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学　位　論　文

Histopathologic characterization of lung adenocarcinoma in relation to fluorine-18-fluorodeoxyglucose uptake on positron emission tomography

（原発性肺腺癌における PET に際して FDG 取り込みを左右する病理組織学的特徴の検討）

北　海　道　大　学

道　免　寛　充

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Histopathologic Characterization of Lung Adenocarcinoma in Relation to Fluorine-18-fluorodeoxyglucose Uptake on Positron Emission Tomography

Hiromitsu Domen[1,2], Yasuhiro Hida[3], Shozo Okamoto[4], Kanako C. Hatanaka[1], Yutaka Hatanaka[1], Kichizo Kaga[3], Nagara Tamaki[4], Satoshi Hirano[2] and Yoshihiro Matsuno[1,*]

[1]Department of Surgical Pathology, Hokkaido University Hospital, Sapporo, [2]Department of Gastroenterological Surgery II, Hokkaido University Graduate School of Medicine, Sapporo, [3]Department of Cardiovascular and Thoracic Surgery, Hokkaido University Graduate School of Medicine, Sapporo and [4]Department of Nuclear Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan

*For reprints and all correspondence: Yoshihiro Matsuno, Department of Surgical Pathology, Hokkaido University Hospital, North 14, West 5, Kita-ku, Sapporo 060-8648, Japan. E-mail: ymatsuno@med.hokudai.ac.jp

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Background: Fluorine-18-fluorodeoxyglucose uptake on positron emission tomography is reported to have prognostic significance in patients after resection of lung adenocarcinoma. However, its relationship with histopathologic features remains unknown.
Methods: We conducted a retrospective analysis of 205 patients who had undergone surgical resection of primary lung adenocarcinoma (>1.0 cm) after preoperative fluorine-18-fluorodeoxyglucose-positron emission tomography between January 1999 and December 2008 at Hokkaido University Hospital. Fluorine-18-fluorodeoxyglucose uptake was measured by the maximum standardized uptake value. A histopathologic review was performed according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification, and various histopathologic factors were evaluated semiquantitatively. Correlations between these clinicopathologic factors and the maximum standardized uptake value (high ≥2.0 vs low <2.0) were analyzed.
Results: Univariate analysis of clinicopathologic factors demonstrated that the following were significantly correlated with a high maximum standardized uptake value: an elevated carcinoembryonic antigen level, larger tumor size, upgraded pT, pN, pStage, non-lepidic histology, abundant fibroblastic/hyalinized stroma, necrosis, presence of pleural involvement, lymphatic and vascular invasion and more intra- and extracellular mucin. Multivariate analysis demonstrated that a tumor size of >2.0 cm, non-lepidic histology and abundant fibroblastic/hyalinized stroma were significantly correlated with the high maximum standardized uptake value.
Conclusion: More histopathologic factors are known to correlate with poor prognosis in lung adenocarcinomas showing high maximum standardized uptake values than in those showing low maximum standardized uptake values. Therefore, prognostication of patients with a resectable lung adenocarcinoma on the basis of preoperative fluorine-18-fluorodeoxyglucose uptake is histopathologically valid. Such observations may also help us to clarify the pathobiological mechanism responsible for the increased fluorine-18-fluorodeoxyglucose uptake in lung adenocarcinomas with a poor prognosis.

Key words: fluorine-19-fluorodeoxyglucose – positron emission tomography – lung adenocarcinoma – maximum standardized uptake value – histopathology

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INTRODUCTION

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related death in both men and women (1). A surgery with curative intent provides the best chance of cure, but can only be considered for Stage I or II disease, and selected cases of Stage III disease. Moreover, ∼50% of patients who undergo complete curative resection suffer from tumor recurrence (2). Therefore, preoperative prognostication is necessary in order to optimize the therapeutic strategy for patients with NSCLC. A non-invasive molecular imaging tool that would be potentially helpful for this purpose is positron emission tomography (PET). Fluorine-18-fluorodeoxyglucose (FDG)-PET allows visualization of cells, such as cancer cells, in the body which have increased glucose uptake and metabolism. FDG uptake reflects the malignant potential and prognosis of various cancers, such as those of the esophagus (3), pancreas (4), breast (5) and thyroid (6).

