Early lung cancer with lepidic pattern: adenocarcinoma *in situ*, minimally invasive adenocarcinoma, and lepidic predominant adenocarcinoma

Wilko Weichert and Arne Warth

Purpose of review
This review gives a comprehensive overview on recent developments in the classification of neoplastic lung lesions with lepidic growth patterns, comprising the adenocarcinoma (ADC) precursor lesions atypical adenomatous hyperplasia (AAH), adenocarcinoma *in situ* (AIS), and minimally invasive adenocarcinoma (MIA) as well as lepidic predominant adenocarcinoma (LPA).

Recent findings
The concept of a continuum between the precursor lesions AAH and AIS to MIA and frankly invasive ADC is backed by a wealth of recent data showing a gradual decrease in overall survival from 100% for AAH, AIS, and MIA to moderately lower rates for LPA. Further, it has been shown that the morphologic categorization of these tumors can be done with reasonable reliability and that nonmucinous lepidic tumors show distinct molecular alterations with high rates of epidermal growth factor receptor mutations. Importantly, lepidic tumor growth is also mirrored by specific characteristics in computed tomography images, arguing for a combined assessment of histomorphology and imaging data for an optimized classification of lepidic neoplasms.

Summary
The validity and clinical importance of the novel concept of ADC precursor lesions and LPA have been confirmed by clinical, radiological, morphological, and molecular data. Thereby, it has evolved into a valuable tool to aid in clinical decision-making.

Keywords
adenocarcinoma *in situ*, computed tomography, histology, lepidic, minimally invasive adenocarcinoma

INTRODUCTION

Adenocarcinoma (ADC) is the most common subtype of lung cancer. Over the last decade, clinical, radiological, and pathological efforts including molecular and morphological analyses have revealed multiple novel disease classifiers. These findings need to be translated and integrated into the clinical setting in order to improve patients' outcome.

Morphology-based categorization of ADC has recently gained attention, as clinically relevant findings have been put forward in this field. To account for this, in 2011, a revised classification for pulmonary ADC was introduced by joint international, multidisciplinary lung cancer specialists representing the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) [1]. Major aspects of this classification comprise a revised concept of ADC precursor lesions and a semi-quantitative assessment of ADC growth pattern. This classification has been validated independently in different cohorts worldwide and was proven to be an important, in some studies even stage-independent, predictor of survival [2–14]. First studies indicate that the classification is

Institute for Pathology, Heidelberg University, Heidelberg, Germany

Correspondence to Arne Warth, MD, Institute for Pathology, University Hospital Heidelberg, Im Neuenheimer Feld 224, D-69120 Heidelberg, Germany. Tel: +49 6221 56 39968; fax: +49 6221 56 5251; e-mail: arne.warth@med.uni-heidelberg.de

Curr Opin Pulm Med 2014, 20:309–316
DOI:10.1097/MCP.0000000000000065

KEY POINTS

- The morphological IASLC/ATS/ERS classification of pulmonary ADCs is of high prognostic relevance and reproducibly applicable.
- The novel concept of a continuum of lepidic lung tumors is a consequent step from the tumor-biologic point of view and its prognostic meaning has been validated independently in multiple studies around the globe.
- Lepidic tumor growth is mirrored by specific characteristics in computed tomography images (ground glass opacities), thus allowing for a combined assessment of histomorphology and imaging data for an optimized classification of lepidic neoplasms.

reproducibly applicable [15–17]. Most recently, retrospective analysis of more than 6000 resected ADCs of the Japan lung cancer registry underscored the independent prognostic impact of histomorphological subtyping [18▪]. In advanced tumor stages, the semi-quantitative assessment of growth pattern was also suggested to be of predictive value for adjuvant treatment [12,19]. However, there are also some conflicting data claiming that assessment of growth patterns does not add relevant prognostic information to established staging systems [20]. In this review, we focus on the most recent findings and clinical implications of the IASLC/ATS/ERS classification of ADC with emphasis on tumors with lepidic growth, which comprise the ADC precursor lesions atypical adenomatous hyperplasia (AAH) and adenocarcinoma *in situ* (AIS) as well as minimally invasive adenocarcinoma (MIA) and lepidic predominant adenocarcinoma (LPA).

THE LEPIDIC PATTERN

Until it was suggested to discontinue the use of the term 'bronchiolo-alveolar carcinoma' (BAC) [1], BAC had been used for a broad spectrum of morphologically and molecular diverse tumors, thus leading to confusion and a lack of comparability of study data. The respective growth patterns of former BACs in the stricter sense are now designated as 'lepidic'. There have been considerable discussions about the origin of the term 'lepidic' itself, which were most recently resolved in a historical overview [21▪]. 'Lepidic' refers to neoplastic tumor cell growth along pre-existing alveolar structures in a flat manner, without forming papillary or micropapillary structures (Fig. 1). Lepidic growth is usually accompanied by thickened alveolar walls but typically lacks inflammation. Stromal, vascular or pleural invasion must be absent. The different tumors with lepidic growth are now classified in a continuous spectrum ranging from AAH to AIS to MIA and, ultimately, LPA (Table 1).

