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Solitary pulmonary nodule evaluation with ^{99m}Tc-methoxy isobutyl isonitrile in a tuberculosis-endemic area

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ABSTRACT: **High prevalence of tuberculosis increases the odds for nonmalignant solitary pulmonary nodules (SPNs). Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose is the method of choice for the identification of malignant SPNs requiring curative surgery. However, PET is not widely available. Technetium-99m methoxy isobutyl isonitrile (MIBI) is inexpensive, widely available and shows increased uptake in malignant SPNs. The aim of the present study was to prospectively evaluate the diagnostic value of MIBI single photon emission computed tomography to distinguish between benign and malignant SPNs in a tuberculosis-endemic area.**

In total, 49 patients with radiologically indeterminate SPNs (single lesion $\leqslant$6 cm in diameter) were prospectively evaluated with MIBI. The final diagnosis was established with bronchoscopy, fine-needle aspiration, surgical resection or clinical follow-up for $\geqslant$2 yrs.

A total of 12 (92%) out of 13 malignant lesions showed increased uptake of MIBI, while no uptake was observed in 33 (92%) out of 36 benign lesions. MIBI uptake indicated malignancy with a sensitivity and specificity of 92% and a negative predictive value of 97%.

In this tuberculosis-endemic area, technetium-99m methoxy isobutyl isonitrile single photon emission computed tomography evaluation of solitary pulmonary nodules had a high negative predictive value. Therefore, it has the potential to prevent unnecessary surgical resections of benign nodules and serve as a low-cost alternative when positron emission tomography is not available.

KEYWORDS: **Diagnosis, lung cancer, solitary pulmonary nodule, technetium-99m-labelled methoxy isobutyl isonitrile, tuberculosis**

Most solitary pulmonary nodules (SPNs) are discovered incidentally on chest radiographs and practically all patients undergo further diagnostic evaluation, since malignancy cannot be ruled out [1]. Survival in bronchial carcinoma is closely related to the stage of the disease at the time of diagnosis and an SPN represents a potentially curable stage amenable to surgery. SPNs are also frequently encountered in patients infected with *Mycobacterium tuberculosis*. In populations with a high prevalence of tuberculosis (TB), routine exploratory surgery for benign SPNs potentially causes excess perioperative morbidity and mortality, as well as unnecessary costs for a healthcare system with limited financial resources.

The Cape Town Metropole (Cape Town, South Africa) has a very high prevalence and incidence of TB (678 patients per 100,000 individuals in 2003) as well as a high incidence of bronchial carcinoma, with ~27% of the population being active smokers. Radiological features detected on chest radiographs (CXR) and computed tomography (CT) are insufficient to reliably differentiate between benign and malignant SPNs. The best predictors of malignancy are a larger lesion diameter and the observation of fine linear strands extending outwards from the nodule (spiculated lesion). Conversely, laminated or central calcification patterns (granuloma), as well as popcorn lesions (hamartoma), are indicative of benign lesions. However, most SPNs do not clearly fit these criteria and are thus termed ''indeterminate'' [2]. Additional evaluations are needed for such lesions.

Fluorine-18 fluorodeoxyglucose (FDG)-positron emission tomography (PET) has become the method of choice to evaluate such SPN but availability and cost still limit its widespread use [3, 4]. There are also several reports indicating

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false-positive results of FDG-PET in patients with active TB [4–6]. Radiopharmaceuticals containing either technetium-99m (^{99m}Tc) or thallium-201 (^{201}Tl) are more affordable than FDG since they can be produced on site and do not need a cyclotron facility. These markers accumulate in lung carcinoma and, therefore, pulmonary lesions can be evaluated with widely available gamma cameras [7–11]. Methoxy isobutyl isonitrile (MIBI) is taken up primarily by mitochondria and studies have shown favourable characteristics in the evaluation of SPN, albeit only in settings with low incidence of benign lesions [10–12]. The present study was conducted to evaluate MIBI for the differentiation of benign from malignant pulmonary nodules in a population with high prevalence of TB and no access to a PET facility.

METHODS

Study design and patients

The present prospective single-centre study was performed at Tygerberg Academic Hospital, a tertiary university hospital in Cape Town, South Africa, with a drainage area of ~1.5 million people. Patients referred to the lung unit with single pulmonary lesions $\leqslant$6 cm in diameter on CXR were included if the lesion was an SPN completely surrounded by aerated lung, without evidence of satellite lesions, adenopathy or characteristic signs of malignant (spiculated margin) or benign (calcification: laminated, central or popcorn type) lesions [13]. Although the classical definition of SPNs considers lesions $\leqslant$3 cm, the present authors chose to investigate lesions $\leqslant$6 cm, since tuberculomas of nearly double that size have been reported [14]. Location and maximal diameter of all indeterminate SPNs were recorded from the chest CT and/or CXR prior to enrolment of patients. Written informed consent was obtained from all patients before inclusion in the study, which was approved by the Committee for Human Research of Stellenbosch University (Cape Town, South Africa).

