A 3.5-mm bronchofiberscope with a lighted tip that is visible at the surgical field is inserted into the orifice of the exposed targeted segmental bronchus. After selectively starting high-frequency oscillation (40 Hz, working pressure 2 kg/cm^2, HFO JET VENTILATOR, MERA, Tokyo, Japan), the diseased segments are inflated with air while the preserved segments appear collapsed, and a line is quickly and clearly formed between the inflated and the deflated parenchyma, demonstrating the anatomical intersegmental plane. This method is contrary to conventional inflation-deflation. The target bronchus is tied and cut with a suture or stapler to keep the segment inflated following being filled by jet ventilation. The surgeon can selectively introduce the tip of the fiberscope into each segmental/subsegmental bronchus and sequentially inflate segments/subsegments when more than one is scheduled for removal. At the proximal portion around the hilum, the intersegmental plane is approached along the intersegmental vein, and the plane is divided along the inflation-deflation line at the peripheral site using electrocautery. The margin must be greater than the diameter of the tumour and comprise at least 2 cm of unaffected lung tissue for controlling local recurrence. A few adjacent segments or subsegments should be removed unless the margin is sufficient. Air leakage at the bare surface of the preserved lung is controlled using an absorbable polyglycolic acid felt and a fibrin sealant consisting of fibrinogen and thrombin. Sampling or dissection of segmental, lobar, hilar and mediastinal lymph nodes followed by intraoperative frozen section analysis is mandatory to determine the applicability of segmentectomy. Standard lobectomy should proceed instead when the surgical margin is judged imperfect or any diseased lymph node is found. The chest is routinely drained using a single chest tube under water seal.

Although the simplest segments in order of easiest to hardest to remove are the upper division (S^{1-3}) and lingular segments (S^{4+5}) of the left upper lobe, the superior (S^6) and the basilar (right S^{7-10} or left S^{8-10}) segments of either lower lobe, we have aggressively performed complicated resection of segments/subsegments such as the left S^3 segment + S^{1+2}a subsegment (Fig. 2).

Patients

We performed radical hybrid VATS segmentectomy in which the intersegmental plane was divided using electrocautery without any stapling between April 2004 and October 2010 in 102 consecutive patients with clinical T1N0M0 NSCLC who could tolerate lobectomy. Surgical-pathologic staging was performed according to the New International Staging System for Lung Cancer [11]. Operative mortality was defined as death during hospitalization for pulmonary resection or within 30 days of the procedure, whichever was longer. Pathological cancer staging proceeded in accordance with the guidelines established by the American Joint Committee on Cancer [12]. Each patient provided his/her informed written consent based on the protocol approved by the institute's review board before surgery. After surgery, every patient was essentially evaluated every 3 months for the first 2 years and at 6-month intervals thereafter.

Statistical analysis

Overall and disease-free survival rates were estimated using the Kaplan-Meier method. Overall survival was defined as elapsed time from surgery until death from any cause or last follow-up. Disease-free survival was defined as elapsed time from surgery until the first diagnosis of local, regional or distant recurrent disease or until the last follow-up. We performed multivariate analyses using the Cox proportional hazards model to identify predictors of postoperative recurrence. Data were statistically analysed using SPSS software (version 10.5, SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 lists the characteristics of the 102 patients (52 women and 50 men; median age, 67 years; range, 34–89 years). Tumour size ranged from 8 to 29 mm (median; 18 mm). Most of the patients had an adenocarcinoma (91/102, 89.2%), of which a high proportion contained a bronchioloalveolar carcinoma component (58/91, 63.7%). Pathological assessments showed that curative resections were achieved with free surgical margins in all patients. Of all 102 patients with cT1N0M0 (stage-IA) disease, 84 (82.4%) were clinically staged as having T1a disease. Final pathological examination demonstrated that 92 (90.2%), 8 (7.8%), and 1 (1%) each had pathological stage IA, IB, IIA and IIIA disease, respectively. Table 2 shows the locations of the burdened segments. Actually, segmentectomy can be performed in any lobe except in the middle lobe, and no conversions to incisions longer than 8 cm were required in this series.

The operative results are shown in Table 3. The median operative time measured from skin incision to skin closure and median bleeding during surgery were 129 min (range, 60–274 min) and 50 ml (range, 10–350 ml), respectively. The median length of the skin incision for utility access was 50 mm (range, 40–80 mm). Postoperative complications developed in 10 patients (9.8%), with the most common being prolonged air leak in 4 patients (3.9%). Three patients (2.9%) had a late alveolo-pleural fistula requiring tube drainage, which is characteristic of our procedure as the intersegmental plane is divided without using a stapler. In 66 patients (64.7%), no air leak was observed at the time of surgery. The median postoperative duration of chest tube drainage was 1 day, that is, the drain was usually removed on the day following the procedure. None of the patients died while in hospital or during the 30 days after the procedure. Five deaths from cancer and four from other causes occurred during a median follow-up of 61 months (range, 8–84 months). Pleural dissemination/malignant effusion and mediastinal lymph node metastasis developed in two patients each and distant metastasis occurred in seven. Local margin recurrence that developed in one patient after lingulectomy was treated by completion left upper lobectomy, who has since remained recurrence free.

The overall and disease-free 5-year survivals of all patients were 89.8 and 84.7%, respectively (Fig. 3). Univariate analyses demonstrated that being male ($P = 0.0049$), having cancer other than adenocarcinoma ($P < 0.0001$) or a high CEA value ($P = 0.0070$) significantly and negatively affected disease-free survival (Fig. 4). Multivariate analysis showed that histological type ($P = 0.0133$) significantly correlated with risk for recurrence, whereas age ($P = 0.9880$), tumour size ($P = 0.4827$), skin incision ($P = 0.5623$), gender ($P = 0.0847$), side ($P = 0.9681$), lobe ($P = 0.4679$) and CEA value ($P = 0.6217$) did not (Table 4). Adenocarcinoma was therefore a significantly better independent prognostic determinant of recurrence.