ATYPICAL ADENOMATOUS HYPERPLASIA AND ADENOCARCINOMA *IN SITU*

AAH is a localized, small (usually 0.5 cm or less) lepidic proliferation of mildly to moderately atypical type II pneumocytes and/or Clara cells lining alveolar walls, replacing normal bronchioloalveolar epithelium of the terminal respiratory unit and, sometimes, respiratory bronchioles. AAH is an

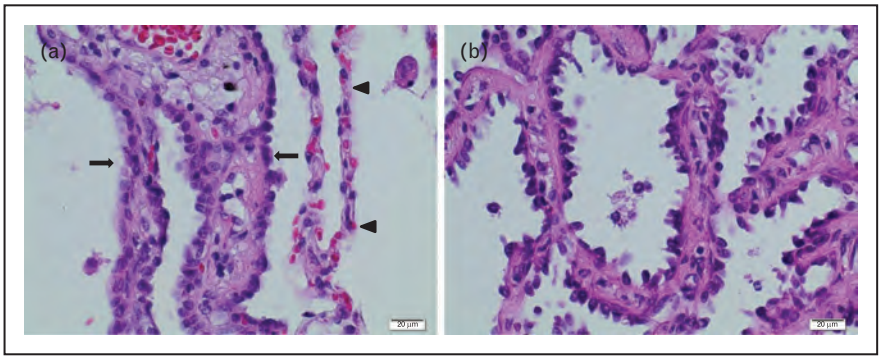

FIGURE 1. Histomorphological features of atypical adenomatous hyperplasia and adenocarcinoma *in situ* (AIS). (a) Lepidic growth of an atypical adenomatous hyperplasia (AAH; arrows) adjacent to normal lung (arrowheads). In direct comparison, the nuclei of AAH are enlarged and hyperchromatic but show only mild atypia. The alveolar walls are thickened but invasive tumor growth is not present. From AAH, there is a continuum to morphologic changes usually seen in AIS. (b) In AIS, the size of the nuclei is further increased, the nuclei are usually more hyperchromatic, and there is also a higher degree of variability in cellular and nuclear size and shape (pleomorphism). Although there is no invasive tumor growth, stromal thickening as a reaction to the neoplastic proliferation is evident.

Table 1. Key characteristics of lepidic pulmonary neoplasms

Neoplasm	Acronym	Size	Invasive foci	Other characteristics	Nuclear characteristics	5-year disease-free survival
Atypical adenomatous hyperplasia	AAH	≤5 mm	None	No angioinvasion, no pleural invasion, no tumor necrosis	Slight pleomorphism, modest hyperchromasia	100%
Adenocarcinoma *in situ*	AIS	>5 mm (not mandatory), ≤30 mm	None	No angioinvasion, no pleural invasion, no tumor necrosis	Moderate pleomorphism, distinct hyperchromasia	100%
Minimally invasive adenocarcinoma	MIA	>5 mm (not mandatory), ≤30 mm	One or more, each focus measuring ≤5 mm	No angioinvasion, no pleural invasion, no tumor necrosis	Moderate pleomorphism, distinct hyperchromasia	100%
Lepidic predominant adenocarcinoma	LPA	/	>5 mm	Also tumors without invasive foci/with microinvasion measuring >30 mm and tumors of any size with pleura/ angioinvasion or necrosis	Moderately to marked pleomorphism, strong hyperchromasia with inhomogenous chromatin structure	≈90%

Note that the morphology criteria represent a continuum; clear-cut delineation on the basis of cytomorphology alone is not advisable.

accepted precursor lesion for ADC and frequently observed as a coincident finding in both neoplastic and nonneoplastic resection specimens. There is a continuum of morphologic changes between AAH and AIS, making a clear-cut distinction of both entities challenging. In AIS, cellular atypia might be more pronounced than in AAH. Overall, cell density, pleomorphism, and cell size can aid in the delineation. Furthermore, AAH must be separated from reactive pneumocyte hyperplasia.

AIS is defined as a small to moderately sized (≤3 cm), solitary neoplastic lesion with pure lepidic growth. Typical cytologic features of AIS include bland, small, monomorphous nuclei with fine chromatin and inconspicuous pinpoint nucleoli. Nuclear groves and nuclear pseudo-inclusions can be prominent. A cell arrangement in orderly strips and small flat monolayers is also a characteristic feature of AIS. Cellular atypia is usually slightly more pronounced than in AAH; in addition, these lesions are usually larger than 0.5 cm. AIS is further subdivided into nonmucinous and mucinous variants, but according to literature and in our own experience virtually all cases are nonmucinous. AIS has been demonstrated to be associated with a 100% 5-year disease-free survival in multiple studies [3,7,11,13,14,22,23,24▪,25,26▪▪]. However, one recent study reported a slightly impaired 5-year overall survival of 98% [27].

