Role of ground-glass opacity in pure invasive and lepidic component in pure solid lung adenocarcinoma for predicting aggressiveness

Takahiro Mimae, MD, PhD,[a] Yoshihiro Miyata, MD, PhD,[a] Yasuhiro Tsutani, MD, PhD,[a] Yoshihisa Shimada, MD, PhD,[b] Hiroyuki Ito, MD, PhD,[c] Haruhiko Nakayama, MD, PhD,[c] Norihiko Ikeda, MD, PhD,[b] and Morihito Okada, MD, PhD[a]

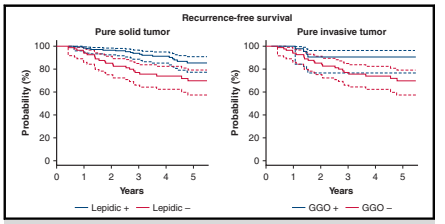
ABSTRACT

Objective: Lung adenocarcinoma often includes noninvasive components with postoperative lepidic morphology on pathologic specimens that appear on preoperative high-resolution computed tomography (HRCT) images as ground-glass opacity (GGO). We aimed to disclose the role of GGO on the aggressiveness of pathologically confirmed pure invasive tumors in patients with early-stage lung adenocarcinoma.

Methods: The prognosis of 932 patients with clinical stage 0-IA and pathologic node-negative lung adenocarcinoma who underwent lobectomy at 3 institutions between 2010 and 2016 was investigated according to the status of GGO and lepidic components.

Results: The recurrence-free survival (RFS) of patients with pathologically confirmed pure invasive tumors was worse without (n = 81) than with (n = 43) GGO (69.7%; 95% confidence interval [CI], 57.3%-79.2% vs 90.5%; 95% CI, 76.6%-96.3%, $P = .028$). The RFS of patients with radiologically confirmed pure solid tumors was worse without (n = 81), than with (n = 173) a lepidic component (69.7%; 95% CI, 57.3%-79.2% vs 85.3%; 95% CI, 77.2%-90.7%, $P = .0012$). Multivariable Cox regression analysis of overall survival and RFS revealed that pure solid and pure invasive tumors, respectively, determined by HRCT and pathologic assessment together comprised an independent prognostic factor like vascular or pleural invasion for patients with early-stage lung adenocarcinoma.

Conclusions: Tumors of non–small cell lung cancer with pure solid and pure invasive components were more aggressive than those with some GGO and lepidic components. Complementary HRCT and pathologic findings can predict the malignant aggressiveness of adenocarcinoma. (JTCVS Open 2022;11:300-16)



Prognosis is worse for tumors without than with GGO and lepidic components.

CENTRAL MESSAGE

Complementary findings of high-resolution computed tomography and pathology predict malignant aggressiveness of lung adenocarcinoma.

PERSPECTIVE

Lung adenocarcinoma tumors that show pure solid component on the preoperative HRCT and pure invasive component on the postoperative pathologic examination had more malignant aggressiveness than others. These findings require validation in other cohorts.

Video clip is available online.

Non–small cell lung cancer (NSCLC) tumors, especially adenocarcinoma, usually consist of invasive and noninvasive components.[1] Pathologic invasive and noninvasive (lepidic) components of tumors are recognized as areas that are solid/consolidated and ground-glass opacity (GGO), respectively, on high-resolution computed tomography (HRCT) images.[1-4] In general, the behavior of pathologic pure invasive tumors is more malignant than tumors containing some or comprising solely noninvasive components.[5] The prognosis is similarly worse for patients with pure solid rather than partly solid or pure GGO tumors on HRCT.[6] However, pathologic pure invasive tumors can have some GGO on HRCT images, and pathologic findings have shown that some pure solid tumors contain a noninvasive/lepidic component. The prognosis is better for patients who have pure solid tumors on HRCT images with than without pathologically confirmed lepidic components.[7]

From the [a]Department of Surgical Oncology, Hiroshima University, Hiroshima; [b]Department of Surgery, Tokyo Medical University, Tokyo; and [c]Department of Thoracic Surgery, Kanagawa Cancer Center, Yokohama, Japan.

This study was supported by grants from the Japan Society for the Promotion of Science (JSPS) KAKENHI (20K09177).

Received for publication Dec 13, 2021; revisions received April 16, 2022; accepted for publication April 27, 2022; available ahead of print June 22, 2022.

Address for reprints: Morihito Okada, MD, PhD, Department of Surgical Oncology, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, Japan, 734-8551 (E-mail: morihito@hiroshima-u.ac.jp).

2666-2736

https://doi.org/10.1016/j.xjon.2022.04.041

Abbreviations and Acronyms

CI = confidence interval
CT = computed tomography
FDG = ^{18}F-fluorodeoxyglucose
GGO = ground-glass opacity
HRCT = high resolution computed tomography
HU = Hounsfield units
NSCLC = non–small cell lung cancer
OS = overall survival
PET = positron emission tomography
RFS = recurrence-free survival
SUVmax = maximum standardized uptake value

However, whether the prognoses of patients who have pathologic pure invasive tumors with and without a GGO component are comparable remains unclear.

Here, we aimed to define the roles of GGO components in pathologic pure invasive tumors and of pathologic lepidic components of pure solid tumors by comparing prognoses according to the status of GGO and lepidic components.

METHODS

Patient Population

We initially collected information about 1486 consecutive patients with pathologic node-negative, clinical stage 0-IA lung adenocarcinoma that was treated by lobectomy or sublobar resections with curative intent at Kanagawa Cancer Center, Tokyo Medical University, and Hiroshima University Hospital between January 2010 and December 2016. Among these patients, we excluded 554 who underwent sublobar resections including wedge resection and segmentectomy for clinical stage 0-IA lung adenocarcinoma to avoid selection bias. The institutional review boards at the participating institutions approved this retrospective review of a prospective database and waived the requirement for informed consent from individual patients (June 13, 2018, E1216). All tumors were staged according to the TNM Classification of Malignant Tumors, Eighth edition.[8,9] Patients were not routinely assessed by endobronchial ultrasonography and mediastinoscopy at the participating institutions. Lymph node metastasis was determined as negative when the short axis of mediastinal or hilar lymph nodes was <1 cm on HRCT, and when ^{18}F-fluorodeoxyglucose (FDG) did not accumulate in such nodes on FDG-positron emission tomography (PET) images. The inclusion criteria included preoperative staging determined by HRCT and FDG-PET/computed tomography (CT) and curative surgery without induction therapy. All patients with clinical stage 0-IA lung adenocarcinoma were assessed by PET, even when the tumors were GGO predominant. Patients with incompletely resected tumors (R1 or R2) were excluded.

Surgical Indications

The intensive inclusion criteria for sublobar resections are as follows: peripherally located, ≤2 cm, and GGO-dominant NSCLC treated by wedge resection; peripherally located, ≤2 cm, and solid dominant NSCLC, or peripherally located, 2-3 cm, GGO-dominant NSCLCs treated by segmentectomy. Compromised patients were also treated by sublobar resection. Other clinical stage 0-IA lung adenocarcinomas, including centrally located, small, or GGO-dominant tumors, were treated by lobectomy. When a preoperative diagnosis was not confirmed for peripherally located tumors in patients scheduled to undergo lobectomy, tumors intraoperatively obtained during wedge resection or segmentectomy were frozen and pathologically analyzed. Then, confirmed malignancies were treated by lobectomy. Centrally located lung tumors that could not be completely removed by sublobar resection were treated by lobectomy with diagnostic and curative intent.

Pathologic Examinations

Surgically resected specimens were routinely fixed for macroscopic assessment in 10% buffered formalin and cut into serial slices 5- to 7-mm thick. Hematoxylin and eosin–stained tissues were histologically diagnosed. Tissues were immunohistochemically assessed when a diagnosis could not be established by hematoxylin and eosin staining. Visceral pleural invasion was assessed as present or absent, and at least 1 tumor cell cluster visible in a lymphatic or blood vessel was considered to indicate lymphatic or vascular invasion, respectively. In addition, lymphatic and vascular invasion was immunohistochemically assessed by D2-40 and Elastica van Gieson staining, and pleural invasion was evaluated by visualizing elastic tissue fibers using the same stain where possible. Histologic type was determined by 2 pathologists according to the Fourth edition of the World Health Organization classification of tumors of the lung, pleura, thymus, and heart.[10] The findings of stained specimens were reviewed twice by at least 2 appropriately qualified pathologists, including at least one with a minimum of 20 years of experience at each institution.

HRCT Imaging

Chest images were acquired using 16-row multidetector CT. High-resolution images of tumors were acquired under the following parameters: 120 kVp; 200 mA; section thickness, 1-2 mm; pixel resolution, 512 × 512; scan duration, 0.5-1.0 seconds; a high spatial reconstruction algorithm with a 20-cm field of view; mediastinal window settings of 40 Hounsfield units (HU) and width, 400 HU and lung window settings of –600 HU and width, 1600 HU. The size of a solid component (consolidation) was defined as its maximal dimension in the lung window, excluding GGO. We defined GGO as a hazy increase in lung attenuation that did not obscure underlying vascular markings that appeared as areas of residual high density. Radiologists from the participating institutions reviewed all CT images and determined tumor sizes.

