Prognostic impact of a ground glass opacity component in the clinical T classification of non-small cell lung cancer

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ABSTRACT

Objective: To determine whether solid component size and the presence of a ground glass opacity (GGO) component are independently associated with survival outcomes in patients with early-stage non-small cell lung cancer (NSCLC) using the eighth edition Lung Cancer Stage Classification.

Methods: We retrospectively evaluated 1029 surgically resected early-stage NSCLCs. T categories were assigned based on solid component size using the eighth classification. All tumors were classified into 1 of 2 groups: the GGO group or the solid group. We evaluated the prognostic impact of several clinicopathological variables in clinical T classification using a Cox proportional hazard model.

Results: On multivariable analysis, the presence of a GGO component (hazard ratio [HR], 0.314; 95% confidence interval [CI], 0.181-0.529; $P < .001$) and solid component size (HR, 1.021; 95% CI, 1.006-1.036; $P = .006$) were identified as independently significant prognostic factors of overall survival. However, after accounting for the presence of a GGO component, neither maximum tumor size nor solid component size added to the prediction of long-term survival. Moreover, tumor size significantly affected survival outcome only in the solid group (HR, 1.020; 95% CI, 1.006-1.034; $P = .004$). Survival was excellent at $\geq 90\%$ despite the revised T categories, provided that the tumor had a ground glass appearance. Meanwhile, tumor size significantly affected survival only in the solid group ($P < .001$).

Conclusions: The presence of a GGO component is a significant prognostic factor in early-stage NSCLC. External validation is required to assess whether it should be adopted as a novel factor in clinical T staging. (J Thorac Cardiovasc Surg 2017;154:2102-10)

Maximum tumor size significantly differentiated survival outcome in the solid group only.

Central Message

Our results suggest that presence of a ground glass opacity component has the ability to distinguish differences in survival even for the same clinical T stage in early-stage non-small cell lung cancer.

Perspective

The results of this study demonstrate disparate clinicopathological and oncologic outcomes of early-stage non-small cell lung cancer based on the presence of a ground glass opacity (GGO) component, even in the same clinical T category. External validation is required to assess whether the GGO component should be adopted as a novel factor in clinical T staging.

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Previous studies have indicated that radiologic pure-ground glass opacity (GGO) or part-solid tumors with GGO components have a favorable prognosis in patients with early-stage non-small cell lung cancer (NSCLC).^{1,2} In lung adenocarcinomas, computed tomography (CT) findings of

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Abbreviations and Acronyms
CT = computed tomography
CTR = consolidation tumor ratio
FDG = 18F-fluorodeoxyglucose
GGO = ground glass opacity
HU = Hounsfield Unit
NSCLC = non–small cell lung cancer
OS = overall survival
PET = positron emission tomography
RFS = recurrence-free survival

GGOs vs solid sections tend to correspond to the pathological lesions of lepidic vs invasive patterns of adenocarcinomas, respectively.³ Data are also accumulating in both the radiology and pathology literature to support the concept that invasive component size is a better predictor of survival than total tumor size in resectable NSCLCs, including lung adenocarcinoma.^{4–6} Traditionally, however, a radiologically determined solid lung tumor without a GGO component tends to have a more highly malignant nature than one with a part-solid component. Moreover, postoperative nodal involvement is found in approximately 15% to 20% of cases even in small lung tumors.^{7,8}

The eighth edition Lung Cancer Stage Classification suggests that the clinical T category be determined according to the invasive component, ie, solid component size excluding the GGO component.⁹ However, the presence of a GGO component is considered to greatly influence the favorable

prognosis of NSCLC.¹⁰ In this context, however, one cannot distinguish a radiologic part-solid tumor from a solid one with no GGO component, because both will lie in the same clinical T category if they present the same solid component size. It is important to assess the potential risk of stage migration in this situation.

To resolve this problem, in this study we aimed to determine whether solid component size and presence of a GGO component are independently associated with survival outcomes after resection of early-stage NSCLCs using the eighth edition clinical T-stage classification.

