Predictive significance of standardized uptake value parameters of FDG-PET in patients with non-small cell lung carcinoma

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Abstract

^{18}F–fluoro-2-deoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is widely used to diagnose and stage non-small cell lung cancer (NSCLC). The aim of this retrospective study was to evaluate the predictive ability of different FDG standardized uptake values (SUVs) in 74 patients with newly diagnosed NSCLC. ^{18}F-FDG PET/CT scans were performed and different SUV parameters (SUV_{max}, SUV_{avg}, $SUV_{T/L}$, and $SUV_{T/A}$) obtained, and their relationship with clinical characteristics were investigated. Meanwhile, correlation and multiple stepwise regression analyses were performed to determine the primary predictor of SUVs for NSCLC. Age, gender, and tumor size significantly affected SUV parameters. The mean SUVs of squamous cell carcinoma were higher than those of adenocarcinoma. Poorly differentiated tumors exhibited higher SUVs than well-differentiated ones. Further analyses based on the pathologic type revealed that the SUV_{max}, SUV_{avg}, and $SUV_{T/L}$ of poorly differentiated adenocarcinoma tumors were higher than those of moderately or well-differentiated tumors. Among these four SUV parameters, $SUV_{T/L}$ was the primary predictor for tumor differentiation. However, in adenocarcinoma, SUV_{max} was the determining factor for tumor differentiation. Our results showed that these four SUV parameters had predictive significance related to NSCLC tumor differentiation; $SUV_{T/L}$ appeared to be most useful overall, but SUV_{max} was the best index for adenocarcinoma tumor differentiation.

Key words: ^{18}F-FDG PET/CT; Standardized uptake value (SUV); Prediction; Non-small cell lung cancer

Introduction

Lung cancer is the largest contributor to cancer death worldwide (1). ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) positron emission tomography (PET) has been widely used in the diagnosis and staging of non-small cell lung cancer (NSCLC) (2,3). Increased FDG uptake by lung cancer cells, measured as the maximum standardized uptake value (SUV_{max}), has been reported to predict the biologic aggressiveness of both early and advanced NSCLC (4-10); however, the reliability of SUV_{max} remains controversial. Some studies found no correlation between SUV_{max} and patient prognosis or lung cancer aggressiveness (11,12). Reasonable explanations for this include the following: 1) SUV_{max} reportedly varies among PET scanners (13); 2) uncontrolled factors such as glucose level, duration of the uptake period, body weight, body composition, and recovery coefficient introduce considerable variations in SUV_{max} (14); 3) different acquisition and image reconstruction parameters also affect SUV_{max} (15). Recent studies have shown that the average SUV (SUV_{avg}), ratio of tumor SUV_{max} to liver SUV ($SUV_{T/L}$), and the ratio of tumor SUV_{max} to the blood pool SUV of aorta ($SUV_{T/A}$) could provide better predictive values (16,17). The purpose of this study was to assess the predictive significance of these SUV parameters in patients with newly diagnosed NSCLC.

Patients and Methods

Study population

This was a retrospective study. Seventy-four consecutive NSCLC patients who were histologically diagnosed between April 2011 and December 2012 were included in this study. They had not undergone surgery, chemotherapy, or radiation therapy and did not have extensive liver metastases. All patients in the study received integrated PET/CT scans with the same PET/CT system within 1 week before surgery or biopsy. The tumor-node-metastasis (TNM) staging system was used, and the histologic tumor type was categorized according to the World Health Organization (WHO) classification system (18,19). The study was

Table 1. Baseline characteristics and standardized uptake values (SUVs) of the study population (n = 74).

