Indications for sublobar resection of clinical stage IA radiologic pure-solid lung adenocarcinoma

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ABSTRACT

Objectives: The aim of this study was to identify clinical factors associated with lepidic growth in resected clinical stage IA radiologic pure-solid lung adenocarcinoma for identifying a possible sublobar resection candidate in the population.

Methods: Clinicopathologic data were reviewed for 200 surgically resected clinical stage IA pure-solid lung adenocarcinomas. Radiologic pure-solid tumor was defined as a tumor without a ground-glass opacity component, that is, a consolidation tumor ratio equal to 1.0. Lepidic predominant adenocarcinoma included adenocarcinomas in situ, minimally invasive adenocarcinomas, and lepidic predominant invasive adenocarcinomas.

Results: A total of 57 patients (29%) had lepidic predominant adenocarcinoma. The 5-year overall survival of clinical stage IA pure-solid adenocarcinoma was 83.4% and that of lepidic predominant adenocarcinoma and nonlepidic predominant adenocarcinoma was 98.1% versus 76.6% ($P = .0012$). A multivariate analysis revealed that maximum standardized uptake value was an independently significant variable of lepidic predominant adenocarcinoma ($P < .0001$) and a significant prognostic factor ($P = .034$). The predictive criterion of lepidic predominant adenocarcinoma was maximum standardized uptake value 3.3 or less based on a receiver operating characteristic curve, and 77 patients (39%) who met this criterion showed less pathologic invasiveness regarding lymphatic ($P = .0012$) and vascular ($P < .0001$) invasions, nodal metastasis ($P = .0007$), and better overall survival than those who did not (maximum standardized uptake value ≤ 3.3 vs > 3.3 rates being 91.7% vs 78.6%, $P = .0031$). Moreover, the 3-year locoregional recurrence-free survival of the sublobar resection arm was significantly worse than that of the lobectomy arm when the tumor showed maximum standardized uptake value greater than 3.3 (62.7% vs 82.9%, $P = .0281$).

Conclusions: Higher maximum standardized uptake value may be useful for identifying patients with clinical stage IA radiologic pure-solid lung adenocarcinoma in whom sublobar resection should not be considered, even if technically feasible. (J Thorac Cardiovasc Surg 2017;154:1100-8)

Lobectomy showed better local control in patients with high standardized uptake value.

Central Message

Higher SUVmax may be useful for identifying patients with stage IA radiologic pure-solid lung adenocarcinoma in whom sublobar resection should not be considered.

Perspective

The primary aim of this study was to elucidate clinical factors associated with lepidic growth in resected clinical stage IA radiologic pure-solid lung adenocarcinoma. As a result, SUVmax was a promising clinical variable for identifying lepidic predominance among them and was associated with differential survival in patients with sublobar versus lobar resection.

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Lung adenocarcinomas have recently become the most common histologic subtypes of non-small cell lung cancers.^{1,2} Since 2011, the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ETS) have characterized

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Abbreviations and Acronyms

AIS	= adenocarcinoma in situ
CT	= computed tomography
FDG	= 18F-fluorodeoxyglucose
GGO	= ground-grass opacity
IASLC/ATS/ETS	= International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society
JCOG	= Japan Clinical Oncology Group
LPA	= lepidic predominant adenocarcinoma
MIA	= minimally invasive adenocarcinoma
OS	= overall survival
PET	= positron emission tomography
RFS	= recurrence-free survival
SUVmax	= maximum standardized uptake value

lung adenocarcinomas as a heterogeneous group on the basis of the comprehensive histologic subtypes.² This classification associates well with the prognosis and indicates a favorable oncologic outcome for adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and lepidic predominant invasive adenocarcinoma.

