Table 3
Postrecurrence survival analyses

Factors	Univariate analysis			Multivariate analysis		
	Number	Median PRS (months)	*p*-value	HR	95% CI	*p*-value
Age at recurrence (median: 66)						
< 66	76	18.9				
≥ 66	94	15.8	0.242			
Gender						
Male	118	15.5		1		
Female	52	25.6	< 0.001	0.487	0.297-0.801	0.005
Smoking status						
Never smoker	59	25.0				
Ever smoker	111	14.1	0.006			
T category						
T1	87	15.8				
T2	83	19.6	0.476			
Tumor size						
0-30 mm	132	16.9				
> 30 mm	38	20.9	0.632			
Pathological vascular invasion						
Absent	53	15.8				
Present	113	17.0	0.088			
Pleural invasion						
Absent	115	15.8				
Present	53	18.8	0.393			
Histology						
Adenocarcinoma	124	20.9				
Nonadenocarcinoma	46	12.4	< 0.001			
Differentiation						
Well or moderate	97	20.8		1		
Poor	65	14.1	0.002	1.810	1.194-2.743	0.005

Type of surgery						
Single lobectomy	162	17.3	0.152			
Bilobectomy or pneumonectomy	8	19.5				
Adjuvant therapy						
Without	134	15.9	0.547			
With	36	21.0				
Postrecurrence therapy						
Without	41	7.2		1		
With	118	21.4	0.021	0.542	0.344-0.853	0.008
Recurrence free interval						
≤ 24 months	82	16.2				
> 24months	88	18.4	0.021			
Type of recurrence						
Distant	127	15.8				
Local only	43	18.8	0.087			
Number of recurrent sites						
Single	132	16.8				
Multiple	38	18.6	0.305			

PRS: postrecurrence survival, HR: hazard ratio, CI: confidence interval

Table 4
Postrecurrence survival analyses in 118 patients who underwent postrecurrence therapy

Factors	Univariate analysis			Multivariate analysis		
	Number	Median PRS (months)	*p*-value	HR	95% CI	*p*-value
Age at recurrence						
< 66	63	22.4				
≥ 66	55	19.5	0.151			
Gender						
Male	79	20.0				
Female	39	27.2	0.002			
Smoking status						
Never smoker	43	27.6				
Ever smoker	75	17.6	0.035			
Histology						
Adenocarcinoma	84	24.4		1		
Nonadenocarcinoma	34	13.9	< 0.001	2.136	1.273-3.585	0.004
Differentiation						
Well or moderate	66	23.1				
Poor	46	18.8	0.019			
Lung metastasis						
Absent	68	19.8				
Present	49	21.4	0.053			
Brain metastasis						
Absent	96	19.6				
Present	21	22.6	0.584			
Bone metastasis						
Absent	100	21.9		1		
Present	17	15.8	0.001	3.288	1.783-6.062	< 0.001
Liver metastasis						
Absent	110	21.9		1		
Present	7	10.5	0.001	4.518	1.793-11.379	0.001
Chemotherapy						
Without	15	9.6		1		

With	103	22.7	0.009	0.478	0.236-0.975	0.040
Surgical resection						
Without	110	20.8				
With	8	33.7	0.209			
EGFR-TKI therapy						
Without	91	17.0		1		
With	27	41.4	0.002	0.460	0.245-0.862	0.015
Second line therapy						
Without	52	14.0				
With	66	27.2	0.004			
Recurrence free interval						
≤ 24 months	59	17.0				
> 24 months	59	22.4	0.394			
Type of recurrence						
Distant	85	20.8				
Local only	33	21.8	0.086			
Number of recurrent sites						
Single	89	21.0				
Multiple	29	20.8	0.049			

PRS: postrecurrence survival, HR: hazard ratio, CI: confidence interval, CT: chemotherapy, EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor

Table 5
Postrecurrence survival of patients with stage I non-small cell lung cancer in previous series

Series	No. of patients	Incidence of recurrence (%)	PRS	Type of recurrence	Independent favorable factors of PRS
Martini (1995) [6]	598	159 (26.6)	NR	L/ D	NR
Al-Kattan (1997) [1]	123	36 (29.3)	NR	L/ D	NR
Nakagawa (2008) [4]	397	87 (21.9)	67.7% (1y) 34.4% (3y)	L/ D	Symptom at recurrence (-) Cervico-mediastinum meta. (-) Liver meta. (-) PRT (Surgery/ non-surgery)
Hung (2009) [2]	933	74 (7.9)	48.7% (1y) 17.6% (2y)	L	PRT (Surgery, CT and/or RT)
Hung (2010) [3]	933	166 (17.8)	30.2% (1y) 15.1% (2y)	D	Disease-free interval > 16 mo PRT
Our series (2012)	919	170 (18.5)	73.5% (1y) 51.4% (2y)	L/ D	PRT Female

PRS: postrecurrence survival, L: Local recurrence, D: Distant recurrence, NR: not reported,
PRT: postrecurrence therapy, CT: chemotherapy, RT: radiotherapy

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Prognostic value of preoperative FDG-PET in stage IA lung adenocarcinoma

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ABSTRACT

Background: Maximum standardized uptake value (SUVmax) of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been found to have prognostic value. We previously reported the correlation between SUVmax and pathological invasive area, and determined an SUVmax cut-off value of 2.15 for predicting the recurrence potential of an invasive area of diameter 5 mm. Here, we evaluate the validity of FDG-PET for prediction of recurrence in pathological stage IA lung adenocarcinoma.
Methods: From February 2006 to May 2008, 100 patients with pathological stage IA lung adenocarcinoma underwent complete resection at our hospital. Tumors were classified as air-type or solid-type based on thin-section computed tomography (TS-CT) findings and the influence of TS-CT classification, SUVmax, and clinicopathologic features were evaluated in terms of the incidence of recurrence.
Results: Unlike air-type adenocarcinomas, recurrent disease was detected in 8 of 62 solid-type adenocarcinomas. SUVmax and diameter of invasive area were significantly correlated with recurrence and a shorter time to recurrence. All 8 recurrent cases had pathological invasive area >5 mm. All except one case of recurrence were solid-type adenocarcinomas with SUVmax ≥ 2.15. Three-year disease-free survival rates were 100% in air-type adenocarcinomas, 97.1% in solid-type adenocarcinomas with SUVmax < 2.15, and 74.1% in solid-type adenocarcinoma with SUVmax ≥ 2.15.
Conclusion: Combined evaluation of TS-CT classification and SUVmax had significant value in predicting recurrence in stage IA lung adenocarcinoma, reflecting the aggressiveness of primary lung adenocarcinoma. Prediction of tumor aggressiveness could contribute to decision-making regarding the choice of surgical procedure and treatment after surgery.

