High Tumor Metabolic Activity as Measured by Fluorodeoxyglucose Positron Emission Tomography Is Associated with Poor Prognosis in Limited and Extensive Stage Small-Cell Lung Cancer

Young Joo Lee,[1,2] Arthur Cho,[3] Byoung Chul Cho,[1,2] Mijin Yun,[3] Se Kyu Kim,[2] Joon Chang,[2] Jin Wook Moon,[2] In Kyu Park,[4] Hye Jin Choi,[1,2] and Joo-Hang Kim[1,2]

Abstract

Purpose: We investigated the prognostic effect of incorporating metabolic assessment by ^{18}F-fluoro-2-deoxyglucose uptake on positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) into a conventional staging system in small-cell lung cancer (SCLC).

Experimental Design: Seventy-six consecutive patients with pathologically proven SCLC were enrolled. All patients underwent standard treatment after pretreatment ^{18}F-FDG-PET/CT scanning. The mean values of maximal standardized uptake values (meanSUV_{max}) of the malignant lesions upon ^{18}F-FDG-PET/CT were calculated. The Cox proportional hazards model was used with performance status, lactate dehydrogenase, stage, and meanSUV_{max}.

Results: Patients with high meanSUV_{max} were significantly related with the established poor prognostic factors, such as higher lactate dehydrogenase ($P = 0.04$) and extensive disease (ED; $P = 0.01$). Furthermore, in multivariate analysis, patients with high meanSUV_{max} were associated with poor survival outcomes compared with patients with low meanSUV_{max} [adjusted hazard ratio, 3.74; 95% confidence interval (95% CI), 1.67-8.37; $P = 0.001$, for death and adjusted hazard ratio, 2.25; 95% CI, 1.21-4.17; $P = 0.01$ for recurrence/progression]. In subgroup analysis, limited disease (LD) with high meanSUV_{max} showed significantly shorter overall survival than LD with low meanSUV_{max} [high versus low meanSUV_{max}, 20.1 months (95% CI, 7.9-23.2) versus 35.3 months (95% CI, 27.6-42.9); $P = 0.02$]. ED with high meanSUV_{max} had significantly shorter overall survival than ED with low meanSUV_{max} [high versus low meanSUV_{max}, 9.5 months (95% CI, 4.9-13.9) versus 17.7 months (95% CI, 12.0-20.1); $P = 0.007$]. These findings were replicated in progression-free survival analysis.

Conclusions: In SCLC, tumor metabolic activity as assessed by FDG-PET is a significant prognostic factor and identifies subgroups of patients at higher risk of death in both LD and ED SCLC.

Small-cell lung cancer (SCLC) represents 15% to 20% of all lung cancers (1). SCLC has distinct characteristics, including rapid tumor doubling time, high growth fraction, and early dissemination, all of which lead to frequent relapse and poor prognosis, despite initially favorable responses to treatment (2).

A two-tiered staging system is typically used to classify SCLC. This system, which was introduced by the Veterans Administration Lung Study Group in 1957 (3), divides SCLC into limited disease (LD) and extensive disease (ED), based on suitability for radiotherapy. This staging system anatomically defines the extent of the disease and selects a subset of patients in whom a combined treatment modality can improve survival. Moreover, tumor stage is the most important prognostic factor of SCLC over performance status, weight loss, gender, lactate dehydrogenase (LDH), and albumin (4, 5). However, despite its practical usefulness and prognostic advantage, the two-stage system is inadequate for predicting survival in some patients. This is particularly relevant for data from a few studies that have shown that the addition of radiotherapy to chemotherapy provides a survival benefit in a favorable subset of ED patients (6, 7). Furthermore, data reported by Shepherd et al. (8) has shown that patients with very limited SCLC, including stage I or II classified by the tumor-node-metastasis system, have improved prognoses compared with patients with usual limited SCLC who present with advanced mediastinal adenopathy. These data suggest that the two-tiered staging system based only on anatomic imaging may define prognostically heterogeneous groups. Thus, more discriminative prognostic markers would be needed, allowing better stratification for appropriate therapy and more accurate predictions of treatment outcome and survival.

Positron emission tomography (PET) imaging using ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) is a novel imaging technique

Authors' Affiliations: [1]Yonsei Cancer Center, [2]Department of Internal Medicine, [3]Division of Nuclear Medicine, Department of Diagnostic Radiology, and [4]Department of Thoracic and Cardiovascular Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea

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Note: Y.J. Lee and A. Cho contributed equally to this work.

