expectation maximization corresponding to a pixel size of 4×4 mm, with section spacing of 2.66 mm.

PET data were evaluated semiquantitatively on the basis of the contrast ratio (CR) obtained as reported previously. Briefly, the regions of interest (ROIs) were chosen in the nodules or lymph nodes and cerebellum. The highest activities in the tumor or lymph node ROI (T or L) and in the cerebellum ROI (C) were measured. The CR was calculated by T/C in each nodule or L/C in each lymph node as an index of FDG-uptake. The primary tumors or lymph nodes with a CR ≥0.25 were diagnosed as having a viable tumor as reported previously.[7] The decrease in CR after neoadjuvant treatment was calculated using the following formula: CR after neoadjuvant treatment/CR before neoadjuvant treatment.

CT scanning and CT data analysis

Spiral CT was performed using a ProSeed SA (General Electric Health care, Milwaukee, Wisconsin, USA). The entire thorax was scanned in 1-cm-thick sections with maximal inspiration. World Health Organization (WHO) response criteria were used for efficacy analysis of the tumor.[8] The criterion of CT definition for suspected metastasis of the lymph node was a short-axis diameter of 1 cm or larger. The area of the tumor was calculated as the multiplication of the longest diameter and the shortest diameter. The decrease in tumor area on CT after neoadjuvant treatment was calculated using the following formula: tumor area after neoadjuvant treatment/tumor area before neoadjuvant treatment.

Pathologic response

Pathologic response was defined according to the article of The Japan Lung Cancer Society.[9] A major pathologic response was defined as a residual tumor less than one-third the size of the original tumor. A minor pathologic response was defined as residual tumor greater than or equal to one-third of the original tumor. The pathologic response was determined by comparing the ratios of FDG-uptake and tumor area on CT before and after neoadjuvant treatment in the 15 available patients.

Statistical analysis

True positive (TP), true negative (TN), false positive (FP) and false negative (FN) results of PET for residual tumor and lymph nodes were compared with the results of pathologic diagnosis. Sensitivity was calculated as TP/TP+FN, specificity as TN/TN+FP, positive predictive values (PPV) as TP/TP+FP, negative predictive values (NPV) as TN/TN+FN and accuracy as TP+TN/total. The differences between major pathologic response and minor pathologic response of the tumor by FDG-uptake and size on CT were examined by the Mann-Whitney *U* test. The data obtained by FDG-PET and CT were compared by the chi-squared test. The data were considered statistically significant at $p<0.05$. All values are expressed as the mean±SD.

Table 2. FDG-PET, CT, and residual viable tumor cells in the primary site

	Viable tumor cells	
	+	−
PET positive	16	2
PET negative	4	0
CT positive	20	2
CT negative	0	0

FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; CT, computed tomography.

Results

Detection of residual viable tumor at the primary site

While the effects of neoadjuvant treatment determined by CT were partial response in 12 and no change in 10 (Table 1), pathologic examination of the resected tumor showed that there were no viable cells in two patients. The results of the correlation between FDG-PET, CT and viable tumor cells are shown in Table 2. There were 16 patients with TP, four with FN and two with FP results by FDG-PET, 20 patients with TP and two patients with FP results by CT. There were no significant differences in the results of FDG-PET and CT.

Lymph node staging with PET and CT

A comparison of clinical (after neoadjuvant treatment) and pathologic lymph node status determined by FDG-PET and CT is shown in Table 3. FDG-PET and CT accurately predicted nodal status in 11 (50%) and 10 patients (45%), respectively. A comparison of clinical and pathologic node status in N1, N2 and N3 stations determined by FDG-PET and CT is shown in Table 4. Sensitivity, specificity, PPV, NPV and accuracy of FDG-PET and CT are summarized in Tables 5 and 6. PPV by FDG-PET (0.29) was significantly lower than that by CT (0.64) ($p=0.04$) in the N2 lymph node stations. However, there were no significant differences in the other results of FDG-PET and CT.

Table 3. Comparison of clinical and pathological nodal status by FDG-PET and CT

PET	Pathological nodal status			
	N0	N1	N2	N3
N0	5	2	2	0
N1	0	1	1	0
N2	2	3	4	1
N3	0	0	0	1

CT	Pathological nodal status			
	N0	N1	N2	N3
N0	5	2	2	0
N1	0	1	1	0
N2	2	3	4	2
N3	0	0	0	0

FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; CT, computed tomography.

Table 4. Comparisons between clinical and pathologic nodal status with FDG-PET and CT

		Lymph node metastasis	
		+	−
N1 station (n=24)	PET positive	4	5
	PET negative	1	14
	CT positive	2	1
	CT negative	3	18
N2 station (n=72)	PET positive	8	20
	PET negative	6	38
	CT positive	7	4
	CT negative	7	54
N3 station (n=7)	PET positive	2	0
	PET negative	2	3
	CT positive	0	0
	CT negative	4	3

FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; CT, computed tomography.

Table 5. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for lymph node staging by FDG-PET after neoadjuvant treatment

Test	N1 lymph nodes	N2 lymph nodes	N3 lymph nodes	All lymph nodes
Sensitivity	0.80	0.57	0.50	0.61
Specificity	0.74	0.66	1.00	0.69
PPV	0.44	0.29	1.00	0.36
NPV	0.93	0.86	0.60	0.86
Accuracy	0.75	0.64	0.71	0.67

PPV, positive predictive value; NPV, negative predictive value; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography.

Table 6. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for lymph node staging by CT after neoadjuvant treatment

Test	N1 lymph nodes	N2 lymph nodes	N3 lymph nodes	All lymph nodes
Sensitivity	0.40	0.50	0.00	0.39
Specificity	0.95	0.93	1.00	0.94
PPV	0.67	0.64	0.00	0.64
NPV	0.86	0.89	0.43	0.84
Accuracy	0.83	0.85	0.43	0.82

PPV, positive predictive value; NPV, negative predictive value; CT, computed tomography.

Pathologic response

In the 15 patients who underwent FDG-PET before and after neoadjuvant treatment, the ratios of FDG-uptake before and after neoadjuvant treatment in the major pathologic response patients (0.34±0.19) were significantly lower than those in the minor response patients (0.73±0.10)(p=0.003)(Fig. 1A). The ratios of tumor size on CT before and after neoadjuvant treatment in the major pathologic response patients (0.39±0.15) were also significantly lower than those in the minor pathologic response group (0.78±0.25)(p=0.009) (Fig. 1B). There was no significant difference in the ability of FDG-uptake or tumor size on CT to predict pathologic response.

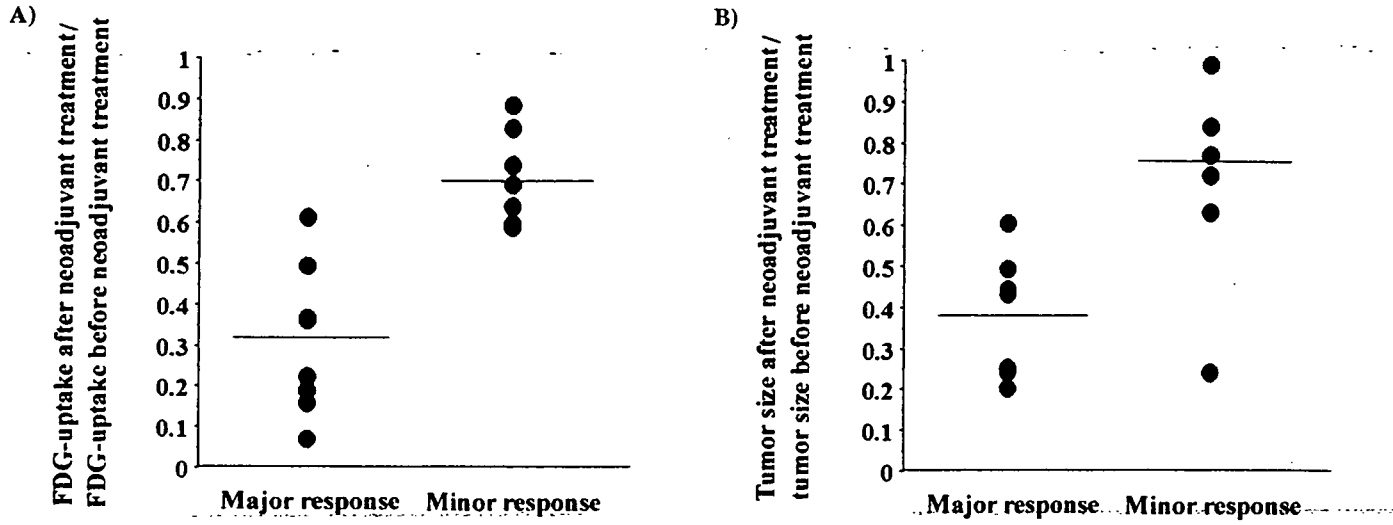

Fig. 1.

