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ORIGINAL ARTICLE

Prognostic significance of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of stage I lung adenocarcinoma: A retrospective study based on analysis of 110 Chinese patients

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Abstract

Background: The aim of this study was to investigate the relationship between predominant subtype, classification, and prognosis in Chinese stage I lung adenocarcinoma patients according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) International Multidisciplinary Lung Adenocarcinoma Classification.

Methods: Between 2000 and 2010, 110 patients with stage I lung adenocarcinoma underwent surgery at Xuanwu Hospital. Two pathologists independently reclassified all resected specimens according to the IASLC/ATS/ERS classification. Survival curves were plotted using the Kaplan–Meier method. The Cox proportional hazard model was used for multivariate analysis.

Results: There were no cases of adenocarcinoma in situ, and three cases of minimally invasive adenocarcinoma. There were 107 cases of invasive adenocarcinoma: 12 lepidic, 32 acinar, 30 papillary, 18 micropapillary, and 15 solid predominant subtypes. Patients with micropapillary and solid predominant tumors had significantly poorer disease-free survival compared to those with other subtypes of predominant tumors ($P = 0.021$). Multivariate analysis revealed that the new classification ($P = 0.003$) and T stage ($P = 0.034$) were independent predictors of disease-free and overall survival, respectively.

Conclusion: The predominant subtype in the primary tumor was associated with prognosis in resected stage I lung adenocarcinoma.

Introduction

Lung cancer is the most common cause of cancer-related death worldwide.[1] In the past few decades, lung cancer mortality rates have significantly increased in both urban and rural areas in China, and pulmonary adenocarcinoma has become the most common histological subtype, with a growing incidence.[2,3] Surgical resection is the preferred treatment for non-small cell lung cancer (NSCLC). With continuous developments in diagnosis and treatment techniques, the early detection rate for lung cancer is gradually increasing, thus more and more patients with early lung cancer are eligible for surgical resection. However, the long-term survival of patients with early-stage lung cancer is not optimistic. The five-year survival rate of patients with resected stage I NSCLC is reported at 50–70%.[4,5] Postoperative survival is significantly different in patients with stage I NSCLC who have undergone surgery. Studies have shown that the main reason for poor prognosis in these patients is postoperative recurrence.[6–8] Therefore, developing strategies to predict patients who may experience recurrence post surgery and who might benefit from adjuvant treatment is of great importance.

It is well known that the pathological classification of tumors guides the treatment strategy and prognosis of

cancer patients. However, the 2004 World Health Organization (WHO) classification system has a crucial flaw in that most adenocarcinomas (ADCs) (more than 80%) are inevitably categorized as mixed subtype because invasive tumors usually consist of highly heterogeneous components.[9] As a result, the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (IASLC/ATS/ERS), sponsored a project to develop an International Multidisciplinary Lung Adenocarcinoma Classification.[10] Recently, several studies have reported the prognostic value of the new classification.[11–13] Only a few reports have focused on the early stages of NSCLC in Chinese patients.[14] There are ethnic differences in epidemiology and the clinical behavior of lung cancer between different races.[15,16] This study reviewed a series of consecutive stage I NSCLC patients who underwent surgery at Xuanwu Hospital using the new IASLC/ATS/ERS classification in an attempt to evaluate the prognostic significance of this classification system in Chinese patients.

Methods

Patients

We reviewed the surgical database and archival slides to identify ADC patients (including patients with ground glass opacity) with pathologic stage I (including IA and IB) NSCLC, who underwent surgery between January 2000 and December 2010 at Xuanwu Hospital. These patients underwent complete resection (lobectomy) of the lung cancer with mediastinal lymph node dissection, therefore the surgical margin was >5 cm. In all, 110 cases met the 2004 WHO criteria for ADC and were considered as stage I according to the 7th Tumor Node Metastasis (TNM) classification. Recurrence or metastasis was confirmed by chest computed tomography (CT), brain magnetic resonance imaging, and bone scan, as well as ultrasound and/or CT of the abdomen. The exclusion criteria were: (i) preoperative chemotherapy or radiation therapy, (ii) death from other disease not related to NSCLC, and (iii) cases lost during follow-up. The ethics committee on human research at Xuanwu Hospital approved this study.