Meanwhile, the presence of a ground-grass opacity (GGO) component is considered to denote a good prognosis, and in most cases the pathologic features are minimally invasive because of a significant correlation with histologic lepidic growths.³⁻⁷ They are considered to be feasible candidates of sublobar resection.⁸ Traditionally, however, a radiologic pure-solid lung adenocarcinoma without any GGO component is assumed to show a highly malignant nature, and postoperative nodal involvement is found in approximately 15% to 20% of cases, even in those with small-sized lesions.^{4,9-11}

Several institutional retrospective studies have recently suggested that survival and recurrence may be identical between lobectomy and sublobar resection in patients with small-sized lung cancers.¹²⁻¹⁵ To elucidate the efficacy of sublobar resection for small-sized lung cancers based on these retrospective studies, prospective clinical trials have been conducted for c-T1a radiologic invasive part-solid or pure-solid lung cancers in both Japan¹⁶ and the United States.¹⁷ Unlike a part-solid lung cancer, however, whether sublobar resection is an appropriate surgical mode for radiologic pure-solid lung cancers remains unclear because of their highly invasive nature.¹⁰ A major problem in routine practice is the fact that identifying histologic lepidic predominance in radiologic pure-solid lung adenocarcinoma on the basis of preoperative findings on thin-section

computed tomography (CT) scan is a challenge. This is due to a lack of useful clinical parameters other than GGO components. If the event could be identified preoperatively, that would enable surgeons to select appropriate candidates of sublobar resections even among patients with radiologic pure-solid lung adenocarcinomas.

Therefore, in the current study, we retrospectively reviewed surgically resected clinical stage IA radiologic pure-solid lung adenocarcinoma at Juntendo University School of Medicine. The primary aim of this study was to identify clinical factors associated with histologic lepidic growth in resected, clinical stage IA radiologic pure-solid lung adenocarcinoma. The secondary aim was to determine whether these clinical factors for histologic lepidic growth were associated with differential survival in the overall population and in patients who underwent sublobar versus lobar resection.

MATERIALS AND METHODS

Study Population

Between January 2008 and March 2013, 238 patients underwent surgical resection for clinical stage IA radiologic pure-solid lung adenocarcinomas in a single institute. Among them, 200 patients with a preoperative evaluation of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) were retrospectively evaluated in this study (Figure 1). Any clinical stage IA lung adenocarcinoma with a GGO component was excluded from the study. Tumors without preoperative histologic confirmation were all proven by intraoperative frozen-section diagnosis. The database has been maintained prospectively, and missing data were missing for the variables in this study. The inclusion criteria were preoperative staging determined by thin-section CT and FDG-PET/CT scans, and complete resection without preoperative chemotherapy or radiotherapy. With regard to the clinical nodal assessment, clinical N0 meant nonenlarged lymph nodes on CT scan and negative FDG uptake by the lymph nodes. Invasive modalities for mediastinal lymph node staging, such as mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration, were not routinely used preoperatively because they were evaluated 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 Evaluations on Thin-Section Computed Tomography Scan

For all patients, findings of the preoperative thin-section CT scan were reviewed in detail by the authors (A.H., T.M., and K.S.). Tumor size was determined preoperatively on the basis of the thin-section CT scan with 2-mm collimation at Juntendo University School of Medicine. The lung was photographed with a window level of -500 to -700 H and a window depth of 1000 to 2000 H as a “lung window,” and a window level of 30 to 60 H and a window depth of 350 to 600 H as a “mediastinal window.” The consolidation tumor ratio was defined as the ratio of the maximum size of consolidation to the maximum tumor size on thin-section CT scan.⁷ In the current study, a radiologic pure-solid tumor was defined as a lung tumor showing only consolidation without GGO on thin-section CT, that is, consolidation tumor ratio was equal to 1.0.^{4,9,10}

Positron Emission Tomography

Positron emission tomography (PET) was performed, and the maximum standardized uptake value (SUVmax) was recorded for all patients in this

FIGURE 1. Flow chart of patients in the study. *FDG-PET*, 18F-Fluorodeoxyglucose positron emission tomography; *SUVmax*, maximum standardized uptake value.