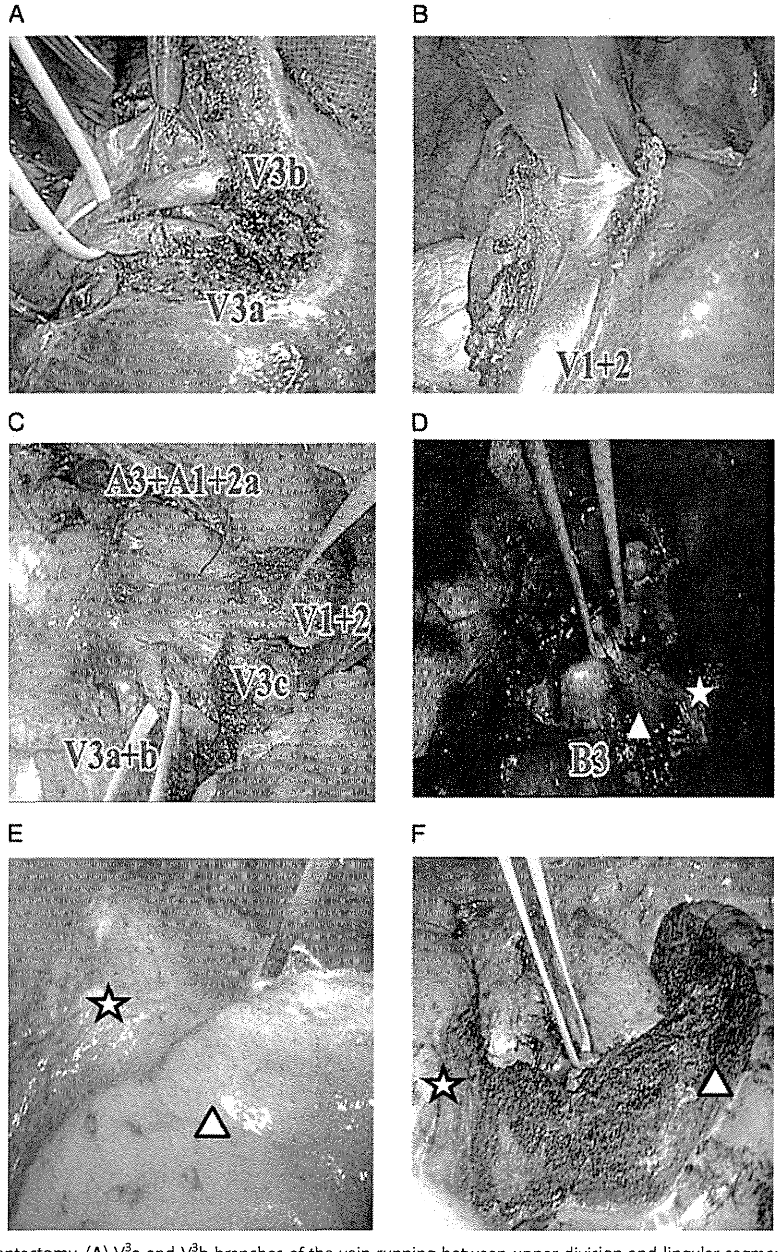

Figure 2: Left $S^3+S^{1+2}a$ segmentectomy. (**A**) V^3a and V^3b branches of the vein running between upper division and lingular segment are identified and sufficiently exposed to distal portion. (**B**) Vein branch V^{1+2} is also exposed to distal site, and $V^{1+2}a$, $V^{1+2}b+c$ and V^{1+2} superior can be identified. $V^{1+2}a$ runs between S^3c and $S^{1+2}a$, and $V^{1+2}b+c$ runs between $S^{1+2}a$ and $S^{1+2}b+c$. (**C**) First two arterial branches (A^3 and $A^{1+2}a$) and vein branches ($V^{1+2}a$, $V^{1+2}b+c$, V^3a, V^3b and V^3c) are adequately exposed. Intersegmental branches of vein ($V^{1+2}b+c$, V^3b) are saved for venous return from preserved adjacent segments. (**D**) Bronchofiberscope through the double-lumen tube inserted into the orifice of the targeted segmental bronchus (B^3) in addition to $B^{1+2}a$ (star), where high-frequency oscillation is applied. $V^{1+2}b+c$ (triangle) is preserved. (**E**) Inflation–deflation line between and inflated (resected) $S^{1+2}a$ subsegment (triangle) and deflated (preserved) $S^{1+2}b+c$ subsegment (star) along which anatomical intersubsegmental plane is dissected with cautery. (**F**) Saved parenchyma of $S^{1+2}b+c$ (triangle) and S^4 (star) is fully inflated after removal of $S^3+S^{1+2}a$.

DISCUSSION

The present study examined the relatively long-term outcomes of patients undergoing hybrid VATS segmentectomy, in which the intersegmental plane identified by the path of the intersegmental veins and by selective inflation of jet ventilation was divided by electrocautery without using a stapler. Because of the unavoidable selection bias in retrospective study, we could not compare the results between VATS segmentectomy and VATS lobectomy, which should be investigated in a prospective trial. The present study nevertheless showed that hybrid VATS segmentectomy is safe for treating patients with small clinical stage-I NSCLC and the results are excellent.

The approach via two skin incisions including a median minithoracotomy incision of 5 cm and a thoracoscope hole of 1 cm was minimally invasive, and none of our patients needed

Table 1: Patient characteristics (n = 102)

Age (years)	
Median	67
Range	34–89
Sex	
Female	52
Male	50
Size of tumour on HR-CT (mm)	
Median	18
Range	8–29
Histology	
Adenocarcinoma	91
Squamous cell	7
Adenosquamous	2
Large cell	1
Carcinoid	1
Serum CEA	
≤5.0 ng/ml	89
>5.0 ng/ml	13
Clinical stage	
IA	102 (T1a: 84, T1b: 18)
Pathologic stage	
IA	92
IB	8
IIA	1
IIIA	1

CEA, carcinoembryonic antigen.

Table 2: Location of burdened lung (n = 102)

Right upper lobe: 30
S^1: 8, $S^1 + S^2$a: 1, S^2: 9, S^2b + S^3a: 6, $S^2 + S^3$a: 1, S^3: 5
Right lower lobe: 26
S^6: 16, $S^6 + S^8$: 1, $S^7 + S^8$: 1, S^8: 3, $S^8 + S^9$: 2, $S^9 + S^{10}$: 1, S^7–S^{10}: 2
Left upper lobe: 22
$S^{1+2} + S^3$: 10, S^{1+2}a: 1, S^{1+2}: 3, $S^3 + S^{1+2}$a: 1, S^3a + b + $S^4 + S^5$: 1, $S^4 + S^5$: 6
Left Lower lobe: 24
S^6: 16, S^8: 2, S^9: 2, $S^9 + S^{10}$: 3, S^8–S^{10}: 1

a, posterior subsegment; b, anterior subsegment; S^1, apical; S^2, posterior; S^{1+2}, apicoposterior; S^3, anterior; S^4, superior; S^5, inferior; S^6, superior; S^7, medial basal; S^8, anterior basal; S^9, lateral basal; S^{10}, posterior basal.

conversion to thoracotomy requiring an incision of ≥8 cm in length. The perioperative complication rates were very low (9.8%, 10/102) and no operative mortality occurred. Since the selection of patients was not random in this series, which may have produced a bias in the selection of patients for specific procedures, we cannot describe the prognosis in detail even at a median follow-up of more than 5 years. The locoregional and distant recurrence rates were low at 4.9% (5/102) and 6.9% (7/102), respectively. The overall and disease-free 5-year survival rates of 89.8 and 84.7%, respectively, were comparable to previously published data [4, 13]. The outcomes of recent studies including ours indicate that VATS segmentectomy for recent smaller and more indolent tumours should be satisfactory from an oncological viewpoint [13, 14]. The ongoing clinical trial

Table 3: Surgical results (n = 102)

Operation time (min)	
Median	129
Range	60–275
Bleeding (ml)	
Median	50
Range	10–350
Utility access incision (mm)	
Median	50
Range	40–80
Complication	10
Prolonged air leak (>7 days)	4
Late alveolopleural fistula	3
Supraventricular arrhythmia	2
Interstitial pneumonia	1
Operative mortality	0
Mortality during follow-up	9
Cancer death	5
Other	4
Recurrence	12
Locoregional	
Dissemination	2
Mediastinum	2
Margin	1
Distant	
Lung	4
Brain	2
Meningitis	1

Follow-up of alive patients (month) median: 61 (range: 8–84).

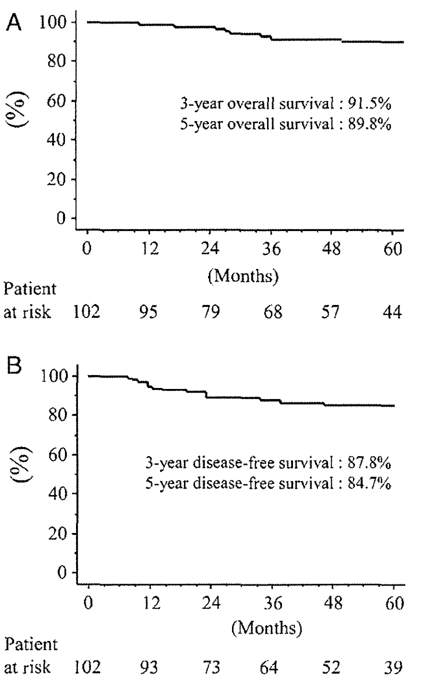

Figure 3: Postoperative Kaplan-Meier curves following radical hybrid VATS segmentectomy. (**A**) Overall survival; (**B**) disease-free survival.

comparing the surgical results between lobectomy and sublobar resection conducted by the Cancer and Leukemia Group B (CALGB 140503) and by the Japan Clinical Oncology Group/West