METHODS
Study Population

Between 2008 and 2013, we retrospectively evaluated 1029 consecutive patients showing clinically node-negative early-stage NSCLC with a solid component <50 mm (clinical stage 0-IIA based on the eighth edition TNM classification) in our surgically resected series. The medical record of each patient was reviewed, and the clinical T descriptor was reclassified at our institution based on the eighth edition TNM staging.^{9,11} The database has been maintained prospectively, and so there were no missing data for the variables used in this study. The inclusion criteria were preoperative staging determined by thin-section computed tomography (CT) scan and complete resection without preoperative chemotherapy and/or radiotherapy. With regard to the clinical nodal assessment, clinical N0 represented nonenlarged lymph nodes <10 mm in the short axis on CT scan or negative 18F-fluorodeoxyglucose uptake by lymph nodes on positron emission tomography (FDG-PET). Invasive modalities for mediastinal lymph node staging, such as mediastinoscopy and endobronchial ultrasound-guided transbronchial needle aspiration, were not used routinely preoperatively if they did not meet the size criteria for clinical nodal involvement as evaluated

FIGURE 1. Flowchart of patients (A), and the relationship between the seventh and eighth editions of the Lung Cancer Stage Classification (B). The percentage indicates the shift rate from the seventh edition to the eighth edition. NSCLC, Non–small cell lung cancer.

TABLE 1. Clinicopathological characteristics based on presence of a GGO component

Characteristic	Clinical stage I NSCLC		P value*
	GGO group (n = 503)	Solid group (n = 526)	
Age (y), mean $\pm$ SD (range)	65.0 $\pm$ 10.9 (24-88)	68.2 $\pm$ 9.8 (35-89)	<.001
Male sex, number (%)	178 (35)	345 (66)	<.001
Right side, number (%)	315 (63)	298 (57)	.065
Pack-years of smoking, mean $\pm$ SD (range)	14.0 $\pm$ 25.5 (0-200)	34.1 $\pm$ 36.3 (0-208)	<.001
VC (%), mean $\pm$ SD (range)	99.7 $\pm$ 15.9 (51.4-147.0)	97.2 $\pm$ 17.2 (44.8-150.9)	.014
FEV ₁ (%), mean $\pm$ SD (range)	76.5 $\pm$ 7.8 (44.2-107.9)	72.8 $\pm$ 12.0 (27.2-99.4)	<.001
CEA (ng/mL), mean $\pm$ SD (range)	2.8 $\pm$ 2.5 (0.2-21.1)	6.6 $\pm$ 10.0 (0.4-82.7)	<.001
Maximum tumor size (mm), mean $\pm$ SD (range)	18.2 $\pm$ 9.1 (5-60)	25.8 $\pm$ 10.6 (5-50)	<.001
Solid component size (mm), mean $\pm$ SD (range)	9.2 $\pm$ 9.0 (0-50)	25.8 $\pm$ 10.6 (5-50)	<.001
Consolidation tumor ratio, mean $\pm$ SD (range)	0.42 $\pm$ 0.31 (0-0.96)	1.0	<.001
Air bronchogram (presence), number (%)	322 (64)	239 (46)	<.001
Pleural tail (presence), number (%)	187 (37)	240 (46)	.005
Clinical T category, number (%)			<.001
Tis	134 (27)	0 (0)	
T1mi	88 (17)	0 (0)	
T1a	100 (20)	32 (6)	
T1b	127 (25)	167 (32)	
T1c	44 (9)	179 (34)	
T2	10 (2)	148 (28)	
Operative mode (lobectomy vs sublobar resection), number (%)	262 (52)	444 (85)	<.001
Histological classification, number (%)			
AAH/AIS/MIA	9 (5)/114 (22)/55 (11)	0 (0)/6 (1)/3 (1)	<.001
Lepidic predominant invasive adenocarcinoma	140 (28)	48 (9)	
Invasive adenocarcinoma	184 (37)	302 (57)	
Squamous cell carcinoma	1 (0)	126 (24)	
Other NSCLC	0 (0)	41 (8)	
Nodal involvement (N1/N2), number (%)	5 (1)/5 (1)	64 (12)/75 (14)	<.001
Lymphatic invasion (presence), number (%)	40 (8)	268 (51)	<.001
Vascular invasion (presence), number (%)	36 (7)	303 (58)	<.001
Pathological stage (stage I), number (%)	485 (96)	338 (64)	<.001
Adjuvant chemotherapy (yes), number (%)	102 (20)	207 (39)	<.001

NSCLC, Non-small cell lung cancer; GGO, ground glass opacity; SD, standard deviation; VC, vital capacity; FEV₁, forced expiratory volume in 1 second; CEA, carcinoembryonic antigen; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma. *Student *t* test, χ^2 test, or Wilcoxon rank-sum test.

by thin-section CT or FDG-PET/CT. The medical record of each patient was reviewed retrospectively under a waiver of authorization approved by the Institutional Review Board of Juntendo University School of Medicine, Tokyo, Japan.