Follow-up Evaluation

Starting from the day after lung resection, all patients were followed up quarterly by a physical examination and chest radiography, as well as biannually by chest and abdominal CT for the first 2 years. Subsequent follow-up comprised biannual radiography of the chest and physical examinations, as well as annual CT assessments of the chest. Sites of recurrence were defined as locoregional, a new first lesion in surgical stumps of lung, hilar, mediastinal or supraclavicular lymph nodes, or the thoracic wall, and distant new first lesions that developed at sites other than locoregional.

Statistical Analyses

Continuous and categorical variables were analyzed using nonparametric Mann–Whitney *U* tests, Kruskal–Wallis tests, and χ^2 or Fisher exact tests. Rates of overall (OS) and recurrence-free (RFS) survival were calculated from Kaplan–Meier curves, and 2 or more groups were compared using univariable log-rank analyses. Prognostic factors were determined by multivariable analyses of OS and RFS using Cox regression. Background variables with potential differences between patients with pure solid and pure invasive tumors and others were adjusted using propensity score stratification. Propensity scores were calculated using a logistic regression model based on preoperative characteristics that included age (≥70 or <70 years), sex, smoking status (Brinkman index ≥400 or <400), lymphatic invasion, vascular invasion, pleural invasion, and histologic subtype (solid/micropapillary or others). Stratified propensity scores were included as covariates in multivariate regression models. All data were

statistically analyzed using EZR, version 1.37 (Saitama Medical Centre, Jichi Medical University), which is a graphical user interface for R, version 3.4.4 (R Foundation for Statistical Computing).[11] More precisely, EZR is a modified version of R commander version 2.4-0 that was designed to add statistical functions that are frequently used in biostatistics.

RESULTS

Clinicopathologic Findings of Patients Based on GGO or a Lepidic Component

Tables 1, 2, and E1 show the clinicopathologic characteristics of all included patients who had tumors with a lepidic component or GGO. Greater Brinkman indices, larger solid tumors, greater maximum standardized uptake values (SUVmax), more advanced cT and pT factors, and more pathologic invasion including lymphatic, vascular, and pleural invasion were associated with pathologic pure invasive tumors compared with tumors that had lepidic components (Table 1). Figure E1 shows representative HRCT findings of lung adenocarcinoma tumors with GGO and without a lepidic component. More male than female patients had pure solid tumors. Patients with pure solid tumors had greater Brinkman indices, larger solid tumors, greater SUVmax, more advanced cT- and pT-factors, larger pathologic invasive size, and a greater frequency of lymphatic, vascular, and pleural invasion compared with tumors containing GGO (Table 2).

Prognosis According to the Status of GGO or a Lepidic Component

The OS was better for patients with tumors containing a lepidic component or GGO than for those with pathologic pure invasive, or pure solid tumors. The 5-year OS rates for all patients based on the presence or absence of a lepidic component were 95.3% (95% confidence interval [CI], 93.3%-96.8%) versus 84.8% (95% CI, 76.1%-90.5%, $P < .0001$; Figure 1, *A*). Those for a GGO component were 96.0% (95% CI, 94.0%-97.3%) versus 87.8% (95% CI, 81.6%-91.9%), $P = .00028$ (Figure 1, *B*). Among patients with pure solid tumors on HRCT images, OS was better for those with, than without pathologically defined lepidic components and excellent for those with tumors that contained GGO on HRCT regardless of lepidic components. The 5-year OS rates for patients with pure solid and pure or mixed GGO tumors based on presence or absence of lepidic components were, respectively, 92.6% (95% CI, 84.8%-96.5%) versus 77.9% (95% CI, 65.5%-86.3%), $P = .0017$ (Figure 1, *C*) and 95.9% (95% CI, 93.7%-97.3%) versus 97.6% (95% CI, 84.3%-99.7%), $P = .57$ (Figure 1, *D*). The OS was likewise better for patients who had pathologically pure invasive tumors with than without GGO on HRCT and excellent for patients with tumors containing pathologic lepidic components regardless of GGO. The 5-year OS rates for patients with pure invasive (Figure 1, *E*) and pure or mixed (Figure 1, *F*) lepidic tumors

TABLE 1. Clinicopathologic characteristics of patients according to lepidic component status

Variable	With lepidic (n = 808)	Pure invasive (n = 124)	*P*
Age, y	68 (62-74)	66.50 (62-75)	.4
Sex			
Female	453 (56.1%)	54 (43.5%)	.012
Male	355 (43.9%)	70 (56.5%)	
Brinkman index	0 (0-425)	480 (0-968)	<.001
Side			
Right	563 (69.7%)	78 (62.9%)	.15
Left	245 (30.3%)	46 (37.1%)	
Whole tumor size, cm	2.2 (1.6-2.7)	2.0 (1.5-2.6)	.009
Solid tumor size, cm	1.4 (0.9-2.0)	1.9 (1.4-2.3)	<.001
GGO rate, %	34.05 (10-60)	0 (0-10)	<.001
cT-factor			
Tis	44 (5.4%)	0 (0%)	<.001
T1mi	69 (8.5%)	3 (2.4%)	
T1a	164 (20.3%)	11 (8.9%)	
T1b	353 (43.7%)	63 (50.8%)	
T1c	178 (22.0%)	47 (37.9%)	
Pathologic whole size, cm	2.1 (1.5-2.7)	2.0 (1.5-2.5)	.51
Pathologic invasive size, cm	1.1 (0.5-1.7)	2.0 (1.5-2.5)	<.001
Subtypes			
AIS	59 (7.4%)	0 (0%)	NA
MIA	67 (8.4%)	0 (0%)	
Lepidic	272 (34.0%)	1 (0.8%)	
Papillary	239 (29.8%)	71 (57.3%)	
Acinar	129 (16.1%)	17 (13.7%)	
Solid	18 (2.2%)	24 (19.4%)	
Micropapillary	4 (0.5%)	2 (1.6%)	
Mucinous	13 (1.6%)	9 (7.3%)	
Lymphatic invasion			
0	735 (91.0%)	84 (67.7%)	<.001
1	73 (9.0%)	40 (32.3%)	
Vascular invasion			
0	714 (88.4%)	69 (55.6%)	<.001
1	94 (11.6%)	55 (44.4%)	
Pleural invasion			
0	734 (90.8%)	84 (67.7%)	<.001
1	52 (6.4%)	26 (21.0%)	
2	17 (2.1%)	7 (5.6%)	
3	5 (0.6%)	7 (5.6%)	
Pulmonary metastasis			
0	799 (98.9%)	121 (97.6%)	.21
1	9 (1.1%)	3 (2.4%)	
pT factor			
Tis	42 (5.2%)	0 (0%)	NA
T1mi	156 (19.3%)	0 (0%)	
T1a	166 (20.5%)	9 (7.3%)	
T1b	276 (34.2%)	36 (29.0%)	
T1c	74 (9.2%)	27 (21.8%)	
T2a	72 (8.9%)	38 (30.6%)	

(Continued)

TABLE 1. Continued

Variable	With lepidic (n = 808)	Pure invasive (n = 124)	P
T2b	4 (0.5%)	3 (2.4%)	
T3	18 (2.2%)	9 (7.3%)	
T4	0 (0%)	2 (1.6%)	

Values are shown as median (interquartile range) or n (%). *GGO*, Ground-glass opacity; *AIS*, adenocarcinoma in situ; *MIA*, minimally invasive adenocarcinoma; *NA*, not applicable.

based on the presence of absence of GGO components were 97.6% (95% CI, 84.3%-99.7%) versus 77.9% (95% CI, 65.5%-86.3%), $P = .012$ (Figure 1, *E*) and 95.9% (95% CI, 93.7%-97.3%) versus 92.6% (95% CI, 84.8%-96.5%), $P = .33$ (Figure 1, *F*), respectively. The tendency was the same for RFS (Figure 2, *A-F*) as follows: 5-year RFS rates for all patients based on the presence or absence of lepidic (92.4% [95% CI, 90.0%-94.3%] vs 76.8% [95% CI, 67.6%-83.7%]), $P < .0001$ (Figure 2, *A*) and GGO (93.9% [95% CI, 91.6%-95.6%] vs 80.2% [95% CI, 73.6%-85.3%]), $P < .0001$ (Figure 2, *B*) components. The 5-year RFS rates for patients with pure solid and pure GGO or mixed GGO tumors based on the presence or absence of lepidic components were 85.3% (95% CI, 77.2%-90.7%) versus 69.7% (95% CI, 57.3%-79.2%), $P = .0012$ (Figure 2, *C*) and 94.1% (95% CI, 91.7%-95.8%) versus 90.5% (95% CI, 76.6%-96.3%), $P = .28$ (Figure 2, *D*), respectively. Five-year RFS rates for patients with pure invasive and pure or mixed lepidic tumors based on the presence or absence of GGO components were, respectively, 90.5% (95% CI, 76.6%-96.3%) versus 69.7% (95% CI, 57.3%-79.2%), $P = .028$ (Figure 2, *E*) and 94.1% (95% CI, 91.7%-95.8%) versus 85.3% (95% CI, 77.2%-90.7%), $P = .0076$ (Figure 2, *F*). The prognoses, OS, and RFS of patients with pure solid tumors having pathologic lepidic components were comparable with those who had pathologic pure invasive tumors with GGO components (Figure E2).