study. In all cases, a PET/CT scan was performed at the Yotsuya Medical Cube (Tokyo, Japan) to remove the standardized uptake value variability among interinstitutional PET scanners. The technique used for the FDG-PET/CT scanning was as follows: All patients fasted for at least 6 hours before the FDG injection to minimize their blood insulin levels and normal tissue glucose uptake. The subjects were injected intravenously with 3.5 MBq/kg of ^{18}F -FDG, and static emission images were obtained 60 minutes after the injection. Image acquisition was then performed using a Discovery ST PET/CT scanner (GE Medical Systems, Waukesha, Wis). Emission scanning was performed from the head to mid-thigh in 6 bed positions. The acquired PET data were reconstructed to volumetric images with a two-dimensional-OSEM (ordered-subsets expectation-maximization) algorithm (2 iterations/15 subsets) incorporating a CT-based attenuation correction. All PET/CT images were interpreted by 1 or 2 experienced nuclear medicine radiologists. A workstation (Xeleris; Elegems, Haifa, Israel) was used for image display and analysis, and the *SUVmax* of the primary tumor was obtained.

Operation Policy

Lobectomy with systemic lymph node dissection is a standard surgical mode for a radiologically pure-solid tumor in patients at Juntendo University School of Medicine, whereas segmentectomy is now performed for part-solid or pure-solid lung cancers according to the Japan Clinical Oncology Group (JCOG 0802¹⁶) (Videos 1 and 2). Furthermore, sublobar resection is selected as an optimal treatment strategy for peripheral pure-solid lesions if the tumor is located favorably for complete resection with a sublobar approach and is intraoperatively assessed as N0 by frozen-section evaluation. In contrast, it is occasionally indicated for some patients with pure-solid tumor who are not lobectomy tolerable, such as very elderly patients and high-risk patients with cardiopulmonary disease.

Pathologic Evaluations

All patients in the present study were reclassified according to the TNM Classification of Malignant Tumors, 7th edition.¹⁸ Clinical stage IA pure-solid lung adenocarcinomas were classified according to the IASLC/ATS/ETS classification as AIS and MIA; invasive adenocarcinomas were

VIDEO 1. The video of left upper division segmentectomy for lung cancer. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)30899-1/addons](http://www.jtcvsonline.org/article/S0022-5223(17)30899-1/addons).

VIDEO 2. The video of right upper lobectomy for lung cancer. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)30899-1/addons](http://www.jtcvsonline.org/article/S0022-5223(17)30899-1/addons).

subdivided into lepidic predominant and other subtypes.² Invasive adenocarcinomas were classified according to the predominant subtype after comprehensive histologic subtyping, which implies a semiquantitative estimation of the percentage of different subtypes in 5% increments.² In the current study, we defined lepidic predominant adenocarcinoma (LPA) as a tumor that showed the lepidic component most frequently including AIS, MIA and lepidic predominant invasive adenocarcinoma; non-LPA was defined as other invasive adenocarcinoma.

Follow-up Policy

The routine follow-up evaluation included a physical examination, chest radiography, chest CT scan, and blood tests including measurements of tumor markers every 6 to 12 months. If any symptom or sign of recurrence was observed, further evaluation was performed, including CT, brain magnetic resonance imaging, and PET. Locoregional recurrence was defined as occurrence within the residual same lobe and hilum or mediastinal lymph

nodes, which was essentially diagnosed by cytologic or histologic confirmation based on biopsy or surgical resection.

Statistics

Chi-square test was used to compare the factors. Unpaired *t* test was used if continuous variables were normally distributed, and if not, Wilcoxon rank-sum test was used. Multivariable logistic regression model was fit to identify the clinical factors of LPA using SPSS Statistics 21 (IBM Inc, New York, NY). Forward and backward stepwise procedures were used to determine the combination of factors that were essential for identifying LPA and the survival outcomes. Overall survival (OS) and recurrence-free survival (RFS) functions were estimated using the Kaplan–Meier method and compared by log-rank test across the different groups. The date of surgical resection was set as the starting point and the date of death or survival follow-up as the end point of OS. Moreover, the time of occurrence of the first event including relapse and death, or

TABLE 1. Comparison of clinicopathologic factors based on the lepidic component frequency

