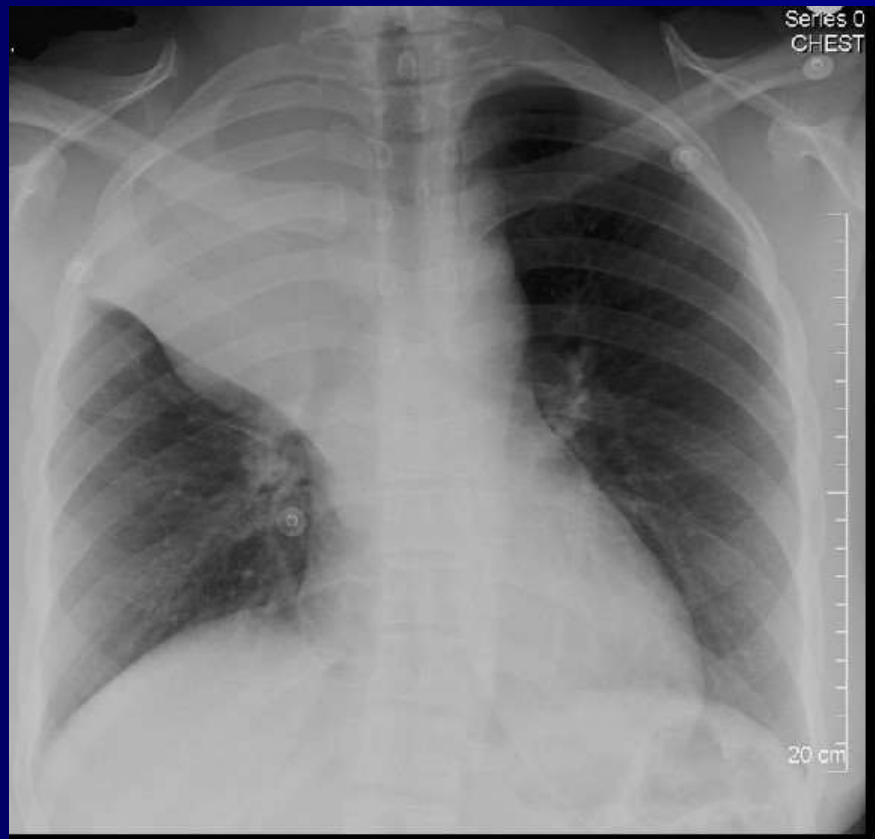



Figure A

Figure B

# Bronchoscopy

**Tumour visualisation and endobronchial staging (extension to- / distance from carina; obturation )**

Cytology sampling (brushing, lavage fluid) and core-cut biopsy

Treatment options (brachytherapy, PDT, plasma-coagulation, electro-cauterisation of bulky endobronchial masses)

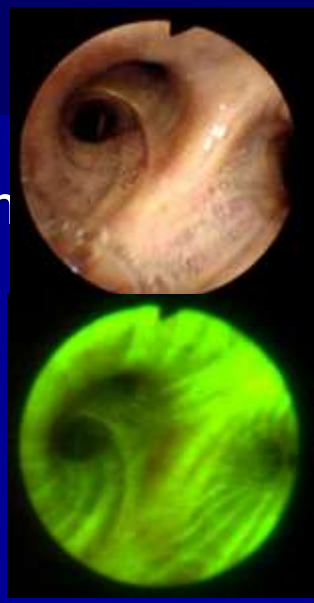
**Basic first-choice investigation in every patient with lung tumour suspection; should precede open surgery**

**- safe, low-risk "invasive" technique**

**N/A** – unstable cardiovascular conditions and arrhytmias, acute kidney or liver failure, cerebral palsy (6 weeks)

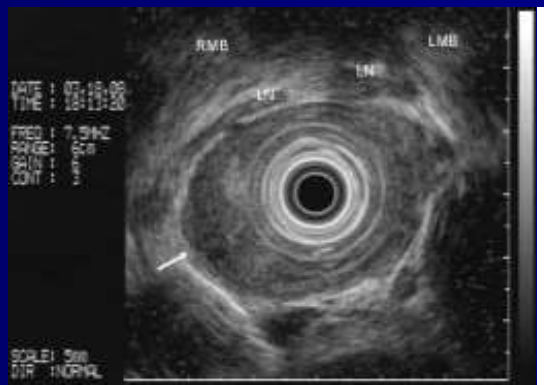
**Consider increased risk** – allergy to local anesthetics, lack of cooperation (consider complete anesthesia), risk of bleeding

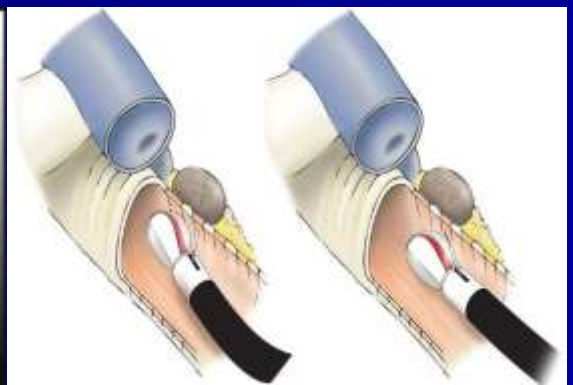
# New bronchoscopy techniques



**autofluorescent bronchoscopy** – borders of tumour invasion
Ca in situ / dysplasia – increased sensitivity

**EBUS + TBNA** (endobronchial ultrasound + transbronchial needle aspiration) – **staging** of the disease, regional LN involvement, visualisation of a parenchymal mass and transbronchial puncture, depth of infiltration of the bronchial wall



