Bronchogenic carcinoma/PGS

Bronchogenic carcinoma is one of the most common types of tumors. It occurs rather in old age, it is usually associated with exposure to risk factors , especially smoking. In addition to local symptoms, distant symptoms are also relatively common, whether caused by metastatic spread or paraneoplatical symptoms.

In 2-5% of cases, lung tumors are multicentric, either synchrotronically or metatronically. Molecular analysis confirmed that about half of the cases have demonstrably different clonal origins, so it is definitely not an early orthotopic metastatic spread, but a real duplication. Bronchogenic carcinoma occurs in several histological types with different biological behavior, the division into small cell and non-small cell carcinomas is essential. The basic therapeutic modality is chemotherapy , surgery only makes sense at lower clinical stages.

Epidemiology

Lung tumors are relatively common. In the United States, bronchogenic cancer accounts for 12.4% of all newly diagnosed tumors and 17.6% of tumor-related deaths. The age-standardized annual incidence is 62 patients per 100,000, more often men. The incidence is increasing worldwide, at the beginning of the 20th century it was an uncommon disease. Five-year survival is 15.6%.

The most significant risk factor for bronchogenic carcinoma is cigarette smoking , which can increase the risk of cancer by up to sixty times depending on the intensity of smoking and the depth of inhalation. Smoking cigars and pipes is also associated with a higher risk of cancer, but this risk is thought to be lower compared to cigarette smoking. An association with marijuana smoking is possible, but few studies have been performed to confirm this assumption and especially to quantify the risk. Similarly, not only active smoking but also passive smoking is a risk factor.

There is also a genetic predisposition to lung cancer. A higher risk of developing lung cancer is a positive family history of the disease before the age of 60. A number of polymorphisms are studied as a molecular correlate of this susceptibility. Gender differences in sensitivity are obscured by different numbers of smokers and differences in smoking intensity between men and women. While in the past lung tumors were significantly predominant in men, today differences are blurred. In non-smokers, a number of studies have confirmed that the age-standardized incidence is significantly higher in women. Nutritional factors, especially the lack of some micronutrients, may also contribute to the development of lung cancer. A somewhat unexpected finding of several intervention studies was the finding that administration of higher doses of beta carotene and vitamin A is rather risky also in terms of the development of lung cancer. It is interesting that the protective factor is also a higher intake of fruits and vegetables, especially cruciferous. Conversely, for example, red meat or fats are also considered a risk factor for lung tumors. The effect of obesity is not entirely clear.

There is an association between some diseases, especially chronic obstructive pulmonary disease and interstitial pulmonary fibrosis . In the case of COPD, lung tumors share the same risk factors, especially smoking, but a more detailed analysis shows that COPD is an independent risk factor for tumor development. The possibility of associating lung tumors with infections is still debated, but the results are contradictory and weak. For example, a relationship with Ebstein and Barr, HPV, Ch. pneumoniae or tuberculosis.

Environmental risk factors include air pollution. Similarly, regular exposure to wood smoke or from biomass or from coal burned in the household. Some occupational exposures, such as asbestos , arsenic or beryllium , are also a risk for the development of lung cancer . [1] [2]

Classification [modify | edit source]

The term bronchogenic carcinoma includes several different types of tumors that may have different behaviors. Roughly, bronchogenic carcinomas are divided into two groups with clearly different behavior: small cell and non-small cell tumors. [3]

This division is also conditioned by historical experience that while patients with small cell carcinoma primarily benefit from chemotherapy, in the early stages of non-small cell carcinoma patients benefit from surgery. A more detailed classification according to the histological structure , which was also used in the classification according to WHO 2004, is the following:

1. 1.Squamous cell carcinoma incl. certain types of clear cell carcinoma
2. 2.Small cell carcinoma
3. 3. Adenocarcinoma incl. bronchioloalveolar carcinoma and several types of clear cell carcinoma
4. 4.Large cell carcinoma
5. 5.Adenosquamous carcinoma,
6. 6.Sarcomatoid carcinoma / carcinosarcoma incl. lung blastoma and lung endodermal tumor.

