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ORIGINAL ARTICLE **CME**

Dual-phase Fluorodeoxyglucose Positron Emission Tomography / Computed Tomography for Differentiation of Tuberculoma from Malignancy in Patients Presenting with Solitary Pulmonary Nodules: Local Experience in a Single Centre

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ABSTRACT

Objectives: *To evaluate whether dual-phase fluorodeoxyglucose (FDG) positron emission tomography / computed tomography (PET/CT) can differentiate tuberculoma from malignancy in patients presenting with solitary pulmonary nodules.*

Methods: *This was a retrospective study of patients referred to our centre for evaluation of a solitary pulmonary nodule from December 2003 to September 2008. FDG PET/CT studies were performed using a hybrid PET/CT scanner. Imaging was taken 1 hour and 3.5 hours after injection of the tracer. The maximum standardised uptake value (SUVmax) of the lung lesion in 1 hour and 3.5 hours imaging was designated as SUVe and SUVd, respectively. The difference between them (SUVd – SUVe) was designated as ΔSUV. Results were correlated with the final (histological or clinical) diagnoses. Patients with primary lung cancer and tuberculosis were selected for the analysis.*

Results: *A total of 26 patients (15 males, 11 females) were investigated during the study period. Among them, 21 (10 males, 11 females) had primary bronchogenic carcinoma and 5 had a tuberculoma (all males). They were followed up for a mean duration of 37 months (range, 6 to 63 months). The malignant nodules had a mean SUVe of 5.2 (range, 0.7 to 15.7) and mean SUVd of 6.5 (range, 0.7 to 19.7), respectively. Tuberculomas had a mean SUVe of 5.1 (range, 1.4 to 9.1) and mean SUVd of 5.6 (range, 1.0 to 8.9), respectively. No statistical significance was found between the two patient groups in terms of SUVe ($p = 0.871$, Mann-Whitney U test). The mean ΔSUV of malignant solitary pulmonary nodules was 1.3 (range, -1.2 to 7.7) while that of tuberculomas was 0.5 (range, -1.8 to 2.3). Thus, there was no statistically significant difference between the two groups in terms of ΔSUV ($p = 0.72$, Mann-Whitney U test).*

Conclusions: *Tuberculomas behave similarly to solitary malignant pulmonary nodules. Dual-phase FDG PET/CT cannot accurately differentiate between them.*

Key Words: *Carcinoma, bronchogenic; Fluorodeoxyglucose F18; Neoplasms; Solitary pulmonary nodule; Tomography, emission-computed*

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中文摘要

雙相氟化脱氧葡萄糖正電子發射/計算機斷層顯像分辨孤立性肺結節患者中的肺癌和結核瘤：本地單中心經驗分享

龔本霆、江萬銨、黃治平、朱競新、歐陽定勤、唐卓敏

目的：探討雙相氟化脱氧葡萄糖正電子發射/計算機斷層顯像（FDG PET/CT）是否能分辨孤立性肺結節患者中的肺癌和結核瘤。

方法：本回顧性研究包括有2003年12月至2008年9月因患有孤立性肺結節而轉介至本中心的病人。利用PET/CT聯合掃描機作出FDG PET/CT檢查。病人注射示踪劑1及3.5小時後作影像檢查，而肺部病變的最大標準化攝取值（SUVmax）分別設定為SUVe（1小時後）和SUVd（3.5小時後）。兩者的差值（即SUVd–SUVe）為ΔSUV。結果與最終診斷（即組織學或臨床）作相關性分析。患有原發性肺癌及肺結核的病人結果將用作分析用途。