1. Introduction

The recent increasing use of thin-section computed tomography scanning (TS-CT) has facilitated the detection of small-sized peripheral lung adenocarcinoma. Surgical resection offers a significant chance of cure for patients with early stage non-small-cell lung cancer (NSCLC); however, even in cases of stage IA adenocarcinoma, some patients experience recurrence within 5 years after surgery.

Many investigators have reported the relationship between TS-CT findings and aggressiveness and survival in patients with lung adenocarcinoma [1]. On TS-CT images, solid areas of a nodule may reflect collapsed alveoli, foci of fibrosis, or tumors with an invasive growth pattern, whereas areas of ground-glass opacity (GGO) represent components of bronchioloalveolar carcinoma (BAC) [1–4]. The authors focused on solid areas seen on TS-CT and reported that small pulmonary adenocarcinomas could be classified according to attenuation on TS-CT images as either 'air-containing-type' (air-type) or 'solid-density-type' (solid-type) [2,4]. No microscopic evidence of metastasis has been revealed in air-type adenocarcinomas, nor any relapses or deaths after resection. In contrast, patients with solid-type adenocarcinomas demonstrated a poor prognosis. Unlike air-type tumors, some solid-type tumors have pathological invasive areas; however, it is difficult to discriminate these areas from the solid component based on the TS-CT findings. The size of the invasive area is related to tumor aggressiveness [1]. Invasive areas of diameter ≤5 mm are reported to have a good prognosis; compared with true BAC type, a small component of invasive tumor does not adversely affect prognosis [1].

Several recent studies have demonstrated the prognostic value of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) for primary lung cancer [5–9]. We previously reported a

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significant correlation between SUVmax (maximum standardized uptake value) and the pathological invasive area of primary lung adenocarcinoma, and determined an SUVmax cut-off value of 2.15 for predicting recurrence potential for an invasive area of diameter 5 mm [10]. Based on this cut-off value, sensitivity was 88.3% and specificity was 84.6% [10]. On the basis of these findings, we evaluated the validity of cut-off SUVmax on FDG-PET to predict recurrence in pathological stage IA lung adenocarcinoma.

2. Materials and methods

2.1. Patients

We retrospectively reviewed the TS-CT and PET reports of 100 patients (39 male, 61 female) who had undergone complete surgical resection of peripheral adenocarcinomas with pathologic T1N0M0 (stage IA) at Kanagawa Cancer Center Hospital, Japan, from March 2006 to May 2008. Of these patients, 40 underwent segmentectomy or wedge resection. Preoperative TS-CT and whole-body FDG-PET were performed on all patients for staging and evaluation of resectability. None of the patients received neo-adjuvant chemotherapy or radiation therapy.

2.2. TS-CT evaluation

All 100 patients underwent TS-CT scanning within 4 weeks prior to surgery. TS-CT images were acquired using an Aquillion CT scanner (Toshiba Medical Systems, Tokyo, Japan). TS-CT images targeted to the tumors were obtained serially at 120 kVp and 200 mAs, with 1–2 mm section thickness, pitch of 1, 1–2 mm section spacing, 512 × 512 pixel resolution, and 1 s scanning time, using a high-spatial-reconstruction algorithm with a 20-cm field of view. All scans were imaged using mediastinal window settings (level, 40 Hounsfield units (HU); width, 400 HU) and lung window settings (level, −600 HU; width, 1600 HU). The TS-CT findings were evaluated and the maximum diameters of the tumor on mediastinal and lung window setting images were measured. The ratio of the maximum diameter of the tumor on mediastinal windows to that on lung windows was calculated. Tumors were defined as air-type for ratio values ≤50% or as solid-type for ratio values > 50%.

2.3. FDG-PET/CT evaluation

All PET/CT studies were performed within 4 week prior to surgery using a lutetium oxyorthosilicate-based whole-body PET/CT scanner (Biograph 16 HI-REZ; Siemens). ^{18}F-FDG (FDG scan Injectable; Nihon Medi-physics Co. Ltd.) was purchased via a delivery system. All patients fasted for at least 6 h before intravenous administration of 130–371 (mean ± SD, 251.4 ± 63.7) MBq ^{18}F-FDG. Prior to tracer administration, the blood sugar level was checked. All measured values were less than 140 mg/dl. Whole-body scanning was performed as an additional scan, from the top of the skull to the middle of the thigh, 60 min after administration of ^{18}F-FDG, with 3 min per bed position. CT images were used for anatomic landmarking. All PET images were reconstructed using iterative algorithms with CT-based attenuation correction. The data were reconstructed with a 128 × 128 matrix and 2-mm slice thickness. SUVmax was evaluated for the maximum value within a region of interest (ROI) drawn around the pulmonary lesion. Tumors were classified as having a high or low SUVmax using an SUVmax cut-off point of 2.15.

2.4. Pathological evaluation

Hematoxylin and eosin, and elastica van Gieson staining were performed on all sections to evaluate the diameter of invasive area, lymphatic and vascular invasion, and pleural involvement. Immunohistochemical evaluations were performed using the avidin–biotin–peroxidase complex method with 3-μm-thick sections of formalin-fixed, paraffin-embedded specimens. A monoclonal antibody against the Ki-67 antigen (MIB-1; MBL, Nagoya, Japan; 1:100 dilution) was used to assess the proportion of proliferating tumor cells. The Ki-67 labeling index was defined as the ratio of MIB-1-stained tumor cells to all tumor cells counted, multiplied by 100. To evaluate the Ki-67 labeling index, stained tumor cells were counted in at least three high-power fields that showed the highest positivity for each section.

