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Correlation of quantified metabolic activity in nonsmall cell lung cancer with tumor size and tumor pathological characteristics

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Abstract

The aim of this study was to evaluate the relationship between maximum standardized uptake value (SUV_{max}) with tumor size and tumor pathological characteristics as well as suggesting equations between SUV_{max} and tumor size in patients with nonsmall cell lung cancer (NSCLC) to help differentiate between pathology types.

We retrospectively analyzed the fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) findings of 98 patients with NSCLC. Statistical differences were considered significant when $P < .05$. Correlation between SUV_{max} and other variables was determined by Pearson and Spearman correlation. Both linear and nonlinear regression analysis were used to determine equations between SUV_{max} and tumor size to help differentiate between pathology types.

The mean SUV_{max} in patients with squamous cell carcinoma was significantly higher than that of adenocarcinoma (21.35 ± 1.73 vs 13.75 ± 0.89, $P = .000$). The results of regression analysis indicated that among all equations determined with relative accuracy, the "cubic equation" has the highest accuracy when considering the relationship between SUV_{max} and tumor size in patients with adenocarcinoma. In patients with squamous cell carcinoma, the most accurate equation was obtained using the "quadratic equation."

There was a significant correlation between SUV_{max} and tumor differentiation and tumor size in patients with adenocarcinoma. SUV_{max} of patients with squamous cell carcinoma also had a significant correlation with tumor size. Overall SUV_{max} of patients with NSCLC could be predicted by tumor size value. In patients with squamous cell carcinoma compared with those with adenocarcinoma, SUV_{max} with less accuracy can be determined by tumor size. Linear regression analysis line slope can be used as an index for distinguishing adenocarcinoma from squamous cell carcinoma.

Abbreviations: CT = computed tomography, FDG-PET = fluorodeoxyglucose-positron emission tomography, NSCLC = nonsmall cell lung cancer, SCC = squamous cell carcinoma, SUV_{max} = standardized uptake value (maximum).

Keywords: adenocarcinoma, FDG PET/CT, maximum standardized uptake value, NSCLC, squamous cell carcinoma

1. Introduction

Nonsmall cell lung cancer (NSCLC) is one of the most frequent tumors, which mainly include squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma is the second most common subtype after adenocarcinoma in NSCLC patients. The prognosis of the tumors with squamous cell carcinoma component has been reported to be worse than that of adenocarcinoma.[1,2]

Fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) imaging is based on glucose metabolism of tumor cells and has been applied primarily as a staging and restaging tool that can guide subsequent patient care. Furthermore, ^{18}F-FDG PET/CT is useful for the assessment of an indeterminate lung nodule, metastatic nodules, and assessment of response to chemotherapy.[3–19] Quantification of FDG uptake by the tumor cells using SUV_{max} index[20] can be easily performed and is the most widely used quantitative parameter for the analysis of ^{18}F-FDG PET images and estimation of metabolic activity.

Some researchers have shown that NSCLC with different pathological types and sizes produce different SUV_{max} values on PET/CT.[21–26] Zhu et al[21] demonstrated that higher primary tumor SUV_{max} predicts higher extensional or metastatic potential in patients with NSCLC. Khalaf et al[22] demonstrated that the SUV_{max} cutoff of 2.5 is a useful tool in the evaluation of large pulmonary nodules (> 1.0 cm); however, it has no or minimal value in the evaluation of small pulmonary nodules (≤ 1.0 cm). It can be concluded that the SUV_{max} of individual mediastinal lymph nodes is a predictor of malignancy.[23] The results of Sim et al[24] indicated that the likelihood of malignancy increases with increasing SUV_{max}. Ming et al[25] demonstrated that increasing SUV_{max} is associated with increasing tumor, node, and metastasis

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(TNM) stage. They found no evidence of an association of increasing SUV_{max} with a shorter survival. Özgül et al[26] concluded that SUV_{max} was significantly associated with tumor size. Hsu et al[27] demonstrated that patients with a reference tumor ≤ 3 cm and SUV ≤ 3.1 had an expected 5-year survival of 100%. Patients with a reference tumor > 3 cm and SUV > 3.1 had an expected 5-year survival rate of 53.3%. Eugene et al[28] concluded that in patients with stage I NSCLC, circulating blood counts showed weak but significant correlation to tumor FDG uptake. They indicated that although total white blood cell (WBC) count was a significant univariate variable, tumor FDG uptake was a superior and independent predictor of outcome. Oikonomou et al[29] showed that adding radiomic features in staging PET/CT improves the prognostication in early-stage lung cancer patients treated with stereotactic body radiotherapy and may impact decision-making for identifying patients who will benefit from adjuvant therapy or even surgery. Shanyuan et al[30] showed that SUV_{max} of primary tumor was a predictor of lymph node involvement for potential stereotactic body radiotherapy candidates. Katsuyuki et al[31] reported that pretreatment SUV_{max} is a prognostic indicator for outcomes in patients with stage I NSCLC treated with carbon ion radiotherapy. Other methods based on diffusion magnetic resonance (MR) imaging for detection, characterization, grading, and staging of lung cancer were presented.[32–35] Razek et al[32] demonstrated the correlation between the apparent diffusion coefficient (ADC) value and prognostic parameters of lung cancer in patients underwent diffusion weighted MRI. In this paper, ADC values of 31 patients with lung cancer were calculated and correlated with tumor grade and size as well as associated mediastinal lymph nodes. They concluded that there was a significant difference in the ADC value between poorly and well-differentiated to moderately differentiated lung cancer ($P=.03$) as well as between patients with N0 and N3 mediastinal lymphadenopathy ($P=.043$). The ADC value of lung cancer correlated with tumor grade ($r=-0.481$, $P=.043$) and metastatic mediastinal nodes ($r=-0.422$, $P=.018$). They concluded that lower ADC value of the lung cancer is associated with higher pathological tumor grade and metastatic lymph nodes. Razek[33] concluded that the diffusion MR imaging can be used in detection, characterization, grading, and staging of lung cancer as well as it can be used for the diagnosis and characterization of mediastinal and pleural tumors. There is no exposure to ionizing radiation, and no need for administration of external tracer or contrast medium. Furthermore, Razek et al[34] concluded that ADC value is a noninvasive, reliable, and reproducible imaging parameter that may help to assess and characterize thymic epithelial tumors. Razek et al[35] also reported that there is a significant difference ($P<.001$) in ADC of benign and malignant mediastinal lesions in children.