It has been shown that mixed types are relatively often diagnosed using this classification. In the group of adenocarcinomas, subtypes with a significantly different prognosis were shown to exist. In 2011, the classification of lung adenocarcinomas was published as a collective work of the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS), which took into

account a number of other factors. [4] In particular, the consideration of prognostic subtypes of all types of tumors, including response and sensitivity to biological therapy of tumors, was reflected in the WHO classification of lung tumors from 2015. [5]

Squamous cell carcinoma

Squamous cell carcinoma (syn. Squamous cell carcinoma) is more common in men, accounting for 44% of lung cancers in men and 25% of lung cancers in women. It usually grows centrally, but can occur peripherally or subpleurally. About half of the patients experience symptoms of bronchial obstruction (infection, cough, haemoptysis). In the center of the tumor locus, necrotic disintegration can occur relatively frequently to form a central cavity. In the mucosa of the bronchi adjacent to the tumor, squamous metaplasia is common, including the finding of carcinoma in situ; these changes can extend up to several centimeters from the tumor. It is assumed that this squamous cell metaplasia is the initial lesion that gave rise to malignancy.

The key to microscopic diagnosis in routine staining is the demonstration of keratinization and intercellular bridges. Keratin can only be in individual cells, typical forms are keratin beads. Detection of intracytoplasmic drops of mucindoes not rule out the diagnosis of squamous cell carcinoma, but immunohistochemical examination is indicated, because solid adenocarcinoma and mucoepidermoid carcinoma in particular enter the differential diagnostic balance. Immunohistochemical examination should be supplemented whenever the sample is small and the typical morphological features of squamous cell carcinoma are not clearly evident.

The main immunochemical markers of squamous cell carcinoma are CK5 / 6 (positive), p63 (positive), p40 (deltaNp63) (positive) and TTF-1 (negative), these are recommended in differential diagnosis. Squamous cell carcinoma is usually reactive with both low and high molecular weight keratins and involucrine.

Immunoreactivity with vimentin, EMA, HMF6-2, S-100 protein, Leu-M1 and CEA can also be detected, while cytokeratin CK7 is usually negative.

Grading of squamous cell carcinoma into well, moderately and poorly differentiated is performed based on the amount of keratin and intercellular bridges in the predominant tumor component:

- **Grade 1** : Significant keratinization and clearly visible intercellular bridges.
- **Grade 2** : Keratin pearls are declining, intercellular bridges are less visible. On the contrary, necrosis tends to be more frequent.
- **Grade 3** : Significant loss of differentiation, virtually complete disappearance of keratin pearls and intercellular bridges.

The WHO classification distinguishes four histological variants:

1. **The small cell variant** has small cells that keratinize only focally. It is difficult to distinguish from small cell carcinoma. The nuclei of the small cell variant are more vesicular and have better defined nucleoli, the nests of tumor cells are sharply demarcated, the tumor tree is more mature and there is less necrosis in the tumor .
2. **The light cell variant** is usually conditioned by the accumulation of glycogen , but keratinization is still evident.
3. **The papillary variant** is a very well differentiated discrete intrabronchial lesion with either no apparent stromal invasion or only minimal invasion. Necrosis practically does not occur.
4. **The basaloid variant** represents an uncommon and very aggressive subtype with morphological features of basal cell carcinoma.

Other morphological features may occasionally occur in squamous cell carcinoma. An increased number of mitochondria can give rise to the oncocytoid appearance of tumor cells. Keratin can react to the body like a foreign body, and huge cells from foreign bodies can appear in the tumor. Relatively massive infiltration by neutrophils or other inflammatory cells may also occur . On the periphery of the tumor it is possible to observe lepidic [note. 1] spread to the respiratory tract.

