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ORIGINAL ARTICLE

Metabolic Tumor Volume Measured by F-18 FDG PET/CT can Further Stratify the Prognosis of Patients with Stage IV Non-Small Cell Lung Cancer

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Abstract
Purpose This study aimed to further stratify prognostic factors in patients with stage IV non-small cell lung cancer (NSCLC) by measuring their metabolic tumor volume (MTV) using F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT).
Materials and Methods The subjects of this retrospective study were 57 patients with stage IV NSCLC. MTV, total lesion glycolysis (TLG), and maximum standardized uptake value (SUVmax) were measured on F-18 FDG PET/CT in both the primary lung lesion as well as metastatic lesions in torso. Optimal cutoff values of PET parameters were measured by receiver operating characteristic (ROC) curve analysis. Kaplan-Meier survival curves were used for evaluation of progression-free survival (PFS). The univariate and multivariate Cox proportional hazards models were used to select the significant prognostic factors.
Results Univariate analysis showed that both MTV and TLG of primary lung lesion (MTV-lung and TLG-lung) were significant factors for prediction of PFS ($P<0.001$, $P=0.038$, respectively). Patients showing lower values of MTV-lung and TLG-lung than the cutoff values had significantly longer mean PFS than those with higher values. Hazard ratios (95 % confidence interval) of MTV-lung and TLG-lung measured by univariate analysis were 6.4 (2.5–16.3) and 2.4 (1.0–5.5), respectively. Multivariate analysis revealed that MTV-lung was the only significant factor for prediction of prognosis. Hazard ratio was 13.5 (1.6–111.1, $P=0.016$).
Conclusion Patients with stage IV NSCLC could be further stratified into subgroups of significantly better and worse prognosis by MTV of primary lung lesion.

Keywords Metabolic tumor volume · Stage IV non-small cell lung cancer · F-18 FDG PET/CT · Progression-free survival

Introduction

Lung cancer is the leading cause of cancer death in the world, and 80–85 % of lung cancer cases are classified as non-small cell lung cancer (NSCLC) [1]. The outcome for patients with NSCLC remains quite poor despite improvements in radiotherapy and chemotherapy in the past decade [2]. Tumor-node-metastasis (TNM) stage is currently the most important prognostic factor for survival in NSCLC, in which stage IV is the most advanced stage. However, all patients with stage IV NSCLC do not show similar prognosis. The 1-year overall survival rate for patients with tumor nodules in both lungs (M1a) was 45 %, and that for distant extrapulmonary metastases or distant metastases (M1b) was 22 % [3, 4]. We experience different survival among patient with same M1a or M1b stages in practice. Given the consistent improvement in the survival of patients who have been treated with chemotherapy over those receiving supportive care alone, clinicians struggle to stratify these patients into different prognostic groups [5].

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Positron emission tomography/computed tomography (PET/CT) using F-18 fluorodeoxyglucose (FDG) has already been successfully applied in oncological practice. Standardized uptake value (SUV)-based PET parameter can predict therapeutic outcome and overall survival in many types of malignancies [6–12]. Recently, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been reported as additional diagnostic and prognostic imaging biomarkers for maximum SUV (SUVmax) [13–15]. MTV and TLG are valuable markers in the prediction of prognosis in NSCLC patients, mostly in operable or up to stage III patients [16–18]. Liao et al. [16] reported that whole-body measurement of MTV successfully predicted survival in stage IV NSCLC. Clinical variables including TNM staging system, histological type, performance status, and smoking status are known to predict the prognosis of NSCLC patients [19–21]. This study aimed to further stratify patients with stage IV NSCLC by measuring MTV using F-18 FDG PET/CT and compared it with various clinical factors for prediction of prognosis.

Materials and Methods

Patients

The subjects of this retrospective study were 57 patients (median age, 67 years; range, 32–82 years) with stage IV NSCLC (50 adenocarcinoma, 7 squamous cell carcinoma). They were enrolled from January 2007 to June 2011.