Histological evaluation

All resected specimens were formalin fixed and stained with hematoxylin and eosin in the routine manner. Two pathologists, blinded to clinical data, independently reviewed each of the slides. The average number of slides reviewed from each case was 9.4 (range 6–37). The percentage of each histological component was semiquantitatively recorded in terms of 5% increments in every slide. Repeated examination was used to resolve any discrepancies in assignment of the histologic subtype between the two pathologists. Histological classification was performed according to the IASLC/ATS/ERS criteria of lung ADCs and the 2004 WHO classification. According to the IASLC/ATS/ERS classification, tumors were reclassified as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive ADCs, which were further divided into lepidic-predominant, acinar-predominant, papillary-predominant, micropapillary-predominant, and solid-predominant. The predominant pattern was defined according to the most dominant pattern.

Follow-up

Follow-up evaluations were performed every three months for the first two years after surgery, every six months in the third to fifth years, and annually thereafter. Each patient's history, physical examination, thoracic CT, brain magnetic resonance imaging, tumor markers, bone scan and ultrasound and/or CT of the abdomen were recorded. The final follow-up occurred on 31 December 2015. The median follow-up time from surgery to the censored date was 79 months (range 13–162).

Statistical analysis

Disease-free survival (DFS) was defined as the period ranging from the date of surgery to the date when recurrence or metastases was diagnosed. Overall survival (OS) was defined as the time from the date of surgery to the date of death or last follow-up. To compare categorical and continuous variables between the groups, chi-square and paired independent sample *t* tests were used as appropriate. Survival curves were calculated using the Kaplan–Meier method. The log-rank test was used to compare DFS and OS between the different subtypes of lung ADC. Multivariate analyses were performed with adjustment for possible prognostic variables. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox's proportional hazards model. $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Results

Clinicopathologic characteristics

Patients' clinicopathologic features, including age, gender, smoking status, and stage are listed in Table 1. Of the 110 stage I patients, 58 were men and 52 were women. The median patient age was 58.7 years (range 27–78). There were 42 non-smokers and 68 previous or current smokers. The pathologic stage was IA in 43 patients and

Table 1 Univariate analysis of patient survival according to clinicopathologic characteristics

	Number	Five-year DFS rate (%)	*P*	Five-year OS rate (%)	*P*
Gender			0.840		0.723
Male	58	59.7		77.4	
Female	52	63.2		78.3	
Age			0.102		0.372
<65	42	65.4		78.9	
≥65	68	59.3		68.3	
Smoking status			0.472		0.135
Never	42	73.2		81.4	
Former/current	68	65.6		73.5	
Pathologic T classification			0.052		0.026
T1 (Ia)	43	76.4		90.6	
T2 (Ib)	67	63.6		73.2	
Pleural involvement			0.045		0.067
Yes	48	58.1		74.2	
No	62	76.3		83.6	
Lymphatic and/or vessel invasion			0.048		0.076
Yes	23	69.4	0.048	71.7	0.076
No	87	44.8		78.9	

DFS, disease-free survival; OS, overall survival.

IB in 67 patients. Lymphatic and/or vessel invasion was observed in 23 patients and pleural involvement in 48.

According to the IASLC/ATS/ERS classification, none of the patients had AIS and three had MIA. Among 107 cases of invasive ADC, 12 were lepidic, 32 were acinar, 30 were papillary, 18 were micropapillary, and 15 were solid predominant subtypes.

