BRJ
Biomedical Research Journal

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

Kyuichi Kadota[1], Ming-Ching Lee[1], and Prasad S. Adusumilli[1,2]

[1]Thoracic Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, USA.
[2]Center for Cell Engineering, Memorial Sloan-Kettering Cancer Center, New York, USA.

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

Key words: Lung, adenocarcinoma, histological classification, prognosis.
***Corresponding Author:** Prasad S. Adusumilli, Thoracic Service, Department of Surgery, Center for Cell Engineering, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA.
Email: adusumip@mskcc.org

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 (Borczuk *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: Historical perspective

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), micropapillarypredominant (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

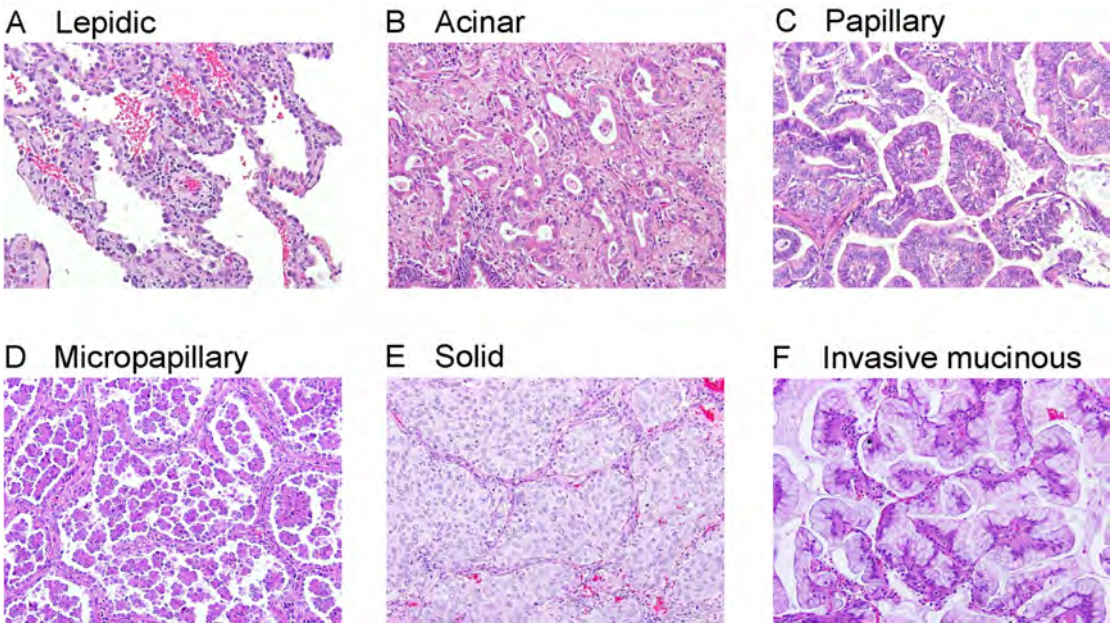

Figure 1. Histologic pattern (hematoxylin and eosin stain; original magnification: ×100 magnification).
(A) Non-mucinous lepidic pattern. (B) Acinar pattern. (C) Papillary pattern. (D) Micropapillary pattern. (E) Solid pattern. (F) Invasive mucinous pattern.

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 thatare 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

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

Histologic subtype	United States (N = 514)		Germany (N = 500)		Japan (N = 440)		Japan (N = 904)	
	% of patients	DFS % (5-yr)	% of patients	DFS (mean)	% of patients	DFS % (5-yr)	% of patients	OS % (5-yr)
AIS	0.2	100	0.0	NA	4.5	100	7.6	98
MIA	1.6	100	0.0	NA	7.5	100	3.7	
Lepidic	5.6	90	8.2	72.6 mo.	8.2	94	15.0	93
Acinar	45.1	84	41.4	61.7 mo.	13.9	70	10.8	67
Papillary	27.8	83	4.6	37.7 mo.	40.7	67	37.4	74
Micropapillary	2.3	67	6.6	33.8 mo.	4.3	0	6.7	62
Solid	13.0	70	36.6	51.2 mo.	17.7	43	13.7	58
Inv. mucinous	2.5	76	2.4	88.1 mo.	2.3	89	5.0	76
Colloid	1.8	71	0.0	NA	0.7	NA	0.0	NA
Enteric	0.0	NA	0.2	NA	0.0	NA	0.0	NA
Fetal	0.0	NA	0.0	NA	0.2	NA	0.0	NA

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

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). As for the diagnostic markers, thyroid transcription factor-1 (TTF-1) and Napsin A have been validated as adenocarcinoma markers, and p40 and p63 as squamous cell carcinoma markers (Bishop *et al*., 2012; Rekhtman *et al*., 2011; Turner *et al*., 2012).