All patients underwent routine staging procedures including history taking, physical examination, blood tests for cells and chemistry panels, CT of the chest and abdomen, brain MRI and FDG PET/CT. Cancer staging was determined by the 7th edition of the American Joint Committee on Cancer (AJCC) Staging Manual. All staging workups were completed before initiation of therapy. Patients were excluded from analysis if any of the following criteria were present: (1) previous diagnosis of other malignant diseases; (2) previous surgical approach for primary lung cancer. Informed consent was waived due to this study's retrospective design.

PET/CT Imaging

FDG PET/CT studies were performed using a combined PET/CT scanner (Discovery ST System, GE Medical Systems, Milwaukee, WI, USA). All patients fasted for at least 6 h prior to the intravenous administration of FDG. Their blood glucose levels were measured before the injection of FDG; if the level was over 8.3 mmol/l, FDG PET/CT was deferred. Image acquisition for torso PET/CT was obtained from the skull base to the upper thigh. Scanning started at approximately 1 h after the injection of 7.4 MBq FDG per kilogram of body weight. CT images used parameters with a peak voltage of 120 kVp, a tube current automated from 10 to 130 mA, a rotation time of 0.7 s, a field of view of 50 cm, a scan length of 40–50 s and a slice thickness of 3.75 mm. Immediately following the CT acquisition, PET data were acquired in the same anatomical locations with a 15.7 cm axial field of view in the two-dimensional (2-D)

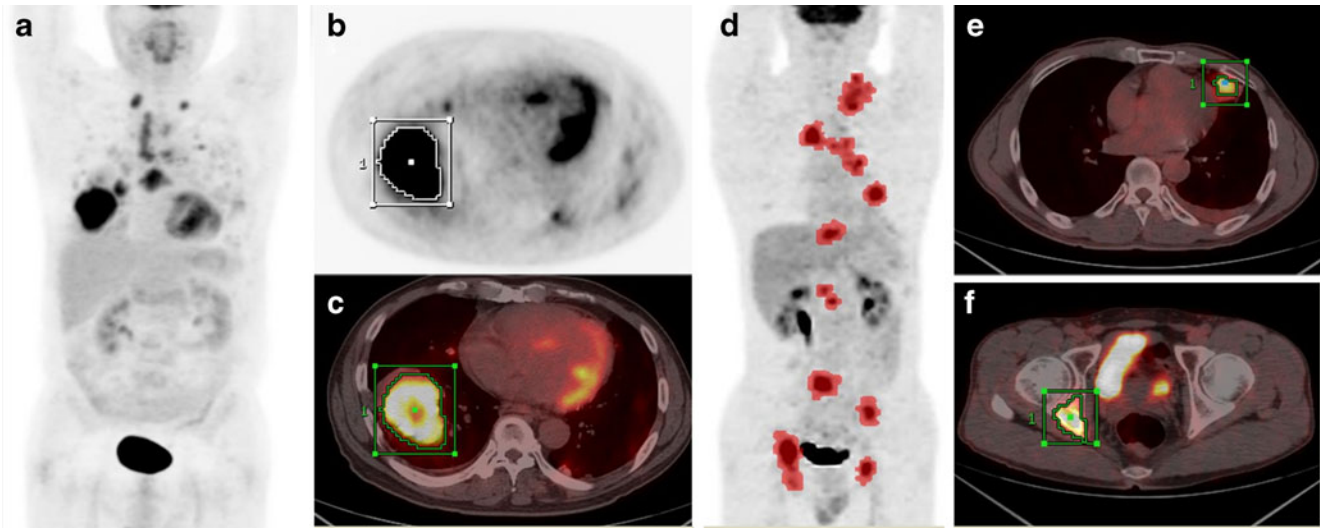

Fig. 1 Measurement of metabolic tumor volume (MTV) of primary lung and metastatic tumor lesions in torso using standardized uptake value (SUV)-based automated contouring program. **a–c** A 64-year-old male patient with multiple lung metastases (M1a). Volume of interest (VOI) was drawn in the primary tumor. **d–f** A 51-year-old male patient with multiple osseous metastases (M1b). *Pink-dotted* lesions on maximum intensity projection image (**d**) show a tumoral lesion exceeding SUV intensity above 2.5

mode with a 150 s/bed position. The CT data were used for attenuation correction and the images were reconstructed using a conventional iterative ordered subsets expectation maximization (OSEM) algorithm.

