Review Article

Validation of the new IASLC/ATS/ERS lung adenocarcinoma classification: a surgeon's perspective

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Abstract: The conclusions from the new IASLC/ATS/ERS lung adenocarcinoma classification portend important clinical consequences. The interpretation of the histological, biomolecular and radiological correlates of this classification not only allows for the definitive abandonment of the bronchoalveolar carcinoma definition but provides surgeons with significant clues to better understand the adenocarcinoma subsets and their surgical management. Indeed, the information will benefit surgeons who are fully involved in the lung cancer CT screening programs as well as in the diagnostic and therapeutic pathways of both early and locally advanced lung cancer. Moreover, intriguing perspectives are disclosing on the inclusion of the surgical modality among the ones used in the oligometastatic disease status. On the other hand, the new adenocarcinoma classification also emphasizes the need for surgeons working in a multidisciplinary environment to be thoroughly cognizant of the ever evolving lung cancer biomolecular knowledge and, in particular, of the potentially druggable somatic mutations in line with the modern professional profile of the so-called "surgeon scientist".

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The recently introduced new classification of lung adenocarcinoma has a relevance which goes beyond the features of an updated histological perspective on a lung cancer histotype (1). The primum movens of this new classification was to overcome the concept of bronchoalveolar carcinoma which had been known to portend a better prognostic outlook compared to other types of adenocarcinomas (1). At the same time, the resurgence of interest for radiologically detected lesions characterized by ground glass appearance and a non predominant solid component has raised the question about how to best manage these lesions (1). Screening programs will contribute to earlier detection of lung cancer and possible identification of GGOs which would have otherwise gone undetected or be mistakenly diagnosed as of inflammatory origin (2). Finally, the tumor genomic era has brought about the so called "oncogenic addiction", i.e., the focus on genetic mutations as the main driver of phenotypic changes of lung tumors. In this setting, the relevance of biomarkers as predictors of response to treatment has become a guiding principle in current clinical research on adenocarcinoma.

The adenocarcinoma histological revolution—beyond "bronchoalveolar" the conclusions from the new IASLC/ATS/ERS lung adenocarcinoma classification (1)

(I) The recognition of the existence of a histological counterpart for squamous dysplasia and squamous carcinoma in situ is the first significant result of this intriguing perspective revolution. Indeed, atypical adenomatous hyperplasia (AAH) is considered a preinvasive lesion often found concomitant with

invasive adenocarcinomas in resected lungs with which AAH shares genetic and epigenetic alterations. AAH is defined as the proliferation of atypical type II pneumocytes and/or Clara cells along the alveolar or bronchiolar walls. Often following a recognized continuum with AAH, adenocarcinoma *in situ* (AIS) is characterized by non-mucinous growth of neoplastic cells in the alveoli (lepidic growth) without signs of invasion of surrounding structures. These small (less than 3 cm) tumors were previously classified as bronchoalveolar carcinomas (BAC) and are associated with superb (i.e., 100%) prognosis after surgical resection;

(II) The recognition of the existence of an intermediate subtype between preinvasive and invasive adenocarcinomatous growths represents another relevant feature of the new classification. Minimally invasive adenocarcinoma (MIA) is a small (less than 3 cm), non necrotic, and solitary tumor characterized by lepidic pattern predominance and non mucinous growth. Typically, resection of MIA is associated to 100% disease specific survival;

(III) The recognition of the existence of non-mucinous lesions with the characteristics of AIS or MIA but measuring more than 3 cm in diameter are defined as "lepidic predominant adenocarcinoma (LPA) suspect for AIS or MIA". Invasive, non mucinous adenocarcinomas are characterized by heterogenous subtypes in addition to the lepidic pattern and by the presence of tumor cells in the myofibroblastic stroma. Moreover, if the tumor infiltrates blood vessels or the pleura or again if it is partially necrotic, the adenocarcinoma is defined as LPA. Complete resection of these lesions carries a 90% 5-year survival.

The recognition that invasive mucinous adenocarcinomas are usually multiple, bilateral and tend to involve more than one lobe suggests aerogenous spread. The same predominance observed in non mucinous invasive adenocarcinomas (with lepidic, acinary, papillary, micropapillary and solid patterns) can be found also in this subset (3). Histologically, they are characterized by proliferation of mucin producing goblet or columnar cells. In this setting, other variants of invasive adenocarcinomas are colloid, fetal or enteric adenocarcinomas.

Clinicopathological correlation (1)

The new histopathological subtypes of adenocarcinoma are characterized by distinct clinical features which may assist physicians in the diagnosis and treatment of this tumor (1). As an example, the presence of a solid component may correspond to an invasive behavior.