A: Distributions of the ratios of FDG-uptake in patients with a major and a minor pathologic response. The ratios of FDG-uptake in patients with a major pathologic response (0.34±0.19) were significantly lower than those in the group with minor pathologic response (0.73±0.10)(p=0.003).

B: Distributions of the ratios of the size in patients with a major and a minor pathologic response. The ratios of tumor size in patients with a major pathologic response (0.39±0.15) were also significantly lower than those in the group with minor pathologic response (0.78±0.25)(p=0.009).

Discussion

Surgical resection has limited success in curing locally advanced non-small cell lung cancer. Recently, combined modality treatment for locally advanced non-small cell lung cancer has been performed.[2] However, accurate staging of lung cancer is still difficult after neoadjuvant treatment.[10-12] FDG-PET, which does not use the criterion of size, might be more accurate for detecting the actual presence of tumor in the lymph nodes than CT. In mediastinal lymph node staging of lung cancer without neoadjuvant treatment, sensitivity and specificity are reported to be 0.71-0.91 and 0.67-0.94, respectively.[2-4,13] Several studies have shown good results for FDG-PET for the staging of lung cancer, even in patients who had received neoadjuvant treatment.[14-16] Akhurst et al. reported that FDG-PET could accurately detect residual viable primary tumor,[15] and Cerfolio et al. showed that FDG-PET had a higher PPV and NPV than CT for detecting residual tumor and paratracheal lymph nodes in patients who had received preoperative chemotherapy.[16] On the other hand, Port et al. reported that FDG-PET did not accurately predict nodal stage after neoadjuvant treatment.[17]

The current study showed that FDG-PET had a low PPV (0.29) when diagnosing mediastinal lymph nodes after neoadjuvant treatment. There were 20 FP lymph nodes (28%) among the 72 N2 lymph nodes. This poor result is thought to be due to inflammatory lesions with invasion of macrophages and lymphocytes in the lymph nodes caused by chemotherapy or radiation therapy. These lesions may be responsible for the increased uptake of FDG and the FP findings reported previously.[18]

Port et al. showed that FDG-PET did not reliably predict pathologic response to preoperative chemotherapy in non-small cell lung cancer.[17] However, the current study demonstrates that the FDG-uptake of the primary tumor before and after neoadjuvant treatment was a good predictor of pathologic response of the tumor. We defined a major pathologic response as 'residual tumor less than one-third the size of the primary tumor'. According to this definition, FDG-uptake could reflect the pathologic response of the primary tumor.

Lymph node downstaging of locally advanced non-small cell lung cancer by neoadjuvant treatment correlates with long-term survival.[19,20] FDG-PET did not offer any advantages over CT in the mediastinal lymph node and could not predict the lymph node downstaging of non-small cell lung cancer patients who received neoadjuvant treatment. Therefore, surgical intervention such as endoscopic biopsy or mediastinoscopy will be needed for accurate staging, since surgery after induction treatment is beneficial only in patients with pathologic downstaging.

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Original Articles

[F-18]Fluorodeoxyglucose Positron Emission Tomography Can Predict Pathological Tumor Stage and Proliferative Activity Determined by Ki-67 in Clinical Stage IA Lung Adenocarcinomas

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Objective: To predict a malignant grade of lung cancer by fluorodeoxyglucose positron emission tomography (FDG-PET) scanning, we investigated the correlation between FDG uptake and pathological tumor stage, proliferative activities determined by Ki-67 and cyclin D1, and an alteration of p53, in clinical stage (c-stage) IA lung adenocarcinomas.
Methods: FDG-PET was performed for 71 patients with c-stage IA lung adenocarcinomas. FDG uptake was measured by a contrast ratio (CR) between the tumor and contralateral lung. Ki-67, cyclin D1 and p53 staining scores were examined by immunohistochemistry.
Results: The lesions with ground-glass opacity were found in 26 patients, and solid lesions in 45 by computed tomography. The pathological tumor stages (p-stage) were stage IA in 59 and more advanced stages in 12. The latter had significantly higher CR value than the former ($P < 0.001$). Patients with CR $\geqslant$ 0.55 could be predicted to be at advanced tumor stages, with a sensitivity of 0.83 and a specificity of 0.82. The CR and staining scores of Ki-67 were significantly correlated with each other ($P < 0.0001$), and both the values were significantly higher in advanced tumor stages than in p-stage IA, and were also significantly higher in tumors with intratumoral lymphatic, vascular and pleural involvements than in those without such features ($P < 0.05$–0.0001).
Conclusions: In c-stage IA lung adenocarcinomas, the FDG uptake can predict p-stage and tumor proliferative activity determined by Ki-67. For c-stage IA lung adenocarcinomas showing CR $\geqslant$ 0.55, mediastinoscopy or neoadjuvant chemotherapy is indicated.

Key words: positron emission tomography – lung cancer – adenocarcinoma – tumor stage – proliferative activity – tumor suppressor gene

INTRODUCTION

It has been reported that tumor proliferative activity and alterations of tumor suppressor genes could be prognostic factors in non-small cell lung cancer (NSCLC). Some authors have demonstrated that proliferative activities determined by Ki-67 (1) and cyclin D1 (2–5), and an alteration of p53 were correlated with the prognosis of NSCLC patients (4,6,7). In recent years, F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) has been frequently used for the diagnosis and staging of lung cancer (8–10). FDG uptake has been reported to be correlated not only with the prognosis in NSCLC patients (11,12) but also with the proliferative activity (13,14) and alteration of p53 (7) of the tumor. However, we previously reported that the FDG uptake in NSCLC tumors was dependent on histological types, that is, FDG-uptake of adenocarcinomas correlated with the pathological tumor stage and tumor invasiveness, but that of the other histological types did not (15,16). Therefore, we consider that the correlation between the FDG

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uptake and the proliferative activity or alteration of p53 should be examined in adenocarcinomas, but not in NSCLC including all histological types. Furthermore, FDG uptake is known to be higher in larger tumors (17,18). Therefore, in the present study, we measured the FDG uptake in clinical stage IA adenocarcinomas and investigated its relationships with the pathological tumor stage, intratumoral invasiveness, proliferative activity determined by Ki-67 and cyclin D1 and the alteration of p53.

PATIENTS AND METHODS

PATIENTS

Between December 2001 and February 2005, FDG-PET was performed for 386 patients with pulmonary nodules. Of these, 301 patients had malignant tumors and 178 of the 301 patients had lung adenocarcinoma. Of the 178 adenocarcinoma patients, 77 were diagnosed as clinical stage IA by PET and thin section computed tomography (TSCT: <2 mm in thickness). They were treated by segmentectomy or lobectomy and lymph node dissection. Of these, we excluded six adenocarcinomas < 1 cm, because the spatial resolution of the PET scanner is 0.7–0.8 cm, making it difficult to image the pulmonary nodules that are <1 cm (16). Therefore, we studied 71 patients with clinical stage IA adenocarcinoma with a size range of 1–3 cm.

FDG-PET SCANNING

Patients were instructed to fast for at least 4 h before intravenous (i.v.) administration of F-18 FDG. The dosage of F-18 FDG administered was 125 μCi/kg (4.6 MBq/kg) for non-diabetic patients and 150 μCi/kg (5.6 MBq/kg) for diabetic patients. PET imaging was performed ~60 min after administration of FDG with a POSICAM.HZL m-POWER (Positron Co., Houston, TX, USA). No attenuation-corrected emission scans were initially obtained in two-dimensional, high-sensitivity mode for 4 min per bed position, and taken from the vertical skull through the mid-thighs. Immediately thereafter, a two-bed-position attenuation-corrected examination was performed with 6 min for the emission sequence and 6 min for the transmission sequence at each bed position.

PET IMAGE PROCESSING AND DATA ANALYSIS

The images were usually reconstructed in a 256 × 256 matrix by using ordered subset expectation maximization corresponding to a pixel size of 4 × 4 mm, with section spacing of 2.66 mm. FDG uptake was evaluated by contrast ratio (CR) with contralateral lung, as previously reported (15,16,19). Briefly, the regions of interest (ROI) were placed in the nodules and contralateral normal lung. Highest standardized uptake ratios in the tumor ROI (T) and in the contralateral lung ROI (N) were measured. The CR value was calculated by using the formula $[(T - N)/(T + N)]$ in each nodule as an index of FDG uptake.

PATHOLOGICAL ANALYSIS

Hematoxylin and eosin and Elastica-van Gieson stainings were performed in all sections to investigate the intratumoral lymphatic and vascular invasions and pleural involvement. Pleural involvement was classified as p0, p1, p2 and p3; that is, a p0 tumor did not extend beyond the pleural elastic layer; a p1 tumor invaded the visceral pleural elastic layer, but did not reach the pleural surface; a p2 tumor included tumor exposure on the pleural surface; and a p3 tumor invaded the parietal pleura or the chest wall. The tumor stages were based on the TNM classification of the International Union Against Cancer (20): p2 tumors were classified as T2, p3 tumors were classified as T3 and tumors with intrapulmonary metastases within the same lobe were classified as T4.