Assessment of MTV, TLG, and SUVmax of Primary Lung Lesion

MTV, TLG and SUVmax of primary lung lesion were measured (MTV-lung; TLG-lung; and SUVmax-lung). Image display and analysis were performed using an Advantage Workstation 4.4 (GE Medical Systems, Milwaukee, WI, USA), which provided multiplanar reformatted images. SUVmax based on body weight and MTV were determined by the attenuation-corrected PET data using volume viewer software. Of the various methods described for determining metabolic volume, a fixed threshold of SUV 2.5 was used [18, 22, 23]. The boundaries of tumor were drawn large enough to incorporate each target lesion in the axial, coronal and sagittal FDG PET/CT images. The contour around the target lesions inside the boundaries was automatically produced, and the voxels presenting SUV intensity>2.5 within the contouring margin were incorporated to define the tumor volumes (Fig. 1a–c). TLG was calculated by multiplying the mean SUV (SUVmean) of the primary tumor by metabolic volume of the tumor [8]. The SUVmax, MTV and TLG of primary lung lesions were recorded as SUVmax-lung, MTV-lung, and TLG-lung, respectively.

Assessment of MTV, TLG, and SUVmax of all Tumor Lesions in Torso PET/CT

In addition to the primary lung lesion analysis, MTV, TLG and SUVmax were also measured by torso PET/CT. We drew rectangular shaped volumes of interest (VOIs) fully encasing the primary tumor, regional lymph node and all distant metastases in the axial, coronal and sagittal PET/CT images. The boundaries of voxels presenting SUV intensity were automatically produced with a threshold of SUV exceeding 2.5. Normal organs which showed physiologic FDG uptake (such as the heart, stomach, liver, intestines, kidney, ureter and bladder) were manually subtracted from the VOI. Inflammation or other benign FDG-avid lesions were selected based on histopathological reports, other imaging modalities such as contrast-enhanced CT and response to therapy, and were excluded from the measurement (Fig. 1d–f). Finally, SUVmax, MTV and TLG in torso tumor lesions were recorded as SUVmax-torso, MTV-torso and TLG-torso, respectively.

Statistical Analysis

The threshold value allowing differentiation between the two groups of patients was selected by the receiver operating characteristic (ROC) method. All PET parameters were compared with each of the dichotomized variables by *t*-test. Progression-free survival (PFS) was measured from the date of FDG PET/CT scan to the date of disease progression/death or last follow-up. Kaplan-Meier estimates and the log rank test were performed to assess the equality of the survival functions across variables in PFS. Cox proportional hazard model was used to develop the univariate and multivariate models describing the association of the independent variables with PFS. Independent variables included age, sex, histological type of lung cancer, M staging of TNM classification, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status, SUVmax-lung, MTV-lung, TLG-lung, SUVmax-torso, MTV-torso, TLG-torso. Estimated hazard

Table 1 Patient characteristics

Characteristic	Number (%)
Total patients	57
Age (years)	
Median age	67
Range	32–82
Sex	
Male	27 (47 %)
Female	30 (53 %)
Smoker	27 (47 %)
Diabetes	6 (11 %)
Hypertension	14 (25 %)
Histological type	
Adenocarcinoma	50 (88 %)
Squamous cell carcinoma	7 (12 %)
M staging	
M1a	20 (35 %)
M1b	37 (65 %)
EGFR mutation	
Negative	43 (75 %)
Positive	14 (25 %)
ECOG performance status	
0	13 (23 %)
1	37 (65 %)
2	5 (9 %)
3	2 (3 %)
Initial chemotherapy regimen	
Platinum-based combination chemotherapy	52 (91 %)
Tyrosine kinase inhibitor	5 (9 %)
Palliative radiotherapy for metastatic lesion	16 (28 %)

EGFR epidermal growth factor receptor, *ECOG* Eastern Cooperative Oncology Group

Table 2 Comparison of SUV-based PET parameters of primary lung lesion and clinical variables

