Original Article

Ratio of maximum standardized uptake value to primary tumor size is a prognostic factor in patients with advanced non-small cell lung cancer

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Purpose: Ratio of maximum standardized uptake value to primary tumor size (SUV_{max}/tumor size) was previously demonstrated to be a more important indicator of prognosis than primary tumor SUV_{max} alone in surgically resected non-small cell lung cancer (NSCLC). The aim of this study was to investigate whether SUV_{max}/tumor size was associated with response to first-line therapy and prognosis in patients with advanced NSCLC.

Patients and methods: A retrospective review of patients who had a pretreatment ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) before receiving first-line therapy for advanced (III & IV) NSCLC was performed. Survival curves were stratified by median SUV_{max} and SUV_{max}/tumor size by the Kaplan-Meier method and statistical differences were assessed using the log-rank test. Multivariate proportional hazards (Cox) regression analyses were applied to test the SUV_{max}'s and SUV_{max}/tumor size's independency of other prognostic factors for the prediction of survival.

Results: In total 181 patients were enrolled into the current study. Median overall survival (OS) was 15.4 months (range, 3.1-64.0 months), progression-free survival (PFS) was 5.6 months (range, 0.8-29.1 months), and post-progression survival (PPS) was 8.2 months (range, 0-51.3 months). The statistical analysis data indicated that only clinical response to first-line therapy (P=0.000, OR =6.555) was independent prognostic factors for PFS, stage (P=0.028, OR =1.673) was associated with PPS independently, and for OS, SUV_{max}/tumor size (P=0.050, OR =1.656) and clinical response (P=0.002, OR =2.803) were all independent prognostic factors.

Conclusions: SUV_{max}/tumor size may be an important indicator of prognosis in patients with advanced NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT); maximum standardized uptake value (SUV_{max}); therapeutic response; prognosis

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Introduction

Lung cancer is the leading cause of cancer-associated death in the world (1). Most non-small cell lung cancer (NSCLC) patients are diagnosed at a relatively late stage, and platinum-based first line chemotherapy is prescribed as a part of standard treatment for advanced NSCLC patients. However, the factor that may predict survival and treatment response is limited.

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is a well-established technique for diagnosis and staging in cancer (2,3). The association between higher maximum standardized uptake value (SUV_{max}) in ^{18}F-FDG PET/CT and poor prognosis or treatment response in cancer patients has been reported in several prior studies (4,5). SUV, a semi-quantitative measurement of FDG uptake, in the primary tumor site of NSCLC has been demonstrated to be correlated with proliferation (4,5) and aggressiveness (6,7).

In 2013, Stiles *et al*. (8) established the SUV_{max} to tumor size ratio (SUV_{max}/tumor size) in his study. SUV_{max}/tumor size was revealed to be associated with survival in 530 patients who were undergoing resection and histologically diagnosed NSCLC, and was stronger than SUV_{max} alone. However, the association between SUV_{max} or SUV_{max}/tumor size and therapy response or survival in advanced NSCLC patients is still unclear.

The aim of this study is to evaluate the predicting and prognostic significance of pretreatment SUV_{max} or SUV_{max}/tumor size in advanced NSCLC patients.

Patients and methods

Study population

The retrospective study protocol was approved by the Hospital Ethics Committee. Patients hospitalized from January 2007 to July 2011 in Department of Respiratory Medicine were included. Inclusion criteria were: (I) histologically or cytologically diagnosed NSCLC; (II) had a pretreatment ^{18}F-FDG PET/CT scanning; (III) in stage IIIB and IV, including those in stage IIIA but not able to surgery or not accept the operation; (IV) had no history or concurrent diagnosis of another type of cancer; (V) overall survival (OS) >3 months; (VI) the clinical data should be available.

Ratio of SUV_{max} to primary tumor size

Scans were performed by a dedicated 16-slice whole-body PET/CT scanner after the patients injected with pyrogen-free ^{18}F-FDG 10 to 15 mCi. SUV_{max} values were obtained by drawing the regions of interest over the most intense slice of the primary tumor by correcting for the injected dose and the patient's weight. The tumor diameter in the primary site was also analyzed.

Therapy response and survival analyses

Therapeutic response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) by CT scans or ^{18}F-FDG PET/CT performed after two cycles of chemotherapy. Clinical responses were classified as disease control rate (DCR) and progressive disease (PD). OS was defined as the time in months between the pathological diagnosis and the date of death, progression-free survival (PFS) as the time between pathological diagnosis and progression disease, and post-progression survival (PPS) as the time between progression disease and the date of death. Patients who were alive were censored at the time of the last clinical follow-up.