PREDICTING ADVANCED TUMOR STAGES FROM FDG UPTAKE

Receiver operating characteristics (ROC) curve (21) was constructed according to the CR value, and the cut-off value was determined for predicting the pathological stages that were more advanced than stage IB.

IMMUNOHISTOCHEMICAL ANALYSIS

Immunostaining was performed by using the Dako envision system (Dako Cytomation, Glostrup, Denmark). The antibodies for Ki-67(monoclonal mouse antibody MIB-1, 1 : 100 dilution), cyclin D1 (monoclonal mouse antibody DCS-1, 1 : 50 dilution) and p53 (monoclonal mouse antibody, DO7, 1 : 400 dilution) were purchased from Dako Co. Sections of 4 μm were cut from the paraffin blocks. Immunostaining was performed with antigen-retrieval techniques.

EVALUATION OF IMMUNOHISTOCHEMICAL STAINING

Ki-67

According to the method of Martin et al. (1), the labeling index of Ki-67 was measured by determining the percentage of cells with positive nuclei in >1000 tumor cells in >4 fields.

Cyclin D1 and p53

The Allred score used to examine the staining scores of cyclin D1 as well as p53 was obtained by determining the percentage of positive tumor cells and staining intensity (22). Briefly, a percentage score was measured by determining the percentage of positive tumor cells in >1000 tumor cells in >4 fields (0, none; 1, <1/100; 2, 1/100–1/10; 3, 1/10–1/3; 4, 1/3–2/3; 5, >2/3). An intensity score was measured by the average of staining intensity (0, none; 1, weak; 2, intermediate; and 3, strong). The sum of the percentage score and the intensity score was used as the Allred score.

STATISTICAL ANALYSIS

The values of CR and staining scores of Ki-67, cyclin D1 and p53 were compared between the pathological stage IA and the

Table 1. Patients' characteristics

Gender	
Male	45
Female	26
Age (years)	62 ± 10 (33–83)*
Size (mm)	19 ± 7 (10–30)*
CT findings	
GGO	26
Solid	45
Pathological stage	
IA	59
≥IB	12
T2N0M0	3
T1N1M0	4
T2N1M0	1
T1N2M0	1
T4N0M0	2
T4N2M0	1

*Mean ± standard deviation (range), GGO: ground-glass opacity.

more advanced stages and between the two groups with or without intratumoral lymphatic, vascular invasion and pleural involvement, by the non-parametric Mann–Whitney's *U*-test. The correlations between the CR values and the staining scores of Ki-67, cyclin D1 and p53 were analyzed by using the non-parametric Spearman's rank test. All values in the text and tables are given as mean ± standard deviation.

RESULTS

Table 1 shows patients' characteristics. The lesion showing ground-glass opacity (GGO) image were found in 26 patients, and the solid lesions in 45 patients at visual TSCT findings. The pathological tumor stages were T1N0M0 in 59 patients and more advanced in 12 patients (i.e. T2N0M0 in 3, T1N1M0 in 4, T2N1M0 in 1, T1N2M0 in 1, T4N0M0 in 2 and T4N2M1 in 1).

Figure 1 shows the distribution of CR values in 59 patients with pathological stage IA and 12 patients with more advanced stages. The mean CR value of the 12 patients with advanced stages was 0.66 ± 0.12, which was significantly higher than 0.32 ± 0.18 of the 59 patients with pathological stage IA ($P < 0.001$).

Figure 2 depicts the ROC curve for predicting tumor stages more advanced than IB, showing the optimal CR cut-off value to be 0.55, of which sensitivity, specificity and accuracy were 0.83, 0.81 and 0.82, respectively. While 10 of the 12 patients (83%) with the advanced stage showed CR values ≥ 0.55, 48 of the 59 patients (81%) with pathological stage IA showed CR values < 0.55 (Table 2).

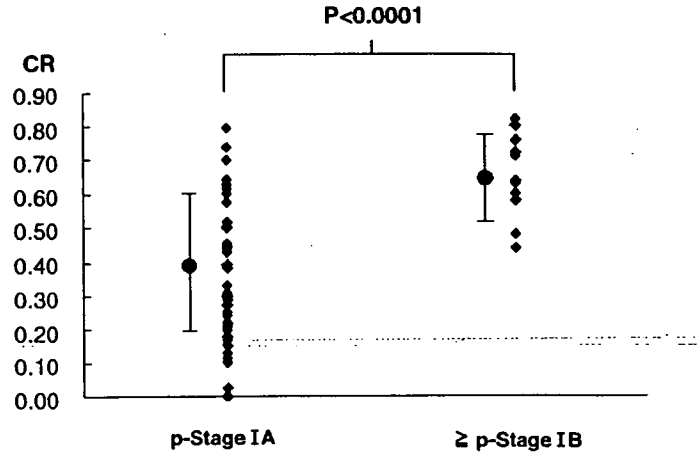

Figure 1. The distribution of CR values in the 59 patients with pathological stage IA and 12 patients with stages advanced more than IA. (CR = contrast ratio).

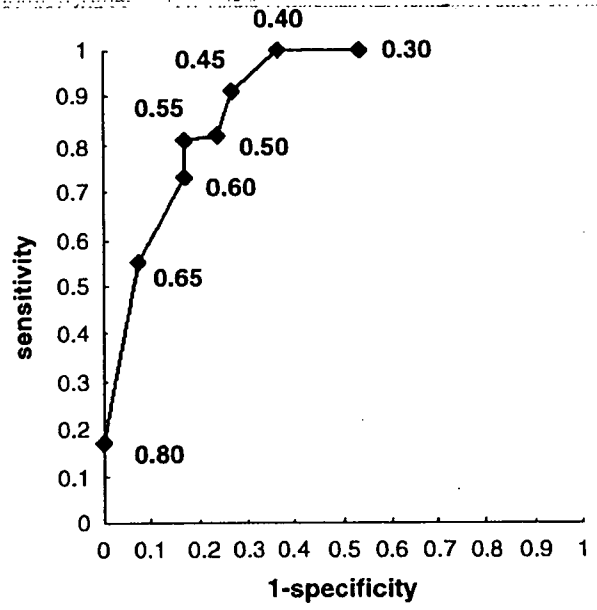

Figure 2. The ROC curve and CR values for predicting tumor stages more advanced than IA. (ROC = receiver operating characteristics; CR = contrast ratio).

Figures 3–5 show the distribution of staining scores of Ki-67, cyclin D1 and p53 in the 59 patients with pathological stage IA and 12 patients with more advanced stages. The mean score for Ki-67 in the 12 patients with advanced stages was 18.0 ± 11.0, which was significantly higher than 9.4 ± 12.0 for the 59 patients with pathological stage IA ($P = 0.012$). However, the mean scores for cyclin D1 in the advanced tumor stages and pathological stage IA were 3.9 ± 1.7 and 4.1 ± 1.8, respectively, of which difference was not significant. The mean scores for p53 in the advanced tumor stages and pathological stage IA were 3.3 ± 3.6 and 2.6 ± 2.6, respectively, of which difference was also not significant.

Table 2. Pathological tumor stage with the cut-off value of CR at 0.55

Pathological tumor stage	CR ≥ 0.55	CR < 0.55	Total
IA	11	48	59
≥IB	10	2	12
Total	21	50	71

≥IB: advanced stage more than IB.

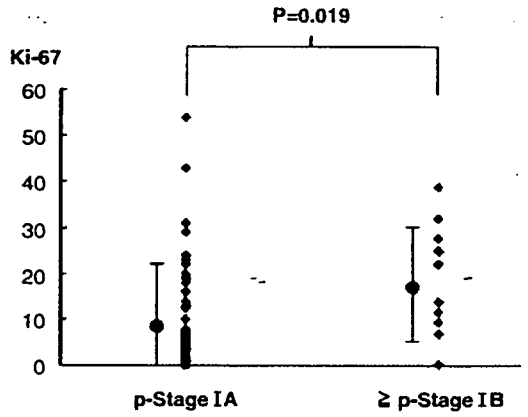

Figure 3. The distribution of Ki-67 staining scores in the 59 patients with pathological stage IA and 12 patients with stages advanced more than IA.