However, it is still unclear whether there is a linear or nonlinear relationship between SUV_{max} of NSCLCs and tumor size, and what is the best representation of the relationship between these 2 variables. Therefore, one of the main purposes of this study is to determine the most accurate equation between SUV_{max} and tumor size in patients with different pathological types of NSCLC. Furthermore, a new index for distinguishing adenocarcinoma from squamous cell carcinoma based on the FDG-PET/CT data is suggested in this paper. The work limit is that the nodules less than 1 cm were hard to image by PET/CT. The spatial resolution of current generation of PET scanners is 7 to 8 mm, which can hardly image pulmonary nodules <1 cm.[36]

2. Materials and methods

2.1. Patients

Ninety-eight patients, diagnosed with NSCLC at our hospital, were retrospectively evaluated. These patients underwent FDG PET/CT scans before the initiation of treatment. Study design and protocol were reviewed and approved by institutional review board (IRB).

2.2. ^{18}F-FDG PET/CT imaging

All PET/CT imaging was acquired using a Discovery 690 VCT (GE Healthcare, Milwaukee, WI) that is equipped with 64-slice CT (Light Speed VCT; GE Healthcare, Milwaukee, Wisconsin). All patients fasted for at least 4 to 6 hours before ^{18}F-FDG PET scanning and whole-blood glucose concentrations were less than 150 mg/dL before ^{18}F-FDG administration. Whole-body image acquisition was started about 45 to 60 minutes after intravenous injection of 370 to 555 MBq of ^{18}F-FDG (4.6 MBq/kg or 0.125 mCi/kg). The emission scan time per bed position was 2.5 minutes. The PET data were reconstructed using a standard iterative algorithm with attenuation correction based on the CT scan data. SUV_{max} was determined by drawing regions of interest on the attenuation corrected FDG-PET images around the tumor. It was then calculated by the software contained within the advantage work station (GE, ADW 4.5 PET/CT work station) according to the following formula[37]:

$$SUV_{\max} = \frac{C(\mu Ci/ml)}{\frac{ID(\mu Ci)}{w(kg)}}.$$

Maintenance and calibration of PET/CT camera and also the work station remained optimal according to manufacturer guideline to assure consistent and reproducible results. Figures 1 and 2 demonstrate FDG-PET/CT scan in 2 NSCLC patients with adenocarcinoma and squamous cell carcinoma pathology, respectively.

2.3. Statistical analysis

The SPSS software version 22.0 (The International Business Machines Corporation (IBM), Armonk, NewYork) was used to perform the statistical analysis and construct figures. The statistical differences of SUV_{max} among the groups (categorized according to the patients' age, gender, tumor size, pathological type, and tumor differentiation) were evaluated by independent sample t test. Descriptive data were expressed as the mean ± standard error of mean. Correlation between SUV_{max} and tumor size and patients' age was calculated by Pearson correlation. Spearman correlation was used to evaluate the correlations between SUV_{max} and pathological type, tumor differentiation, and patients' gender. Both linear and nonlinear (including Logarithmic, Inverse, Quadratic, Cubic, Compound, Power, S-curve, Growth, Exponential) regression equations were fitted to a scatter curve of SUV_{max} and tumor size. Results were considered to be statistically significant when a P value was less than .05.

3. Results

There were 98 patients with NSCLC and their characteristics are demonstrated in Table 1. All patients underwent FDG PET/CT scans before the initiation of treatment. The mean age of these 98 patients was 63.59 ± 1.02 years (range: 35–88). Among them, 72 patients were male with a mean age of 66.01 ± 1.05 years

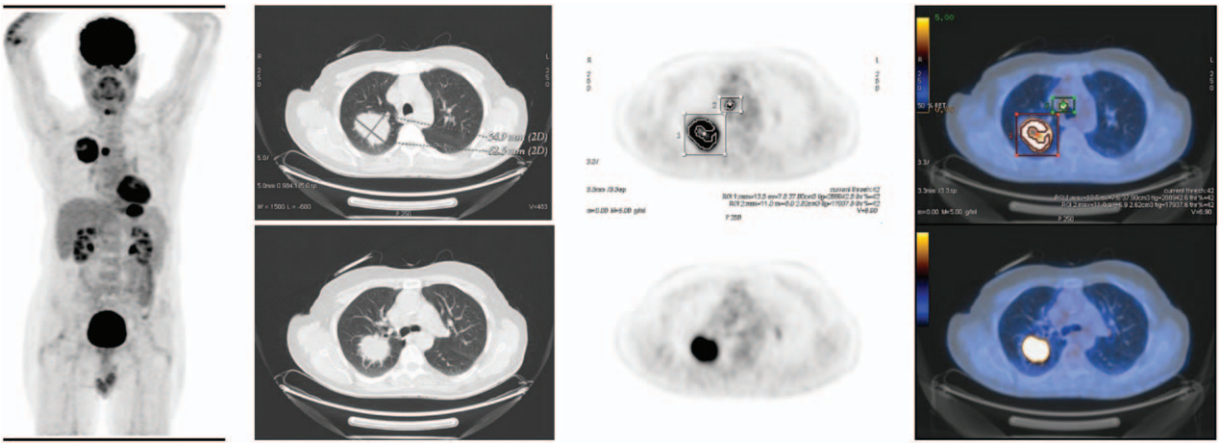

Figure 1. FDG-PET/CT scan, which was performed for the staging of a patient with adenocarcinoma type of NSCLC.

