Nuclear Science and Techniques **21** (2010) 306–311

Dual time point FDG PET imaging in evaluating pulmonary nodules with low FDG avidity

CHEN Xiang ZHAO Jinhua* SONG Jianhua XING Yan
WANG Taisong QIAO Wenli

Department of Nuclear Medicine, Shanghai First People's Hospital, Shanghai Jiaotong University, Shanghai, China

Abstract A standardized uptake value(SUV) of 2.5 is frequently used as criteria to evaluate pulmonary lesions. However, false results may occur. Some studies have shown the usefulness of delayed PET for improving accuracy, while others recently have shown fewer promising results. This study was designed to investigate the accuracy of dual time point (DTP) FDG PET imaging in the evaluation of pulmonary lesions with an initial SUV less than 2.5. DTP FDG PET studies were conducted about 1 and 2 hours after FDG injection, and pulmonary lesions with an initial SUV less than 2.5 were identified. Nodules with pathologic results or imaging follow up were included. The differences in SUV and retention index (RI) between benign and malignant pulmonary lesions were analyzed. Receiver operating characteristics (ROC) analysis was performed to evaluate the discriminating validity of SUV and RI. 51 lesions were finally included. A RI greater than 0% was observed in 64% of the benign lesions; 56% had a RI greater than 10%. Among the malignancies, 80.8% had a RI greater than 0%, and 61.5% had a RI greater than 10%. We found no significant differences in SUV and RI between benign and malignant lesions. The area under the ROC curve did not differ from 0.5 whether using SUV or the retention index. Utilizing a SUV increase of 10%, the sensitivity was 61.5%, specificity 44% and accuracy was 52.9%. Dual time point FDG PET may not be of benefit in the evaluation of pulmonary nodules with low FDG avidity.

Key words Dual time point; Delayed imaging; FDG; Positron emission tomography; Lung nodules

1 Introduction

^{18}F-FDG PET has demonstrated its use of differentiating benign and malignant lung lesions. A standardized uptake value (SUV) of 2.5 is often used as criteria for malignancy in interpreting the images of FDG PET. However, FDG is not a tumor-specific radiotracer. Increased FDG uptake can be seen in numerous inflammatory or infectious processes, whereas some well-differentiated malignancies (bronchoalveolar carcinoma, well-differentiated adenocarcinoma, and carcinoid tumors) may not demonstrate high FDG uptake. Some authors have claimed that dual time point imaging may improve the accuracy of FDG PET[1–3], because malignant lesions showed increased SUV over time while benign lesions showed decreased or stable SUV over time, but other groups obtained less promising results when looking specifically at lesions with low FDG uptake[4,5].The purpose of our study was to investigate the accuracy of dual time point FDG PET imaging for determining the nature of pulmonary nodules when the initial 1-h maximum SUV is less than 2.5.

2 Patients and methods

2.1 Patients

All patients who underwent dual time point FDG PET of pulmonary nodules from June 2007 to August 2009

* Corresponding author. *E-mail address:* zjh1963@gmail.com
Received date: 2010-07-15

at our institution were retrospectively reviewed. The enrolled patients met all the criteria as follows: 1) without a history of known malignancy; 2) receiving PET/CT scan for either initial assessment of an indeterminate pulmonary nodule, or follow-up of indeterminate pulmonary nodules; 3) the pulmonary nodules in diameter of no more than 3 cm, and less than 2.5 of a 1-h maximum SUV; and 4) the pulmonary nodules of pathological results or with sufficient clinical follow up.

