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Prognostic value of 2-[^{18}F]fluoro-2-deoxy-D-glucose uptake as measured by PET scan in patients with non-small cell lung cancer

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Abstract. This study aimed to evaluate the prognostic value of 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) uptake determined by positron emission tomography (PET) in patients with non-small cell lung cancer (NSCLC) in relation to disease stage and/or tumor histology. A retrospective review of 144 patients with newly diagnosed lung cancer undergoing PET imaging was performed. Differences in survival were compared by univariate and multivariate analyses. Univariate analysis identified three prognostic factors: stage, lesion size and the standardized ^{18}F-FDG uptake value. The latter was a better prognostic predictor in lung cancer patients with early-stage disease than in those at advanced stages. Multivariate analysis revealed that the most important prognostic factors were tumor-node-metastasis (TNM) stage and the standardized ^{18}F-FDG uptake value. Patients with standardized uptake values (SUVs) >8 had a 2.5 times higher mortality rate than those with values ≤8. A one-unit increase in SUV corresponded with a 7% increase in the hazard of death. SUVs provided stronger prognostic stratification in patients with adenocarcinoma than in those with squamous cell carcinoma (SCC). Furthermore, the best choice of prognostic predictor differed between the two types of lung cancer: the SUV was best for SCC, while TNM stage was most significant for adenocarcinoma. In conclusion, ^{18}F-FDG uptake in primary lung lesions is an independent prognostic predictor in patients with NSCLC, especially those with adenocarcinoma or early-stage disease. Further stratification of patients with the same TNM stage based on SUVs may allow for the modification of individual treatment strategies, resulting in improved outcome.

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Introduction

Lung cancer is one of the leading causes of cancer-related death worldwide, with non-small cell lung cancer (NSCLC) being the main type. Accurate staging of NSCLC plays an important role in stratifying patients for optimal treatment regimens and improving prognosis. 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET) and PET/computerized tomography (CT) are non-invasive imaging techniques for the evalation of unidentified pulmonary nodules, the diagnosis of lung cancer, the staging of mediastinal lymph nodes and the evaluation of distant metastases and response to therapy (1,2). In many countries, FDG PET is now included in the standard staging procedures for lung cancer, and its prognostic value is being evaluated. Previous studies have shown that FDG PET may provide prognostic information (3-13). One of the most frequently used criteria is the standardized uptake value (SUV) of FDG. While some studies show a significant correlation between SUV and survival, it is unclear whether SUV can act as an independent prognostic factor (14). The objective of this study was to determine whether SUV is an independent prognostic predictor in NSCLC patients and, if so, whether it has different prognostic values in patients at different stages of the disease or with different histology.

Materials and methods

Patients. Patients with newly diagnosed NSCLC undergoing FDG PET imaging at the PET center of Huashan Hospital were considered eligible for participation in this study. Indications for PET imaging included strongly suspected lung cancer based on chest radiographs and CT or a pathologically proven new diagnosis of lung cancer. Patients were excluded if they had received chemotherapy or radiotherapy before PET imaging,

or if they had an expected survival time of <3 months. A total of 156 NSCLC patients, 112 men and 44 women, with a mean age of 62 years (range 30-84) were enrolled.

Each patient was assigned a stage according to the revised international staging system of the UICC. Clinical staging methods included physical examination, thoracic CT, bone scan, head CT or magnetic resonance imaging, mediastinoscopy and PET. To simplify staging, patients were categorized into group I (stages I and II) or group II (stages III and IV).

PET imaging. PET imaging was performed with either a Siemens ECAT EXACT HR+ PET or a Siemens Biograph Sensation 16 PET/CT (Siemens Medical Solutions, Knoxville, TN, USA). Patients fasted for at least 6 h prior to the PET scan and were dosed with 5.55-7.4 MBq/kg of ^{18}F-FDG intravenously, followed by PET 1 h after administration of FDG. The blood sugar level before FDG injection was <7 mMol/l for each subject.

