Metabolic tumor volume derived from ^{18}F-FDG PET/CT as a prognostic parameter for non-small cell lung cancer (NSCLC) patients

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Abstract
To determine whether the prognostic stratification of non-small cell lung cancer (NSCLC) patients could be made by fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT)-derived parameters such as maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG). A total of 106 patients who were initially diagnosed with NSCLC with clinical stage III or stage IV at our hospital from January 2015 to January 2018 were included. The metabolic and volumetric parameters of ^{18}F-FDG PET/CT were systematically collected, and their optimal cut-off values were determined on the basis of the receiver operating characteristic (ROC) curves. Kaplan-Meier methods and log-rank test were used to evaluate the relationships between ^{18}F-FDG PET/CT-derived parameters and overall survival (OS) of NSCLC patients. The univariate and multivariate Cox analysis were conducted to identify the independent predictors of OS. The optimal cut-off value of SUVmax was 8.94 and area under the curve (AUC) for identifying patients with mortality risk was 0.618 (95% confidence interval [CI]: 0.490-0.745), with a sensitivity of 78.6% and specificity of 53.3%. The optimal cut-off value of MTV40 was 12.44 and the AUC value was 0.785 (95%CI: 0.676-0.893), with a sensitivity of 85.7% and specificity of 71.7%. Furthermore, the ROC curves identified 71.95 as the optimal cut-off value of TLG40, and the AUC value, sensitivity and specificity were 0.782 (95%CI: 0.681-0.883), 78.6% and 70.4%, respectively. The Kaplan-Meier curves showed that SUVmax (HR for SUVmax >8.94: 3.501, 95%CI: 1.133-10.817, P=0.029), MTV40 (HR: 6.926 for MTV40 >12.44, 95%CI: 2.244-21.378, P=0.001) and TLG40 (HR: 4.314 for TLG40 >71.95, 95%CI: 1.503-12.381, P=0.007) were significantly associated with poor OS of NSCLC patients. However, only MTV40 (HR: 4.235, 95%CI: 1.324-13.526, P=0.015) was shown to have an independent role in the multivariate Cox analysis. Metabolic tumor volume had a superiority in predicting the prognosis of NSCLC patients compared with other metabolic and volumetric parameters, suggesting that it might be a valuable prognostic marker.

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Introduction

In the recent decade, the prevalence of lung cancer presents a trend of growing up year by year, and it has become the leading cause of cancer-related deaths around the world [1, 2]. Non-small cell lung cancer (NSCLC) is the most common pathological subtype, which accounts for 80% of all lung cancer cases. Surgical resection was still the primary treatment option for early NSCLC patients. Due to aggressive biological characteristics and lack of early symptoms, however, NSCLC was frequently diagnosed at the advanced stage of disease, making these patients lost opportunity of curative surgery [3]. It has been reported that the 5-year overall survival of locally advanced and metastatic NSCLC patients is less than 10% [4].

The tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) was the major clinical tool for prognostic assessment and treatment decision of NSCLC patients [5, 6]. Currently, the preoperative and/or pretreatment clinical staging of the primary NSCLC was mainly dependent on radiological imaging examinations. As a novel functional imaging technique, fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) imaging has established an excellent diagnostic value for lymph node involvement and distant metastases of lung cancer [7-9]. Unlike traditional imaging technique such as CT scan and magnetic resonance imaging (MRI), ^{18}F-FDG PET/CT provided important information on glucose uptake and metabolism of the neoplastic lesion, which reflected the proliferative ability of tumor [10, 11]. To date, various metabolic and volumetric parameters of ^{18}F-FDG PET/CT, including maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG), have been used to evaluate meta-

bolic activity of tumor. More importantly, emerging evidence has suggested that these metabolic parameters had a significant prognostic value for lung cancer patients. It has been shown that increased values of metabolic and volumetric parameters were significantly associated with high risk of recurrence and poor survival outcome in NSCLC patients [11-15]. However, this conclusion has been challenged by some studies, which demonstrated that these metabolic parameters did not provide additional prognostic value for NSCLC patients [16-18]. In view of inconsistent findings about this topic, the current study was designed to determine whether the prognostic stratification of NSCLC patients could be made by metabolic and volumetric parameters of ^{18}F-FDG PET/CT.

