General Thoracic and Cardiovascular Surgery (2022) 70:455–462
https://doi.org/10.1007/s11748-021-01758-3

ORIGINAL ARTICLE

High-grade tumor classified by new system is a prognostic predictor in resected lung adenocarcinoma

Chihiro Yoshida[1] · Hiroyasu Yokomise[1] · Emi Ibuki[2] · Tetsuhiko Go[1] · Reiji Haba[2] · Kyuichi Kadota[3]

Received: 21 July 2021 / Accepted: 7 December 2021 / Published online: 20 January 2022

Abstract

Objectives A grading system for pulmonary adenocarcinoma has not been established; hence, the International Association for the Study of Lung Cancer (IASLC) pathology panel developed a new grading system for invasive adenocarcinoma. We aimed to evaluate the prognostic significance of the IASLC grading system for invasive pulmonary adenocarcinoma.

Methods We conducted a retrospective analysis of 471 Japanese patients with resected lung adenocarcinoma. Tumors were classified in accordance with the IASLC grading system and 2015 World Health Organization classification. We analyzed recurrence-free probability (RFP) and overall survival (OS) using the log-rank test and compared the two grading systems using the Cox proportional hazards model.

Results Grade 3 tumors of the IASLC system and high-grade tumors of the 2015 World Health Organization classification were present in 38% and 17% of patients, respectively. The 5-year RFP was lower in patients with IASLC Grade 3 tumors (45%) than in patients with IASLC Grade 1 and 2 tumors (91% and 83%, respectively). The 5-year RFP of patients with IASLC Grade 2 tumors (83%) was higher than of those with 2015 World Health Organization intermediate tumors (69%). On multivariate analysis for recurrence, IASLC Grade 3 was an independent prognostic factor of worse RFP. We showed similar results on analysis for the OS.

Conclusions The prognostic significance of IASLC Grade 3 tumors on recurrence-free probability was confirmed through both univariate and multivariate analyses. Thus, the IASLC Grade 3 tumor is an independent factor of poor prognosis in patients with resected lung adenocarcinoma.

Keywords Adenocarcinoma · Histologic subtype · Lung · Prognosis · Tumor grading

Introduction

The predominant subtype in the 2015 World Health Organization (WHO) lung tumor classification has been identified as a prognostic indicator for patients with resected lung adenocarcinoma in various countries [1–5]. The histologic subtype can be used to stratify patients with lung adenocarcinoma into three prognostic groups: low grade (lepidic predominant), intermediate grade (acinar or papillary predominant), and high grade (solid or micropapillary predominant) [2]. Moreover, classification and stratification by the predominant pattern are suggested to be predictive of response to adjuvant chemotherapy [6].

Pulmonary adenocarcinomas are histologically heterogeneous and present with multiple combinations of patterns and proportions. When classified according to the predominant pattern alone, the acinar subtype is the most prevalent (estimated at 40–50% of patients) and carries the widest spectrum of prognoses [2, 3, 7–9]. In addition to the five major histologic patterns, several other patterns such as the cribriform pattern have been reported in the lungs. The cribriform pattern in lung adenocarcinoma was recognized in the 2015 WHO classification; however, a new subtype was not created, and this pattern was rather described as a part of a high-grade pattern of the acinar subtype [10]. These complex glandular patterns (high-grade acinar) have been found to be associated with a high mitotic rate, tumor

✉ Kyuichi Kadota
ychihiro.sky@gmail.com

[1] Department of General Thoracic Surgery, Faculty of Medicine, Kagawa University, Kagawa, Japan

[2] Department of Diagnostic Pathology, Faculty of Medicine, Kagawa University, Kagawa, Japan

[3] Department of Pathology, Faculty of Medicine, Shimane University, 89-1 Enya, Izumo, Shimane 693-8501, Japan

necrosis, and lymphovascular invasion in the lungs [11, 12]. Furthermore, current evidence supports that these complex glandular patterns carry a poor prognosis similar to that of high-grade histologic types (solid and micropapillary) [9, 11–16]. However, the lack of appreciation of these patterns may have led to uncertainty in tumor classification and poor reproducibility because some investigators may have classified these patterns as intermediate grade (acinar) or high grade (solid). Thus, it is crucial to identify these "nontraditional patterns" and to classify them as complex glands separately from the conventional acinar pattern.