Factors	c-Stage IA pure-solid lung adenocarcinoma		P value*
	LPA (N = 57)	Non-LPA (N = 143)	
Clinical variables			
Age (y)	66.1 ± 9.9 (44-88)	67.2 ± 10.1 (35-89)	.522
Sex (male)	27 (47)	92 (64)	.038
Side (right)	36 (63)	81 (57)	.430
Location (peripheral/central)	46 (81)/11 (19)	93 (65)/50 (35)	.040
Lobe			
RU/RM/RL	18 (32)/4 (7)/14 (24)	46 (32)/10 (7)/25 (17)	.801
LU/LL	13 (23)/8 (14)	35 (25)/27 (19)	
Pack-y of smoking	0 ± 30.0 (0-95)	30.0 ± 50.0 (0-180)	<.001
COPD (stage I)	49 (86)	107 (75)	.093
CEA (ng/mL)	2.3 ± 2.6 (0.6-14.3)	3.8 ± 6.5 (0.7-82.7)	<.001
SUVmax	2.5 ± 3.2 (0.7-18.5)	5.6 ± 5.6 (0.7-23.4)	<.001
Maximum tumor size (mm)	17.5 ± 6.0 (9-30)	20.5 ± 6.0 (7-30)	.002
Clinical T status (c-T1a/c-T1b)	40 (70)/17 (30)	75 (52)/68 (48)	.063
Radiologic pleural tail (present)	25 (44)	77 (54)	.214
Air bronchogram (absent)	42 (74)	73 (58)	.052
History of cancer (present)	4 (7)	23 (16)	.110
Operative variable			
Lobectomy/sublobar resection	42 (74)/15 (26)	123 (86)/30 (14)	.062
Pathologic variables			
Histologic classification			
AIS	3 (5)	0	<.001
MIA	3 (5)	0	
Lepidic predominant invasive ad	51 (90)	0	
Acinar predominant	0	60 (42)	
Papillary predominant	0	43 (30)	
Solid predominant	0	40 (28)	
Nodal involvement (N1/N2)	1 (2)/4 (7)	19 (13)/26 (18)	.003
Lymphatic invasion (present)	17 (30)	69 (48)	.018
Vascular invasion (present)	13 (23)	81 (57)	<.001
Pathologic stage			
IA/IB	46 (81)/5 (9)	62 (43)/29 (20)	<.001
IIA/IIB	1 (2)/0 (0)	18 (13)/6 (4)	
IIIA/IIIB	4 (6)/1 (2)	27 (19)/1 (1)	

Categoric data are shown as numbers (%), and continuous data are shown as mean ± standard deviation if normally distributed and median ± interquartile range if not normally distributed (range). The following factors were analyzed as a continuous variable: age, pack-y of smoking, CEA, SUVmax, and maximum tumor size. LPA, Lepidic predominant adenocarcinoma; RU, right upper; RM, right middle; RL, right lower; LU, left upper; LL, left lower; COPD, chronic obstructive pulmonary disease; CEA, carcinoembryonic antigen; SUVmax, maximum standardized uptake value; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma. *P value in chi-square test, Student *t* test, or Wilcoxon rank-sum test.

TABLE 2. Univariable and multivariable analyses for the prediction of lepidic predominant clinical stage IA pure-solid lung adenocarcinoma

Variables	Univariable			Multivariable		
	OR	95% CI	P value*	OR	95% CI	P value*
Sex (male)	2.00	1.08-3.74	.029	0.99	0.95-1.03	.667
Side (right)	1.32	0.70-2.44	.399			
Location (peripheral)	2.27	1.08-4.76	.032	1.61	0.69-3.85	.267
Lobe (upper)	1.10	0.59-2.03	.772			
Pack-y of smoking	0.98	0.97-0.99	.002	0.90	0.80-1.03	.072
COPD (stage I)	2.06	0.89-4.76	.091			
CEA (ng/mL)	0.86	0.78-0.96	.005	0.91	0.80-1.04	.112
SUVmax	0.77	0.63-0.83	<.001	0.76	0.65-0.88	<.001
Maximum tumor size (mm)	0.92	0.87-0.97	.002	1.01	0.94-1.09	.763
Air bronchogram (absent)	0.50	0.25-0.97	.041	0.53	0.25-1.14	.102
History of cancers (no)	2.54	0.84-7.71	.100			