Imaging interpretation. Two experienced investigators independently evaluated the PET scan results. In the event of disagreement, a consensus was reached before the results were used for analysis. Focal intense uptake was considered a positive result. Low-grade uptake with diffused areas or no uptake was confirmed along with the information provided by the CT image. SUV was calculated automatically from the PET image by selecting the region of interest (ROI) and using the equation SUV = activity concentration within the tissue defined by ROI/(injected dose/body weight), which gives the relative metabolic activity of a given lesion. The maximum SUV (SUVmax) was defined as the maximum FDG uptake within the region of the primary tumor on the PET image, and the mean SUV (SUVmean) was defined as the mean concentration of FDG uptake in the ROI. The SUVmax, which was less variable than the SUVmean, was used throughout data analysis.

Data collection and statistical analysis. Parameters used to describe patients included age, gender, lesion size, tumor-node-metastasis (TNM) stage, SUV, histology, survival status and survival time. Survival time was defined as the time between the date of PET imaging and the date the patients succumbed to the disease or the date of the last follow-up. Statistical analysis was performed with the SPSS11.5 statistical package. Categorical variables were male vs. female, group I vs. II and squamous cell carcinoma (SCC) vs. adenocarcinoma, while numeric variables were age ≤65 vs. >65 and lesion size ≤3 cm vs. >3 cm. Since, based on previous reports, the cut-off points for the SUV varied considerably (3-5,7-12), we used a log-rank test to determine the SUV cut-off point with the most statistical significance.

The significance of the differences in SUV between the two groups was evaluated by a two-tailed Student's t-test. Survival probabilities for the patient subgroups as defined by the co-variables were calculated by the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis was accomplished with the Cox proportional hazards model, with forward stepwise covariate entry (likelihood ratio method) and significance levels of 0.05 for entry and 0.1 for removal. Reported P-values were two-sided, and P<0.05 was considered statistically significant.

Table I. Patient characteristics

Variable	No. of patients	Deceased patients
Gender		
Male	105	49
Female	39	12
Age		
>65	67	31
≤65	77	30
Tumor size (cm)		
>3	81	42
≤3	63	19
TNM stage		
I+II	72	16
III+IV	72	45
Histology		
Adenocarcinoma	107	45
SCC	37	16
SUV		
>8	62	37
≤8	82	24

Results

A total of 156 patients with NSCLC were enrolled in the present study, including 107 patients with adenocarcinoma, 37 with SCC, eight with bronchioalveolar carcinoma and four with adenosquamous carcinoma. Due to small sample size, the latter two groups were excluded from analysis. Patient numbers in stages I, II, III and IV were 53, 19, 32 and 40, respectively, resulting in an equal number of 72 patients in groups I and II. During the follow-up period, 61 patients succumbed to the disease. The median follow-up period for the remaining 83 patients was 24 months (range 14-65). Patient characteristics are summarized in Table I.

Standardized uptake value. The mean SUV of primary lesions in the 144 patients was 7.8±4.3 (median 7.5), with a range of 1.0-23.8. Twelve patients had a SUV <2.5, and 10 of these had stage I disease. Patients with advanced disease (group II) had higher SUVs than those in early stages (group I) (8.7±4.2 vs. 6.7±4.2, P<0.05). Lesions with larger tumor size (>3 cm) had higher SUVs than those with smaller tumor size (9.2±4.2 vs. 6.6±4.3, P<0.05). No statistical differences were found for SUVs between genders or age groups. Of note is that patients with SCC had higher SUVs than those with adenocarcinoma (10.2±5.4 vs. 6.9±3.5, P<0.05).

Optimal standardized uptake cut-off value based on univariate survival analysis. Based on the log-rank test, a cut-off SUV of eight was the best discriminative value for predicting prognosis in all patients, with a SUV of nine for patients with adenocarcinoma and of eight for patients with SCC (Table II).

Relationship between SUV cut-off values and survival based on the log-rank test.

