The new WHO classification of lung cancer

Prof. Dr. Philipp A. Schnabel
Inst. Allgemeine & Spezielle Pathologie
Universitätsklinikum des Saarlandes
Gebäude 26
66421 Homburg/Saar
GERMANY
philipp.schnabel@uks.eu

AIMS AND STRUCTURE

It is aimed to present the “new” (2015) 4th edition of the “WHO classification of tumours of the lung” (21) and the most important developments since the 3rd edition dating from 2004 (19). During the course, relevant histopathological, immunohistochemical and/or molecular findings will be demonstrated and discussed. This review will focus on the underlined chapters:

- Introduction (Aims and structure)
- Small biopsies, immunohistochemical and molecular testing
- Adenocarcinoma
- Squamous cell carcinoma
- Neuroendocrine tumours
- Large cell carcinoma, Adenosquamous carcinoma, Sarcomatoid carcinoma
- Other tumours
- Summary and outlook

Small biopsies, immunohistochemical and molecular testing

The new WHO classification is not only applicable on resection specimen, but also on small biopsies and cytological material, for the first time (21). This is very important, because from about two thirds of the patients with lung cancer, only small biopsy / and or cytology specimen are taken. There are recommendations how to deal with this material to achieve a correct diagnosis with a minimum of material, because immunohistochemical and/or molecular analyses may be required (18, 21). These recommendations are based on the paper from Travis WD, Brambilla E et al. about the new adenocarcinoma classification published in the JTO in 2011 (20). From this paper an algorithm for the work-up of non-resection lung cancer specimens diagnostic workflow has been introduced into the new WHO classification (Fig. 1.06; here Fig. 1). The use of immunohistochemistry is recommended for those cases, in which the diagnosis is unclear, in which a histologic distinction between adenocarcinoma and squamous cell carcinoma cannot be made or in which a neuroendocrine morphology is detected. A minimum of antibodies / sections should be taken in order to save material for molecular analyses. For the distinction between squamous cell and adenocarcinoma in the first line p40 vs. TTF1 should be applied (21). Only if there is no clear result with these two antibodies, further antibodies can be applied (21, 24). Molecular testing differs fundamentally between adenocarcinoma and squamous cell carcinoma. For adenocarcinoma, already some drugs are approved, for which molecular testing is recommended. For squamous cell carcinoma, mostly different mutations/translocations are known, but at the moment, no specific drug is approved. Nevertheless, many compounds are in clinical testing / trials, and the situation may change rapidly (5, 21).

It is a strength of the new WHO classification that not only recommendations for molecular testing are given, but also known histomorphological – molecular pathologic / genetic correlations are presented (21).

For cytology specimen, the use of the cell block technique is recommended (9, 21).
Adenocarcinoma

At first, it is noteworthy to state that in the new WHO classification two new entities have been defined (21):

- Adenocarcinoma in situ (AIS)
- Minimal invasive adenocarcinoma (MIA)

The first shows a lepidic (non-mucinous) growth pattern without any invasive component, in the latter an invasive growth is restricted to less than 0.5 cm. Both diagnoses can only be made in resection specimen and not in biopsies (21).

The term “lepidic” had already been introduced in the JTO in 2011 (2, 20). It replaces the old term “brochiolo-alveolar”, which has been abolished, because it had been applied with different meanings.

In the new WHO classification, as in the 2011 JTO paper, five different differentiation patterns of pulmonary adenocarcinoma have been defined (2, 20, 21):

- Lepidic adenocarcinoma
- Acinar adenocarcinoma
- Papillary adenocarcinoma
- Micropapillary adenocarcinoma
- Solid adenocarcinoma

For resection specimen, the predominant growth pattern should be reported after carefully looking through all sections from all tumor blocks and determining the percentage of each growth pattern in 5% increments (21, 25). There are some promising radiological – pathological correlations (10, 22).

For biopsies, because of the sampling error, the different growth patterns, which can be detected, should be reported (21).

In the new WHO classification, the “variants of adenocarcinoma” have been restricted to four entities:

- Invasive mucinous adenocarcinoma (Mixed non-mucinous and mucinous adenocarcinoma)
- Colloid adenocarcinoma
- Fetal adenocarcinoma
- Enteric adenocarcinoma

As mentioned above, there are now chapters on:

- Minimal invasive adenocarcinoma
- Preinvasive lesions:
  - Atypical adenomatous hyperplasia
  - Adenocarcinoma in situ

Squamous cell carcinoma

In the new WHO classification, the number of subtypes has been reduced to three, which makes the diagnosis easier and avoids rare subtypes with confusing names (21):