結果：研究期間共有26名病人，包括15男11女，其中21人（10男11女）患有原發性支氣管癌，另5名男病人患有結核瘤。病人的隨訪期平均為37個月（介乎6至63個月）。惡性結節的SUVe平均值為5.2（介乎0.7至15.7）、SUVd平均值為6.5（介乎0.7至19.7）。結核瘤的SUVe平均值為5.1（介乎1.4至9.1）、SUVd平均值為5.6（介乎1.0至8.9）。比較兩組病人的SUVe值並無統計顯著性（$p = 0.871$，曼—惠特尼*U*檢定）。惡性孤立性肺結節的ΔSUV平均值為1.3（介乎-1.2至7.7），而結核瘤的相應值為0.5（介乎-1.8至2.3）。因此，兩個組別的ΔSUV值並無顯著統計學差異（$p = 0.72$，曼—惠特尼*U*檢定）。

結論：結核瘤的表現與惡性孤立性肺結節類似，所以雙相FDG PET/CT檢查並不能分辨兩種病患。

INTRODUCTION

Fluorodeoxyglucose (FDG) positron emission tomography / computed tomography (PET/CT) is playing a vital role in management of patients with various kinds of malignancies. One of its major clinical applications is detection and staging of bronchogenic carcinoma. In addition, it has an important role in characterisation of solitary pulmonary nodules (SPNs). In this study, they were defined as intraparenchymal lung lesions equal to or smaller than 3 cm in diameter, and not associated with atelectasis or adenopathy.

FDG PET/CT has been proven to be a useful non-invasive tool for differentiation of benign and malignant SPNs.[1-3] It is crucial to differentiate between the two as malignant SPNs have an overall mortality rate of up to 85%.[4] There are a number of well-known false-positive causes of enhanced FDG uptake, particularly associated with this clinical scenario. Infection or granulomatous disease such as tuberculoma can present as a hypermetabolic SPN in FDG PET imaging.[5,6] It is believed that dual-phase FDG PET study helps to differentiate the two as FDG uptake tends to decrease or remain stable in benign lesions, while FDG uptake of malignant lesions tends to increase with time.[7,8] In contrast to benign conditions causing false-positive FDG uptake, malignant lesions such as bronchoalveolar carcinomas or carcinoid tumours are associated with low FDG uptake. In our locality, the prevalence of tuberculosis (TB) is higher than that in other developed countries. According to the latest local statistics provided by the Centre for Health Protection, there were a total of 5132 new TB notifications in 2010; the notification rate being 72.6 per 100,000 inhabitants. By contrast, according to the latest local statistics provided by the Hong Kong Cancer Registry, there were 4365 new cases of lung cancers in 2009. Hence it is crucial to know whether FDG PET/CT has high accuracy in differentiating malignancy from pulmonary tuberculoma in patients referred because of a SPN. A recent study of 28 patients suffering from SPNs receiving dual-phase FDG PET/CT in a TB endemic region (Mainland China) found added value in SPNs with a standardised uptake value (SUV) of less than 2.5 at early phase.[9]

According to this article,[9] the addition of delayed phase scanning resulted in correct diagnosis of three malignant lesions with an initial SUV value of less than 2.5. The aim of our study was to assess if dual-phase PET/CT can accurately differentiate benign pulmonary tuberculoma from malignant SPN in our locality, which has a high TB prevalence rate.

METHODS

In this retrospective study, individuals referred for PET/CT examination to assess a solitary lung lesion with subsequent pathologically confirmed pulmonary tuberculoma or a solitary malignancy were recruited during the period December 2003 to September 2008. Pathological confirmation entailed either biopsy or a surgical specimen. All the patients had undergone contrast CT thorax before PET/CT examination. Patients with multiple lung nodules, positive mediastinal adenopathy or a known history of lung cancer diagnosed by conventional imaging (CT or magnetic resonance imaging) were excluded. There were a total of 26 patients (15 men and 11 women). Their ages ranged from 35 to 81 (mean, 59) years. The patient follow-up period ranged from 6 to 63 (mean, 37) months.