Survival analysis

The five-year DFS and OS rates of all patients were 64.5% and 82.3%, respectively. Patients with MIA showed 100% five-year DFS and OS. The five-year DFS rate of patients with lepidic, acinar, papillary, micropapillary, and solid predominant subtypes were 91.7%, 62.5%, 66.7%, 44.5%, and 46.7%, respectively. The five-year OS rates were 90.9%, 87.5%, 86.5%, 72.8% and 61.6%, respectively. The five-year recurrence rate of patients with MIA, lepidic, acinar, papillary, micropapillary, and solid predominant subtypes were 0%, 8.4%, 28.1%, 31.2%, 44.8%, and 46.7%, respectively. No postoperative mortality occurred in this study. The results of univariate analysis of clinicopathologic factors are shown in Table 1. Pleural invasion and lymphatic and/or vessel invasion were significantly associated with shorter DFS ($P = 0.045$ and $P = 0.048$, respectively), but not OS. In contrast, patients with pathologic T2 stage showed poorer OS ($P = 0.052$) but not DFS ($P = 0.026$).

Table 2 Univariate analysis of patient survival according to histologic subtype

	Number	Five-year DFS rate (%)	*P*	Five-year OS rate (%)	*P*
Minimally invasive adenocarcinoma	3	100.0	0.012	100.0	0.073
Lepidic predominant	12	91.7	0.009	90.9	0.071
Acinar predominant	32	62.5	0.984	87.5	0.134
Papillary predominant	30	66.7	0.569	86.5	0.259
Micropapillary predominant	18	44.5	0.035	72.8	0.143
Solid predominant	15	46.7	0.037	61.6	0.095

DFS, disease-free survival; OS, overall survival.

Table 2 shows the results of univariate analyses of histologic subtype. MIA ($P = 0.012$), lepidic predominant ($P = 0.003$), micropapillary predominant ($P = 0.037$) and solid predominant ($P = 0.035$) subtypes were predictive factors of DFS, but not OS.

Figures 1 and 2 show the results of survival curves according to subtypes. There was a significant difference in DFS ($P = 0.021$) between the six different histologic subtypes using the new classification; however, the survival curves did not reveal any difference in OS ($P = 0.340$).

The different subtypes were divided into three groups, according to clinical outcomes. Good prognostic groups included AIS, MIA, and lepidic predominant. Intermediate prognostic groups included acinar predominant, papillary predominant, and variants of invasive ADC. Poor prognostic groups included micropapillary predominant and solid predominant. There was a statistically significant difference of $P = 0.002$ in five-year DFS between the groups (Fig 3). However, there was no statistically significant difference in terms of the five-year OS between the groups ($P = 0.077$).

A multivariate Cox regression model was constructed including age, gender, T-status, smoking status, lymphatic and/or vessel invasion, pleural involvement, and histologic subtype (micropapillary and solid predominant vs. other subtypes). Histologic subtype was a significant independent prognostic factor for DFS ($P = 0.003$), while T stage had independent prognostic value for OS ($P = 0.034$) (Table 3).

Discussion

Since publication of the new lung adenocarcinoma classification in 2011, many countries around the world have begun to review archived lung adenocarcinoma specimens according to the new criteria. Most of these studies support that the new classification subtype, as with TNM staging, is an independent prognostic factor for patient survival.[17] We

