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Presence of a Ground-Glass Opacity Component Is the True Prognostic Determinant in Clinical Stage I NSCLC

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ABSTRACT

Introduction: Recent studies have suggested that including presence or absence of ground-glass opacity (GGO) may improve the tumor descriptor (T descriptor) classification in clinical stage I NSCLC. In this study, we analyzed prognostic implications of presence or absence of GGO, size of the solid component, and predominant histology to identify the true prognostic determinant for early-stage NSCLC.

Methods: We retrospectively examined 384 patients with clinical stage I NSCLC (solid: 242, part solid: 142) who underwent complete resection between 2009 and 2013.

Results: Survival curves of the whole cohort revealed good separation using the current TNM classification. Nevertheless, the part-solid group had a favorable prognosis irrespective of solid component size. Conversely, patients in the solid tumor group with tumors between 3 and 4 cm had a worse prognosis than patients whose tumors were less than or equal to 3 cm. Thus, we propose the following novel T descriptor classification: IA, part-solid tumors; IB, solid tumors less than or equal to 3 cm; and IC, solid tumors between 3 and 4 cm. This novel classification system stratified patient prognosis better than the current classification. On pathologic evaluation, the part-solid group always had better prognoses than the solid group in each subgroup divided by pathologic grade.

Conclusions: These results suggest that presence of GGO is the true prognostic determinant of stage I NSCLC, irrespective of the size of the solid component. Our novel T descriptor classification system could more accurately predict prognoses of clinical stage I NSCLC cases.

Introduction

Surgical resection is the standard of care for early-stage NSCLC. Nevertheless, there remains appreciable risk of postsurgical recurrence, even after complete surgical resection. Currently, the Union for International Cancer Control (UICC) TNM staging system is the only established prognostic modality to stratify risk of recurrence. To improve survival predictions, the TNM system has been revised several times. In the current eighth edition of the TNM guidelines for NSCLC, the most important tumor descriptor (T descriptor) is maximum size of the tumor's solid component, excluding any ground-glass opacity (GGO).[1] This seems to be reasonable because on pathologic examination, GGO components from thin-section computed tomography (TS-CT) usually correspond to preinvasive lesions, whereas solid components correspond to invasive regions.[2,3] Because size of the tumor's solid component is well correlated with patient survival in early-stage NSCLC,[4,5] the current TNM staging guidelines for NSCLC define T descriptor in 1-cm increments.

Nevertheless, recent studies of patients with surgically resected stage I NSCLC have reported that the prognosis of patients who have tumors with a GGO component (part-solid tumors) is significantly better than patients with pure solid tumors (solid tumors), even if the solid component of both tumors has the same diameter.[6–11] These results suggest that the presence of GGO component should be considered in the T descriptor. In addition, the reason why the prognosis of solid tumors is worse than that of GGO tumors is unknown, and detailed pathologic studies investigating this aspect of NSCLC have not yet been performed. A grading system based on the predominant pathologic subtype has been used for invasive adenocarcinomas[12]; however, the International Association for the Study of Lung Cancer recently proposed a new grading system.[13]

In this study, we investigated the influence of presence or absence of GGO and of solid tumor size in the T descriptor by analyzing the prognoses of patients with stage I NSCLC to propose a new T descriptor classification that incorporates GGO status of the primary tumor. We also evaluated the correlation between GGO status and pathologic subtypes, including a grading system of invasive adenocarcinoma, to evaluate whether pathologic grading can explain the prognostic differences between patients with solid and part-solid tumors.

Materials and Methods

Inclusion Criteria

We retrospectively extracted patient information from the surgical databases of Kindai University Hospital and Yamagata Central Hospital. We identified 1133 patients with NSCLC who underwent pulmonary resection between January 2009 and December 2013 in these hospitals. Among these patients, we ultimately included 384 who underwent complete resection by lobectomy or pneumonectomy for clinical stage I NSCLC (according to the UICC TNM eighth edition guidelines).[1] The median follow-up period of all 384 patients was 77 months. This study was approved by the institutional review boards (IRB number 31-200 in Kindai University Faculty of Medicine and IRB number 137 in Yamagata Central Hospital). Written informed consent was waived by the IRBs and opt-out was performed.

