**The New International Multidisciplinary Histological Classification of Lung Adenocarcinoma and Clinical Implications for Indian Physicians**

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In 2011, a new histologic classification of lung adenocarcinomas (IASLC/ATS/ERS) was proposed based on the recommendations of an international and multidisciplinary panel that included thoracic medical oncologists, pulmonologists, radiologists, molecular biologists, thoracic surgeons and pathologists. 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. The prognostic value of this classification has been validated in large, independent cohorts from multiple countries. Patients with adenocarcinomas *in situ* and minimally invasive adenocarcinomas experienced no recurrence. Patients with micropapillary or solid predominant tumors would be classified as high risk for recurrence or cancer-related death. Patients with acinar and papillary predominant tumors might be classified as an intermediate-risk group, but further investigation is needed for papillary subtype. This classification, coupled with additional prognostic factors (nuclear grade, cribriform pattern, high Ki-67 labeling index, TTF-1 negativity, immune markers and SUVmax on FDG-PET), which we have published on extensively, could further stratify patients into prognostic subgroups that may help with clinical management. This new classification for the most common type of lung cancer is important for oncologists practicing in India, as its implementation would require only hematoxylin and eosin (H&E) histology slides, the most common type of stain used at hospitals. It can be implemented with basic pathologist training and no additional costs. Furthermore, implementation and analyses would identify if this classification is valid for Indian patients or a specific modification is required.

**INTRODUCTION**

Lung cancer is the leading cause of cancer deaths worldwide (Jemal *et al.*, 2011; Siegel *et al.*, 2012). Over the past decade, the rate of adenocarcinoma (the most frequent subtype of lung cancer) has increased in a majority of the countries (Devesa *et al.*, 2005; Youlden *et al.*, 2008). Currently, the single most important factor that determines prognosis for patients with lung adenocarcinomas is tumor-nodal-metastasis (TNM) stage (Edge *et al.*, 2009). Lung adenocarcinoma is a heterogeneous tumor with great 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 molecular genetic information (Travis *et al.*, 2004). Despite the updating, there is limited clinical

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utility in the 2004 WHO classification of lung adenocarcinomas, since more than 90% of adenocarcinomas are classified as a mixed subtype even though they have a wide variety of clinical outcomes (Motoi et al., 2008; Travis et al., 2011; Yoshizawa et al., 2011). Increasing evidence suggests that histologic pattern scan identifies significant prognostic subsets of patients with lung adenocarcinomas (Barletta et al., 2010; Borczuk et al., 2009; Motoi et al., 2008; Nakazato et al., 2010; Sica et al., 2010; Yim et al., 2007). Multiple studies have shown that patients with pure lepidic (noninvasive) adenocarcinomas had 100%, 5-year disease-free survival (Koike et al., 2009; Noguchi et al., 1995; Sakurai et al., 2004; Vazquez et al., 2009). Other studies showed that patients with lepidic predominant minimally invasive (≤ 5 mm invasion) adenocarcinomas had near 100% survival (Borzczuk et al., 2009; Maeshima et al., 2010; Yim et al., 2007). Lepidic predominant invasive tumors also correlate with a favorable prognosis in patients with resected lung adenocarcinomas (Lee et al., 2009; Lin et al., 2006; Yokose et al., 2000). In contrast, the micropapillary pattern bodes a poor prognosis in patients with lung adenocarcinomas (Miyoshi et al., 2003; Nagano et al., 2010). In the WHO classification, the diagnostic criteria are based primarily on H&E examination with recognition of importance of integration of immunohistochemical, histochemical, and molecular studies. 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 define prognosis, advances in radiologic-pathologic correlations, molecular biology, and thoracic medical oncology for lung adenocarcinomas over the past decade have been reported. On chest computed tomography (CT) of lung adenocarcinomas, the correlations between lepidic growth and ground-glass opacity and between invasive components and solid components, have been identified and predict histologic subtypes for patient prognosis. CT has also been used for improving preoperative clinical decision-making of surgical procedures (i.e., lobectomy versus limited resection) (Nakata et al., 2003; Okada et al., 2006; Suzuki et al., 2002; Takashima et al., 2002).