Table 1
Patient and tumor characteristics[a].

CT finding	Air-type (n = 38)	Solid-type (n = 62)	p-Value
Median age (range) (yr)	67(44–77)	68(40–83)	.112
Gender (male/female)	14/24	25/37	.729
SUVmax	0.97 ± 0.95	3.28 ± 3.12	<.001
Low (<2.15)	35(92.1)	35(56.5)	<.001
High (≥2.15)	3(7.9)	27(43.5)	
Tumor size (mm)	18.6 ± 5.4	20.5 ± 5.7	.602
0–20 mm	25(65.8)	29(46.8)	.217
21–30 mm	13(34.2)	33(53.2)	
Type of surgical procedure			
Lobectomy	9(23.7)	51(82.3)	< .001
Sublobar resection	29(76.3)	11(17.7)	
Histology			
BAC	24(63.2)	13(21.0)	< .001
Mucinous BAC	0(0)	3(4.8)	
Non-BAC	14(36.8)	46(74.2)	
Lymphatic or vascular invasion			
Negative	38(100)	46(74.2)	< .001
Positive	0(0)	16(25.8)	
Invasive area size (mm)			
≤5	–	36(58.1)	
>5	–	26(41.9)	
Ki-67 index			
<25	–	50(80.6)	
≥25	–	12(19.4)	

[a] Data are presented as median (range) or number (%) of patients. SUVmax = maximum standard uptake value; BAC = bronchioloalveolar carcinoma.

2.5. Statistical analysis

Statistical analysis was performed using SPSS software (Dr. SPSS II. for Windows, Tokyo, Japan, released 2001). Disease-free survival was calculated and drawn using the Kaplan–Meier method, and groups were compared using the log-rank statistic. An exact χ^2 test was used to analyze the relationship between risk of recurrence and histopathological findings, SUVmax, tumor size, and type of surgery. Differences were considered statistically significant when $p < 0.05$.

3. Results

3.1. Patient characteristics

The characteristics of patients and tumors are listed in Table 1. Based on the TS-CT findings, there were 38 patients with air-type adenocarcinomas and 62 patients with solid-type adenocarcinomas. The majority of air-type adenocarcinomas (92.1%) showed low SUVmax (<2.15); for solid-type adenocarcinomas, 35 cases (56.5%) showed low SUVmax and the remaining 27 cases (43.5%) showed high SUVmax (≥2.15).

Of the air-type adenocarcinomas, 24 (63.2%) were classified as BAC without stromal destruction and the others were classified as mixed-type adenocarcinoma. In contrast, of the solid-type adeno-

Table 2
Correlation of SUVmax and histologic findings in solid-type adenocarcinomas[a].

	Low SUVmax (<2.15) (n=35)	High SUVmax (≥2.15) (n=27)	p-Value
Histology			
BAC	12(34.4)	1(3.7)	
Adenocarcinoma with ≤ 5 mm invasive area	16(45.7)	4(14.8)	
Adenocarcinoma with > 5 mm invasive area	4(11.4)	22(81.5)	
mucinousBAC	3(8.6)	0(0)	
Lymphatic or vascular invasion			
Negative	33(94.3)	13(48.1)	< .001
Positive	2(5.7)	14(51.9)	
Ki-67 index			
<25	34(97.1)	16(59.2)	< .001
≥25	1(2.9)	11(40.8)	

[a] Data are presented as number (%) of patients.

carcinomas, 46 (74.2%) were classified as non-BAC. All 3 cases of mucinous-BAC appeared as solid type on TS-CT. No patient with air-type adenocarcinoma had lymphatic or vascular invasion. Among patients with solid-type adenocarcinoma, 16 (25.8%) had lymphatic and vascular invasion, 26 (41.9%) had invasive area > 5 mm, and 12 (19.4%) had Ki-67 index ≥25%.

3.2. Type of surgical procedure

Of the air-type adenocarcinomas, 9 (23.7%) received lobectomy, while the other 29 underwent sublobar resection (i.e., segmentectomy or wedge resection) because of their small size. Among the solid-type adenocarcinomas, 51 (82.3%) underwent lobectomy, while 11 (17.7%) underwent sublobar resection because of the advanced age or pulmonary hypofunction of the patient.

3.3. Correlation of SUVmax and pathological invasive area in solid-type adenocarcinomas

Table 2 shows the results of further analysis of the relationship in solid-type adenocarcinomas between SUVmax cut-off value of 2.15 and pathological invasive factors, such as the existence of invasive area >5 mm, lymphatic or vascular invasion, and Ki-67 index. Among the 35 solid-type adenocarcinomas with low SUVmax, 12 (34.4%) were diagnosed to be BAC and 16 (45.7%) were adenocarcinomas with invasive area ≤5 mm, while 22 (81.5%) of 27 adenocarcinomas with high SUVmax had an invasive area >5 mm. Lymphatic or vascular invasion was observed in 2 (5.7%) of 35 solid-type adenocarcinomas with low SUVmax, but was observed in 14 (51.9%) of 27 solid-type adenocarcinomas with high SUVmax. Only one adenocarcinoma with low SUVmax had Ki-67 ≥25; there was a lower frequency of high Ki-67 index in adenocarcinomas with low SUVmax compared with those with high SUVmax.

3.4. Disease-free survival data

None of the air-type adenocarcinomas had recurrent disease. In contrast, 8 (12.9%) of the 62 solid-type adenocarcinomas had recurrent disease: 6 had lung metastasis and 2 had bone metastasis. The median follow-up time to recurrence was 14.6 months (range, 9.1–29.4 months).

Table 3 shows the association of recurrence and prognostic significance for each histopathologic factor and molecular marker, in relation to time to recurrence, in solid-type adenocarcinomas. SUVmax, lymphatic and vascular invasion, size of invasive area, and Ki-67 index were significantly correlated with recurrence and

Table 3
Risk factors for recurrence and prognostic predictors in stage IA solid-type adenocarcinomas[a].

