Original Article

Glucose-corrected standardized uptake value (SUV\textsubscript{gluc}) is the most accurate SUV parameter for evaluation of pulmonary nodules

Amin Haghighat Jahromi\textsuperscript{1}, Farshad Moradi\textsuperscript{2}, Carl K Hoh\textsuperscript{1}

\textsuperscript{1}Department of Radiology, University of California, San Diego, La Jolla, CA 92093, USA; \textsuperscript{2}Department of Radiology, Stanford University, Stanford, CA 94305, USA

Received August 2, 2019; Accepted August 22, 2019; Epub October 15, 2019; Published October 30, 2019

Abstract: Standardized uptake values (SUVs) of \textsuperscript{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) are widely used to help characterize pulmonary nodules. The purpose of this study is to assess the accuracy of the SUV corrected by blood glucose levels (SUV\textsubscript{gluc}), compared to four other commonly used semi-quantitative methods: maximal SUV normalized to body weight (SUV\textsubscript{max}), ratio of SUV of nodule to cerebellum (SUV\textsubscript{cer}), SUV normalized to body surface area (SUV\textsubscript{bsa}) and SUV normalized to body mass index (SUV\textsubscript{bmi}). 52 patients with lung nodules had FDG PET scans, consecutively imaged between 7/1/2015 and 6/7/2016. Histopathologic result of the nodules, obtained within two months after the FDG PET scan, demonstrated 10 benign and 42 malignant lung nodules. The SUV\textsubscript{gluc} was defined as SUV\textsubscript{max} $\times$ blood glucose level/100. The average SUV\textsubscript{max} was 2.8 for benign nodules and 7.7 for malignant nodules. No significant difference in the receiver operating characteristic (ROC) area under the curves (AUCs) were found between the SUV\textsubscript{max} (0.84) and the SUV\textsubscript{cer} (0.87) or SUV\textsubscript{bsa} (0.86), or SUV\textsubscript{bmi} (0.86) with \textit{p}-values greater than 0.05; however, the ROC AUC for the SUV\textsubscript{gluc} (0.90) was larger than that for the SUV\textsubscript{max} with \textit{p}-value of 0.03. These results suggest that SUV\textsubscript{gluc} may assist in more accurately representing the glucose metabolism of malignant lung nodules by accounting for the patient’s blood glucose level (BGL). The simplicity of the SUV\textsubscript{gluc} method avoids an additional reference ROI, uses preexisting clinical data, \textit{i.e.} pre-injection blood glucose level, and retains the familiar SUV reference values.

Keywords: Glucose-corrected SUV, PET, lung nodule, blood glucose level

Introduction

\textsuperscript{18}F-fluorodeoxyglucose positron emission tomography (\textsuperscript{18}F-FDG PET) is a commonly used imaging modality to assess the risk of benign versus malignant pulmonary nodules, noninvasively [1]. Although the accuracy of PET for diagnosing malignancy is heterogeneous, it is widely accepted for the clinical diagnosis and staging of lung cancer in patients with suspicious lung nodules [2]. Standardized uptake value (SUV) is a simple method to obtain semiquantitative index of FDG uptake, however multiple factors can affect SUV, thus limit its reliability including: body surface area, lean body mass, blood glucose level, or other perturbing factors [3]. In this study, we compared accuracy of SUV\textsubscript{max} (normalized by body weight) and four other corrected SUV parameters including: ratio of SUV of nodule to cerebellum (SUV\textsubscript{cer}), SUV normalized to body surface area (SUV\textsubscript{bsa}), SUV normalized to body mass area (SUV\textsubscript{bma}) and SUV corrected by blood glucose level (SUV\textsubscript{gluc}).

Materials and methods

Patient selection

This study was designed as a retrospective single-center study in the University of California San Diego medical center including Hillcrest and Thornton hospitals. It was approved by the institutional review board (IRB) and was Health Insurance Portability and Accountability Act (HIPAA) compliant. Documentation in our database was anonymous. Patients were considered eligible for this study if they underwent FDG PET-CT study between July 2015 and June 2016 and had a pathological diagnosis of the nodule within 2 months after the imaging. The
FDG PET imaging

All patients were asked to fast for at least 6 hours prior to their scan. Blood glucose levels were measured immediately before the FDG injection. Patients were intravenously injected with 370-740 MBq FDG, within a 5-10 second interval. Following an uptake period of approximately 1 hour in a quiet room at rest, multi-station 3-dimensional (3D) PET acquisition with CT, for attenuation correction, was performed for approximately 60 min, using a GE Discovery VCT scanner. PET images were acquired, after the CT scan, at a rate of 2 minutes/bed position, in the 3D acquisition mode. CT images were then reconstructed onto a 512 × 512 matrix. PET images were reconstructed using a standard whole body 3D iterative reconstruction: 2 iterations; 28 subsets onto a 128 × 128 matrix with attenuation correction, decay correction, and scatter correction. The photon energy window was 425-650 keV. Slice thickness was 3.27 mm and reconstruction diameter was 70 cm. Pixel size was 5.47 mm × 5.47 mm with spatial resolution of 5 mm.