MINIMALLY INVASIVE ADENOCARCINOMA

MIA is a small to moderately sized solitary lesion (≤3 cm) with lepidic pattern and circumscribed invasive foci. Mucinous variants of MIA are rare. The number of invasive foci is variable; however, most often only one distinct area of microinvasion is present. By definition, the invasive areas must be 5 mm or smaller in greatest dimension in any one focus. The invasive component to be measured in MIA is defined as being of any histological pattern other than lepidic (i.e. acinar, papillary, micropapillary and/or solid) or comprising single nests of tumor cells infiltrating myofibroblastic stroma. The category MIA is not applied to tumors invading lymphatics, blood vessels, or pleura or to tumors containing necrosis. When multiple independent tumors are present, AIS and MIA should only be diagnosed if the lesions are regarded as synchronous primaries rather than intrapulmonary metastases. Approximately one third of ADCs have a significant lepidic component and of these nearly one third are believed to be minimally invasive [28].

MIA has been demonstrated to have a 100% 5-year disease-free survival in multiple studies [3,7,13,14,22,23,24▪,25,26▪▪,29–31]. One study reported a slightly diminished 5-year overall survival of 98% [27].

The delineation of invasive foci in MIA from AIS with sclerotic septal widening or alveolar collapse can be challenging, as the latter two morphologic states might resemble acinar tumor growth. To ease the evaluation of parenchymal invasion, in some cases the use of elastic stains demonstrating a destruction of the elastic structures can be helpful to differentiate true invasion from alveolar collapse [28]. However, early invasion will not necessarily

result in a destruction of elastic fibers. Furthermore, a recent study pointed out that one must be aware not to misinterpret biopsy-site changes from prior biopsies as tumor-related stromal reactions [32]. Regardless of these shortcomings, the introduction of MIA as a new entity placed between AIS and LPA is a logical step from the tumor-biological point of view and helpful for pathologists in cases in which the features for stromal invasion versus alveolar collapse are controversial. However, in the strict sense, the definitive delineation of microinvasive foci is not critical from the clinical viewpoint (see below).

In contrast, exact delineation of MIA from LPA is of utmost importance, as both entities are associated with a significantly different prognosis. In addition, Yeh *et al.* [33▪] demonstrated that not only invasion *per se* but also different stromal invasion categories in combination with specific ADC patterns were associated with variations in patient survival. Another work quoted that even small micropapillary components in an MIA might be associated with a worse prognosis [28]. The acinar (91%) and the papillary pattern (9%) were described as the predominant invasive components in a series of 43 MIAs [26▪▪], which further complicates the delineation of MIA from AIS, as both patterns are the ones most readily confused with lepidic tumor growth (see below). This might also explain why there was only a fair reproducibility in the delineation of invasive from noninvasive ADC patterns among international pulmonary pathologists [15]. In frozen sections, the differentiation of AIS from MIA is difficult because of multifactorial reasons (e.g. intraoperative consultation of more than one pathologist necessary; more than one sample of frozen sections needed) as demonstrated by root cause analysis of 224 consecutive cases [34].

LEPIDIC PREDOMINANT ADENOCARCINOMA

LPA typically consists of slightly to moderately atypical neoplastic cells growing along the surface of alveolar walls. Architecture and cytomorphology are comparable with the criteria described for AIS and MIA. However, at least one invasive focus measuring more than 5 mm in greatest dimension must be present. The diagnosis of LPA rather than MIA is also made if the tumor invades lymphatics, blood vessels, or pleura and if the tumor contains necrosis. The average percentage of the lepidic pattern in LPA was recently reported to be 50% (range: 40–85%) with acinar (81%) and papillary (17%) as the predominant accompanying invasive components [26▪▪]. In several retrospective studies, 5-year disease-free survival of LPA ranged between 85.7 and 100% [3,13,14,23,24▪,25,26▪▪,27,33▪]; survival for these tumors is thereby considerably better than for ADC with any other predominant pattern. A higher percentage of the lepidic pattern correlated with a lower risk for recurrence [26▪▪]. As multifocality is a typical feature of tumors with predominant lepidic growth, the prognostic impact of synchronous lesions was analyzed by different groups. In a series of 39 patients with multifocal ground glass lesions and negative lymph nodes, Gu *et al.* [35▪] recently reported a 100% overall survival after anatomic resection of the dominant tumor and wedge resection of all other accessible ground glass opacities (GGO), which is in line with data from previous studies [36–39].

