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Quantification of metabolic tumor activity and burden in patients with NSCLC: Is manual adjustment of semi-automatic gradient based measurements necessary?

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Abstract

Purpose: Metabolic tumor burden (MTB) measurements including metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been shown to have prognostic value in non-small cell lung cancer (NSCLC). Calculating MTB typically utilizes software to semi-automatically draw volumes of interest (VOIs) around the tumor, which are subsequently manually adjusted by the radiologist to include the entire tumor. The manual adjustment step can be time-consuming and observer-dependent. We compared the agreement of MTB values obtained from the semi-automatic method with and without manual adjustment in NSCLC patients.

Methods: This IRB approved prospective study included 134 patients with histologically proven NSCLC who underwent ¹⁸F-FDG-PET/CT. The MTB of the primary tumor was measured with a semi-automatic gradient-based method without manual adjustment (semi-automatic gradient method) and with manual adjustment (manually adjusted semi-automatic gradient method) by two radiologists by using the MIM PETedge tool. The paired t-test, Wilcoxon signed-rank test, and

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest:

Piotr Obara, Haiping Liu, Kristen Wroblewski, Chen-Peng Zhang, Peng Hou, Yulei Jiang, Chen Ping and Yonglin Pu declare that they have no conflict of interest.

Research involving Human Participants:

The study was done under IRB approval of the First Affiliated Hospital of Guangzhou Medical University.

Informed consent:

Informed consent was obtained from the research subjects.

concordance correlation coefficient (CCC) were calculated to evaluate agreement between MTB measures obtained with these two methods, as well as agreement between the two radiologists for each method.

Results: SUV_{max} values were identical between the two methods. No statistically significant difference was present for SUV_{peak} , MTV and TLG values between the two methods ($p=0.23$, 0.45 and 0.37 , respectively). Excellent agreement between the two methods was found in terms of CCC ($CCC > 0.98$ for all measures). Inter-observer reliability was excellent for all measures ($CCC > 0.90$).

Conclusion: The semi-automatic gradient-based tumor-segmentation method can be used without the additional manual adjustment step for metabolic tumor burden quantification of primary NSCLC tumors.

Keywords

non-small cell lung cancer; metabolic tumor burden; PET/CT; metabolic tumor volume; total lesion glycolysis

Introduction

^{18}F -FDG positron emission tomography (^{18}F -FDG-PET) exams are commonly used in patients with non-small cell lung cancer (NSCLC) for initial evaluation, staging, radiation therapy planning, and treatment response monitoring [1–4]. In addition to qualitative evaluation by visual inspection, ^{18}F -FDG -PET imaging provides several semi-quantitative or quantitative measurements of radioactivity concentration, such as with the standardized uptake value (SUV) [5]. SUV_{max} and SUV_{peak} are routinely used in clinical and research settings [6]. More recently, measures of metabolic tumor burden (MTB) have been explored, including metabolic tumor volume (MTV) and total lesion glycolysis (TLG). MTV indicates the volume of metabolically active tumor. Total lesion glycolysis (TLG) is the product of SUV_{mean} and MTV; it combines the volumetric and metabolic information from ^{18}F -FDG-PET [7]. Metabolic tumor burden measurements of MTV and TLG as well as SUV_{max} of the primary tumor in patients with NSCLC have been shown to have prognostic value and utility in monitoring treatment response [8–16].

A critical step in calculating MTB values is the delineation of tumor margin in PET images; accuracy and efficiency of this step are necessary for MTB measures to be used in routine clinical practice. Completely manual tumor margin delineation by the radiologist involves hand drawing a region of interest around the tumor margin; this is not only time-intensive but also tends to have poor inter-observer agreement [17]. Manual adjustment following a semi-automatic gradient method has been used to accomplish this goal and MTB measurements with this method have been found to be associated with patient's overall survival [12–14, 16]. With this method, the initial semi-automatic tumor contouring requires the radiologist to identify the tumor center and its major and minor axes on a single 2-D slice of a 3-D PET image set. By utilizing a gradient method based on spatial derivatives, the software automatically draws a volume of interest (VOI) to delineate tumor margin, and subsequently calculate various tumor metabolic measures such as SUV_{max} , MTV, or TLG

from the VOI[18]. The second step requires the radiologist to adjust the software-generated VOI to make sure that it includes the entire tumor and that no tissue outside the tumor is included. This manual adjustment step can also be time-consuming and observer-dependent.