All patients were fasted at least six hours before intravenous FDG injection. Scanning was initiated 60 minutes after administration. Images were taken from the head to the proximal thigh with the PET/CT scanner (Discovery LS, GE Healthcare, USA) with a spatial resolution 6.6 mm in the centre of the field of view. FDG (370 MBq) was injected intravenously. Seven bed positions were performed with three minutes per bed position. In the delayed image, five minutes per bed position was performed in order to partially compensate for the count decay. A four-slice CT was performed for attenuation correction, lesion localisation and characterisation. The CT scanner had a rotating anode oil-cooled X-ray tube installed, which operated at 140 kV. It operated from 120 mA to 200 mA, according to the patient size. Rotate-fixed ring geometry was used. Images were acquired in the helical mode with slice thicknesses of 5 mm (beam coverage of 2 cm in each gantry rotation). Cross-sectional reconstruction images with matrix size of 512 × 512 were produced. The obtained images were reconstructed using an ordered subsets expectation maximisation iterative reconstruction algorithm. Regions of interests were drawn for FDG uptake quantification on visible

Table. Patient characteristics.

Patient No.	Sex	Age at examination (years)	Lesion size (mm)	SUVe	SUVd	ΔSUV	1-Year survival (%)
1	M	49	21	7.4	8.9	1.5	TB
2	M	47	20	9.1	7.3	-1.8	TB
3	M	35	15	1.4	1	-0.4	TB
4	M	80	30	4.6	6.9	2.3	TB
5	M	53	17	3.2	4	0.8	TB
6	M	72	15	15.7	17.8	2.1	Adeno CA
7	M	70	30	12.7	19.7	7.0	Adeno CA
8	M	68	25	7.5	10.1	2.6	Adeno CA
9	M	58	15	0.7	0.7	0	Adeno CA
10	F	57	10	4.1	5.5	1.4	Adeno CA
11	M	68	18	2.0	2.7	0.7	Adeno CA
12	F	45	14	3.7	4.2	0.5	Adeno CA
13	M	48	17	5.2	4	-1.2	SCLC
14	F	67	16	3.5	6	2.5	Adeno CA
15	F	69	18	1.6	2.3	0.7	Adeno CA
16	M	55	10	2.3	1.5	-0.8	Adeno CA
17	F	50	30	4.0	4.3	0.3	Adeno CA
18	M	53	28	9.8	9.7	-0.1	Adeno CA
19	M	81	23	2.8	3.7	-0.9	Adeno CA
20	F	63	21	2.0	1.8	-0.2	Adeno CA
21	F	58	27	6.2	6.5	0.3	Adeno CA
22	M	56	18	1.5	1.3	-0.2	Adeno CA
23	F	61	18	4.2	3.6	-0.6	Adeno CA
24	F	63	12	1.2	1.1	-0.1	Adeno CA
25	F	39	30	10.7	18.4	7.7	Adeno CA
26	F	56	26	8.6	11.8	3.2	Adeno CA

Abbreviations: SUV = standardised uptake value; SUVe = SUVmax in early (1 hour) image; SUVd = SUVmax in the delayed (3.5 hour) image; ΔSUV = SUVd – SUVe; TB = tuberculosis; Adeno CA = adenocarcinoma lung cancer; SCLC = small-cell lung carcinoma.

lesions with increased uptake, and the maximum SUV (SUVmax) was semi-quantitatively analysed with the equation:

$$SUV = \frac{A}{ID/BW}$$

where A represents the decay- and attenuation-corrected activity in tissue (in MBq per ml), ID represents the injected dose of FDG (in MBq), and BW represents the patient's body weight (in g).

In this study, PET/CT images were taken at 1 hour and 3.5 hours after FDG injection. SUVe was defined as the SUVmax in early (1 hour) image while SUVd was defined as SUVmax in the delayed (3.5 hour) image. ΔSUV was defined as SUVd minus SUVe. These values were used for further statistical analysis.

