LUNG CANCER

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Cancer mortality

- Cancer deaths accounted for 23.1% of all deaths in the United States in 2017.
- It is second only to cardiovascular deaths as a major cause of mortality.
- For both men and women, lung cancer was the major cause of cancer death and accounted for 5.1% of all deaths
- More people die of lung cancer than of prostate, breast, and colorectal cancer combined

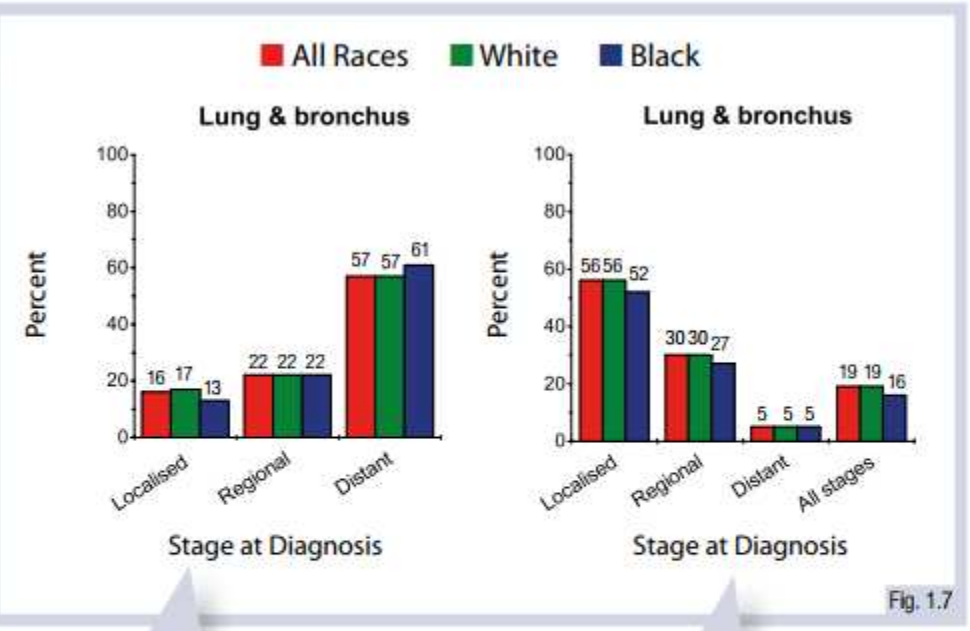


Fig. 1.7

Stage distribution by race, United States, 2008-2014

5-year relative survival rates by race and stage at diagnosis, United States, 2008-2014

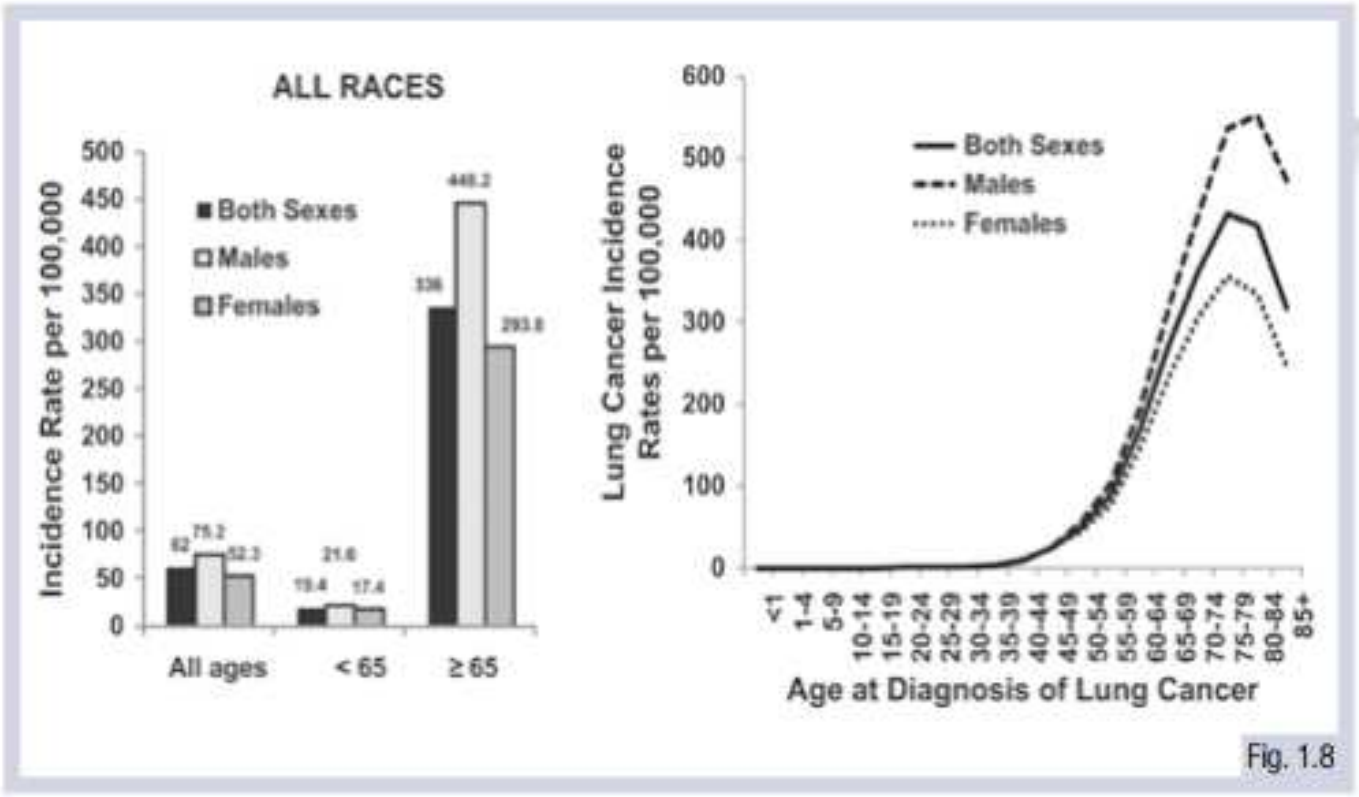

ALL RACES
Incidence Rate per 100,000
500
450
400
350
300
250
200
150
100
50
0
Both Sexes
Males
Females
62
75.2
52.3
19.4
21.6
17.4
336
448.2
293.8
All ages
< 65
≥ 65
Lung Cancer Incidence Rates per 100,000
600
500
400
300
200
100
0
Both Sexes
Males
Females
<1
1-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85+
Age at Diagnosis of Lung Cancer

Fig. 1.8

Mediastinal tumors

- Anterior mediastinum (60%)
- Substernal goiter
- Germ cell tumor or teratoma
- Thymoma
- Non-Hodgkin's lymphoma
- Nodular sclerosing Hodgkin's disease
- Middle mediastinum
- Bronchogenic or esophageal cysts
- Most common site for hyperparathyroid states
- Posterior mediastinum
- Neuroblastoma (children)

Table II. Summary of anterior mediastinal masses

Type of Mass	Epidemiology	Gender Predilection	Important Labs	Imaging	Treatment
Thymoma	0.13 cases per 100,000, with mean age 40-60	Equal	β HCG AFP, T3, T4, TSH gamma globulins ACTH, ADH serum antiacetylcholine receptor antibody	CXR CT Scan FDG-PET	Surgical resection
Thymic Carcinoma	1% of thymic malignancies, mean age of 46	Men	Same as for thymoma	CT	Surgical resection
Thymolipoma	5% of thymic masses	Equal	CBC Gamma globulins TSH	CXR CT MRI	Complete Surgical Resection
Thymic Cyst	1-3% of anterior mediastinal masses	No information found	For large multilocular thymic cyst: HIV	CXR	Complete Surgical Resection
Hodgkins Lymphoma	8500 cases annually, bimodal distribution (mean ages 2-65)	Male in young adults	CBC, ESR, BMP, LFT, LDH, lipid panel, calcium, βHCG, HIV Lymph node biopsy	CXR FDG-PET (for staging)	Stage dependent Chemotherapy +/- radiation
Non-Hodgkins Lymphoma	19.5 cases per 100,000 per year, 3.4% of all cancer deaths	Men	CBC, BMP, LDH SPEP, Lymph node biopsy	FDG –PET (for staging)	Stage dependent radiation +/- Chemotherapy
Germ Cell Tumors/ Teratoma	1-10% of tumors originating in the mediastinum	Equal	AFP hHCG	CXR CT of chest + abdomen Scrotal U/S	Complete Surgical resection +/- adjuvant chemotherapy
Substernal Goiter	5-10% of mediastinal masses	No data available	TSH, T3, T4	CT scan Radionucleotide	Above brachiocephalic vein: observe Below Brachiocephalic vein: resection

Table III. Summary of Middle compartment tumors

Type of Mass	Epidemiology	Gender Predilection	Important Labs	Imaging	Treatment
Esophageal tumors	16,940 new cases of esophageal cancer diagnosed annually	Equal	General labs	PET-CT Barium swallow Endoscopic ultrasound Biopsy	Radiation Chemotherapy +/- resection
Parathyroid adenoma	80-85% of hyperparathyroid cases	No data available	BMP, Ca^{+} PTH, serum 25-hydroxyvitamin D, 24 hour urinary Ca^{+}	Ultrasound Sestamibi Scan SPECT/CT	Resection or hormone replacement therapy in mild cases.
Bronchogenic cyst	5-10% of pediatric mediastinal masses	No data available	General labs	CXR, CT, MRI	Complete resection
Esophageal Ductal Cyst	5-10 % of mediastinal cysts	No data available	General labs	CT Endoscopic ultrasound	Resection through thoracotomy or VATs
Tracheal Tumors	Incidence of 0.1 out of 100,000 per year	No data available.	General labs	CXR, CT, PET-CT, bronchoscopy	Resection reconstruction Radiation
Pericardial cyst	1 out of 100,000 per year	No data available	General labs	CXR, CT, MRI, echocardiogram	Resection or aspiration vs. observation

Table IV. Summary of Posterior compartment tumors

Type of Mass	Epidemiology	Gender Predilection	Important Labs	Imaging	Treatment
Neurogenic tumors	19-39% of all mediastinal masses	No data available	General labs	CXR, CT, MRI	Surgical resection
Thymic neuroendocrine tumor	0.13 cases per 100,000	Male	Urine 5-HIAA Serum chromogranin Serum cortisol	CT, MRI Radiolabeled Somatostatin imaging FDG-PET	Surgery +/- radiation

Thymomas

- One third of patients are asymptomatic.
- Another third of patients present with local symptoms such as cough, dyspnea or chest pain.
- The remaining third present with autoimmune disorders, most commonly myasthenia gravis.
- Circulating antibodies that block acetylcholine receptors at the postsynaptic neuromuscular junction.

Thymomas

- Thymomas are subdivided into different types (so-called A, AB, B1, B2, and B3) based upon:
- The atypia of tumor cells
- The relative proportion of the associated non-tumoral lymphocytic component
- Resemblance to the normal thymic architecture.
- Thymic carcinomas are similar to their extrathymic counterpart, the most frequent subtype being squamous cell carcinoma.

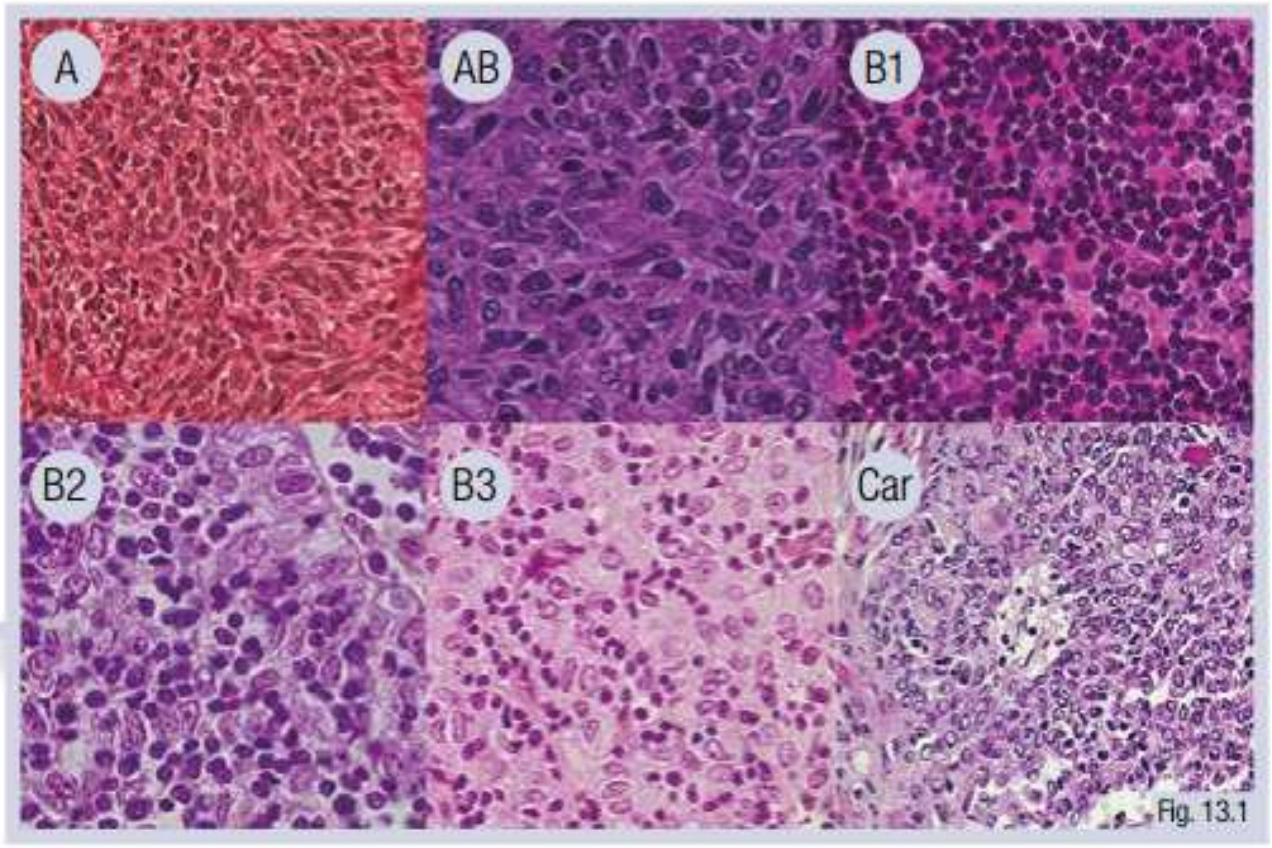


Fig. 13.1

TNM Staging

T – Primary Tumour

T1	Tumour encapsulated or extending into the mediastinal fat, may involve the mediastinal pleura.
T1a	No mediastinal pleural involvement
T1b	Direct invasion of the mediastinal pleura
T2	Tumour with direct involvement of the pericardium (partial or full thickness)
T3	Tumour with direct invasion into any of the following; lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or vein
T4	Tumour with direct invasion into any of the following; aorta (ascending, arch or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, or oesophagus

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in anterior (perithymic) lymph nodes
N2	Metastasis in deep intrathoracic or cervical lymph nodes

M – Distant Metastasis

M0	No pleural, pericardial or distant metastasis
M1	Distant metastasis
M1a	Separate pleural or pericardial nodule(s)
M1b	Distant metastasis beyond the pleura or pericardium

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T Any T	N1 N0, N1	M0 M1a
Stage IVB	Any T Any T	N2 Any N	M0, M1a M1b

TNM, Tumour, Node, Metastasis.

Fig. 13.2

Pulmonary nodule

- 0.1% discovered on routine chest x-ray,
- BUT up to 30% on thin-slice CT
- 25% are benign
- If benign lesion is not diagnosed on chest x-ray, CT of the chest with contrast is required.
- High resolution of peripheral nodules
- May also identify unsuspected lymphadenopathy and other lesions.

Pulmonary nodule

- Changes on chest x-ray compatible with increased probability of malignancy:
- Upper lobe location
- Marginal spiculation
- More than 5 nodules
- >3cm diameter

Pulmonary nodule

- Solid pulmonary nodules
- Focal scar
- Granuloma
- Extrapulmonary lymph nodes
- Frequently found in pre-fissure
- Smooth, regular contour
- Malignancy (primary or metastatic)

Pulmonary nodule

- Subsolid pulmonary nodules
- Result of infection or hemorrhage
- Transient
- However, may represent part of pulmonary adenocarcinoma spectrum
- Ground glass change with or without solid areas

Evaluation of pulmonary nodule

- Transthoracic needle biopsy under CT guidance required for nodule where benign diagnosis is suspected that requires specific medical therapy.
- Bronchoscopy indicated if:
- Nodule deep within parenchyma or
- Or has an air bronchogram
- Or the risk of pneumothorax is high.
- Thoracoscopy preferred if peripheral nodule.
- Endobronchial ultrasound guided biopsy or fine needle aspiration more effective than mediastinoscopy to identify involved nodes
- Open biopsy if suspect that the lesion is malignant and surgical treatment indicated.

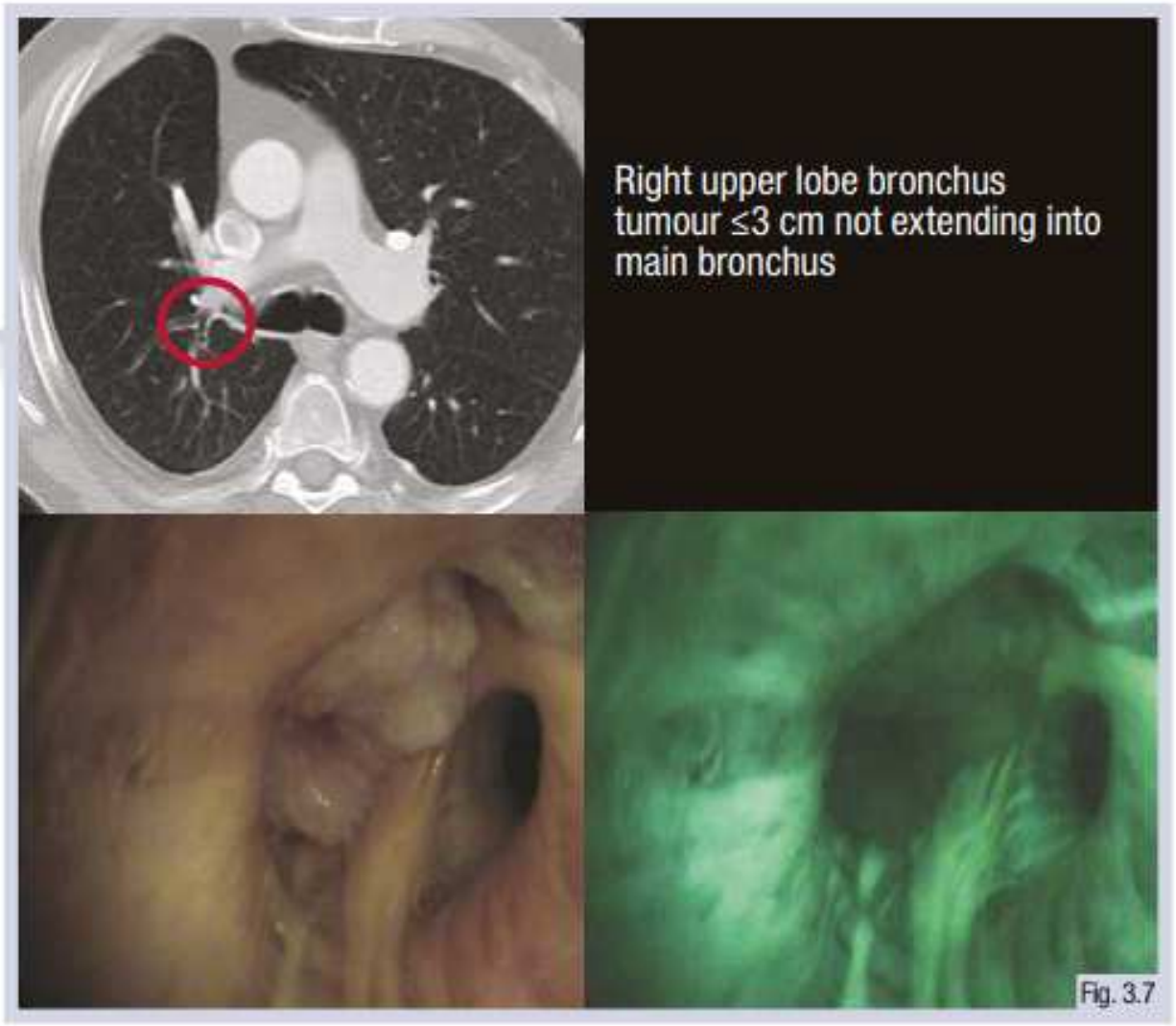

Right upper lobe bronchus
tumour ≤3 cm not extending into
main bronchus

Fig. 3.7

Evaluation of pulmonary nodule

- CT scan of chest and upper abdomen are done in all patients to detect nodal and extra-nodal disease.
- Cranial magnetic resonance imaging (MRI) is required for patients with stage IB-III lung cancer.
- Positron emission tomography (PET) has a complementary role to CT for two reasons:
- Detection of unexpected LN involvement or distant metastatic organ spread in 4%–12% of stage I-III lung cancer.
- Determination of the nature of some equivocal lesions on conventional CT imaging.

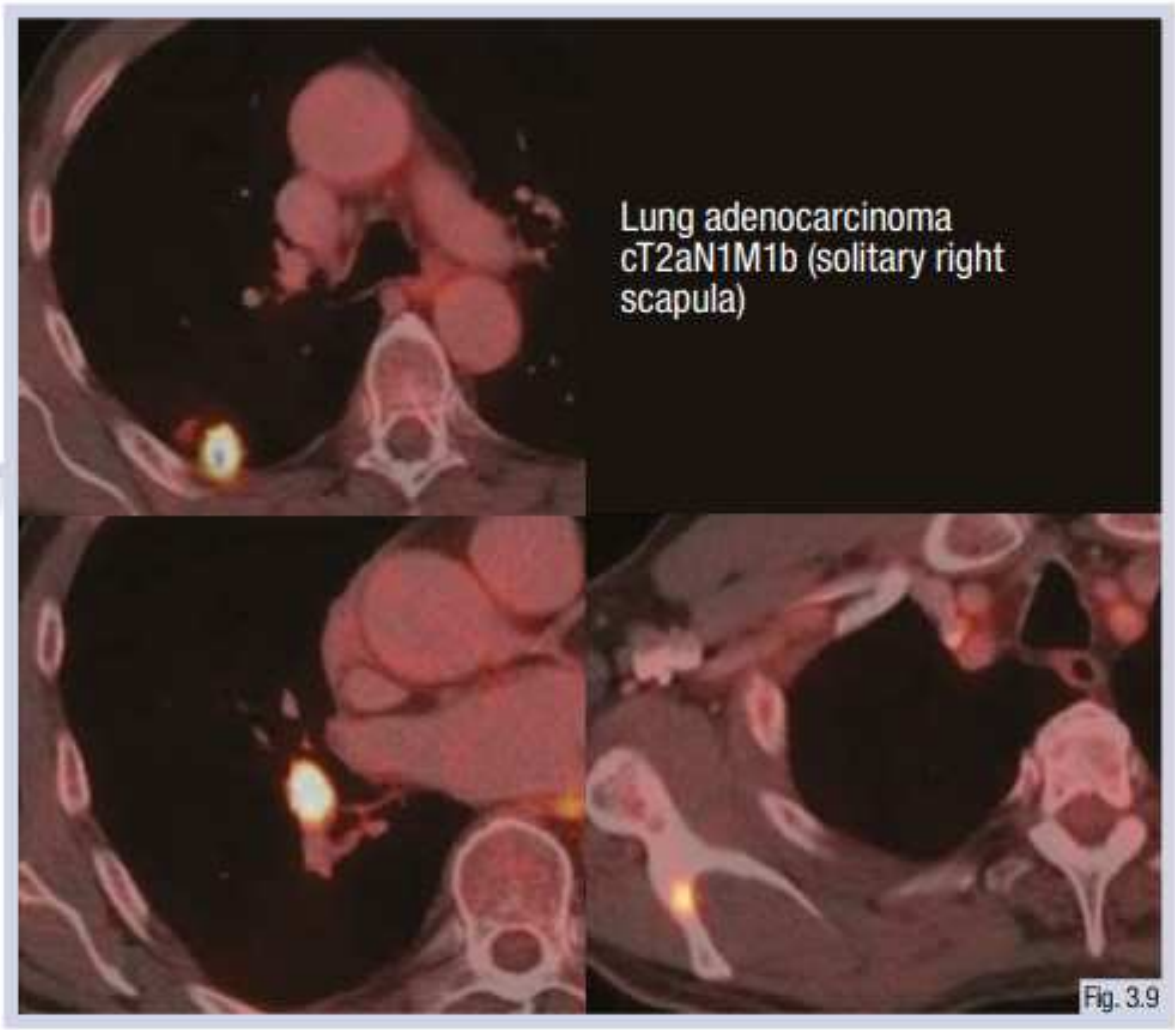


Fig. 3.9

Evaluation of pulmonary nodule

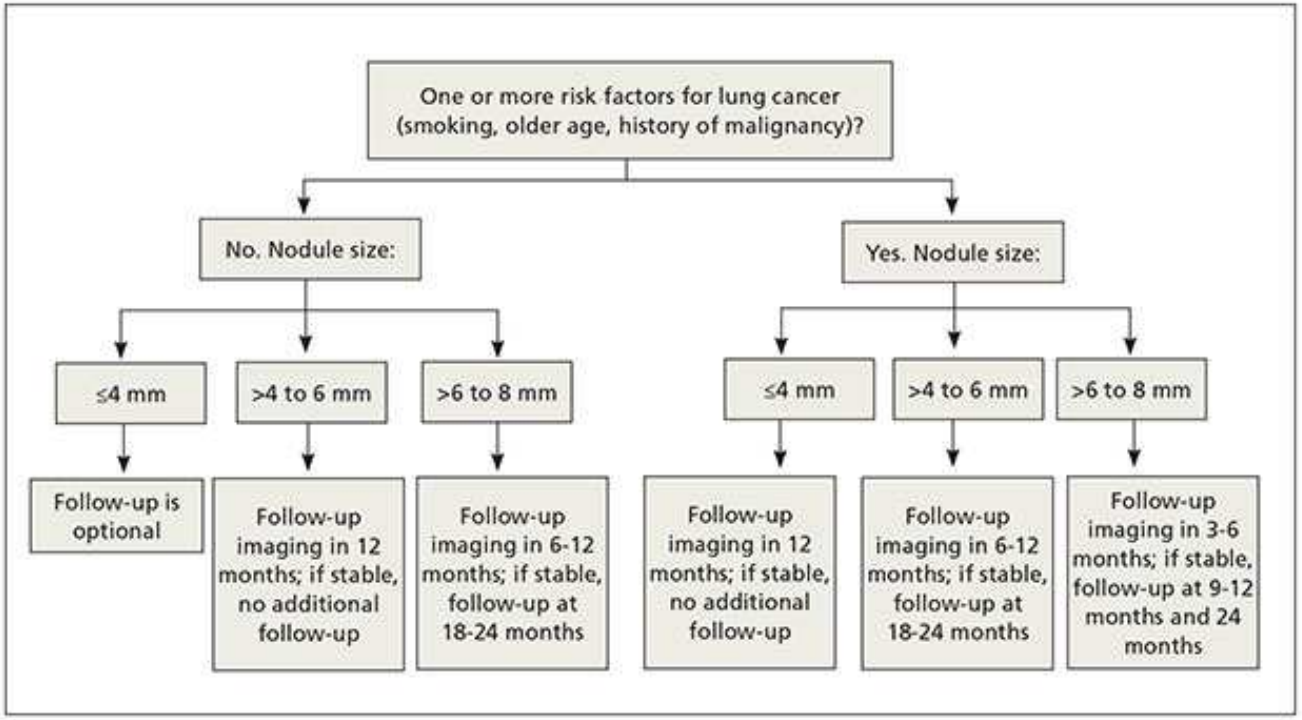
- False-negative PET findings in mediastinal LN staging occur in presence of:
- a central tumor
- N1 nodes
- tumor >3 cm
- enlarged LNs on CT
- False-positive PET findings in mediastinal LNs are due to the fact that fluorodeoxyglucose (FDG) uptake is not tumor specific.

https://www.mdedge.com/familymedicine/article/106108/oncology/pulmonary-nodule-x-ray-algorithmic-approach

Accessed 12/10/2019

ALGORITHM 2

Follow-up on solid nodules ≤8 mm depends on lung cancer risk, nodule size*[1]



* Decisions at every step should be based on an informed patient's preference/values.

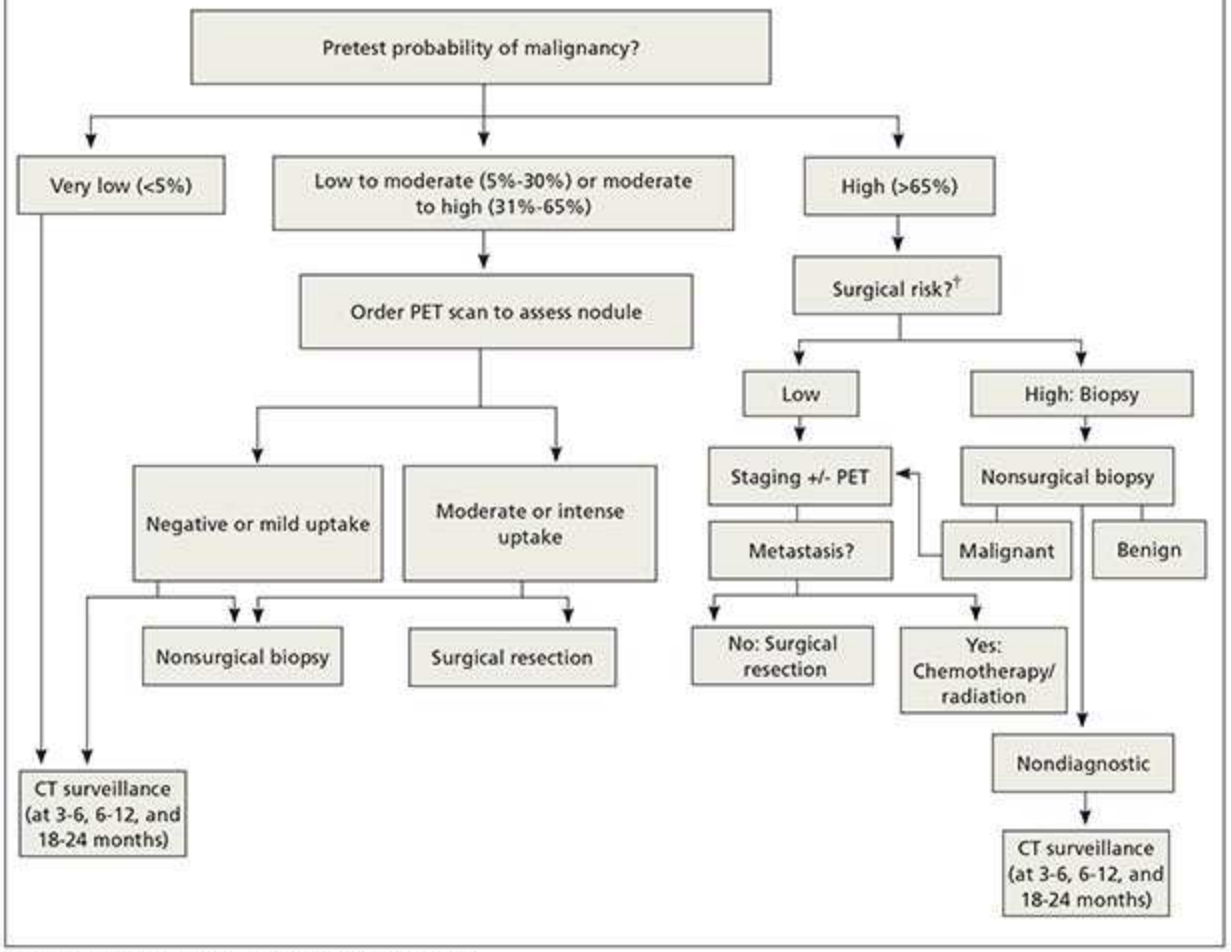
Source: Gould MK et al. *Chest*. 2013.[1]

https://www.mdedge.com/familymedicine/article/106108/oncology/pulmonary-nodule-x-ray-algorithmic-approach

Accessed 12/10/2019

ALGORITHM 1

Risk of lung cancer guides management of solid nodules >8 mm to 3 cm*[1]



CT, computed tomography; PET, positron emission tomography.