Clinical and radiological examinations

The primary procedure for establishing a diagnosis was fibreoptic bronchoscopy after obtaining a contrasted chest CT. Patients with lesions that did not fulfil the definition of an SPN on CT were excluded. A radiologist without knowledge of previous results interpreted the CT images. Routine specimens obtained were sputum for microbiology and cytology, as well as bronchoscopic samples for microbiology, cytology and histopathology. Patients with an established diagnosis were treated accordingly. Patients with inconclusive results after routine work-up were presented to a panel of clinical experts (interdisciplinary tumour board) who decided on whether to recommend transthoracic fine-needle aspiration, surgical resection or observation with serial CXR for $\geqslant$2 yrs.

Imaging protocol

MIBI scanning was performed before any invasive diagnostic procedure. After intravenous administration of 740 MBq ^{99m}Tc-MIBI in the contralateral arm to the lesion, planar views of the chest area (anterior, posterior and left and right lateral) and single photon emission CT (SPECT) images of the chest were acquired. Image acquisition commenced 5–10 min after the administration of the radiopharmaceuticals using a dual-headed gamma camera (Helix; Elscint, Haifa, Israel) equipped with low-energy high-resolution collimators. The planar views were acquired for 5 min each. The acquisition parameters for the SPECT studies included a step-and-shoot mode over 30 min with 120 projection angles over 360° rotation, 15 s per frame acquisition time and a 64×64 matrix. No attenuation correction was carried out.

SPECT data were reconstructed by filtered back projection using a Butterworth filter with a cut-off frequency value of 0.8. SPECT studies were viewed in the coronal, axial and sagittal planes and in reprojection three-dimensional cine mode. Iterative reconstruction, currently the preferred method, only became available at the present authors' institution toward the end of the study period. In fact, the last 11 patients were analysed using both reconstruction methods but the results did not differ.

Definitions, scoring and statistical methods

A diagnosis was considered established when mycobacteria were recovered or cultured from a clinical specimen or on unequivocal microbiological, cytological or histopathological evidence obtained from biopsy or resection specimens from the lesion. The lesion was classified as granuloma when cytological or histological evidence of a chronic inflammatory process was documented and no increase in nodule size was observed during $\geqslant$2 yrs of radiological follow-up. Tuberculous granuloma met the same criteria, but acid-fast bacilli were detected and mycobacterial cultures were negative. Active TB was diagnosed when mycobacterial cultures were positive for samples obtained from the lesion and/or the lesion size diminished during anti-TB treatment. Malignant tumours were diagnosed when two independent pathologists diagnosed malignancy in a specimen obtained from the SPN. In a few cases with nondiagnostic specimens, radiological follow-up documenting lesion growth and/or metastatic spread was used to diagnose malignancy.

Planar and reconstructed SPECT images were evaluated for intensity of uptake and scored independently by two experienced nuclear medicine physicians (H. Bouma, A. Ellmann) as independent image readers. They were blinded to all diagnoses and laboratory results available at the time of image reading. Localisation of SPN and all radiological information (CXR and/or CT) were known to the two image readers at the time of evaluation of the SPECT scanning to classify the acquired images qualitatively (subjective visual evaluation) for abnormal accumulation of MIBI corresponding to the location of the nodule on the CXR or CT scan. Image assessment included subjective consideration of background activity in the field of view. Readers classified each scan for planar and SPECT images separately into one of four categories: 0=negative scan, no uptake in the region of interest; 1=minimal uptake; 2=intermediate uptake; and 3=high uptake in the region of interest. Categories 1–3 were considered positive. Positive scans were graded into three categories to permit stratified analysis of inflammatory lesions, which are often associated with a lower degree of uptake than malignant lesions. A consensus between readers was requested when individual readings lead to discordant categorisation between positive or negative scans. The mean MIBI score for each patient was calculated from the four values derived from separate assessments of planar and SPECT images (score range 0–3). Any score >0 represented a positive result. Negative and

positive results were compared with the clinical diagnosis as the gold standard. In a *post hoc* analysis, a MIBI score >1 was also used to define a positive result. Basic descriptive statistical tests were performed.

RESULTS

Patient population

Between August 2000 and November 2003, 53 consecutive patients met inclusion criteria. Of these, 49 had SPNs according to the present authors' definition. A total of 13 patients had a past history of TB. Four patients were excluded after CT scanning for having multiple lesions (two patients), pleural-based lesions (one patient) or lesions >6 cm in diameter (one patient). The demographical data and lesion characteristics of these 49 patients are presented in table 1. Seven nodules were >3 cm in diameter: four were malignant (3.5, 4.4, 5.0 and 5.8 cm) and three were benign (4.0, 4.5 and 6 cm).