# Thoracic CT scanning

- low specificity (60%), good sensitivity 80 – 95%

High **reliability** in chest wall invasion detection

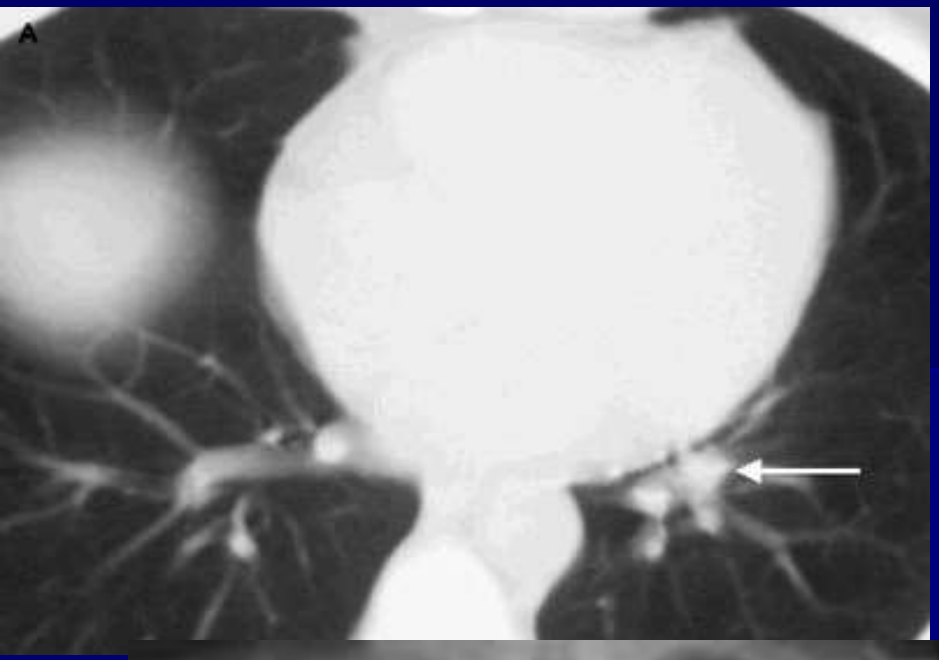
Poor **reliability** in mediastinal pleura invasion detection (usually confirmed during open thoracic surgery)