Radiologic Evaluation

For all patients, preoperative TS-CT scans were independently reviewed by two investigators, and patients were classified into the part-solid or solid groups based on the presence of GGO component as described in previous reports.[6–11] CT images were evaluated on a monitor display with a window level of 600 to 700 Hounsfield units and a window width of 1500 to 2000 Hounsfield units. Solid components were defined as areas of increased opacification that completely obscured the underlying vascular structures on TS-CT. GGO components were defined as areas of increased hazy density that did not obscure the underlying vascular structure.[3,14]

Pathologic Evaluation

Pathologic diagnoses were made by two expert pathologists (TKa or NY) according to the WHO classification. Lung adenocarcinoma was classified into adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive adenocarcinoma, which was further divided into lepidic predominant, acinar predominant, papillary predominant, micropapillary predominant, solid predominant, or invasive mucinous adenocarcinoma. As previously reported,[12] the predominant pattern was defined as the pattern with the largest percentage throughout the tissue. Invasive adenocarcinomas were further classified into the following three groups: grade 1, lepidic predominant; grade 2, acinar or papillary predominant; and grade 3, solid or

Table 1. Characteristics of the 384 Included Patients With Clinical Stage I NSCLC

Characteristics	Total (N = 384)	Part Solid (n = 142)	Solid (n = 242)	*p* Value (Part Solid vs. Solid)
Institution, n (%)				
Kindai University	215 (56)	97 (45)	118 (55)	
Yamagata Central	169 (44)	45 (27)	124 (73)	
Sex, n (%)				
Male	215 (56)	56 (26)	159 (74)	
Female	169 (44)	86 (51)	83 (49)	<0.001
Age				
Median (IQR), y	69 (64-75)	68 (64-72)	70 (64-77)	0.099
Smoking, n (%)				
Yes	219 (57)	58 (26)	161 (74)	
No	165 (43)	84 (51)	81 (49)	<0.001
Clinical stage, n (%)				
IA1	65 (17)	58 (89)	7 (11)	
IA2	154 (40)	65 (42)	89 (58)	
IA3	118 (31)	16 (14)	102 (86)	
IB	47 (12)	3 (6)	44 (94)	<0.001
Operative procedure				
Pneumonectomy	3 (1)	0 (0)	3 (100)	
Lobectomy	381 (99)	142 (37)	239 (63)	0.299
Pathologic nodal involvement, n (%)				
N0	330 (86)	136 (41)	194 (59)	
N1/2	54 (14)	6 (11)	48 (89)	<0.001

IQR, interquartile range.

micropapillary predominant, according to predominant pattern-based grading system. We also performed an exploratory analysis among the Kindai cohort using the new International Association for the Study of Lung Cancer grading system, which is as follows: grade 1, lepidic predominant; grade 2, acinar or papillary predominant (both with 0% or <20% high-grade patterns); and grade 3, any tumor with greater than or equal to 20% high-grade patterns (solid, micropapillary, or complex gland).[13]

Statistical Analyses

Statistical analyses were performed using JMP software, version 15.0 (SAS Institute Inc., Cary, NC). Continuous variables were compared using the Mann–Whitney *U* test, whereas categorical variables were compared using the chi-square test. Recurrence-free survival (RFS) was defined as the interval from the day of surgery to the first event (relapse or death from any cause). Overall survival (OS) was defined as the interval from the day of surgery to death from any cause. RFS and OS were analyzed using the Kaplan–Meier method, and statistical differences in RFS or OS between groups were compared using the log-rank test. Univariate and multivariate Cox proportional hazard regression analyses were performed to assess the prognostic impact of clinical or pathologic factors on RFS and OS. A *p* value less than 0.05 was considered statistically significant.

Results

Patient Characteristics

Clinical and demographic characteristics of the included patients are summarized in Table 1. Among the 384 patients, 65 (17%) were classified as stage IA1, 154 (40%) as stage IA2, 118 (31%) as stage IA3, and 47 (12%) as stage IB according to the current TNM classifications (eighth edition). Pathologic nodal involvement (pN1 or pN2) was recorded in 54 patients (14%). In our cohort, 242 patients (63%) had pure solid tumor (solid group). Compared with patients whose tumors had a GGO component (part-solid group), the solid group was significantly correlated with male sex ($p < 0.001$), current smokers ($p < 0.001$), and presence of the pathologic nodal involvement ($p < 0.001$). The median size of the solid tumor component in the solid group was significantly larger than that in the part-solid group (1.7 cm versus 0.7 cm, $p < 0.001$). Similar clinicopathologic differences were observed between the part-solid and solid groups in patients with clinical stage I lung adenocarcinoma (Supplementary Table 1).

