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Adenocarcinoma classification: patterns and prognosis

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Key words

Lung • Adenocarcinoma • Classification • Pathology • Prognosis

Summary

Lung cancer is the most frequent human malignancy and the principal cause of cancer-related death worldwide. Adenocarcinoma is now the main histologic type, accounting for almost half of all the cases. The 2015 World Health Organization has adopted the classification recently developed by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society. This new adenocarcinoma classification has incorporated up-to-date advances in radiological, molecular and oncological knowledge, providing univocal diagnostic criteria and terminology. For resection specimens, new entities have been defined such as adenocarcinoma in situ and minimally invasive adenocarcinoma to designate adenocarcinomas, mostly nonmucinous and ≤ 3 cm in size, with either pure lepidic growth or predominant lepidic growth with ≤ 5 mm invasion, respectively. For invasive adenocarcinoma, the new classification has introduced histological subtyping according to the predominant pattern of growth of the neoplastic cells: lepidic (formerly non mucinous brochioloalveolar adenocarcinoma), acinar, papillary, micropapillary, and solid. Of note, micropapillary pattern is a brand new histologic subtype. In addition, four variants of invasive adenocarcinoma are recognized, namely invasive mucinous (formerly mucinous brochioloalveolar adenocarcinoma), colloid, fetal, and enteric. Importantly, three variants that were considered in the previous classification have been eliminated, specifically mucinous cystadenocarcinoma, signet ring cell, and clear cell adenocarcinoma. This review presents the changes introduced by the current histological classification of lung adenocarcinoma and its prognostic implications.

Introduction

The relative frequency of adenocarcinoma of the lung has been increasing steadily over the past few decades, as opposed to squamous cell carcinoma, most likely as a result of spreading of low nicotine-tar cigarettes [1]. Therefore, nowadays adenocarcinoma represents by far the most frequent histologic type of lung cancer, accounting for more than 40% of the total. It slightly predominates in male patients, but not infrequently occurs in women, also relatively young, and in individuals who have never smoked.

Over the last decade, the unprecedented advances in the understanding of lung adenocarcinoma, with regard to radiology, molecular biology, and medical oncology, made necessary a reconsideration of its classification in view of the new knowledge, which involved not only pathologists, but also radiologists, molecular biologists, clinicians, and surgeons. As a matter of fact, the latest WHO classification is the result of an integrated multidisciplinary approach.

Histological classification

Preinvasive lesions

Precursor lesions of invasive adenocarcinoma by current classification comprise two entities: atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS) (Fig. 1). Both lesions show a lepidic type of growth, which was previously named as "bronchioloalveolar", a term discontinued because of its ambiguity. This growth pattern is characterized by a proliferation of cuboidal to columnar cells with variably atypical nuclei and occasional intranuclear inclusions, growing alongside preexistent alveolar walls. Immunohistochemically, these lesions are always positive for CK7, napsin A, and

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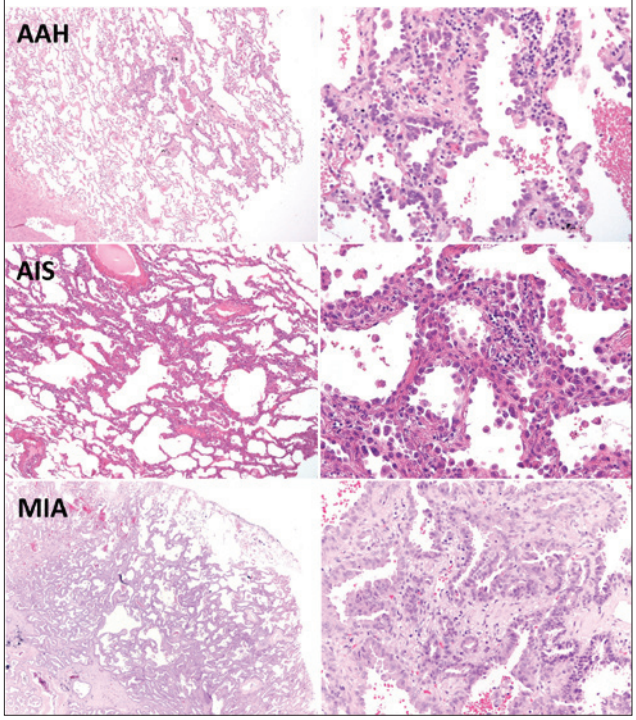
Fig. 1. Examples of precursor lesions of invasive adenocarcinoma of the lung.



