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Consistency of Metabolic Tumor Volume of Non-Small Cell Lung Cancer Primary Tumor Measured from ^{18}F -FDG PET/CT at Two Different Tracer Uptake Times

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Abstract

Objectives—To test the hypothesis that MTV of primary NSCLC is not sensitive to differences of FDG uptake time, and to compare this consistency of MTV measurement with that of SUV and total lesion glycolysis (TLG).

Methods—Under institutional review board approval, 134 consecutive histologically proven NSCLC patients underwent ^{18}F -FDG PET/CT scans at about one hour (early) and two hours (delayed) after intravenous injection of ^{18}F -FDG. MTV, SUV, and TLG, all of the primary tumor, were measured. Student's t-test and Wilcoxon signed-rank test for paired data were used to compare MTV, SUV, and TLG between the two scans. The intraclass correlation coefficient (ICC) was used to assess agreement in PET parameters between the two scans and between measurements made by two observers.

Results—MTV was not significantly different ($p = 0.17$) between the two scans. However, SUV_{max} , SUV_{mean} , SUV_{peak} , and TLG increased significantly from the early to the delayed scans ($p < 0.0001$ for all). The median percentage change between the two scans in MTV (1.65%) was smaller than in SUV_{max} (11.76%), SUV_{mean} (10.57%), SUV_{peak} (13.51%), and TLG (14.34%), ICC of MTV (0.996) was greater than that of SUV_{max} (0.933), SUV_{mean} (0.952), SUV_{peak} (0.928), and TLG (0.982). Inter-observer agreement between the two radiologists was excellent for MTV, SUV, and TLG on both scans (ICC: 0.934–0.999).

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Disclosure

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Conclusions—MTV is not sensitive to common clinical variations in FDG uptake time, its consistency is greater than that for SUV_{max} , SUV_{mean} , SUV_{peak} , and TLG, and it has excellent inter-observer agreement.

Keywords

FDG; metabolic tumor burden; metabolic tumor volume; non-small-cell lung cancer; total lesion glycolysis

INTRODUCTION

In clinical practice, ^{18}F -FDG PET/CT has become an important imaging modality for the diagnosis and staging[1], as well as prognosis estimation and monitoring of therapeutic response[2, 3], of non-small cell lung cancer (NSCLC) patients. The standardized uptake value (SUV), which quantifies tumor glucose metabolic activity, is a widely used PET-derived parameter. However, SUV measurement is affected by many factors, such as FDG uptake time, patient physiology, instrument calibration, and image-acquisition and reconstruction methods [4–7]. Among these factors, FDG uptake time is not easy to standardize in different patients, and even in the same patient with repeat scans, because of scheduling and patient compliance issues [8]. SUV is known to increase with increased FDG uptake time from one hour to two hours after FDG injection by an average of 23.0% (range 24.8 to 109.8%, median 21.6%) [9].

NSCLC metabolic tumor volume (MTV) measured on PET/CT has been shown recently to be a significant prognostic factor independent of TNM stage and other clinical and pathological prognostic factors such as age, gender, performance status, tumor histology, and treatment received [10–21]. Furthermore, MTV has been shown to be a better prognostic factor for NSCLC than SUV [10, 13, 15]. We recently showed that a semiautomatic gradient-based tumor-segmentation method can be used without additional time-consuming manual adjustment for MTV measurement[22]. To adopt MTV into clinical practice, it is important to determine its reproducibility. A number of studies of different cancers, in different parts of the world, and with different PET/CT scanners have consistently demonstrated significant correlation between patient survival and MTV[10–13, 15–21, 23, 24]. MTV has also been shown to be not sensitive to image-reconstruction algorithms [25]. Moreover, MTV has been shown to have low inter-observer variability [10, 13, 19]. However, to our knowledge, the consistency of MTV measurement at different FDG uptake time has not been fully studied, with only two abstracts published [26, 27]. Thus, the purpose of this study was to test the hypothesis that MTV of primary NSCLC tumor is not sensitive to FDG uptake time between one and two hours after FDG injection, and to compare the consistency of MTV with that of SUV and total lesion glycolysis (TLG)..

