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The Applications of Corrected Standardized Uptake Values in the Diagnosis of Peripheral Lung Lesions

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Abstract: Fluorine 18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) imaging has been widely used to diagnose many types of tumors. However, many factors can affect the accuracy of standardized uptake values (SUVs). In this study, we aimed to explore the applications of corrected SUVs in the diagnosis of peripheral solitary pulmonary lesions.

A retrospective study was undertaken in 69 patients with peripheral solitary pulmonary lesions. Whole-body PET/CT was acquired approximately 60 min after ^{18}F-FDG injection. The lesions were found to be malignant in 57 cases and benign in 12 cases. Of the 69 cases, 68 were correctly diagnosed, and only 1 was misdiagnosed by the corrected SUVs. The diagnostic accuracy rate was 98.5%. The sensitivity, specificity, positive predictive value, and negative predictive value of the corrected SUV were 100%, 91.7%, 98.3%, and 100%, respectively.

^{18}F-FDG PET/CT with corrected SUVs is of great value for improving diagnostic accuracy in peripheral lung lesions.

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Abbreviations: ^{18}F-FDG = fluorine 18-fluorodeoxyglucose, CT = computed tomography, GLUT1 = glucose transporter type 1, PET = positron emission tomography, PET/CT = positron emission tomography/computed tomography, ROC = receiver-operator characteristic, ROI = region of interest, SUV = standardized uptake value, SUVave = average standardized uptake value, SUVmax = maximal standardized uptake value.

INTRODUCTION

Positron emission tomography (PET) with integrated computed tomography (CT) imaging is the most advanced functional imaging technique at the current time. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) can be used as an imaging agent based on the principle of elevated glucose metabolism in malignant tumors.[1] Fluorine 18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) can assess fundamental alterations in the cellular metabolism of glucose that are common to all neoplasms, and ^{18}F-FDG PET/CT has become the most commonly used radiopharmaceutical for PET studies of cancer. Most lung cancers are FDG-avid, except for some low-grade malignant tumors such as tumors that are part of well-differentiated lung cancer and bronchioloalveolar cancer. Some benign diseases, such as tuberculosis, granuloma, inflammation, and fungal infections, can also show different degrees of ^{18}F-FDG metabolism. The standardized uptake value (SUV) of FDG-PET is a semiquantitative simplified measurement of the FDG accumulation rate in tissues, and the maximum SUV (SUVmax) in the target lesion is widely used because of its simplicity.[2] The most commonly used SUVmax cutoff value for benign and malignant lung lesions is 2.5.[3] FDG-avid lesions with a SUVmax of $\geq$2.5 have been previously associated with a higher probability of malignancy.[4] However, many factors can affect the accuracy of SUV, such as weight, plasma glucose level, length of uptake period, partial-volume effects, and the recovery coefficient.[5–8] The liver SUV is thought to remain stable over time, and some research has shown that all of the SUVs in the mediastinum and most of the SUVs in the liver remain stable over time.[9] The liver SUV has also been previously described as remaining constant between patients.[7,10] In this research, the corrected SUV, which was defined as the lesion SUVmax divided by the liver SUVmax, was used to diagnose the peripheral lung lesions.

MATERIALS AND METHODS

Patient Population

Sixty-nine patients (44 males, 25 females; age range: 39–81 years; mean age: 60 years) with peripheral solitary pulmonary lesions were enrolled in this study. All of the patients had a definitive diagnosis based on biopsy results. Each patient received a whole-body ^{18}F-FDG scan described below. This study was approved by the ethics committee of our institution.