(range: 43–88) and 26 patients were female with a mean age of 56.88 ± 2.02 years (range: 35–76). Of the 98 patients, 59 patients had adenocarcinoma and 39 patients had squamous cell carcinoma. The mean age of the 59 patients diagnosed with adenocarcinoma was 61.32 ± 1.29 years and the mean age of the 39 patients diagnosed with squamous cell carcinoma was 67.02 ± 1.59 years. Of the 59 patients diagnosed with adenocarcinoma, 37 were male with a mean age of 64.95 ± 1.32 years and 22 patients were female with a mean age of 55.23 ± 2.14 years. Also, of the 39 patients diagnosed with squamous cell carcinoma, 35 were male with a mean age of 67.14 ± 1.66 years and 4 patients were female with a mean age of 66.00 ± 3.58 years. The tumor size is defined as the greatest transaxial dimension of the tumor in the lung window (level, −700 to −550 H; width, 1200–1600 H). The tumor size in 98 NSCLC patients ranged from 14 to 140 mm with a mean of 55.16 ± 2.62 mm. Mean size of tumors in male and female patients with NSCLC were 60.27 ± 3.09 and 41.00 ± 3.80 mm, respectively. Mean size of tumors in patients with adenocarcinoma was 47.44 ± 2.86 mm (range: 14–106), while mean size of tumors in patients with squamous cell carcinoma was 66.85 ± 4.37 mm (range: 27–140). The mean size of tumors in patients with squamous cell carcinoma was significantly higher than those of adenocarcinoma ($P = .000$).

Table 2 demonstrates the statistical differences of mean SUV_{max} between different groups, which are classified on the basis of patients' age, gender, tumor size, pathological type, and tumor differentiation degree. There was no significant statistical difference between mean SUV_{max} of males and females (17.57 ± 1.14 vs 14.58 ± 1.61, $P = .166$) with NSCLC. As the median age of patients with NSCLC is 64 years, a comparison was made between 2 groups of patients (<64 and ≥ 64 years). The results of Table 2 demonstrate that there is no significant difference between NSCLC patients under the age of 64 years and those above 64 years (16.00 ± 1.24 vs 17.49 ± 1.42, $P = .436$). The median size of NSCLC tumors was 52.5 mm. Larger NSCLC tumors (≥52.5 mm) significantly had a higher mean SUV_{max} than smaller (<52.5 mm) tumors (21.13 ± 1.38 vs 12.42 ± 0.97, $P = .000$). The mean SUV_{max} in patients with squamous cell carcinoma (21.35 ± 1.73) was significantly ($P = .000$) higher than that of patients with adenocarcinoma (13.75 ± 0.89). In patients with NSCLC, moderately differentiated tumors significantly showed higher mean SUV_{max} than well-differentiated tumors (18.12 ± 2.37 vs 8.19 ± 0.88, $P = .000$). Also, poorly differentiated tumors significantly had higher mean SUV_{max} than well differentiated tumors (19.44 ± 1.14 vs 8.19 ± 0.88, $P = .000$). However, there was no significant difference between the mean

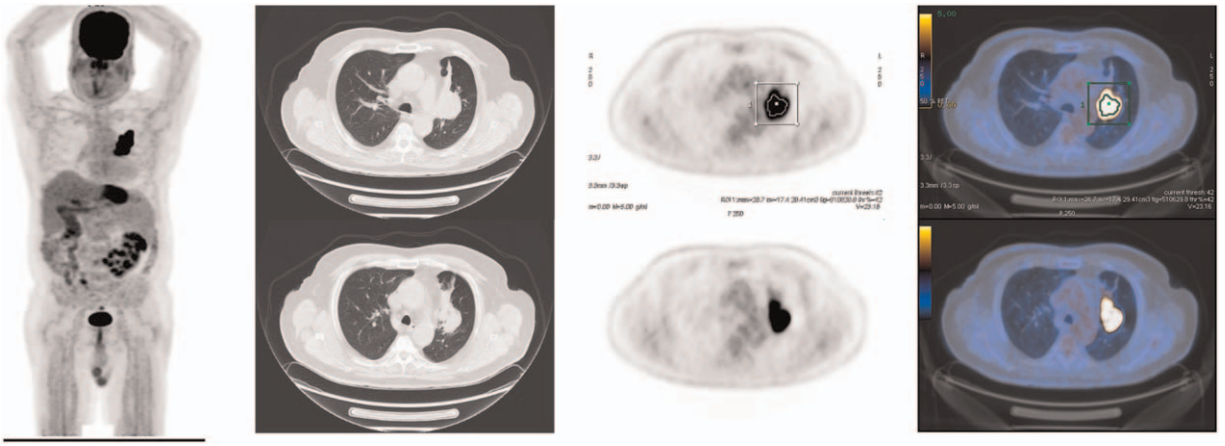

Figure 2. FDG-PET/CT scan, which was performed for the staging of a patient with squamous cell carcinoma type of NSCLC.

Table 1

Patients characteristics.

	Number	Male/Female (number)	Age, y	Male/Female age, y	Tumor size, mm	Male/Female tumor size, mm
NSCLC	98	72/26	63.59 ± 1.02	(66.01 ± 1.05) /(56.88 ± 2.02)	55.16 ± 2.62	(60.27 ± 3.09) /(41.00 ± 3.80)
Adenocarcinoma	59	37/22	61.32 ± 1.29	(64.95 ± 1.32) /(55.23 ± 2.14)	47.44 ± 2.86	(53.62 ± 3.68) /(37.04 ± 3.64)
Squamous cell carcinoma	39	35/4	67.02 ± 1.59	(67.14 ± 1.66) /(66.00 ± 3.58)	66.85 ± 4.37	(67.31 ± 4.79) /(62.75 ± 9.19)

NSCLC = nonsmall cell lung cancer.