MATERIALS AND METHODS

Patient Population

This single-institution prospective study was conducted with approval from the institutional review board of the First Affiliated Hospital of Guangzhou Medical University. Written

informed consent was obtained from all patients after risks associated with additional radiation exposure from a second (delayed) FDG PET/CT scan were explained to patients. Patients were enrolled prospectively from 26 September 2013 to 31 January 2014. All out-patients and in-patients referred for PET/CT for evaluation of proven, or suspected, NSCLC were invited to participate. The inclusion criteria were: (1) consent to undergo two PET/CT scans at one hour and two hours after FDG tracer injection, (2) have histologically confirmed NSCLC, (3) have a measurable ^{18}F -FDG-avid primary NSCLC tumor, and (4) have not had NSCLC-specific treatment. Part of the data from this study has been used previously in an analysis of the agreement between a semi-automatic gradient-based method for metabolic tumor burden estimation and manual adjustment of tumor volume estimation after the semi-automatic method[22].

PET/CT Protocol

All PET/CT studies were performed at the First Affiliated Hospital of Guangzhou Medical University with an 8-section PET/CT scanner (Discovery ST 8, GE Healthcare, WI, USA) according to the following standard clinical protocol. After a patient fasted for at least 6 hours and had blood glucose levels less than 7.0 mmol/L, patient blood glucose level, weight, and height were recorded, and ^{18}F -FDG of 3.70–5.55 MBq per kilogram of body weight was administered intravenously. The patient was asked to void his or her bladder immediately before the PET/CT scan. Approximately 60 min (mean $\pm$ SD: 65.7 ± 9.4 min; median: 65 min; range: 50–93 min) after ^{18}F -FDG injection, a whole-body unenhanced CT scan was performed from the base of the skull to mid-thigh, at 140 kVp, 150 mAs, 3.75 mm slice thickness, pitch 1.675, and 512×512 image matrix. Immediately afterward, a whole-body PET was performed covering the same anatomical area. The acquisition time was 3.5 minutes per cradle position, with a total of six or seven cradle positions. PET emission data were reconstructed by using a two-dimensional ordered-subset expectation maximization algorithm and a 128×128 image matrix with the CT data used for attenuation correction.

After this whole-body scan, two nuclear medicine physicians (H. L. and P. H., with 6 and 4 years of PET/CT experience, respectively) reviewed the PET/CT images to determine whether a second (delayed) scan was indicated. The delayed scan was considered indicated if there was an FDG-avid tumor. If the delayed scan was indicated, a second PET scan of the entire thorax was performed approximately two hours (mean $\pm$ SD: 128.5 ± 11.1 min, median: 128 min, range: 103–160 min) after ^{18}F -FDG injection following the same imaging protocol as the early whole-body PET/CT scan. The time interval between the early and delayed PET/CT scans was approximately one hour (mean $\pm$ SD: 62.8 ± 6.7 min, median: 62.5 min, range: 48–79 min). PET/CT image fusion was performed on an Xeleris post-processing workstation (GE Healthcare, WI, USA).

PET, CT, and fused PET/CT images were reviewed in the axial, coronal, and sagittal planes (Fig. 1).

Measurements of PET Parameters

PET/CT images were analyzed (blinded to clinical data) at the University of Chicago. Two board-certified radiologists (Y. P., with 10 years PET/CT experience, and C. Z., with 7 years

of nuclear medicine and PET experience, both proficient in the MIM software) independently measured MTV, TLG, SUV_{max} , SUV_{mean} , and SUV_{peak} of the primary NSCLC tumor with the PETedge tool (MIM Software, Cleveland, OH, USA), a semi-automatic and gradient-based method for tumor segmentation (Fig. 1) [10, 13, 18, 25]. Briefly, a radiologist first identified the approximate center of the tumor. Then, the radiologist identified the major and minor axes of the tumor in one plane, and the software automatically drew a volume of interest (VOI). The software also automatically calculated SUV_{max} , SUV_{mean} , SUV_{peak} , MTV, and TLG of the tumor VOI. These data were recorded. In this study, SUV_{max} was defined as the maximum activity concentration of ^{18}F -FDG within the tumor VOI as a fraction of the injected FDG dose per body weight, and SUV_{mean} was defined as the average concentration of ^{18}F -FDG within the tumor VOI as a fraction of the injected FDG dose per body weight [10], whereas SUV_{peak} was defined as the average SUV within a 12-mm diameter sphere centered at the highest uptake region of the tumor VOI [28].

We defined percentage changes of these PET parameters (for SUV also known as the retention index, or RI [9]) between the early and delayed scans as follows.

$$\Delta SUV = \frac{(SUV_{delayed} - SUV_{early})}{SUV_{early}} \times 100 \quad (1)$$

$$\Delta MTV = \frac{(MTV_{delayed} - MTV_{early})}{MTV_{early}} \times 100 \quad (2)$$

$$\Delta TLG = \frac{(TLG_{delayed} - TLG_{early})}{TLG_{early}} \times 100 \quad (3)$$

Note that a positive value indicates a higher parameter value on the delayed scan, compared with the early scan, and a negative value indicates a lower parameter value on the delayed scan.

