Review Article

Implementing the new IASLC/ATS/ERS classification of lung adenocarcinomas: results from international and Chinese cohorts

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Abstract: A new histologic classification of lung adenocarcinoma was proposed by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) in 2011 to provide uniform terminology and diagnostic criteria for multidisciplinary strategic management. This classification proposed a comprehensive histologic subtyping (lepidic, acinar, papillary, micropapillary, and solid pattern) and a semi-quantitative assessment of histologic patterns (in 5% increments) in an effort to choose a single, predominant pattern in invasive adenocarcinomas. The prognostic value of this classification has been validated in large, independent cohorts from multiple countries. In patients who underwent curative-intent surgery, those with either an adenocarcinoma *in situ* (AIS) or a minimal invasive adenocarcinoma have nearly 100% disease-free survival and are designated "low grade tumors". For invasive adenocarcinomas, the acinar and papillary predominant histologic subtypes were usually designated as "intermediate grade" while the solid and micropapillary predominant histologic subtypes were designated "high grade" tumors; this was based on the statistic difference of overall survival. This classification, coupled with additional prognostic factors [nuclear grade, cribriform pattern, high Ki-67 labeling index, thyroid transcription factor-1 (TTF-1) immunohistochemistry, immune markers, and ^{18}F-fluorodeoxyglucose uptake on positron emission tomography (PET)] that we have published on, could further stratify patients into prognostic subgroups and may prove helpful for individual patient care. With regard to Chinese oncologists, the implementation of this new classification only requires hematoxylin and eosin (H&E) stained slides and basic pathologic training, both of which require no additional costs. More importantly, this new classification system could provide informative data for better selection and stratification of clinical trials and molecular studies.

Keywords: Lung; adenocarcinoma; histologic classification; prognosis

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Introduction

Lung cancer is the leading cause of cancer death worldwide (1). Over the past decade, the rate of adenocarcinoma (the most frequent subtype of lung cancer) has increased in most countries (2,3). Currently, the single most important factor that determines prognosis for patients with lung adenocarcinomas is tumor-nodal-metastasis stage (4). Lung adenocarcinoma is a heterogeneous tumor with variation in pathological profile. Histologic classifications of lung cancers have been published by the World Health Organization (WHO) in 1967, 1981, 1999, and 2004, and the most recent revision has introduced relevant clinical and genetic information (5). Despite this, there is still limited clinical utility in the 2004 classification of lung adenocarcinomas since more than 90% of adenocarcinomas are classified as a mixed subtype even though they have a variety of clinical outcomes (6-8). Increasing evidence

suggests that histologic patterns can identify significant prognostic subsets of patients with lung adenocarcinomas (8-13). Multiple studies have shown that patients with pure lepidic (noninvasive) adenocarcinomas had 100%, 5-year disease-free survival (14-17). Other studies showed that patients with lepidic predominant, minimally invasive (≤5 mm invasion) adenocarcinomas had a near 100% survival (9,10,18). Lepidic predominant invasive tumors also correlate with a favorable prognosis in patients with resected lung adenocarcinomas (19-21). In contrast, the micropapillary pattern has been identified as a poor prognostic factor in patients with lung adenocarcinomas (22,23). To address the advances in the prognostic pathological findings identified over the last decade, a new histologic classification is needed to provide histological subtypes with uniform terminology and diagnostic criteria.

In addition to the pathologic findings that can define prognosis, there have been advances in radiologic-pathologic correlations, molecular biology, and thoracic medical oncology for lung adenocarcinomas over the past decade. On chest computed tomography (CT) of lung adenocarcinomas, the correlations between lepidic growth and ground-glass opacities, and between invasive components and solid components, have been identified and used for predicting histologic subtypes and patient prognosis. CT has also been used for improving preoperative clinical decision-making of surgical procedures (i.e., lobectomy *vs*. limited resection) (24-27).