Clinicopathologic Findings and Prognosis of Patients Based on GGO and Lepidic Component

We assessed the clinicopathologic characteristics and prognosis of 851 patients with tumors containing GGO or lepidic components and 81 with pure solid and pathologic pure invasive tumors based on the above results. More male than female patients had both pure solid and pathologic pure invasive tumors, and these were associated with high Brinkman indices, large solid tumors, a high SUVmax, more advanced cT and pT factors, larger pathologic invasive size, and a greater frequency of lymphatic, vascular, and pleural invasion than other types of tumors (Table 3). The OS and RFS did not significantly differ among cT factors in patients with both pure solid and pathologic pure invasive tumors (Figure E3, *A* and *B*; $P = .61$

TABLE 2. Clinicopathologic characteristics of patients according to GGO status

Variable	With GGO (n = 678)	Pure solid (n = 254)	P
Age, y	68 (61-73)	68.5 (63-76)	.08
Sex			
Female	377 (55.6%)	130 (51.2%)	.24
Male	301 (44.4%)	124 (48.8%)	
Brinkman index	0 (0-420)	117.5 (0-840)	<.001
Side			
Right	472 (69.6%)	169 (66.5%)	.38
Left	206 (30.4%)	85 (33.5%)	
Whole tumor size, cm	2.3 (1.7-2.8)	2.0 (1.5-2.4)	<.001
Solid tumor size, cm	1.2 (0.7-1.8)	2.0 (1.5-2.4)	<.001
GGO rate, %	42 (25-62)	0 (0-0)	<.001
cT-factor			
Tis	44 (6.5%)	0 (0.0%)	NA
T1mi	72 (10.6%)	0 (0.0%)	
T1a	168 (24.8%)	7 (2.8%)	
T1b	287 (42.3%)	129 (50.8%)	
T1c	107 (15.8%)	118 (46.5%)	
Pathologic whole size, cm	2.2 (1.5-2.8)	2.0 (1.5-2.5)	.016
Pathologic invasive size, cm	1.0 (0.4-1.7)	1.6 (1.2-2.2)	<.001
Subtypes			
AIS	57 (8.4%)	2 (0.8%)	NA
MIA	62 (9.2%)	5 (2.0%)	
Lepidic	254 (37.6%)	19 (7.6%)	
Papillary	198 (29.3%)	112 (45.0%)	
Acinar	82 (12.1%)	64 (25.7%)	
Solid	6 (0.9%)	36 (14.5%)	
Micropapillary	2 (0.3%)	4 (1.6%)	
Mucinous	15 (2.2%)	7 (2.8%)	
Lymphatic invasion			
0	620 (91.4%)	199 (78.3%)	<.001
1	58 (8.6%)	55 (21.7%)	
Vascular invasion			
0	624 (92.0%)	159 (62.6%)	<.001
1	54 (8.0%)	95 (37.4%)	
Pleural invasion			
0	634 (93.5%)	184 (72.4%)	<.001
1	29 (4.3%)	49 (19.3%)	
2	11 (1.6%)	13 (5.1%)	
3	4 (0.6%)	8 (3.1%)	
Pulmonary metastasis			
0	673 (99.3%)	247 (97.2%)	.022
1	5 (0.7%)	7 (2.8%)	
pT factor			
Tis	40 (5.9%)	2 (0.8%)	NA
T1mi	147 (21.7%)	9 (3.5%)	
T1a	148 (21.8%)	27 (10.6%)	
T1b	211 (31.1%)	101 (39.8%)	
T1c	65 (9.6%)	36 (14.2%)	
T2a	46 (6.8%)	64 (25.2%)	

(Continued)

TABLE 2. Continued

Variable	With GGO (n = 678)	Pure solid (n = 254)	*P*
T2b	7 (1.0%)	0 (0.0%)	
T3	13 (1.9%)	14 (5.5%)	
T4	1 (0.1%)	1 (0.4%)	

Values are shown as medians (interquartile range) or n (%). *GGO*, Ground-glass opacity; *AIS*, adenocarcinoma in situ; *MIA*, minimally invasive adenocarcinoma; *NA*, not applicable.

and .62). In contrast, the prognosis, OS, and RFS were excellent for patients with tumors containing GGO or lepidic components, except for those staged as cT1c (Figure E3, *C* and *D*). In addition, patients with tumors without GGO and lepidic components had a significantly worse OS and RFS than patients with other types of tumors staged as cT1b and cT1c. The 5-year OS rates for patients with cT1b tumors based on pure solid and pure invasive types compared with others that consisted partly or entirely of GGO or lepidic components were, respectively, 82.7% (95% CI, 66.8%-91.5%) versus 96.4% (95% CI, 93.3%-98.1%), $P = .0022$ (Figure 3, *A*). Five-year RFS rates for patients with cT1b pure solid and pure invasive tumors compared with others that consisted partly or entirely of GGO or lepidic components were 74.2% (95% CI, 58.1%-84.8%) versus 94.7% (95% CI, 91.3%-96.7%), $P < .0001$ (Figure 3, *B*). Five-year OS rates for patients with cT1c pure solid and pure invasive tumors compared with others that consisted partly or entirely of GGO or lepidic components were 70.0% (95% CI, 47.5%-84.3%) versus 92.2% (95% CI, 86.1%-95.7%), $P = .0025$ (Figure 3, *C*). The 5-year RFS rates for patients with cT1c pure solid and pure invasive tumors and others that consisted partly or entirely of GGO or lepidic components were 60.9% (95% CI, 39.0%-77.0%) versus 83.0% (95% CI, 75.9%-88.2%) (Figure 3, *D*; $P = .0094$). Multivariable Cox regression analysis of OS and RFS revealed that pure solid tumors on HRCT along with pathologically confirmed, pure invasive tumors comprised an independent factor for a poor prognosis with hazard ratios of 3.2 (95% CI, 1.5-6.7) and 1.9 (95% CI, 1.0-3.4) like vascular or pleural invasion, among patients with early-stage lung adenocarcinoma (Table 4). The results of multivariable analyses of OS and RFS with propensity score matching (Table E2) also revealed that a pure solid and pure invasive component comprised an independent poor prognostic factor with hazard ratios of 3.4 (95% CI, 1.6-7.1) and 2.2 (95% CI, 1.2-4.1). When pure GGO tumors were excluded, the results of multivariable Cox regression analyses of OS and RFS were similar (Table E3). We found that 31 (70%) of 44 pathologically confirmed cTis tumors had a part-invasive component and none had a pure invasive component. Thirteen (16%) and 31 (3.6%) patients with pure solid and pure invasive tumors and other types of tumors experienced recurrence. Sites of recurrence did not significantly differ between them (Table E4).

Comment

The present study examined the role of GGO findings on preoperative HRCT images to predict the prognoses of patients with lung adenocarcinoma that is pathologically confirmed as pure invasive; that is, without lepidic components. The role of lepidic components in postoperative pathologic findings was also validated in patients with pure solid lung adenocarcinoma tumors without GGO components. Tumors with a GGO component were associated with an excellent prognosis even when only an invasive component was pathologically detected. Moreover, tumors that did not have GGO or lepidic components were associated with a worse prognosis than those that consisted of only GGO or lepidic components or some of either.

To pathologically assess all parts of tumors is usually difficult, but CT imaging offers the advantage of being able to visualize 1- to 2-mm slices. However, a GGO component does not always correspond to a noninvasive lepidic component. For instance, inflammation, edema, or fibrosis often appear as GGO components around tumor lesions on HRCT images.[12] Spread through airway spaces or a papillary component without massive invasiveness might be also recognized as GGO components.[13] Thus, tumors with GGO components on HRCT do not always have pathologically confirmed lepidic components, whereas pathologic findings of lepidic components irrefutably define non-invasive tumors. In addition, a collapsed lepidic component is detected as a solid component on HRCT images that usually represents a pathological invasive component.[14,15] Another explanation for why a solid component sometimes appears non-invasive on HRCT might be central fibrotic foci due to alveolar collapse without active fibroblasts. Moreover, tumor density on HRCT images can be ambiguous, which complicates classification of a tumor area as solid or as a GGO component. In fact, ~70% of pure GGO tumors pathologically had a part-invasive component as previously reported.[13,16] Therefore, pathologic assessment is more effective than CT or HRCT in detecting invasive or non-invasive components.

