Review Article

Surgical pathology of early stage non-small cell lung carcinoma

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Abstract: The histologic classification of non-small cell lung carcinoma (NSCLC), particularly adenocarcinoma (ADC), has undergone extensive study in recent decades, ultimately resulting in an extensively updated classification system. The 2015 World Health Organization (WHO) classification of ADC provides greatly improved prognostic information in comparison to the 2004 WHO classification. Several issues still require further investigation: lepidic predominant ADC, prognostic significance of poor prognostic subtypes such as micropapillary carcinoma, the more recently described concept of spread of tumor through airspaces (STAS), and the utility of sublobar resections. While limited resection appears to be suitable for tumors with a ground glass radiographic appearance, which typically correspond to adenocarcinoma in situ (MIS) or minimally invasive adenocarcinoma (MIA) histologically, the role of sublobar resection in radiographic solid tumors is not as clear, and the impact of histologic subtypes with a poor prognosis needs further evaluation. Squamous cell carcinoma (SCC) has not been as extensively studied and the current classification lacks subclassification with significant prognostic information.

Keywords: Adenocarcinoma (ADC); lepidic; micropapillary; spread of tumor through airspaces (STAS); squamous cell carcinoma (SCC); solid

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Introduction

Non-small cell lung carcinomas (NSCLCs) have historically included adenocarcinoma (ADC), squamous cell carcinoma (SCC) and large cell carcinoma, the last being increasingly rare with improved ancillary techniques (1). Advances in chemotherapy and molecular targeted therapy, in particular, have made accurate subclassification essential for treatment. ADC is currently the most common histologic subtype of NSCLC and following the 1995 landmark study by Noguchi, *et al.* (2), much focus has been directed toward subtyping of ADCs in regard to prognostic significance, ultimately culminating in a comprehensive update of the histologic classification of ADC in 2011, which has subsequently been incorporated into the 2015 World Health Organization (WHO) classification of lung tumors (1). This classification scheme is based almost exclusively on studies of small ADCs less than three centimeters (2-6). As such, while the prognostic significance of the classification in larger tumors has not been well validated, its value has otherwise been supported in several studies focusing on smaller tumors (7). As with any classification system, additional issues potentially impacting prediction of tumor behavior and prognosis have arisen and need to be addressed. Additionally, the evolution of lung cancer screening programs with increased detection of small tumors, combined with an ongoing debate regarding the efficacy of sublobar resections for small tumors, increases the need for reliable prognostic markers for non-small cell carcinomas.

This paper will focus primarily on ADCs. The updated classification will be reviewed with focus on prognostic subgroups, followed by evolving issues regarding particular patterns of adenocarcinoma with poor prognostic implications, namely micropapillary and solid patterns as

well as the recently described concept of "spread of tumor through alveolar spaces" (STAS). Discussion of ADC will be limited to focus on the most commonly encountered subtypes presenting as discrete tumors in patients with early stage disease. Tumors which are either very rare (i.e., fetal ADC) or more typically present as non-discrete pneumonic spread (invasive mucinous ADC, colloid ADC) will not be discussed. Literature focusing on prognostic features in SCC is much more limited at this time but will be addressed briefly. Finally, the implications of histology in regard to the issue of sublobar resections will be addressed.

Squamous cell carcinoma

Unlike ADC, SCC does not currently have a classification system that permits prognostic significance of predominant histologic subtypes. The absence, presence, and degree of keratinization have traditionally defined the grading. In the current updated classification scheme, histologic subtypes have been divided into "keratinizing" and "non-keratinizing" subtypes but they are not associated with prognostic or clinical significance. Kadota *et al*. However, attempted to look at single cell invasion and tumor budding to assess possible favorable/unfavorable prognostic indicators of death and recurrence in patients with SCC. The prognostic significance of histology, as well as the parameters mentioned above, requires additional study and validation before patients with SCC can be stratified into prognostic and therapy groups (1,8).