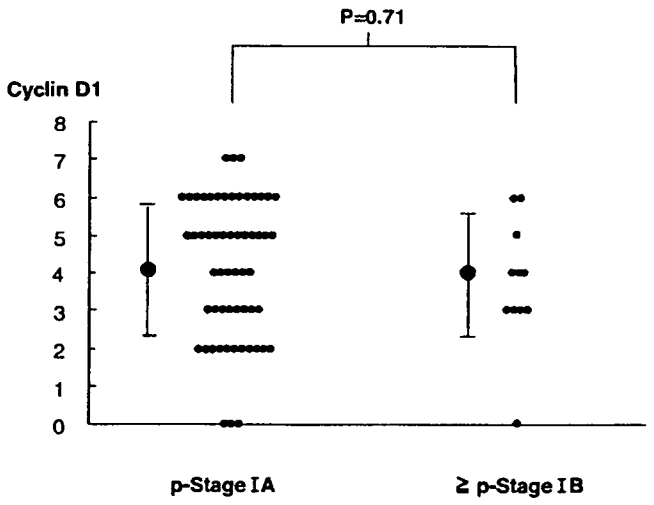

Figure 4. The distribution of cyclin D1 staining scores in the 59 patients with pathological stage IA and 12 patients with stages advanced more than IA.

Table 3 shows the mean values of CR, Ki-67, cyclin D1 and p53 staining scores in tumors with or without intratumoral lymphatic, vascular and pleural involvements. Tumors with intratumoral lymphatic, vascular and pleural involvements had significantly higher values of both CR and Ki-67 staining scores ($P < 0.05$–0.001). However, there were no significant differences of tumor invasiveness in the cyclin D1 and p53 staining scores.

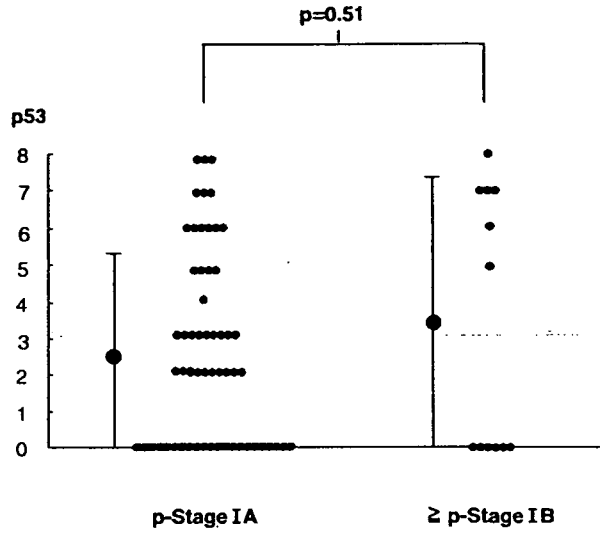

Figure 5. The distribution of p53 staining scores in the 59 patients with pathological stage IA and 12 patients with stages advanced more than IA.

Table 4 shows the mean values of CR and Ki-67 staining scores in tumors with stage IA and advanced stages in tumors with GGO and solid images. In 26 tumors with GGO image, 25 were stage IA and the other one was stage IB. The GGO tumors showed significantly lower CR and Ki-67 staining scores than the solid tumors ($P < 0.001$). The mean values of CR of the 25 GGO tumors with stage IA was 0.17 ± 0.14, while the CR of the one tumor with stage IB was 0.48. The mean values of Ki-67 staining scores of the 25 GGO tumors with stage IA was 4.7 ± 6.9, while the CR of the one tumor with stage IB was 0.16. In 45 tumors with solid image, 34 were stage IA and 11 were more advanced than stage IB. The mean values of CR of the 34 solid tumors with stage IA was 0.43 ± 0.20, which was significantly lower than 0.67 ± 0.11 of the 11 tumors with more advanced stages ($P < 0.001$). The mean values of Ki-67 staining scores of the 34 solid tumors with stage IA was 13 ± 13, which was lower than 21 ± 10 of the 11 solid tumors with more advanced stages ($P = 0.056$).

The CR value and Ki-67 staining scores were significantly correlated with each other ($r = 0.42$, $P < 0.0001$) (Fig. 6). However, both cyclin D1 and p53 scores did not show any correlation with the CR values ($r = 0.05$ and 0.07, respectively).

DISCUSSION

Although the standard uptake value (SUV) has been frequently used for evaluation of FDG-PET, it has been reported that several factors can affect the SUV, such as body size (23), blood glucose level (24), time after injection (25) and lesion size (17,18). In fact, the mean SUV of malignant pulmonary nodules has been reported to be various, ranging from 5.5 to 10.1 (26–29). We previously compared the results of SUV, CR with contralateral lung and CR with cerebellum for pulmonary nodules, and reported that the CR with contralateral lung or

Table 3. Correlation between intratumoral invasiveness and CR values and staining scores of Ki-67, cyclin D1 and p53

Invasiveness	Number of patients	CR	Ki-67	p53	Cyclin D1
ly (−)	38	0.29 ± 0.21	5.6 ± 8.1	2.2 ± 2.3	3.9 ± 1.8
(+)	33	0.48 ± 0.21*	17 ± 13*	3.4 ± 3.1	4.3 ± 1.8
v (−)	58	0.34 ± 0.23	9.9 ± 12	2.9 ± 2.7	4.1 ± 1.8
(+)	13	0.55 ± 0.20**	17 ± 12***	2.1 ± 3.0	3.8 ± 1.7
p 0	63	0.34 ± 0.20	9.7 ± 12	2.5 ± 2.6	4.1 ± 1.8
1–2	8	0.63 ± 0.13*	21 ± 8.3**	4.5 ± 3.6	3.8 ± 2.0

CR, contrast ratio; ly, lymphatic invasion; v, vascular invasion; p, pleural involvement.
*$P < 0.001$.
**$P < 0.01$.
***$P < 0.05$.

Table 4. The values of CR and Ki-67 of tumors with stage IA and advanced stages in tumors with solid and GGO images

Tumor findings and pathological stage	CR	Ki-67
GGO		
All cases ($n = 26$)	0.18 ± 0.14	4.5 ± 6.8
Stage IA ($n = 25$)	0.17 ± 0.14	4.7 ± 6.9
Stage IB ($n = 1$)	0.48	0.16
Solid		
All cases ($n = 45$)	0.48 ± 0.2*	15 ± 13*
Stage IA ($n = 34$)	0.43 ± 0.20	13 ± 13
≥Stage IB ($n = 11$)	0.67 ± 0.11†	21 ± 10

GGO, ground-glass opacity; CR, contrast ratio.
*The differences of CR or Ki-67 staining scores between the GGO and solid lesions were $P < 0.001$.
†The difference of CR between the tumors with stage IA and ≥stage IB was $P < 0.001$.

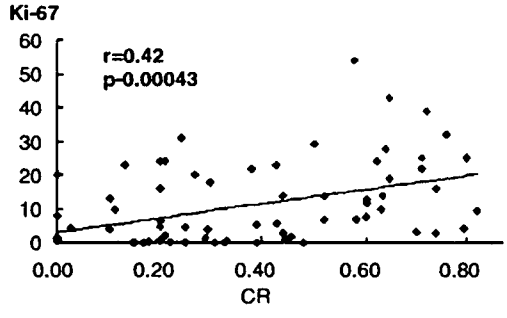

Figure 6. The correlation between CR values and Ki-67 staining scores in the 71 patients with clinical stage IA.: $r = 0.42$; $P = 0.00043$.

cerebellum showed significantly higher sensitivity than the SUV (19). We therefore used the CR value with contralateral lung in the present study.

The present study has demonstrated the following points: (i) tumors with high FDG uptake (CR ≥ 0.55) could be identified as those at stages that are more advanced than stage IB with the sensitivity of 0.83 and the specificity of 0.81; (ii) FDG uptake and Ki-67 staining scores correlated with the pathological tumor stage and intratumoral invasiveness, although cyclin D1 and p53 did not show such correlation; and (iii) FDG uptake and Ki-67 scores were significantly correlated with each other.

Earlier reports have indicated that adenocarcinomas with GGO image are usually N0 stage and show low FDG uptake on PET (15,16,30). The present study is basically in agreement with these results, that is, adenocarcinomas with GGO image showed lower FDG uptake than those with solid one. However, one adenocarcinoma with GGO image was stage IB, which showed rather high CR than 25 stage IA tumors. In tumors with solid image, the 11 tumors with advanced stages showed significantly higher CR values than the 34 tumors with stage IA. Therefore, the FDG uptake on PET could be an independent factor for predicting pathological stage in clinical T1N0M0 lung adenocarcinomas.

It has been reported that 25% of clinical stage IA adenocarcinomas are pathologically advanced tumor stage (31). Recently, neoadjuvant chemotherapy has been reported to improve survival in clinical stages IB, II and IIIA of NSCLC (32). The present study showed that the CR value of 0.55 could be the cut-off value for predicting advanced tumor stages more than IB. Therefore, we propose that to improve patients' prognosis in clinical stage IA adenocarcinoma, mediastinoscopy or neoadjuvant chemotherapy should be performed for clinical stage IA adenocarcinoma with CR ≥ 0.55.

The Ki-67 antigen exists in the nucleus of proliferating cells and has been reported to be a prognostic factor in lung cancer (1). Vesselle et al. (14) reported that the FDG uptake correlated with Ki-67 staining scores in 39 patients with NSCLC. They also described that the correlation between the FDG-uptake and Ki-67 staining scores was stronger in stage I than in stages I–III. Their report supported the present study, showing a significant correlation between the FDG uptake and Ki-67 staining scores in clinical stage IA lung adenocarcinomas.