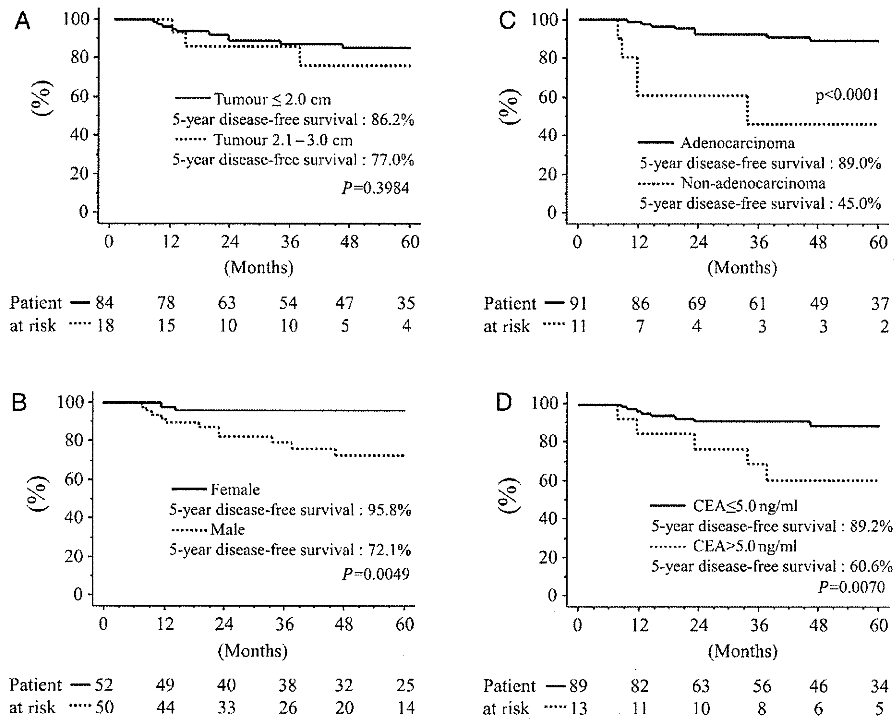

Figure 4: Disease-free survival following radical hybrid VATS segmentectomy, according to (**A**) tumour size, (**B**) gender, (**C**) histology and (**D**) serum CEA value.

Table 4: Multivariate analysis of factors predicting recurrence

Variable	Hazard ratio	95% confidence interval	*P*-value
Continuous factors			
Age	0.999	0.926–1.078	0.9880
Tumour size	1.069	0.887–1.288	0.4827
Skin incision	1.011	0.974–1.050	0.5623
Categorized factors			
Gender			
Male	Reference		
Female	0.240	0.047–1.216	0.0847
Side			
Right	Reference		
Left	1.028	0.269–3.919	0.9681
Lobe			
Upper	Reference		
Lower	0.599	0.151–2.387	0.4679
Histology			
AD	Reference		
Non-AD	6.775	1.488–30.839	0.0133
CEA			
≥5.0 ng/ml	Reference		
>5.0 ng/ml	1.452	0.330–6.383	0.6217

AD, adenocarcinoma; CEA, carcinoembryonic antigen.

Japan Oncology Group (JCOG0802/WJOG4607L) [15] will demonstrate the role of segmentectomy for patients with NSCLC 2 cm or smaller. The former randomly assigns patients to undergo segmentectomy or wedge resection and lobectomy, but the latter cannot permit wedge resection as a sublobar resection although surgeons in both trials can freely select the access technique by VATS or by thoracotomy.

The primary target of ideal function-saving surgery is to preserve the pulmonary parenchyma, and the secondary aim is to reduce trauma through selecting the appropriate surgical approach. As you know from accumulated experience, complete VATS approach can be used in simple lobectomy for lung cancer. However, we have applied a hybrid VATS approach to more technically demanding surgical procedures for treating lung cancer, such as bronchoplasty, angioplasty and atypical segmentectomy [9]. Segmentectomy allows optimal resection of small deep non-palpable lesions with suspected malignancy, which helps preserve lung function. Under these conditions, the hybrid VATS approach can provide safe surgical margins, although lobectomy even using a complete VATS approach must not be an option for any small undiagnosed tumour. The three-dimensional view provided by direct vision through hybrid VATS enables surgeons to understand the appropriate margins, thus minimizing the likelihood of missing diseased lung tissue or removing an excessive volume of healthy tissue. The advantages of treating lung cancer with VATS using only monitor visualization are arguable for the patient, although the surgeon seems to get a great sense of achievement. Whether or not direct vision is applied in VATS is in essence a peripheral matter. Thoracic surgeons need to balance the benefits and disadvantages of complete VATS, for example, to avoid lobectomy thoughtlessly performed for a tiny undiagnosed tumour. The most important aspects of cancer surgery are radicality and the preservation of functionality for the patients.

The key to successful high-quality procedures using the hybrid VATS approach is the upside-down backhand grip on long scissors for incisive dissection, and the long needle holder for bronchoplasty or angioplasty developed by Belsey (Frenchay Hospital; Bristol, UK) and Pearson (Toronto General Hospital; Toronto, ON, Canada) to facilitate deep manoeuvring. This skill was advanced before the introduction of VATS and we consider it suitable for manoeuvring through a small access thoracotomy in this heyday of VATS. In general, segmentectomy is technically more demanding than lobectomy because it requires a thorough three-dimensional knowledge of all relevant bronchoarterial relationships and possible anomalies of the arterial branches. Sharp dissection with scissors that can accurately and rapidly expose the segmental hilar structures is important for radical hybrid VATS segmentectomy.

We concluded that hybrid VATS segmentectomy is a safe and useful option for patients with small N0 NSCLC who can tolerate lobectomy. The accurate identification of the intersegmental plane and dissection along an adequate cutting line by electrocautery prevents local failure and maintains lung function that are crucial during radical segmentectomy even through the VATS approach. Minimally invasive strategies will be applied to ever more challenging segmentectomies such as radical atypical resection of segments and/or subsegments, and thus become a standard approach for treating lung cancer.

Conflict of interest: none declared.

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Prediction of pathologic node-negative clinical stage IA lung adenocarcinoma for optimal candidates undergoing sublobar resection

Yasuhiro Tsutani, MD, PhD,[a] Yoshihiro Miyata, MD, PhD,[a] Haruhiko Nakayama, MD, PhD,[b] Sakae Okumura, MD, PhD,[c] Shuji Adachi, MD, PhD,[d] Masahiro Yoshimura, MD, PhD,[e] and Morihito Okada, MD, PhD[a]

Objective: Patients with pathologic node-negative early lung cancer may be optimal candidates for sublobar resection. We aimed to identify predictors of pathologic lymph node involvement in clinical stage IA lung adenocarcinoma.

Methods: The data from a multicenter database of 502 patients with completely resected clinical stage IA lung adenocarcinoma were retrospectively analyzed to determine the relationship between the lymph node metastasis status and tumor size on high-resolution computed tomography (HRCT) or maximum standardized uptake value (SUVmax) on [18F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT). Revised SUVmax was used to correct interinstitutional discrepancies.

Results: In multivariate analyses, either a solid tumor size on HRCT ($P = .001$) or an SUVmax on FDG-PET/CT ($P = .049$) was an independent predictor of lymph node metastasis. The predictive criteria of pathologic node-negative early lung cancer were a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5. Patients who met the predictive criteria of pathologic node-negative disease had less pathologic invasiveness, such as lymphatic, vascular, or pleural invasion ($P < .001$), and better disease-free survival ($P < .0001$) than those who did not, and 86 (40.4%) of the 213 patients with T1b (2-3 cm) tumors met the predictive criteria.