Patient Preparation and Scanning

All of the patients fasted with no sugary drink for at least 6 hours before the PET/CT examination. The blood glucose concentration was controlled $<$11.1 mmol/L. Intravenous ^{18}F-FDG was injected at a dose of 0.2 mCi/kg. After resting for 60 min, the patients were given 300–500 mL of pure drinking water followed by bladder emptying before the examination. A GE Discovery VCT PET/CT was used for the scan. While breathing calmly, the full-body CT scanning was conducted from the skull base to the middle of the femur with the following scanning parameters: voltage, 120 kV; current, 130 mA; slice thickness, 3.75 mm; and interlayer spacing, 3.27 mm. For the diagnostic chest CT scan, the patient was trained to breathe correctly before the examination, and the scanning was conducted from the thoracic inlet to the adrenal level using the following scanning parameters: voltage, 120 kV; current, 200 mA; matrix, 512 $\times$ 512; slice thickness, 5 mm; interlayer spacing, 5 mm; and thickness of a reconstructed slice, 2.5 mm,

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TABLE 1. Comparisons of benign and malignant lesions

	Benign (n = 12)	Malignant (n = 51)	*t* Value	*P* Value
Maximum diameter (cm)	1.89 ± 0.87	2.70 ± 0.91	2.824	0.006
Volume (cm^3)	7.32 ± 0.88	15.22 ± 16.34	2.367	0.025
Lesion SUVmax (g/mL)	3.63 ± 2.89	7.52 ± 4.22	3.874	0.001
Lesion SUVave (g/mL)	2.23 ± 1.37	4.59 ± 2.36	4.171	0.000
Liver SUVmax (g/mL)	2.40 ± 0.60	2.41 ± 0.65	0.078	0.938
Corrected SUV	1.55 ± 1.25	3.18 ± 1.76	3.784	0.001

SUV = standardized uptake values.

with the interlayer spacing at 2.5 mm. Using standardized algorithms, the lung window width was 1000 Hu at a window level of −700 Hu, and the mediastinal window width was 350 Hu at a window level of 40 Hu. The PET scanning conditions were as follows: under modest quiet breathing, the imaging acquisition range was consistent with the full-body CT scanning. The scanning time for each bed position was 3 min.

Data Analysis and Processing

The region of interest (ROI) was drawn on the slice that showed clear radioactivity aggregation. The SUVmax of segment 6 of the liver was measured. The corrected SUV was defined as the lesion SUVmax divided by the liver SUVmax. The scanning images were reviewed by physicians proficient in clinical PET/CT imaging diagnosis. The diagnostic results were judged by two senior radiologists to achieve consensus. In cases of disagreement, the whole department participated in a discussion to reach a final conclusion.

Statistical Analysis

Statistical Package for Social Science (SPSS Inc, Chicago, IL, USA) software (version 13.0) was used for the statistical analysis. Count data and measurement data were analyzed using the chi-squared test and *t* test, respectively. The diagnostic efficiency of the corrected SUV was analyzed using the chi-squared test. The correlation between tumor size and the corrected SUV was assessed using correlation analysis.

RESULTS

Pathologic Results

The diameters of the lesions ranged from 0.7 to 4.7 cm, with an average diameter of 2.6 cm. Fifty-seven of the 69 cases were found to be malignant by pathologic testing, and these included 34 cases of adenocarcinoma, 16 cases of squamous cell carcinoma, 2 cases of bronchioloalveolar carcinoma, 3 cases of neuroendocrine carcinoma, 1 case of adenosquamous carcinoma, and 1 case of metastatic tumor of papillary carcinoma. In addition, there were 12 benign lesions, which included organizing pneumonia, cryptococcus infection and tuberculosis.

Comparisons of Benign and Malignant Lesions

The maximum diameter, volume, SUVmax, average standardized uptake value (SUVave), and corrected SUV of the benign lesions were significantly different from the malignant lesions ($P < .05$), and there was no significant difference in the liver SUVmax between the 2 groups ($P = .938$) (Table 1). The CT signs (shape, margin, lobulation, pleural indentation) of the benign lesions were significantly different from the malignant lesions ($P < .05$), and the calcification did not show a significant difference between the 2 groups ($P = .531$) (Table 2).

