

## Revised World Health Organization Classification of Lung Tumours. Important Changes and Implications

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### ABSTRACT

This article focuses on the main changes applying to the diagnosis of lung cancer according to the recently published latest edition of the WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. The now recommended diagnostic approach for pathologists is attributed to subsequent new clinical and therapeutic implications. The most important change regards achieving a precise as possible diagnosis on small biopsies or cytologic specimens, providing the basis for the best possible tumour-specific therapy. At the same time, tumour tissue must be conserved for additional molecular analyses which are a prerequisite for certain targeted therapeutic approaches. In the future, this challenge is likely to increase even further in the light of additional upcoming treatment strategies.

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**Key words:** Non-small cell lung cancer; Classification; Histology; Molecular pathology

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### EDITORIAL

The World Health Organization (WHO) has recently published the newest edition of their WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart<sup>[1]</sup>. The previous edition was published in 2004, which is a relatively long time span considering the advances in diagnostics and treatment, especially in the field of lung cancer. This article focuses on the main changes applying to the diagnosis of lung cancer from the pathologist's point of view, including subsequent clinical implications. Beforehand it should be noted that the seminal interdisciplinary publication regarding the classification of Adenocarcinomas of the lung, published in 2011 by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society, has largely been adopted, with minor modifications<sup>[2]</sup>.

An important new point is the recommendation for use of immunohistochemistry for small biopsies (when possible) as well as for resection specimens when no clear morphological patterns are discernible. In the prior classification, diagnosis was based on routine light microscopy using hematoxylin-eosin (HE) and mucin stains, with the exception of large cell neuroendocrine carcinoma (LCNEC) requiring additional immunohistochemical confirmation. The fact that various tumour entities can be very difficult, if not impossible to diagnose reliably by this approach, was not crucial since treatment strategies did not differ. Such problematic tumours to classify by standard microscopy include solid adenocarcinoma, non-keratinizing squamous cell carcinoma, large cell carcinoma, neuroendocrine tumours and sarcomatoid carcinoma. Due to evolving tumour therapies with specific drugs given according to histology, precise classification is now essential. In squamous cell cancer, anti-VEGFR antibodies have been shown to cause haemorrhages and the folate antimetabolite pemetrexed lacks efficacy, however both drugs play an important role for the treatment of non-squamous cancer<sup>[3,4]</sup>. On the other hand, anti-PDL1 antibodies seem to be more effective for patients with squamous cell cancer<sup>[5]</sup>.

Tyrosine kinase inhibitors (TKI) of the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibitors are also fundamental for the treatment of adenocarcinoma, or for cases when an adenocarcinoma cannot be excluded<sup>[2]</sup>. So following an era where standardized criteria were not needed and the diagnosis of non-small cell lung cancer – not otherwise specified (NSCLC-NOS) was rather encouraged on biopsies to prevent discrepancies with the resection specimen, now the diagnosis NSCLC-NOS should be avoided as much as possible. When clear morphologic patterns are present, no immunohistochemistry is recommended unless the issue is differentiation between a pulmonary adenocarcinoma and a pulmonary metastasis. Clear patterns include acinary, papillary and lepidic growth in adenocarcinoma and keratinization and intercellular bridges (desmosomes) in squamous cell carcinoma. If such features are lacking, a limited panel of immunohistochemical stains is recommended on biopsies in order to preserve tumour tissue in case additional molecular analyses (EGFR mutation and ALK rearrangement for adenocarcinoma) are needed. An accurate and preserving antibody panel includes TTF1 or Napsin-A as markers for adenocarcinoma and p40 or CK 5/6 for squamous cell carcinoma. We have experienced that dual staining combining a nuclear with a membranous/cytoplasmic marker using two different staining dyes, gives good results while conserving tumour tissue for additional work-up<sup>[6]</sup>. When no definite diagnosis can be made with conventional stains but the immunohistochemical profile is unequivocal, the recommended diagnosis is: favour adenocarcinoma or squamous cell carcinoma. For cases showing two distinctly different areas of differentiation the diagnosis should be: possible adenosquamous carcinoma, since this entity may only be diagnosed definitively on the resection specimen. If a reliable diagnosis can still not be made, then the recommended term is now non-small cell cancer (NSCC) -NOS not NSCLC-NOS, since metastatic disease to the lung must be excluded clinically. In daily routine, the diagnosis of NSCC-NOS can be avoided in about 90% of cases. The entity of large cell carcinomas (LCC) should only be diagnosed on the resection specimen, not on biopsy. Additional immunohistochemical stains for undetermined cases on biopsy include cytokeratins (for confirmation) as well as S100 (melanoma) and CD45 (haematological neoplasia). Depending on the clinically suspected primary tumour, metastasis to the lung may be confirmed or ruled out by respective markers (e.g. hormone receptors, prostate specific antigen).