One major advantage of PET is that it allows FDG uptake to be measured prior to surgery or other treatments. It has been demonstrated consistently that the maximal uptake of FDG in NSCLC is an independent prognostic factor for survival (7–10), particularly in patients with lung adenocarcinoma (11–15). However, the significance or mechanism responsible for differences in FDG uptake among cases has not yet been clarified histopathologically.

Until now, the most reliable prognostic factor in patients with a resected NSCLC has been pathologic tumor-node-metastasis (pTNM), along with several histopathologic factors such as tumor size (16), vascular invasion (17) and pleural involvement (18). Additional histopathologic features, such as the presence of an active fibroblastic stroma or mucus production, serve as prognostic factors in cases of adenocarcinoma (19,20).

The purpose of the present study was to clarify the correlation between FDG uptake and the histopathologic characteristics of adenocarcinoma, in order to assess the prognostic significance of FDG-PET, and also to help clarify the pathobiological mechanism responsible for the increased FDG uptake in cases with a poor prognosis. It was anticipated that the data obtained would facilitate more accurate interpretation of preoperative imaging in individual patients, and yield information that might assist in the development of a novel, more specific and sensitive imaging modality.

PATIENTS AND METHODS

Patients

We conducted a retrospective analysis of 220 patients who had undergone surgical resection of lung adenocarcinoma after preoperative FDG-PET between January 1999 and December 2008 at Hokkaido University Hospital. Nine patients with tumors ≤1.0 cm in diameter and three patients with plasma glucose levels >150 mg/dl were excluded, based on the findings of previous studies (21,22). Thus, a final total of 205 patients [median age 67 years (range 31–92 years), median tumor size 2.5 (1.1–7.7) cm, median carcinoembryonic antigen (CEA) level 3.0 (0.5–104.7) ng/ml] were included in the study (Table 1).

FDG-PET data Analysis

Patients fasted for at least 6 h prior to tracer injection (4.5 MBq/kg FDG). After 60 min, FDG-PET images were obtained with an ECAT EXACT 47(Siemens-Asahi, Tokyo, Japan) or ECAT EXACT HR+ (Siemens-Asahi) system.

Table 1. Patient characteristics

Variables	No. of patients	SUVmax	
		Median	Quartile points
Age (years)			
<60	46	1.8	0.7–4.5
≥60	159	2.1	1.2–4.2
Sex			
Male	93	2.3	1.2–4.7
Female	112	1.9	1.1–3.4
Tumor size (cm)			
1.0–2.0	62	1.2	0.7–2.0
>2.0	143	2.5	1.5–4.9
CEA (ng/ml)			
<3.0	94	1.5	0.8–2.4
≥3.0	111	2.6	1.5–5.3
pT			
T1	133	1.5	0.8–2.4
T2	55	4.1	2.2–6.7
T3	12	4.4	2.1–8.0
T4	5	2.6	1.8–5.1
pN			
N0	166	1.6	0.9–2.8
N1	18	5.8	2.4–8.1
N2	20	4.7	2.7–7.1
N3	1	6.2	N.A
pStage			
IA	118	1.4	0.7–2.3
IB	36	2.5	1.5–4.8
IIA	6	2.5	1.7–5.5
IIB	15	5.5	2.4–7.8
IIIA	24	4.6	2.5–7.1
IIIB	2	9.4	6.2–12.5
IV	4	4.5	3.2–6.7

SUVmax, the maximum standardized uptake value.

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Whole-body images were collected with 2 min/bed emission scan and reconstructed using the ordered subset expectation maximization method with correction for attenuation. A region of interest (ROI) was drawn over the primary tumor; when necessary, a computed tomography scan was used to help localize the tumor. The maximum standardized uptake value (SUVmax) was then calculated for each tumor [median SUVmax 2.0 (0−14.4)]. The pixel with the maximum uptake within the ROI was used to determine the SUVmax. The median SUVmax was used as a cut-off threshold for defining groups of patients.