Cyclin D1 is known to regulate the G_1-to-S phase transition during the cell cycle, and its expression in tumor cells is reported to correlate with their proliferative activity. However, several immunohistochemical studies on involvement of cyclin D1 in lung cancer had shown different results (2–5). While some authors reported the opposite finding, that is, the cyclin D1 staining scores was a predictor of poor prognosis of NSCLC (4,5), others have questioned its role as a predictor (3).

On the other hand, another report described that the negative staining for cyclin D1 correlated with poor prognosis (2). While these previous studies examined the expression of cyclin D1 in NSCLC including all histological types, the present study investigated the clinical stage IA adenocarcinomas, showing that cyclin D1 scores did not correlate with the FDG uptake, pathological tumor stage or tumor invasiveness. Our results indicate that Ki-67 is a better marker for the proliferative activity and malignant grade of adenocarcinomas than cyclin D1.

An alteration of p53 is reported to be a poor prognostic factor in many types of tumors including lung cancer (6), although one recent report has denied it (2). While Sasaki et al. (7) reported that the FDG uptake in tumors with the alteration of p53 tended to be higher than in those without, the present study did not find any correlation of p53 staining scores with the FDG uptake, tumor stage and intratumoral invasiveness in clinical stage IA lung adenocarcinomas. The differences between the report by Sasaki et al. and ours were (i) the number of the patients (28 versus 71 patients); (ii) histological types (NSCLC including all histological types versus adenocarcinoma); (iii) size of tumors (17,18) (no details about specific sizes versus 1–3 cm); (iv) measurement of FDG uptake (SUV versus CR). As described in our previous reports, the FDG uptake should be measured by CR and not by SUV, and should also be evaluated in adenocarcinomas with limited tumor size (16,19). Therefore, we believe that the alteration of p53 does not correlate with FDG uptake and therefore cannot be a dictator for the malignant grade in clinical stage IA lung adenocarcinomas.

We conclude that the FDG uptake can predict pathological tumor stage and tumor proliferative activity determined by Ki-67, but cannot predict the alteration of p53 in clinical stage IA lung adenocarcinomas. These results should be useful in determining the indication for mediastinoscopy or neoadjuvant chemotherapy in patients with clinical stage IA lung adenocarcinoma.

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Prognostic Significance of [^{18}F]Fluorodeoxyglucose Uptake on Positron Emission Tomography in Patients With Pathologic Stage I Lung Adenocarcinoma

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BACKGROUND. [^{18}F]Fluoro-2-deoxyglucose uptake on positron emission tomography (FDG-PET) has been frequently used for diagnosis and staging of lung cancer. The prognostic significance of FDG uptake on PET was evaluated in patients with pathologic Stage I lung adenocarcinoma (tumor stages were based on the TNM classification of the International Union Against Cancer).

METHODS. Disease-free survival of 98 patients with pathologic Stage I lung adenocarcinoma who were treated by curative resection was examined in relation to sex, age, histologic grade of differentiation, surgical procedure, tumor stage, and FDG uptake measured as the maximum standardized uptake value (SUV).

RESULTS. Sixty-three patients were had Stage IA disease and 35 patients had Stage IB disease. Six patients each with Stage IA and Stage IB disease developed disease recurrence after a mean postsurgical follow-up period of 31 months. Ten (23%) of the 43 patients with SUV $\geq$ 3.3 developed a recurrence compared with 2 (4%) of the 55 patients with SUV < 3.3 (P = .020). Ten (20%) of the 51 patients with moderately or poorly differentiated adenocarcinoma developed disease recurrence, compared with 2 (4%) of the 47 patients with well-differentiated adenocarcinoma (P = .056). Multivariate analysis demonstrated that histologic grade of differentiation was not correlated with the frequency of tumor recurrence (P = .286), whereas SUV was found to be marginally correlated (P = .079).

CONCLUSIONS. FDG uptake appears to be predictive of disease-free survival in patients with Stage I lung adenocarcinoma. FDG uptake could yield important information for determining the likely value of postoperative adjuvant chemotherapy in such patients. *Cancer* **2006;107:2468–73.** © *2006 American Cancer Society.*

KEYWORDS: lung cancer, positron emission tomography, prognosis, recurrence.

Although patients with Stage II or Stage III nonsmall cell lung cancer (NSCLC) can generally be considered candidates for postoperative chemotherapy, it is still difficult to determine whether it would be useful for patients with Stage I after complete resection. To determine the potential usefulness of postoperative adjuvant chemotherapy in patients with Stage I NSCLC, it is important to clarify the prognostic factors in these patients.

In recent years, [^{18}F]fluoro-2-deoxyglucose uptake on positron emission tomography (FDG-PET) has been used frequently for diagnosis and staging of lung cancer.[1–3] It has also been reported that FDG uptake on PET can be a prognostic factor in patients with NSCLC.[4,5] However, FDG uptake is dependent on the histologic cell type of NSCLC (i.e., FDG uptake by adenocarcinoma is correlated with pathologic tumor stage and tumor invasiveness, whereas that of other histologic types is not).[6,7] We considered that the prognostic

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TABLE 1
Patient Characteristics and Number of Patients With Recurred Patients

	No. of patients	No. of recurred patients	Hazards ratio (95% CI)	P
Sex				
Male	56	9		
Female	42	3	0.40 (0.11–1.48)	.169
Age, y				
≥60	64	7		
<60	34	5	0.99 (0.22–2.12)	.949
Histologic grade of differentiation				
Well	47	2		
Moderately	39	6	4.39 (0.96–20.09)	.057*
Poorly	12	4		
Surgery				
Pneumonectomy	1	1		
Lobectomy	80	9	0.97 (0.21–4.51)	.970†
Segmentectomy	17	2		
Pathologic stage‡				
IA	63	6		
IB	35	6	0.67 (0.22–2.11)	.497
SUV				
≥3.3	43	10		
<3.3	55	2	6.05 (1.32–27.65)	.020

95% CI indicates 95% confidence interval; SUV, standardized uptake value.
* P value was calculated between the well-differentiated adenocarcinoma and the moderately or poorly differentiated one.
† P value was calculated between the pneumonectomy or lobectomy group and segmentectomy group.
‡ Tumor stages were based on the TNM classification of the International Union Against Cancer.

significance of FDG uptake should be examined in adenocarcinomas, but not in NSCLC including all histologic types. Therefore, in the current study, we examined the prognostic significance of FDG uptake in patients with pathologic Stage I lung adenocarcinoma.

MATERIALS AND METHODS

Between December 2001 and January 2005, FDG-PET was performed on 377 patients with pulmonary tumors. Of these patients, 232 had NSCLC and underwent surgery. Of these 232 patients, 109 had pathologic Stage I disease. We excluded 6 patients whose tumors measured <1 cm in greatest dimension because the spatial resolution of the PET scanner is 0.7 to 0.8 cm, making it difficult to image pulmonary nodules that are <1 cm in size.[6] We also excluded 4 patients with squamous cell carcinoma and 1 patient with carcinosarcoma. There was no patient with bronchioloalveolar cell carcinoma. As a result, 98 patients with pathologic Stage I adenocarcinoma who underwent FDG-PET scanning followed by major pulmonary resection with systematic lymph node dissection were eligible to participate in this study (Table 1). The medical records of each patient were examined with regard to sex, age, operative procedure, tumor stage (Stage IA or Stage IB), and histologic grade of differentiation. The tumor stages were based on the TNM classification of the International Union Against Cancer.[8] Patients were excluded if they had undergone any chemotherapy or radiotherapy before PET scanning. The histologic grade was classified as well, moderately, or poorly differentiated.

PET Data Analysis

The FDG-PET data were evaluated semiquantitatively on the basis of maximum standardized uptake value (SUV). To measure the maximum SUV, a region of interest (ROI) was placed over the tumor after correction for radioactive decay. The maximum activity in the tumor ROI was then calculated as tumor activity/injected dose / body weight.

Follow-up and Assessment of Tumor Recurrence

Patients were followed for cancer recurrence. Follow-up data were obtained every 3 months for the first 2 years and every 6 months thereafter. Chest and abdominal computed tomography (CT) scans were performed every 6 months. Each follow-up visit was supplemented by chest radiography, serum biochemistry, tumor marker assay, and any other test required to examine suspected tumor recurrence. In addition, if patients became symptomatic or demonstrated abnormal laboratory findings, appropriate testing (i.e., brain CT and bone scintigraphy) was performed as well. Recurrence was defined as any unequivocal occurrence of new cancer foci in a disease-free patient.