Recent advances in molecular biology, in partner with medical oncology advances, have shown that activating mutations in the tyrosine kinase domain of *epidermal growth factor receptors* (*EGFR*) can predict better responsiveness to *EGFR* tyrosine kinase inhibitors (TKI) than conventional platinum-based chemotherapy in patients with non-small cell lung cancer (NSCLC) (28-32). These mutations are most frequently observed in females, in never smokers, and in Asian patients with adenocarcinomas (28-34). *EGFR* mutations have also been associated with lepidic pattern adenocarcinomas, formerly known as a bronchioloalveolar carcinoma patterns (34-39). This association has led to the hypothesis that tumors with lepidic pattern adenocarcinomas may be correlated with the *EGFR* mutations and may predict responses to TKI (40-42). In contrast, *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) and *v-raf murine sarcoma viral oncogene homolog B* (*BRAF*), the downstream molecules in the *EGFR* signaling pathway, were considered resistant to *EGFR*-TKI treatment and exhibited poor prognosis (34,43-50). In addition, the *KRAS* mutation has shown a correlation with invasive mucinous adenocarcinomas, formerly known as mucinous bronchioloalveolar carcinomas (51-55). A recently discovered *anaplastic lymphoma kinase (ALK)* rearrangement can predict responsiveness to a new targeted agent (crizotinib) (56-58). *ALK* rearrangements exclusively occur in lung adenocarcinomas and they are correlated with specific histological findings such as signet-ring cell features, extracellular mucin, and cribriform patterns (59-61).

History of the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) histologic classification of lung adenocarcinoma

To provide an international and multidisciplinary approach to the development of a new histologic classification system for identifying prognostic subtype, the IASLC/ATS/ERS selected as panel members thoracic medical oncologists, pulmonologists, radiologists, molecular biologists, thoracic surgeons, and pathologists based on their special interest and expertise in lung adenocarcinomas (6). First, the panel performed a systematic review of the literature on lung adenocarcinomas and generated a series of key questions by specialty. The search strategy initially yielded 11,368 relevant articles. Of these, 312 met the specified eligibility criteria for a full-text review. After review, and in conjunction with each specialty group, a writing committee developed the recommendations for histologic classification. Following a multidisciplinary discussion that took place between 2008 and 2009, this classification system was subsequently modified, and separate projects were initiated by the panel members in an effort to validate the proposed system (7,11,62). On the basis of this multidisciplinary approach, the panel recommended 10 significant changes to the diagnostic classification of lung adenocarcinomas in order to improve precision in predicting clinical outcome and therapeutic benefits. These recommendations are detailed in the 2011 joint publication by the IASLC, ATS, and ERS proposing the new classification system (6).

The 2011 IASLC/ATS/ERS lung adenocarcinoma histologic classification and advantage

The IASLC/ATS/ERS lung adenocarcinoma histologic classification system was proposed in the *Journal of Thoracic Oncology* in 2011 (6). According to this new classification,

Table 1 Advantage of the new IASLC/ATS/ERS classification system

Clinicians
AIS and MIA can define patients who have near 100% disease-specific survival
Established the first simple way to grade lung adenocarcinoma low, intermediate, and high architectural grades and correlated them with clinical outcomes
Comprehensive histologic subtyping can be useful to distinguish multiple primary tumors from intrapulmonary metastases
To identify the "micropapillary predominant subtype" in early stage lung adenocarcinoma because of its poor prognosis
Radiologists
Providing detailed histologic information for modern radiologic findings (i.e., different subtype of "ground glass nodule")
Surgeons
Better predict the risk of recurrence in surgically resected lung adenocarcinomas
The new classification can help surgeon choose the optimal procedure (i.e., "limited resection" or "lobectomy") in early stage lung adenocarcinoma patients
Pathologists
Better stratify the former term bronchioloalveolar carcinoma into AIS, MIA, lepidic predominant subtype, and invasive mucinous adenocarcinoma
To provide better stratification of the "mixed subtype" lung adenocarcinoma according to the 1999/2004 WHO classification

Abbreviation: IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society; AIS, adenocarcinoma *in situ*; MIA, minimal invasive adenocarcinoma; WHO, World Health Organization.