2.2 ^{18}F-FDG PET/CT scan

Imaging from vertex of the head to mid thighs was obtained using an integrated in-line PET/CT scanner (Discovery; GE Healthcare STE PET/CT). All patients ingested nothing but water for approximately 6 h. Serum glucose level was measured before injection of the radiotracer to ensure a level of less than 150 mg/dL. Image acquisition for the scan started at ~60 min after injection of 4.07–4.44 MBq/kg (0.11–0.12 mCi/kg) of FDG. Two hours after injection, a second CT was obtained (limited to the chest) followed by PET of the chest. Reconstructed images were obtained by ordered -subset expectation maximization (OSEM) technique using 8 subsets and 2 iterations in a 128 × 128 matrix for PET and 512×512 matrix for CT. Emission scanning for the PET was performed moving caudal to cranial with 3min/bed acquisitions.

2.3 Image Interpretation

Four nuclear medicine physicians were involved in the interpretation of the studies. All were fellowship trained and board certified in nuclear medicine. The region of interest was drawn in the pulmonary nodules on the slice demonstrating maximum intensity. Size and 1-h and 2-h SUVs of the pulmonary nodules were recorded. All SUVs was maximum SUV. The retention index (RI) in the pulmonary nodules was calculated by RI = [(2-h SUV – 1-h SUV)/1-h SUV]×100%.

Maximal SUV was chosen for analysis because it is more reproducible than mean SUV. Since the goal of this study was to quantify the diagnostic benefit of DTP, so the information provided by CT was not used for diagnosis.

Determination of benignity or malignancy of lesions was based upon the criteria of (1) histology in cases of tissue sampling, (2) disappearance or improvement of lesions without intervening oncologic therapy, and (3) disappearance of lesions after anti-tuberculosis therapy.

2.4 Statistical Considerations

Significance of the differences in SUV and RI between benign and malignant pulmonary nodules was statistically analyzed with the T test. Statistical significance was set at $P<0.05$. The ROC curve was used to evaluate SUV and RI suitable as a cutoff for malignancy.

3 Results

Among the 51 nodules, which met the selection criteria and were included in the study, 9 nodules were smaller than 1cm, 25 were 1–2 cm, and 17 were over 2 cm, while 25 nodules were benign and 26 were malignant (Table 1). The differences in 1-h SUV, 2-h SUV, RI, and size between the benign and malignant pulmonary nodules were not statistically significant (Table 2).

It was found that 16 (64%) of the 25 benign lesions had further increases in SUV on delayed images (RI > 0%). 14 of the 25(56%) benign lesions had a RI greater than 10% (Fig.1, Fig.2). 21 (80.8%) of the 26 malignant lesions exhibited further increases in maximal SUV on delayed images. 16 (61.5%) of the 26 malignant lesions had a RI greater than 10% (Fig.3). We analyzed the RI value for differenting malignant and benign pulmonary nodules, using threshold of 0%, 10%, 20% and 30%, but all of them could not come to satisfactory diagnostic efficacy (Table 3). ROV curve analysis showed that the AUC (area under the receiver operating characteristic curve) did not differ from 0.5, which was the half probability, whether using SUV or RI (Table 4, Fig.4). No clear cutoff was found due to the decline in sensitivity and 1-specificity as RI and SUV increased.

Table 1 Type of pulmonary lesions included in dual time point PET imaging analysis.

Pathology	Malignant	Benign
Adenocarcinoma	13	
Bronchoalveolar carcinoma	11	
Quamous cell carcinoma	2	
Focal fibrosis		2
Sclerosing hemangioma		1
Hamartoma		1
Adenoma		1
Tuberculous granuloma		7
Fungal granuloma		1
Inflammation		2
Disappearance or improvement of lesions without intervening oncologic therapy		7
Disappearance of lesion after anti-tuberculosis therapy		3
Total	26	25

Table 2 Comparison of ^{18}F-FDG PET results for benign and malignant pulmonary nodules.