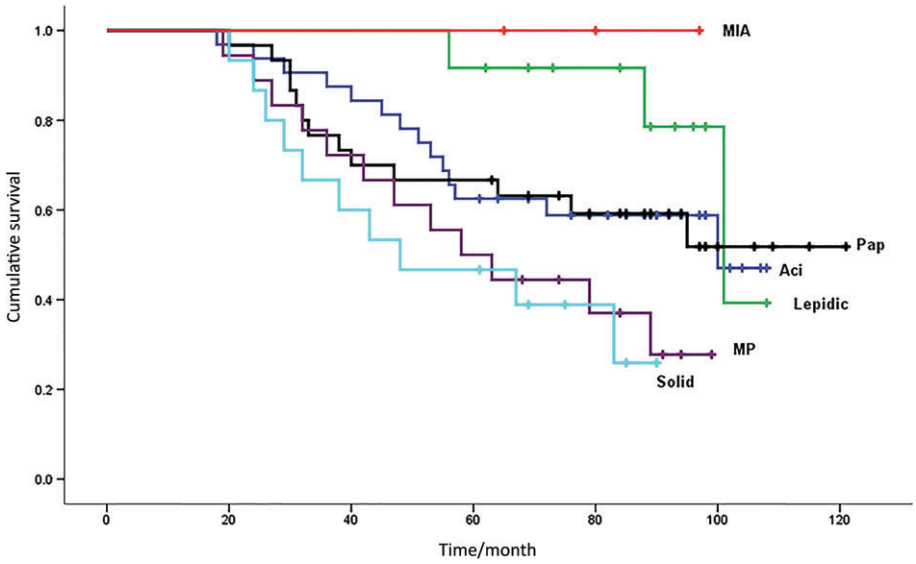

Figure 1 Probability of disease-free survival for all histologic predominant groups (P = 0.021). Aci, acinar; MIA, minimally invasive adenocarcinoma; MP, micropapillary predominant; Pap, papillary.

examined 110 Chinese cases of stage I ADC according to the new classification system. Consistent with a previous study examining 179 Japanese cases of stage I ADC, our results also confirmed the prognostic value of the new classification system; however, the incidence of different patterns varied.[11] For example, the incidence of micropapillary predominant ranged from 2.3% to 15.2% and the frequency of solid predominant ranged from 8.1% to 37.6% in the Japanese study.[10,18–20] In our cohort, the frequencies of the micropapillary predominant and solid predominant patterns were 16.3% and 13.6%, respectively. This variability might have been caused by variations between geographical regions as well as ethnic populations, as the incidence of genetic mutations, such as epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene homolog, is quite different between Asian and Western populations.[21,22] Investigating the potential genetic and/or habitual factors that determine such differences poses an interesting subject.

Several studies have investigated the prognostic value of the new classification on DFS and OS.[12,13] In our study, univariate and multivariate analysis showed that pathological subtype was the only factor affecting five-year DFS according to subtype, but there was no significant difference in five-year OS. On the contrary, the T stage has the opposite result. Although our data showed no significant differences in five-year OS according to the different pathological subtypes, there was a trend of poor five-year OS in the micropapillary and solid predominant patterns, as illustrated by the survival curve. This may be a result of the

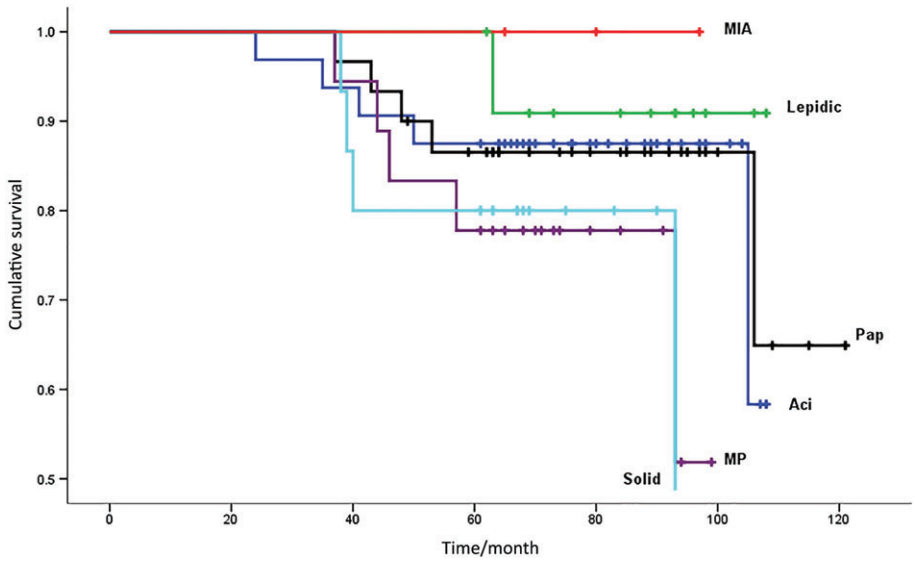

Figure 2 Probability of overall survival for all histologic predominant groups. Aci, acinar; MIA, minimally invasive adenocarcinoma; MP, micropapillary predominant; Pap, papillary.