For evaluation of inter-observer agreement, data obtained by the two radiologists were compared. To ensure that the two radiologists analyzed the same tumor in each patient, they reviewed 15 cases of both primary and metastatic tumors with relatively large discrepancy in the data and made sure that they had analyzed the same primary tumor in all cases.

NSCLC Diagnosis

The diagnosis of NSCLC was made through histopathological examination of resection specimens or through cytopathological examination of bronchoscope biopsy samples, transthoracic needle biopsy samples, or pleural fluid samples. Resected tumors were classified according to the WHO classification of lung neoplasms [29]. All patients were followed up for at least one year.

Statistical Analysis

Normality of the distribution of PET parameter data was evaluated by using the Kolmogorov-Smirnov test. Data for SUV_{max} , SUV_{mean} , and SUV_{peak} were approximately normally distributed, but data for MTV and TLG were not normally distributed. These data are presented here in terms of mean $\pm$ standard deviation (SD), median, and range.

Student's t-test for paired data was performed to compare SUV_{max} , SUV_{mean} , and SUV_{peak} between the early and delayed PET scans, but a non-parametric Wilcoxon signed-rank test was used to compare MTV and TLG between the two PET scans. Intra-class correlation coefficient (ICC) was calculated to evaluate the agreement between each PET parameter measured from the two PET scans. The ICC was also calculated to assess inter-observer agreement between measurement made by the two radiologists [30]. The ICC was generated by a two-way random-effects model of absolute agreement, and was reported as a point estimate together with an estimate of the 95% confidence interval (CI). Statistical significance was considered at the $\alpha = 0.05$ level. Statistical analyses were performed using Stata Version 13 (Stata Corp., College Station, TX).

RESULTS

Patient Cohort

During the study period, we screened 230 consecutive patients who had proven, or suspected, NSCLC. Of these, 187 were determined to be eligible for inclusion. Of the 187 patients, seven declined to participate, 19 did not receive pathological diagnosis, two did not have a measurable primary tumor, and 25 had diagnoses other than NSCLC (small cell lung cancer, $n = 10$; inflammation or infection, $n = 7$; metastatic tumor, $n = 4$; mediastinal tumor, $n = 2$; and tuberculosis, $n = 2$). Thus, 53 patients were excluded, and 134 patients were included in this study (Fig. 2).

The mean age of the 134 patients (50 females and 84 males) was 60.8 years with standard deviation of 10.8 years. There were 37 patients with stage I, 15 patients with stage II, 43 patients with stage III and 39 patients with stage IV NSCLC. There were 89 patients with adenocarcinoma, 32 patients with squamous carcinoma and 13 patients with other types of NSCLC.

Agreement of PET Parameters between the Early and Delayed Scans

Table 1 shows results of SUV_{max} , SUV_{mean} , SUV_{peak} , MTV, and TLG measured from the early and delayed PET scans by one of the radiologists (Y. P.). There were statistically significant differences ($p < 0.0001$ for all) in SUV_{max} , SUV_{mean} , SUV_{peak} , and TLG between the early and delayed PET scans, with the delayed scans producing higher mean and median values. However, there was no statistically significant difference ($p = 0.17$) for MTV between the early and delayed PET scans (Table 1). The median percentage change in MTV (1.65%) was smaller than that of SUV_{max} (11.76%), SUV_{mean} (10.57%), SUV_{peak} (13.51%), and TLG (14.34%), between the two scans (Table 2). The ICC between the early and delayed scans was also higher for the MTV (0.996) than for SUV_{max} (0.933), SUV_{mean} (0.952), SUV_{peak} (0.928), and TLG (0.982) (Table 3).

Inter-observer Agreement

Inter-observer agreement between the two radiologists was excellent (ICC: 0.934–1.000) for SUV_{max} , SUV_{mean} , SUV_{peak} , TLG, and MTV, and for both the early and delayed PET scans, with ICC for SUV_{max} being the highest (Table 4).