Nature	Size(cm)	1-h SUV	2-h SUV	Retention index(%)
Benign(n=25)	1.54±0.58	1.67±0.58	1.90±0.84	19.33±25.06
Malignant(n=26)	1.79±0.55	1.60±0.58	1.88±0.80	22.67±23.76
P	0.15	0.66	0.93	0.63

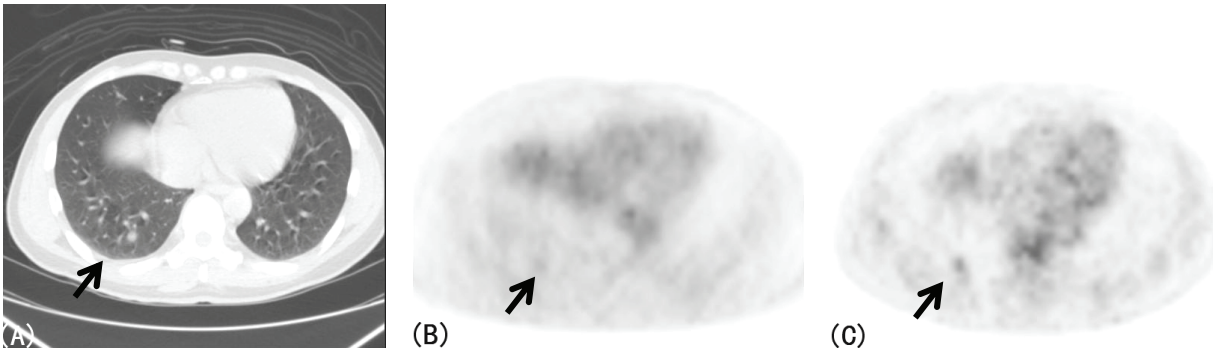

Fig. 1 Noncontrast axial CT (A) showing a 8-mm indeterminate right lower lobe pulmonary nodule, with SUVs of 0.7 and 1.6 on 1-h (B) and 2-h imaging (C), respectively. The patient had a surgery and the histopathologic result was non-tuberculous granuloma.

Fig. 2 Noncontrast axial CT(A) showing a 1.5×1.3 cm indeterminate left lower lobe pulmonary nodule, with SUVs of 2.1 and 3.6 on 1-h (B) and 2-h imaging (C), respectively. The patient had a surgery and the histopathologic result was tuberculous granuloma.

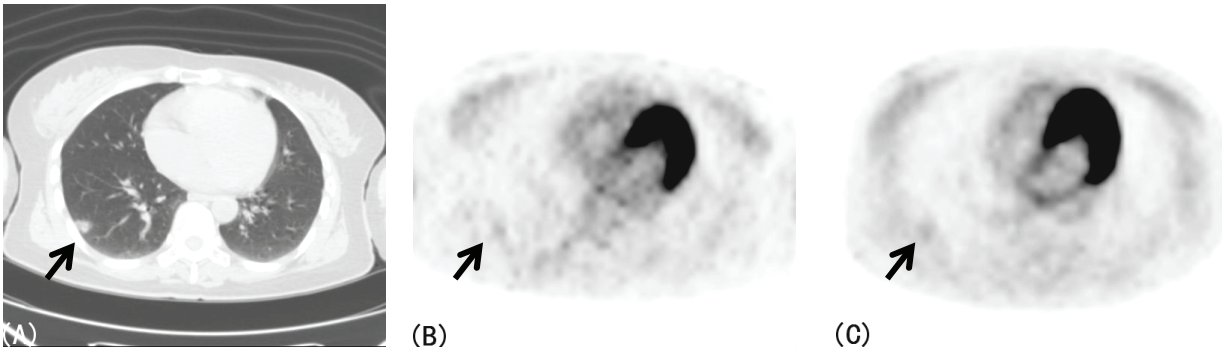

Fig. 3 Noncontrast axial CT(A) showing a 1.2-cm indeterminate right lower lobe pulmonary nodule, with SUVs of 0.7 and 1.0 on 1-h (B) and 2-h imaging (C), respectively. The patient had a surgery and the histopathologic result was bronchioalveolar cell carcinoma without lymphatic metastasis.

Table 3 Threshold of retention index on the diagnostic efficacy.