We conducted this study to determine whether the semi-automatic gradient method without manual adjustment can be used to replace the method with manual adjustment by evaluating the agreement in metabolic and volumetric measurements of the primary tumor obtained with these two methods in 134 NSCLC patients.

Methods

Patient selection/demographics

This study was done under IRB approval. All patients with pathologically confirmed diagnosis of NSCLC and a baseline PET/CT scan between 09/26/2013 and 01/31/2014 at Guangzhou Medical University Hospital, which showed a measurable ^{18}F -FDG-avid primary tumor, were enrolled in this prospective study.

PET/CT technique

All patients underwent a whole-body ^{18}F -FDG PET/CT scan in accordance with the National Cancer Institute guidelines [3]. The ^{18}F -FDG PET images were obtained from a PET/CT scanner (GE Discovery ST, GE, Milwaukee, WI, USA) equipped with high-resolution bismuth germanate (BGO) detector blocks and an 8-slice CT scanner. Patients fasted for at least 4–6 hours before intravenous administration of 3.70–5.55 MBq/kg of ^{18}F -FDG. Serum glucose levels were tested via finger-stick sampling before ^{18}F -FDG injection and a value less than 7.0 mmol/L was required for the PET/CT study to be performed. A whole-body CT scan without IV contrast was performed for PET attenuation correction, by using a standard protocol: 140 kVp, 150 mA, slice thickness 3.75 mm, pitch 1.675, and imaging matrix 512×512 . About sixty minutes following injection of ^{18}F -FDG, a whole-body static PET scan was acquired for about 21–25 min, starting at the thighs and proceeding to the head, with an acquisition time of 3.5 min per cradle position, by using the 2D acquisition mode with image matrix of 128×128 . PET images were reconstructed by using the ordered subsets expectation maximization (OSEM) iterative algorithm. CT imaging matrices were converted to 128×128 and were used for attenuation correction for PET images.

Primary tumor segmentation and metabolic evaluation

All PET image analyses were done with the PETedge tool of the MIMvista software (MIMvista Corp, Cleveland, OH, USA) at the University of Chicago. After a radiologist indicated the approximate tumor center and drew the major and minor axes of tumor on a single 2-D axial image of a 3-D image set, which were shown automatically on sagittal and coronal planes, the software used a gradient-based (spatial derivatives) method to automatically generate volumes of interest (VOIs) and segment the tumor [18]. The tumor segmentation generated by the software in this manner was what we defined as the “semi-automatic gradient method.” The radiologist can also manually adjust the software-generated VOIs by visual inspection to ensure that the VOI contour matched the

metabolically active tumor boundary exactly; we defined this as the “manually adjusted semi-automatic gradient method.” The manual adjustment step used the software’s 3-D ball tool, which is a manual adjustment tool for the tumor contour.

Two radiologists (YP and CZ with more than 7 years of clinical nuclear medicine and FDG PET experience) independently segmented each patient’s primary tumor twice with both the semi-automatic gradient method and manually adjusted semi-automatic gradient method (Figure 1). Subsequently, the following MTB and SUV measurements were obtained based on the segmentation results from each radiologist with each method: SUV_{max} , SUV_{peak} , MTV, and TLG. A 1.2-cm-diameter sphere within the tumor was used to calculate SUV_{peak} .

Statistical analysis

The differences between values obtained from the semi-automatic gradient method versus manually adjusted semi-automatic gradient method were evaluated by using the paired t-test for normally distributed SUV measures, and the Wilcoxon signed-rank test was used for the non-normally distributed MTV and TLG. A natural logarithmic transformation was also applied to MTV and TLG in order to obtain more normally distributed data for these measures, and differences in $\log(MTV)$ and $\log(TLG)$ measured with the two methods were evaluated by using the paired t-test. Subsequently, measurement agreement between the two methods, and inter-radiologist agreement from each method, were assessed with concordance correlation coefficients (CCCs) [19].