Recent advances in molecular biology in conjunction with medical oncology have demonstrated that activating mutations in the tyrosine kinase domain of epidermal growth factor receptors (EGFR) predicts responsiveness to EGFR tyrosine kinase inhibitors (TKI) in patients with non-small cell lung cancer (NSCLC) (Lynch et al., 2004; Paez et al., 2004; Pao et al., 2004). The mutations are most frequently observed in females, in non-smokers and in Asian patients with adenocarcinomas (Lynch et al., 2004; Paez et al., 2004; Pao et al., 2004; Shigematsu et al., 2005; Tam et al., 2006). EGFR mutations have also been associated with lepidic pattern adenocarcinomas, formerly known as bronchioloalveolar carcinoma (BAC) patterns (Blons et al., 2006; Hsieh et
al., 2005; Marchetti et al., 2005; Tam et al., 2006). The association led to the hypothesis that tumors with lepidic pattern adenocarcinomas may be correlated with the EGFR mutations and may predict responses to TKI (Kim et al., 2004; Miller et al., 2004; Zakowski et al., 2009). In addition, incidence of the specific secondary EGFR mutation (T790M) is the main molecular mechanism responsible for acquired resistance to EGFR-TKIs (Suda et al., 2010; Yun et al., 2008). Kirsten rat sarcoma viral oncogene homolog (KRAS) is one of the downstream molecules in the EGFR signaling pathway (Mitsudomi and Yatabe, 2007; Riely et al., 2009). In contrast to EGFR mutations, KRAS mutations predict resistance to TKI treatment in patients with NSCLC (Eberhard et al., 2005; Pao et al., 2005) and are correlated with a history of cigarette smoking and poor patient prognosis (Ahrendt et al., 2001; Marks et al., 2008; Mascaux et al., 2005; Tam et al., 2006). In addition, the KRAS mutation shows a correlation with invasive mucinous adenocarcinoma, formerly known as mucinous BAC (Casali et al., 2010; Finberg et al., 2007; Hata et al., 2010; Kakegawa et al., 2011; Marchetti et al., 1996). A recently discovered anaplastic lymphoma kinase (ALK) rearrangement predicts sensitivity to a targeted agent (Crizotinib) (Kwak et al., 2010; Shaw et al., 2009). ALK rearrangements exclusively occur in adenocarcinomas and are correlated with specific histological findings such as signet-ring cell features, extracellular mucin, and cribriform patterns (Inamura et al., 2009; Jokoji et al., 2010; Rodig et al., 2009).

**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 thoracic medical oncologists, pulmonologists, radiologists, molecular biologists, thoracic surgeons, and pathologists as panel members, based on their special interest and expertise in lung adenocarcinoma (Travis et al., 2011). The panel performed a systematic review of the literature on lung adenocarcinoma 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 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 (Sica et al., 2010; Thunnissen et al., 2012; Yoshizawa et al., 2011). 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 (Travis et al., 2011).