**LN involvement** 59 - 99% reliability (CT versus peroperative findings), based on LN size cut-offs.

E.g. LN diameter less than 10mm – low (5 to 10%) mts likelihood

**High-resolution CT scanning – carcinomatous lymfangiopathy**

**Virtual bronchoscopy** – poststenotic tumour growth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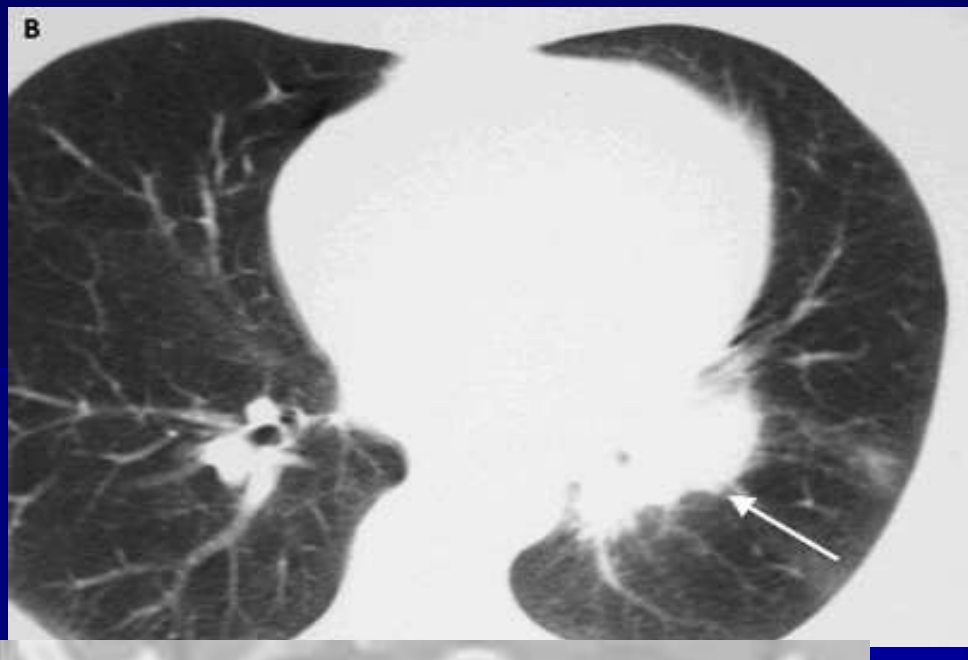
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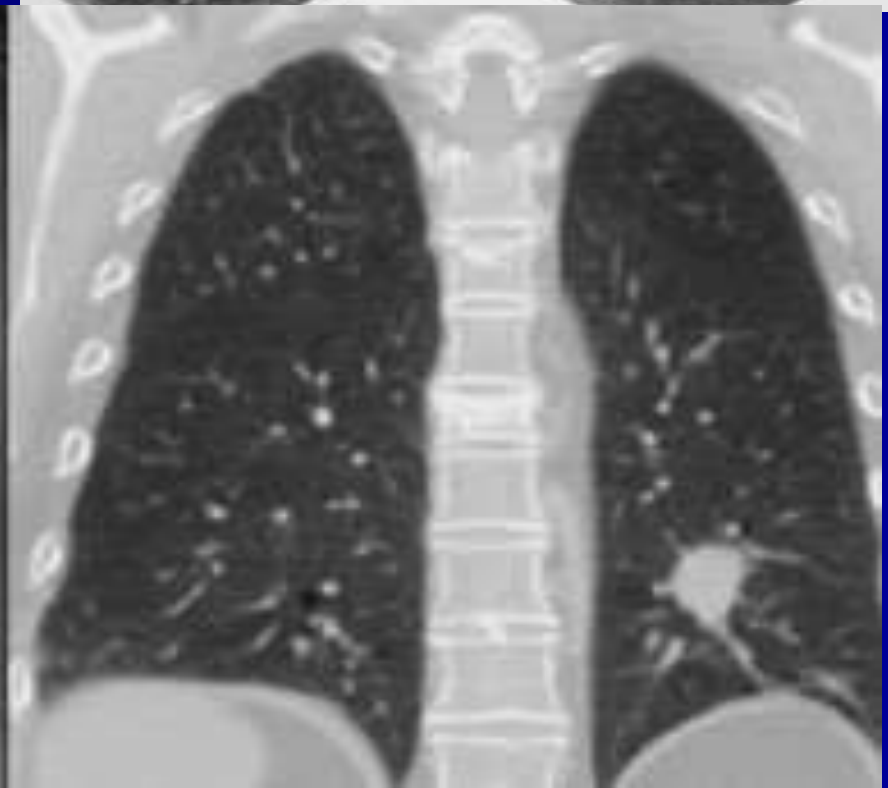
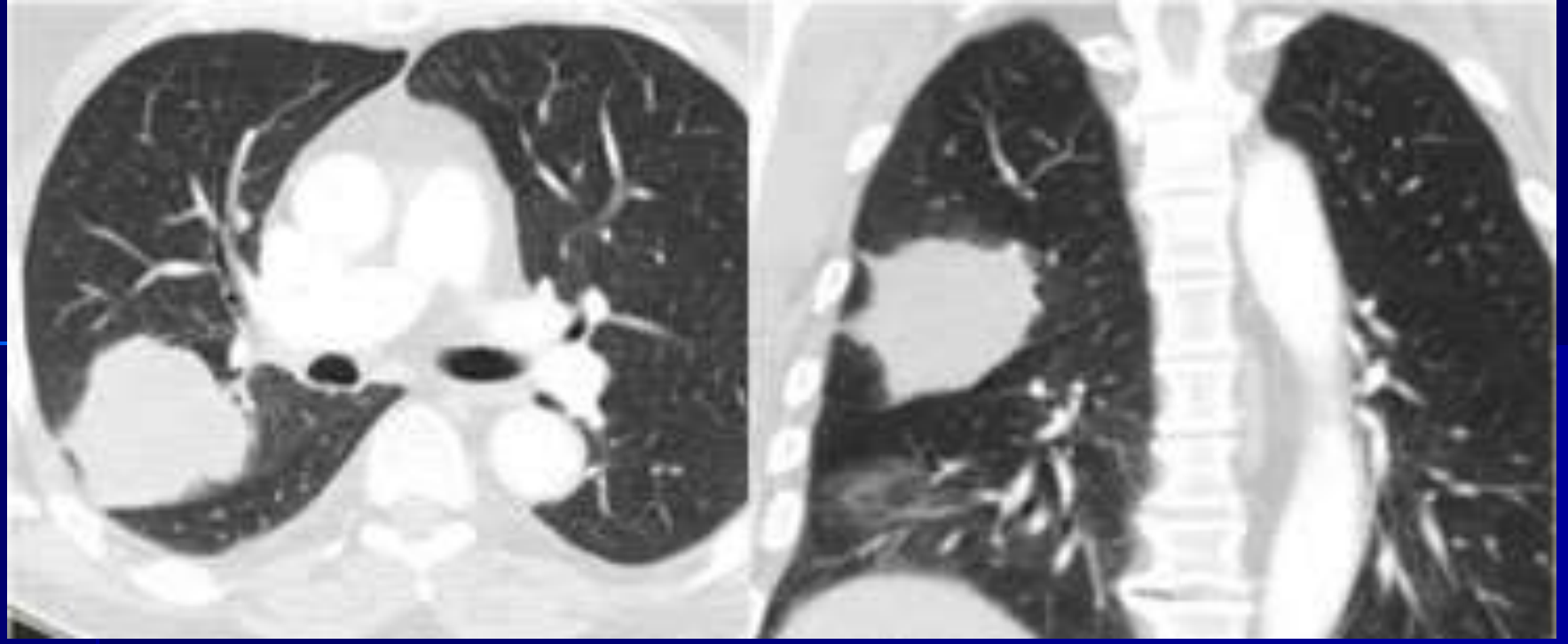
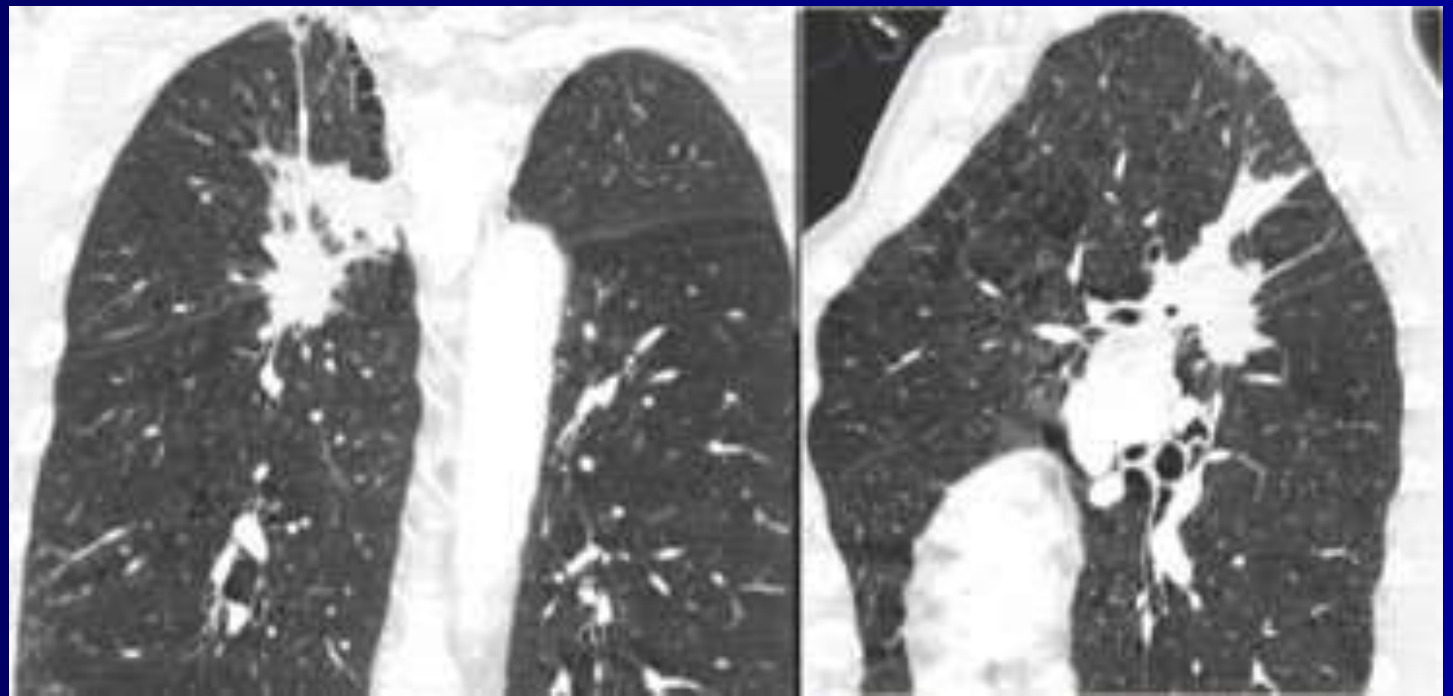
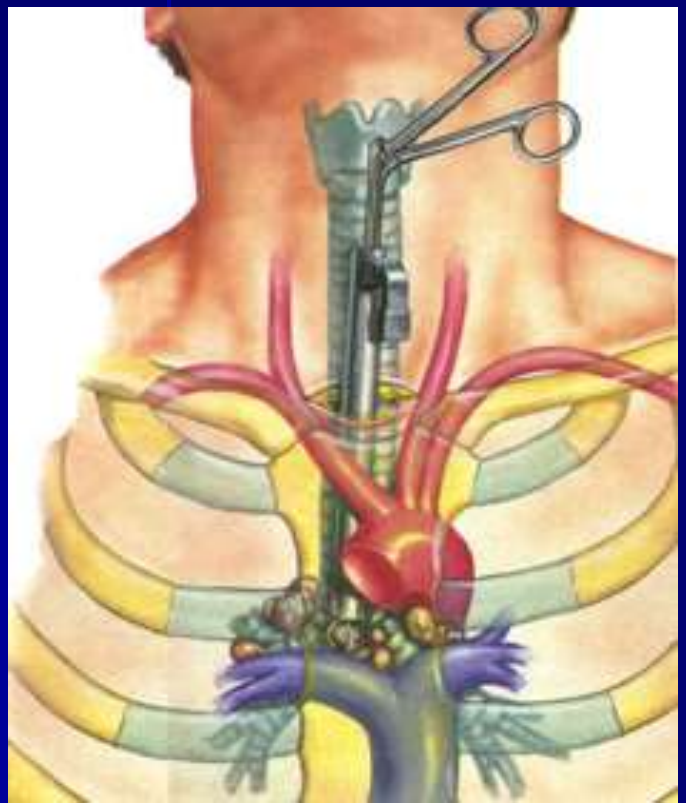