The proportion of the lepidic growth in LPA is of high prognostic value. Stratification for survival in dependence of ADC diameter is better when instead of the overall tumor diameter only the adjusted nonlepidic ('invasive') tumor diameter is taken into account [12]. This observation strengthens comparable findings by Yoshizawa *et al.* [13] and was also underscored by recent data of two series of $n = 603$ [40▪] and $n = 191$ [24▪] stage I ADC in which the 'invasive' size was of higher prognostic impact than the total tumor size. In both studies, the total tumor size even failed to reach prognostic relevance, whereas the invasive tumor size was found to be an independent prognosticator in multivariate analysis. This is supported by data of Zhang *et al.* [41], who analyzed 215 small peripheral ADC, and Xu *et al.* [28], who analyzed 87 resected ADCs with lepidic growth. Both studies found that histomorphological subtyping is more reliable to predict the N0 status than the tumor size. In addition, the size of the invasive foci has been demonstrated as an independent predictor of survival for pulmonary ADC in preceding studies [42].

If a noninvasive pattern is present in a small biopsy, it should be referred to as lepidic growth. The diagnosis of AIS or MIA cannot be firmly established without entire histologic sampling of the tumor. To achieve this, patients necessarily must be subjected to surgery. For lesions suspicious for AIS or MIA with a diameter of larger than 3 cm (based on imaging analyses; compare Fig. 2), the term 'lepidic predominant ADC' should be applied including a comment that an invasive component cannot be excluded [43▪].

DIAGNOSTIC REPRODUCIBILITY OF THE LEPIDIC GROWTH

With a mean correlation coefficient of 0.78, lepidic growth is associated with a good interobserver agreement [17]. However, the delineation from papillary or acinar growth has been found

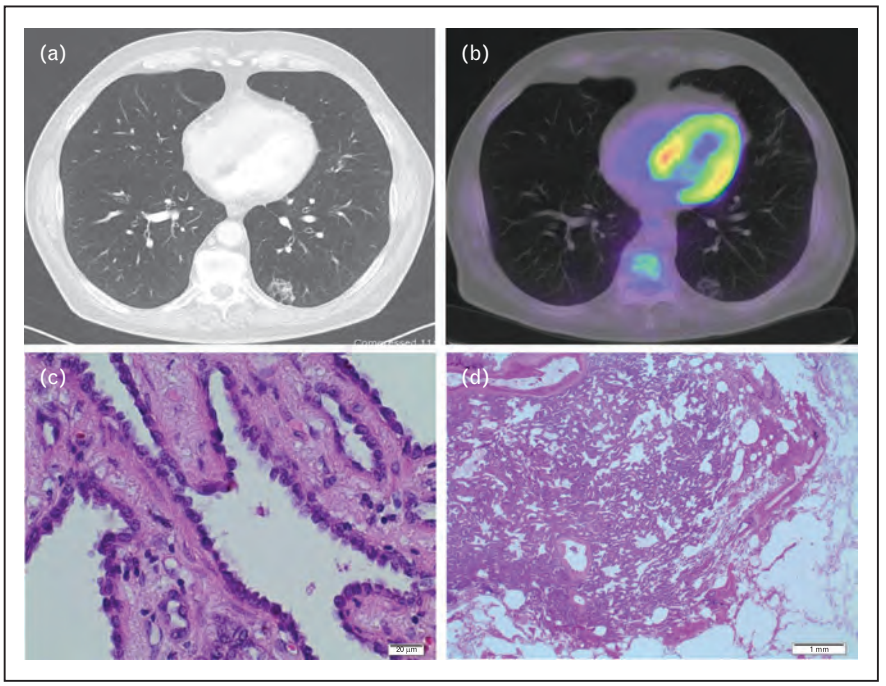

FIGURE 2. Interplay of histomorphology and radiological imaging. Case of a 72-year-old male with a lung lesion with dominance of ground-glass opacities in segment 10 of the left lower lobe (a). On positron emission tomography (PET)/computed tomography (CT) images, the lesion was found PET-negative (b). Transthoracic core needle biopsy showed a small lung tissue fragment with lepidic growth (c). Subsequent lobectomy accompanied by systematic lymph node dissection revealed an adenocarcinoma *in situ* (d). CT and PET images were kindly provided by C.P. Heussel and U. Haberkorn, Thoraxklinik and University Hospital Heidelberg, Germany, respectively.

challenging, but training sessions improve the interobserver agreement [16]. Furthermore, cases with obscuring inflammation as well as lepidic involvement of emphysematous areas can be difficult with respect to correct pattern interpretation. This underlines the need for international efforts in this regard, which was further emphasized by an interobserver study on the reproducibility of histopathological subtypes and invasion demonstrating that more precise definitions and better education on the interpretation of existing terminology are required to improve proper diagnosis of purely in-situ disease [15]. Furthermore, Thunnissen *et al.* [44] analyzed three-dimensional reconstructions of pulmonary ADCs from serial sections for the influence of surgical atelectasis on the diagnosis of a 'lepidic' pattern. It was shown that for reliable ADC subtyping, pathologists must be aware of artifacts because of compressed or collapsed tissue to avoid misclassification of the lepidic pattern as papillary growth.