Statistical Analysis

The SUVe and ΔSUV for tuberculoma and malignant lesions were compared. The non-parametric Mann-Whitney test was used to compare SUVe as well as ΔSUV values in the two groups of patients. Statistical analysis was performed using the Statistical Package for the Social Sciences (Windows version 15.0; SPSS Inc, Chicago [IL], USA), and statistical significance was assumed when the p value was less than 0.05.

RESULTS

A total of 26 patients (15 males, 11 females) were recruited during the defined study period and their details are summarised in the Table. On histological examination, 21 patients (10 males, 11 females) had primary bronchogenic carcinoma and five had tuberculomas (all males). They were followed up for a mean duration of 37 (range, 6-63) months. Their mean size was 20 (ranged, 10-30) mm. The malignant nodules had a mean SUVe of 5.2 (range, 0.7-15.7) and a mean SUVd of 6.5 (range, 0.7-19.7). Tuberculomas had a mean SUVe of 5.1 (range, 1.4-9.1) and a mean SUVd of 5.6 (range, 1.0-8.9). As illustrated in Figure 1, there was no statistically significant difference between the two patient groups in terms of SUVe (p = 0.871). The mean ΔSUV of malignant SPNs was 1.3 (range, -1.2 to 7.7) while mean ΔSUV of tuberculoma was 0.5 (range, -1.8 to 2.3), and as illustrated in Figure 2 there was no statistically significant difference between the two patient groups (p = 0.72).

Among those with malignant SPNs, 12 and 8 patients respectively demonstrated interval increase and decrease in SUVmax. Among those with tuberculomas,

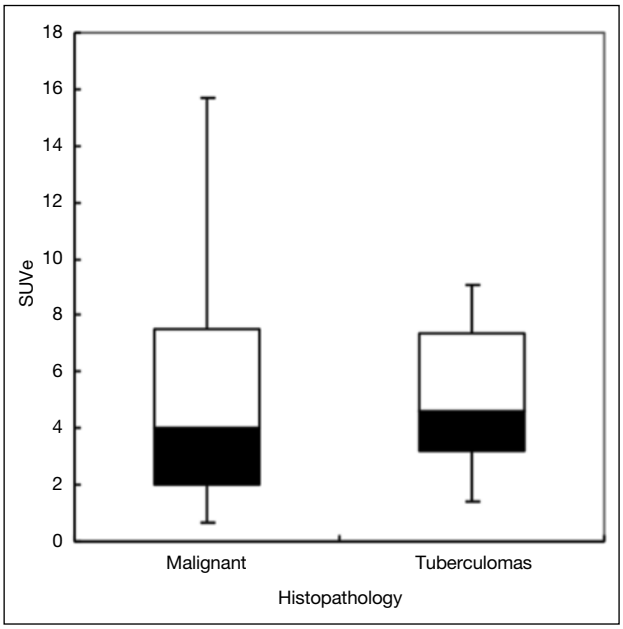

Figure 1. Comparison of SUVe in patients with malignant solitary pulmonary nodules and pulmonary tuberculomas. There is no statistically significant difference between the two groups (p = 0.871). SUVe = maximum standardised uptake value in early (1 hour) image. The horizontal lines within the boxes represent the medians, the lower and upper bounds of the boxes represent the 25th and 75th percentiles, and the I bars represent the range.

