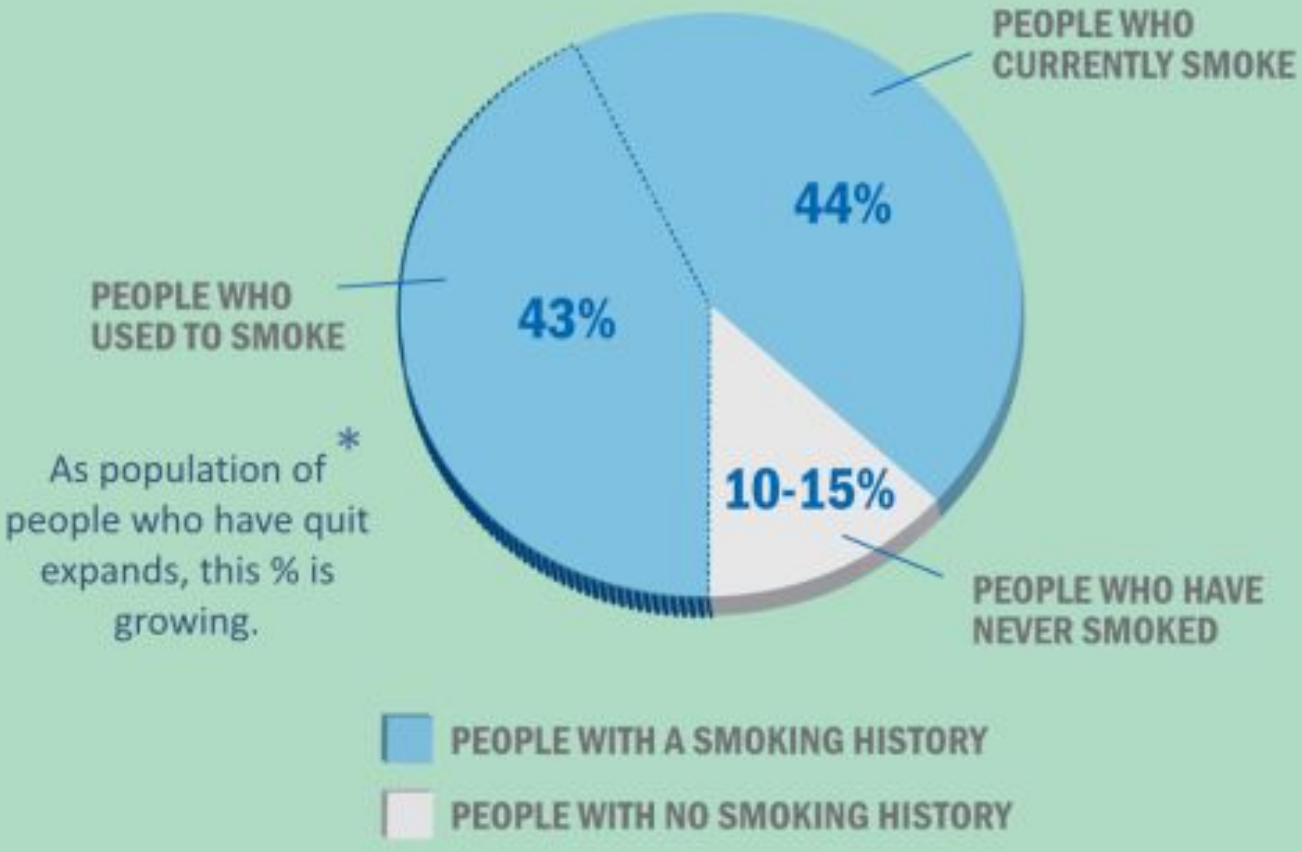
Lung Cancer: Risk

Lung cancer can affect anyone



American Cancer Society. Cancer Facts & Figures 2012; Thun, MJ, et al. PLOS Medicine, 2008. Tong, L, et al. Cancer, 1996; Burns DM. Cancer, 2000. 89:2506–2509.

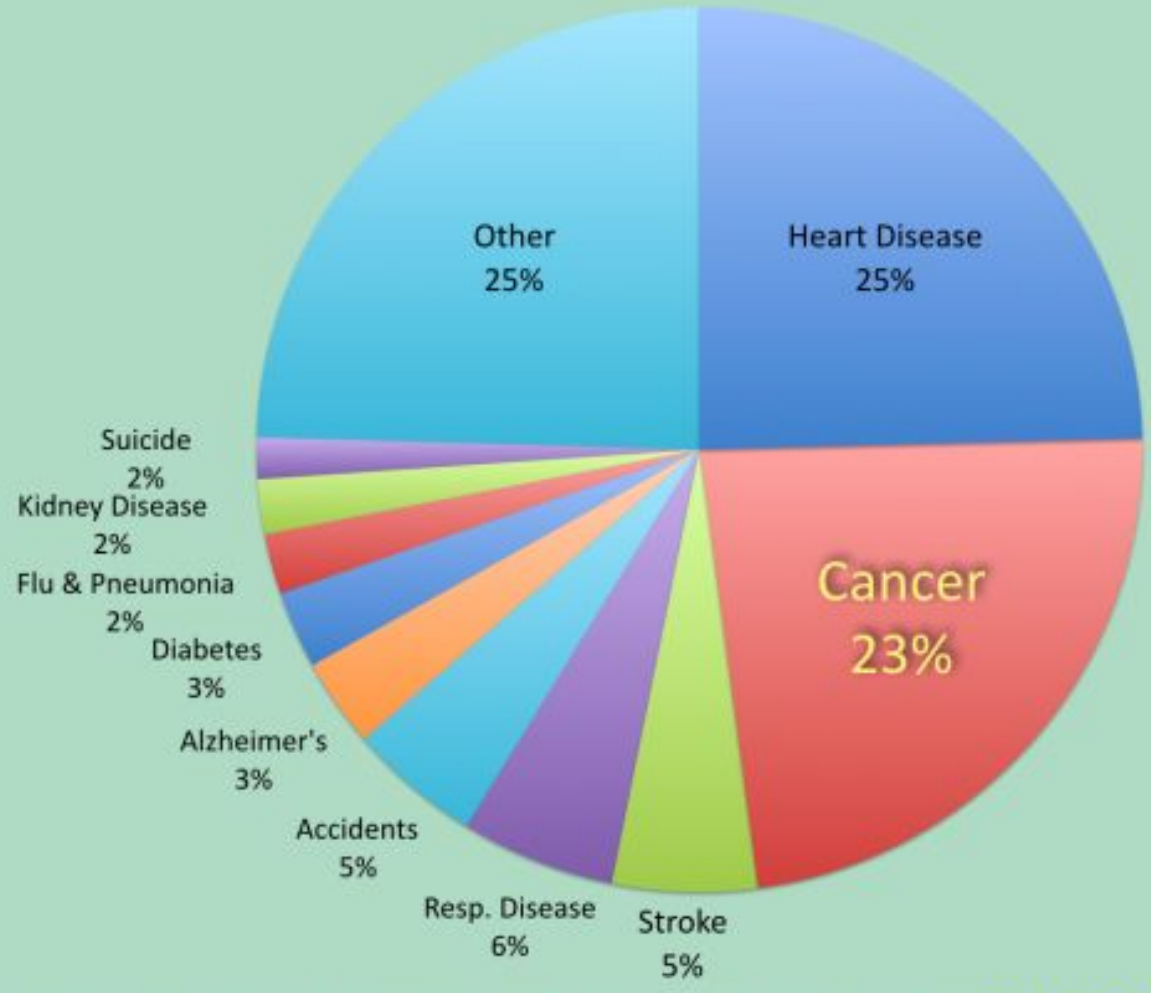
Lung Cancer Can Affect Anyone

Age @ diagnosis

	20-34	35-44	45-54	55-64	65-74	75-84	85+
Female	0.3%	1.9%	8.8%	19.9%	30.6%	29.5%	9.0%
Male	0.2%	1.5%	8.8%	21.8%	31.9%	28.7%	7.1%

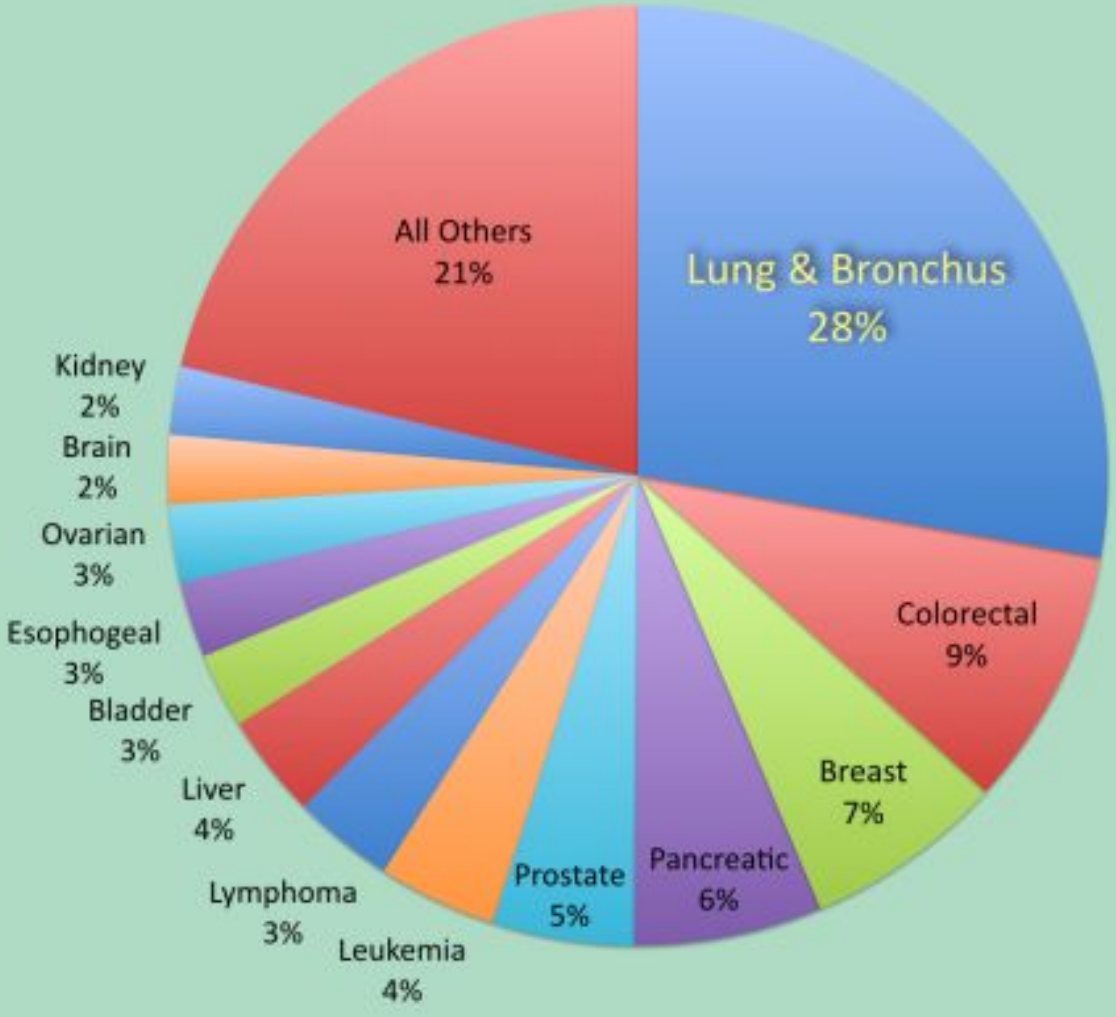
SEER Cancer Statistics Review 1975-2007

Leading Causes of Death in the US



Centers for Disease Control & Prevention, Leading Causes of Death, Final Data for 2009; www.cdc.gov/nchs/fastats/lcod.htm

Leading Causes of Cancer Death in the US



American Cancer Society. Cancer Facts & Figures 2012.

Risk Factors

- **Smoking**
- **Genetic predisposition**
  - Genetic trait : Li Fraumeni syndrome (P_{53} mutation)
  - Gene polymorphisms:
    - DNA repair genes : XRCC1
    - COX 2
    - Interleukin 6
- **Occupational & Environmental exposure**
  - Asbestos exposure: Occupational or residential (**silicate type fibers**)
  - Foundry workers and welders: Ni, Co, Cd
  - Uranium mine workers: Inhaled Radon
  - Air pollution:
    - Diesel exhaust
    - Metal fumes
    - Air sulfate and PAH content
- **Dietary influence**
  - Folate & B_{12} deficiency
  - Inadequate antioxidant consumption

- Smoking & histological changes
- ↓ Ciliary cells
- Epithelial cells hyperplasia
- Metaplasia to squamous cell
- Atypical hyperplasia

Anatomic classification

- Central bronchial carcinoma: segmental or larger bronchi, account for ¾ cases, consist of squamous and small cell lung cancer
- Peripheral: small bronchi or bronchioles, account for ¼ cases , adenocarcinoma is the main histological type

Histological classification (WHO)

1980

Squamous cell
- well, medium or badly differentiated

Small undifferentiated cell
- lymphocyte-like (avenine cell)
- intermediate cell (fusiform cell, polyhedral cell, etc)

Adenocarcinoma
- well, medium or badly differentiated, bronchoalveolar/papillary

Large cell
- accompanied with mucus differentiation
- accompanied with multilamellar structure
- cytomegalic, megalocyte
- hyalocyte

T – Primary Tumour		
Tx		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1		Tumour 3 cm or less in greatest diameter surrounded by lung or visceral pleura, without evidence of main bronchus
	T1a(mi)	Mininally invasive adenocarcinoma
	T1a	Tumour 1 cm or less in greatest diameter
	T1b	Tumour more than 1 cm but not more than 2 cm
	T1c	Tumour more than 2 cm but not more than 3 cm
T2		Tumour more than 3 cm but not more than 5 cm; or tumour with any of the following features: Involves main bronchus (without involving the carina), invades visceral pleura, associated with atelectasis or obstructive pneumonitis that extends to the hilar region
	T2a	Tumour more than 3 cm but not more than 4 cm
	T2b	Tumour more than 4 cm but not more than 5 cm
T3		Tumour more than 5 cm but not more than 7 cm or one tha directly invades any of the following: chest wall, phrenic nerve, parietal pericardium, or associated separate tumour nodule(s) in the same lobe as the primary
T4		Tumours more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary

International Association for the Study of Lung Cancer, 2015

N – Regional Lymph Nodes		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
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)

M – Distant Metastasis		
M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleaural or pericardial nodules or malignant pleural or pericardial effusion
	M1b	Single extrathoracic metastasis in a single organ
	M1c	Multiple extrathoracic metastases in one or several organs

International Association for the Study of Lung Cancer, 2015

Lung Cancer Stage Classification (8th Edition)

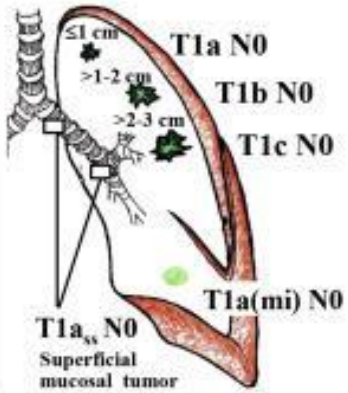
General Note:
All Stage 1-III tumors are M0

Tx, Nx should be used only if no information at all is available about T or N stage (including no clinical staging information).

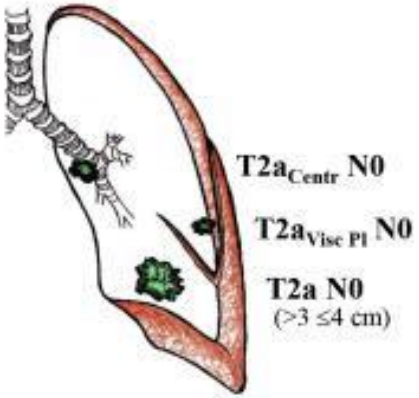
Mx is not allowed, because symptoms and physical exam information is always available.