Correlation Between the Presence of GGO and Prognosis

Figure 1 illustrates RFS and OS curves based on the current clinical stage in all patients, in the part-solid group, and in the solid group. The current TNM classification predicted the prognosis of patients well in the whole cohort (Fig. 1*A* and *B*); however, it did not predict
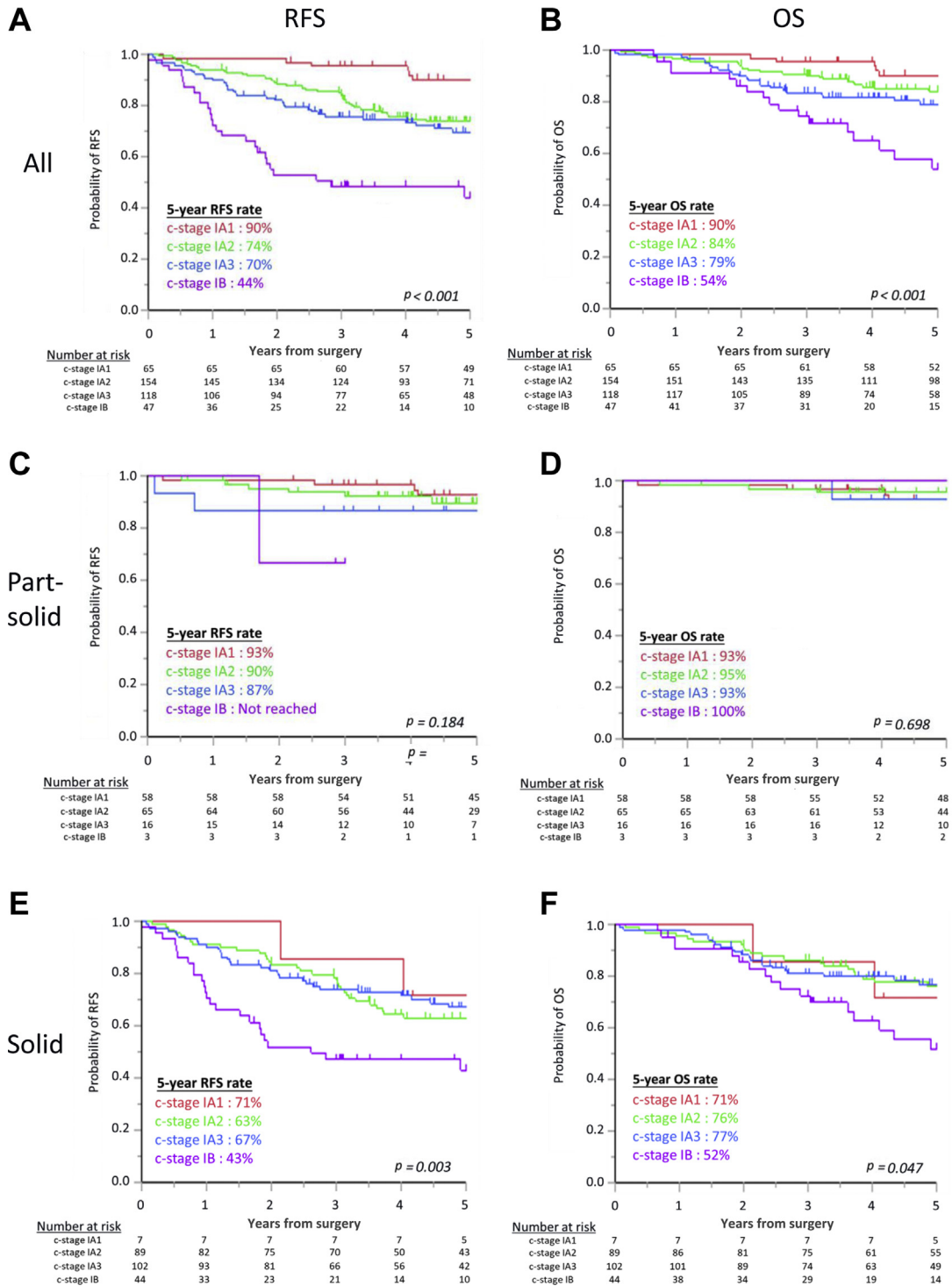
Figure 1. RFS and OS curves by c-stage in (*A*, *B*) all patients, (*C*, *D*) the part-solid group, and (*E*, *F*) the solid group. The current TNM classification system accurately predicted the prognosis of the whole cohort (5-y RFS: IA1, 90%; IA2, 74%; IA3, 70%; IB, 44%, $p < 0.001$; 5-y OS: IA1, 90%; IA2, 84%; IA3, 79%; IB, 54%, $p < 0.001$); however, it did not accurately predict prognosis in the part-solid group or c-stage IA1 to 3 of the solid group. c-stage, clinical stage; OS, overall survival; RFS, recurrence-free survival.

prognosis in the part-solid group (Fig. 1*C* and *D*). In the solid group, there was a statistically significant difference in RFS and OS; however, the survival curves were similar between c-stage IA1, IA2, and IA3 groups (Fig. 1*E* and *F*). To exclude a possibility of stage migration (influence of patients with cN0pN1/2 disease), we

performed an analysis that excludes these patients; however, the results were the same (Supplementary Fig. 1A–F). We also performed a subgroup analysis based on histology (adenocarcinomas/non-adenocarcinomas). The current classification was well associated with prognosis of patients with adenocarcinoma in the whole cohort (Supplementary Fig. 2A and B); however, it did not predict the prognosis of the solid group in either the adenocarcinoma or non-adenocarcinoma subgroup (Supplementary Fig. 2C–F).

