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

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Objective: This study aimed to compare malignant behavior and prognosis between solid tumors and mixed tumors with a ground-glass opacity component on high-resolution computed tomography.

Methods: We examined 436 of 502 consecutive patients with clinical stage IA adenocarcinoma who had undergone preoperative high-resolution computed tomography and F-18-fluorodeoxyglucose positron emission tomography/computed tomography; 66 patients with tumors with pure ground-glass opacity components were excluded. Tumor type (solid, $n = 137$; mixed, $n = 299$) and surgical results were analyzed for all patients and their matched pairs.

Results: In all patients, solid tumors showed a significantly greater association ($P < .001$) with lymphatic, vascular, and pleural invasion and lymph node metastasis compared with mixed tumors. The disease-free survival was also worse in patients with solid tumors ($P = .0006$). Analysis of 97 pairs matched for solid component size confirmed that solid tumors were significantly associated with lymphatic, vascular, and pleural invasion ($P = .008$, $P = .029$, $P = .003$, respectively) and poor prognosis. When maximum standardized uptake value and solid component size were matched ($n = 79$), the differences in pathologic prognostic parameters and disease-free survivals between patients with solid and mixed tumors disappeared.

Conclusions: Solid tumors exhibit more malignant behavior and have a poorer prognosis compared with mixed tumors, even when the solid component size is the same in both tumor types. However, differences in malignant behavior can be identified using maximum standardized uptake values determined by F-18-fluorodeoxyglucose positron emission tomography/computed tomography. (J Thorac Cardiovasc Surg 2013;146:17-23)

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The recent development of high-resolution computed tomography (HRCT) and low-dose computed tomography (CT) screening has improved the detection of small lung cancers, especially lung adenocarcinomas.¹⁻³ These often contain a nonsolid component that presents as a ground-

glass opacity (GGO) on HRCT and is closely associated with bronchioloalveolar carcinoma.^{4,5} We have previously reported the benefits of comparing solid component size (the maximum dimension of the solid component excluding GGO) on HRCT with whole tumor size for predicting the pathologic invasiveness of tumors or the prognosis of clinical stage IA lung adenocarcinomas.⁶ It remains unclear whether GGO-containing tumors have the same malignant behavior and prognosis as pure solid tumors after matching for solid component size.

Whether or not differences exist in malignant behavior between pure solid tumors and mixed tumors with a GGO component on HRCT remains controversial. Therefore, we used HRCT to compare malignant behavior, including lymphatic, vascular, and pleural invasion, and prognosis between solid tumors and mixed tumors having a GGO component in patients with clinical stage IA lung adenocarcinoma.

PATIENTS AND METHODS

Between August 1, 2005, and December 31, 2009, we enrolled 502 patients with clinical T1N0M0 stage IA lung adenocarcinoma who were admitted to 1 of the following 4 institutions: Hiroshima University, Kanagawa Cancer Center, Cancer Institute Hospital, and Hyogo Cancer Center. HRCT and F-18-fluorodeoxyglucose positron emission tomography/CT

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Abbreviations and Acronyms

CT	= computed tomography
DFS	= disease-free survival
FDG-	= F-18-fluorodeoxyglucose positron
PET	emission tomography
FOV	= field of view
GGO	= ground-glass opacity
HRCT	= high-resolution computed tomography
SUV	= standardized uptake value
SUVmax	= maximum standardized uptake value

(FDG-PET/CT) followed by curative R0 resection were performed in all patients, who were staged according to the seventh edition of the TNM classification of malignant tumors.⁷ Mediastinoscopy and endobronchial ultrasonography were not routinely performed because HRCT revealed no swelling of mediastinal or hilar lymph nodes and FDG-PET showed no accumulation in these lymph nodes in all patients. Sublobar resections (segmentectomy or wedge resection) were performed if the tumor mainly comprised a GGO component or had no lymph node metastasis on intraoperative assessment. Tumors with pure GGO were excluded from the analyses because they are noninvasive and have an extremely good prognosis.^{8,9} We obtained appropriate approval for this multicenter study from the institutional review board of each institution, which waived the requirement for informed consent from individual patients because this was a retrospective review of medical records from a prospective database.