Image analysis

All PET images were reviewed and further analyzed using the Agfa Impax software by a board certified academic nuclear medicine physician. Focal activity corresponding to the pulmonary nodule on CT was manually identified on PET images. SUV of the dominant nodule was obtained by manually placing a circular ROI at the site of the maximum FDG uptake in the PET images and the maximal activity (SUV<sub>max</sub>) was recorded. SUV<sub>max</sub> was calculated as decay-corrected activity of tissue volume (kBq/mL)/injected FDG activity per body mass (kBq/g). SUV<sub>bmi</sub> was calculated from SUV<sub>max</sub> by normalizing activity based on body mass index (BMI) = Weight (kg)/Height<sup>2</sup> (m). SUV<sub>bsa</sub> was calculated from SUV<sub>max</sub> by normalizing activity based on body surface area (BSA) = (Weight (kg) * Height (cm)/3600)<sup>1/2</sup>. The average SUV value of the cerebellum reference region was used to calculate the SUV<sub>cer</sub>, defined as the ratio of SUV<sub>max</sub> divided by the average cerebellar SUV. Corrected SUV for the blood glucose level (SUV<sub>gluc</sub>) was calculated based on BGL immediately before the FDG injection (Table 1).

Statistical analysis

All data were expressed as mean ± SD (standard deviation). Differences were analyzed by the paired T-test and considered to be significant at a P-value less than 0.05. Since the sensitivity and specificity of a test depends on the selected threshold value, a more rigorous comparison of diagnostic accuracy was performed using ROC analysis using ROCKIT (1.1B2, University of Chicago, IL, USA).

Results

Histopathological and patient characteristics analysis

Following <sup>18</sup>F-FDG PET, the final diagnosis was confirmed pathologically by subsequent biopsy within 2 months in all 52 patients. It revealed 42 malignant nodules, consisting of 20 adenocarcinoma, 15 squamous cell carcinoma, and 7 other malignancies. The other 10 nodules were benign. The average glucose level was 104.8 mg/dL (range 77 to 235). The rest of the patient characteristics are shown in Table 2.

---

**Table 1.** Definition and area under the curve (AUC) in the receiver operating characteristic (ROC) curve of SUV parameters

<table>
<thead>
<tr>
<th>SUV parameter</th>
<th>Definition</th>
<th>AUC in the ROC curve</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>decay-corrected activity of tissue volume/injected activity per body mass</td>
<td>0.84</td>
<td>Not applicable</td>
</tr>
<tr>
<td>SUV&lt;sub&gt;bmi&lt;/sub&gt;</td>
<td>(SUV&lt;sub&gt;max&lt;/sub&gt;/body weight) × BMI</td>
<td>0.86</td>
<td>0.15</td>
</tr>
<tr>
<td>SUV&lt;sub&gt;bsa&lt;/sub&gt;</td>
<td>(SUV&lt;sub&gt;max&lt;/sub&gt;/body weight) × BSA</td>
<td>0.86</td>
<td>0.43</td>
</tr>
<tr>
<td>SUV&lt;sub&gt;cer&lt;/sub&gt;</td>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;/SUV&lt;sub&gt;cer&lt;/sub&gt;</td>
<td>0.87</td>
<td>0.32</td>
</tr>
<tr>
<td>SUV&lt;sub&gt;gluc&lt;/sub&gt;</td>
<td>SUV&lt;sub&gt;max&lt;/sub&gt; × blood glucose level/100</td>
<td>0.90*</td>
<td>0.03***</td>
</tr>
</tbody>
</table>

*SUV<sub>gluc</sub> has the highest AUC among semiquantitative parameters. **P-value is in comparison to SUV<sub>max</sub>. ***SUV<sub>gluc</sub> is the only SUV parameter which significantly improves diagnostic accuracy of SUV<sub>max</sub> in differentiating benign vs. malignant lung nodules (P = 0.03).
**Table 2.** Patient characteristics and SUV values. Mean and Standard deviation (parentheses) values are reported