Source: Gould MK et al. *Chest*. 2013.[1]

* Decisions at every step should be based on an informed patient's preference/values.

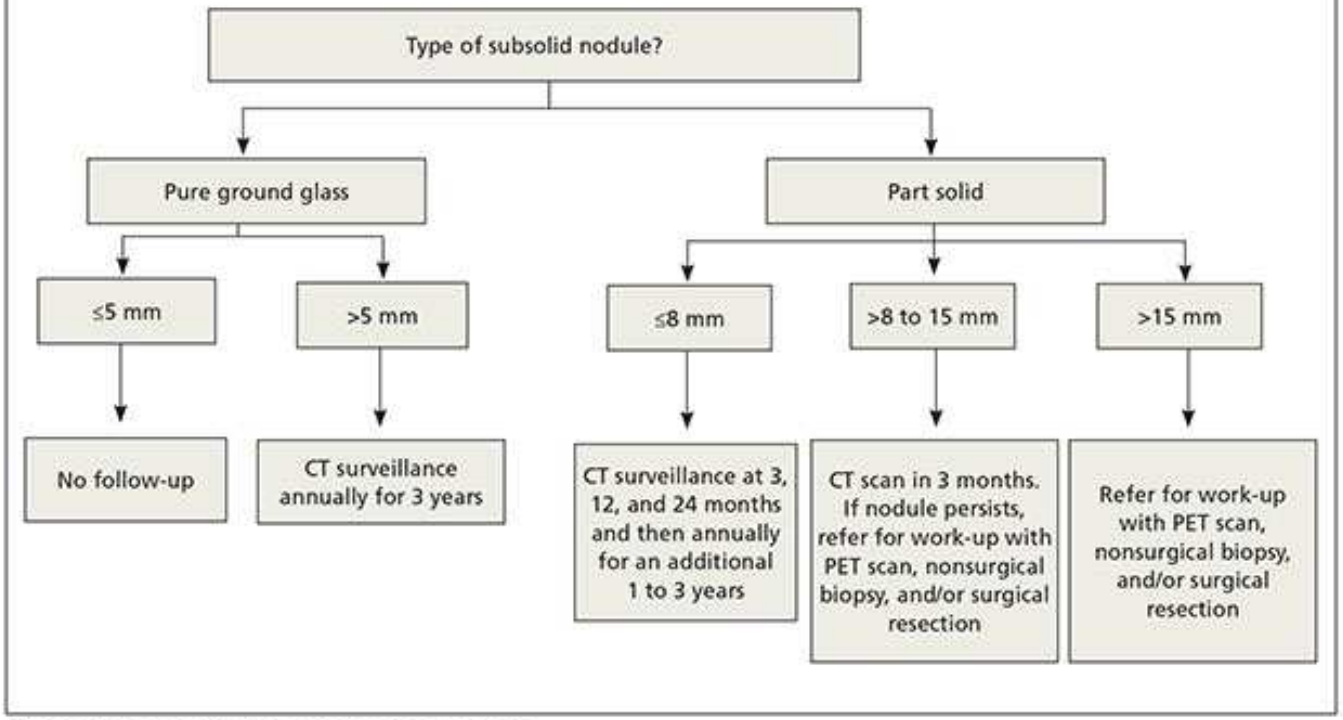
† A high-risk surgical candidate with a high-risk lung nodule may not go on to surgical resection but instead to stereotactic radiotherapy, which also may be considered for a patient with a nondiagnostic biopsy. These decisions should be guided by specialists.

https://www.mdedge.com/familymedicine/article/106108/oncology/pulmonary-nodule-x-ray-algorithmic-approach

Accessed 12/10/2019

ALGORITHM 3

Managing newly detected subsolid nodules*[1]



CT, computed tomography; PET, positron emission tomography.

* Decisions at every step should be based on an informed patient's preference/values.

Pulmonary hamartoma

- Benign
- Often incidental finding on chest-xray
- Rounded radio-opacity ("coin lesion")
- Usually solitary
- Well circumscribed
- Usually cartilage in which are entrapped elements of respiratory epithelium
- Clonal neoplasm
- 6p21 or 12q14-15 mutations

Adenocarcinoma

- Most prevalent non-small cell carcinoma
- 38.5% of non-small cell lung carcinoma
- More common in women
- Most common type of lung cancer in male non-smokers
- More common in those of sub-Saharan African origin
- Age 60 - 70

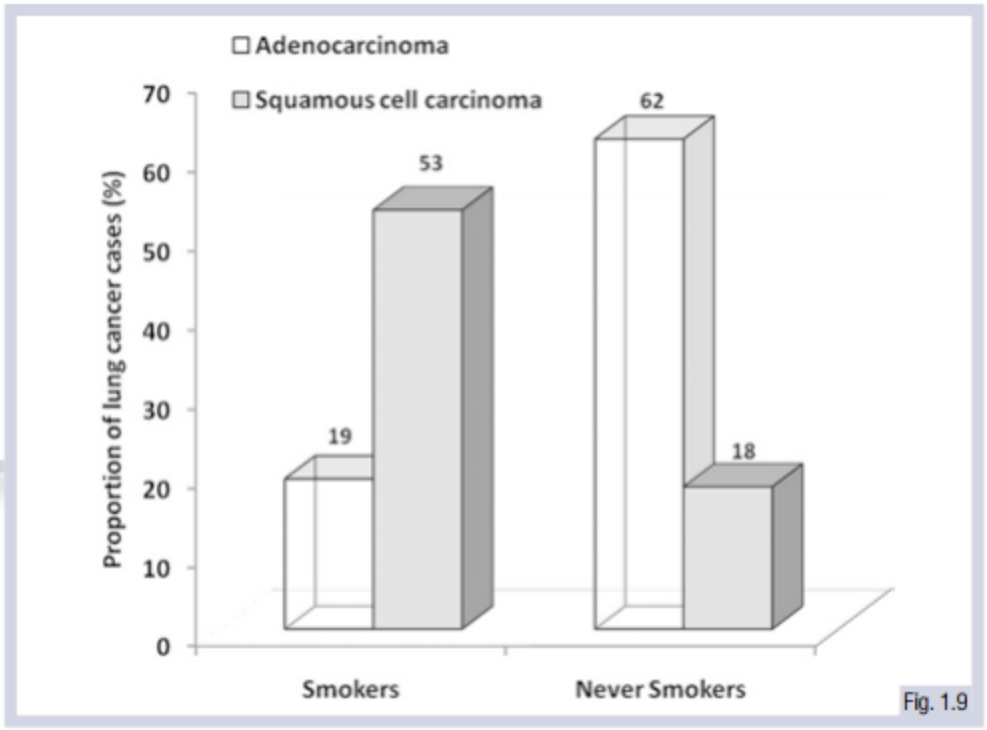

Adenocarcinoma
Squamous cell carcinoma
Proportion of lung cancer cases (%)
70
60
50
40
30
20
10
0
19
53
62
18
Smokers
Never Smokers

Fig. 1.9

Chemoprevention

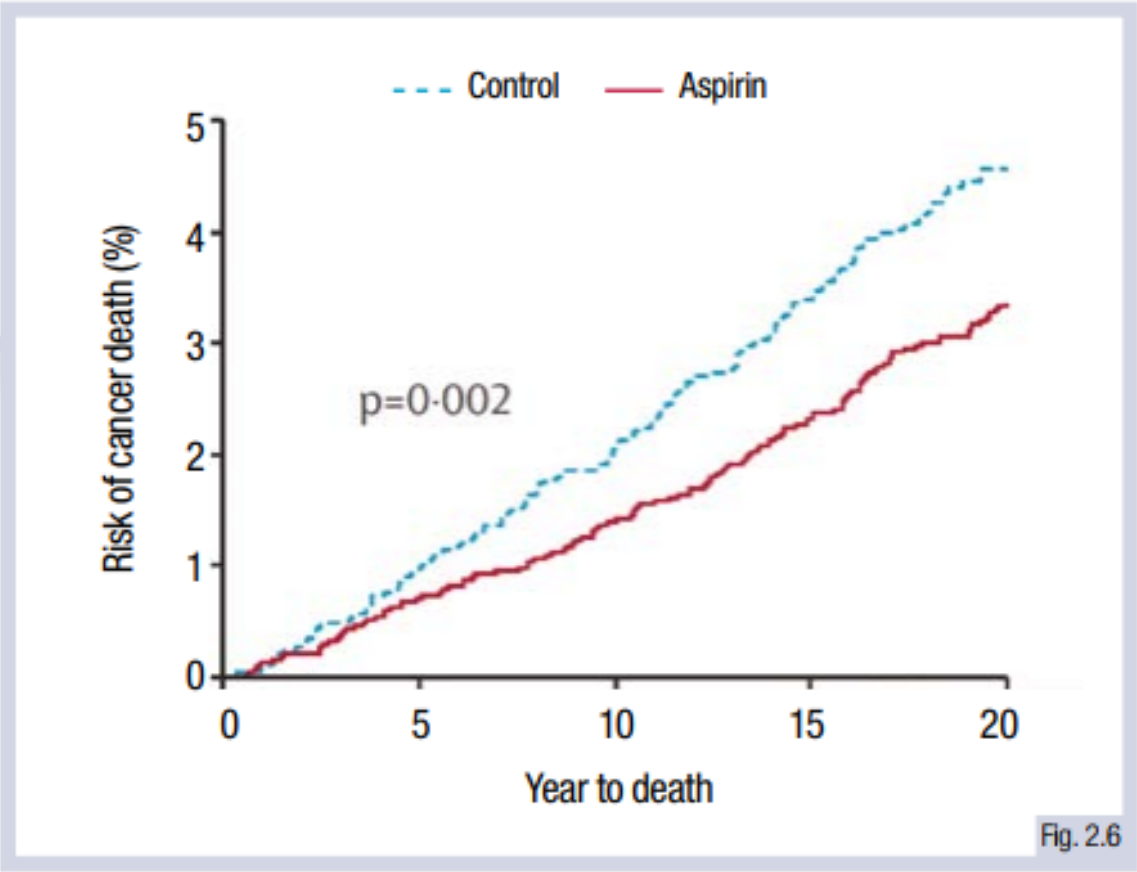


Fig. 2.6

Adenocarcinoma

- Sites
- More common in upper lobe
- More common as peripheral tumor
- Brain often only site of metastasis
- Bone, liver, and adrenal metastatic sites (in descending order)

  Risk for brain metastasis increases with tumor size and lymph node stage

Adenocarcinoma

- Prognostic factors
- Favorable
- Lepidic
- Unfavorable:
- Size larger than 2.5 cm
- Visceral pleural invasion
- Micropapillary or solid type

Pathologic description

- Gross
- Usually tan-white cut surface
- May have central area of scar or necrosis
- Usually well defined but non encapsulated
- Minimally invasive lesion is usually solitary,
- Histopathology
- Continuous spectrum
- If invasive (extent > 5 mm), named by predominant pattern
- 5 histologic patterns
- Mucinous and non mucinous subtypes

Adenocarcinoma

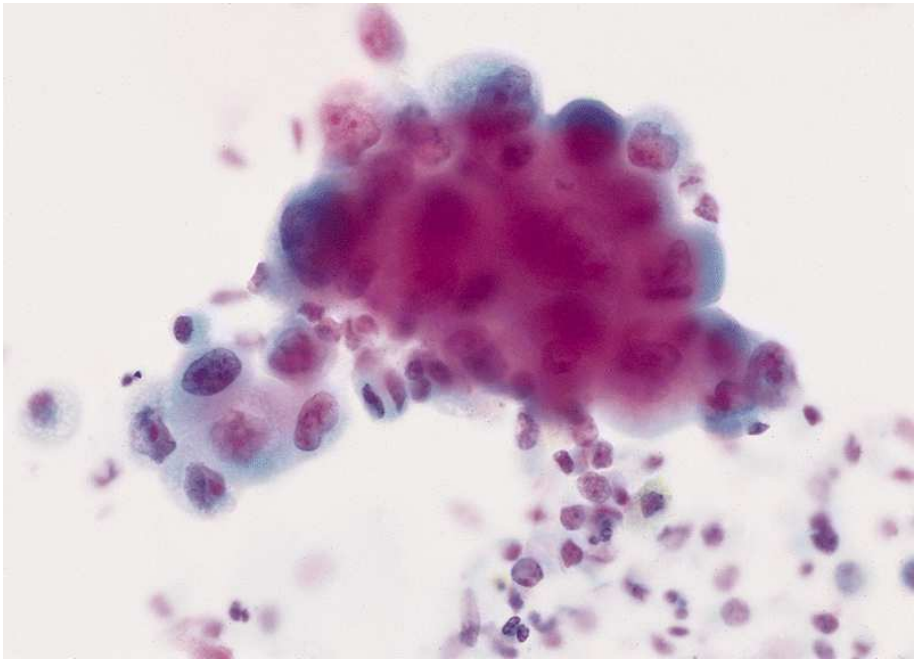
Small apical mass with some surrounding fibrosis and emphysematous change.

Pigmentation within the mass is apparent.

Fig. 12-1

Colby, TV, Koss, MN, Travis, WD., "Tumors of the lower respiratory tract. " Atlas of Tumor Pathology, Third Series, Fascicle 13. Armed Forces Institute of Pathology, Washington, D.C. 1995.

Bornchial wash cytology



Bronchial wash specimen shows cells that overlap and form a three-dimensional group. Atypical features of the nuclei can be seen at the edge of the group. Some of the cells have prominent nucleoli.

Typical for adenocarcinoma.

Fig. 12-24

Colby, TV, Koss, MN, Travis, WD., "Tumors of the lower respiratory tract. " Atlas of Tumor Pathology, Third Series, Fascicle 13. Armed Forces Institute of Pathology, Washington, D.C. 1995.

World Health Organization classification

- Pre-invasive patterns

  Atypical adenomatous hyperplasia precedes lepidic pattern

  Multifocal, asymptomatic

  Adenocarcinoma in situ if >0.5cm
- May have ground glass pattern on x-ray.
- Bronchorrhea common.

World Health Organization classification

- Minimally invasive carcinoma
- A lepidic tumor less than 3 cm in size with <5mm or >10% invasion
- Invasive carcinoma
- Lepidic (usually non-mucinous adenocarcinoma)
- Acinar
- Papillary
- Micropapillary
- Solid

World Health Organization classification

- Other adenocarcinoma types
- Mucinous adenocarcinoma
- Colloid adenocarcinoma
- Fetal
- Enteric.
- TTF1 present (14q13.3)
- CK7 (keratin) positive (12q13.13)

Histologic patterns

- Lepidic

  Type II pneumocytes and Clara cells

  Proliferate to line alveolar walls (lepidic)

  Lacks architectural complexity

  No lymphovascular or perineural invasion

  Usually minimally invasive

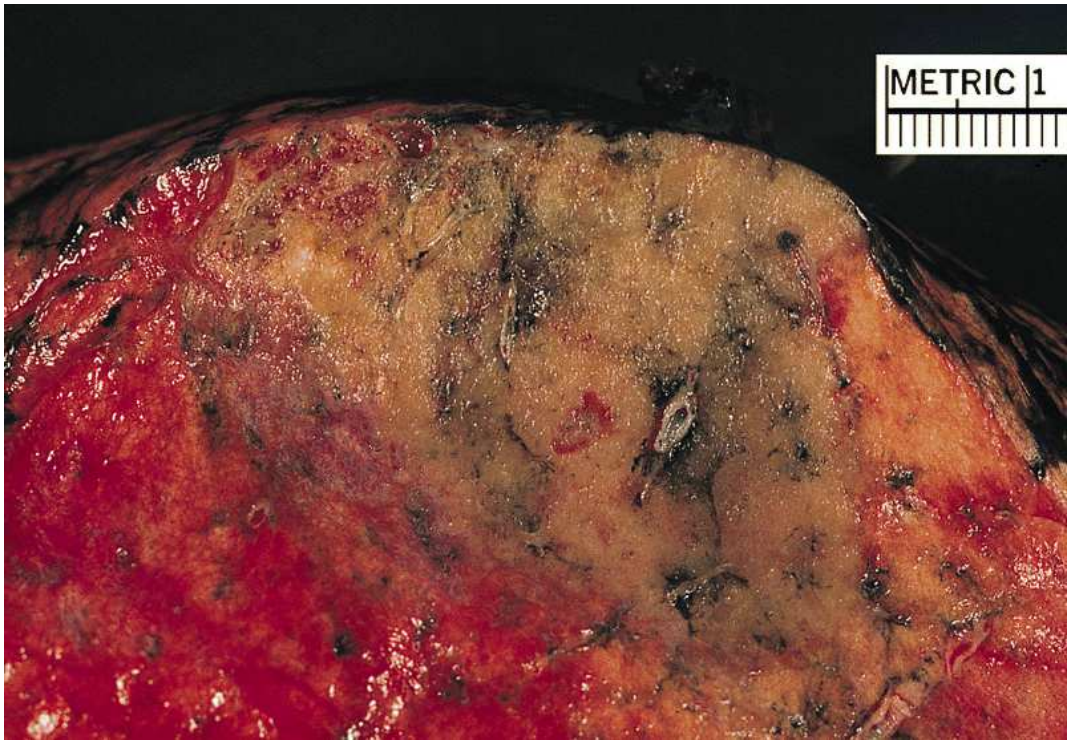
  Once known as "bronchioalveolar carcinoma"

  Non-mucinous

  No Thyroid transcription factor 1 (TTF1)

  K-ras mutation

Adenocarcinoma

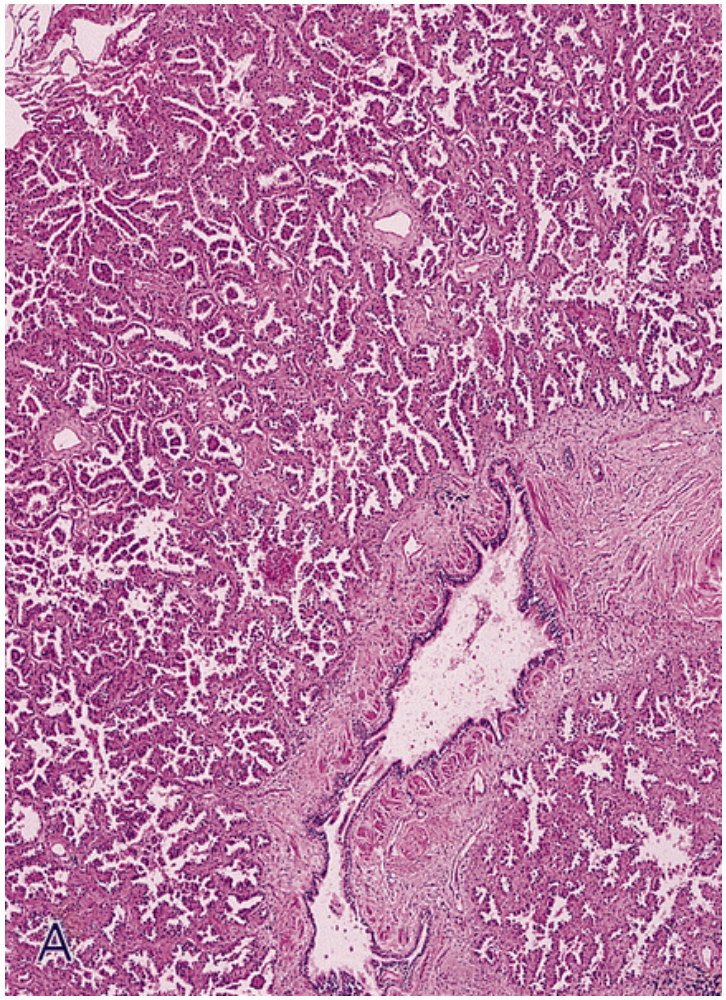


The superior portion of this upper lobe (left) is almost entirely consolidated by mucinous tumor with lepidic growth. Despite the consolidation, there is an absence of necrosis and hemorrhage, and the architecture is maintained.

Fig. 13-1.

Colby, TV, Koss, MN, Travis, WD., "Tumors of the lower respiratory tract. " Atlas of Tumor Pathology, Third Series, Fascicle 13. Armed Forces Institute of Pathology, Washington, D.C. 1995.

Adenocarcinoma



Resection specimen from a Clara cell non-mucinous adenocarcinoma. There is a proliferation of eosinophilic cells with cytoplasmic protrusions lining the alveolar walls.

Lepidic growth

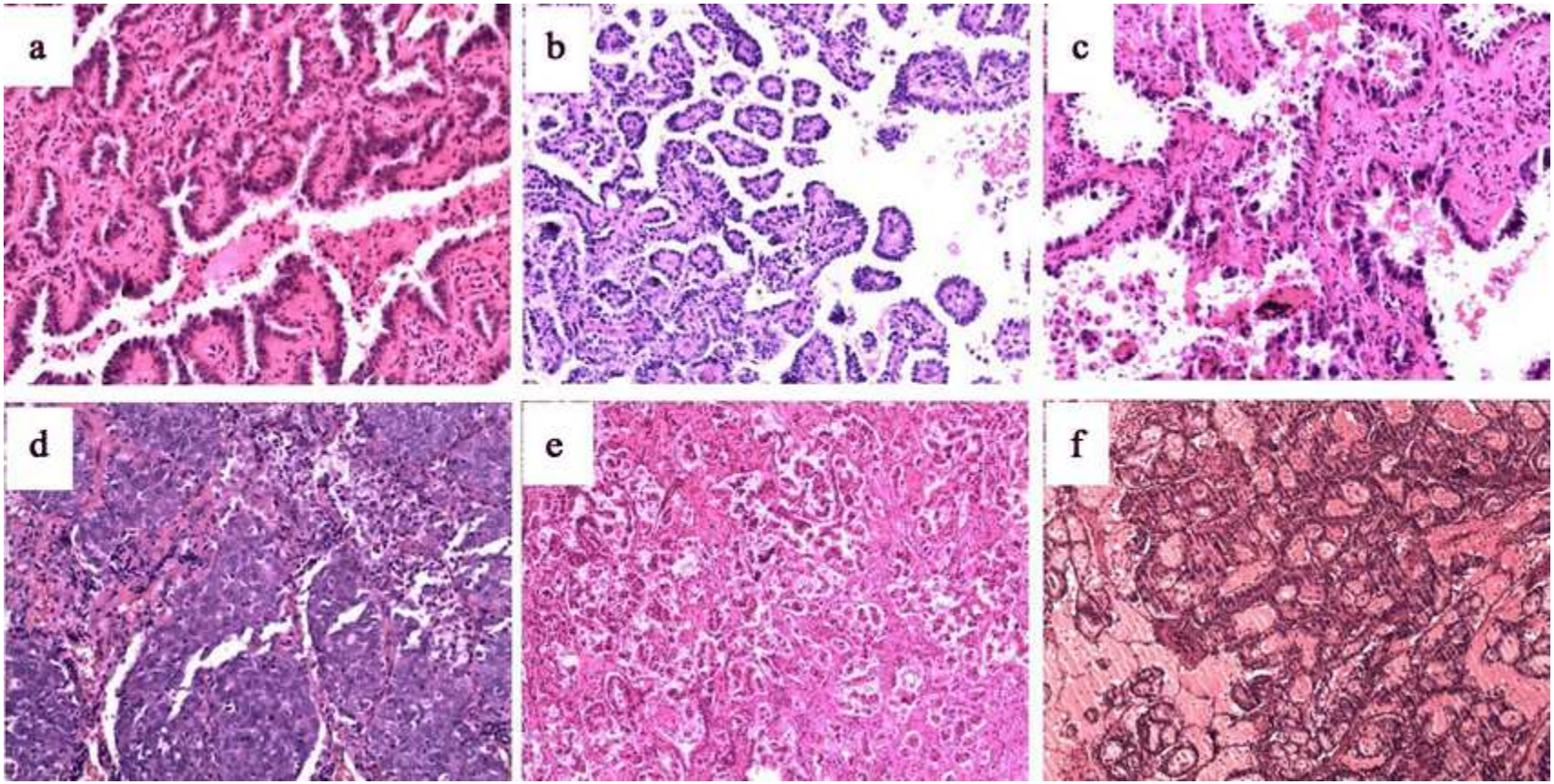
Fig. 13-10A

Colby, TV, Koss, MN, Travis, WD., "Tumors of the lower respiratory tract. " Atlas of Tumor Pathology, Third Series, Fascicle 13. Armed Forces Institute of Pathology, Washington, D.C. 1995.

Histologic patterns

- Acinar
- Gland forming
- Round or oval glands invading a fibrous stroma
- Papillary
- Malignant cuboidal or columnar cells replace alveolar lining
- Contains fibrovascular cores
- Micropapillary
- Tufting lack fibrovascular cores
- Solid
- Sheets of neoplastic cells

Adenocarcinoma subtypes



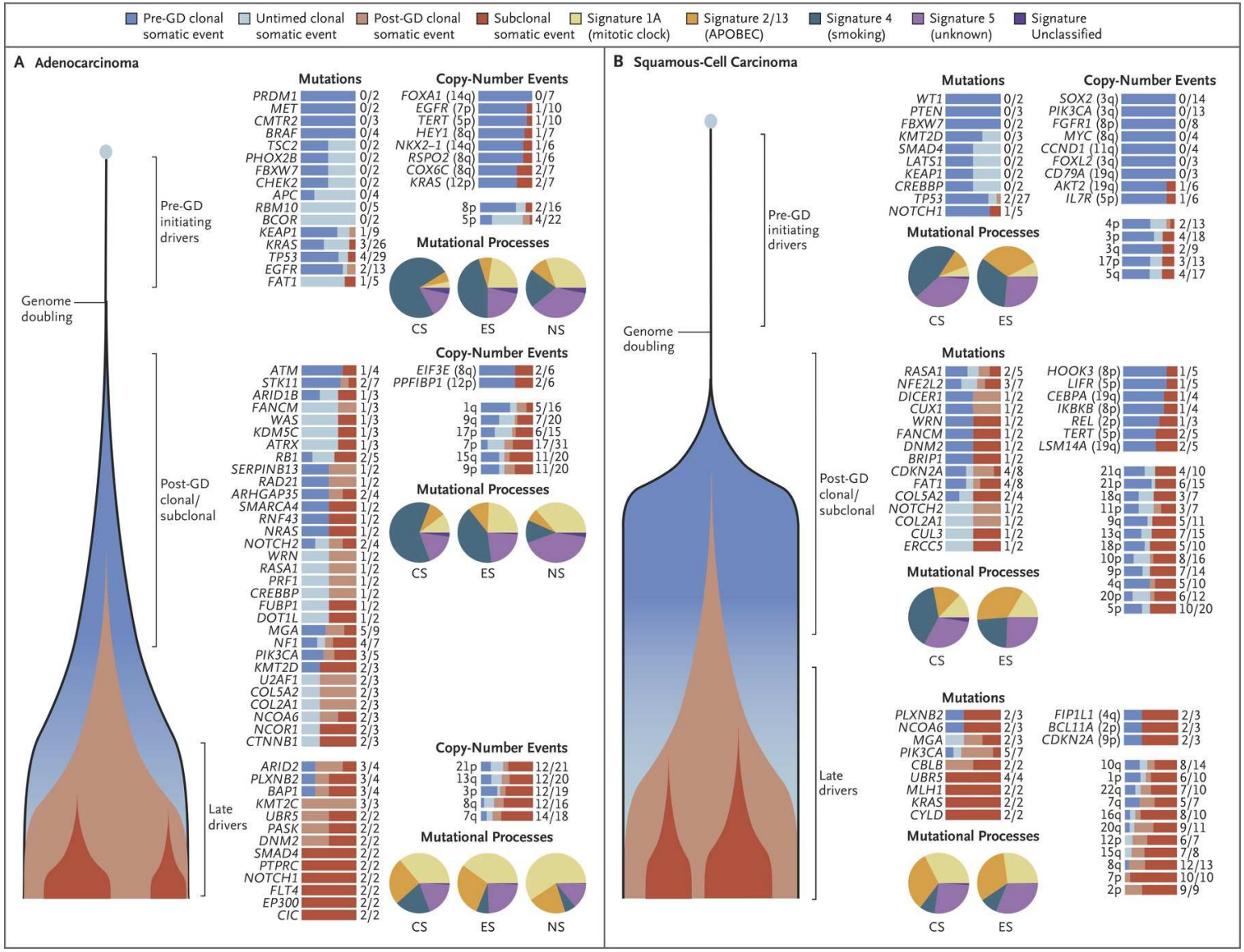
https://www.researchgate.net/publication/277252711/figure/fig1/AS:423261164052481@1477924733116/Lung-adenocarcinoma-histologic-subtypes-hematoxylin-and-eosin-stain-x40-a-lepidic.png
Accessed 01/20/2020

Lymph node metastasis based on predominant pattern of pulmonary adenocarcinomas	
Lepidic:	7%
Acinar:	46%
Papillary:	43%
Solid:	51%
Micropapillary:	76%

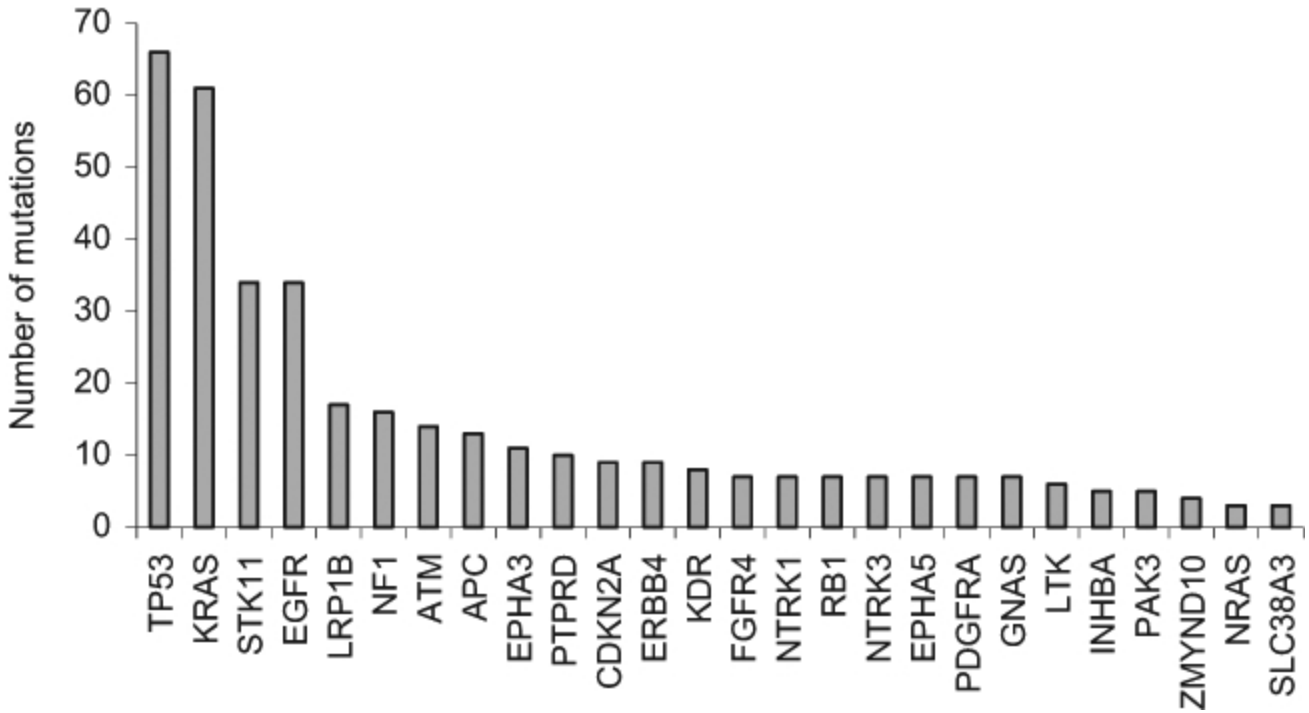
Fig. 4.6

Molecular description

- p53 and CDKN2A (p15) checkpoints lost early in course of evolution of non small cell carcinoma of epithelial cell origin
- Biallelic loss
- 90% PD-L1 positive
- Due to targeted therapy, molecular testing is routine



https://www.nejm.org/doi/10.1056/NEJMoa1616288 Accessed 05/05/2020



Gruelich, H, “The genomics of lung carcinoma,” Genes Cancer. 2010 Dec; 1(12): 1200–1210.
doi: 10.1177/1947601911407324
Accessed 05/20/20

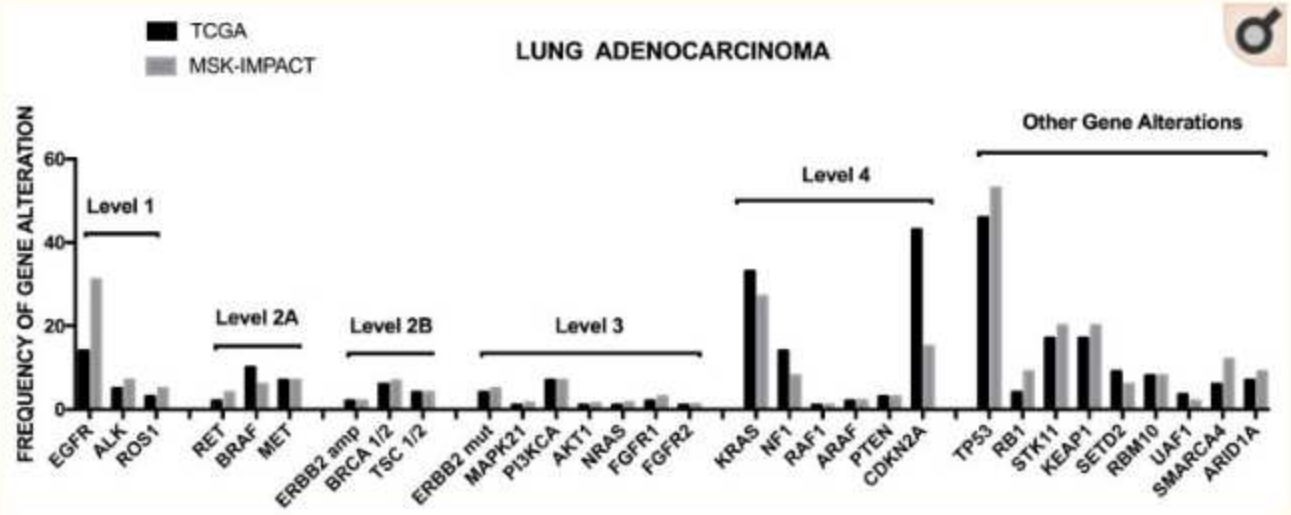


Figure 2

Frequency of main genetic alterations, subdivided into various levels according to the degree of therapeutic actionability of genetic events, in two groups of lung adenocarcinoma patients: TCGA data sets based on the analysis of non-metastatic patients and MSK-IMPAC data based on the analysis of recurrent/metastatic lung adenocarcinomas. Date are reported in [13,19].

