Update on histologic classification of non-small cell lung cancer

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Abstract

Given the recent advances in personalized medicine in lung cancer that are mostly observed in adenocarcinomas, an international multidisciplinary group of lung cancer specialists has recommended a new sub-classification of resected adenocarcinomas, and a histologic classification in small biopsies and cytologic material that constitutes the majority of specimens. Whereas the classification of adenocarcinomas has been shown to have better correlation with prognosis than the current WHO classification, it has brought many questions that need to be addressed. In order to further classify poorly-differentiated NSCLC while preserving tissue for molecular testing in small samples, a minimal 2-marker panel of immunohistochemistry (TTF-1 and 63/p40) has been recommended. In the current WHO classification, squamous cell carcinoma and large cell carcinoma categories include several variants, some of which are based solely on cytomorphologic features and do not appear to have biologic significance. Thus, a new, biology-based sub-classification is also warranted in those categories.

Keywords adenocarcinoma; biopsy; cytology; immunohistochemistry; lung; NSCLC

Introduction

The recent advance in personalized medicine has sifted a paradigm of non-small cell lung cancer (NSCLC) treatment. The personalized treatment is a concept that takes into consideration specific characteristics of a disease in order to offer the best-suited therapy and starts with the histological diagnosis in lung cancer. Non-small cell lung cancer (NSCLC) is a histologically heterogeneous group composed primarily of adenocarcinoma, squamous cell carcinoma, and large cell carcinomas. Of those, most of the advances in lung cancer target therapy occurred in adenocarcinoma. The shift to personalized therapy and triage for molecular tests has brought many new challenges. In particular, pathologists are now obliged to sub-classify NSCLC in small biopsy samples. In response to these challenges, a multidisciplinary group of lung cancer specialists including pathologists, radiologists, oncologists and surgeons have joined forces under the leadership of three professional societies, namely the International Association for the Study of Lung Cancer

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(IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS) to reevaluate the histological classification of lung cancer and integrate the classification with clinical and radiographic information.[1] These professionals have recommended major changes in the structure of the previous 2004 World Health Organization classification (WHO) in resected adenocarcinomas, but more importantly, have put forth recommendations for sub-classifying in small biopsies and cytologic material, which constitutes the majority of specimens for tissue diagnosis of lung cancer.

In this review, we will discuss the major changes and associated issues and questions in the adenocarcinoma classification and the classification in small specimens including the application of a minimal panel of immunomarkers. We will also touch upon issues associated with the current classifications of squamous cell carcinoma and large cell carcinoma.

Adenocarcinoma

The 2004 WHO classification hinted to the association of different patterns of adenocarcinoma with prognosis. The correlation between histological patterns and prognosis was further exploited and became the basis for the 2011 IASLC/ATS/ERS classification. The most important change occurred in the group of tumors previously known as bronchioloalveolar carcinoma (BAC). The 2011 IASLC/ATS/ERS classification recommends the discontinuation of the term BAC.[1] Instead, these tumors are now classified into three different categories: adenocarcinoma in situ (AIS), minimally-invasive adenocarcinoma (MIA) and lepidic predominant adenocarcinoma (LPA).

AIS is a tumor composed entirely of a lepidic growth pattern without parenchymal, lymphovascular or pleural invasion or necrosis. AIS is defined as a small adenocarcinoma measuring 3 cm or less in greatest dimension. These tumors have a pure ground glass opacity (GGO) depicted by CT scan. MIA is a tumor similar to AIS, that is composed predominantly of lepidic patterns, but it contains small amounts of invasive components, most often in the form of acinar and papillary patterns. By definition, the tumor is 3 cm or less in greatest dimension and the invasive component is 0.5 cm or smaller (Figure 1). MIA can present radiographically as pure GGOs or mixed GGO-solid components. Both AIS and MIA have excellent prognosis with no recurrence after 5 years following complete excision of the lesion.[1,2] The term MIA was coined after observation that even with a strict definition of AIS as a pure lepidic tumor, lepidic predominant adenocarcinomas with small foci of invasion had a similar prognosis as AIS. Most reports in the field used 0.5 cm as a cut-off for definition of the entity.[2,3]

MIA is a new entity and as such it brings many questions that still need to be addressed. For example: how to measure the invasive component, if more than one foci of invasion is seen? Should an interstitial scar, if present, be included in the measurement of invasion? These questions need careful consideration, but in a practical point of view, the availability of the category of MIA offers the pathologists some leeway in reporting these well-differentiated adenocarcinomas when there is doubt as to the diagnosis of AIS.