True Prognostic Determinants for Clinical Stage I NSCLC

Therefore, we next analyzed our cohort to determine the prognosis of patients with clinical stage I NSCLC by including GGO status. Table 2 illustrates the results of Cox proportional hazard regression models for RFS and OS in all patients, the part-solid group, and the solid group. In the whole cohort, GGO status (solid versus part solid) and clinical stage (IB versus IA1/IA2/IA3) were independent prognostic factors of RFS and OS in multivariate analysis. Nevertheless, clinical stage was not a prognostic factor of RFS or OS in the part-solid group. In contrast, clinical stage (IB versus IA1/IA2/IA3) was an independent prognostic factor of RFS and OS in the solid group.

A Revised Clinical Classification System for Stage I NSCLC

On the basis of these data, we propose a new T classification system for stage I NSCLC (Table 3), in which we defined a novel clinical T1a subgroup as part-solid tumors with solid components of less than or equal to 4 cm (n = 142, 37%), a novel T1b subgroup as solid tumors with tumor diameters of less than or equal to 3 cm (n = 198, 52%), and a novel T1c subgroup as solid tumors with tumor diameters between 3 and 4 cm (n = 44; 11%). This proposed novel clinical staging classification predicted patient outcomes well in terms of RFS and OS (Fig. 2A and B). In addition, a similar trend was observed for both patients with adenocarcinoma (Fig. 2C and D) and nonadenocarcinoma (Fig. 2E and F).

Correlation Between GGO Status and Pathologic Classification

To explore the underlying reasons for the prognostic differences between part-solid tumors and solid tumors, we performed further analysis to evaluate the correlation between GGO status and the pathologic classification of tumors. The representative cases for each category were displayed in Supplementary Figure 3. Detailed pathologic classifications for the part-solid and solid groups by tumor size are summarized in Supplementary Table 2A (whole cohort) and in Supplementary Table 2B (adenocarcinoma only). These data are summarized in Figure 3A–C by grouping adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic predominant tumors into grade 1, acinar and papillary predominant tumors into grade 2, and micropapillary and solid predominant tumors into grade 3, following a previous study.[12] As found in Figure 3, the proportion of patients with grade 1 lesions was always higher in the part-solid group compared with that in the solid group in each subgroup. It is noteworthy that the part-solid group was almost entirely dominated by grade 1 and 2 lesions regardless of tumor size. In contrast, between 7% and 17% of solid tumors greater than 1 cm were classified as grade 3.

We first compared RFS and OS between patients with grade 1, 2, and 3 lesions. As found in Figure 4A and B, pathologic grade 1 disease was significantly associated with better prognosis in terms of both RFS and OS (RFS: $p < 0.001$, OS: $p < 0.001$). Conversely, there were only small prognostic differences between patients with grade 2 and grade 3 lesions. We then compared 5-year RFS and OS between the part-solid and solid groups among patients who were classified into each pathologic grade (Fig. 4C and D). The 5-year RFS of the part-solid group was always better than that of the solid group, even if both tumors had the same pathologic grade. The same trend was observed in 5-year OS data.

Discussion

The T descriptor in the UICC TNM eighth edition is based on the size of the invasive component according to radiologic or pathologic findings. In our data set, we observed that this classification well separated 5-year RFS and OS (Fig. 1A and B). Nevertheless, we also observed that the current classification did not predict patient outcomes in subgroup analysis (part-solid and solid groups) (Fig. 1C–F). This is consistent with recent studies that reported a better prognosis for patients who have tumors with GGO component compared with that for patients who have pure solid tumors, even within the same stage.[4,5,15,16] Thus, we sought to propose a better TNM staging system. Nevertheless, it should be noted that the TNM staging system has a rigid hierarchical structure: clinical, surgical, and pathologic. Therefore, it would be a future task to consider how to apply these suggestions for clinical T factor into the entire TNM staging system.