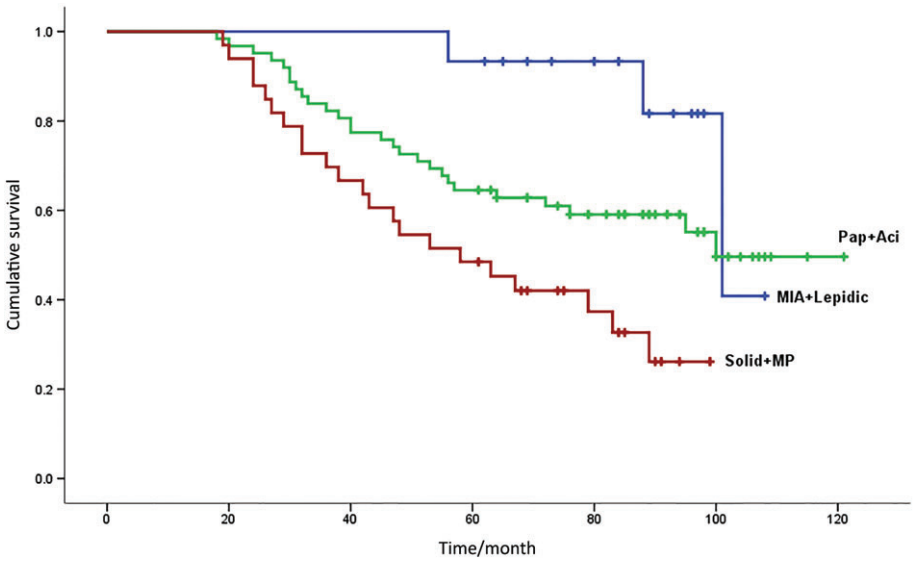

Figure 3 Probability of disease-free survival for three different prognostic groups (P = 0.002). Aci, acinar; MIA, minimally invasive adenocarcinoma; MP, micropapillary predominant; Pap, papillary.

small number of cases and the lack of follow-up in our study. In addition, different pathological subtypes can be distributed in different T stage patients, which may have caused the insignificant five-year DFS rate. Therefore, in order to verify our results, future studies should include larger sample sizes and conduct follow-up for longer time periods.

Yoshizawa *et al.* divided stage I lung ADCs into low (AIS and MIA), intermediate (lepidic, acinar, and papillary predominant ADC), and high grade (solid, micropapillary, colloid predominant, and invasive mucinous ADC) in order to significantly stratify the patients with poor DFS.[18] The high-grade group had the worst prognosis compared to the intermediate and low-grade groups. Hung *et al.* reported that lepidic predominant had a lower recurrence risk, whereas micropapillary and solid predominant had a higher recurrence risk.[20] Similarly, our results indicated that lepidic predominant had a lower risk of recurrence, while micropapillary and solid predominant had higher risk of recurrence. Furthermore, the lepidic predominant pattern had a similar DFS and OS compared to MIA. Our results indicate that lepidic predominant should be included as low-grade rather than intermediate-grade and we propose that patients with micropapillary or solid predominant patterns may be candidates for adjuvant therapy.