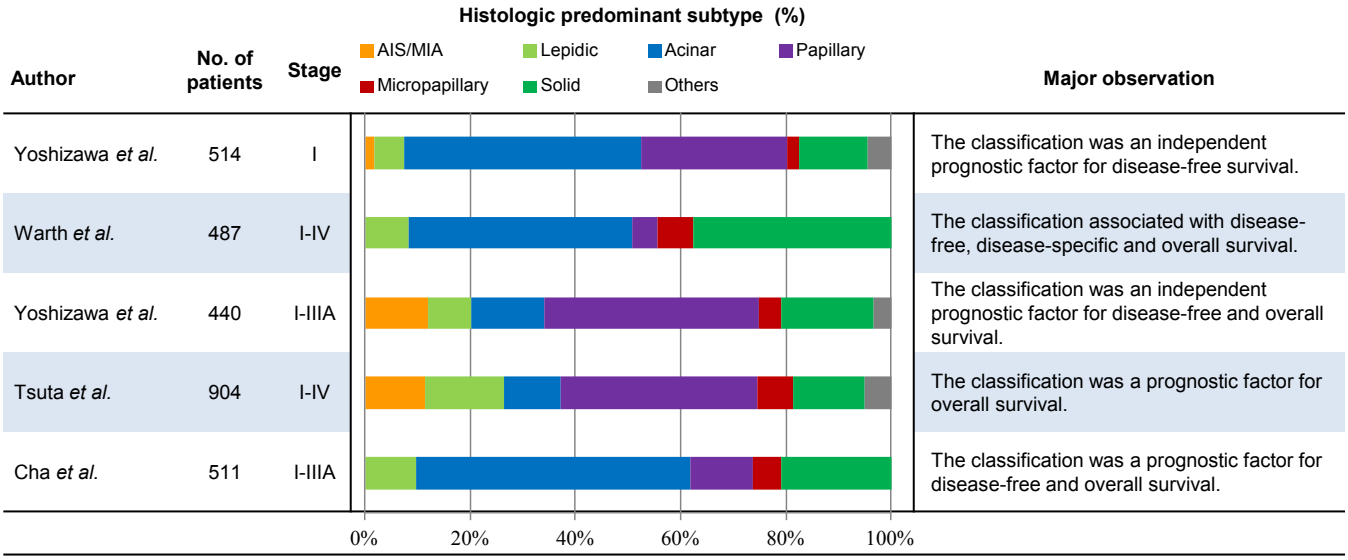
tumor size ≤3 cm with pure lepidic pattern, but without lymphatic, vascular, pleural invasion or tumor necrosis was defined as adenocarcinoma *in situ* (AIS). If tumor size ≤3 cm with a lepidic predominant pattern and contained ≤5 mm stromal invasion it was defined as minimally invasive adenocarcinoma (MIA). If tumor had >5 mm stromal invasion it was defined as an invasive adenocarcinoma. For invasive adenocarcinomas, comprehensive histologic subtyping by recording the percentage of each histological component (lepidic, acinar, papillary, micropapillary, or solid) in 5% increments is suggested to choose a single predominant pattern. Variant invasive adenocarcinomas included invasive mucinous adenocarcinomas (formerly mucinous bronchioloalveolar carcinomas), colloid, enteric, and fetal (low and high grade) adenocarcinomas.

This new classification provides not only uniform terminology and diagnostic criteria for pathologists, but it is also predictive and it provides prognostic data that may help oncologists, thoracic surgeons, and radiologists improve patient outcomes (*Table 1*).