Single or multiple AAH, AIS and MIA usually measure less than 2 cm in diameter with AAH typically being 5 mm or less. Ground glass appearance is a characteristic feature of AAH and AIS albeit the degree of attenuation of a pure non solid nodule may be higher in the latter. Conversely, MIA usually presents as a partly solid nodule with a predominance of ground glass appearance. As in AIS, the mucinous component is associated to an increasingly solid component of the nodule.

Invasive non mucinous, adenocarcinoma is characterized by lesions measuring in excess of 2 cm and size is related to the potential for metastatic spread (especially to the CNS). Histological heterogeneity is a typical feature of this subset of adenocarcinomas. The different subgroups are classified according to the predominant pattern (lepidic predominant, acinary, papillary, micropapillary, solid). Invasiveness is recognized by the presence of patterns other than lepidic and myofibroblastic stroma associated with invasive neoplastic cells.

Histological and biomolecular correlates

The morphologic (i.e., architectural) differentiation patterns of adenocarcinoma described above, in other words, grading, are indeed related to prognosis. As an example, solid or micropapillary architecture is associated to poor prognosis whereas nonmucinous lepidic portends a favorable outlook (3). Conversely, papillary and acinary morphologies are related to an intermediate prognosis. Next generation sequencing has identified several somatic mutations that are potentially druggable and often mutually exclusive. As an example, EGFR mutations (i.e., exons 19 and 21) were first found to predict response to tyrosine kinase inhibitors (TKI), such as erlotinib and gefitinib, in East Asians patients of female gender and with little or no smoking history (1). To date, eight randomized clinical trials have demonstrated that first line treatment with TKIs in advanced NSCLC patients harboring activating EGFR mutations is associated with significant improvement in response rate, progression-free survival, quality of life and tolerability, compared to platinum-based chemotherapy (4). Several phase III trials have demonstrated the following: (I) improvement of progression-free survival in patients with EGFR mutations subjected to TKI therapy compared to conventional platinum-based chemotherapy; (II) adverse

outcome in adenocarcinoma patients without mutations treated with gefitinib; (III) gefitinib is associated with both prolonged progression free survival and higher response rate than docetaxel in EGFR mutated patients; (IV) EGFR copy number and not mutation is related to better response to erlotinib than gefitinib for advanced adenocarcinoma (1,5). These results established EGFR TKIs as the current standard first line treatment of patients with advanced NSCLC harbouring activating EGFR mutations.

Radiological correlates (1)

The classification of the equivalent radiological patterns of adenocarcinoma histotypes includes pure GGNs, solid and semi-solid nodules (1,6). Although some degree of variability exists among subsets, AAH is typically associated with single or multiple pure GGNs (1). These lesions are usually less than 5 mm in size whereas non-mucinous AIS are usually less than 2 cm in size and also present as pure GGN, albeit both solid and semi-solid nodular patterns can be observed (1). Conversely, mucinous AIS is usually associated with a solid pattern (1). The variability of radiological pattern is a typical feature of MIAs most of which measure less than 2 cm (1).

Validation of the new IASLC/ATS/ERS lung adenocarcinoma classification

Since the publication of the new adenocarcinoma classification, several retrospective institutional reports have attempted to validate the new classification system. As an example, Yanagawa and colleagues reviewed 191 patients with resected adenocarcinomas subjected to lobectomy in 91% (7). Interestingly, 59% of the patients from Japan were never smokers or women (58%) with a median age of 67 years (7). In this series, the authors found AIS in 5.8% and MIA in 8.9% of the patients. Lepidic, papillary, acinary and solid predominance were seen in 26.7%, 27.2%, 20.9%, and, 10.5%, respectively (7). The lepidic predominance was detected with maximal frequency in AIS and MIA whereas was completely absent in the solid subset. The associated 5-year progression free survival rates were 100% for AIS and MIA and in excess of 85% for the other growth patterns except solid predominance (54%) (7). On multivariate analysis, invasive tumor size (HR =2.04) and solid subset (HR =4.08) were significantly associated with progression-free survival (7). The frequent, albeit not exclusive, association between lepidic component and EGFR mutation was confirmed in a series of resected specimens (8). In this setting, the prognostic relevance of EGFR and KRAS mutations with the latter significantly found in mucinous subsets was reported in a series of 440 resected Japanese patients (9) for whom genetic mutations were used to direct adjuvant therapies. A striking difference in 5-year survival between micropapillary subset (0%) and the other histotypes was observed, with the best survival confirmed for AIS and MIA as well as growths with predominant lepidic components (9). An interesting prognostic stratification was proposed by Yoshizawa who identified low (i.e., AIS and MIA), intermediate (i.e., non-mucinous lepidic, papillary, and, acinar), and, high-grade (i.e., invasive mucinous, solid, colloid, and micropapillary) subsets in 541 patients with resected stage I adenocarcinomas (9). Conversely, in a recent series from Melbourne, 69 patients with resected N2 disease were analyzed for frequency of EGFR and KRAS mutations (10). While the former (EGFR) were more significantly detected in association with the acinar and micropapillary subsets, the latter (KRAS) were seen more frequently in the solid component (10). In this series, the acinar subset had a better prognosis compared to the non acinar ones [HR =0.45 (10)].

