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

Takashi Ohtsuka, MD, PhD[1]
Hiroaki Nomori, MD, PhD[2]
Ken-ichi Watanabe, MD[1]
Masahiro Kaji, MD, PhD[1]
Tsuguo Naruke, MD, PhD[1]
Keiichi Suemasu, MD, PhD[1]
Kimiichi Uno, MD, PhD[3]

[1] Department of Thoracic Surgery, Saiseikai Central Hospital, Tokyo, Japan.

[2] Department of Thoracic Surgery, Graduate School of Medicine, Kumamoto University, Kumamoto, Japan.

[3] Nishidai Clinic, Tokyo, Japan.

Address for reprints: Hiroaki Nomori, MD, Department of Thoracic Surgery, Graduate School of Medicine, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan; Fax: (011) 81-96-373-5532; E-mail: hnomori@qk9.so-net.ne.jp

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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

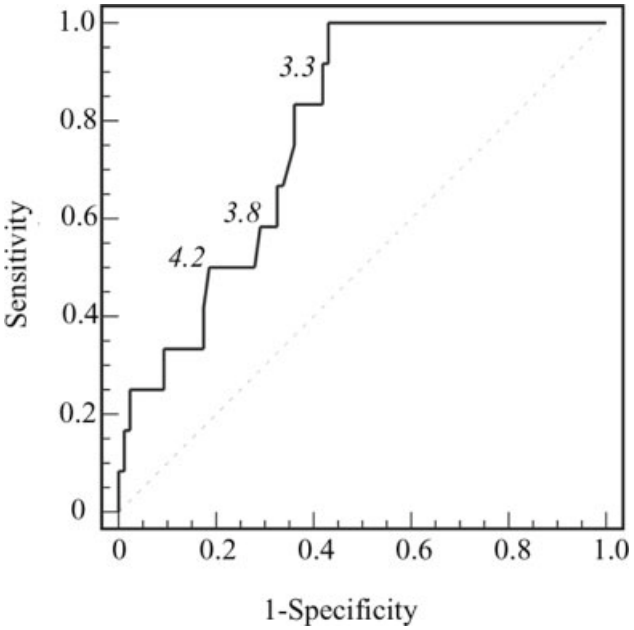

FIGURE 1. The receiver operating characteristic (ROC) curve of the standardized uptake value (SUV) for the prediction of recurrence. Cutoff values for SUV are shown in italics.

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.

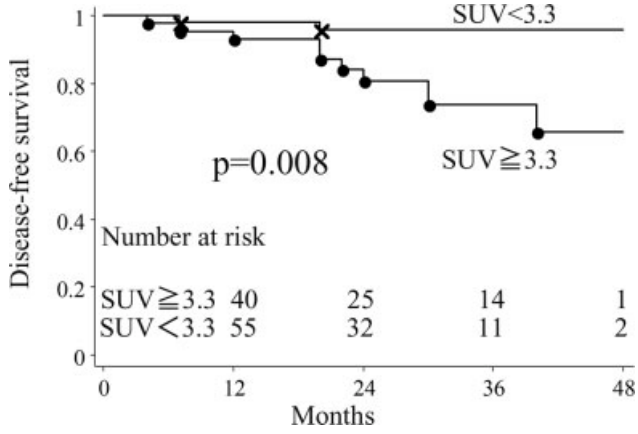

FIGURE 2. Disease-free survival of the 98 patients with pathologic Stage I adenocarcinoma according to the standardized uptake value (SUV) of the primary tumor.

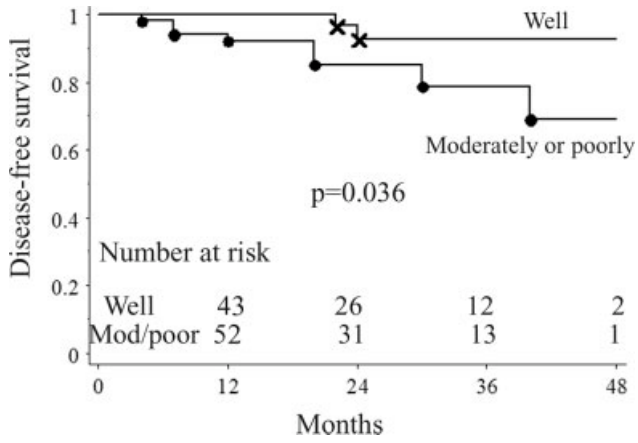

FIGURE 3. Disease-free survival of the 98 patients with pathologic Stage I adenocarcinoma according to the histologic grade of differentiation. Mod/poor indicates moderately/poorly differentiated.

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 $\geq$60 years or age <60 years), histologic grade of differentiation (well, moderately, or poorly differentiated), surgical procedure (pneumonectomy, lobectomy, or segmentectomy), and SUV ($\geq$3.3 or <3.3) and results of *P* value and hazard ratio by univariate analysis. Sixty-four patients were age $\geq$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 $\geq$ 3.3 and 55 patients had an SUV < 3.3.

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

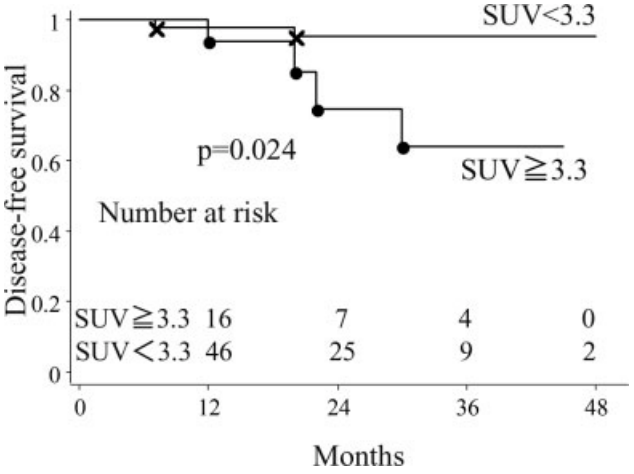

FIGURE 4. Disease-free survival of the 63 patients with pathologic Stage IA adenocarcinoma according to the standardized uptake value (SUV) of the primary tumor.

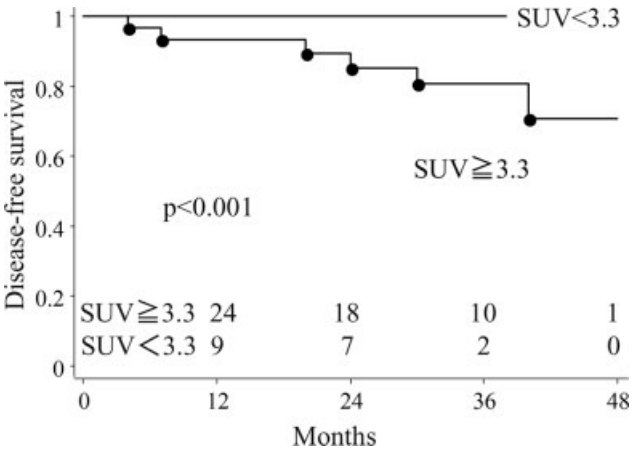

FIGURE 5. Disease-free survival of the 35 patients with pathologic Stage IB adenocarcinoma according to the standardized uptake value (SUV) of the primary tumor.

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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