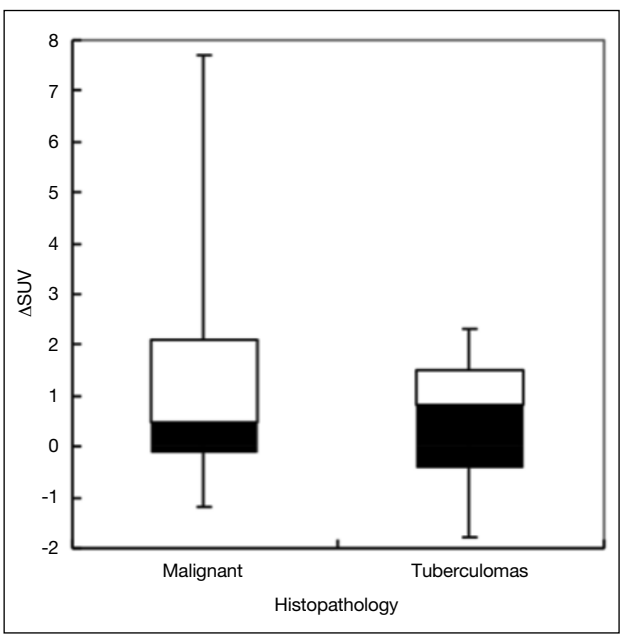

Figure 2. Comparison of ΔSUV in patients with malignant solitary pulmonary nodules and pulmonary tuberculomas. There is no statistically significant difference between the groups (p=0.72). ΔSUV = maximum standardised uptake value (SUVmax) in the delayed (3.5 hour) image – SUVmax in early (1 hour) image. The horizontal lines within the boxes represent the medians, the lower and upper bounds of the boxes represent the 25th and 75th percentiles, and the I bars represent the range.

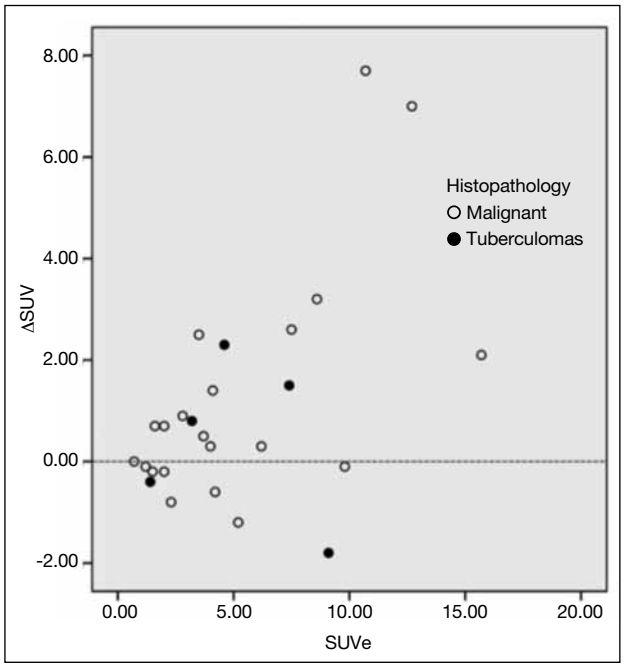

Figure 3. Plotting of ΔSUV against SUVe per patient.
Abbreviations: SUV = standardised uptake value; SUVe = SUVmax in early (1 hour) image; SUVd = SUVmax in the delayed (3.5 hour) image; ΔSUV = SUVd – SUVe.

three demonstrated interval increase while two patients demonstrated interval decrease in SUVmax. Plotting ΔSUV over SUVe per patient (Figure 3) suggested that increased and decreased SUVmax in delayed images occurred in both patient groups. Considerable overlap in SUVe and SUVd values in the two groups was evident, which jeopardises the clinical utility of dual-phase FDG PET/CT for this clinical scenario in our locality.

DISCUSSION

Characterisation of SPNs remains a challenge in the 21st century, particularly in TB endemic regions. Unlike most of the developed western countries, where the incidence of pulmonary tuberculoma is low, the prevalence rate of TB in our locality is high. According to local statistics, the number of new cases of TB reported annually is comparable if not significantly higher than the number of new cases of lung cancer. For local physicians, it is therefore important to differentiate the two types of lesions, as the subsequent management of these patients is very different.