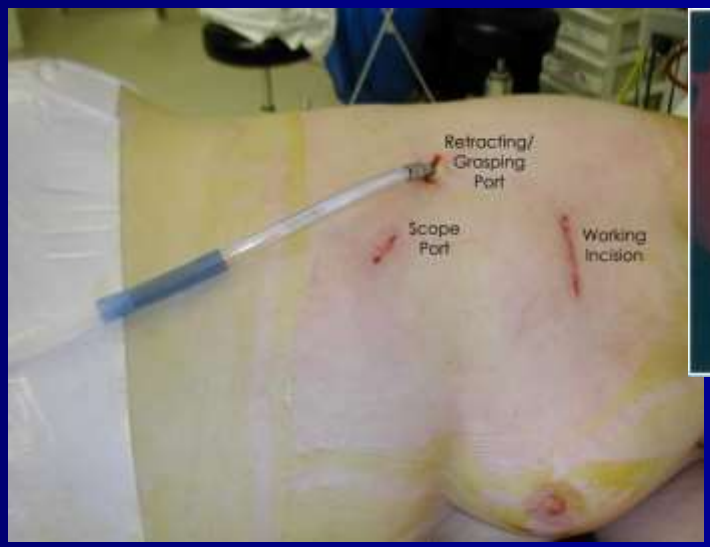


# Mediastinoscopy

- suprasternal approach
- mediastinal LN biopsy and staging;  in some cases thoracotomy may be avoided



# Thoracoscopy / VATS




# TNM classification and staging

- 8th revision TNM (*TNM in Lung Cancer* of the International Association for the Study of Lung Cancer (IASLC) Staging Committee in 2018)
- **applicable for NSCLC** (non-small cell lung cancer)

  **SCLC - staging only LD, ED** (limited/extensive disease)
- each NSCLC disease stage determines the treatment and prognosis
- aim of the TNM staging – to make a decision on the best suitable treatment option
- basic question – surgical curability (resecability) and the extent needed (limited resection, lobectomy, bi-lobectomy, pneumonectomy)