Table 2

The statistical differences of the mean SUV_{max} in patients with NSCLC, adenocarcinoma, and squamous cell carcinoma.

	Variable	Number of patients	SUV_{max}	*P*
Nonsmall cell lung cancer	Gender			
	Male	72	17.57 ± 1.14	.166
	Female	26	14.58 ± 1.61	
	Age, y			
	<64	47	16.00 ± 1.24	.436
	≥ 64	51	17.49 ± 1.42	
	Tumor size, mm			
	<52.5	49	12.42 ± 0.97	.000
	≥ 52.5	49	21.13 ± 1.38	
	Pathological type			
	Adenocarcinoma	59	13.75 ± 0.89	.000
	Squamous cell carcinoma	39	21.35 ± 1.73	
	Tumor differentiation			
	Well	21	8.19 ± 0.88	.000
	Moderate	19	18.12 ± 2.37	
	Well	21	8.19 ± 0.88	.000
	Poor	58	19.44 ± 1.14	
	Moderate	19	18.12 ± 2.37	.584
	Poor	58	19.44 ± 1.14	
Adenocarcinoma	Gender			
	Male	37	13.77 ± 1.01	.983
	Female	22	13.73 ± 1.71	
	Age, y			
	<61	27	15.14 ± 1.29	.153
	≥ 61	32	12.58 ± 1.21	
	Tumor size, mm			
	<49	29	9.69 ± 1.04	.000
	≥ 49	30	17.68 ± 1.02	
	Tumor differentiation			
	Well	18	7.02 ± 0.67	.000
	Moderate	6	13.05 ± 1.78	
	Well	18	7.02 ± 0.67	.000
	Poor	35	17.33 ± 1.01	
	Moderate	6	13.05 ± 1.78	.103
	Poor	35	17.33 ± 1.01	
Squamous cell carcinoma	Gender			
	Male	35	21.59 ± 1.88	.695
	Female	4	19.30 ± 4.38	
	Age, y			
	<67	17	19.97 ± 2.60	.492
	≥ 67	22	22.42 ± 2.36	
	Tumor size, mm			
	<78	29	18.84 ± 1.57	.012
	≥ 78	10	28.64 ± 4.43	
	Tumor differentiation			
	Well	3	15.23 ± 1.79	.460
	Moderate	13	20.46 ± 3.20	
	Well	3	15.23 ± 1.79	.267
	Poor	23	22.65 ± 2.31	
	Moderate	13	20.46 ± 3.20	.578
	Poor	23	22.65 ± 2.31	

NSCLC = nonsmall cell lung cancer, SUV = standard uptake value.

SUV_{max} of NSCLC patients with poorly and moderately differentiated tumors (19.44 ± 1.14 vs 18.12 ± 2.37, $P = .584$).

Table 2 also demonstrates that in patients with adenocarcinoma, the mean SUV_{max} of males was not significantly different from females (13.77 ± 1.01 vs 13.73 ± 1.71, $P = .983$). No significant statistical difference was observed in adenocarcinoma patients aged under 61 years compared with those above 61 years (12.58 ± 1.21 vs 15.14 ± 1.29, $P = .153$). In patients with adenocarcinoma, the mean value of SUV_{max} in tumors greater than or equal to 49 mm was significantly higher than tumors smaller than 49 mm (17.68 ± 1.02 vs 9.69 ± 1.04, $P = .000$). Furthermore, poorly and moderately differentiated tumors significantly had higher mean SUV_{max} (17.33 ± 1.01 and 13.05 ± 1.78, respectively) than well-differentiated tumors (7.02 ± 0.67) ($P = .000$ and $P = .000$, respectively). However, the mean SUV_{max} of poorly differentiated tumors was not significantly different from moderately differentiated tumors (17.33 ± 1.01 vs 13.05 ± 1.78, $P = .103$).

Furthermore, Table 2 demonstrates that there was no significant difference between mean values of SUV_{max} in males and females with squamous cell carcinoma ($P = .695$), and no significant difference was found between older and less than 67 years old patients (22.42 ± 2.36 vs 19.30 ± 4.38, $P = .492$). Larger squamous cell carcinoma tumors (≥ 78 mm) significantly showed a higher mean value of SUV_{max} than smaller (<78 mm) tumors (28.64 ± 4.43 vs 18.84 ± 1.57, $P = .012$). In patients with squamous cell carcinoma, there was no significant difference between the mean SUV_{max} of poorly and well differentiated tumors (22.65 ± 2.31 vs 15.23 ± 1.79, $P = .267$), also between tumors with moderate and well differentiation (20.46 ± 3.20 vs 15.23 ± 1.79, $P = .460$), and between poorly and moderately differentiated tumors (22.65 ± 2.31 vs 20.46 ± 3.20, $P = .578$).

The correlation coefficient values between SUV_{max} and tumor size, pathological type, tumor differentiation, patients' age, and gender in patients with NSCLC are summarized in Table 3. Pearson correlation was used to calculate the correlation between SUV_{max} and tumor size and patients' age, while correlation between SUV_{max} and pathological type, tumor differentiation, and patients' gender was determined by Spearman correlation.

In patients with NSCLC, there was a positive and significant correlation between the SUV_{max} and pathological types ($R = 0.368$, $P = .000$). Also, SUV_{max} of NSCLC patients had a positive and significant correlation with tumor differentiation ($R = 0.526$, $P = .000$) and tumor size ($R = 0.554$, $P = .000$). SUV_{max} of NSCLC patients was not significantly correlated with patients' age ($R = 0.120$, $P = .239$) and patients' gender ($R = 0.125$, $P = .222$).