Validation and implementing studies of the 2011 IASLC/ATS/ERS lung adenocarcinoma histologic classification

Current international cohorts validate the IASLC classification had prognostic value

A review of five published studies that validated the 2011 IASLC/ATS/ERS lung adenocarcinoma histological classification using a large cohort (more than 300 patients as a study sample) is shown in *Figure 1* (7,63-66). The study cohorts consisted of one from Unites States, Germany, and South Korea, and two from Japan. All five studies included patients who underwent curative-intent surgery. The study from the United States validated the new classification by using a homogeneous cohort composed of only stage I patients (7) while the other studies from Japan, Germany, and South Korea used patients with both early- and advanced-stage lung adenocarcinomas (63-66). The majority of cases (48-78%) seen globally were adenocarcinomas of the acinar and papillary predominant histologic subtypes. Based on the new IASLC/ATS/ERS classification, five of these large cohorts demonstrated the significant difference between clinical prognoses among the five predominant histologic subtypes. In addition, based on the similarity of survival rate, three prognostic groups with low, intermediate, and high architectural grades were proposed (7). The low grade was comprised of AIS and MIA, and it had a near 100% 5-year survival rate. The intermediate grade consisted of acinar and papillary predominant adenocarcinomas. High grade tumors included solid and micropapillary predominant adenocarcinomas and they presented with a poor outcome. Several additional cohorts also validated the prognostic difference between these three tumor grade groups (67-70).



Author	No. of patients	Stage	Major observation
Yoshizawa *et al.*	514	I	The classification was an independent prognostic factor for disease-free survival.
Warth *et al.*	487	I-IV	The classification associated with disease-free, disease-specific and overall survival.
Yoshizawa *et al.*	440	I-IIIA	The classification was an independent prognostic factor for disease-free and overall survival.
Tsuta *et al.*	904	I-IV	The classification was a prognostic factor for overall survival.
Cha *et al.*	511	I-IIIA	The classification was a prognostic factor for disease-free and overall survival.

*Percentages refer to each individual histologic predominant subtype with the total 100% in each cohort.
AIS , adenocarcinoma *in situ*; MIA, minimal invasive adenocarcinoma.

Figure 1 The application of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification in lung adenocarcinoma using a large cohort (more than 300 patients as a study sample).

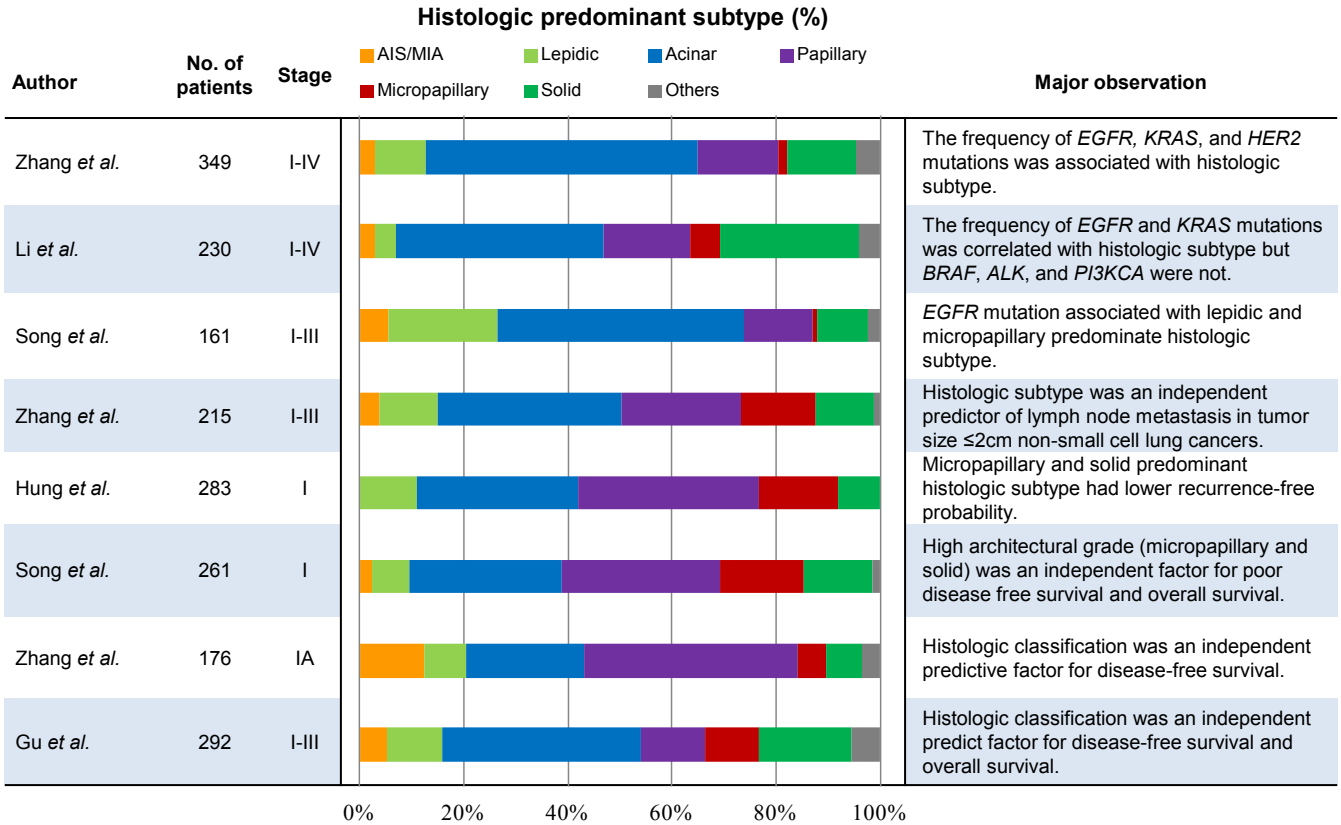
The association between radiologist features of CT/positron emission tomography (PET)-CT and the IASLC classification

