CHAPTER 52

CLASSIFICATION OF LUNG CANCER

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Lung cancer is the most common cancer worldwide and is still responsible for the most cancer deaths according to the World Health Organization (WHO), more than double the next two highest cancers of liver and lower gastrointestinal tract [1,2].

Due in part to remarkable advances over the past decade in our understanding of lung cancer, particularly in area of medical oncology, molecular biology, and radiology, there is a pressing need for a revised classification, based not on pathology alone, but rather on an integrated multidisciplinary approach to classification of lung cancer. The 2015 World Health Organization (WHO) Classification of Tumors of the Lung, Pleura, Thymus and Heart has just been published with numerous important changes from the 2004 WHO classification.

The most significant changes are as follows: (1) main changes of lung adenocarcinoma as proposed by the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification (2) reclassifying squamous cell carcinomas into keratinizing, nonkeratinizing, and basaloid subtypes with the nonkeratinizing tumors requiring immunohistochemistry proof of squamous differentiation, (3) restricting the diagnosis of large cell carcinoma only to resected tumors that lack any clear morphologic or immunohistochemical differentiation with reclassification of the remaining former large cell carcinoma subtypes into different categories, (4) grouping of neuroendocrine tumors together in one category, (5) adding NUT carcinoma, (6) changing the term sclerosing hemangioma to sclerosing pneumocytoma, (7) changing the name hamartoma to "pulmonary hamartoma," (8) creating a group of PEComatous tumors that include (a) lymphangioleiomyomatosis, (b) PEComa, benign (with clear cell tumor as a variant) and (c) PEComa, malignant, (9) introducing the entity pulmonary myxoid sarcoma with an EWSR1–CREB1 translocation, (10) adding the entities myoepithelioma and myoepithelial carcinomas, which can show EWSR1 gene rearrangements, (11) recognition of usefulness of WWTR1–CAMTA1 fusions in diagnosis of epithelioid hemangioendotheliomas, (12) adding Erdheim–Chester disease to the lymphoproliferative tumor, and (13) a group of tumors of ectopic origin to include germ cell tumors, intrapulmonary thymoma, melanoma and meningioma.

Classification of lung carcinomas by histopathologic subtype provides important information about prognosis and is necessary for optimal treatment. The lung cancer classification organized by WHO in 2015 is shown in Table 1 [2,4,5].

Compared with the 2004 WHO Classification, there are multiple major changes for the common lung cancers most of which follow the 2011 lung adenocarcinoma classification sponsored by the

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Table 8. 2015 WHO criteria for the diagnosis of pulmonary neuroendocrine tumors

Tumor type	Criteria
Typical carcinoid	• Carcinoid morphology and <2 mitoses/2 mm^2 (10 HPFs), lacking necrosis and >0.5 cm
Atypical carcinoid	• Carcinoid morphology with 2 to 10 mitoses/2 mm^2 (10 HPFs) or necrosis (often punctuate)
Large cell neuroendocrine carcinoma	• Neuroendocrine morphology (organoid nesting palisading rosettes, trabeculae); • High mitotic rate >10/2 mm2 (10 HPFs), median of 70/2 mm2; • Necrosis (often large zones); • Cytologic features of a NSCLC: large cell size, low nuclear to cytoplasmic ratio, vesicular or fine chromatin, and/or frequent nucleoli; some tumors have fine nuclear chromatin and lack nucleoli but qualify as NSCLC because of large cell size and abundant cytoplasm; and • Positive immunohistochemical staining for one or more NE markers (other than neuron-specific enolase) and/or NE granules by electron microscopy
Small cell neuroendocrine carcinoma	• Small size (generally less than the diameter of three resting lymphocytes); • Scant cytoplasm; • Nuclei: finely granular nuclear chromatin, absent or faint nucleoli; • High mitotic rate: >11 mitoses/2 mm2 (10 HPFs), median of 80/2 mm2 (10 HPFs); and • Frequent necrosis, often in large zones

HPF: high-power field; NSCLC: non-small cell lung carcinoma; NE: neuroendocrine.

Within the group of pulmonary neuroendocrine tumors, typical and atypical carcinoids share a number of features and are similar to carcinoid lesions arising at other sites. Small cell carcinomas and large cell neuroendocrine carcinomas are characterized clinically by a more aggressive course and pathologically by a much higher mitotic rate compared with pulmonary carcinoids (11 or more mitoses per 10 high power fields) [4]. A high Ki-67 score may help distinguish small cell and large cell neuroendocrine carcinoma from pulmonary carcinoids, especially in small biopsies, but staining for Ki-67 is not part of the diagnostic criteria.

NUT Carcinoma

Carcinomas associated with chromosomal rearrangement in the NUT gene are called NUT carcinomas. These are poorly differentiated carcinomas genetically defined by the presence of *NUT* gene rearrangement [27,28]. This consists of a chromosomal translocation between the *NUT* gene (*NUTM1*) on chromosome 15q14 and other genes: *BRD4* on chromosome 19p13.1 (70%), *BRD3* on chromosome 9q34.2 (6%), or an unknown partner gene (24%).Although it was originally thought to be a diseasebof children and younger adults, NUT carcinoma can affect people of any age, affecting males and females equally. NUT carcinoma is a very aggressive tumor with a median survival of 7 months.

Other Primary Tumors Of The Lung

Besides lung carcinomas as described above other types of tumors can arise from lung, including mesenchymal tumors, lymphohistiocytic tumors, melanoma, germ cell tumors and others (Table 1) [4].

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