Characteristics	Number	SUV_{max}	SUV_{avg}	$SUV_{T/L}$	$SUV_{T/A}$
Age					
<60 years	32	6.9 ± 3.0	5.7 ± 2.4	4.0 ± 2.1	4.5 ± 2.2
≥60 years	42	9.1 ± 4.8	7.2 ± 3.7	5.0 ± 2.5	5.9 ± 3.1
P		0.022*	0.041*	0.063	0.027*
Gender					
Male	54	8.7 ± 4.3	6.9 ± 3.2	4.9 ± 2.4	5.4 ± 2.9
Female	20	6.6 ± 3.8	5.7 ± 3.4	3.5 ± 2.0	4.3 ± 2.3
P		0.053	0.189	0.018*	0.041*
Tumor size					
<3 cm	35	5.8 ± 2.8	4.8 ± 2.2	3.5 ± 2.2	3.9 ± 2.1
≥3 cm	39	10.3 ± 4.3	8.2 ± 3.2	5.4 ± 2.2	6.6 ± 2.7
P		0.000*	0.000*	0.000*	0.000*
Pathological type					
Adenocarcinoma	50	7.4 ± 3.9	5.9 ± 2.9	4.0 ± 2.2	4.8 ± 2.8
Squamous cell carcinoma	24	9.8 ± 4.6	7.9 ± 3.6	5.5 ± 2.5	6.3 ± 2.6
P		0.035*	0.025*	0.017*	0.032*
Tumor differentiation					
Well	15	5.7 ± 2.8	4.7 ± 2.4	2.9 ± 1.5	3.5 ± 1.7
Moderate	22	8.0 ± 3.9	6.7 ± 3.4	4.3 ± 2.2	5.2 ± 2.5
Poor	37	9.2 ± 4.6	7.2 ± 3.3	5.3 ± 2.5	6.1 ± 3.0
P		0.027*	0.039*	0.004*	0.010*
Clinical stage					
I	12	7.1 ± 5.5	5.7 ± 4.6	3.5 ± 2.7	4.0 ± 2.9
II	9	8.3 ± 3.7	6.4 ± 1.8	4.8 ± 1.5	6.3 ± 3.1
III	23	8.3 ± 3.4	6.6 ± 2.6	4.8 ± 2.1	5.5 ± 2.2
IV	30	8.4 ± 4.6	6.9 ± 3.5	4.6 ± 2.6	5.4 ± 3.0
P		0.835	0.757	0.409	0.274