<table>
<thead>
<tr>
<th></th>
<th>All patient</th>
<th>Benign</th>
<th>Malignant</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N, number</strong></td>
<td>52</td>
<td>10</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>72.8±17.6</td>
<td>73.9±18.1</td>
<td>72.6±17.6</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>168.3±9.5</td>
<td>164.0±9.5</td>
<td>169.3±9.3</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Blood glucose level, mg/dL</strong></td>
<td>104.8</td>
<td>92.9±8.4</td>
<td>107.7±32.2</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Body Mass Index, kg/m²</strong></td>
<td>25.6±5.4</td>
<td>27.4±6.4</td>
<td>25.2±5.1</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Body Surface Area, m²</strong></td>
<td>1.83±0.25</td>
<td>1.82±0.25</td>
<td>1.84±0.25</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>SUV&lt;sub&gt;max&lt;/sub&gt;</strong></td>
<td>6.8±4.8</td>
<td>2.8±1.7</td>
<td>7.7±4.8</td>
<td>0.003*</td>
</tr>
<tr>
<td><strong>SUV&lt;sub&gt;bma&lt;/sub&gt;</strong></td>
<td>0.18±0.13</td>
<td>0.07±0.04</td>
<td>0.20±0.13</td>
<td>0.003*</td>
</tr>
<tr>
<td><strong>SUV&lt;sub&gt;bmi&lt;/sub&gt;</strong></td>
<td>1.5±1.2</td>
<td>0.60±0.57</td>
<td>1.8±1.2</td>
<td>0.005*</td>
</tr>
<tr>
<td><strong>SUV&lt;sub&gt;bmi&lt;/sub&gt;</strong></td>
<td>2.4±1.7</td>
<td>1.0±0.6</td>
<td>2.7±1.7</td>
<td>0.003*</td>
</tr>
<tr>
<td><strong>SUV&lt;sub&gt;gluc&lt;/sub&gt;</strong></td>
<td>6.8±4.5</td>
<td>2.6±1.6</td>
<td>7.9±4.3</td>
<td>0.0005*</td>
</tr>
</tbody>
</table>

Mean ± standard deviation (parentheses) values are reported. *All SUV parameters are significantly different between the benign vs. malignant pulmonary nodules, whereas weight, height, BGL, or BMI are not.

---

**Figure 1.** The ROC curves of SUV<sub>gluc</sub>, SUV<sub>cer</sub>, SUV<sub>bmi</sub>, SUV<sub>bma</sub>, and SUV<sub>max</sub>. AUC for SUV<sub>gluc</sub>, SUV<sub>cer</sub>, and SUV<sub>bma</sub> is not significantly different from SUV<sub>max</sub> (P = 0.32, 0.15, and 0.43, respectively). The SUV<sub>gluc</sub> has the largest AUC, significantly different from SUV<sub>max</sub> (AUC = 0.90 vs. 0.84, P = 0.03), thus the most accurate SUV parameter to distinguish malignant from benign pulmonary nodules.

---

**Figure 3** shows a representative FDG PET projection image of a patient with left upper lobe lung adenocarcinoma, BGL = 166 mg/dL, with SUV<sub>max</sub> = 6.3 and SUV<sub>gluc</sub> = 10.5.

---

**Discussion**

The radiopharmaceutical tracer FDG follows a three compartment model with a net uptake rate of 

\[ K = \frac{k_1k_3}{k_2+k_3} \]  

(Figure 2). SUV<sub>max</sub> is proportional to this uptake rate (K) whereas glucose metabolism rate (GMR) is proportional to 

\[ K \times [\text{Glucose}] \]  

[3, 4]. The rational for SUV<sub>gluc</sub> is analogous to the calculation of the GMR which involves the scaling of the FDG uptake rate with

---

Weight, Height, BGL, BMI and BSA were not significantly different between benign and malignant pulmonary nodules (P>0.05). All five SUV parameters were significantly different between benign and malignant nodules (P<0.05) with SUV<sub>gluc</sub> having the smallest p value = 0.0005 (Table 2).