While there are many positive aspects of the new classification system, it is not without its limitations. One such limitation is that the histologic subtyping is primarily estimated using postoperatively resected specimens and not via preoperative small biopsies or cytology specimens (11). Therefore, it is preferable to use a preoperative surrogate biomarker in conjunction with imaging tools to predict patient prognosis. One such imaging tool is ^{18}F-fluorodeoxyglucose-PET (FDG-PET), which is a standard imaging modality currently used in clinical practice. FDG-PET measures the metabolic activity of tumors and the maximum standardized uptake value (SUVmax) on FDG-PET has shown to correlate with prognosis in lung cancer patients (71-73). With this in mind, we investigated the association between the histologic predominant subtypes of the IASLC/ATS/ERS classification and SUVmax of PET. Our studies revealed that a high SUVmax correlated with high grade histologic subtypes in stage I lung adenocarcinomas. High SUVmax (≥3.0) was associated with a poor prognosis of recurrence and it could further stratify patients with intermediate architectural grade tumors (acinar or papillary predominant histologic subtypes) into two prognostic subsets (74). This result was validated by two other studies that showed that the presence of high architectural grade tumors (i.e., micropapillary and solid predominant histologic subtypes) were associated with a higher SUVmax value (66,75). These results may help clinicians to identify the patients with a higher preoperative risk of recurrence and assist them in selecting patients for neoadjuvant treatment or extended surgery.

The association between genetic mutation analysis and the IASLC/ATS/ERS classification

Following the aforementioned, genetic mutation variants are related to the treatment responsiveness of different targeting inhibitors. The identification of the correlation between histology and these molecular abnormalities becomes clinically relevant when choosing which patients will receive properly targeted cancer therapies and predict treatment responsiveness (76).

Currently, *EGFR* mutations occur most frequently in AIS, MIA, and lepidic predominant histologic subtypes; they are relatively rare in solid predominant lung adenocarcinomas. Conversely, *KRAS* mutations were associated with invasive mucinous adenocarcinomas and the solid morphologic pattern in lung adenocarcinomas (8,63,64,77-81). In identical studies, especially those that