Data are reported as means ± SD. SUV_{max}: maximum SUV; SUV_{avg}: average SUV; $SUV_{T/L}$: ratio of tumor SUV_{max} to liver SUV; $SUV_{T/A}$: ratio of tumor SUV_{max} to the blood pool SUV of aorta. One-way ANOVA followed by the LSD *post hoc* test was used for statistical analyses.
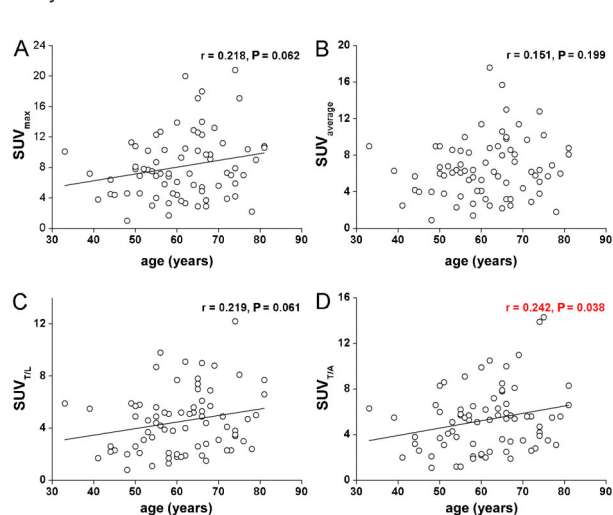
Figure 1. Correlation analyses between age and standardized uptake values (SUVs). SUV_{max}: maximum SUV; SUV_{avg}: average SUV; $SUV_{T/L}$: ratio of tumor SUV_{max} to liver SUV; $SUV_{T/A}$: ratio of tumor SUV_{max} to the blood pool SUV of aorta.
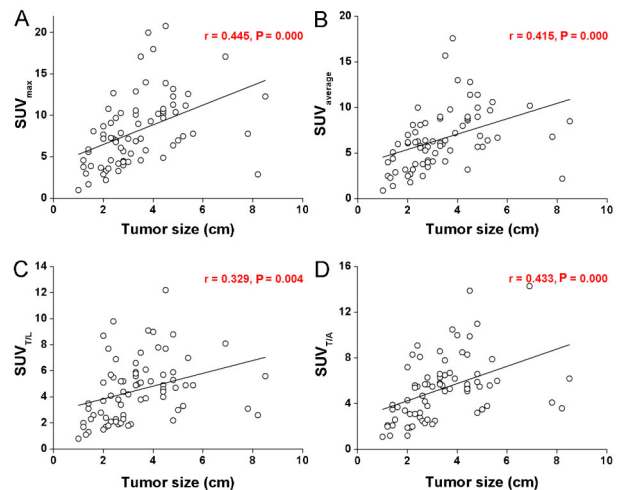
Figure 2. Correlation analyses between tumor size and standardized uptake values (SUVs). SUV_{max}: maximum SUV; SUV_{avg}: average SUV; $SUV_{T/L}$: ratio of tumor SUV_{max} to liver SUV; $SUV_{T/A}$: ratio of tumor SUV_{max} to the blood pool SUV of aorta.
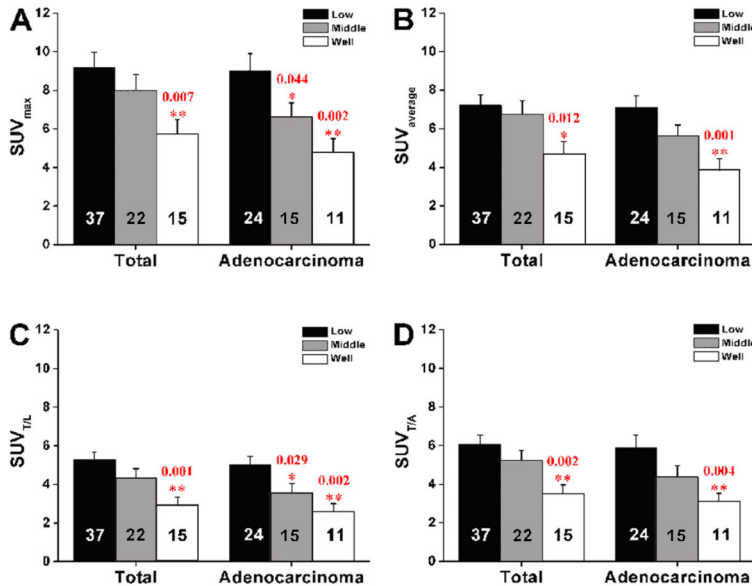
Figure 3. Tumor differentiation-based group difference for standardized uptake values (SUVs). One-way ANOVA followed by the LSD *post hoc* test was used for statistical analyses. See Figure 1 for explanation of SUVs.

conducted with the approval of the Institutional Ethics Committee of Xi'an Jiaotong University.

PET/CT scan

Patients were asked to fast for at least 6 h before examination, and serum glucose levels were confirmed to be below 160 mg/dL. PET/CT scanning was performed on a Gemini 64 TF scanner (Philips, The Netherlands) 40-60 min after intravenous FDG administration (3.7-4.4 MBq/kg). Non-contrast CT images were obtained with a multi-detector spiral CT scanner (Philips Gemini TF 16 PET/CT) immediately prior to PET scanning with an acquisition time of 1.5 min/bed position during shallow breathing. The scan field was from the vertex to the upper thighs. PET data were reconstructed using an ordered-subset expectation maximization algorithm. CT data were used for attenuation correction and anatomic localization. Co-registered images were displayed by means of the SYNTEGRA software (Philips).

PET/CT results were interpreted by two experienced nuclear medicine physicians in a blinded manner. SUV_{max} and SUV_{avg} were determined by drawing a region of interest (ROI) around the primary tumor on the transaxial slices and calculating values with the following equation: tumor activity concentration/injected dose/body weight. $SUV_{T/L}$ and $SUV_{T/A}$ were defined as primary tumor SUV_{max} divided by liver SUV_{max} and aorta blood pool SUV_{max}, respectively.