Radiologic Evaluation

For all patients, preoperative thin-section CT scan findings were reviewed in detail by A.H., T.M., and K.S. Tumor size was determined preoperatively based on these thin-section CT findings. In addition, all tumors were subsequently evaluated to estimate the extent of GGO by the same thin-section CT scan with 2-mm collimation. The lung was photographed with a window level of -500 to -700 Hounsfield Units (HU) and a window depth of 1000 to 2000 HU as a "lung window," and a window level of 30 to 60 HU and a window depth of 350 to 600 HU as a "mediastinal window." The consolidation tumor ratio (CTR) was defined as the ratio of the maximum size of consolidation to the maximum tumor size on thin-section CT scan.¹ A pure GGO tumor

was defined as a lung tumor without a solid component (ie, CTR = 0), a part-solid tumor was defined as a lung tumor with both GGO and solid components (ie, $0 < \text{CTR} < 1.0$), and a pure-solid tumor was defined as a tumor showing only consolidation without GGO (ie, CTR = 1.0).^{1,7,10}

Clinicopathological Evaluation

According to the eighth edition classification, tumors were defined based on solid component size as follows⁹: Tis, 0 mm (pure GGO); T1mi, ≤ 5 mm (with a GGO component); T1a, 6 to 10 mm (part-solid tumor) or 1 to 10 mm (pure-solid tumor); T1b, 11 to 20 mm; T1c, 21 to 30 mm; T2 (including T2a and T2b), 31 to 50 mm. Furthermore, all tumors were classified into either the GGO group or the solid group based on the simple presence of a GGO component (Figure 1). Histological type of lung adenocarcinoma was assigned according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system.³

TABLE 2. Cox proportional hazard model based on the clinicopathological variables

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value*	HR (95% CI)	P value*
Age (years)	1.056 (1.039-1.073)	<.001	1.042 (1.024-1.061)	<.001
Female sex	0.364 (0.268-0.492)	<.001	0.486 (0.340-0.695)	<.001
Pack-year smoking	1.010 (1.006-1.013)	<.001	1.002 (0.997-1.006)	.469
VC (%)	0.976 (0.967-0.984)	<.001	0.988 (0.979-0.997)	.008
FEV ₁ (%)	0.989 (0.976-1.002)	.098	1.019 (1.005-1.034)	.007
Serum CEA level (ng/mL)	1.042 (1.032-1.051)	<.001	1.007 (0.996-1.018)	.194
Solid component size (mm)	1.058 (1.048-1.068)	<.001	1.021 (1.006-1.036)	.006
GGO presence (yes)	0.115 (0.074-0.177)	<.001	0.314 (0.181-0.529)	<.001
Air bronchogram (no)	1.278 (0.973-1.678)	.078	1.257 (0.924-1.710)	.145
Pleural tail (no)	0.866 (0.659-1.139)	.304	0.999 (0.746-1.339)	.995
Multiple GGOs (absence)	5.276 (1.310-21.26)	.019	1.917 (0.467-7.868)	.367
Operative mode (lobectomy)	2.696 (1.840-3.950)	<.001	0.983 (0.637-1.518)	.939
Histology (adenocarcinoma)	0.363 (0.270-0.486)	<.001	1.184 (0.832-1.683)	.348
Pathological node (present)	0.243 (0.183-0.324)	<.001	0.530 (0.377-0.746)	<.001
Lymphatic invasion (present)	0.265 (0.200-0.350)	<.001	0.676 (0.463-0.987)	.042
Vascular invasion (present)	0.245 (0.184-0.326)	<.001	0.849 (0.568-1.268)	.423
Adjuvant chemotherapy (yes)	1.075 (0.800-1.445)	.631	1.673 (1.218-2.299)	.001

HR, Hazard ratio; CI, confidence interval; VC, vital capacity; FEV₁, forced expiratory volume in 1 second; CEA, carcinoembryonic antigen; GGO, ground glass opacity.
*Cox proportional hazard model.