The prognosis was worse for patients with pure solid and pure invasive tumors than with GGO or lepidic components and notably comparable between patients with pure solid and pure invasive tumors in clinical cT1b and cT1c tumors. Based on these findings, true, pure, invasive clinical T1 tumors might be associated with a comparably poor prognosis regardless of tumor size. That is, classifying T1 true pure invasive NSCLC might be better with another method, such as genomic sequencing or molecular profiling data to name a couple examples, instead of the current 3 subcategories, although classification of T1a, T1b, and T1c is necessary for tumors containing GGO or lepidic

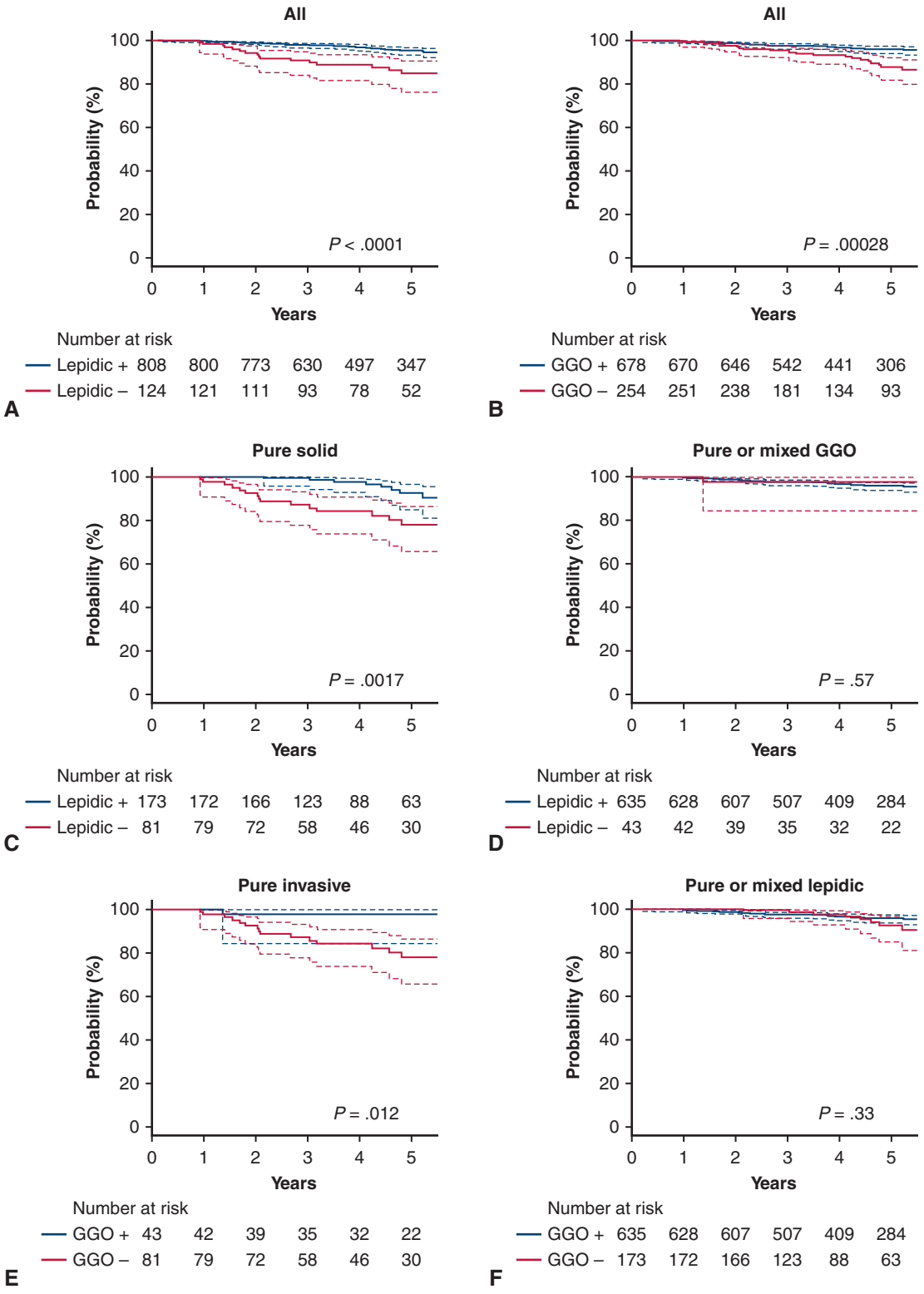


FIGURE 1. Overall survival of patients with clinical stage 0-IA and pathologic node-negative non–small cell lung cancer according to lepidic and GGO component status. Overall survival of all patients based on presence and absence of (A) lepidic, and (B) GGO components. Overall survival of patients with (C) pure solid, and (D) pure GGO or mixed GGO tumors based on presence and absence of lepidic components, respectively. Overall survival of patients with (E) pure invasive and (F) pure or mixed lepidic tumors based on presence and absence of GGO components, respectively. All *P* values were determined bylog rank tests. *GGO*, Ground-glass opacity.

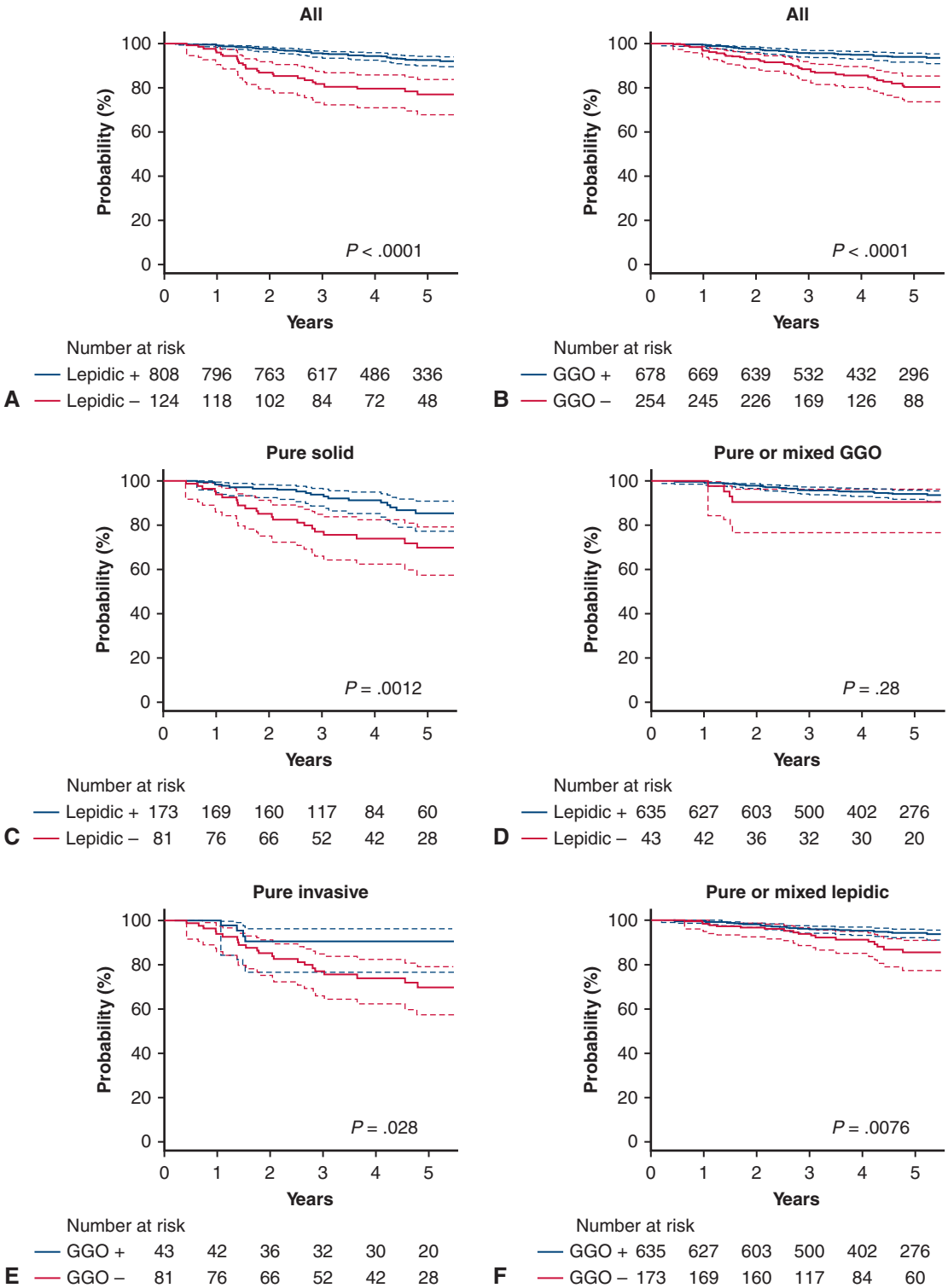


FIGURE 2. Recurrence-free survival of patients with clinical stage 0-IA and pathologic node negative non–small cell lung cancer based on lepidic and GGO component status. Recurrence-free survival of all patients based on presence or absence of (A) lepidic and (B) GGO components. Recurrence-free survival of patients with (C) pure solid and (D) pure GGO or mixed GGO tumors based on presence or absence of lepidic components, respectively. Recurrence-free survival of patients with (E) pure invasive and (F) pure or mixed lepidic tumors based on presence or absence of GGO components, respectively. All *P* values were determined by log rank tests. *GGO*, Ground-glass opacity.