In this study, we found that the 5-year OS of the part-solid group was quite good (>90%) irrespective of the size of the solid component (Fig. 1D). Conversely, the 5-year RFS and OS of the solid group were poorer than the part-solid group (Fig. 1E and F). In addition, we observed

Table 2. Cox Proportional Hazard Regression Model for RFS and OS in All Patients, the Part-Solid Group and the Solid Group

Variables	RFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
All (N = 384)								
Age (≥70 vs. <70)	1.48 (1.02-2.15)	0.042	1.27 (0.87-1.86)	0.222	2.34 (1.50-3.65)	<0.001	2.08 (1.33-3.27)	0.001
Sex (male vs. female)	1.71 (1.15-2.53)	0.008	1.30 (0.76-2.22)	0.341	2.29 (1.43-3.68)	<0.001	1.64 (0.90-3.01)	0.109
Smoking (yes vs. no)	1.58 (1.07-2.35)	0.022	1.05 (0.62-1.80)	0.848	1.90 (1.20-3.02)	0.007	1.16 (0.64-2.11)	0.619
GGO status (solid vs. part solid)	5.01 (2.85-8.80)	<0.001	4.04 (2.25-7.25)	<0.001	4.57 (2.47-8.44)	<0.001	3.46 (1.83-6.51)	<0.001
Clinical stage								
IA2/IA3/IB vs. IA1	4.60 (2.02-10.48)	<0.001			3.54 (1.54-8.14)	0.003		
IA3/IB vs. IA1/IA2	2.28 (1.56-3.35)	<0.001			2.02 (1.31-3.11)	0.001		
IB vs. IA1/IA2/IA3	3.45 (2.21-5.40)	<0.001	2.35 (1.48-3.72)	<0.001	2.94 (1.73-4.99)	<0.001	1.95 (1.14-3.34)	0.016
Part solid (n = 142)								
Age (≥ 70 vs. <70)	1.96 (0.68-5.66)	0.213	1.97 (0.67-5.75)	0.216	4.13 (1.09-15.59)	0.036	4.28 (1.13-16.17)	0.032
Sex (male vs. female)	0.89 (0.30-2.67)	0.839	0.47 (0.13-1.65)	0.238	1.30 (0.40-4.25)	0.668	0.89 (0.23-3.42)	0.861
Smoking (yes vs. no)	2.13 (0.74-6.15)	0.162	2.72 (0.79-9.37)	0.133	1.95 (0.61-6.22)	0.258	2.17 (0.58-8.11)	0.250
Clinical stage								
IA2/IA3/IB vs. IA1	2.06 (0.64-6.59)	0.224			1.73 (0.52-5.83)	0.375		
IA3/IB vs. IA1/IA2	2.42 (0.66-8.83)	0.180			1.68 (0.36-7.81)	0.507		
IB vs. IA1/IA2/IA3	5.68 (0.72-45.09)	0.100	3.67 (0.43-31.17)	0.233	NA	NA	NA	NA
Solid (n = 242)								
Age (≥70 vs. <70)	1.38 (0.92-2.07)	0.117	1.19 (0.79-1.81)	0.403	1.98 (1.23-3.19)	0.005	1.86 (1.15-3.00)	0.012
Sex (male vs. female)	1.41 (0.90-2.19)	0.134	1.73 (0.95-3.15)	0.072	1.89 (1.11-3.22)	0.020	1.96 (0.99-3.87)	0.054
Smoking (yes vs. no)	1.02 (0.67-1.57)	0.924	0.79 (0.44-1.40)	0.413	1.32 (0.79-2.19)	0.283	1.00 (0.52-1.92)	0.991
Clinical stage								
IA2/IA3/IB vs. IA1	1.78 (0.44-7.24)	0.419			1.35 (0.33-5.52)	0.677		
IA3/IB vs. IA1/IA2	1.30 (0.86-1.97)	0.217			1.17 (0.73-1.87)	0.508		
IB vs. IA1/IA2/IA3	2.35 (1.48-3.73)	<0.001	2.31 (1.44-3.70)	<0.001	2.12 (1.23-3.64)	0.007	2.06 (1.19-3.55)	0.010

CI, confidence interval; GGO, ground-glass opacity; HR, hazard ratio; NA, not available; OS, overall survival; RFS, recurrence-free survival.

Table 3. Cox Proportional Hazard Regression Model for RFS and OS in All Patients, the Proposed Novel Clinical Staging Classification for Stage I NSCLC

Novel T Descriptor	Description
T1a (stage IA)	Part-solid tumors, the size of solid component is ≤4 cm
T1b (stage IB)	Solid tumors, the size of solid component is ≤3 cm
T1c (stage IC)	Solid tumors, the size of solid component >3 cm but does not exceed 4 cm