Author	No. of patients	Stage	Major observation
Zhang *et al.*	349	I-IV	The frequency of *EGFR, KRAS*, and *HER2* mutations was associated with histologic subtype.
Li *et al.*	230	I-IV	The frequency of *EGFR* and *KRAS* mutations was correlated with histologic subtype but *BRAF*, *ALK*, and *PI3KCA* were not.
Song *et al.*	161	I-III	*EGFR* mutation associated with lepidic and micropapillary predominate histologic subtype.
Zhang *et al.*	215	I-III	Histologic subtype was an independent predictor of lymph node metastasis in tumor size ≤2cm non-small cell lung cancers.
Hung *et al.*	283	I	Micropapillary and solid predominant histologic subtype had lower recurrence-free probability.
Song *et al.*	261	I	High architectural grade (micropapillary and solid) was an independent factor for poor disease free survival and overall survival.
Zhang *et al.*	176	IA	Histologic classification was an independent predictive factor for disease-free survival.
Gu *et al.*	292	I-III	Histologic classification was an independent predict factor for disease-free survival and overall survival.

*Percentages refer to each individual histologic predominant subtype with the total 100% in each cohort.
AIS, adenocarcinoma *in situ;* MIA, minimal invasive adenocarcinoma.

Figure 2 The application of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification in lung adenocarcinoma in the clinical studies based on Chinese population.

used East Asian patients, a higher incidence of *EGFR* mutations were observed in micropapillary pattern lung adenocarcinomas (64,82-85). However, the some studies did not show this correlation (77-79,86). The implementation of more clinical trials will be needed to investigate the long term benefits garnered from TKI treatment in patients with micropapillary lung adenocarcinomas.

Current validation for Chinese population

Ethnic differences in the epidemiology and the clinical behavior of lung cancer between East Asians and Caucasians have been acknowledged since the introduction of *EGFR* TKIs and the subsequent discovery of activating *EGFR* mutations (87,88). To understand the relationship between the new IASLC histologic subtyping classification and genetic mutations in the Chinese population, three studies were proposed. The *EGFR* mutation was positively associated with lepidic, acinar, and micropapillary predominant histologic subtypes and negatively associated with solid predominant histologic subtypes (77,84,85). In contrast, the *KRAS* mutation was positively associated with invasive mucinous adenocarcinomas (77,84). These results were similar to other studies conducted on Western populations except for two of them that showed that *EGFR* mutations positively correlated with the micropapillary histologic subtype (84,85). Further studies were warranted to confirm that there was a difference between *EGFR* mutation incidence rate of the micropapillary histologic subtype in East Asian and Caucasian populations.

With the regard to the validation of the prognostic value of the new IASLC/ATS/ERS classification, there were five studies that demonstrated that the histologic subtypes were independent predictors for a patient's clinical outcome (67-70,89). These results (shown in *Figure 2*) confirm that the new classification system will be applicable to the

Chinese population and could be useful in the selection patients for personalized therapies.

The IASLC/ATS/ERS classification and surgical procedure options

We further investigated the prognostic significance of the histologic pattern in small (≤2 cm) stage I lung adenocarcinoma patients who underwent different surgical procedures (limited resection vs. lobectomy) (90). We saw that patients who had a micropapillary morphologic pattern of ≥5% and were treated with limited resection (wedge resection or segmentectomy) had a higher incidence of locoregional recurrence while those treated with lobectomy had a lower incidence locoregional recurrence. This suggests that this histologic pattern has a greater chance of locoregional recurrence in comparison to other histologic morphologies. It is the important to note that there was a reduced probability of recurrence in cases with a surgical margin of ≥1 cm. The results of our study suggest that patients treated with limited resection and whose tumors are determined to have a micropapillary of ≥5% (this is determined by the use of permanent sections) may require a complete lobectomy or further adjuvant treatment. Although limited resections had a higher locoregional recurrence rate in early stage I lung adenocarcinoma with micropapillary ≥5%, it might be useful to investigate the utility of extended surgeries, such as lobectomies, in those types of patients. However, identifying the presence of small percentage of micropapillary morphologic patterns on preoperative imaging, core biopsies and intraoperative frozen sections is difficult and unreliable (91,92). Further studies were warranted to overcome this condition.