Statistical analyses

Statistical analyses were performed using the SPSS statistical software program (version 18.0 for windows). The continuous variables SUV_{max}, tumor size, and SUV_{max}/tumor size were dichotomized by a median split. Survival was calculated with the Kaplan-Meier method, and groups were compared with the log-rank test. Multivariate analysis was carried out with the Cox proportional hazards model. A significance level of 0.05 was used for covariate entry. P values less than 0.05 were considered to be statistically significant.

Results

Patient characteristics

Total 237 consecutive advanced NSCLC patients were enrolled. However, 49 patients were excluded because they took no therapy, transferred to other hospitals or died within 3 months. In 188 patients who had pretreatment ^{18}F-FDG PET/CT, six patients with concurrent chemo-radiotherapy and one patient with a second primary extra-pulmonary cancer were excluded. Final 181 patients were included in the further analysis.

The characteristics of the 181 patients were listed in *Table 1*,

Table 1 Clinical characteristics of total 181 patients with advanced non-small cell lung cancer

Patient characteristic	Data, n (%)
No. of patients	181
Age (years)	
<65	112 (61.9)
≥65	69 (38.1)
Gender	
Female	65 (35.9)
Male	116 (64.1)
Smoke status	
Non-smoker	95 (52.5)
Smoker	86 (47.5)
Loss of weight	
Yes	27 (14.9)
No	154 (85.1)
Histology	
AC	127 (70.2)
SCC	52 (28.7)
Other	2 (1.1)
Differentiation	
Well	82 (45.3)
Moderate	48 (26.5)
Poor	51 (28.2)
TNM stage	
III	44 (24.3)
IV	137 (75.7)
Tumor diameter (cm)	
<3.7	94 (51.9)
≥3.7	87 (48.1)
First-line therapy	
Chemotherapy	157 (86.7)
EGFR-TKI	24 (13.3)
Clinical response	
DCR	139 (76.8)
PD	42 (23.2)
PFS (median/mean ± SD, months)	5.6 (7.2±5.6)
PPS (median/mean ± SD, months)	8.2 (9.9±8.0)
OS (median/mean ± SD, months)	15.4 (17.0±10.4)

AC, adenocarcinoma; SCC, squamous carcinoma; TNM, tumor-node-metastasis; DCR, disease control rate (CR + PR + SD); PD, progressive disease; PFS, progression free survival; PPS, post-progression survival; OS, overall survival.

with a mean age of 60.6 years (range, 29-87 years). A total of 116 patients were males (64.1%). The number of patients in stage III and IV was 44 and 137, respectively. All 181 patients received first-line therapy, including 157 patients received platinum-based chemotherapy according to the tumor histology and left 24 patients with unknown mutation status received EGFR-TKI therapy. After two courses of treatment, patients took whole body tumor scan and clinical response was evaluated. Among these patients, 139 (76.8%) patients got DCR and 42 (23.2%) patients had PD.

There were 59 (32.6%) patients survived till April 1st, 2013. In all patients, the median PFS was 5.6 months, the median PPS was 8.2 months and the median OS was 15.4 months.

SUV_{max} and SUV_{max}/tumor size analyses

In the study population, the median tumor SUV_{max} was 8.0 (range, 1.3-25.4), and the median SUV_{max}/tumor size was 2.2 (range, 0.5-7.5). The distribution of clinical characteristics for SUV_{max} subgroup and SUV_{max}/tumor size subgroup is presented in *Table 2*.

Patients with pretreatment SUV_{max} ≥8.0 had a higher prevalence of age ≥65 years (P=0.003), males (P=0.013), smokers (P=0.001), tumor diameter ≥3.7 cm (P=0.000) and squamous cell carcinoma (P=0.000), while patients with higher pretreatment SUV_{max}/tumor size only tended to be older (≥65 years) (P=0.001).

Either the SUV_{max} or the SUV_{max}/tumor size were no significantly different in therapeutic response (P=0.5808 and P=0.2009, respectively). In EGFR-TKI subgroup, SUV_{max} had significant difference between DCR and PD (P=0.0072), while in the group of chemotherapy treatment, SUV_{max}/tumor size was statistically different in DCR and PD (P=0.0068) (*Figure 1*).