Diagnostic Efficiency of Corrected SUV

The receiver operator characteristic (ROC) curve of the corrected SUV showed that the area under the ROC curve was 0.781 (Fig. 1). The corrected SUV of 1.1 was used as the cutoff point to achieve optimal sensitivity and specificity. Sixty-eight cases were correctly diagnosed, and only 1 case was misdiagnosed by corrected SUV. The diagnostic accuracy rate was 98.5%. The sensitivity, specificity, positive predictive value, and negative predictive value of the corrected SUV were 100%, 91.7%, 98.3%, and 100%, respectively. The diagnostic accuracy rate using an SUVmax of 2.5 as the threshold was 88.7%, and the sensitivity, specificity, positive predictive value, and negative predictive value were 94.7%, 58.3%, 90.2%, and 70.0%, respectively. The difference in accuracy between using an SUVmax of 2.5 and a corrected SUV of 1.1 as the threshold was significant ($P < .05$). The 3 cases, that is, 2 cases of adenocarcinoma and 1 case of chronic organizing pneumonia, that were misdiagnosed using an SUVmax of 2.5 as the

TABLE 2. Comparison of the CT signs of benign and malignant lesions

	Benign (n = 12)	Malignant (n = 57)	χ^2 Value	*P* Value
Quasi-circular	4 (33.3%)	4 (7%)	6.6	0.026
Spicule sign	3 (25%)	39 (68%)	7.775	0.008
Lobulation sign	3 (25%)	39 (68%)	7.775	0.008
Pleural indentation	3 (25%)	40 (70%)	5.610	0.022
Calcification	7 (67.9%)	26 (90.0%)	0.644	0.531

CT = computed tomography.

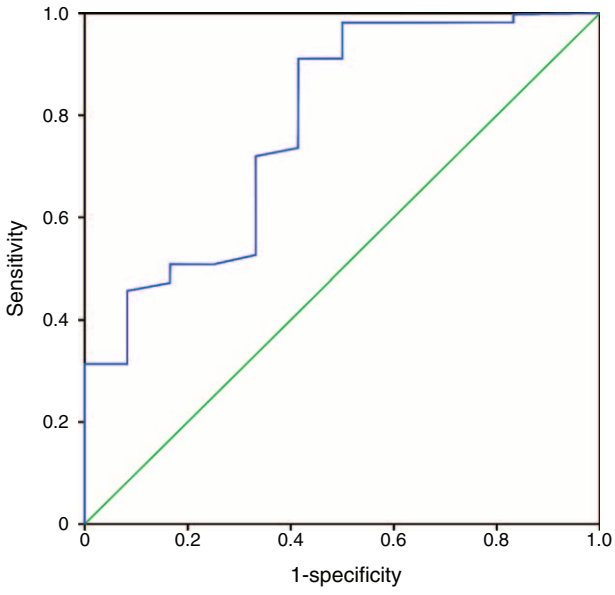

FIGURE 1. Receiver operator characteristic curve of corrected standardized uptake value.

threshold were correctly diagnosed using the corrected SUV of 1.1 as the threshold (Figs. 2–4).

Correlation Analysis of the SUV and the Lesion Volume

There was a significant positive correlation between the corrected SUV and the lesion volume (Fig. 5). SUVmax, SUVave, and corrected SUV were positively correlated with lesion volume (Table 3), and with the volume of adenocarcinoma (Table 4).

DISCUSSION

The incidence of lung cancer has rapidly increased, and this disease currently represents the main cause of cancer mortality worldwide.[11] It is difficult to make a differential diagnosis between benign and malignant peripheral isolated lung lesions in the clinic.[12] ^{18}F-FDG is the most commonly used radiotracer at the present time, and SUVmax is a semiquantitative indicator. Because of the uncontrolled proliferation of tumor cells, more energy is required, and their glucose metabolism is significantly increased. Scheepers et al[13] showed that increased FDG uptake was related to the upregulation of glucose transporter type 1 (GLUT1). GLUT1 is the main carrier involved in the transmembrane transport of glucose and is closely related to glucose metabolism. Some studies have shown that increased GLUT1 expression is a characteristic of many malignant cells.[14–16]