TABLE 3. Clinicopathologic characteristics of patients according to GGO and lepidic component status

Variable	With GGO or lepidic (n = 851)	Pure solid + pure invasive (n = 81)	*P*
Age, y	68 (62-74)	69 (63-76)	.18
Sex			
Female	472 (55.5%)	35 (43.2%)	.036
Male	379 (44.5%)	46 (56.8%)	
Brinkman index	0 (0-480)	525 (0-1000)	<.001
Side			
Right	590 (69.3%)	51 (63.0%)	.26
Left	261 (30.7%)	30 (37.0%)	
Whole tumor size, cm	2.2 (1.6-2.7)	1.8 (1.5-2.4)	.001
Solid tumor size, cm	1.4 (0.9-2.0)	1.8 (1.5-2.4)	<.001
GGO rate, %	33 (10-59)	0 (0-0)	<.001
cT-factor			
Tis	44 (5.2%)	0 (0%)	<.001
T1mi	72 (8.5%)	0 (0%)	
T1a	173 (20.3%)	2 (2.5%)	
T1b	372 (43.7%)	44 (54.3%)	
T1c	190 (22.3%)	35 (43.2%)	
Pathologic whole size, cm	2.1 (1.5-2.8)	2.0 (1.5-2.5)	.093
Pathologic invasive size, cm	1.1 (0.5-1.8)	2.0 (1.5-2.5)	<.001
Subtypes			
AIS	59 (7.0%)	0 (0%)	NA
MIA	67 (7.9%)	0 (0%)	
Lepidic	273 (32.3%)	0 (0%)	
Papillary	267 (31.6%)	43 (53.1%)	
Acinar	133 (15.8%)	13 (16.0%)	
Solid	22 (2.6%)	20 (24.7%)	
Micropapillary	4 (0.5%)	2 (2.5%)	
Mucinous	19 (2.3%)	3 (3.7%)	
Lymphatic invasion			
0	766 (90.0%)	53 (65.4%)	<.001
1	85 (10.0%)	28 (34.6%)	
Vascular invasion			
0	744 (87.4%)	39 (48.1%)	<.001
1	107 (12.6%)	42 (51.9%)	
Pleural invasion			
0	770 (90.5%)	48 (59.3%)	<.001
1	59 (6.9%)	19 (23.5%)	
2	17 (2.0%)	7 (8.6%)	
3	5 (0.6%)	7 (8.6%)	
Pulmonary metastasis			
0	842 (98.9%)	78 (96.3%)	.078
1	9 (1.1%)	3 (3.7%)	
pT-factor			
Tis	42 (4.9%)	0 (0%)	NA
T1mi	156 (18.3%)	0 (0%)	
T1a	168 (19.7%)	7 (8.6%)	
T1b	290 (34.1%)	22 (27.2%)	
T1c	86 (10.1%)	15 (18.5%)	
T2a	83 (9.8%)	27 (33.3%)	
T2b	7 (0.8%)	0 (0%)	
T3	18 (2.1%)	9 (11.1%)	
T4	1 (0.1%)	1 (1.2%)	

(Continued)

TABLE 3. Continued

Values are shown as medians (interquartile range) or n (%). *GGO*, Ground-glass opacity; *AIS*, Adenocarcinoma in situ; *MIA*, minimally invasive adenocarcinoma; *NA*, not applicable.

components based on prognosis. Contrary findings have been reported by Hattori and colleagues.[17] Thus, further validation with more patients is needed to conclude this. Similar to previous results,[18] in tumors containing GGO and/or lepidic components, the prognosis of patients with solid tumors >2 cm was worse than those with solid tumors ≤2 cm. The prognosis was excellent even when HRCT revealed pure solid tumors, if the pathologic findings revealed lepidic components; this was consistent with previous findings.[7] Moreover, the finding that the prognosis was excellent even for patients with pathologically confirmed pure invasive tumors that contained a GGO component on HRCT is a novel insight. Figure 4 and Video 1 summarize the present findings.

The 5-year RFS rate of 69.7% in patients with pure solid and pure invasive tumors was poor as the result of the clinical stage IA. One reason might be that ∼45% of cT1 pure solid and pure invasive tumors were pT2 or worse might be involved. In contrast, the 5-year RFS rate in patients with cT1 pure solid tumors was 80.2% was slightly worse than expected for clinical stage IA and pN0 lung adenocarcinoma after lobectomy but was better than previous outcomes of clinical stage IA.[17,19] Thus, the recurrence rate in our cohort was not abnormally high, even considering that previous studies did not exclude patients who were pathologic node-positive, because the rate of node positivity was not high among patients with clinical stage IA. The prognosis was significantly worse for patients with pure solid and pure invasive tumors than those with pure solid tumors. This was because we focused on both findings of pure solid and pure invasive components. Furthermore, this certainly resolves the question of whether the prognosis is poor for patients with pathologically confirmed "pure" invasive tumors regardless of preoperative HRCT findings of GGO components. The prognosis is worse for patients with pure solid tumors than part-solid or pure GGO tumors, and for patients with pure invasive than with part-invasive or pure lepidic tumors.[17,19,20] However, GGO confirmed by HRCT together with a pathologically confirmed lepidic component predicts lung adenocarcinoma tumor aggressiveness more precisely than either modality alone.

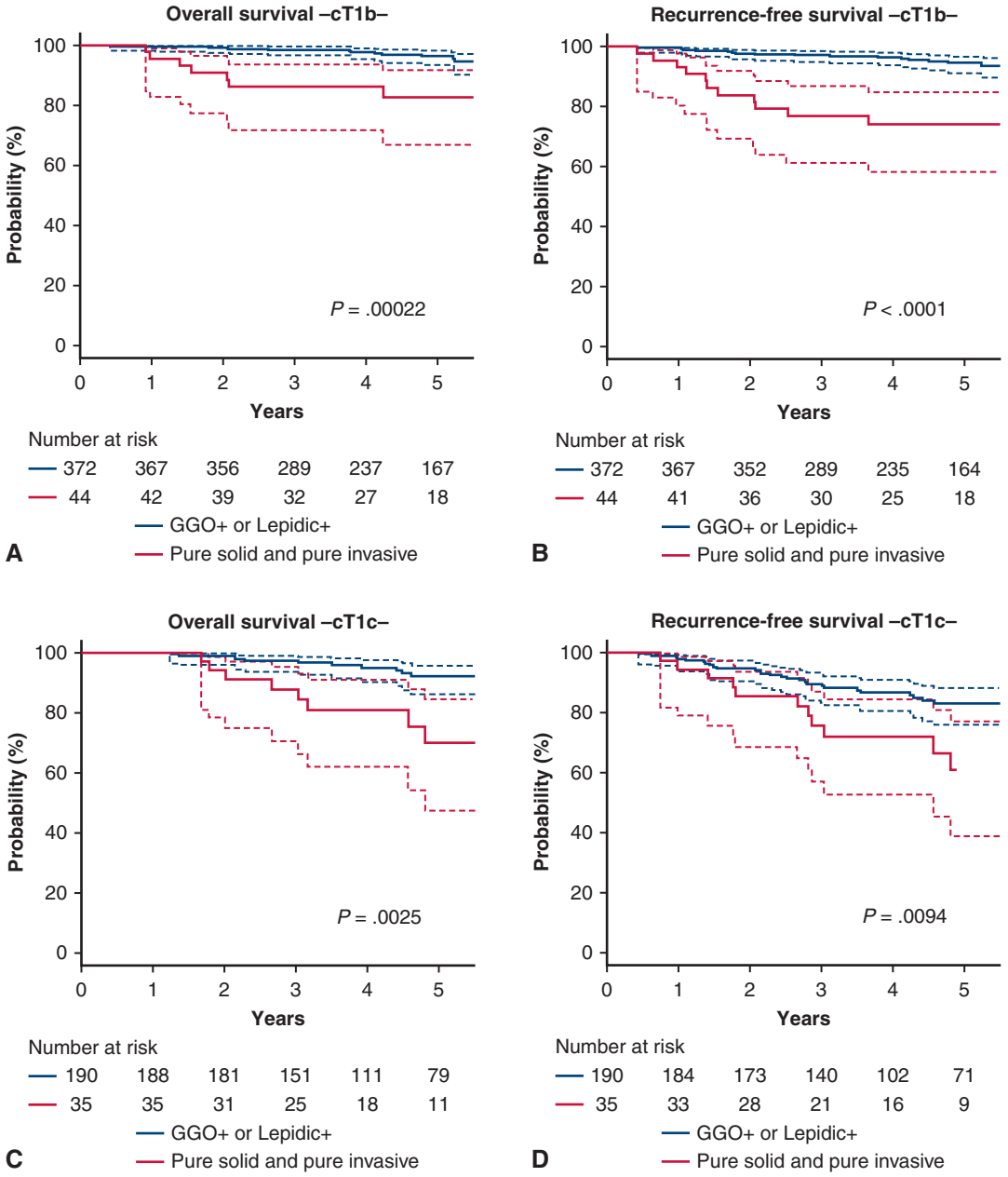


FIGURE 3. Overall survival and recurrence-free survival of patients with clinical stage IA and pathologic node-negative, non–small cell lung cancer according to status of lepidic components, GGO component, and clinical T-factors. A, Overall survival of patients with cT1b tumors based on pure solid and pure invasive tumors compared with tumors solely or partly containing either GGO or lepidic components. B, Recurrence-free survival of patients with cT1b pure solid and pure invasive tumors compared with tumors solely or partly containing either GGO or lepidic components. C, Overall survival of patients with cT1c pure solid and pure invasive tumors compared with tumors solely or partly containing either GGO or lepidic components. D, Recurrence-free survival of patients with cT1c pure solid and pure invasive tumors compared with tumors solely or partly containing either GGO or lepidic components. *GGO*, Ground-glass opacity.