	Recurrence (no. (%))	χ^2 Test p-value	Log-rank test p-value
Tumor size (mm)			
0–20 mm	5(15.2)	.573	.590
21–30 mm	3(10.3)		
SUVmax			
Low (<2.15)	1(2.9)	.007	.008
High (≥2.15)	7(25.9)		
Type of surgery			
Lobectomy	8(15.7)	.159	.173
Segmentectomy	0(0)		
Histology			
BAC	0(0)	.074	.082
Non-BAC	8(17.4)		
Lymphatic or vascular invasion			
Negative	1(2.1)	<.001	<.001
Positive	7(43.8)		
Invasive are size (mm)			
≤5	0(0)	<.001	<.001
>5	8(30.8)		
Ki-67 index			
<25	3(6.0)	.001	<.001
≥25	5(41.7)		

[a] Data are presented as number (%) of patients.

a shorter time to recurrence. Among these predictors, SUVmax is the only preoperative factor, with the others being pathological factors. Our examination revealed no significant association between tumor size and recurrence. All cases of recurrence underwent lobectomy. In agreement with the findings of previous reports, no relapse was found in solid-type adenocarcinomas with invasive area ≤5 mm; in contrast, relapse was observed in 8 (30.8%) solid-type adenocarcinomas with invasive area >5 mm. Patients with solid-type adenocarcinomas with invasive area ≤5 mm had a 100% 3-year disease-free survival rate, which was significantly better than that for patients with solid-type adenocarcinomas having invasive area >5 mm ($p = .0003$) (Fig. 1).

When solid-type adenocarcinomas were stratified according to SUVmax on preoperative FDG-PET, the disease-free survival in solid-type adenocarcinomas with high SUVmax was significantly lower than that in solid-type adenocarcinomas with low SUVmax ($p = .0077$); however, no significant difference was found in Kaplan–Meier curves between air-type adenocarcinomas and solid-type adenocarcinomas with low SUVmax. Three-year disease-free survival rates were 100% in air-type adenocarcinomas,

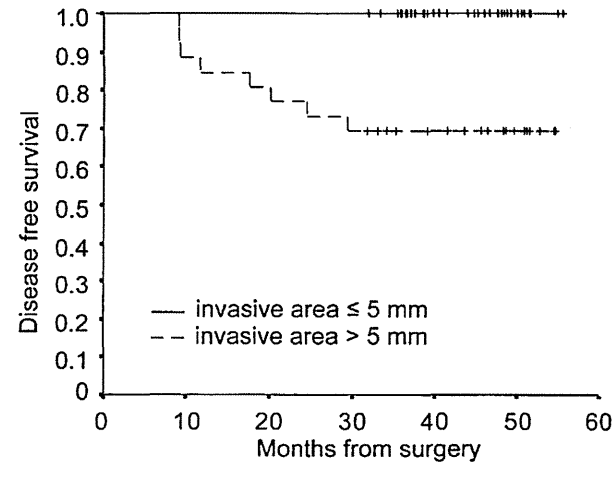

Fig. 1. Disease-free survival for solid-type adenocarcinoma stratified by the presence of pathological invasive area.

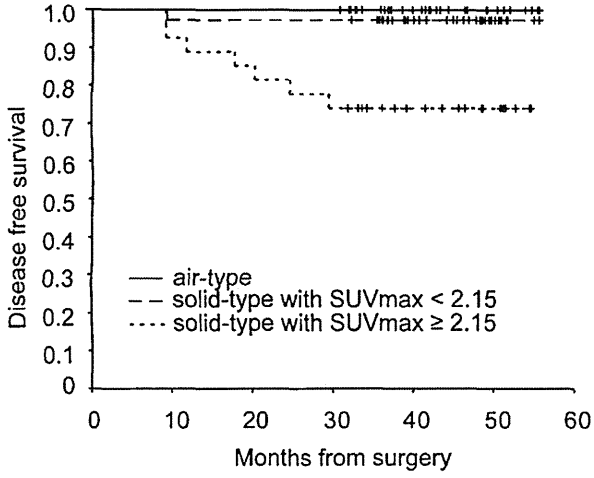

Fig. 2. Disease-free survival for patients with air-type adenocarcinoma or solid-type adenocarcinoma stratified by cut-off value of SUVmax.

97.1% in solid-type adenocarcinomas with low SUVmax, and 74.1% in solid-type adenocarcinomas with high SUVmax (Fig. 2).

4. Discussion

Numerous studies have reported recurrence rates for patients with NSCLC treated by surgical resection with curative intent. In patients with pathological stage I disease, 5-year recurrence rates of 20–39% are reported [11,12], with most recurrences detected within the first 4 years following curative intent surgery [12]. The prediction by preoperative radiological findings of adenocarcinoma with invasive characteristics could play a crucial role in treatment decisions.

In the present study, we reported the preoperative TS-CT and FDG-PET findings to indicate tumor differentiation. A previous study investigated the prognostic value of the ratio of the GGO component in small-sized lung adenocarcinoma of diameter ≤20 mm, reporting a 5-year disease-free survival rate of 100% in patients with air-type tumors on TS-CT who underwent limited resection, but a rate of 60% in patients with solid-type tumors [13]. This classification, based on the ratio of GGO component on TS-CT, could become a useful preoperative indicator when deciding the surgical procedure. Previous studies regarding classification based on the findings of TS-CT are reported for small-sized lung adenocarcinomas of ≤20 mm or less in diameter [2,4,13]. In the present study, we examined peripheral lung adenocarcinomas ≤30 mm in diameter with median follow-up of 42 months. We found no relapse in air-type adenocarcinomas ≤30 mm in diameter, the as same as for adenocarcinomas ≤20 mm in diameter. These results suggest that classification based on the findings of TS-CT could be appropriate for adenocarcinomas ≤30 mm in diameter.

