Tumours of the lung

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Worldwide incidence

World largest „epidemic” in 20th century…
Tobacco is the major contributor in developed world
Indoor pollution in developing world
Outdoor pollution

Epidemiology of lung cancer

- The diseases was rare in the 19th century (it was frequently observed among miners). Lung cancer became frequent in first half of 20th century
- **incidence** in men has started to decline, but **among women, lung cancer incidence and mortality is still increasing**
- In general a disease of later life

- 17% of all cancers in men, 9% of new cancers in women
- Adenocarcinoma can develop in patients younger than 40 years
- **65-70% of patients are already inoperable** at presentation
- **5-year survival: 14-20%**

The role of smoking

- 1950s: relationship of smoking and lung cancer was revealed
- **10-20 fold risk** of lung cancer in smokers
- „1 pack year" equating to 20 cigarettes per day for 1 year
- In case of stop smoking the risk begins to decline but **it takes about 15 years** to approach the same risk as in non-smokers
- the switch to **low-tar cigarette**s has led smokers to inhale more deeply and thereby **contributed to the increased incidence of peripheral tumours (adenocarcinoma maily)**
- Passive smoking associated with smaller risk: equivalent to 1 cig a day
- polycyclic hydrocarbons linked to squamous cell cc
- nitrosamines linked to adenocarcinoma
- **genetic susceptibility**: variation in the amounts of **P450 cytochromes**

Environmental carcinogens

polycyclic hydrocarbons from the combustion of fossil fuels (vehicles in western world but domestic coal combustion is still significant in east)

Ionising radiation

Uranium ore miners have 30 times higher risk
Risk is 67 times greater in heavy smokers exposed to irradiation
Role of **indoor radon**
therapeutic irradiation (e.g.: radiotherapy as a part of breast cancer treatment)

Asbestos

much **higher levels of exposure** are required to produce pulmonary carcinoma than mesothelioma
promoting agent rather than a primary carcinogen

Other risk factors

Idiopathic pulmonary fibrosis (IPF)
HPV

Precancerous lesions

Normal bronchial epithelium

↓ injury

Reserve cell hyperplasia

↓ benzpyrene, nitrosamines

Squamous metaplasia

↓ benzpyrene, nitrosamines

Dysplasia

↓ 8 years

Carcinoma in situ

↓ 4 years

Invasive cancer

Precancerous lesions

Atypical adenomatous hyperplasia (AAH)

adenocarcinoma-in-situ

AAH composed of hyperplastic type II alveolar epithelial cells or bronchiolar Clara cells.

AAH is <5 mm in diameter.

The cells in AAH have dense chromatin, prominent nucleoli and sparse cytoplasm.

Multifocal AAH may develop

Frequently found in the neighborhood of invasive carcinoma

Adenocarcinoma-in-situ

- Previously called bronchioloaveolar carcinoma - BAC
- The lesional cells grow along the alveolar walls without destroying them.
- Non-mucinous lesion
- Lesion greatest diemater is **no greater than 3cm**
- **100% 5-year survival** if completely resected

Microinvasive carcinoma

- invasion **no greater than 5 mm**
- prominent central scarring
- acini vary in size, lining cells are irregular
- metastatic potential, but prognosis is very good in general

Old histological **classification** of lung cancer

Non - small cell lung cancer (NSCLC)

Squamous cell carcinoma (SCC)
Adenocarcinoma
Adenosquamous carcinoma
Large cell carcinoma (LCLC)

Carcinoid
Atypical carcinoid
Large Cell Neuroendocrine Cc

Sarcomatoid carcinoma
others

Small cell lung cancer (SCLC)