Based on the present prognostic data, patients with true invasive T1 tumors without lepidic and GGO components might be candidates for postoperative adjuvant therapy regardless of tumor size in the future. However, whether adjuvant therapy improves the prognosis in such patients with pure solid and pure invasive tumors should be determined in a prospective study. In contrast, almost all patients with tumors containing lepidic or GGO components could conceivably be cured by surgical resection alone even if HRCT indicates a pure solid tumor or pathologic findings indicate pure invasive tumors. Regardless, considering both pathologic and CT or HRCT imaging findings is

TABLE 4. Multivariable Cox regression analysis of OS and RFS

Survival	Status	HR (95% CI)	*P*
OS			
Age, y	≥70 vs <70	4.7 (2.5-8.9)	<.0001
Sex	Male vs female	2.0 (1.0-4.4)	.067
Brinkman index	≥400 vs <400	1.5 (0.7-3.2)	.25
Lymphatic invasion	Yes vs no	0.9 (0.4-1.9)	.71
Vascular invasion	Yes vs no	2.2 (1.1-4.4)	.036
Pleural invasion	Yes vs no	1.4 (0.7-2.8)	.41
Subtype	Solid or micropapillary vs others	0.9 (0.4-2.3)	.87
Tumor type	Pure solid and pure invasive vs others	3.2 (1.5-6.7)	.0025
RFS			
Age, y	≥70 vs <70	2.6 (1.6-4.1)	<.0001
Sex	Male vs female	1.5 (0.8-2.7)	.18
Brinkman index	≥400 vs <400	1.2 (0.6-2.1)	.64
Lymphatic invasion	Yes vs no	1.4 (0.8-2.5)	.24
Vascular invasion	Yes vs no	2.7 (1.5-4.7)	.00085
Pleural invasion	Yes vs no	2.1 (1.2-3.6)	.0088
Subtype	Solid or micropapillary vs others	1.3 (0.7-2.6)	.42
Tumor type	Pure solid and pure invasive vs others	1.9 (1.0-3.4)	.035

OS, Overall survival; *HR*, hazard ratio; *CI*, confidence interval; *RFS*, recurrence-free survival.

important to predict the postoperative prognosis of patients with lung adenocarcinoma. Re-evaluation to identify GGO components is recommended when postoperative pathologic findings show pure invasive tumors.

This study has some limitations. Evidence is weaker in retrospective than in prospective studies. This study included only patients with complete preoperative CT and postoperative pathologic data. Our database does not have

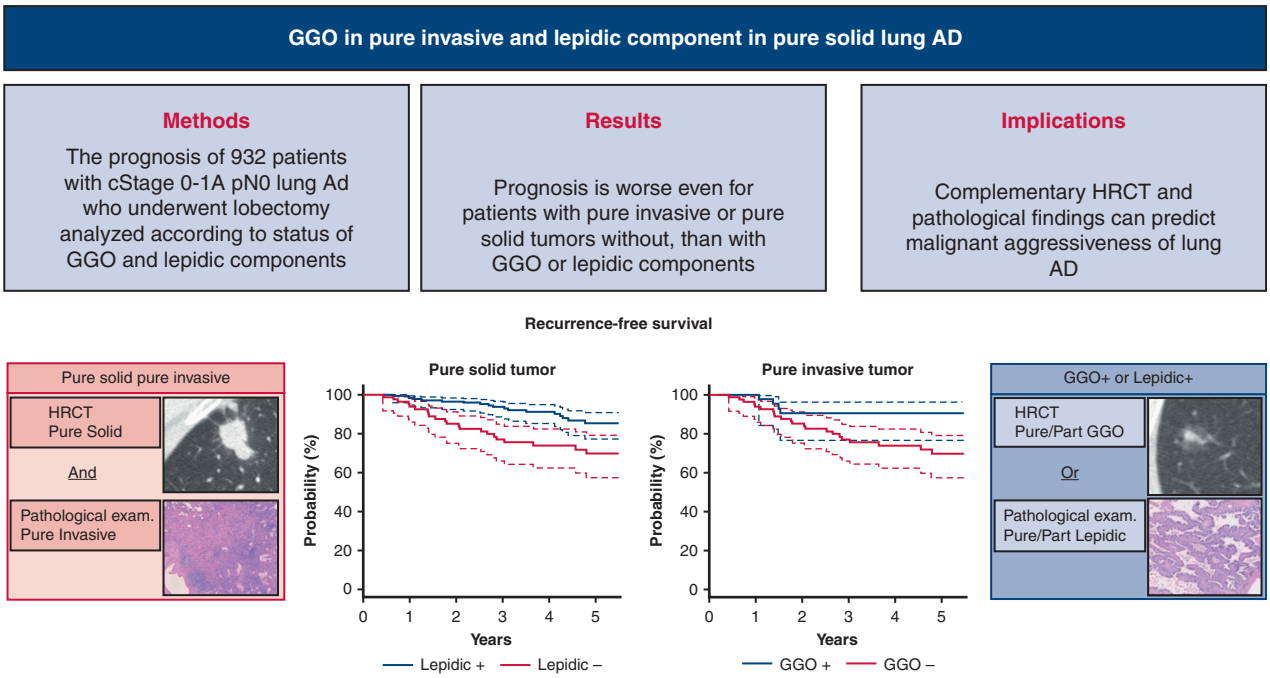
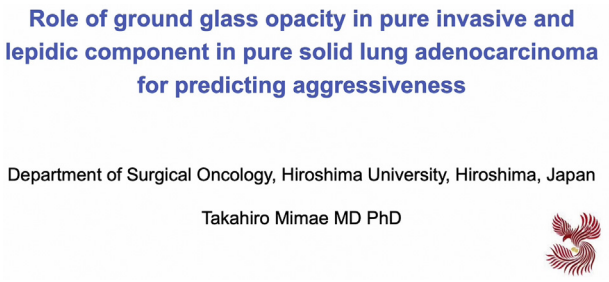


FIGURE 4. Recurrence-free survival is significantly worse for patients with pure solid tumors on high-resolution computed tomography without than with lepidic components and for those with postoperative pathologic findings of pure invasive tumors without, than with ground glass opacity components. *GGO*, Ground-glass opacity; *AD*, adenocarcinoma; *cStage*, clinical stage; *pN0*, pathalogical node negative; *HRCT*, high-resolution computed tomography.



VIDEO 1. Summary of key figures. Video available at: https://www.jtcvs.org/article/S2666-2736(22)00209-1/fulltext.

the pathologic data about spread through airway spaces. Nevertheless, our findings provide important insights to consider when deciding strategies for treating lung disease.

In conclusion, lung adenocarcinoma tumors without GGO on preoperative HRCT images accompanied by a pathologic lepidic component were more malignant and aggressive than such tumors comprising partly or entirely GGO or lepidic components. The present findings provide useful information for the development of novel postoperative adjuvant therapeutic strategies. Pathologic and CT findings together can predict the malignant aggressiveness of NSCLC tumors. Further studies of a larger patient cohort after pulmonary resection are needed to confirm the present results.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

This manuscript has been professionally proof-checked by a native English speaker with more than 25 years of experience in medical and life science editing.