Requests for reprints: Joo-Hang Kim, Yonsei Cancer Center, Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, 250 Seongsanno, Seodaemun-gu, CPO Box 8044, 120-752 Seoul, Republic of Korea. Phone: 82-2-2228-8131; Fax: 82-2-392-1508; E-mail: kjhang@yuhs.ac.

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Translational Relevance

The heterogeneity of the conventional staging system by the Veterans Administration Lung Study Group has continued to be a matter of debate in the management of small-cell lung cancer. An introduction of ^{18}F-fluoro-2-deoxyglucose uptake on positron emission tomography/computed tomography imaging technology can provide more accurate prognostic information because the metabolic process precedes gross anatomic changes. Our study will be helpful for better stratification for appropriate therapy and more accurate predictions of treatment outcome and survival in the small-cell lung cancer clinics.

based on the increased rate of glucose uptake in malignant cell. An association between tumor glycolytic activity and tumor proliferation prognosis remains controversial. A number of studies have found that the rate of ^{18}F-FDG uptake is correlated with tumor growth rate (9, 10) or survival in a variety of malignant tumors (11–14). However, some studies have reported that ^{18}F-FDG uptake is not an independent prognostic factor of survival (15–17). Although contradictory results have also been reported, ^{18}F-FDG-PET has continued to be proposed as a noninvasive measurement of the biological aggressiveness of the tumor and prognostic factor of patient outcome. More recently, ^{18}F-FDG-PET imaging has been increasingly applied to the staging of SCLC due to high sensitivity and specificity for differentiating ED from LD (18–20). Regarding the tumor characteristics, FDG uptake by PET may also have a major role in predicting the survival of SCLC.

Therefore, we conducted the present study to determine if a model including a conventional tumor stage and ^{18}F-FDG uptake in pretreatment PET/computed tomography (CT) imaging is more accurate for predicting survival than the tumor stage alone in patients with SCLC.

Materials and Methods

Patients. From February 2003 to December 2007, we enrolled consecutive patients with newly diagnosed, histologically or cytologically proven, and untreated SCLC. Complete staging procedures included history taking and physical examination, chest radiography, bone scintigraphy (if needed), magnetic resonance imaging of brain, and hematologic and biochemical tests as well as ^{18}F-FDG-PET/CT scanning within 2 wk before the first treatment. Patients who had any lesions that could not be confirmed by ^{18}F-FDG-PET/CT image underwent further anatomic imaging or pathologic biopsy. This study was approved by the institutional review board of the Yonsei University College of Medicine (Seoul, Republic of Korea). All patients gave written, informed consent before enrollment.

Treatment and response evaluation. Patients with LD underwent concurrent chemoradiotherapy, which consisted of six cycles of chemotherapy and thoracic radiotherapy. Irradiation on the chest was initiated on day 1 of the second cycle of chemotherapy with 1.8 Gy once daily in 30 fractions. Both LD and ED patients underwent combined chemotherapy with an IP or EP regimen as the first-line treatment. The IP regimen consisted of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 40 mg/m^2 on days 1 and 8. The EP regimen consisted of etoposide 100 mg/m^2 on days 1 to 3 and cisplatin 70 mg/m^2 on day 1. Both regimens were repeated every 3 wk. Patients with LD who showed a complete response or partial response after chemoradiotherapy received prophylactic cranial irradiation, which consisted of 25 Gy in 2.5-Gy fractions.

Response evaluation was done with a CT scan every two cycles, according to the guidelines of the Response Evaluation Criteria in Solid Tumor Committee (21). After completion of treatment, patients were evaluated with CT scans every 3 mo for 1 y, every 6 mo in the following year, and yearly thereafter.

PET imaging. All patients fasted for at least 6 h before an ^{18}F-FDG-PET/CT scan. When plasma glucose level before administration of ^{18}F-FDG was below 130 mg/dL, scanning was done. Scanning was initiated 60 min after administration of FDG. Low-dose noncontrast CT scans were obtained for nonuniform attenuation correction. Images from the neck to the proximal thighs were obtained using the Phillips Gemini PET/CT scanner (Phillips-ADAC Medical Systems) with a spatial resolution of 5.3 mm in the center of the field of view. Data were acquired in a three-dimensional mode after the i.v. administration of 370 to 444 MBq of ^{18}F-FDG. After PET imaging, contrast-enhanced CT images were acquired (i.v. bolus 60% w/v at 1.5-2.0 mL/s). The obtained PET images were reconstructed using an iterative reconstruction algorithm, specifically the low-action maximal likelihood algorithm.