The SUV is a semiquantitative simplified measurement of the rate of FDG accumulation in tissues, and FDG-avid lesions with an SUVmax of $\geq$2.5 have been previously associated with a higher probability of malignancy.[4] However, many factors can affect the accuracy of SUV, including patient weight, blood glucose level, length of uptake period, partial-volume effect, recovery coefficient, and type of ROI.[6–8] Many studies have shown that an SUVmax cutoff value of 2.5 has low specificity.[17] Tuberculosis, fungal infections, sarcoidosis, and rheumatoid nodules are known causes of false-positive results. Small tumors and some other types of tumors (neuroendocrine carcinoma and bronchoalveolar carcinoma) can lead to false-negative results.[18] It has been reported that SUVs in normal tissues are usually not stable over time,[19] except for the liver SUV, which is quite stable over time and therefore can be used for comparisons with suspected malignant lesions.[20]

The SUVmax of the liver background was selected as the denominator, and the SUVmax of peripheral solitary pulmonary lesions was selected as the numerator to calculate the corrected SUV. Correcting the SUV decreased the effects of individual differences and systemic errors to some extent.[21] An analysis of

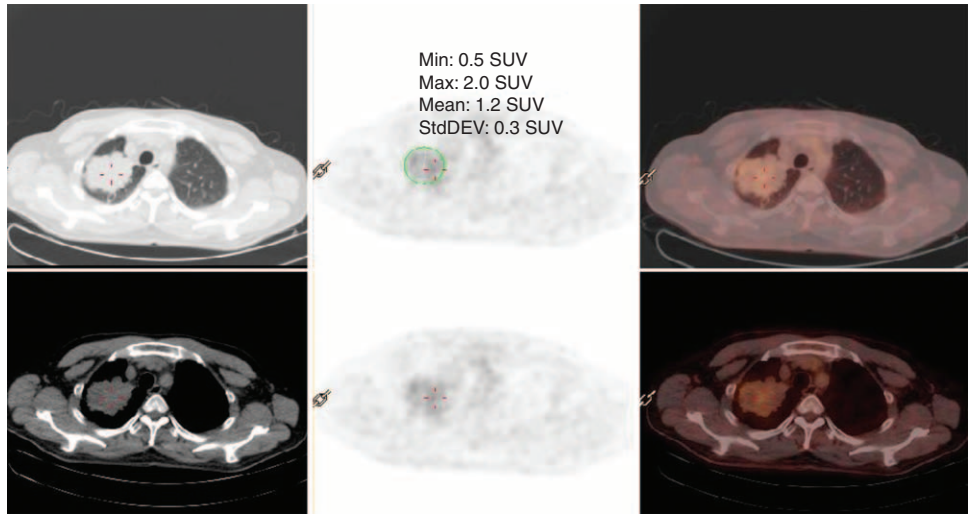

FIGURE 2. Male, 57 years' old. Suffered from pulmonary tuberculosis 7 years ago but cured. A mass with air bronchogram was observed in the superior lobe of right lung 40 days ago. Fluorine 18-fluorodeoxyglucose uptake was slightly increased. SUVmax was 2.0, liver SUVmax was 1.7, and corrected SUV was >1.1. Needle biopsy indicated poorly differentiated adenocarcinoma. SUV = standardized uptake values.