Statistical analysis

All analyses were conducted using the SPSS software package (version 18.0, SPSS Inc., USA). The statistical differences of SUVs among the groups were determined using one-way analysis of variance (ANOVA), and LSD *post hoc* testing was performed to determine the specific differences between the two groups when $P < 0.05$. Multiple stepwise regression analyses were applied to test the merit of SUVs to predict NSCLC outcomes. Differences were considered significant when $P < 0.05$.

Results

From April 2011 through December 2012, a total of 74 consecutive patients with a mean age of 61 ± 10 years (median = 62 years; range = 33-81 years) were enrolled in the study. The median SUV_{max} was 7.25 (range = 1.0-20.8), and the median SUV_{avg} was 6.2 (range = 0.9-17.6). The median $SUV_{T/L}$ and $SUV_{T/A}$ were 4.4 (range = 0.8-12.2) and 5.4 (range = 1.2-14.3), respectively. The

Table 2. Multiple stepwise regression analysis in patients with non-small cell lung cancer (n = 74).

	Unstandardized coefficients		Standardized coefficients	*t*	P
	B	Std. error	Beta		
$SUV_{T/L}$	0.117	0.037	0.346	3.134	0.002*

Dependent variable: tumor differentiation degree. $SUV_{T/L}$: ratio of tumor maximum standardized uptake value (SUV_{max}) to liver SUV.
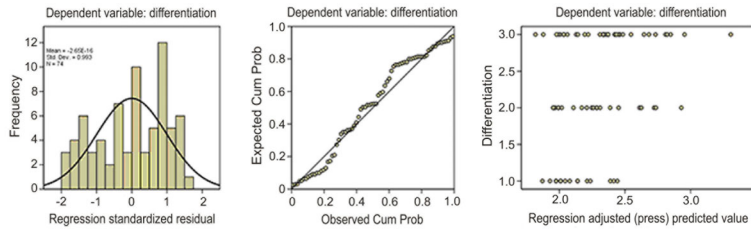
Figure 4. Multiple stepwise regression analysis of patients with non-small cell lung cancer (NSCLC).

demographic and clinical characteristics and SUVs of the population are summarized in Table 1. The mean $SUV_{T/L}$ and $SUV_{T/A}$ of males were significantly higher than those of female subjects (P = 0.018, 0.041). Significantly higher SUV_{max}, SUV_{avg}, and $SUV_{T/A}$ were observed in patients ≥ 60 years of age compared to those <60 years (P = 0.022, 0.041, and 0.027, respectively). Only $SUV_{T/A}$ positively correlated with patients' age (r = 0.242, P = 0.038; Figure 1). No significant relationships were observed between different SUV parameters and clinical stages (all P>0.05, Table 1).

Tumor size was an important factor related to SUV on PET. The median size of the primary tumor was 3.05 cm (range = 1.0-8.5 cm), and the mean SUVs of tumors ≥ 3 cm were statistically higher than those <3 cm (P = 0.000, Table 1). Further analysis revealed that SUVs significantly correlated with tumor size. Their values increased in a tumor size-dependent manner (Figure 2).

Table 1 shows that tumor pathologic type and differentiated grade were significantly related to SUV_{max} (P = 0.035 and 0.027), SUV_{avg} (P = 0.025 and 0.039), $SUV_{T/L}$ (P = 0.017 and 0.004) and $SUV_{T/A}$ (P = 0.032 and 0.010). Poorly differentiated tumors exhibited higher SUVs than well-differentiated tumors (P<0.05, Figure 3). We performed further analyses based on pathologic type and found that in patients with adenocarcinoma, SUV_{max} (P = 0.005), SUV_{avg} (P = 0.007), and $SUV_{T/L}$ (P = 0.018) were significantly different among the differentiation groups. Specifically, the values of poorly differentiated tumors were statistically higher than those of moderately or well-differentiated tumors (P<0.05, Figure 3).

Multiple stepwise regression analyses revealed that of the four SUV parameters, $SUV_{T/L}$ was the primary predictor for tumor differentiation (Table 2 and Figure 4), while in patients with adenocarcinoma, SUV_{max} was the best independent factor for determining tumor differentiation (Table 3 and Figure 5).