References

1. 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.
2. Aherne EA, Plodkowski AJ, Montecalvo J, Hayan S, Zheng J, Capanu M, et al. What CT characteristics of lepidic predominant pattern lung adenocarcinomas correlate with invasiveness on pathology? *Lung Cancer*. 2018;118:83-9.
3. Collins J, Stern EJ. Ground-glass opacity at CT: the ABCs. *AJR Am J Roentgenol*. 1997;169:355-67.
4. Suzuki K, Asamura H, Kusumoto M, Kondo H, Tsuchiya R. "Early" peripheral lung cancer: prognostic significance of ground glass opacity on thin-section computed tomographic scan. *Ann Thorac Surg*. 2002;74:1635-9.
5. Takahashi Y, Ishii G, Aokage K, Hishida T, Yoshida J, Nagai K. Distinctive histopathological features of lepidic growth predominant node-negative adenocarcinomas 3-5 cm in size. *Lung Cancer*. 2013;79:118-24.
6. Tsutani Y, Miyata Y, Yamanaka T, Nakayama H, Okumura S, Adachi S, et al. Solid tumors versus mixed tumors with a ground-glass opacity component in patients with clinical stage IA lung adenocarcinoma: prognostic comparison using high-resolution computed tomography findings. *J Thorac Cardiovasc Surg*. 2013;146:17-23.
7. Miyoshi T, Aokage K, Katsumata S, Tane K, Ishii G, Tsuboi M. Ground-glass opacity is a strong prognosticator for pathologic stage IA lung adenocarcinoma. *Ann Thorac Surg*. 2019;108:249-55.
8. Detterbeck FC, Chansky K, Groome P, Bolejack V, Crowley J, Shemanski L, et al. The IASLC lung cancer staging project: methodology and validation used in the development of proposals for revision of the stage classification of NSCLC in the forthcoming (eighth) edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2016;11:1433-46.
9. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11:39-51.
10. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. *World Health Organization Classification of Tumours of the Lung, Pleura, Thymus and Heart*. 4th ed. IARC; 2015.
11. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*. 2013;48:452-8.
12. Fan L, Liu SY, Li QC, Yu H, Xiao XS. Multidetector CT features of pulmonary focal ground-glass opacity: differences between benign and malignant. *Br J Radiol*. 2012;85:897-904.
13. Koezuka S, Mikami T, Tochigi N, Sano A, Azuma Y, Makino T, et al. Toward improving prognosis prediction in patients undergoing small lung adenocarcinoma resection: radiological and pathological assessment of diversity and intratumor heterogeneity. *Lung Cancer*. 2019;135:40-6.
14. Ikehara M, Saito H, Kondo T, Murakami S, Ito H, Tsuboi M, et al. Comparison of thin-section CT and pathological findings in small solid-density type pulmonary adenocarcinoma: prognostic factors from CT findings. *Eur J Radiol*. 2012;81:189-94.
15. Lee KH, Goo JM, Park SJ, Wi JY, Chung DH, Go H, et al. Correlation between the size of the solid component on thin-section CT and the invasive component on pathology in small lung adenocarcinomas manifesting as ground-glass nodules. *J Thorac Oncol*. 2014;9:74-82.
16. Mimae T, Miyata Y, Tsutani Y, Mimura T, Nakayama H, Okumura S, et al. What are the radiologic findings predictive of indolent lung adenocarcinoma? *Jpn J Clin Oncol*. 2015;45:367-72.
17. Hattori A, Suzuki K, Takamochi K, Wakabayashi M, Aokage K, Saji H, et al. Prognostic impact of a ground-glass opacity component in clinical stage IA non–small cell lung cancer. *J Thorac Cardiovasc Surg*. 2021;161:1469-80.
18. Mimae T, Tsutani Y, Miyata Y, Imai K, Ito H, Nakayama H, et al. Solid tumor size of 2 cm divides outcomes of patients with mixed ground glass opacity lung tumors. *Ann Thorac Surg*. 2020;109:1530-6.
19. Watanabe Y, Hattori A, Nojiri S, Matsunaga T, Takamochi K, Oh S, et al. Clinical impact of a small component of ground-glass opacity in solid-dominant clinical stage IA non–small cell lung cancer. *J Thorac Cardiovasc Surg*. 2022;163:791-801.e4.
20. Sasada S, Nakayama H, Miyata Y, Tsubokawa N, Mimae T, Yoshiya T, et al. Comparison of malignant grade between pure and partially invasive types of early lung adenocarcinoma. *Ann Thorac Surg*. 2015;99:956-60.

Key Words: adenocarcinoma, computed tomography, histology, surgery, prognosis

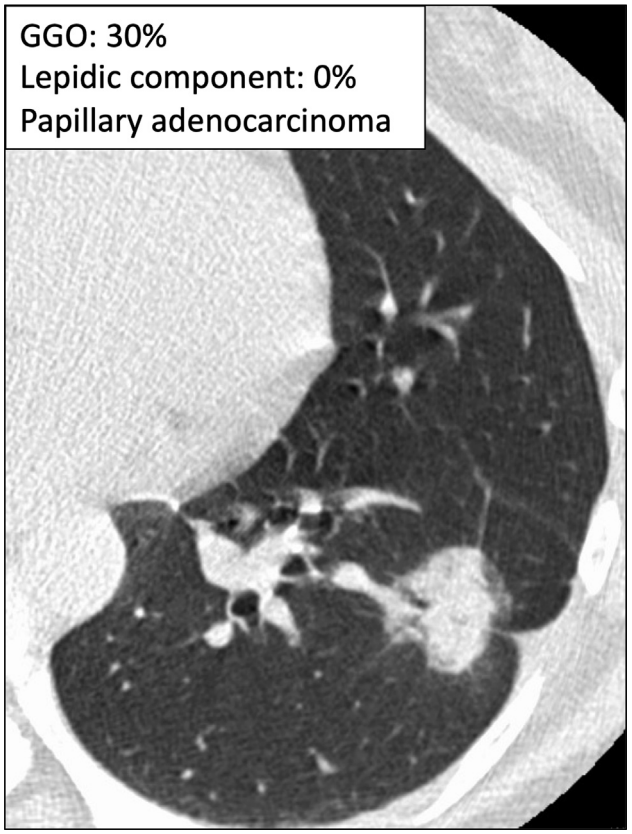


FIGURE E1. Representative high-resolution computed tomography findings of lung adenocarcinoma tumors with 30% GGO and no lepidic component. Histologic subtype is papillary adenocarcinoma. *GGO*, Ground-glass opacity.

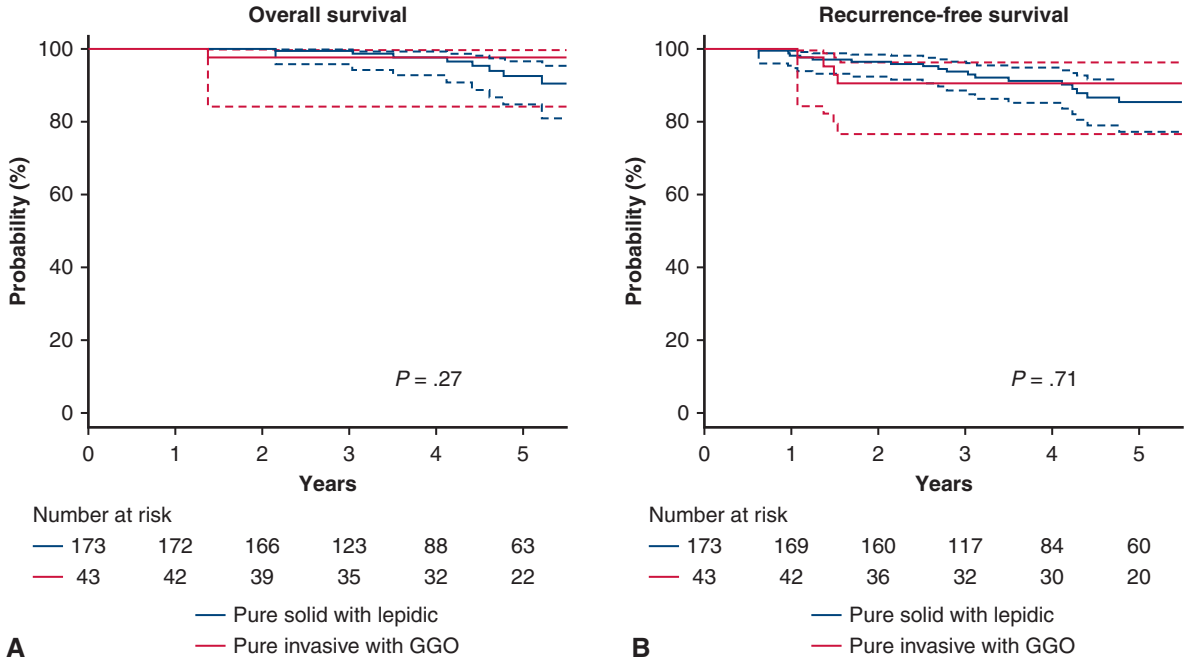


FIGURE E2. OS and RFS of patients with clinical stage 0 or IA and pathologic node-negative, non–small cell lung cancer according to status of lepidic and GGO components. Five-year (A) OS and (B) RFS rates for patients with pure solid tumors having pathologic pure or mixed lepidic components and those with pathologic pure invasive tumors having pure or mixed GGO (92.6% (95% CI, 84.8%-96.5%) versus 97.6% (95% CI, 84.3%-99.7%), $P = .27$, and 85.3% (95% CI, 77.2%-90.7%) versus 90.5% (95% CI, 76.6%-96.3%), $P = .71$, respectively. *GGO*, Ground-glass opacity; *OS*, overall survival; *RFS*, recurrence-free survival; *CI*, confidence interval.