Subjects and Methods

Patients and data collection

This is a single-institution retrospective cohort study, and a total of 106 patients who were initially diagnosed with primary NSCLC at our hospital from January 2015 to January 2018 were included. All patients received ^{18}F-FDG PET/CT examination before treatment and were classified as clinical stage III or stage IV according to the 7th TNM staging system of the AJCC. Those patients who had the history of other malignancies and/or underwent any adjuvant treatment before imaging examination were not eligible for this study. All enrolled patients received first-line platinum-based chemotherapy and additional targeted therapy/immunotherapy if indicated.

The demographic data and clinicopathologic characteristics of 106 NSCLC patients were systematically collected from electronic medical record. All patients were retrospectively characterized based on age (>65 vs ≤65 years), gender (female vs male), BMI (≥25 vs <25kg/m^2), smoking history (yes vs No), histological type (squamous cell carcinoma vs adenocarcinoma), tumor size (≥4.0 vs <4.0cm), the serum level of pretreatment carcinoembryonic antigen (CEA)(>5 vs ≤5ng/mL), the expression of CYFRA21-1 (positive vs negative) and clinical TNM stage (stage IV vs stage III).

^{18}F-FDG PET/CT examination and relevant metabolic parameters

The whole-body PET/CT scanning was conducted according to a standard clinical procedure. To maintain a relatively low level of blood glucose, all patients need to fast for at least 6 hours before PET/CT examination. After intravenous injections of ^{18}F-FDG for 1 hour, the whole-body image acquisition was obtained in each subject. The values of relevant metabolic parameters and imaging measurements were calculated from PET data. A region of interest was manually drawn around the most active lesion. The ^{18}F-FDG uptake was quantitatively assessed by SUVmax, which was defined as the ratio of the maximum activity concentration and the injected dose adjusted by body weight. In other word, SUVmax represented the maximum metabolic activity of the tumor within the region of interest. Metabolic tumor volume was considered as a volume parameter with increased glycolytic activity and it quantified the metabolic volume of the primary tumor. In this study, MTV was calculated as the sum in cubic centimeters of the lesion volume, and the threshold of MTV was set as 40% (MTV40). In addition, TLG was defined as the product of SUVmean and MTV, which taken into account metabolic activity and metabolic volume of the tumor. Correspondingly, TLG40 was calculated by multiplying MTV40 by SUVmean of the lesion.

Statistical analysis

The means and standard deviations (SD) were used to describe statistics if continuous variables complied with normal distribution, and the median and range were used if not. The optimal cut-off values of SUVmax, MTV40 and TLG40 were determined on the basis of the receiver operating characteristic (ROC) curves, respectively. In this study, the primary endpoint was overall survival (OS), which was defined as the time interval from the diagnosis of NSCLC to the death owing to any cause or the last follow-up. The prognostic value of metabolic parameters was evaluated by Kaplan-Meier methods and log-rank test. Furthermore, the univariate and multivariate Cox regression analysis were conducted to identify the independent prognostic factors for NSCLC patients. Data processing and statistical analysis were carried out using SPSS software 23.0 version, and a P-value of <0.05 was considered statistically significant.

Results

Patient characteristics and metabolic parameters of ^{18}F-FDG PET/CT

A total of 106 consecutive NSCLC patients with clinical stage III or stage IV were eligible for this analysis. Table 1 showed the demographic data and baseline characteristics of these NSCLC patients. This patient cohort consists of 70 male (66.0%) and 36 female (34.0%), with a mean age of 64.6±9.4 years (range: 36-85 years). Of these patients, 62.3% (66/106) had the history of smoking, and lung adenocarcinoma was detected in 70.8% (75/106) of patients. The mean of tumor size was 4.1±2.3cm. The clinical stage was determined based on the 8th edition of TNM staging system of the AJCC. Fifty patients (47.2%) had advanced NSCLC (clinical stage III) and fifty-six patients (52.8%) had metastatic NSCLC (clinical stage IV). The level of blood glucose for all patients was 6.34± 1.25mmol/mL at the time of ^{18}F-FDG PET/CT examination.