OS, overall survival; RFS, recurrence-free survival; T descriptor, tumor descriptor.
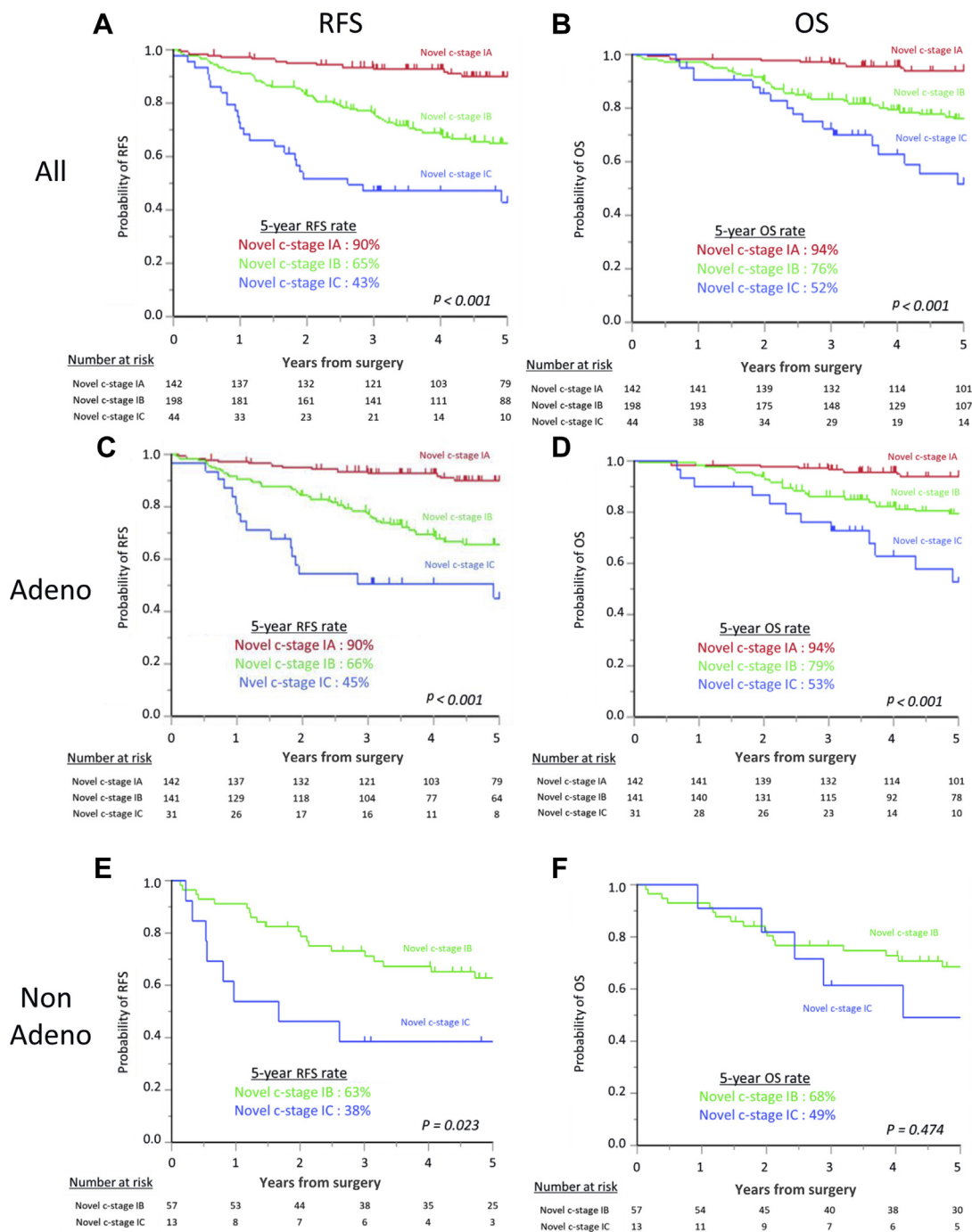