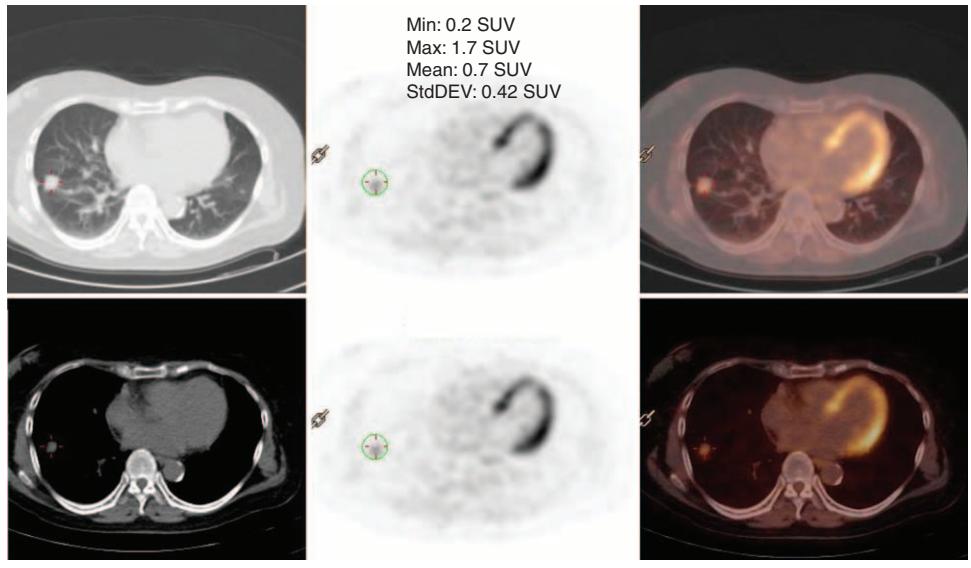

FIGURE 3. Female, 75 years' old, with cough, chest distress, shortness of breath for 2 weeks. Chest computed tomography showed a nodule with irregular shape in inferior lobe of right lung 1 week ago. Fluorine 18-fluorodeoxyglucose uptake was slightly increased. SUVmax was 1.7, liver SUVmax was 1.4, and corrected SUV is >1.1. Needle biopsy indicated grade II peripheral adenocarcinoma SUV = standardized uptake values.

our study showed that the corrected SUV was significantly higher in malignant cases than in benign cases ($P < 0.05$), which suggests that a high corrected SUV value in a solitary peripheral pulmonary lesions may indicate malignancy. Using a corrected SUV of 1.1 as the threshold, the sensitivity, specificity, positive predictive value, and negative predictive values were higher than when using an SUVmax of 2.5 as the threshold. The accuracy rate using an SUVmax of 2.5 as the threshold was 88.7% in this study; in addition, 3 malignant cases were misdiagnosed as benign, and 5 benign cases were misdiagnosed as malignant. The accuracy rate using the corrected SUV of 1.1 as the threshold was 98.5%, with only 1 case being misdiagnosed as malignant. The difference between the accuracy using an SUVmax of 2.5 and a corrected SUV of 1.1 as the threshold was significant ($P < 0.05$). These results suggest that the corrected SUV may be valuable for diagnosing pulmonary lesions in clinical practice.

It has been demonstrated in many prior studies that the size of the primary lesion is correlated with SUV.[18,22–25] As proposed by Vesselle et al,[25] glucose metabolism reflects the