Retention index	Sensitivity	Specificity	Accuracy
>0%	80.8%(21/26)	36%(9/25)	58.80%
>10%	61.5%(16/25)	44%(14/25)	52.90%
>20%	50%(13/26)	60%(15/25)	54.90%
>30%	23%(6/26)	80%(20/25)	51.00%

Table 4 Comparison of AUC of ROC curves between SUV and RI in discrimination of the benign or malignant of pulmonary nodules.

SUV and RI	Area under the curve(AUC)	*P* value
1-hour SUV	0.462	0.638
2-hour SUV	0.493	0.932
Retention index	0.584	0.304

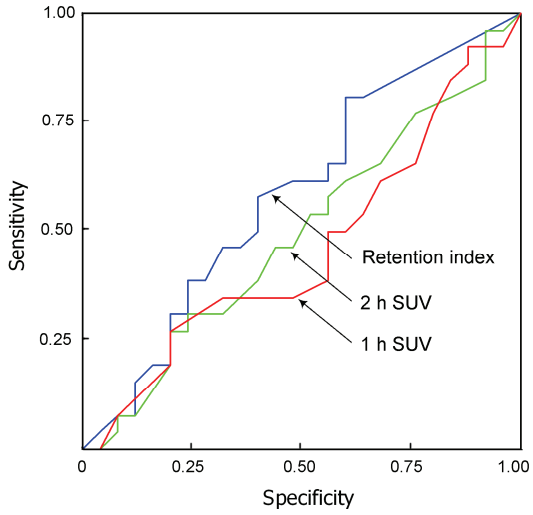

Fig.4 The ROC curve for retention index, 1-h SUV, and 2-h SUV.

4 Discussion

SUV is a semi-quantitative number that normalizes lesion uptake to the injected dose of radioactivity per unit of body weight. It is widely used to assess metabolic activity in lesions. A SUV of 2.5 is frequently used as the criteria for malignancy in evaluating pulmonary nodules with high accuracy[6,7]. However, there are many reports of malignant nodules with low FDG uptake such as bronchoalveolar carcinoma which typically demonstrate SUV<2.5 and benign lesions with SUV of >2.5 such as infectious or inflammatory nodules[3,7,8].

Since Zhuang H *et al.*[3] first proposed utilizing dual time point FDG PET imaging to distinguish malignant from benign lesions, multiple reports of dual time point FDG PET imaging in the evaluation of many kinds of tumors with encouraging results have

been published. Using a 10% increase in delayed SUV as the criteria for pulmonary malignancy, Matthies *et al*.[1] showed the sensitivity of 100% and the specificity of 89%. Adopting the same threshold, Xiu Y *et al*.[9] reported that in evaluation of lung nodules with only borderline increased FDG uptake (initial SUV < 2.5), dual time point imaging yielded a sensitivity of 81% and a specificity of 87%. Their results raised hope that dual point imaging might provide an accurate means for identifying malignant pulmonary nodules with low FDG uptake. Unfortunately, recent two studies do not support the claim, using a 10% threshold, they demonstrated a sensitivity of 40% and 61%, and a specificity of 62% and 58%, respectively[4,5].

Our results demonstrate similar findings to Chen C J and Cloran F J *et al*.[4,5], that the use of dual time point imaging does not provide significant improvement in distinguishing malignant from benign nodules with low FDG avidity. We found no significant difference in RI between benign and malignant nodules. ROC analysis showed that SUV and RI are not useful for making discrimination. Utilizing the threshold of 10%, our study demonstrated a sensitivity of 61.5% and a specificity of 44% which is consistent with Chen C J and Cloran F J *et al*. Therefore our results do not support the use of dual time point imaging for further assessment of pulmonary nodules with low FDG uptake.