PET has been emerged as a useful non-invasive imaging technique to differentiate benign and malignant lesions. We designed this study to discover whether FDG PET/CT, with the assistance of dual-phase technique, could accurately differentiate benign pulmonary tuberculomas and malignant SPNs. There have been studies suggesting that the dual-phase technique could improve the diagnostic accuracy of PET/CT for differentiating benign from malignant disease,[10-12] since malignancy usually demonstrated progressive FDG accumulation. This phenomenon was attributed to an increased ratio of hexokinase to glucose-6-phosphatase,[7] leading to a further rise of SUVmax in the delayed image. In our study, interestingly we found that three out of five pulmonary tuberculomas demonstrated increased FDG uptake in the delayed image (as illustrated in Figure 4). We deliberately performed the second image at 3.5 hour instead of 2 hours, to ensure an adequate delay (as previously reported).[13]

According to our study, both pulmonary tuberculoma and malignant SPNs shared similar metabolic behaviour. Sun et al[14] demonstrated a consistent and progressive rise in FDG accumulation in turpentine-induced granulomatous inflammation in dynamic PETs involving animals. Other studies demonstrated substantial expression of hexokinase in granulomatous tissue.[15,16] *Mycobacterium tuberculosis* was believed to be responsible for the progressive FDG accumulation in tuberculomas in the delayed imaging. High glucose levels are required to build their impermeable mycobacterial wall, characterised by an outer layer of mycolic acids.[17]

We found that the dual-phase technique was unreliable in differentiating the two types of lesions, which was consistent with other studies highlighting the limitations of the dual-phase technique.[18-20] Sathekge et al[21] found that dual time-point FDG PET/CT could not differentiate benign from malignant SPNs in TB endemic areas (such as South Africa). Chen et al[20] suggested that dual-phase FDG PET could not improve the diagnostic performance of PET for pulmonary diseases in geographic regions with a high risk of granulomatous inflammation. Had PET/CT been found useful in differentiating tuberculomas from malignant SPNs, undertaking futile biopsies and thoracotomy could be reduced. Based on our results, together with those of others, we believe that biopsies remain an essential tool for differentiating the two types of lesions.

This study had limitations. First, in order to accurately explore the efficacy of dual-phase FDG PET studies, we included only patients with pathological findings as the reference gold standard. However, this requirement