Conclusions: Either a solid tumor size or an SUVmax was a significant independent predictor of nodal involvement in clinical stage IA lung adenocarcinoma. The pathologic node-negative status criteria of a solid tumor size of less than 0.8 cm on HRCT or an SUVmax of less than1.5 on FDG-PET/CT may be helpful for avoiding systematic lymphadenectomy for clinical stage IA lung adenocarcinoma, even in cases of T1b (2-3 cm) tumor. (J Thorac Cardiovasc Surg 2012;■:1-7)

Recent advances in radiography, such as high-resolution computed tomography (HRCT) and the widespread practice of low-dose helical computed tomography (CT) for screening of tumors, have resulted in an increase in the early detection of smaller non–small cell lung cancer (NSCLC), especially adenocarcinoma.[1-3] Several studies have reported that the survival is similar in patients with small peripheral NSCLC between those treated with segmentectomy and those treated with lobectomy.[1,4-8] In determining the indications for sublobar resection, prediction of the pathologic node-negative (pN0) status is important.[4-8] We[9] previously reported that solid tumor size on HRCT and maximum standardized uptake value (SUVmax) on [18F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) were useful for predicting pathologic invasiveness or prognosis in clinical stage IA lung adenocarcinoma. We hypothesized that solid tumor size on HRCT and SUVmax on FDG-PET/CT had a predictive value for lymph node metastasis. Therefore, we retrospectively investigated the preoperative predictive value of solid tumor size and SUVmax for pN0 status to select optimal candidates for sublobar resection in clinical stage IA lung adenocarcinoma. The primary end point of this study was lymph node involvement.

From the Department of Surgical Oncology,[a] Hiroshima University, Hiroshima; the Department of Thoracic Surgery,[b] Kanagawa Cancer Center, Yokohama; the Department of Thoracic Surgery,[c] Cancer Institute Hospital, Tokyo; and the Departments of Radiology[d] and Thoracic Surgery,[e] Hyogo Cancer Center, Akashi, Japan.
Disclosures: Authors have nothing to disclose with regard to commercial support.
Received for publication Feb 16, 2012; revisions received June 7, 2012; accepted for publication July 10, 2012.
Address for reprints: Morihito Okada, MD, PhD, Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, 1-2-3-Kasumi, Minami-ku, Hiroshima City, Hiroshima 734-0037, Japan (E-mail: morihito@hiroshima-u.ac.jp).
0022-5223/$36.00
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http://dx.doi.org/10.1016/j.jtcvs.2012.07.012

PATIENTS AND METHODS

Patients

We enrolled 502 patients with clinical T1 N0 M0 stage IA lung adenocarcinoma from 4 institutions in Japan (Hiroshima University, Kanagawa Cancer Center, Cancer Institute Hospital, and Hyogo Cancer Center) between August 1, 2005, and December 31, 2009, to evaluate the significance of FDG-PET/CT.[10] The data from all 502 patients from this multicenter database were retrospectively analyzed in the present study. HRCT and FDG-PET/CT followed by curative R0 resection were performed for all patients who were staged according to the TNM Classification of Malignant

Abbreviations and Acronyms

CT	= computed tomography
DFS	= disease-free survival
FDG	= [18F]-fluoro-2-deoxy-D-glucose
GGO	= ground-glass opacity
HRCT	= high-resolution computed tomography
NSCLC	= non–small cell lung cancer
PET	= positron emission tomography
SUVmax	= maximum standardized uptake value

Tumours, 7th edition.[11] Mediastinoscopy or endobronchial ultrasonography was not routinely performed because all patients received preoperative HRCT and FDG-PET/CT; HRCT revealed no swelling of mediastinal or hilar lymph nodes and FDG-PET showed no accumulation in those lymph nodes. Sublobar resection was allowed in cases of complete removal of the disease using a procedure for a peripheral T1a N0 M0 tumor. Wedge resection without lymph node assessment was allowed for a pure ground-glass opacity (GGO) tumor, which was regarded as a node-negative noninvasive tumor in a prospective study.[12] Segmentectomy with hilar and mediastinal lymph node dissection was allowed for a GGO-mixed tumor. If lymph node involvement was evident by intraoperative frozen section of any lymph node, the procedure was converted to standard lobectomy. All of the other patients underwent standard lobectomy. The inclusion criteria included preoperative staging determined by HRCT and FDG-PET/CT, curative surgery without neoadjuvant chemotherapy or radiotherapy, and a definitive histopathologic diagnosis of lung adenocarcinoma. Patients with incompletely resected tumors (R1 or R2) and those with multiple tumors or previous lung surgery were excluded from the database. This multicenter study was approved by the institutional review boards of the participating institutions, all of which waived the requirement for informed consent from individual patients for this retrospective review of the prospective database.

Table 1 summarizes the characteristics of the 502 patients enrolled in this study. The mean follow-up period after surgery was 19.8 ± 12.2 months, during which disease recurred in 29 (5.8%) patients. There were 9 (1.8%) local recurrences, including mediastinal lymph node metastasis, 3 (0.6%) local and distant recurrences, and 17 (3.4%) distant recurrences. The median whole tumor and solid tumor sizes on HRCT were 2.0 cm and 1.2 cm, respectively. The median SUVmax was 2.0. Lymphatic, vascular, and pleural invasion was evident in 76 (15.1%), 92 (18.3%), and 56 (11.2%) patients, respectively, and lymph nodes were involved in 38 (7.8%).

High-Resolution Computed Tomography

Sixteen-row multidetector CT was used to obtain chest images independent of subsequent FDG-PET/CT examinations. For high-resolution images of the tumors, the following parameters were used: 120 kVp, 200 mA, 1 to 2-mm section thickness, 512 × 512-pixel resolution, 0.5 to 1.0-second scanning time, a high-spatial reconstruction algorithm with a 20-cm field of view, 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 tumor size as the maximum dimension of the solid component of the lung windows, excluding GGO.[11] CT scans were reviewed and tumor sizes determined by radiologists from each institution for the purpose of this study.

FDG-PET/CT

Patients were instructed to fast for more than 4 hours before intravenous injection of 74 to 370 MBq FDG and then to relax for at least 1 hour before FDG-PET/CT scanning. Blood glucose levels were calculated before the tracer injection to confirm a level of less than150 mg/dL.[12] Patients with blood glucose levels of 150 mg/dL or more were excluded from PET/CT acquisition. For imaging, Discovery ST (GE Healthcare, Little Chalfont, United Kingdom), Aquiduo (Toshiba Medical Systems Corporation, Tochigi, Japan), or Biograph Sensation16 (Siemens Healthcare, Erlangen, Germany) integrated 3-dimensional PET/CT scanners were used. Low-dose nonenhanced 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 by following a standard protocol. Immediately after CT, PET covered the identical axial field of view for 2 to 4 minutes per table position, depending on the condition of the patient and the scanner performance. An iterative algorithm with CT-derived attenuation correction was used to reconstruct all PET images with a 50-cm field of view. An anthropomorphic body phantom (NEMA NU2-2001; Data Spectrum Corp, Hillsborough, NC) was used to minimize variations in SUVs among the institutions. A calibration factor was analyzed by dividing the actual SUV by the gauged mean SUV in the phantom background to decrease interinstitutional SUV inconsistencies; the final SUV used here is referred to as the revised SUVmax.[13,14] The adjustment of interinstitutional variations 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 of each institute relative to the SUVmax of the control institute. The original SUVmax values were determined by radiologists from each institution for the purpose of this study.

Follow-up Evaluation

All patients who underwent lung resection were followed up from the day of surgery. Postoperative follow-up procedures, including a physical examination and chest radiograph every 3 months and chest and abdominal CT examinations every 6 months, were performed for the first 2 years. Afterward, a physical examination and chest radiograph were performed every 6 months, and a chest CT examination was performed every year.

Statistical Analysis

Data are presented as numbers (percents) or the median unless otherwise stated. Multiple logistic regression analyses were performed to determine the independent continuous variables related to whole tumor size, solid tumor size, SUVmax, and carcinoembryonic antigen for prediction of pathologic lymph node metastasis. In addition, receiver operating characteristic curves of solid tumor size and SUVmax were used for determining the criteria of pN0. The χ^2 test for categorical variables was used to compare frequencies and Fisher's exact test was applied to small samples. 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 Kaplan-Meier method was used to analyze the duration of DFS, and the log–rank test was used to assess differences in DFS. SPSS software (version 10.5; SPSS Inc, Chicago, Ill) was used to statistically analyze the data.