No surgical intervention in general

WHO 2015 Classification of lung tumours

Histologic Type and Subtypes	ICDO code[a]
Epithelial tumors	
Adenocarcinoma	8140/3
Lepidic adenocarcinoma[e]	8250/3[d]
Acinar adenocarcinoma	8551/3[d]
Papillary adenocarcinoma	8260/3
Micropapillary adenocarcinoma[e]	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma[e]	8253/3[d]
Mixed invasive mucinous and nonmucinous adenocarcinoma	8254/3[d]
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma[e]	8144/3
Minimally invasive adenocarcinoma[e]	
Nonmucinous	8256/3[d]
Mucinous	8257/3[d]
Preinvasive lesions	
Atypical adenomatous hyperplasia	8250/0[d]
Adenocarcinoma in situ[e]	
Nonmucinous	8250/2[d]
Mucinous	8253/2[d]
Squamous cell carcinoma	8070/3
Keratinizing squamous cell carcinoma[e]	8071/3
Nonkeratinizing squamous cell carcinoma[e]	8072/3
Basaloid squamous cell carcinoma[e]	8083/3
Preinvasive lesion	
Squamous cell carcinoma in situ	8070/2
Neuroendocrine tumors	
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Carcinoid tumors	
Typical carcinoid tumor	8240/3
Atypical carcinoid tumor	8249/3
Preinvasive lesion	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	8040/0[d]
Large cell carcinoma	8012/3
Adenosquamous carcinoma	8560/3
Sarcomatoid carcinomas	
Pleomorphic carcinoma	8022/3
Spindle cell carcinoma	8032/3
Giant cell carcinoma	8031/3
Carcinosarcoma	8980/3
Pulmonary blastoma	8972/3
Other and Unclassified carcinomas	
Lymphoepithelioma-like carcinoma	8082/3
NUT carcinoma[e]	8023/3[d]
Salivary gland-type tumors	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial-myoepithelial carcinoma	8562/3
Pleomorphic adenoma	8940/0
Papillomas	
Squamous cell papilloma	8052/
Exophytic	8052/
Inverted	8053/
Glandular papilloma	8260/
Mixed squamous and glandular papilloma	8560/
Adenomas	
Sclerosing pneumocytoma[e]	8832/
Alveolar adenoma	8251/
Papillary adenoma	8260/
Mucinous cystadenoma	8470/
Mucous gland adenoma	8480/
Mesenchymal tumors	
Pulmonary hamartoma	8992/
Chondroma	9220/
PEComatous tumors[e]	
Lymphangioleiomyomatosis	9174/
PEComa, benign[e]	8714/
Clear cell tumor	8005/
PEComa, malignant[e]	8714/3
Congenital peribronchial myofibroblastic tumor	8827/1
Diffuse pulmonary lymphangiomatosis	
Inflammatory myofibroblastic tumor	8825/1
Epithelioid hemangioendothelioma	9133/3
Pleuropulmonary blastoma	8973/3
Synovial sarcoma	9040/3
Pulmonary artery intimal sarcoma	9137/3
Pulmonary myxoid sarcoma with *EWSR1–CREB1* translocation[e]	8842/3[d]
Myoepithelial tumors[e]	
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Lymphohistiocytic tumors	
Extranodal marginal zone lymphomas of mucosa-associated Lymphoid tissue (MALT lymphoma)	9699/3
Diffuse large cell lymphoma	9680/3
Lymphomatoid granulomatosis	9766/1
Intravascular large B cell lymphoma[e]	9712/3
Pulmonary Langerhans cell histiocytosis	9751/1
Erdheim–Chester disease	9750/1
Tumors of ectopic origin	
Germ cell tumors	
Teratoma, mature	9080/0
Teratoma, immature	9080/1
Intrapulmonary thymoma	8580/3
Melanoma	8270/3
Meningioma, NOS	9530/0
Metastatic tumors	

(*Continued*)

[a]The morphology codes are from the ICDO.[2] Behavior is coded /0 for benign tumors, /1 for unspecified, borderline or uncertain behavior, /2 for carcinoma in situ and grade III intraepithelial neoplasia, and /3 for malignant tumors.

[b]The classification is modified from the previous WHO classification[3] taking into account changes in our understanding of these lesions.

