Deciphering Lung Adenocarcinoma Heterogeneity

Subjects: Oncology

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pulmonary enteric carcinoma colorectal cancer immunochemistry mutation analyses

1. Introduction

Lung cancer is one of the most frequently diagnosed cancers worldwide and the leading cause of cancer-related death. The worldwide lung cancer mortality rate amounted to 1.59 million deaths in 2012, accounting for 19.4% of the total cancer deaths, while in terms of incidence, it is second only to prostate and breast cancers among men and women, respectively [1].

Over the past decade, a significant reduction in lung cancer mortality has been observed for both sexes in the United States [2], mostly driven by the introduction of lung cancer screening and precision medicine in clinical practice [3]. Conversely, lung cancer-related mortality is rising in the female European population, requiring different approaches in terms of both diagnostic and therapeutic interventions [4].

Based on morphological features, lung cancer has been historically classified as small cell lung cancer (SCLC—15%) and non-small cell lung cancer (NSCLC—75%), the latter including adenocarcinoma (ADC—60%), squamous cell carcinoma (Sq—30%) and other less common subtypes (10%) (**Figure 1**).

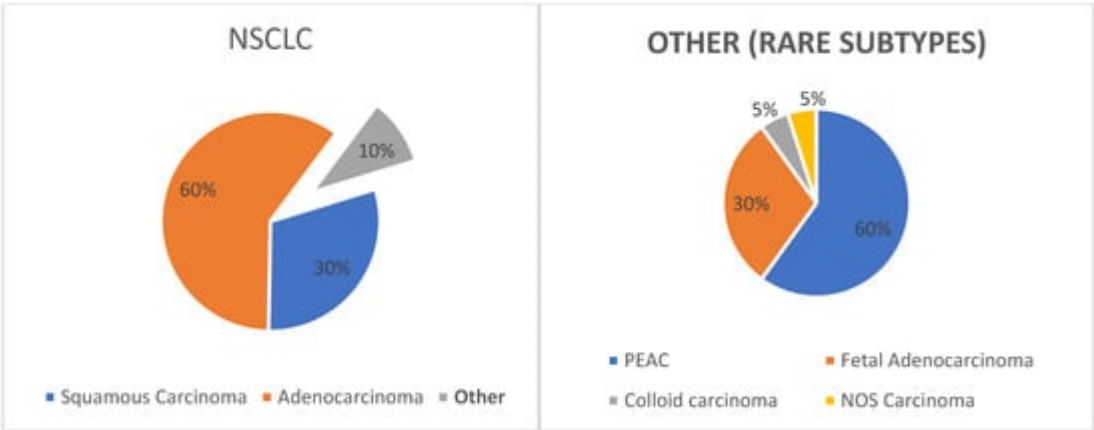

Figure 1. NSCLC and classification of rare variants based on World Health Organization (WHO) 2021 classification. PEAC: pulmonary enteric adenocarcinoma; NOS: not otherwise specified.

A sex-specific difference in the incidence of lung cancer subtypes has been reported, with women most likely to develop adenocarcinoma rather than squamous cell carcinoma, which is most commonly detected in men [5]. Even if tobacco smoking remains the main risk factor, being involved in the development of almost 70% of lung cancer cases, the increasing proportion of non-small cell lung cancer diagnoses in people who have never smoked has led to the hypothesis that this subgroup of tumors should be considered a separate entity [6] with specific molecular and genetic features, since they are typically found in younger female patients harboring oncogenic driver alterations, especially the adenocarcinoma subtype. Other environmental risk factors include air pollution, occupational exposure (asbestosis, metals, etc.) and chronic obstructive pulmonary disease [7].

The recent introduction of innovative therapies (e.g., targeted therapies and immunotherapy) in clinical practice has certainly changed the therapeutic management of lung cancer patients, but only a limited proportion of them currently experience long-term clinical benefits in real-world scenarios, while the 5-year survival rate in the overall lung cancer population remains poor, especially for patients affected by SCLC and other rare histological subtypes, which exhibit relevant differences in terms of epidemiology, molecular characteristics and prognosis [8].

In recent years, both improvements in molecular techniques, such as next-generation sequencing (NGS), and immunohistochemistry have led to a better classification of lung adenocarcinoma subtypes and the biological mechanisms underlying these entities. The 2015 WHO classification introduced many important changes largely owing to the remarkable progress in understanding genetics and molecular-targeted therapies [9]. The more recent 2021 World Health Organization (WHO) classification provided a detailed and updated categorization of lung adenocarcinomas with a special focus on rare histological types, including the enteric, fetal and colloid types, as well as not otherwise specified adenocarcinomas, overall accounting for about 5–10% of all cases. With this new classification, thanks to the introduction of new immunohistochemistry biomarkers and molecular testing, many of the more sophisticated approaches to pathologic diagnosis have led to more precise pathologic and genetic classification of lung tumors. Moreover, the understanding of the biological mechanism underlying lung cancer transformation has been improved, leading to more personalized medicine, even for rare lung cancers.