Regarding metabolic parameters of ^{18}F-FDG-PET/CT, the median of SUVmax, MTV40 and TLG40 for the primary tumor was 9.27 (range: 1.93-26.78), 8.28 (range: 0.99-131.68) and 44.4 (range: 1.82-1156.58), respectively. The ROC curves indicated that the optimal cut-off value of SUVmax was 8.94 and the area under curve (AUC) for identifying patients with mortality risk was 0.618 (95%CI: 0.490-0.745), with a sensitivity of 78.6% and specificity of 53.3% (Figure 1). The ROC curves identified 12.44 as the optimal cut-off value of MTV40 and its AUC value for survival prediction was 0.785 (95%CI: 0.676-0.893), with a sensitivity of 85.7% and specificity of 71.7% (Figure 1). In addition, the optimal cut-off point of TLG40 was 71.95 on the basis of ROC curve analysis. The AUC

value was 0.782 (95%CI: 0.681-0.883), and the sensitivity and specificity were 78.6% and 70.4%, respectively (Figure 1).

The relationships between metabolic parameters of ^{18}F-FDG PET/CT and survival outcome of NSCLC patients

The median of follow-up period was 12.1 months (range, 1.4-29.7 months), and 17 patients (16.0%) died during follow-up period. Based on the identified threshold of SUVmax, all patients were divided into high SUVmax (>8.94, n=46) and low SUVmax (≤8.94, n=60) group. The Kaplan-Meier curves showed that SUVmax >8.94 group had a worse OS in comparison to SUVmax ≤8.94 group (HR: 3.501, 95%CI: 1.133-10.817, P=0.029) (Figure 2). In terms of MTV40, NSCLC patients were classified into MTV40 >12.44 (n=68) and MTV40 ≤12.44 group (n=38) based on its optimal cut-off value. The result revealed a significant correlation between high MTV40 value and poor OS (HR: 6.926, 95%CI: 2.244-21.378, P=0.001) (Figure 3). Similarly, we also found that TLG40>71.95 (n=41) was significantly associated with worse OS in NSCLC patients (HR: 4.314, 95%CI: 1.503-12.381, P=0.007) (Figure 4).

Table 1. *Demographic and clinicopathological features of 106 NSCLC patients.*

Variables	n (%)
Age (years)	
≤65	51 (48.1%)
>65	55 (51.9%)
Mean±SD	64.6±9.4
Range	36-85
Sex	
Male	70 (66.0%)
Female	36 (34.0%)
BMI (kg/m^2)	
<25 kg/m^2	73 (68.9%)
≥25 kg/m^2	34 (32.1%)
Mean±SD	23.3±3.3
Smoking history	
No	40 (37.7%)
Yes	66 (62.3%)
Histological type	
Adenocarcinoma	75 (70.8%)
Squamous cell carcinoma	31 (29.2%)
Tumor size (cm)	
<4.0	59 (55.7%)
≥4.0	47 (44.3%)
Mean±SD	4.1±2.3
CEA	
≤5ng/mL	67 (63.2%)
>5ng/mL	39 (36.8%)
CYFRA21-1	
Negative	47 (44.3%)
Positive	59 (55.7%)
clinical TNM stage	
Stage III	50 (47.2%)
Stage IV	56 (52.8%)