	SUVmax-lung	*P*	MTV-lung	*P*	TLG-lung	*P*
Age						
<67	10.4±4.3	0.054	35.8±35.9	0.049	174.6±210.2	0.081
≥67	12.9±5.2		67.4±74.3		364.7±500.0	
Sex						
Male	10.7±4.3	0.128	35.6±45.4	0.035	181.2±256.1	0.060
Female	12.7±5.4		68.8±69.0		392.6±510.7	
Histological type						
Squamous cell carcinoma	14.8 ±7.4	0.245	65.0±51.4	0.521	383.1±326.6	0.486
Adenocarcinoma	11.2±4.3		49.4±61.0		267.1±418.8	
M staging						
M1a	9.7±3.2	0.012	35.9±38.1	0.151	177.8±216.1	0.161
M1b	12.7±5.3		59.7±67.6		337.3±474.3	
Smoking						
Positive	12.5±5.4	0.193	67.5±70.0	0.057	386.6±514.5	0.064
Negative	10.8±4.2		36.8±44.9		186.6±253.7	
ECOG Performance status						
0 or 1	11.7±5.0	0.604	56.1±62.2	<0.001	310.1±427.9	0.157
2 to 3	10.7±4.2		17.4±10.2		76.1±40.7	

ECOG Eastern Cooperative Oncology Group, *SUVmax-lung* maximum standardized uptake value of primary lung lesion, *MTV-lung* metabolic tumor volume of primary lung lesion, *TLG-lung* total lesion glycolysis of primary lung lesion

ratio (HR) with 95 % confidence interval (CI) was presented for each variable. A value of *P* less than 0.05 was considered statistically significant. The statistical software package for social science (SPSS, version 19.0.0; SPSS, Chicago, IL, USA) and MedCalc statistical package (version 12.0.0.0, MedCalc Software, Mariakerke, Belgium) were used for statistical testing.

Results

Patient Characteristics

The characteristics of 57 patients are summarized in Table 1. The median age of the patients was 67 years (range, 32–82 years). Most of patients (91 %) received

Table 3 Comparison of SUV-based PET parameters of torso lesions and clinical variables

	SUVmax-torso	*P*	MTV-torso	*P*	TLG-torso	*P*
Age						
<67	12.2±4.6	0.187	296.7±284.0	0.904	975.4±884.7	0.925
≥67	14.0±5.5		285.1±402.6		950.2±1072.2	
Sex						
Male	12.8±5.4	0.646	216.3±245.8	0.096	702.2±756.3	0.040
Female	13.4±5.1		372.3±432.5		1249.0±1136.8	
Histological type						
Squamous cell carcinoma	15.1±7.1	0.272	229.2±292.0	0.630	836.3 ±819.9	0.724
Adenocarcinoma	12.8±4.9		298.7±362.0		978.7 ±1012.9	
M staging						
M1a	10.9±4.3	0.014	147.5±172.5	0.006	488.1±573.7	0.001
M1b	14.2±5.4		367.3±400.3		1217.0±1070.9	
Smoking						
Positive	13.1±5.3	0.923	362.8±420.0	0.142	1202.6±1118.6	0.079
Negative	13.0±5.3		224.9±269.5		744.0±807.6	
ECOG Performance status						
0 or 1	13.2±5.3	0.630	289.1±362.4	0.952	956.9±1001.0	0.930
2 to 3	12.2±4.7		297.9±296.4		992.1±942.0	

SUVmax-torso maximum standardized uptake value of torso tumor lesion, *MTV-torso* metabolic tumor volume of torso tumor lesion, *TLG-torso* total lesion glycolysis of torso tumor lesion

platinum-based combination chemotherapy as a first therapeutic regimen, while five patients were treated by tyrosine kinase inhibitor. Palliative radiotherapy for metastatic lesion was given to 16 patients (28 %). The median follow-up period from the time of FDG PET/CT scan was 414.5 days (range, 19–1,643 days). During the follow-up, disease progression was developed in 30 patients (53 %). Mean PFS was 279 days (range, 19–1,643 days).