Adenocarcinoma

Over the past decades, it has been recognized that ADCs comprise a heterogeneous groups of tumors with different behaviors. Prognosis and survival are influenced by various factors including histologic subtype, size of tumors, type of surgical resection, and molecular profile (1). The clinical heterogeneity of lung ADC has made pathologic classification challenging. In 1995, Noguchi *et al*. (2) recognized that tumors with pure lepidic growth had a 100% 5-year survival and this definition was subsequently used in the 1999 WHO as the definition for what was then termed bronchioloalveolar carcinoma (BAC) and was retained in the 2004 WHO classification (2,9). At that time, however, the majority of ADCs fell into the so-called "mixed subtype" of ADC, a category which provided little if any prognostic information to the clinician (9-11).

In attempt to address the need for a prognostically relevant classification, a multidisciplinary classification was published jointly by the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the International Association for the study of Lung Cancer (IASLC) in 2011, which was also adopted into the recently published 2015 WHO classification (1,9) (*Table 1*). In this classification, tumors with pure lepidic growth were reclassified as adenocarcinoma in situ (AIS) and the term BAC was eliminated. A new category of minimally invasive adenocarcinoma (MIA) was also introduced based upon data supporting that tumors with lepidic growth and an invasive component less than or equal to 5 mm have the same prognosis as those with pure lepidic growth. The mixed category was replaced with the recommendation that ADC be classified based on the predominant histologic subtype (lepidic, papillary, acinar, solid or micropapillary) (*Figures 1-5*), with a further recommendation that each component be recorded in 5% increments (1). The new categories of AIS and MIA have been proposed as Tis and T1a (mi) for the upcoming eighth edition of the TNM classification of lung carcinoma (12).

This new classification system stratifies tumors into morphological subgroups that have biologic relevance and may impact clinical decision-making. The prognostic significance of the histological classification system proposed by the IASLC has been validated by numerous studies and correlated with patient outcomes (3,7). While patients with AIS and MIA are reported to have 100% five-year disease free survival (DFS), the various histologic subtypes are associated with significant differences in DFS and overall survival (OS) (13-23). Overall, among the five invasive ADC subtypes comprised of lepidic, acinar, papillary, micropapillary, and solid predominant patterns, the lepidic predominant group had the best prognosis, papillary and acinar predominant intermediate prognosis, and solid and micropapillary predominant exhibited the poorest. Yoshizawa's categorization by comprehensive histologic subtyping defined three overall prognostic groups by 5-year DFS. DFS for the low grade group, AIS and MIA, was 100%, intermediate grade comprised of non-mucinous lepidic predominant, papillary predominant, and acinar predominant achieved 90%, 83%, and 84% DFS, respectively, and finally, the high-grade histologic variants, including micropapillary predominant and solid predominant attained 67% and 70% DFS, respectively. Overall, there were significant differences in DFS among the low, intermediate, and high prognostic groups: 100%, 84% and 71%. Studies evaluating solid and micropapillary

Table 1 2015 World Health Organization classification of adenocarcinomas

Pre-invasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma in situ
Non-mucinous
Mucinous (rare)
Adenocarcinoma
Minimally invasive adenocarcinoma
Non-mucinous
Mucinous (rare)
Lepidic predominant adenocarcinoma
Acinar predominant adenocarcinoma
Papillary predominant adenocarcinoma
Micropapillary predominant adenocarcinoma
Solid predominant adenocarcinoma
Invasive mucinous adenocarcinoma
Mixed invasive mucinous and non-mucinous adenocarcinoma
Colloid adenocarcinoma
Fetal adenocarcinoma
Enteric adenocarcinoma

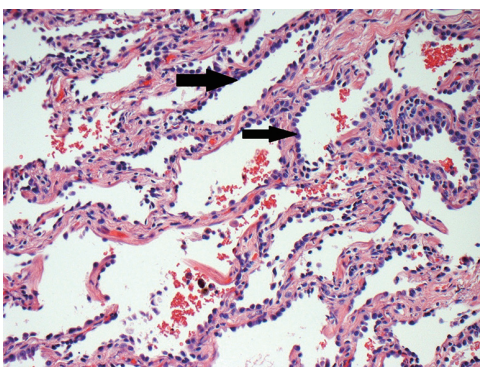

Figure 1 Lepidic pattern of adenocarcinoma. Lepidic growth refers to growth of tumor cells along alveolar septa without invasion of destruction of lung architecture (arrows). This pattern may occur as a component of virtually any lung adenocarcinoma, but when this pattern comprises 100% of a resected tumor the term adenocarcinoma in situ is used. Hematoxylin and Eosin 400×.