RESULTS

Possible predictors of lymph node metastasis were investigated (Table 2). Multivariate analysis showed that solid tumor size or SUVmax, but not whole tumor size and carcinoembryonic antigen, were independent predictors of lymph node metastasis.

Figure 1 shows the receiver operating characteristic area under the curve values for solid tumor size and SUVmax used in determining the criteria of pN0. When using solid tumor size and SUVmax for predicting pN0, patients with a solid tumor size of less than 0.8 cm or an SUVmax of

TABLE 1. Patient characteristics

Variable	n = 502
Age (y, range)	66 (31-86)
Gender	
Male	223 (44.4%)
Female	279 (55.6%)
Whole tumor size (cm, range)	2.0 (0.6-3.0)
Solid tumor size (cm, range)	1.2 (0-3.0)
SUVmax (range)	2.0 (0-27.7)
CEA (ng/mL, range)	2.4 (0-113.8)
Procedure	
Lobar resection	320 (63.7%)
Sublobar resection (wedge + segmentectomy)	182 (36.3%)
Lymphatic invasion	
Negative	426 (84.9%)
Positive	76 (15.1%)
Vascular invasion	
Negative	410 (81.7%)
Positive	92 (18.3%)
Pleural invasion	
Negative	446 (88.8%)
Positive	56 (11.2%)
Lymph node metastasis	
Negative	464 (92.4%)
Positive	38 (7.6%)

SUVmax, Maximum standardized uptake value; *CEA,* carcinoembryonic antigen.

less than 1.5 were observed to have no lymph node metastasis. We defined the predictive criteria of pN0 as a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5.

Table 3 shows the number of patients who met the criteria of pN0 as indicated by solid tumor size, SUVmax, and a combination of the two. Using this combination, the number of patients expected to have pN0 was 169 (58.5%) of 289 for clinical T1a ($\leq$2 cm) and 86 (40.4%) of 213 for clinical T1b (2-3 cm) tumors. Figure 2 shows examples of tumors larger than 2 cm that met the predictive criteria of pN0.

A significant difference in DFS for all T1 tumors was identified between patients with a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5 (n = 255; 3-year DFS rate, 100%) and those with a solid tumor size of 0.8 cm or more and an SUVmax of 1.5 or more (n = 247; 3-year DFS rate, 81.8%; $P < .001$) (Figure 3, *A*). Even when cases were categorized into cT1a and cT1b, significant differences in DFS were observed between patients with a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5 and the remainder (Figure 3, *B* and *C*). Moreover, a significant difference in

TABLE 2. Multivariate analysis of possible predictors of lymph node metastasis

Valuables	OR (95% CI)	*P*
Model 1		
Whole tumor size (cm)	1.42 (0.76-2.66)	.28
SUVmax	1.09 (1.00-1.29)	.049
CEA (ng/mL)	1.04 (0.99-1.08)	.097
Model 2		
Solid tumor size (cm)	2.44 (1.49-4.00)	<.001
SUVmax	1.04 (0.93-1.16)	.47
CEA (ng/mL)	1.03 (0.99-1.07)	.14

OR, Odds ratio; *CI,* confidence interval; *SUVmax,* maximum standardized uptake value; *CEA,* carcinoembryonic antigen.

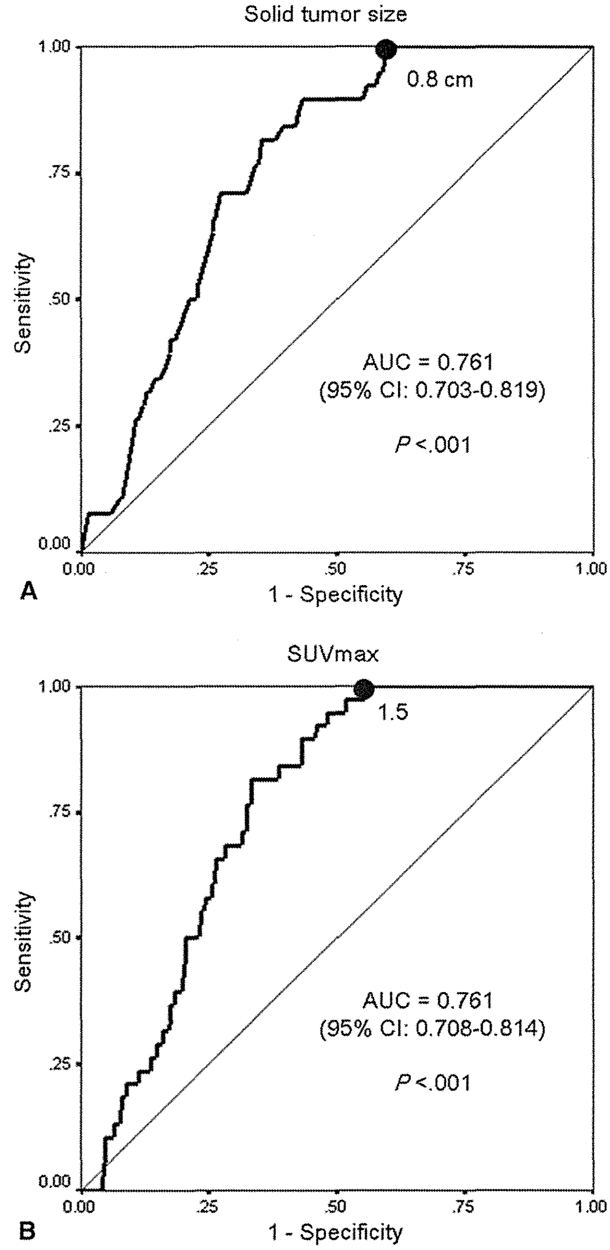

FIGURE 1. Receiver operating characteristic area under the curve *(AUC)* for detecting lymph node metastasis for solid tumor size (A) and maximum standardized uptake value *(SUVmax)* (B). Solid tumor size: AUC, 0.761 (95% confidence interval *[CI],* 0.703-0.819; $P < .001$). SUVmax: AUC, 0.761 (95% CI, 0.708-0.814; $P < .001$).

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TABLE 3. Number of patients without nodal metastasis according to solid tumor size, SUVmax, and a combination of the two

	cT1 (n = 502)	cT1a (n = 289)	cT1b (n = 213)
Solid tumor size < 0.8 cm	187 (37.3%)	131 (45.3%)	56 (26.3%)
SUVmax < 1.5	206 (41.0%)	138 (47.8%)	68 (31.9%)
Solid tumor size < 0.8 cm or SUVmax < 1.5	255 (50.8%)	169 (58.5%)	86 (40.4%)

SUVmax, Maximum standardized uptake value.

DFS was observed between patients with T1a tumor with a solid tumor size of 0.8 cm or more and an SUVmax of 1.5 or more and those with T1b tumor with a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5 ($P = .0015$; Figure 3, *D*).

Significant differences in pathologic invasiveness (lymphatic, vascular, or pleural invasion) were identified between patients with a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5 and those with a solid tumor size of 0.8 cm or more and an SUVmax of 1.5 or more (Table 4); a few patients who met the predictive criteria of pN0 had pathologic invasiveness (9/255, 3.5%). Even in the cases categorized as cT1a or cT1b, significant differences in pathologic invasiveness were observed between the patients with a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5 and those with a solid tumor size of 0.8 cm or more and an SUVmax of 1.5 or more (Table 4).