TTF1, and show an extremely low proliferation index (below 5%). Notably, the diagnosis requires a surgical specimen with complete sampling of the lesion to exclude the presence of an overtly invasive component, hence they cannot be diagnosed on cytological or bioptic samples.

1. Atypical adenomatous hyperplasia

AAH is a centroacinar lesion of small dimensions (≤ 0.5 cm), constituted by a clonal proliferation of atypical polygonal cells, lining the alveolar walls and associated with mild septal thickening. The cells are cuboidal or low columnar, sometimes hobnailing, and show mild to moderate atypia. In general, the background lung does not show significant fibrosis or inflammation. Apart from AIS, the differential diagnosis includes entrapped alveoli, peribronchiolar metaplasia, and pneumocytic hyperplasia with reactive atypia [2].

AAH usually cannot be detected by radiological imaging, or correspond to small ground-glass opacities at high-resolution CT scan, therefore in most instances, they represent incidental findings in lung surgical samples resected for other diseases.

2. Adenocarcinoma in situ

AIS is a neoplastic lesion, > 0.5 cm and ≤ 3 cm in size, composed mostly of nonmucinous cells with an exclusively lepidic pattern of growth and without features of invasion (either stromal, vascular, pleural or STAS-see below). AIS often shows relatively abrupt outer margins, and its cells are columnar with overlapping nuclei and a more pronounced cytologic atypia if compared to AAH. AIS corresponds to the tumor previously designed as nonmucinous bronchioloalveolar carcinoma and is staged as pTis. A mucinous variant of AIS can also occur, but it is extremely rare. The latter shows subtle atypia, still basally located nuclei, intracytoplasmic mucin, and occasionally goblet cells.

The differential diagnosis includes AAH and minimally invasive adenocarcinoma (MIA), which are two ends of the same disease spectrum. It is likely that this distinction has a minimal clinical impact since these three entities have an excellent prognosis. In addition, the differential diagnosis includes also reactive cellular atypia due to inflammatory diseases. On CT scans these lesions appear as ground-glass opacities, sometimes difficult to distinguish from lung inflammatory changes.

Minimally invasive adenocarcinoma

MIA is a new tumor entity first included in the new WHO classification, defined as a solitary lesion ≤ 3 cm in size, with a predominant lepidic pattern and with foci of invasion ≤ 0.5 cm. When multiple foci stromal of invasion are present, only the size of the largest invasive area should be considered for classification.

The invasive component may have acinar, papillary, micropapillary, or solid architecture or consists of single cells dispersed in desmoplastic stroma. Vascular/pleural invasion and tumor necrosis rule out this diagnosis. Cytologically, MIA is almost invariably nonmucinous, with a cell morphology overlapping with AIS. Microinvasive areas can be found close to central scars. MIA according to the WHO classification is considered as pT1a(mi). The main differential diagnosis is with AIS. On CT scan, the lepidic component appears as a ground-glass opacity, whereas the microinvasive areas sometimes correspond to small solid areas.

Invasive adenocarcinoma

The latest classification has addressed the utmost heterogeneity of growth patterns of invasive adenocarcinoma of the lung with the introduction of the subtyping according to the predominant pattern. These patterns are often found in combination within the same tumor, therefore, lung adenocarcinoma is now classified based on the pattern most represented in cross-sectional area of histological sections (so-called predominant pattern), with reporting of the percentage of all the other identifiable patterns in 5% increments. It is our impression that a 5% increment may lead to a low agreement among pathologists, and a 10% increment evaluation may be more realistic. Nevertheless, this accurate histologic stratification is useful when dealing with multiple lung adenocarcinomas, because their morphologic comparison may help to differentiate multiple synchronous or metachronous primaries from intrapulmonary metastases [3], but more importantly it carries prognostic information, which will be discussed further on. Moreover, it is known that some morphologic features tend to be associated with specific molecular alterations, which