Results

A total of 134 patients met the inclusion criteria and were included in the study. Information regarding patient demographics, diagnosis method, histology type, and stage are summarized in Table 1. Of these, only 121 patients were evaluated for SUV_{peak} because in 13 patients the small tumor size (less than 1.2 cm) did not meet the criteria for determining this measure.

There was no statistically significant difference observed between values obtained using the semi-automatic gradient method versus manually adjusted semi-automatic gradient method (Table 2). The median (range) MTV values, in ml, was 14.50 (1.22–529.69) and 12.99 (1.42–529.39) from the semi-automatic gradient method and from manually adjusted semi-automatic gradient method, respectively ($p=0.45$, Wilcoxon signed-rank test). Similarly, the mean (SD) MTV were similar for the two methods, with values in ml of 37.62 (67.36) and 37.34 (67.47), respectively. The median (range) TLG value, in ml, was 82.47 (4.14–4228.87) and 85.17 (3.83–4197.61) from the semi-automatic gradient method and from manually adjusted semi-automatic gradient method, respectively ($p=0.37$, Wilcoxon signed-rank test). Similar results were found when comparing logarithmically transformed MTV and TLG values between the two methods ($p=0.52$ and $p=0.72$, respectively). The mean (standard deviation) of SUV_{peak} was 10.07 (4.78) and 10.12 (4.80) from the semi-automatic gradient method and from manually adjusted semi-automatic gradient method, respectively ($p=0.23$, from paired t-test). SUV_{max} was identical between the two methods in every case, with a mean (SD) of 12.10 (5.83); therefore, further statistical analysis was not performed for this measure.

Figure 2 shows scatterplots of the differences in MTV and TLG measured with the semi-automatic gradient method and the manually adjusted semi-automatic gradient method, versus SUV_{max} of the primary tumor. There was no evidence in these scatterplots to suggest that the differences in MTV and TLG measured with the two methods were dependent on SUV_{max} of the primary tumor.

Excellent agreement between the semi-automatic gradient method and manually adjusted semi-automatic gradient method was found for all measures in terms of CCC, with the lower bound of 95% confidence interval being 0.98 or greater for all measures (Table 3).

Excellent agreement was also seen between the two radiologists for both the semi-automatic gradient and manually adjusted semi-automatic gradient method methods in terms of CCC, with the lower bound of 95% confidence interval being 0.86 or greater for all measures (Table 4).

Discussion

We demonstrate in this study excellent agreement between MTB measurements of the primary tumor in NSCLC obtained with the semi-automatic gradient method and manually adjusted semi-automatic gradient method, as well as between MTB measurements obtained independently by two radiologists. These results suggest that the additional time-consuming step of manually adjusting semi-automatically selected VOIs may be avoided without significantly affecting MTB values.

MTV and TLG can provide an estimate of the true metabolically active tumor volume. MTV and TLG of the primary tumor and of the whole body have been shown to have prognostic value in patients with NSCLC independent of stage, and better prognostic value than SUV_{max} or SUV_{mean} [9–16]. The efficiency and objectivity of the semi-automatic method for calculating MTV and TLG values may help facilitate the use of MTB as a prognostic factor.

PET tumor SUV measurement is also important for evaluating tumor response to therapy [8]. PET Response Criteria in Solid Tumors (PERCIST) based on tumor SUV_{peak} measurements has been adopted as the new standard method for PET-based evaluation of treatment effectiveness [20]. The close similarity of SUV_{peak} obtained from the two methods in our study suggests that the semi-automatic method without manual adjustment can be more efficient for PERCIST assessment without sacrificing accuracy. Whole-body MTB quantification may also be valuable for standardized assessment of treatment response because of its demonstrated prognostic value, and the faster semi-automatic method can make MTB more practical to use clinically.