The 2011 IASLC/ATS/ERS lung adenocarcinoma histologic classification

The IASLC/ATS/ERS lung adenocarcinoma histologic classification system was proposed in the Journal of Thoracic Oncology in 2011 (Travis et al., 2011). According to this new classification, a tumor should be reviewed by using comprehensive histological subtyping, recording the percentage of each histological component (lepidic, acinar, papillary, micropapillary, or solid) in 5% increments and choosing a single predominant pattern. In addition, total tumor size and invasive tumor size are measured. Tumor invasion was defined as: (1) histologic pattern other than lepidic (acinar, papillary, micropapillary or solid); (2) active myofibroblastic stroma correlated with invasive tumor cells; and (3) presence of lymphatic, vascular, or pleural invasion. Invasive tumor size was measured in two distinct ways comprising (1) cases where the tumor was small and the invasive area could be measured on a single slide, the invasive size was measured at either ×20 or ×40 magnification on the microscope, using a ruler; and (2) cases where the tumor was large and the invasive area could not be measured on a single slide, the invasive size was calculated by multiplying the total tumor size by the percentage of the invasive component (Yoshizawa et al., 2011). Adenocarcinoma in situ (AIS) is defined as a ≤ 3 cm tumor with a pure lepidic pattern, but without lymphatic, vascular, or pleural invasion or tumor necrosis. Minimally invasive adenocarcinoma (MIA) is defined as a ≤ 3 cm tumor with a lepidic predominant pattern and ≤ 5 mm stromal invasion, but with no lymphatic, vascular, or pleural invasion or tumor necrosis. It is important to understand that AIS and MIA should only be considered for diagnosis when a tumor is completely resected and the entire tumor area is histologically investigated (Travis et al., 2011). In addition, the CT findings and gross appearance of a tumor should be considered to ensure that a solid component is sampled from the tumor that appeared to be solid on the CT scan (Travis et al., 2011). Lepidic growth was classified into two patterns, nonmucinous and mucinous, according to the absence or presence of an intracellular mucinous feature. AIS and MIA were further subgrouped as nonmucinous, mucinous, or mixed mucinous/nonmucinous. Invasive adenocarcinomas (> 5 mm invasion size) were further divided into lepidic predominant (Figure 1A), acinar predominant (Figure 1B), papillary predominant (Figure 1C), micropapillary predominant (Figure 1D), solid predominant (Figure 1E), invasive mucinous adenocarcinoma (Figure 1F), colloid predominant adenocarcinoma, enteric adenocarcinoma and fetal adenocarcinoma (low and high grade).

Application of the IASLC/ATS/ERS adenocarcinoma classification to biopsy or cytologic specimens is challenging as these...
may not be representative of the total tumor due to histologic heterogeneity; there may also be a discrepancy between the initial and the final histologic diagnoses in a resection specimen (Travis et al., 2011). A recent study suggested that it may be unreliable and difficult to identify high grade histologic (solid and micropapillary) pattern on cytology specimens (Rodriguez et al., 2013). However, nuclear grade on cytologic specimens may provide support for the classification of tumors into different prognostic groups preoperatively (Sigel et al., 2012). This will be used in conjunction with the IASLC/ATS/ERS adenocarcinoma classification.

The IASLC/ATS/ERS histologic subtyping is primarily validated for early-stage lung adenocarcinomas. Testing for EGFR mutation in patients with advanced lung adenocarcinomas is also recommended by the IASLC/ATS/ERS classification because response and outcome to EGFR- TKIs can be predicted by presence of an EGFR mutation (Travis et al., 2011). According to the guidelines proposed by the College of American Pathologists, in order to do accurate testing for EGFR mutation, laboratories should use testing methods that allow the detection of mutation in specimens with ≥ 50% cancer cell content. Despite this, laboratories are strongly encouraged to use more sensitive tests that are able to detect mutations in specimens with as little as 10% cancer cells (Lindeman et al., 2013).

Regarding molecular findings, there may be important differences between the primary tumor and metastases of lung adenocarcinomas. However, further investigations are needed as the mutation status of metastases is unpredictable between
primary tumors and metastases (Travis et al., 2011).

Moreover, specific treatments (i.e., gefitinib, bevacizumab and pemetrexed) should be guided by histological types (adenocarcinoma versus squamous cell carcinoma) on the basis of dramatic advances in thoracic medical oncology over the past few years. Hence, IASLC/ATS/ERS classification recommends using immunohistochemistry to classify lung cancers into adenocarcinomas or squamous cell carcinomas; this being especially true if the tumor cannot be classified by light microscopy alone (Travis et al., 2011).