El-Telbani, A, Ma, PC, “Cancer genes in lung cancer,” Genes Cancer. 2012; 3(7-8): 467–480. doi: 10.1177/1947601912465177
Accessed 05/20/20

Significant gene mutations

MUTATED GENE	ASIAN PRIMARY TUMOR	ASIAN METASTASES	WHITE PRIMARY TUMOR	WHITE METASTASES	BLACK PRIMARY TUMOR	BLACK METASTASES
DDR	10.3	12.7	18.4	21.7	17.8	28.3
EFGR	53	59	18.7	21.5	30	28.2
KRAS	12.2	9.7	35.7	31	26.1	24.3

Percentage occurrence by race in public databases
Differences are significant

Molecular description

- Epidermal growth factor receptor (EGFR) mutations at 7p11.2:
- 10-15% of lung adenocarcinoma
- 49% in Asia
- Rare in mucinous subtype
- More common in never smokers, women

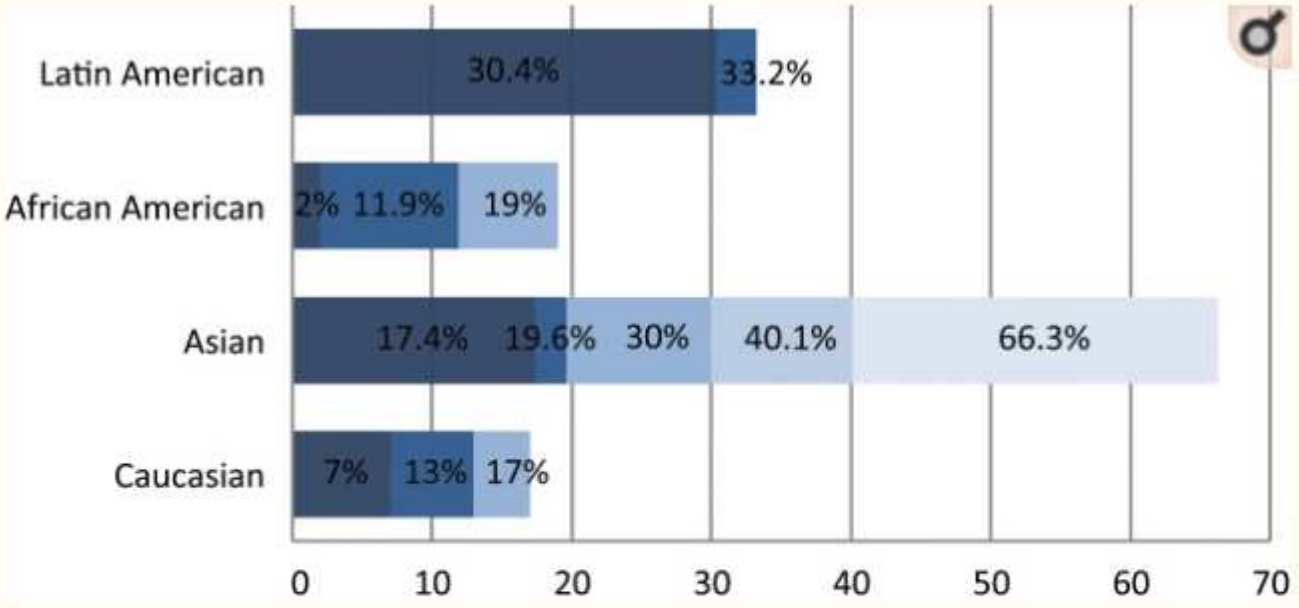


Figure 2.

Spectrum of *EGFR* oncogenic driver mutations among different racial groups with NSCLC. The different color shades represent *EGFR* mutational rates reported by different studies. Data on the African American and Latin American cohorts are based on a limited number of studies available.[46,55-58] Data on the Asian and white cohorts are abundant over recent years, and several representative studies were selected for graphical representation here.[23,24,28,46,56,101,143]

El-Telbani, A, Ma, PC, "Cancer genes in lung cancer," Genes Cancer. 2012; 3(7-8): 467–480.
doi: 10.1177/1947601912465177
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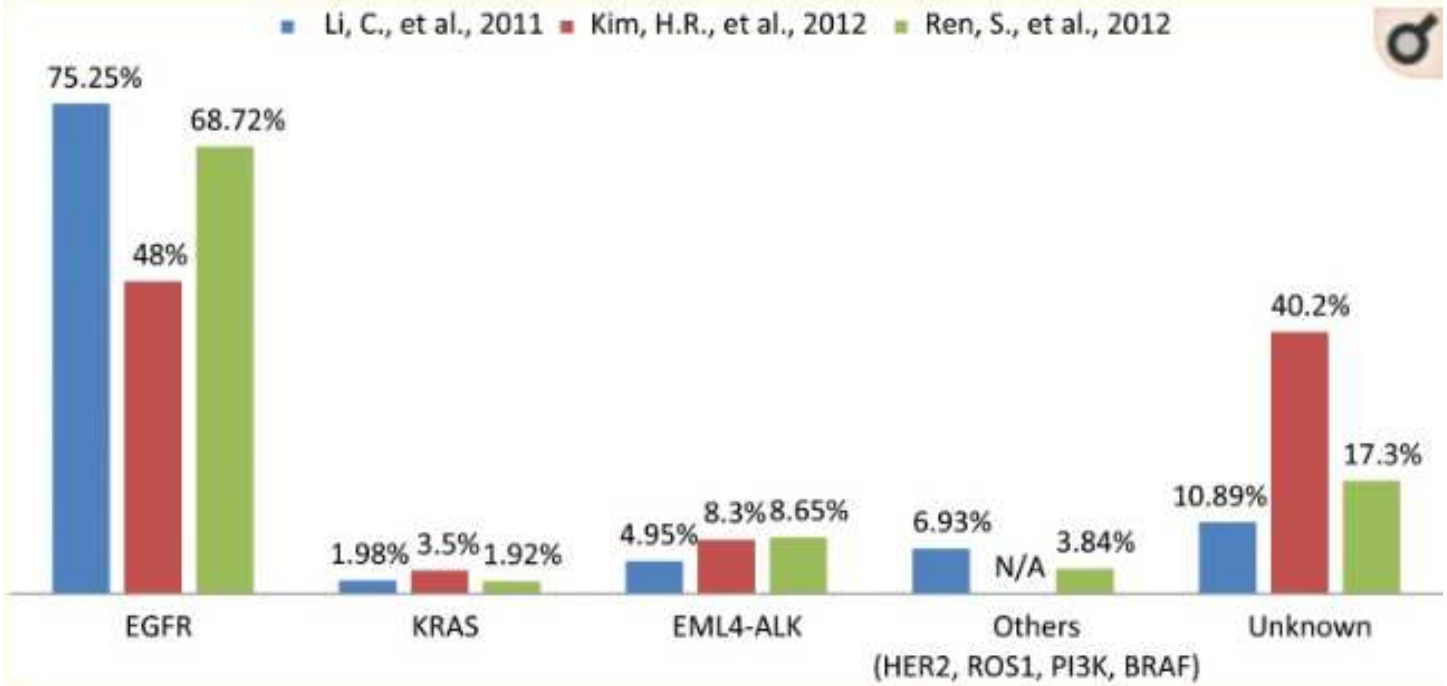


Figure 3.

Spectrum of oncogenic driver mutations in Asian never smokers with lung adenocarcinoma.[31-33] The data were collected from 3 different studies to represent the mutational frequency range of different genes among the same population. N/A = not available.

El-Telbani, A, Ma, PC, "Cancer genes in lung cancer," Genes Cancer. 2012; 3(7-8): 467–480. doi: 10.1177/1947601912465177
Accessed 05/20/20

Molecular description

- K-RAS gene mutation at 12p12.1
- GTPase
- 15-25% of lung cancer
- But 0% in China, 5% in Taiwan, 11% in Japan
- 76% in mucinous subtype
- Smokers and non-smokers have different point mutations
- $G_{12}C$ is most common mutated allele (13%)
- Patients with KRAS mutation have a poorer prognosis
- Do not overlap with EFGR, ALK, or ROS1 mutations

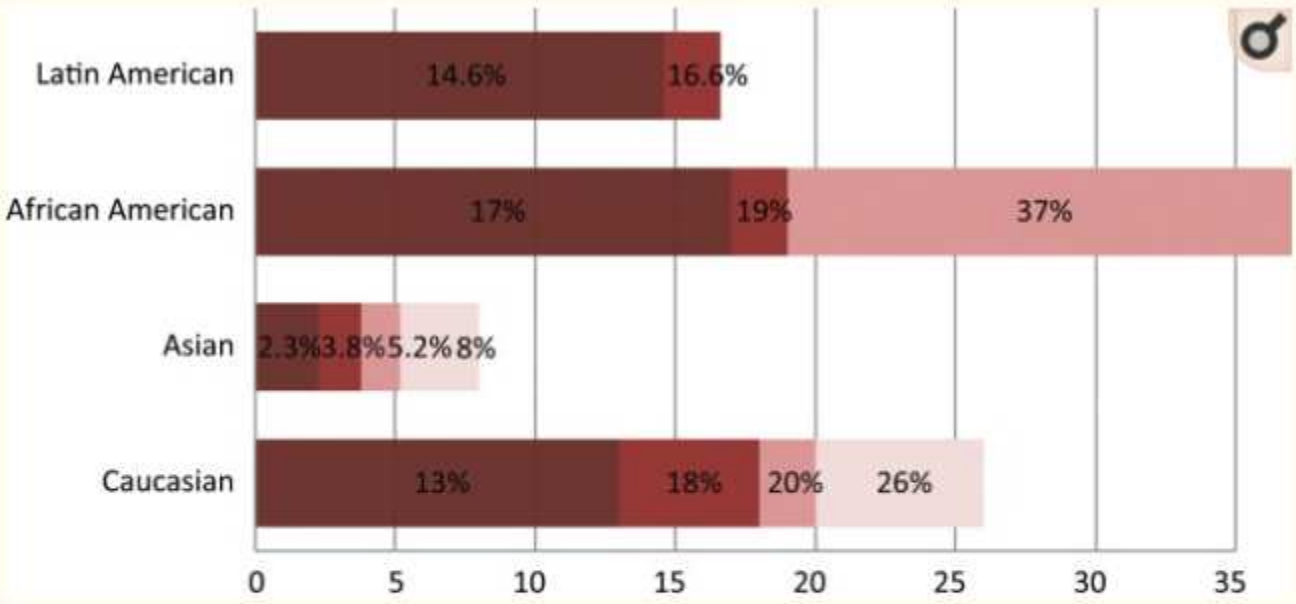


Figure 4.

Spectrum of *KRAS* oncogenic driver mutations among different racial groups with NSCLC. The different color shades represent *KRAS* mutational rates reported by different studies. Data on the African American and Latin American cohorts are based on a limited number of available studies.[46,56-58,73] Data on the white cohort are based on multiple studies including 2 meta-analyses of 22 studies with 1,470 NSCLC patients.[23,46,56,71-73] Data on the Asian cohort are based on studies conducted in the Chinese and Korean populations.[143-145]

El-Telbani, A, Ma, PC, "Cancer genes in lung cancer," Genes Cancer. 2012; 3(7-8): 467–480. doi: 10.1177/1947601912465177
Accessed 05/20/20

Molecular description

- Fusion between EML4 at 2p21 and ALK at 2p23.2-23.1:
- Present in 2-7%
- Tyrosine kinase
- Mucinous (signet cells noted)
- More common in nonsmokers or light smokers
- Younger age
- Do not overlap with EFGR or ROS1 mutations

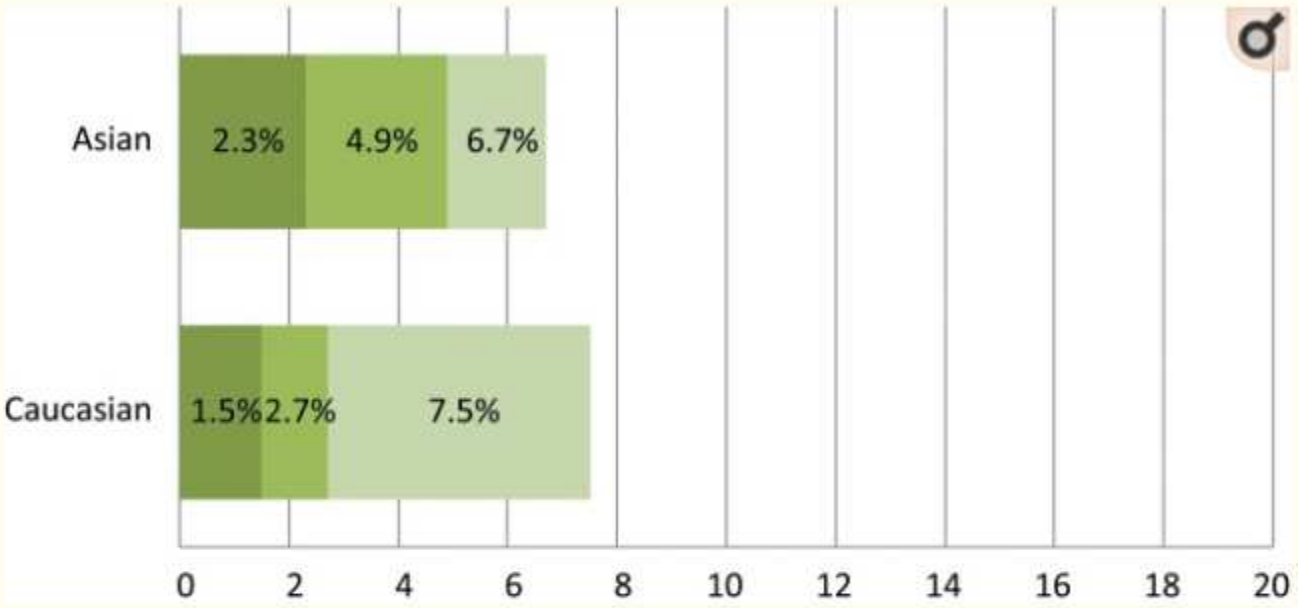


Figure 7.

Spectrum of *EML4-ALK* oncogenic driver fusions among different racial groups with NSCLC.[114,116,119,120,122,124,146] The different color shades represent *EML4-ALK* rates reported by different studies. Data among human populations other than white and Asian are lacking thus far.

El-Telbani, A, Ma, PC, "Cancer genes in lung cancer," Genes Cancer. 2012; 3(7-8): 467–480.
doi: 10.1177/1947601912465177
Accessed 05/20/20

Molecular description

- ROS1 gene at 6q22.1
- Receptor tyrosine kinase similar to ALK and insulin receptor
- 1-2% of cancers
- Young women
- Non-smokers
- Adenocarcinoma that is EFGR, KRAS, and ALK negative

Molecular description

- ROS1/NTRK fusion
- Neurotrophin receptor kinase
- Three types
- 3% of lung cancers (histologic type unimportant)
- 75% of secretory breast and thyroid cancers
- Activate RAS-ERK, PI3K, PLC pathways

Molecular description

- MET gene at 7q31.2
- Activates RAS-ERK, PI3K, PLC pathways
- MET amplification and MET exon 14 skipping mutation are associated with poor prognosis and EGFR acquired resistance
- If MET exon 14 mutation, other drivers rare

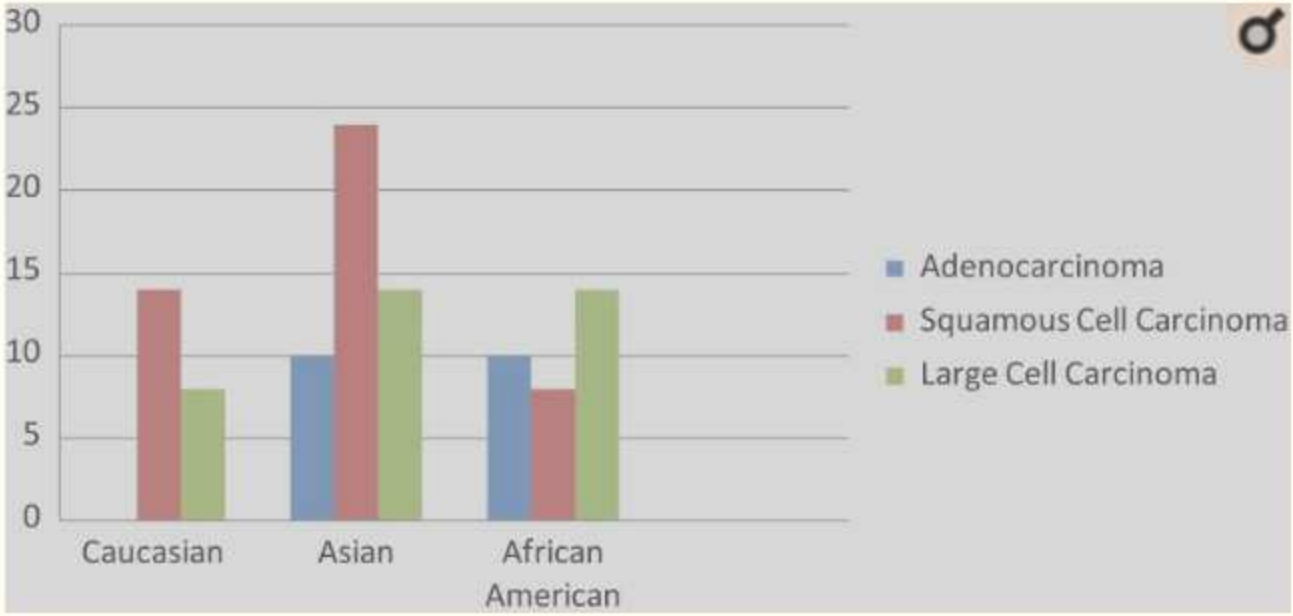


Figure 5.

Spectrum of *MET* mutations among different racial groups with NSCLC.[89] The frequency of *MET* mutations is presented in accordance of the findings with the histological subtypes of lung cancer and racial groups.

El-Telbani, A, Ma, PC, “Cancer genes in lung cancer,” Genes Cancer. 2012; 3(7-8): 467–480. doi: 10.1177/1947601912465177
Accessed 05/20/20

Molecular description

- STK11/LB1 mutations at 19p13.3
- Third most common mutation in adenocarcinoma
- Inhibit phosphorylation of AMPK-mTOR
- Decrease in infiltrating CD8+ cells
- Promote PD-1/PDL-1 inhibitor resistance

- BRAF gene at 7q34 V600E mutation
- Poor response to platinum based therapy

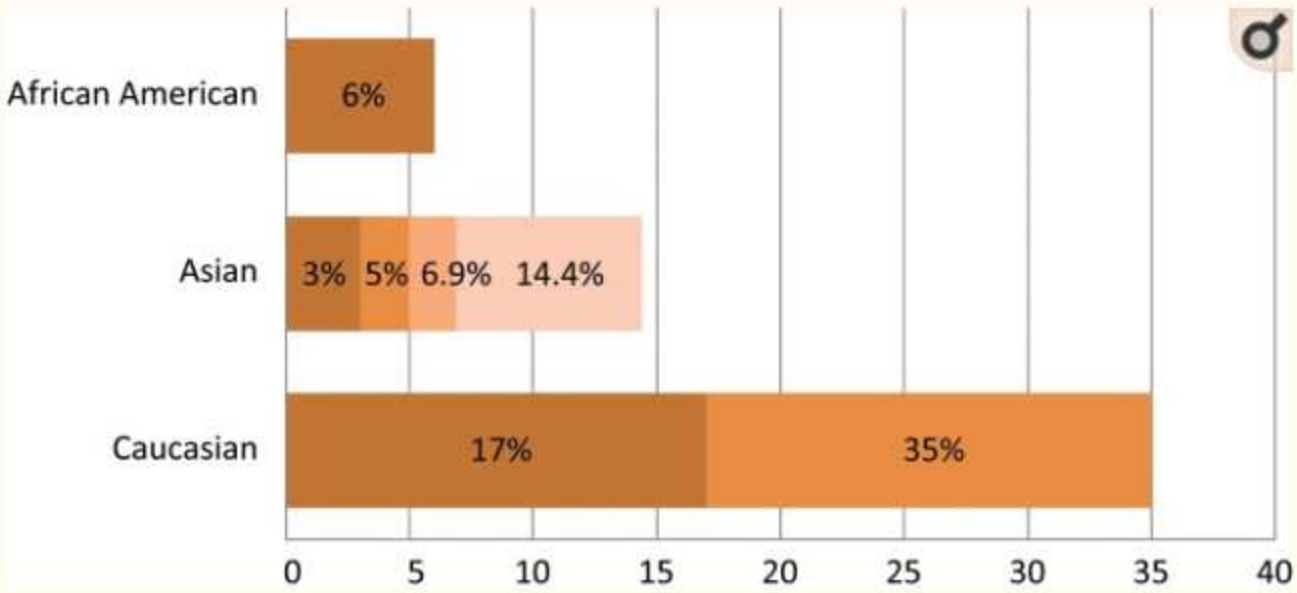


Figure 6.

Spectrum of *LKB1* oncogenic mutations among different racial groups with NSCLC.[100-102,104] The different color shades represent *LKB1* mutational rates reported by different studies.

El-Telbani, A, Ma, PC, “Cancer genes in lung cancer,” Genes Cancer. 2012; 3(7-8): 467–480. doi: 10.1177/1947601912465177
Accessed 05/20/20

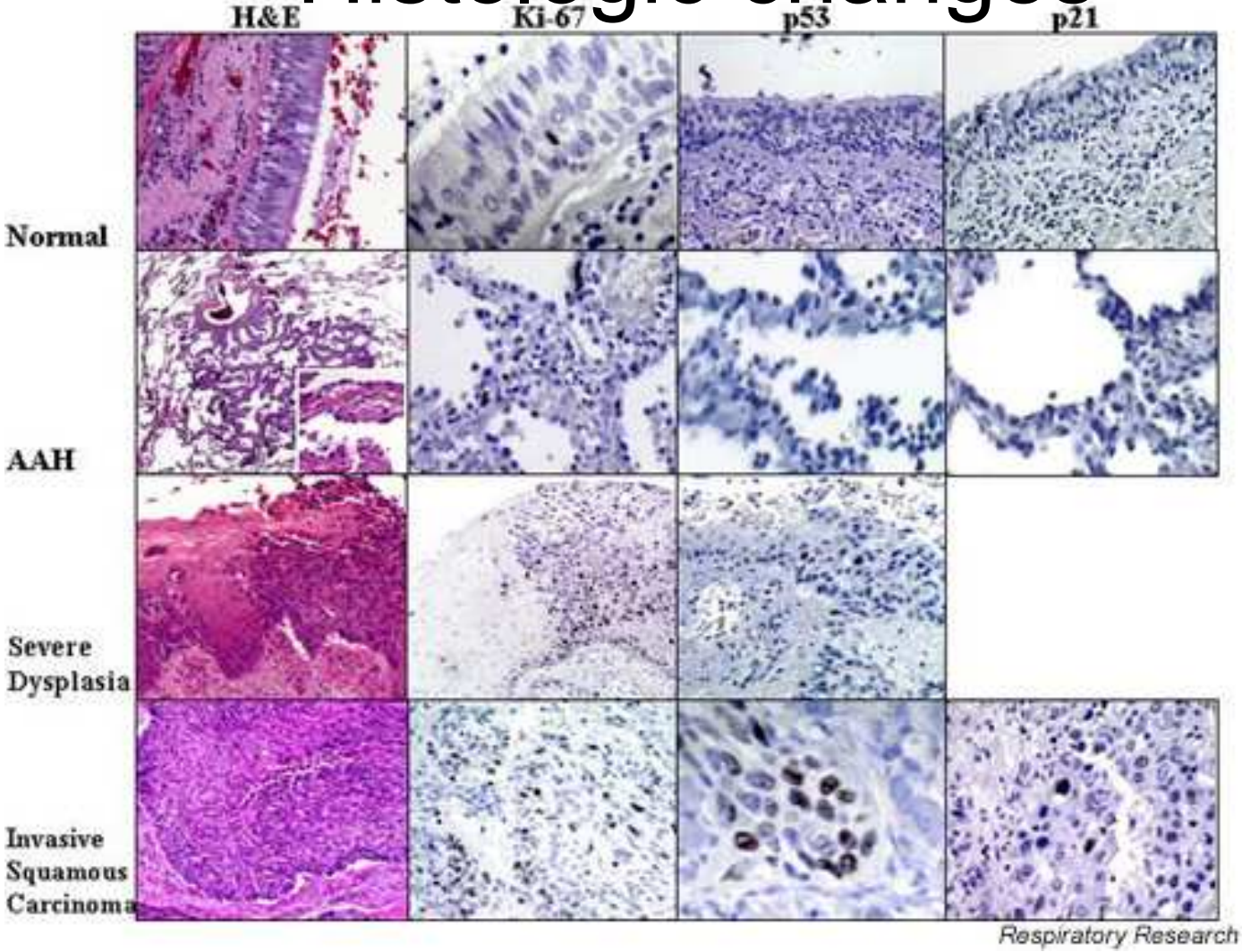
Molecular description

- RET at 10q11.2
- Adenocarcinoma
- 64% never smokers, 24% former smokers
- Initiate RAS/MAPK, PI3K/AKT, and PLC pathways
- Germline mutations of RET lead to MEN2, whereas somatic mutations lead to sporadic medullary thyroid carcinoma.
- RET rearrangements independent of EGFR, KRAS mutations and ALK or ROS1 rearrangements

Molecular description

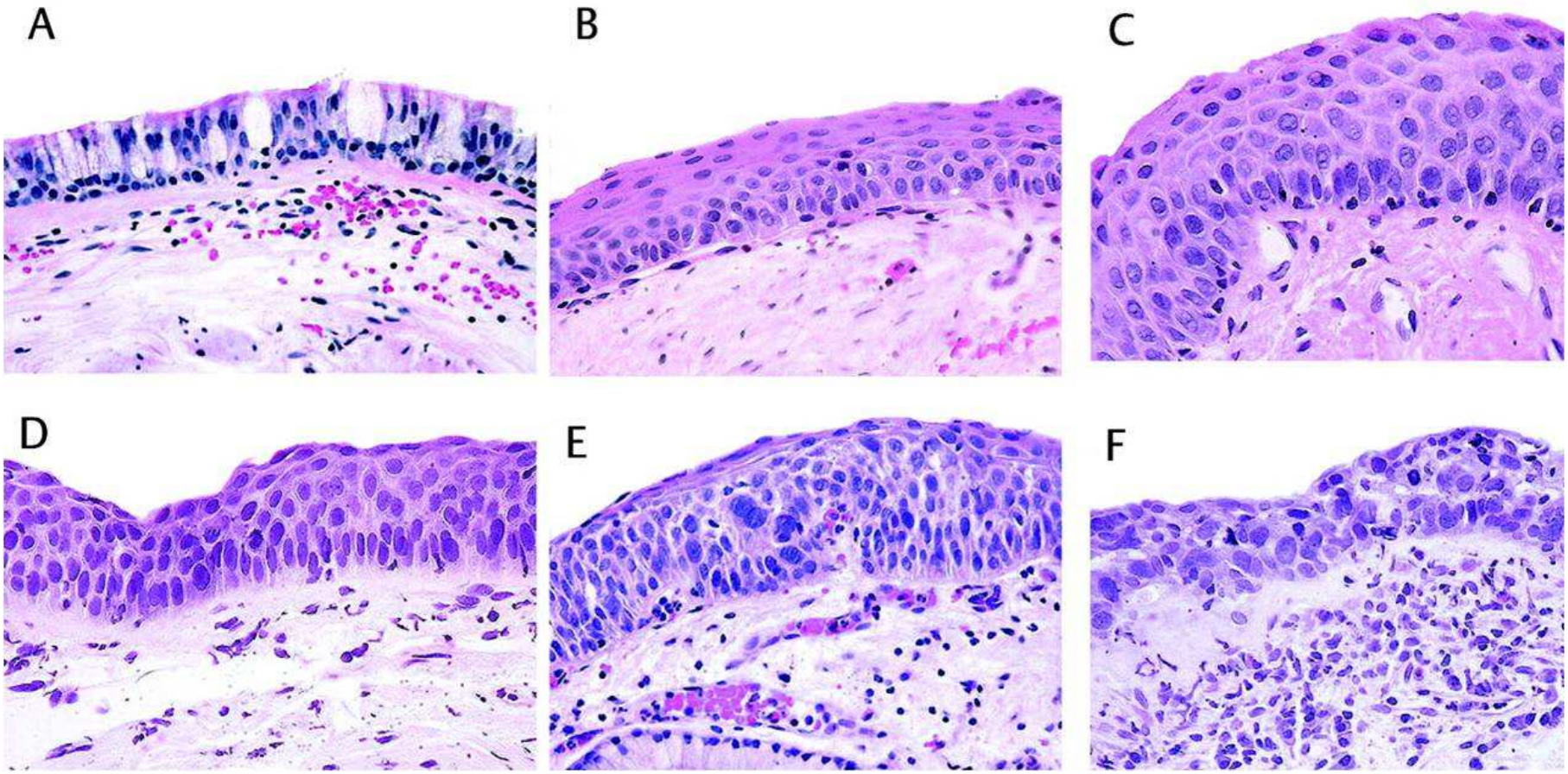
- SHOX2 at 3q25.32
- Idiopathic short stature syndrome
- DNA methylation common.
- May use to identify micro-metastases in mediastinal lymph nodes.

