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Major Hystologic Types of Lung Cancer

Yusupov Baxtiyor Lutfidin o'g'li
Assistant of Pathologic anatomy and forensic medicine, Ferghana Medical Institute of Public Health

Annotation. *Worldwide, lung cancer is the most common cause of major cancer incidence and mortality in men, whereas in women it is the third most common cause of cancer incidence and the second most common cause of cancer mortality. Significant progress has been made in the understanding of lung cancer biology, due in large part to advancement in the understanding of tumor biology and pathogenesis. Acquisition of key somatic mutations acts as a sentinel event in lung carcinogenesis, essential for tumor cell growth and division.*
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Lung cancer can be diagnosed pathologically either by a histologic or cytologic approach. The new International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) Lung Adenocarcinoma Classification has made major changes in how lung adenocarcinoma is diagnosed. It will significantly alter the structure of the previous 2004 World Health Organization (WHO) classification of lung tumors. Not only does it address classification in resection specimens, but it also makes recommendations applicable to small biopsies and cytology specimens, for diagnostic terms and criteria for other major histologic subtypes in addition to adenocarcinoma. The major histologic types of lung cancer are squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and large cell carcinoma. These major types can be subclassified into more specific subtypes such as lepidic predominant subtype of adenocarcinoma or the basaloid variant of large cell carcinoma. More detailed reviews of the pathology, cytology, and molecular biology of lung cancer can be found elsewhere.

Histologic classification of lung cancer:

Although lung cancer can be divided into many subtypes, historically the most important distinction was between small cell lung carcinoma (SCLC) and non–small cell lung carcinoma (NSCLC). This situation is because of the major clinical differences in presentation, metastatic spread, and response to therapy. However, in the past decade, there has been a major transformation in the approach to diagnosis of NSCLC, so now more attention is given to its precise classification in small biopsies and cytology. Because 70% of lung cancers present in advanced stages, most patients are unresectable and the diagnosis is based on small biopsies and cytology. The main reason for this new importance to classify NSCLC further is because the choice of therapies now is dependent on histology. For example, patients with adenocarcinomas and NSCLC not otherwise specified (NSCLC-NOS) are eligible for EGFR tyrosine kinase inhibitors (TKIs) if an EGFR mutation is present; they are also eligible for either pemetrexed-based or bevacizumab-based regimens. In contrast, if the diagnosis is squamous cell

carcinoma, patients are not eligible for these therapies. The implications of these new therapeutic paradigms for lung cancer classification are profound and are outlined in this review.

Preinvasive lesions: the pathology of preinvasive lesions for lung cancer has attracted increasing interest in recent years because of the growing importance of early detection of lung cancer using screening of high-risk patients by fluorescence bronchoscopy and by spiral or helical computed tomography (CT). In addition, the concepts of preinvasive lesions have evolved over the past several decades, with none mentioned in the 1967 WHO classification of lung tumors and only bronchial squamous dysplasia and CIS in the 1981 WHO histologic classification of lung tumors. In the 1999 WHO classification 2 new lesions were described: AAH and DIPNECH, and these were maintained in the 2004 WHO classification. So in the 1999 and 2004 WHO classification, there were only 3 preinvasive lesions. Now, in the 2011 IASLC/ATS/ERS Classification of Lung Adenocarcinoma, AIS was added as a new preinvasive lesion for adenocarcinoma.

Squamous Dysplasia and CIS: bronchial carcinogenesis is conceptualized as a multistep process involving transformation of the normal bronchial mucosa through a continuous spectrum of lesions, including basal cell hyperplasia, squamous metaplasia, dysplasia, and CIS. Associated with the morphologic changes are a series of molecular events that accumulate as the squamous lesions progress through increasing dysplasia to CIS and invasive squamous cell carcinoma. Such changes include allelic loss at the 3p region, which is an early event found in 78% of preinvasive bronchial lesions. Followed by a series of other molecular events such as loss of heterozygosity at 9p21 (p16), 17p loss (hyperplasia), telomere activation, telomerase reactivation, retinoic acid receptor (RAR) β loss (mild dysplasia), p53 mutation, vascular endothelial growth factor overexpression (moderate dysplasia), p16 inactivation, Bcl-2 overexpression, and cyclin D1 and E overexpression (CIS). Squamous dysplasia may be mild, moderate, or severe depending on the severity of cytologic atypia and the thickness of the abnormality within the bronchial epithelium. CIS shows full thickness involvement of the epithelium by marked cytologic atypia. There is a continuum of morphologic changes, but these categories can be separated with good reproducibility. Care must be taken not to confuse dysplasia with reactive atypia associated with inflammation or granulation tissue. CIS with involvement of submucosal glands must also be separated from microinvasive squamous cell carcinoma.