LEPIDIC GROWTH AND IMAGING MODALITIES

Lepidic growth can be predicted by imaging modalities to a certain extent. In computed tomography (CT), lepidic growth is mirrored by GGO, thus allowing the rough estimation of the 'lepidic' fraction of a tumor (e.g. pure GGO, part-solid nodule) already prior to surgery or in advanced tumor stages when only palliative treatment is feasible [11,45,46▪,47]. This has been demonstrated to be of prognostic value, especially in early-stage lung ADC [48–53]. On univariate analysis, the presence of a positive air bronchogram, size of nodule, and mass of nodule were significant factors that differentiated invasive ADC from AIS or MIA. On multivariate analysis, size and mass of nodule were significant determinants for invasive ADC [54]. In a series of 114 lesions with pure GGO, Ichinose *et al.* [55] reported that after morphological workup, 14% of the cases were diagnosed as MIA and only 12% as invasive cancer. Differential diagnosis of part-solid nodules includes focal inflammation, focal fibrosis, and organizing pneumonia. Furthermore, maximum standardized uptake values (SUVmax) on positron emission tomography (PET)/CT and mean apparent diffusion coefficient values have been reported to correlate well with the histologic differentiation of pulmonary ADC [56]. In pure GGO lesions, PET-positive tumors are associated with foci of invasion [55].

CLINICAL IMPLICATIONS OF THE CLASSIFICATION OF TUMORS WITH LEPIDIC GROWTH

One of the most profound changes in the new ADC classification are the elimination of the term BAC and a concomitant tighter delineation of lesions that were formerly summarized in this category, including solitary small noninvasive AIS, minimal invasive ADCs, mixed subtype invasive ADCs with a lepidic component and tumors now categorized as invasive mucinous carcinomas. This hopefully will lead to a more precise and comparable classification of the respective tumors in the future. Introduction of the new entities AIS and MIA is consistent with tumor biology and in line with the classification of tumors in other organs. Beyond tumor architecture, other parameters like mitotic count or nuclear grading might be helpful for a meaningful prognostic assessment of ADC in the future [5].

From a clinical point of view, a classification should reflect the patients' prognosis to allow for tailored treatment decisions. This has been achieved with the novel classification. With respect to prognosis of tumors with lepidic growth, it is of utmost importance to delineate between MIA and LPA, whereas the differentiation of AIS and MIA from each other seems to have no prognostic relevance. Concerning staging, AIS and MIA are classified as pTis and pTmia, respectively, and should not be considered for multiple nodule upstaging. For a definite separation of the lepidic tumors, surgical resection is a prerequisite, which, in cases in which a definite classification is necessary, hampers the use of alternative treatment options.

Advances in imaging allow for an early detection of lung cancer, while increasing numbers of precursor lesions are expected to be diagnosed in the future. A large trial demonstrated that small nodules smaller than 10 mm or smaller than 500 mm^3 that are clearly 100% pure GGO lesions on CT might be considered for close follow-up rather than immediate resection [57]. Whether some of these lesions can be treated by limited resection is a prevailing question and a subject of intensive investigations [58]. However, although most cases of AIS or MIA will likely be cured by complete resection [26▪▪], a small percentage of LPA will recur. Thus, it is of utmost importance to further characterize these lesions in a multidisciplinary setting in order to identify criteria allowing for risk-adjusted treatment decisions.

With respect to predictive biomarkers used for patient stratification, nonmucinous lepidic growth is significantly associated with mutations in the epidermal growth factor receptor but not V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations [25,59–62]. Tumors with mucinous lepidic growth and papillary projections, now designated as invasive mucinous ADC, are associated with KRAS mutations [27,62–64]; however, these tumors now form a separate entity and are not part of the lepidic tumor spectrum anymore.

CONCLUSION

Taken together, the validity and clinical importance of the novel concept of a continuum of lepidic lung tumors have been confirmed by clinical, radiological, morphological, and molecular data. Thereby, it has evolved into a valuable tool to aid in clinical decision-making.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Travis WD, Brambilla E, Noguchi M, *et al.* International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011; 6:244–285.
2. Cha MJ, Lee HY, Lee KS, *et al.* Micropapillary and solid subtypes of invasive lung adenocarcinoma: clinical predictors of histopathology and outcome. J Thorac Cardiovasc Surg 2013; 147:921–928.
3. Gu J, Lu C, Guo J, *et al.* Prognostic significance of the IASLC/ATS/ERS classification in Chinese patients-A single institution retrospective study of 292 lung adenocarcinoma. J Surg Oncol 2013; 107:474–480.
4. Hung JJ, Jeng WJ, Chou TY, *et al.* Prognostic value of the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification on death and recurrence in completely resected stage I lung adenocarcinoma. Ann Surg 2013; 258:1079–1086.
5. Kadota K, Suzuki K, Kachala SS, *et al.* A grading system combining architectural features and mitotic count predicts recurrence in stage I lung adenocarcinoma. Mod Pathol 2012; 25:1117–1127.
6. Kadota K, Yeh YC, Sima CS, *et al.* The cribriform pattern identifies a subset of acinar predominant tumors with poor prognosis in patients with stage I lung adenocarcinoma: a conceptual proposal to classify cribriform predominant tumors as a distinct histologic subtype. Mod Pathol 2013. [Epub ahead of print]
7. Russell PA, Wainer Z, Wright GM, *et al.* Does lung adenocarcinoma subtype predict patient survival?: a clinicopathologic study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. J Thorac Oncol 2011; 6: 1496–1504.
8. Sica G, Yoshizawa A, Sima CS, *et al.* A grading system of lung adenocarcinomas based on histologic pattern is predictive of disease recurrence in stage I tumors. Am J Surg Pathol 2010; 34:1155–1162.
9. Song Z, Zhu H, Guo Z, *et al.* Prognostic value of the IASLC/ATS/ERS classification in stage I lung adenocarcinoma patients–based on a hospital study in China. Eur J Surg Oncol 2013; 39:1262–1268.
10. Sterlacci W, Savic S, Schmid T, *et al.* Tissue-sparing application of the newly proposed IASLC/ATS/ERS classification of adenocarcinoma of the lung shows practical diagnostic and prognostic impact. Am J Clin Pathol 2012; 137:946–956.