Adenocarcinoma

Pulmonary adenocarcinomas are relatively more common in women and non-smokers because their association with smoking is less close than in other types of lung tumors. They arise on the basis of atypical adenomatous hyperplasia .

Adenocarcinomas are more often localized on the periphery of the lung, so they can be asymptomatic for a relatively long time and are usually diagnosed at a more advanced stage, but it is possible to occur anywhere in the lung. It is not uncommon for synchrotron or metatronic occurrences of several deposits. Macroscopically, adenocarcinoma usually presents as a poorly demarcated gray-yellow lesion. With particularly abundant mucin production, the tumor may have a gelatinous appearance. The necrotic decay of a larger area, cavitation, occurs only very rarely. Peripheral localization often involves pleural retraction. Sometimes there is significant fibro-production to scarring around the tumor. Occasionally there is consolidation of the lung, which macroscopically resembles consolidation in pneumonia. Sometimes even a relatively small tumor can grow through the pleura and subsequently spread massively in the pleural cavity.

A typical microscopic sign of adenocarcinoma is the formation of glandular structures and the production of mucin. Sometimes it is not possible to diagnose solely on the basis of hematoxylin-eosin staining and it is necessary to clarify mucin production by histochemical techniques. Immunohistochemistry should be performed for

definitive diagnosis. Pulmonary adenocarcinomas expressing cytokeratin incl. CK7, often, but certainly not always, is a demonstrable nuclear positivity of TTF-1. Inscription A and surfactant protein tend to be positive. P63 protein positivity is infrequent and usually only weak and focal. Almost a third of adenocarcinomas express synaptophysin, chromogranin, NSE, CD56 or CD57. Immunohistochemistry has an irreplaceable place in deciding whether it is primarily a lung tumor or whether it is a metastasis of adenocarcinoma from other sites.

The usual grading scheme is based on the degree of difference of adenocarcinoma:

- **Grade 1** : Well-differentiated glandular or acinar structures represent more than 90% of the tumor area.
- **Grade 2** : Relatively well-differentiated glandular or acinate structures with poorly formed lumens represent at least 50% of the tumor area.
- **Grade 3** : Poorly differentiated structures.
- Other approaches to grading are studied in the literature, which are based, for example, on mitotic activity.

The classification of adenocarcinomas underwent relatively fundamental changes compared to the 2004 WHO classification. The original classification proved to be unsatisfactory, with more than 90% of all cases being diagnosed as a mixed type. For this reason, the classification of lung adenocarcinomas according to ASLC / ATS / ERS [4] was introduced , which was in principle also taken into account in the new WHO classification 2015 [5] :

- Pre-invasive lesions:
  - Atypical adenomatous hyperplasia
- Adenocarcinoma in situ:
  - unmucinous
  - mucinous
  - Mixed mucinous and non-muninous
- Minimally invasive adenocarcinoma (less than 3 cm, in case of predominantly lepid growth pattern less than 5 mm invasion)
  - unmucinous
  - mucinous
  - mixed mucinous and non-muninous
- Invasive adenocarcinoma
  - predominantly lepidic
  - predominantly acinar
  - predominantly papillary
  - predominantly micropapillary
  - predominantly solid with mucin production
  - Variants of invasive adenocarcinoma
  - invasive mucinous adenocarcinoma
  - colloidal
  - fetal (low and high grade)
  - enteric

The classification respects the frequent mixed nature of invasive adenocarcinomas, so the tumor is classified according to the dominant component, any other component that represents more than 5% of the tumor should be mentioned. Subtype information is also of prognostic significance, for example, the predominantly lepidic form of lung adenocarcinoma has an excellent prognosis.

The growth patterns of invasive adenocarcinoma are as follows:

- **The lepid pattern** is characterized in that the tumor cells spread along the alveolar septa without evidence of stromal, vascular or pleural invasion.
- **The acinar pattern** consists of acins and tubules from cubic to columnar mucin-producing cells.
- **The papillary pattern** is characterized by papillary growth with a pronounced fibrovascular core.