The following factors were analyzed as a continuous variable: pack-y of smoking, carcinoembryonic antigen, SUVmax, and maximum tumor size. OR, Odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CEA, carcinoembryonic antigen; SUVmax, maximum standardized uptake value. *P value in logistic regression analysis.

date of evaluating survival or recurrence was set as the end point of the RFS. Continuous variables that were normally distributed were summarized by mean and standard deviation; those not normally distributed were summarized by median and interquartile range.

RESULTS

The overall clinicopathologic characteristics of clinical stage IA radiologic pure-solid lung adenocarcinoma are summarized in Table 1. Histologic subtype of LPA was identified in approximately one third of the patients, the majority of which were lepidic predominant invasive adenocarcinomas, whereas the non-LPA subtypes were fairly evenly distributed.

FIGURE 2. Receiver operating characteristic curve reveals that the optimal cutoff value for predicting LPA is an SUVmax of 3.3 (area under the curve, 0.764; sensitivity, 72.7%; specificity, 66.7%). AUC, Area under the curve; SUVmax, maximum standardized uptake value; CI, confidence interval.

Table 2 shows univariable and multivariable analyses for identifying lepidic predominant clinical stage IA pure-solid lung adenocarcinoma. From a multivariable analysis, SUVmax is an independent variable of LPA in this population ($P < .0001$). The receiver operating characteristic curve revealed that the optimal cutoff value for identifying LPA was an SUVmax of 3.3 (Figure 2) (area under the curve, 0.764; sensitivity, 72.7%; specificity, 66.7%). Furthermore, the Cox proportional hazard analysis for the OS demonstrated that SUVmax ($P = .034$) and pathologic nodal involvement ($P = .030$) were independent significant prognostic factors (Table 3).

The 5-year OS and RFS of clinical stage IA radiologic pure-solid lung adenocarcinoma were 83.4% and 67.5%, respectively, with a median follow-up period of 43.3 months for the OS and 41.8 months for the RFS. Furthermore, the 5-year OS and RFS were significantly different between the LPA and non-LPA groups (5-year OS, 98.1% vs 76.6%, $P = .0012$; 5-year RFS, 78.8% vs 59.9%, $P = .0024$) (Figure E1). Furthermore, we divided clinical stage IA pure-solid lung adenocarcinomas into 2 categories based on SUVmax, that is, an SUVmax 3.3 or less arm ($n = 77$) and an SUVmax greater than 3.3 arm ($n = 123$) based on the results of a multivariable analysis and receiver operating characteristic curve. Pathologically, lymphatic or vascular invasion, and nodal metastasis were less common in patients with an SUVmax 3.3 or less than those with an SUVmax greater than 3.3. LPA was shown in 38 patients (49%) in the SUVmax 3.3 or less arm, but in 19 patients (15%) in the SUVmax greater than 3.3 arm ($P < .0001$). The 5-year OS of the SUVmax 3.3 or less arm was significantly better than that of the SUVmax greater than 3.3 arm (91.7% vs 78.6%, $P = .0031$). Furthermore, we investigated the clinicopathologic features in the 2 study arms based on the operative modes (Table 4). With regard to the oncologic outcomes, the 3-year locoregional RFS was similar between the sublobar resection arm ($n = 18$) and the lobectomy arm