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 at 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

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.

ACKNOWLEDGMENTS

We thank Alex Torres for his editorial assistance.

CONFLICT OF INTEREST

The authors claim no conflict of interest.

REFERENCES

Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, *et al.* Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011a;365(5):395-409.

Aberle DR, Berg CD, Black WC, Church TR, Fagerstrom RM, Galen B, *et al.* The National Lung Screening Trial: overview and study design. *Radiology* 2011b;258(1):243-253.

Ahrendt SA, Decker PA, Alawi EA, Zhu Yr YR, Sanchez-Cespedes M, Yang SC, *et al.* Cigarette smoking is strongly associated with mutation of the K-ras gene in patients with primary adenocarcinoma of the lung. *Cancer* 2001;92(6):1525-1530.

Barletta JA, Yeap BY, Chirieac LR. Prognostic significance of grading in lung adenocarcinoma. *Cancer* 2010;116(3):659-669.

Bishop JA, Teruya-Feldstein J, Westra WH, Pelosi G, Travis WD, Rekhtman N. p40 (DeltaNp63) is superior to p63 for the diagnosis of pulmonary squamous cell carcinoma. *Mod Pathol* 2012;25(3):405-415.

Blons H, Cote JF, Le Corre D, Riquet M, Fabre-Guilevin E, Laurent-Puig P, Danel C. Epidermal growth factor receptor mutation in lung cancer are linked to bronchioloalveolar differentiation. *Am J Surg Pathol* 2006;30(10):1309-1315.

Borczuk AC, Qian F, Kazeros A, Eleazar J, Assaad A, Sonett JR, *et al.* Invasive size is an independent predictor of survival in pulmonary adenocarcinoma. *Am J Surg Pathol* 2009;33(3):462-469.

Casali C, Rossi G, Marchioni A, Sartori G, Maselli F, Longo L, *et al.* A single institution-based retrospective study of surgically treated bronchioloalveolar adenocarcinoma of the lung: clinicopathologic analysis, molecular features, and possible pitfalls in routine practice. *J Thorac Oncol* 2010;5(6):830-836.

Devesa SS, Bray F, Vizcaino AP, Parkin DM. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. *Int J Cancer* 2005;117:294-299.

Eberhard DA, Johnson BE, Amler LC, Goddard AD, Heldens SL, Herbst RS, *et al.* Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005;23(25):5900-5909.

Edge SB, Byrd DR, Compton CC, Fritz, A.G., Greene, F.L., Trotti, A. American Joint Committee on Cancer Cancer Staging

Manual. 7th ed. New York, NY: Springer; 2009:253-270.

Felip E, Rosell R, Maestre JA, Rodríguez-Paniagua JM, Morán T, Astudillo J, *et al.* Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *J Clin Oncol* 2010;28:3138-3145.

Finberg KE, Sequist LV, Joshi VA, Muzikansky A, Miller JM, Han M, *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(3):320-326.

Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pages C, *et al.* Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 2006;313(5795):1960-1964.

Hata A, Katakami N, Fujita S, Kaji R, Imai Y, Takahashi Y, *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(8):1197-1200.

Hsieh RK, Lim KH, Kuo HT, Tzen CY, Huang MJ. Female sex and bronchioloalveolar pathologic subtype predict EGFR mutations in non-small cell lung cancer. *Chest* 2005;128(1):317-321.

Inamura K, Takeuchi K, Togashi Y, Hatano S, Ninomiya H, Motoi N, *et al.* EML4-ALK lung cancers are characterized by rare other mutations, a TTF-1 cell lineage, an acinar histology, and young onset. *Mod Pathol* 2009;22(4):508-515.

Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61(2):69-90.

Jokoji R, Yamasaki T, Minami S, Komuta K, Sakamaki Y, Takeuchi K, Tsujimoto M. Combination of morphological feature analysis and immunohistochemistry is useful for screening of EML4-ALK-positive lung adenocarcinoma. *J Clin Pathol* 2010;63(12):1066-1070.

Kadota K, Colovos C, Suzuki K, Rizk NP, Dunphy MP, Zabor EC, *et al.* FDG-PET SUVmax combined with IASLC/ATS/ERS histologic classification improves the prognostic stratification of patients with stage I lung adenocarcinoma. *Ann Surg Oncol* 2012a;19(11):3598-3605.