11. Takahashi M, Shigematsu Y, Ohta M, *et al.* Tumor invasiveness as defined by the newly proposed IASLC/ATS/ERS classification has prognostic significance for pathologic stage IA lung adenocarcinoma and can be predicted by radiologic parameters. J Thorac Cardiovasc Surg 2014; 147:54–59.

12. Warth A, Muley T, Meister M, *et al.* The novel histologic International Association for the Study of Lung Cancer/American Thoracic Society/ European Respiratory Society classification system of lung adenocarcinoma is a stage-independent predictor of survival. J Clin Oncol 2012; 30:1438–1446.

13. Yoshizawa A, Motoi N, Riely GJ, *et al.* Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. Mod Pathol 2011; 24:653–664.

14. Zhang J, Wu J, Tan Q, *et al.* Why do pathological stage IA lung adenocarcinomas vary from prognosis?: a clinicopathologic study of 176 patients with pathological stage IA lung adenocarcinoma based on the IASLC/ATS/ERS classification. J Thorac Oncol 2013; 8:1196–1202.

15. Thunnissen E, Beasley MB, Borczuk AC, *et al.* Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study. Mod Pathol 2012; 25:1574–1583.

16. Warth A, Cortis J, Fink L, *et al.* Training increases concordance in classifying pulmonary adenocarcinomas according to the novel IASLC/ATS/ERS classification. Virchows Arch 2012; 461:185–193.

17. Warth A, Stenzinger A, von Brunneck AC, *et al.* Interobserver variability in the application of the novel IASLC/ATS/ERS classification for pulmonary adenocarcinomas. Eur Respir J 2012; 40:1221–1227.

18. ■ Sakurai H, Asamura H, Miyaoka E, *et al.* Differences in the prognosis of resected lung adenocarcinoma according to the histological subtype: a retrospective analysis of Japanese lung cancer registry data. Eur J Cardiothorac Surg 2014; 45:100–107.

This is a large-scale study on the prognostic impact of histomorphological subtyping in pulmonary ADCs.

19. Campos-Parra AD, Aviles A, Contreras-Reyes S, *et al.* Relevance of the novel IASLC/ATS/ERS classification of lung adenocarcinoma in advanced disease. Eur Respir J 2014. [Epub ahead of print]

20. Weissferdt A, Kalhor N, Marom EM, *et al.* Early-stage pulmonary adenocarcinoma (T1N0M0): a clinical, radiological, surgical, and pathological correlation of 104 cases. The MD Anderson Cancer Center Experience. Mod Pathol 2013; 26:1065–1075.

21. ■ Jones KD. Whence lepidic?: the history of a Canadian neologism. Arch Pathol Lab Med 2013; 137:1822–1824.

This is an excellent historical overview on the origin of the term 'lepidic'.

22. Ahn S, Hwangbo W, Kim H, Kim CH. Naked cuticle Drosophila 1 expression in histologic subtypes of small adenocarcinoma of the lung. Korean J Pathol 2013; 47:211–218.

23. Woo T, Okudela K, Mitsui H, *et al.* Prognostic value of the IASLC/ATS/ERS classification of lung adenocarcinoma in stage I disease of Japanese cases. Pathol Int 2012; 62:785–791.

24. ■ Yanagawa N, Shiono S, Abiko M, *et al.* New IASLC/ATS/ERS classification and invasive tumor size are predictive of disease recurrence in stage I lung adenocarcinoma. J Thorac Oncol 2013; 8:612–618.

This study clearly demonstrates the prognostic impact of the invasive tumor size in early stage lung cancer.

25. Yoshizawa A, Sumiyoshi S, Sonobe M, *et al.* Validation of the IASLC/ATS/ ERS lung adenocarcinoma classification for prognosis and association with EGFR and KRAS gene mutations: analysis of 440 Japanese patients. J Thorac Oncol 2013; 8:52–61.