Stage 0

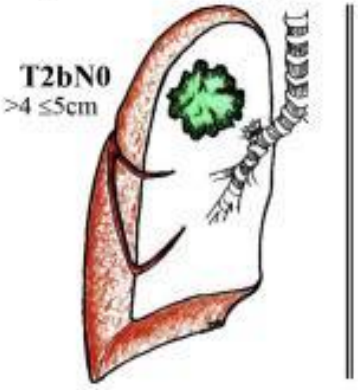
Stage IA

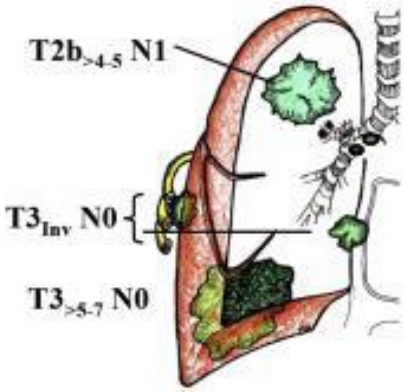


Stage IB

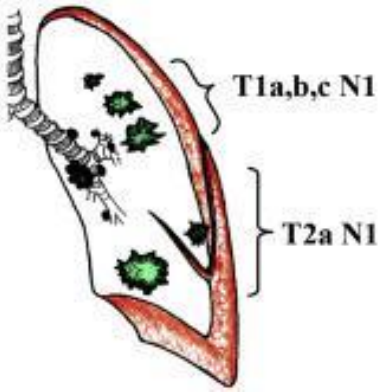


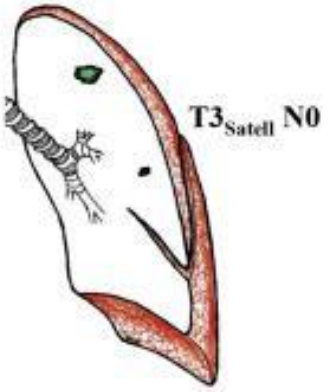
Stage IIA



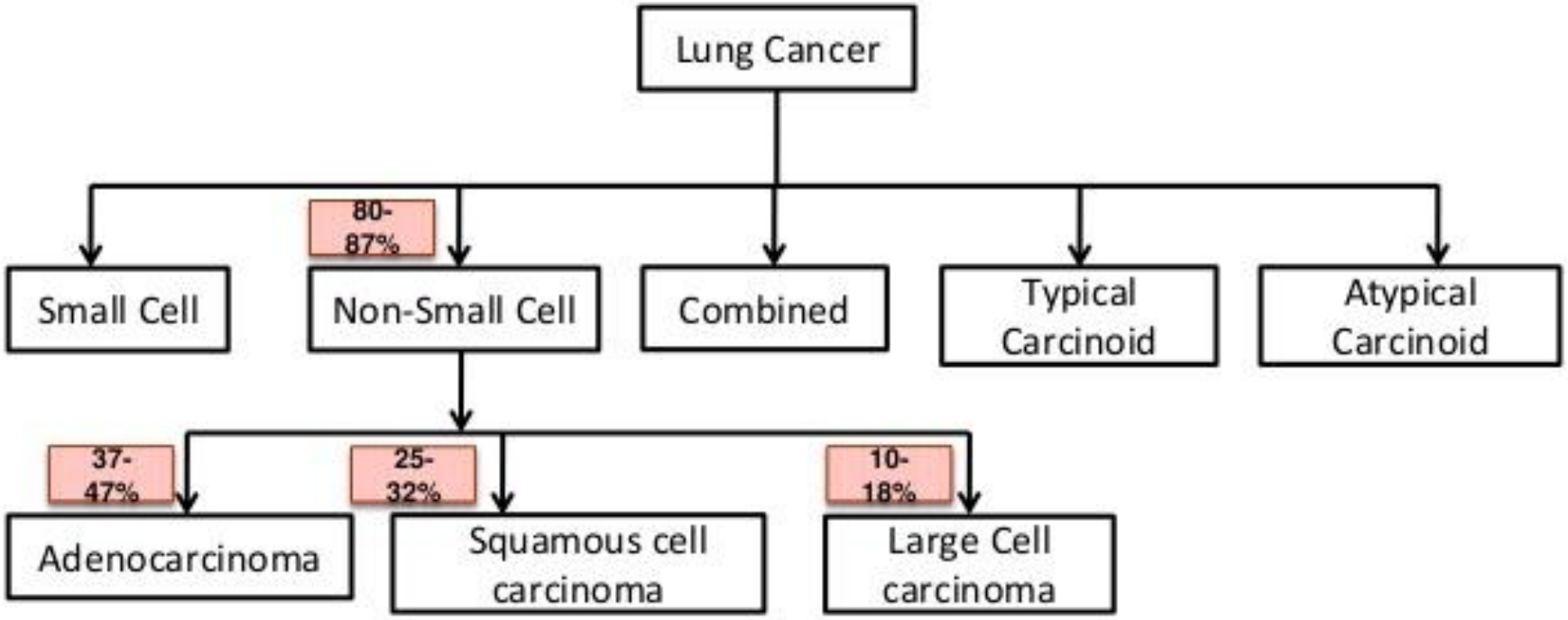


Stage IIB





Classification
(*Histologically*)



DiPiro J. Lung Cancer. In: Pharmacotherapy: A Pathophysiological Approach, 2014

Non-Small Cell Lung Cancer (NSCLC)

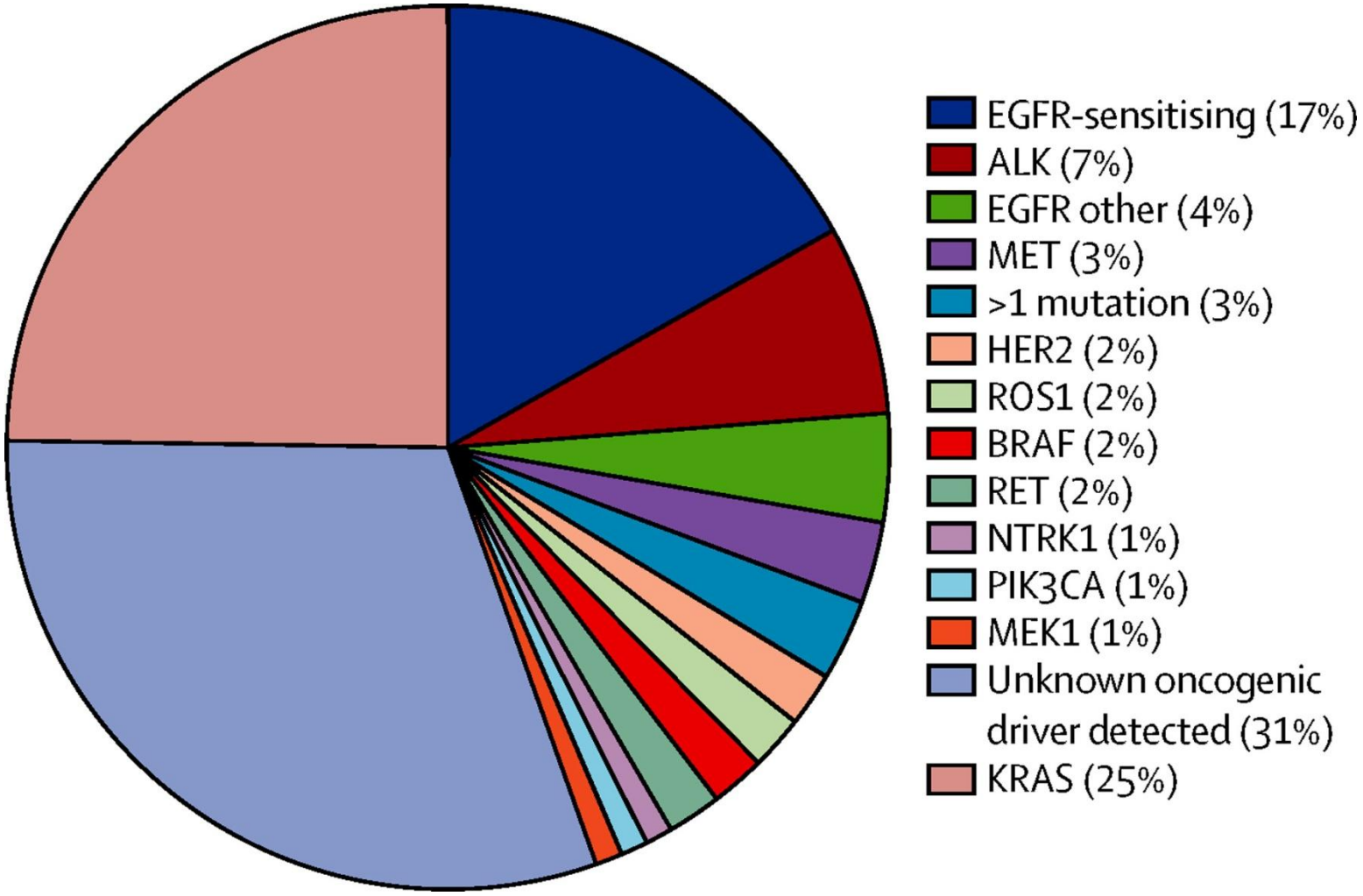
NSCLC constitutes 85% to 90% of all lung cancers

- NSCLC divided into:
  - Squamous (epidermoid carcinoma): ~25% of all NSCLC
  - Non-Squamous: ~75% of all NSCLC
    - Adenocarcinoma: cancer that originates from the mucus secreting cells, most common form
    - Large cell (undifferentiated) carcinoma: heterogenous epithelial neoplasms
    - Other types: occur less frequently

2015 Lung Cancer Statistics (United States)	
NSCLC and SCLC (Small Cell Lung Cancer)	
Estimated New Cases	Estimated Deaths
221,200	158,040

(*sources: Seer Cancer Statistics, http://seer.cancer.gov/statfacts/html/lungb.html; American Cancer Society, http://www.cancer.org/cancer/lungcancer-non-smallcell/)*

NSLC


EGFR-sensitising (17%)
ALK (7%)
EGFR other (4%)
MET (3%)
>1 mutation (3%)
HER2 (2%)
ROS1 (2%)
BRAF (2%)
RET (2%)
NTRK1 (1%)
PIK3CA (1%)
MEK1 (1%)
Unknown oncogenic driver detected (31%)
KRAS (25%)

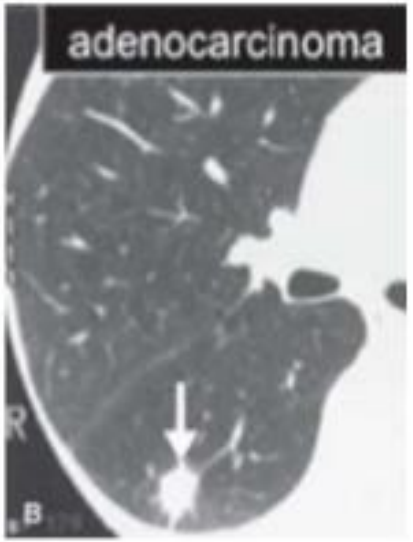
- Squamous cell carcinomas

- Identical to extrapulmonary (i.e., head and neck) squamous cell carcinomas .
- Occur centrally .
- Classically associated with a history of smoking.
- Pattern is that of an infiltrating nest of tumor cells with central necrosis , resulting in cavitation.

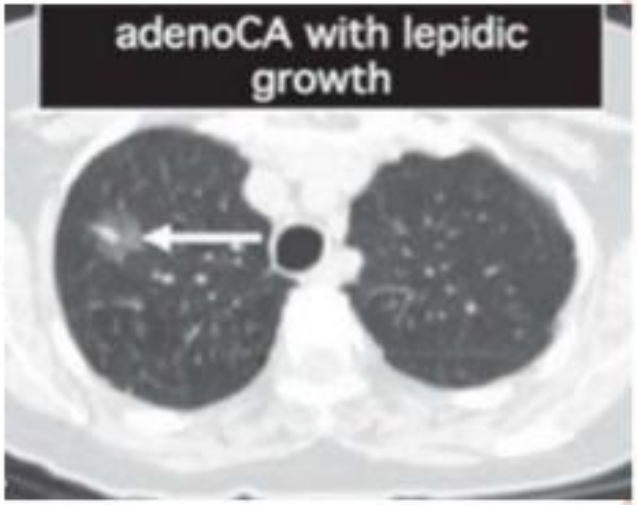
:Abeloff's Clinical Oncology, 4th ed

- ADENOCARCINOMA ~ 30-40% ; most common subtype

- composed of malignant glandular epithelium, varying in degree of differentiation.
- Most common cell type in non-smokers.
- smaller than other bronchogenic carcinomas.
- located in lung periphery
- Radiologic feature – peripheral nodule / peripheral mass
- 5 yr survival = 17%



- ***BRONCHOALVEOLAR CARCINOMA*** : is a type of adenocarcinoma ; m/c in women and non-smokers
- arises from epithelium of terminal bronchiole or alveolus
- almost always peripheral ; may present as pneumonia like consolidation ,as a solitary nodule or forms multiple colaescing nodules.



Morphology of bronchogenic carcinoma

Adenocarcinomas

Two forms:

1. Bronchial – derived carcinoma.

Peripheral
Develops on site of prior pulmonary inflammation or injury (scar carcinoma); less clearly linked to smoking.
Tend to metastasize widely at an early stage.

2. Bronchioloalveolar carcinoma

Involve peripheral parts as a single nodule or more often as multiple diffuse nodules.
Less clearly related to smoking; columnar to cuboidal tumor cells line alveolar walls and multiple densities on x-ray.
The disease often mimicks interstitial pneumonia

Lung Cancer:
Symptoms at Presentation

- Due to primary tumor:
  - Cough, hemoptysis, chest pain, wheezing, dyspnea, & fever.
- Thoracic extension of tumor:
  - Chest pain, SVC syndrome, hoarseness, & dysphagia.

Symptoms and Signs of Lung Cancer

Symptoms and signs from primary tumor

Central Tumors	Peripheral Tumors
Cough	Pain
Hemoptysis	Shortness of breath
Shortness of breath	Pleural effusion
Wheezing	Cough
Postobstructive pneumonia	

Symptoms and signs from regional spread

Superior vena cava obstruction (superior vena cava syndrome)
Recurrent laryngeal nerve palsy (hoarseness)
Phrenic nerve palsy (elevated hemidiaphragm and worsening dyspnea)
Brachial nerve root compression (Horner syndrome)
Brachial nerve root compression by superior sulcus tumors
Esophageal compression (dysphagia)
Airway compression (dyspnea and superior)

Symptoms and signs from metastatic spread

Brain metastases
Spinal cord compression
Bone pain
Liver metastases
Hepatomegaly

Paraneoplastic syndromes	Commonly associated histology
Hypercalcemia	Squamous cell carcinoma
Trousseau syndrome	Adenocarcinoma
Clubbing	All types
Hypertrophic pulmonary osteoarthropathy	Non-small cell carcinoma
SIADH	Small cell carcinoma
Ectopic ACTH production	Small cell carcinoma
Eaton-Lambert syndrome	Small cell carcinoma
Central nervous system	Multiple

SIADH: Syndrome of inappropriate secretion of antidiuretic hormone
ACTH: Adrenocorticotropic hormone

LUNG CANCER SCREENING PROGRAM

RISK ASSESSMENT TOOL

If all three apply to you:

- ❑ Between the ages of 55 and 80*
- ❑ Smoking at least a pack a day for at least 30 years or two packs a day for 15 years
- ❑ Still smoking or stopped within 15 years

High Risk
Talk to your doctor about Low Dose screening Chest CT.

Checked two of the above, plus one or more of the following:

- ❑ Exposure to radon
- ❑ Exposure to asbestos or other cancer causing agents such as arsenic, beryllium, cadmium, chromium, nickel, coal smoke, soot, silica or diesel fumes
- ❑ History of other cancers
- ❑ Family members who have had lung cancer
- ❑ Personal history of lung disease
- ❑ Second hand smoke exposure

Intermediate Risk
Talk to your doctor to see if screening may be appropriate.

If you have checked fewer than three of the above...

Low Risk
Any questions, talk to your doctor.

* U.S. Preventive Services Task Force (USPSTF). Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014 Mar 4;160(5):330-8

www.LungCancerInitiativeNC.org

Non–Small-Cell Lung Cancer Diagnosis and Staging

Evaluation	Purpose
Physical examination	Identify signs
Chest x-ray	Determine position, size, number of tumors
Bronchoscopy	Determine location of tumor, obtain biopsy
Fine-needle aspiration	Cytology
CT scan	Identify chest-wall invasion, mediastinal lymphadenopathy, distant metastases
PET scan	Mediastinal, lymph-node and extrathoracic staging
Laboratory analysis	Detect changes in hormone production, and hematologic manifestations of lung cancer
Mediastinoscopy	Visualize and sample mediastinal lymph nodes

Investigations

- **Investigations to confirm the disease**
  - Sputum cytology (sensitivity 65% - 75%)
  - Transthoracic FNAC (sensitivity 87% - 91%)
  - Bronchoscopic biopsy (70% - 80%)
  - **TT-FNAC associated with**
    - Pneumothorax (27%)
    - Hemoptysis (5%)
    - Local bleeding (11%)
- **Investigations to assess the stage**
  - Imaging
  - Bronchoscopy
  - Mediastinoscopy
  - VATS
- **Investigations to assess fitness for treatment**
  - Hemogram
  - Renal and liver function tests
  - Pulmonary function tests

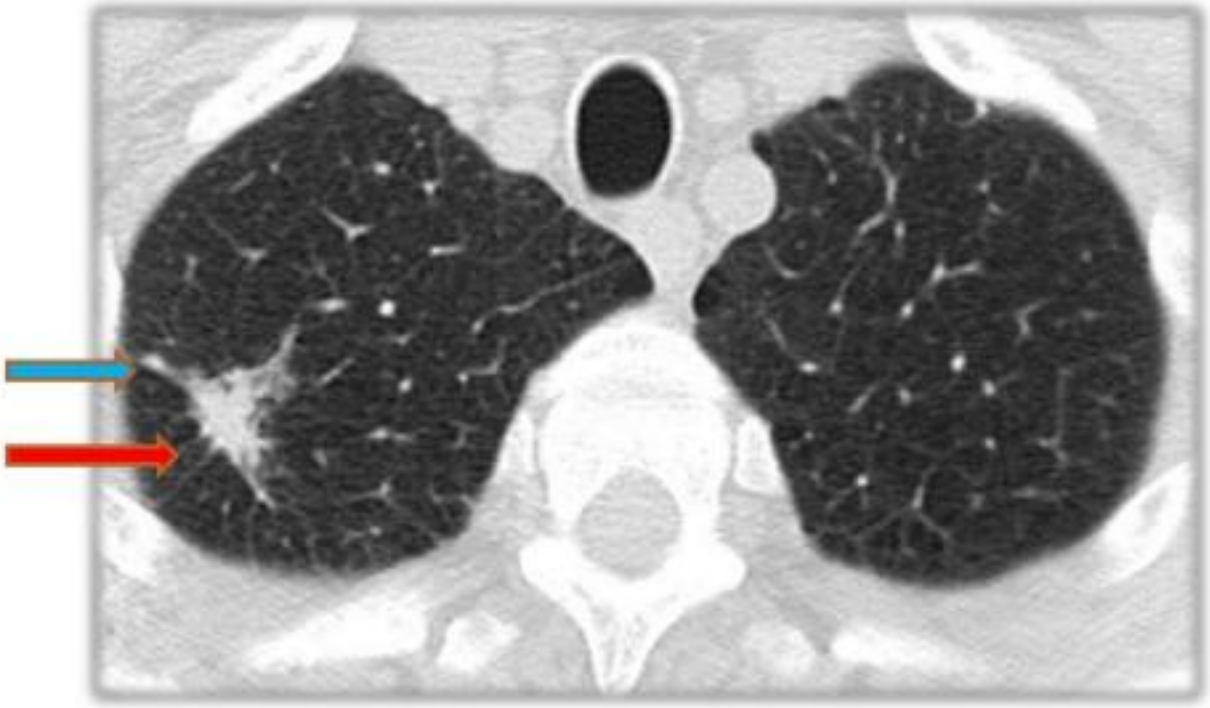
Common Immunohistochemical Markers Used in the Diagnosis of Lung Tumors