Histologic changes



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC107849/figure/F1/ Accessed 12/10/2019

Histology of bronchial epithelium

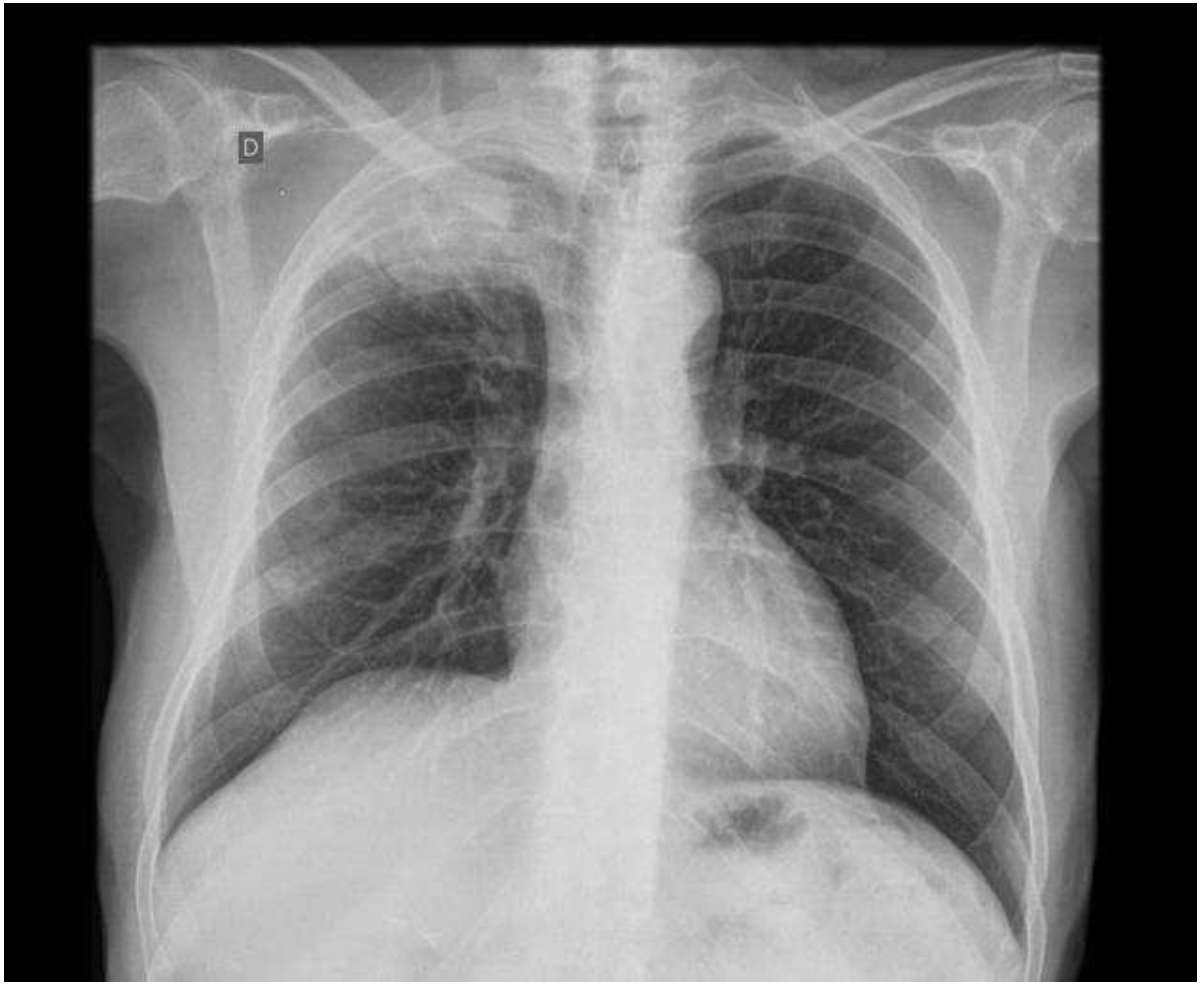


(A) Normal two-layered epithelium; (B) squamous metaplasia; (C) mild dysplasia; (D) moderate dysplasia; (E) severe dysplasia; (F) carcinoma in situ. http://homepage.smc.edu/wissmann_paul/physiology/dysplasia.htm Accessed 12/10/2019

Squamous carcinoma

- Presents with
- Cough and dyspnea
- Increased sputum production
- Weight loss
- Chest pain
- Extrapulmonary manifestations include
- Acanthosis nigricans,
- Hypertrophic pulmonary osteoarthropathy (clubbing)
- Horner's syndrome
- Enophthalmos, ptosis, miosis, anhidrosis
- Due to apical lung tumors (Pancoast tumors)

Primary apical lung cancer



Pancoast tumor

3-5% of squamous carcinomas

Usual complaint is arm pain.

25% may have Horner's syndrome

https://radiopaedia.org/articles/pancoast-tumour Fig. 2 Accessed 12/10/2019

Squamous carcinoma

- 20% of non-small cell carcinoma (squamous)
- 95% are bronchogenic carcinoma
- 2.9% of non-small cell carcinoma (large cell)
- 55–60 years or older
- 2% occur before age 40 years
- More common in men.
- Relative risk of smokers vs. nonsmokers is 10:1, but is 20:1 for > 40 cigarettes/day (two packs/day)
- Cumulative probability of developing lung cancer in those who smoke one or more packs of cigarettes daily is 10-15%.

Smoking cessation

Fig. 2.3

Smoking cessation

- Even after 16 years of smoking cessation, the relative risk for development of lung cancer is four times higher than those who have never smoked.
- Nicotine receptor therapy and the atypical antidepressant, buproprion, with support is the most effective cessation therapy at 6 months as compared to with unaided attempts at cessation
- 12% remain tobacco-free

Squamous carcinoma

- Cigarette smoking leads to squamous metaplasia of basal cells or metaplastic goblet cells
- 10% of smokers have atypia or hyperplasia of bronchial epithelium
- The most potent carcinogens in cigarette smoke are the polycyclic aromatic hydrocarbons (PAHs) and the aromatic amines, N-nitrosamines
- Benzo [a] pyrene is an initiator and phenol derivatives act as promoters.
- CYP1A1 is a cytochrome P450 enzyme that activates carcinogens through hydroxylation of vacant position on aromatic ring
- Mediated via aryl hydrocarbon receptor

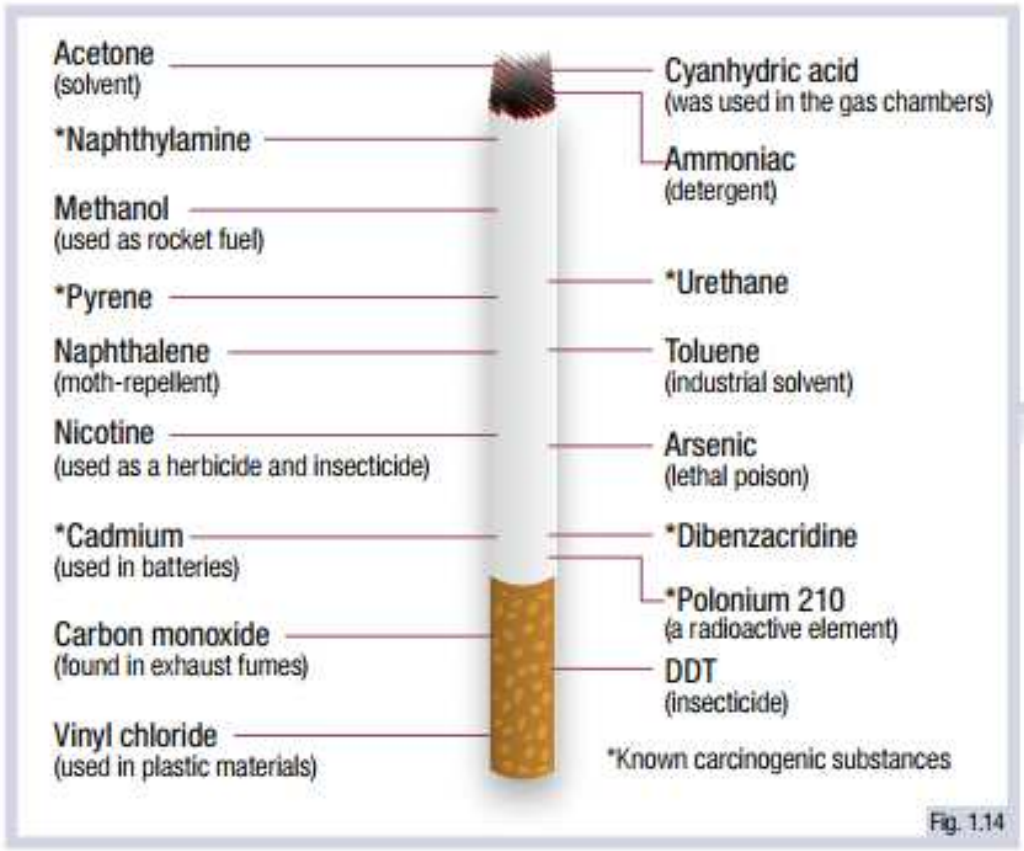

Acetone
(solvent)
*Naphthylamine
Methanol
(used as rocket fuel)
*Pyrene
Naphthalene
(moth-repellent)
Nicotine
(used as a herbicide and insecticide)
*Cadmium
(used in batteries)
Carbon monoxide
(found in exhaust fumes)
Vinyl chloride
(used in plastic materials)
Cyanhydric acid
(was used in the gas chambers)
Ammoniac
(detergent)
*Urethane
Toluene
(industrial solvent)
Arsenic
(lethal poison)
*Dibenzacridine
*Polonium 210
(a radioactive element)
DDT
(insecticide)
*Known carcinogenic substances

Fig. 1.14

Squamous carcinoma

- Other risk factors
- Radiation exposure
- Uranium (and Radon gas)
- Relative risk with uranium exposure is 4:1 for nonsmokers, 10:1 for smokers
- Asbestos
- Relative risk is 5:1 for nonsmokers, 50-90:1 for smokers
- 20% lung cancer, 10% mesothelioma, 10% GI carcinomas
- Also exposure to arsenic, beryllium, chromate, coal, gold ore, iron, mustard gas, nickel, radon, vinyl chloride

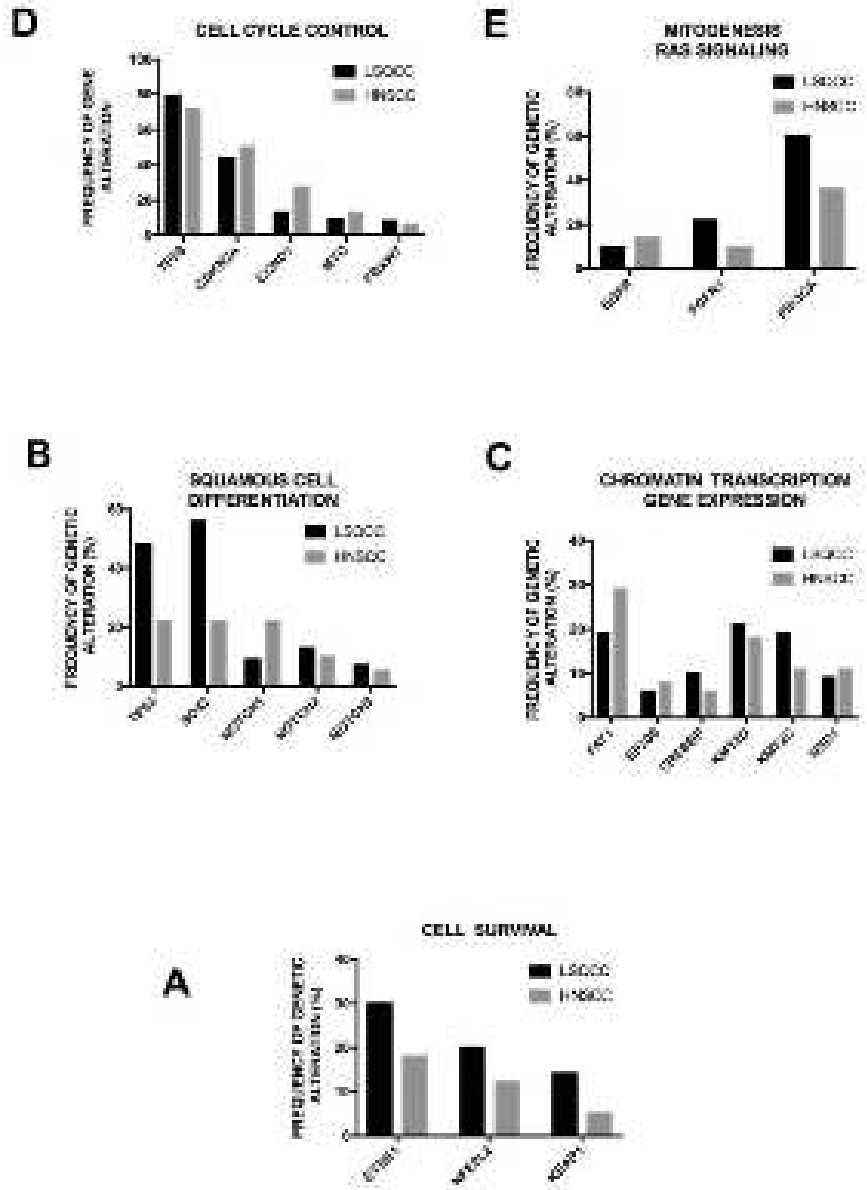


Figure 3

Pattern of frequently altered genes in Lung and Head and Neck squamous cell carcinoma subdivided according to their biologic function. A: Cell Survival; B: Squamous Cell Differentiation; C. Chromatin Transcription Gene Expression; D: Cell Cycle Control; E: Mitogenesis, RAS Signaling.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6116004/

Squamous carcinoma in situ

- A multifocal and clonal condition strongly associated with cigarette smoking ("field cancerization")
- Focal to full thickness replacement of epithelium by squamous cells with increased nuclear to cytoplasmic ratio, nuclear pleomorphism, mitotic activity but intact basement membrane
- Cannot differentiate those lesions which will progress

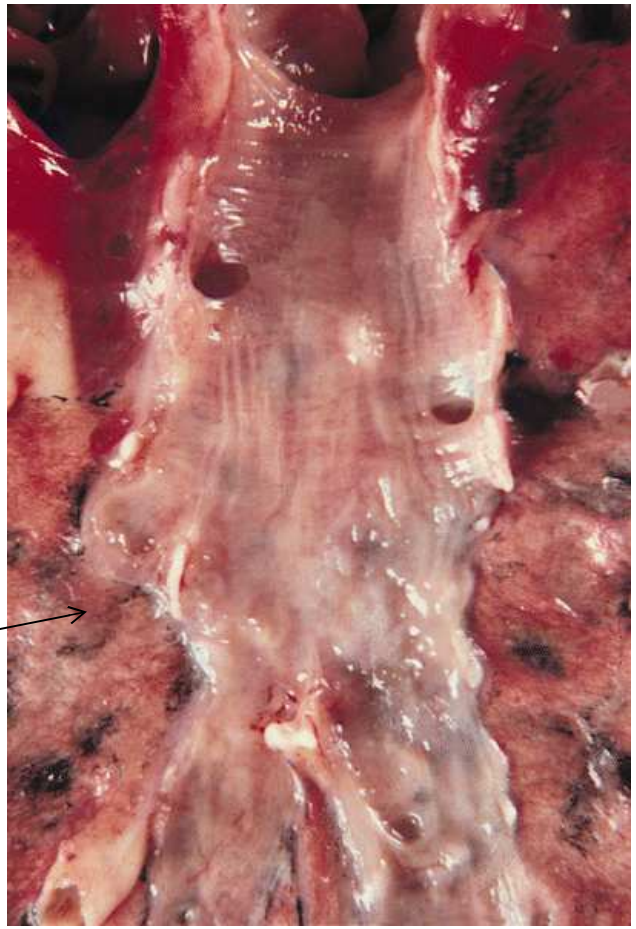
Squamous carcinoma in situ

- Squamous dysplasia (CIS) tends to arise in large central airways around bifurcations trachea
- High grade squamous dysplasia (CIS) is associated with an increased risk of invasive squamous cell carcinoma

Gross description

- Usually central portion of lung affecting larger bronchi but may be peripheral
- Invades peribronchial soft tissue, lung parenchyma and nearby lymph nodes
- May compress pulmonary artery and vein
- Peripheral tumors often have nodular growth with central necrosis and cavitation
- Surrounding lung may exhibit lipid pneumonia, bronchopneumonia, atelectasis
- Calcification is unusual

Squamous carcinoma in situ



Carcinoma in situ with foci of early invasion. The latter foci can be seen grossly as areas of nodular thickening (lower right) in a subsegmental bronchus adjacent to a bronchial bifurcation. (arrow)

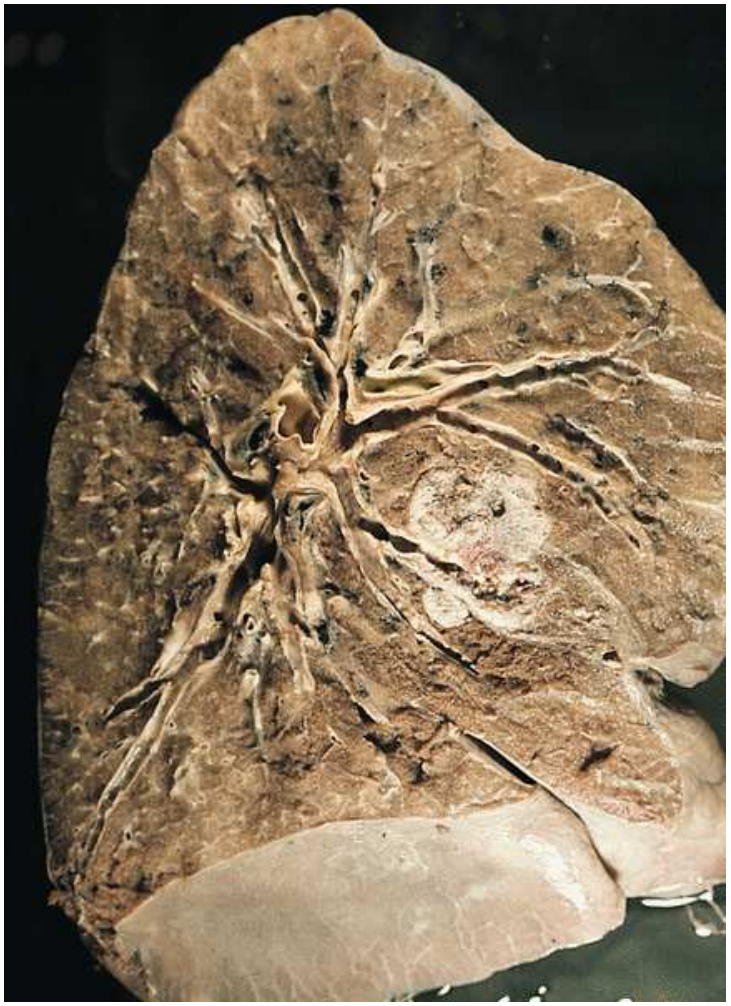
Fig. 10-2

Colby, TV, Koss, MN, Travis, WD., "Tumors of the lower respiratory tract. " Atlas of Tumor Pathology, Third Series, Fascicle 13. Armed Forces Institute of Pathology, Washington, D.C. 1995.

Spread and classification

- Spreads along bronchus distally and proximally, into lung parenchyma to mediastinum or pleura
- Causing pleural seeding, pleural effusion, involvement of diaphragm and chest wall
- 50% have nodal involvement at resection (usually hilar, mediastinal and supraclavicular)
- Also metastases to adrenals (50%), liver (30%), brain, bone
- Also to opposite lung, pericardium, kidneys
- Low dose CT scanning best screening test.

Squamous carcinoma



This non-small cell carcinoma (squamous) involves a segmental bronchus, which is eroded and destroyed by the capitating mass. The tumor has a white, granular appearance due to keratinization.

The high frequency of positive exfoliative cytology specimens from such cases results from the degree of bronchial involvement.

Fig. 11-1

Colby, TV, Koss, MN, Travis, WD., "Tumors of the lower respiratory tract. " Atlas of Tumor Pathology, Third Series, Fascicle 13. Armed Forces Institute of Pathology, Washington, D.C. 1995.

Early carcinoma of hilar type

- Arises in major bronchi
- Confined to bronchial wall with no lymph node metastases
- Usually squamous carcinoma
- May be polypoid, nodular, superficially infiltrating or mixed
- Longitudinal mucosal folds show changes at tumor border
- Superficial tumor has thickened and fused folds
- 90% 5-year survival

Early squamous cell carcinoma of peripheral type

- Defined as tumor 2 cm or less in peripheral lung
- No lymph node or distal metastases

Rapid growth

Often have glandular cell characteristics

Alveolar space filling

Tumor cells fill alveoli but don't destroy elastic septa

Expanding type

Growth destroys elastic septa

Mixture

Subtypes

- Subtypes
- Clear cell
- Numerous clear tumor cells containing glycogen
- Small cell (epithelial origin)
- Small tumor cells with focal keratinization
- Distinct nucleoli
- Sharply outlined tumor nests
- Less necrosis than small cell neuroendocrine carcinoma
- MYC-C mutation

Subtypes

- Papillary
- Basaloid squamous cell carcinoma:

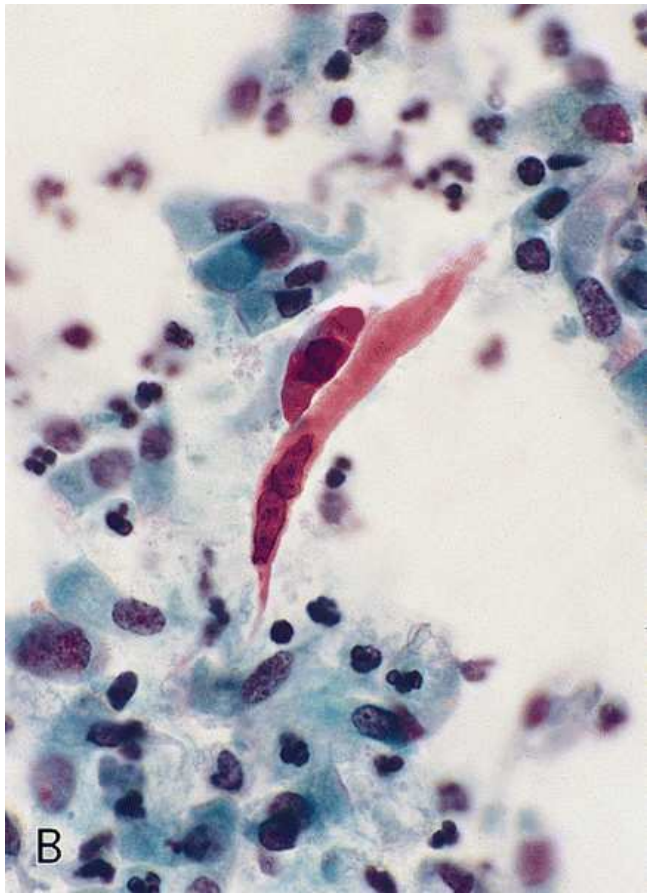
  Very aggressive subtype
- Spindle cell squamous cell carcinoma:

  Also called sarcomatoid carcinoma

Histopathology

- Sheets or islands of large polygonal malignant cells containing keratin (individual cells or keratin pearls) and intercellular bridges
- Adjacent bronchial dysplasia or carcinoma in situ is common
- At advancing tumor border, tumor cells usually destroy alveoli or fill alveolar spaces
- Rarely spreads beneath basement membrane
- May have focal areas of intracytoplasmic mucin

Sputum cytology



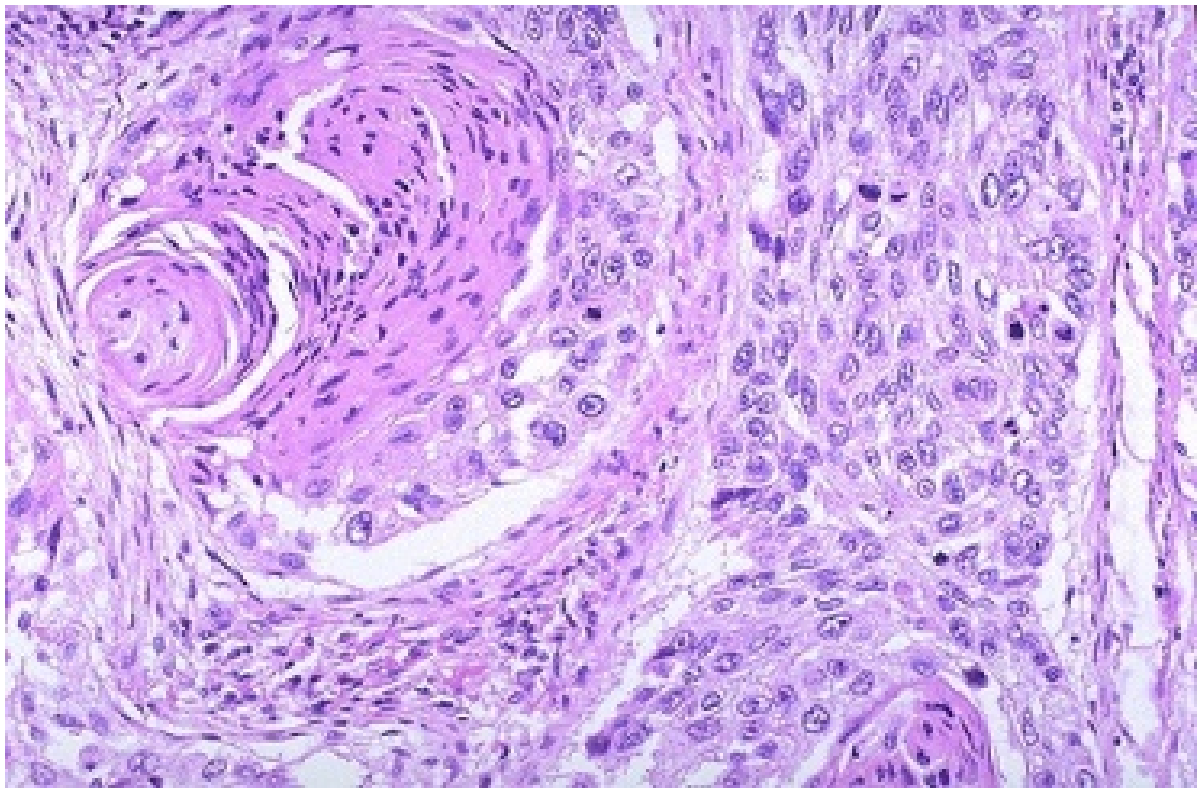
There are large bizarre-shaped keratinized cells with hyperchromatic nuclei, some of which show cytoplasmic orangophilia.

Typical for squamous carcinoma.

Fig. 11-13B

Colby, TV, Koss, MN, Travis, WD., "Tumors of the lower respiratory tract. " Atlas of Tumor Pathology, Third Series, Fascicle 13. Armed Forces Institute of Pathology, Washington, D.C. 1995.

Squamous carcinoma



https://webpath.med.utah.edu/jpeg1/NEO097.jpg
Accessed 01/20/2020

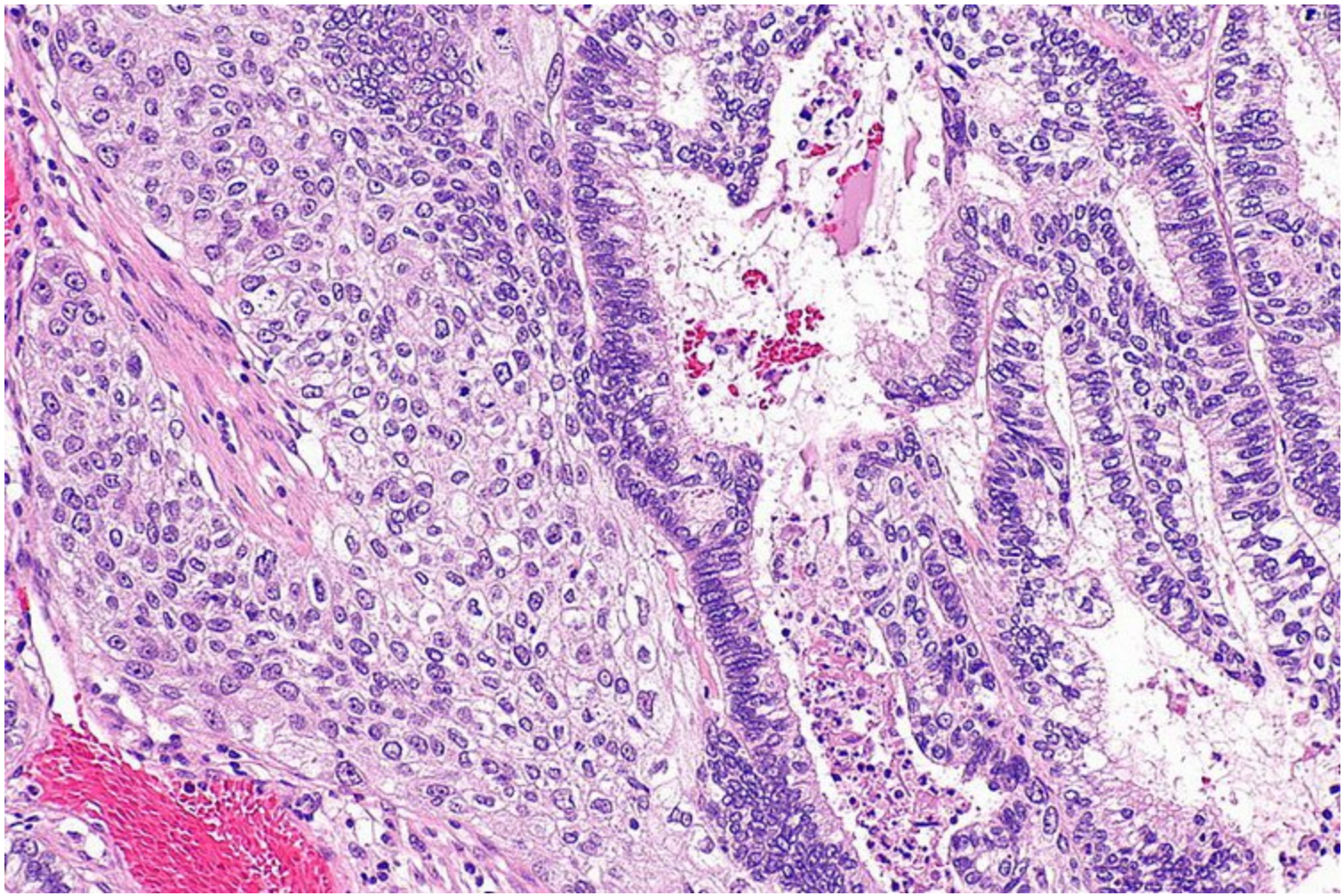
Stratification

- Classify as well, moderately or poorly differentiated based on amount of keratinization present in predominant component
- Important to examine margins carefully for intraepithelial spread

Adenosquamous carcinoma

- 1-5% of lung cancers
- Substantial amounts of malignant squamous and glandular differentiation (at least 10% of each component within tumor)
- 90% peripheral, often associated with scars
- Lobulated or speculated
- Poorer prognosis than either component alone

Adenosquamous carcinoma

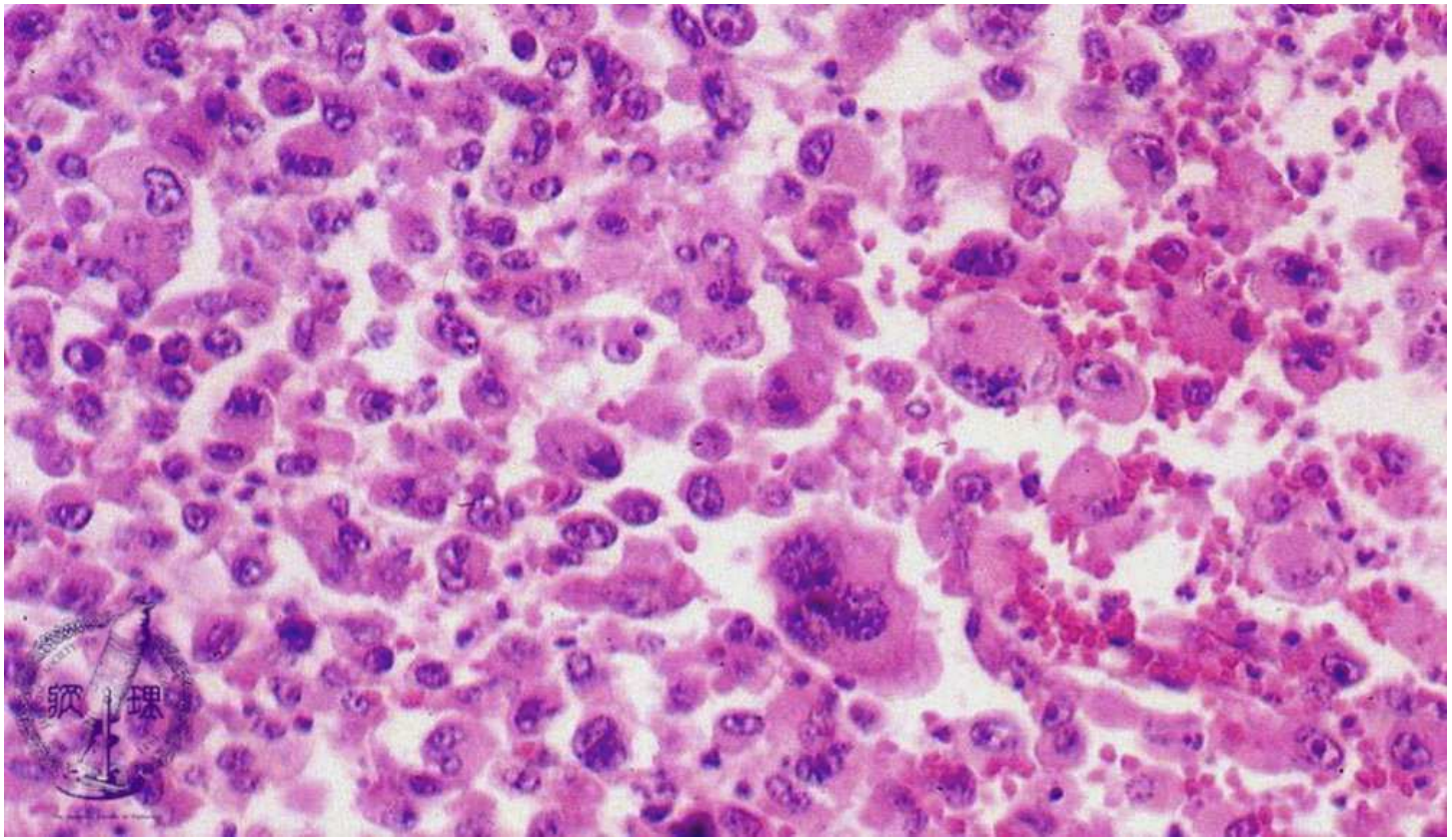


https://www.dovemed.com/diseases-conditions/adenosquamous-carcinoma-of-lung/ Accessed 01/20/2020

Large cell carcinoma

- Lack any clear morphologic or immunohistochemical differentiation

Large cell carcinoma



Lack any clear morphologic or immunohistochemical differentiation
http://pathology.or.jp/corepicturesEN/05/c17/images/14.jpg
Accessed 01/20/2020

Carcinosarcoma

- 0.1% of lung tumors
- More common in men
- Smoking history
- Over 60 years-old
- Central
- Mixture of non small cell lung cancer (typically squamous cell carcinoma or adenocarcinoma) and sarcomatous heterologous elements
- Monoclonal tumor with divergent lines of differentiation, leading to mixture of carcinomatous and sarcomatous elements
- Poor prognosis

Histopathology

- Epithelial component 10-85%
- Usually adenocarcinoma
- OR large cell carcinoma
- OR squamous cell carcinoma
- Usually poorly differentiated
- At least 10% neoplastic spindle or giant cells
- Spindle cells resemble malignant fibrous histiocytoma or fibrosarcoma
- Giant cells usually bizarre with multilobulated nuclei with abundant eosinophilic cytoplasm

Histopathology

- Heavy neutrophilic infiltrate with occasional ingested white blood cells
- Numerous mitotic figures
- Stroma often myxoid
- Massive necrosis common
- Vascular invasion in 58%

Giant cell carcinoma

- Upper lobe
- Frequently metastasize to intestine
- Subtype of sarcomatoid carcinoma consisting of purely giant, pleomorphic tumor cells
- Should not show differentiated non small cell components
- Tumor stains for cytokeratins
- May stain for human chorionic gonadotropin

Small cell carcinoma of epithelial origin

Cross section of this surgically resected tumor shows peribronchial and perivascular infiltration by a white soft tumor which also involves a hilar lymph node (arrow).