In contrast, the micropapillary pattern is characterized by small papillary aggregates of cells with only a completely indistinct fibrovascular nucleus.

Neuroendocrine tumors

The precursor lesion from which the neuroendocrine tumors originate is hyperplasia of cells of the neuroendocrine system, which is defined primarily by a size of up to 2 mm. Hyperplasia progresses to a tumorlet, which is defined by a size of up to 5 mm. The finding of hyperplasia of neuroendocrine cells and tumorlet is relatively common in a number of chronic lung diseases. The condition can be diffuse and multiple carcinoids are relatively common.

Neuroendocrine tumors include the following types:

1. typical carcinoid
2. atypical carcinoid

3. small cell carcinoma
4. large cell neuroendocrine carcinoma

In general, the diagnosis of a neuroendocrine tumor is based on the finding of typical neuroendocrine features in hematoxylin-eosin staining:

1. rosette creation
2. trabecular formation
3. palisade
4. lacy and organoid arrangement of cells
5. in light microscopy, chromatin has the characteristic appearance of "pepper and salt".

With the exception of large cell neuroendocrine tumors, clear staining is usually sufficient to make a diagnosis.

A typical carcinoid:

A typical carcinoid is low-grade neuroendocrine carcinoma (NEC grade I), defined as a well-differentiated neuroendocrine lesion larger than 5 mm in diameter. It represents about 1-2% of lung tumors. In more than one third of cases, tumorlets also appear, which cannot be considered as metastases.

A typical carcinoid can occur centrally or peripherally, the central occurrence is more frequent, representing about 70% of cases. A centrally occurring tumor manifests as an endobronchial growing mass with symptoms of obstruction, a peripherally localized tumor may be asymptomatic. In cross-section, a typical carcinoid is usually a well-defined yellow to yellow-brown nodular deposit.

Microscopically, neuroendocrine growth is evident with a number of typical patterns: organoid, trabecular, rosetiform, pseudoglandular and microacinar. Mitoses are usually not more common than 2 per 10 HPF (2 mm^2), when the proliferation marker Ki67 is examined , the mitotic activity is less than 5%. Necrosis does not occur in a typical carcinoid; on the contrary, nuclear polymorphism may occur. Immunohistochemically, positive markers are neuroendocrine differentiation (chromogranin , synaptophysin and CD56). Cytokeratin can be negative in up to 20% of cases, so it is advisable to examine another epithelial angigen, such as EMA , if negative .

Typical carcinoid has a good prognosis, five-year survival is about 90%.

Atypical carcinoid

Atypical carcinoid is a neuroendocrine carcinoma of moderate malignancy (NEC grade II), similar to a typical carcinoid. It is similar to a typical carcinoid, differing mainly in the histological picture indicating higher restlessness. The diagnosis of an atypical carcinoid can be made with an otherwise typical carcinoid where at least one of the following conditions is met:

- Mitotic activity is higher, usually 2-10 mitoses per ten HPF (2 mm^2). The proliferation marker Ki67 is positive in 5 to 20%.
- Necrosis is present in the tumors. Atypical carcinoids are characterized by necrosis of the nature of comedon necrosis.
- The prognosis of atypical carcinoid is worse compared to typical carcinoid.

Large cell neuroendocrine carcinoma

Large cell neuroendocrine carcinoma is a neuroendocrine tumor of high malignancy (NEC grade III). It is less common, accounting for about 9% of all lung cancers. Macroscopically, it usually appears as a lesion with necrosis that grows infiltratively into adjacent structures. It is usually located peripherally, but central location is possible.