Consequently, the International Association for the Study of Lung Cancer (IASLC) pathology committee conducted a systematic study to evaluate a set of histologic features that had been described as prognostic indicators and established a grading system for resected invasive pulmonary adenocarcinoma. The IASLC grading system proposed the following: Grade 1, well-differentiated adenocarcinoma (lepidic predominant tumors with no or $<20\%$ of high-grade patterns [solid, micropapillary, and/or cribriform patterns]); Grade 2, moderately differentiated adenocarcinomas (acinar or papillary predominant tumors with no or $<20\%$ of high-grade patterns); and Grade 3, poorly differentiated (any tumor with $\geq 20\%$ of high-grade patterns) (Online Resource 1) [17].

To further validate the prognostic significance of tumors graded by the IASLC grading system, we analyzed a series of 471 Japanese patients with resected lung adenocarcinoma and compared the IASLC grade with the 2015 WHO classification (low grade, lepidic predominant; intermediate grade, acinar or papillary predominant; and high grade, solid or micropapillary predominant).

Methods

Patients

This retrospective study was approved by the Institutional Review Board of Kagawa University. The need for informed consent was waived by the Institutional Review Board due to the retrospective nature of the study. We reviewed the data of 471 patients with therapy-naïve stage I–IIIA lung adenocarcinoma who had undergone a radical surgical resection by more than a segmentectomy with systematic lymph node dissection at Kagawa University between 1999 and 2016. Cases with multifocal invasive carcinomas, stage IIIB–IV lung carcinomas, adenocarcinoma in situ, minimally invasive adenocarcinomas, multifocal adenocarcinomas, invasive mucinous adenocarcinoma, and other variants of adenocarcinoma were excluded from the study.

Clinical data were collected from a prospectively maintained lung carcinoma database. Initial CT was performed 3 months after surgery; thereafter, chest and abdominal CT were routinely performed every 6 months. Disease recurrence was confirmed by clinical, radiological, or pathological assessment. The disease TNM (tumor, node, metastasis) staging was based on the eighth edition of the American Joint Committee on Cancer TNM Staging Manual [18].

Histologic evaluation

Hematoxylin and eosin-stained slides were reviewed by two pathologists blinded to the patients' clinical outcomes using an Olympus BX53 upright microscope (Olympus Corporation, Tokyo, Japan) with a standard 22-mm-diameter eyepiece. The tumors were graded using both the IASLC grading system and an architectural approach based on the predominant subtypes of the 2015 WHO lung tumor classification [1]. The presence of lymphatic and vascular invasions was noted if at least one tumor cell cluster was visible.

Statistical analyses

Associations between categorical variables were analyzed using the Chi-square test. Recurrence-free probability (RFP) was defined as the time from surgical resection to the date of disease recurrence. Overall survival (OS) was defined as the time from surgical resection to the date of death or last follow-up. RFP and OS were estimated using the Kaplan–Meier method, and nonparametric group comparisons were performed using the log-rank test. Multivariate analyses were performed using a Cox proportional hazards regression model. Furthermore, multivariate models were built to include factors that were significant in the univariate analysis. Any association between pathologic factors were checked, and a factor was included in the model only if any strong association was discovered. All statistical tests were two-sided, with a significance level of 0.05. Statistical analyses were conducted using SPSS Statistics for Windows (version 23.0; IBM Corporation, Armonk, New York).

Results

Patient clinicopathologic characteristics and outcomes

The median age of the 471 patients was 70 years (range 26–92 years), and more than half of the patients were male individuals ($n=255$, 54%). Most patients had pathologic stage I disease ($n=357$, 76%). Furthermore, 428 (91%) patients underwent at least lobectomy, and 43 (9%) underwent segmentectomy. Ninety-three patients (20%) received adjuvant therapy. During the study period, 123 patients (26%) experienced recurrence and 104 (22%) died. The median follow-up period for the patients who

were alive at the time of the last follow-up was 60 months (mean 64 ± 38 months).

Among all patients, higher pathologic stage ($p < 0.001$), lymphatic invasion ($p < 0.001$), vascular invasion ($p < 0.001$), and tumor spread through air spaces (STAS; $p < 0.001$) were found to be significantly associated with a lower RFP. Male sex ($p = 0.002$), surgical procedure ($p = 0.017$), higher pathologic stage ($p < 0.001$), lymphatic invasion ($p < 0.001$), vascular invasion ($p < 0.001$), and STAS ($p < 0.001$) were found to be significantly associated with a worse OS (Table 1).