[c]This table is reproduced from the 2015 WHO Classification by Travis et al.[1]

[d]These new codes were approved by the International Agency on Cancer Research/ WHO Committee for ICDO.

[e]New terms changed or entities added since 2004 WHO Classification.[3]

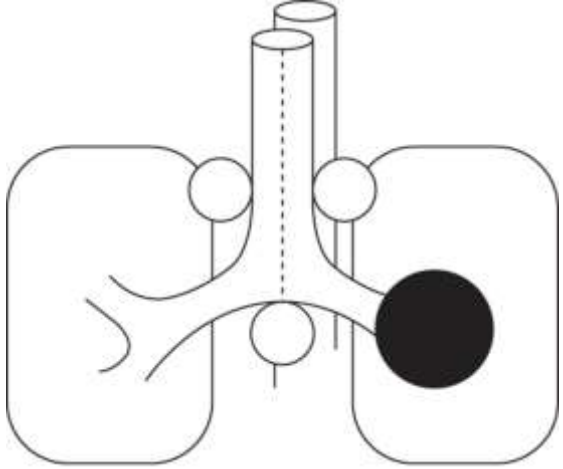
LCNEC, large cell neuroendocrine carcinoma, WHO, World Health Organization; ICDO International Classification of Diseases for Oncology.

Histologic Type and Subtypes

Epithelial tumors

- Adenocarcinoma
  - Lepidic adenocarcinoma[e]
  - Acinar adenocarcinoma
  - Papillary adenocarcinoma
  - Micropapillary adenocarcinoma[e]
  - Solid adenocarcinoma
  - Invasive mucinous adenocarcinoma[e]
- Minimally invasive adenocarcinoma[e]
  - Nonmucinous
  - Mucinous
- Preinvasive lesions
  - Atypical adenomatous hyperplasia
  - Adenocarcinoma in situ[e]
- Squamous cell carcinoma
  - Keratinizing squamous cell carcinoma[e]
  - Nonkeratinizing squamous cell carcinoma[e]
  - Basaloid squamous cell carcinoma[e]
- Preinvasive lesion
  - Squamous cell carcinoma in situ
- Neuroendocrine tumors
  - Small cell carcinoma
    - Combined small cell carcinoma
  - Large cell neuroendocrine carcinoma
    - Combined large cell neuroendocrine carcinoma
  - Carcinoid tumors
    - Typical carcinoid tumor
    - Atypical carcinoid tumor
- Preinvasive lesion
  - Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
- Large cell carcinoma
- Adenosquamous carcinoma
- Sarcomatoid carcinomas

Squamous cell carcinoma



- Classically **central in origin**
- The cut surface is often granular or friable
- Large tumours **frequently cavitate** because of central necrosis
- Irregular nests and strands of tumour cells with squamous differentiation
- Keratinisation in well differentiated lesion
- Keratin forms concentrically laminated squamous „**pearls”**
- The **basaloid variant** shows peripheral palisade, basaloid cytomorphology. The tumour cells are small and have hyperchromatic nuclei. It represents a more aggresive, unpredictable behaviour.

Adenocarcinoma

- The most frequent type (circa 50%)
- there is a higher proportion of adenocarcinoma in non-smokers and the young.
- **Mostly in the periphery of the lung**, central localisation means worse prognosis
- different mutations can be detected into bronchial and peripheral subtypes
- TTF-1, NapsinA positive IHC in 80-90%