Histological subtypes were classified according to the predominant subtype after comprehensive histologic subtyping, which implies a semi-quantitative estimation of the percentage of different subtypes in 5% increments.

Surgical Policy

With regard to the operative modes at our institution, if a tumor shows a pure-GGO or radiologically noninvasive appearance (ie, CTR <0.5), then the patient is a candidate for limited surgical resection, including wedge resection or segmentectomy.^{1,2,12} Major lung resection with systematic or lobe-selective mediastinal lymph node dissection is warranted for radiologically invasive lung cancer with a part-solid or solid tumor (0.5 ≤ CTR ≤ 1.0).^{1,2,13} Intentional segmentectomy with systematic or selective lymph node dissection is now indicated for radiologically invasive part-solid or solid lung tumors (0.5 ≤ CTR ≤ 1.0) 2 cm or smaller, according to a prospective randomized trial in Japan.¹⁴ In that trial, nonanatomic wedge resection was performed in a few elderly patients and patients considered at high cardiopulmonary risk.

Statistics

The χ^2 test was used to compare the factors. For continuous variables, the unpaired *t* test was used to compare normally distributed variables, and the Wilcoxon rank-sum test was used to compare non-normally distributed variables. A Cox proportional hazard model was fit to identify the significant prognostic factors for survival using SPSS version 21 (IBM, Armonk, NY). Forward and backward stepwise procedures were used to determine the combination of factors essential for the survival outcomes. Overall survival (OS) was estimated using the Kaplan-Meier method and compared across the different groups using the log-rank test. The date of surgical resection was set as the starting point of OS, and the date of death or survival at follow-up was set as the endpoint of OS. The time of occurrence of the first event including relapse and death, or the date of evaluating survival or recurrence, was set as the endpoint of recurrence-free survival (RFS). Continuous

variables were summarized as mean ± standard deviation for normally distributed variables and as median and interquartile range for non-normally distributed variables. A difference was considered statistically significant at a *P* value < .05.

RESULTS

Among the 1029 patients, 134 (13%) were classified as Tis, 88 (9%) as T1mi, 132 (13%) as T1a, 294 (29%) as T1b, 223 (21%) as T1c, and 158 (15%) as T2. Among these, 32 T1a (24%), 167 T1b (57%), 179 T1c (80%), and 148 T2 (94%) lesions were classified as the solid group. All of the Tis and T1mi lesions belonged to the GGO group (Figure 1, A). The relationship between the seventh and eighth editions of the Clinical Lung Cancer Stage Classification is shown in a cross table in Figure 1, B.

Clinicopathological characteristics of the patients by group are summarized in Table 1. Significant differences were observed between the GGO and solid groups regarding several clinicopathological factors.

We evaluated OS in the 1029 eligible patients with NSCLC. The eighth edition classification clearly delineates the differences in 5-year OS: 99.2% in Tis, 95.8% in T1mi, 96.3% in T1a, 78.6% in T1b, 65.4% in T1c, and 56.5% in T2 (*P* < .0001) (Figure E1). The median follow-up period for the entire cohort was 53.0 ± 31.5 months. The number of deaths was 207. Table 2 presents data for a Cox proportional hazard model for survival in early-stage NSCLC. Our multivariable analysis, which eliminated any possible confounding between solid component size and maximum

TABLE 3. Clinicopathological characteristics based on the presence of a GGO component in clinical stage I NSCLC