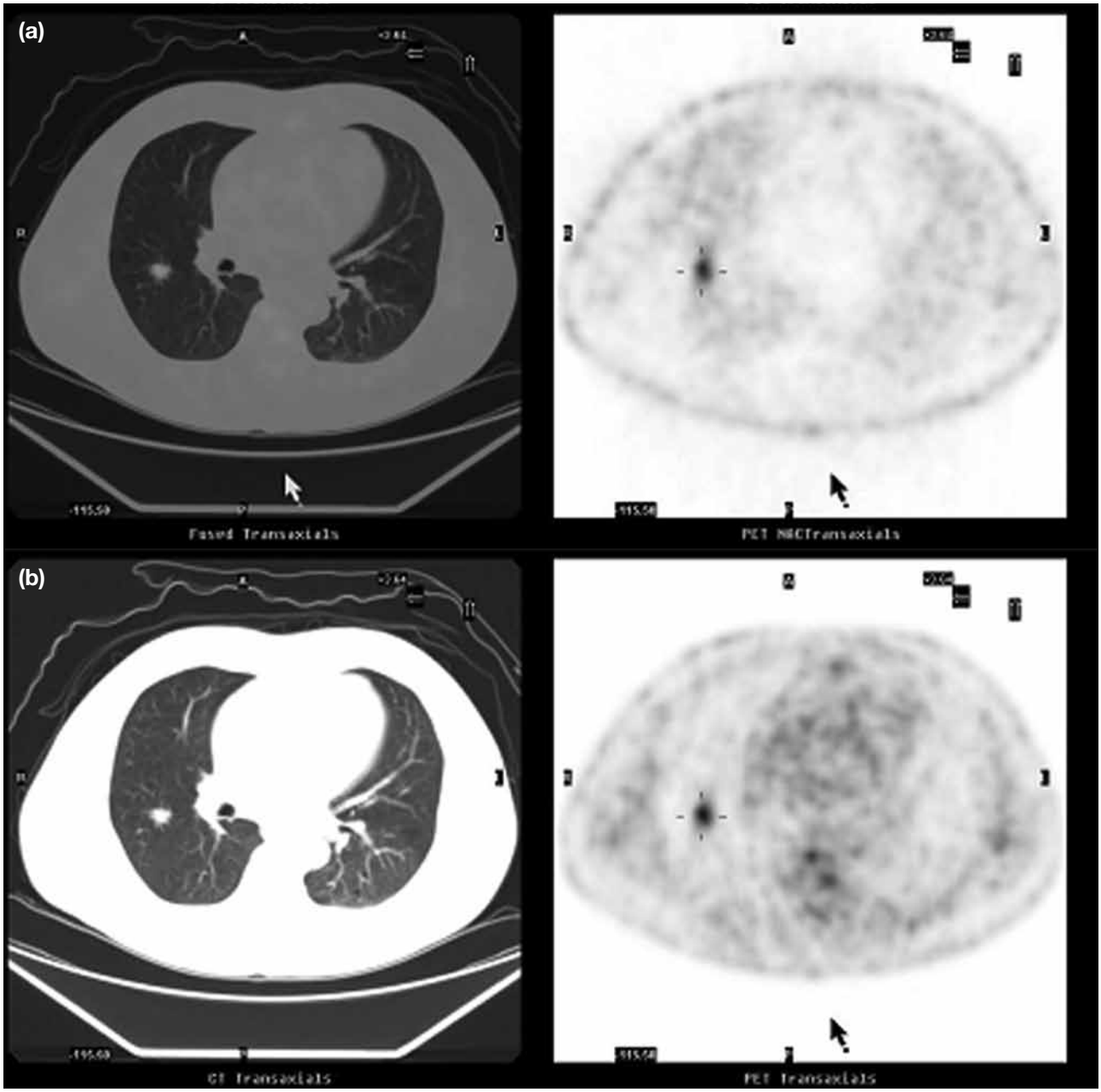

Figure 4. A 53-year-old man with a 1.7-cm solitary pulmonary nodule (SPN) in the right lung, which appears hypermetabolic in both (a) early (SUVmax 3.2) and (b) delayed (SUVmax 4.0) images. He is subsequently proven to suffer from tuberculoma. The delayed image demonstrates an interval increase in FDG uptake as illustrated, which shares the same characteristics as a malignant SPN.

excluded patients suffering from malignant nodules or tuberculomas without pathological findings. This requirement might have caused selection bias. Second, the number of patients included in this study was small. In fact, all 26 of our patients were referred for PET/CT because the underlying nature of the SPN could not be reliably ascertained from previous contrast CT thorax, and histological and microbiological studies. These patients therefore belonged to a highly selected group with SPNs of an unknown nature. Even with a small sample size, our study showed that pulmonary tuberculoma could demonstrate high FDG uptake similar to malignant SPNs. Pulmonary tuberculomas could also show interval increase in FDG metabolism in the delayed image. Conversely, malignant SPNs could show interval decrease in FDG metabolism in the delayed image. Thus, dual-phase FDG PET/CT was not reliable enough to differentiate between these

SPNs. Larger-scale studies are required to further strengthen our findings. Lastly, in this study we put less emphasis on the morphological CT features. Indeed, its ultimate aim was to ascertain whether there was a significant difference between the metabolic behaviour of malignant SPNs and pulmonary tuberculomas. In the delayed thoracic images, all the CT features remained static (e.g. Hounsfield unit, size, lesion morphology) while FDG metabolism would vary. However, this does not imply that the CT component of the PET/CT ratio has no role in assessing SPNs.

CONCLUSION

According to our data, pulmonary tuberculoma can demonstrate interval increase in FDG metabolism in the delayed image. Conversely, malignant SPNs can also demonstrate interval decrease in FDG metabolism in the delayed image. Therefore, dual-phase FDG PET/CT may not be reliable enough to differentiate pulmonary tuberculomas from malignant SPNs.

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