Univariate survival analyses

In univariate analyses, as for the primary outcome OS, age (P=0.013, HR =1.585) and tumor diameter (P=0.004, HR=1.686), loss of weight (P=0.022, HR =1.759), histology (P=0.044, HR =1.411), clinical response (P=0.000, HR =3.921), SUV_{max} (P=0.001, HR =1.927), SUV_{max}/tumor size (P=0.000, HR =2.127) were significant prognostic factors (*Table 3*).

SUV_{max} (P=0.000, HR =1.876) and SUV_{max}/tumor size (P=0.000, HR =1.979) were significant prognostic factors

Table 2 Distribution of clinical characteristics stratified by pretreatment SUV_{max} and the ratio of SUV_{max} to tumor size

Variables	SUV_{max}			SUV_{max}/tumor size		
	<8.0	≥8.0	P value	<2.2	≥2.2	P value
Age (years)			0.003			0.001
<65	65	47		66	46	
≥65	25	44		24	45	
Sex			0.013			0.162
Male	50	66		36	29	
Female	40	25		54	62	
Smoke status			0.001			0.354
Non-smoker	58	37		49	46	
Smoker	32	54		41	45	
Loss of weight			0.327			0.350
No	75	79		78	76	
Yes	15	12		12	15	
Stage			0.121			0.448
III	18	26		21	23	
IV	72	65		69	68	
Tumor diameter (cm)			0.000			0.356
<3.7	67	27		45	49	
≥3.7	23	64		45	42	
Histology			0.000			0.830
AC	75	52		65	62	
SCC	13	39		24	28	
Other	2	0		1	1	
Differentiation			0.056			0.285
Well	48	34		46	36	
Moderate	23	25		22	26	
Poor	19	32		22	29	

SUV_{max}, maximum standardized uptake value; AC, adenocarcinoma; SCC, squamous carcinoma.

for PFS, together with sex (P=0.048, HR =1.376), age (P=0.016, HR =1.467), smoke status (P=0.045, HR =1.364), loss of weight (P=0.033, HR =1.580), tumor diameter (P=0.010, HR =1.487), histology (P=0.005, HR =1.488), and clinical response (P=0.000, HR =7.944).

And for PPS, age (P=0.039, HR =1.464), loss of weight (P=0.039, HR =1.666), tumor diameter (P=0.011, HR =1.596), stage (P=0.024, HR =1.672), clinical response (P=0.000, HR =2.155), SUV_{max} (P=0.017, HR =1.558) and SUV_{max}/tumor size (P=0.006, HR =1.665) were significant prognostic factors.

Kaplan-Meier survival curves showed significant differences in OS, PFS and PPS when patients stratified by SUV_{max}/tumor size or SUV_{max}, suggesting that SUV_{max}/tumor size or SUV_{max} was correlated with survival in advanced NSCLC patients (*Figure 2*).

Multivariate survival analyses

The statistical analysis data indicated that only clinical response to first-line therapy (P=0.000, OR =6.555) was independent prognostic factors for PFS, stage (P=0.028, OR =1.673) was associated with PPS independently, and for OS, SUV_{max}/tumor size ratio (P=0.050, OR =1.656) and clinical response (P=0.002, OR =2.803) were independent prognostic factors (*Table 4*).