Association between clinicopathologic features and the IASLC grade

High-grade tumors classified by the 2015 WHO classification were present in 17% ($n = 78$), whereas Grade 3 tumors classified by the IASLC grade were present in 38% ($n = 181$) of all tumors. Among all patients, IASLC Grade 3 tumors were more frequently identified in male individuals ($p < 0.001$) and those who underwent lobectomy ($p = 0.045$), those with higher pathologic stages ($p < 0.001$), lymphatic invasion ($p < 0.001$), vascular invasion ($p < 0.001$), STAS ($p < 0.001$), and more distant recurrence ($p < 0.001$) (Online Resource 2). In the subgroup of stage I patients, IASLC Grade 3 tumors were more frequently identified in male

Table 1 Clinicopathologic characteristics and their associations with patient's outcomes in all stages

Variables	*N*	5-year RFP (%)	*p*	5-year OS (%)	*p*
Age (years)			0.15		0.43
≤ 65	163	66		74	
> 65	308	72		72	
Sex			0.73		**0.002**
Female	216	70		79	
Male	255	69		67	
Surgical procedure			0.64		**0.017**
Segmentectomy	43	63		60	
Lobectomy	428	70		74	
Pathologic stage			**< 0.001**		**< 0.001**
Stage I	357	80		80	
Stage II	50	57		54	
Stage IIIA	64	19		45	
Lymphatic invasion			**< 0.001**		**< 0.001**
Absent	282	84		84	
Present	189	47		53	
Vascular invasion			**< 0.001**		**< 0.001**
Absent	292	84		86	
Present	179	47		51	
STAS			**< 0.001**		**< 0.001**
Absent	250	86		86	
Present	221	51		57	
2015 WHO classification[a]			**< 0.001**		**< 0.001**
Low	88	91		90	
Intermediate	305	69		73	
High	78	48		54	
IASLC grade[b]			**< 0.001**		**< 0.001**
Grade 1	88	91		90	
Grade 2	202	83		86	
Grade 3	181	45		51	

Significant *p* values are shown in bold

STAS spread through air spaces

[a]The 2015 World Health Organization (WHO) classification for adenocarcinoma

[b]The International Association for the Study of Lung Cancer (IASLC) grading system for invasive adenocarcinoma

individuals ($p < 0.001$) and those with higher pathologic stages ($p < 0.001$), larger invasive tumor size ($p < 0.001$), lymphatic invasion ($p < 0.001$), vascular invasion ($p < 0.001$), STAS ($p < 0.001$), and more distant recurrence ($p < 0.001$) (Online Resource 3).

Association between patient outcomes and the IASLC grade

The 5-year RFP of patients with IASLC Grade 3 tumors (45%) was lower than that of patients with Grade 1 and 2 tumors (91% and 83%, respectively) (Fig. 1A). Moreover, we compared the outcomes of previously established grades (low grade, lepidic; intermediate grade, acinar, papillary; and high grade, solid, micropapillary) based on the 2015 WHO classification and IASLC grade among all patients. The number of patients with IASLC Grade 1 was the same as those with 2015 WHO low-grade tumors. This indicated that there was no lepidic-predominant tumor with a significant portion exhibiting a high-grade pattern. In contrast, there were fewer patients with IASLC Grade 2 tumors than those with 2015 WHO intermediate-grade tumors and more patients with IASLC Grade 3 tumors than those with 2015 WHO high-grade tumors (Table 1).

Although the 5-year RFP of patients with IASLC Grades 1 and 3 tumors and that of patients with 2015 WHO low- and high-grade tumors were almost the same, the 5-year RFP of patients with IASLC Grade 2 tumors (83%) was higher than that of patients with 2015 WHO intermediate-grade tumors (69%) (Fig. 1A, B). In addition, according to the multivariate analysis for recurrence, IASLC Grade 3 was an independent prognostic factor for a worse RFP (hazard ratio [HR], 1.83; $p = 0.018$) (Table 3). In a subgroup of stage I patients, the prognostic significance of IASLC Grade3 was confirmed on univariate analysis (Table 2, Supplementary Fig. 1) and on multivariate analysis (Table 3).