	All patients		Adeno		SCC	
SUV cut-off	χ^2	P-value	χ^2	P-value	χ^2	P-value
5	11.85	0.0006	6.54	0.0106	6.13	0.0133
6	10.28	0.0013	6.28	0.0122	4.38	0.0363
7	9.19	0.0024	5.54	0.0185	4.38	0.0363
8	18.89	<0.0001	12.44	0.0004	7.88	0.0050
9	17.78	<0.0001	14.16	0.0002	5.20	0.0226
10	15.76	0.0001	13.55	0.0002	2.99	0.0838

SCC, patients with squamous cell carcinoma; Adeno, patients with adenocarcinoma.

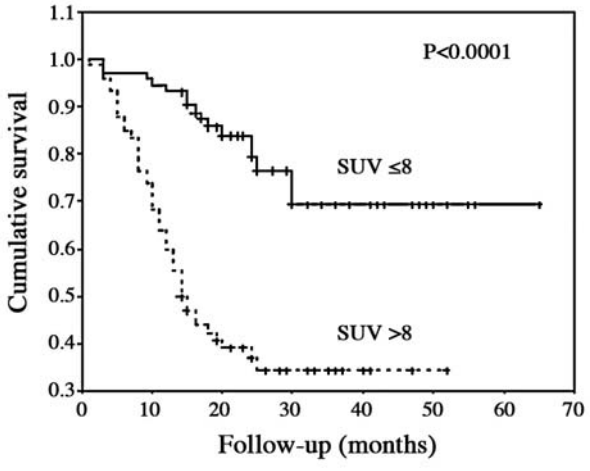

Figure 1. Survival curves among NSCLC cases stratified by the SUV of the ^{18}F-FDG PET (Kaplan-Meier method).

Univariate analysis for all patients. In the present study, 62 patients had tumor lesions with a SUV >8 and a mean survival of 26.2 months [95% confidence interval (CI) 20.9-31.5), while 82 had tumor lesions with a SUV ≤8 and a mean survival of 47.9 months (95% CI 42.2-53.7) (Fig. 1).

Survival was also affected by TNM stage and lesion size. Advanced stage and larger lesion size were correlated with poorer prognosis. The mean survival times of groups I and II were 51.2 months (95% CI 45.2-57.2) and 25.3 months (95% CI 20.6-30.1), respectively (P<0.0001). The mean survival times of patients with a lesion size ≤3 cm and >3 cm were 47.4 months (95% CI 40.8-54.0) and 29.6 months (95% CI 24.9-34.3), respectively (P=0.0064).

SUVs provided stronger prognostic stratification in group I than in group II (P=0.0053 vs. P=0.0094). Gender, age and tumor type had no predictive value in prognosis (P>0.05).

Univariate analysis for patients with adenocarcinoma or SCC. In patients with adenocarcinoma, the significant prognostic predictors were SUV, TNM stage and lesion size, with TNM stage being the most significant (P<0.0001). In patients with SCC, the significant predictors were SUV and TNM stage, with SUV being more significant than TNM stage. SUV was a better predictor for patients with adenocarcinoma than for those with SCC (P=0.0002 vs. P=0.005).

Table III. COX proportional hazards model for 144 patients (using dichotomized variables).

Variable	P-value	HR	95% CI HR
Stage, group II vs. I	<0.001	3.732	2.090-6.663
Tumor SUV, >8 vs. ≤8	0.001	2.504	1.483-4.226

Multivariate analysis for all patients. On the basis of the results of the univariate analyses, variables with the potential to be predictive factors were entered as candidate variables in the multivariate COX analysis. The variables for all patients and for those with adenocarcinoma included primary tumor size, SUV and stage. For those with SCC, the variables were SUV and stage.

Stage and SUV were significant prognostic factors, while lesion size had no statistical significance. Patients with advanced stages of disease or higher SUVs had poorer prognoses (Table III). The mortality of patients with a SUV >8 was 2.5 times higher than that of those with a SUV ≤8. We incorporated the SUV as a continuous variable in the multivariate analysis and found it to be a significant predictor (P=0.008) with a hazard ratio (HR) of 1.07 (95% CI 1.02-1.10), indicating that a one-unit increase in SUV corresponded with a 7% increase in the hazard of death.