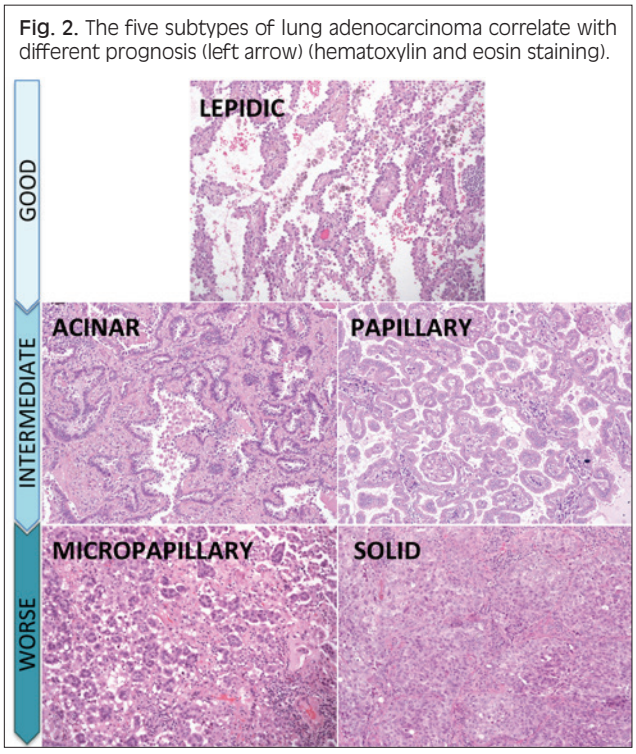


Fig. 2. The five subtypes of lung adenocarcinoma correlate with different prognosis (left arrow) (hematoxylin and eosin staining).

make cancer susceptible and eligible to specific targeted therapeutics. The degree of cytological atypia does not have impact on the classification. The **five subtypes** of lung adenocarcinoma based on the WHO classification are the following (Fig. 2):

1. **Lepidic predominant adenocarcinoma** is composed of nonmucinous adenocarcinoma cells, usually quite bland, which grow along the alveolar walls and contains an invasive focus greater than 0.5 cm, or is greater than 3 cm in size, or shows vessel/pleura infiltration. Usually, the invasive foci are easily identified at low magnification as irregular glands immersed in a desmoplastic stroma, papillae, micropapillae, or solid areas. Sometimes, recognizing invasive features can be challenging: useful clues are the shape of malignant glands, inconsistent with normal alveoli (too small, angulated, or branched), the increase of cytological atypia, and the presence of interstitial desmoplastic reaction. Importantly, in this subtype the histologic report should include the dimension of the largest focus of invasion and the percentage of the invasive component, as measured on histological section. In CT scan, adenocarcinomas with lepidic predominance show a prevalent ground-glass appearance with focal solid areas corresponding to the invasive component.
2. **Acinar predominant adenocarcinoma** is mainly composed of neoplastic glands arranged in acini. The glandular structures may have different configurations ranging from small tubules through angulated and branched cords, to more complex irregular glands. Cribriform areas are generally included in the spectrum of acinar adenocarcinoma, and lead to a worsening prognosis (see below). Cytoplasmic features may vary from vacuolated and clear to basophilic or eosinophilic, and sometimes the cell cytoplasm contains mucin. Occasionally, in autolytic samples the acini collapse or pseudopapillary structures take over, so that acinar pattern is difficult to recognize.
3. **Papillary predominant adenocarcinoma** is mostly composed of neoplastic cells lining fibrovascular cores of variable size and ramification [4]. Papillary structures occasionally show morules and/or psammoma bodies [5]. The neoplastic cells are cuboidal or columnar, with variable cytomorphological features from bland monomorphic cells, similar to papillary thyroid carcinoma, to highly pleomorphic cells, analogous to high-grade serous carcinoma of the female genital tract.
4. **Micropapillary predominant adenocarcinoma** is mostly composed of papillary tufts, lacking fibrovascular cores. Micropapillae may be folding on alveolar surface, floating within alveoli and sometimes infiltrating the stroma as small clusters reminiscent of invasive implants of serous borderline tumor of the ovary. Psammoma bodies are sometimes observed. The diagnosis of micropapillary subtype should be performed with caution in autolytic specimens, since adenocarcinoma cells tend to dissociate in an artifactual micropapillary-like fashion.
5. **Solid predominant adenocarcinoma** is mostly composed of solid nests, sometimes with a vaguely squamoid appearance. The cell cytoplasm may be clear, dark eosinophilic or basophilic and usually the nuclei are highly pleomorphic. Intracellular mucin should be present in at least 5% each of 2 high-power fields, and histochemical stains are helpful in confirming intracytoplasmic mucin droplets. Solid predominant pattern is the most common in lung adenocarcinomas. Differentiation from other solid growth carcinomas, like non-keratinizing squamous cell carcinoma or large cell neuroendocrine carcinoma, can be difficult on morphological base, therefore in these cases immunohistochemistry should be applied to support the diagnosis.