# T staging

| TNM 8th - Primary tumor characteristics | |
|---|---|
| $T_x$ | Tumor in sputum/bronchial washings but not be assessed in imaging or bronchoscopy |
| $T_0$ | No evidence of tumor |
| $T_{is}$ | Carcinoma in situ |
| **$T_1$** | ≤ 3 cm surrounded by lung/visceral pleura, not involving main bronchus |
| $T_{1a(mi)}$ | Minimally invasive carcinoma |
| $T_{1a}$ | ≤ 1 cm |
| $T_{1b}$ | > 1 to ≤ 2 cm |
| $T_{1c}$ | > 2 to ≤ 3 cm |
| **$T_2$** | > 3 to ≤ 5 cm *or* involvement of main bronchus without carina, regardless of distance from carina or invasion visceral pleural *or* atelectasis or post obstructive pneumonitis extending to hilum |
| $T_{2a}$ | >3 to ≤4cm |
| $T_{2b}$ | >4 to ≤5cm |
| **$T_3$** | >5 to ≤7cm in greatest dimension *or* tumor of any size that involves chest wall, pericardium, phrenic nerve *or* satellite nodules in the same lobe |
| **$T_4$** | > 7cm in greatest dimension *or* any tumor with invasion of mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, spine *or* separate tumor in different lobe of ipsilateral lung |
| **$N_1$** | Ipsilateral peribronchial and/or hilar nodes and intrapulmonary nodes |
| **2** | Ipsilateral mediastinal and/or subcarinal nodes |
| **3** | Contralateral mediastinal or hilar; ipsilateral/contralateral scalene/ supraclavicular |
| **$M_1$** | Distant metastasis |
| $M_{1a}$ | Tumor in contralateral lung or pleural/pericardial nodule/malignant effusion |
| $M_{1b}$ | Single extrathoracic metastasis, including single non-regional lymphnode |
| $M_{1c}$ | Multiple extrathoracic metastases in one or more organs |

| | TNM 7th EDITION | TNM 8th EDITION |
|---|---|---|
| T | - | Tis |
| | - | Tmi |
| | - | Tss |
| | T1a (≤2 cm) → | T1a (≤1 cm) |
| | T1b (>2 -3 cm) | T1b (>1-2cm) |
| | | T1c (>2-3cm) |
| | T2a (>3-5 cm) → | T2a (>3cm but ≤4cm) |
| | T2b (>5-7 cm) | T2b (>4cm but ≤5cm) |
| | T3 (>7 cm) → | T4 |
| | T3 - atelectasis/pneumonitis involving whole lung) | T2 atelectasis/pneumonitis irrespective of involving lobe or whole lung |
| | T3 tumor involving the main bronchus <2cm distance to carina → | T2 -tumor involving the main bronchus irrespective of distance to carina |
| | T3 -invasion of the diaphragm → | T4 (invasion of the diaphragm) |
| N | No changes | |
| M | M1b - distant metastasis → | M1b - single extrathoracic metastasis |
| | | M1c - multiple extrathoracic metastases |

# T - Staging – summary

- Thoracic CT scanning is required to perform the correct T staging
- **CT** – superior in local extent and finding satellite nodules
- CT – not sufficient in N- staging and mediastinal invasion

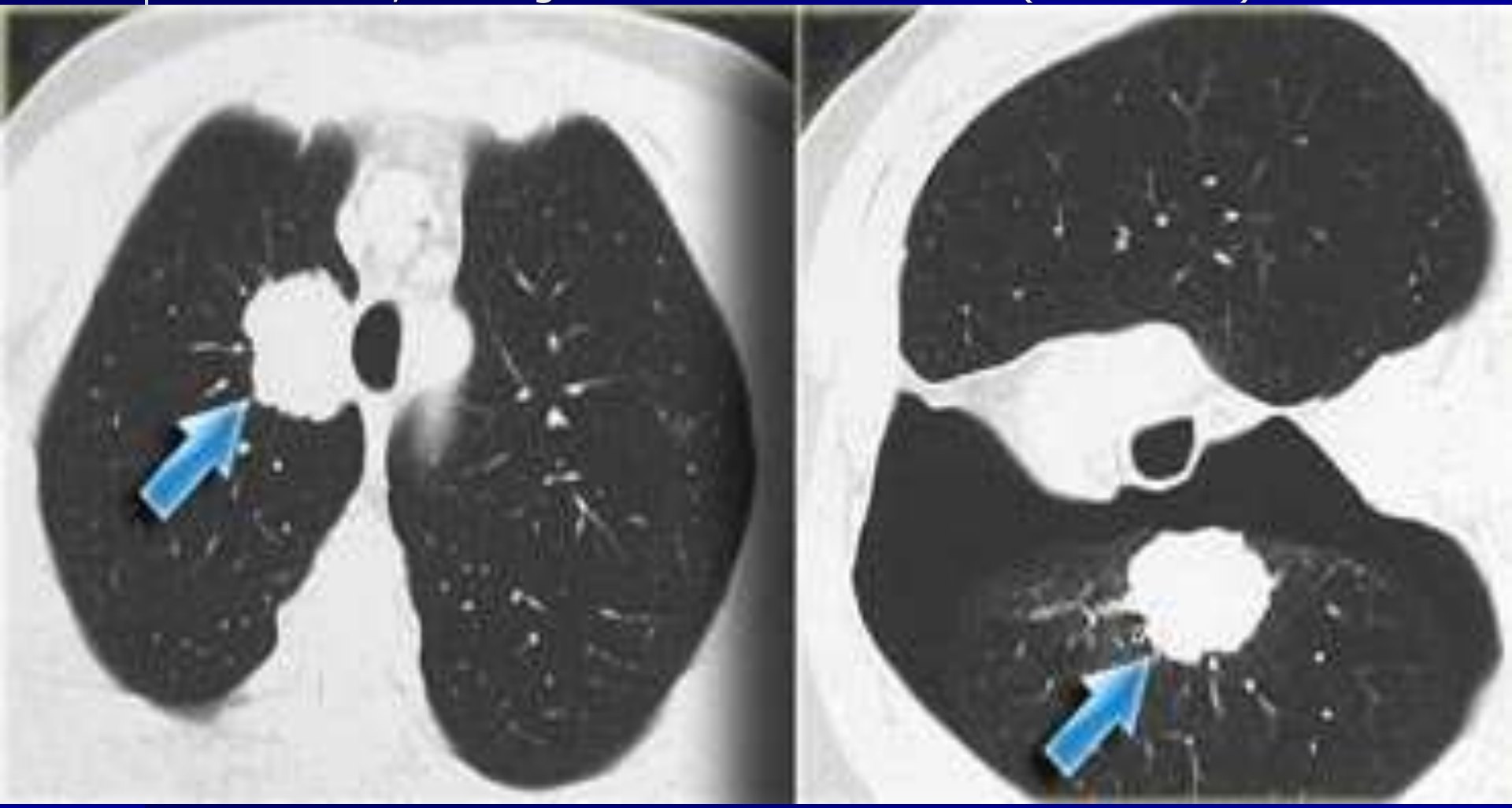
**MR** – superior to CT in case of
- mediastinal involvement
-neural structures involvement (Pancoast tumour, vertebral invasion)