Regarding adenocarcinomas, the term bronchioloalveolar carcinoma (BAC) is now obsolete, as these tumours are referred to as lepidic adenocarcinoma and the corresponding mucinous BAC is now invasive mucinous adenocarcinoma. In addition, the term adenocarcinoma in-situ (AIS) has been added for purely lepidic, solitary tumours smaller than 3 cm and without invasion (stroma, pleura, vasculature and air space). For such tumours with an invasion less than 0.5cm the term microinvasive adenocarcinoma (MIA) is applied. Should there be invasive areas on multiple slides, the percentage of the invasive tumour multiplied by the largest tumour diameter can be used as an estimate (e.g.: tumour diameter: 2.6 cm; invasive tumour: 15%; estimated invasive area:  $0.15 \times 2.6 = 0.39$  cm). When reporting a lepidic adenocarcinoma on biopsy it is therefore important to comment that invasion cannot be excluded. Other adenocarcinoma patterns that have additional implications are micropapillary and solid variants, as they are associated with a worse prognosis. For adenocarcinomas of the fetal, enteric or colloid type, it should be noted that a metastasis must be excluded.

Concerning neuroendocrine tumours, performing the respective immunohistochemistry (synaptophysin, chromogranin, CD56) is

only recommended when neuroendocrine features are evident by routine microscopy (organoid nesting, trabecular growth, rosette-like structures, peripheral palisading). The reason for this is that 10-20% of NSCLC show immunohistochemical evidence of neuroendocrine differentiation, however this is not a separate class of tumours as there is no proven significance<sup>[7]</sup>. Mitotic count should be performed in the area with the highest activity and reported per 2 mm<sup>2</sup>, not per high power field (hpf) since these may differ according to the microscope. If neuroendocrine morphology is evident on routine stains (HE) and the respective immunohistochemistry is positive, the recommended diagnosis on biopsy is: possible LCNEC. The definite diagnosis of LCNEC is made on the resection specimen. If neuroendocrine immunohistochemistry is negative, the recommended diagnosis is: suspected LCNEC. On resection specimen this entity is now termed large cell carcinoma with neuroendocrine morphology. For NSCC with spindle cells or giant cells on biopsy, these features should be mentioned, however the corresponding diagnosis of a pleomorphic carcinoma should only be made on resection specimen. Clear cell and rhabdoid morphology are now considered as features of a defined carcinoma and do not represent separate entities as in the former classification. When diagnosing a squamous cell carcinoma, three subtypes are distinguishable: keratinizing, non-keratinizing and basaloid (> 50%). Previous subtypes, including small cell and papillary carcinoma are no longer specified.

Tumour grading is still an issue and has not yet been resolved. For neuroendocrine tumours grading is inherent. Certain other entities, such as LCC or pleomorphic carcinoma are always considered high grade tumours. For adenocarcinomas, an architectural approach has been suggested, with lepidic architecture corresponding to grade 1, acinary and papillary to grade 2 and solid and micropapillary to grade 3<sup>[2]</sup>. This method has resulted in a prognostically significant stratification of adenocarcinomas and is also an objective and reproducible means of grading<sup>[6]</sup>. Nuclear atypia as well as tumour budding have also been discussed and seem to play a role in the context of tumour grading, although there is still no established grading system for most lung cancers<sup>[8,9]</sup>.

In summary, the pathologist is now confronted with providing a precise as possible diagnosis on small biopsies, while conserving tumour tissue at the same time for further molecular testing. In the light of additional upcoming targeted treatment strategies, this situation is even likely to increase, leading to more challenges in the field of lung cancer diagnostics and treatment.

## CONFLICT OF INTERESTS

The author declare that they do not have conflict of interests.

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