TABLE 3. Cox proportional hazard analysis for overall survival

Variables	Univariable			Multivariable		
	HR	95% CI	P value*	HR	95% CI	P value*
Sex (male)	0.59	0.26-1.35	.211			
Side (right)	0.82	0.38-1.75	.604			
Location (peripheral)	0.99	0.43-2.27	.991			
Lobe (upper)	1.89	0.88-4.08	.103			
Pack-y of smoking	1.01	0.99-1.01	.090			
COPD (stage I)	0.59	0.26-1.36	.216			
CEA (ng/mL)	1.04	1.02-1.06	<.001	1.02	0.99-1.04	.163
SUVmax (≤3.3)	0.23	0.08-0.67	.007	0.27	0.08-0.91	.034
Maximum tumor size (mm)	1.07	1.00-1.14	.044	1.02	0.94-1.11	.612
Air bronchogram (absent)	1.02	0.47-2.22	.966			
History of cancers (no)	0.47	0.19-1.17	.107			
Operation (lobectomy)	1.65	0.50-5.48	.416			
Nodal involvement (present)	3.02	1.41-6.49	.004	4.24	1.15-15.6	.030
Pathologic stage (IA)	0.525	0.24-1.13	.100			
Lymphatic invasion (present)	3.18	1.39-7.30	.006	2.05	0.63-6.76	.236
Vascular invasion (present)	2.70	1.18-6.17	.019	1.02	0.34-3.67	.965
LPA (no)	12.86	1.74-94.9	.012	6.32	0.80-50.0	.081

The following factors were analyzed as a continuous variable: pack-y of smoking, carcinoembryonic antigen, and maximum tumor size. *HR*, Hazard ratio; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *CEA*, carcinoembryonic antigen; *SUVmax*, maximum standardized uptake value; *LPA*, lepidic predominant adenocarcinoma. **P* value in Cox proportional hazard analysis.

(*n* = 59) of patients with an SUVmax of 3.3 or less (Figure 3, A, 92.9% vs 98.2%, *P* = .9761), whereas that of the sublobar resection arm (*n* = 17) was significantly worse than that of the lobectomy arm (*n* = 106) of patients with an SUVmax greater than 3.3 (Figure 3, B, 62.7% vs 82.9%, *P* = .0281).

DISCUSSION

Our first study aim was to determine whether clinical factors can be used to identify lepidic growth in patients with

clinical stage IA radiologic pure-solid lung adenocarcinomas. In general, radiologic pure-solid lung adenocarcinomas without a GGO component have been found to exhibit a more malignant behavior and have a poorer prognosis compared with part-solid lung adenocarcinomas.^{4,9,10,19,20} However, the most critical finding in this study was that the SUVmax level correlated well with the histologic subtypes based on the IASLC/ATS/ETS classification even for cases of clinical stage IA radiologic pure-solid lung adenocarcinoma without GGO components

TABLE 4. Clinicopathologic characteristics based on the operative modes in each maximum standardized uptake value group

Clinical factors	SUVmax ≤3.3 (N = 77)			SUVmax >3.3 (N = 123)		
	Lobectomy (n = 59)	Sublobar (n = 18)	P value*	Lobectomy (n = 106)	Sublobar (n = 17)	P value*
Age (y)	67.2 ± 9.8 (48-86)	64.6 ± 11.2 (43-88)	.350	66.6 ± 10.1 (35-89)	70.1 ± 8.7 (59-83)	.176
Sex (male)	35 (59)	7 (39)	.177	65 (61)	12 (71)	.593
Location (peripheral)	43 (73)	15 (83)	.535	66 (62)	15 (88)	.052
Pack-y smoking	24.4 ± 30.1 (0-120)	10.3 ± 16.1 (0-50)	.061	31.7 ± 39.3 (0-180)	33.3 ± 26.4 (0-92)	.870
FEV1%	74.6 ± 8.8 (43-89)	75.7 ± 6.4 (62-86)	.619	75.4 ± 9.5 (48-97)	74.6 ± 12.8 (50-97)	.764
VC (%)	97.6 ± 15.4 (67-129)	97.9 ± 19.0 (55-126)	.951	98.4 ± 15.7 (49-133)	88.2 ± 20.8 (51-118)	.068
CEA (ng/mL)	3.7 ± 3.3 (0.6-18.2)	2.6 ± 2.2 (0.5-8.9)	.190	8.5 ± 13.0 (0.5-82.7)	12.0 ± 14.4 (1.1-45.6)	.318
SUVmax	2.2 ± 0.8 (0.7-3.3)	1.5 ± 0.7 (0.7-3.2)	.0002	7.6 ± 3.7 (3.4-23.4)	7.3 ± 4.1 (3.8-19.0)	.698
Maximum tumor size (mm)	19.0 ± 8.0 (7-30)	10.012.0 (8-20)	<.001	21.4 ± 5.6 (10-30)	18.8 ± 25.4 (12-28)	.073
c-T status (T1a)	35 (59)	18 (100)	<.001	50 (47)	12 (71)	.111
Lymphatic invasion (present)	20 (34)	2 (11)	.077	58 (55)	6 (35)	.191
Vascular invasion (present)	19 (32)	2 (11)	.129	70 (66)	3 (18)	<.001
Nodal metastases (present)	8 (14)	1 (6)	.676	39 (37)	2 (12)	.053
p-stage IA disease	40 (68)	15 (83)	.247	43 (41)	10 (59)	.192
LPA	26 (44)	12 (67)	.112	16 (15)	3 (18)	.726