PET interpretation. Two experienced nuclear medicine specialists who were unaware of the clinical information were responsible for reading the ^{18}F-FDG-PET/CT images. In the cases of discrepancy, a consensus was reached and was used for analysis. Positive malignant FDG uptake was defined as an abnormal increase in comparison with the background activity in the surrounding tissue. The standardized uptake values (SUV) were generated for malignant lesions, such as primary tumor, lymph nodes, and metastatic lesions except brain metastasis. The SUV was measured by region-of-interest analysis and calculated as the dose detected in the lesion divided by the injected dose, with correction for body weight (μCi/g). The maximal SUV (SUV_{max}) was the peak SUV in one pixel with the highest counts within the region of interest. For further analyses, we chose the malignant

Table 1. Patient characteristics

Characteristics	Overall	MeanSUV$_{max}$		
		Low (<8.7*)	High (≥8.7*)	P †
Age (y)				0.49
<65	37 (49%)	17 (45%)	20 (53%)	
≥65	39 (51%)	21 (55%)	18 (47%)	
Gender				0.68
Male	66 (87%)	33 (87%)	33 (87%)	
Female	10 (13%)	5 (13%)	5 (13%)	
Performance (ECOG)				0.61
0, 1	70 (92%)	36 (95%)	34 (90%)	
2	6 (8%)	2 (5%)	4 (10%)	
LDH (units/L)				0.04
<455	43 (57%)	26 (69%)	15 (39%)	
≥455	33 (43%)	12 (31%)	23 (61%)	
Tumor stage ‡				0.01
Limited disease	41 (54%)	26 (68%)	15 (39%)	
Extensive disease	35 (46%)	12 (32%)	23 (61%)	
Chemotherapy (median)				0.49
<2 cycles	6 (8%)	2 (5%)	4 (10%)	
≥2 cycles	70 (92%)	36 (95%)	34 (90%)	
Total	76	38	38	

Abbreviations: ECOG, Eastern Cooperative Oncology Group.
*The median value of meanSUV$_{max}$.
† Frequency, tested by the χ^2 test.
‡ Staging according to the Veterans Administration Lung Study Group staging system.

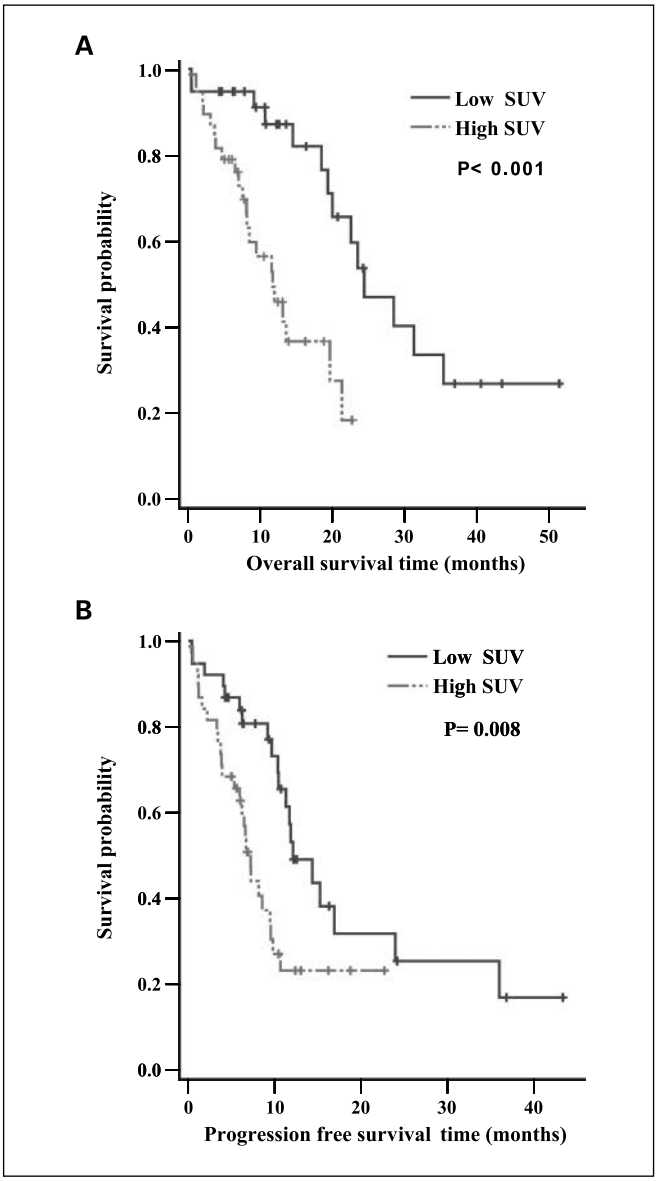

Fig. 1. Kaplan-Meier survival curves for (*A*) overall survival ($P < 0.001$) and (*B*) PFS ($P = 0.008$) of two groups divided on the basis of the median value of meanSUV$_{max}$ upon pretreatment ^{18}F-FDG PET/CT of 76 patients with SCLC.

lesion with highest SUV$_{max}$ per each organ and calculated the mean (meanSUV$_{max}$) from the SUV$_{max}$ values of chosen lesions.