High-Resolution Computed Tomography

Chest images were obtained using 16-row multidetector CT independently of subsequent FDG-PET/CT examinations. High-resolution images of the tumors were acquired using the following parameters: 120 kVp; 200 mA; section thickness, 1 to 2 mm; pixel resolution, 512 × 512; scanning time, 0.5 to 1 seconds; a high spatial reconstruction algorithm with a 20-cm field of view (FOV); and mediastinal (level, 40 HU; width, 400 HU) and lung (level, -600 HU; width, 1600 HU) window settings. GGO was defined as a misty increase in lung attenuation that did not obscure underlying vascular markings. We defined solid component size as the maximum dimension of the solid component in the lung windows after excluding the GGO component.⁶ Solid tumors were defined as pure solid tumors without a GGO component, whereas mixed tumors were defined as tumors with a GGO component regardless of the GGO proportion.

F-18-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

Patients were instructed to fast for more than 4 hours before intravenous injection of 74 to 370 MBq of FDG. After injection, they were instructed to relax for at least 1 hour before FDG-PET/CT scanning. Blood glucose was calculated before tracer injection to confirm a level of less than 150 mg/dL.¹⁰ Patients with blood glucose values 150 mg/dL or greater were excluded from PET/CT image acquisition. Images were obtained using Discovery ST (GE Healthcare, Little Chalfont, UK), Aquiduo (Toshiba Medical Systems Corporation, Tochigi, Japan), or Biograph Sensation16 (Siemens Healthcare, Erlangen, Germany) integrated PET/CT scanners. Low-dose, unenhanced CT images of 2- to 4-mm section thickness for attenuation correction and localization of lesions identified by PET were obtained from the head to the pelvic floor of each patient using a standard protocol. Immediately after CT, PET covered the identical axial FOV for 2 to 4 minutes per table position depending on the condition of the patient and scanner performance. All PET images with a 50-cm FOV were reconstructed using an iterative algorithm with CT-derived attenuation

correction. Variations in standardized uptake values (SUVs) among institutions were minimized using an anthropomorphic body phantom. A calibration factor was obtained by dividing the actual SUV by the gauged mean SUV in the phantom background to decrease interinstitutional SUV inconsistencies; the final SUV used is referred to as the revised maximum SUV (SUVmax).^{11,12} Adjustment of interinstitutional variability in SUV narrowed the range from 0.89 to 1.24 to 0.97 to 1.18 when the SUVmax ratio was expressed as the SUVmax reported by each institute relative to the SUVmax reported by the control institute.

Follow-up Evaluation

All patients who underwent lung resection were followed up from the day of surgery. Postoperative follow-up procedures, including physical examination and chest roentgenography every 3 months and chest and abdominal CT examinations every 6 months, were performed for the first 2 years. Thereafter, physical examination and chest roentgenography were performed every 6 months, whereas chest CT examination was performed every year. Recurrence was determined by radiographic features or histologic evidence.

Statistical Analysis

Data are presented as numbers (%) or mean ± standard deviation unless otherwise stated. Frequencies were compared using the chi-square test for categorical variables, and the Fisher exact test was applied to small samples in all cohort patients. McNemar tests were used for analyses of matched-pair patients. Mann-Whitney *U* tests and *t* tests were used to compare continuous variables in all cohort patients. Wilcoxon tests were used for analyses of matched-pair patients. Disease-free survival (DFS) was defined as the time from the date of surgery until the first event (relapse or death from any cause) or last follow-up. The duration of DFS was analyzed using the Kaplan-Meier method. Differences in DFS were assessed using the log-rank test. We applied matching to balance the assignment of the included patients and correct for tumor type (solid or mixed), which confounded survival. The variables were solid component size or SUVmax. Solid and mixed tumor pairs with an equivalent solid component size or SUVmax were selected by a 1-to-1 match. All 436 patients were pooled and sorted in ascending order according to their solid component size or SUVmax. The selection process began from the first 2 cases with the lowest solid component size or SUVmax. If 1 case exhibited a solid tumor and the other case exhibited a mixed tumor, both were selected as a matched pair. If this was not the case, then 4 cases were included. In the same way, solid and mixed tumors were matched by their solid component size or SUVmax in 1:1, 2:2, 3:3, or 4:4 blocks. A patient who did not have a suitable match within the acceptable rank range was excluded from further analysis, and the matching process moved down the sort list until all possible matched pairs were included. The selected patients formed well-matched 1:1 pairs in both groups. Data were analyzed using the Statistical Package for the Social Sciences (v 10.5; SPSS Inc, Chicago, Ill).