The latest WHO classification has also revised substantially the special forms of lung adenocarcinoma (Tab. I). Three entities have been eliminated, namely mucinous cystadenocarcinoma, signet ring cell, and clear cell adenocarcinoma. Currently, mucinous cystadenocarcinoma is included in colloid adenocarcinoma, the presence of signet ring cells should be indicated in an addendum, while clear cell adenocarcinomas are now classified according to their growth pattern without mentioning clear cell morphology. Moreover, two new entities have been introduced, the invasive mucinous and the enteric adenocarcinoma, therefore, besides the different growth patterns, the following **four variants** of adenocarcinoma are recognized (Fig. 3), and can be associated with other subtypes of lung adenocarcinoma.

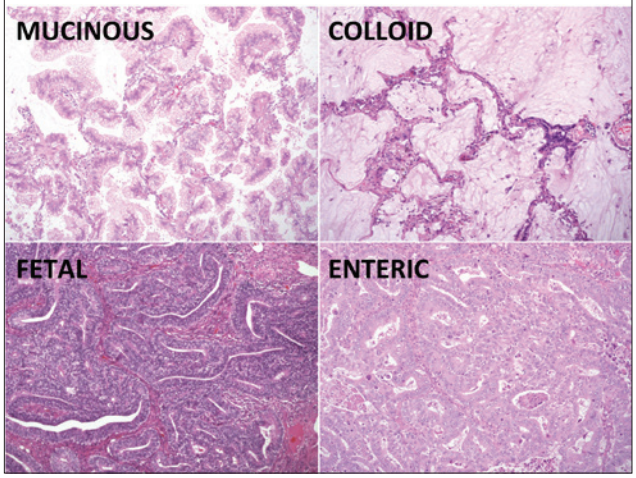
Tab. I. Comparison between 2015 WHO classification and 2004 WHO classification.

2015 WHO classification	2004 WHO classification
Preinvasive lesions	
Atypical adenomatous hyperplasia	Atypical adenomatous hyperplasia
Adenocarcinom *in situ*	Non mucinous bronchioloalveolar carcinoma
Invasive lung adenocarcinoma subtypes	
Minimally invasive adenocarcinoma	
Lepidic predominant	Mixed
Acinar predominant	Mostly mixed, some acinar
Papillary predominant	Mostly mixed, some papillary
Micropapillary predominant	Mostly mixed, some papillary
Solid predominant	Mostly mixed, some solid
Lung adenocarcinoma variants	
Invasive mucinous	Mucinous bronchioloalveolar carcinoma
Colloid	Mucinous ("colloid") Mucinous cystadenocarcinoma
Fetal	Fetal
Enteric	Mucinous adenocarcinoma
	Signet ring*
	Clear cell*

* Currently classified according to growth pattern with an addendum that indicates the presence of signet ring cell elements, but not clear cells.