Categoric data are shown as numbers (%), and continuous data are shown as mean ± standard deviation if normally distributed and median ± interquartile range if not normally distributed (range). The following factors were analyzed as a continuous variable: pack-y of smoking, FEV1%, vital capacity (%), CEA, SUVmax, and tumor size. *SUVmax*, Maximum standardized uptake value; *FEV1*, forced expiratory volume in 1 second; *VC*, vital capacity; *CEA*, carcinoembryonic antigen; *LPA*, lepidic predominant adenocarcinoma. **P* value in chi-square test, Student *t* test, or Wilcoxon rank-sum test.

FIGURE 3. The 3-year locoregional RFS is presented on the basis of the operative mode. It is similar between the sublobar resection arm and the lobectomy arm of patients with an SUVmax of 3.3 or less (A, 92.9% vs 98.2%, $P = .9761$), whereas that of the sublobar resection arm is significantly worse than that of the lobectomy arm of patients with an SUVmax of 3.3 or greater (B, 62.7% vs 82.9%, $P = .0281$). *SUVmax*, Maximum standardized uptake value; *RFS*, recurrence-free survival.

on thin-section CT scan, that is, SUVmax value was a promising clinical variable for identifying lepidic predominance among them.

These findings suggest that there are a subset of patients with adenocarcinoma who may be adequately treated with sublobar resection on the basis of clinical factors. To further explore this question, we stratified the patients on the basis of the SUVmax, which we identified as strongly associated with lepidic growth, to determine whether the approach to resection was associated with differential survival. Our finding that patients with a high SUVmax who underwent sublobar resection had worse survival suggests that higher SUVmax value may be useful for identifying patients with stage IA radiologic pure-solid lung adenocarcinoma in whom sublobar resection should not be considered.

Controversy still surrounds the appropriate operative modes for early-stage NSCLC with solid nodules.^{12,15,21-23} We speculate that the dispute regarding segmentectomy versus lobectomy for small-sized lung cancer to date would be due to a migration of part-solid and pure-solid tumors in the initial patient selection. The oncologic outcomes of the radiologic part-solid lung adenocarcinomas were excellent and definitely different from those of pure-solid tumors.^{4,24} Therefore, we focused exclusively on radiologic pure-solid tumors to address this matter. Moreover, pure-solid lung adenocarcinomas showed the histologic predominance of a wide variety of components including not only lepidic but also acinar, papillary, and solid as shown in the current study. Among them, lung adenocarcinomas demonstrating

lepidic component predominance showed less invasiveness, and the oncologic outcomes of such adenocarcinomas are fully acceptable despite the operative mode used even for tumors that showed a radiologic pure-solid appearance.