The 5-year OS for patients with IASLC Grade 3 tumors (51%) was lower than that of patients with IASLC Grade 1 and 2 tumors (90% and 86%, respectively). Moreover, the 5-year OS for patients with IASLC Grade 2 tumors (86%) was higher than that of patients with 2015 WHO intermediate-grade tumors (73%) (Table 1). According to the multivariate analysis for survival, IASLC Grade 3 was an independent prognostic factor for worse OS (HR, 2.99; $p < 0.001$) (Table 3). The prognostic significance of IASLC Grade 3 in stage I patients was confirmed on univariate (Table 2) and multivariate (Table 3) analyses.

Moreover, patients with IASLC Grade 2 tumors were stratified according to a < 5% cut-off of high-grade patterns and patients with IASLC Grade 1 and 2 tumors were stratified according to the presence of STAS as high-grade histological features. Among patients with IASLC Grade 2 tumors, the 5-year RFP of those with ≥ 5% high-grade patterns was lower than that of patients with < 5% high-grade patterns (Grade 2, 69% vs. 88%, $p < 0.001$, respectively) (Fig. 2A). Moreover, the 5-year RFP of patients with STAS-positive tumors was lower than that of patients with STAS-negative tumors (Grade 1, 67% vs. 91%, $p < 0.001$, and Grade 2, 69% vs. 89%, $p < 0.001$, respectively) (Fig. 2B, C). According to the multivariate analysis for recurrence, STAS was an independent prognostic factor for worse RFP compared with patients without STAS (HR, 2.45; $p < 0.001$). The prognostic significance of STAS-positive tumors in stage I patients was confirmed on multivariate analysis (Table 3).

Discussion

In this study, we showed that IASLC Grade 3 tumors and 2015 WHO high-grade tumors were present in 38% and 17% of the same set of patients, respectively. We also found that in patients with resected lung adenocarcinoma, IASLC Grade 3 was an independent predictor of worse

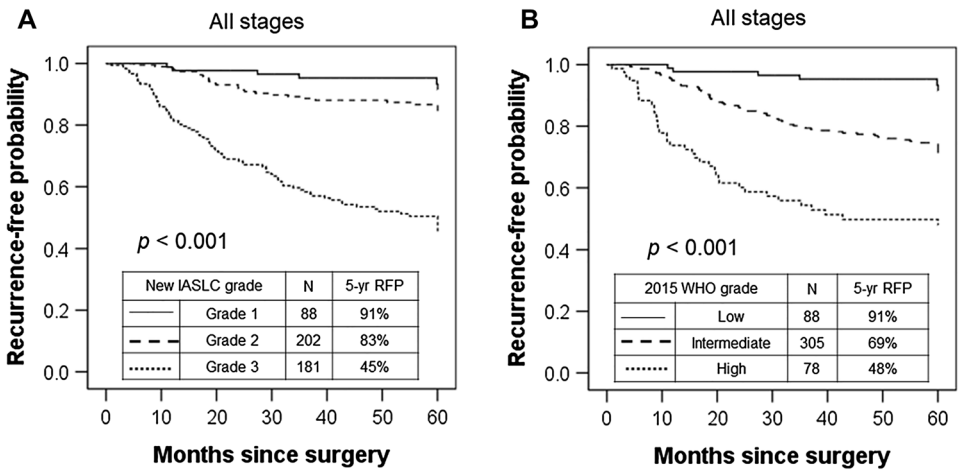

Fig. 1 Prognostic significance of tumors classified in accordance with **A** the IASLC grading system and **B** 2015 WHO classification. **A**, **B** IASLC Grade 3 and 2015 WHO high-grade tumors are statistically significant prognostic factors for RFP, with the difference more pronounced in the IASLC grading system than in the 2015 WHO classification. *IASLC* International Association for the Study of Lung Cancer, *RFP* recurrence-free probability, *WHO* World Health Organization

Table 2 Clinicopathologic characteristics and their associations with patient's outcomes in stage I

Variables	*N*	5-year RFP (%)	*P*	5-year OS (%)	*P*
Age (years)			0.77		0.13
≤65	114	79		85	
>65	243	80		77	
Sex			0.17		**0.003**
Female	170	83		87	
Male	187	77		73	
Surgical procedure			**0.034**		**0.006**
Limited resection	39	63		63	
Lobectomy	318	82		82	
Invasive tumor size			**<0.001**		**<0.001**
<2 cm	228	85		87	
>2 cm	129	70		66	
Lymphatic invasion			**<0.001**		**<0.001**
Absent	264	86		85	
Present	93	63		65	
Vascular invasion			**<0.001**		**<0.001**
Absent	257	88		89	
Present	100	60		57	
STAS			**<0.001**		**<0.001**
Absent	219	89		87	
Present	138	65		68	
2015 WHO classification[a]			**<0.001**		**<0.001**
Low	88	91		90	
Intermediate	228	80		82	
High	41	57		52	
IASLC grade[b]			**<0.001**		**<0.001**
Grade 1	88	91		90	
Grade 2	176	88		88	
Grade 3	93	55		57	