Characteristic	T1a (n = 132)			T1b (n = 294)	
	GGO (n = 100)	Solid (n = 32)	P value*	GGO (n = 127)	Solid (n = 167)
Male sex, number (%)	34 (34)	15 (47)	.211	51 (40)	109 (65)
Age (years), mean $\pm$ SD (range)	65.8 $\pm$ 10.6 (35-88)	67.1 $\pm$ 9.8 (49-88)	.549	67.7 $\pm$ 9.4 (40-88)	66.6 $\pm$ 10.3 (35-89)
Pack-year smoking, mean $\pm$ SD (range)	17.4 $\pm$ 29.4 (0-125)	22.6 $\pm$ 30.6 (0-110)	.383	17.3 $\pm$ 27.0 (0-162)	29.9 $\pm$ 32.9 (0-208)
CEA (ng/mL), mean $\pm$ SD (range)	2.3 $\pm$ 1.3 (0.3-7.3)	4.0 $\pm$ 7.8 (0.5-45.6)	.038	3.2 $\pm$ 2.6 (0.5-21.1)	5.9 $\pm$ 8.0 (0.4-57.0)
Maximum tumor size (mm), mean $\pm$ SD (range)	17.4 $\pm$ 5.7 (7-34)	9.2 $\pm$ 1.3 (5-10)	<.001	22.7 $\pm$ 5.2 (11-38)	16.7 $\pm$ 2.6 (11-20)
Solid component size (mm), mean $\pm$ SD (range)	8.3 $\pm$ 1.7 (0-10)	9.2 $\pm$ 1.3 (5-10)	.009	15.5 $\pm$ 2.7 (11-20)	16.7 $\pm$ 2.6 (11-20)
Multiple GGOs (presence), number (%)	10 (10)	1 (3)	.294	11 (9)	4 (2)
Operation (lobectomy), number (%)	56 (56)	15 (47)	.418	104 (82)	131 (78)
Histology (adenocarcinoma), number (%)	100 (100)	27 (84)	.001	127 (100)	128 (77)
Nodal involvement (yes), number (%)	0 (0)	3 (9)	.013	4 (3)	32 (19)
Pathological whole size (mm), mean $\pm$ SD (range)	15.7 $\pm$ 6.1 (4-35)	9.5 $\pm$ 2.5 (2-14)	<.001	21.4 $\pm$ 7.1 (5-40)	17.4 $\pm$ 5.3 (6-32)
Lymphatic invasion (presence), number (%)	7 (7)	4 (13)	.461	21 (17)	87 (52)
Vascular invasion (presence), number (%)	4 (4)	6 (19)	.013	16 (13)	78 (47)
Pathological stage I disease, number (%)	100 (100)	29 (91)	.044	123 (97)	131 (78)

GGO, Ground glass opacity; SD, standard deviation; CEA, carcinoembryonic antigen. *Student *t* test, χ^2 test, or Wilcoxon rank-sum test.

tumor size, revealed that presence of a GGO (hazard ratio [HR], 0.314; 95% confidence interval [CI], 0.181 to 0.529; $P < .001$) and solid component size (HR, 1.021; 95% CI, 1.006 to 1.036; $P = .006$) were independent significant prognostic factors of survival.

Based on the results of our multivariable analysis, we investigated the clinicopathological characteristics of clinical T1a-T2 NSCLCs based on the presence of a GGO component (Table 3). Histologically, adenocarcinoma was more frequent in the GGO group than in the solid group. Pathologically, lymphatic or vascular invasion and nodal metastasis were less common in the GGO group than in the solid group, especially in the clinical T1a-1c category.

Based on our Cox proportional hazard model findings, we performed a further multivariable analysis to identify the significant clinicopathological variables according to the presence or absence of a GGO component on thin-section CT (Table 4). Among the 526 tumors in the solid group (CTR = 1.0; 51%), multivariable analysis identified carcinoembryonic antigen titer, maximum tumor size, nodal metastasis, and adjuvant chemotherapy administration were independently significant clinicopathological factors in OS ($P = .006$, $.004$, $< .001$, and $< .001$, respectively). Among the 503 tumors (49%) in the GGO group, however, neither maximum tumor size nor solid component size was predictive of long-term survival after accounting for the presence of a GGO component.