Pathologic Evaluation

The surgically resected specimens were processed routinely, including intrabronchial instillation of 10% formalin in a bath of the same fixative for 2−7 days, and cut into slices at ∼5 mm intervals. A representative tumor section was taken from the largest cut surface in each case. The paraffin-embedded tissues were cut into sections 4 μm thick and stained with hematoxylin and eosin for routine histologic examination. Representative sections were also stained with elastica-Masson to aid evaluation of intratumoral venous invasion and pleural involvement. The slides were reviewed independently by two investigators (H.D. and Y.M.) who were blinded to the SUVmax for each case, and discrepancies were resolved by a joint review of the slides through a multiheaded microscope.

Histologic type was evaluated according to the criteria and nomenclature described in the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) histologic classification (23). For further analysis in this study, these histologic types were categorized as (i) adenocarcinoma *in situ* (AIS) type: non-mucinous/mucinous adenocarcinoma *in situ* (lepidic component100%), (ii) lepidic type: micro invasive/invasive adenocarcinoma with lepidic growth (lepidic component <100−10%) and (iii) non-lepidic type: invasive adenocarcinoma without or with only minimal lepidic growth (lepidic component <10%). Disease stage in each case was determined according to the tumor-node-metastasis classification system of the International Union Against Cancer (24).

The following histopathologic factors were evaluated semiquantitatively: fibroblastic tumor stroma, necrosis, pleural involvement, lymphatic invasion, vascular invasion, intracellular mucin and extracellular mucin. The histologic features and scoring criteria for these histopathologic factors are shown in Table 2. The percentage area of active fibroblasts or hyalinization in the total fibrotic area was scored according to a previous report (25): Score 0 (none), Score 1 (a focus of alveolar collapse-type fibrosis occupying ≥10% of the total tumor area, and active fibroblasts or hyalinization in <10% of the total fibrotic area), Score 2 (active fibroblasts in ≥10% of the total fibrotic area, and hyalinization in <10% of the total fibrotic area) or Score 3 (hyalinization in >10% of the total fibrotic area). Cases with scores of 0 and 1 were placed in a non-fibroblastic group and those with scores of 2 and 3 in a fibroblastic group. Pleural involvement was evaluated histologically in accordance with a previous report (26).

Statistical Analysis

Statistical analysis was performed using the JMP software system (JMP for Windows. version 8.0, USA). The relationships between various clinicopathologic factors (age, sex, tumor size, serum CEA level, pT, pN, pStage, histologic type and other histopathologic factors) and SUVmax were evaluated using the Wilcoxon test. SUVmax was dichotomized at its median value of 2.0. The relationships between these factors and dichotomized SUVmax were evaluated using Fisher's exact test.

Table 2. Histologic factors and scoring criteria

Histologic factors	Scoring			
	0	1	2	3
Fibrosis	No fibrotic tissue	With foci of alveolar structure collapse	With active fibroblastic proliferation	With hyalinization
Necrosis[a]	≤10%	10%<, ≤20%	20%<, ≤50%	50%<, ≤100%
Pleural involvement	No pleural involvement	Tumor extending beyond the visceral pleural elastic layer but not extending to the pleural surface	Tumor extending to the visceral pleural surface but not involving the parietal pleura	Tumor involving the parietal pleura or extending to organs adjacent to the lung
Lymphatic/ vascular invasion[b]	Not found	A few	Occasionally found	Prominent
Intracellular/ extracellular mucin[c]	≤10%	10%<, ≤20%	20%<, ≤50%	50%<, ≤100%

[a]The percentage of necrotic tissue in the total tumor area.
[b]Lymphatic or vascular invasion was determined by identification of tumor cells in the lumen of lymphatic or vascular channels.
[c]The percentage of the total tumor area showing intra- or extracellular mucin production.

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Multivariate analysis was performed using multiple logistic regression analysis to assess the joint effects and interactions of the variables. Differences at $P < 0.05$ were considered to be statistically significant.

RESULTS

Histopathologic Analysis

Among 205 adenocarcinomas, there were 25 adenocarcinomas *in situ* (22 non-mucinous and 3 mucinous, AIS type, Fig. 1b), 92 microinvasive adenocarcinomas and invasive adenocarcinomas with a lepidic pattern of growth (lepidic type) and 88 adenocarcinomas with other types of predominant growth pattern, including acinar, papillary/micropapillary and solid (non-lepidic type, Fig. 1a). The median SUVmax was 0.59 for the AIS type, 1.5 for the lepidic type and 4.4 for the non-lepidic type (Fig. 2).