1. **Invasive mucinous adenocarcinoma** corresponds mainly to those tumors formerly classified as mucinous bronchioloalveolar carcinomas. These tumors grow predominantly in lepidic pattern, sometimes with acinar, papillary or micropapillary invasive foci and intra-alveolar mucin. These tumors have indistinct margins and frequently involve lung multifocally, probably due to intrapulmonary spread by aerogenous dissemination. The neoplastic cells are columnar, with minimal cytological atypia and contain intracytoplasmic mucin, usually apical, which may give the appearance of goblet cells. By immunohistochemistry, these tumors typically coexpress CK7 and CK20, are positive in less than 30% of the cases for TTF1 and napsin A and are almost always negative for CDX2 [6 7]. Metastases from biliopancreatic tract can closely resemble primary invasive mucinous adenocarcinoma, and this differential diagnosis requires clinical correlation. Molecularly, this tumor constantly harbors somatic *KRAS* mutation. Clinically, invasive mucinous adenocarcinoma hardly metastasizes distantly or to lymph nodes and, radiologically, appears as a ground-glass or consolidative area. Peculiar pathological and molecular characteristics make these tumors a unique entity. However, emerging evidences suggest that a subgroup of acinar predominant adenocarcinomas composed of nonmucinous columnar cells may belong to this entity [8].
2. **Colloid adenocarcinoma** is characterized by the presence of large lakes of extracellular mucin filling and destroying the alveolar spaces. Neoplastic cells are generally few, with minimal nuclear atypia, floating in the mucus lakes or covering the fibrous septa [9]. By immunohistochemistry, colloid adenocarcinomas typically express CDX2, but also CK7, CK20, and TTF1. Radiologically, they appear as solitary and peripheral nodules, with low attenuation at contrast-enhanced CT scan.
3. **Fetal adenocarcinoma** is a rare tumor characteristically occurring in women in their fourth decade of life. It is composed of glands with glycogen-rich, clear cytoplasm, and subnuclear vacuoles, resembling fetal pseudoglandular lung or endometrial glands [10]. Squamoid morules with eosinophilic cytoplasm and optically clear nuclei are frequently observed, contributing to the resemblance with endometrioid adenocarcinoma. This variant is generally low-grade, but high-grade forms have been reported, which must have at least 50% of classical fetal morphology, by definition. Immunohistochemically, the neoplastic cells express TTF1 and

Fig. 3. Representative images of the four variants of lung adenocarcinoma (hematoxylin and eosin staining).



nuclear-catenin [11]. The aberrant localization of the latter protein is due to a somatic mutation in exon 3. The main differential diagnosis is with pulmonary blastoma, that characteristically shows a distinct sarcomatoid, primitive-blastomatous stroma.

4. **Enteric adenocarcinoma** is a newly introduced entity that includes those primary lung tumors having the same histological and immunohistochemical features as colorectal adenocarcinoma [11]. Therefore, they are composed by pseudostratified, columnar cells with hyperchromatic nuclei and basophilic cytoplasm, which form large glands, often with central dirty necrosis. By definition, they must express at least one marker of enteric differentiation, including CK20, CDX2, and MUC2, and enteric pattern must constitute at least 50% of the entire tumor. Pure enteric adenocarcinomas are quite rare, and to make this diagnosis it is necessary to clinically exclude a metastasis from colorectal adenocarcinoma to the lung.

Distinguishing among adenocarcinoma different patterns and subtypes usually is not particularly difficult, with an interpersonal agreement varying from good to moderate, depending on the studies [12 13]. The main problems arise in the differentiation of lepidic from acinar and papillary pattern [14], and of papillary from micropapillary pattern, especially in cases with a less than optimal tissue fixation.

Prognostication

Many clinical and pathological factors have been found to be associated with patient outcome. The clinical prognostic factors for lung adenocarcinoma patients include gender, age, smoking history and stage [15 16].

Several studies have revealed and confirmed the prognostic value of the recent classification [17-20]. As mentioned above, the precursor lesions AAH, AIS, and MIA have all an excellent prognosis, with about 100% survival rate. In fact, in lepidic lesions the main prognostic factor is the size of invasive component [21 22]. Coherently, adenocarcinomas with predominant lepidic pattern have a better prognosis than the other subtypes of invasive adenocarcinoma, with survival inversely correlated with the size of the invasive component [23 24]. Moreover, the smaller the solid component identified by CT scan, the better the prognosis [21].

The prognostic relevance of histologic subtypes is demonstrated in early stage disease, where lepidic subtype is associated with good prognosis, acinar and papillary subtypes show intermediate prognosis, whereas micropapillary and solid subtypes correlate with the worst prognosis [17-20]. Sica et al. proposed a grading system for lung adenocarcinomas based exclusively on histologic pattern, with grade 1 corresponding to lepidic growth, grade 2 to acinar and papillary, and grade 3 to solid and micropapillary [17]. The two prevalent grades were combined into a score, which proved to predict prognosis in a large series of lung adenocarcinomas. Kadota et al. [25] and von der Thusen et al. [26] proposed two different grading systems, both combining histologic pattern and mitotic count. The best grading system for lung adenocarcinoma has still to be determined.