Cutoff Values of PET Parameters for PFS

The area under the curve (AUC) of MTV-lung was 0.52, and its cutoff value was 68.26. AUC and cutoff values of TLG-lung and SUVmax-lung were 0.50 and 194.16, 0.51 and 11.20, respectively. AUC and cutoff values of MTV-torso, TLG-torso, and SUVmax-torso were 0.58 and 656.20, 0.59 and 442.20, 0.53 and 11.20, respectively.

Table 4 Univariate and multivariate analyses for progression-free survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*
Age (years)				
<67	1.088 (0.526–2.252)	0.820		
≥67				
Sex				
Male	1.287 (0.593–2.796)	0.523		
Female				
Histological type				
Squamous cell	1.507 (0.452–5.022)	0.504		
Carcinoma				
Adenocarcinoma				
M staging				
M1a	1.726 (0.783–3.807)	0.176		
M1b				
Smoking				
Positive	1.464 (0.670–3.198)	0.339		
Negative				
ECOG performance status				
0 or 1	2.451 (0.577–10.411)	0.224		
2 to 3				
SUVmax-lung				
≤11.20	1.416 (0.626–3.199)	0.403		
>11.20				
MTV-lung (cm^3)				
≤68.26	6.377 (2.500–16.266)	<0.001	13.487 (1.637–111.101)	0.016
>68.26				
TLG-lung				
≤194.16	2.395 (1.049–5.472)	0.038	2.304 (0.303–17.506)	0.420
>194.16				
SUVmax-torso				
≤11.20	1.253 (0.595–2.641)	0.552		
>11.20				
MTV-torso (cm^3)	1.569 (0.208–11.832)	0.662		
≤656.20				
>656.20				
TLG-torso	1.816 (0.826–3.992)	0.138		
≤442.20				
>442.20				

HR hazard ratio, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group, *SUVmax* maximum standardized uptake value, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis

Prognosis Stratification by Using SUVmax, MTV and TLG

Comparison of PET variables of primary lung lesion is summarized in Table 2. MTV was lower in younger patients (less than 67 years old), in male patients, and in patients showing higher ECOG performance status. SUVmax was lower in M1a group.

Comparison of PET variables of tumor in the torso region is summarized in Table 3. Values of SUVmax-torso, MTV-torso and TLG-torso were significantly higher in patients with M1b stage than in those with M1a stage.

Results of univariate and multivariate analyses of clinical and PET variables for PFS are shown in Table 4. Univariate analysis showed that MTV-lung and TLG-lung were significant factors for prediction of PFS. However, all torso PET parameters did not show any statistical significance. Patients showing lower values of MTV-lung and TLG-lung than the cutoff values had significantly longer mean PFS than those with higher values (329.8±367.2 vs 107.7±57.7 days, respectively, $P<0.001$; 374.0±395.8 vs 128.2±95.5 days, respectively, $P=0.038$). There was a good correlation among three PET parameters of primary tumor (SUVmax-lung and MTV-lung, $r=0.601$, $P<0.001$; SUVmax-lung and TLG-lung, $r=0.658$, $P<0.001$; and MTV-lung and TLG-lung, $r=0.974$, $P<0.001$). Multivariate analysis revealed that MTV-lung was the only significant factor for prediction of prognosis (HR and 95 % *CI*=13.487 and 1.637–111.101, respectively).

The Kaplan-Meier survival graphs showed a statistically significant difference in PFS between the groups categorized by MTV-lung ($P<0.001$) and TLG-lung ($P=0.033$), but SUVmax-lung ($P=0.401$) did not (Fig. 2a–c). In subgroup analysis, MTV-lung ($P<0.001$) and TLG-lung ($P=0.043$) were showed statistical differences in only M1b patients, but SUVmax-lung ($P=0.335$) did not. (Fig. 2d–f).