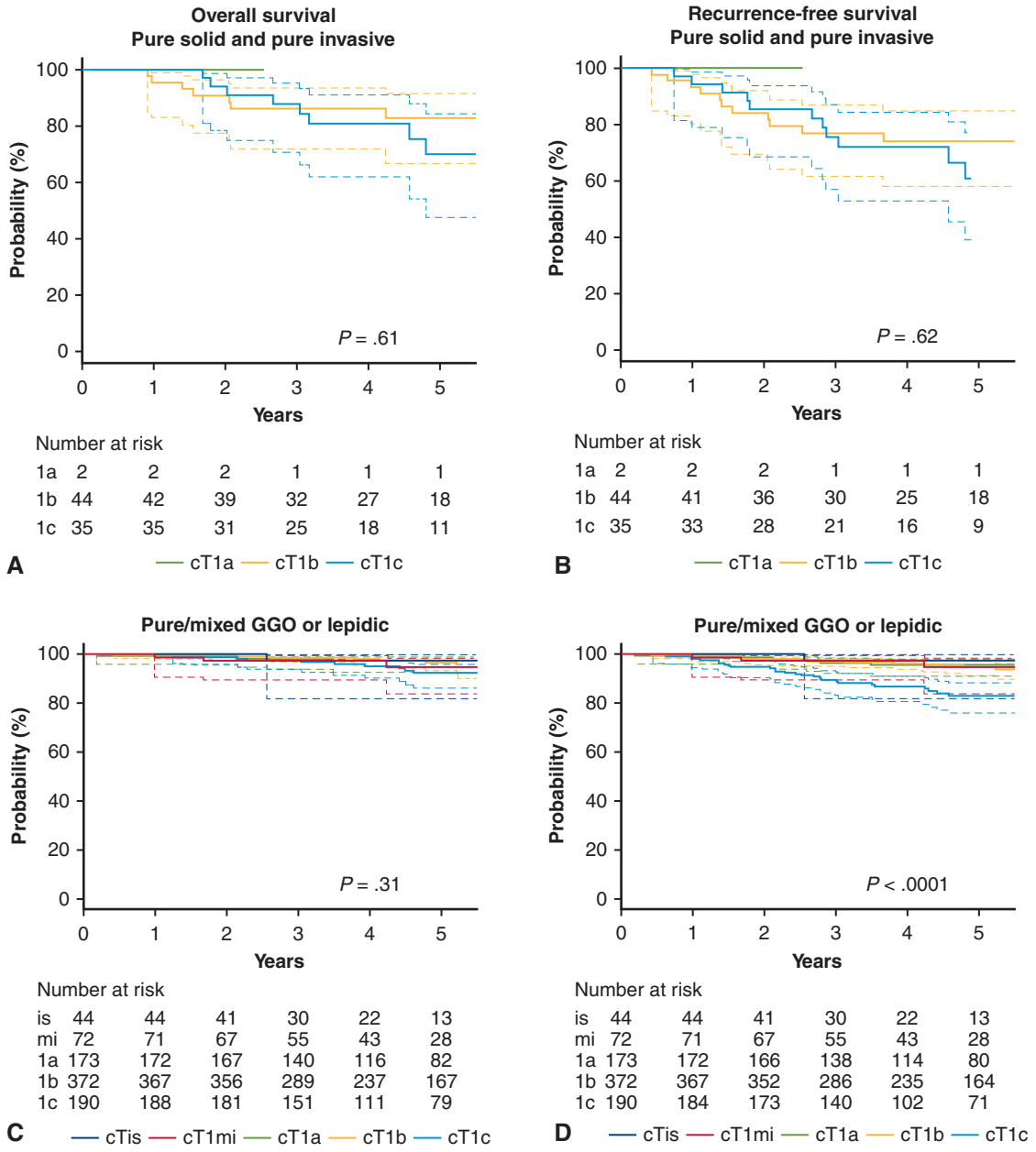


FIGURE E3. OS and RFS of patients with clinical stage 0 or IA and pathologic node-negative, non–small cell lung cancer according to status of lepidic components, GGO components, and clinical T-factors. Five-year (A) OS and (B) RFS rates for patients with cT1a, cT1b, and cT1c pure solid and pure invasive tumors 100% (95% CI, 100%-100%), 82.7% (95% CI, 66.8%-91.5%), and 70.0% (95% CI, 47.5%-84.3%), $P = .61$, respectively, and 100% (95% CI, 100%-100%), 74.2% (95% CI, 58.1%-84.8%), and 60.9% (95% CI, 39.0%-77.0%), $P = .62$, respectively. Five-year (C) OS and (D) RFS rates for patients with cTis, cT1mi, cT1a, cT1b, and cT1c tumors containing lepidic or GGO components: 97.2% (95% CI, 81.9%-99.6%), 94.7% (95% CI, 83.7%-98.3%), 96.8% (95% CI, 92.5%-98.7%), 96.4% (95% CI, 93.3%-98.1%), and 92.2% (95% CI, 86.1%-95.7%), respectively, $P = .31$, and 97.2% (95% CI, 81.9%-99.6%), 94.7% (95% CI, 83.7%-98.3%), 95.6% (95% CI, 90.9%-97.9%), 94.7% (95% CI, 91.3%-96.7%), and 83.0% (95% CI, 75.9%-88.2%), respectively, $P < .0001$. *GGO*, Ground-glass opacity; *OS*, overall survival; *RFS*, recurrence-free survival; *CI*, confidence interval.

TABLE E1. Clinicopathologic characteristics of patients

Variables	All (n = 932)
Age, y	68 (62-74)
Sex	
Female	507 (54.4%)
Male	425 (45.6%)
Brinkman index	0 (0-559)
Side	
Right	641 (68.8%)
Left	291 (31.2%)
Whole tumor size, cm	2.1 (1.6-2.7)
Solid tumor size, cm	1.5 (0.9-2)
GGO rate, %	30 (0-53)
cT factor	
Tis	44 (4.7%)
T1mi	72 (7.7%)
T1a	175 (18.8%)
T1b	416 (44.6%)
T1c	225 (24.1%)
Pathologic whole size, cm	2.1 (1.5-2.7)
Pathologic invasive size, cm	1.2 (0.6-1.8)
Subtypes	
AIS	59 (6.4%)
MIA	67 (7.2%)
Lepidic	273 (29.5%)
Papillary	310 (33.5%)
Acinar	146 (15.8%)
Solid	42 (4.5%)
Micropapillary	6 (0.6%)
Mucinous	22 (2.4%)
Lymphatic invasion	
0	819 (87.9%)
1	113 (12.1%)
Vascular invasion	
0	783 (84.0%)
1	149 (16.0%)
Pleural invasion	
0	818 (87.8%)
1	78 (8.4%)
2	24 (2.6%)
3	12 (1.3%)
Pulmonary metastasis	
0	920 (98.7%)
1	12 (1.3%)
pT factor	
Tis	42 (4.5%)
T1mi	156 (16.7%)
T1a	175 (18.8%)
T1b	312 (33.5%)
T1c	101 (10.8%)
T2a	110 (11.8%)
T2b	7 (0.8%)
T3	27 (2.9%)
T4	2 (0.2%)

Values are shown as medians (interquartile range) or n (%). *GGO*, Ground-glass opacity; *AIS*, adenocarcinoma in situ; *MIA*, minimally invasive adenocarcinoma.

TABLE E2. Multivariable Cox regression analysis of OS and RFS using propensity score matching

Survival	Status	HR (95% CI)	*P*
OS			
Propensity score	–	–	–
Tumor type	Pure solid and pure invasive vs others	3.4 (1.6-7.1)	.0010
RFS			
Propensity score	–	–	–
Tumor type	Pure solid and pure invasive vs others	2.2 (1.2-4.1)	.010

Propensity scores for pure solid and pure invasive tumor calculated using age, sex, smoking, lymphatic invasion, vascular invasion, pleural invasion, and subtype. *HR*, Hazard ratio; *CI*, confidence interval; *OS*, overall survival; *RFS*, recurrence-free survival.

TABLE E3. Multivariable Cox regression analysis of OS and RFS excluding patients with cStage 0

Survival	Status	HR (95% CI)	*P*
OS			
Age, y	≥70 vs <70	5.0 (2.6-9.7)	<.0001
Sex	Male vs female	2.1 (1.0-4.5)	.063
BI	≥400 vs <400	1.5 (0.7-3.1)	.32
Lymphatic invasion	Yes vs no	0.9 (0.4-1.9)	.70
Vascular invasion	Yes vs no	2.2 (1.1-4.5)	.035
Pleural invasion	Yes vs no	1.4 (0.7-2.8)	.40
Subtype	Solid or micropapillary vs others	0.9 (0.4-2.3)	.87
Tumor type	Pure solid and pure invasive vs others	3.2 (1.5-6.7)	.0024
RFS			
Age, y	≥70 vs <70	2.6 (1.6-4.2)	<.0001
Sex	Male vs Female	1.5 (0.8-2.7)	.18
BI	≥400 vs <400	1.1 (0.6-2.0)	.74
Lymphatic invasion	Yes vs no	1.4 (0.8-2.4)	.25
Vascular invasion	Yes vs no	2.6 (1.5-4.7)	.00093
Pleural invasion	Yes vs no	2.1 (1.2-3.6)	.0091
Subtype	Solid or micropapillary vs others	1.3 (0.7-2.6)	.41
Tumor type	Pure solid and pure invasive vs others	1.9 (1.0-3.4)	.035

OS, Overall survival; *HR*, hazard ratio; *BI*, brinkman index; *RFS*, recurrence-free survival; *CI*, confidence interval.

TABLE E4. Recurrence sites in patients according to GGO and lepidic component status

Variable	With GGO or lepidic (n = 851)	Pure solid + pure invasive (n = 81)	*P*
Recurrence			
Absent	820 (96.4%)	68 (84.0%)	<.0001
Present	31 (3.6%)	13 (16.0%)	
Recurrence site			
Locoregional	12 (38.7%)	7 (53.8%)	.45
Distant	14 (45.2%)	3 (23.1%)	
Locoregional + distant	4 (12.9%)	2 (15.4%)	
Unknown	1 (3.2%)	1 (7.7%)	

GGO, Ground-glass opacity.