Fig. 14-2

Colby, TV, Koss, MN, Travis, WD., "Tumors of the lower respiratory tract. " Atlas of Tumor Pathology, Third Series, Fascicle 13. Armed Forces Institute of Pathology, Washington, D.C. 1995.

Malignant PEComa

- Derived from perivascular epithelioid cells
- Clear cells with glycogen rich cytoplasm, prominent nucleoli, high mitotic activity
- Necrosis
- Molecular description
- Loss of function mutation of TSC2 at 16p13.3
- Negative regulator of mTOR

- Other variant is lymphangioleiomyomatosis

Lymphangioleiomyomatosis

- Women of child bearing age
- Presents with dyspnea or spontaneous pnuemothorax
- Gross pathology
- Cystic dilation of terminal airways
- Interstitial thickening
- Obstruction of lymphatic vessels

Lymphangioleiomyomatosis

- Histopathology
- Derived from perivascular epithelioid cells
- Proliferation of perivascular epithelioid cells
- Express markers of both melanocytes and smooth muscle cells
- Estrogen receptor positive
- Molecular description
- Loss of function mutation of TSC2 at 16p13.3
- Negative regulator of mTOR

Inflammatory myofibroblastic tumor

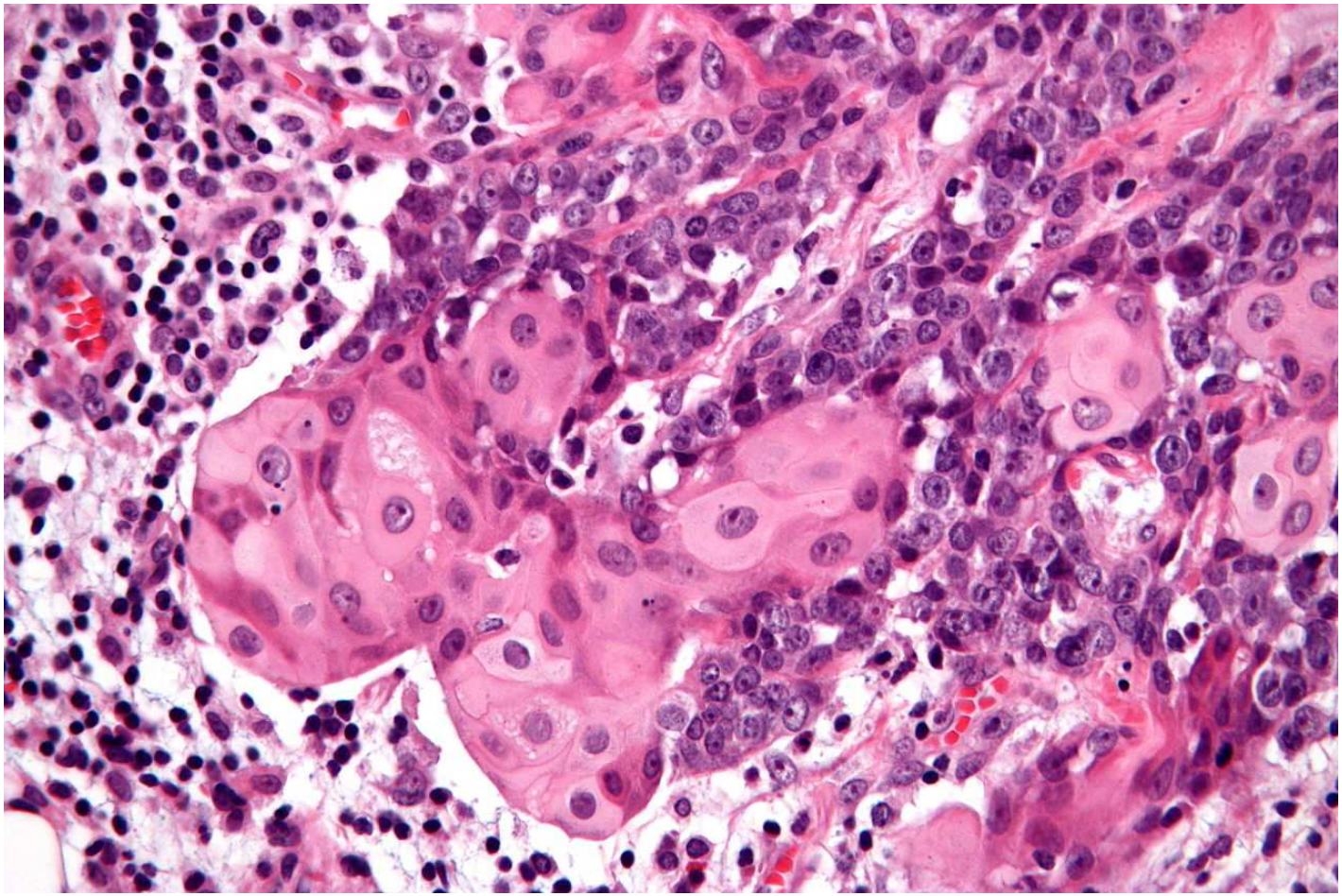
- May present with fever, cough, and hemoptysis
- More common in children
- Equal male to female ratio
- Single, well defined peripheral mass on x-ray
- 25% have calcium deposits
- Gray white lesion on gross examination
- Spindle shaped fibroblasts and myofibroblasts and a leukocyte inflammatory infiltrate on microscopic exam
- ALK mutation at 2p23.2-23.1

Pleomorphic carcinoma

- <1% lung tumors
- 90+% in men, smokers
- Age 65 years
- Nodal metastases common
- Contains at least 10% spindle cells or giant cells

NUT carcinoma

- Any age or sex
- Poorly differentiated
- Large cells with eosinophilic cytoplasm and prominent nucleoli
- Foci of keratinization
- NUT gene rearrangement at 15q14
- Fusion partner not known
- Median survival is 7 months



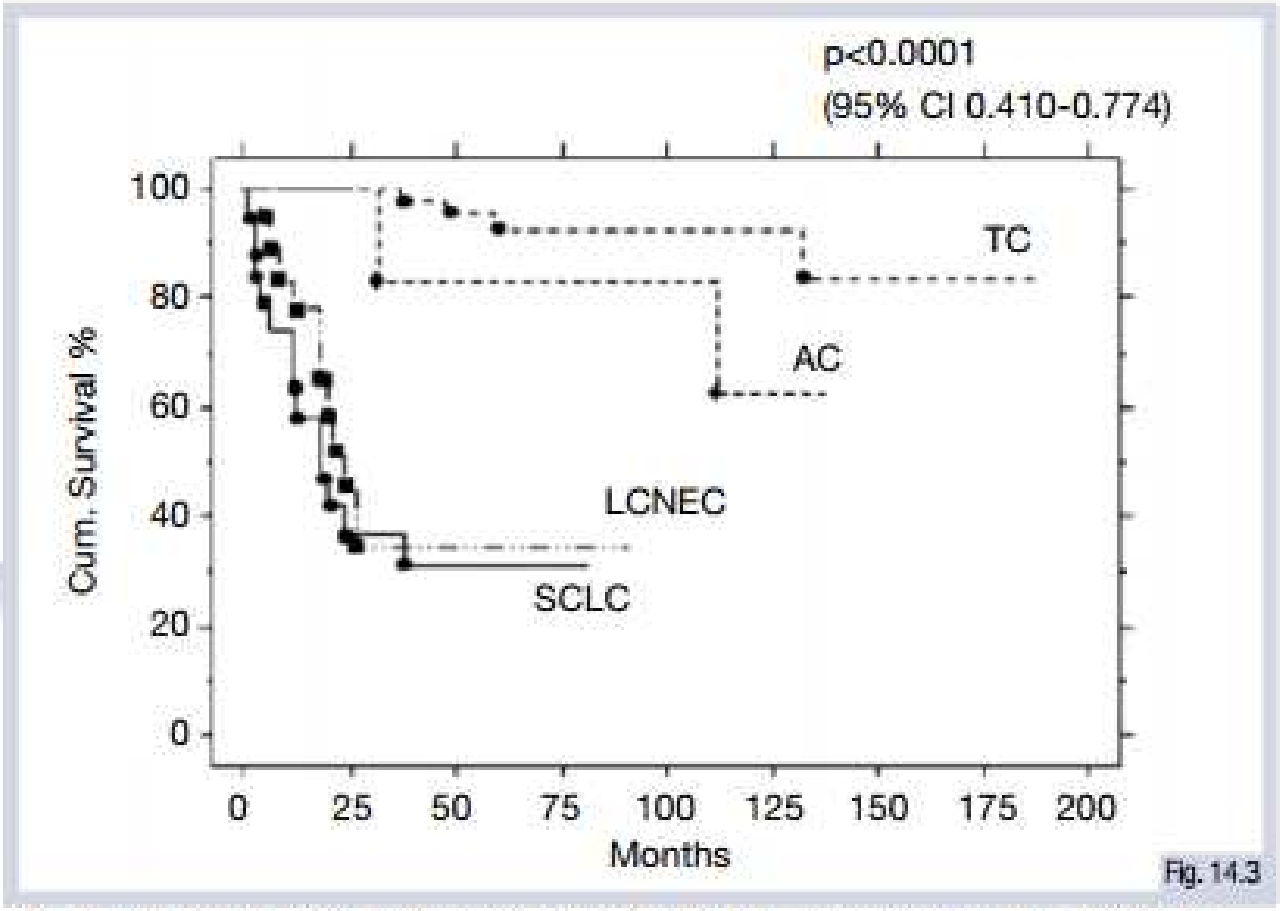
https://en.wikipedia.org/wiki/NUT_midline_carcinoma#/media/File:NUT_midline_carcinoma_-_very_high_mag.jpg

Neuroendocrine tumors

- 4 major categories, including typical carcinoid (TC), atypical carcinoid (AC), small cell carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNEC).

Histological type	Necrosis	Mitotic count
TC	Absent	<2/10 HPF
AC	Present focal	2–10/10 HPF
LCNEC	Present (extensive)	>10 HPF, usually >30 HPF
SCLC	Present (extensive)	>10 HPF, usually >60 HPF

AC, Atypical carcinoid; HPF, high-power field; LCNEC, large cell neuroendocrine carcinoma; SCLC, small cell lung cancer; TC, typical carcinoid.



AC, Atypical carcinoid; CI, confidence interval; LCNEC, large cell neuroendocrine carcinoma; SCLC, small cell lung cancer; TC, typical carcinoid.

Small cell carcinoma

- 15% of all lung cancers
- Older men
- Smokers.
- Central growth
- Rarely a peripheral nodule
- Submucosal growth
- Origin likely the Kultchitsky (basal neuroendocrine) cell.
- Metastasis to liver, adrenals, bone, bone marrow, brain; often widespread
- Metastases to brain common
- SIADH, Lambert-Eaton associated syndromes

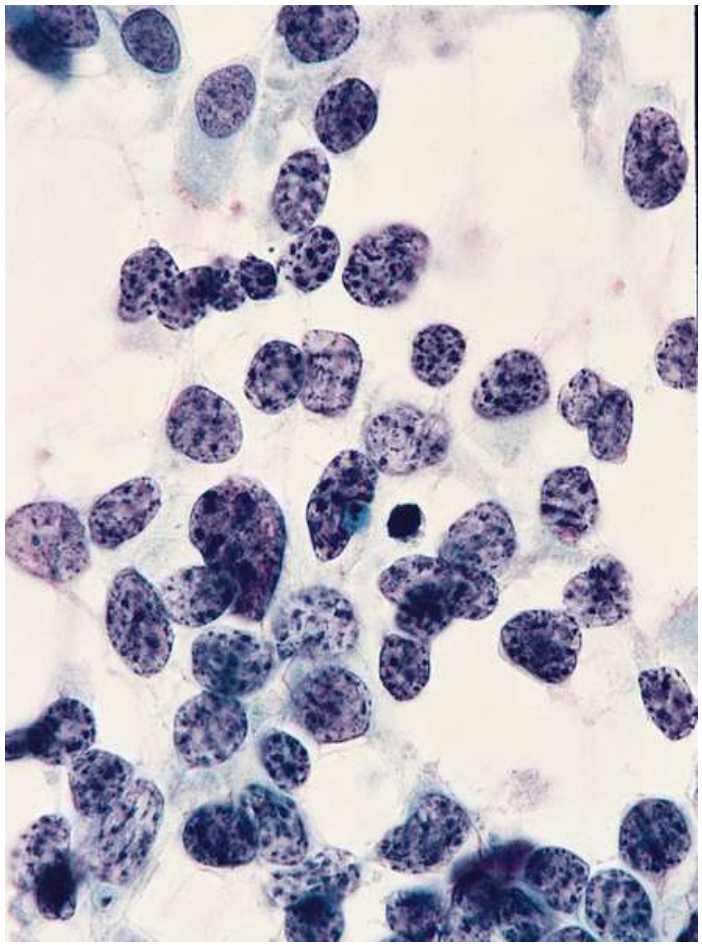
Gross description

- Central or hilar mass
- White-tan, soft, friable, necrotic
- Peripheral nodules are circumscribed, with fleshy cut surface

Cytology

- Oval, elongated, hyperchromatic nuclei with absent nucleoli
- Smooth membrane
- Scant but granular cytoplasm
- Nuclear molding
- Individual cells or loose clusters
- Necrosis and apoptosis of individual cells and tumor background
- Hypercellular

Touch preparation cytology



The tumor cells from this touch preparation vary in size and shape but demonstrate scant cytoplasm, finely granular chromatin, and absent nucleoli.

Fig. 14-12

Colby, TV, Koss, MN, Travis, WD., "Tumors of the lower respiratory tract. " Atlas of Tumor Pathology, Third Series, Fascicle 13. Armed Forces Institute of Pathology, Washington, D.C. 1995.

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Histopathology

- Biopsy
- Small round blue cells with minimal cytoplasm
- Nuclear with finely dispersed chromatin, no distinct nucleoli
- Nuclear molding, smudging
- High mitotic rate
- Stroma is thin, delicate, scant
- Fibrovascular
- Necrosis and apoptosis of individual cells common
- Occasional giant cells

Histopathology

- Patterns
  - Sheets
  - Clusters
  - Ribbons
  - Rosettes
  - Peripheral palisading
- Basophilic nuclear material lining blood vessel walls (Azzopardi phenomenon)

Small cell carcinoma

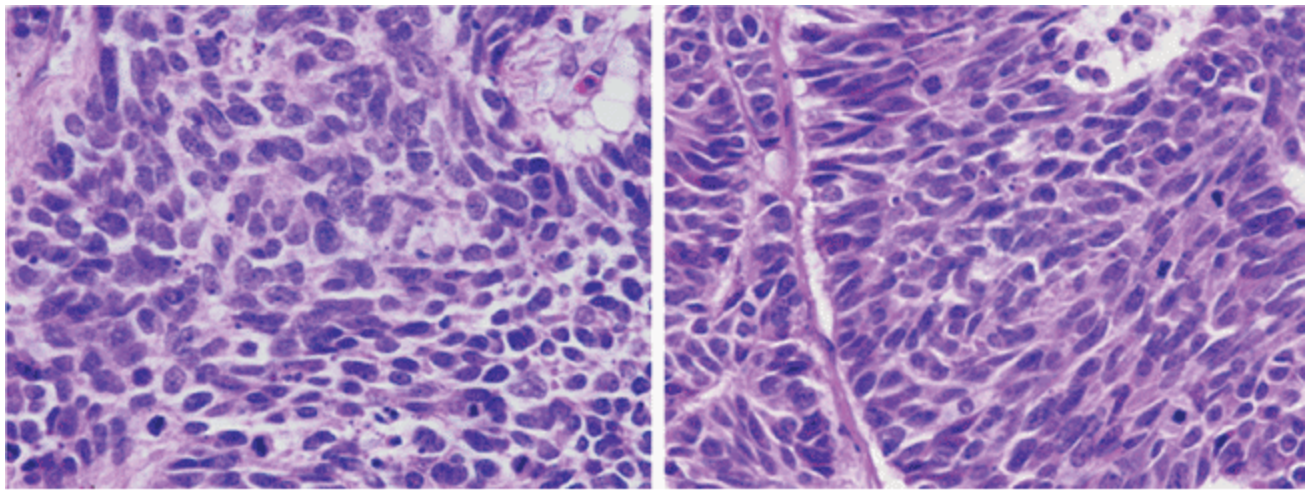


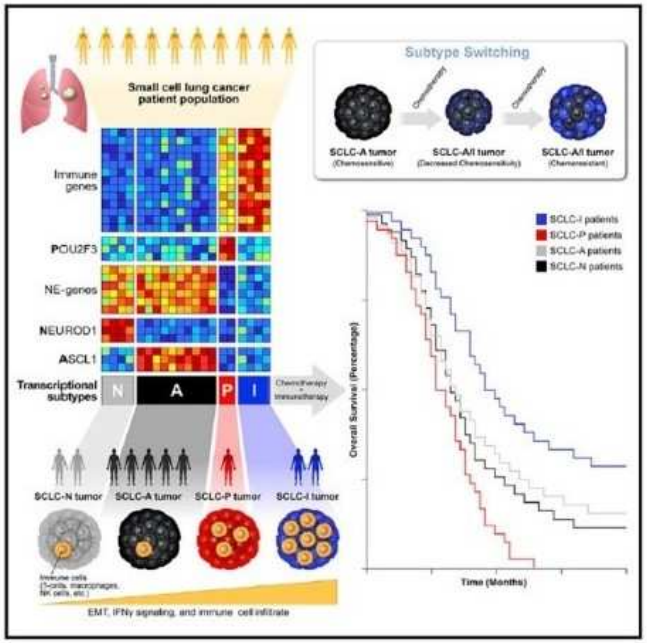
Fig. 11-1 Accessed 04/27/2010

Monotonous "small round blue cells" with foci of necrosis and hyperchromatic nuclei are seen. Occasionally, the cells organize in a rosette formation with high mitotic counts. Cellular atypia or pleomorphism with a high nuclear-to-cytoplasmic ratio can be seen at higher magnification. The cell shape is usually round to oval with occasional spindle morphology.

Cancer Cell

Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities

Graphical Abstract



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In Brief

Gay et al. provide a classification for four subtypes of small cell lung cancer, each with unique molecular features and therapeutic vulnerabilities. An inflamed, mesenchymal subtype predicts benefit with the addition of immunotherapy to chemotherapy. Intratumoral switching between chemosensitive and chemoresistant subtypes accompanies therapeutic resistance.

SCLC subtypes

- SCLC-A
- 51%, High ASCL1 expression
- High expression of delta-like ligand 3, an inhibitory Notch ligand
- High expression of SLFN11
- Putative DNA/RNA helicase that blocks replication at stressed replication forks in the presence of DNA damage, leading to cell death
- SCLC-N
- 23%, High NEUROD1
- High expression of Somatostatin receptor 2

SCLC subtypes

- SCLC-P
- 18%, High POU2F3
- SCLC-I
- “Inflamed” subtype
- Lack expression of the ASCL1, NEUROD1, and POU2F3 transcription factors
- Exhibit epithelial-mesenchymal transition
- Have high expression of genes related to immune cell infiltration and immune checkpoints, HLA genes, and IFN-γ activation
- High expression of Bruton tyrosine kinase (BTK)

SCLC subtypes

- SCLC-A subtype has increased sensitivity to BCL2 inhibitors
- SLFN11 a marker for platinum, topoisomerase I/III, and PARP inhibitor therapy
- SCLC-N subtype has increased susceptibility to aurora kinase inhibitors
- SCLC-P subtype is particularly vulnerable to PARP inhibitor therapy (independent of absent SLFN11 expression) and antimetabolites.
- SCLC-I subtype has increased sensitivity to checkpoint inhibitors

Molecular description

- Deletion of 3p with loss of MLH1, VHL is earliest change
- p53 mutations due to deletion at 17p (90%)
- RB1 loss of function at 13q14 (80 - 100%)
- PTEN mutation (15 - 20%)
- Wild type c-Kit upregulation (80 - 90%)
- MYC (MYC, MYCL1 or MYCN) amplification (20%)
- Telomerase activation (90%)
- Bcl-2 (72%)
- IGF/IGFR (90%)
- IGF, Bcl2 over-expression allow evasion of apoptosis.
- Rare EGFR mutations and ALK rearrangements

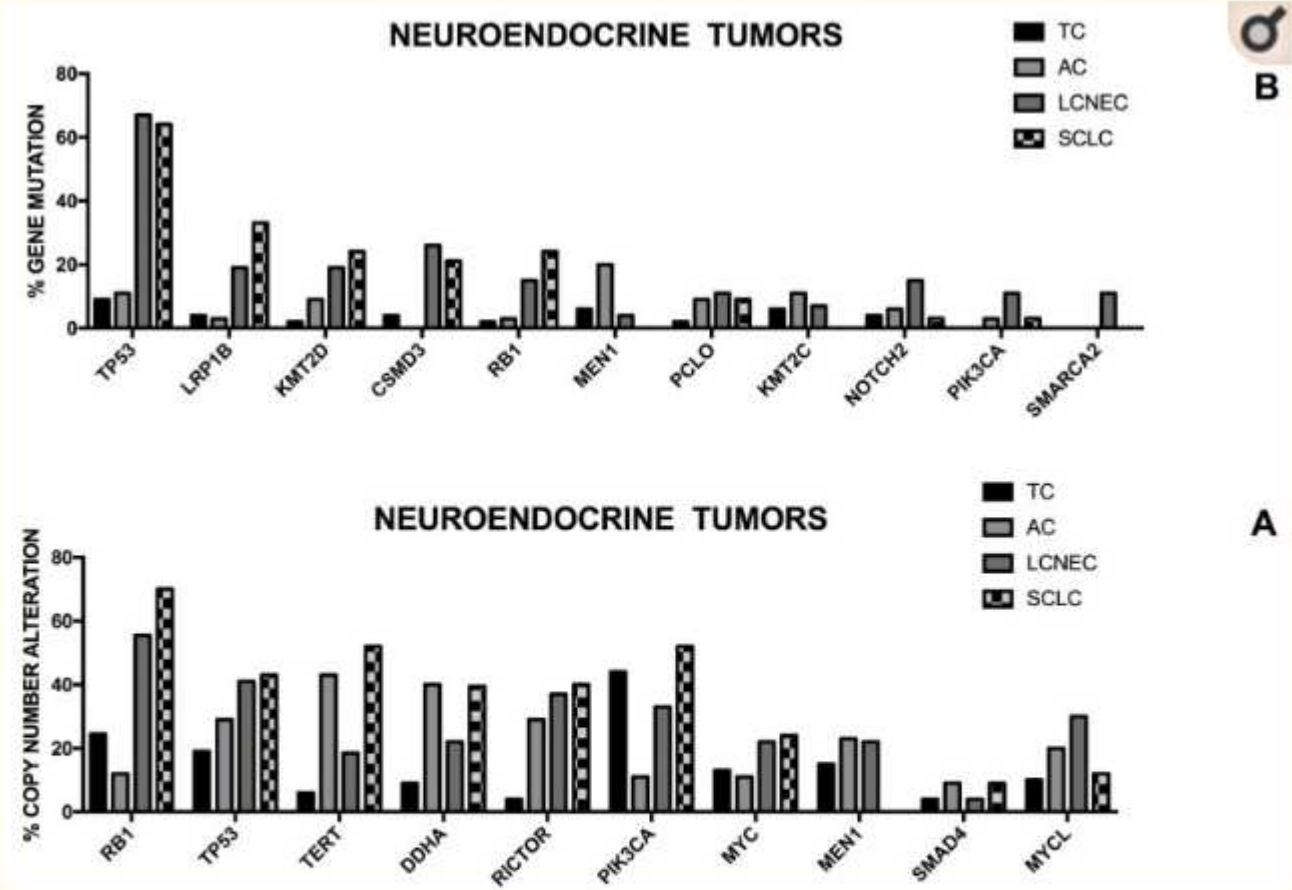


Figure 4

Genetic abnormalities observed in neuroendocrine lung cancers classified into four subtypes: TC (Typical Carcinoid); AC (Atypical Carcinoid); LCNEC (Large Cell Neuro Endocrine Carcinoma); SCLC (Small Cell Lung Carcinoma). A: Copy Number Alterations; B: Gene Mutations The data plotted in this figure were reported by Simbolo et al. [123].

DIPNECH

- Diffuse pulmonary neuroendocrine hyperplasia as precursor lesion for carcinoid
- Defined by 5 or more pulmonary neuroendocrine cells in at least 3 separate small airways combined with 3 or more carcinoid tumorlets
- Pre-invasive proliferation of pulmonary neuroendocrine cells

Carcinoid

- Centrally located bronchial carcinoids may present with cough, wheezing, or hemoptysis due to airway obstruction
- Carcinoids located distally often asymptomatic
- Rarely metastasize
- Paraneoplastic syndromes are uncommon and usually present in the setting of liver metastases

  Carcinoid syndrome

  2-10% of cases

  Cushing syndrome

  4% of cases

Carcinoid

- Epidemiology
- < 1% of all lung cancers
  < 60 years of age
  Women
- Risk factors:
  Mutation in MEN1 gene
  Unrelated to smoking
- Sites
- Anywhere from the trachea to the distal bronchioles
- 85%, central airways

Carcinoid

- Generally central, polypoid.
- A penetrating lesion that fans out in the peribronchial tissue ("collar button") is seen with a minority.
- Bronchoscopy shows polypoid endobronchial lesion in central airway

- Typical carcinoids have no p53 mutations or abnormalities of BCL2 or BAX expression that are found in 20-40% of atypical carcinoids.

Carcinoid syndrome

- Pulmonary carcinoids produce biogenic amines that are released directly into circulation and affect the left side of the heart.
- Rectal carcinoids produce biogenic amines that are released directly into the inferior vena cava and affect the right side of the heart.
- Intestinal carcinoids produce biogenic amines that are released directly into the portal system and are detoxified by the liver.
- Affect the right side of the heart when the liver is no longer capable of detoxifying the biogenic amines. Usually this is due to liver metastasis.