:Harrison's Principles of Internal Medicine, 18e

Histology	Positive Immunohistochemical Markers
Squamous cell carcinoma	Cytokeratin (CK) cocktail, e.g., AE1/AE3 CK5/6 , CK7 rare
Adenocarcinoma	Cytokeratin cocktail, e.g., AE1/AE3 CK7 , TTF-1 Neuroendocrine markers rare, e.g., CD56, NSE
Large cell carcinoma	Cytokeratin , TTF-1 rare Neuroendocrine markers rare (e.g., CD56, NSE)
Large cell neuroendocrine carcinoma	Cytokeratin cocktail, e.g., AE1/AE3 TTF-1 , CD56 , Chromogranin Synaptophysin
Small cell carcinoma	Cytokeratin cocktail (tends to be patchy) TTF-1 , CD56 , Chromogranin Synaptophysin

TUMOR SHAPE AND SIZE-

- Tumor at lung apex may appear as pleural thickening.
- Majority of peripheral tumors may be spherical or oval
- **CORONA RADIATA** - numerous strands radiating from the nodule into surrounding lung
- Peripheral line shadow or '**TAIL' SIGN** - linear opacity that extends from a peripheral nodule to the visceral pleura



Adverse Prognostic Factors

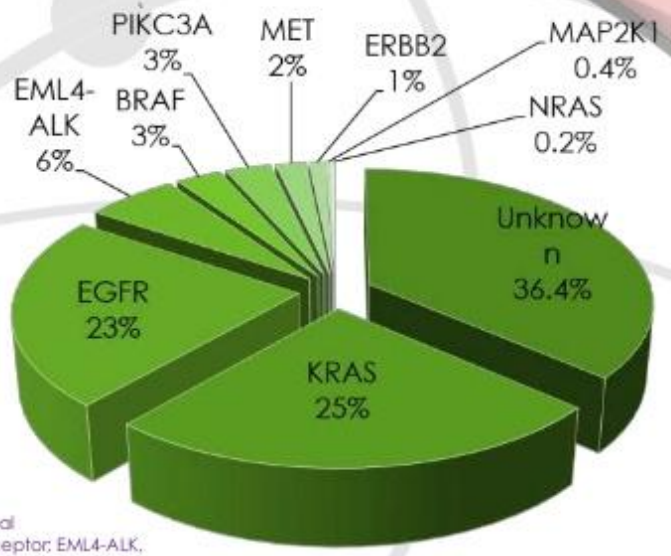
- Age > 65
- Performance status > 2
- Advanced stage
- Presence of mediastinal lymphadenopathy
- Tumor hypercalcemia
- Surgical procedure : Limited resection
- Positive resection margins
- Biological markers:
  - COX 2
  - p 53
  - EGFR
  - erbB2

Selected mutations in NSCLC

(Adenocarcinoma; Patients were smokers or non-smokers)

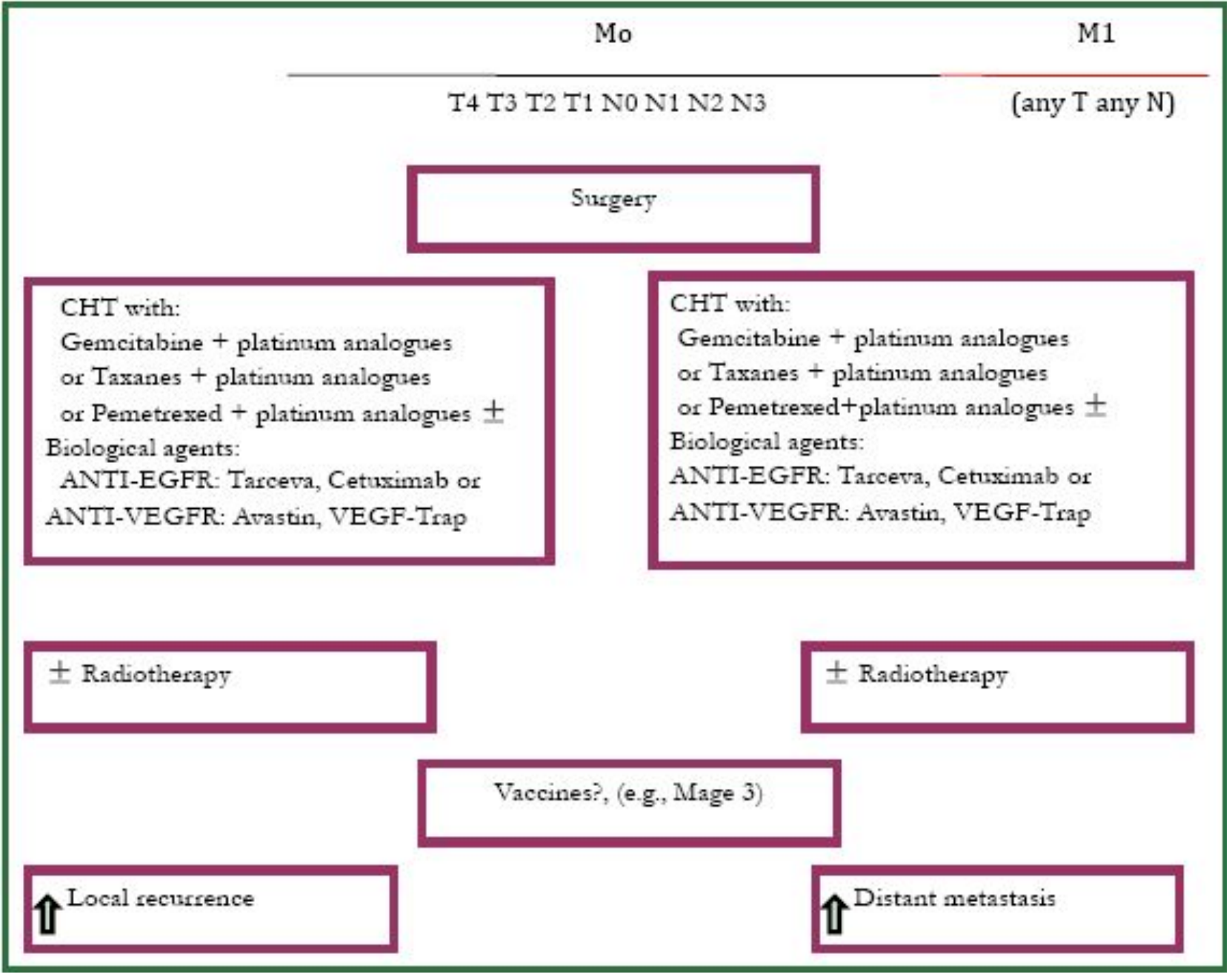
Molecular pathology(4)

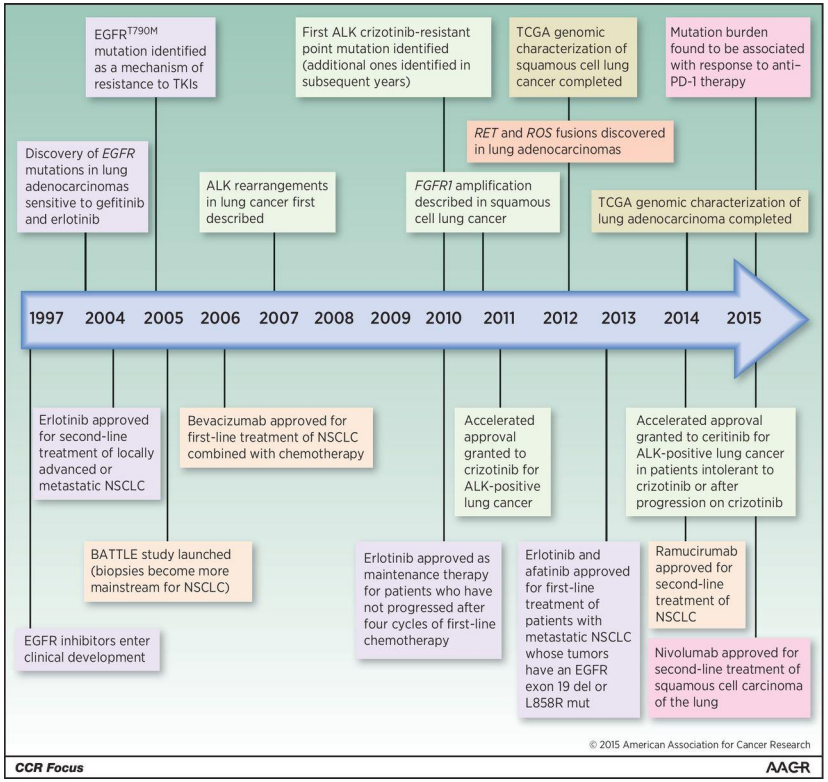
- KRAS (ALK/BRAF/PI3K)
- EGFR (ALK inhibitors)
- EML4-ALK
- BRAF (EGFR TKI)
- MET (Kinase domain mut.)
- ERBB2/HER2 (EGFR TKI)
- MAP2K1(MEK inhibitor-sens.)
- NRAS (MEK inhibitor-sens.)

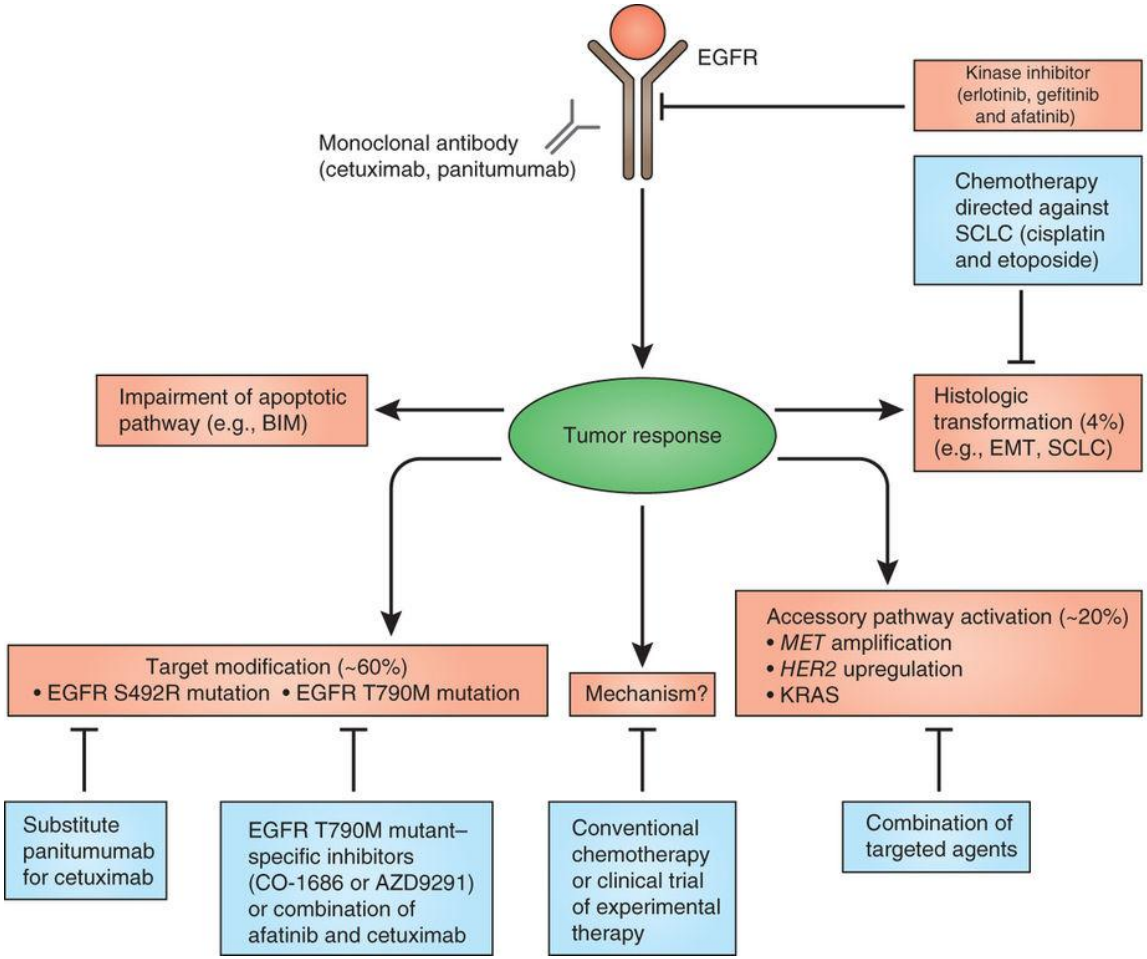


BRAF, proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B1; EGFR, epidermal growth factor receptor; EML4-ALK, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase; ERBB2/HER2, Receptor tyrosine-protein kinase erbB-2; MAP2K1, dual specificity mitogen-activated protein kinase kinase 1; MET, proto-oncogene (hepatocyte growth factor receptor); mut., mutation; NRAS, Neuroblastoma RAS viral oncogene homolog; PI3K, Phosphatidylinositol-4,5-bisphosphate 3-kinase; PIKC3A, Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit a; sens., sensitive; TRKI, tyrosine kinase inhibitor

4. Cheng L, Alexander RE, Maclennan GT, Cummings OW, Montironi R, Lopez-Beltran A, et al. Molecular pathology of lung cancer: key to personalized medicine. Modern pathology 2012;25(3):347-69.

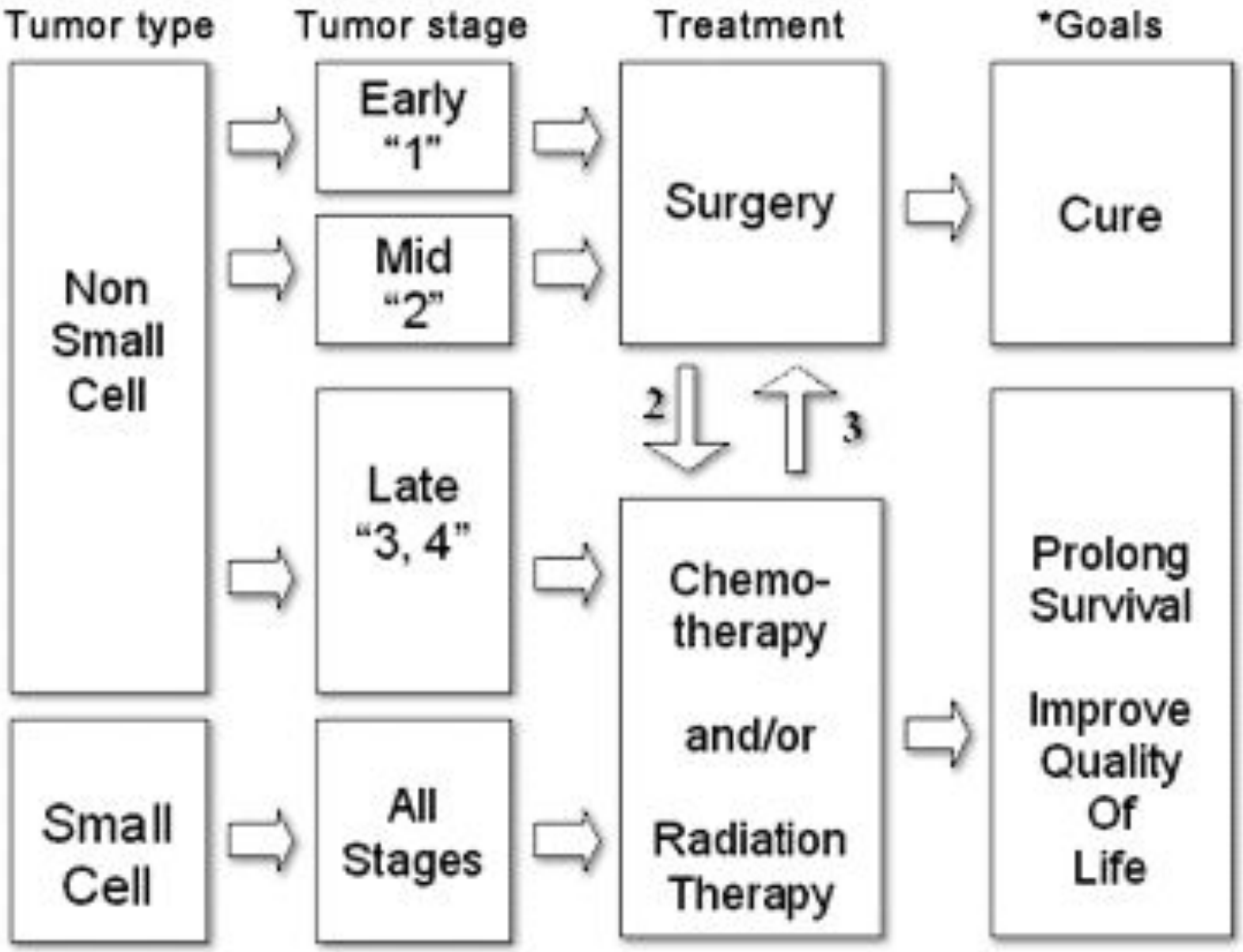

Mo
M1
T4 T3 T2 T1 N0 N1 N2 N3
(any T any N)
Surgery
CHT with:
Gemcitabine + platinum analogues
or Taxanes + platinum analogues
or Pemetrexed + platinum analogues ±
Biological agents:
ANTI-EGFR: Tarceva, Cetuximab or
ANTI-VEGFR: Avastin, VEGF-Trap
CHT with:
Gemcitabine + platinum analogues
or Taxanes + platinum analogues
or Pemetrexed+platinum analogues ±
Biological agents:
ANTI-EGFR: Tarceva, Cetuximab or
ANTI-VEGFR: Avastin, VEGF-Trap
± Radiotherapy
± Radiotherapy
Vaccines?, (e.g., Mage 3)
⇧ Local recurrence
⇧ Distant metastasis