In our evaluation of OS and RFS of patients in the GGO and solid groups, respectively (Figures 2 and 3), the new clinical T categories significantly separated both OS (T1a, 87.7%, T1b, 70.4%; T1c, 59.6%; T2, 54.1%; $P < .001$) (Figure 2, A) and RFS (T1a, 82.7%; T1b, 62.1%; T1c, 53.6%; T2, 41.6%; $P < .001$) (Figure 3, A) in the solid group with a median follow-up time of 49.0 ± 31.5 months for OS. Furthermore, survival curves in the solid group were clearly separated between adjacent groups, yielding significant OS differences between T1a and T1b ($P = .033$) and between T1b and T1c ($P = .038$) (Figure 2, A). Significant differences in OS (Figure 2, B) and RFS (Figure 3, B) were observed among the T categories of the GGO group; however, despite the revised T categories, 5-year OS was excellent at $\geq 90\%$ provided that the tumor had a GGO appearance, with a median follow-up time of 54.5 ± 29.3 months (Tis, 99.2%; T1mi, 95.8%; T1a, 98.9%; T1b, 90.2%; T1c, 91.0%; T2, 90.0%; $P = .004$; Tis vs T1mi, $P = .061$; T1mi vs T1a, $P = .123$; T1a vs T1b, $P = .007$; T1b vs T1c, $P = .919$) (Figure 2, B).

DISCUSSION

The results of this study clearly demonstrate that the clinicopathological and oncologic outcomes of early-stage NSCLCs differ significantly between part-solid and pure-solid tumors even in the same clinical T category. The OS curve was clearly split in accordance with the new clinical

TABLE 3. Continued

T1b (n = 294)	T1c (n = 223)			T2 (n = 158)		
	GGO (n = 44)	Solid (n = 179)	P value*	GGO (n = 10)	Solid (n = 148)	P value*
<.001	16 (36)	115 (64)	.001	5 (50)	106 (72)	.164
.348	68.6 ± 8.9 (44-86)	68.3 ± 9.7 (38-86)	.877	72.1 ± 7.25 (62-83)	70.2 ± 8.9 (48-88)	.517
.001	16.2 ± 25.7 (0-80)	40.3 ± 42.1 (0-180)	.003	27.8 ± 40.4 (0-100)	33.6 ± 32.4 (0-175)	.589
<.001	5.0 ± 4.0 (1.0-20.3)	6.7 ± 10.1 (0.5-80.5)	.038	6.1 ± 5.6 (1.9-16.9)	7.8 ± 11.9 (0.8-82.7)	.644
<.001	32.7 ± 5.8 (25-46)	25.5 ± 3.0 (21-30)	<.001	44.7 ± 7.6 (35-60)	39.7 ± 5.7 (31-50)	.072
<.001	24.8 ± 2.9 (21-30)	25.5 ± 3.0 (21-30)	.200	39.8 ± 5.6 (31-50)	39.7 ± 5.7 (31-50)	.973
.029	4 (9)	1 (1)	.006	0 (0)	2 (1)	1.000
.557	40 (91)	158 (88)	.792	10 (100)	140 (95)	1.000
<.001	44 (100)	120 (67)	<.001	9 (90)	85 (57)	.050
<.001	6 (14)	59 (33)	.015	0 (0)	45 (28)	.063
<.001	33.3 ± 11.5 (17-55)	27.1 ± 9.3 (10-55)	<.001	46.2 ± 17.7 (31-85)	40.7 ± 12.6 (17-65)	.196
<.001	7 (16)	93 (52)	<.001	5 (50)	84 (57)	.749
<.001	8 (18)	118 (66)	<.001	7 (70)	101 (68)	1.000
<.001	35 (80)	107 (60)	<.001	6 (60)	81 (55)	1.000

T classification; however, both pathological characteristics and oncologic outcomes differed significantly based on the presence of a GGO component in each clinical T category. Thus, our results suggest that thorough distinction between radiologically pure-solid and part-solid lung cancers is crucial when considering clinical T classification in early-stage NSCLC.

The aim of this study was to determine whether solid component size and presence of a GGO component are independently associated with survival outcomes of early-stage NSCLC using the eighth edition clinical T-stage classification. Our multivariable analysis identified the presence of a GGO component as a significant predictive factor, whereas whole tumor size of solid component size was not associated with survival when the presence of a GGO component in patients with early-stage NSCLC was accounted for. Generally, CTR or solid component size on thin-section CT scan is considered more prognostic than maximum tumor size in NCSLC^{5,6,9}; however, these factors might not be considered in the prediction of long-term survival in patients with NSCLC with a GGO component owing to the prevalence of less-invasive or lepidic-predominant adenocarcinomas in the population.¹⁰ On the other hand, radiologically determined pure-solid lung cancers without a GGO component exhibit more malignant behavior and show several histological types