Dipnech is a rare condition in which the peripheral airways are diffusely involved by neuroendocrine (NE) cell hyperplasia and tumorlets. The clinical presentation resembles interstitial lung disease manifest by airway obstruction caused by bronchiolar fibrosis in approximately half of the patients. The remaining patients typically present with multiple incidentally discovered pulmonary nodules, often found during follow-up for an extrathoracic malignancy. Because carcinoid tumors are frequently found in patients with DIPNECH and the tumors are often multiple, this is believed to represent a preinvasive lesion for carcinoid tumors. There is a distinctive CT appearance consisting of centrilobular nodules and pulmonary nodules, which correspond to the tumorlets and carcinoid tumors, respectively. Furthermore, in patients who present with clinical manifestations of interstitial lung disease, the CT can be normal or it can show mosaic perfusion from air trapping, bronchial wall thickening, and bronchiectasis.

Squamous cell carcinoma: historically, two-thirds of squamous cell carcinomas presented as central lung tumors, whereas many among the remaining third are peripheral. However, recent reports document that an increasing percentage of squamous cell carcinomas are found in the periphery, exceeding 50% in some studies. The morphologic features that suggest squamous differentiation include intercellular bridging, squamous pearl formation, and individual cell keratinization. In well-differentiated tumors these features are readily apparent; however, in poorly differentiated tumors they are difficult to find. Squamous cell carcinoma arises most often in segmental bronchi and involvement of lobar and mainstem bronchus occurs by extension. Squamous cell carcinoma can have papillary, clear cell, small cell and

basaloid subtypes. However, this subtyping needs updating because it does not address well the morphologic spectrum of appearances of lung squamous cell carcinoma and it does not allow for meaningful correlations with clinical, prognostic, or molecular features. For example, the small cell variant probably should be discarded, because most of these cases would better be classified as basaloid variants and the term small cell creates confusion with true small cell carcinoma. Papillary squamous cell carcinomas often show a pattern of exophytic endobronchial growth.

Adenocarcinoma: the 2011 IASLC/ATS/ERS lung adenocarcinoma classification recommends multiple major changes. First, it is recommended to no longer use the term BAC because the tumors formerly classified under this term are now classified into 5 different tumors. Second, there are new concepts of AIS (see preinvasive lesions) and MIA. Third, it is recommended to no longer use the term mixed subtype, but rather to use comprehensive histologic subtyping to estimate the percentage of histologic patterns in 5% increments within a tumor with final classification according to the predominant subtype. Fourth, tumors with a predominant component formerly called nonmucinous BAC should be classified as LPA. Fifth, micropapillary adenocarcinoma is recognized as a new subtype with a poor prognosis. Sixth, invasive mucinous adenocarcinoma is the term recommended for those tumors formerly classified as mucinous BAC. Sixth, specific terminology and diagnostic criteria are proposed for tumors in small biopsies and cytology specimens along with recommendations for strategic management of tissue and EGFR mutation testing in patients with advanced adenocarcinoma.

Small cell carcinoma: small cell lung cancer is a rare fast-growing lung cancer. Small cell lung cancer can affect anyone, but it typically affects people who have a long history of tobacco use, specifically smoking cigarettes. Healthcare providers can cure some people if the disease is found early; for others, they can help them live longer. There are two types of small cell lung cancer: Small cell carcinoma: This is the most common form of small cell lung cancer. Combined small cell carcinoma: Combined small cell carcinoma represents about 2% to 5% of all small cell carcinomas. This small cell type is a combination of non-small cell and small cell lung cancer cells. Large cell carcinoma: large cell lung cancer is categorized as such by how the cancer cells look under a microscope. The cells do not clearly look like adenocarcinoma or squamous cell lung cancer, and they are distinguished from small cell lung cancer cells by their larger size. In the past, about 10% of all lung cancers were classified as large cell. However, as more exact ways of diagnosing lung cancer have come into use, this percentage is dropping to possibly as low as 2%. Many lung cancers that would have been considered large cell in the past are now being identified as lung adenocarcinoma or squamous cell lung cancer.

Adenosquamous carcinoma accounts for 0.6% to 2.3% of all lung cancers and it is defined as a lung carcinoma having at least 10% squamous cell and adenocarcinoma by light microscopy. Similar to large cell carcinoma enormous confusion has been introduced by use of immunostains. The current WHO definition recognizes this tumor if the 10% of squamous and adenocarcinoma components are diagnosable by light microscopy. This diagnosis should be made only if the adenocarcinoma and squamous components are both recognizable by light microscopy and not purely by immunohistochemistry. This diagnosis may be suspected, but cannot be made by small biopsy or cytology, because a resection specimen is needed.

All in all, characterization of histologic type of lung cancer plays an increasingly pivotal role in the multidisciplinary approach in the diagnosis and management of lung cancer. Recognizing the biological diversity of lung cancer, a comprehensive and accurate tumor classification has been developed, which is important for treatment and prognosis. Pathology of lung cancer has expanded to cover both tissue diagnosis and selection of specific subtypes of lung cancers for further molecular testing. Confirmatory histologic diagnosis directs surgical resection of early-stage disease, whereas

pathologic classification and molecular testing enable selection of tumor type–tailored adjvuant therapy and genotype-based treatment regimen to improve the survivals of advanced-stage patients**.**

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