26. ■■ Kadota K, Villena-Vargas J, Yoshizawa A, *et al.* Prognostic significance of adenocarcinoma in situ, minimally invasive adenocarcinoma, and nonmucinous lepidic predominant invasive adenocarcinoma of the lung in patients with stage I disease. Am J Surg Pathol 2014. [Epub ahead of print]

This is a large-scale study on more than 1000 early-stage ADCs with relevant prognostic data for the tumors with lepidic growth.

27. Tsuta K, Kawago M, Inoue E, *et al.* The utility of the proposed IASLC/ ATS/ERS lung adenocarcinoma subtypes for disease prognosis and correlation of driver gene alterations. Lung Cancer 2013; 81:371–376.

28. Xu L, Tavora F, Battafarano R, Burke A. Adenocarcinomas with prominent lepidic spread: retrospective review applying new classification of the American Thoracic Society. Am J Surg Pathol 2012; 36:273–282.

29. Noguchi M, Morikawa A, Kawasaki M, *et al.* Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer 1995; 75:2844–2852.

30. Sakurai H, Maeshima A, Watanabe S, *et al.* Grade of stromal invasion in small adenocarcinoma of the lung: histopathological minimal invasion and prognosis. Am J Surg Pathol 2004; 28:198–206.

31. Suzuki K, Yokose T, Yoshida J, *et al.* Prognostic significance of the size of central fibrosis in peripheral adenocarcinoma of the lung. Ann Thorac Surg 2000; 69:893–897.

32. Doxtader EE, Mukhopadhyay S, Katzenstein AL. Biopsy-site changes in lung adenocarcinoma with prior core needle biopsy: a potential pitfall in the assessment of stromal invasion. Am J Surg Pathol 2013; 37:443–446.

33. ■ Yeh YC, Wu YC, Chen CY, *et al.* Stromal invasion and micropapillary pattern in 212 consecutive surgically resected stage I lung adenocarcinomas: histopathological categories for prognosis prediction. J Clin Pathol 2012; 65:910–918.

This is an interesting study on the prognostic relevance of stromal invasion and the micropapillary pattern in early-stage ADCs with lepidic growth.

34. Walts AE, Marchevsky AM. Root cause analysis of problems in the frozen section diagnosis of in situ, minimally invasive, and invasive adenocarcinoma of the lung. Arch Pathol Lab Med 2012; 136:1515–1521.

35. ■ Gu B, Burt BM, Merritt RE, *et al.* A dominant adenocarcinoma with multifocal ground glass lesions does not behave as advanced disease. Ann Thorac Surg 2013; 96:411–418.

This is a retrospective clinicopathological study on patients with pulmonary lesions with ground-glass opacity, their outcome, and their correlation with histological findings.

36. Kim HK, Choi YS, Kim J, *et al.* Management of multiple pure ground-glass opacity lesions in patients with bronchioloalveolar carcinoma. J Thorac Oncol 2010; 5:206–210.

37. Mun M, Kohno T. Efficacy of thoracoscopic resection for multifocal bronchioloalveolar carcinoma showing pure ground-glass opacities of 20 mm or less in diameter. J Thorac Cardiovasc Surg 2007; 134:877–882.

38. Nakata M, Sawada S, Yamashita M, *et al.* Surgical treatments for multiple primary adenocarcinoma of the lung. Ann Thorac Surg 2004; 78:1194–1199.

39. Tsutsui S, Ashizawa K, Minami K, *et al.* Multiple focal pure ground-glass opacities on high-resolution CT images: clinical significance in patients with lung cancer. AJR Am J Roentgenol 2010; 195:W131–138.

40. ■ Tsutani Y, Miyata Y, Mimae T, *et al.* The prognostic role of pathologic invasive component size, excluding lepidic growth, in stage I lung adenocarcinoma. J Thorac Cardiovasc Surg 2013; 146:580–585.

This study shows significant data concerning the prognostic impact of the total tumor size and the invasive tumor size.

41. Zhang Y, Sun Y, Shen L, *et al.* Predictive factors of lymph node status in small peripheral nonsmall cell lung cancers: tumor histology is more reliable. Ann Surg Oncol 2013; 20:1949–1954.

42. Borczuk AC, Qian F, Kazeros A, *et al.* Invasive size is an independent predictor of survival in pulmonary adenocarcinoma. Am J Surg Pathol 2009; 33:462–469.

43. ■ Travis WD, Brambilla E, Riely GJ. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. J Clin Oncol 2013; 31:992–1001.

This is a concise review of the clinical implications of the novel IASLC/ATS/ERS classification of pulmonary ADCs.

44. Thunnissen E, Belien JA, Kerr KM, *et al.* In compressed lung tissue microscopic sections of adenocarcinoma in situ may mimic papillary adenocarcinoma. Arch Pathol Lab Med 2013; 137:1792–1797.