RESULTS

Of the 502 patients, 66 who had tumors with pure GGO components were excluded; the remaining 436 patients were included in this analysis. Of the 436 study patients, 137 had solid tumors and 299 had mixed tumors. The mean follow-up period after surgery was 20.2 ± 12.5 months, during which the disease recurred in 29 patients (6.7%). The mean follow-up period was similar for solid and mixed tumors (21.4 ± 12.8 months and 19.7 ± 12.4 months, respectively, *P* = .235). Of the 29 cases of recurrence, 9 (2.1%) were local (including mediastinal lymph node metastasis), 3 (0.7%) were local and distant, and 17

(3.9%) were distant. Age, sex, and whole tumor size on HRCT were not significantly different between patients with solid and mixed tumors. Solid tumors were significantly correlated with a large solid component size, a high SUVmax, and the presence of lymphatic, vascular, and pleural invasion and lymph node metastasis ($P < .001$, $P < .001$, $P < .001$, $P < .001$, $P < .001$, $P = .001$, respectively; Table 1).

Local recurrence occurred in 5 patients (3.6%) with solid tumors (1 involving the bronchial stump and 4 involving the mediastinal lymph nodes) and 4 patients (1.3%) with mixed tumors (1 involving the residual lung after segmentectomy and 3 involving the mediastinal lymph nodes). A significant difference in DFS was identified between patients with solid tumors ($n = 137$; 2-year DFS, 83.1%) and those with mixed tumors ($n = 299$; 2-year DFS, 94.2%; $P = .0006$; Figure 1, A).

After matching for solid component size, there were 97 well-matched solid and mixed tumor pairs. Significant differences were identified in whole tumor size, SUVmax, and lymphatic, vascular, and pleural invasion between the 2 tumor types ($P < .001$, $P < .001$, $P = .008$, $P = .029$, $P = .003$, respectively, Table 2). Solid tumors were significantly correlated with a small whole tumor size, a high SUVmax, and the presence of pathologic invasiveness.

Furthermore, a difference in DFS was identified between patients with solid tumors ($n = 97$; 2-year DFS, 83.5%) and

those with mixed tumors ($n = 97$; 2-year DFS, 91.8%; Figure 1, B) after matching for solid component size.

After matching for SUVmax, there were 96 well-matched solid and mixed tumor pairs. No significant differences in clinical characteristics, except for solid component size, were found between the 2 tumor types (Table 3).

A difference in DFS was identified between patients with solid tumors ($n = 96$; 2-year DFS, 87.1%) and those with mixed tumors ($n = 96$; 2-year DFS, 90.4%; Figure 1, C) after matching for SUVmax.

After matching for solid component size and SUVmax, there were 79 well-matched solid and mixed tumor pairs. No significant differences in clinical characteristics, except for whole tumor size, were found between the 2 tumor types (Table 4).

Furthermore, there was no difference in DFS between patients with solid tumors ($n = 79$; 2-year DFS, 87.0%) and patients with mixed tumors ($n = 79$; 2-year DFS, 83.9%; Figure 1, D) after matching for solid component size and SUVmax.

Figure 2 shows examples of solid and mixed tumors with the same solid component size (1.0 cm). Regardless of tumor type, tumors with low SUVmax were not associated with lymphatic invasion, whereas those with high SUVmax were.