Semi-automatic tumor segmentation and contouring rely on the software's ability to detect the true margin of the tumor. Two common algorithms used for tumor delineation are the gradient- and threshold-based methods [21,22]. Our study used the gradient method, which has been shown to be more accurate than the threshold method for tumor segmentation [18, 23,24]. MTV estimates from the gradient method are also insensitive to the tumor to background ratio and, for this reason, are expected to be less sensitive to the length of ^{18}F -

FDG uptake before PET imaging [18]. More sophisticated segmentation techniques have also been developed, including locally-adaptive region-growing, an iterative technique combining local background correction and adaptive thresholding, as well as other techniques employing fuzzy logic and spatial context to help identify the tumor boundary more accurately [17, 25–30]. Although tumor location in the lung may affect accuracy, several studies employing these algorithms demonstrated good correlation of semi-automatically generated tumor volume with pathological specimens [24, 30–36]. While semi-automatically derived measurements are more reproducible overall than those obtained from completely manual tumor delineation, the reproducibility of each semi-automatic algorithm varies and further testing must be performed before application of any of these methods to patient care [17, 25, 29, 37].

All of the methods above calculate tumor volume by segmenting the metabolically active region of a tumor seen on PET images. Theoretically, CT and MR images can also be used for estimation of whole-body tumor volume. However, the boundary of the metabolically active tumor can be difficult to differentiate from the surrounding anatomy based on CT or MR, and thus PET/CT is more accurate for this purpose. A study comparing tumor-volume measurement from CT, MRI, and PET for head and neck cancer showed that PET-derived MTV is the closest to the reference tumor volume from surgical specimens [38]. Another study of NSCLC showed that PET/CT images produce more accurate tumor-size measurement than PET alone or CT alone [39]. Other studies have also shown that PET/CT is more accurate than CT or MRI for characterization of various cancers, including NSCLC [40–46]. Another advantage of PET/CT is that oncologic PET/CT scans are already routinely performed from “eyes to thighs” [47], thus facilitating whole-body metabolic tumor burden measurements for staging without incurring an additional imaging study.

Our study has several limitations. First, all the measurements were performed with one particular software tool and one particular initial semi-automatic segmentation method. It is possible that the agreement between the derived MTB values from the semi-automatic gradient method versus from manually adjusted semi-automatic gradient method that we have observed may not hold for software tools from other vendors. However, continued development of segmentation methods should lead to even more accurate and efficient calculation of metabolic tumor values. Second, although there is a possibility of bias toward agreement between the two segmentation methods, because the agreement would have been greatest if the observers simply did not manually adjust the VOIs, this study was not done for the purpose of comparing the two segmentation methods, but to compare VOIs measured from PET scans at two time points (results not reported here). Therefore, the observers simply tried to measure the VOIs as accurately as possible, and we expect the possibility of this bias to be minimal. Third, the spatial resolution of PET in our study was determined by a 128×128 matrix size, which is no longer considered state-of-the-art, compared with 192 or 256 matrices; it is unknown whether the software will perform better or worse in generating accurate tumor contours with larger matrices. Fourth, we compared MTB measurements of only the primary tumor in a limited number of patients with untreated NSCLC and we did not exclude the central necrosis in the tumor. Finally, given the high contrast between bright metabolically active tumor and dark background lung parenchyma, it is possible that the software performs better in delineating primary lung tumor contours

than it will for tumor in other parts of the body where the tumor to background contrast is less pronounced. Further studies are needed to confirm that the semi-automatic method is equally accurate as the method with manual adjustment for a more heterogeneous patient population with metastasis in other locations.

Conclusion

We have demonstrated excellent agreement for metabolic PET measurement of the primary tumor obtained from the semi-automatic gradient method and manually adjusted semi-automatic gradient method in NSCLC patients. Given the close similarity in MTB values obtained with these two methods, the semi-automatic method can be used to provide better efficiency in metabolic tumor burden evaluation, and improve the utility of MTB in both research and clinical practice. However, we recommend that a final review of the VOI boundary by a radiologist should always be performed when using semi-automatic method.

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Figure 1:
PET images of a 63-year-old woman with a new diagnosis of NSCLC (adenocarcinoma), showing the measurements of MTV, TLG and maximum and peak SUVs of the primary tumor obtained with the MIMvista PETedge tool by using both the semi-automatic gradient methods without (A, semi-automatic gradient method) and with manual adjustment (B, manually adjusted semi-automatic gradient method).

Figure 2:

Scatterplots of (A) the differences in MTV, and (B) the differences in TLG, measured with the semi-automatic gradient method and with the semi-automatic gradient method followed by manual adjustment, versus SUV_{max} of the primary tumor. These scatterplots show that

the differences in MTV and TLG measured with the two methods are not dependent on SUV_{max} of the primary tumor.