Among a total of 122 cases (59%), there was significant proliferation of active fibroblasts with plump nuclei and often with prominent nucleoli, occasionally accompanied by hyalinized collagenous fibrosis in some cases (fibrosis score 2 or 3, Fig. 1a). These cases were categorized as a fibroblastic group, while the other 83 cases (41%) without active fibroblastic proliferation were categorized as a non-fibroblastic group (score 0 or 1, Fig. 1b). The median SUVmax was 3.02 in the fibroblastic group and 1.1 in the non-fibroblastic group, respectively (Fig. 3).

Coagulation necrosis >10% of the tumor area was found in 30 cases (score 1 + 2 + 3, Table 3). Pleural involvement was found in 41 cases. Lymphatic and blood vascular invasion was found in 38 and 63 cases, respectively. Intracellular and extracellular mucin production by tumor cells was evident in 41 and 34 cases, respectively (Table 3).

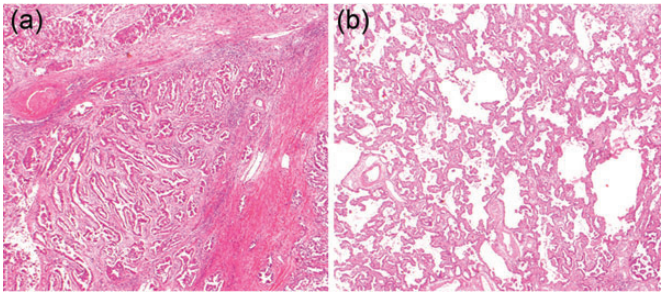

Figure 1. Representative histologic features of tumors (hematoxylin–eosin, original magnification ×100).The tumor on the left (a) is categorized as non-lepidic type, fibroblastic (Score 3). The tumor on the right (b) is categorized as adenocarcinoma *in situ* (AIS) type, non-fibroblastic (Score 0). The maximum standardized uptake value (SUVmax) of these representative tumors was 12.5 (a) and 0.53 (b).

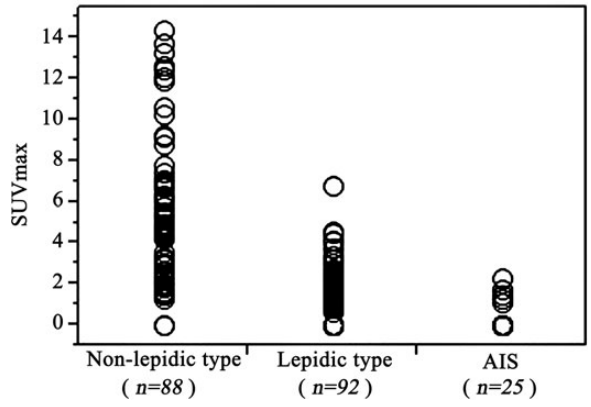

Figure 2. Association between the histologic type and the SUVmax. The 205 cases comprised 25 (12%) that were AIS type, 92 (45%) that were lepidic type and 88 (43%) that were non-lepidic type. The median (quartile points) of SUVmax was 0.59 (0.4–1.1), 1.5 (0.9–2.3) and 4.4 (2.3–6.3), respectively.

Univariate Analysis

The results of univariate analysis of clinicopathologic factors in relation to SUVmax are shown in Table 4. Neither age nor sex showed a significant correlation with SUVmax. In contrast, an elevated CEA level (>3.0), larger tumor size (>2.0 cm), higher pT (pT2–4), pN (pN1–3), pStage (pStage II–IV), histologic invasion, non-lepidic type, the presence of an abundant fibroblastic or hyalinized stroma, abundant necrosis (>10%), pleural involvement and lymphatic or vascular invasion were significantly correlated with an SUVmax higher than the median ($P < 0.01$ for all factors). Furthermore, the presence of abundant intracellular mucin ($P = 0.038$) and extracellular mucin ($P = 0.040$) was also significantly correlated with an SUVmax higher than the median.