However, rare entities are still difficult to diagnose and manage in most centers because of the low incidence of these tumors, for which reliable data and prospective trials are still lacking.

Most of the evidence is currently derived from retrospective studies employing data collection, case reports published in the literature, subgroup analyses of clinical trials or international guidelines for these rare tumors' common counterparts.

Consequently, there is no standard of care for the management of rare variants of lung cancer, while treatment algorithms are defined by each center and international, univocal guidelines are still lacking.

2. Fetal Adenocarcinoma

Fetal lung adenocarcinoma is a very rare cancer described in 1982 as a subtype of pulmonary blastoma. Well-differentiated fetal adenocarcinoma (WDFA) accounts for 0.5% of all lung neoplasms [10]; it is more commonly detected in young female smokers and is usually associated with a good prognosis [11]. Reports describing the radiological features of this disease are limited, but it is usually characterized by round-shaped, well-defined solid lesions with oval or lobulated borders and high FDG-PET uptake [12]. From the histological point of view, WDFA is characterized by neoplastic glands and tubules lined with non-ciliated columnar cells, with some of them resembling endometrial glands and squamous morula cells with a fibroblastic stroma [12][13]. Rounded cells with eosinophilic cytoplasm are frequently observed [12]. These glands are rich in glycogen, as demonstrated by periodic acid–Schiff (PAS) reaction staining. Immunohistochemistry is usually positive for epithelial markers associated with vimentin and synaptophysin [13]; beta-catenin and WNT signaling pathway abnormalities are crucial in the pathogenesis of WDFA, with upregulation of c-myc and cyclin-D1 frequently reported in these tumors. Moreover, diagnosis can be challenging using only small biopsy specimens, and anatomical resection with surgical specimens should be preferentially considered. Differential diagnosis must be considered with regard to pulmonary blastoma—which is a biphasic tumor with a sarcomatous and carcinomatous component characterized by aggressive behavior—fibrous solitary tumors, Castleman's disease, inflammatory pseudotumors, lymphoma and sarcoidosis. WDFAs are usually smaller than 5 cm and rarely spread to lymph nodes or the pleural surface. For this reason, surgical approaches are usually preferred and associated with good survival outcomes [14].

Indeed, following surgical resection, 5-year and 10-year survival rates have been reported to be around 80% and 75%, respectively. [14]. Combined treatment with radiotherapy and chemotherapy (based on platinum doublets) should be considered for patients with locally advanced disease, while metastatic disease can be treated with chemotherapy alone, although prognosis remains poor [14].

In contrast, high-grade fetal adenocarcinoma (HGFA) is a poorly differentiated variant, less frequently diagnosed compared to WDFA and predominantly occurring in male patients [12]. HGFA is characterized by disorganized glands with large vesicular nuclei, prominent nucleoli, anisonucleosis and adenocarcinoma foci [13]. Morula differentiation is absent, and positive stains for p53 and alpha-fetoprotein (AFP) are evident. Treatment consists of systemic chemotherapy, although responses are rare, so prognosis remains poor.

3. Colloid Adenocarcinoma

Colloid adenocarcinoma (CA) of the lung was first described in 1992 and identifies a group of very rare lung tumors characterized by abundant extracellular mucin associated with scant neoplastic epithelium, distorting the alveolar space [15]. In recent years, these tumors have been reported under different designations, including "Mucinous Cystadenoma" and "Mucinous Cystic Adenocarcinoma". Recently, this entity was included in the 2021 WHO classification as a rare subtype. Although these tumors can show indolent biological behavior, they sometimes spread to distant sites, including lymph nodes, bone and brain [16]. CA occurs more frequently in females and smokers, with a median age at diagnosis of 65 years [17].

Macroscopically, CA usually presents as a large lesion predominantly composed of gelatinous/mucinous material. Microscopically, it is characterized by an abundant mucin matrix with some tumor cells floating in the mucous, including both cuboidal and columnar cells, with small nuclei and without atypia or mitotic activity [16]; fragments of alveolar walls are frequently noted.

Regarding immunohistochemistry features, research on colloid cancer has shown some overlapping findings with PEAC, including strong expression of CK7 and moderate expression of CK20, CDX-2 and MUC2 [17]. TTF-1 and napsin-A are normally negative, while weak expression of surfactant protein-A (SP-A) can be present [16]. However, some CAs may show positive TTF-1 staining due to tumor heterogeneity [17]. Some reports suggest that *KRAS* mutations on codon 12 or 13 could be found in CA [16].

This entity usually presents as a peripheral and solitary nodular intrapulmonary mass, which may be discovered incidentally during a routine radiographic evaluation [17]. The main treatment is surgery; although most patients have favorable outcomes, some of them develop recurrences, especially when associated with a major non-colloid part or KRAS mutations. Although there are no established diagnostic criteria, this designation is used for tumors that are composed exclusively of colloid cancer or have only small foci of non-colloidal tissue [17].

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