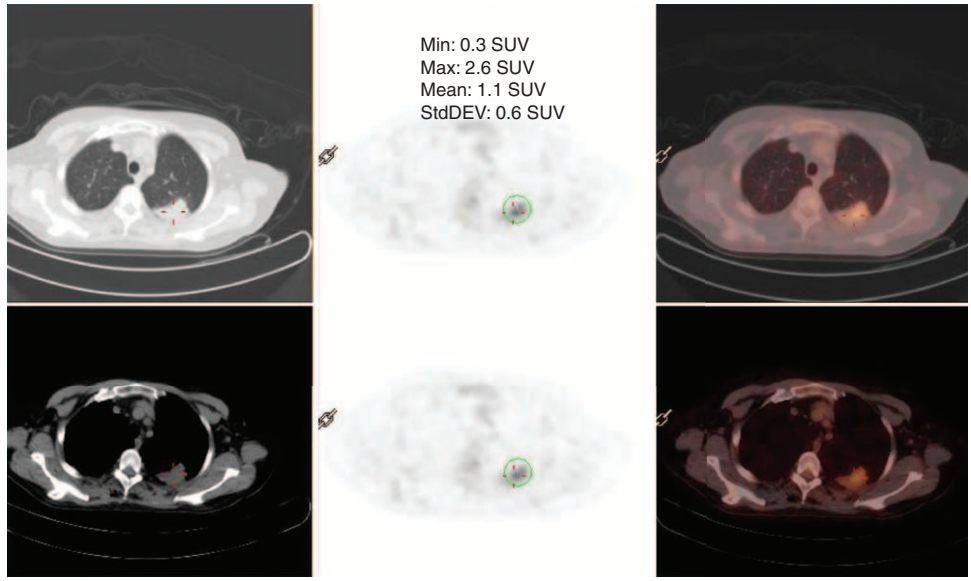

FIGURE 4. Female, 69 years' old, with cough, expectoration accompanied by hemoptysis for half a month. A mass with thin and long burrs was observed in superior lobe of the left lung. Fluorine 18-fluorodeoxyglucose uptake was slightly increased. SUVmax was 2.6, liver SUVmax was 3.2, and corrected SUV was <1.1. Needle biopsy indicated organizing pneumonia. SUV = standardized uptake values.

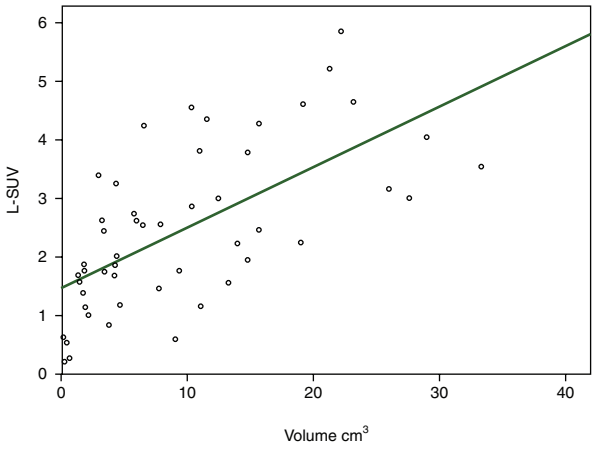

FIGURE 5. Correlation of the corrected SUV and the lesion volume. L-SUV represents the liver- corrected SUV. SUV = standardized uptake values.

activity of tumor cell proliferation, and a lesion's SUV is positively correlated with its proliferation rate. In this study, the results indicate that lesion size is indeed positively correlated with SUV, that is, the bigger lesion, the larger the SUV. Port et al[26] reported that the pathologic type of lung cancer is also an important predictive factor of SUV. Thus, our study aimed to clarify the correlation between SUV and lesion size in lung adenocarcinoma, and the correlation factor was larger when other types of lung cancer were excluded.

Studies have shown that respiratory movements can potentially result in the underestimation of pulmonary lesion SUV.[27] Several methods have been investigated to manage this respiratory motion problem, including the respiratory gating technique,[28] CT protocol-based methods,[29–32] and breathing instructions.[33] Due to various reasons, we did not adopt the respiratory gating technique or CT protocol-based methods. However, to minimize the impact of respiratory motion on SUV, we encouraged the patients to adopt modest, quiet breathing to minimize the respiratory motion. In addition, we avoided lesions at the bottom of the lung because they are markedly affected by respiratory motions.[34]

The diagnosis of a peripheral lung lesion is one of the challenges in clinical practice. For peripheral lung lesions that do not show significant changes on long-term follow-up observations, clinicians are hesitant about whether to perform surgery. Because early diagnosis and early treatment are very important for improving prognosis, radiologists have always made efforts to increase diagnostic efficiency in peripheral lung lesions. Our study suggests 2 important points. First, because there are many factors influencing SUVmax, the diagnosis of benign and malignant lesions cannot be based on the lesion's SUVmax alone, but the corrected SUV can be utilized to increase diagnostic accuracy. Second, lung lesion SUV is positively correlated with lesion size, that is, the larger the lesion, the larger the SUV.