Epidermal growth factor receptor mutations have recently been discovered and EGFR-tyrosine kinase inhibitor treatment now plays an important role in treating advanced NSCLC, especially in patients with EGFR mutations.[23–25] EGFR mutation has proven to be more common in ADC;[26] however, the relationship between EGFR mutation and subtype in the new lung adenocarcinoma classification is not clear, despite being investigated in several studies.[27,28] EGFR mutation and histology subtype data are conflicting. Zhang *et al.* investigated 349 lung ADC cases and found that EGFR mutations were more frequent in acinar-predominant tumors.[28] However, in Shim *et al.* and Song *et al.*'s studies, EGFR mutations were more frequent in micropapillary-predominant tumors.[27,29] Therefore, future studies should focus on the correlation between lung ADC subtype and EGFR mutation in order to provide clinical evidence for the treatment of lung ADC subtypes.

Table 3 Multivariate survival analysis for DFS and OS

	DFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Gender (male vs. female)	1.037	0.671–1.682	0.843	1.235	0.689–2.324	0.566
Age (≥65 vs. <65)	1.576	0.985–2.979	0.081	1.712	0.782–3.446	0.233
Smoking status (smoker vs. non-smoker)	0.847	0.371–1.684	0.534	1.215	0.671–2.153	0.549
T stage (T2 vs. T1)	1.598	0.769–2.982	0.134	2.585	1.084–2.673	0.034
Pleural involvement (yes vs. no)	1.305	0.704–2.343	0.539	0.939	0.461–1.402	0.869
Lymphatic and/or vessel invasion (yes vs. no)	1.823	1.129–3.496	0.057	1.901	1.189–3.882	0.076
Histologic subtype (MP and solid vs. other subtypes)	2.381	1.474–3.645	0.003	1.930	1.188–5.070	0.636

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; MP, micropapillary predominant; OS, overall survival.

In conclusion, the new IASLC/ATS/ERS classification in Chinese stage I lung adenocarcinoma patients has prognostic value. This new classification might be valuable for screening patients with a high risk of recurrence who may be eligible for postoperative adjuvant therapy.

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Disclosure

No authors report any conflict of interest.