- Keratinizing
- Non-keratinizing
- Basaloid squamous cell carcinoma

- Preinvasive lesion
  - Squamous cell carcinoma in situ
Neuroendocrine tumors

In the new WHO classification, all entities of pulmonary neuroendocrine tumors are shown together in one chapter, for the first time (1, 3, 4, 14–16, 21). In previous editions of the WHO classification, small cell carcinoma and carcinoids were found in separate chapters, whereas large cell neuroendocrine carcinoma (LCNEC) was listed in the chapter of large cell carcinomas (19). In the 3rd edition of the WHO classification LCNEC was the only entity, for the diagnosis of which routinely immunohistochemistry was recommended (19). In the new edition the spectrum of indications for immunohistochemistry is much broader (see above). Not only the visibility of all neuroendocrine lung tumors presented in one chapter is much better than before, also the diagnostic criteria are more precise (1, 3, 4, 12, 14, 16, 23, 27). Thus, visibility, diagnosis and differential diagnosis of these tumors is ameliorated. They are grouped into high grade tumors (small cell and large cell neuroendocrine carcinoma), intermediate and low grade tumors (atypical and typical carcinoids), and the preinvasive diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), and for each of these there are characteristic molecular alterations (1, 3, 4, 6–8, 11, 12, 14, 16, 17, 21):

- Small cell carcinoma
- Large cell neuroendocrine carcinoma
- Carcinoid tumor
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Large cell carcinoma

With the use of immunohistochemistry the proportion of large cell carcinoma will decrease in the future (13, 21). Formerly, large cell carcinoma was diagnosed, in the absence of histopathologic features for adenocarcinoma or squamous cell carcinoma and in the presence of a large cell morphology. If there was a neuroendocrine morphology, this had to be confirmed by at least positivity of one immunohistochemical neuroendocrine marker for the diagnosis of large cell neuroendocrine carcinoma (LCNEC; see above; 19).

Adenosquamous carcinoma

The diagnosis of adenosquamous carcinoma can usually be made in resection specimen, because a minimum of 10% of each component is required (21). If in small biopsies two components with histopathologically, histochemically or immunohistochemically clear adenoid and squamous differentiation can be distinguished, then the term “NSCLC NOS, possible adenosquamous carcinoma” should be applied (Fig. 1; 20). Then, the same testing for molecular alterations should be applied as for adenocarcinoma (Fig. 1; 20).

Sarcomatoid carcinoma

If these tumors show a component of adenocarcinoma or squamous cell carcinoma histologically or with immunohistochemistry, the respective molecular testing can be applied. The subgroups are (21):

- Pleomorphic, spindle cell, and giant cell carcinoma
- Carcinosarcoma
- Pulmonary blastoma

The following entities are listed according to the new WHO classification (21).

Other and unclassified carcinomas

- Lymphoepithelioma-like carcinoma
- NUT carcinoma
Salvary gland-type tumors

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Epithelial-myoepithelial carcinoma
- Pleomorphic adenoma

Papillomas

- Squamous cell papilloma
- Glandular papilloma
- Mixed squamous cell and glandular papilloma

Adenomas

- Sclerosing pneumocytoma
- Alveolar adenoma
- Mucinous cystadenoma
- Mucus gland adenoma

Mesenchymal tumors

- Pulmonary hamartoma
- Chondroma
- PEComatous tumors
- Congenital peribronchial myofibroblastic tumor
- Diffuse pulmonary lymphangiomatosis
- Inflammatory myofibroblastic tumor
- Epitheloid haemangiendothelioma
- Pleuropulmonary blastoma
- Synovial sarcoma
- Pulmonary artery intimal sarcoma
- Pulmonary myxoid sarcoma with EWSR1-CREB1 translocation
- Myoepithelial tumors / myoepithelial carcinoma
- Other mesenchymal tumors

Lymphohistiocytic tumors

- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Diffuse large B-cell lymphoma
- Lymphomatoid granulomatosis
- Intravascular large B-cell lymphoma
- Pulmonary Langerhans cell histiocytosis
- Erdheim-Chester disease

Tumors of ectopic origin

- Germ cell tumors
- Intrapulmonary thymoma
- Melanoma
- Meningioma

Metastases to the lung

SUMMARY AND OUTLOOK

In the new “WHO classification of tumors of the lung” (4th edition 2015) the authors have achieved some essential improvements in comparison with previous editions:
As a multidisciplinary classification it integrates clinical, radiological, macroscopic histopathological, immunohistochemical, and molecular findings for the (differential) diagnosis of lung tumors.

It applies also to small biopsies and cytology specimen, not only for resection specimen.

It includes recommendations for molecular testing based on the specimen available and on the current knowledge about the implication of the different molecular alterations of adenocarcinoma and squamous cell carcinoma.

It provides histo-/cytomorphologic, immunohisto-/cyto-chemical and molecular typing (and in part grading) of lung tumors with high prognostic and predictive relevance.

An interdisciplinary discussion of consequences for diagnostic and therapeutic decisions is mandatory (not only in tumourboards).

Established (diagnostic and) therapeutic algorithms including (new) relevant histo-/cytomorphological, immunohisto-/cyto-chemical and molecular biomarkers should be re-evaluated/validated in randomized studies.

In the course presentation histopathologic (patterns) immununohisto-/cytochemical, and molecular parameters in the new WHO classification will be shown for adenocarcinoma, squamous cell carcinoma, neuroendocrine tumors, and selected rare carcinoma, in relation to to prognosis and prediction. Consequences of these findings for diagnostic and therapeutic decisions will be discussed.

REFERENCES


**Fig. 1:** Algorithm for the work-up of non-resection lung cancer specimens (from 20, 21)