EGFR
Kinase inhibitor (erlotinib, gefitinib and afatinib)
Monoclonal antibody (cetuximab, panitumumab)
Chemotherapy directed against SCLC (cisplatin and etoposide)
Impairment of apoptotic pathway (e.g., BIM)
Tumor response
Histologic transformation (4%) (e.g., EMT, SCLC)
Target modification (~60%)
• EGFR S492R mutation • EGFR T790M mutation
Mechanism?
Accessory pathway activation (~20%)
• MET amplification
• HER2 upregulation
• KRAS
Substitute panitumumab for cetuximab
EGFR T790M mutant–specific inhibitors (CO-1686 or AZD9291) or combination of afatinib and cetuximab
Conventional chemotherapy or clinical trial of experimental therapy
Combination of targeted agents
Neil Smith

Treatment by Stages of Cancer

Stage	Description	Treatment Options
Stage Ia – Ib	Tumor localized in lung	Surgical resection
Stage IIa – IIb	Tumor spread to local lymph nodes	Surgical resection
Stage IIIa	Tumor spread to regional lymph nodes in trachea, chest above diaphragm	Chemotherapy followed by radiation or surgery
Stage IIIb	Tumor spread to contra lateral lymph nodes	Combination of Chemotherapy and Radiation
Stage IV	Tumor metastasis to organs outside chest	Chemotherapy and or palliative care


Tumor type
Tumor stage
Treatment
*Goals
Non Small Cell
Small Cell
Early "1"
Mid "2"
Late "3, 4"
All Stages
Surgery
Chemo-therapy
and/or
Radiation Therapy
2
3
Cure
Prolong Survival
Improve Quality Of Life

Lung Cancer Treatment Options

- Surgery
  - If in good general health, stage I and II lung cancer patients are usually treated with surgery. More advanced stages must be evaluated individually for the possibility of surgery. Some patients have small tumors that can be removed surgically, but they may suffer from other medical problems or may be opposed to surgery. In these cases, important treatment options like CyberKnife® offer an alternative.
- Conventional radiation therapy
  - Conventional radiation therapy administers a broad beam of low dose radiation from only a few directions. Generally, treatment is offered with chemotherapy and radiation combined.
- Stereotactic radiosurgery
  - Stereotactic radiosurgery is a noninvasive method of treating tumors with high dose radiation precisely aimed from different angles. Systems like the CyberKnife can offer effective treatment of lung tumors while carrying a low risk of side effects.

Surgery

- Surgery is done in early stage NSCLC (stage I, II & IIIA)
- Only about 20% of patients suitable for curative surgery
- In these the tumor has not extended beyond broncho pulmonary lymph nodes
- Lobar resection with hilar and mediastinal lymph node sampling is the standard surgical treatment .

Patterns of failure after Sx

- Patients who fail after surgery, present with extrathoracic disease 70% of the time, local recurrence in 20% and local and distant metastasis in 10%.
- Tumors measuring 1-2 cm have a mediastinal nodal metastasis rate of 17% as compared to those measuring 2 to 3 cm, when the rate is 37%
- Median overall survival was 9.1 years (stage T1) and 6.5 years (stage T2).
- Overall survival at 5 years was 72% (stage T1) and 55% (stage T2).
- Local recurrence-free survival at 5 years was 95% (stage T1) and 91% (stage T2)

Martini et al J Thor Cardiov Surg 1995
Su et al J Thor Cardiov Surg 2014

TABLE 7: Combination chemotherapy regimens recommended for NSCLC

Regimen	Agents	Treatment Dose and schedule	Treatment interval
PT	Platinol Taxol	75 mg/m^2 IV on day 2 135 mg/m^2 IV on day 1 (24-h infusion)	3 weeks
CP	Carboplatin Paclitaxel	AUC of 6 mg/mL/min IV on day 1 225 mg/m^2 IV on day 1 (3-h infusion)	3 weeks
PG	Platinol Gemcitabine	100 mg/m^2 IV on day 1 1,000 mg/m^2 IV on days 1, 8, and 15	4 weeks
PD	Platinol Docetaxel	75 mg/m^2 IV on day 1 75 mg/m^2 IV on day 1	3 weeks
PV	Platinol Vinorelbine	100 mg/m^2 IV on day 1 25 mg/m^2 IV on days 1, 8, 15, and 22	4 weeks
PCB	Paclitaxel Carboplatin Bevacizumab	200 mg/m^2 IV on day 1 (3-hr infusion) AUC of 6 mg/mL/min IV on day 1 15 mg/kg IV	3 weeks
PC[a]	Pemetrexed Cisplatin	500 mg/m^2 IV on day 1 75 mg/m^2 IV on day 1	3 weeks

AUC = area under the concentration-time curve

[a]Carboplatin may be substituted in patients with poor performance status. Dexamethasone (4 mg by mouth twice daily) should be started a day before and a day after pemetrexed. All patients should also receive folic acid (350–1,000 mg/d) started about a week before and thereafter while taking pemetrexed. Vitamin B_{12} (1,000 mg IM) should be started about 1 to 2 weeks before pemetrexed and every 9 weeks during therapy.

Role of radiotherapy

- **Localized early stage disease (I, II,IIIa) (Resectable)**

a) Alternative to surgery (medical contraindication / patients choice

b) As adjuvant to surgery

- **Locally advanced disease (III) (Unresectable)**

  Radical RT

  — Alone

  — With chemotherapy

- **Stage IV** - treatment remains palliative
  - Symptoms palliation
  - Local RT for consolidation
  - RT to bone / brain mets

- **Brachytherapy**
  - Alone (very early endobronchial disease
  - For boost or Palliative tratment

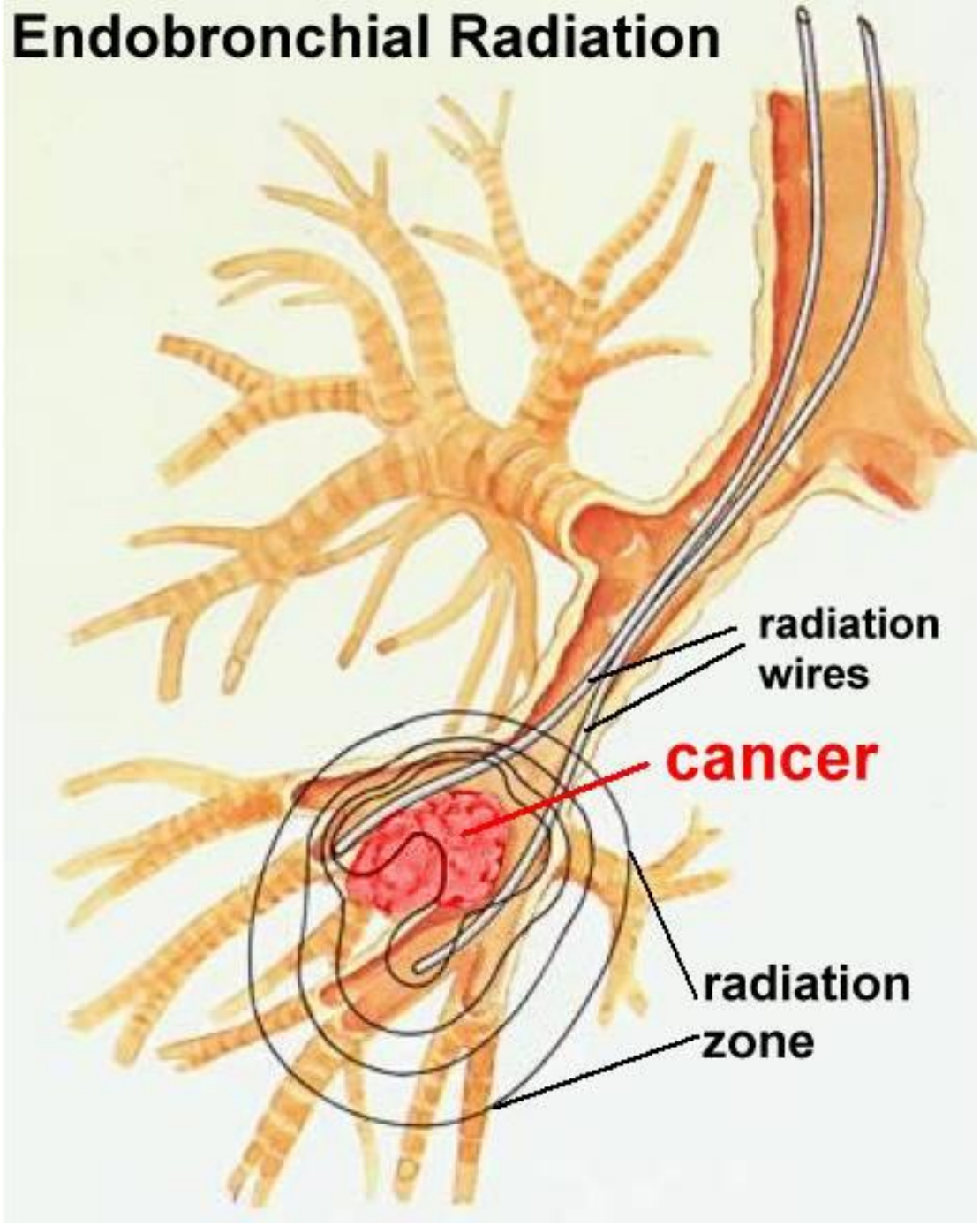
Curative radiotherapy

- Indications for **curative definitive radiotherapy**:
  - Histologically proven squamous cell carcinoma.
  - Medically inoperable patients with localised tumors.
  - Unimpaired functional status with or without symptoms (WHO < 2).
  - Weight loss lesser than 6%.
  - No evidence of distant metastasis.

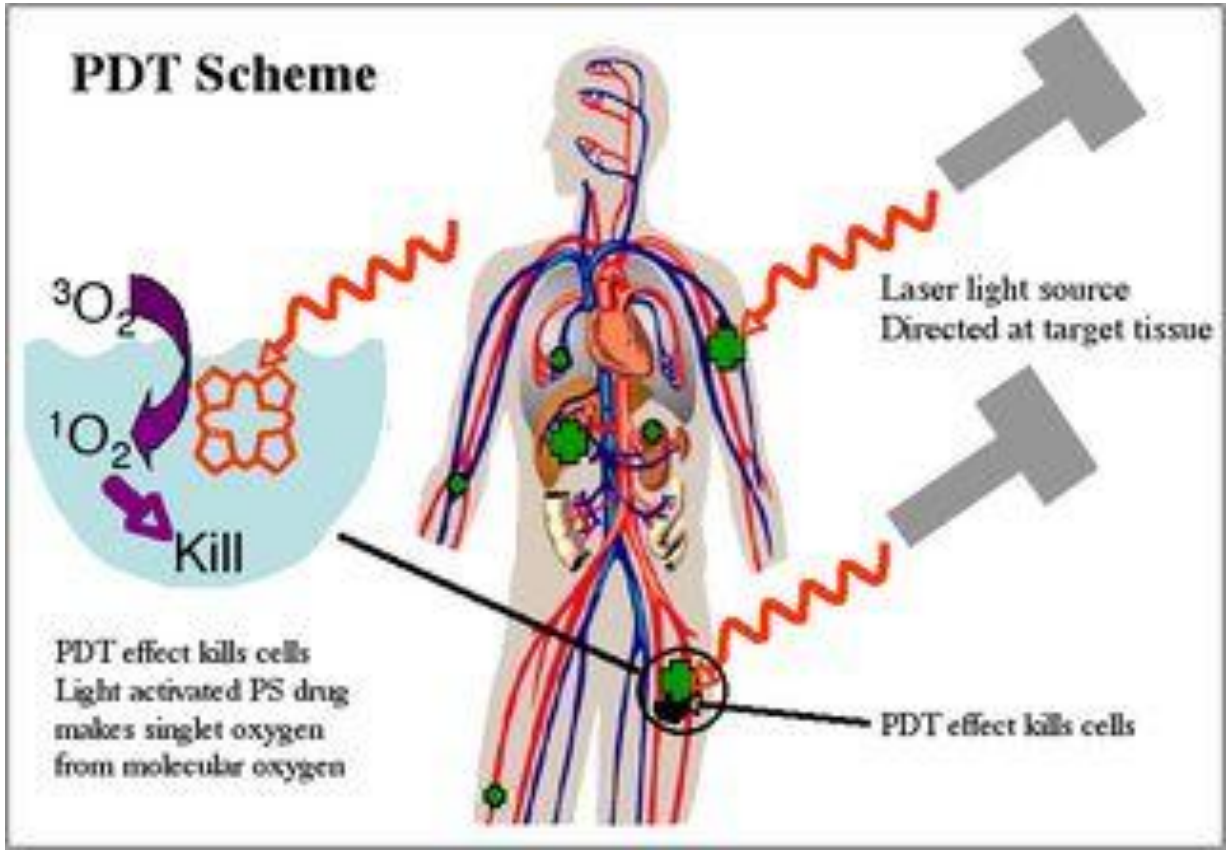
- **Contraindications** for curative definitive radiotherapy are:
  - SVC syndrome.
  - Paralysis of recurrent laryngeal nerve.
  - Paralysis of phrenic nerve.
  - Pleural or pericardial effusions.
  - Extensive infection including abscess formation
  - Destructive involvement of chest wall.
  - Superior sulcus tumors

Table 1 Results and limitations of the main available bronchoscopic techniques used for curative treatment of endobronchial lesions

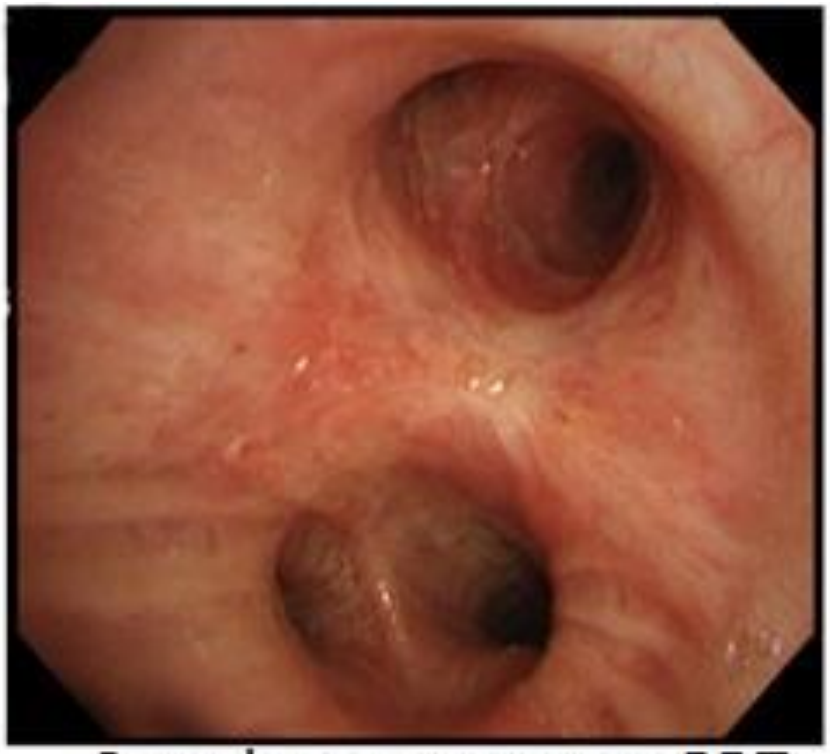
Methods	Principle	Indications	Results/advantages	Limitations
Photodynamic therapy	Local activation of a photosensitizing agent using a specific wave-length (630 nm) Phototoxic reaction	Maximum 6–7 mm depth lesions; extensive/ multiple lesions	Tumor response 70%; 5-year survival 70% for TIS or stage I; widely studied	Cost; sunburn
Brachytherapy	Radioactive isotopes (Iridium 192) delivered through a graduated radio-opaque catheter	Radio-occult lesions, <3 cm infiltration; inoperable patients; contralateral recidive after pneumonectomy; incomplete resection surgery	2 years-survival rate 92%; 2 years-local control rate 86%; depth of action; synergistic association with external radiation therapy; widely studied	Risk of fatal hemoptysis; radiation bronchitis/ necrosis/fistula/ stenosis
Cryotherapy	Cold cytotoxic effect (dehydration, crystallisation)	Endobronchial superficial lesions; no cartilaginous invasion; <3 mm depth	91% histological remission; no fire risk; cheap; no risk of stenosis or perforation	Limited thickness of action (3 mm)
Thermocaogulation	Thermic destruction of the tissue by a high-frequency electric current	From severe dysplasia to micro invasive carcinoma	80% complete response rate; cheap; quick; available in many centers	Risk of bleeding; stenosis; perforation; poor littérature