Statistical analysis. Overall survival (OS) was calculated as the time interval between the date of ^{18}F-FDG-PET/CT scanning and the date of death or last follow-up. Progression-free survival (PFS) was assessed from the date of ^{18}F-FDG-PET/CT scanning until the date of first recurrence or death. Survival time was estimated by the Kaplan-Meier method and the survival difference between groups was assessed by the log-rank test. The Cox proportional hazards model was used for a multivariate analysis of survival. The SPSS 12.0 for Windows software was used for statistical analyses.

Results

Patient characteristics. The patient baseline characteristics are presented in Table 1. In total, 88 eligible patients were enrolled. Four patients died early due to treatment-related toxicities and eight patients refused to continue the treatment and were lost to follow-up. Thus, 76 patients were analyzed. The median age of the patients was 56 years (range, 50-78 years). Initial chemotherapy regimens included IP (80%) and EP (20%). The median number of cycles of chemotherapy given was 6 (range, 2-6). The median relative dose intensities of irinotecan, etoposide, and platinum were 0.94 [95% confidence interval (95% CI), 0.89-0.96], 0.93 (95% CI, 0.87-1.01), and 0.83 (95% CI, 0.78-0.86), respectively. All LD patients received thoracic radiation, with a median total dose of 54.0 Gy (95% CI, 38.7-58.1). Among the 35 patients with LD who showed complete remission or partial remission after chemoradiotherapy, 31 patients underwent a scheduled prophylactic cranial irradiation and four patients took palliative radiotherapy for overt brain metastases, which developed before the prophylactic cranial irradiation. Follow-up data were available through May 2008. The median follow-up time was 22.3 months (95% CI, 17.1-25.4). The median OS and PFS were 18.6 months (95% CI, 16.3-22.8) and 9.8 months (95% CI, 8.4-11.2), respectively.

SUV and responses. A total of 76 patients underwent ^{18}F-FDG-PET/CT imaging. The median plasma glucose level before ^{18}F-FDG-PET/CT imaging was 96 mg/dL (range, 81-120 mg/dL). The total number of lesions analyzed was 326; primary tumors were 23%, lymph node 31%, distant metastasis 35%, and unspecified site 11%. The median number of lesions analyzed per patient was 4. The median size of the lesions included in the analysis was 2.2 cm and was not different between LD and ED patients (Mann-Whitney *U* test, $P = 0.26$). The meanSUV$_{max}$ of the 76 patients ranged from 2.9 to 36.0, with a median value of 8.7. When patients were divided into two groups according to the median value of meanSUV$_{max}$, the patients with high meanSUV$_{max}$ were more likely to have higher LDH ($P = 0.04$) and to be ED ($P = 0.01$), compared with the patients with low meanSUV$_{max}$ (Table 1). For the responses to the first treatment, the high meanSUV$_{max}$ group did not

Table 2. Multivariate analysis of survival

Characteristics (reference group)	Overall survival		PFS	
	HR (95%CI)	*P*	HR (95% CI)	*P*
ECOG (0,1)	3.12 (1.03-9.47)	0.04	2.05 (0.71-5.91)	0.18
LDH (<455 units/L)	2.90 (0.57-8.65)	0.19	4.10 (1.18-8.23)	0.02
Tumor stage (limited disease)	2.87 (1.30-6.34)	0.009	3.51 (1.78-6.91)	<0.001
MeanSUV$_{max}$ (<8.7)	3.74 (1.67-8.37)	0.001	2.25 (1.21-4.17)	0.01

NOTE: In the Cox proportional hazard model, Eastern Cooperative Oncology Group, LDH, tumor stage, and meanSUV$_{max}$ were included.

differ significantly from the low meanSUV$_{max}$ group (CR+PR; 76% versus 74%, P = 0.79).

SUV and survival. High meanSUV$_{max}$ was associated significantly with shorter OS [median OS for high meanSUV$_{max}$ versus low meanSUV$_{max}$, 11.7 months (95% CI, 7.5-15.9) versus 24.3 months (95% CI, 17.3-31.4); P < 0.001; Fig. 1A]. A univariate analysis of OS determined that age and gender were not the significant predictors but performance status, LDH, stage, and meanSUV$_{max}$. In a multivariate analysis of OS, performance status, stage, and meanSUV$_{max}$ remained significant predictors (Table 2). High meanSUV$_{max}$ was associated with a higher risk of death, with an adjusted hazard ratio of 3.74 (95% CI, 1.67-8.37; P = 0.001), compared with low meanSUV$_{max}$.