Figure 2. RFS and OS curves by the novel clinical staging system in (*A, B*) all patients, (*C, D*) patients with adeno, and (*E, F*) patients with nonadeno. The novel clinical staging classification accurately predicted the prognosis of the whole cohort (5-y RFS: IA, 90%; IB, 65%; IC, 43%, *p* < 0.001; 5-y OS: IA, 94%; IB, 76%; IC, 52%, *p* < 0.001). Adeno, adenocarcinoma; c-stage, clinical stage; OS, overall survival; RFS, recurrence-free survival.
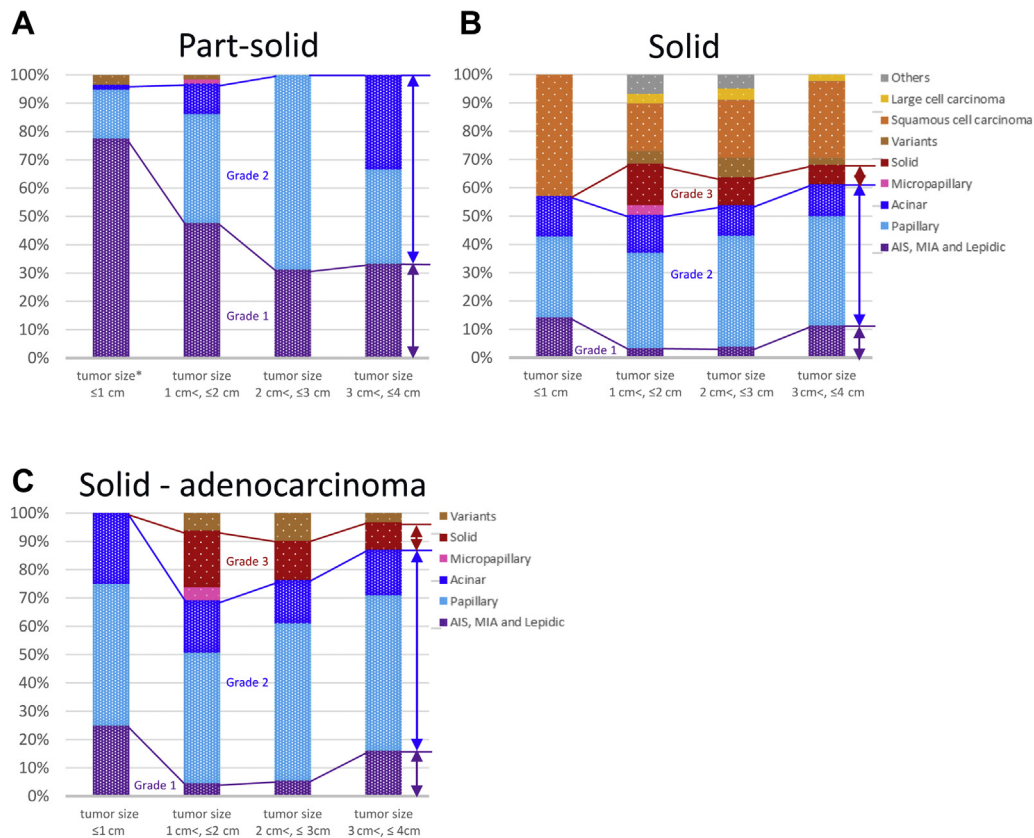
Figure 3. Proportion of pathologic subtypes by clinical stage in (*A*) the part-solid group, (*B*) the solid group, and (*C*) patients with adenocarcinoma among the solid group. *Solid component size. AIS, adenocarcinoma in situ; lepidic, invasive lepidic predominant adenocarcinoma; MIA, minimally invasive adenocarcinoma; micropapillary, invasive micropapillary predominant adenocarcinoma; papillary, invasive papillary predominant adenocarcinoma; solid, invasive solid predominant adenocarcinoma.

poorer prognosis in patients with large (>3 cm) solid tumors compared with that in patients who had small (≤3 cm) solid tumors. Following these observations and validation by multivariate analysis, we propose a new T descriptor (Table 3). We observed that this novel clinical staging system predicted patient prognosis better than the current TNM classification (Supplementary Table 3).

The reasons why the part-solid group had better prognosis than the solid group are unclear. In this study, we analyzed pathologic differences between these groups; however, patient prognosis in the solid group was always worse than in the part-solid group, even with the same pathologic grade. The International Association for the Study of Lung Cancer has recently proposed a new grading system, in which any tumor with greater than or equal to 20% high-grade patterns, such as solid, micropapillary, and complex glandular patterns, is classified as grade 3. Therefore, we applied this novel scoring system on the Kindai cohort.[13] Nevertheless, the results were the same; the part-solid group had a better prognosis than the solid group regardless of the new pathologic grade (Supplementary Fig. 4A–D).

This study had some limitations. One is its retrospective design and that it only included a relatively small cohort of patients from two institutions in Japan. Our cohort did not have data for adjuvant therapies that may affect prognosis. Another limitation is the lack of a clear definition for part-solid and pure solid tumors, as previous studies reported there would be inter- and intraobserver variability in defining a nodule into a pure solid or a part-solid tumor. There is currently no general worldwide consensus as to the optimal method of evaluating the extent of GGO. In this study, at least two investigators reviewed TS-CT scans and assigned patients into the two groups according to the definition used in previous reports[6–11]; however, we realize that it is difficult to uniformly measure the size of the solid component given the various types of pulmonary nodules.[17,18] It would be desirable to validate the results of this study in a larger cohort.