Table 4 summarizes the correlation coefficient values between SUV_{max} and tumor size, tumor differentiation, patients' age, and gender in patients with adenocarcinoma and squamous cell carcinoma. This table summarizes a positive and significant correlation between SUV_{max} and tumor differentiation ($R = 0.719$, $P = .000$) in patients with adenocarcinoma. Furthermore, a positive and significant correlation was observed between SUV_{max} and tumor size ($R = 0.533$, $P = .000$). There was no significant correlation between SUV_{max} and patients' age ($R = -0.133$, $P = .314$) and patients' gender ($R = 0.030$, $P = .822$).

Furthermore, SUV_{max} of patients with squamous cell carcinoma had a positive and significant correlation with tumor size ($R = 0.440$, $P = .005$), while a significant correlation was not found between SUV_{max} of patients with squamous cell carcinoma and tumor differentiation ($R = 0.216$, $P = .186$). Also, SUV_{max} of these patients was not significantly correlated with patients' age ($R = 0.157$, $P = .340$) and patients' gender ($R = 0.041$, $P = .803$).

Regression analysis was used to determine the relation between the SUV_{max} and tumor size. In this regard, 2 types of linear and nonlinear regression analysis have been used. In both types of analyses, the algorithm uses the least squared error value to determine the pattern between the 2 variables. The SUV_{max} was considered as a dependent variable and tumor size was considered as an independent variable. Also, analysis of variance (ANOVA) was used to determine whether the regression model can significantly predict the relationship between variables (SUV_{max} and tumor size).

Figure 3 and Table 5 summarize the results of linear and nonlinear (including Logarithmic, Inverse, Quadratic, Cubic, Compound, Power, S-curve, Growth, Exponential) regression analysis and the obtained equations between SUV_{max} and tumor size in patients with NSCLC.

Regarding the results, using linear and nonlinear regression analysis, tumor size can significantly ($P = .000$) predict SUV_{max} in patients with NSCLC. Although all linear and nonlinear equations with relative precision determine the behavior between SUV_{max} and tumor size, the most accurate [the lowest P value ($P = 2.20 \times 10^{-10}$) and the maximum $R^2 = 0.344$] relationship between SUV_{max} and tumor size was obtained using the "power equation."

The results of linear and nonlinear regression analysis between SUV_{max} and tumor size in patients with adenocarcinoma are summarized in Fig. 4 and Table 6.

On the basis of these results, SUV_{max} significantly ($P = .000$) can be predicted by tumor size value in patients with adenocarcinoma. Among all types of linear and nonlinear equations with relative accuracy to determine the relationship between SUV_{max} and tumor size in patients with adenocarcino-

Table 3

The correlation coefficient values between SUV_{max} and tumor size, pathological type, tumor differentiation, patients' age, and gender in patients with NSCLC.

	Correlation coefficient	P
Pathological type	0.368	.000
Tumor differentiation	0.526	.000
Tumor size	0.554	.000
Age	0.120	.239
Gender	0.125	.222

NSCLC = nonsmall cell lung cancer, SUV = standard uptake value.

Table 4

The correlation coefficient values between SUV_{max} and tumor size, tumor differentiation, patients' age, and gender in patients with adenocarcinoma and squamous cell carcinoma.

Pathological type of NSCLC	Correlation coefficient	P
Adenocarcinoma		
Tumor differentiation	0.719	.000
Tumor size	0.533	.000
Age	−0.133	.314
Gender	0.030	.822
Squamous cell carcinoma		
Tumor differentiation	0.216	.186
Tumor size	0.440	.005
Age	0.157	.340
Gender	0.041	.803

NSCLC = nonsmall cell lung cancer.

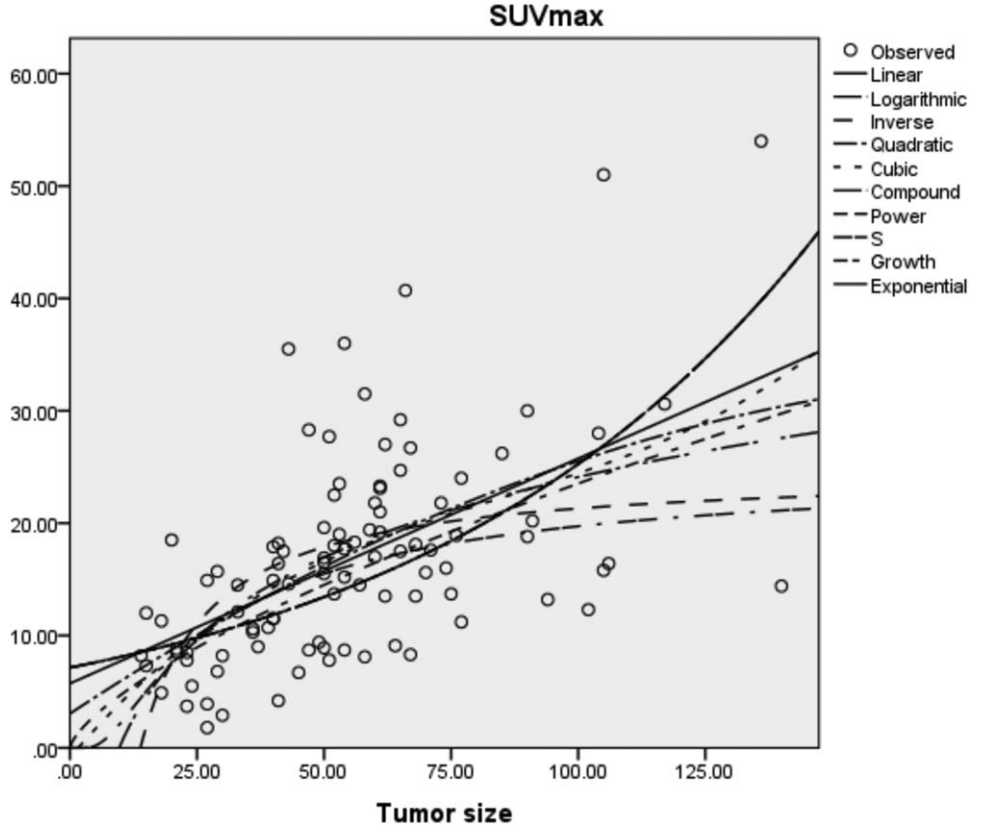

Figure 3. Results of regression analysis between SUV_{max} and tumor size in patients with NSCLC.

ma, the "cubic equation" has the highest accuracy ($P = 6.49 \times 10^{-7}$ and $R^2 = 0.434$).