Table 3. Responses to first-line treatment in two groups according to meanSUV$_{max}$ at each stage

Response	Limited disease			Extensive disease		
	Low SUV	High SUV	P*	Low SUV	High SUV	P*
CR+PR	20 (77%)	15 (100%)	0.07	8 (67%)	14 (63%)	0.73
SD+PD	6 (23%)	0 (0%)		4 (33%)	9 (39%)	

NOTE: In each stage, patients were divided into groups with low SUV (meanSUV$_{max}$ <8.7) and the group with high SUV (meanSUV$_{max}$ ≥8.7), according to the median value of the meanSUV$_{max}$.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*Frequency, as tested by the Fisher's exact test.

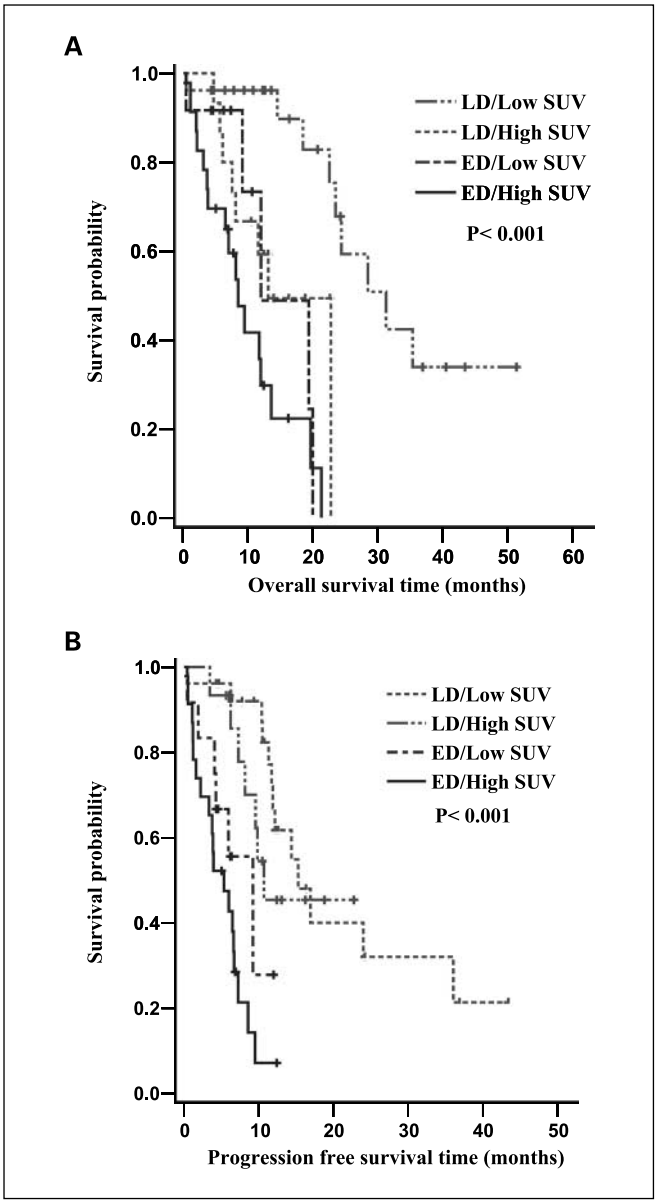

Fig. 2. Kaplan-Meier survival curves for (*A*) overall survival (P < 0.001) and (*B*) PFS (P < 0.001) of four groups divided according to the combined criteria of meanSUV$_{max}$ and tumor stage in 76 patients with SCLC. Low SUV, meanSUV$_{max}$ <8.7; high SUV, meanSUV$_{max}$ ≥8.7.

Similar to the results obtained for OS, high meanSUV$_{max}$ was significantly associated with an increased risk of recurrence/progression after the initial treatment [median PFS for high meanSUV$_{max}$ versus low meanSUV$_{max}$, 7.3 months (95% CI, 6.3-8.3) versus 12.2 months (95% CI, 8.5-15.8); P = 0.008; Fig. 1B]. In a univariate analysis of PFS, age, gender, and performance status were not significant predictors but LDH, stage, and meanSUV$_{max}$. In a multivariate analysis of PFS, LDH, stage, and meanSUV$_{max}$ confirmed to be independent predictors (Table 2). The high meanSUV$_{max}$ group had a higher risk of recurrence/progression, with an adjusted hazard ratio of 2.25 (95% CI, 1.21-4.17, P = 0.01), compared with the low meanSUV$_{max}$ group. Similar associations between meanSUV$_{max}$ and survival outcome were observed when meanSUV$_{max}$ was analyzed as a continuous variable.