References

1 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74–108.
2 Yang L, Parkin DM, Li L, Chen Y. Time trends in cancer mortality in China: 1987–1999. *Int J Cancer* 2003; **106**: 771–83.
3 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. (Published erratum appears in *CA Cancer J Clin* 2011; 61: 134). *CA Cancer J Clin* 2011; **61**: 69–90.
4 Hung JJ, Jeng WJ, Hsu WH, Chou TY, Huang BS, Wu YC. Predictors of death, local recurrence, and distant metastasis in completely resected pathological stage-I non-small-cell lung cancer. *J Thorac Oncol* 2012; **7**: 1115–23.
5 Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Prognostic factors in patients with stage IB non-small cell lung cancer according to the seventh edition TNM classification. *Chest* 2011; **139**: 855–61.
6 Martini N, Bains MS, Burt ME *et al.* Incidence of local recurrence and second primary tumors in resected stage I lung cancer. *J Thorac Cardiovasc Surg* 1995; **109**: 120–9.
7 Harpole DH Jr, Herndon JE II, Young WG Jr, Wolfe WG, Sabiston DC Jr. Stage I nonsmall cell lung cancer. A multivariate analysis of treatment methods and patterns of recurrence. *Cancer* 1995; **76**: 787–96.
8 Hung JJ, Jeng WJ, Hsu WH, Huang BS, Wu YC. Time trends of overall survival and survival after recurrence in completely resected stage I non-small cell lung cancer. *J Thorac Oncol* 2012; **7**: 397–405.
9 Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *World Health Organization Classification Of Tumors. Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart*. IARC Press, Lyon 2004; 9–67.
10 Travis WD, Brambilla E, Noguchi M *et al.* International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma. *J Thorac Oncol* 2011; **6**: 244–85.
11 Woo T, Okudela K, Mitsui H *et al.* Prognostic value of the IASLC/ATS/ERS classification of lung adenocarcinoma in stage I disease of Japanese cases. *Pathol Int* 2012; **62**: 785–91.
12 Yoshizawa A, Sumiyoshi S, Sonobe M *et al.* Validation of the IASLC/ATS/ERS lung adenocarcinoma classification for prognosis and association with EGFR and KRAS gene mutations: Analysis of 440 Japanese patients. *J Thorac Oncol* 2013; **8**: 52–61.
13 Gu J, Lu C, Guo J *et al.* Prognostic significance of the IASLC/ATS/ERS classification in Chinese patients-A single institution retrospective study of 292 lung adenocarcinoma. *J Surg Oncol* 2013; **107**: 474–80.
14 Song Z, Zhu H, Guo Z, Wu W, Sun W, Zhang Y. Prognostic value of the IASLC/ATS/ERS classification in stage I lung adenocarcinoma patients--based on a hospital study in China. *Eur J Surg Oncol* 2013; **39**: 1262–8.
15 Ahn MJ, Lee J, Park YH *et al.* Korean ethnicity as compared with white ethnicity is an independent favorable prognostic factor for overall survival in non-small cell lung cancer before and after the oral epidermal growth factor receptor tyrosine kinase inhibitor era. *J Thorac Oncol* 2010; **5**: 1185–96.
16 Kawaguchi T, Matsumura A, Fukai S *et al.* Japanese ethnicity compared with Caucasian ethnicity and never-smoking status are independent favorable prognostic factors for overall survival in non-small cell lung cancer: A collaborative epidemiologic study of the National Hospital Organization Study Group for Lung Cancer (NHSGLC) in Japan and a Southern California Regional Cancer Registry databases. *J Thorac Oncol* 2010; **5**: 1001–10.
17 Okada M. Subtyping lung adenocarcinoma according to the novel 2011 IASLC/ATS/ERS classification: Correlation with patient prognosis. *Thorac Surg Clin* 2013; **23**: 179–86.
18 Yoshizawa A, Motoi N, Riely GJ *et al.* Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: Prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. *Mod Pathol* 2011; **24**: 653–64.
19 Warth A, Muley T, Meister M *et al.* The novel histologic International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system of lung adenocarcinoma is a stage-independent predictor of survival. *J Clin Oncol* 2012; **30**: 1438–46.
20 Hung JJ, Jeng WJ, Chou TY *et al.* Prognostic value of the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification on death and recurrence in completely resected stage I lung adenocarcinoma. *Ann Surg* 2013; **258**: 1079–86.

21 Okudela K, Woo T, Kitamura H. KRAS gene mutations in lung cancer: Particulars established and issues unresolved. *Pathol Int* 2010; **60**: 651–60.
22 Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T. Mutations of the epidermal growth factor receptor gene in lung cancer: Biological and clinical implications. *Cancer Res* 2004; **64**: 8919–23.
23 Mitsudomi T, Morita S, Yatabe Y *et al.* Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. *Lancet Oncol* 2010; **11**: 121–8.
24 Maemondo M, Inoue A, Kobayashi K *et al.* Gefitinib or chemotherapy for non-small cell lung cancer with mutated EGFR. *N Engl J Med* 2010; **362**: 2380–8.
25 Shepherd FA, Rodrigues Pereira J, Ciuleanu T *et al.* Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; **353**: 123–32.
26 Mok TS, YL W, Thongprasert S *et al.* Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361**: 947–57.
27 Shim HS, Lee H, Park EJ, Kim SH. Histopathologic characteristics of lung adenocarcinomas with epidermal growth factor receptor mutations in the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification. *Arch Pathol Lab Med* 2011; **135**: 1329–34.
28 Zhang Y, Sun Y, Pan Y *et al.* Frequency of driver mutations in lung adenocarcinoma from female never-smokers varies with histologic subtypes and age at diagnosis. *Clin Cancer Res* 2012; **18**: 1947–53.
29 Song Z, Zhu H, Guo Z, Wu W, Sun W, Zhang Y. Correlation of EGFR mutation and predominant histologic subtype according to the new lung adenocarcinoma classification in Chinese patients. *Med Oncol* 2013; **30**: 645.