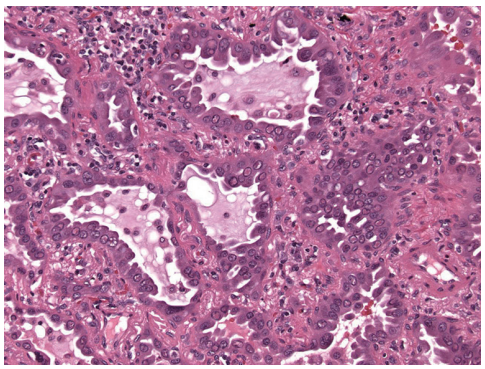

Figure 2 Acinar pattern of adenocarcinoma. Acinar growth is characterized by invasive tumor with well-formed glandular structures set in a fibrous stroma. Hematoxylin and Eosin 400×.

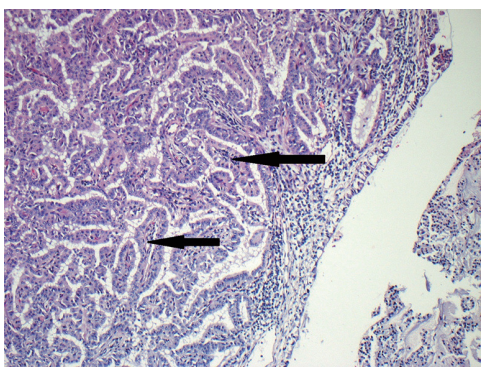

Figure 3 Papillary pattern of adenocarcinoma. Papillary adenocarcinoma is characterized by malignant cells covering fibrovascular cores (arrows). Hematoxylin and Eosin 200×.

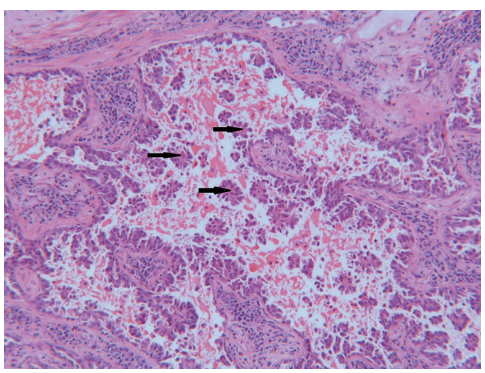

Figure 4 Micropapillary pattern of adenocarcinoma. Micropapillary adenocarcinoma is characterized by tufts of tumor cells surrounding a sclerotic center but lacking a fibrovascular core (arrows).The micropapillary tufts are frequently found within glandular spaces, as in this example, or may be seen within alveolar spaces or within retraction spaces in a fibrotic stroma. Hematoxylin and Eosin 200×.

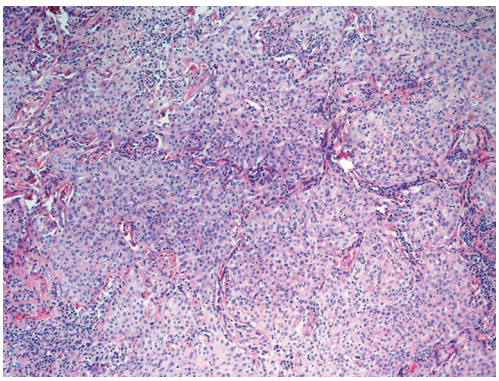

Figure 5 Solid pattern of adenocarcinoma. Solid adenocarcinoma essentially lacks overt features of differentiation by light microscopy and generally requires evidence of differentiation by mucin stains or immunohistochemistry such as TTF-1 to properly classify. Hematoxylin and Eosin 400×.

predominant tumors have demonstrated 5-year survival rates of 30–40% (13-18,20,24).

Molecular implications

Studies are ongoing to assess potential correlations between the updated classification system and the presence of certain targetable driver mutations, particularly EGFR and ALK. While there is a tendency for EFGR mutations to occur more frequently in lepidic, papillary, and micropapillary carcinomas, the latter particularly in Asian populations, EGFR mutations may be encountered in any of the histologic subtypes. Similarly, ALK rearrangements have been most commonly associated with the solid subtype, particularly if there is an associated signet ring component, but gene rearrangements have been reported in all subtypes (25-29).