Subgroup analysis by stage. A strong association between meanSUV$_{max}$ and survival was also found within each stage. LD with high meanSUV$_{max}$ showed significantly shorter OS than LD with low meanSUV$_{max}$ [median OS for high meanSUV$_{max}$ versus low meanSUV$_{max}$, 20.1 months (95% CI, 7.9-23.2) versus 35.3 months (95% CI, 27.6-42.9); P = 0.02; Fig. 2A]. ED with high meanSUV$_{max}$ also had significantly shorter OS than the same stage with low meanSUV$_{max}$ [median OS for high meanSUV$_{max}$ versus low meanSUV$_{max}$, 9.5 months (95% CI, 4.9-13.9) versus 17.7 months (95% CI, 12-20.1); P = 0.007; Fig. 2A].

This finding was replicated in a PFS analysis. In patients with LD, median PFS of high meanSUV$_{max}$ was shorter than those of low meanSUV$_{max}$ [median PFS for high meanSUV$_{max}$ versus low meanSUV$_{max}$, 10.7 months (95% CI, 6.8-14.5) versus 23.5 months (95% CI, 19.4-37.9); P = 0.05; Fig. 2B]. In patients with ED, high meanSUV$_{max}$ was associated significantly with shorter PFS [median PFS for high meanSUV$_{max}$ versus low meanSUV$_{max}$, 6.0 months (95% CI, 2.2-9.8) versus 10.5 months (95% CI, 7.6-13.3); P = 0.04; Fig. 2B].

Among the LD patients, the high meanSUV$_{max}$ group showed a better response than the low meanSUV$_{max}$ group, although the difference was not statistically significant (CR+PR; 100% versus 77%, P = 0.07; Table 3). Distant metastases developed more frequently in the LD with high meanSUV$_{max}$ group than in the LD with low meanSUV$_{max}$ group without statistical significance (71.4% versus 52.8%, P = 0.07).

Three prognostically homogenous groups. Dividing the subjects into four groups using the combined criteria of meanSUV$_{max}$ and stage, the LD patients with high meanSUV$_{max}$

showed no significant difference in OS compared with the ED patients with low meanSUV$_{max}$ [median OS for LD with high meanSUV$_{max}$ versus ED with low meanSUV$_{max}$, 20.1 months (95% CI, 7.9-23.2) versus 17.7 months (95% CI, 12-20.1); P = 0.53]. When the two series with similar survival were treated as a single group, LD with low meanSUV$_{max}$, LD with high meanSUV$_{max}$ and ED with low meanSUV$_{max}$, and ED with high meanSUV$_{max}$ were defined as group 1, 2, and 3, respectively. The three groups defined by the combined criteria showed significant differences in OS [median OS for groups 1, 2, and 3 were 31.1 (95% CI, 20.1-42.2), 19.3 (95% CI, 6.0-32.7), and 8.5 months (95% CI, 5.5-11.5), respectively; P < 0.001; Fig. 3A]. When group 1 was used as the reference group, adjusted hazard ratios for death in groups 2 and 3 were 5.47 (95% CI, 1.64-18.24) and 14.44 (95% CI, 4.52-46.14), respectively (P < 0.001; Table 4). These findings were replicated in the PFS analysis (Fig. 3B; Table 4).

SUV values. We tested three variables based on the SUV$_{max}$: meanSUV$_{max}$ (median = 8.7, 95% CI, 8.2-10.5), which was defined as the mean of the SUV$_{max}$; primarySUV$_{max}$ (median = 9.3, 95% CI, 8.9-11.2), which was the SUV$_{max}$ measured in the primary lesion; and peakSUV$_{max}$ (median = 9.9, 95%CI, 9.9-12.1), which was the highest of the SUV$_{max}$ values. In Spearman's test with three SUV variables, there were significant correlation between meanSUV$_{max}$ and primarySUV$_{max}$ (ρ = 0.54, P = 0.04), between meanSUV$_{max}$ and peakSUV$_{max}$ (ρ = 0.55, P = 0.03), and especially between primarySUV$_{max}$ and peakSUV$_{max}$ (ρ = 0.88, P = 0.001). However, in a multivariate survival analysis, a significant association with OS was found only for meanSUV$_{max}$. When primarySUV$_{max}$ and peakSUV$_{max}$ were used as the SUV variable for the analysis of OS, adjusted hazard ratios for death were 1.26 (95% CI, 0.60-2.06; P = 0.53) and 1.17 (95% CI, 0.56-2.46; P = 0.66), respectively. Similar results were obtained for the analysis of PFS.