Significant *p* values are shown in bold

STAS spread through air spaces

[a]The 2015 World Health Organization (WHO) classification for adenocarcinoma

[b]The International Association for the Study of Lung Cancer (IASLC) grading system for invasive adenocarcinoma

clinical outcomes (recurrence and survival) after adjustments for significant clinicopathologic factors and was associated with characteristics of aggressive tumor behavior such as larger invasive tumor size, higher pathologic stage, lymphovascular invasion, and histological features such as STAS. Therefore, our findings highlight the significant prognostic value of the IASLC grading system for invasive adenocarcinoma.

Moreover, patients with tumors having ≥5% high-grade patterns (solid, micropapillary, and/or complex glandular patterns), even those with IASLC Grade 2 tumors, had a poor prognosis. Although STAS was not included in the IASLC grading system, its incidence was a poor prognostic factor regardless of tumor grade. Based on these results, we suggest that Grade 2 tumors should be recognized as having a poor prognosis if they have a high-grade pattern of ≥5% or histological features such as the incidence of STAS.

In the 2015 WHO classification, tumors are graded using an architectural approach based on the predominant subtype: low (lepidic subtype), intermediate (papillary or acinar subtype), or high grade (micropapillary or solid subtype) [2, 6]. Therefore, according to this classification of lung carcinomas, cribriform arrangements are regarded as a pattern of acinar adenocarcinoma despite the previously reported association between the pattern and worse clinical outcomes in patients with lung adenocarcinoma [9, 13–15]. Kadota et al. [16] reported that the cribriform-predominant subtype (currently a subcategory of the acinar subtype) is an independent factor of poor prognosis, with respect to recurrence and survival, among patients with resected lung

Table 3 Multivariate analysis

Variables		HR	95% CI	*p*
RFP in all stages				
Pathologic stage	Stage III vs. stage I–II	2.13	1.42–3.19	**< 0.001**
Lymphatic invasion	Present vs. absent	1.30	0.80–2.10	0.29
Vascular invasion	Present vs. absent	1.96	1.26–3.04	**0.003**
STAS	Present vs. absent	2.45	1.54–3.92	**< 0.001**
2015 WHO classification[a]	High vs. low, intermediate	1.16	0.75–1.78	0.50
IASLC grade[b]	Grade 3 vs. grade1–2	1.83	1.11–3.02	**0.018**
RFP in stage I				
Surgical procedure	Segmentectomy vs. lobectomy	3.20	1.60–6.40	**< 0.001**
Invasive tumor size	> 2 cm vs. ≤ 2 cm	1.15	0.66–1.99	0.63
Lymphatic invasion	Present vs. absent	1.14	0.62–2.11	0.68
Vascular invasion	Present vs. absent	2.16	1.17–3.98	**0.014**
STAS	Present vs. absent	1.97	1.06–3.69	**0.033**
2015 WHO classification[a]	High vs. low, intermediate	0.97	0.50–1.89	0.93
IASLC grade[b]	Grade 3 vs. Grade 1–2	3.38	1.73–6.60	**< 0.001**
OS in all stages				
Sex	Male vs. female	1.52	1.00–2.30	0.051
Surgical procedure	Segmentectomy vs. lobectomy	4.25	2.34–7.74	**< 0.001**
Pathologic stage	Stage III vs. stage I–II	1.33	0.85–2.09	0.21
Lymphatic invasion	Present vs. absent	1.27	0.75–2.16	0.37
Vascular invasion	Present vs. absent	1.95	1.20–3.18	**0.007**
STAS	Present vs. absent	1.82	1.12–2.94	**0.015**
2015 WHO classification[a]	High vs. low, intermediate	0.88	0.55–1.40	0.58
IASLC grade[b]	Grade 3 vs. Grade 1–2	2.99	1.72–5.21	**< 0.001**
OS in stage I				
Sex	Male vs. female	1.56	0.88–2.77	0.13
Surgical procedure	Segmentectomy vs. lobectomy	3.58	1.84–6.98	**< 0.001**
Invasive tumor size	> 2 cm vs. ≤ 2 cm	1.57	0.86–2.84	0.14
Lymphatic invasion	Present vs. absent	0.94	0.50–1.77	0.85
Vascular invasion	Present vs. absent	2.24	1.17–4.30	**0.016**
STAS	Present vs. absent	1.61	0.87–2.95	0.13
2015 WHO classification[a]	High vs. low, intermediate	1.06	0.53–2.15	0.87
IASLC grade[b]	Grade 3 vs. Grade 1–2	2.74	1.36–5.54	**0.005**