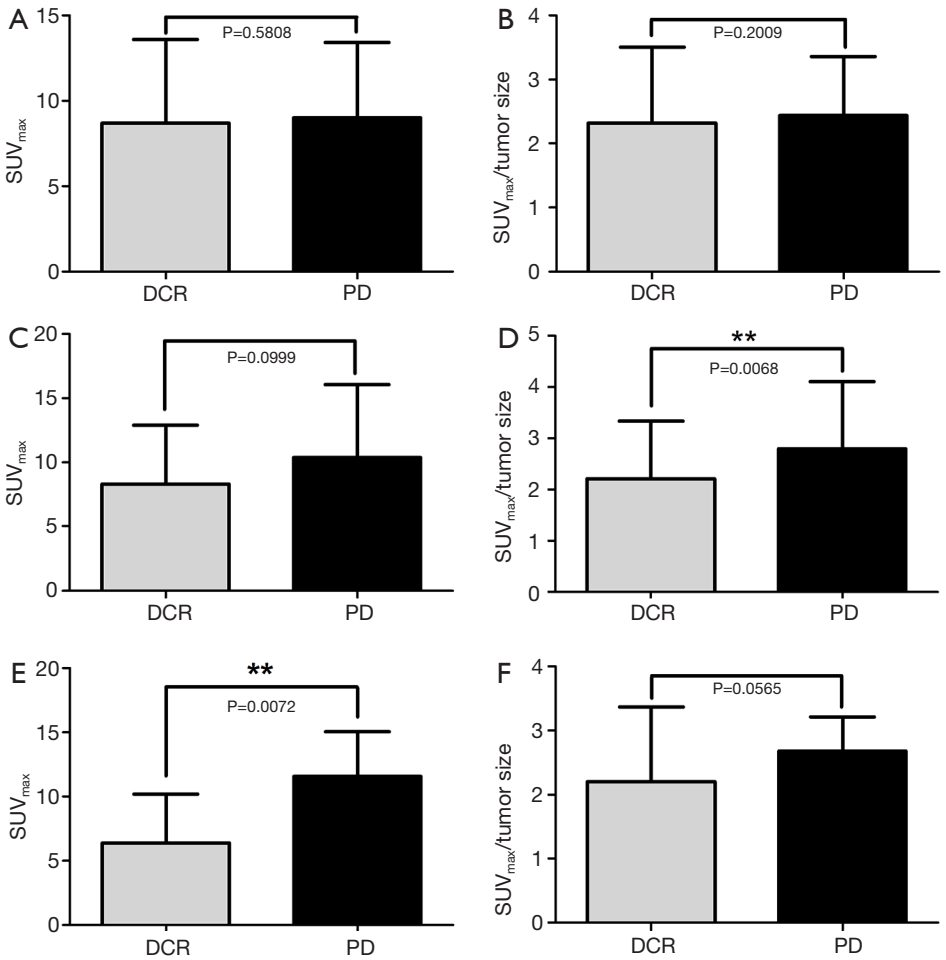

Figure 1 Relationship of SUV_{max}, SUV_{max}/tumor size and RECIST responses (A and B); relationship of SUV_{max}, SUV_{max}/tumor size and RECIST responses in subgroup of chemotherapy (C and D); relationship of SUV_{max}, SUV_{max}/tumor size and RECIST responses in subgroup of EGFR-TKI therapy (E and F). SUV_{max}, maximum standardized uptake value; RECIST, the Response Evaluation Criteria in Solid Tumors; DCR, disease control rate; PD, progressive disease.

Discussion

Our study is the first clinical study to evaluate the prognostic value of SUV_{max}/tumor size in advanced NSCLC patients. SUV_{max}/tumor size is demonstrated to be significantly correlated with survival of patients in this present study. As a promising functional marker, SUV_{max}/tumor size is an available factor for predicting outcome in advanced NSCLC patients.

As we known, a tumor did not always have a uniform shape and a homogeneous composition, so tumor diameter could not represent the real tumor burden. Other functional parameters, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were suggested to have prognostic value in previous studies (9,10). MTV and TLG were integrated both tumor volume and biologically relevant metabolic data and was defined as the mean standardized uptake value multiplied by the MTV. However, the volumetric functional assessment could only be made consistently with the advance of image analysis tools and 3-dimensional display techniques. SUV_{max}/tumor size, taken the real tumor burden the tumor diameter together, is much more simple to perform than MTV or TLG and have the efficiency in clinic, making the result more feasible and credible (11,12).

Stiles *et al.* (8) provided the evidence in his study that SUV_{max}/tumor size was a stronger independent predictor of survival than SUV_{max} alone. However, all the patients