**PET** limited role in T-staging; crucial in N- and M-staging

# T staging – a case study

CT scans showing T4 stage TU mass in upper right lobe, in tight proximity to paratracheal space, with suspected mediastinal invasion. FNA procedure complicated with pneumothorax: TU mass freely movable with the collapsed lung, completely separated from mediastinum and trachea.

As a result, T4 stage had to be corrected to (a favorable) T2



# N - staging

N1

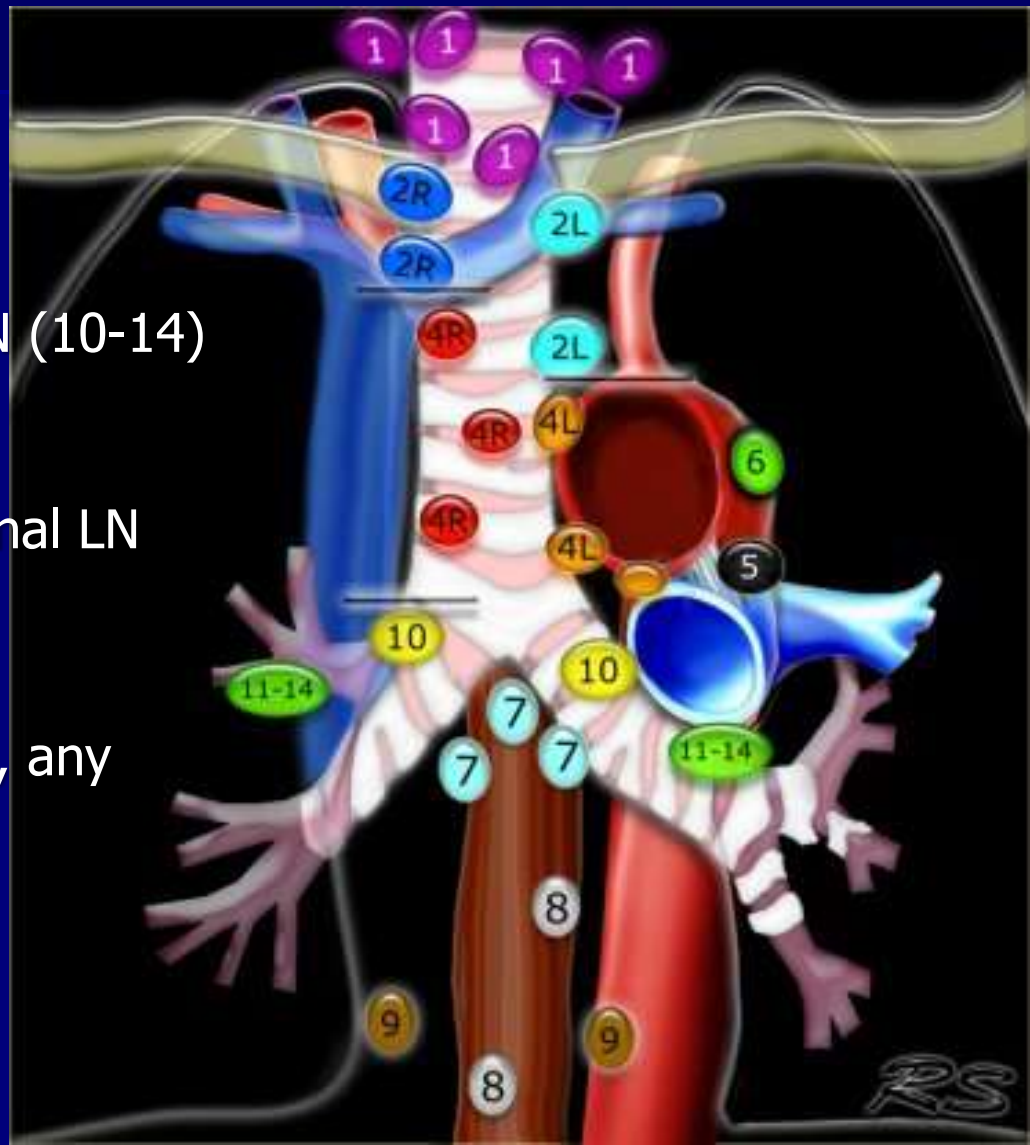
ipsilateral intrapulmonary to hilum LN (10-14)