Multivariate analysis for adenocarcinoma and SCC. In patients with adenocarcinoma, TNM stage and SUV affected survival, with stage being the better predictive factor (P<0.001, HR = 4.707, 95% CI 2.232-9.925). In the case of SCC, SUV was the more significant prognostic factor (P=0.018, HR = 11.708, 95% CI 1.517-90.271).

Discussion

For NSCLC, the TNM staging system is an important tool used by clinicians to estimate prognosis and select the optimal

treatment modalities. Since TNM staging does not consistently give a satisfactory explanation for differences in survival, it is important to identify other prognostic factors. The amount of FDG uptake can be presented by semi-quantitative measures such as SUV and compared between patients. Previous studies have correlated FDG uptake with lung tumor doubling time (15) and proliferation markers such as Ki67 (16). FDG uptake in the primary tumor correlates with poor survival (3-13). Most of these studies were based on comparisons of survival between groups of patients with high and low SUVs, defined by applying cut-offs for SUV ranging from 5 to 20 (3-5,7-12). For SUVs, there is apparently no true cut-off point, but rather a transition zone in which the prognosis gradually worsens. This is substantiated by the results of the present study, in which a range of SUVs from 5 to 10 had discriminatory value, with the most discriminatory being 8.

In a study of 2,700 lung cancer patients who underwent surgery, only 39% of the clinical staging results were consistent with pathological staging (17). Considering that PET scans are more sensitive and accurate than conventional staging methods such as CT (18), and that the post-PET stage provides a stronger prognostic stratification (6), in the present study we determined the TNM stage by combining a conventional staging system with PET findings.

In this study, univariate and multivariate analyses showed SUV to be an independent prognostic predictor for NSCLC patients. Cerfolio *et al* (11) reported that SUV is a better prognostic predictor than stage. However, our study and many others have shown that though SUV is a prognostic predictor independent of stage, TNM stage is the most valuable predictor of survival. We incorporated SUV as a continuous variable in multivariate analysis and observed a 7% increase in the hazard of death after a one-unit increase in SUV. This is in agreement with the results of Downey *et al* (9) and Borst *et al* (10), who observed a 7 and 6% increase in the hazard of death, respectively. Since patients of the same TNM stage may have a varying prognosis and recurrence, it is important for clinicians to subdivide these patients into different groups and to select different treatment strategies for them. The present study indicates that the determination of SUVs is an effective non-invasive method for subdividing patients, and is useful in developing strategies for individually adapted treatment. In brief, the SUV, in combination with conventional prognostic factors, may indicate whether a patient is an appropriate candidate for more aggressive treatment.

We also explored whether SUVs have different prognostic value for patients with different cancer stages or histology. SUVs provided stronger prognostic stratification in group I than in group II. The reason may be that large differences in survival were not expected in group II, since more than half of the patients had stage IV disease with a relatively low survival probability. We therefore speculate that SUV is a better predictor of survival or recurrence in early-stage lung cancer patients than in advanced-stage patients. A limitation of this study is that, since the patients were divided into only two groups according to stage, the prognostic value of SUVs for patients with different stages of cancer needs to be confirmed by further comparison.

Our study furthermore indicates that SUV may be a better prognostic predictor in adenocarcinoma than in SCC. The reason is possibly related to the higher expression of the glucose transporter (19) and, thus, to the relatively higher FDG uptake in SCC than in adenocarcinoma. Multivariate analysis demonstrated that the best choice of prognostic predictor differs between these two cell types of lung cancer, with SUV being the best predictor for SCC and TNM stage being the most significant factor (better than SUV) for adenocarcinoma. However, since the number of patients with SCC was relatively small, this result warrants further study.

In conclusion, ^{18}F-FDG uptake based on PET scan is an independent prognostic predictor in NSCLC patients, especially for those with adenocarcinoma or early-stage disease. These results may help physicians subdivide patients with the same TNM stage in order to develop strategies that optimize individual treatments and improve clinical outcome.

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