Statistical Analysis

Receiver operating characteristic (ROC) curves of SUV for the prediction of recurrence were generated using MedCalc (Medisoftware, Mariakerke, Belgium) by plotting sensitivity versus 1-specificity for varying thresholds of SUV. The best combination between sensitivity and specificity was found. Patients with disease recurrence who exceeded the SUV threshold were defined as true-positive and patients without disease recurrence whose SUVs were less than this were defined as true-negative. Patients with disease recurrence whose SUVs were below the threshold were defined as false-negative, and patients without disease recurrence who exceeded the SUV threshold were defined as false-positive. Sensitivity was calculated as true-positive/true-positive + false-negative, and specificity was calculated as true-negative/true-negative + false-positive. The ROC curve was used to determine the cutoff value that yielded the optimal sensitivity and specificity.

The duration of disease-free survival was measured from the date of surgery until the first evidence of disease recurrence or the last date of follow-up for

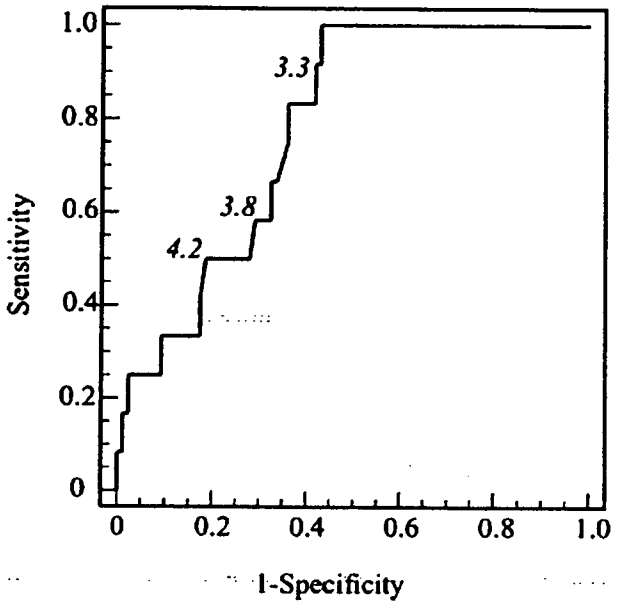

FIGURE 1. The receiver operating characteristic (ROC) curve of the standardized uptake value (SUV) for the prediction of recurrence. Cutoff values for SUV are shown in italics.

patients who remained alive and free of disease. The disease-free interval was analyzed according to the Kaplan-Meier method, and the differences in disease-free survival were assessed by using the log-rank test. Univariate and multivariate analyses (Cox proportional hazards model) were performed to determine independent prognostic predictors.[9] All variables with $P < .1$ in the univariate analysis were entered in the multivariate analysis. Differences at $P < .05$ were defined as being statistically significant.

RESULTS

Disease-Free Survival and Univariate Analysis

The median follow-up period after surgery in the 98 patients was 31 months (range, 14–50 months). There was no surgical death or loss to follow-up. Twelve patients (i.e., 6 patients each with Stage IA and Stage IB disease) developed disease recurrence after surgery. The ROC curve showed that the optimal cutoff value for predicting recurrence was 3.3 (area under the curve, 0.784; standard error of 0.081) (Fig. 1). Using an SUV of 3.3 yielded a sensitivity of 0.917 and a sensitivity of 0.628, a positive predictive value of 0.256, and a negative predictive value of 0.982. The distribution of mean SUV was 3.81 and the standard deviation was 3.75 (range, 0.87–26.2).

Table 1 shows the patient characteristics including sex, age (age ≥60 years or age <60 years), histologic grade of differentiation (well, moderately, or poorly differentiated), surgical procedure (pneumonectomy, lobectomy, or segmentectomy), and SUV (≥3.3 or <3.3) and results of *P* value and hazard ratio by univariate analysis. Sixty-four patients were age ≥60 years and 34 were age <60 years. There were 56 male and 42 female patients. Surgical procedures included pneumonectomy in 1 patient, lobectomy in 80 patients, and segmentectomy in 17 patients. Histologically, the tumors were well differentiated in 47 patients, moderately differentiated in 39 patients, and poorly differentiated in 12 patients. Sixty-three patients had Stage IA disease and 35 had Stage IB disease. Forty-three patients had tumors with an SUV ≥ 3.3 and 55 patients had an SUV < 3.3.

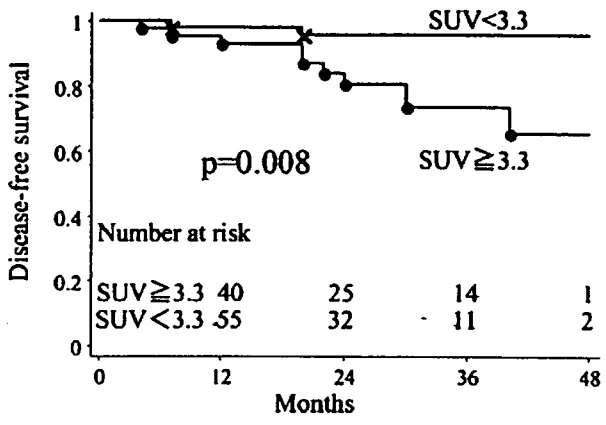

FIGURE 2. Disease-free survival of the 98 patients with pathologic Stage I adenocarcinoma according to the standardized uptake value (SUV) of the primary tumor.

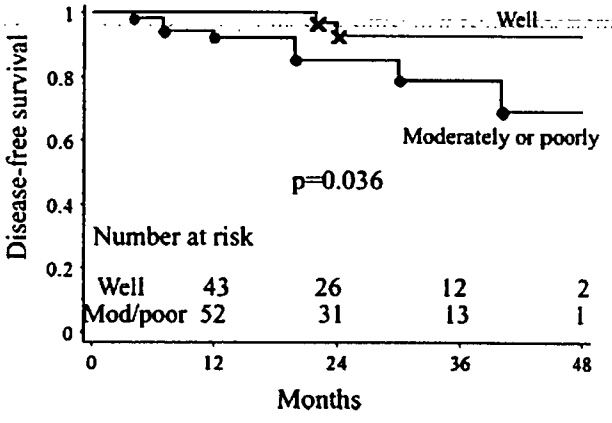

FIGURE 3. Disease-free survival of the 98 patients with pathologic Stage I adenocarcinoma according to the histologic grade of differentiation. Mod/poor indicates moderately/poorly differentiated.

As shown in Figure 2, there was a significant difference in disease-free survival between the those patients with an SUV ≥ 3.3 and those with an SUV < 3.3 ($P = .008$). A significant difference was also noted

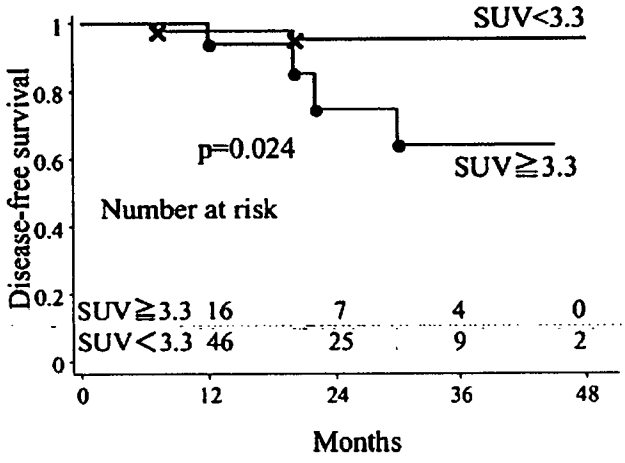

FIGURE 4. Disease-free survival of the 63 patients with pathologic Stage IA adenocarcinoma according to the standardized uptake value (SUV) of the primary tumor.

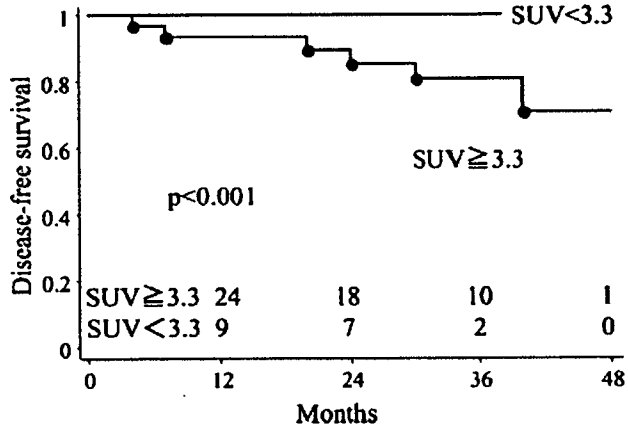

FIGURE 5. Disease-free survival of the 35 patients with pathologic Stage IB adenocarcinoma according to the standardized uptake value (SUV) of the primary tumor.

between moderately or poorly differentiated adenocarcinomas and well-differentiated adenocarcinomas (Fig. 3) ($P = .036$). For both Stage IA and IB disease, patients with an SUV $\geq$ 3.3 demonstrated more frequent disease recurrence than those with an SUV < 3.3 (Stage IA, $P = .024$ and Stage IB, $P < .001$) (Figs. 4 and 5).