**Diagnostic value of five SUV parameters in differentiating benign and malignant pulmonary nodules**

We found SUV<sub>max</sub> to have the lowest diagnostic accuracy for detecting malignant lung nodules with area under the curve (AUC) = 0.84, in the receiver operating characteristic (ROC) curve, compared to other four semiquantitative corrected SUV parameters. The use of alternative semiquantitative methods including SUV<sub>bma</sub> (AUC = 0.86), SUV<sub>bmi</sub> (AUC = 0.86), and SUV<sub>cer</sub> (AUC = 0.87), increased AUC in the ROC however this increase was not statistically significant (P>0.05), however only for SUV<sub>gluc</sub> (AUC = 0.88) this increase was statistically significant (P = 0.03) (Figure 1). Therefore AUC for SUV<sub>gluc</sub> showed the highest diagnostic accuracy for detecting malignant lung nodules.
SUV\textsubscript{gluc} for the evaluation of pulmonary nodules

PET Image Arterial ROI

\[
\begin{align*}
C_p & \quad k_1 \quad C_E \\
& \quad k_2 \quad k_3 \quad C_T
\end{align*}
\]

PET Image Tissue ROI

\[
\begin{align*}
C_p & \quad k_1 \quad C_E \\
& \quad k_2 \quad k_3 \quad C_T
\end{align*}
\]

Figure 2. FDG tracer kinetic model, follows a three compartment model with a net uptake rate of \( K = k_1k_3/k_2+k_3 \). \( C_p \) = plasma concentration of FDG tracer, \( C_E \) = extracellular concentration, \( C_T \) = tissue concentration.

the blood glucose level. Therefore, SUV\textsubscript{gluc} defined as \( \text{SUV\textsubscript{max}} \times \text{BGL} (\text{mg/dL})/100 \) is a better marker of GMR, especially in higher blood glucose levels, where SUV\textsubscript{max} is of limited value. Glucose and \(^{18}\text{F-FDG}\) compete to enter the cells using the same glucose transporters. High BGL reduces \(^{18}\text{F-FDG}\) uptake in the tissue by competitive inhibition and by altered the biodistribution of FDG. The reason for fasting prior to the start of the PET study is to achieve low blood glucose levels for better target-to-background image contrast [5-7]. The end effect is the high blood glucose falsely reduces SUV\textsubscript{max}, but not SUV\textsubscript{gluc}, due to competitive inhibition of FDG uptake. Although prior publications have shown the advantage of SUV\textsubscript{gluc} over SUV\textsubscript{max} in evaluation of lymphoma patients [8], predicting the prognosis of pancreatic cancer [8], and brain tumors [9], one study found no advantage of SUV\textsubscript{gluc} over SUV\textsubscript{max} on SUV-survival correlation in esophageal cancer [10]. It is unclear whether glucose normalization improves diagnosis accuracy or treatment response monitoring of malignant tumors [11]. To our knowledge, only one study has reported the application of the SUV\textsubscript{gluc} in lung nodules, where the SUV\textsubscript{gluc} was found not to be beneficial in differentiating lung nodules; however, only patients with glucose levels less than 150 mg/dl were studied [12]. We speculate that limiting the patients in that study to those with BGL<150 mg/dl masked the statistical significance of the advantage of SUV\textsubscript{gluc} over SUV\textsubscript{max} because this advantage is related to BGL as SUV\textsubscript{gluc} = SUV\textsubscript{max} \times \text{BGL}/100 (Table 1). In fact, patients with normal BGL do not need glucose correction and those with high BGL will benefit from SUV\textsubscript{gluc}. Therefore, to overcome this shortcoming, we included all the patients with BGL ranging from 77 to 235 mg/dL. Another study suggests that for BGL<200 mg/dL, correction of blood glucose is not necessary however the accuracy of SUV\textsubscript{gluc} versus other SUV indicators for differentiating lung nodules was not evaluated [13]. Limitations of our study include the retrospective nature and having a single center study; however, it helps the uniformity of the data. Also, we did not evaluate the SUV in the same patient after injection of glucose, to raise BGL and study the effect of BGL on the same patient’s pulmonary nodule.

In summary, our study demonstrates that the SUV\textsubscript{gluc} is the most accurate semiquantitative method to differentiate malignant from benign lung nodules. The method is relatively simple to adopt clinically since the BGL is readily available as part of routine PET protocols, and there is no need for an additional reference ROI to define.

Acknowledgements

Amin Haghighat Jahromi is supported by National Institute of Health grant (NIH T32 Grant 4T32EB005970-09).
SUV\textsubscript{gluc} for the evaluation of pulmonary nodules

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Carl K Hoh, Department of Radiology, University of California, San Diego, La Jolla, CA 92093, USA. Tel: 619-543-1975; Fax: 619-543-1975; E-mail: ckhoh@ucsd.edu

References