Kadota K, Suzuki K, Kachala SS, Zabor EC, Sima CS, Moreira AL, *et al.* A grading system combining architectural features and mitotic count predicts recurrence in stage I lung adenocarcinoma. *Mod Pathol* 2012b;25(8):1117-1127.

Kadota K, Nitadori J, Sarkaria IS, Sima CS, Jia X, Yoshizawa A, *et al.* Thyroid transcription factor-1 expression is an independent predictor of recurrence and correlates with the IASLC/ATS/ERS histologic classification in patients with stage I lung adenocarcinoma. *Cancer* 2013a;119(5):931-938.

Kadota K, Yeh Y, Sima CS, Rusch VW, Moreira AL, Adusumilli PS, Travis WD. 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* 2013b;Nov 1. Doi: 10.1038/modpathol. 2013b.188. [Epub ahead of print].

Kakegawa S, Shimizu K, Sugano M, Miyamae Y, Kaira K, Araki T, *et al.* Clinicopathological features of lung adenocarcinoma with KRAS

mutations. *Cancer* 2011;117(18):4257-4266.

Kim YH, Ishii G, Goto K, Nagai K, Tsuta K, Shiono S, *et al*. Dominant papillary subtype is a significant predictor of the response to gefitinib in adenocarcinoma of the lung. *Clin Cancer Res* 2004;10(21):7311-7317.

Koike T, Togashi K, Shirato T, Sato S, Hirahara H, Sugawara M, *et al.* Limited resection for noninvasive bronchioloalveolar carcinoma diagnosed by intraoperative pathologic examination. *Ann Thorac Surg* 2009;88(4):1106-1111.

Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, *et al.* Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010;363(18):1693-1703.

Lee HY, Han J, Lee KS, Koo JH, Jeong SY, Kim BT, *et al.* Lung adenocarcinoma as a solitary pulmonary nodule: prognostic determinants of CT, PET, and histopathologic findings. *Lung Cancer* 2009;66(3):379-385.

Lin DM, Ma Y, Zheng S, Liu XY, Zou SM, Wei WQ. Prognostic value of bronchioloalveolar carcinoma component in lung adenocarcinoma. *Histol Histopathol* 2006;21(6):627-632.

Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, *et al.* Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *Arch Pathol Lab Med* 2013;137(6):828-860.

Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350(21):2129-2139.

Maeshima AM, Tochigi N, Yoshida A, Asamura H, Tsuta K, Tsuda H. Histological scoring for small lung adenocarcinomas 2 cm or less in diameter: a reliable prognostic indicator. *J Thorac Oncol* 2010;5(3):333-339.

Mahmoud SM, Paish EC, Powe DG, Macmillan RD, Grainge MJ, Lee AH, *et al.* Tumor-infiltrating CD8+ lymphocytes predict clinical outcome in breast cancer. *J Clin Oncol* 2011;29(15):1949-1955.

Marchetti A, Buttitta F, Pellegrini S, Chella A, Bertacca G, Filardo A, *et al*. Bronchioloalveolar lung carcinomas: K-ras mutations are constant events in the mucinous subtype. *J Pathol* 1996;179(3):254-259.

Marchetti A, Martella C, Felicioni L, Barassi F, Salvatore S, Chella A, *et al.* EGFR mutations in non-small-cell lung cancer: analysis of a large series of cases and development of a rapid and sensitive method for diagnostic screening with potential implications on pharmacologic treatment. *J Clin Oncol* 2005;23(4):857-865.

Marks JL, Broderick S, Zhou Q, Chitale D, Li AR, Zakowski MF, *et al*. Prognostic and therapeutic implications of EGFR and KRAS mutations in resected lung adenocarcinoma. *J Thorac Oncol* 2008;3(2):111-116.

Mascaux C, Iannino N, Martin B, Paesmans M, Berghmans T, Dusart M, *et al.* The role of RAS oncogene in survival of patients with lung cancer: a systematic review of the literature with meta-analysis. *Br J Cancer* 2005;92(1):131-139.

Miller VA, Kris MG, Shah N, Patel J, Azzoli C, Gomez J, *et al.* Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. *J Clin Oncol* 2004;22(6):1103-1109.

Mitsudomi T, Yatabe Y. Mutations of the epidermal growth factor receptor gene and related genes as determinants of epidermal growth factor receptor tyrosine kinase inhibitors sensitivity in lung cancer. *Cancer Sci* 2007;98(12):1817-1824.