Endobronchial Radiation
radiation wires
cancer
radiation zone

Photodynamic therapy

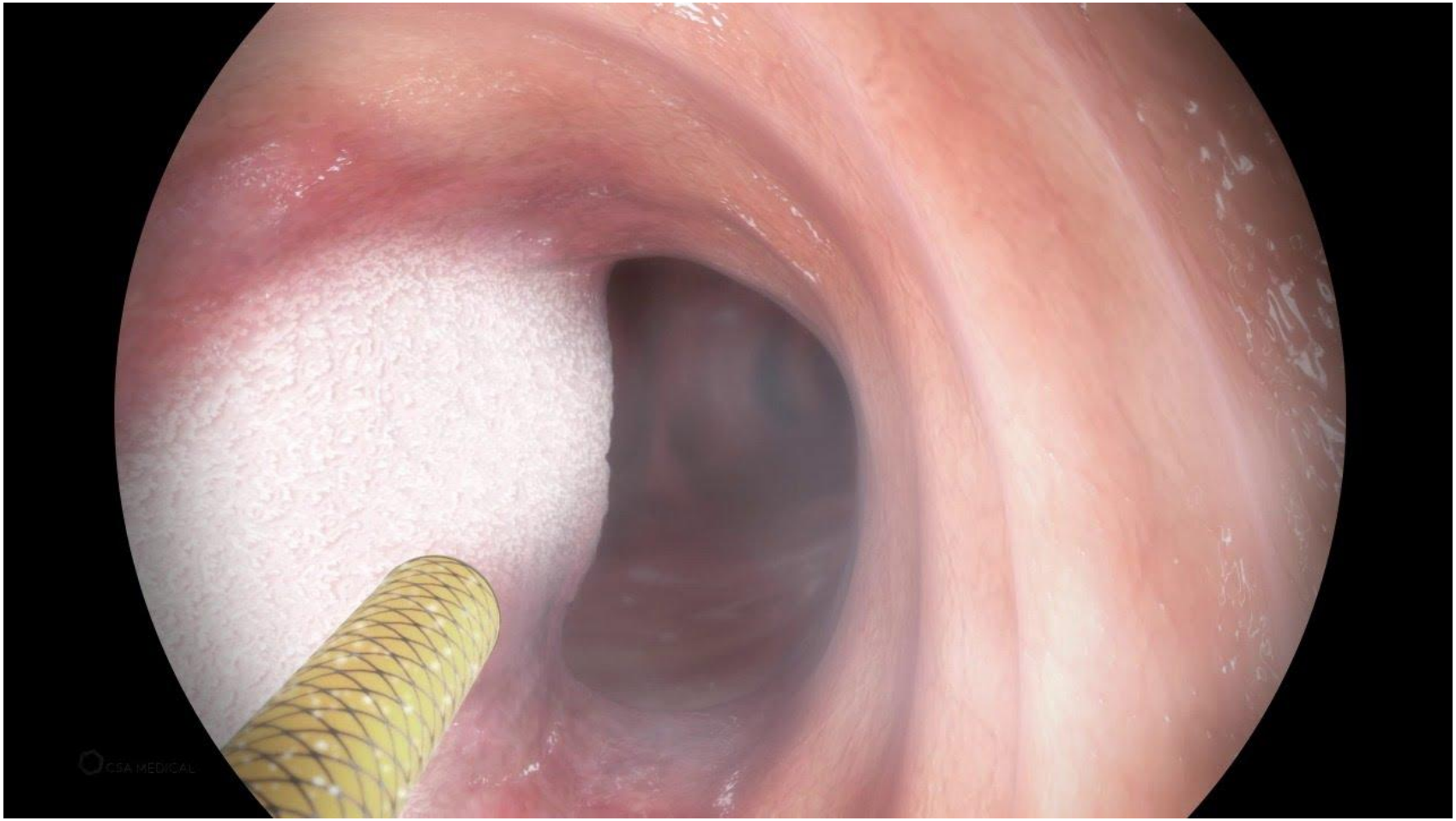


Endobronchial tumour completely obstructing left upper lobe bronchus

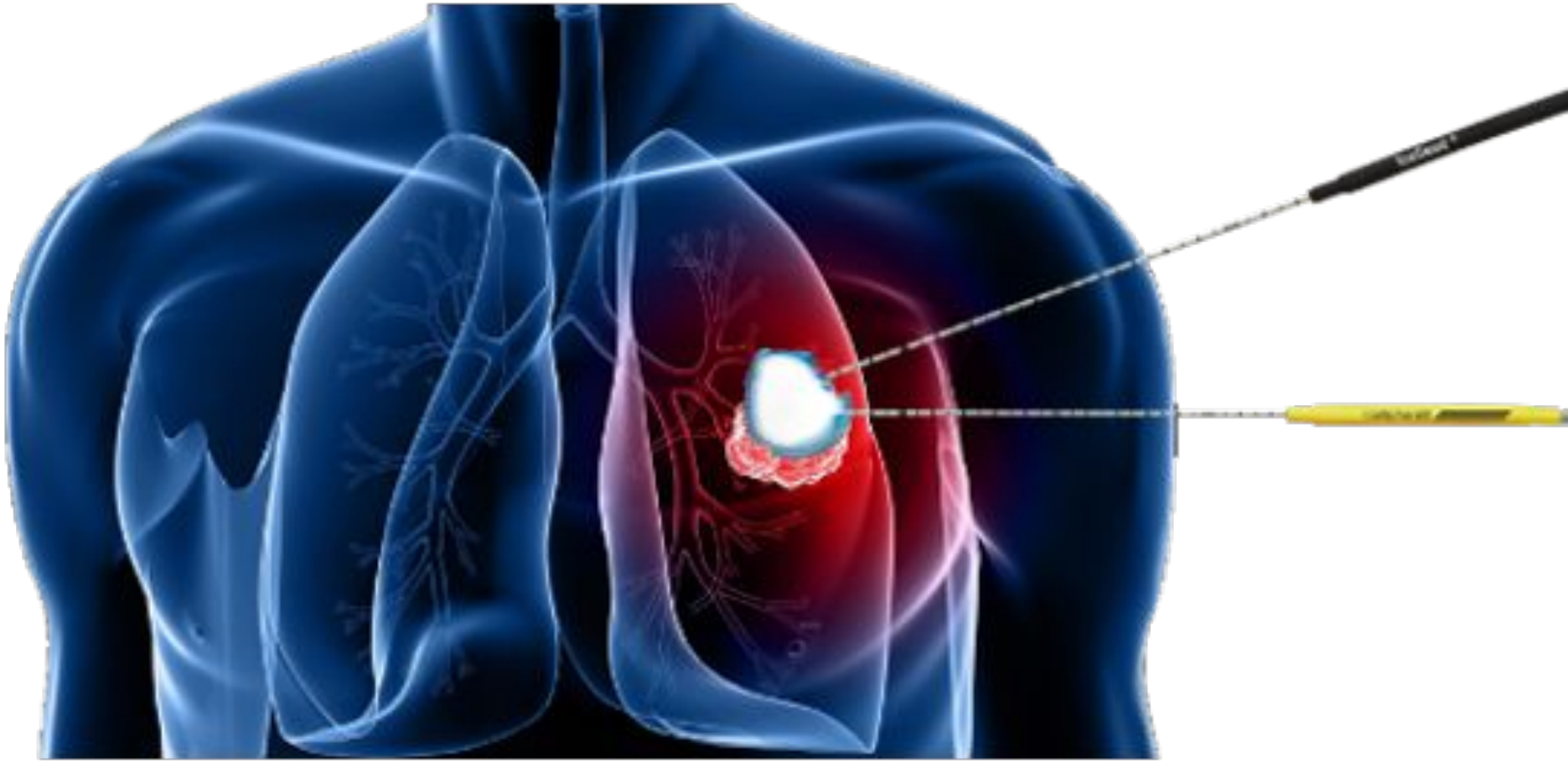


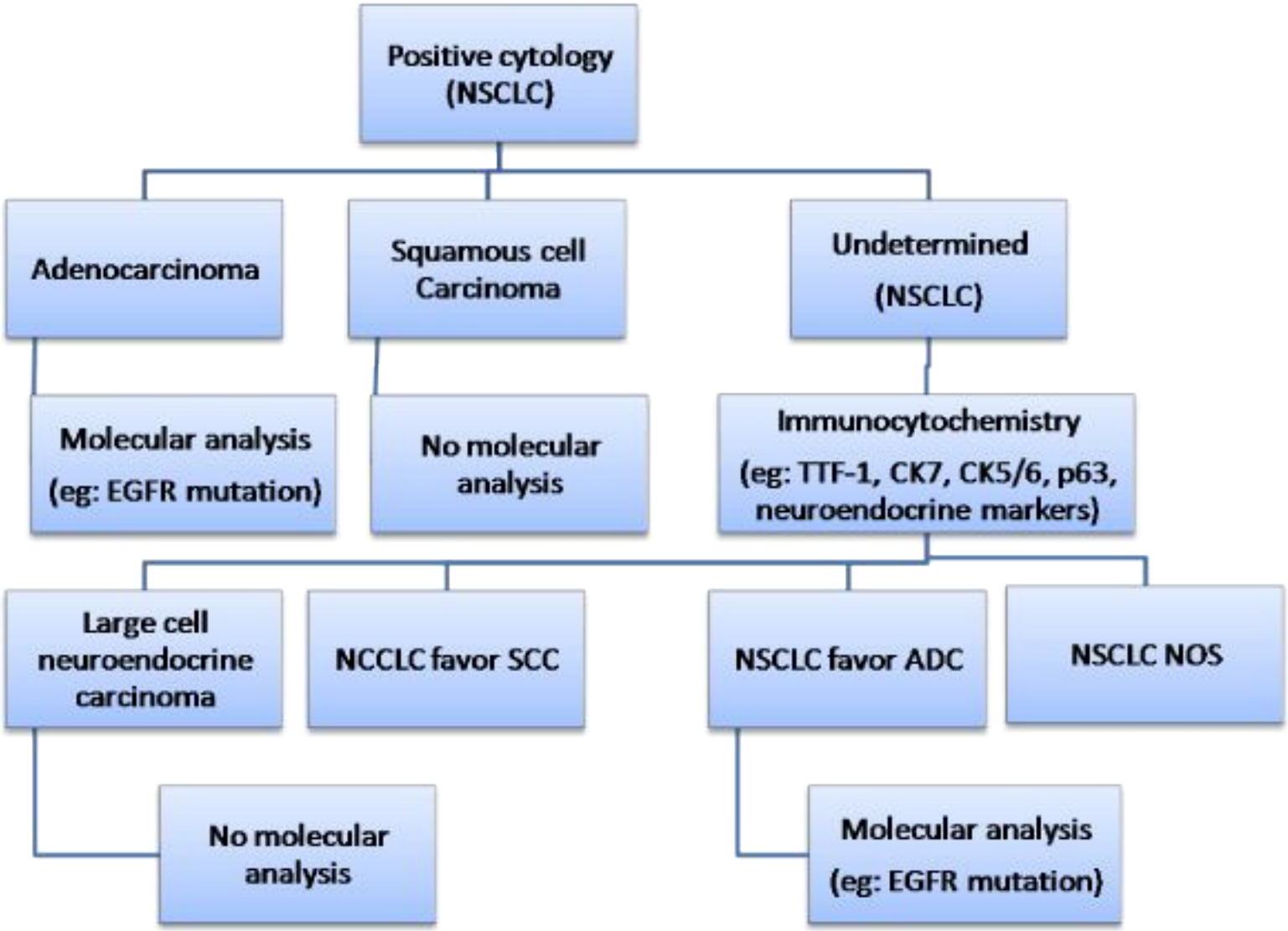
Complete response to PDT, follow up bronchoscopy 1 year post PDT

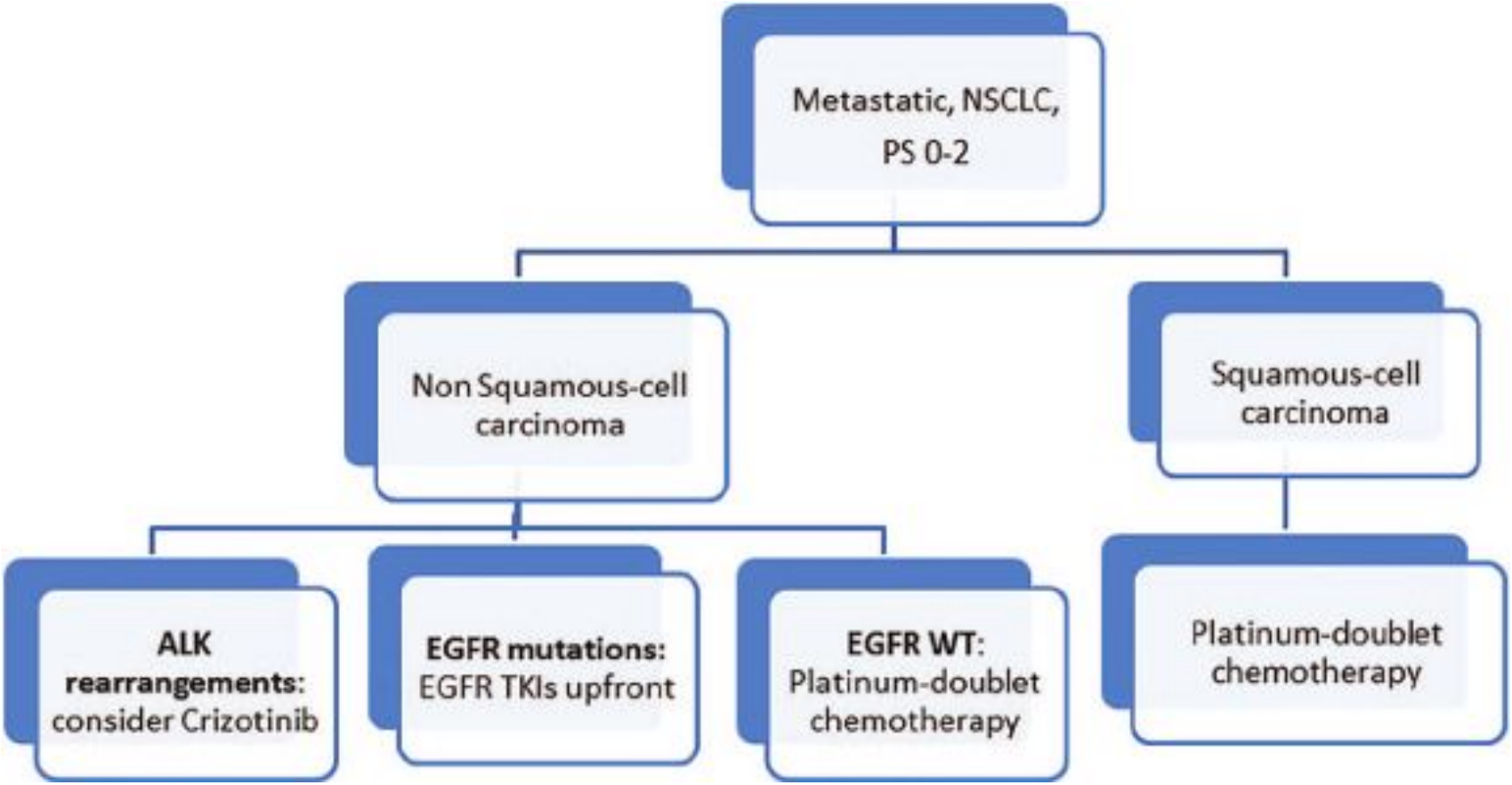
Cryotherapy



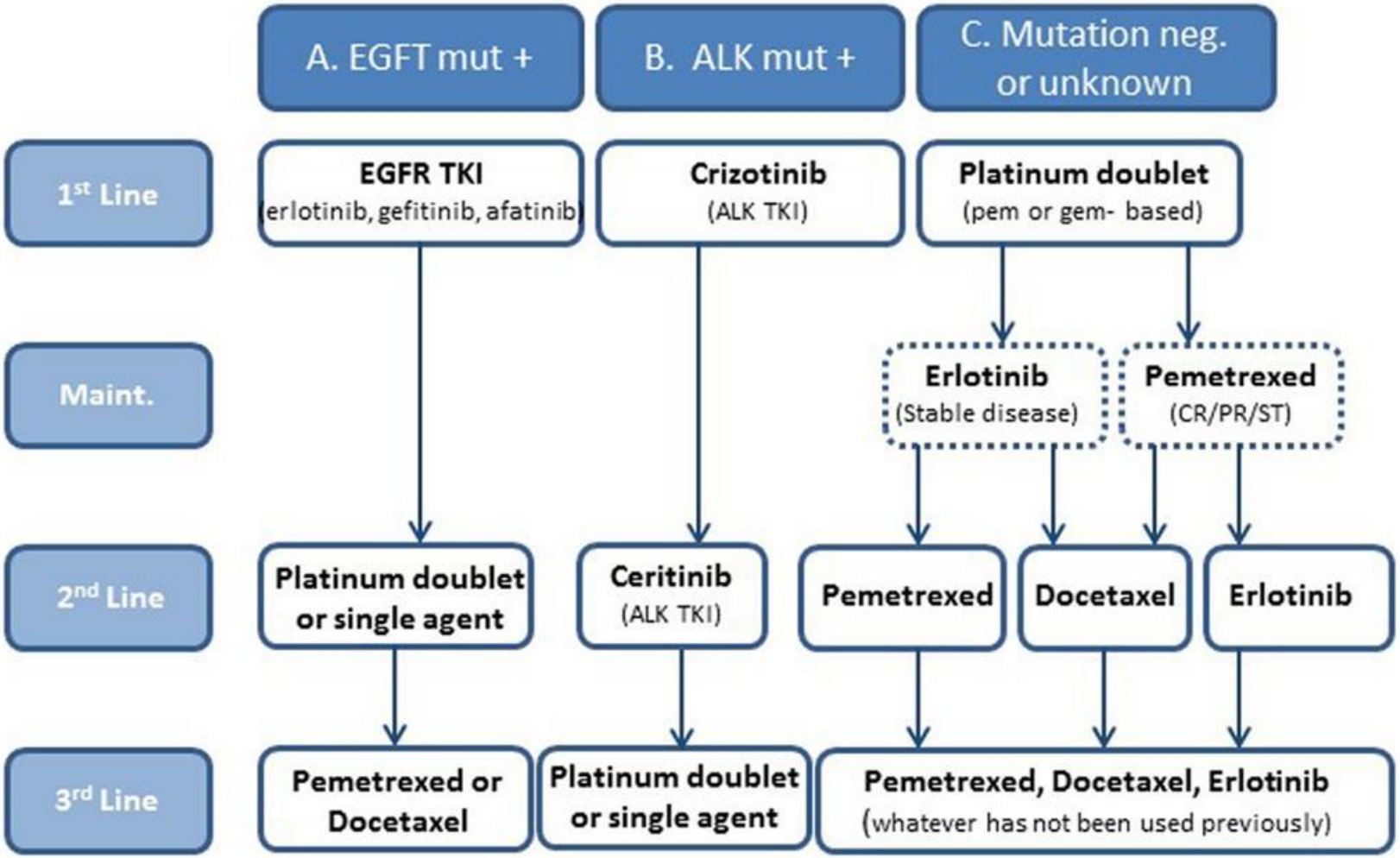
Transthoracic cryoablation




Positive cytology (NSCLC)
Adenocarcinoma
Squamous cell Carcinoma
Undetermined (NSCLC)
Molecular analysis (eg: EGFR mutation)
No molecular analysis
Immunocytochemistry (eg: TTF-1, CK7, CK5/6, p63, neuroendocrine markers)
Large cell neuroendocrine carcinoma
NCCLC favor SCC
NSCLC favor ADC
NSCLC NOS
No molecular analysis
Molecular analysis (eg: EGFR mutation)