N2

ipsilateral mediastinal and/or subcarinal LN

N3

contralateral hilum or mediastinal LN, any cervical or supraclavicular LN

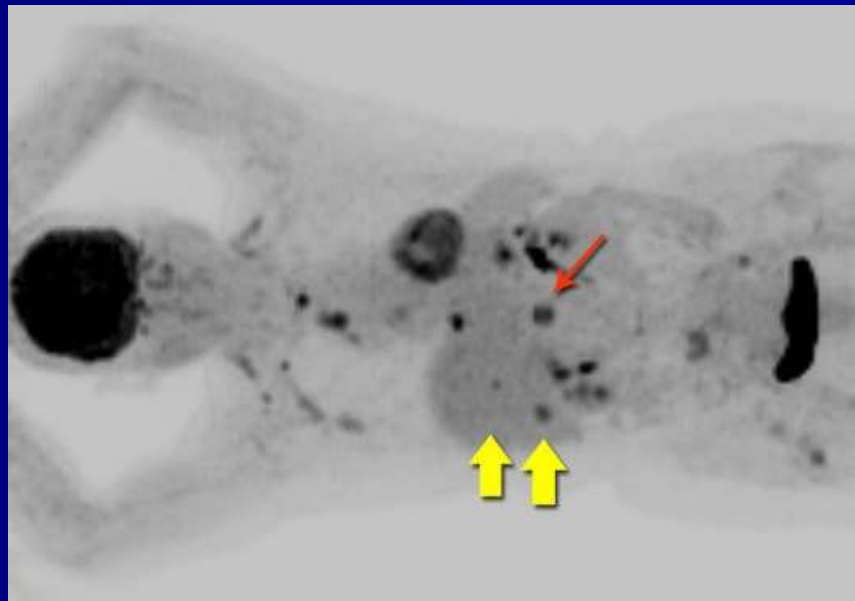


# M - staging

**M1**: distant metastases present

- **M1a** separate nodules in the contralateral lung, or pleural nodules / malignant pleural or pericardial effusion

- **M1b** any other site



# Staging – summary

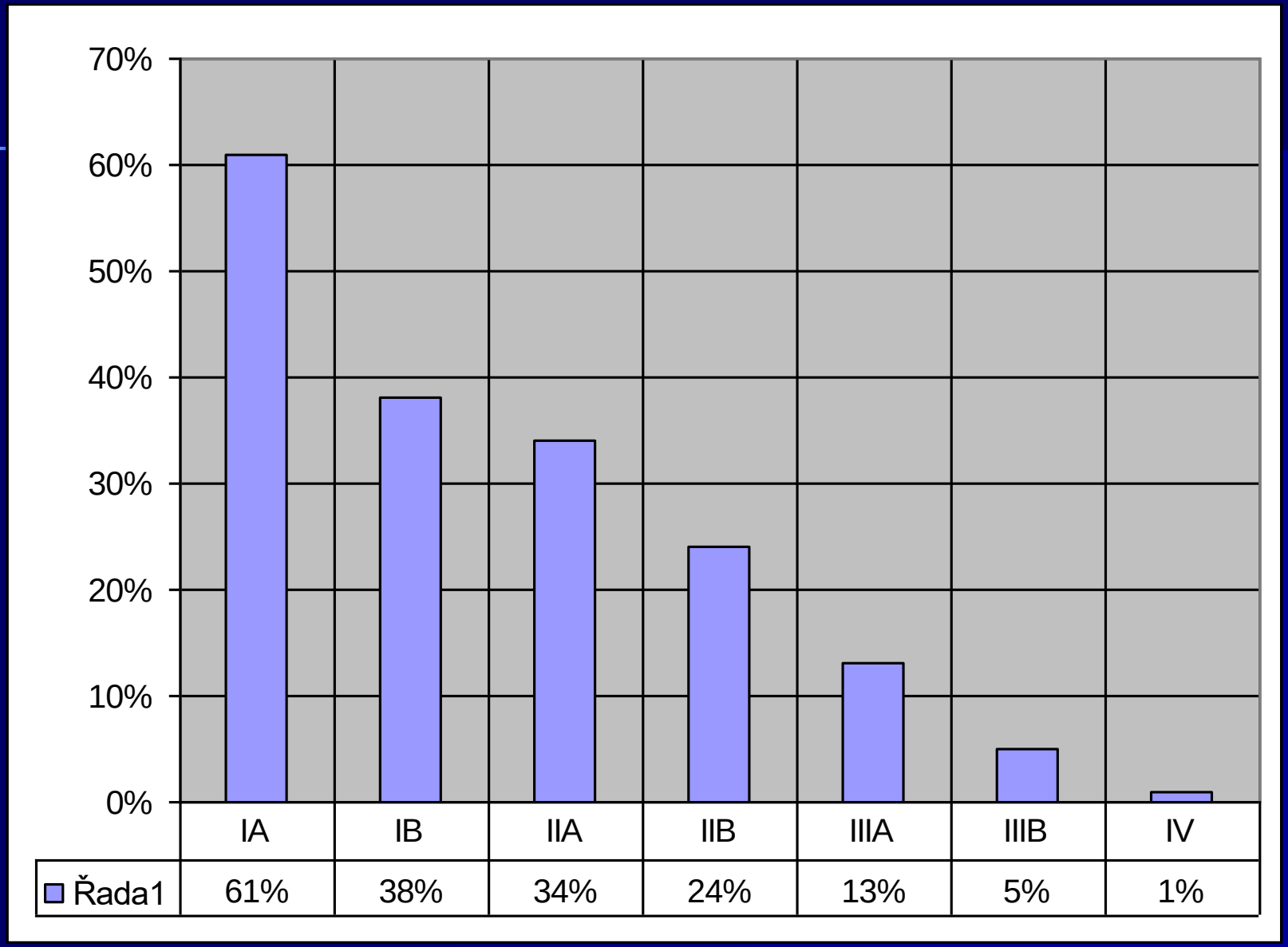
In NSCLC, stages IA to IIIA (green) are curable by surgery

| | T1a | T1b | T2a | T2b | T3 | T4 |
|---|---|---|---|---|---|---|
| N0 | IA | | IB | IIA | IIB | IIIA |
| N1 | IIA | | IIA | IIB | IIIA | IIIA |
| N2 | IIIA | | IIIA | | IIIA | IIIB |
| N3 | IIIB | | IIIB | | IIIB | IIIB |