Figure 5 and Table 7 demonstrate linear and nonlinear regression analysis between SUV_{max} and tumor size in patients with squamous cell carcinoma.

The obtained results demonstrate that in patients with squamous cell carcinoma compared with those with adenocarcinoma, tumor size with less precision can determine the SUV_{max}. In these patients, the most accurate equation was obtained using the "quadratic equation."

Using linear regression analysis, it can be assumed that the linear regression analysis line slope in patients with squamous cell carcinoma is more significant than in patients with adenocarcinoma, which can be used as an index (with a threshold level of 0.170) for the diagnosis of these 2 types of tumors based on the linear regression curve.

Table 5

The linear and nonlinear equations between SUV_{max} and tumor size in patients with NSCLC.

Linear	$SUV_{max} = 0.2 \times$ (Tumor size) + 5.728
Logarithmic	$SUV_{max} = -23.452 + 10.327 \times \ln$(Tumor size)
Inverse	$SUV_{max} = 24.730 - 342.619/$(Tumor size)
Quadratic	$SUV_{max} = -0.01 \times$ (Tumor size)$^2 + 0.298 \times$ (Tumor size) + 3.047
Cubic	$SUV_{max} = 1.814 \times 10^{-5} \times$ (Tumor size)$^3 - 0.05 \times$ (Tumor size)$^2 + 0.535 \times$ (Tumor size) − 0.872
Compound	$SUV_{max} = 7.140 \times 1.013^{(Tumorsize)}$
Power	$\ln(SUV_{max}) = \ln(0.945) + 0.698 \times \ln$(Tumor size)
S	$SUV_{max} = e^{[3.223 - 24.140/(Tumor\ size])}$
Growth	$SUV_{max} = e^{[1.966 + 0.013 \times (Tumor\ size])}$
Exponential	$SUV_{max} = 7.14 \times e^{0.013 \times (Tumorsize)}$

NSCLC = nonsmall cell lung cancer, SUV_{max} = standardized uptake value (maximum).

4. Discussion

Although some papers have previously reported that NSCLC with different pathological types and sizes produce different SUV_{max} values on PET/CT,[21–26] we found no previous reports demonstrating statistical differences of SUV_{max} for different groups classified based on patients' age, gender, tumor size, pathological type, and tumor differentiation degree. Zhu et al[21] showed statistical differences of SUV_{max} for tumor size and tumor differentiation degree, while Khalaf et al[22] demonstrated statistical differences of SUV_{max} only based on tumor size. Sim et al[24] showed SUV_{max} values for groups classified based on pathological type and tumor differentiation degree and Ming et al[25] showed statistical differences of SUV_{max} based on patients' gender, tumor size, and pathological type. In our paper, the statistical differences of mean SUV_{max} between different groups (patients' age, gender, tumor size, pathological type and tumor differentiation degree) are summarized in Table 2.

The results of the present study indicated that there was no significant statistical difference between mean SUV_{max} of males and females in patients with NSCLC. No significant difference was found between patients under the age of 64 years and those who were over 64 years old. Larger NSCLC tumors (≥ 52.5 mm) exhibited a significantly higher mean SUV_{max} than smaller NSCLC tumors (<52.5 mm).

We found that the mean value of SUV_{max} in patients with squamous cell carcinoma was significantly higher than that of

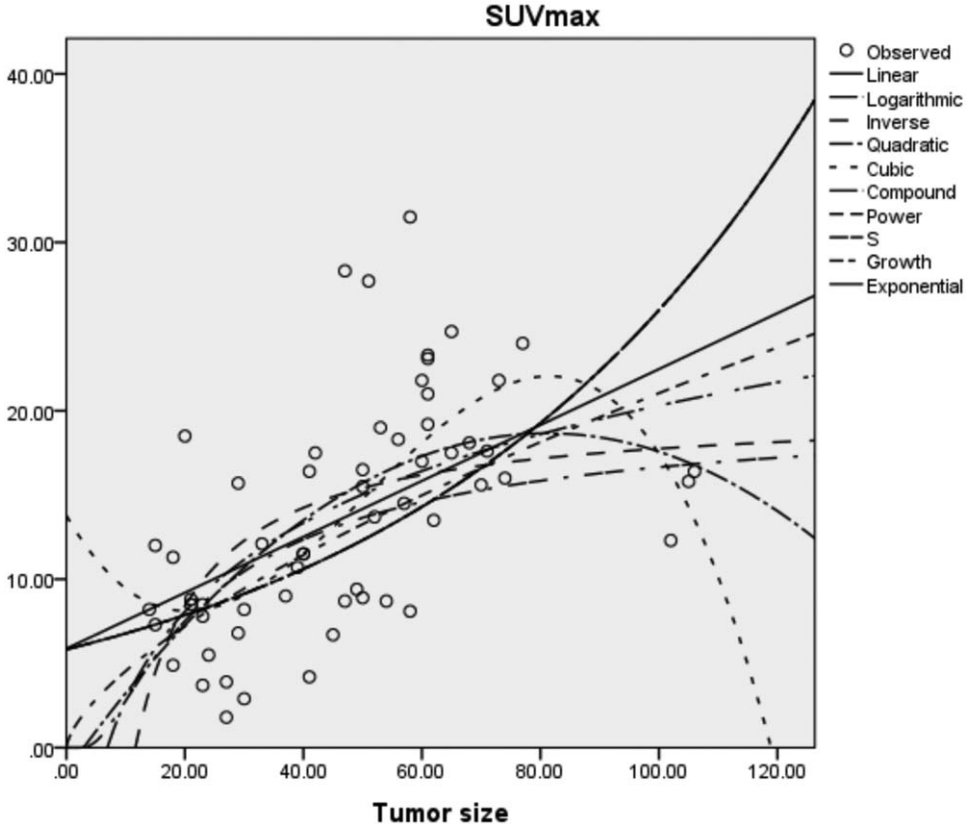

Figure 4. Results of regression analysis between SUV_{max} and tumor size in patients with adenocarcinoma.