Regarding the new pathologic grading system, we could only perform an analysis on the Kindai cohort because of a lack of data; however, even in the Kindai cohort, pathologic information on complex glandular
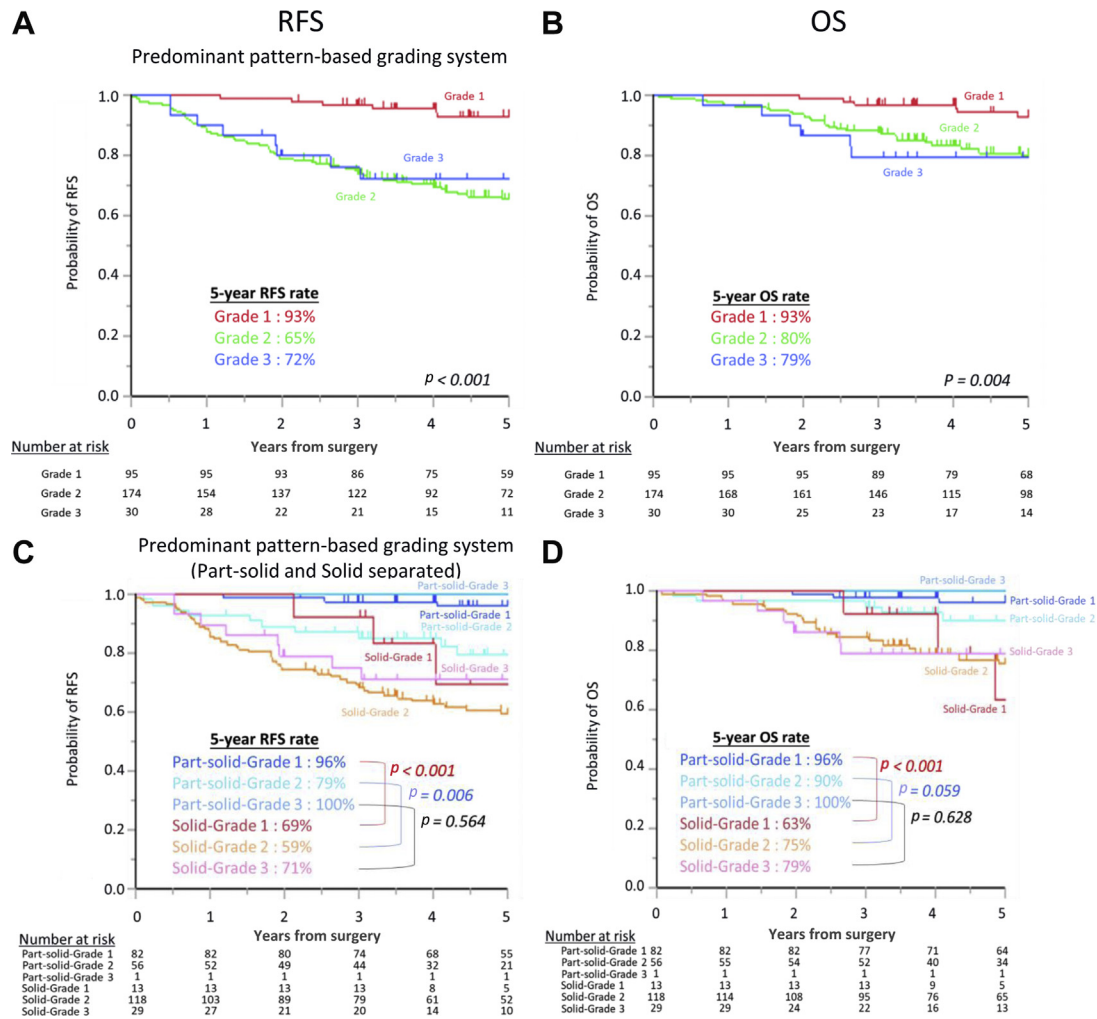
Figure 4. (*A, C*) RFS and (*B, D*) OS curves in patients with adenocarcinoma by pathologic grade based on the predominant pattern. The whole adenocarcinoma cohort (*A* and *B*) was divided into part-solid and solid groups (*C* and *D*). The 5-year OS in the part-solid group was always better than in the solid group, even if both tumors had the same pathologic grade: grade 1: 96% versus 63% (*p* < 0.001); grade 2: 90% versus 75% (*p* = 0.059); and grade 3: 100% versus 79% (*p* = 0.628), respectively. OS, overall survival; RFS, recurrence-free survival.

patterns (cribriform pattern characterized by nests of neoplastic cells with sieve-like perforations, poorly formed glands in a continuous spectrum between solid and acinar patterns, fused and irregular glands in desmoplastic stroma, and poorly formed glands in a ribbon-like formation with irregular borders, small cell clusters, and single cells infiltrating desmoplastic stroma) is not recorded. Such information should be incorporated in future analyses.

In conclusion, our results suggest that the presence of GGO is the true determinant of prognosis irrespective of the size of the solid component. A novel T descriptor classification system might be useful for more accurately predicting the prognosis of patients with clinical stage I NSCLC.

CRediT Authorship Contribution Statement

Tetsuya Mitsudomi: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing - review & editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100321.

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