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

We summarized the published studies that validated the 2011 IASLC/ATS/ERS lung adenocarcinoma histologic classification using a large cohort (more than 300 patients as a study sample) in Table 1 (Tsuta et al., 2013; Warth et al., 2012; Yoshizawa et al., 2011; Yoshizawa et al., 2013). There was one study from the United States (n = 514) (Yoshizawa et al., 2011), one from Germany (n = 500) (Warth et al., 2012), and two from Japan (n = 440 and 904) (Tsuta et al., 2013; Yoshizawa et al., 2013). The study from the United States validated the new classification by using a homogeneous cohort composed of only stage I

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**Table 1. Published studies validating the IASLC/ATS/ERS lung adenocarcinoma classification (study sample > 300 patients)**

<table>
<thead>
<tr>
<th>Histologic subtype</th>
<th>United States (N = 514)</th>
<th>Germany (N = 500)</th>
<th>Japan (N = 440)</th>
<th>Japan (N = 904)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of patients DFS % (5-yr)</td>
<td>% of patients DFS (mean)</td>
<td>% of patients DFS % (5-yr)</td>
<td>% of patients OS % (5-yr)</td>
</tr>
<tr>
<td>AIS</td>
<td>0.2 100</td>
<td>0.0 NA</td>
<td>4.5 100</td>
<td>7.6 98</td>
</tr>
<tr>
<td>MIA</td>
<td>1.6 100</td>
<td>0.0 NA</td>
<td>7.5 100</td>
<td>3.7 67</td>
</tr>
<tr>
<td>Lepidic</td>
<td>5.6 90</td>
<td>8.2 72.6 mo.</td>
<td>8.2 94</td>
<td>15.0 74</td>
</tr>
<tr>
<td>Acinar</td>
<td>45.1 84</td>
<td>41.4 61.7 mo.</td>
<td>13.9 70</td>
<td>10.8 67</td>
</tr>
<tr>
<td>Papillary</td>
<td>27.8 83</td>
<td>4.6 37.7 mo.</td>
<td>40.7 67</td>
<td>37.4 74</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>2.3 67</td>
<td>6.6 33.8 mo.</td>
<td>4.3 0</td>
<td>6.7 62</td>
</tr>
<tr>
<td>Solitude</td>
<td>13.0 70</td>
<td>36.6 51.2 mo.</td>
<td>17.7 43</td>
<td>13.7 58</td>
</tr>
<tr>
<td>Inv. mucinous</td>
<td>2.5 76</td>
<td>2.4 88.1 mo.</td>
<td>2.3 89</td>
<td>5.0 76</td>
</tr>
<tr>
<td>Colloid</td>
<td>1.8 71</td>
<td>0.0 NA</td>
<td>0.7 NA</td>
<td>0.0 NA</td>
</tr>
<tr>
<td>Enteric</td>
<td>0.0 NA</td>
<td>0.2 NA</td>
<td>0.0 NA</td>
<td>0.0 NA</td>
</tr>
<tr>
<td>Fetal</td>
<td>0.0 NA</td>
<td>0.0 NA</td>
<td>0.2 NA</td>
<td>0.0 NA</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; OS, overall survival; NA, not applicable

patients (Yoshizawa et al., 2011), while the other studies comprised of patients with both early and advanced stage diseases (Jokoji et al., 2010; Rodriguez et al., 2013; Thunnissen et al., 2012).