Prognostic factors not included in the 2011 IASLC/ATS/ERS lung adenocarcinoma histologic classification

According to the aforementioned large cohort validation studies, the 2011 IASLC/ATS/ERS lung adenocarcinoma histologic classification has great prognostic value (7,63,64). In addition to this, we have recently published studies that discuss the use of several prognostic factors that are based on morphological analysis (histologic features such as nuclear feature, cribriform subtype, and presence of a micropapillary pattern), immunohistochemical analysis [Ki-67 labeling index and thyroid transcription factor-1 (TTF-1)], and immune markers (tumor-infiltrating lymphocyte and cytokine receptor expression), when investigating a large cohort comprised of stage I lung adenocarcinoma patients (90,93-96).

Using a cohort of stage I lung adenocarcinoma patients, we evaluated all of the nuclear features (nuclear diameter, nuclear atypia, nuclear/cytoplasmic ratio, chromatin pattern, prominence of nucleoli, intranuclear inclusions, mitotic count, and atypical mitoses) and identified nuclear diameter, nuclear atypia, mitotic count, and atypical mitoses as predictors of an increased risk of recurrence (93). Among these features, we discovered that mitotic count was an independent risk factor of recurrence. Using this information, we established a combined architectural (based on the 2011 IASLC/ATS/ERS classification) and mitotic count grading system. This new system was able to better stratify patients for risk of recurrence when compared with the stratification system used in the 2011 IASLC/ATS/ERS classification alone.

We reported the prognostic significance of the cribriform pattern as a predominant subtype. In conjunction with the 2011 IASLC/ATS/ERS classification, we proposed using the cribriform pattern as a distinct histologic subtype with a poor prognosis (94). The recurrence-free probability for patients with cribriform predominant tumors was significantly lower than it was for patients with acinar or papillary predominant tumors and comparable to patients with micropapillary or solid predominant tumors. These findings give credence to the hypothesis that the cribriform pattern was an independent prognostic factor.

In addition to mitotic count, Ki-67 also represents a proliferation of tumor cells. Based on immunohistochemical analysis using tissue microarrays on stage I lung adenocarcinomas, we reported a high Ki-67 labeling index; this was indicative of a predictor of recurrence (93). While TTF-1 is known as a positive diagnostic marker for differentiating between lung adenocarcinomas and squamous cell carcinomas, TTF-1 negativity is an independent risk factor of recurrence in stage I lung adenocarcinomas (95). More importantly, tumoral TTF-1 expression status was able to further stratify patients with intermediate grade tumors (acinar and papillary predominant subtype) based on their risk of recurrence.

Recent evidence suggests that the immune microenvironment has prognostic significance in solid cancers (97,98). We investigated the prognostic significance of tumor-infiltrating immune cells in tumor and tumor-related stroma, tumoral cytokine, and cytokine receptor expression via immunohistochemical analysis using tissue

microarrays in two large, independent cohorts (training and validation; n=478 for each) of patients with stage I lung adenocarcinomas. We identified high forkhead box P3 (FoxP3)/CD3 lymphocyte infiltration ratio in tumor-related stroma, tumoral interleukin-7 receptor (IL-7R) overexpression, and a loss of IL-12Rβ2 expression as poor independent prognostic indicators of recurrence (96). All of these immune markers were able to further stratify the risk of recurrence in each histological grade based on the 2011 IASLC/ATS/ERS classification.

Future potential of the 2011 IASLC/ATS/ERS classification

Clinical trails comparing limited resections and lobectomies should also stratify patients according to these histologic architectural grades and morphologic subtypes. This is because patients with high architectural grade tumors (micropapillary and/or solid predominant subtypes) may be suitable for lobectomies while those with low grade tumors are more suitable for limited resections. The recent randomized trials that assessed low-dose CT screening for lung cancer (99-101) suggested that an increasing number of patients will be diagnosed with adenocarcinomas with lepidic growth at an early stage. This may ultimately contribute to a reduced disease-related mortality rate for those types of patients in the future. Therefore, it is important to recognize the clinical characterization of early-stage lung adenocarcinomas with lepidic predominant patterns. Since AIS and MIA are very curable, if completely resected, they have become of great interest to surgeons who may be considering limited resection over standard lobectomy as a treatment option.