The tumor cells themselves are large with abundant eosinophilic cytoplasm. Nuclear chromatin has a typical "pepper and salt" structure, with prominent nucleoli visible. The mitotic activity of the cells is high, typically dozens of mitoses per 10 HPF (2 mm^2). The histological pattern is typically organoid. Tumor cells are diffusely stained with cytokeratin and rather weakly with neuroendocrine markers (synaptophysin, chromogranin, CD56). About half of the cases are stained with TTF1. Signs of neuroendocrine differentiation can also be demonstrated ultrastructurally.

Small cell carcinoma

Small cell (neuroendocrine) carcinoma is a neuroendocrine tumor of high malignancy (NEC grade III). It represents about 20% of all lung cancers. Epidemiologically, there is a very strong association with smoking, it occurs only rarely in non-smokers. Small cell carcinoma with clinical behavior incl. responses to therapy, in course and in origin, differ significantly from other lung tumors, so the distinction between at least small cell and non-small cell carcinomas is extremely important.

Small cell carcinoma was clearly defined as a separate entity in the late 1950s. There was a terminological division between European and American pathology schools, with European pathologists using the older term oatmeal cancer (following the older term oatmeal sarcoma because mesenchymal origin was originally thought), while American pathologists preferred the term small cell carcinoma. [6]

The tumor presents macroscopically as a soft, friable mass. It usually appears centrally around the great bronchus, localization on the periphery is possible, but uncommon. Obliteration of the respective bronchus is possible at a later stage of the disease, but primary endobronchial growth is extremely unusual.

Histologically, small cell carcinoma cells may not be really small, they can be up to three times the size of a mature lymphocyte. The key to diagnosis is mainly the cytological characteristics of tumor cells. In their most common form, the cells are actually smaller, round to oval, so they can resemble lymphocytes . Sometimes the cells can take on a spindle shape. Tumor cells have very little cytoplasm, they may not be evident in routine staining. The nucleus of tumor cells is finely granular and markedly hyperchromatic with inconspicuous nucleoli. Abundant mitoses and marked necrotic deposits are evident in the tumor. The growth pattern of a small cell tumor is usually solid, but streaked formations, ribbons, rosettes and pseudorosions, tubules, and ducts may also appear.

When processing cytological samples in particular, an artifact appears quite often: Nuclear molging. The liver is elongated and deformed, it clumps together, chromatin diffuses. When tumor resection or metastatic nodules are processed directly, the cytoplasm tends to be more abundant than in cytological specimens and specimens from small biopsies; it is thus possible that the indistinct cytoplasm is to some extent an artifact. In general, especially in bronchoscopic samples, a relatively high number of artificially crushed cells has a diagnostic value, increasing the likelihood that it is indeed a small cell carcinoma.

Immunohistochemically, small cell carcinomas are stained with a number of cytokeratins and neuroendocrine markers, and TTF-1 positivity is common.

References

Footnotes

Jump up↑ The adjective lepidický is derived from the Greek word >> lepis << (bark, skin, membrane). The term was coined by John George Adami (1862-1926), a professor of pathology at McGill University, as a term describing a tumor arising from superficial cells. Sometimes the term is mistakenly given an etymological origin based on a comparison with butterflies, because the Latin name of the order of butterflies is Lepidoptera ; in fact, it is only the same origin of words. The term was practically forgotten for almost the entire twentieth century, it is mentioned only in a few books. At present, the meaning of the term has shifted and I link it exclusively to lung pathology. This is because a lepidally growing tumor is the proliferation of tumor cells along the surface of intact alveolar walls without noticeable stromal or vascular invasion.. Source: JONES, KD. Whence lepidic? The history of a Canadian neologism. Arch Pathol Lab Med [online] . 2013, vol 137, no. 12, pp. 1822-4, also available from < https://pinnacle-secure.allenpress.com/action/getSharedSiteSession?redirect=http%3A%2F%2Fwww.archivesofpathology.org%2Fdoi%2Fpdf%2F10.5858% 2Farpa.2013-0144-HP & rc = 0 & code = coap-site >. ISSN 1543-2165.

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External links

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