DISCUSSION

In this study, we have found that MTV is not significantly different between PET/CT scans at one hour or two hours after FDG injection. To our knowledge, the consistency of NSCLC MTV measurement obtained at different FDG uptake times has not been fully studied previously. Kitao et al reported in an abstract of 30 NSCLC patients that the average primary-tumor MTV, estimated based on tumor segmentation by means of a fixed SUV of 2.5, at one hour (54 ± 103 ml) vs. two hours (57 ± 110 ml) after FDG injection, was not significantly different ($p = 0.159$) [27]. However, MTV estimated based on tumor segmentation by means of 45% of SUV_{max} significantly decreased (-16% , $p < 0.01$) from one hour (17 ± 17 ml) to two hours (15 ± 15 ml) after FDG injection, and MTV estimated based on tumor segmentation by means of an adaptive region-growing method significantly increased (16% , $p < 0.05$) from one hour (47 ± 71 ml) to two hours (58 ± 91 ml) after FDG injection. The MTV estimated based on tumor segmentation by means of 45% of SUV_{max} was smaller than MTV values estimated based on tumor segmentation by means of a fixed SUV of 2.5 or the adaptive region-growing method. In our study, we found that MTV of the primary NSCLC tumor, estimated based on gradient-based segmentation, did not change significantly between one hour and two hours after FDG injection [26].

The difference in the reported consistency of MTV over time may be explained by tissue SUV change over time and by different tumor segmentation methods used. It has been shown that SUV of the primary NSCLC tumor increases over time from one hour to three hours post FDG injection [9, 31] and SUV of the lung background decreases over this time period [32]. This is consistent with our finding in this study in which SUV_{max} (11.76%), SUV_{mean} (10.57%), and SUV_{peak} (13.51%) all increased from one hour to two hours post FDG injection. For MTV estimated based on tumor segmentation by means of 45% of SUV_{max} , the tumor size may be affected by this change of SUV over time, with the increase in tumor SUV decreasing the tumor size. This is consistent with the report of Kitao et al. The gradient-based segmentation method, which we used in this study, may have an advantage in this regard, because the tumor segmentation has been shown to be not sensitive to the ratio of tumor to background SUV [25]. Therefore, the gradient-based segmentation method may be more reliable for evaluation of MTV change over time.

The tumor segmentation method based on adaptive region-growing may also suffer from similar problems. With this method, a radiation oncologist first manually draws a rough region of interest (ROI) that encloses a tumor. Then the algorithm examines neighboring voxels of the ROI and determines whether any neighboring voxels should be added to the ROI. If a neighboring voxel has intensities equal to, or greater than, the product of the mean intensity of the ROI and an arbitrary percent threshold, then the voxel will be added to the ROI. However, the transition from tumor to background does not always occur at a fixed arbitrary threshold [33]. The increase of tumor SUV over time suggests that tumor

segmentation based on this method may be sensitive to the increase of tumor SUV over time.

In this study, we have also found that the median percentage change in MTV (1.65%) between the two PET scans one hour and two hours post FDG injection is smaller than that for SUV_{max} (11.76%), SUV_{mean} (10.57%), SUV_{peak} (13.51%), and TLG (14.34%). Furthermore, the ICC between these two PET scans is higher for MTV (0.996) than for SUV_{max} (0.933), SUV_{mean} (0.952), SUV_{peak} (0.928), and TLG (0.982). These results suggest that MTV of the primary NSCLC tumor is less sensitive to common clinical variations of FDG uptake time than SUV and TLG. This consistency of MTV, combined with low inter-observer variability [10, 13, 19] and low inter-scanner variability [25], suggest that MTV may be a reproducible PET marker for NSCLC patients.

In this study, we have also shown excellent inter-observer agreement for MTV as well as other PET measurements: SUV_{max} , SUV_{mean} , SUV_{peak} , and TLG, on both the early and delayed PET scans (ICC: 0.934–1.000). The SUV_{max} has the highest inter-observer agreement, which is consistent with prior reports[10, 13, 19, 34].

One limitation of this study is that we evaluated only one tumor segmentation method: a gradient-based method via commercially available computer software. Three other commonly used tumor segmentation methods have been evaluated by Kitao et al [27]. Our study showed that MTV of the primary NSCLC tumor estimated with the gradient-based segmentation method is relatively stable over common clinical variations of FDG uptake time (one to two hours) in a large cohort of 134 patients.

In conclusion, the primary NSCLC tumor MTV is not sensitive to common clinical variations of FDG uptake time (one to two hours). The consistency of MTV over time is substantially greater than that for SUV_{max} , SUV_{mean} , SUV_{peak} , and TLG. This consistency, combined with low inter-observer variability and low inter-scanner variability, suggest that MTV may be a reproducible PET marker for NSCLC patients.

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Fig. 1.