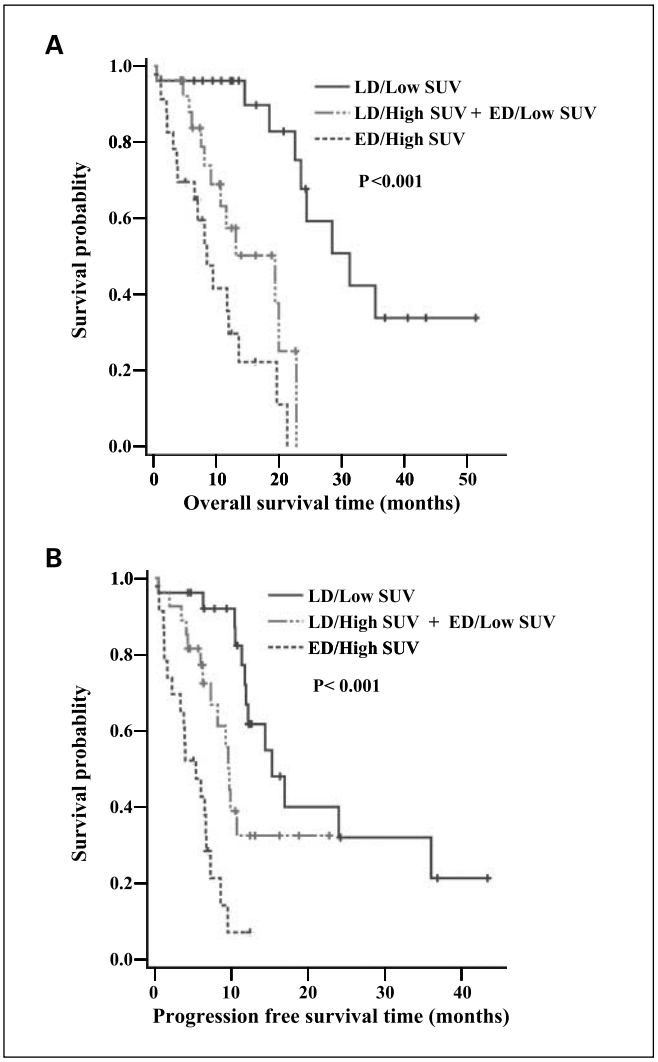

Fig. 3. Kaplan-Meier survival curves for (*A*) overall survival (P < 0.001) and (*B*) PFS (P < 0.001) of three prognostically homogenous groups identified by the combined criteria of meanSUV$_{max}$ and tumor stage in 76 patients with SCLC. Low SUV, meanSUV$_{max}$ <8.7; high SUV, meanSUV$_{max}$ ≥8.7.

Discussion

To our knowledge, this is the first study to evaluate clinical usefulness of ^{18}F-FDG uptake in predicting survival in SCLC patients, using carefully staged subjects who underwent homogenous treatments. In a multivariate analysis, meanSUV$_{max}$ was revealed as another significant predictor of survival of SCLC together with well-defined existing prognostic factors, such as performance status, LDH, and tumor stage. Moreover, stratifying subjects by the combined criteria of meanSUV$_{max}$ and two-tiered staging system, we found that patients with ED and high meanSUV$_{max}$, those with one of these risk factors and those without both of these risk factors had significantly different prognoses.

In the classification of SCLC, the heterogeneity of a two-stage Veterans Administration Lung Study Group system has continued to be a matter of debate. Recently, the International Association for the Study of Lung Cancer has attempted to overcome these limitations of the Veterans Administration Lung Study Group system through application of the tumor-node-metastasis system (22). Similar to the International Association for the Study of Lung Cancer study, the present study confirmed that metabolic stage can be used to identify subgroups with distinct prognosis within the broad definitions of LD- or ED-SCLC. This result is supported by the fact that ^{18}F-FDG-PET imaging can provide more accurate prognostic information because the metabolic process precedes gross anatomic changes. As a consequence, the combined criteria of an anatomic assessment of total tumor load in the body and a metabolic assessment of tumor aggressiveness seemed to be adequate to achieve high discriminative power for prediction of survival in SCLC. Simple prognostic factors, such as LDH, can also be included in a model to predict survival in combination with tumor stage. However, ^{18}F-FDG uptake has an advantage of site specificity because it is accompanied with anatomic information. In addition, it is applicable to the full spectrum of the SCLC populations, in contrast to LDH, which is rarely elevated in LD (23, 24).