Seventeen (27%) of the 63 patients with Stage IA disease and 26 (74%) of the 35 patients with Stage IB disease had tumors with an SUV $\geq$ 3.3 (Table 2). Among the 12 patients with disease recurrence, 4 (67%) of the 6 patients with Stage IA disease and all (100%) of the 6 patients with Stage IB disease had tumors with an SUV $\geq$ 3.3 (Table 3). None of the 9 patients with Stage IB disease who had an SUV < 3.3 (see Table 2) developed disease recurrence.

TABLE 2
Correlation between Pathologic Stage and FDG Uptake Measured by SUV

Stage*	No. of patients	SUV $\geq$ 3.3	SUV < 3.3
IA	63	17	46
IB	35	26	9
Total	98	44	54

FDG indicates [^{18}F]fluoro-2-deoxyglucose; SUV, standardized uptake value.
* Tumor stages were based on the TNM classification of the International Union Against Cancer.

TABLE 3
Correlation between Number of Patients With Recurrence and FDG Uptake Measured by SUV

Stage*	No. of recurrence	SUV $\geq$ 3.3	SUV < 3.3
IA	6	4	2
IB	6	6	0
Total	12	11	1

FDG indicates [^{18}F]fluoro-2-deoxyglucose; SUV, standardized uptake value.
* Tumor stages were based on the TNM classification of the International Union Against Cancer.

TABLE 4
Multivariate Analysis of Variables for Predicting Disease-Free Survival

Variables	Hazards ratio	95% CI	*P*
SUV ($\geq$3.3 or <3.3)	4.2	0.8-21.5	.079
Histologic grade of differentiation (well or moderately/poorly)	2.4	0.5-12.2	.286

95% CI indicates 95% confidence interval; SUV, standardized uptake value.

Univariate analysis showed that patients with an SUV $\geq$ 3.3 and moderately or poorly differentiated adenocarcinomas demonstrated more frequent disease recurrence compared with those with an SUV < 3.3 and well-differentiated tumors ($P = .020$ and $P = .056$, respectively) (Table 1). Both of the patients with recurrence of well-differentiated adenocarcinoma (shown in Table 1) had an SUV $\geq$ 3.3. There were no significant correlations noted between disease recurrence and other variables including sex, age, surgical procedure, and pathologic stage.

Multivariate Analysis

Multivariate analysis showed that although SUV with a cutoff value of 3.3 did not achieve statistical significance, it was able to predict tumor recurrence well ($P = .079$) (Table 4). Histologic grade of cell differentiation was found to have no correlation with tumor recurrence ($P = .286$).

DISCUSSION

Although TNM staging is the most important prognostic factor in patients with NSCLC, it is well known that approximately 30% of patients with Stage I disease die due to disease recurrence within 5 years after surgery.[10,11] Although some studies have shown that postoperative adjuvant chemotherapy can increase survival in NSCLC patients with Stage IB or Stage II disease,[12–14] to our knowledge it has been unclear which population would benefit most from adjuvant chemotherapy. In addition, to our knowledge there have been no data to indicate the value of adjuvant chemotherapy for patients with pathologic Stage IA NSCLC.

We recently reported that clinical Stage IA lung adenocarcinomas with high FDG uptake had more frequent lymph node metastasis, higher tumor invasiveness, and proliferative activity as determined by Ki-67 staining than those with low FDG uptake.[15] The present study also revealed that patients with adenocarcinomas showing an SUV $\geq$ 3.3 had poorer disease-free survival than those with an SUV $<$ 3.3, for patients with both Stage IA and Stage IB disease. Although further research will be needed to define the usefulness of adjuvant chemotherapy for patients with pathologic Stage I disease, our data suggest that patients with pathologic Stage I disease with an SUV $\geq$ 3.3 could be candidates for adjuvant chemotherapy. We also found that none of 9 patients with Stage IB disease demonstrating an SUV $<$ 3.3 developed disease recurrence. Although several studies have reported the benefit of adjuvant treatment for Stage IB NSCLC,[12–14] it appears that we should refer to SUV before administering adjuvant chemotherapy for patients with Stage IB lung adenocarcinoma.

Although the results of the current study demonstrated that the SUV cutoff value for predicting tumor recurrence was 3.3, Cerfolio et al.[4] and Vansteenkiste et al.[5] reported it to be 10 and 7, respectively. The difference between our result and theirs can be explained as follows: 1) the previous 2 reports examined NSCLC patients with Stage I–IV disease, including patients who were not considered candidates for surgical treatment, but we examined only patients with pathologic Stage I disease who were treated by complete resection and mediastinal lymph node dissection; and 2) the previous 2 reports examined patients with all histologic types of NSCLC, but the present study was limited to adenocarcinoma. Because it is reasonable that patients with advanced disease would have a higher SUV and poorer prognosis than those with early-stage disease, SUV could be concluded to be an important prognostic factor when examining patients with Stage I–IV disease. Cerfolio et al.[4] analyzed their own data in detail and reported that NSCLC patients with an SUV $\geq$ 10 had a higher frequency of disease recurrence than those with an SUV $<$ 10 for Stage IB and Stage II disease, whereas this difference was not significant for patients with Stage IA disease. In addition, it has been reported that the relation between FDG uptake and tumor aggressiveness is significant in adenocarcinoma, but not in other histologic types of NSCLC.[3,6,7] Therefore, we examined the prognostic significance of SUV to determine the potential value of postoperative adjuvant treatment for patients with Stage IA and Stage IB adenocarcinoma, and found that the cutoff value was 3.3.

It has been reported that patients with well-differentiated adenocarcinoma generally have a better postoperative prognosis than those with moderately or poorly differentiated adenocarcinoma at pathologic Stage IA.[16] Although the current study also yielded similar results, the prognostic importance of histologic grade of differentiation was found not to be significant in multivariate analysis. In fact, both patients who developed disease recurrence of well-differentiated adenocarcinoma had tumors with an SUV $\geq$ 3.3. Our results demonstrated that the maximum SUV could be a more reliable factor for predicting recurrence than histologic grade of differentiation in patients with pathologic Stage I adenocarcinoma. However, it should be kept in mind that the small number of enrolled patients is a major limitation of this study, especially for multivariate analysis.

We conclude that FDG uptake measured by maximum SUV has potential value as an independent prognostic factor in patients with Stage I lung adenocarcinoma after surgery, and therefore could yield important information for determining the usefulness of adjuvant chemotherapy in such patients.

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Characteristics of Advantages of Positron Emission Tomography over Computed Tomography for N-staging in Lung Cancer Patients

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Objective: We analyzed the characteristics of advantages of positron emission tomography (PET) over computed tomography (CT) for N-staging in lung cancer patients.
Methods: Preoperative PET and CT scans were performed for 2057 lymph node stations in 205 patients with peripheral-type lung cancer. The advantages of PET over CT for N-staging were analyzed among lymph node locations and histological subtypes.
Results: The pathological N-stages were N0 in 143 patients, N1 in 31, N2 in 24 and N3 in 7. PET was able to diagnose N0, N2 and N3 diseases more accurately than CT ($P = 0.03$, 0.01 and 0.02, respectively), but there was no significant difference between the two modalities for N1 disease. In the upper mediastinal lymph node stations, both false-negative and false-positive were significantly less frequent with PET than with CT ($P = 0.001$). In the lower mediastinal and supra clavicle lymph nodes, PET showed a lower frequency of false-negative than CT ($P = 0.04$ and 0.003, respectively), but there was no significant difference in the frequency of false-positive between the two modalities. Among histological types, PET could stage adenocarcinoma with less frequent false-negative and squamous cell carcinoma with less frequent false-positive than CT ($P = 0.02$ and 0.005, respectively).
Conclusion: For N-staging, PET was superior to CT for the following: (1) more accurate for N0, N2 and N3 diseases but not for N1; (2) lower frequency of false-positive in the upper mediastinal nodes; and (3) lower frequencies of false-negative in adenocarcinoma and false-positive in squamous cell carcinoma. Recognizing these advantages of PET could make the N-staging of lung cancer more accurate.

Key words: positron emission tomography – computed tomography – lymph node stage – lung cancer – adenocarcinoma

INTRODUCTION

CT scanning has been a usual procedure of N-staging of lung cancer. However, CT scanning is not sufficiently sensitive or specific for diagnosing lymph node metastasis, because size is the only criterion used to differentiate benign from malignant lymph nodes (1). In recent years, ^{18}F-fluorodeoxyglucose (FDG)-PET scanning has been used for the staging of lung cancer (2–7). Because of the biological nature of FDG, FDG-PET has been reported to be able to detect metastatic lymph nodes more accurately than CT. A meta-analysis by Dwamena et al. of PET scanning of 514 patients in 14 studies showed that the mean sensitivity and specificity of PET scanning for N-staging were 0.79 (range: 0.62–0.97) and 0.91 (range: 0.79–0.99), respectively, both being superior to those of CT scanning, i.e. 0.60 (range: 0.25–0.89) and 0.77 (range: 0.44–0.95) (1). However, the advantages of PET over CT for lymph node staging of lung cancers have not been fully characterized. In this study we examined the characteristics of advantages of PET over CT for lymph node staging, especially among various lymph node locations and histological types.