Table 3 Univariate analysis of survival in 181 patients with advanced NSCLC

Variables	PFS		PPS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)						
<65	1		1		1	
≥65	1.467 (1.076-2.002)	0.016	1.464 (1.019-2.104)	0.039	1.585 (1.102-2.280)	0.013
Sex						
Male	1		1		1	
Female	1.376 (1.003-1.887)	0.048	1.139 (0.783-1.657)	0.497	1.294 (0.890-1.883)	0.178
Smoke status						
Non-smoker	1		1		1	
Smoker	1.364 (1.006-1.848)	0.045	1.177 (0.823-1.683)	0.371	1.268 (0.887-1.813)	0.192
Loss of weight						
No	1		1		1	
Yes	1.580 (1.038-2.404)	0.033	1.666 (1.027-2.704)	0.039	1.759 (1.085-2.850)	0.022
Stage						
IIIA/IIIB	1		1		1	
IV	1.040 (0.729-1.484)	0.829	1.672 (1.068-2.617)	0.024	1.538 (0.983-2.405)	0.059
Tumor diameter (cm)						
<3.7	1		1		1	
≥3.7	1.487 (1.098-2.013)	0.010	1.596 (1.113-2.289)	0.011	1.686 (1.177-2.414)	0.004
Histology						
AC	1		1		1	
SCC						
Other	1.488 (1.125-1.967)	0.005	1.239 (0.881-1.742)	0.218	1.411 (1.010-1.972)	0.044
Differentiation						
Well	1		1		1	
Moderate						
Poor	1.088 (0.906-1.305)	0.366	1.156 (0.930-1.437)	1.191	1.124 (0.905-1.394)	0.290
First-line therapy						
Chemotherapy	1		1		1	
EGFR-TKI	1.080 (0.683-1.708)	0.743	1.471 (0.899-2.406)	0.125	1.460 (0.893-2.389)	0.132
Clinical response						
DCR	1		1		1	
PD	7.944 (5.268-11.98)	0.000	2.155 (1.450-3.202)	0.000	3.921 (2.596-5.921)	0.000
SUV_{max}						
<8.0	1		1		1	
≥8.0	1.816 (1.334-2.474)	0.000	1.558 (1.084-2.240)	0.017	1.927 (1.340-2.772)	0.000
SUV_{max}/tumor size						
<2.2	1		1		1	
≥2.2	1.979 (1.454-2.694)	0.000	1.665 (1.156-2.399)	0.006	2.127 (1.476-3.066)	0.000

NSCLC, non-small cell lung cancer; PFS, progression free survival; PPS, post-progression survival; OS, overall survival; AC, adenocarcinoma; SCC, squamous carcinoma; DCR, disease control rate (CR + PR + SD); PD, progressive disease; SUV_{max}, maximum standardized uptake value.