Discussion

SUV is a semi-quantitative index of radiolabeled glucose uptake in tumor tissue and correlates with some prognostic factors, including tumor differentiation (20). SUV_{max} has been reported to relate to tumor grade, clinical stage, and pathologic type (21). In the present study, we also noted a higher SUV_{max} in squamous cell carcinoma than in adenocarcinoma, and found that poorly differentiated tumors showed a higher SUV_{max} than well-differentiated tumors. The same results were obtained for SUV_{avg}.

In clinical practice, some uncontrolled factors affect SUV, such as blood glucose level, the time window between FDG administration and image acquisition, serum insulin levels, and renal clearance of FDG (22,23). As such, the use of $SUV_{T/L}$ and $SUV_{T/A}$ has been proposed to minimize variability. Shiono et al. (17) reported that these ratios could significantly predict the risk of disease recurrence in patients with lung cancer, but no more data were published to support this concept. The present study enrolled 74 newly diagnosed NSCLC patients and applied the same method to obtain the SUV ratios ($SUV_{T/L}$ and $SUV_{T/A}$) for each patient. Statistical analyses demonstrated that both values correlated with tumor differentiation. Specifically, poorly differentiated tumors had higher SUV ratios than well-differentiated tumors. Further multiple stepwise regression analysis showed that among these parameters (SUV_{max}, SUV_{avg}, $SUV_{T/L}$, and $SUV_{T/A}$), $SUV_{T/L}$ was an independent determinant for tumor differentiation in NSCLC patients. However, none of these parameters were found to be useful in predicting NSCLC clinical stage.

Pathologic type was related to SUVs. In our study, squamous cell carcinomas exhibited significantly higher SUVs than adenocarcinomas. Conversely, SUV_{max}, SUV_{avg}, and $SUV_{T/L}$ correlated with tumor differentiation in adenocarcinoma, and SUV_{max} was the best independent

Table 3. Multiple stepwise regression analysis in patients with lung adenocarcinoma (n = 50).

	Unstandardized coefficients		Standardized coefficients	t	P
	B	Std. error	Beta		
$SUV_{T/L}$	0. 094	0.027	0.443	3.428	0.001*

Dependent variable: tumor differentiation degree. $SUV_{T/L}$: ratio of tumor maximum standardized uptake value (SUV_{max}) to liver SUV.
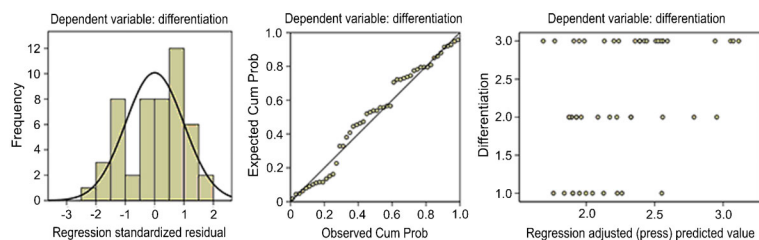
Figure 5. Multiple stepwise regression analysis in patients with lung adenocarcinoma.

determining factor for tumor differentiation, which was inconsistent with the result in the entire study population. Further investigation is needed to understand this finding.

Furthermore, tumor size, age, and gender were also associated with differences in SUV parameters. The values were increased for larger tumors, and patients ≥ 60 years of age had higher values than those <60 years. We also observed statistical differences in SUV ratios between male and female subjects. Males had significantly higher $SUV_{T/L}$ and $SUV_{T/A}$ ratios than females. More data are required to confirm these findings.

Based on the results above, we came to the following preliminary conclusions: 1) SUV_{max}, SUV_{avg}, $SUV_{T/L}$, and $SUV_{T/A}$ relate to tumor differential grade and might be useful for predicting NSCLC patient prognosis; 2) of these parameters, $SUV_{T/L}$ exhibited the strongest predictive value for tumor differentiation overall, but SUV_{max} was better than other parameters for predicting lung adenocarcinoma differentiation; and 3) age, gender, tumor size, and pathologic type dramatically affected SUV parameters and should therefore be taken into account during imaging interpretation. Because of the limitations associated with retrospective studies, further prospective investigations should be designed and performed to acquire more data on the prognostic significance of different SUV parameters in NSCLC patients.

Acknowledgments

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