Significant *p* values are shown in bold type

RFP recurrence-free probability, *STAS* spread through air spaces, *HR* hazard ratio, *CI* confidence interval, *OS* overall survival, *WHO* World Health Organization, *IASLC* International Association for the Study of Lung Cancer

[a]The 2015 WHO classification for adenocarcinoma

[b]The IASLC grading system for invasive adenocarcinoma

adenocarcinoma, and that it was associated with aggressive pathology. To detect tumors with high-grade patterns, it was necessary to classify them as complex glands separate from the conventional acinar pattern. Based on the IASLC grading system, tumors with ≥ 20% high-grade patterns were classified as poorly differentiated because these tumors behave more aggressively, similar to those with a predominantly high-grade pattern. Hence, this grading system offers a superior prognostic grouping compared to the 2015 WHO classification.

In this study, even in stage I disease, IASLC Grade 3 tumors had more distant recurrences than Grade 1 and 2 tumors. Considering these results, we propose that the high-grade pattern such as IASLC Grade 3 tumors should be accurately detected, and that careful follow-up after surgery and indication for adjuvant therapy should be considered. However, as a potential limitation of our study, it is important to note that the patients' epidermal growth factor receptor status, which may affect the prognosis of those with lung adenocarcinoma, was unclear.

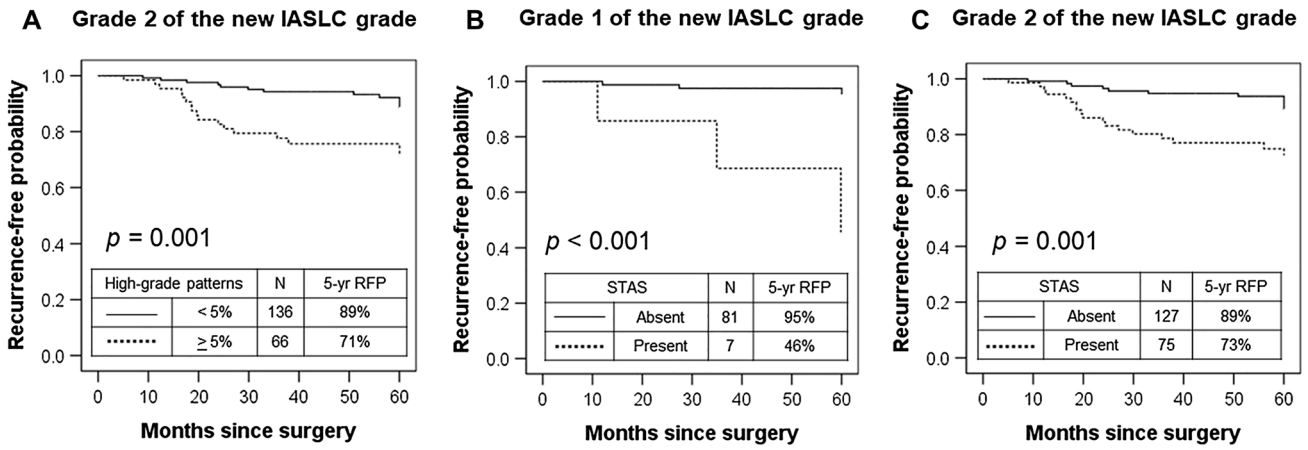

Fig. 2 Association between ≥5% high-grade patterns, STAS, and RFP. **A** Among patients with IASLC Grade 2 tumors, the 5-year RFP of patients with ≥5% high-grade patterns was lower than that of those with <5% high-grade patterns (71% vs. 89%, $p=0.001$). **B** Among patients with IASLC Grade 1 and **C** among patients with IASLC Grade 2 tumors, the 5-year RFP of patients with STAS-positive tumors was lower than that of those with STAS-negative tumors (Grade 1: 46% vs. 95%, $p<0.001$; Grade 2: 73% vs. 89%, $p=0.001$, respectively). *IASLC* International Association for the Study of Lung Cancer, *RFP* recurrence-free probability, *STAS* spread through air spaces