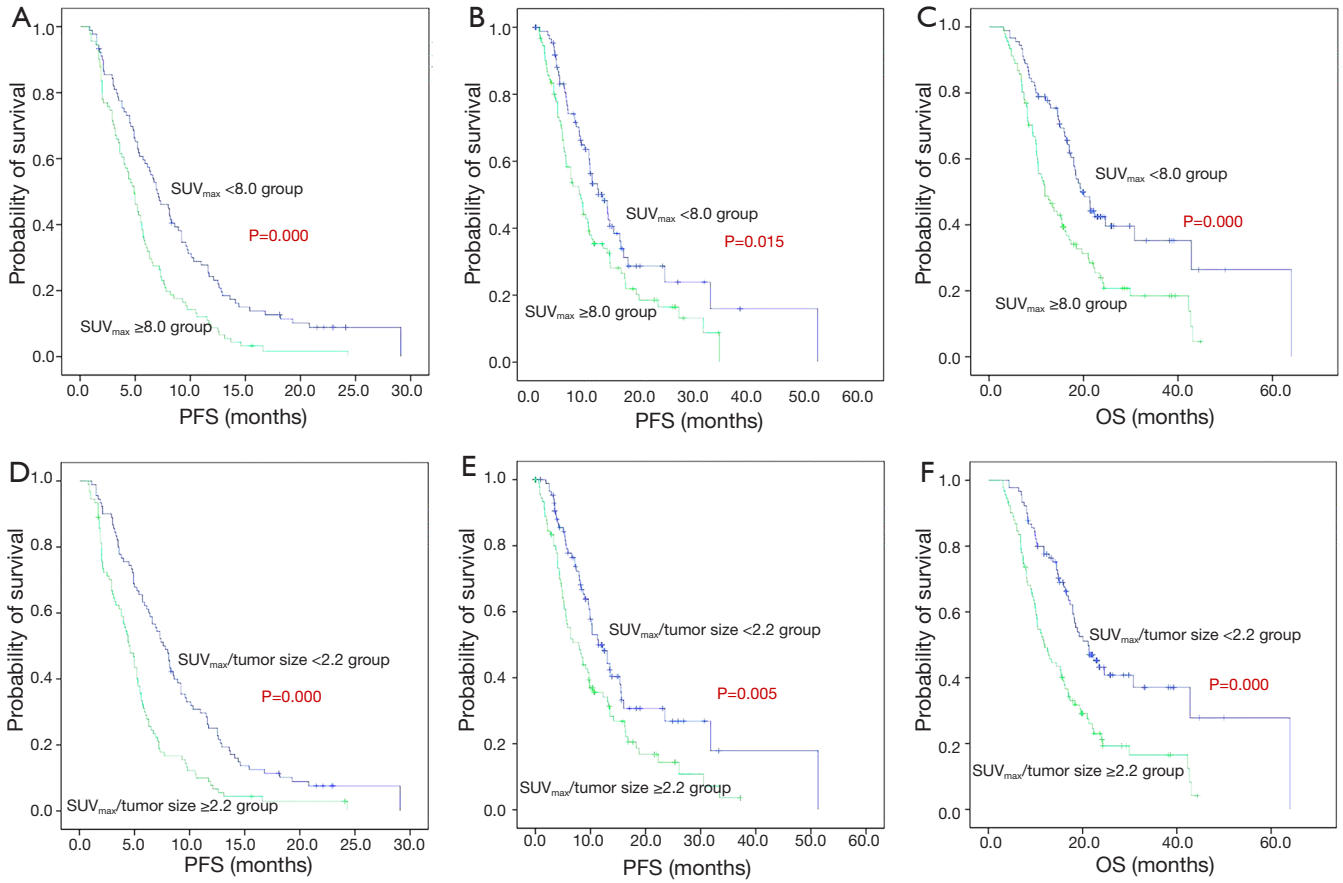

Figure 2 Kaplan-Meier demonstrating differences in patients with high and low primary tumor ^{18}F-FDG PET SUV_{max} (A-C), SUV_{max}/tumor size (D-F). Differences in OS (C and F, P=0.000 and 0.000, respectively), PFS (A and C, P=0.030 and 0.005, respectively), and PPS (B and E, P=0.000 and 0.000, respectively). ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography; SUV_{max}, maximum standardized uptake value; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival.

Table 4 Multivariate Cox regression analysis of survival in 181 patients with advanced NSCLC

Variables	PFS		PPS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.058 (0.748-1.496)	0.750	1.394 (0.951-2.044)	0.089	1.220 (0.827-1.800)	0.315
Sex	0.962 (0.635-1.458)	0.856	–	–	–	–
Smoke status	1.231 (0.814-1.860)	0.325	–	–	–	–
loss of weight	1.302 (0.827-2.049)	0.254	1.309 (0.781-2.194)	0.307	1.324 (0.795-2.206)	0.281
Tumor diameter	1.258 (0.855-1.851)	0.244	1.533 (0.989-2.376)	0.056	1.511 (0.976-2.338)	0.064
Histology	1.201 (0.845-1.709)	0.308	–	–	1.404 (0.974-2.024)	0.069
Stage	–	–	1.673 (1.056-2.651)	0.028	–	–
Clinical response	6.555 (4.142-10.372)	0.000	1.568 (0.998-2.463)	0.051	2.803 (1.752-4.483)	0.000
SUV_{max}	1.086 (0.671-1.756)	0.737	0.955 (0.568-1.607)	0.863	1.003 (0.591-1.702)	0.991
SUV_{max}/tumor size	1.438 (0.936-2.207)	0.097	1.476 (0.905-2.407)	0.119	1.656 (1.000-2.742)	0.050

NSCLC, non-small cell lung cancer; PFS, progression free survival; PPS, post-progression survival; OS, overall survival; SUV_{max}, maximum standardized uptake value.

enrolled in that study were at an early stage (IA-IIIA). In current research, we demonstrated that SUV_{max}/tumor size ratio was only affected by age. In survival analysis, SUV_{max}/tumor size was an independent predictor of OS, PFS and PPS.

In addition, high value of FDG uptake suggested more vigorous tumor cell metabolism and more rapid growth and there were many studies identified the relationship between functional parameters in PET/CT and therapeutic response in several tumors (13). We also analyzed the relationship between SUV_{max} or SUV_{max}/tumor size and the response of first-line therapy. However, the correlation was not significant in this study.

This study had its limitations. First, it was retrospective research and study population was from just a single center. Second, the use of EGFR-TKI was proved to be associated with survival in NSCLC (14,15), and 100 patients in our study had used iressa or tarceva, which might affect the survival. Despite these limitations, we included patients strictly and made a relatively large patient cohort and the current study provided important insight into the prognostic importance of pretreatment SUV_{max}/tumor size.

Taken together, our results is first to demonstrate the SUV_{max} to primary tumor size in ^{18}F-FDG PET/CT is associated with survival in patients with advanced NSCLC, and might be an important indicator rather than SUV_{max} alone. Although it was a respective study, our study indicated the potential usefulness of a new predictor for advanced NSCLC patients. To confirm these findings, additional larger, prospective and randomized studies were needed.

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