Other 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 (Tsuta et al., 2013; Yoshizawa et al., 2011; Yoshizawa et al., 2013). Despite this, there was a limitation of this classification that was identified. The limitation was that the majority of tumors (50–70%) classified as having intermediate grade histology (acinar or papillary predominant subtype) may actually include a heterogeneously prognostic subgroup. We propose that another prognostic factor, preferably one based on morphological analysis, is needed for this majority group. We have recently published studies that discuss the use of several prognostic factors that are based on morphological analysis, such as histologic findings (nuclear feature, cribriform subtype, and presence of micropapillary pattern), immunohistochemical analysis (Ki-67 labeling index and TTF-1), immune markers (tumor-infiltrating lymphocyte and cytokine receptor expression) and radiologic biomarkers (maximum standard uptake value [SUVmax] on 18F-fluorodeoxyglucose [FDG] uptake on positron emission tomography [PET]), when investigating a large cohort comprising stage I lung adenocarcinoma patients (Kadota et al., 2012a; Kadota et al., 2012b; Kadota et al., 2013a; Kadota et al., 2013b; Nitadori et al., 2013; Suzuki et al., 2013).

Using a cohort of stage I lung adenocarcinoma patients, we evaluated all the nuclear features including 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 risk of recurrence (Kadota et al., 2012b). 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 stratification done using the 2011 IASLC/ATS/ERS classification per se.

We also reported the prognostic significance of the cribriform pattern as a predominant subtype. In addition to the 2011 IASLC/ATS/ERS classification, we proposed using this as a distinct histologic subtype with poor prognosis (Kadota et al., 2013b). The recurrence-free probability for patients with cribriform predominant tumors was significantly lower than it was for patients with acinar or papillary predominant tumors; however, it was comparable to the probability for patients with micropapillary or solid
predominant tumors. These findings give credence to the hypothesis that cribriform pattern was an independent prognostic factor.

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). We identified the presence (≥ 5%) of micropapillary patterns as the risk factor of recurrence in patients treated with limited resection but not for those treated with lobectomy (Nitadori et al., 2013). Interestingly, in the limited resection group, tumors that presented a micropapillary pattern correlated with locoregional recurrence.

In addition to the mitotic count, Ki-67 also represents proliferation of tumor cells. Based on immunohistochemical analysis using tissue microarrays on stage I lung adenocarcinomas, we reported a high Ki-67 labeling index (threshold, 10%) which was indicative of it being a predictor of recurrence (Kadota et al., 2012b). Whereas, 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 (Kadota et al., 2013a). More importantly, tumoral TTF-1 expression status further stratified patients with intermediate grade tumors (acinar and papillary predominant subtype) based on their risk of recurrence.

Recent evidence suggests that the immune microenvironment also has prognostic significance in solid cancers (Galon et al., 2006; Mahmoud et al., 2011). 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 2 large, independent cohorts (training and validation; n = 478 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 (Suzuki et al., 2013).

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.

SUVmax on FDG-PET has been recognized as a prognostic factor in lung cancer. Accordingly, we investigated the prognostic value of SUVmax on FDG-PET in patients with stage I lung adenocarcinoma (Kadota et al., 2012a). High SUVmax (≥ 3.0) was associated with a poor prognosis of recurrence and it further stratified the risk of recurrence in patients with intermediate grade histology (acinar or papillary predominant tumors). We observed that a high SUVmax correlated with high grade histology based on the 2011 IASLC/ATS/ERS classification.

**Future potential of the 2011 IASLC/ATS/ERS classification**

As stated earlier, the use of the 2011 IASLC/ATS/ERS classification as a powerful
prognostic evaluator has been validated many times over by large, independent data sets from multiple countries (Jokoji et al., 2010; Motoi et al., 2008; Rodriguez et al., 2013; Thunnissen et al., 2012). Recently, our group has proposed the use of other prognostic factors, in addition to those already used by the 2011 IASLC/ATS/ERS classification, based on a study of a large, homogeneous cohort comprising patients with stage I lung adenocarcinomas (Kadota et al., 2012a; Kadota et al., 2012b; Kadota et al., 2013a; Kadota et al., 2013b; Nitadori et al., 2013; Suzuki et al., 2013). CT scans of lung adenocarcinomas have suggested a correlation between ground-glass opacity (an air density-containing area on a CT scan) and lepidic growth patterns (Nakata et al., 2003; Suzuki et al., 2002; Takashima et al., 2002). Results from the recent randomized trials assessing low-dose CT screening for lung cancer (Aberle et al., 2011a; Aberle et al., 2011b; van lersel et al., 2007) suggest 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. Hence, it is important to recognize the clinical characterization of early-stage lung adenocarcinoma with lepidic predominant pattern. Since AIS and MIA are curable if completely resected, it is of interest to surgeons considering limited resection over standard lobectomy as a treatment option.