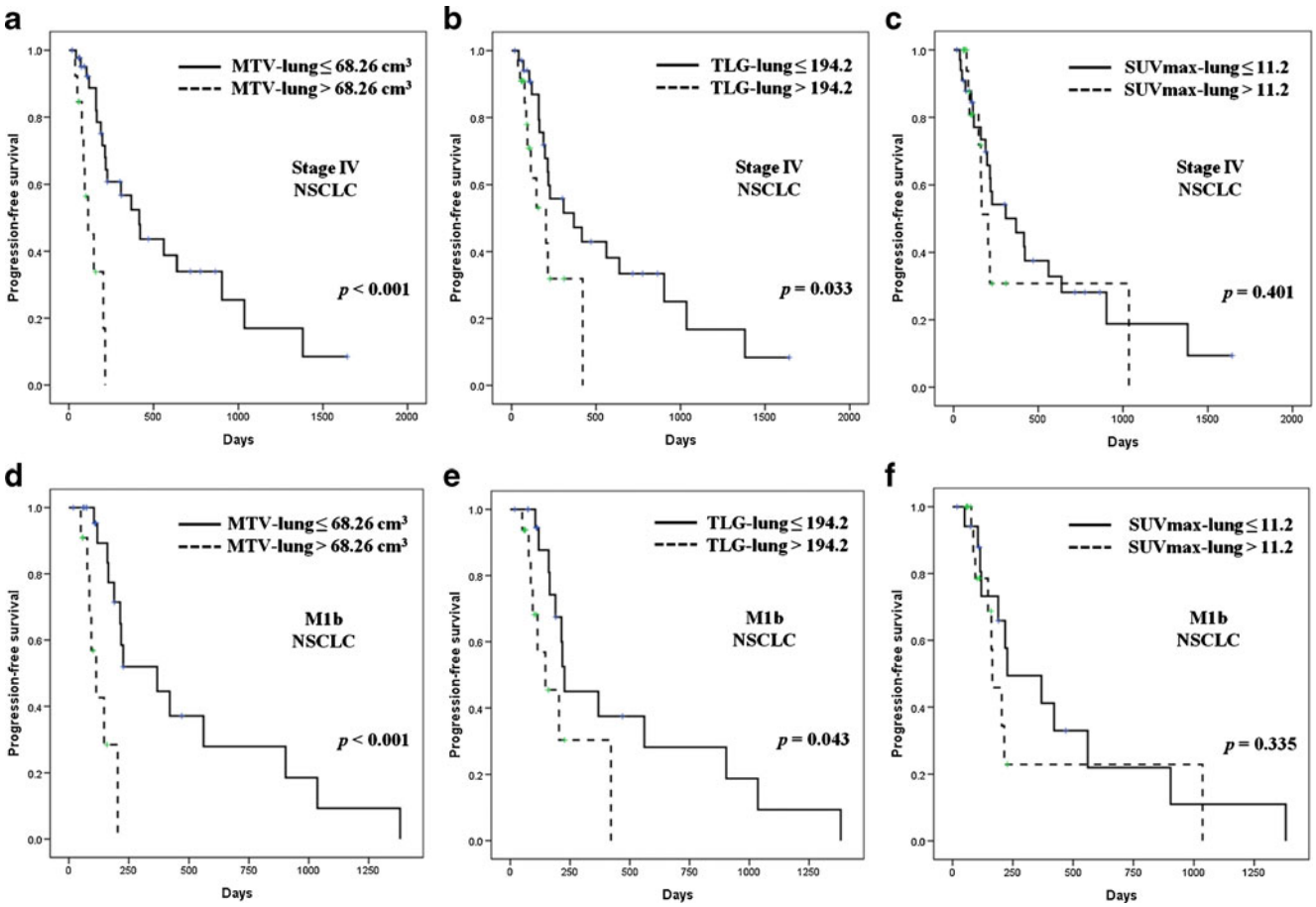

Fig. 2 Prognosis stratification by metabolic tumor volume in stage IV non-small cell lung cancer (NSCLC) patients with the Kaplan-Meier survival graphs. (**a**) MTV-lung and (**b**) TLG-lung successfully distinguished patients with longer prognostic-free survival (PFS). In a subgroup of M1b, (**d**) MTV-lung and (**e**) TLG-lung also could distinguish patients with longer PFS. However, SUVmax-lung could not stratify prognosis (**c, f**). *MTV-lung* metabolic tumor volume of primary lung lesion, *TLG-lung* total lesion glycolysis of primary lung lesion, *SUVmax-lung* maximum standardized uptake value of primary lung lesion

Discussion

In this study, MTV-lung and TLG-lung can differentiate stage IV NSCLC patients into two subgroups of longer and shorter PFS. Moreover, these two parameters can divide PFS even in M1b patients. Multivariate analysis showed that MTV-lung was the only significant predictive factor in the risk stratification of this study group. TLG was dependent on MTV because it was calculated by multiplying the SUVmean by MTV.