Because of the refined resolution of thin-section CT scan, we can predict tumor invasiveness more precisely on the basis of the preoperative radiologic characteristics, namely, the presence of a GGO component. In routine practice, however, it is sometimes difficult to distinguish them on the basis of the findings on thin-section CT scan if the tumors have a radiologic pure-solid appearance because of the complete absence of a GGO component. In general, a radiologic pure-solid appearance is considered to exhibit histologic nonlepidic components. However, there exists LPA showing a radiologic pure-solid appearance on thin-section CT scan because of the collapse of alveolar and intestinal fields. Thus, identifying LPAs is key to select patients with radiologic pure-solid lung adenocarcinoma for whom sublobar resection may be indicated.

Although definitive preoperative patient selection is mandatory especially when indicating sublobar resection for a radiologic pure-solid lung adenocarcinoma, our results showed that a lower SUVmax level of the tumor was a significant clinical factor of LPA, and patients who met our criterion showed less pathologic invasiveness and better OS than those who did not. Moreover, the 3-year locoregional RFS of the sublobar resection arm was significantly different than that of the lobectomy arm based on the SUVmax level of the tumor. This indicates that the SUVmax of

tumors is a promising clinical parameter that may be useful for identifying patients in whom sublobar resection should not be considered if the patient is a candidate for lobectomy, even if technically feasible, but this requires further study. The greatest concern regarding the indication for sublobar resection in patients with radiologic pure-solid lung adenocarcinoma is the potential risk for pathologic nodal metastasis and subsequent locoregional recurrence. Moreover, their frequencies are extremely high compared with those of part-solid tumors. Therefore, the decision to proceed with sublobar resection should be made with caution in patients with pure-solid lung adenocarcinomas.

SUVmax on PET and GGO appearances are significant preoperative variables for surgical outcome in clinical stage IA lung adenocarcinoma.⁸ Furthermore, we elucidated that SUVmax would be useful in quantitative assessments to subdivide radiologic pure-solid lung adenocarcinomas into lepidic predominant or nonlepidic predominant lesions in the current study. In principal, lobectomy with nodal dissection is the mainstay definitive locoregional surgical management for patients with clinical stage IA pure-solid lung adenocarcinomas, especially when it showed a high SUVmax (ie, SUVmax >3.3) because of its truly highly invasive nature. In contrast, segmentectomy may be an optimal surgical mode for cases with a low SUVmax because they have similar locoregional RFSs compared with cases of the lobectomy arm, although further validation study is necessary to confirm the result. Our primary objective was to explore the clinical factors correlated with the histologic lepidic growth component in this cohort, with the understanding that being able to determine the clinical variables that identify a high frequency of lepidic component would potentially validate the concept of selecting sublobar resection for clinical stage IA radiologic pure-solid lung adenocarcinoma. On the basis of the results of the current study, SUVmax level of clinical stage IA radiologic pure-solid lung adenocarcinoma may provide a clue for identifying sublobar resection candidates in the future.

Study Limitations

This study was limited by its retrospective nature in a single center and the relatively small number of the patients undergoing sublobar resection for clinical stage IA radiologic pure-solid lung adenocarcinoma to prevent locoregional recurrence. In Japan, the prospective JCOG0802 study has completed enrolling cases, and the final result is awaited regarding appropriate operative modes for patients with radiologic invasive lung cancers. We hope to validate our recent results as an additional study in this prospective setting. Furthermore, variables of SUVmax on PET limit the generalizability of our results in daily practice. There are variations in SUVmax quantification among several institutions, and SUVmax is easily influenced by many factors, such as patient preparation procedures, scan acquisition,

image reconstruction, and data analysis. To overcome this disadvantage, the standardized uptake value needs to be revised and PET procedures standardized. Thus, further investigations are warranted in the future.

CONCLUSIONS

Although any final decision regarding the efficacy of sublobar resection for radiologically invasive small-sized lung cancers should be based on the results of the prospective studies conducted by the JCOG and Cancer and Leukemia Group B, a lower SUVmax of the tumor was a significant clinical factor of histologically LPAs, and higher SUVmax value may be useful for identifying patients with clinical stage IA radiologic pure-solid lung adenocarcinoma in whom sublobar resection should not be considered, even if it is technically feasible.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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