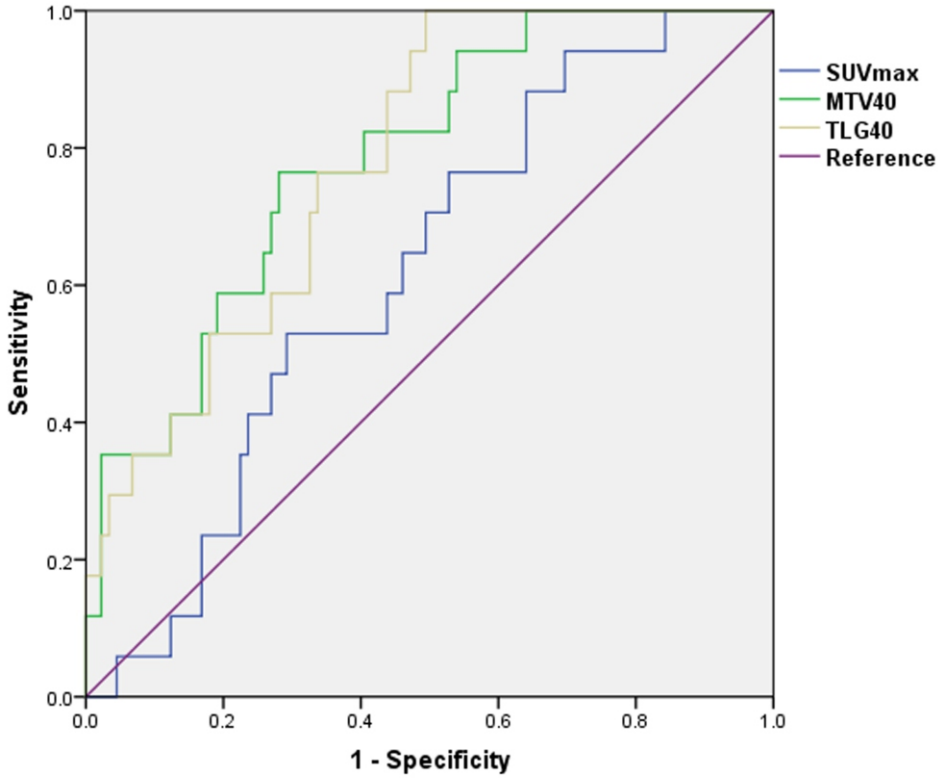

Figure 1. The ROC curves of metabolic and volumetric parameters derived from ^{18}F-FDG PET/CT.

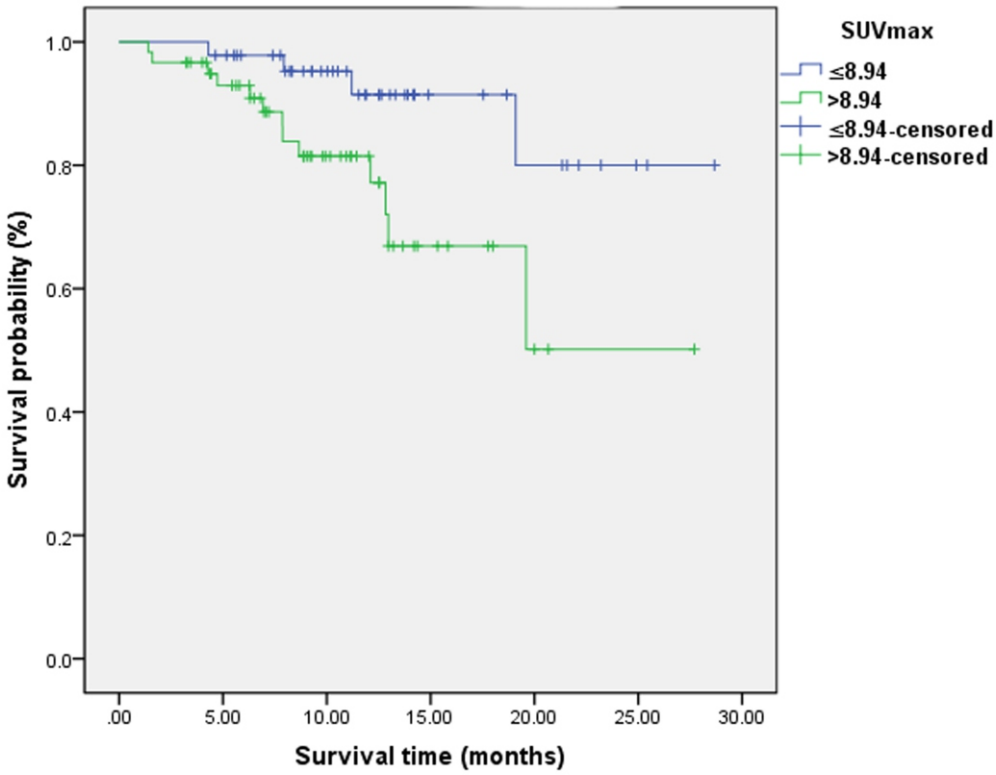

Figure 2. Comparison of overall survival in NSCLC patients according to the SUVmax.