Metastatic, NSCLC, PS 0-2
Non Squamous-cell carcinoma
Squamous-cell carcinoma
ALK rearrangements: consider Crizotinib
EGFR mutations: EGFR TKIs upfront
EGFR WT: Platinum-doublet chemotherapy
Platinum-doublet chemotherapy

Squamous and Non-Squamous Mutation Positive

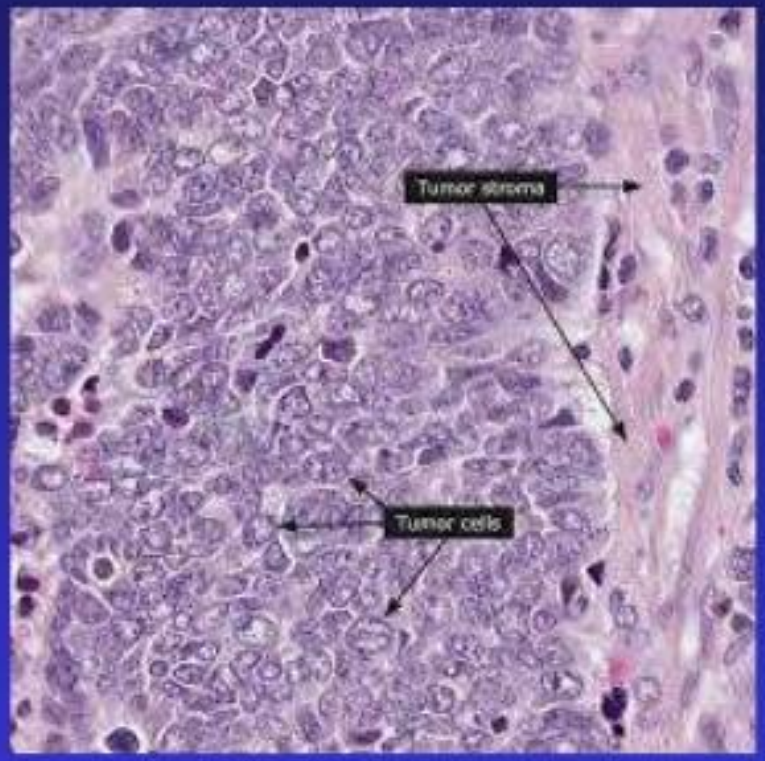


NSCLC vs SCLC

	NSCLC	SCLC
Incidence	80%	16%
Origin	Epithelial cells of the lung	Nerve producing cells of the lung (bronchi)
Classification	• Squamous cell • Large cell • Adenocarcinoma	• Limited stage • Extensive stage
Metastatic potential	Less than SCLC	Rapid metastatic potential
Treatment	• Surgery • Chemotherapy • Radiotherapy	• Chemotherapy • Radiotherapy
5 year survival	• Stage I : 57 – 67% • Stage II : 39 – 55% • Stage III : 5 – 25% • Stage IV : < 1%	• Limited 20% • Extensive < 1%

Patho physiology

- Small cells with scant cytoplasm
- Ill- defined cell borders
- Finely granular nuclear chromatin
- Absent or inconspicuous nucleoli
- Extensive Necrosis
- High mitotic count



Staging system

- Limited stage disease (LD)
  - Confined to the ipsilateral hemithorax
  - All known disease can be encompassed within a single radiation port
- Extensive stage disease (ED)
  - Disease in the contralateral hemithorax and distant metastases

5 Year Survival Rates – By Stage

- Non-Small Cell Lung Cancer
  - IA 58-73%
  - IB 43-58%
  - IIA 36-46%
  - IIB 25-36%
  - IIIA 19-24%
  - IIIB 7-9%
  - IV 2-13%
- Small Cell Lung Cancer
  - Limited 18-38%
  - Extensive 1%

Small cell carcinoma

- Originated from Kultschitzky (K cell) or argyrophilic cell in mucus gland of airway
- Evidence from immunohistochemistry and special tumor markers indicate SCLC has characters of **neuroendocrinal** tissues
- Paraneoplastic syndrome: serotonin, histamine, kinin, catecholamine, etc
- Polymorphic: avenine, lymphoid, and fusiform

SMALL CELL CARCINOMA

Strongly a/w smoking

Variants-
1. Small cell (pure)

2. Combined small cell/ non small cell

IHC-
Chromogranin A (specific)
synaptophysin (sensitive)
NSE
N CAM (CD 56)
bombesin

Paraneoplastic syndromes

- SIADH – Small cell – Hyponatremia

  Resolves within 1–4 weeks of initiating chemotherapy.

  Demeclocycline can be a useful

- ACTH-producing tumors – Small cell-Hypokalemia

  No changes in body habitus. Metyrapone and ketoconazole not effective.

  Treatment is effective management of underlying SLCS

:Harrison's Principles of Internal Medicine, 18e

SMALL CELL LUNG CANCER
NCCN GUIDELINES

Diagnostic Evaluation

Biopsy or cytology of primary or metastatic site

H&P	CXR
Path Review	Chest CT
CBC	Head MRI (or CT)
Chemistries	Bone Scan

Limited Stage

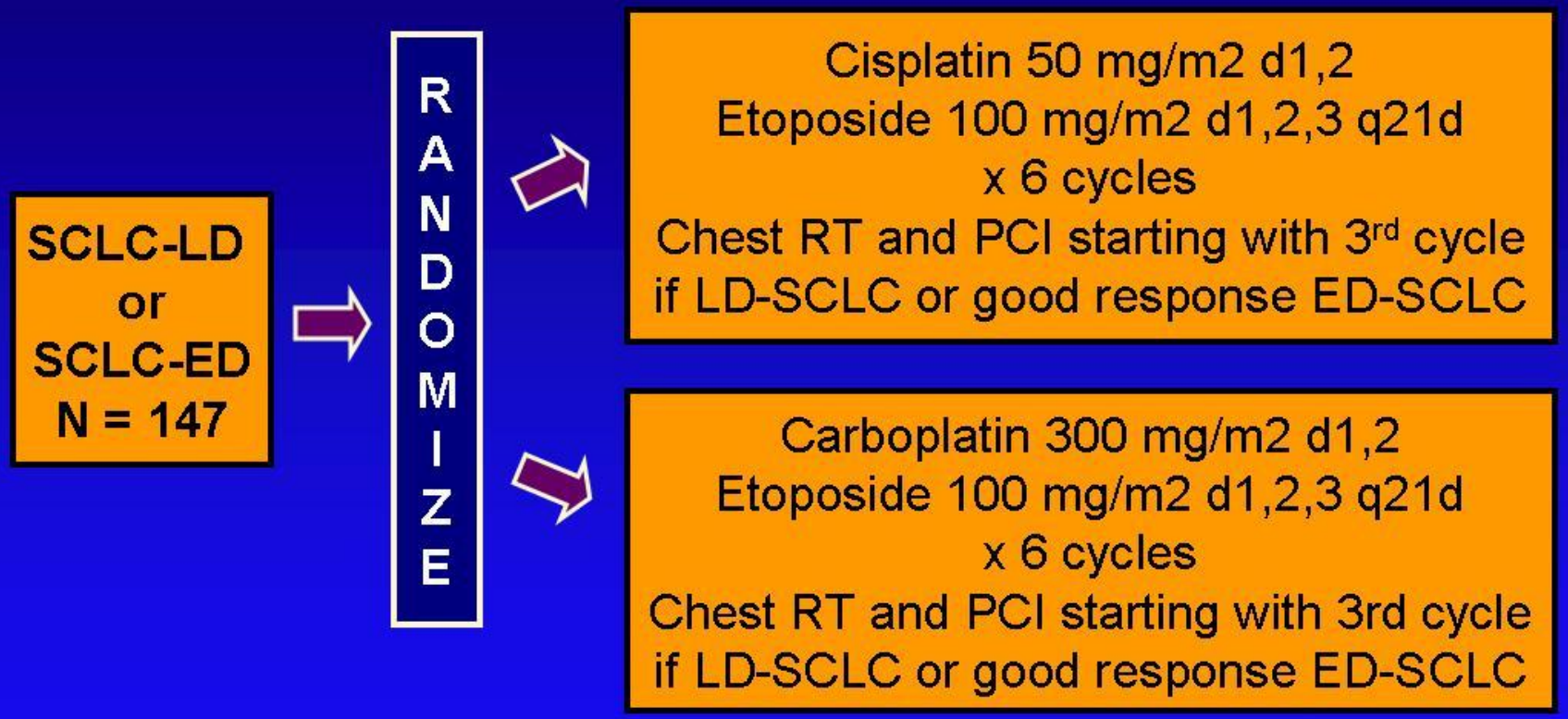
Unilateral marrow aspiration/biopsy

Thoracentesis if pleural effusion visible on CXR

Extensive Stage

Plain film x-rays of bone scan abnormalities of weight-bearing areas

Cisplatin vs. Carboplatin in SCLC (LD-SCLC or ED-SCLC)



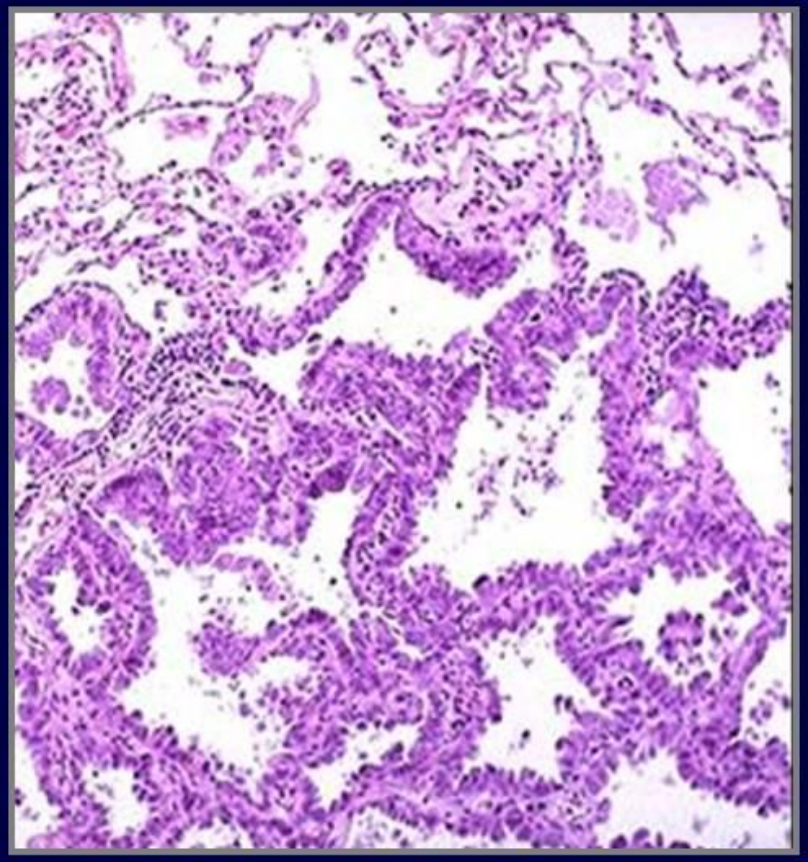
Skarlos, Ann Oncol 5: 601, 1994

PCI = Prophylactic Cranial Irradiation
RT = Radiation Therapy

Bronchioloalveolar carcinoma

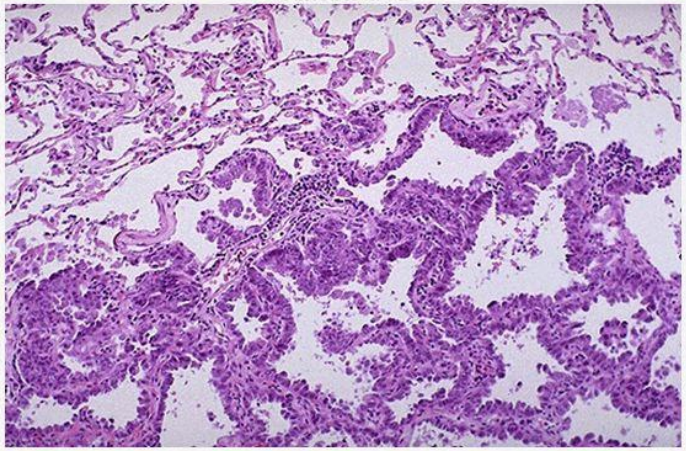
- Bronchioloalveolar carcinoma is a subtype of adenocarcinoma and represents 2-6% of all lung cancers.It typically arises distal to the terminal bronchioles and spreads along the preexisting alveolar septa without causing significant amounts of lung destruction
- The cells secrete mucin and surfactant apoprotein-- can lead to bronchorrhea
- Bronchioloalveolar carcinoma can manifest as a single peripheral nodule or mass usually in the upper lung.Most commonly, this nodule is well-circumscribed

BAC: Microscopic & Radiographic View



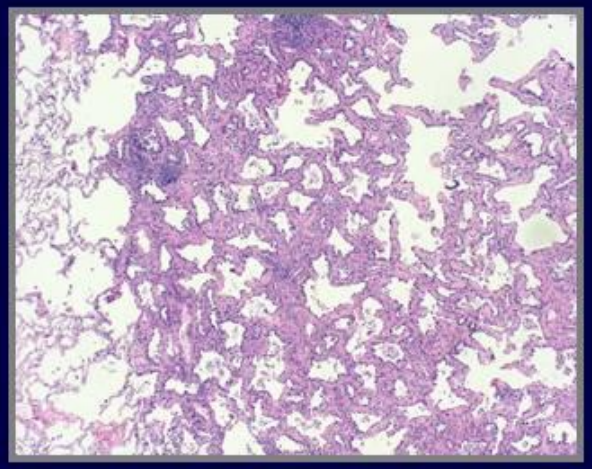
Bronchioloalveolar carcinoma

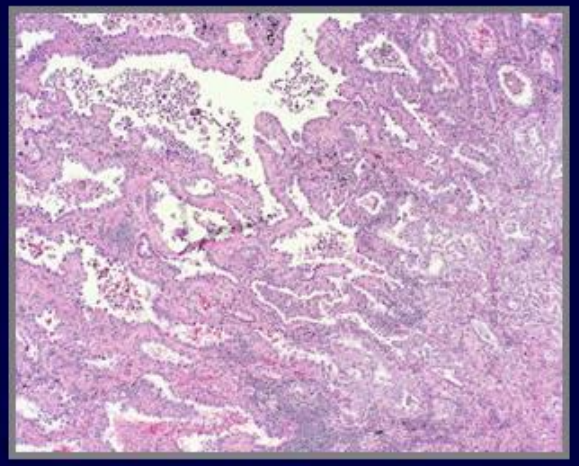
- Almost always peripheral
- Usually appears as multiple nodules with pneumonia like consolidation
- Nodules have mucoid feel
- Microscopic growth pattern is characteristic and resembles butterflies on a fence
- Mucinous and non mucinous subtypes
- Nonmucinous tumors are surgically resectable