that have a poorer prognosis compared with part-solid lung cancers.^{7,8,15}

Especially in lung adenocarcinomas, the significant differences in clinicopathological and oncologic outcomes between pure-solid and part-solid tumors may be related to their distinctive carcinogenesis. The difference in how pure-solid and part-solid lesions progress undoubtedly accounts for the difference in survival to some extent. Histologically, most part-solid lung adenocarcinomas remain predominantly lepidic.¹⁰ Clinically, previous studies have shown a significant difference in maximum standardized uptake value on FDG-PET between part-solid and pure-solid lung cancers.^{8,16} In particular, lung adenocarcinoma is thought to follow a multistep linear progression in which a precursor lesion progresses to adenocarcinoma in situ, followed by invasive adenocarcinoma, including many predominantly lepidic lesions.¹⁷ We would expect some of the pure-solid tumors to reflect a nonlinear progression, derived from de novo invasive adenocarcinomas.¹⁸ Thus, resolving the different natural histories of tumors with and without a GGO component from a pathological or genetic standpoint is important.

Radiologically determined pure-solid lung cancer is considered highly invasive and includes several histological types other than lung adenocarcinoma. A previous study demonstrated the importance of solid component size only in adenocarcinoma⁹; however, preoperative histological

TABLE 4. Cox proportional hazard model in the solid and GGO groups

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value*	HR (95% CI)	P value*
Solid group (CTR = 1.0)				
Female sex	0.637 (0.460-0.881)	.006	0.681 (0.491-0.946)	.022
Pack-year smoking	1.003 (1.000-1.007)	.084		
Serum CEA level (ng/mL)	1.026 (1.016-1.036)	<.001	1.015 (1.004-1.026)	.006
Maximum tumor size (mm)	1.030 (1.017-1.044)	<.001	1.020 (1.006-1.034)	.004
Air bronchogram (no)	1.210 (0.904-1.620)	.201		
Pleural tail (no)	1.104 (0.825-1.477)	.506		
Multiple GGOs (no)	2.683 (0.376-19.17)	.084		
Histology (adenocarcinoma)	0.765 (0.565-1.035)	.082		
Nodal involvement (no)	0.456 (0.339-0.613)	<.001	0.535 (0.385-0.744)	<.001
Lymphatic invasion (no)	0.564 (0.415-0.766)	<.001	0.764 (0.525-1.114)	.162
Vascular invasion (no)	0.532 (0.386-0.732)	<.001	0.811 (0.544-1.208)	.302
Adjuvant chemotherapy (no)	1.607 (1.181-2.186)	.003	1.931 (1.406-2.652)	<.001
GGO group (0 ≤ CTR <1.0)				
Female sex	0.286 (0.121-0.674)	.004	0.294 (0.108-0.800)	.017
Pack-year smoking	1.015 (1.005-1.025)	.003	1.003 (0.989-1.017)	.662
Serum CEA level (ng/mL)	1.129 (1.036-1.231)	.006	1.112 (0.907-1.276)	.079
Maximum tumor size (mm)	1.054 (1.017-1.092)	.004	0.993 (0.914-1.079)	.870
Solid component size (mm)	1.053 (1.016-1.090)	.004	1.004 (0.924-1.090)	.930
Air bronchogram (no)	0.155 (0.036-0.663)	.012	0.222 (0.045-1.082)	.063
Pleural tail (no)	0.529 (0.234-1.20)	.128		
Multiple GGOs (no)	2.094 (0.281-15.58)	.470	2.707 (0.371-19.78)	.326
Nodal involvement (no)	0.417 (0.056-3.096)	.392		
Lymphatic invasion (no)	0.308 (0.114-0.832)	.020	0.385 (0.133-1.116)	.079
Vascular invasion (no)	0.502 (0.149-1.688)	.265		
Adjuvant chemotherapy (no)	1.795 (0.533-6.045)	.345		

HR, Hazard ratio; CI, confidence interval; CTR, consolidation tumor ratio; CEA, carcinoembryonic antigen; GGO, ground glass opacity. *Cox proportional hazard model.

confirmation might not be done in most cases due to the early detection of small-sized tumors and the advancement of pre-operative radiologic diagnosis of lung cancer by thin-section

CT scan. Therefore, we analyzed patients with NSCLC to reflect the real prognostic impact of a GGO component in the future clinical T staging for all NSCLC patients.