The validation of the new IASLC/ATS/ERS lung adenocarcinoma classification carries remarkable clinical implications. As an example, the ideal surgical management of stage I adenocarcinoma subsets like AIS and MIA is being reconsidered (11). In fact, given the low incidence of N+ disease with these subsets, sublobar resections can entail the same prognostic outlook as lobectomy for AIS and MIA in terms of overall and disease free survival rates (11). Indeed, when, on frozen section, wedge resection yields AIS or MIA, a decision to proceed to segmentectomy or lobectomy may be also justified. In fact, the reported 1% recurrence rate compares favorably with the literature and supports the resort to segmentectomy (11), even though the final word will presumably derive from randomized trials like the currently recruiting North American Cancer and Leukemia Group B 140503 (ClinicalTrials.gov #00499330) and the Japanese JCOG0802/WJOG4607L (11). Another controversial issue relates to the comparison between wedge and segmentectomy for AIS and MIA. Given the impossibility of obtaining a definitive preoperative diagnosis of AIS and MIA (1), a prospective, randomized trial does not seem a viable option to resolve this dilemma. One important clinical aspect remains the interpretation of CT scan to tailor the best surgical approach for patients with stage I AIS or MIA. In particular, Brambilla and

Travis have emphasized the need to measure the solid or invasive component of GGOs as the major predictor of postoperative recurrence and survival instead of calculating the diameter on the entire lesion inclusive of the ground glass component (12). Sakurai and colleagues reported on the survival stratification according the different subsets of adenocarcinoma from the data of 7,921 resected patients registered in the Japanese Joint Committee of Lung Cancer Registry (13). This significant series confirmed the remarkable separation in 5-year survival rates among tumors with solid predominance (54%), an intermediate group including the acinar, papillary and mixed subsets (63%, 73%, and,74%, respectively) and the formerly defined BAC (90%) (13). Of all the BAC tumors, 8% were stages II to IV; according to the authors, this finding explained the relatively high 9% recurrence rate after resection of BAC in this series (13). Interestingly, the predicting ability of the solid predominance seems to be independent of the extent of resection. In fact, Tsutani and coworkers demonstrated the lack of statistically significant difference in recurrence-free survival and recurrence pattern between segmentectomy and lobectomy in 327 patients with solid predominant adenocarcinoma (14). In this setting, an appropriate extent of resection for clinical stage I pure/dominant GGOs may be wedge resection for clinical stage IA and segmentectomy for stage IB (15). In addition, on the basis that a significant part of adenocarcinoma are mixed subtypes, Sica *et al.* proposed a grading system based on the predominant two constituting patterns, being those with predominant solid pattern high grade tumors (16). Another interesting clinical implication from the new adenocarcinoma classification results from the outcomes of the National Lung Screening Trial (NLST) (2). The 20% reduction in lung cancer mortality, 24% positive findings (of which 96% false positives), and, the need for 320 individuals to be screened to avoid one lung cancer death have provided the United States Preventive Service Task Force with enough evidence to recommend lung cancer screening in high risk population (17). The implementation of lung cancer screening programs based on early involvement of qualified surgeons (18,19) will likely increase the detection rate of bilateral lung synchronous or metachronous lesions.

Conclusions

The new IASLC/ATS/ERS lung adenocarcinoma classification represents an ideal *trait d'union* among the different components of the diagnostic and therapeutic pathways of NSCLC (1). The multispecialty effort that plays such a fundamental role in lung cancer management is accurately reflected in this classification since it is the crossroads of vanguard concepts in biomolecular medicine, pathology, radiology, medical and radiation oncology and surgery (1,20). From a surgical standpoint, the emphasis on minimally invasive thoracic surgery has never been so appropriately reinforced as in the management of AIS and MIA, virtually curable disease subsets with resection only (1). Furthermore, the need to establish a consistent and valid approach to screen detected lesions will make VATS and robotic thoracic surgery essential components of the modern surgical armamentarium since we can no longer afford the morbidity, the prolonged hospitalizations, inactivity and the related costs which traditional open surgery entails (21-23). Unlike potential therapeutic alternatives for local control of early stage lung cancer, minimally invasive thoracic surgery is associated with the provision of specimens for biomolecular assessment, a fundamental step on the way of totally integrated individualized medicine (24).

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