M zero

M 1a/ M 1b - any T / N – stage **IV**

# 5-year survival by stage (NSCLC)



# Treatment - NSCLC

Based on the TNM staging and classification

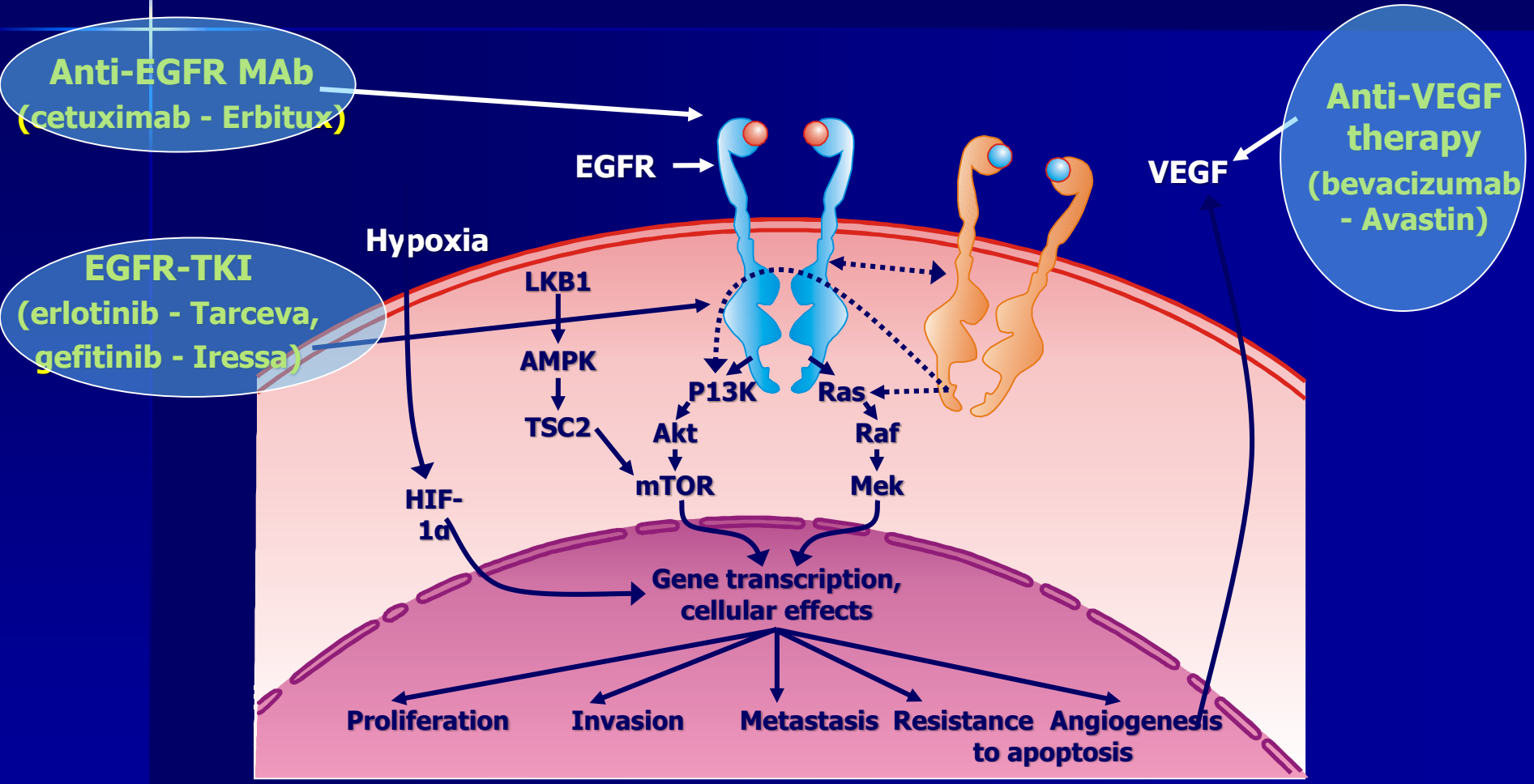
**IA** – surgery, no other treatment required. Radiation therapy (RT) in case of no surgery, consider local treatment options.

**IB-IIIA** – surgery followed by adjuvant chemotherapy (CHT), RT. In case of no surgery - CHT, RT.

**IIIB** – systemic CHT, RT (reduction in the tumour size, improvement in QoL, improvement in survival). In selected patients down-staging achievable – surgery can be performed thereafter.

**IV** – palliative CHT, RT (symptom relieve).

# Molecular – targeted – treatment of the NSCLC




Herbst, et al. NEJM 2008

# Treatment - SCLC

- In Limited Disease - RT (chest involvement only) 45-50 Gy + CHT (concommitant or sequential).

  - 1-st line CHT (platinum-based, combined)

  - 2-nd line – late relapse (after 3 mo) – 1-st line drugs will be effective again;  early relapse (less than 3 mo) – change drug !

- In Extensive Disease - CHT with palliative intention, RT to alleviate metastases-related symptoms (bone, brain).

- Preventive brain RT is recommended in SCLC both LD and ED (no impact on survival, improves QoL).

# Palliative options for SCLC and NSCLC

- **Superior vena cava syndrome**

  antiedematous treatment – high-dose dexamethason (24-40 mg/d), diuretics.

- **Malignant pleural effusion**

  drainage followed by pleurodesis (talcum)

- **Bulky endobronchial mass - obturation**

  – laser, electrocauterisation, cryotherapy, brachytherapy, PDT, stenting

Thank you for your attention