While several previous clinical trials applied adjuvant chemotherapy to stage I NSCLC patients, the treatment yielded no clinical benefit (Felip et al., 2010; Strauss et al., 2008). 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 recently identified by other groups, such as nuclear grade, cribriform pattern, TTF-1 negativity, high Ki-67 labeling index, immune markers, and SUVmax on FDG-PET, provided better prognostic stratification than the 2011 IASLC/ATS/ERS classification alone (Kadota et al., 2012a; Kadota et al., 2012b; Kadota et al., 2013a; Kadota et al., 2013b; Nitadori et al., 2013; Suzuki et al., 2013). Therefore, we believe that the new classification, which includes the previously mentioned factors, is crucial for identification of stage I lung adenocarcinoma patients at a high-risk of recurrence who may benefit from adjuvant chemotherapy, thus improving their overall survival rate.

The application of the new classification system in small specimens, including cytology, is challenging and requires further investigation. In those small specimens, there may be other morphologic findings, such as nuclear grade (nuclear atypia and diameter), which could help stratify patients based on their risk of recurrence or cancer-related death (Kadota et al., 2012b; Sigel et al., 2012).

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. To confirm reproducibility and improve identification of each histologic pattern using the new classification system, development of precise definitions combined with better training in the interpretation of the system's terminology is necessary.

**Indian context**

With the number of lung cancer diagnoses increasing and the need for management of cancer growing in India, this new classification system is both timely and much needed. The new IASLC/ATS/ERS classification, while requiring a certain amount of additional training for pathologists interested in lung cancer, can be implemented early in hospitals performing H&E staining. Furthermore, the H&E slide can be easily re-reviewed by pathologists at other treatment centres to confirm the diagnosis. Unlike molecular testing, perceived as complex with requirement of resources and advanced equipment, the IASLC/ATS/ERS classification system is easy to implement with low maintenance costs. Awareness of this new classification system and appropriate collaboration with high-volume centers for validation of the predominant histological subtype on H&E slides will assist treating physicians in stratifying prognosis of their patients. There is the possibility that this new classification system may identify differences in Indian patient's histologic subtypes which will form the basis for a modified classification for lung cancer management in Indian patients. However, in order to apply the new classification system to clinical practice in India, prognostic value of histologic subtypes should be confirmed and validated using cohorts of Indian patients.

**SUMMARY**

The 2011 IASLC/ATS/ERS classification system has been proven to have powerful prognostic value in four large cohorts (> 300 patients) across multiple countries (Jokoji et al., 2010; Rodriguez et al., 2013; Thunnissen et al., 2012; Yoshizawa et al., 2011). Patients with AIS and MIA show 100% DFS with no recurrent diseases. Patients with micropapillary or solid predominant tumors are 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 may be classified as an intermediate-risk group, although further investigation will 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), combined with the 2011 IASLC/ATS/ERS classification, will further stratify patients into prognostic subgroups for recurrence and cancer-related deaths. Ultimately, this may aid in clinical management and decision making, particularly for patients with early-stage lung adenocarcinomas, and provide informed decision-making as to the option of adjuvant chemotherapy.

To emphasize that the new classification...
system of lung adenocarcinomas, in the predominant type of lung cancer observed in India, is readily implementable at any hospital in the country with a pathology laboratory handling routine H&E staining. The reproducibility of the classification system and the prognostic importance for patients with lung cancer in this setting requires further investigation.

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CONFLICT OF INTEREST
The authors claim no conflict of interest.

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