Editorial Commentary

Towards a clinically applicable histomolecular classification of lung adenocarcinomas?

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Lung adenocarcinoma is the most common histological type of lung cancer. It has been clear for several years that lung adenocarcinomas represent a very heterogeneous group in terms of prognosis and molecular features. Historically, the classification of these tumors was defined based on histopathology. The various WHO classifications of 1967, 1981, 1999, 2004, 2015, and 2021 have allowed for better definition and subtyping of certain entities (1). This subtyping correlates with prognosis for certain entities and with certain molecular abnormalities. For example, the recognition of invasive mucinous adenocarcinoma, which has a higher frequency of *KRAS* mutations and a higher proportion of oncogenic fusions than non-mucinous adenocarcinomas (1).

Nevertheless, this histopathological subtyping reaches its limits because it does not correlate perfectly with molecular abnormalities, it is not perfectly reproducible, it is improved by the use of immunohistochemistry, and above all it is not completely able to predict the therapeutic response (2-4). Excerpt for the histopathological type, histopathological subtyping of lung adenocarcinomas has limited use for the therapy of lung adenocarcinomas where stage, PD-L1 status and molecular biology have an important place.

The discovery of recurrent molecular abnormalities in adenocarcinomas has led to diagnostic advances with molecularly defined entities. For example, the individualization of *SMARCA4*-deficient thoracic tumors or *NUT* cell carcinoma (5,6). Nevertheless, it is on the therapeutic level that molecular abnormalities have had an impact with clinical significance. On the opposite, while adenocarcinomas with *ALK* rearrangements reach a different population from other lung adenocarcinomas, have a different histopathological appearance, and different therapy, they are not recognized as a specific subtype whereas in other cancers some subtypes are defined by oncogenic fusions (7).

At the molecular level, the identification of oncogenic driver mutations in lung adenocarcinomas has led to improved overall patient survival and progression-free survival due to the availability of targeted therapies. Some of the frequent oncogenic drivers such as *EGFR* and *KRAS* mutations are mutually exclusive in untreated lung adenocarcinoma and occur in different populations. *EGFR* mutations are more frequent in non-smokers and in Asian patients, whereas *KRAS* mutations are more frequent in smokers (8,9). However, even though adenocarcinomas with oncogenic driver mutations or rearrangements share some common clinical or histopathological

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features, adenocarcinoma subtyping is not based on these mutations (1). This can be contrasted with what has been described for other primary locations such as tumors of the central nervous system where, despite a lesser therapeutic range, gliomas have been subtyped according to the rearrangements or mutations present (10). For gliomas, the notion of histomolecular classification is no longer debated, whereas for lung adenocarcinomas, the notion of histomolecular classification is discussed (11).

Among the main works allowing a histomolecular classification of lung adenocarcinomas, The Cancer Genome Atlas (TCGA) initiative is a major work (12). A work from TCGA looked at mutation profiles, structural rearrangements, copy number alterations, DNA methylation, mRNA, miRNA and protein expression of 230 lung adenocarcinomas (12). The authors proposed 6 subtypes by integrating histopathological data (12). Among the different molecular alterations, even though some mutations are recurrent, they are not used alone in current pathology for the classification of lung adenocarcinomas. Furthermore, several molecular classifications have been proposed with different systems but none of them has a clinical implication (13).

DNA methylation is an important factor among the epigenetic factors modifying the expression of certain genes. Indeed, methylation of a gene allows to modify its expression without modifying its sequence. For example, the methylation of a promoter usually leads to the repression of its expression. In brain tumor pathology, as well as in sarcomas, a classification system has been developed that allows to predict the histopathological type more precisely than the histopathological examination, based on the methylation profile (14,15). Moreover, in glioblastoma, *MGMT* promoter methylation is an important factor in predicting response to treatment.

In lung adenocarcinomas, gene methylation is not of major practical clinical interest to date. Nevertheless, Guidry *et al.* have identified several subgroups of lung adenocarcinomas with a distinct cell composition, a distinct DNA methylation age and these groups are correlated with clinical outcome (16). In the work of Guidry *et al.* the authors showed by studying the tumor microenvironment that immunologically warm tumors were richer in CD8 T cells and B cells and had lower levels of eosinophils (16). Nevertheless, overall survival was not correlated with immune phenotypes in this study (16). The composition of the microenvironment differed in patients with a history of smoking, where there was an increase in $CD8^+$ T cells, Tregs, B cells and neutrophils with low levels of NK cells, eosinophils and $CD4^+$ T cells (16). The composition of the microenvironment varied according to ethnic group, but due to the small number of patients in each subgroup it was not possible to draw definite conclusions regarding the subgroup (16).

Among the correlations between the microenvironment and driver mutations, the main differences in the work of Guidry *et al.* were shown in adenocarcinomas with *KRAS* or *TP53* mutations where $CD4^+$ T cells were decreased in case of either mutation (16).

DNA methylation allows an age calculation that correlates with biological age in humans. Using the Horvath clock approach to mDNA age, the authors showed a trend toward better survival in patients with mDNA ages greater than 75 years compared with younger patients (16). Interestingly, patients with *STK11*, *KEAP1*, and *ATM* mutations had a lower mDNA age (16). This if of interest because *STK11* and *KEAP1* mutations are correlated to poor response to immunotherapy (17). Patients with higher mDNA age had lower levels of Tregs and $CD19^+$ B lymphocytes. In addition, these patients had higher levels of $CD56^+$ NK cells, $CD4^+$ T cells and $CD14^+$ monocytes/macrophages (16). A work from our group found that lepidic, papillary components and *EGFR* mutations are frequent in patients with lung adenocarcinoma who are over 75 years old reinforcing the fact that lung adenocarcinomas might be different in older patients (9).

Guidry *et al.* used an unsupervised hierarchical clustering technique and individualized 6 molecular groups (16). Data from some of the subgroups are limited due to small numbers of patients, for example, subgroup 6 which includes only 5 tumors. However, data from some subgroups may be of interest for prognosis and therapy, with subgroup 1 with the highest mDNA age having no reported patient deaths and a trend toward better survival compared with groups 2 to 5 (16).

The data of Guidry *et al.* although limited because of the small number of patients, seems interesting to identify subgroups of patients with different prognosis that could benefit from personalized adjuvant therapy, beyond chemotherapy (16,18). Moreover, most patients with lung adenocarcinoma present at a metastatic stage. However, the tumor microenvironment seems to differ according to the metastatic site, and it is not certain that the data obtained on the primary site can be extrapolated to the metastatic sites (19).

In total, the data proposed by Guidry *et al.* could be of

clinical interest, it allows the identification of subgroups, although promising it could be interesting to verify the response to adjuvant therapies according to the proposed subtypes in an ancillary study (16). Molecular classification of lung adenocarcinoma remains an issue, but multiple approaches might be useful to identify specific subgroups in order to propose the most adequate treatment for patients.

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