patients with adenocarcinoma. The obtained results show that poorly and moderately differentiated tumors had higher mean SUV_{max} than well-differentiated tumors in patients with NSCLC; however, no significant difference was found between the mean SUV_{max} of NSCLC patients with poorly and moderately differentiated tumors.

In our study, we also found that in patients with adenocarcinoma, there was no significant difference between males and females, as well as between the patients younger than 61 years compared with those over 61 years of age. Larger adenocarcinoma tumors ($\geq$ 49 mm) significantly had a higher mean value of SUV_{max} than smaller adenocarcinoma tumors (<49 mm). Furthermore, the mean SUV_{max} values of poorly and moderately differentiated adenocarcinoma tumors were significantly higher than those of well-differentiated tumors; however, no significant difference was observed between the mean SUV_{max} of poorly and moderately differentiated tumors.

In patients with squamous cell carcinoma, no significant difference was observed between mean values of SUV_{max} in males and females, as well as between the patients <67 years and those $\geq$ 67 years of age. Larger squamous cell carcinoma tumors ($\geq$ 78 mm) significantly demonstrated a higher mean value of SUV_{max} than smaller (<78 mm) ones. No significant difference was found between the mean SUV_{max} of poorly, moderately, and well-differentiated tumors in patients with squamous cell carcinoma.

Compared with our study, in which the correlation coefficient values between SUV_{max} and tumor size, pathological type, tumor differentiation, patients' age, and gender in patients with NSCLC were investigated (Tables 3 and 4), previous reports have been demonstrated correlation coefficient values between SUV_{max} and only 2 or 1 of the aforementioned variables. Zhu et al[21] demonstrated correlation coefficient values between SUV_{max} and tumor size and tumor differentiation degree, while Khalaf et al[22] and Ming et al[25] calculated correlation coefficient values between SUV_{max} and pathological type. Sim et al[24] showed correlation coefficient values between SUV_{max} and tumor differentiation degree and pathological type.

We performed further analysis and found that SUV_{max} of NSCLC patients exhibited a positive and significant correlation with pathological types. In these patients, there was a positive and significant correlation between the SUV_{max} and tumor differentiation, as well as between SUV_{max} and tumor size, while SUV_{max}

Table 6

The linear and nonlinear equations between SUV_{max} and tumor size in patients with adenocarcinoma.

Linear	$SUV_{max} = 0.166 \times (\text{Tumor size}) + 5.880$
Logarithmic	$SUV_{max} = -14.703 + 7.602 \times \ln(\text{Tumor size})$
Inverse	$SUV_{max} = 20.090 - 234.053/(\text{Tumor size})$
Quadratic	$SUV_{max} = -0.003 \times (\text{Tumor size})^2 + 0.495 \times (\text{Tumor size}) - 1.416$
Cubic	$SUV_{max} = -0.000122 \times (\text{Tumor size})^3 + 0.019 \times (\text{Tumor size})^2 - 0.607 \times (\text{Tumor size}) + 13.778$
Compound	$SUV_{max} = 5.840 \times 1.015^{(\text{Tumorsize})}$
Power	$\ln(SUV_{max}) = \ln(0.982) + 0.666 \times \ln(\text{Tumor size})$
S	$SUV_{max} = e^{[3.011 - 19.889/(\text{Tumor size})]}$
Growth	$SUV_{max} = e^{[1.765 + 0.015 \times (\text{Tumor size})]}$
Exponential	$SUV_{max} = 5.84 \times e^{0.015 \times (\text{Tumorsize})}$

SUV_{max} = standardized uptake value (maximum).