An incorporation of meanSUV$_{max}$ to a two-tiered staging system identified a subgroup of patients at a higher risk for death within the same stage. New treatment strategies are required for these higher risk groups identified by meanSUV$_{max}$. For example, LD patients with high meanSUV$_{max}$ need to take more enhanced systemic chemotherapy than the low meanSUV$_{max}$ group because they relapsed more frequently as

Table 4. Survival of patients classified according to tumor stage and meanSUV$_{max}$

Survival (95% CI)	Group 1	Group 2		Group 3	P
	LD	LD	ED	ED	
	Low SUV	High SUV	Low SUV	High SUV	
Death/*n*	9/26	13/27		17/23	
Median OS, mo	31.1 (20.1-42.2)	19.3 (6.0-32.7)		8.5 (5.5-11.5)	<0.001
HR of death	Reference	5.26 (1.50-18.42)		15.70 (4.60-53.60)	<0.001
Recurrence/*n*	13/26	14/27		19/23	
Median PFS, mo	15.3 (10.1-20.4)	9.7 (8.8-10.6)		5.4 (2.3-8.5)	<0.001
HR of recurrence	Reference	3.00 (1.27-7.07)		10.49 (4.13-26.62)	<0.001

NOTE: In the Cox proportional hazard model, Eastern Cooperative Oncology Group, LDH and meanSUV$_{max}$/tumor stage (groups 1, 2, 3) were included as variables and group 1 (the LD with low SUV) was treated as the reference group.
Abbreviations: Low SUV, meanSUV$_{max}$ <8.7; high SUV, meanSUV$_{max}$ ≥8.7; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

distant metastasis. Combinations of chemoradiotherapy and induction chemotherapy or chemoradiotherapy and consolidation chemotherapy using non–cross-resistant drugs may help these higher risk subsets in the LD-SCLC (25–27). Furthermore, risk-adapted therapies also have to apply to patients with ED. Especially, more effective complements to standard systemic chemotherapy, such as maintenance therapy using new chemotherapeutic drugs or target agents, may be useful for ED patients with high meanSUV$_{max}$ (28–31).

In terms of response, the relationship between tumor response and FDG uptake remain controversial. Lee et al. (32) suggested that high SUV tumors exhibit higher response to chemotherapy but shorter time to progression. However, another report by Na et al. (33) came to a rather different conclusion that high SUV predict both unfavorable response and survival. In the present study, there was no correlation between meanSUV$_{max}$ and response rate. Several factors may explain this discrepancy. First, it may come from an inaccuracy of response evaluation tools. The specificity for the differentiation of residual cancer from scar tissue or fibrosis is decreased in the conventional imaging techniques. Second, the relationships among pretreatment SUV, response rate, and survival may be quite different depending on the biological intrinsic characteristics of tumor cells, treatment modality, and chemotherapeutic agents. Therefore, it is difficult to reach definitive conclusions from the previous results until now. More inclusive studies are warranted to deduce consistent conclusions.

Although SUV is widely used as a semiquantitative index to assess the tissue glucose metabolic rate, there is no standard method for the measurement or calculation of FDG. In the present study, SUV$_{max}$ was chosen as a calculation tool for tumor uptake because of its reproducibility. In addition, we hypothesized that the average of all the SUV$_{max}$ values identified would represent a surrogate marker for real tumor metabolic activity in SCLC. Consequently, of the three SUV variables tested, the meanSUV$_{max}$ showed the strongest association with survival in SCLC. This suggests that meanSUV$_{max}$ represents the metabolic activity of the total ongoing process in the entire body. This result may be due to the biological characteristics of SCLC; that is, an early, active, and extensive dissemination. However, this calculation method for FDG needs to be validated in further prospective studies.

Our study had several limitations. First, although the median size of total lesions was larger than 2.0 cm and was not different between LD and ED subgroups, some lesions with diameter less than 2.0 cm may encounter partial volume effect. Second, because all FDG-PET abnormal lesions were measured, the number of false positives included in the analysis may be increased although possible imaging methods and pathologic biopsy were done in the case with discrepancy in PET image and CT findings.

In conclusion, the assessment of metabolic activity by pretreatment ^{18}F-FDG-PET/CT well predicted prognosis of SCLC patients. Incorporation of metabolic measurements by FDG-PET into a two-tiered staging system is more accurate for predicting survival than the tumor stage alone and identifies three subgroups with different prognosis. This criterion with high discriminative power will be useful for stratifying patients in randomized clinical studies and ultimately for selecting appropriate therapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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