Conclusion

In conclusion, IASLC Grade 3 tumor is an independent factor of poor prognosis in patients with resected lung adenocarcinoma, with respect to recurrence and survival. Moreover, they are associated with aggressive pathology. This finding was validated in independent cohorts comprising more than 400 patients with resected lung adenocarcinoma.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11748-021-01758-3.

Author contributions CY: data curation, formal analysis, investigation, visualization, and writing-original draft preparation. KK: conceptualization, funding acquisition, methodology, writing-reviewing and editing. EI: resources. TG: validation. RH: project administration. HY: supervision.

Funding This work was supported in part by JSPS KAKENHI (Grant number JP20K07392).

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

References

1. Travis W, Brambilla E, Nicholson A, Marx A, Burke A. WHO classification of tumours of the lung, pleura, thymus and heart. Lyon: IARC; 2015.
2. 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;24:653–64.
3. 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;30:1438–46.
4. 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;81:371–6.
5. 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;6:244–85.
6. Tsao MS, Marguet S, Le Teuff G, Lantuejoul S, Shepherd FA, Seymour L, et al. Subtype classification of lung adenocarcinoma predicts benefit from adjuvant chemotherapy in patients undergoing complete resection. J Clin Oncol. 2015;33:3439–46.
7. 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;8:52–61.
8. Woo T, Okudela K, Mitsui H, Tajiri M, Yamamoto T, Rino Y, 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.
9. Warth A, Muley T, Kossakowski C, Stenzinger A, Schirmacher P, Dienemann H, et al. Prognostic impact and clinicopathological correlations of the cribriform pattern in pulmonary adenocarcinoma. J Thorac Oncol. 2015;10:638–44.
10. Travis WD, World Health Organization, International Agency for Research on Cancer, International Association for the Study of Lung Canceer, International Academy of Pathology. WHO classification of tumors of the lung, pleura, thymus and heart. Lyon and Oxford: IARC Press, Oxford University Press; 2015.

11. Xu L, Tavora F, Burke A. Histologic features associated with metastatic potential in invasive adenocarcinomas of the lung. Am J Surg Pathol. 2013;37:1100–8.
12. Mäkinen JM, Laitakari K, Johnson S, Mäkitaro R, Bloigu R, Pääkkö P, et al. Histological features of malignancy correlate with growth patterns and patient outcome in lung adenocarcinoma. Histopathology. 2017;71:425–36.
13. Moreira AL, Joubert P, Downey RJ, Rekhtman N. Cribriform and fused glands are patterns of high-grade pulmonary adenocarcinoma. Hum Pathol. 2014;45:213–20.
14. Kuang M, Shen X, Yuan C, Hu H, Zhang Y, Pan Y, et al. Clinical significance of complex glandular patterns in lung adenocarcinoma: clinicopathologic and molecular study in a large series of cases. Am J Clin Pathol. 2018;150:65–73.
15. Kadota K, Yeh YC, Sima CS, Rusch VW, Moreira AL, Adusumilli PS, et al. The cribriform pattern identifies a subset of acinar predominant tumors with poor prognosis in patients with stage I lung adenocarcinoma: a conceptual proposal to classify cribriform predominant tumors as a distinct histologic subtype. Mod Pathol. 2014;27:690–700.
16. Kadota K, Kushida Y, Kagawa S, Ishikawa R, Ibuki E, Inoue K, et al. Cribriform subtype is an independent predictor of recurrence and survival after adjustment for the eighth edition of TNM staging system in patients with resected lung adenocarcinoma. J Thorac Oncol. 2019;14:245–54.
17. Moreira AL, Ocampo PSS, Xia Y, Zhong H, Russell PA, Minami Y, et al. A grading system for invasive pulmonary adenocarcinoma: a proposal from the International Association for the Study of Lung Cancer Pathology Committee. J Thorac Oncol. 2020;15:1599–610.
18. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al. AJCC cancer staging manual. 8th ed. New York: Springer; 2017. p. 431–56.