Most of the air-type adenocarcinomas in the present study were BAC. Stromal destruction was revealed in some air-type adenocarcinomas, which are conventionally categorized as having mixed subtypes in the WHO typing, but none showed vascular or lymphatic invasion. In contrast, 74.2% of solid-type adenocarcinomas were non-BAC, 25.8% had vascular or lymphatic invasion, and most had pathological invasive area. Pathological invasive area is known to be associated with prognosis. A diameter of invasive area ≤5 mm is reported to have a good prognosis; a small component of invasive tumor does not adversely affect prognosis, in comparison with the true-BAC type [1]. Of the solid-type adenocarcinomas, 58.1% had invasive area ≤5 mm. Despite the appearances of solid-type adenocarcinomas on TS-CT, no relapses or deaths after resection occurred for invasive area ≤5 mm. This finding indicates that prediction using the diameter of pathological invasive area on solid-type adenocarcinomas could contribute to decisions regarding the choice of surgical procedure and treatment after surgery.

In a previous work, we studied the correlation between SUVmax and pathological invasive area, and reported that an SUVmax cut-off point of 2.15 was the best discriminative value for predicting invasive area >5 mm in solid-type adenocarcinomas ≤30 mm [10]. In the present study, preoperative SUVmax predicted pathological invasive area >5 mm with high accuracy for solid-type lung adenocarcinomas. Of the solid-type adenocarcinomas studied, eight relapsed during the follow-up period of 9.1–29.4 months, and the 3-year disease-free survival was 87%. All eight cases of relapse had invasive area >5 mm. All except one case of relapse were solid-type adenocarcinomas with high SUVmax on preoperative FDG-EPT. Significant difference was found for disease-free survival between solid-type adenocarcinomas with high SUVmax and those with low SUVmax. No statistically significant difference was found regarding disease-free survival between solid-type adenocarcinomas with low SUVmax compared with air-type adenocarcinomas. Therefore, we consider that intentionally limited surgery would be suitable for candidates with solid-type adenocarcinoma with low SUVmax, without lowering the disease-free survival rate. SUVmax on preoperative FDG-PET would be a valuable preoperative indicator for predicting the risk of relapse following curative surgery in stage IA adenocarcinoma.

Because tumor size is known to have prognostic relevance, a new T category was added to the seventh edition of the Tumor, Node, and Metastasis Classification, to include the subclassifications T1a (≤20 mm) and T1b (>20 mm, ≤30 mm). The 5-year postoperative survival rate decreased significantly as tumor size increased [14]. In the present study, no significant difference was found regarding disease-free survival between T1a and T1b adenocarcinomas. Several limitations may have influenced the finding of no significant difference in disease-free survival: (1) the sample size is small; (2) the follow-up period could be insufficient.

The monoclonal antibody Ki-67 detects a nuclear antigen that is present through the cell cycle. Tumor Ki-67 expression is known to be a molecular marker of tumor proliferation, and its overexpression leads to a poorer prognosis in non-small lung cancer [15]. As previously reported, Ki-67 index ≥25% is a prognostic indicator for solid-type adenocarcinomas. In the present study, however, three of the eight cases of relapse had Ki-67 index <25%, which indicates that Ki-67 index does not have a definite prognostic value regarding relapse after resection.

It is important to consider the possibility of false-negative FDG-PET. Despite showing low SUVmax, one patient with solid-type adenocarcinoma had distal relapse to the spine 9.3 months after surgery; the Ki-67 index was 3.8%, which is much lower than the Ki-67 cut-off point of 25%. False-negative PET scan occurs most commonly in small-size tumors because of the partial volume effect [16]. Because SUVmax is affected by Ki-67 expression [17] as well as invasive area, an adenocarcinoma with low Ki-67 index could show low SUVmax, even if the adenocarcinoma had invasive area >5 mm.

The present results suggest that evaluation of SUVmax on FDG-PET in addition to classification by TS-CT findings could predict a poorer prognosis in some patients with solid-type adenocarcinoma. In cases of stage IA lung cancer, the nodule should first be classified as air-type or solid-type according to the TS-CT findings. Solid-type nodules should then be evaluated for tumor aggressiveness by SUVmax on FDG-PET. Patients with IA solid-type adenocarcinomas with high SUVmax would have a high potential for relapse and would therefore benefit from adjuvant therapy. In contrast, limited surgery may be suitable for patients with solid-type adenocarcinoma with low SUVmax. In the present study, however, most of

the patients with solid-type tumors underwent lobectomy and all of the cases of relapse underwent lobectomy. Therefore, we did not demonstrate the validity of limited surgery for these patients. Further prospective studies are required concerning intentionally limited surgery for patients with small-sized solid-type adenocarcinomas showing low SUVmax.

5. Conclusion

Combined evaluation of the preoperative TS-CT findings and SUVmax on FDG-PET has significant value for predicting recurrence in stage IA lung adenocarcinoma, reflecting the aggressiveness of primary lung adenocarcinoma. Prediction of tumor aggressiveness could contribute to decisions regarding the choice of surgical procedure and post-resection treatment.

Conflict of interest statement

None declared.

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

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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;144:1365-71)

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.

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

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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

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 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.

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.

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 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 (≤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.

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.