Another clinical question that has arisen is whether a lobectomy is necessary in patients diagnosed with AIS or MIA, since these tumors have a very low risk of recurrence. If a partial resection is to
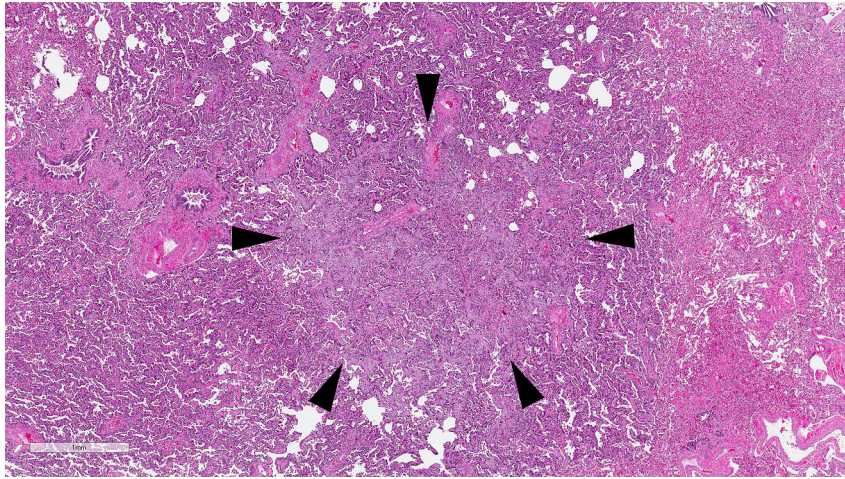
Figure 1 Minimally invasive adenocarcinoma (MIA) consisting predominantly of lepidic pattern with a small component of invasive adenocarcinoma that measures less than 0.5 cm. The invasive component can be seen as a slightly distinct area in the center of the image (arrows). Higher magnifications show the presence of acinar pattern adenocarcinoma (not shown).

be performed for these tumors, can they be diagnosed confidently in a frozen section slide? Hopefully, these questions will be answered in a near future. Yeh YC et al. has shown that intra-operative frozen section has low sensitivity and moderate inter-observer reproducibility for the diagnosis of AIS, but good specificity for high-grade patterns of adenocarcinoma.[4] When faced with a surgical excision of a lesion with GGO, information on the presence of high-grade patterns may be helpful for the surgeon to determine the extent of resection at the time of surgery.

All other patterns of adenocarcinomas should be considered invasive. The 2011 classification recommends that these tumors be classified by the predominant pattern. Several investigators have demonstrated that the predominant pattern of adenocarcinoma is associated with different risks of recurrence in Stage 1 adenocarcinomas.[2,5−7] A lepidic predominant adenocarcinoma (invasive component larger than 0.5 cm) has a good prognosis with a low risk of recurrence in 5 year follow-up. In contrast, acinar and papillary predominant tumors have an intermediate-risk of recurrence. Approximately 80% of acinar and papillary predominant tumors are recurrence free after 5 years following excision. Solid or micropapillary predominant adenocarcinomas are considered high-risk tumors with more than 30% chance of recurrence within 5 years after resection. Although this risk stratification classification was established in Stage 1 tumors, it has been shown that the pattern-associated prognostic impact is also relevant for higher stage tumors (Stage II and III).[6,7]

One of the most important criticisms of this proposed classification is reproducibility for determination of the predominant pattern. Recently an international group of pulmonary pathologists demonstrated that there is good agreement among specialists for the diagnosis of predominant pattern (kappa 0.7); however, the agreement rate fell sharply when non-traditional patterns were present.[8] Non-traditional patterns such as cribriform (Figure 2), fused glands (Figure 3), small infiltrative nests, and isolated tumors cells are not recognized by the WHO classification. When confronted with these variants most specialists place these patterns randomly into acinar or solid predominant categories, which pose a problem not only for reproducibility, but also for prognostic determination. Recently, several

publications have identified cribriform[9,10] and other variants[10] as high-grade patterns as demonstrated by the high recurrence risk. These tumors should not be placed into the acinar predominant tumors that carry an intermediate-risk prognosis.

Another important issue is the emphasis on the predominant pattern only, when it is well known that pulmonary adenocarcinomas are highly heterogeneous. If patterns are associated with prognosis, what would be the best way to classify heterogeneous tumors that have minor components of high-risk patterns? Recent publications have shown that the presence of a small amount of micropapillary pattern in an otherwise lepidic predominant adenocarcinoma is associated with a higher recurrence rate.[11] In addition, whereas the proposed classification appears intrinsically associated with tumor grading, there are no clear guidelines for grading of adenocarcinomas as of today. Whether the tumors should be graded by the predominant pattern or a combination of the predominant plus a secondary or the most poorly-differentiated component is still open to debate.[5] These questions will certainly need to be addressed in order to come up with a better prognosis based classification.

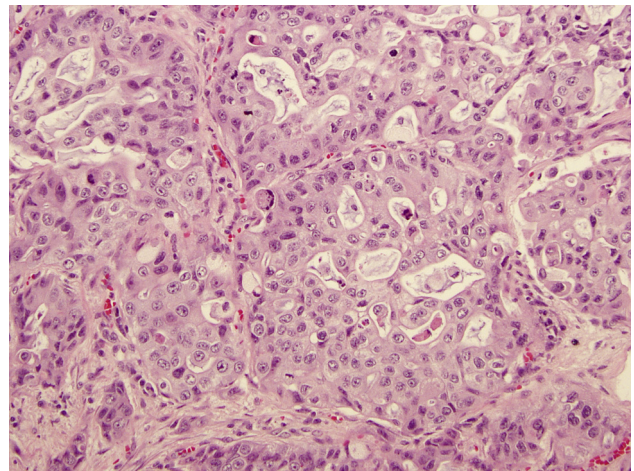**Figure 2** Cribriform pattern of adenocarcinoma. This pattern is characterized by the presence of back-to-back glands in a nested appearance.

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