Belgian consensus guidelines for the subtyping of NSCLC

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For many years in lung cancer diagnosis, pathologists had to differentiate between small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) for treatment purposes. In recent years, clinical observations with new drugs demonstrated different outcomes depending on the NSCLC histological subtype. Therefore, the Belgian Mesothelioma Registry, whose members are all particularly interested in lung pathology, proposed guidelines for the subtyping of NSCLC based on the recent literature, taking specific Belgian reimbursement modalities into account.

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Introduction

Increasingly, cancer treatments are both patient- and tumour-tailored leaving the "one-size-fits-all" for a more targeted strategy. This is particularly true of primary pulmonary carcinoma. For many years, pathologists have had to distinguish between small cell (SCLC) and non-small cell lung carcinoma (NSCLC) because of particular prognosis, outcome and treatment modalities. This diagnostic algorithm has recently evolved and, also, pathologists actually need to subdivide NSCLC into adenocarcinoma and squamous cell carcinoma. This change is based on the following clinical observations: patients with advanced lung cancer treated with bevacizumab run an increased risk of life-threatening haemorrhage if they have squamous cell carcinoma.[1] Patients with non-squamous histology respond significantly better to pemetrexed than those with squamous cell carcinoma.[2-4] EGFR mutation is strongly associated with adenocarcinoma histology and patients with advanced NSCLC and EGFR mutation have a better outcome and better response to tyrosine kinase inhibitors as a primary therapy, whereas patients without EGFR mutations seem to have a better outcome with chemotherapy.[5] In all these studies, diagnosis was based solely on histology as advised by the WHO classification.[6] This classification is built on large surgical specimen, but in daily practice, the pathologist mostly (85% of lung cancer patients) receives small biopsy fragments or cytological material. Therefore, the Belgian Mesothelioma Registry has decided to propose a consensus guideline for the subtyping of NSCLC using special stains and immunohistochemical markers according to the literature and taking specific Belgian reimbursement modalities into account.

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Algorythm description

In the diagnostic work-up of primary lung cancer, different ways to obtain tumour material are available, from specimen obtained by bronchoscopic examination such as bronchial biopsies or lavage and US-guided transbronchial fine needle aspiration (FNA) to transthoracic punctures, pleural fluid and US-guided transoesophageal FNA of metastatic mediastinal lymph nodes. For cytological material cell blocks are mandatory to preserve as much material as possible for complementary techniques.

The first diagnostic step is to distinguish a SCLC from a NSCLC, based on histological or cytological characteristics confirmed by the immunohistochemical expression of neuroendocrine markers (i.e. synaptophysin, chromogranin, CD56) in SCLC.

When facing a NSCLC, a histological picture based on gland formation or the presence of keratinized cells, pearls and intercellular bridges is sufficient to distinguish an adenocarcinoma from a squamous cell carcinoma. In case of a NSCLC not otherwise specified (NOS), special stains such as Periodic Acid Schiff (PAS) after diastase-demonstrating mucin production by tumour cells, is enough to render a diagnosis of adenocarcinoma (the solid variant of adenocarcinoma is defined as the presence of a minimum of 5 mucus containing cells in 2 High Power Fields). The immunohistochemical panel proposed by the workgroup includes 4 different antibodies in accordance with specific Belgian reimbursement modalities, recognized in the literature as being able to differentiate between lung adenocarcinoma and squamous cell carcinoma in most cases, although none is 100% specific. Usually, pulmonary adenocarcinomas are characterized by nuclear expression of thyroid transcription factor-1 (TTF-1), however negative, in up to 30% of cases, and cytoplasmic positivity for the surfactant protein A (SPA) and cytokeratin 7 (CK7). High-molecular-weight cytokeratins (HMWCK) and p63 are not expressed. Squamous cell carcinomas show nuclear staining for p63 and a positivity of HMWCKs, but expression of CK7 and TTF-1 is only seldom seen. The proposed panel includes CK7, TTF-1, p63 and either cytokeratin 5,6 or cytokeratin 34βE12 (HMWCKs).[7-9] A concordant panel with a positivity of CK7 associated or not associated with TTF-1 expression is in favour of an adenocarcinoma, whereas p63 expression associated or not associated with a HMWCK pleads for a squamous cell carcinoma. A discordant panel with aberrant immunohistochemical expression such as the association of a CK7 and p63 positivity is in favour of a non-squamous cell carcinoma (which may be either an adenocarcinoma or a large cell carcinoma) when CK7 is positive, with the exception of a diffuse and strong positivity of p63 and CK34βE12/CK5.6 favouring an SCC diagnosis. In case of absence of immunohistochemical expression of all