DISCUSSION

The present study demonstrated, as expected, that solid tumors were associated with highly malignant variables, such as large solid component size, high SUVmax, and lymphatic, vascular, and pleural invasion and lymph node metastasis in all cohort patients. In addition, patients with solid tumors had worse DFS than those with mixed tumors. A retrospective study has previously shown that pure solid tumors have malignant potential with nodal or pleural involvement and worse DFS compared with predominantly solid tumors with a GGO component.¹³ Other studies have also revealed that tumors with a predominant GGO component are less invasive and have a more favorable prognosis in patients with clinical stage IA lung adenocarcinomas.^{4,8,14} Our study is consistent with these findings.

With regard to the tumor size on HRCT, solid component size is more useful than whole tumor size for predicting pathologic invasiveness and prognosis. In our previous study, solid component size was found to have a higher predictive value for lymphatic, vascular, and pleural invasion compared with whole tumor size; furthermore, solid component size was an independent prognostic factor for DFS.⁶ It was not clear whether mixed tumors and solid tumors have similar malignant behaviors and prognoses when both have the same solid component size on HRCT. Therefore, we conducted a matched analysis to compare solid and mixed tumors after matching for solid component size in both tumor types. Even after matching for solid component

TABLE 1. Comparison of solid and mixed tumor characteristics in all cohort patients

	Solid tumors (n = 137)	Mixed tumors (n = 299)	P
Age (y)	65.5 ± 10.5	65.7 ± 8.8	.85
Sex			.12
Male	71 (51.8%)	130 (43.5%)	
Female	66 (48.2%)	169 (56.5%)	
Whole tumor size (cm)	2.1 ± 0.6	2.0 ± 0.6	.69
Solid component size (cm)	2.1 ± 0.6	1.1 ± 0.7	<.001
SUVmax	4.9 ± 3.3	2.6 ± 2.9	<.001
Lymphatic invasion			<.001
Negative	89 (65.0%)	270 (90.3%)	
Positive	48 (35.0%)	29 (9.7%)	
Vascular invasion			<.001
Negative	79 (57.7%)	264 (88.3%)	
Positive	58 (42.3%)	35 (11.7%)	
Pleural invasion			<.001
Negative	100 (73.0%)	278 (93.0%)	
Positive	37 (27.0%)	21 (7.0%)	
Lymph node metastasis			<.001
Negative	114 (83.2%)	284 (95.0%)	
Positive	23 (16.8%)	15 (5.0%)	
Procedure			.001
Lobectomy	111 (81.0%)	190 (63.5%)	
Segmentectomy	9 (6.6%)	48 (16.1%)	
Wedge resection	17 (12.4%)	61 (20.4%)	

SUVmax, Maximum standardized uptake value.

FIGURE 1. DFS curves of patients according to tumor type on HRCT. A, In all cohort patients, 2-year DFS of 94.2% (mean DFS of 47 months; 95% confidence interval [CI], 46-48 months) and 83.1% (mean DFS of 42 months; 95% CI, 39-45 months) were identified for mixed and solid tumors, respectively ($P = .0006$). B, In patients matched for solid component size, 2-year DFS of 91.8% (mean DFS of 46 months; 95% CI, 43-48 months) and 83.5% (mean DFS of 42 months; 95% CI, 38-45 months) were identified for mixed and solid tumors, respectively. C, In patients matched for SUVmax, 2-year DFS of 90.4% (mean DFS of 42 months; 95% CI, 39-44 months) and 87.1% (mean DFS of 42 months; 95% CI, 38-46 months) were detected for mixed and solid tumors, respectively. D, In patients matched for solid component size and SUVmax, 2-year DFS of 83.9% (mean DFS of 43 months; 95% CI, 40-47 months) and 87.0% (mean DFS of 43 months; 95% CI, 40-47 months) were detected for mixed and solid tumors, respectively.