TABLE 3. Correlation between the SUV and the lesion volume

	Diameter		Volume	
	***r* Value**	***P* Value**	***r* Value**	***P* Value**
SUVmax	0.616	0.000	0.536	0.000
SUVave	0.644	0.000	0.617	0.000
Corrected SUV	0.609	0.000	0.523	0.000

SUVave = average standardized uptake value, SUVmax = maximum standardized uptake value.

TABLE 4. Correlation between the SUV and the volume of adenocarcinoma

	Diameter		Volume	
	***r* Value**	***P* Value**	***r* Value**	***P* Value**
SUVmax	0.507	0.006	0.565	0.001
SUVave	0.555	0.002	0.621	0.000
Corrected SUV	0.601	0.001	0.656	0.000

SUVave = average standardized uptake value, SUVmax = maximum standardized uptake value.

REFERENCES

1. Koolen BB, Vogel WV, Vrancken Peeters MJ, et al. Molecular imaging in breast cancer: from whole-body PET/CT to dedicated breast PET. *J Oncol.* 2012;2012:438647.
2. Kosaka T, Yamaki E, Tanaka S, et al. Preoperative 18F-fluorodeoxyglucose positron emission tomography can predict the tumor malignancy of small peripheral lung cancer. *Ann Thorac Cardiovasc Surg.* 2014;20:968–973.
3. Padma S, Sundaram PS, George S. Role of positron emission tomography computed tomography in carcinoma lung evaluation. *J Cancer Res Ther.* 2011;7:128–134.
4. Kim SK, Allen-Auerbach M, Goldin J, et al. Accuracy of PET/CT in characterization of solitary pulmonary lesions. *J Nucl Med.* 2007;48:214–220.
5. Keyes JW Jr. SUV: standard uptake or silly useless value? *J Nucl Med.* 1995;36:1836–1839.
6. Lee JR, Madsen MT, Bushnel D, et al. A threshold method to improve standardized uptake value reproducibility. *Nucl Med Com.* 2000;21:685–690.
7. Ramos CD, Erdi YE, Gonen M, et al. 18F-FDG PET standardized uptake values in normal anatomical structures using iterative reconstruction segmented attenuation correction and filtered back-projection. *Eur J Nucl Med.* 2001;28:155–164.
8. Young H, Baum R, Cremerius U, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. *Eur J Cancer.* 1999;35:1773–1782.
9. Paquet N, Albert A, Foidart J, et al. Within-patient variability of 18F-FDG: standardized uptake values in normal tissues. *J Nucl Med.* 2004;45:784–788.
10. Zasadny KR, Wahl RL. Standardized uptake values of normal tissues at PET with 2-[fluorine-18]-fluoro-2-dexoy-D-glucose: variations with body weight and a method for correction. *Radiology.* 1993;189:847–850.
11. Jemal A, Siegel R, Ward E, et al. Cancer statistics. *CA Cancer J Clin.* 2009;59:225–249.
12. Ambrosini V, Nicolini S, Caroli P, et al. PET/CT imaging in different types of lung cancer: An overview. *Eur J Radiol.* 2012;81:988–1001.