45. Honda T, Kondo T, Murakami S, *et al.* Radiographic and pathological analysis of small lung adenocarcinoma using the new IASLC classification. Clin Radiol 2013; 68:e21–e26.

46. ■ Lederlin M, Puderbach M, Muley T, *et al.* Correlation of radio- and histomorphological pattern of pulmonary adenocarcinoma. Eur Respir J 2013; 41:943–951.

This is a retrospective study on the correlations between imaging characteristics and histomorphology of pulmonary ADCs.

47. Sawabata N, Kanzaki R, Sakamoto T, *et al.* Clinical predictor of pre or minimally invasive pulmonary adenocarcinoma: possibility of sub-classification of clinical T1a. Eur J Cardiothorac Surg 2014; 45:256–261.

48. Ambrosini-Spaltro A, Ruiu A, Seebacher C, *et al.* Impact of the IASLC/ATS/ ERS classification in pN0 pulmonary adenocarcinomas: a study with radiological-pathological comparisons and survival analyses. Pathol Res Pract 2014; 210:40–46.

49. Cho S, Song IH, Yang HC, *et al.* Predictive factors for node metastasis in patients with clinical stage I nonsmall cell lung cancer. Ann Thorac Surg 2013; 96:239–245.

50. Jiang B, Takashima S, Hakucho T, *et al.* Adenocarcinoma of the lung with scattered consolidation: radiological-pathological correlation and prognosis. Eur J Radiol 2013; 82:e623–e627.

51. Maeyashiki T, Suzuki K, Hattori A, *et al.* The size of consolidation on thin-section computed tomography is a better predictor of survival than the maximum tumour dimension in resectable lung cancer. Eur J Cardiothorac Surg 2013; 43:915–918.

52. Murakawa T, Konoeda C, Ito T, *et al.* The ground glass opacity component can be eliminated from the T-factor assessment of lung adenocarcinoma. Eur J Cardiothorac Surg 2013; 43:925–932.

53. Tsutani Y, Miyata Y, Yamanaka T, *et al.* Solid tumors versus mixed tumors with a ground-glass opacity component in patients with clinical stage IA lung adenocarcinoma: prognostic comparison using high-resolution computed tomography findings. J Thorac Cardiovasc Surg 2013; 146: 17–23.

54. Lim HJ, Ahn S, Lee KS, *et al.* Persistent pure ground-glass opacity lung nodules >/= 10 mm in diameter at CT scan: histopathologic comparisons and prognostic implications. Chest 2013; 144:1291–1299.

55. Ichinose J, Kohno T, Fujimori S, *et al.* Invasiveness and malignant potential of pulmonary lesions presenting as pure ground-glass opacities. Ann Thorac Cardiovasc Surg 2013. [Epub ahead of print]

56. Lee HY, Jeong JY, Lee KS, *et al.* Histopathology of lung adenocarcinoma based on new IASLC/ATS/ERS classification: prognostic stratification with functional and metabolic imaging biomarkers. J Magn Reson Imaging 2013; 38:905–913.

57. van Klaveren RJ, Oudkerk M, Prokop M, *et al.* Management of lung nodules detected by volume CT scanning. N Engl J Med 2009; 361:2221–2229.

58. Van Schil PE, Asamura H, Rusch VW, *et al.* Surgical implications of the new IASLC/ATS/ERS adenocarcinoma classification. Eur Respir J 2012; 39: 478–486.

59. Onozato ML, Kovach AE, Yeap BY, *et al.* Tumor islands in resected early-stage lung adenocarcinomas are associated with unique clinicopathologic and molecular characteristics and worse prognosis. Am J Surg Pathol 2013; 37:287–294.

60. Shim HS, Lee da H, Park EJ, Kim SH. Histopathologic characteristics of lung adenocarcinomas with epidermal growth factor receptor mutations in the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification. Arch Pathol Lab Med 2011; 135:1329–1334.

61. Song Z, Zhu H, Guo Z, *et al.* Correlation of EGFR mutation and predominant histologic subtype according to the new lung adenocarcinoma classification in Chinese patients. Med Oncol 2013; 30:645.

62. Warth A, Penzel R, Lindenmaier H, *et al.* EGFR, KRAS, BRAF and ALK gene alterations in lung adenocarcinomas: patient outcome, interplay with morphology and immunophenotype. Eur Respir J 2013; 43:872–883.

63. Finberg KE, Sequist LV, Joshi VA, *et al.* Mucinous differentiation correlates with absence of EGFR mutation and presence of KRAS mutation in lung adenocarcinomas with bronchioloalveolar features. J Mol Diagn 2007; 9: 320–326.

64. Hata A, Katakami N, Fujita S, *et al.* Frequency of EGFR and KRAS mutations in Japanese patients with lung adenocarcinoma with features of the mucinous subtype of bronchioloalveolar carcinoma. J Thorac Oncol 2010; 5:1197–1200.