Although prior studies have suggested the utility of dual time point imaging in pulmonary nodules[1–3], our results did not demonstrate the same conclusion in those pulmonary nodules with low FDG avidity. The existence of granulomatous diseases in benign lesions may be one of the reasons. Many clinical observations have shown that granulomatous inflammation presents persistently increased FDG uptake just as malignant lesions and human and animal studies have shown substantial expression of hexokinase in granulomatou tissue which explain the further increase in FDG uptake[4,10]. But our and Cloran's study population demonstrated a preponderance of non-granulomatous lesions in benign nodules[5], therefore there are some other factors which impact the efficiency of dual time point imaging.

We think that the physiologic differences between lesions with high FDG uptake and those with low FDG uptake (upregulation of glucose transporter 1 and increased hexoskinase expression) may be the factors for changes in FDG uptake over time. Thus, lesions with increased GLUT1 and hexoskinase will tend to be more FDG avid on standard PET imaging and, demonstrate increasing activity on dual time point imaging. The change of SUV may be smaller in lesions with low FDG avidity than in those with high FDG avidity. On the other hand many factors can affect the accurate determination of SUV[11], such as the patient's serum glucose levels, insulin levels, the time interval between FDG injection and image acquisition, and partial volume effects [12–15]. Considering the formula for computing RI and the low 1-h SUV, even small change of SUV may impact the RI. So the factors that affect SUV may lead to the non-negligible change of RI and interfere with the diagnostic value of dual time point imaging. Malignant lesions used to show further FDG uptake in delayed image, but in our study 5 of 26 malignancies showed the decreased SUV on delayed PET image. Therefore, variability of the RI may be one of the reasons.

Our study had limitations. For example, the data was based on retrospective data and did not reflect ideal prospective data and we included only nodules with follow up results and this might cause selection bias. Additionally, the total number of enrolled lesions with low FDG upake was somewhat small (51), but larger than Cloran F J *et al*. (45). A larger population sampling with a substantially larger number of varied benign and malignant pulmonary lesions is needed to verify our findings.

5 Conclusions

Our study supports the idea that dual time point PET may not provide significant improvement in differentiating between benign and malignant pulmonary nodules with an initial SUV uptake less than 2.5. For them dual time point imaging is not recommended and the information provided by CT may be more important.

References

1 Matthies A, Hickeson M, Cuchiara A, *et al*. J Nucl Med, 2005, **43**: 871–875.

2 Kubota K, Itoh M, Ozaki K, *et al* . Eur J Nucl Med, 2005, **28**: 696–703.

3 Zhuang H, Pourdehnad M, Lambright ES, *et al*. J Nucl Med, **42**: 1412–1417.

4 Chen CJ, Lee BF, YaoWJ, *et al*. AJR, 2008, **191**: 475–479.

5 Cloran FJ, Banks KP, Song WS, *et al*. Lung Cancer, 2010, **68**: 66–71.

6 Patz EF Jr, Lowe VJ, Hoffman JM, *et al*. Radiology, 1993, **188**: 487–490.

7 Bryant AS, Cerfolio RJ. Ann Thorac Surg, 2006, **82**: 1016 –1020.

8 Higashi K, Ueda Y, Seki H, *et al*. J Nucl Med, 1998, **39**: 1016–1020.

9 Xiu Y, Bhutani C, Dhurairaj T, *et al*. Clin Nucl Med, 2007, **32**: 101–105.

10 Sun YL, Jan ML, Kao PF, *et al*. Kaohsiung J Med Sci, 2005, **21**: 258–266.

11 Acton PD, Zhuang H, Alavi A. Radiol Clin North Am,2004, **42**: 1055–1062.

12 Langen KJ, Braun U, Rota Kops E, *et al*. J Nucl Med, 1993, **34**: 355–359.

13 Lindholm P, Minn H, Leskinen-Kallio S, *et al*. J Nucl Med, 1993, **34**: 1– 6.

14 Boerner AR, Weckesser M, Herzog H, *et al*. Eur J Nucl Med, 1999, **26**: 226–230.

15 Hickeson M, Yun MJ, Matthies A, *et al*. Eur J Nucl Med Mol Imaging, 2000, **29**: 1639–1647.