Subtypes (usually mixed pattern)

i. **Lepidic** predominant } slow progression

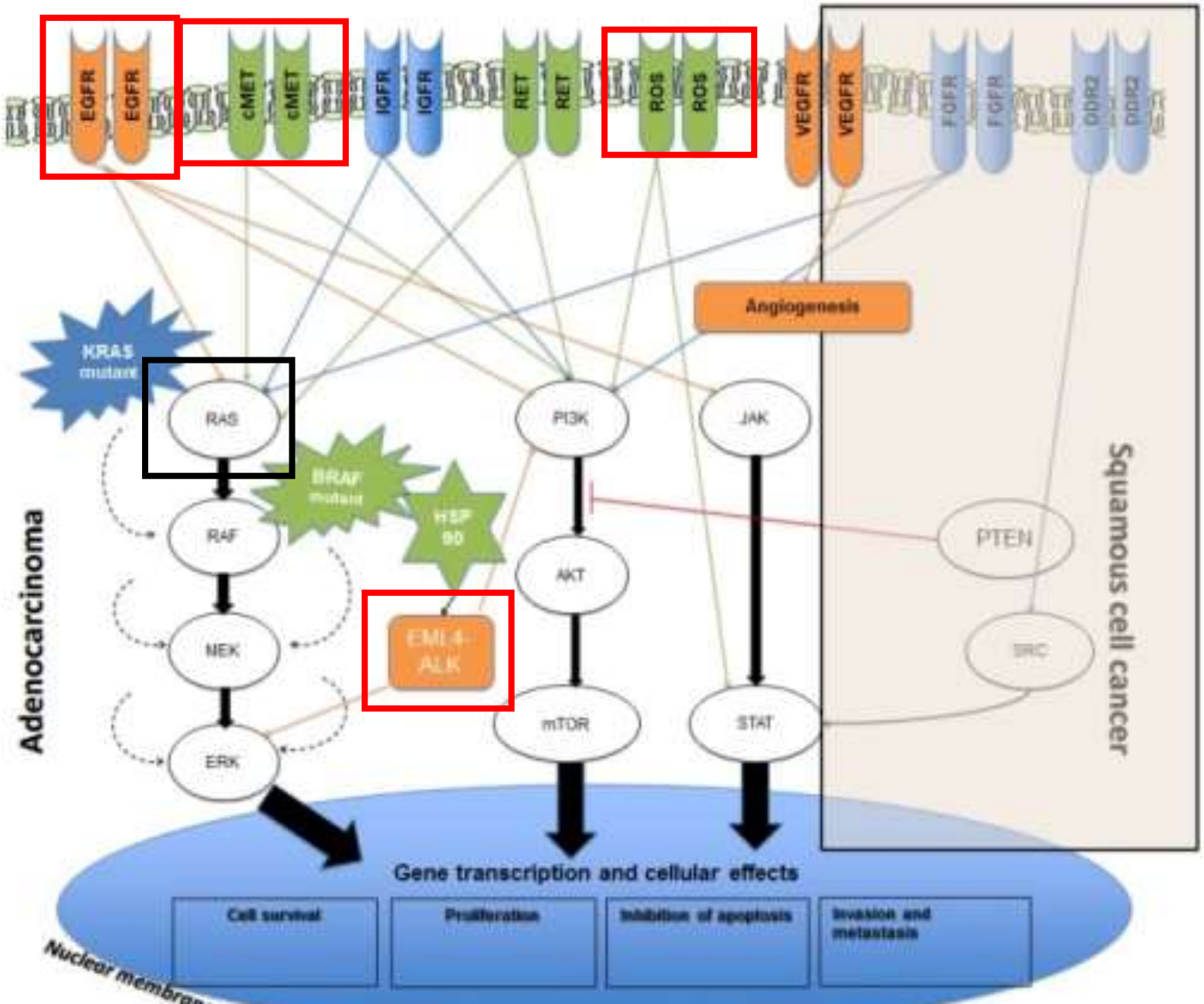
ii. **Acinar** predominant

iii. **Papillary** predominant } moderatly agrressive

iv. **Solid** predominant

v. **Micropapillary** predominant } aggressive

Driver mutations in non-small cell lung cancer



Druggable mutation

Non-druggable mutation

Low mitotic rate
Low proliferation index (Ki67 IHC)