size in both tumor types on HRCT, solid tumors were more frequently correlated with high SUVmax and malignant behavior compared with mixed tumors. In addition, the DFS of patients with solid tumors was worse than that of patients with mixed tumors. This means that solid tumors have more malignant potential than mixed tumors even if both tumor types have the same solid component size on HRCT. This is a new finding. SUVmax on PET/CT is reported to be a predictor of malignant behavior and prognosis in cases of lung adenocarcinomas.^{6,11,12,15-17} SUVmax on PET/CT is a preoperative factor, whereas lymphatic, vascular, and

pleural invasion are postoperative factors. We have previously reported that SUVmax is a significant predictor of malignant behavior.^{6,11,12,16,17}

We experimentally performed a matched analysis to compare solid and mixed tumors after matching for SUVmax. In this matched model, solid tumors and mixed tumors had similar clinical characteristics except solid component size, but there seemed to be a difference in DFS. Although both tumor types have the same SUVmax, solid tumors seem to have a worse potential than mixed tumors.

TABLE 2. Comparison of solid and mixed tumor characteristics in patients matched for solid component size

	Solid tumors (n = 97)	Mixed tumors (n = 97)	P
Age (y)	64.9 ± 10.4	66.1 ± 10.0	.63
Sex			.054
Male	50 (51.5%)	36 (37.1%)	
Female	47 (48.5%)	61 (62.9%)	
Whole tumor size (cm)	1.8 ± 0.5	2.3 ± 0.5	<.001
Solid component size (cm)	1.8 ± 0.5	1.8 ± 0.5	N/A
SUVmax	4.8 ± 3.4	3.0 ± 2.5	<.001
Lymphatic invasion			.008
Negative	63 (64.9%)	81 (83.5%)	
Positive	34 (35.1%)	16 (16.5%)	
Vascular invasion			.029
Negative	62 (63.9%)	76 (78.4%)	
Positive	35 (36.1%)	21 (21.6%)	
Pleural invasion			.003
Negative	71 (73.2%)	88 (90.1%)	
Positive	26 (26.8%)	9 (9.9%)	
Lymph node metastasis			.13
Negative	82 (84.5%)	90 (92.8%)	
Positive	15 (15.5%)	7 (7.2%)	
Procedure			.38
Lobectomy	74 (76.3%)	83 (85.6%)	
Segmentectomy	7 (7.2%)	8 (8.2%)	
Wedge resection	16 (16.5%)	6 (6.2%)	

SUVmax, Maximum standardized uptake value; N/A, not applicable.

TABLE 3. Comparison of solid and mixed tumor characteristics in patients matched for maximum standardized uptake value

	Solid tumor (n = 96)	Mixed tumor (n = 96)	P
Age (y)	65.4 ± 10.4	65.5 ± 9.3	.94
Sex			.26
Male	49	40	
Female	47	56	
Whole tumor size (cm)	2.0 ± 0.6	2.1 ± 0.6	.24
Solid tumor size (cm)	2.0 ± 0.6	1.5 ± 0.7	<.001
SUVmax	4.0 ± 2.6	4.0 ± 2.6	N/A
Lymphatic invasion			.12
Negative	65	74	
Positive	31	22	
Vascular invasion			.47
Negative	62	67	
Positive	34	29	
Pleural invasion			.071
Negative	70	81	
Positive	26	15	
Lymph node metastasis			.54
Negative	80	84	
Positive	16	12	
Procedure			.50
Lobar resection	77	73	
Segmentectomy	6	15	
Wedge resection	13	8	

SUVmax, Maximum standardized uptake value; N/A, not applicable.