Pathologic Subtypes: A Continuum from Pure BAC to Invasive Adenocarcinoma

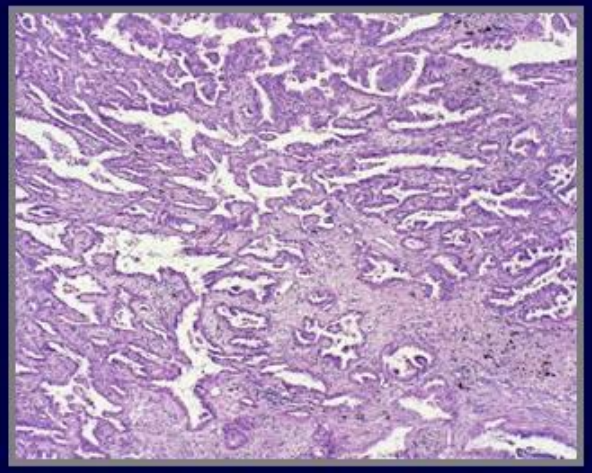
Pure BAC

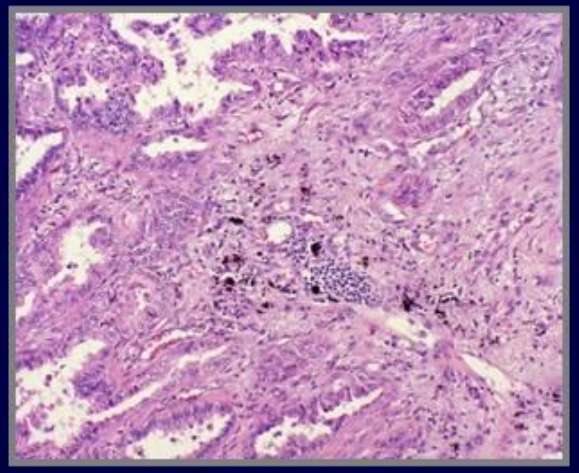




BAC with Invasion

Adeno with BAC





Adeno-carcinoma

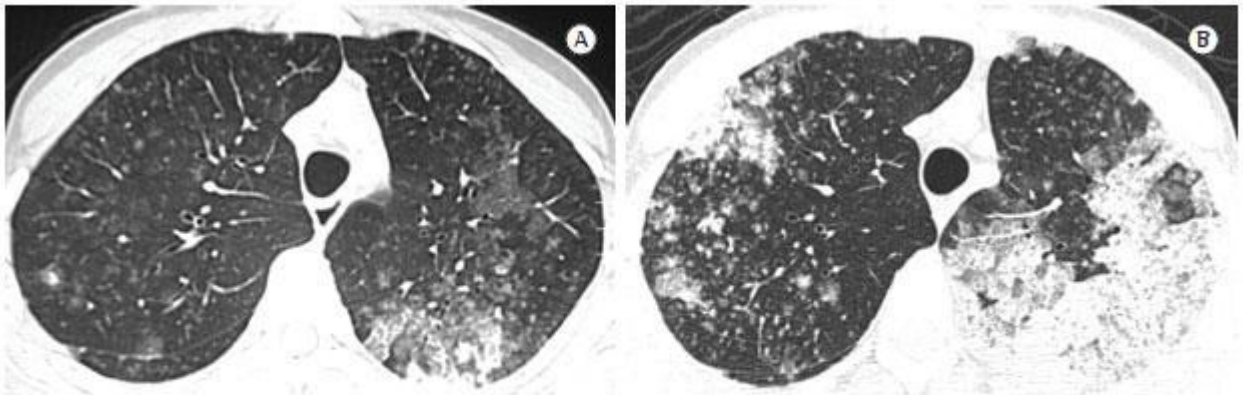
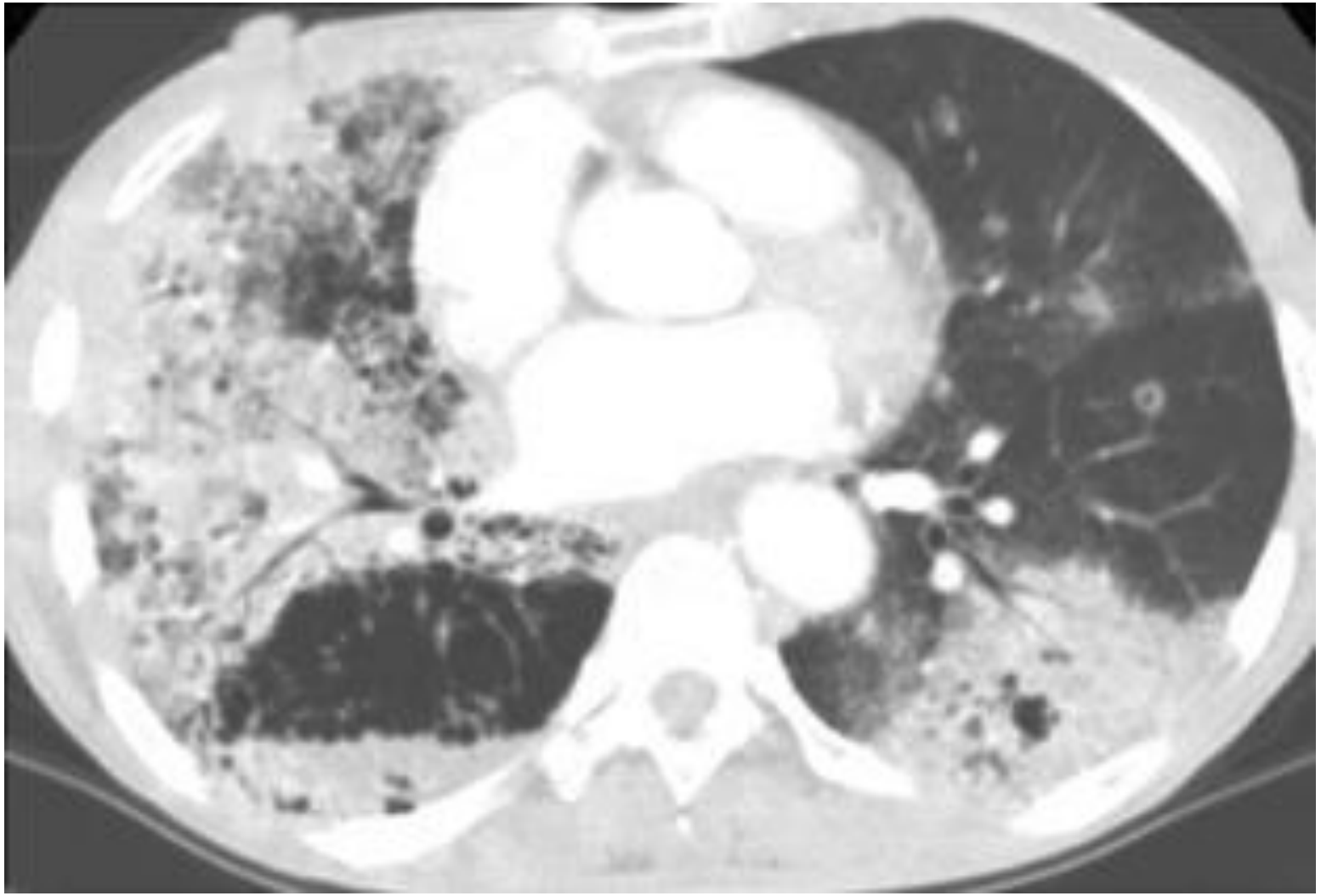
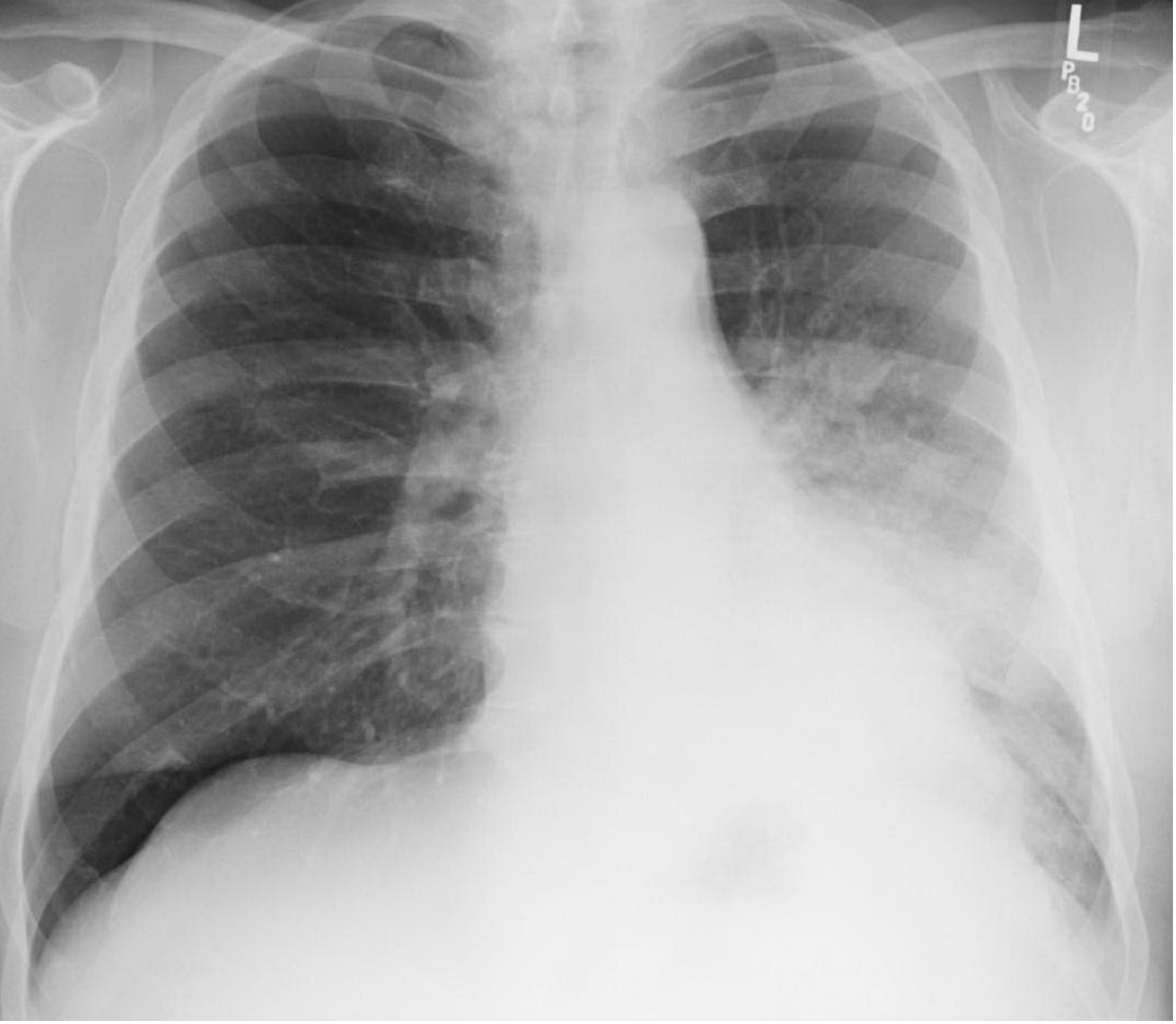
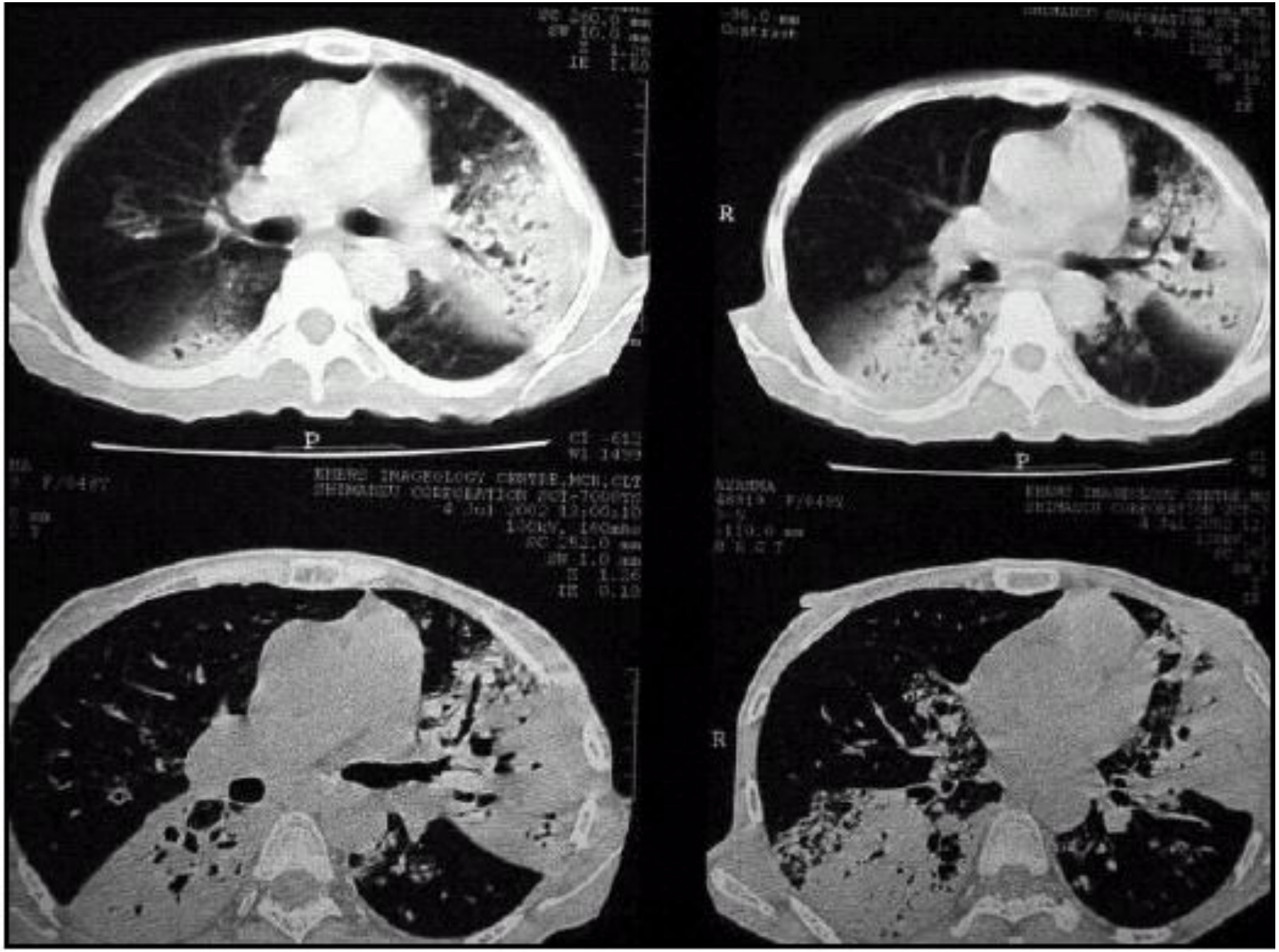


Figure 11 - CT scan of the chest of a 42-year-old female patient with diffuse bronchioloalveolar carcinoma, which was initially interpreted as infection. In a, ground-glass opacity, crazy-paving pattern, air-space nodules, and foci of consolidation. In b, significant worsening of the disease after two months.