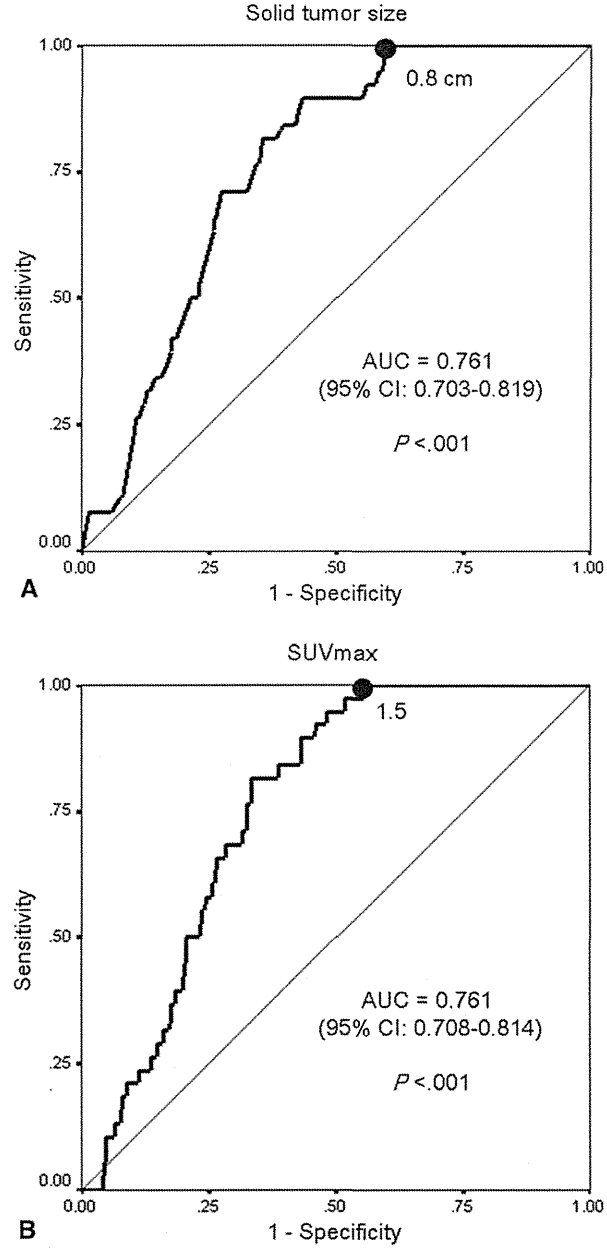

FIGURE 1. Receiver operating characteristic area under the curve *(AUC)* for detecting lymph node metastasis for solid tumor size (A) and maximum standardized uptake value *(SUVmax)* (B). Solid tumor size: AUC, 0.761 (95% confidence interval *[CI],* 0.703-0.819; $P < .001$). SUVmax: AUC, 0.761 (95% CI,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

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

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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.

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 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).

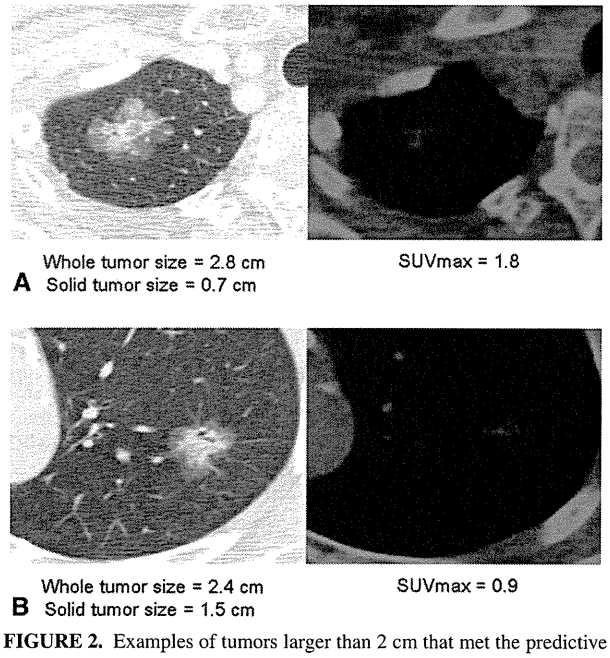

FIGURE 2. Examples of tumors larger than 2 cm that met the predictive criteria of pathologic node negative. A, Whole tumor size, 2.8 cm; solid tumor size, 0.7 cm; maximum standardized uptake value *(SUVmax)*, 1.8. This tumor can be treated with sublobar resection, such as right apical segmentectomy.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