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Table 1.

Patient demographics and tumor characteristics.

Variable	Number	Percentage (%)
Number of patients	134	100
Gender		
Female	50	37.3
Male	84	62.7
Age		
Mean±SD	60.8±10.8	
Median	62	
Range	23–83	
Diagnosis Methods		
Surgery	70	52.2
Bronchoscope biopsy	41	30.6
Transthoracic needle biopsy	21	15.7
Pleural fluid cytopathology	2	1.5
Histology types		
Adenocarcinoma	89	66.4
Squamous cell carcinoma	32	23.9
Other type of NSCLC	13	9.7
TNM Stage		
Stage I A/I B	15/22	11.2/16.4
Stage II A/II B	9/6	6.7/4.5
Stage III A/III B	30/13	22.4/9.7
Stage IV	39	29.1

Note: NSCLC =non-small cell lung cancer.

Table 2.

Comparison of PET measurements obtained with the semi-automatic gradient method and manually adjusted semi-automatic gradient method.

Parameter	Number of patients	Semi-automatic	Manually adjusted semi-automatic	Difference [^]	p-value
SUV _{max}	134				NA [‡]
Mean (SD)		12.10 (5.83)	12.10 (5.83)	0 (0)	
Median		11.78	11.78		
Range		2.25–32.86	2.25–32.86		
SUV _{peak}	121				0.23 [*]
Mean (SD)		10.07 (4.78)	10.12 (4.80)	−0.05 (0.44)	
Median		9.79	9.80		
Range		1.73–27.27	1.73–27.27		
MTV	134				0.45 ^{\$}
Mean (SD)		37.62 (67.36)	37.34 (67.47)	0.28 (5.67)	
Median		14.50	12.99		
Range		1.22–529.69	1.42–529.39		
Log(MTV)	134				0.52 [*]
Mean (SD)		2.81 (1.23)	2.80 (1.22)	0.01 (0.21)	
Range		0.20–6.27	0.35–6.27		
TLG	134				0.37 ^{\$}
Mean (SD)		276.51 (606.71)	278.59 (607.58)	−2.07 (21.38)	
Median		82.47	85.17		
Range		4.14–4228.87	3.83–4197.61		
Log(TLG)					0.72 [*]
Mean (SD)		4.47 (1.49)	4.46 (1.51)	0.01 (0.16)	
Range		1.42–8.35	1.34–8.34		

Note: NA = Not Applicable, Log = natural logarithmic transformation, MTV= metabolic tumor volume, SD = standard deviation, SUV_{max} = maximum standardized uptake value, SUV_{peak} =peak standardized uptake value, TLG= total lesion glycolysis

[^] Semi-automatic – Manually Adjusted

^{*} Differences tested with the paired t-test.

^{\$} Differences tested with the Wilcoxon signed-rank test.

[‡] SUV_{max} was identical between the two methods in every case; therefore, further statistical analysis was not performed for this measure.

Table 3.

Concordance correlation coefficients for PET measurements obtained with the semi-automatic gradient method and manually adjusted gradient method.

Parameter	Number of patients	CCC	95% CI
SUV _{max}	134	1.000	NA
SUV _{peak}	121	0.996	0.994 to 0.997
log (MTV)	134	0.986	0.980 to 0.990
log (TLG)	134	0.994	0.992 to 0.996

Notes: CCC = Concordance correlation coefficients, CI = confidence interval. Other abbreviations are the same as in Table 2.

Table 4.

Inter-observer agreement between two radiologists for PET measurements obtained with the semi-automatic gradient method and manually adjusted gradient method.

Parameter	Method	Number of patients	CCC	95% CI
SUV _{peak}	Semi-automatic	109	0.980	0.971 to 0.986
log (MTV)	Semi-automatic	134	0.902	0.867 to 0.928
log (TLG)	Semi-automatic	134	0.952	0.933 to 0.965
SUV _{peak}	Manual	111	0.989	0.984 to 0.992
log (MTV)	Manual	134	0.903	0.868 to 0.930
log (TLG)	Manual	134	0.952	0.934 to 0.966

Notes: CCC = Concordance correlation coefficients, CI = confidence interval. Other abbreviations are the same as in Table 2.