While several previous clinical trials applied adjuvant chemotherapy to stage I NSCLC patients, that treatment yielded no clinical benefit (102,103). The 2011 IASLC/ATS/ERS classification identified patients in the high-risk group of recurrence such as those with micropapillary and solid predominant tumors. Additionally, the prognostic factors that we recently identified (nuclear grade, cribriform pattern, TTF-1 negativity, high Ki-67 labeling index, immune markers, and SUVmax on FDG-PET), provided better prognostic stratification than did the 2011 IASLC/ATS/ERS classification did alone (74,90,93-96). Therefore, we believe that the new classification system, which includes the previously mentioned factors, could help to identify stage I lung adenocarcinoma patients at a high-risk for recurrence who may benefit from adjuvant chemotherapy. This would, in turn, improve their overall survival rate.

The new IASLC/ATS/ERS adenocarcinoma classification may help in comparing histologic characteristics of synchronous multiple lung adenocarcinomas to determine whether they are intrapulmonary metastases or separate primaries. A combination of comprehensive histologic subtyping and other histologic characteristics have been shown to have a correlation with molecular analyses and clinical behavior (104,105).

The application of the new classification system in small specimens, including cytology, is still challenging and requires further investigation. In those small specimens, there may be other morphologic findings, such as nuclear grade (nuclear atypia and diameter), that could help stratify patients based on their risk of recurrence or cancer-related death (93,106).

Although the prognostic values of the 2011 IASLC/ATS/ERS classification have been validated, reproducibility (interobserver agreement) has not been adequately investigated to identify a predominant pattern in lung adenocarcinomas. The only way to confirm reproducibility and improve identification of each histologic pattern using this new classification system is through the development of more precise definitions combined with better training when interpreting system terminology.

Implications for Chinese physicians

With the number of diagnoses increasing and the need for management of lung cancer growing in the Chinese population, this new classification system is both timely and much needed. While this new classification system requires some training for pathologists interested in lung cancer, it can readily be implemented in any hospital that performs hematoxylin and eosin (H&E) staining. Furthermore, any H&E slide can easily be reviewed by pathologists at other treatment centers to confirm the diagnosis. Unlike molecular testing, which requires complex resources and advanced equipment, the IASLC/ATS/ERS classification system is easy to implement and has low maintenance costs. Awareness of this new classification system and the appropriate collaboration with high-volume centers for validation of the predominant histological subtype on H&E slides will assist treating physicians in stratifying the prognoses of their patients. Of even greater consequence, there is the possibility that this new classification system may identify differences in Chinese patients' histologic subtype. This will form the basis for a modified classification

for lung cancer management in Chinese patients.

Summary

The 2011 IASLC/ATS/ERS classification system has been proven to have powerful prognostic value in five large cohorts (>300 patients) across multiple countries (8,58-60). Patients with AIS and MIA had 100% DFS with no recurrent diseases. Patients with micropapillary or solid predominant tumors would be classified as a high-risk group for recurrence or cancer-related death. Patients with acinar predominant tumors will be classified as an intermediate risk group. Patients with papillary predominant tumors might be classified as an intermediate risk group, although further investigation would be needed. On the basis of our published studies, additional prognostic factors (nuclear grade, cribriform pattern, high Ki-67 labeling index, TTF-1 negativity, immune markers, and SUVmax on FDG-PET) and the 2011 IASLC/ATS/ERS classification system could further stratify patients into prognostic subgroups for recurrence and cancer-related death. Ultimately, this may aid in clinical management and decision making, especially for patients with early-stage lung adenocarcinomas, when deciding whether or not to opt for adjuvant chemotherapy.

This new classification system of lung adenocarcinomas, the predominant type of lung cancer, can be readily implemented at any hospital in China that has the capacity to perform H&E staining. The reproducibility of the classification system and its prognostic importance for patients with lung cancer in this setting require further investigation.

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