Multivariate Analysis

The results of multivariate analysis are shown in Table 5. A tumor size of >2.0 cm (odds ratio, OR, 2.94; 95% confidence interval 1.14–7.95; $P = 0.028$), non-lepidic histology (3.95; 1.54–10.73; <0.01) and an abundant fibroblastic or hyalinized stroma (3.23; 1.28–8.48; 0.014) were significantly correlated with SUVmax higher than the median. Two

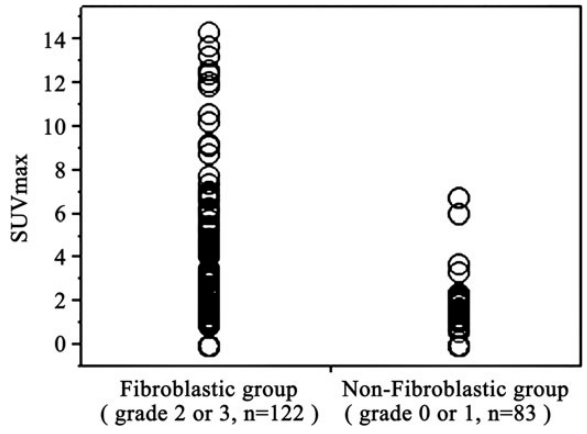

Figure 3. Association between the fibroblastic tumor stroma and the SUVmax. The 205 cases comprised 122 (59%) in the fibroblastic group and 83 (41%) in the non-fibroblastic group. The median (quartile points) of SUVmax was 3.0 (1.9–5.2) and 0.7 (0.5–1.7), respectively.

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Table 3. Summary of histopathologic review

Histologic type	
AIS type	25
Non-mucinous	22
Mucinous	3
Lepidic type	92
Non-lepidic type	88
Fibrosis	
0	21
1	62
2	79
3	43
Necrosis	
0	175
1	14
2	13
3	3
Pleural involvement	
0	164
1	24
2	7
3	10
Lymphatic invasion	
0	167
1	27
2	8
3	3
Vascular invasion	
0	142
1	40
2	16
3	7
Intracellular mucin	
0	164
1	23
2	8
3	10
Extracellular mucin	
0	171
1	11
2	11
3	12

histopathologic factors—non-lepidic histology and an abundant fibroblastic stroma—showed a stronger correlation with a high SUVmax than the other histopathologic factors.

Our additional subgroup analysis revealed a significant correlation between the fibroblastic type, as well as the non-lepidic type, and a higher SUVmax both in the 1.0–2.0 cm group ($P = 0.0002$) and in the >2.0 cm group ($P < 0.0001$).

DISCUSSION

Several reports have claimed that FDG uptake is a prognostic factor in NSCLC (7–10). In recent years, FDG uptake has often been identified as a factor reflecting the grade of malignancy or patient prognosis, especially in lung adenocarcinoma. Several studies have examined the association between FDG uptake and histopathologic factors in lung adenocarcinoma (11–15). Higashi et al. (12) reported that a high SUVmax in pStage I–III lung adenocarcinomas was associated with pleural involvement, vascular or lymphatic invasion. Similarly, Okada et al. (13) analyzed clinical T1N0M0 lung adenocarcinomas ≤3 cm in diameter, and showed that those with a lower SUVmax less frequently showed lymphatic or vascular invasion, and regional lymph node metastasis. Murakami et al. (15) reviewed the thin-section computed tomography scan and PET reports of 100 patients with pStage IA lung adenocarcinoma. They concluded that combined evaluation of such findings with SUVmax had a significant value for predicting recurrence in this group of patients. Very recently, Kadota et al. (27) reported that high SUVmax correlates with high-grade histology (solid and micropapillary), and low SUVmax correlates with low-grade histology (AIS, MIA and lepidic predominant) in the IASLC/ATS/ERS classification (23). Also, they showed that higher SUVmax correlated with the second predominance of high-grade histology among the intermediate histology group. They showed that histology and SUVmax can be used as prognostic stratification of patients in Stage I lung adenocarcinoma. The results in our present study on Japanese patients in any stage are quite consistent with, and thus strongly support their report, because our non-lepidic type group represents high-grade histology in theirs, and their low-grade histology group would be included in our lepidic type group.