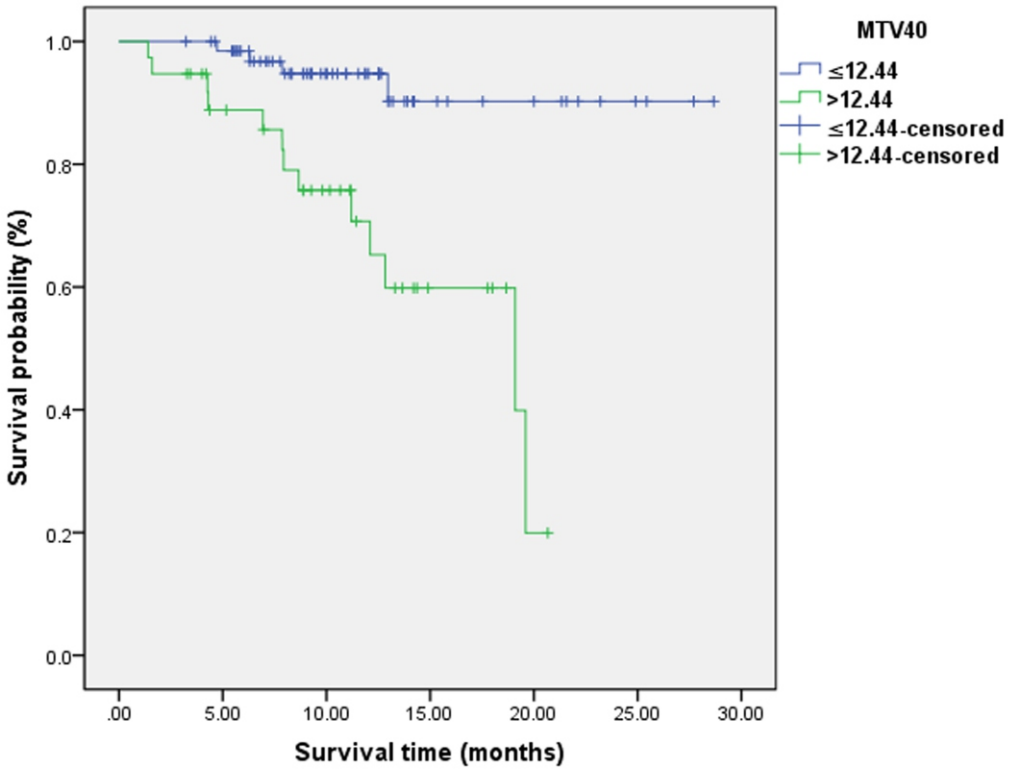

Figure 3. Comparison of overall survival in NSCLC patients according to the MTV40.