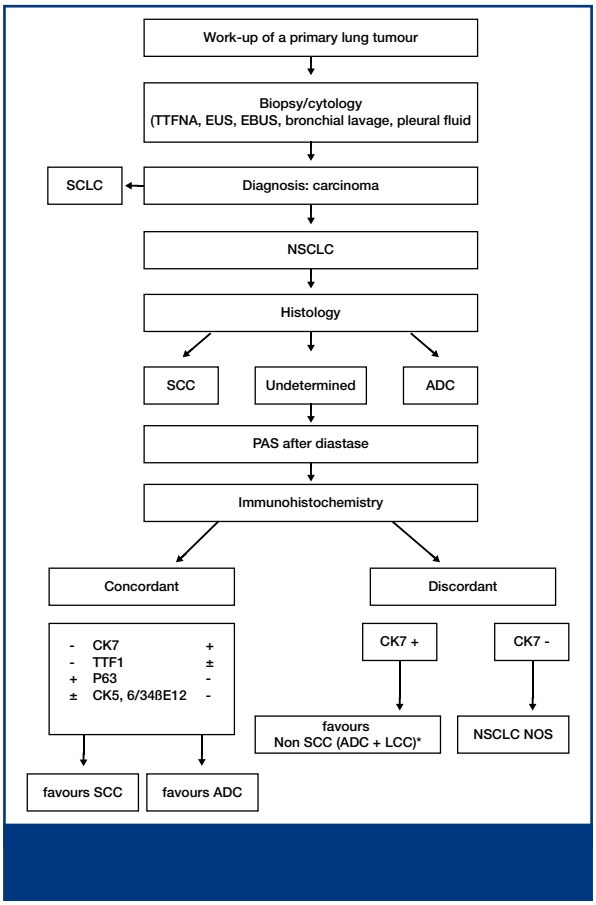

Figure 1. Work-up of a primary lung tumour. SCLC=small cell lung carcinoma; NSCLC=non-small cell lung carcinoma; SCC=squamous cell carcinoma; ADC=adenocarcinoma; LCC=large cell carcinoma; CK=cytokeratin; TTF-1=thyroid transcription factor 1; PAS=periodic acid-Schiff; TTFNA=transthoracic fine needle aspiration; EUS=US-guided transoesophageal puncture; EBUS=US-guided transbronchial puncture; NOS=not otherwise specified; *=with the exception of a strong and diffuse positivity of p63 and CK34bE12/CK5.6 which is in favour of a SCC.

4 markers, a diagnosis of NSCLC NOS should be rendered, although a completely negative tumour should raise the suspicion of a metastatic tumour, the lung being the first metastatic site of most extrathoracic tumours (*Figure 1*). In this last situation, the pathologist can add other markers depending on the patient's clinical history and his personal experience.

In the future, the proposed algorithm may change when new markers already described in the literature such as napsin-A for adenocarcinoma and desmocollin-3 for squamous cell carcinoma, have been validated in larger studies.[10-11]

Conclusion

The Belgian Mesothelioma Registry proposes an algorythm for the subtyping of NSCLC in adenocarcinoma and squamous cell carcinoma based on histological or cytological characteristics, special stains and an immunohistochemical panel taking recent literature in the field and Belgian reimbursement modalities into account.

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