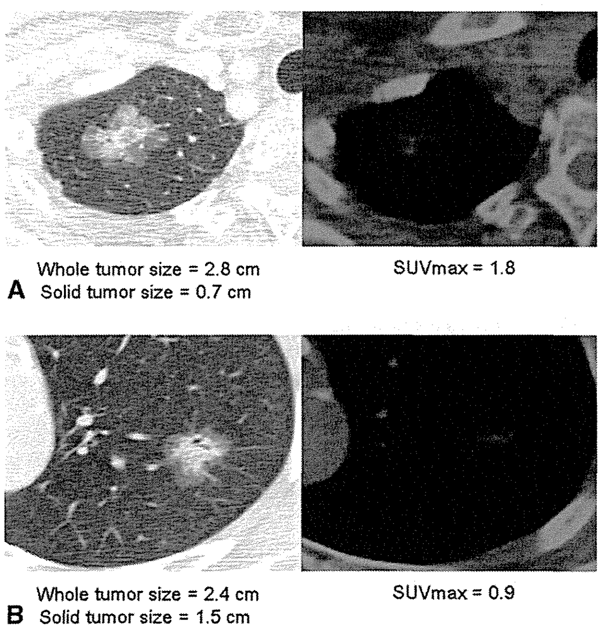

FIGURE 2. Examples of tumors larger than 2 cm that met the predictive criteria of pathologic node negative. A, Whole tumor size, 2.8 cm; solid tumor size, 0.7 cm; maximum standardized uptake value *(SUVmax),* 1.8. This tumor can be treated with sublobar resection, such as right apical segmentectomy. B, Whole tumor size, 2.6 cm; solid tumor size, 1.7 cm; SUVmax, 0.9. This tumor can be treated with sublobar resection, such as left apicoposterior segmentectomy.

DISCUSSION

In 1995, the Lung Cancer Study Group conducted a prospective randomized controlled trial comparing limited resection with lobectomy for clinical T1 N0 M0 NSCLC and concluded that the former resulted in inferior local recurrence and survival.[15] On the other hand, several reports have described how survival was similar between patients treated with segmentectomy and those treated with lobectomy.[1,4-8] Determining the indications for sublobar resection requires that intraoperative frozen sections be examined for all hilar and lobe-specific mediastinal lymph nodes to confirm the intraoperative N staging as N0.[1,4-7] However, intraoperative examination of many lymph nodes is difficult for thoracic surgeons and pathologists in the clinical setting. If pN0 can be predicted from preoperative information, sublobar resection without strict intraoperative lymph node assessment can be performed in patients with clinical stage IA NSCLC.

The present study demonstrated the value of using solid tumor size with HRCT and SUVmax on PET/CT to predict the status of nodal involvement in clinical stage IA lung adenocarcinoma. We[9] reported the usefulness of solid tumor size defined as the maximum dimension of the solid component, excluding GGO, on HRCT compared with that of whole tumor size for predicting pathologic invasiveness of tumors or prognosis in clinical stage IA lung adenocarcinoma. In that study, solid tumor size showed a higher predictive value for pathologic invasiveness than did whole tumor size, and it was an independent prognostic factor for DFS. We[9,10,14,16,17] also reported the usefulness of SUVmax to predict the malignancy grade of tumors with regard to pathologic invasiveness in lung adenocarcinoma. Solid tumor size and SUVmax were useful in predicting both pathologic nodal status and pathologic tumor invasiveness in the current study. Moreover, we found that patients with a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5 had pN0. There were significant differences in DFS between patients who met the predictive criteria of pN0 and those who did not. Furthermore, the incidence of pathologic invasiveness in patients who met the predictive criteria of pN0 was very low. These findings indicate that the predictive criteria of pN0 were reasonable for choosing a treatment strategy in clinical stage IA lung adenocarcinoma.

Interestingly, 40.4% of tumors larger than 2 cm and 58.5% of those 2 cm or smaller met the predictive criteria of pN0. Most previous studies that showed favorable results for segmentectomy set its indication at T1 N0 M0 NSCLC of 2 cm or less.[1,4-6] The ongoing clinical trials comparing surgical results between lobectomy and sublobar resection

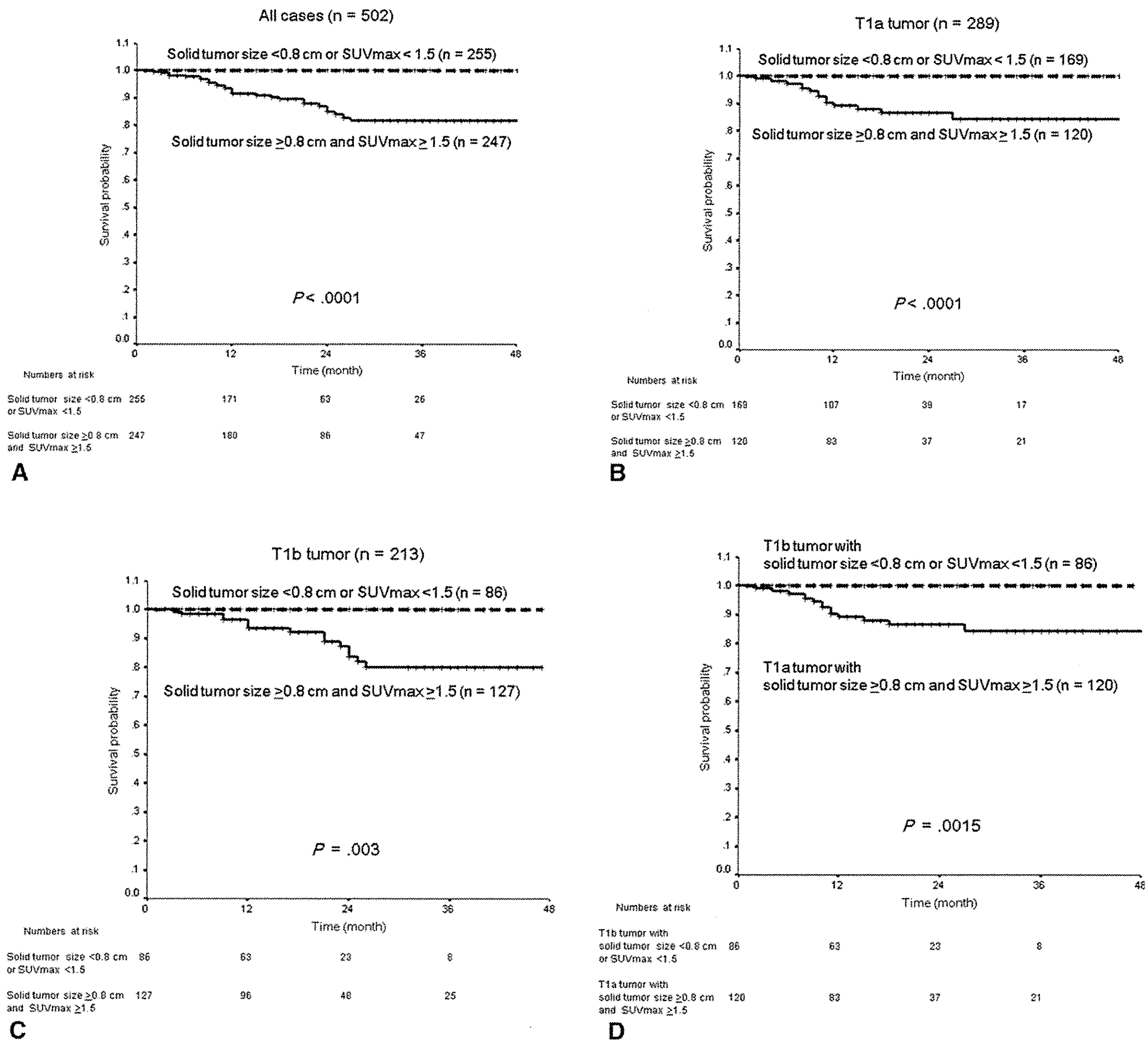

FIGURE 3. Disease-free survival *(DFS)* curves of patients according to the predictive criteria of pathologic node negative using solid tumor size and maximum standardized uptake value *(SUVmax)*. A, Three-year DFS rates of 100% and 81.8% for patients with a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5 and those with a solid tumor size of 0.8 cm or more and an SUVmax of 1.5, respectively ($P < .0001$) in all T1 tumors. B, Three-year DFS rate of 100% and 84.2% for patients with a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5 and those with a solid tumor size of 0.8 cm or more and an SUVmax of 1.5 or more, respectively ($P < .0001$) in T1a ($\leq$2.0 cm) tumors. C, Three-year DFS rate of 100% and 80.1% for patients with a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5 and those with a solid tumor size of 0.8 cm or more and an SUVmax of 1.5 or more, respectively ($P = .003$) in T1b (2-3 cm) tumors. D, Three-year DFS rate of 100% and 84.2% for patients with a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5 in T1b tumors and those with a solid tumor size of 0.8 cm or more and an SUVmax of 1.5 or more in T1a tumors, respectively ($P = .0015$).