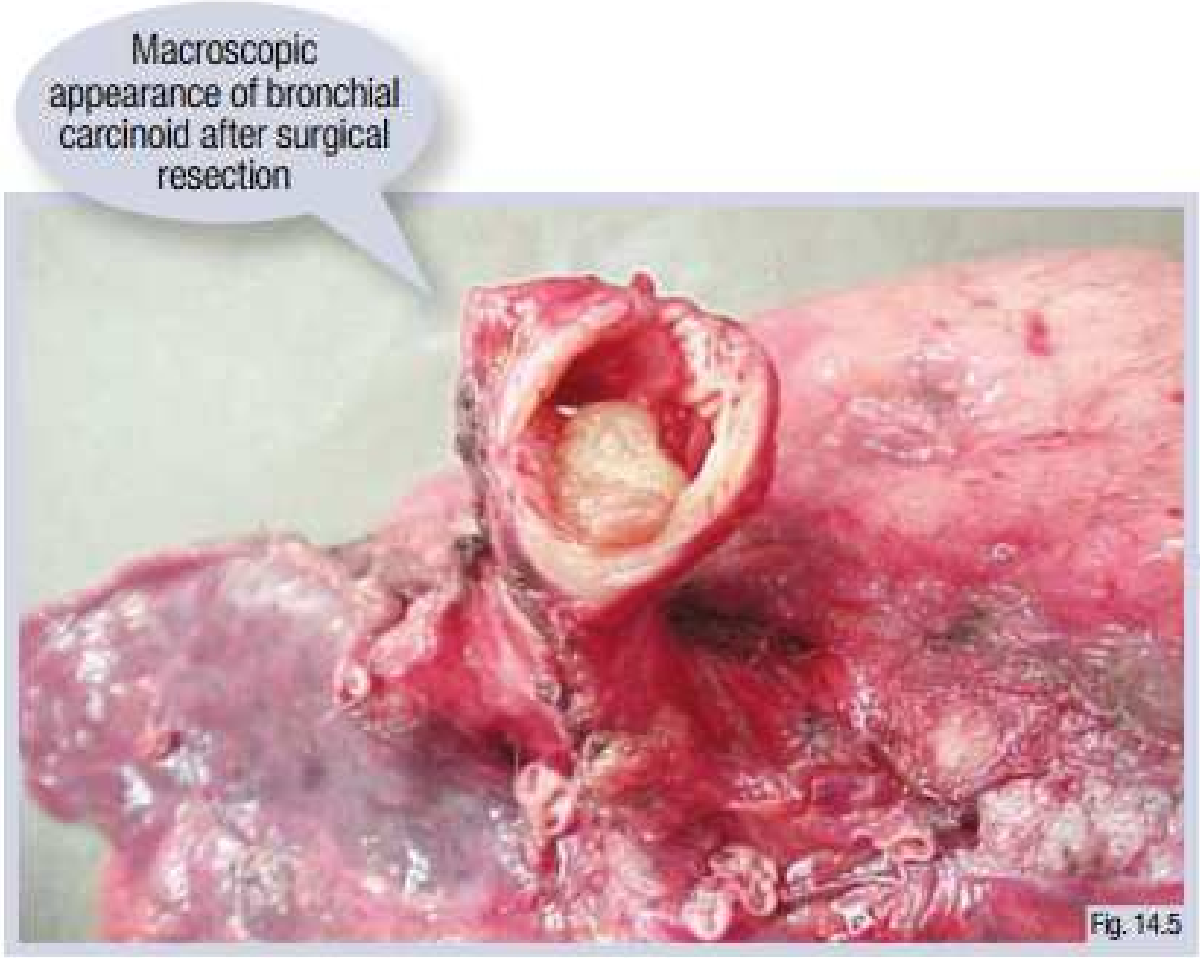
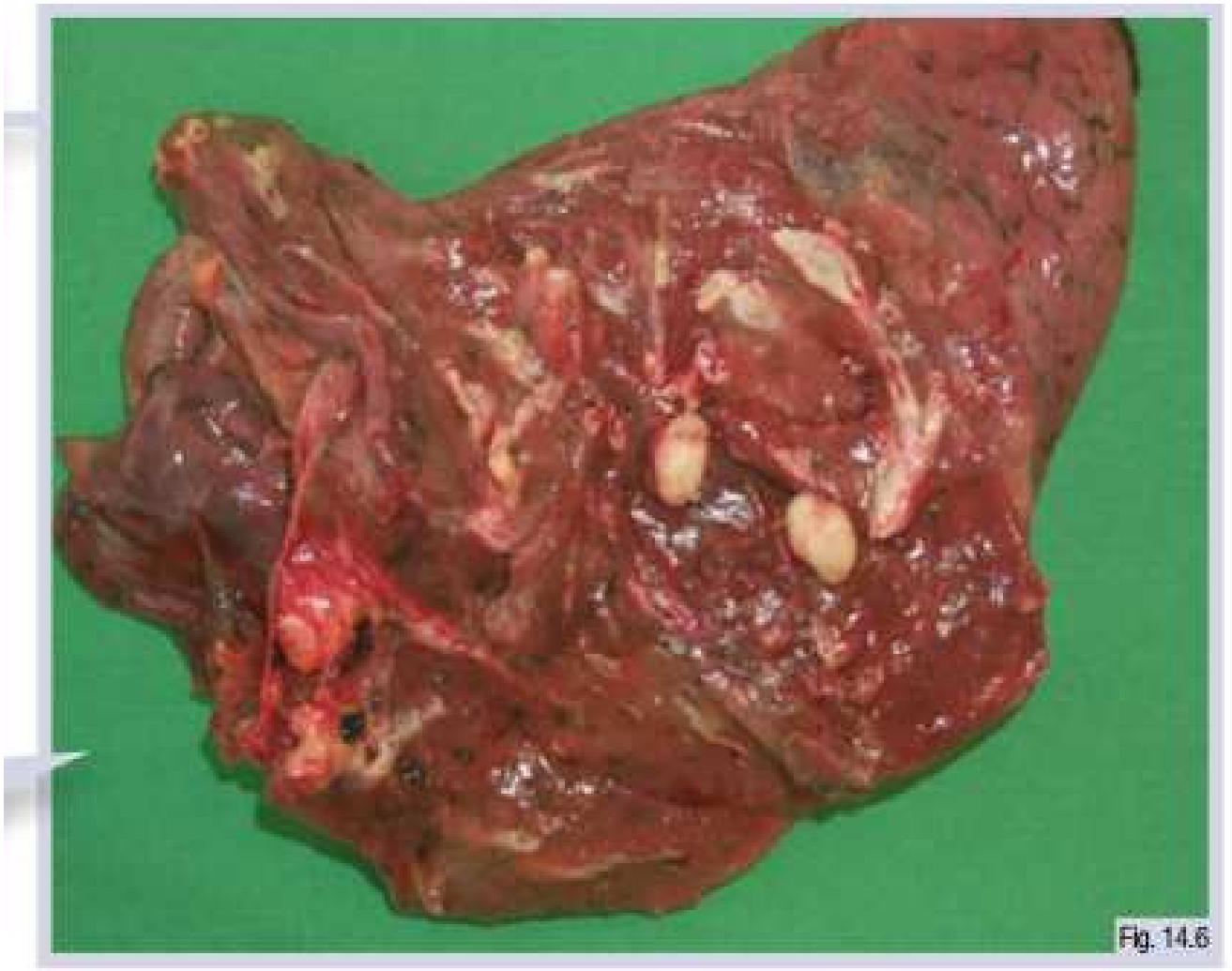
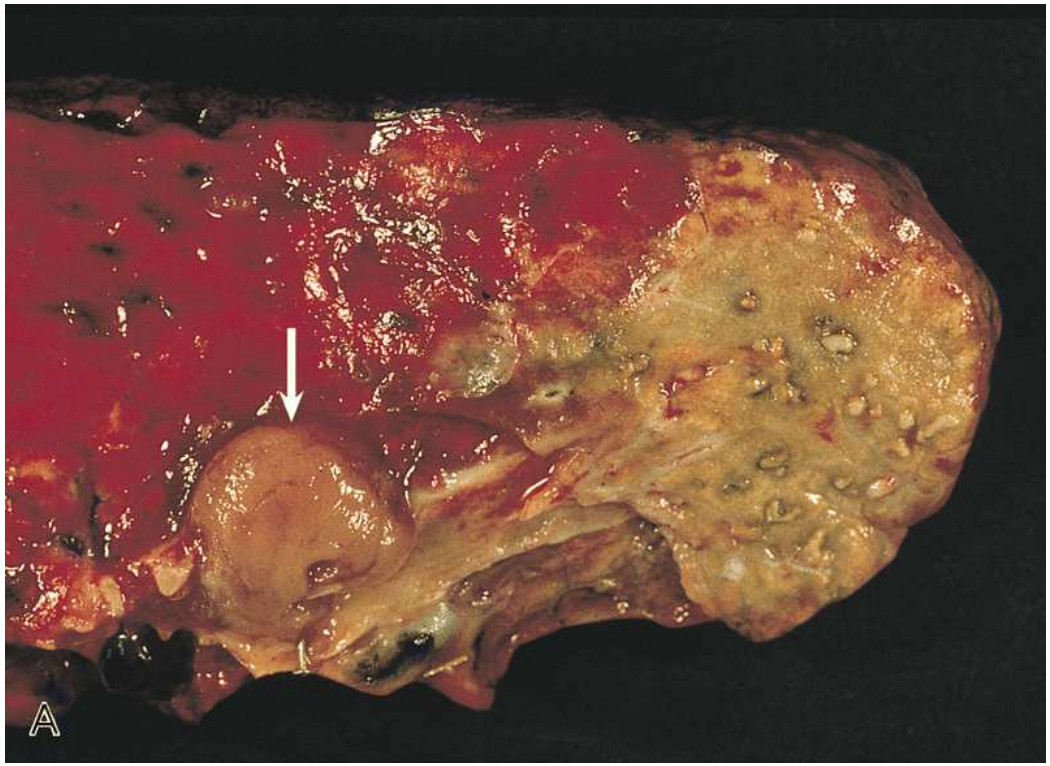

Macroscopic appearance of bronchial carcinoid after surgical resection

Fig. 14.5



10% of patients will have multifocal bronchopulmonary carcinoids

Carcinoid

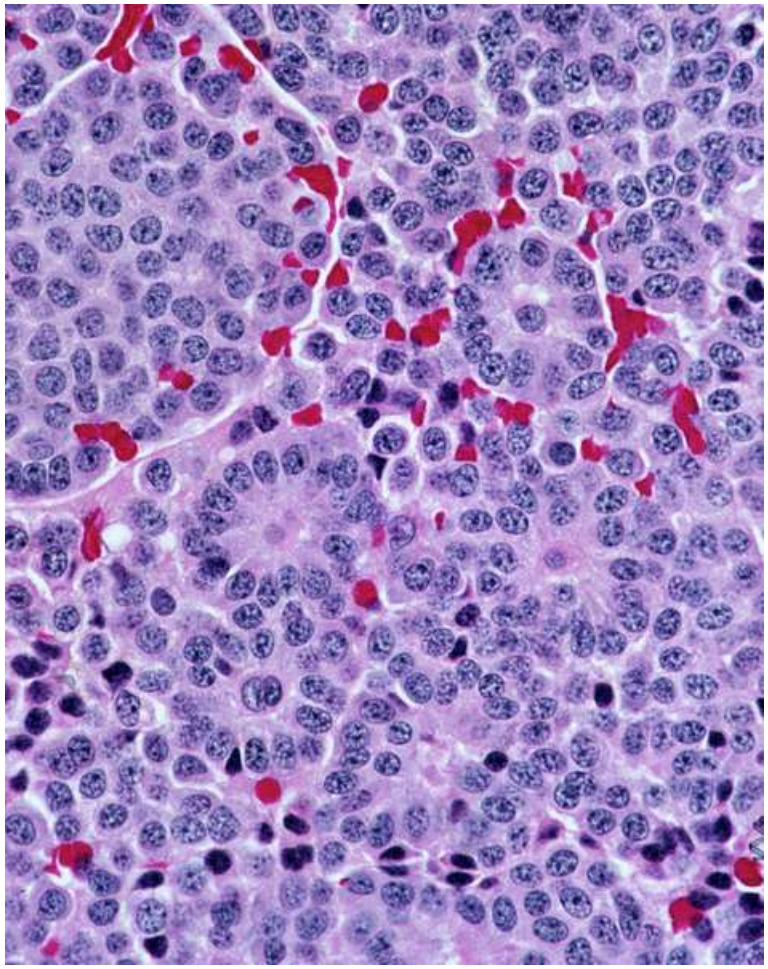


This 2.0-cm, circumscribed, central carcinoid tumor (arrow) impinges on the proximal bronchus to the left upper lobe. The cut surface of the tumor shows a smooth, tan-yellow mass. The lung parenchyma distal to the tumor shows postobstructive pneumonia.

Fig. 17-7A

Colby, TV, Koss, MN, Travis, WD., "Tumors of the lower respiratory tract. " Atlas of Tumor Pathology, Third Series, Fascicle 13. Armed Forces Institute of Pathology, Washington, D.C. 1995.

Carcinoid



Prominent organoid nesting pattern. The tumor cells have a moderate amount of cytoplasm and nuclei with finely granular chromatin. Faint nucleoli are also present. Rosettes are present.

Fig. 17-8R

Colby, TV, Koss, MN, Travis, WD., "Tumors of the lower respiratory tract. " Atlas of Tumor Pathology, Third Series, Fascicle 13. Armed Forces Institute of Pathology, Washington, D.C. 1995.

	NSCLC			SCLC		
	Incidence rate difference (95% CI)	Hazard ratio (95% CI)		Incidence rate difference (95% CI)	Hazard ratio (95% CI)	
		Crude	Adjusted [a]		Crude	Adjusted [a]
All potential PNS	111.2 (107.6–114.9)	4.9 (4.8–5.1)	4.8 (4.7–5.0)	213.5 (200.4–226.6)	8.2 (7.7–8.8)	8.2 (7.6–8.8)
Hematologic conditions	54.2 (52.0–56.4)	14.2 (13.4–15.1)	14.1 (13.3–15.0)	113.4 (104.7–122.1)	27.7 (24.2–31.7)	27.5 (24.0–31.5)
Vasculitis	0.4 (0.1–0.7)	1.6 (1.1–2.1)	1.6 (1.2–2.1)	-0.1 (-0.7–0.6)	1.0 (0.4–2.8)	1.1 (0.4–3.0)
Other vasculopathy	0.1 (-0.0–0.2)	2.4 (1.2–4.8)	2.3 (1.1–4.6)	0.1 (-0.2–0.4)	2.3 (0.3–20.0)	1.8 (0.2–16.3)
Endocrine and metabolic conditions	16.1 (14.7–17.5)	3.4 (3.2–3.6)	3.4 (3.1–3.6)	22.5 (18.3–26.6)	4.5 (3.8–5.4)	4.8 (4.0–5.7)
Neurologic conditions	2.0 (1.1–2.8)	1.4 (1.2–1.5)	1.4 (1.3–1.6)	5.6 (2.9–8.3)	2.0 (1.6–2.5)	2.1 (1.6–2.7)
Neuromuscular junction and muscle	-0.0 (-0.3–0.3)	1.0 (0.7–1.3)	1.0 (0.8–1.3)	1.2 (0.1–2.4)	2.2 (1.3–3.9)	2.5 (1.4–4.4)
Ménière's disease	-0.0 (-0.2–0.1)	0.7 (0.4–1.4)	0.8 (0.4–1.5)	0.2 (-0.3–0.8)	1.8 (0.5–6.3)	2.0 (0.6–6.8)
Circulatory conditions (not described as PNS)	0.3 (0.0–0.6)	1.5 (1.1–2.0)	1.3 (1.0–1.8)	0.6 (-0.3–1.4)	1.8 (0.9–3.9)	1.8 (0.8–3.8)
Asthma	3.4 (2.7–4.1)	2.4 (2.1–2.8)	1.7 (1.5–2.0)	3.1 (1.3–4.8)	1.8 (1.3–2.7)	1.3 (0.9–1.9)
Digestive conditions (not described as PNS)	1.6 (1.1–2.2)	1.9 (1.6–2.2)	1.8 (1.5–2.1)	0.9 (-0.4–2.2)	1.3 (0.8–2.1)	1.2 (0.7–2.0)
Kidney disease	0.1 (-0.0–0.3)	1.6 (0.9–2.7)	1.4 (0.8–2.5)	0.8 (0.0–1.6)	4.0 (1.7–9.4)	4.6 (1.9–11.0)
Dermatologic conditions	0.7 (0.4–1.1)	1.8 (1.4–2.3)	1.7 (1.3–2.2)	-0.1 (-0.8–0.6)	0.9 (0.4–2.2)	0.9 (0.3–2.2)
Rheumatic syndromes	1.2 (0.7–1.7)	1.5 (1.2–1.8)	1.4 (1.2–1.7)	0.9 (-0.4–2.3)	1.2 (0.8–2.0)	1.1 (0.7–1.8)
Non-system-specific	33.4 (31.7–35.1)	21.7 (19.9–23.6)	20.8 (19.1–22.7)	71.8 (65.0–78.6)	39.3 (32.7–47.4)	38.2 (31.7–46.2)

[a] Adjusted for age, sex, residence, calendar period and baseline history of chronic obstructive pulmonary disease, non-insulin dependent diabetes mellitus, hypertension, ischemic heart disease, kidney disease, Charlson Comorbidity Index score (excluding the conditions listed beforehand).

CI confidence interval; NSCLC non-small cell lung cancer; PNS paraneoplastic syndrome(s); SCLC small cell lung cancer

https://doi.org/10.1371/journal.pone.0181564.t003

Tab. 2 Häufige paraneoplastische Syndrome: Ätiologie, klinische Symptomatik und Therapie.

Syndrom	Auftreten bei	Symptome	Therapie*
Hyperkalziämie	v. a. NSCLC (PEC, Adeno)	Anorexie, Nausea, Erbrechen, Polyurie, Polydipsie	forcierte Diurese, Biphosphonate
SIADH	v. a. SCLC	Hyponatriämie, Anorexie, Übelkeit, Erbrechen, Verwirrungszustände, Krämpfe, Somnolenz, Koma	Flüssigkeitsrestriktion, hypertone Kochsalzlösung, Vaptane
EAS/Cushing-Syndrom	EAS: v. a. Bronchuskarzinoid Cushing-Syndrom: v. a. SCLC	periphere Ödeme, proximale Myopathie, Vollmondgesicht, Gewichtsverlust, hypokaliämische Alkalose, Hyperglykämie	Therapie der Grundkrankheit
Anämie	beide	Blässe, Dyspnoe, verminderte Belastbarkeit	Transfusion, Erythropoetin
LEMS	v. a. SCLC	progrediente Muskelschwäche der proximalen unteren Extremitäten, Fatigue, Mundtrockenheit, Ptosis	3,4-Diaminopyridin, intravenöse Immunglobulingabe
Akanthosis nigricans	v. a. NSCLC	warzenartige Hautveränderungen (Achselhöhlen, Gelenkbeugen, im Nacken oder in den Leistenbeugen)	keine spezifische
Dermatomyositis	v. a. SCLC	proximale Myopathie, Erytheme	Glukokortikosteroide
Thrombembolie	beide	Thrombosezeichen, Dyspnoe, thorakale Schmerzen, Hämoptysen	Antikoagulation
Trommelschlegelfinger/HPO	v. a. NSCLC (PEC, Adeno)	nicht-steroidale Antiphlogistika, Biphosphonate	Schwellung der terminalen Phalangen, schmerzhafte symmetrische Arthropathie (Sprung- und Hüftgelenke), periostale Knochenneubildung an den distalen Extremitäten
Kachexie	beide	Gewichtsverlust, Anorexie, Verlust an Muskelmasse, Anämie	Ibuprofen, Medroxyprogesteronazetat, Eicosapentaensäure
Fatigue	beide	physikalische Erschöpfung, verminderte körperliche Aktivität, fehlende Motivation, mentale Erschöpfung	Antidepressiva, Kortikosteroide, Psychostimulantien, Modafinil

* Es ist die spezifische Therapie für das jeweilige Syndrom angeführt (sofern bekannt).
NSCLC: non-small cell lung cancer. SCLC: small cell lung cancer. PEC: Plattenepithelkarzinom. Adeno: Adenokarzinom.

- DOI: 10.1055/s-0030-1256118

Accessed 01/20/2020

Table 1

Paraneoplastic syndromes and their associated antibodies and tumours. The most frequent antibodies and tumours are listed in bold

Neurological syndrome	Antibody	Tumour	References
Encephalomyelitis/limbic encephalitis	**Anti-Hu, anti-Ma2,** anti-CV2/CRMP5, anti-VGKC, anti-Ri, anti-amphiphysin, anti-GABA$_B$R, anti-AMPAR, anti-GAD	**SCLC, testicular tumour,** thymoma, neuroblastoma, prostate carcinoma, breast cancer, Hodgkin's lymphoma	[6,50,63,72–75]
Cerebellar degeneration	**Anti-Yo, anti-Hu,** anti-VGCC, anti-CV2/CRMP5, anti-Ma2, anti-Ri, anti-Tr, anti-GAD, anti-mGluR1-α	**SCLC, ovarian cancer, breast cancer, Hodgkin's lymphoma,** thymoma	[8,48,51,76,77]
Brainstem encephalitis/opsoclonus-myoclonus	**Anti-Ri, anti-Ma2,** anti-Hu, anti-amphiphysin	Breast cancer, ovarian cancer, testicular tumour, SCLC, neuroblastoma (children)	[50,78]
Encephalitis with psychiatric manifestations, seizures, dyskinesias, dystonia and autonomic instability	**Anti-NMDAR**	**Ovarian teratoma,** testis teratoma, SCLC	[5,79]
Neuromyotonia	**Anti-VGKC**	Thymoma, SCLC	[19]
Lambert-Eaton myasthenic syndrome	**Anti-VGCC**	**SCLC**	[80]
Myasthenia gravis	**Anti-AChR**	**Thymoma**	[81]
Subacute sensory neuronopathy	**Anti-Hu,** anti-CV2/CRMP5, anti-amphiphysin	**SCLC,** breast cancer, ovarian cancer	[6,82]
Subacute autonomic neuropathy	Anti-gAChR, anti-Hu	**SCLC,** thymoma	[82]
Stiff-person syndrome	**Anti-amphiphysin,** anti-GAD	**Breast cancer,** SCLC	[83–86]
Cancer-associated retinopathy	Anti-recoverin	**SCLC,** endometrium cancer	[87–89]

SCLC, small cell lung cancer.

doi
: 10.1111/j.1468-1331.2010.03220.x

Extrapulmonary manifestations

- Lambert-Eaton syndrome
- Proximal muscle weakness
- Orthostatic change
- Diplopia but no ptosis (distinguish from myasthenia gravis)
- Improves during the day (distinguish from myasthenia gravis)
- Due to antibodies to presynaptic voltage gated (P/Q) calcium channel

Extrapulmonary manifestations

- Subacute cerebellar degeneration
- Presents with dizziness, nausea, and vomiting
- Ataxia
- Dysarthria
- Vertigo
- Diplopia
- Antibody to Purkinje cell
- May coincide with Lambert-Eaton syndrome
- Also seen in thiamine deficiency
-

Extrapulmonary manifestations

- Limbic encephalitis
- Short-term memory defects
- Seizures
- Psychiatric disturbances
- Anti-Hu antibody
- May also be seen with germ cell tumor of testis (anti-Ma2) or ovarian teratoma (anti-NDAR)
- Indistinguishable from Herpes simplex or HSV-6 encephalitis
- (There are non-neoplastic variants associated with antibody to voltage gated potassium channels)

Extrapulmonary manifestations

- Optic neuritis
- Anti-CV2 antibody (to oligodendroglia)
- Trigeminal neuralgia
- Unilateral stabbing pain
- Poor prognostic sign
- 10-15% have neuroendocrine symptoms
- Gastrin releasing peptide
- Parathormone (hypercalcemia)
- Opioids

Extrapulmonary manifestations

- Pain in distribution of ulnar nerve
- Sensory peripheral neuropathy
- Leukemoid reaction
- Compression or invasion of the superior vena cava is life threatening complication
- Venous congestion
- Circulatory compromise
- Dusky head
- Neck and arm edema

Extrapulmonary manifestations

- Syndrome of inappropriate ADH secretion
- Often presents with confusion and delirium
- Na^+ <125 mEq/L
- U_{Osm} <275 mOsm/kg
- U_{Na+} >40 mEq/L
- Fractional Na^+ excretion >1%
- Cushing Syndrome
- Truncal obesity
- Facial plethora
- Proximal muscle weakness
- Hypokalemia

Pulmonary hyperosteoarthropathy

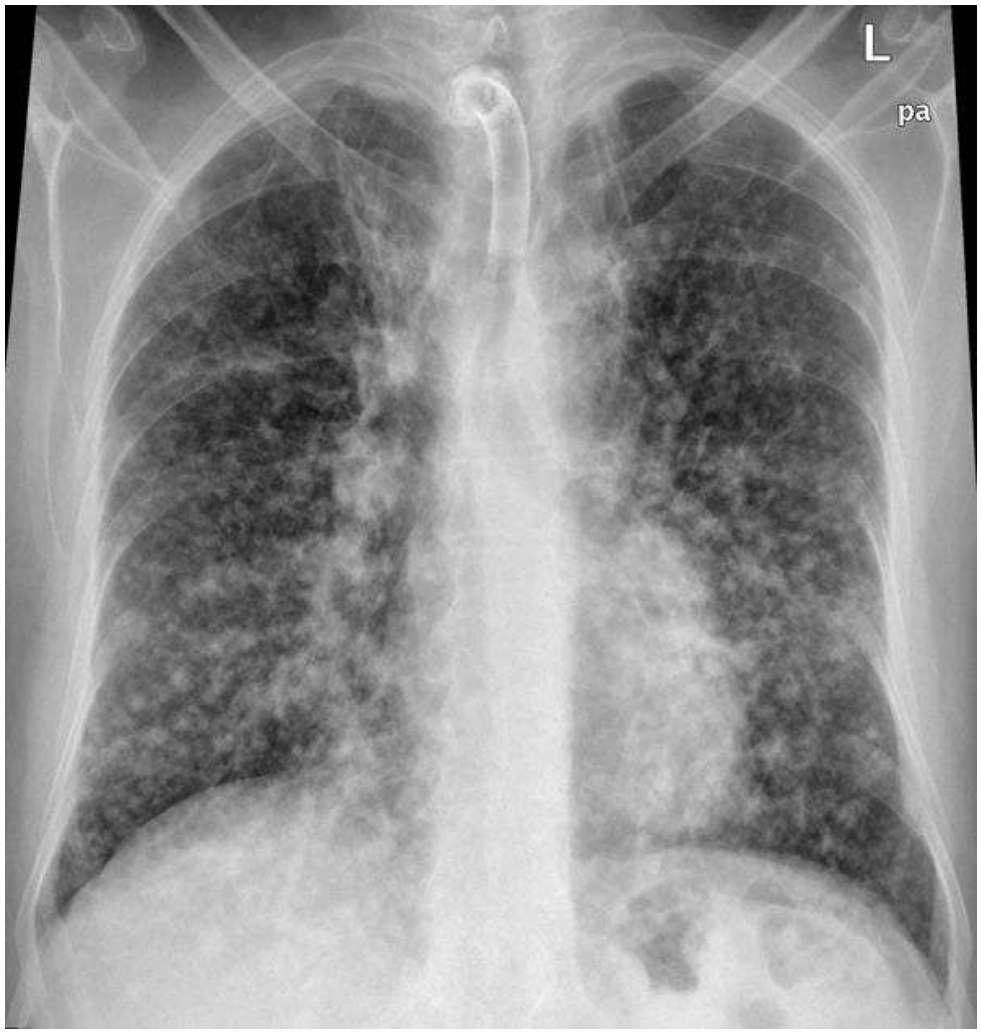
Digital clubbing. Loss of normal nail angle.

Nail changes associated with periostitis (on x-ray) are commonly associated with squamous carcinoma of the lung (5% in some series) but may be seen in mesothelioma and liver cancer.

Clubbing without periostitis is seen in cyanotic heart disease

https://www.mdedge.com/ccjm/article/134382/imaging/hypertrophic-osteoarthropathy-uncommon-presentation-lung-cancer
Fig. 1 Accessed 12/10/2019

Metastatic cancer



Usually single or multiple nodules.

Shown is Hematogenous spread of carcinoma.

Mimics miliary tuberculosis.

https://radiopaedia.org/articles/miliary-tuberculosis?lang=us
Accessed 12/10/2019

Pleural effusion

- Dullness to percussion
- Breath sounds diminished in area of effusion
- Vocal fremitus absent in area of effusion
- Large effusions may restrict breathing
- May shift mediastinum
- Blunting of the costophrenic angle is noted on chest x-ray
- Diaphragm may also be obscured

Etiology of pleural effusion

- Increased hydrostatic pressure in visceral pleura
- Congestive heart failure
- Decreased oncotic pressure
- Nephrotic syndrome
- Obstruction of lymphatic drainage from the visceral pleura
- Lung cancer

Etiology of pleural effusion

- Increased vessel permeability of visceral pleural capillaries
- Pneumonia
- Pulmonary infarction
- Metastasis to the pleura
- Entrance of fluid from retroperitoneum
- Pancreatitis

Types of pleural effusion

- Transudate
- Plasma ultrafiltrate
- Pleural fluid protein <0.5 g/dL
- pH >7.4
- LDH fluid/ LDH plasma <0.6
- Exudate
- Usually inflammatory
- Protein and cell rich fluid
- Pleural protein fluid >0.5 g/dL
- pH <7.4
- LDH fluid/ LDH plasma >0.6

Pleural effusion

- Chylous
- Thoracic duct interrupted
- Turbid, milky appearance (chylomicrons)
- Pleural fluid triglycerides >110 mg/dL

- If from pancreas, amylase present in pleural fluid

Malignant mesothelioma

- Lung encased in fibrous tissue.
- Presents with :
- Chest pain
- Dyspnea (restrictive lung disease)
- Pleural effusion
- Origin
- Arises from mesothelial lining of pleura, peritoneum, pericardium and tunica vaginalis
- pleural mesothelioma is the most common site
- Fibrous plaques may precede development of malignant lesion

Fibrous plaque

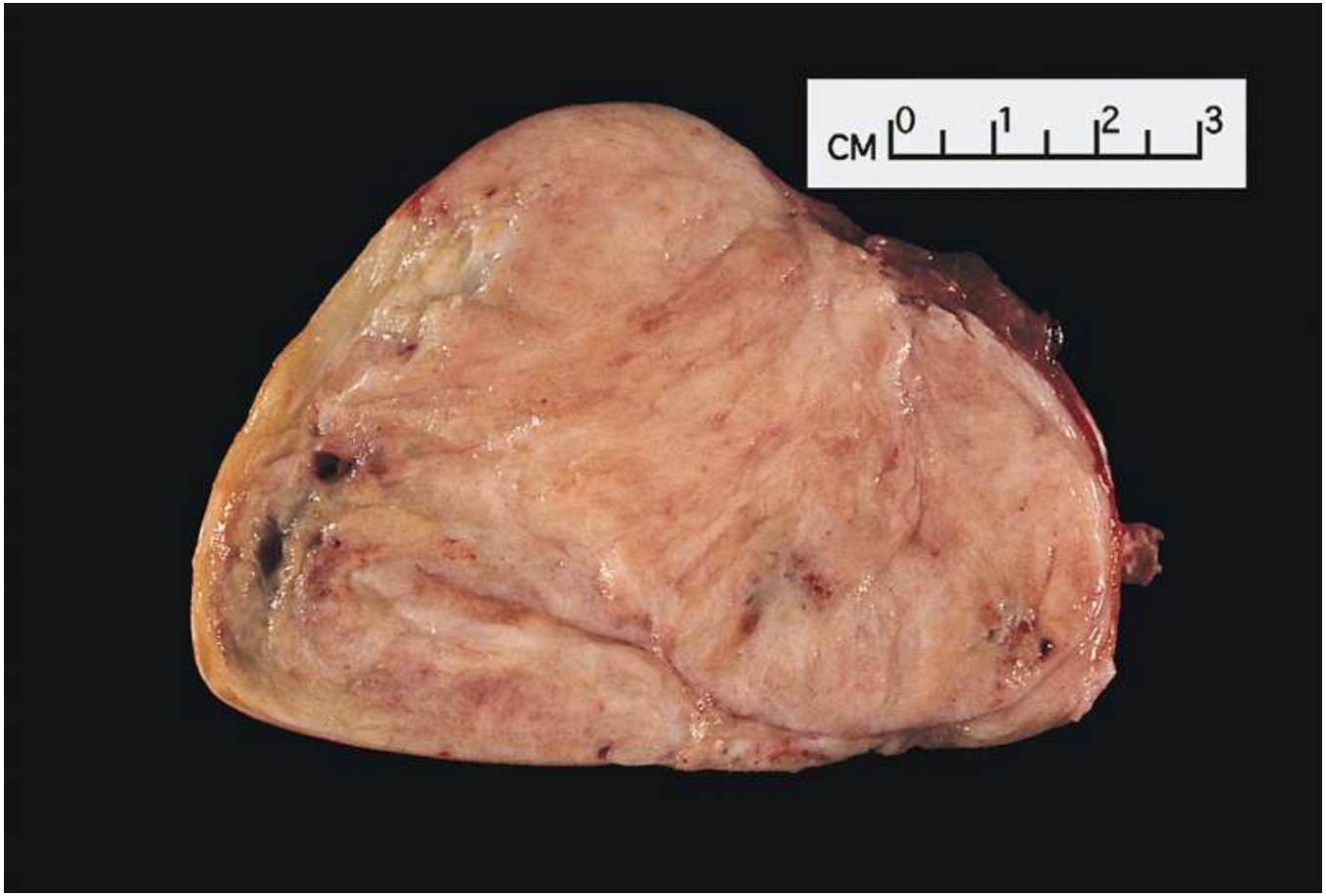


Fig. 6-2

Battifora, Hector, McCaughey, WT Elliott, “Tumors of the serosal membranes,” Atlas of Tumor Pathology. Third Series, Fascicle 15. Armed Forces Institute of Pathology. Washington, DC . 1995.