Miyoshi T, Satoh Y, Okumura S, Nakagawa K, Shirakusa T, Tsuchiya E, Ishikawa Y. Early-stage lung adenocarcinomas with a micropapillary pattern, a distinct pathologic marker for a significantly poor prognosis. *Am J Surg Pathol* 2003;27(1):101-109.

Motoi N, Szoke J, Riely GJ, Seshan VE, Kris MG, Rusch VW, *et al.* Lung adenocarcinoma: modification of the 2004 WHO mixed subtype to include the major histologic subtype suggests correlations between papillary and micropapillary adenocarcinoma subtypes, EGFR mutations and gene expression analysis. *Am J Surg Pathol* 2008;32(6):810-827.

Nagano T, Ishii G, Nagai K, Ito T, Kawase A, Takahashi K, *et al.* Structural and biological properties of a papillary component generating a micropapillary component in lung adenocarcinoma. *Lung Cancer* 2010;67(3):282-289.

Nakata M, Sawada S, Saeki H, Takashima S, Mogami H, Teramoto N, Eguchi K. Prospective study of thoracoscopic limited resection for ground-glass opacity selected by computed tomography. *Ann Thorac Surg* 2003;75(5):1601-1605; discussion 1605-1606.

Nakazato Y, Minami Y, Kobayashi H, Satomi K, Anami Y, Tsuta K, *et al.* Nuclear grading of primary pulmonary adenocarcinomas: correlation between nuclear size and prognosis. *Cancer* 2010;116:2011-2019.

Nitadori J, Bograd AJ, Kadota K, Sima CS, Rizk NP, Morales EA, *et al*. Impact of micropapillary histologic subtype in selecting limited resection vs. lobectomy for lung adenocarcinoma of 2 cm or smaller. *J Natl Cancer Inst* 2013;105(16):1212-1220.

Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S, *et al.* Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer* 1995;75(12):2844-2852.

Okada M, Koike T, Higashiyama M, Yamato Y, Kodama K, Tsubota N, *et al.* Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. *J Thorac Cardiovasc Surg* 2006;132(4):769-775.

Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, *et al.* EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. *Science* 2004;304(5676):1497-1500.

Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, *et al.* EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci USA* 2004;101(36):13306-13311.

Pao W, Wang TY, Riely GJ, Miller VA, Pan Q, Ladanyi M, *et al.* KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. *PLoS Med* 2005;2(1):e17.

Rekhtman N, Ang DC, Sima CS, Travis WD, Moreira AL. Immunohistochemical algorithm for differentiation of lung adenocarcinoma and squamous cell carcinoma based on large series of whole-tissue sections with validation in small specimens. *Mod Pathol* 2011;24(10):1348-1359.

Riely GJ, Marks J, Pao W. KRAS mutations in non-small cell lung cancer. *Proc Am Thorac Soc* 2009;6(2):201-205.

Rodig SJ, Mino-Kenudson M, Dacic S, Yeap BY,

Shaw A, Barletta JA, *et al.* Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. *Clin Cancer Res* 2009;15(16):5216-5223.

Rodriguez EF, Monaco SE, Dacic S. Cytologic subtyping of lung adenocarcinoma by using the proposed International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) adenocarcinoma classification. *Cancer Cytopathol* 2013;Aug 13. doi: 10.1002/cncy.21314. [Epub ahead of print].

Sakurai H, Maeshima A, Watanabe S, Suzuki K, Tsuchiya R, Maeshima AM, *et al.* Grade of stromal invasion in small adenocarcinoma of the lung: histopathological minimal invasion and prognosis. *Am J Surg Pathol* 2004;28(2):198-206.

Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, *et al.* Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009;27(26):4247-4253.

Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, *et al.* Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* 2005;7(5):339-346.

Sica G, Yoshizawa A, Sima CS, Azzoli CG, Downey RJ, Rusch VW, *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(8):1155-1162.

Sigel CS, Rudomina DE, Sima CS, Rekhtman N, Travis WD, Geisinger KR, Moreira AL. Predicting pulmonary adenocarcinoma outcome based on a cytology grading system. *Cancer Cytopathol* 2012;120(1):35-43.

Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62(1):10-29.

Strauss GM, Herndon JE 2nd, Maddaus MA, Johnstone DW, Johnson EA, Harpole DH, *et al.* Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 2008;26:5043-5051.