conducted by the Cancer and Leukemia Group B (CALGB 140503) and by the Japan Clinical Oncology Group/West Japan Oncology Group (JCOG0802/WJOG4607L) also set a T1 N0 M0 NSCLC criterion of 2 cm or smaller for the study subjects.[18] However, approximately 40% of patients with T1 N0 M0 lung adenocarcinoma of more than 2 cm might be candidates for sublobar resection according to the present study because such patients can be predicted as pN0 preoperatively. In fact, no recurrence was seen in patients with T1b tumor who met the predictive criteria, regardless of the surgical procedure. Furthermore, the frequency of pathologic invasiveness of T1b tumors that met the criteria of pN0 was very low. However, adequate surgical margins are required when performing sublobar resection in such patients. To achieve complete resection with adequate surgical margins, we recommend segmentectomy, not wedge resection, for T1b tumors that meet the criteria of pN0. To provide an adequate surgical margin for T1b

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TABLE 4. Comparison of pathologic invasiveness of tumors and lymph node involvement between patients who met the criteria of pathologic node negative and those who did not

All tumors (n = 502)	Solid tumor size < 0.8 cm or SUVmax < 1.5 (n = 255)	Solid tumor size ≥ 0.8 cm and SUVmax ≥ 1.5 (n = 247)	*P*
LY	4 (1.6%)	73 (29.6%)	<.001
V	4 (1.6%)	89 (36.0%)	<.001
PL	3 (1.2%)	55 (22.3%)	<.001
LY or V or PL	9 (3.5%)	131 (53.0%)	<.001
N	0 (0%)	38 (15.4%)	<.001
T1a tumors (n = 289)	**Solid tumor size < 0.8 cm or SUVmax < 1.5 (n = 169)**	**Solid tumor size ≥ 0.8 cm and SUVmax ≥ 1.5 (n = 120)**	***P***
LY	3 (1.8%)	34 (28.3%)	<.001
V	4 (2.4%)	33 (27.5%)	<.001
PL	2 (1.2%)	24 (20.0%)	<.001
LY or V or PL	7 (4.1%)	59 (49.2%)	<.001
N	0 (0%)	16 (13.3%)	<.001
T1b tumors (n = 213)	**Solid tumor size < 0.8 cm or SUVmax < 1.5 (n = 86)**	**Solid tumor size ≥ 0.8 cm and SUVmax ≥ 1.5 (n = 127)**	***P***
LY	1 (1.2%)	39 (30.7%)	<.001
V	0 (0%)	56 (44.1%)	<.001
PL	1 (1.2%)	31 (24.4%)	<.001
LY or V or PL	2 (2.3%)	72 (56.7%)	<.001
N	0 (0%)	22 (17.3%)	<.001

SUVmax, Maximum standardized uptake value; *LY,* lymphatic invasion; *V,* vascular invasion; *PL,* pleural invasion.

tumors by wedge resection is difficult. Local recurrence must be avoided. When performing lobar resection for tumors that meet the predictive criteria of pN0, systematic lymph node dissection such as mediastinal lymph node dissection is not always needed. On the other hand, when performing sublobar resection in patients with tumors of 2 cm or less, wedge resection and segmentectomy with ample surgical margins can be permitted. The extent of resection can be determined according to the tumor size and location. Lobe-specific lymph node dissection or sampling can be allowed for tumors that meet the criteria of pN0. Systematic lymph node dissection is not always needed for these tumors. The use of solid tumor size and SUVmax allows many more patients to be identified, who may benefit from the maintenance of lung function that results from selecting sublobar resection rather than can be identified simply on the basis of peripheral small nodules of 2 cm or less. The proportion of patients with lung adenocarcinoma of 2 cm or less who did not meet the predictive criteria of pN0 was approximately 40%. There are some risks of lymph node metastasis in small lung adenocarcinoma that do not meet the predictive criteria of pN0. When sublobar resection is performed in such cases, intraoperative lymph node assessment, such as examination of frozen sections, is mandatory, and wedge resection cannot be recommended because such a procedure does not allow an approach to the hilar lymph nodes for assessment. If lymph node metastasis is intraoperatively shown, sublobar resection should be converted to standard lobectomy with systematic lymph node dissection.

One of the limitations of this multicenter study using PET is the wide variation in SUV among institutions. Many factors such as preparation procedures, scan acquisition, image reconstruction, and data analysis can affect SUV. In this study, we used an anthropomorphic body phantom to minimize interinstitutional variability in SUV. When performing subgroup analyses of DFS from each institution, DFS of patients with a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5 was significantly better than that of patients with a solid tumor size of 0.8 cm or more and an SUVmax of 1.5 or more (data not shown). Moreover, when using the original SUVmax values, multivariate logistic regression analysis showed that SUVmax was an independent predictor of lymph node metastasis, and DFS of patients with a solid tumor size of less than 0.8 cm or an SUVmax of less than 1.5 was significantly better than that of those with a solid tumor size of 0.8 cm or more and an SUVmax of 1.5 or more (data not shown). These findings are important to other institutions that may use our criteria of pN0.

This study had several limitations. Because the follow-up period was short, long-term follow-up is needed to confirm the results of DFS. In addition, it is sometimes difficult to measure solid tumor size, especially with a large GGO component. Because this was a retrospective study, a validation cohort study is required to confirm our pN0 predictive criteria of solid tumor size on HRCT and SUVmax on FDG-PET/CT.

CONCLUSIONS

Preoperative solid tumor size on HRCT and SUVmax on FDG-PET/CT are useful for prediction of pN0 in clinical stage IA lung adenocarcinoma. The pN0 predictive criteria of solid tumor size less than 0.8 cm or SUVmax less than 1.5 may be helpful for avoiding systematic lymphadenectomy in patients with clinical stage IA lung adenocarcinoma.

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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

Yasuhiro Tsutani, MD, PhD,[a] Yoshihiro Miyata, MD, PhD,[a] Takeharu Yamanaka, PhD,[b] Haruhiko Nakayama, MD, PhD,[c] Sakae Okumura, MD, PhD,[d] Shuji Adachi, MD, PhD,[e] Masahiro Yoshimura, MD, PhD,[f] and Morihito Okada, MD, PhD[a]

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 2012;■:1-7)

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 (FDG-PET/CT) followed by curative R0 resection were performed in all

From the Department of Surgical Oncology,[a] Hiroshima University, Hiroshima, Japan; Research Center for Innovative Oncology,[b] National Cancer Center Hospital East, Kashiwa, Japan; Department of Thoracic Surgery,[c] Kanagawa Cancer Center, Yokohama, Japan; Department of Thoracic Surgery,[d] Cancer Institute Hospital, Tokyo, Japan; and Departments of Radiology[e] and Thoracic Surgery,[f] Hyogo Cancer Center, Akashi, Japan.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Jan 23, 2012; revisions received Sept 14, 2012; accepted for publication Nov 6, 2012.

Address for reprints: Morihito Okada, MD, PhD, Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, 1-2-3-Kasumi, Minami-ku, Hiroshima City, Hiroshima 734-0037, Japan (E-mail: morihito@hiroshima-u.ac.jp).

0022-5223/$36.00

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http://dx.doi.org/10.1016/j.jtcvs.2012.11.019

Abbreviations and Acronyms

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

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 categoric 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.

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.