High mitotic rate
High proliferation index

Carcinoid Atypical carcinoid LCNEC SCLC

Carcinoid: < 2 mitosis per 2 mm^2
Atypical carcinoid: ≥ 2 mitosis per 2 mm^2
Large cell neuroendocrine carcinoma: >10 mitosis per 2 mm^2
Small cell lung cancer: high mitotic activity, characterisitic morphology

Small cell carcinoma (SCLC)

- generally arises **in major airways** (arising from Kulchitsky cells)
- **grows rapidly, early metastasis**
- sensitive to chemotherapy
- surgery can be successful only in case of early stage and highly selected cases (small peripheral tumour)
- 3p, 13q and 17p are affected by chromosomal deletions, p53 mutation

Morphology

small (oat cell) or medium-sized round or elongated cells, arranged in nests or present as single cells

small amount of cytoplasm

nucleus shows finely dispersed chromatin pattern

the **tumour cells are often crushed** in biopsy specimens: masses of haematoxyphil material are seen

Immuno**h**isto**c**hemistry (**IHC**): positive with epithelial and **neuroendocrine** markers (synaptophysin, CD56), mitotic figures in very high number

Neuroendocrine tumours

Carcinoid - typical

At young age
Central/bronchial localization in most of the cases
Mitotic figures are rare (<2 mitosis/2 mm^2), „salt and pepper” chromatin pattern
Intrabronchial (polypoid) growth is characteristic
There is no relationship with smoking
Dense cor neurosecretory granules (chromograninA +)

Carcinoid - atypical

Peripheral in most of the cases
Moderate mitotic activity
Necrosis may be present, significant nuclear atypia

Large cell neuroendocrin carcinoma (LCNEC)

Poorly differentiated neuroendocrine neoplasm
High mitotic activity (high proliferation index with Ki67 immunohistochemistry)
Pronounced nuclear atypia

Large cell carcinoma

Absence of differentiation (keratin or mucin cannot be observed)

Immuno phenotype (IHC): absence of the markers specific for adenocc, squamous cell or neuroendocrine differentiation

Umbrella term for very poorly differentiated epithelial tumours

Morphology

- generally have a moderate amount of cytoplasm, clumped chromatin at the periphery of the nucleus and a prominent nucleolus

Sarcomatoid carcinoma

- carcinomas shows mesenchymal differentiation morphologically
- tumour cells with mesenhymal cell appearance originates from epithelial cells (there is no real sarcoma component present)
- spindle cells or giant cells are present in large number

Frequent paraneoplastic syndromes in lung cancer

1. Inappropriate or ectopic hormone secretion:

secretion of adrenocorticotrophic hormone and antidiuretic hormone by the tumour (SIADH: SCLC)

2. Eaton–Lambert syndrome

myasthenia gravis-like disease (autoantibody produced against antigens on the tumour cell membrane cross-reacts with components of the neuromuscular junction)

3. Parathyroid-related protein production by the tumour

cancer-associated hypercalcaemia in squamous cell carcinoma

4. Adrenocorticotrophic hormone production

glucose intolerance

5. Thrombocytosis, thrombosis

Location of lung cancer

- Decades ago the ratio of central to peripheral tumours was formerly 2 : 1
- Recently, the proportion of central and peripheral tumours is the same

Spread of lung cancer

- Predilection site for metastasis: adrenal gland
- Wirchows node metastasis (lymph node in the left supraclavicular fossa)
- **Pancoast tumour**: pain in the shoulder and arm, involvement of a superior cervical ganglion (sympathetic ganglion) resulting in **Horner's syndrome**: **miosis, anhidrosis**, **ptosis**
- **Superior vena cava syndrome:** compression/obstruction of the vein caused by large metastatic lymph nodes → facial swelling and cyanosis

Lymphangitis carcinomatosa:

- Gross appaerance: pale threads of tumour tissue filling lymphatic vessels
- Microscopic finding: dilated lymphatics filled with nests of carcinoma cells
- Possible primary cancer: the **stomach**, **pancreas**, breast, colon and the **lung itself**.