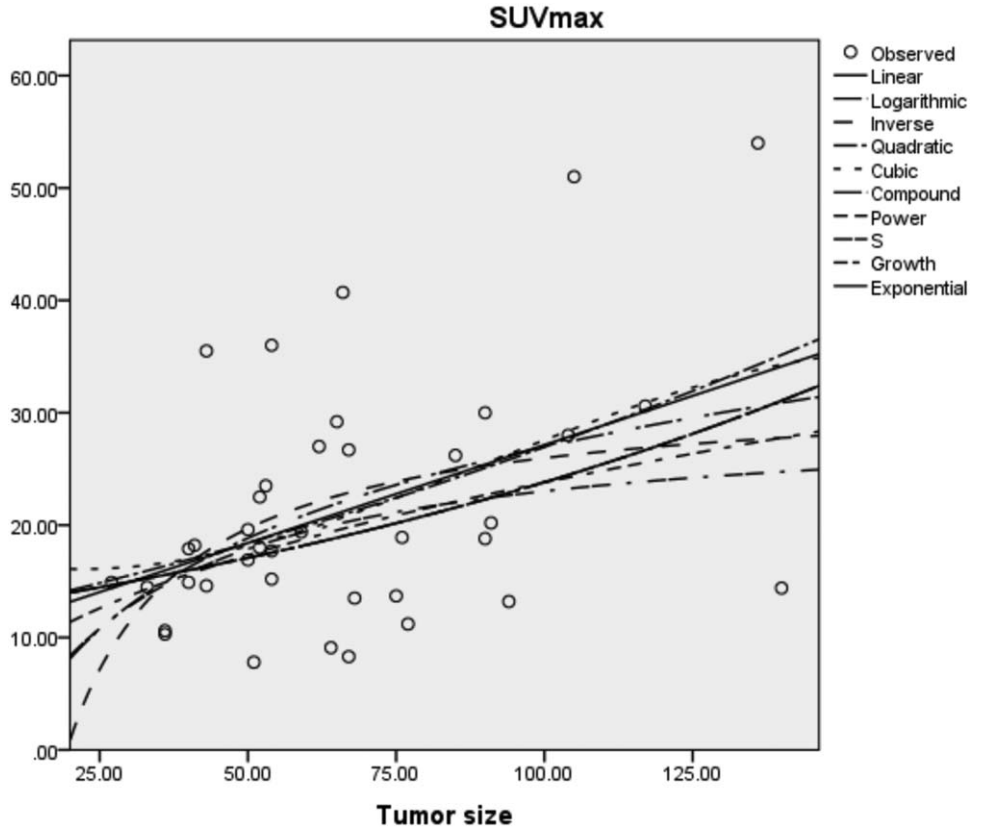

Figure 5. Results of regression analysis between SUV_{max} and tumor size in patients with squamous cell carcinoma.

of NSCLC patients was not significantly correlated with patients' age and patients' gender.

A positive and significant correlation between SUV_{max} and tumor differentiation in patients with adenocarcinoma was found. Furthermore, SUV_{max} of adenocarcinoma patients had a positive and significant correlation with tumor size. There was no significant correlation observed between SUV_{max} and patients' age and gender.

Statistical analysis demonstrated that SUV_{max} of patients with squamous cell carcinoma exhibited a positive and significant correlation with tumor size, whereas a significant correlation was not observed between SUV_{max} of these patients and tumor differentiation. It may be due to the more invasive behavior of this tumor. Furthermore, SUV_{max} of patients with squamous cell carcinoma had no significant correlation with patients' age and patients' gender.

Table 7

The linear and nonlinear equations between SUV_{max} and tumor size in patients with squamous cell carcinoma.

Linear	$SUV_{max} = 0.175 \times (\text{Tumor size}) + 9.678$
Logarithmic	$SUV_{max} = -26.916 + 11.697 \times \ln(\text{Tumor size})$
Inverse	$SUV_{max} = 32.245 - 627.208/(\text{Tumor size})$
Quadratic	$SUV_{max} = -0.000378 \times (\text{Tumor size})^2 + 0.114 \times (\text{Tumor size}) + 11.759$
Cubic	$SUV_{max} = -1.442 \times 10^{-5} \times (\text{Tumor size})^3 + 0.004 \times (\text{Tumor size})^2 - 0.153 \times (\text{Tumor size}) + 17.684$
Compound	$SUV_{max} = 12.253 \times 1.007^{(\text{Tumorsize})}$
Power	$\ln(SUV_{max}) = \ln(2.882) + 0.458 \times \ln(\text{Tumor size})$
S	$SUV_{max} = e^{[3.389 - 25.266/(\text{Tumor size})]}$
Growth	$SUV_{max} = e^{[2.506 + 0.007 \times (\text{Tumor size})]}$
Exponential	$SUV_{max} = 12.253 \times e^{0.007 \times (\text{Tumorsize})}$

SUV_{max} = standardized uptake value (maximum).

The results of the both linear and nonlinear regression analysis indicated that SUV_{max} of patients with NSCLC could be significantly predicted by tumor size value. Among all the linear and nonlinear equations that with relative accuracy determine the relationship between SUV_{max} and tumor size in patients with NSCLC, the "power equation" has the highest accuracy (the lowest P value and the maximum R^2).

We found that in patients with adenocarcinoma, tumor size significantly predicted the SUV_{max} value. Although all linear and nonlinear equations with relative precision determine the behavior between SUV_{max} and tumor size in patients with adenocarcinoma, the most accurate (the lowest P value and the maximum R^2) relationship between SUV_{max} and tumor size was obtained using the "cubic equation."

Our analysis showed that in patients with squamous cell carcinoma, the most accurate equation was obtained using the "quadratic equation," and in these patients, tumor size with less precision can determine the SUV_{max} of tumor than patients with adenocarcinoma.

The results of our study indicated that the linear regression analysis line slope in patients with squamous cell carcinoma is more than in patients with adenocarcinoma, which can be used as an index (with a threshold level of 0.170) for the diagnosis of these 2 types of tumors based on the linear regression curve.

In addition to evaluate the relationship and correlation between SUV_{max} and tumor size and tumor pathological characteristics, we, for the first time, proposed and determined mathematical equations between SUV_{max} and tumor size in

patients with different pathological types of NSCLC to help differentiate between pathology types. Furthermore, we proposed a new index for distinguishing adenocarcinoma from squamous cell carcinoma based on the FDG-PET/CT data. To our best of knowledge, this research work is unique in terms of suggesting mathematical equation for relationship between SUV_{max} of lung tumors with tumor size and pathology, which can be potentially helpful to differentiate tumor type based on PET/CT findings. The limitation of our study is that the nodules less than 1 cm were hard to image by PET/CT. The spatial resolution of current generation of PET scanners is 7 to 8 mm, which can hardly image pulmonary nodules <1 cm.[36]

5. Conclusion

There is a significant correlation between SUV_{max} and tumor differentiation and tumor size in patients with adenocarcinoma. SUV_{max} of patients with squamous cell carcinoma also had a significant correlation with tumor size. Overall SUV_{max} of patients with NSCLC could be predicted by tumor size value. In patients with squamous cell carcinoma compared with those with adenocarcinoma, SUV_{max} with less accuracy can be determined by tumor size. Linear regression analysis line slope can be used as an index for distinguishing adenocarcinoma from squamous cell carcinoma.

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