Suda K, Murakami I, Katayama T, Tomizawa K, Osada H, Sekido Y, *et al.* Reciprocal and complementary role of MET amplification and EGFR T790M mutation in acquired resistance to kinase inhibitors in lung cancer. *Clin Cancer Res* 2010;16(22):5489-5498.

Suzuki K, Asamura H, Kusumoto M, Kondo H, Tsuchiya R. "Early" peripheral lung cancer: prognostic significance of ground glass opacity on thin-section computed tomographic scan. *Ann Thorac Surg* 2002;74(5):1635-1639.

Suzuki K, Kadota K, Sima CS, Nitadori J, Rusch VW, Travis WD, *et al.* Clinical impact of immune microenvironment in stage I lung adenocarcinoma: tumor interleukin-12 receptor beta2 (IL-12Rbeta2), IL-7R, and stromal FoxP3/CD3 ratio are independent predictors of recurrence. *J Clin Oncol* 2013;31(4):490-498.

Takashima S, Li F, Maruyama Y, Hasegawa M, Takayama F, Kadoya M, *et al.* Discrimination of subtypes of small adenocarcinoma in the lung with thin-section CT. *Lung Cancer* 2002;36(2):175-182.

Tam IY, Chung LP, Suen WS, Wang E, Wong MC, Ho KK, *et al.* Distinct epidermal growth factor receptor and KRAS mutation patterns in non-

small cell lung cancer patients with different tobacco exposure and clinicopathologic features. *Clin Cancer Res* 2006;12(5):1647-1653.

Thunnissen E, Beasley MB, Borczuk AC, Brambilla E, Chirieac LR, Dacic S, *et al.* Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study. *Mod Pathol* 2012;25(12):1574-1583.

Travis W, Brambilla E, Muller-Hermelink H, Harris C. World Health Organization Classification of Tumours. Pathology and Genetics. Tumours of the Lung, Pleura, Thymus, and Heart. IARC Press: Lyon, France. 2004.

Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, *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(2):244-285.

Tsuta K, Kawago M, Inoue E, Yoshida A, Takahashi F, Sakurai H, *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(3):371-376.

Turner BM, Cagle PT, Sainz IM, Fukuoka J, Shen SS, Jagirdar J. Napsin A, a new marker for lung adenocarcinoma, is complementary and more sensitive and specific than thyroid transcription factor 1 in the differential diagnosis of primary pulmonary carcinoma: evaluation of 1674 cases by tissue microarray. *Arch Pathol Lab Med* 2012;136(2):163-171.

van Iersel CA, de Koning HJ, Draisma G, Mali WP, Scholten ET, Nackaerts K, *et al.* Risk-based selection from the general population in a screening trial: Selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). *Int J Cancer* 2007;120(4):868-874.

Vazquez M, Carter D, Brambilla E, Gazdar A, Noguchi M, Travis WD, *et al.* Solitary and multiple resected adenocarcinomas after CT screening for lung cancer: histopathologic features and their prognostic implications. *Lung Cancer* 2009;64(2):148-154.

Yim J, Zhu LC, Chiriboga L, Watson HN, Goldberg JD, Moreira AL. Histologic features are important prognostic indicators in early stages lung adenocarcinomas. *Mod Pathol* 2007;20(2):233-241.

Warth A, Muley T, Meister M, Stenzinger A, Thomas M, Schirmacher P, *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(13):1438-1446.

Yokose T, Suzuki K, Nagai K, Nishiwaki Y, Sasaki S, Ochiai A, *et al.* Favorable and unfavorable morphological prognostic factors in peripheral adenocarcinoma of the lung 3 cm or less in diameter. *Lung Cancer* 2000;29(3):179-188.

Yoshizawa A, Motoi N, Riely GJ, Sima CS, Gerald WL, Kris MG, *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(5):653-664.

Yoshizawa A, Sumiyoshi S, Sonobe M, Kobayashi M, Fujimoto M, Kawakami F, *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(1):52-61.

Youlden DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. *J Thorac Oncol* 2008;3(8):819-831.

Yun CH, Mengwasser KE, Toms AV, Woo MS, Greulich H, Wong KK, *et al.* The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci USA* 2008;105(6):2070-2075.

Zakowski MF, Hussain S, Pao W, Ladanyi M, Ginsberg MS, Heelan R, *et al.* Morphologic features of adenocarcinoma of the lung predictive of response to the epidermal growth factor receptor kinase inhibitors erlotinib and gefitinib. *Arch Pathol Lab Med* 2009;133(3):470-407.