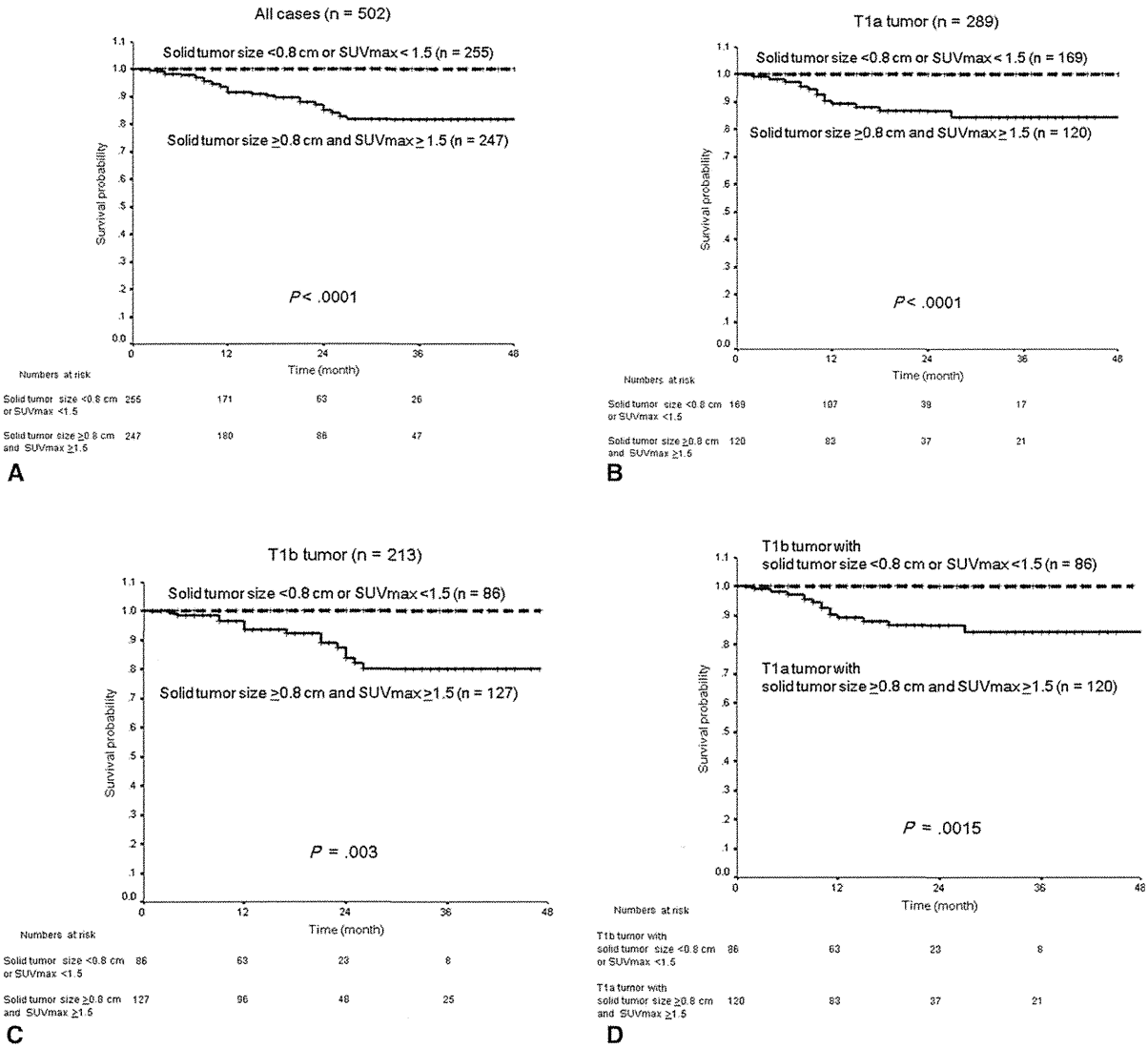

FIGURE 3. Disease-free survival *(DFS)* curves of patients according to the predictive criteria of pathologic node negative using solid tumor size and maximum standardized uptake value *(SUVmax)*. A, Three-year DFS rates of 100% and 81.8% for patients with a solid tumor size of less than 0.8 cm or an 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 (≤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 ($P = .0015$).

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 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

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.

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 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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肺非小細胞癌の術前・術後化学療法

Peri-operative chemotherapy for non small cell lung cancer

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◎肺癌の手術成績は近年向上してきている．しかし，切除可能ではあるがリンパ節転移などにより病期が進んだ症例の切除後の予後は，あまり変わっていない．そのために，手術前後の補助化学療法の開発は避けて通ることはできない．近年，新規抗がん剤の開発により，術後病期Ⅱ～Ⅲ期においてはcisplatin＋vinorelbineによる術後化学療法が標準治療として確立された．今後は個別化治療を通じて分子標的薬などを絡めた新しい治療法を検討することで，予後の改善を求めていく必要がある．抗がん剤の開発による術後化学療法の過去を振り返りつつ，今後の展望について述べる．

Key word：肺非小細胞癌，分子標的薬，術後化学療法，臨床試験，個別化治療，術前化学療法

肺非小細胞癌は，発症例のうち手術適応になる割合は他癌種に比べ低く，25～30%である．その最大の理由は，発見時にすでに遠隔転移をしているからである．切除可能例もすでに遠隔転移している割合が多い．切除例の再発形式の大半は，肺転移を含めた遠隔転移である．これを克服する方法は補助化学療法であろう．そのため，ずいぶん昔からいろいろな化学療法が試みられてきた．多くは薬剤の効果が至らなかったために有効性を証明することができなかったが，現在ではかなり有望な結果が得られるまでになってきている．

近年，分子標的薬の有効性がクローズアップされるなかで，術後化学療法への応用について治験が行われている．これら多様な試みについても言及する．

初期の術後化学療法

非小細胞肺癌の化学療法はcisplatin(CDDP)が出現してから大きな進歩を遂げた．それまでの抗がん剤から格段に奏効率が向上したため，切除不能非小細胞肺癌に対して広く用いられるようになった．

はじめに術後補助化学療法の有効性について報告したのは，1986年のHolmesらのLung Cancer Study Groupであった[1]．彼らは141人のⅡ～Ⅲ期の腺癌と大細胞癌の切除症例に対し，胸腔内にBCGを注入するとともにlevamisoleを18カ月投与する群と，cytoxan 400 mg/m^2＋adriamycin 40 mg/m^2＋CDDP 40 mg/m^2(以下，CAPと略)の化学療法を月1回で半年間投与する群に割り付けた．141人のうち11人がineligibleと判断され，130人が解析対象となった．最終治療の開始からほぼ2年の時点で84/130の再発イベントが発生し，無再発期間において化学療法群が統計学的に良好であったと報告した．これを受けてCAPを用いた多くの臨床試験が行われた．CAPを用いた試験は多く追試されたが，症例数がわずか112例であるNiiranenらの試験[2]を除いて，その有用性を証明することはできなかった．

その後，1980年代になって，抗がん作用がより強力なCDDP＋vindesineやVP-16の併用が非切除例に対する標準治療と考えられるようになり，補助化学療法に関してもCAP療法は行われなくなった．CDDP＋VDS，VBL，VP-16を用いた術

表 1　多数症例による術後化学療法の比較試験

study	protocol	stage	*n*	survival	hazard ratio	*p*-value
ALPI[4]	MVP(±RT) (±RT)	Ⅰ～ⅢA	606 603	55.2 mo 48 mo	0.96	0.58
IALT[5]	CDDP+Vinca(±RT) (±RT)	Ⅰ～ⅢA	932 935	50.8 mo 44.4 mo	0.86	0.03

表 2　術前化学療法の比較試験

source	stage	*n*	chemotherapy	response rate	resection rate	MST
Rosell[6]	ⅢAN2	30 30	MIP ope	53%	77% 90%	26 mo. 8 mo.
Roth[7]	ⅢA	28 32	CEP ope	35%	39% 31%	67 mo. 11 mo.
DePierre[9]	c-ⅠB～Ⅲa	179 176	MIP ope	64%	52% 41%	36 mo. 26 mo.
Gilligan[10]	c-Ⅰ～Ⅲ	258 261	Platin. doublet ope	49%	82% 80%	53 mo. 54 mo.
Pisters[11]	c-ⅠB～Ⅲ	169 167	Cb+paclitaxel-ope ope	41%	98% 96%	62 mo. 41 mo.
Scagliotti[12]	c-ⅠB～Ⅲ	129 141	CDDP+gemcitabin ope	35%	85% 96%	7.8 yr. 4.8 yr.