The univariate analysis in the present study demonstrated that lung adenocarcinoma with a high SUVmax was characterized histopathologically by a scant lepidic growth component, and an abundant fibroblastic tumor stroma (Fig. 1). Multivariate analysis showed that these two histopathologic factors were not only the strongest, but also independently reflected a high SUVmax. In addition, the present data also confirmed previous studies that had indicated that detectable lymphatic or vascular invasion, or pleural involvement, was significantly correlated with a high SUVmax. However, these latter factors were not proven to be independent by multivariate analysis in this largest case series. For the first time, necrosis and intratumoral mucin production were also shown to be correlated with a high SUVmax.

As our data in Table 5 clearly pointed out, SUVmax may be affected, in general, by the tumor volume. However, our additional subgroup analysis revealed a significant correlation

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Table 4. Correlation between clinicopathologic factors and SUVmax

	n	Wilcoxon test *P* value	SUVmax		Odds ratio	95% CI	Fisher's exact test *P* value
			high (≥2.0)	low (<2.0)			
Age (years)							
<60	46	0.513	22	25	1.19	0.62–2.31	0.619
≥60	159		83	76			
Sex							
Male	93	0.123	52	41	0.71	0.41–1.23	0.262
Female	112		53	59			
Tumor size (cm)							
1.0–2.0	62	<0.001	15	47	5.32	2.71–10.42	<0.001
>2.0	143		90	53			
CEA (ng/ml)							
<3.0	94	<0.001	34	60	3.13	1.76–5.55	<0.001
≥3.0	111		71	40			
pT							
T1	133	<0.001	49	84	6.00	3.11–11.58	<0.001
T2 + T3 + T4	72		56	16			
pN							
N0	166	<0.001	71	95	9.09	3.39–24.43	<0.001
N1 + N2 + N3	39		34	5			
pStage							
IA	116	<0.001	38	78	6.25	3.37–11.6	<0.001
IB–IV	89		67	22			
Histologic invasion							
AIS type	25	<0.001	1	24	32.84	4.34–248.1	<0.001
Lepidic type + non-lepidic type	180		104	76			
Lepidic growth component							
AIS type + lepidic type	117	<0.001	31	86	14.66	7.25–29.63	<0.001
Non-lepidic type	88		74	14			
Fibrosis							
0 + 1 (Non-fibroblastic)	83	<0.001	16	67	11.29	5.74–22.20	<0.001
2 + 3 (Fibroblastic)	122		89	33			
Necrosis							
0	175	<0.001	77	98	17.81	4.11–77.13	<0.001
1 + 2 + 3	30		28	2			
Pleural involvement							
0	164	<0.001	70	94	7.83	3.12–19.64	<0.001
1 + 2 + 3	41		35	6			
Lymphatic invasion							
0	167	<0.001	74	93	5.56	2.32–13.35	<0.001
1 + 2 + 3	38		31	7			

Continued

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Table 4. *Continued*

	n	Wilcoxon test *P* value	SUVmax		Odds ratio	95% CI	Fisher's exact test *P* value
			high (≥2.0)	low (<2.0)			
Vascular invasion							
0	142	<0.001	51	91	10.71	4.89–23.46	<0.001
1 + 2 + 3	63		54	9			
Intracellular mucus							
0	164	0.003	78	86	2.12	1.04–4.34	0.038
1 + 2 + 3	41		27	14			
Extracellular mucus							
0	171	0.002	82	89	2.27	1.04–4.94	0.040
1 + 2 + 3	34		23	11			

OR, odds ratio; CI, confidence interval.

Table 5. Multivariate analysis for predicting SUVmax

	OR	95% CI	*P*
Tumor size	2.94	1.14–7.95	0.028
>2.0 cm vs 1.0–2.0 cm			
Lepidic growth component	3.95	1.54–10.73	0.005
Non-lepidic type vs AIS type + lepidic types			
Fibrosis	3.23	1.28–8.48	0.014
Fibroblastic vs non-fibroblastic			

between the fibroblastic type, as well as the non-lepidic type, and a higher SUVmax both in the 1.0–2.0 cm group and in the >2.0 cm group in the present study. This strongly supports that these correlations observed in the whole group can be interpreted as reliably valid, despite adjustment by each tumor size has not been performed.