Prognostic values of MTV and TLG were previously reported in NSCLC patients, mostly only in operable or with stage I-III patients [16–18]. To the best of our knowledge, this is the second report regarding prognostic value of MTV in stage IV NSCLC patients. Liao et al. [24] was the first to report the values of MTV and TLG in stage IV NSCLC. They showed that pretreatment MTV and TLG in primary tumor might be better prognostic measures than SUVmax and SUVmean measurements. Our findings are consistent with that of Liao et al. [24]. In addition, we analyzed the stratification power of MTV-lung and TLG-lung in M1b patients. Both of them successfully classified patients with better prognosis. Interestingly, clinical parameters which were routinely used in clinical practice such as age, sex, histology of lung cancer, TNM classification, smoking history, ECOG performance status and SUVmax also did not show any statistical significance.

In spite of a good correlation among three PET parameters of primary tumor, SUVmax-lung did not predict PFS. Although SUVmax is convenient to measure and widely used, it has some limitations. SUVmax is a single-pixel value representing the most intense F-18 FDG uptake in the tumor and may not be an adequate surrogate marker to represent tumor biology [13]. In addition, SUVmax variability increases as the lesion matrix size and patient size increase [25]. There is also a statistical bias of SUVmax in that large lesions are more intense because of more available counts [26]. Our results are consistent with those of previous reports that have reported that SUVmax-lung is not an independent prognostic factor [27–29].

Liao et al. [24] reported that whole-body MTV had a prognostic value in stage IV NSCLC, while MTV-torso failed to stratify prognosis in this study. The standard imaging protocol for NSCLC in Korea is torso imaging. We measured MTV from torso images instead of instead of the whole body. Sixteen of 57 patients (28.1 %) had brain metastases at the time of diagnosis. This might be one reason for the different results from the whole-body MTV results of Liao et al.'s study. However, there was no statistical difference in PFS according to the presence or absence of brain metastases (mean PFS 218.4±233.9 days, 302.8±368.5 days, respectively P=0.738) in these stage IV patients. Also, there was no statistical difference of disease progression frequency in the two groups (no brain metastasis group, 21/41; brain metastasis group, 7/16; P=0.776). Therefore presence of brain metastasis might not contribute to the disease progression.

We evaluated these PET parameters in M1a staging group, which did not show any statistical significance. The small number of enrolled patients (20 patients of M1a stage in present study) might be influence of statistic value. Further study with large eligible patients will be needed.

The present study had several limitations. First, a small number of patients were included retrospectively. Second, MTV can be affected by the partial volume effect, the time between tracer injection and imaging, and plasma glucose levels. The methods of measuring MTV are still controversial. Further prospective studies on the accurate measurement of MTV involving a larger number of patients are needed to confirm the prediction of prognosis in patients with NSCLC. Third, we used PFS as clinical end point, instead of overall survival. Since the chemotherapeutic regimen was changed after disease progression, we were not able to standardize all chemotherapeutic regimens. Therefore, we did not correlate prognostic factors with overall survival in this study. Forth, MTV was measured using torso instead of whole-body images. But, MTV from torso scan could give more useful information in routine clinical setting, because torso scan in PET/CT is the usual protocol for NSCLC.

In conclusion, MTV of primary lung lesion measured by FDG PET/CT could further stratify patients with stage IV NSCLC into two groups of different prognoses, while new classification of M1a and M1b could not. This observation has a clinical implication in planning palliative treatment decisions for stage IV NSCLC patients.

Conflict of interest The authors declare that they have no conflict of interest.

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