後補助療法は比較的進行例を対象としていたが，いずれも有効性を証明できなかった．

多数例による検証

1995年に，非小細胞肺癌の化学療法に対するメタアナリシスが行われ，術後補助化学療法についても検討され，『*BMJ*』に報告された[3]．その結果，CDDPを用いた場合には術後化学療法施行群のhazard ratioは0.87であり，1,294例の症例数では統計学的有意差を証明することができなかった．そのため，従来よりも多数の症例を集積して検討することが試みられた．多数例の比較試験としてはじめて報告されたのはALPI Study[4]というイタリアで行われた試験である．完全切除されたstageⅠ～Ⅲ 1,209例を対象として，MVP(mitomycin 8 mg/m^2, vindesine 3 mg/m^2, CDDP 100 mg/m^2)を術後3コース行う群と，切除単独の群に割り付けて比較した．Hazard ratioは0.96であり，統計学的有意差はなく，術後化学療法は無効であると考えられた．ついで，国際共同試験としてIALT Study[5]が計画された．本試験は完全切除された非小細胞肺癌病理病期stageⅠ～Ⅲに対する術後補助療法として，CDDPを300 mg/m^{2}以上とvinca alkaloid，あるいはetoposideとを併用する群と，手術単独の群とを比較するものである．症例の集積が悪く1,867例の時点で症例集積を断念した．化学療法群とコントロール群でそれぞれ，MSTはで50.8カ月：44.4カ月，5年生存率は39.4%：34.3%であり，hazard ratioは0.86，log-rankでp=0.03と，化学療法群が有意に良好であった．

術前化学療法

他癌種において術前化学療法のよい成績が報告され，非小細胞肺癌においても術前化学療法が試みられるようになった．当初はそのfeasibilityをみる試験として行われ，術前治療の妥当性が確立されたため，比較試験が行われた．1995年に2つの比較試験がスペイン[6]とアメリカ[7]から報告された．いずれもⅢ期症例を対象として，症例数は各群30例と少数ながら中間解析の時点で大きな隔たりがあったため，有効中止となった．この報告に続いて，日本とフランスで同様の比較試験が行われた．日本の試験[8]は登録が悪く途中で試験

表 3　New drugによる術後化学療法の比較試験

study	stage	protocol	*n*	survival benefit	hazard ratio	possible subset
CALGB9633[15]	ⅠB	Carbo+Taxol×4 none	173 171	2% (5yr)	0.80	>4 cm
BR10[13]	ⅠB～Ⅱ	CDDP+NAV×4 none	242 240	15% (5yr)	0.7	Ⅱ
ANITA[14]	ⅠB～Ⅲa	CDDP+NAV×4 none	407 433	8.6% (5yr)	0.79	Ⅱ, ⅢA

が中止され，長期予後の観察について報告されたが，有意差はなかった．フランスの試験[9]は術前病期ⅠB～Ⅲ期を対象に355例が集積され，術前化学療法に良好な傾向はみられたが，統計学的有意差を検出することはできなかった．いくつかのレジメンを用いて519症例を対象に行われた国際共同治験[10]でも術前治療の有効性は証明できなかった．

Carboplatin＋paclitaxelを用いた術前化学療法試験も行われた[11]．354例が登録された時点で術後化学療法の有効性が証明されたため，倫理性の観点から手術単独群をおくという試験は中止せざるをえなかった．長期観察の結果，化学療法群が5年生存率で手術単独群よりも9%良好でhazard ratioは0.80であったが，統計学的有意差を示すことはできなかった．Scagliotti ら[12]も術前のCDDP＋gemcitabine投与と手術単独を比較し，試験は早期中止されたが，270例の検討ではhazard ratioが0.63と，化学療法群のほうが有意に良好であった．

以上のことを踏まえ，現在では術前に行うことと術後に行うことでは，ほぼ同等の効果であると考えられるようになった．

新規抗がん剤

1990年代に新規抗がん剤がいくつか上市された．そのなかでもっとも早く肺癌に承認されたのがvinorelbineであったため，欧米でCDDP＋vinorelbineを用いた術後化学療法が行われた．ひとつは北アメリカにおけるJBR.10という試験[13]で，術後病期ⅠB～Ⅱを対象に，切除単独とCDDP＋naverubine(CDDP 50 mg/m^2 day 1.8とnaverbine 25 mg/m^2 day 1.8)を4コース行う群とを比較したものである．1994年から482例が登録され，5年生存率は化学療法群で69%，観察群で54%であり，hazard ratioは0.69と化学療法群が良好であった．Subset analysisではstageⅡでは有効であったが，stageⅠBでは有効性を証明できなかった．

ヨーロッパで行われた試験[14]は，stageⅠB～ⅢAを対象に，CDDP＋naverubine(CDDP 100 mg/m^2 day 1とnaverbine 30 mg/m^2 weekly)を4コース行うもので，同じく1994年から開始され，840例が集積された．化学療法群で2%の治療関連死亡がみられたものの，生存中央期間は化学療法群で65.7カ月，観察群で43.7カ月と，hazard ratioは0.80(p=0.017)で，化学療法群が有意に良好であった．Subset analysisでは，こちらもstageⅠB期では有意差はなく，stageⅡ～Ⅲ期でのみ化学療法が有効であるという結果であった．

アメリカでは1996年からstageⅠB症例を対象にcarboplatin＋paclitaxel(carboplatin AUC=6, paclitaxel 200 mg/m^2 every 3 weeks)を4コース投与する群と観察群だけに割り付けて比較する試験が行われた．本試験は中間解析の時点で化学療法群が良好であるとして，344例の時点で中間解析で有効と判断し更なる登録が中止されたが，長期観察の結果，hazard ratioは0.83で，化学療法の有効性を証明できなかった[15]．しかし，腫瘍径が4 cm以上のsubsetについてはhazard ratioが0.69(p=0.48)で，術後化学療法の有効性がみられたと報告された．

現在進行中の臨床試験

個別化をめざしたものとしては，IALT bioなどを通じて過去の試験から類推されたバイオマーカー(ERCC1やBRCA1 mRNAなど)を用いて補助化学療法とバイオマーカーの効果を検証するこ