Since Noguchi et al. first demonstrated that small adenocarcinomas composed entirely of a lepidic growth pattern had an excellent prognosis (19), a number of studies have clarified that the presence of a lepidic growth component, i.e. *in situ* spread of adenocarcinoma, seems to be a crucial prognostic factor (28). Among them, Terasaki et al. reported that mixed-subtype adenocarcinomas showing predominantly lepidic growth tended to be less aggressive than those without this component (29). The results of the present study, in which a significant lepidic growth component in adenocarcinomas was strongly correlated with lower FDG uptake, are consistent with the previous results, both implicating a better post-surgical outcome in such cases. In addition, it will be necessary to clarify the significance of microinvasion in terms of FDG uptake, in comparison with frankly invasive adenocarcinoma, as this was not investigated in the present study.

Several studies have examined the morphologic features associated with a fibroblastic tumor stroma. Shimosato et al. (30) demonstrated that the degree of collagenization in the fibrotic focus was closely correlated with tumor growth and prognosis. They proposed that tumors with little or no collagenization could be considered to be in an early stage of development. Yamashiro et al. (31) reported that histologic invasion could be suggested by tumor cells accompanied by a stromal desmoplastic reaction in adenocarcinoma, and that a greater proportion of invasion into the fibrotic focus was correlated with a poorer prognosis. Noguchi et al. (19) suggested that active fibroblast proliferation in small adenocarcinomas was related to invasive growth and poorer patient survival. These reports, together with the present results, indicate that a high SUVmax would be an indicator of invasive, histologically advanced carcinoma. Thus, the present data have provided histopathologic validation that prognostication of patients after resection of lung adenocarcinoma is possible on the basis of preoperative FDG uptake.

The clinical application of SUVmax has not yet been established due to problems that include the lack of a valid method for determining the SUVmax cutoff value (32,33). In the present study, SUVmax was divided into two groups by setting the median value as the cutoff. Previously, the cutoff value for SUVmax was determined using the median value or the 'best cutoff value' (determined from the log-rank test), or the SUVmax was decided arbitrarily. Other problems with the clinical application of SUVmax include the spatial resolution of FDG-PET, the influence of the blood sugar level on FDG uptake and differences in the FDG-PET protocol and equipment between facilities. Standardization of SUVmax and the optimal threshold for dichotomization based on the SUVmax will need to be established in the near future.

It would be interesting to explore the biological mechanism that upregulates FDG uptake in the microenvironment of adenocarcinoma. Whether accelerated glucose uptake may take place in a number of constituents in non-lepidic adenocarcinoma tissue, such as accompanying stromal fibroblasts as

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well as carcinoma cells itself, should be determined in the future studies. Based on the results obtained in this study, the future study to analyze cellular functional aspects should be further encouraged, including Ki-67 labeling index, mitotic index, metabolism-related protein distribution or cellular atypia in relation to FDG-PET uptake. Furthermore, clarification of alterations in glucose metabolism would facilitate a better understanding of the natural history of lung adenocarcinoma development.

In conclusion, the present study has revealed that lung adenocarcinomas showing a higher SUVmax are associated with more histopathologic factors indicative of a poor prognosis, thus providing pathologic validation for prognostication of patients after resection of lung adenocarcinoma on the basis of preoperative FDG uptake. Scarcity of a lepidic growth component and an abundance of stromal fibroblasts are independently correlated with the high SUVmax, suggesting that these cells play important roles in FDG uptake. The results obtained here would not necessarily contribute to the better prognostication of the patients directly, but instead, provide pathologic validation for preoperative prognostication, as well as some clues to elucidate the pathobiologic mechanisms responsible for the increased FDG uptake in lung adenocarcinomas. The latter would facilitate the future investigations that will enable the more effective stratification of the patients with lung cancer.

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Conflict of interest statement

None declared.

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