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

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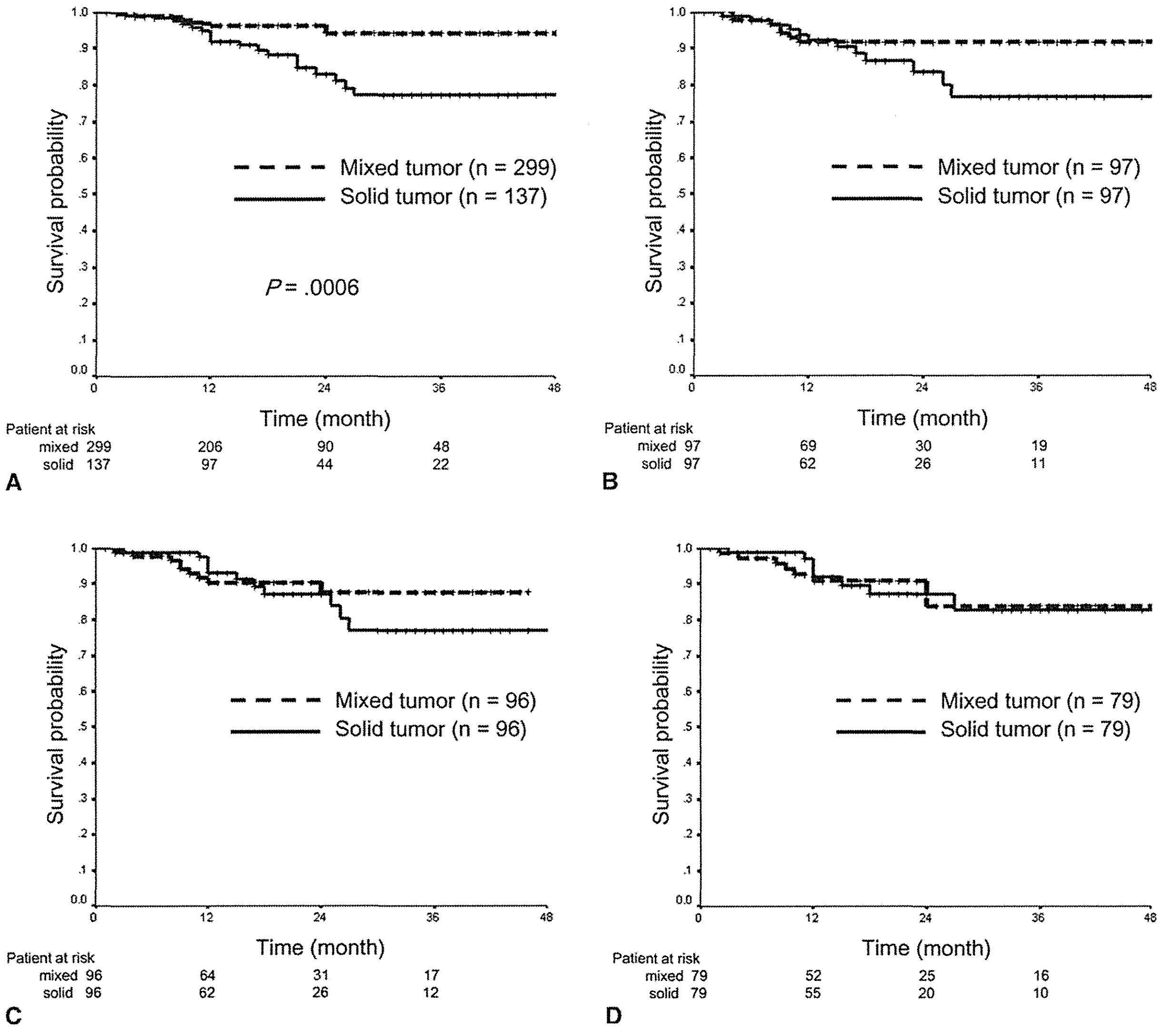

FIGURE 1. DFS curves of patients according to tumor type on HRCT. A, In all cohort patients, 2-year DFS of 94.2% (mean DFS of 47 months; 95% confidence interval [CI], 46-48 months) and 83.1% (mean DFS of 42 months; 95% CI, 39-45 months) were identified for mixed and solid tumors, respectively ($P = .0006$). 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

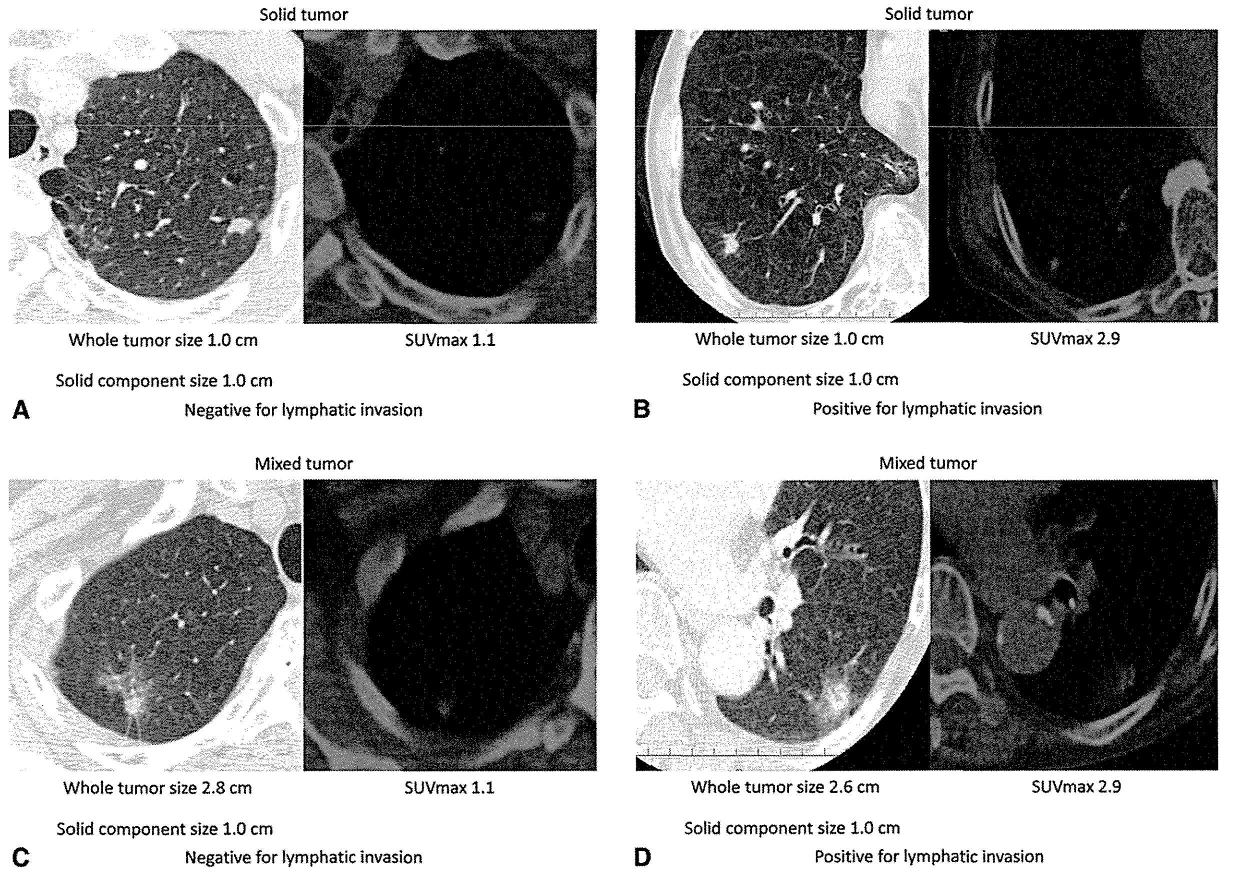

FIGURE 2. Examples of solid and mixed tumors on HRCT. A, Whole tumor size = solid component size: 1.0 cm, SUVmax: 1.1. This solid tumor was negative for lymphatic invasion. B, Whole tumor size = solid component size: 1.0 cm, SUVmax: 2.9. This solid tumor was positive for lymphatic invasion. C, Whole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