Early (a) and delayed (b) PET scans, one and two hours after FDG injection, respectively, of a 74-year-old man with a new diagnosis of NSCLC (squamous cell carcinoma) shown in axial, sagittal, and coronal images. Also shown are primary NSCLC tumor segmented with the MIM PETedge tool for measurement of MTV, TLG, SUV_{max} , SUV_{mean} , and SUV_{peak} .

Fig. 2.

A flow diagram illustrating patient enrollment in this study.

Table 1

Comparison of PET parameters obtained from the early and delayed PET scans.

Parameter	N	The Early PET Scan	The Delayed PET Scan	p-value
SUV_{max}	134			< 0.0001 [*]
Mean±SD		12.10 ± 5.83	13.61 ± 6.45	
Median		11.78	13.19	
Range		2.25 – 32.86	2.85 – 31.45	
SUV_{mean}	134			< 0.0001 [*]
Mean±SD		5.94 ± 2.77	6.56 ± 3.11	
Median		5.73	6.17	
Range		1.19 – 13.62	1.43 – 14.91	
SUV_{peak}	118 [‡]			< 0.0001 [*]
Mean±SD		10.18 ± 4.79	11.54 ± 5.45	
Median		9.94	11.34	
Range		1.73 – 27.27	2.30 – 26.24	
TLG	134			< 0.0001
Mean±SD		276.51 ± 606.71	320.23 ± 715.66	
Median		82.47	87.87	
Range		4.14 – 4228.87	3.99 – 5121.43	
MTV	134			0.17
Mean±SD		37.62 ± 67.36	38.36 ± 68.90	
Median		14.50	14.95	
Range		1.22 – 529.69	1.38 – 515.30	

Note: N = the number of patients; MTV= metabolic tumor volume; SD = standard deviation; SUV_{max} = maximum standardized uptake value; SUV_{mean} = average standardized uptake value; SUV_{peak} = peak standardized uptake value; TLG = total lesion glycolysis.

^{*} Student's t-test for paired data.

^{\$} Wilcoxon signed-rank test.

[‡] SUV_{peak} could not be measured in 16 patients due to small (< 12 mm diameter) tumor size.

Table 2

Percentage change in PET parameters between the early and delayed scans

Parameter [*]	N	Mean $\pm$ SD (%)	Median (min, max) (%)
SUVmax	134	13.76 $\pm$ 15.52	11.76 (–19.82, 92.07)
SUVmean	134	10.78 $\pm$ 10.94	10.57 (–12.12, 56.91)
SUVpeak	118 ^{\$}	13.64 $\pm$ 12.22	13.51 (–12.77, 77.64)
TLG	134	13.95 $\pm$ 15.74	14.34 (–35.37, 64.47)
MTV	134	3.77 $\pm$ 17.24	1.65 (–43.82, 64.96)

Note: N = the number of patients; SD = standard deviation.

^{*} Percentage change () in PET parameters from the early to delayed scans.

^{\$} SUV_{peak} could not be measured in 16 patients due to small (< 12 mm diameter) tumor size.

Table 3

Intraclass correlation coefficient of PET parameters estimated from the early and delayed scans

Parameter	N	ICC	95% CI
SUVmax	134	0.933	[0.694, 0.974]
SUVmean	134	0.952	[0.747, 0.982]
SUVpeak	118*	0.928	[0.630, 0.973]
TLG	134	0.982	[0.971, 0.988]
MTV	134	0.996	[0.994, 0.997]

Notes: N = the number of patients; ICC = intraclass correlation coefficient; CI = confidence interval.

* SUV_{peak} could not be measured in 16 patients due to small (< 12 mm diameter) tumor size.

Table 4

Inter-observer agreement in PET parameters

Parameters	The Early PET Scan			The Delayed PET Scan		
	N	ICC	95% CI	N	ICC	95% CI
SUV _{max}	134	1.000	[1.000, 1.000]	134	0.999	[0.999, 1.000]
SUV _{mean}	134	0.949	[0.820, 0.978]	134	0.952	[0.884, 0.975]
SUV _{peak}	109 [*]	0.980	[0.971, 0.986]	108 [§]	0.953	[0.931, 0.967]
TLG	134	0.990	[0.986, 0.993]	134	0.939	[0.915, 0.956]
MTV	134	0.934	[0.909, 0.953]	134	0.954	[0.936, 0.967]

Notes: ICC = intraclass correlation coefficient; CI = Confidence interval.

^{*} SUV_{peak} was measured by both radiologists in 109 patients due to small (< 12 mm diameter) tumor size in the rest of the cases.

[§] SUV_{peak} was measured by both radiologists in 108 patients due to small (< 12 mm diameter) tumor size in the rest of the cases.