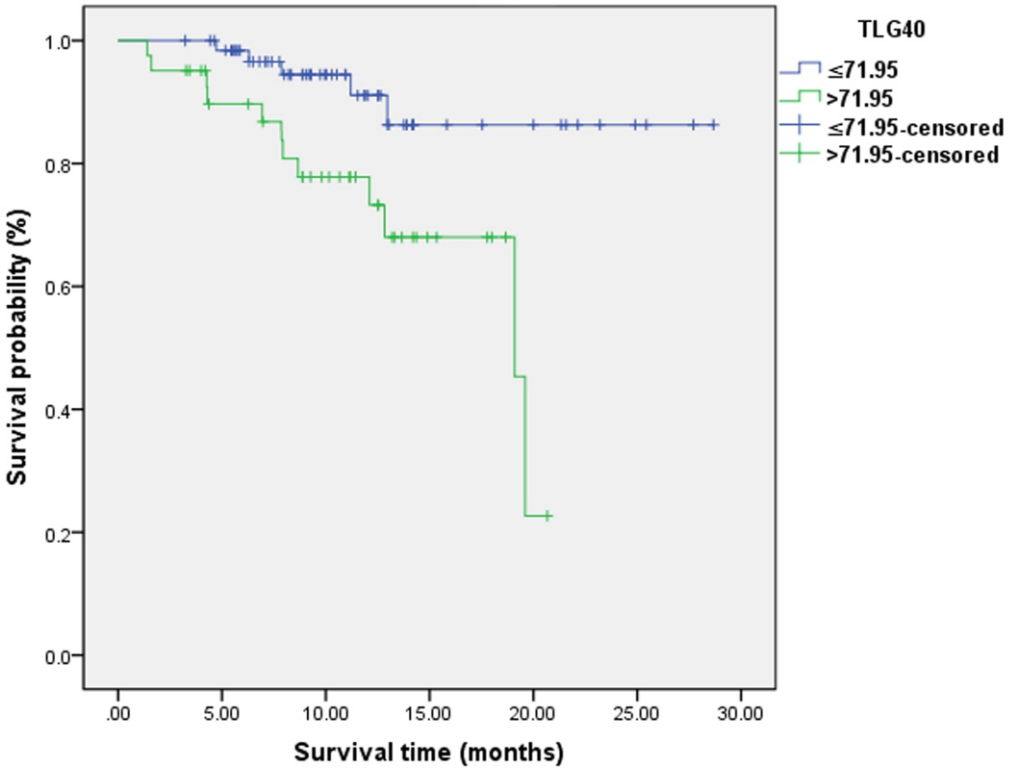

Figure 4. Comparison of overall survival in NSCLC patients according to the SUVmax.

Univariate and multivariate Cox analysis of OS for NSCLC patients

According to the results of the univariate Cox analysis (Table 2), a total of six variables were shown to have a statistically significant correlation to survival outcome of NSCLC patients. They were tumor size (P=0.002), the expression of CYFRA21-1 (P=0.004), clinical TNM stage (P=0.004), SUVmax (P=0.029), MTV40 (P=0.001) and TLG40 (P=0.007). These variables were further analyzed in the multivariate Cox model, and our results demonstrated that tumor size ≥4.0cm (HR: 5.238, 95%CI: 1.484-18.481, P=0.010), clinical stage IV (HR: 6.151, 95%CI: 1.385-27.324, P=0.017) and MTV40 >12.44 (HR: 4.235, 95%CI: 1.324-13.526, P=0.015) were independent predictors of poor OS in NSCLC patients. By contrast, SUVmax and TLG40 lost their statistical significance in the multivariate analysis.

Table 2. *Univariate and multivariate Cox regression analysis of prognostic factors for NSCLC patients.*

	Univariate		Multivariate	
	HR and 95%CI	**P value**	**HR and 95%CI**	**P value**
Age (years)				
>65 vs ≤65	2.526 (0.908-7.028)	0.076		
Sex				
Female vs Male	0.356 (0.102-1.241)	0.105		
BMI (kg/m^2)				
≥25 vs <25	1.239 (0.468-3.279)	0.666		
Smoking history				
Yes vs No	3.180 (0.913-11.080)	0.069		
Histology				
Squamous cell carcinoma vs Adenocarcinoma	1.412 (0.522-3.820)	0.497		
Tumor size (cm)				
≥4.0 vs <4.0	7.331(2.100-25.589)	**0.002**	5.238 (1.484-18.481)	**0.010**
CEA (ng/mL)				
>5 vs ≤5	1.759(0.674-4.593)	0.249		
CYFRA21-1				
Positive vs Negative	8.737(1.979-38.580)	**0.004**	4.203 (0.769-22.975)	0.069
Clinical TNM stage				
Stage IV vs Stage III	8.831(2.002-38.955)	**0.004**	6.151 (1.385-27.324)	**0.017**
SUVmax				
>8.94 vs ≤8.94	3.501(1.133-10.817)	**0.029**	1.841 (0.484-7.001)	0.258
MTV40				
>12.44 vs ≤12.44	6.926 (2.244-21.378)	**0.001**	4.235 (1.324-13.526)	0.015
TLG40				
>71.95 vs ≤71.95	4.314 (1.503-12.381)	**0.007**	3.280 (0.592-18.158)	**0.174**