TABLE 4. Comparison between solid and mixed tumor characteristics in patients matched for solid component size and maximum standardized uptake value

	Solid tumor (n = 79)	Mixed tumor (n = 79)	P
Age (y)	64.4 ± 10.7	66.0 ± 8.9	.27
Sex			.62
Male	37 (46.8%)	41 (51.9%)	
Female	42 (53.2%)	38 (48.1%)	
Whole tumor size (cm)	1.8 ± 0.5	2.2 ± 0.5	<.001
Solid component size (cm)	1.8 ± 0.5	1.8 ± 0.5	N/A
SUVmax	3.7 ± 2.4	3.7 ± 2.6	N/A
Lymphatic invasion			.31
Negative	53 (67.1%)	60 (75.9%)	
Positive	26 (32.9%)	19 (24.1%)	
Vascular invasion			1.0
Negative	56 (70.9%)	56 (70.9%)	
Positive	23 (29.1%)	23 (29.1%)	
Pleural invasion			.71
Negative	62 (78.5%)	65 (82.3%)	
Positive	17 (21.5%)	14 (17.7%)	
Lymph node metastasis			.80
Negative	67 (84.8%)	69 (87.3%)	
Positive	12 (15.2%)	10 (12.7%)	
Procedure			.15
Lobar resection	61 (77.2%)	66 (83.5%)	
Segmentectomy	5 (6.3%)	8 (10.1%)	
Wedge resection	13 (16.5%)	5 (6.3%)	

SUVmax, Maximum standardized uptake value; N/A, not applicable.

In a next step, we evaluated whether mixed tumors exhibited malignant behavior and prognosis similar to those of solid tumors after matching for solid component size and SUVmax. In this matched model, solid tumors and mixed tumors had similar clinical characteristics and DFS. As shown in Figure 2, tumors with equivalent solid component size and SUVmax had the same malignant behavior (eg, lymphatic invasion), regardless of type. The DFS of patients with solid and mixed tumors was also comparable after matching for solid component size and SUVmax. These findings indicate that solid tumors and mixed tumors show similar biological behavior and prognosis when both have the same solid component size on HRCT and the same SUVmax value on PET/CT. In other words, solid component size on HRCT and SUVmax on PET/CT are important factors for evaluating malignant behavior of clinical stage IA lung adenocarcinomas before surgery, and this is regardless of the GGO proportion. Solid and mixed lung adenocarcinoma tumors with low SUVmax reflect pathologic noninvasiveness and may be good candidates for sublobar resection. We have previously reported, in the same population who were evaluated in the current study, that tumors with SUVmax less than 1.5 were not associated with lymph node metastasis or recurrence,^{12,18} and we recommend that individuals with clinical stage IA lung adenocarcinomas with

FIGURE 2. Examples of solid and mixed tumors on HRCT. A, Whole tumor size = solid component size: 1.0 cm, SUVmax: 1.1. This solid tumor was negative for lymphatic invasion. B, Whole tumor size = solid component size: 1.0 cm, SUVmax: 2.9. This solid tumor was positive for lymphatic invasion. C, Whole tumor size: 2.8 cm, solid component size: 1.0 cm, SUVmax: 1.1. This mixed tumor was negative for lymphatic invasion. D, Whole tumor size: 2.6 cm, solid component size: 1.0 cm, SUVmax: 2.9. This mixed tumor was positive for lymphatic invasion. *SUVmax*, Maximum standardized uptake value.

SUVmax less than 1.5 should undergo sublobar resection with adequate surgical margins.¹⁸

One of the strengths of this study is the use of PET/CT in all patients. PET/CT, which is the diagnostic tool of choice for patients with non-small cell lung cancer, improves the sensitivity of preoperative staging and reduces the frequency of futile thoracotomies.¹⁹ In addition, SUVmax on PET/CT is a known prognostic factor for non-small cell lung cancer, especially for adenocarcinoma.^{6,11,12,16,17} For patients with clinical stage IA lung adenocarcinoma who do not undergo PET/CT, tumor type (solid or mixed) is an important factor for predicting malignant behavior and prognosis. Because the follow-up period was short in this study, long-term follow-up is needed to confirm the DFS results.

CONCLUSIONS

In cases of clinical stage IA lung adenocarcinoma, solid tumors are more malignant than mixed tumors even after

matching for solid component size in both tumor types. However, solid tumors have the same malignant potential and prognosis as mixed tumors when both tumor types are matched for solid component size on HRCT and SUVmax on PET/CT.

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