Issues with current histologic classification system

While the updated ADC classification has shown correlation with outcome, as with any classification scheme, some issues require further clarification and investigation. As stated, the current recommendation is to classify ADC by the predominant subtype. However, this concept may not always be clear-cut. For example, in the "lepidic predominant" ADC, the lepidic component may be the predominant pattern present, but actually comprise less than 50% of the total tumor volume. In such cases, the predominant pattern present may be lepidic, but the majority of the tumor consists of various patterns of invasive carcinoma. At least one study has shown that tumors with greater than 50% lepidic growth and those with 10–50% have a 0% and 12% incidence of recurrence, respectively (30).

The percentage of micropapillary pattern needed to impact prognosis is also problematic in regard to behavior and prognosis. The inclusion of the micropapillary subtype was a significant addition to the updated classification. Histologically, this group consists of tumor cells that grow in papillary tufts lacking fibrovascular cores, in contrast to true papillary structures which contain fibrovascular cores. Numerous studies have highlighted the poor prognosis of this histologic pattern in lung carcinoma (13,14,22,31-36). As stated previously, studies have shown that solid and micropapillary predominant tumors have the worst prognosis among the histologic subtypes. Additional evidence suggests that the micropapillary pattern may in and of itself be a robust predictor of both prognosis and survival (14,20) and associated with poor outcomes (21,37). Furthermore, it has recently been suggested that the presence or absence of the micropapillary pattern may be an important prognostic indicator and impact survival (32-34). Rather than use the 5% increment as suggested by the IASLC classification, studies demonstrated that a micropapillary pattern of >1% of the tumor, resulted in metastasis and worse prognosis when compared to patients with no evidence of this histologic subtype (31). In addition, a micropapillary component of greater than 5% is associated with increased recurrence if treated by limited resection rather than lobectomy (22). Furthermore, this histologic subtype has been associated with a higher incidence of locoregional recurrence (38) and lymphovascular invasion (35,36).

A somewhat related issue is the recently described concept of tumor spread through air spaces (STAS). This pattern is defined as tumor cells spreading within air spaces in the lung parenchyma beyond the edge of the main tumor, in micropapillary structures without a central fibrovascular core, or in solid nests or tumor islands (*Figure 6*). While published literature is limited and further investigation is needed to clarify several issues, this pattern has been associated with poor outcomes and lymphatic invasion. The authors also raise the possibility that in patients with small percentages of micropapillary tumor (5%) who do poorly may progress because of "micropapillary STAS". Of potential treatment significance, patients with STAS had a poorer prognosis only when they underwent limited resection, but not in those who underwent lobectomy,

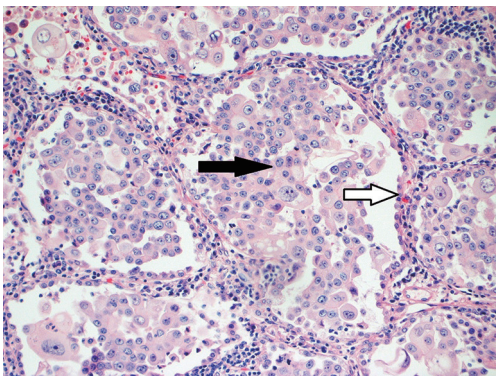

Figure 6 Spread of tumor through airspaces (STAS). STAS is characterized by tumor cells spreading through alveolar spaces away from the main body of the tumor. In this example of the solid variant of STAS, tumor cells are present in airspaces (black arrow) while the surrounding alveolar walls are free of tumor (white arrow). Hematoxylin and Eosin 400×.

suggesting a role for lobectomy even in small lesions (39).

Solid predominant histological component has been associated with high grade clinical behavior. A 70% 5-year DFS has been associated with this aggressive subtype (13,40). Furthermore, it has been shown to be a predictor of early recurrence and poor post-recurrence survival. Patients with this histological subtype had the highest risk of recurrence and earlier recurrence than for intermediate and low-risk histologies with greater extra-thoracic and multisite spread. When compared to low and intermediate histological subtype groups, OS was significantly worse in solid predominant tumors. Furthermore, as these tumors tend to be EGFR negative and KRAS positive, they are not amenable to molecular targeting. For this cohort of patients, adjuvant therapeutic strategies require investigation (41).