BAC, pneumonic form




L
PA20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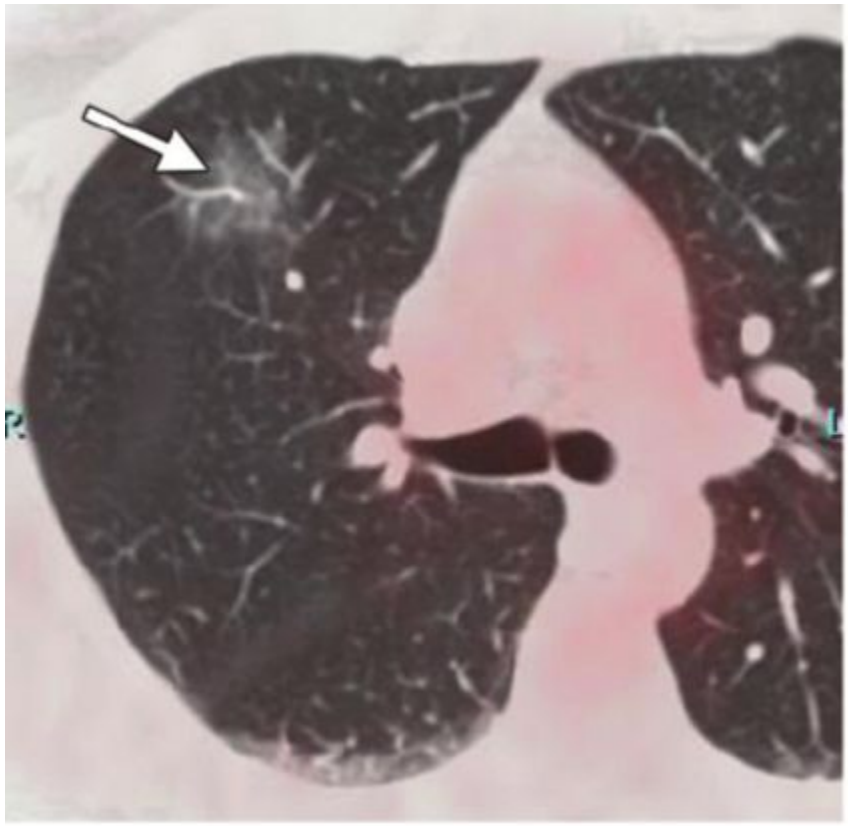
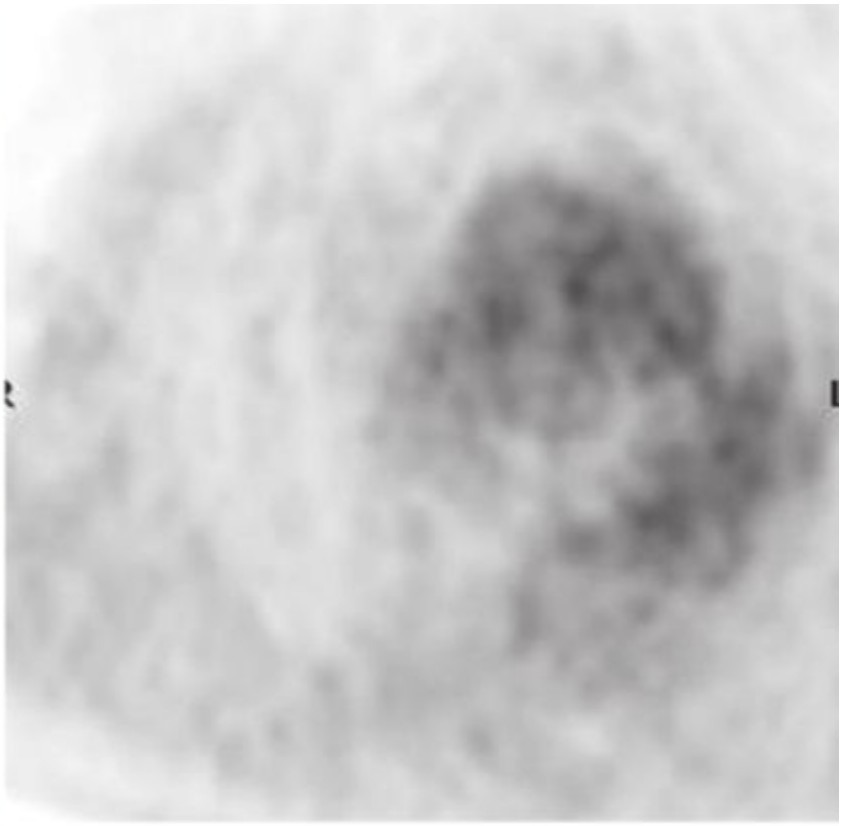
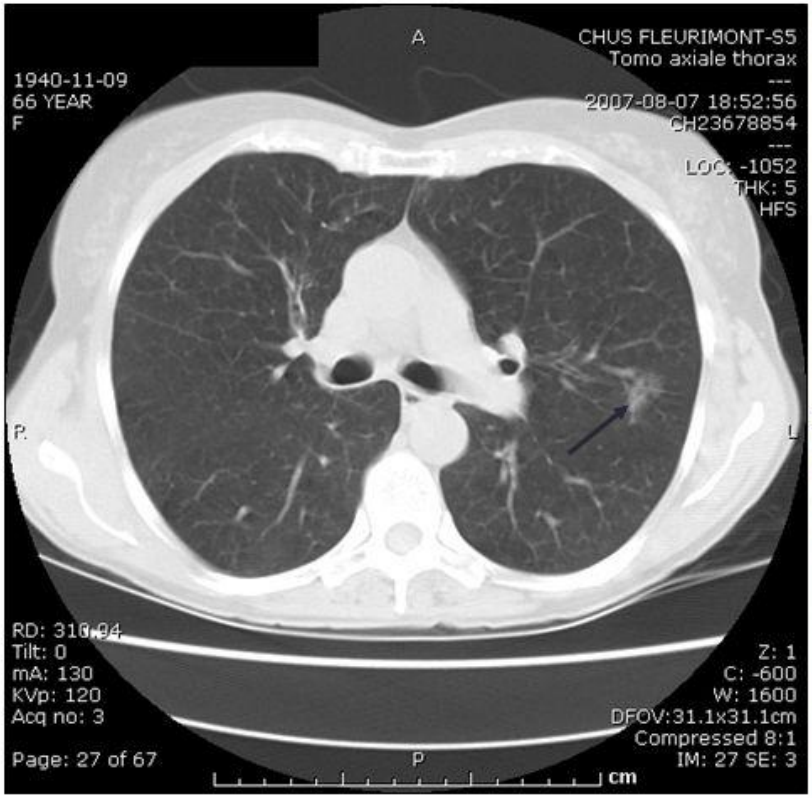
Early manifestations

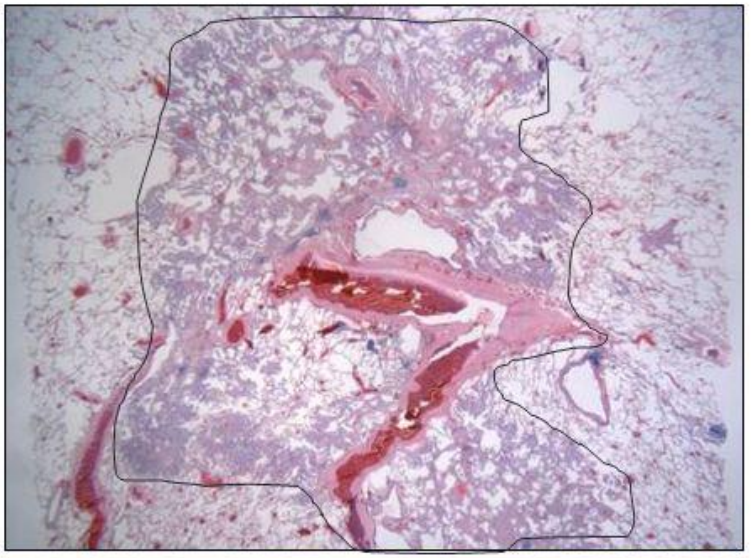


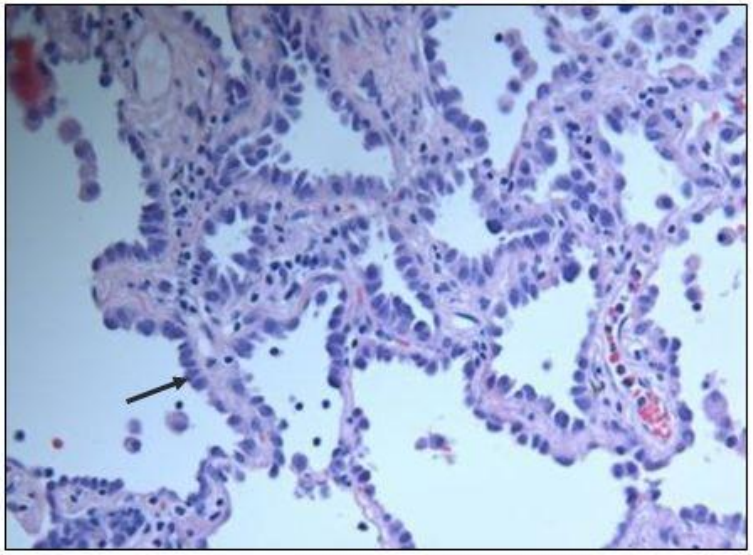
a.



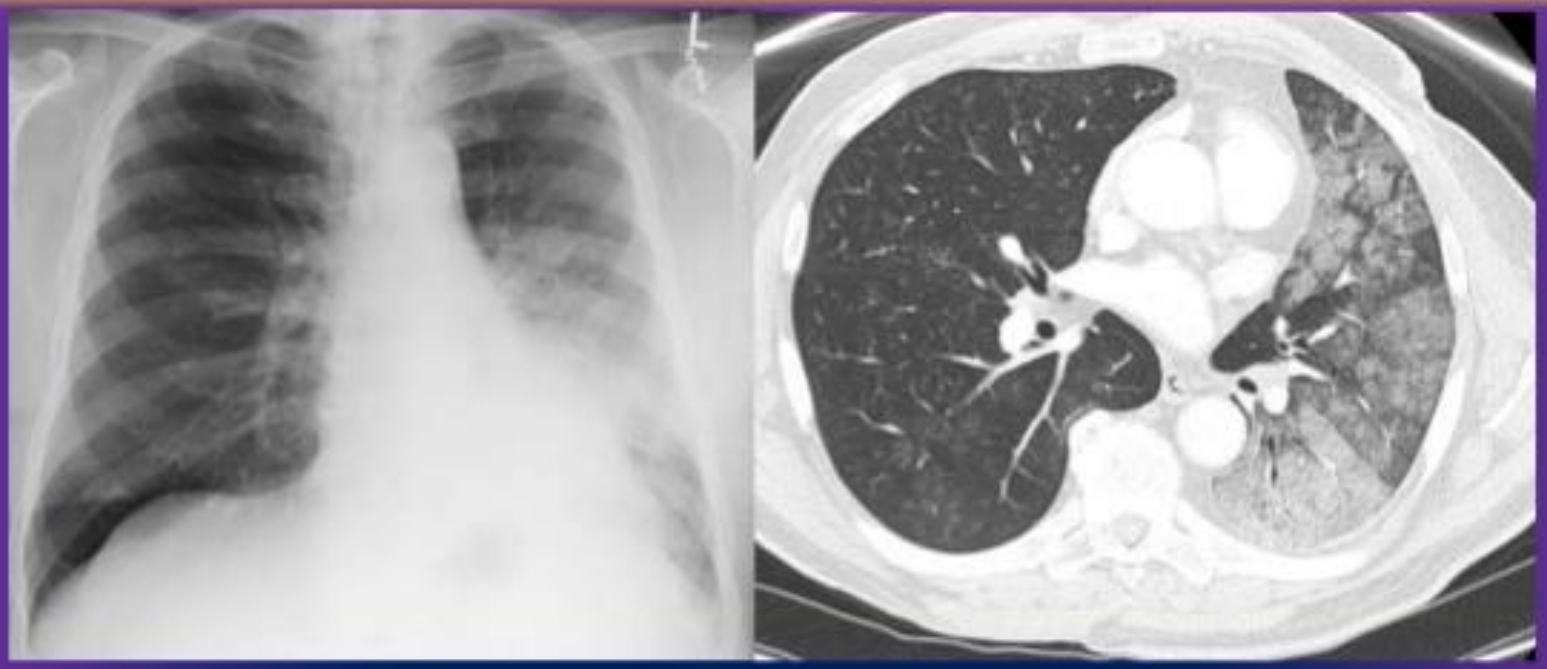
b.







Bronchioloalveolar carcinoma (adenocarcinoma-in-situ)



- Bronchoalveolar Carcinoma--- as ground glass haze in left lower lobe and lingula

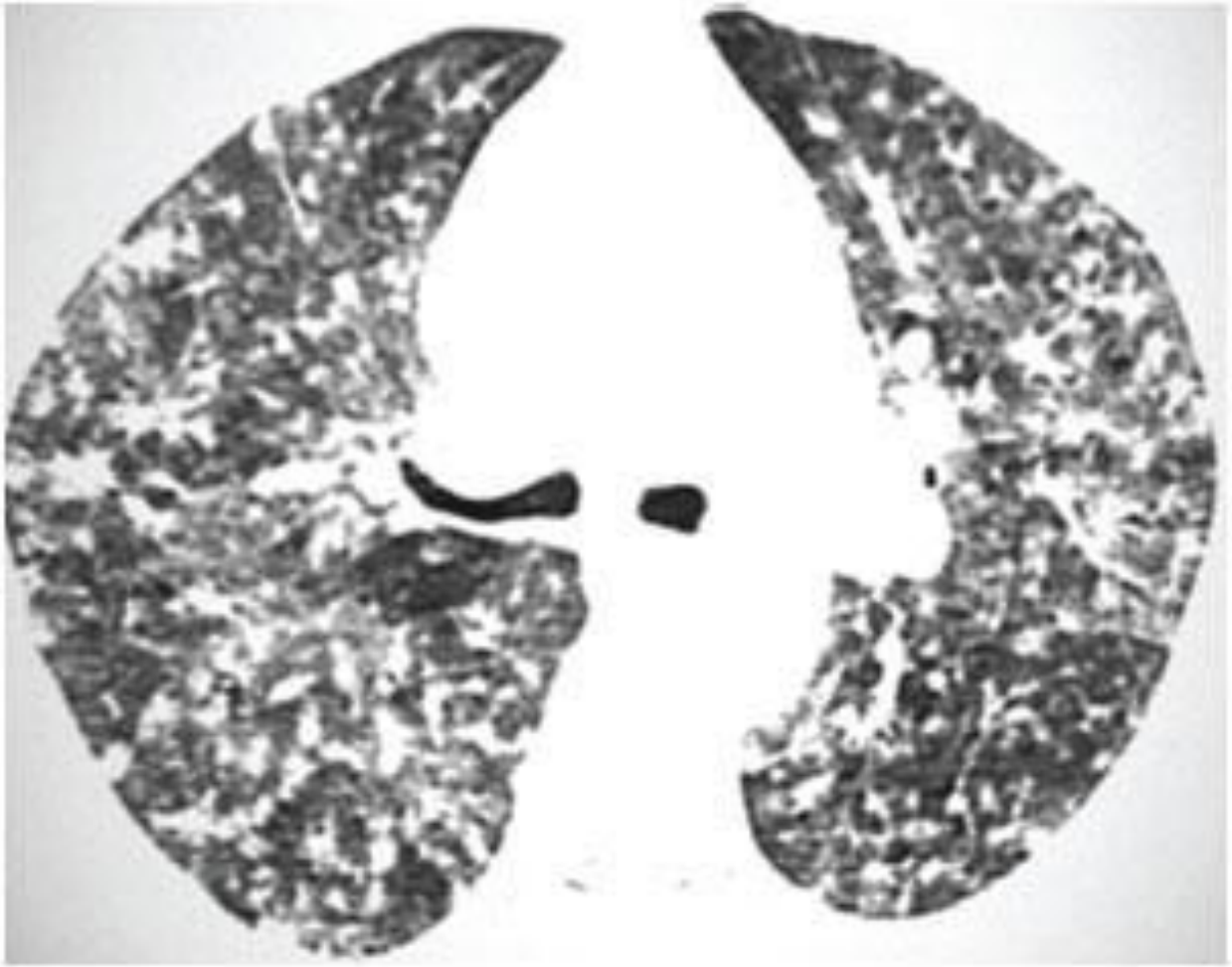
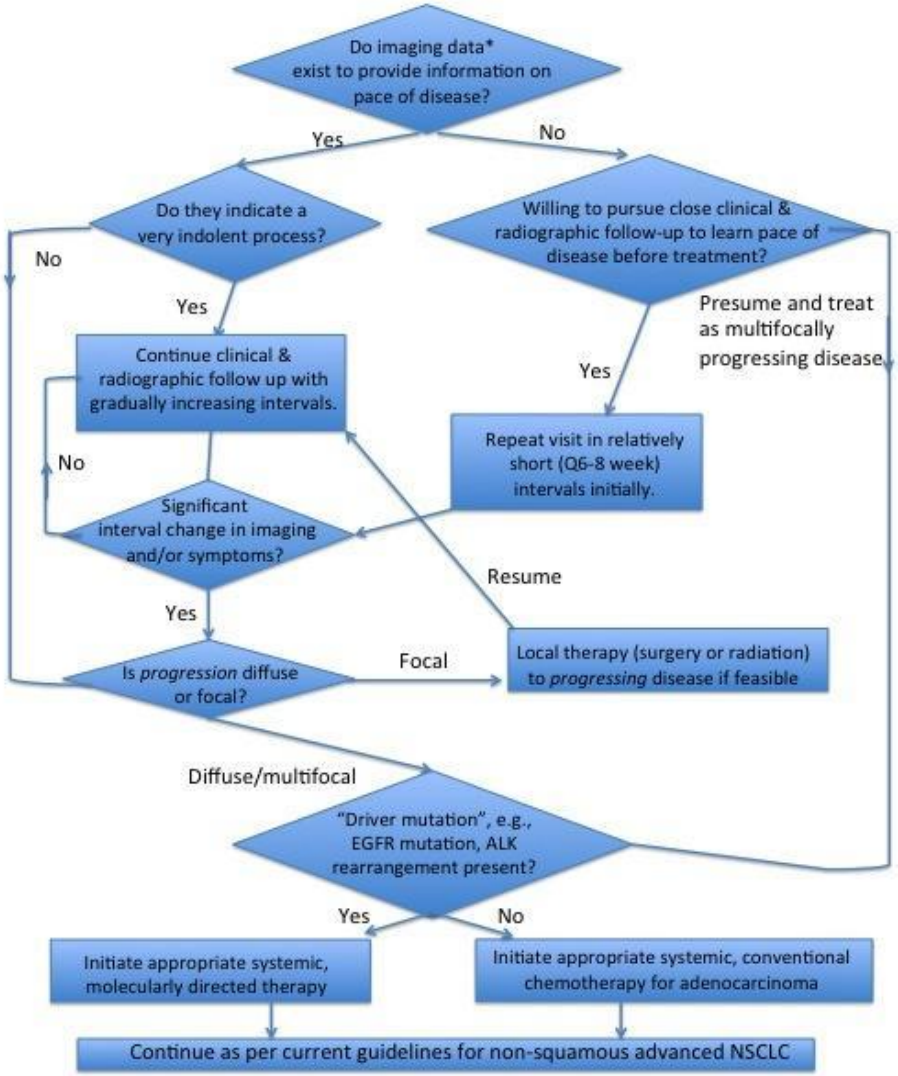


Figure 9 – CT scan of the chest of an 81-year-old male patient with cough and dyspnea diagnosed with diffuse bronchioloalveolar carcinoma showing multiple bilateral pulmonary nodules and scattered ground-glass opacities.

Dr. West Proposed algorithm for management of asymptomatic multifocal BAC



*comparison films showing minimal interval change, and/or PET with very low maximal SUV

AstraZeneca's **Iressa** (ZD1839)

Erlotinib in Bronchoalveolar Carcinoma: Phase II Study

- 98 patients screened, 71 patients eligible, 50 patients for analysis
- Treatment: erlotinib 150 mg po qd
- 26% never smoked; 68% female; 24% 1 prior chemotherapeutic treatment
- Partial responses: 13/50 (26%)
- Responders:
  - male/female: 13% / 32% ($P = .18$)
  - never smoked/smoked: 46% / 19% ($P = .07$)

Miller VA et al. *Proc Am Soc Clin Oncol.* 2003;22: 619. Abstr 2491.