Discussion

Fluorine-18-FDG PET/CT was a novel imaging technique which integrated metabolic and anatomical information of the lesions. The multimodal imaging has been widely used in diagnosis, preoperative/pretreatment clinical staging and recurrence surveillance of various human cancers such as lung cancer [9, 19]. Recent literature has been enriched with interesting findings regarding the clinical applications of ^{18}F-FDG PET/CT in malignant tumors. It has been demonstrated that metabolic parameters derived from ^{18}F-FDG PET/CT was non-inferior to established clinicopathologic variables for the assessment of therapeutic response and long-term survival in NSCLC [20, 21].

In the present study, we investigated the prognostic value of metabolic parameters derived from ^{18}F-FDG PET/CT for locally advanced and metastatic NSCLC patients. Both the Kaplan-Meier curves and univariate Cox analysis demonstrated that metabolic parameters of ^{18}F-FDG PET/CT such as SUVmax, MTV40 and TLG40 were significantly associated with poor OS of NSCLC patients. The multivariate analysis identified MTV40 as a strong prognostic factor, but SUVmax and TLG40 lost their statistical significance. These findings suggested that MTV40 might be a better predictor of OS than SUVmax and TLG40 for NSCLC patients. The prognostic value of MTV has been reported in several studies, Lee et al. (2007) found that the risk of lung cancer progression and related death increased by 2.8 fold with the increase in value of MTV [22]. Consistent with our findings, some studies have shown that MTV had a higher predictive value for the prognostic assessment of NSCLC patients than SUVmax [23, 24]. In a recent study, Pellegrino et al. (2019) found that MTV was only significant prognostic factor for NSCLC patients with stage III or stage IV, suggesting it provided more valuable prognostic information than other ^{18}F-FDG PET/CT derived parameters [25]. Similarly, Sharma et al. (2018) reviewed the metabolic and volumetric parameters of ^{18}F-FDG PET/CT in 60 stage III-IV NSCLC patients who received platinum-based chemotherapy, and they concluded that MTV had a superiority for predicting the prognosis of these patients compared with SUVmax and TLG [24]. It is not surprising that MTV is more reliable to predict the prognosis of NSCLC patients, because it represented both metabolic activity and tumor volume and provide more information about tumor burden and aggressiveness [26]. These findings suggested that MTV might be a promising indicator of prognostic assessment and therapeutic strategies for NSCLC patients.

It is considered that TLG is another significant parameter of differential diagnosis and prognostic assessment in NSCLC. Previous reports showed that survival outcome was significantly poorer in patients with high TLG value [27, 28]. Zhang et al. (2013) carried out a retrospective study to evaluate the relationship between ^{18}F-FDG PET/CT derived parameters and survival outcome of NSCLC patients and found that both MTV and TLG were independent prognostic markers [26]. In this study, however, TLG was not found to have an independent role in survival prediction of NSCLC patients. The possible reason for inconsistent findings from the multivariate Cox analysis was the limited sample size and heterogeneity of study population and treatment options.

This study was limited by its retrospective design, small sample size, single case source and insufficient follow-up period. Future investigation need be further carried out to determine the prognostic value of ^{18}F-FDG PET/CT derived metabolic parameters for NSCLC patients.

In conclusion, our results revealed a significant relationship between metabolic parameters of ^{18}F-FDG PET/CT (SUVmax, MTV40 and TLG40) and survival outcome of NSCLC patients. In particular, MTV40 was identified as an independent predictors of poor OS. These findings further supported the prognostic value of MTV40 for NSCLC patients, and it might be used as a promising prognostic indicator

Ethical approval

The study was approved by the ethics committee of our hospital. Since this study is a retrospective study, no informed consent was needed.

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The authors declare that they have no conflicts of interest.

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