Treatment implications of the new classification system

The histologic issues above are some of many which need to be addressed in the evolving evaluation of the efficacy of sublobar resection which once again has come to the forefront with the advent of CT testing and the increasing detection of small lesions radiographically. The standard of care for early stage lung ADC is lobectomy, but segmentectomies and wedge resections are now more common alternatives, particularly for small (<2 cm) lesions (42). Radiologic evidence has shown the wedge/segmentectomy may be appropriate for small tumors with a ground glass or predominantly ground glass appearance (43,44). These tumors for the most part correspond to AIS and MIA (38). While pure ground glass tumors have a 100% DFS survival after limited resection there are instances, albeit rare, where recurrences have occurred at the resection margin (44).

Studies to evaluate whether limited resection is appropriate for small tumors of mixed ground glass and solid subtypes are ongoing, as consistent conclusive evidence supporting limited resection for invasive tumors is still lacking. The issue of histologic subtype needs to be taken into consideration for these tumors in particular. Given the data demonstrating poor outcomes with aggressive histologic subtypes in small lesions, particularly with micropapillary histology, and studies demonstrating recurrence in patients with small lesions, sublobar resections (22) may need more careful consideration, particularly with small solid or subsolid radiographic lesions for which a micropapillary component may not be excluded. Further evaluation of the impact of micropapillary growth and STAS in sublobar resections is needed. Additionally, better information in regard to confounding variables such as margin distance (which can be difficult to evaluate grossly in both of these patterns) is needed.

Given that the presence of certain ADC subtypes may potentially impact the choice of surgical resection, the accuracy of identifying histologic patterns of ADC at the time of frozen section has received recent attention. Trejo Bittar *et al*., recently evaluated 112 consecutive surgically resected stage 1 lung ADCs in order to determine diagnostic accuracy and interobserver variability in histologic subtyping of lung ADCs at the time of frozen section (45). In this study, primary and secondary histologic patterns were assigned in each case by three pathologists independently, with comparison between interpretation of frozen section and permanent section results. In this study, kappa values ranged from 0.48–0.58 for the primary histologic pattern. Particular attention was also paid to the identification of a micropapillary pattern, which was recognized with a 98% specificity rate when identified but was recognized with only a 13% sensitivity rate. Similarly, Yeh *et al*., evaluated 361 resected stage 1 ADCs in regard to accuracy of pattern identification, and additionally attempted to evaluate the accuracy of the presence of invasion at the time of frozen section in 35 cases (46). Similar to the Trejo Bittar study, agreement on the predominant histologic subtype achieved only a moderate a kappa value of 0.565 and again showed high specificity but low sensitivity for the identification

of a micropapillary component. In regard to evaluation of degree of invasion, the kappa value was only 0.378. Sampling issues and quality of frozen section slides were cited as the most common reasons for discrepancy. These results suggest that identification of ADC subtype by frozen section is not sufficiently reliable to serve as the sole basis for choice of surgical resection.

In regard to other treatment modalities, although adjuvant therapy is not typically used in the case of resectable low stage disease, given the varied diagnostic and prognostic outcomes for patients with different histologic subtypes, the new IASLC/ATS/ERS classification may provide a rationale for stratifying adjuvant chemotherapeutic treatment options among these different subgroups of patients. Brambilla *et al*. have shown that patients with micropapillary and solid histologic subtypes, both associated with poor DFS, obtained significant benefit from treatment with adjuvant chemotherapy when compared to less aggressive histologic subtypes (47).

Conclusions

In summary, the updated 2015 WHO classification of ADCs is a much improved classification in comparison to the 2004 WHO classification in regard to provided information regarding tumor prognosis. Several issues require further study, particularly micropapillary carcinoma and the related concept of STAS, in regard both to prognosis and the potential impact on choice of resection. SCC has been studied much less extensively than ADC and further evaluation of this tumor subtype is needed in regard to both prognosis and treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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