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PATIENTS AND METHODS

Subjects

Between December 2001 and March 2005, 205 patients with peripheral lung cancer more than 1 cm in size prospectively underwent FDG-PET and CT scanning during the month before surgery. A total of 2057 lymph node stations in these 205 patients were evaluated. The histological type of lung cancer was adenocarcinoma in 151 patients, squamous cell carcinoma in 37, large cell carcinoma in eight, small cell carcinoma in two, adenosquamous carcinoma in four, carcinosarcoma in two and atypical carcinoid in one (Table 1). The histological criteria were based on the 1999 World Health Organization classification (8). The pathological N stages were N0 in 143, N1 in 31, N2 in 24 and N3 in seven. The classification of lymph nodes was done according to the original lymph node map of lung cancer (9). All patients underwent pneumonectomy, lobectomy, or segmentectomy with mediastinal lymph node dissection, except for seven patients with clinical N3 disease in whom pathological N-stages were evaluated by mediastinoscopy and/or scalene node biopsy.

FDG-PET Scanning

Patients were instructed to fast for at least 4 h prior to intravenous (IV) administration of ^{18}F-FDG. The administered dosage of ^{18}F-FDG was 125 μCi/kg (4.6 MBq/kg) for non-diabetic patients and 150 μCi/kg (5.6 MBq/kg) for diabetic patients. PET imaging was performed approximately 60 min after administration of the FDG with a POSICAM.HZL m-POWER (Positron Co., Houston, Texas, USA). Initially no attenuation-corrected emission scans were obtained during the two-dimensional, high-sensitivity mode for 4 min per bed position, taken from the vertical-skull through the mid-thighs. Immediately thereafter, a two-bed-position attenuation-corrected examination was performed with 6 min for the emission sequence and 6 min for the transmission sequence at each bed position. The images were usually reconstructed in a 256 × 256 matrix by using ordered subset expectation maximization corresponding to a pixel size of 4 × 4 mm, with section spacing of 2.66 mm.

Table 1. Characteristics of patients

Variable	Data
Age (years)	67 ± 19
Sex	
Male	134
Female	71
Tumor size (cm)	3.0 ± 1.8
Histology	
Adenocarcinoma	151
Squamous cell carcinoma	37
Large cell carcinoma	8
Small cell carcinoma	2
Adenosquamous carcinoma	4
Carcinosarcoma	2
Atypical carcinoid	1
Pathological N stage	
N0	143
N1	31
N2	24
N3	7
Total	205

N Staging by PET Scanning

PET data were evaluated visually and/or semi-quantitatively. Based on visual findings, the lymph nodes showing clearly greater or less FDG-uptake than the mediastinal blood pool were diagnosed as positive and negative, respectively. Two examiners (A.E. and K.U.), who were blinded for the pathological N-stage, evaluated the visual findings of PET. For the lymph nodes showing similar FDG-uptake to the mediastinal blood pool or where there was disagreement between the two examiners, semi-quantitative analysis was used as reported previously (10). Briefly, the regions of interest (ROIs) were placed in the lymph nodes and cerebellum. The highest activities in both the lymph node ROI (L) and the cerebellum ROI (C) were measured. The contrast ratio (CR) was calculated by L/C in each lymph node as an index of FDG uptake. The cut-off value was determined as 0.25, i.e. lymph nodes with CR $\geq$ 0.25 were defined as positive and those with CR $<$ 0.25 as negative.

N Staging by CT Scanning

Spiral CT was performed using a ProSeed SA (General Electric Medical System, Milwaukee, USA). The following acquisition parameters were used: high voltage (120 kV), tube load 160 mA, window level −500 Hounsfield units (HU) and window width 1500 HU. The entire thorax was scanned with 0.5 or 1-cm thick sections at 1 breath hold with maximum inspiration. The criterion of CT definition for suspected metastasis of the lymph node was a short-axis diameter of 1.0 cm or larger. Enhanced CT was additionally conducted for patients with CT-negative and PET-positive lymph nodes. The same two examiners for N-staging by PET evaluated the CT findings. For lymph nodes showing disagreement between the two examiners, N-sages were determined after their discussion.

Statistical Analysis

True-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN) results of PET and CT scanning for lymph node metastasis were compared with the results of pathological diagnosis. Sensitivity was calculated as TP/TP + FN, specificity as TN/TN + FP, positive predictive

value as TP/TP + FP, negative predictive value as TN/TN + FN and accuracy as TP + TN/Total. The advantages of PET over CT were evaluated for each pathological N-stage, lymph node location and each histological type. All data were analyzed for significance by using the Stat View software χ^2 test. Differences at $P < 0.05$ were accepted as significant. All values in the text and tables are given as mean ± SD.

RESULTS

Table 2 shows the correlation between the N-staging by PET and CT and pathological N-stage. PET was able to diagnose N0, N2 and N3 diseases more accurately than CT with significant difference ($P = 0.03$, 0.01 and 0.02, respectively). However, there was no difference between PET and CT in the accuracy in diagnosing N1 disease ($P = 0.4$).

Of the 2057 lymph node stations examined, 15 showed similar FDG-uptake to the mediastinal blood pool. Of those 15 lymph nodes, six showed CR ≥ 0.25 (positive) and the remaining nine showed CR < 0.25 (negative). PET scanning yielded TP in 85 lymph node stations, FN in 46, FP in 11 and TN in 1915 (Table 3). For the same lymph node stations, CT scanning yielded TP in 49 lymph node stations, FN in 82, FP in 22 and TN in 1904. As a result, the sensitivity of PET was 0.65, which was significantly higher than 0.37 of CT ($P < 0.0001$). The positive predictive value of PET was 0.89, which was significantly higher than 0.7 of CT ($P = 0.02$). However, there was no significant difference in specificity, accuracy and negative predictive value between the two diagnostic modalities.

The locations of FP lymph node stations revealed by PET and CT are shown in Table 4. Of the 670 upper mediastinal lymph node stations without metastasis, PET showed FP less frequently than CT ($P = 0.001$). One FP upper mediastinal lymph node, demonstrated by PET was Botallo's lymph node, showed lymphadenitis probably as a result of tuberculosis accompanying the adenocarcinoma. The other locations of FP lymph nodes did not show any difference between PET and CT.

Table 2. Coincidence of N-staging by PET and CT with pathological N-stage

Pathological N-stage	No. of coincidences with pathological N-stage		Difference
	PET	CT	
N0 ($n = 143$)	138	129	$P = 0.03$
N1 ($n = 31$)	19	16	NS
N2 ($n = 24$)	16	7	$P = 0.01$
N3 ($n = 7$)	7	3	$P = 0.02$

PET, positron emission tomography; CT, computed tomography; NS, not significant.

The locations of FN lymph node stations revealed by PET and CT are shown in Table 5. For the upper mediastinal, lower mediastinal and supra-clavicle lymph nodes with metastasis, PET showed FN less frequently than CT ($P = 0.001$, 0.04 and 0.003). However, for hilar lymph nodes, there was no significant difference of FN between PET and CT.

The difference of histological types in patients who were understaged or overstaged by PET and CT are shown in Tables 6 and 7. For adenocarcinoma, PET showed significantly less understaging than CT ($P = 0.02$) (Table 6). For squamous cell carcinoma, PET showed significantly less overstaging than CT (Table 7) ($P = 0.005$). All seven squamous cell carcinoma patients who were overstaged by CT were heavy smokers, whose Brinkman Index was 680–2400 (mean ± SD: 1444 ± 525).

DISCUSSION

Several criteria have been used to detect lymph node metastases of lung cancer using PET scanning, including accumulation of FDG without objective criteria (6, 11),

Table 3. PET and CT analyses with pathological diagnosis

Diagnosis	No. of lymph node stations		Total
	With metastasis	Without metastasis	
PET			
Positive	85	11	96
Negative	45	1915	1961
CT			
Positive	49	22	71
Negative	82	1904	1986
Total	131	1926	2057

PET, positron emission tomography; CT, computed tomography.

Table 4. False positive lymph node stations with PET and CT

Locations of LNS	No. of LNS without metastasis	False positive with		Difference
		PET	CT	
Upper mediastinum	670	1	12	$P = 0.001$
Lower mediastinum	510	4	3	NS
Hilar	745	4	7	NS
SCN	1	1	0	NS
Total	1926	10	22	

PET, positron emission tomography; CT, computed tomography; LNS, lymph node station; SCN, supra clavicle lymph node; NS, not significant.