Etiology of malignant mesothelioma

- Smoking is not a risk factor
- Risk factors include:

  Asbestos exposure:

  - Usually a prolonged latency period
  - No linear dose-response relationship between asbestos exposure and malignant mesothelioma
  - Amphibole (crocidolite) is potent carcinogen
  - Accounts for 95% of asbestos employed
  - Amphibole fibers of a size that permits penetration to small airways

Etiology of malignant mesothelioma

- Chrysotile (serpentine form of asbestos) is not a potent carcinogen

- Radiation
- Erionite
- Potent carcinogenic mineral fiber used in gravel roads
- SV40 virus
- Up to 80% have DNA sequences in the tumor

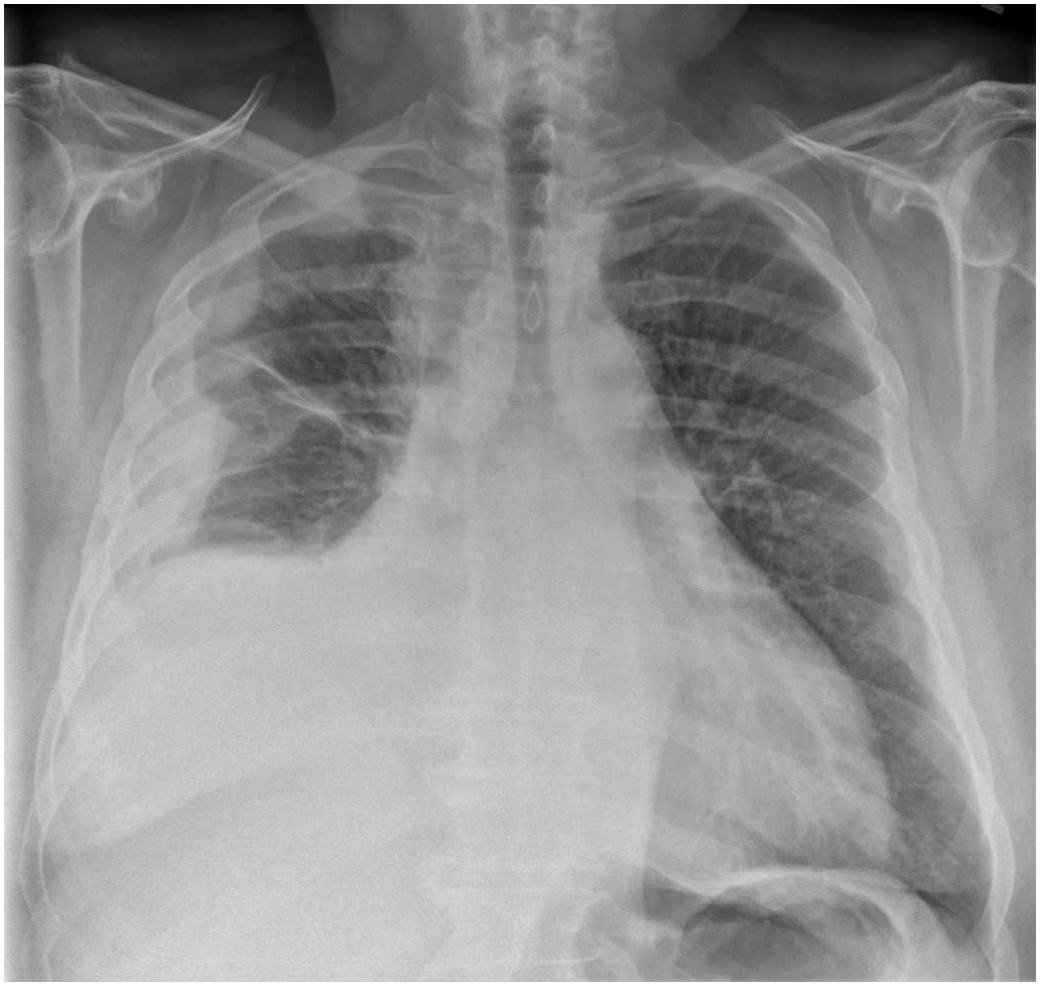
Malignant mesothelioma

- Gross description
- Multifocal studding of lung or pleural surfaces
- Circumferential or nodular pleural thickening

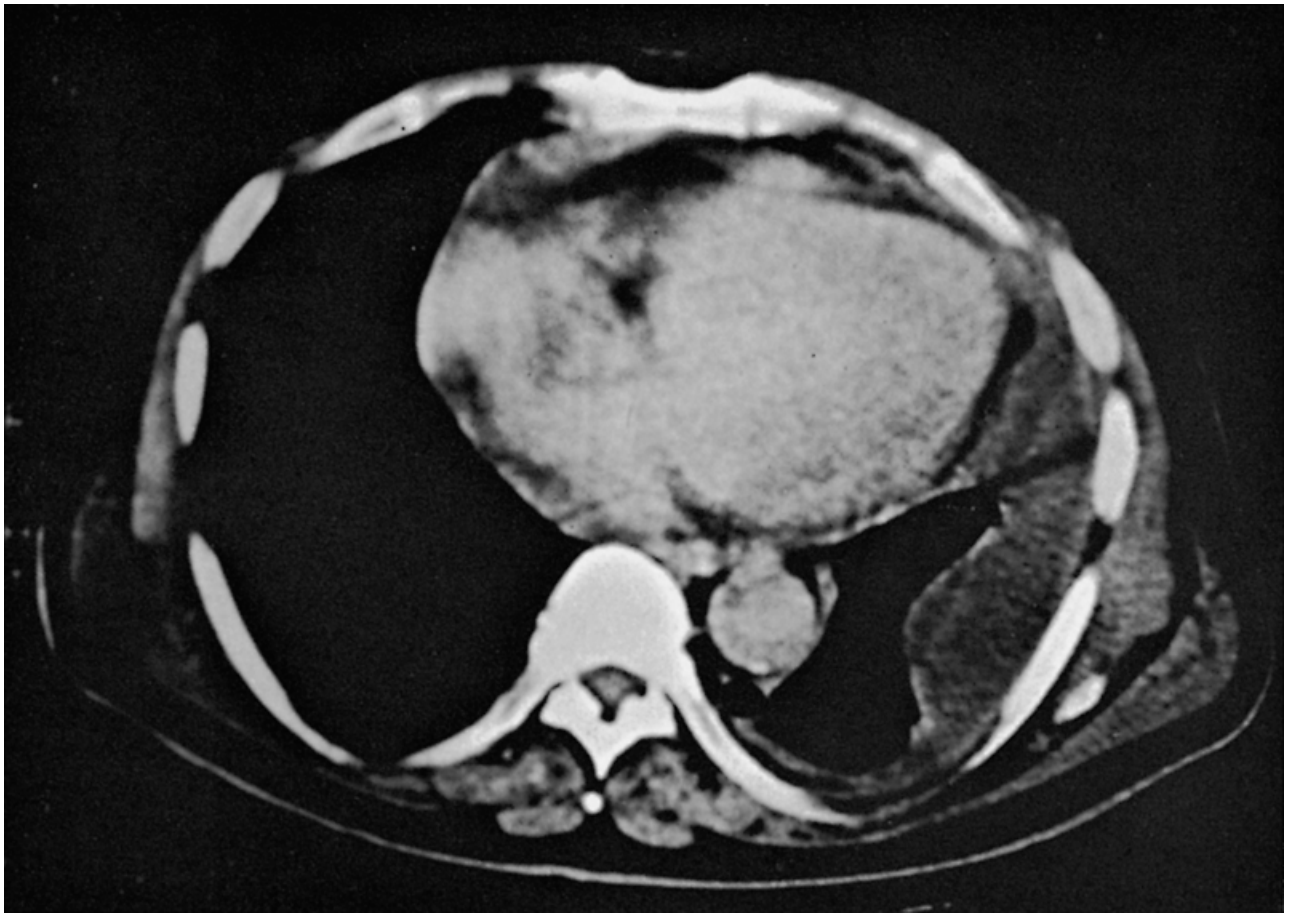
Malignant mesothelioma

Blunting of the right costophrenic angle with pleural plaque noted along right lateral thoracic margin and the medial mediastinal surface.

https://radiopaedia.org/cases/mesothelioma-16
Accessed 12/10/2019



Malignant mesothelioma



In this CT scan, the pleura on the right side shows marked diffuse thickening by tumor.

Fig. 20 from Fascicle 20, 2nd Series., in Battifora, Hector, McCaughey, WT Elliott, “Tumors of the serosal membranes,” Atlas of Tumor Pathology. Third Series, Fascicle 15. Armed Forces Institute of Pathology. Washington, DC . 1995.

Histopathology

- Three broad histopathological features
- Glands are poorly formed
- May see iron covered asbestos fiber in fibrotic plaques.
- Epithelioid (60%)
- Tubulopapillary
- Deciduoid
- Clear cell
- Small cell type
- Sarcomatoid (20%)
- Desmoplastic (may see malignant spindle cells)
- Lymphohistiocytoid types
- Biphasic / mixed (20%)

Histopathology

- Stromal or fat invasion is helpful in diagnosis
- Stain for acid mucopolysaccharide (hyaluronidase resistant)
- Stain for keratin (perinuclear)
- Electron microscopy
- Most useful in epithelioid variant and moderately well differentiated tumors
- Not helpful in sarcomatoid or poorly differentiated tumors
- Long, slender microvilli with tonofilaments but without glycocalyx
- No lamellar bodies
- Adenocarcinoma has short stubby microvilli

Molecular description

- BAP1 (BRCA associated protein 1) germline mutations at 3p21.1 may identify those at increased risk (ubiquination)
- Homozygous deletions of p16 / CDKN2A at 9p21 in 30% of tumors
- Inactivating mutations in NF2 gene at 22q12.2
- Mutations in LATS2 gene at 13q21
- Identified in cell lines only

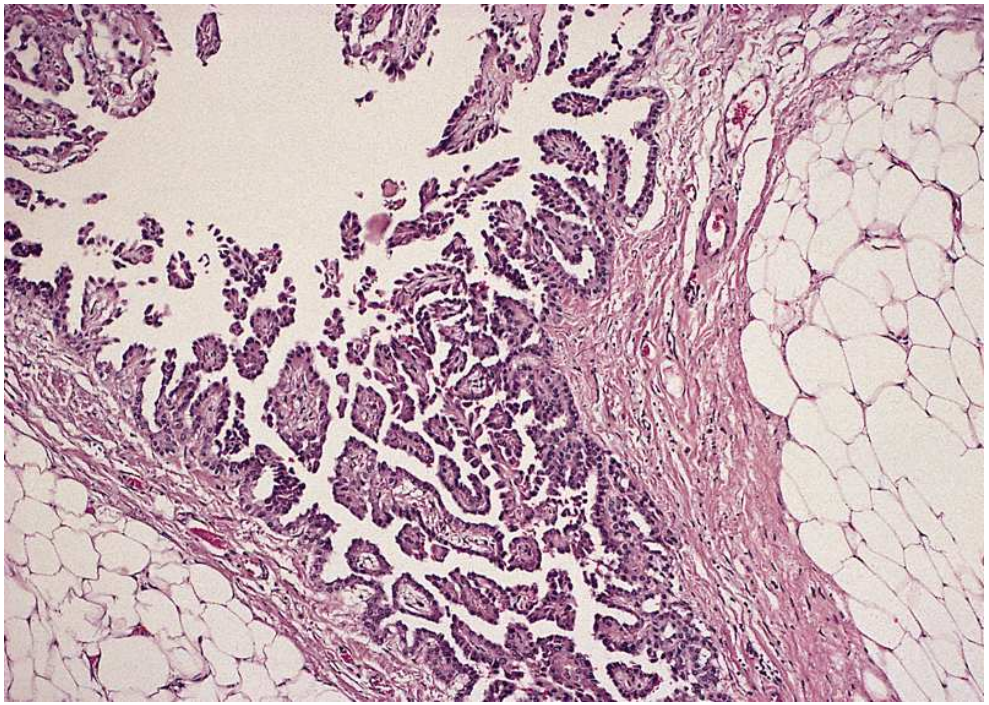
Molecular description

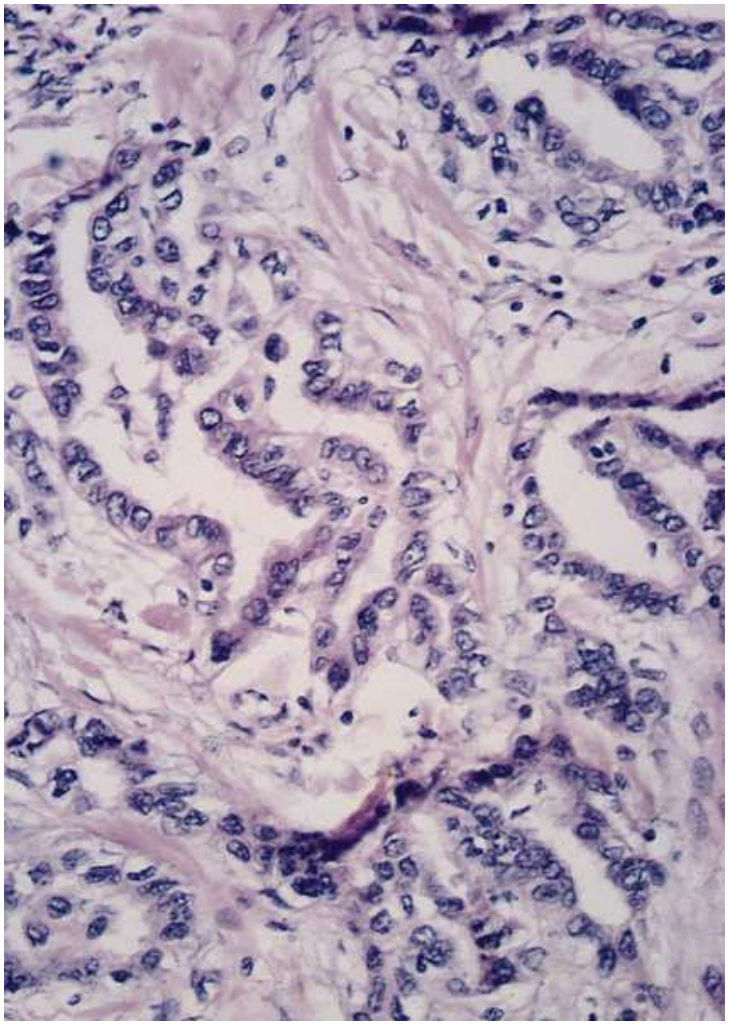
- Del 1p, 3p, 6q, 9p, or 22q common.
- 30% have p16 abnormalities.
- CT best choice for work-up.
- Epithelioid subtype (60% of tumors) more likely to respond to chemotherapy than are mixed or sarcomatoid types.
- Premetrexed and cisplatin as combination of choice.

Asbestos body

https://www.merckmanuals.com/professional/pulmonary-disorders/environmental-pulmonary-diseases/asbestosis
Accessed 12/10/2019

Malignant mesothelioma

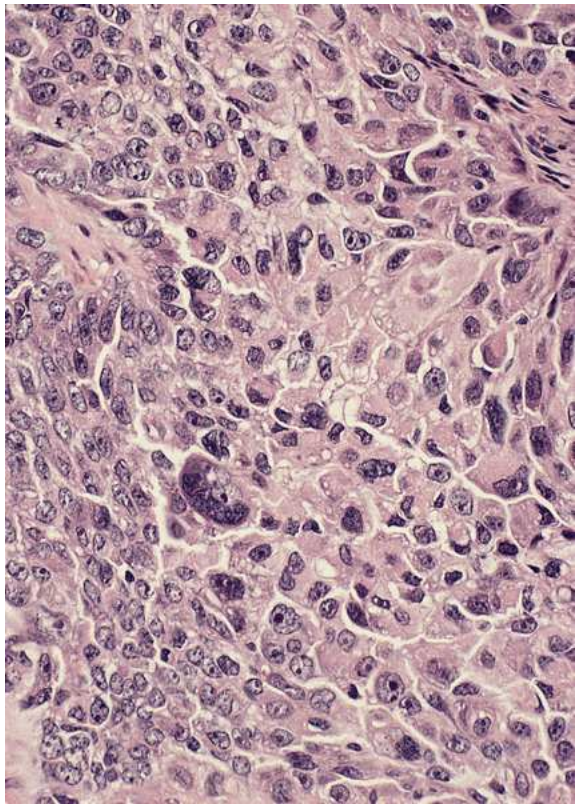




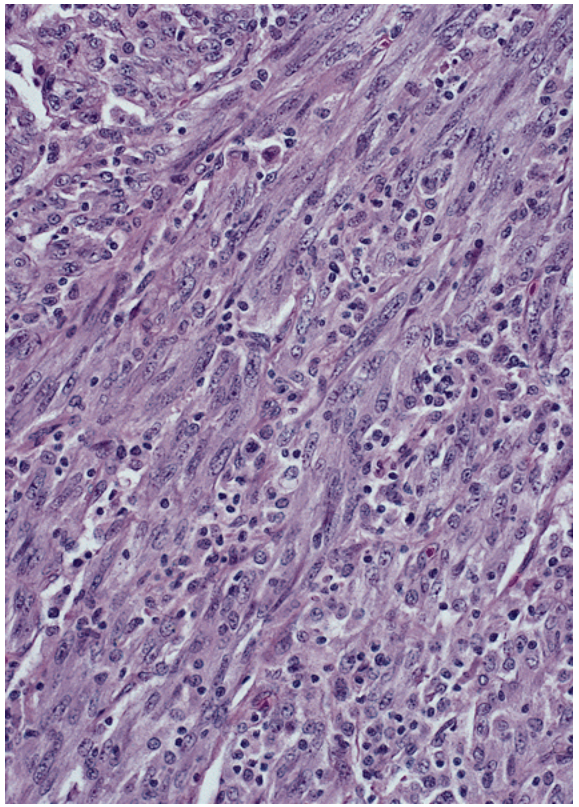
Papillary (left) and tubular (right) patterns

Fig. 4-16 and 4-17.
Battifora, Hector, McCaughey, WT Elliott, “Tumors of the serosal membranes,” Atlas of Tumor Pathology. Third Series, Fascicle 15. Armed Forces Institute of Pathology. Washington, DC . 1995.

Malignant mesothelioma



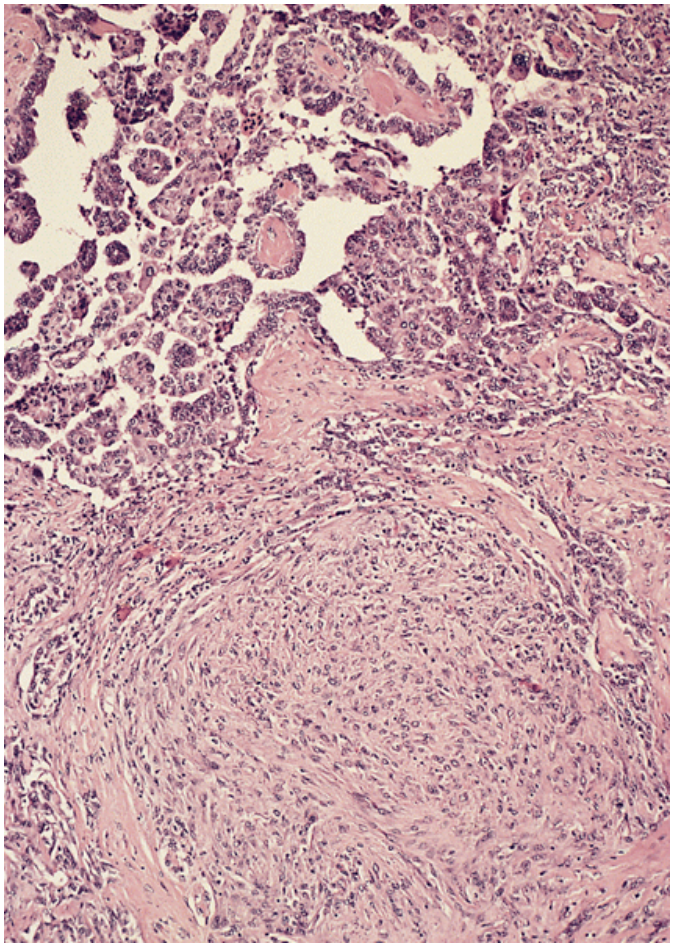
Epithelial pattern



Sarcomatous pattern

Fig. 4-24 and 4-29.
Battifora, Hector, McCaughey, WT Elliott, “Tumors of the serosal membranes,” Atlas of Tumor Pathology. Third Series, Fascicle 15. Armed Forces Institute of Pathology. Washington, DC . 1995.

Malignant mesothelioma

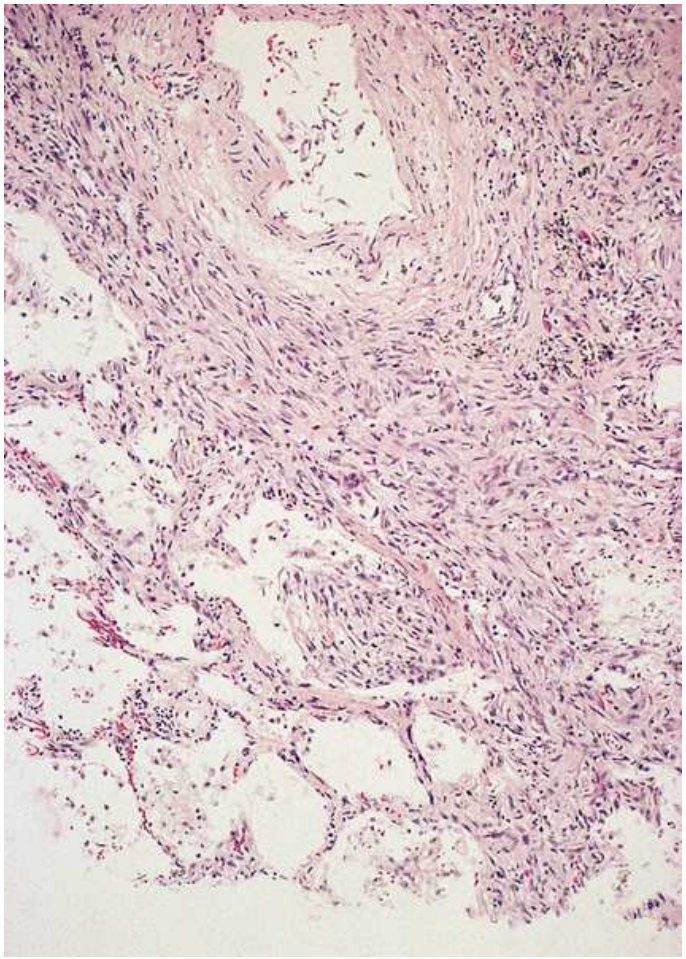


Biphasic pattern

Fig. 4-40L

Battifora, Hector, McCaughey, WT Elliott, “Tumors of the serosal membranes,” Atlas of Tumor Pathology. Third Series, Fascicle 15. Armed Forces Institute of Pathology. Washington, DC . 1995.

Malignant mesothelioma



Invasion of alveoli

Fig. 4-47T

Battifora, Hector, McCaughey, WT Elliott, “Tumors of the serosal membranes,” Atlas of Tumor Pathology. Third Series, Fascicle 15. Armed Forces Institute of Pathology. Washington, DC . 1995.

Diagnostic decision points

- Bronchoscopy with brushings and washings has a 90% yield if central tumor; 60% if peripheral.
- Transtracheal needle aspiration best for right tracheal, subcarinal disease.
- Combination CT and PET scan identifies lymphadenopathy.
- If no lymphadenopathy noted on PET scan, lesion is resectable.
- If lymphadenopathy, guided endobronchial ultrasound essential to evaluate N_2.
- Greater yield than with mediastinoscopy
- May reach periphery (3mm diameter)
- N_2 or N_3 disease is not resectable.

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

https://radiologyassistant.nl/chest/lung-cancer-tnm-8th-edition
Accessed 12/10/2019

Endobronchial staging

- T-descriptor:
- eT1: tumor ≤3 cm not extending into main bronchus
- eT2: tumor involving main bronchus distal to main carina
- eT4: tumor involving main carina and/or distal trachea

Lung cancer staging

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB

https://radiologyassistant.nl/chest/lung-cancer-tnm-8th-edition
Accessed 12/10/2019

Therapeutic approach

- Age is not a limit to therapy.
- If minimum Oxygen consumption <15ml/kg/min, high risk.
- If DLCO>60% and residual volume <50%, can tolerate pneumonectomy.
- If FEV1 2L, can tolerate pneumonectomy; if 1L, lobectomy; if 0.6L, segmentectomy.
- Local recurrence much more likely if limited resection. (Stages I and II)
- With a centrally located tumor, a parenchyma-sparing sleeve resection (SR) can be performed in order to avoid a pneumonectomy.

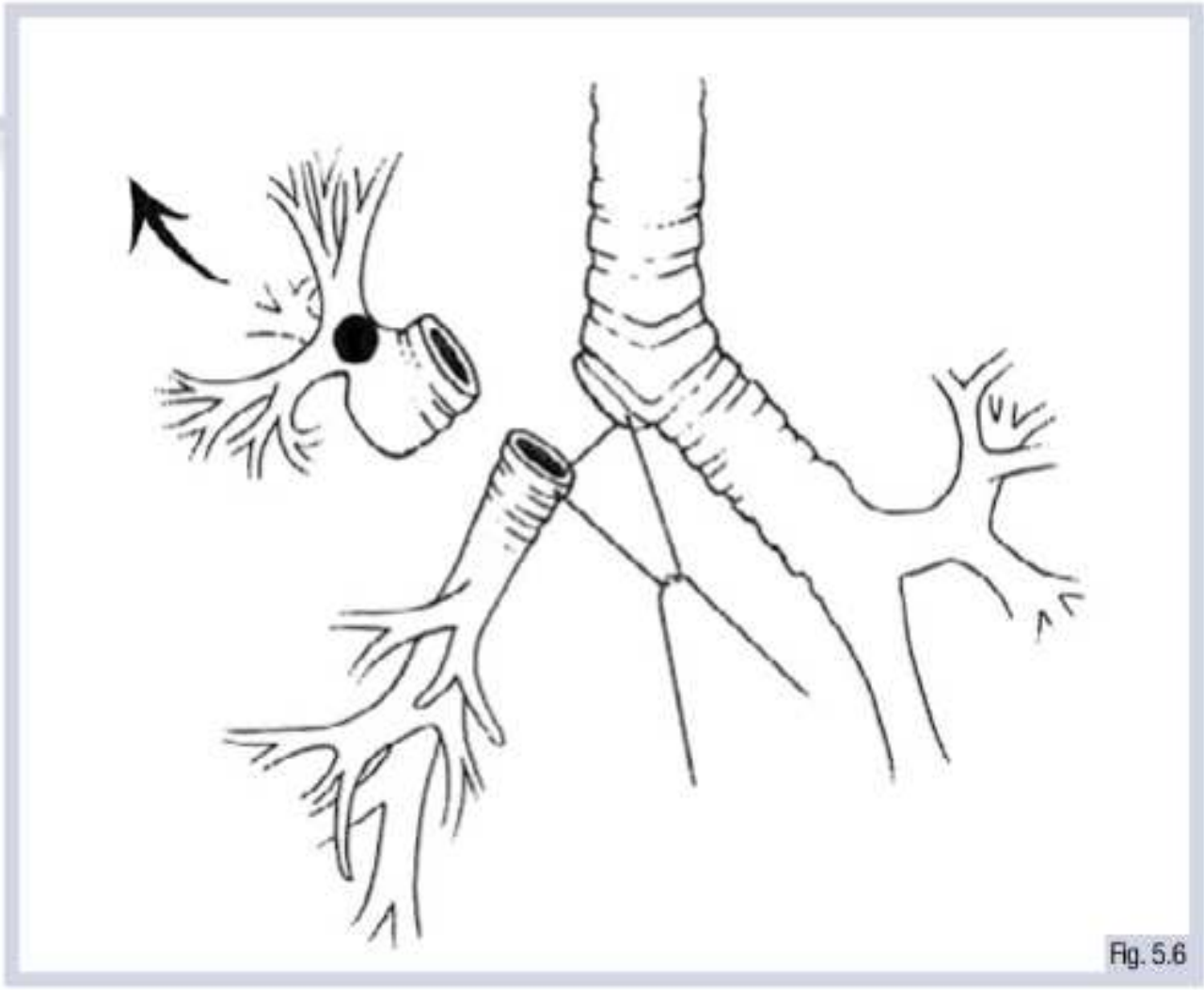
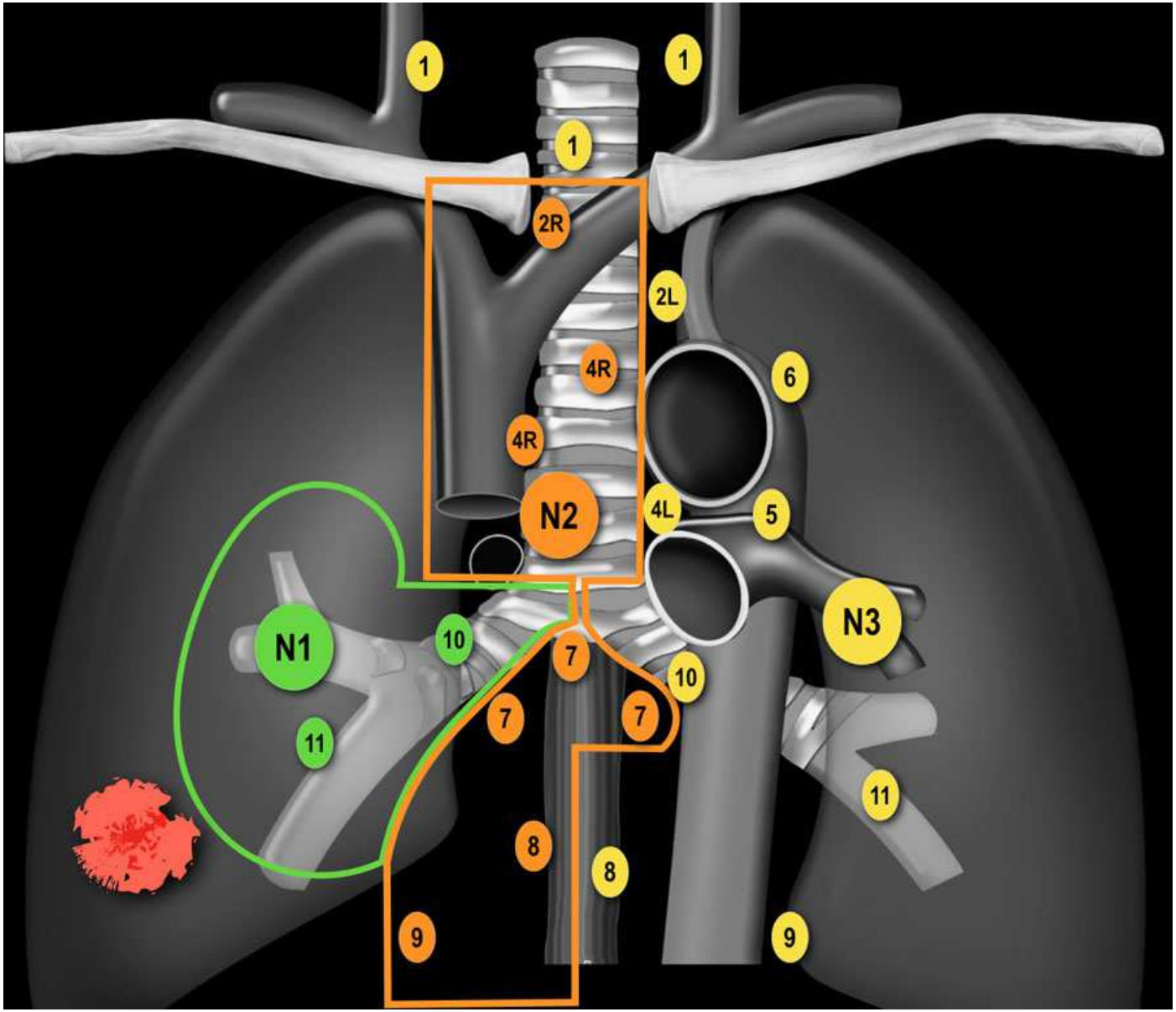


Fig. 5.6

Therapeutic approach

- Lobectomy is generally not possible if there is:
- Transfissural growth.
- Pulmonary vascular invasion.
- Invasion of main bronchus.
- Involvement of upper and lower lobe bronchi.
- Clinically positive N_2 or N_3 disease is not resectable.