It is worth noting that the adverse prognostic impact of micropapillary component seems to be independent to its extent [27]. On the other hand, when solid growth pattern is predominant, metastases to regional lymph nodes occur in > 75% of cases at the time of surgical resection. Furthermore, growing evidences suggest that cribriform arrangement, currently part of acinar subtype, correlates with a poorer prognosis [28 29]. However, the prognostic impact of histologic subtyping in advanced stage patients has to be clarified. Since some recent studies found that histologic subtyping correlates with recurrence risk after sublobar resection, it is plausible that in a near future adenocarcinoma subtype will impact treatment strategy.

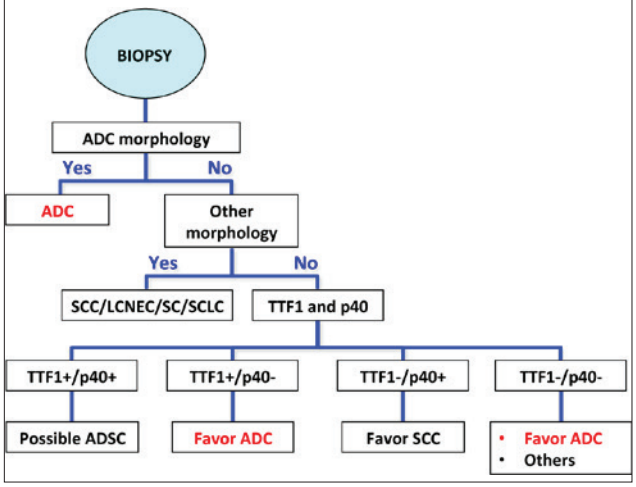
Beyond histological patterns, other morphological parameters have been found to possibly affect the clinical outcome. In particular, two recent studies have investigated the prognostic impact of the presence of spread through air spaces (also known as STAS) in patients with adenocarcinoma. STAS consists of tumor minute micropapillae, solid nests or single cells, spreading via airways outside the main tumor rim. STAS has been found to correlate significantly with micropapillary and solid patterns, high-stage, increased recurrence, worse disease-free and overall survival, suggesting that STAS is an adverse prognostic factor [30 31]. However, further studies are warranted in order to validate these findings.

Diagnosis of adenocarcinoma in small biopsies and cytology

The diagnosis of adenocarcinoma, particularly in small biopsies, requires either the classical histologic features of adenocarcinoma (lepidic, acinar, papillary or micropapillary patterns) or immunohistochemical confirmation by TTF1 (Fig. 4). As an alternative, also the demonstration of mucin production is contemplated, which is however rarely applied in routine practice. Obviously, diagnostic features of squamous cell carcinoma (unequivocal intercellular bridges and keratinization) are banned.

The current recommendation for the diagnosis of lung cancer on small biopsies or cytology samples is to precisely classify the histotype, while the subclassification of adenocarcinoma types is not standard practice and is not recommended. However, considering that only a minority of lung adenocarcinomas can be resected, and as such can be subtyped more precisely on surgical specimens, recent studies have explored the possibility of applying the new WHO classification on cytology samples. Despite some peculiar cytomorphological features have been shown to be more frequently associated with specific adenocarcinoma subtypes (papillary clusters with fibrovascular cores in papillary adenocarcinoma, acinar

Fig. 4. The diagnostic algorithm tree intended for small biopsies combines morphologic and immunohistochemical features. ADC morphology refers to lepidic, acinar, papillary or micropapillary growth patterns, thus the main problems arise with solid growth carcinomas. In these cases, the use of a minimal immunohistochemical panel that combines TTF1 and p40 (or p63, that is less specific) is advised. When TTF1 and p40 are coexpressed, usually highlighting different cell populations, a diagnosis of ADSC should be considered.
Abbreviations: ADC, adenocarcinoma; SCC, squamous cell carcinoma; LCNEC, large cell neuroendocrine carcinoma; SC, sarcomatoid carcinoma; SCLC, small cell lung carcinoma; ADSC, adenosquamous carcinoma.



structures in acinar adenocarcinoma), most studies have concluded that cytology cannot reliably subclassify adenocarcinoma [32-34]. The main problem has been the heterogeneity of morphological patterns observed in most adenocarcinomas [33]. However, in order to guide patient treatment decisions, defining reproducible cytomorphological parameters, in particular associated either with the most aggressive histotypes or, possibly, with predictive genetic alterations, remains a relevant unachieved goal.

Conclusion

The current histological classification takes into account all the recent progress made in understanding the radiological, molecular and biological features of lung adenocarcinoma and is corroborated by relevant prognostic value.

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