13. Scheepers A, Joost HG, Schurmann A. The glucose transporter families SGLT and GLUT: molecular basis of normal and aberrant function. *J Parenter Enteral Nutr.* 2004;28:364–371.
14. Chandler JD, Williams ED, Slavin JL, et al. Expression and localization of GLUT1 and GLUT12 in prostate carcinoma. *Cancer.* 2003;97:2035–2042.
15. Kim SJ, Lee HW, Kim DC, et al. Significance of GLUT1 expression in adenocarcinoma and adenoma of the ampulla of Vater. *Pathol Int.* 2008;58:233–238.
16. Amann T, Maegdefrau U, Hartmann A, et al. GLUT1 expression is increased in hepatocellular carcinoma and promotes tumorigenesis. *Am J Pathol.* 2009;174:1544–1552.
17. Kumar A, Dutta R, Kannan U, et al. Evaluation of mediastinal lymph nodes using F-FDG PET-CT scan and its histopathologic correlation. *Ann Thorac Med.* 2011;6:11–16.
18. Kim SC, Machac J, Krynyckyi BR, et al. Fluoro-deoxy-glucose positron emission tomography for evaluation of indeterminate lung nodules: assigning a probability of malignancy may be preferable to binary readings. *Ann Nucl Med.* 2008;22:165–170.
19. Boellaard R. Standards for PET image acquisition and quantitative data analysis. *J Nucl Med.* 2009;50(Suppl 1):11S–20S.
20. Wahl RL, Jacene H, Kasamon Y, et al. From RECIST to PERCIST:evolving considerations for PET response criteria in solid tumors. *J Nucl Med.* 2009;50(Suppl 1):122S–150S.
21. Laffon E, Adhoute X, de Clermont H, et al. Is liver SUV stable over time in ^{18}F-FDG PET imaging? *J Nucl Med Technol.* 2011;39:258–263.
22. Apostolova I, Wiemker R, Paulus T, et al. Combined correction of recovery effect and motion blur for SUV quantification of solitary pulmonary nodules in FDG PET-CT. *Eur Radiol.* 2010;20:1868–1877.
23. Hara T, Kosaka N, Suzuki T, et al. Uptake rates of 18F-fluorodeoxyglucose and 11C-choline in lung cancer and pulmonary tuberculosis: a positron emission tomography study. *Chest.* 2003;124:893–901.
24. Li Y, Su M, Li F, et al. The value of 18F-FDG-PET/CT in the differential diagnosis of solitary pulmonary nodules in areas with a high incidence of tuberculosis. *Ann Nucl Med.* 2011;25:804–811.
25. Vesselle H, Schmidt RA, Pugsley JM, et al. Lung cancer proliferation correlates with [F-18]fluorodeoxyglucose uptake by positron emission tomography. *Clin Cancer Res.* 2000;6:3837–3844.
26. Port JL, Andrade RS, Levin MA, et al. Positron emission tomographic scanning in the diagnosis and staging of non small cell lung cancer 2 cm in size or less. *J Thorac Cardiovasc Surg.* 2005;130:1611–1615.
27. Erdi YE, Nehmeh SA, Pan T, et al. The CT motion quantitation of lung lesions and its impact on PET-measured SUVs. *J Nucl Med.* 2004;45:1287–1292.
28. Nehmeh SA, Erdi YE, Ling CC, et al. Effect of respiratory gating on reducing lung motion artifacts in PET imaging of lung cancer. *Med Phys.* 2002;29:366–371.
29. Lagerwaard FJ, Van Sornsen de Koste JR, Nijssen-Visser MR, et al. Multiple ''slow'' CT scans for incorporating lung tumor mobility in radiotherapy planning. *Int J Radiat Oncol Biol Phys.* 2001;51:932–937.
30. Nye JA, Esteves F, Votaw JR. Minimizing artifacts resulting from respiratory and cardiac motion by optimization of the transmission scan in cardiac PET/CT. *Med Phys.* 2007;34:1901–1906.
31. Cook RA, Carnes G, Lee TY, et al. Respiration-averaged CT for attenuation correction in canine cardiac PET/CT. *J Nucl Med.* 2007;48:811–818.
32. Huang TC, Mok GS, Wang SJ, et al. Attenuation correction of PET images with interpolated average CT for thoracic tumors. *Phys Med Biol.* 2011;56:2559–2567.
33. Nehmeh SA, Erdi YE, Meirelles GS, et al. Deep-inspiration breath-hold PET/CT of the thorax. *J Nucl Med.* 2007;48:22–26.
34. Torizuka T, Tanizaki Y, Kanno T, et al. Single 20-second acquisition of deep-inspiration breath-hold PET/CT: clinical feasibility for lung cancer. *J Nucl Med.* 2009;50:1579–1584.