FIGURE 2. Comparison of overall survival (OS) by clinical T category in the solid (A) and ground glass opacity (GGO) groups (B). The 5-year OS was excellent at $\geq 90\%$ despite the revised T categories, provided that the tumor had a GGO appearance. In contrast, maximum tumor size had a significant impact on OS only in the solid group ($P < .001$).

FIGURE 3. Comparison of recurrence-free survival (RFS) by clinical T category in the solid (A) and ground glass opacity (GGO) groups (B). Maximum tumor size had a significant impact on RSF only in the solid group ($P < .001$).

In terms of the appropriate operative modes, tumors with a radiologically noninvasive appearance, including c-Tis and c-T1mi lesions, are candidates for limited surgical resection, including wedge resection or segmentectomy.^{1,2,12} In contrast, major lung resection with mediastinal lymph node dissection is warranted for radiologically invasive lung cancers.^{1,2,13} Intentional segmentectomy is under investigation as a future operative strategy for small radiologically invasive lung cancers ($0.5 \leq \text{CTR} \leq 1.0$).¹⁴ Based on the results of our present study, however, the presence of a GGO component should influence the treatment mode in early-stage NSCLC. A tumor with a GGO component is considered a candidate for segmentectomy, even when it has a radiologically invasive appearance, but this requires further investigation.^{19,20} In contrast, lobectomy may be a mainstay for radiologically solid tumors without a GGO component to prevent locoregional recurrence.¹⁹⁻²¹

One of the limitations of this study is the difficulty in determining the extent of GGO. There is no general worldwide consensus as to the optimal method for evaluating the extent of GGO. In Japan, the JCOG0201 study prospectively elucidated the radiological-pathological correlation based on the extent of GGO using thin-section CT scans.¹ In general, thin-section CT is necessary to precisely assess the true degree of a GGO component or solid component. Thus, it is far easier to assess the presence or absence of a GGO component than to measure the size of the solid component of a tumor. The eighth edition classification suggests that tumor size should be determined according to the invasive component size excluding any GGO component⁹; however, it is impossible to uniformly measure solid

component size in many part-solid tumors, given the various types of GGO components, including GGO-dominant, solid-dominant, GGO with scattered consolidations, island-shaped consolidation, and GGO mimicking organizing pneumonia.^{5,10,22,23} The prognosis of part-solid tumors, most of which are lung adenocarcinomas, is favorable for all cases despite the distinct appearance of a solid part due to the presence of a radiological GGO component.¹⁰ In this point, recognition of the presence of a GGO component on thin-section CT scan would be more radical and reproducible compared with the measurement of the solid component in part-solid tumors to evaluate the radiological-pathological correlation and the prognosis.

The principle behind the TNM staging system is the classification of cancers into groups according to the anatomic extent of GGO. The purpose is to evaluate treatment strategies and to give some indication of prognosis for survival. Precise measurement of tumor size is crucial to improve stratification in the future. The results of this study indicate that maximum tumor size should be applied only to radiologically pure-solid lung cancers. In contrast, revised clinical T categories do not function for tumors with a GGO component due to their excellent OS. We recommend Tis as the description for pure GGO, and T1a for all part-solid lesions (Video 1).

Other limitations of this study are its single-center retrospective nature and relatively small number of the patients. We are planning to validate our findings using prospective data from Japanese studies in the near future. Furthermore, global uniformity of the concept and recognition of GGOs is important for generalizing the GGO component as a new clinical T descriptor.

VIDEO 1. A paper presented at The American Association for Thoracic Surgery Centennial in Boston, 2017. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)31798-1/fulltext](http://www.jtcvsonline.org/article/S0022-5223(17)31798-1/fulltext).

In conclusion, the presence of a GGO component has a significant impact on the favorable prognosis of early-stage NSCLCs. External validation is required to assess whether it should be adopted as a novel factor in the clinical T staging of NSCLCs.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: lung cancer, ground glass opacity, T classification, prognosis

FIGURE E1. Overall survival (OS) based on the eighth edition of the clinical T classification in clinical stage I NSCLC. The 5-year OS was 99.2% for Tis, 95.8% for T1mi, 96.3% for T1a, 78.6% for T1b, 65.4% for T1c, and 56.5% for T2 ($P < .0001$).