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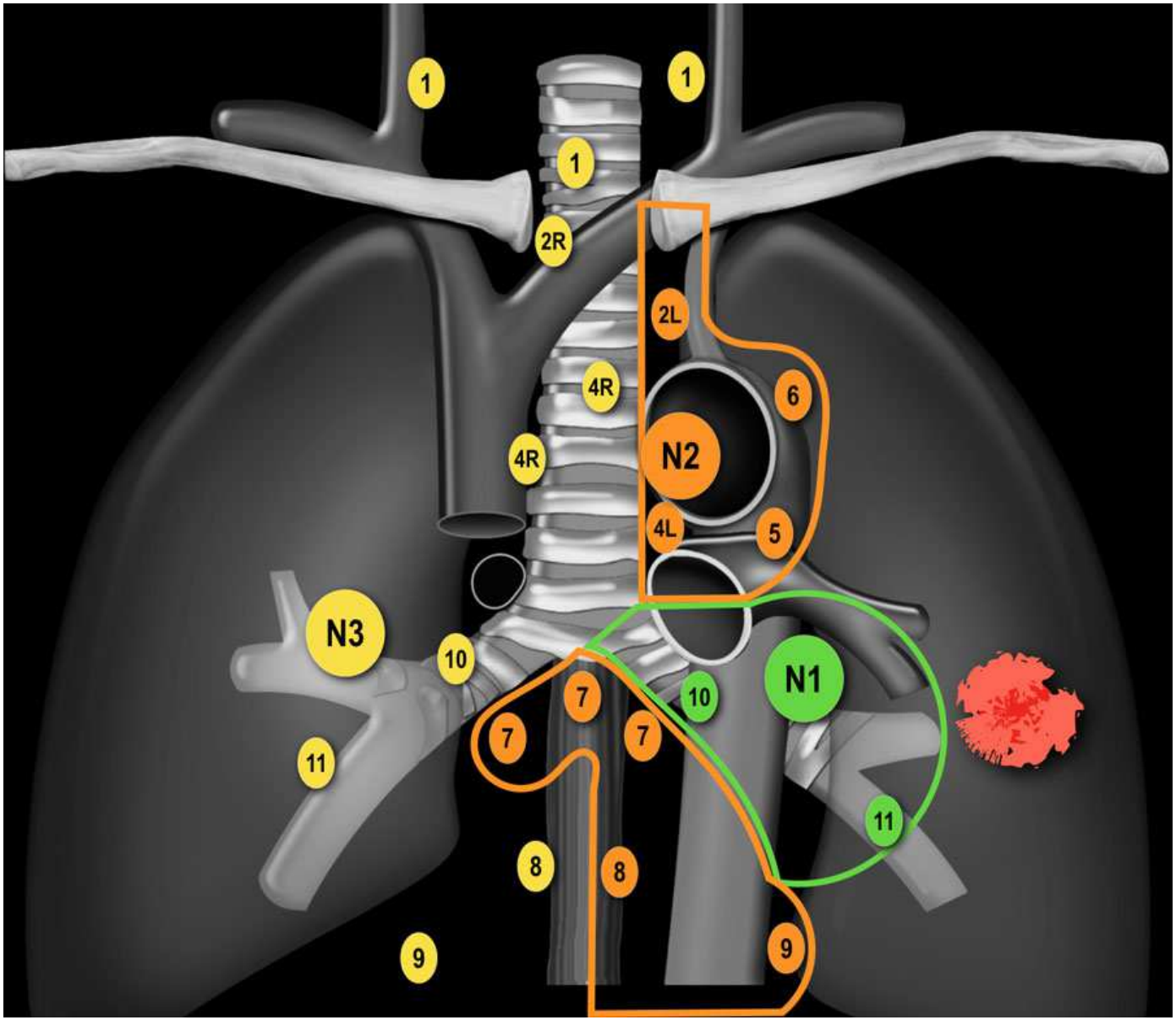

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Pre-treatment testing

- Routine molecular testing:
- EFGR
- BRAF
- ALK
- ROS1
- RET
- MET exon 14 skipping mutation
- PDL-1
- NTRK fusion gene

Therapeutic approach

- Non Small Cell Lung Cancer
- Anatomic segmentectomy for lung cancer <2cm (Stage IA), with brachytherapy if Stage IB.
- Stereotactic ablative radiotherapy (SABR) is the non-surgical treatment of choice for early-stage NSCLC and local control rates in excess of 90% are obtained.
- Low toxicity in patients with COPD and in the elderly

Therapeutic approach

- Stage IIIA patients with microscopic N2 disease survive longer than those with clinical N2 disease (34% vs. 9% at 5 years) following induction, chemoradiation (platinum based), and surgery.
- Stage IIIB patients without malignant pleural effusion (MPE) are treated with sequential chemotherapy (cisplatin and etoposide) and radiation followed by resection
- Yields 53% 5-year survivals.

Therapeutic approach

- Stage IIIB patients with malignant pleural effusion (MPE) receive chemotherapy.
- MPE can be treated surgically with talc pleurodesis or tunneled pleural catheters (TPCs) to prevent recurrence

Therapeutic approach

- Superior sulcus (Pancoast) tumor is best treated with chemotherapy and radiation therapy followed by surgical resection with chest wall resection as well.
- Incompletely resected patients have an average survival of 10-14 months.

Therapeutic approach

- Stage IV patients may have the primary tumor and a single brain or adrenal metastasis resected.
- Chemotherapy with cisplatin-premetrexed lengthens survival time (to beyond 14 months).
- Switch to targeted agent if driver mutation identified

Therapeutic approach

- Stage IV
- ALK rearrangement
- Performance status (PS) of 0-2, AND previously untreated
- Alectinib or brigatinib or lorlatinib.
- Ceritinib or crizotinib if others not available
- RET rearrangement
- PS of 0-2, AND previously untreated
- Selpercatinib or pralsetinib.

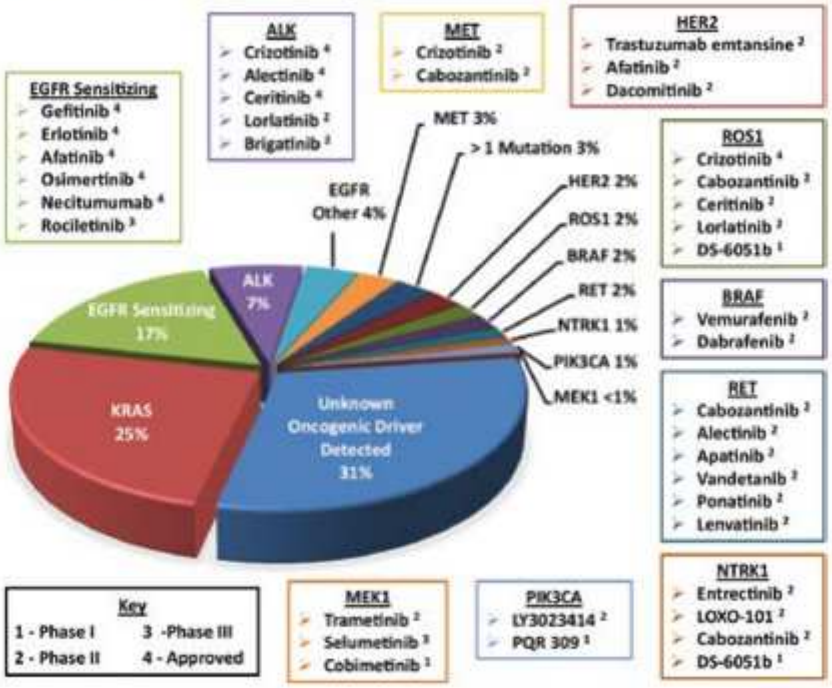
Therapeutic approach

- Stage IV
- PD-L1 expression (tumor proportion score [TPS] ≥ 50%) AND PS 0-1
- Single-agent atezolizumab.
- PD-L1 expression (TPS <50%) AND PS 0-1
- Nivolumab and ipilumumab alone or nivolumab and ipilimumab plus chemotherapy (platinum based if squamous cell carcinoma)
- Adenocarcinoma patients who received an immune checkpoint inhibitor and chemotherapy as first-line therapy
- Paclitaxel plus bevacizumab.
- Adenocarcinoma patients who received chemotherapy with or without bevacizumab and immune checkpoint inhibitor therapy
- Single-agent pemetrexed, docetaxel, or paclitaxel plus bevacizumab.

Therapeutic approach

- Vinorelbine better than supportive care.
- Carboplatin with taxol better than taxol, vinorelbine, or gemcitabine alone.
- Maintenance therapy for non-small cell lung cancer advanced disease.
- Premetrexed is less toxic than docetaxel.
- Cisplatin and premextred together may bring about complete remission.
- Metformin blocks AMP-APK if LKB1 is not mutated.
- Induces apoptosis.
- Also blocks mTOR.

Frequency of molecular aberrations in various driver oncogenes in lung adenocarcinomas and currently available drugs against oncogenic proteins



ALK, Anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor 2.

Fig. 10.1

Therapeutic approach

- If the cancer harbors an EFGR mutation, and no KRAS mutation is present, a tyrosine kinase is first line therapy
- Gefitinib, erlotinib
- Gefitinib and osimertumab prevent development of secondary sites of resistance (to platinum plus pretrexmed chemotherapy)
- Trastuzumab deruxtecan if EGFR mutation, not amplification
- The complication of a skin rash is a good prognostic sign

Therapeutic approach

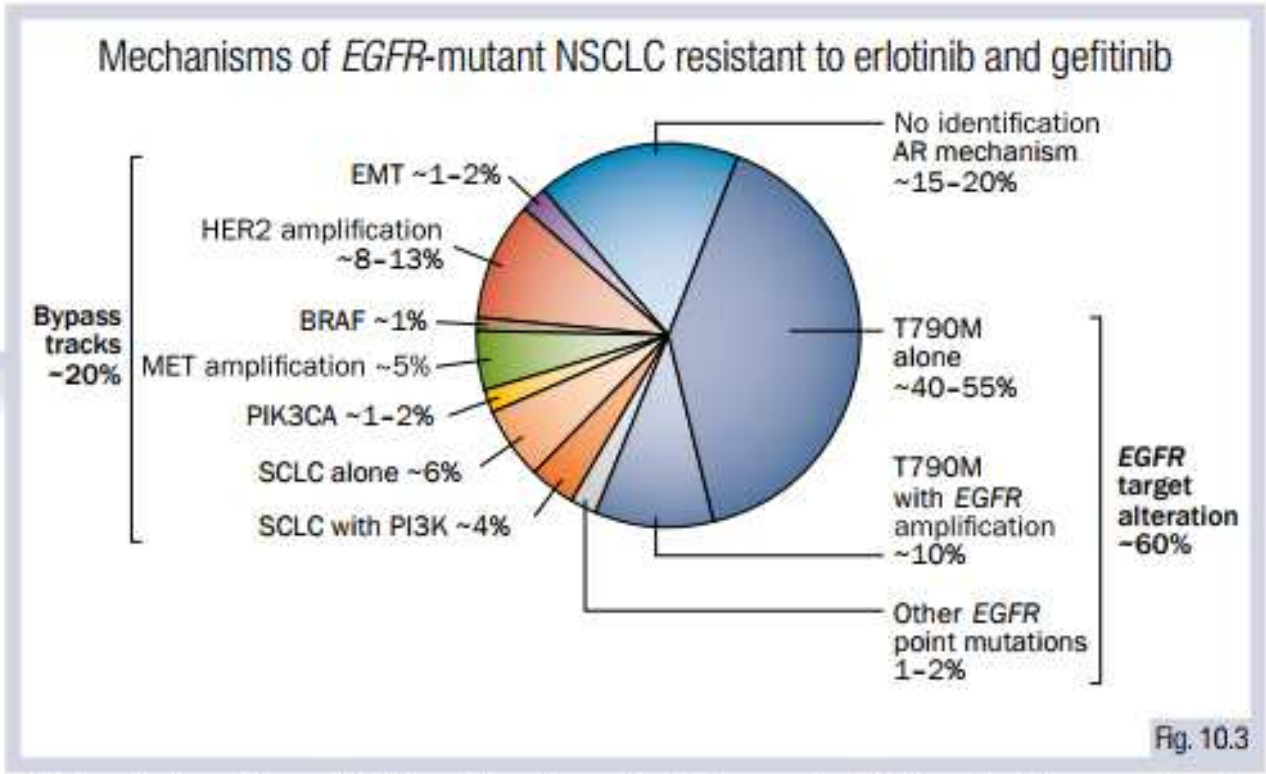
- EGFR amplified cancers unlikely to respond to tyrosine kinase inhibitors.
- The EGFR T790M mutation or BRCA1 expression is associated with shorter survival when erlotinib used.
- 50-60% of acquired resistance mechanisms are associated with EGFR T790M
- Other resistance mechanisms to TKIs include C-MET amplification, HER2 amplification, small cell lung cancer transformation or epithelial mesenchymal transition (EMT).
- BRAF and MEK inhibitors dabrafenib and tretinib used in tandem with BRAF V600E mutation

Therapeutic approach

- HER2 is a receptor tyrosine kinase of the ERBB family with no known identified ligand
- Functions as a preferred dimerization partner.
- 2-4% mutations in non-small cell carcinoma
- Mutually exclusive to other mutations
- Map to exon 20 (usually between residues Glu762 and Cys775)
- In-frame insertional
- Usually resistant to erlotinib or gefitinib
- Typically occur in never/light-smokers.

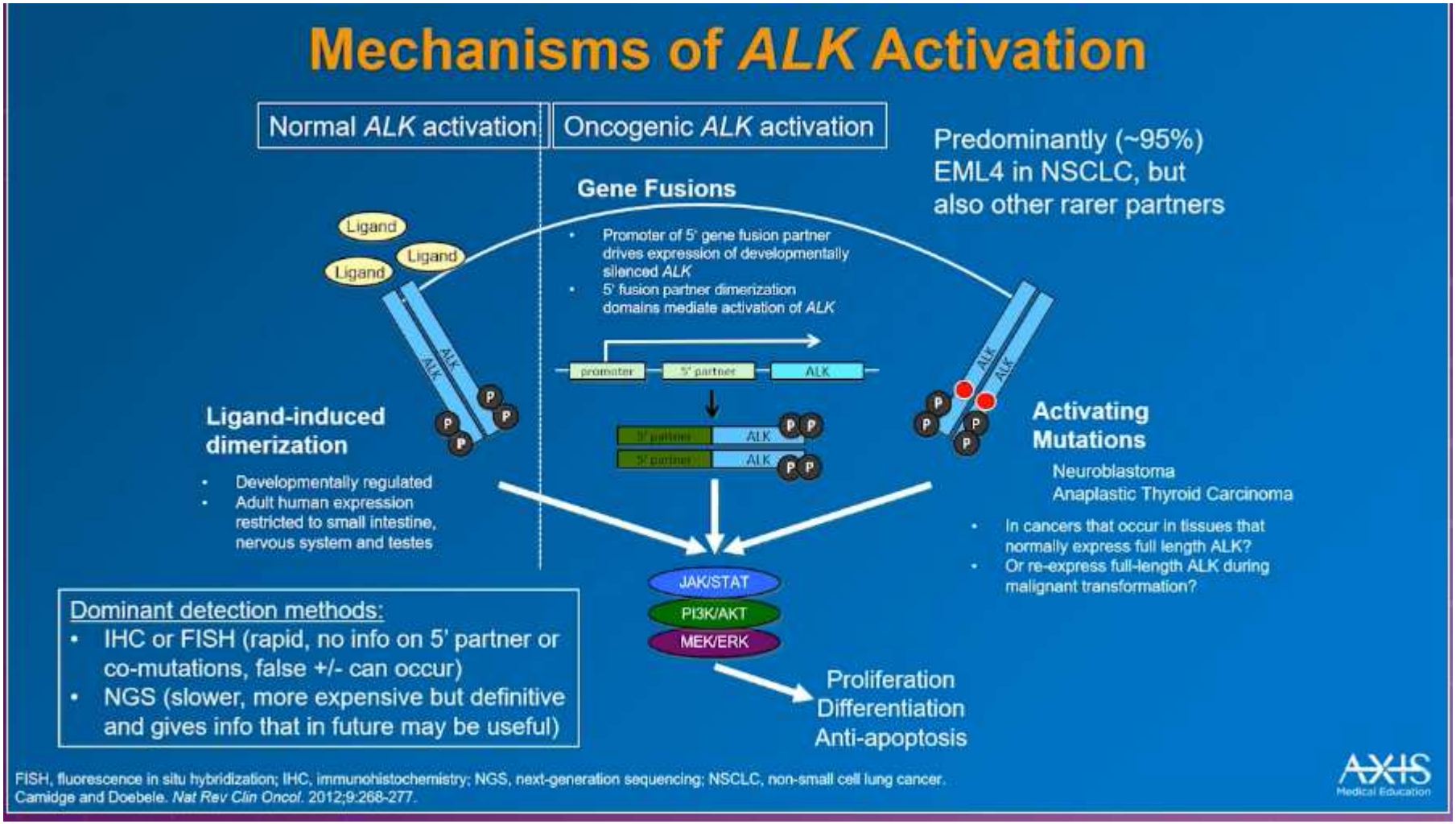
Therapeutic approach

- Homologous to epidermal growth factor receptor (EGFR) exon 20 insertions.
- Over 80% of cases harbor the A775_G776insYVMA insertion/ duplication.
- MET mutation responds to critizonib, capmatanib
- MET copy number gains arise from polysomy or amplification and are associated with resistance.
- 1-5% of non-small cell carcinomas



AR, Acquired resistance; *EGFR*, epidermal growth factor receptor; EMT, epithelial mesenchymal transition; *HER2*, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Mechanisms of *ALK* Activation



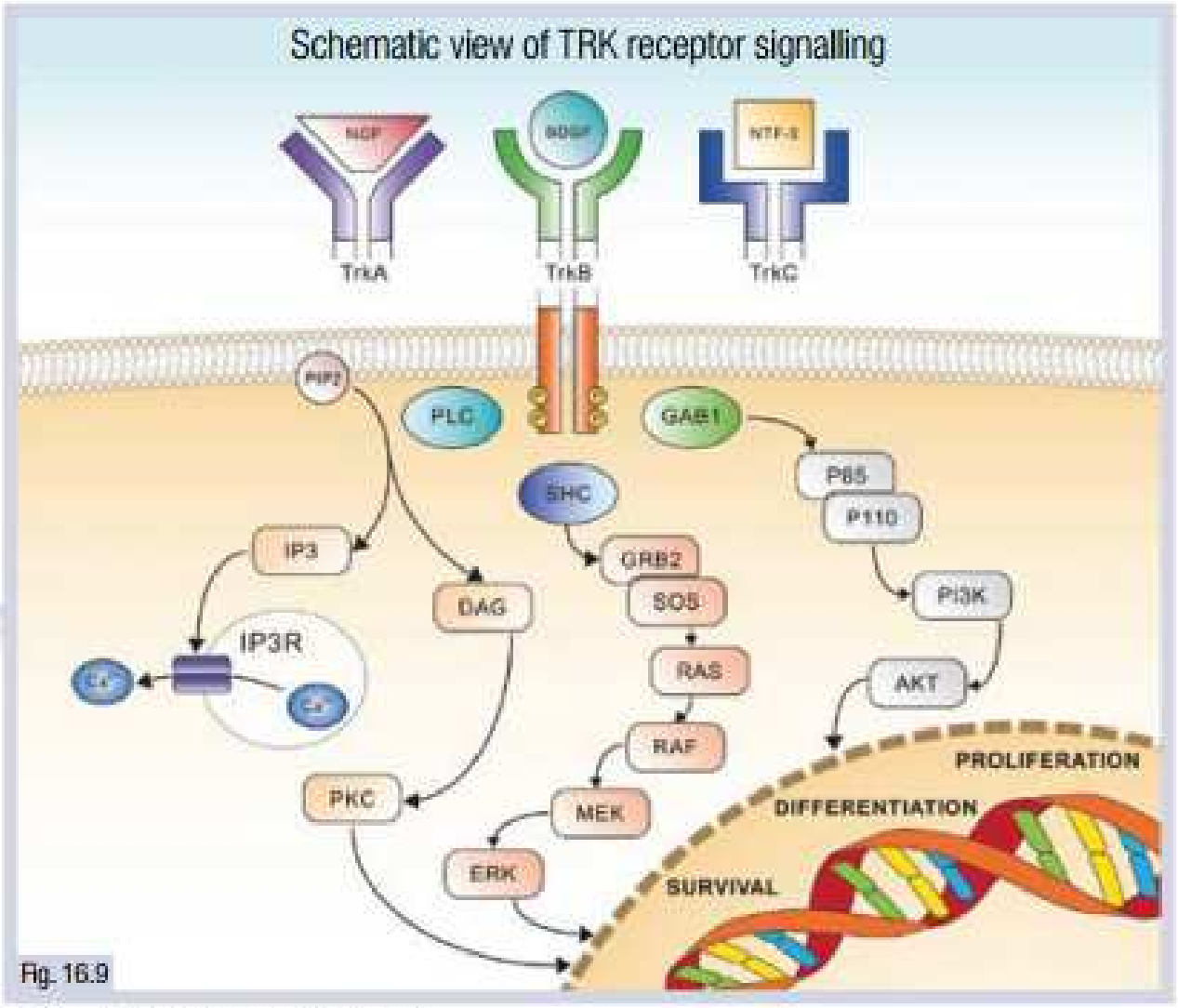
FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer.

Camidge and Doebele. *Nat Rev Clin Oncol*. 2012;9:268-277.

AXIS Medical Education

Therapeutic approach

- The presence of the EML4-ALK fusion product is also associated with shorter survival.
- 3-5% of cases
- Crizotinib, erlotinib
- Crizotinib (ALK inhibitor) also effective if a ROS1 rearrangement is present.
- Brain most common site of relapse in patients treated with crizotinib
- Lorlatinib for relapsed patients; has CNS activity
- Extra-CNS failure is usually local, clonal
- MET or HER2+ appear after ALK inhibitor failure



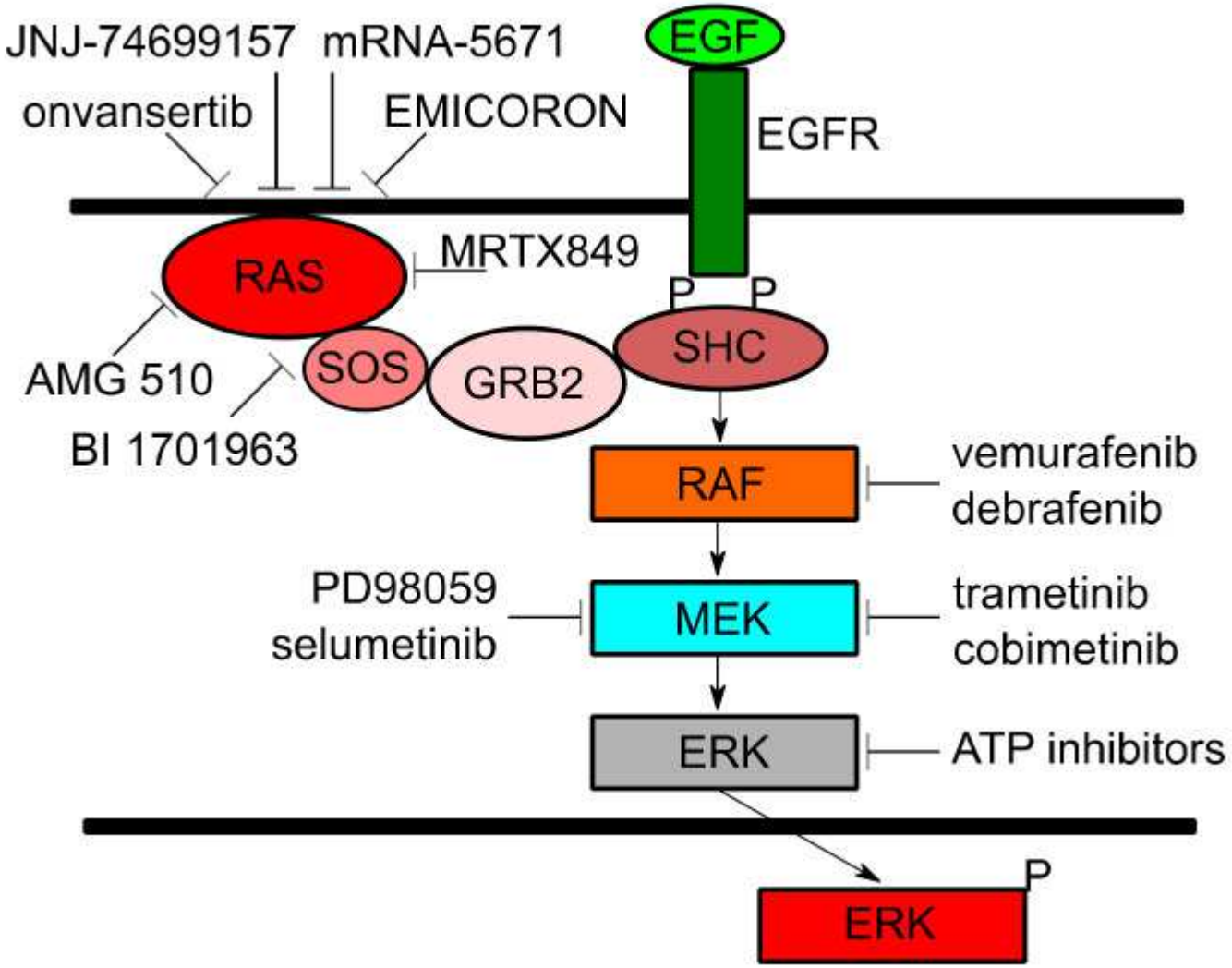
TRK, Tropomyosin receptor kinase.

Therapeutic approach

- ROS1/NTRK fusion responds to larotrectonib (NTRK inhibitor)
- RET mutation responds to cabozantinib, vadentanib, pralcetinib
- KRAS G12C mutation associated with poor response to fluropyrimidines
- Common in tobacco use
- Sotorasib (AMG 510) binds to cysteine residue, holding protein in inactive form
- If fail first line therapy

Therapeutic approach

- LB1 mutated cancers are resistant to PD-L1 inhibitors
- NTRK/ROS1/ALK mutations respond to erectinib
- All have 60+% response rates
- Bevicumuzab (VEGF blocker) now included in first line therapy with chemotherapy
- Bleeding and hypertension as complications



Mustachio LM, Chelariu-Raicu A, Szekvolgyi L, Roszik J. Targeting KRAS in Cancer: Promising Therapeutic Strategies. Cancers (Basel). 2021;13(6):1204. Fig. 1 Published 2021 Mar 10. doi:10.3390/cancers13061204

Therapeutic approach

- Small cell lung cancer
- Lobectomy with mediastinal nodal dissection/sampling in cT1-2N0M0 disease
- Adjuvant radiation therapy only in cases of subtotal resection or pathologic N2 involvement.
- Stereotactic body radiation for stage I to II node-negative patients who are not surgical candidates

Therapeutic approach

- Chemosensitive
- Adjuvant cisplatin based chemotherapy is recommended for completely resected Stages II, IIIA.
- Often used with etoposide
- Chemoradiation without surgery if locally advanced (IIIA included).
- Consolidation radiation therapy continues to play a role in patients who have had good response to initial systemic therapy

Therapeutic approach

- Prophylactic cranial irradiation only for those who enter complete remission
- Nivolumab is directed against the PD-1 receptor expressed on activated lymphocytes and modulates T-cell exhaustion.
- Age does not limit therapy.

Therapeutic approach

- Lymph node metastases are present in more than 15% of cases of typical carcinoid lung neuroendocrine tumors
- 5-year survival exceeds 90%
- Up to 60% of patients with atypical carcinoid have lymph node metastases
- 5-year survival of 61% to 88%.
- Surgical resection (lobectomy or sleeve resection) is considered even in advanced disease

Therapeutic approach

- Available chemotherapy regimens for typical carcinoids and atypical carcinoids include a combination of streptozotocin plus 5-fluorouracil/doxorubicin.
- Octreotide (somatostatin analogue) may be used in symptomatic patients
- Anti-tumor activity even in asymptomatic patients
- Evorlimus (mTOR inhibitor) also effective

Therapeutic approach

- Extrapleural pneumonectomy (EPP) is an aggressive procedure entailing en bloc resection of the parietal and visceral pleura with the enclosed lung, pericardium, ipsilateral diaphragm and mediastinal nodes in treatment of mesothelioma.
- Postoperative morbidity is high (up to 50%), but mortality is <5%
- Pleurectomy/decortication (P/D) allows the removal of the visceral, parietal and pericardial pleura
- Morbidity and mortality are lower, but cytoreduction less effective than EPP
- Better effusion control than talc plurodesis

Therapeutic approach

- Chemotherapy alone with platinum and pretrexmed more effective than EPP or P/D
- In unresectable mesothelioma, the addition of a PD-1 inhibitor to platinum based chemotherapy (with or without a VEGF inhibitor) is associated with better outcomes than platinum and pretrexmed chemotherapy

Therapeutic approach

- Median sternotomy as the standard approach for resectable tumors of the thymus
- Minimally invasive surgery is possible
- Complete exploration of the pleural cavities
- Complete thymectomy, including the tumor, normal thymus and mediastinal fat
- En bloc resection of involved structures: lung, vessels, pleural implants, phrenic nerves

Therapeutic approach

- Chemotherapy is administered as the sole treatment modality for metastatic, unresectable, recurrent disease not eligible for radiotherapy
- 50% of patients overall actually die from tumor progression; causes of death include autoimmune diseases and non-related disorders (each accounting for 25%).

Masaoka–Koga stage	Postoperative radiotherapy (RT) / chemotherapy (ChT)
Stage I	Complete resection: - Thymoma: no postoperative RT - Thymic carcinoma: consider postoperative RT Incomplete resection: Postoperative RT
Stage IIa	Complete resection: - Type A-B2 thymoma: no postoperative RT - Type B3 thymoma–thymic carcinoma: consider postoperative RT Incomplete resection: Postoperative RT Thymic carcinoma: Consider postoperative ChT
Stage IIb	Complete resection: - Type A-B1 thymoma: no postoperative RT - Type B2-B3 thymoma–thymic carcinoma: consider postoperative RT Incomplete resection: Postoperative RT Thymic carcinoma: Consider postoperative ChT
Stage III-IVa	Postoperative RT, with boost on areas of concern Thymic carcinoma: Consider postoperative ChT

Fig. 13.5

Regimen	Agents	Doses
ADOC	Doxorubicin	40 mg/m² / 3 w
	Cisplatin	50 mg/m² / 3 w
	Vincristine	0.6 mg/m² / 3 w
	Cyclophosphamide	700 mg/m² / 3 w
CAP	Cisplatin	50 mg/m² / 3 w
	Doxorubicin	50 mg/m² / 3 w
	Cyclophosphamide	500 mg/m² / 3 w
PE	Cisplatin	60 mg/m² / 3 w
	Etoposide	120 mg/m²/ × 3 / 3 w
VIP	Etoposide	75 mg/m² × 4d / 3 w
	Ifosfamide	1.2 g/m² × 4d / 3 w
	Cisplatin	20 mg/m² × 4d / 3 w
Carbo-Px	Carboplatin	AUC 5 / 3 w
	Paclitaxel	225 mg/m² / 3 w

AUC, Area under the curve.

Fig. 13.6