Diagnosis and outcome

A histological, cytological or microbiological diagnosis was established at initial evaluation in 36 (73%) patients, and 13 (27%) patients were observed. In total, 14 patients underwent surgery, 42 underwent bronchoscopy and three received a transthoracic CT-guided needle biopsy. Some patients required >1 procedure for diagnosis. Table 2 summarises the diagnoses of the 49 patients investigated. Of these, 13 (27%) had malignant tumours (figs 1 and 2) and 36 (73%) had benign lesions.

Four patients with positive scans refused the recommended further invasive work-up and/or surgery and were followed radiologically. All showed progression of lesion size and/or metastasis. Two received palliative treatment and died, one refused treatment and one was lost to follow-up upon

TABLE 1 Descriptive statistics of patients evaluated with methoxy isobutyl isonitrile single photon emission computed tomography

Subjects	49
Males	29 (59)
Age yrs	54.2±14.4
SPN diameter cm	2.24±1.2
Location of SPN	
Right/left upper lobe	12/11
Middle lobe	5
Right/left lower lobe	9/12

Data are presented as n, n (%) or mean±SD, unless otherwise indicated. SPN: solitary pulmonary nodule.

TABLE 2 Distribution of solitary pulmonary nodules according to diagnosis and results from methoxy isobutyl isonitrile (MIBI) single photon emission computed tomography (SPECT) imaging

Clinical diagnosis	Patients n	Results from MIBI-SPECT
Malignant tumours	13	
Adenocarcinoma	6	True positive 12
Squamous cell carcinoma	1	
Nonsmall cell lung cancer	4	
Small cell lung cancer	1	
Poorly differentiated carcinoma	1	False negative 1
Benign lesions	36	
Granuloma	20	True negative 33
Tuberculous granuloma	11	
Rounded pneumonia	2	
Silicosis/granuloma	1	False positive 3
Active tuberculosis	1	
Aspergilloma	1	

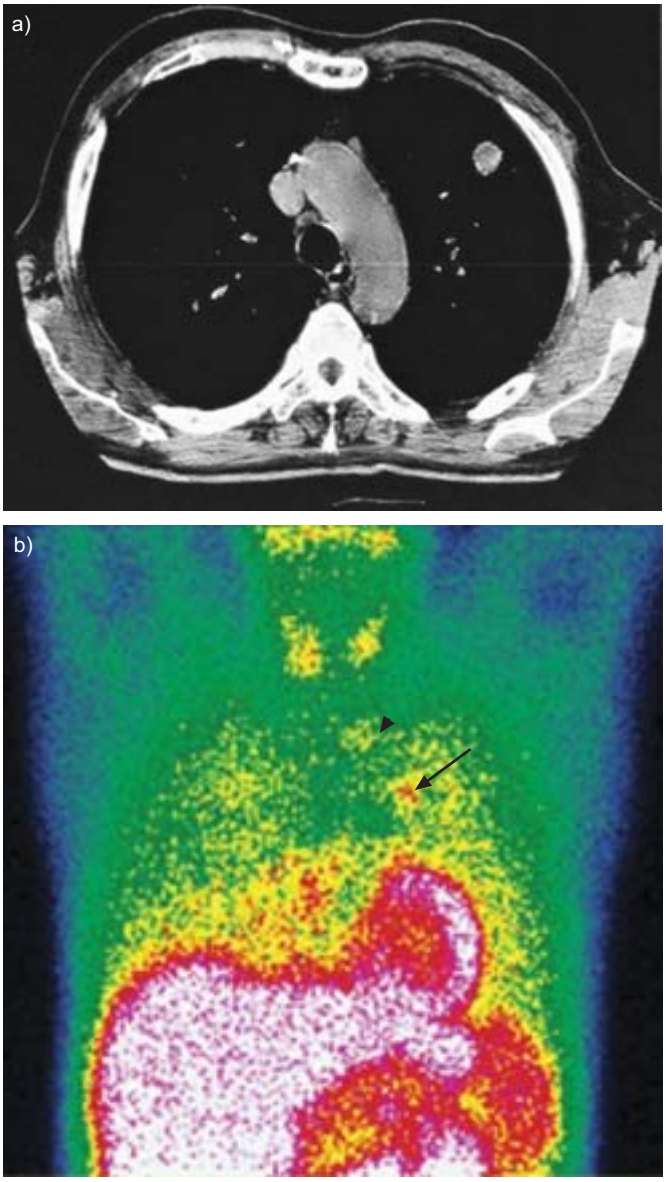

FIGURE 1. Chest computed tomography (CT) of a 61-yr-old male patient with a solitary pulmonary nodule in the left upper lobe. a) The chest CT scan showed a 1-cm lesion without mediastinal or hilar lymphnode enlargement. b) Planar views and coronal slices showed increased uptake in the nodule (score 3; arrow), as well as uptake in ipsilateral mediastinal lymphnode (arrowhead). Surgical resection showed adenocarcinoma in the nodule and in the N2 lymphnode.

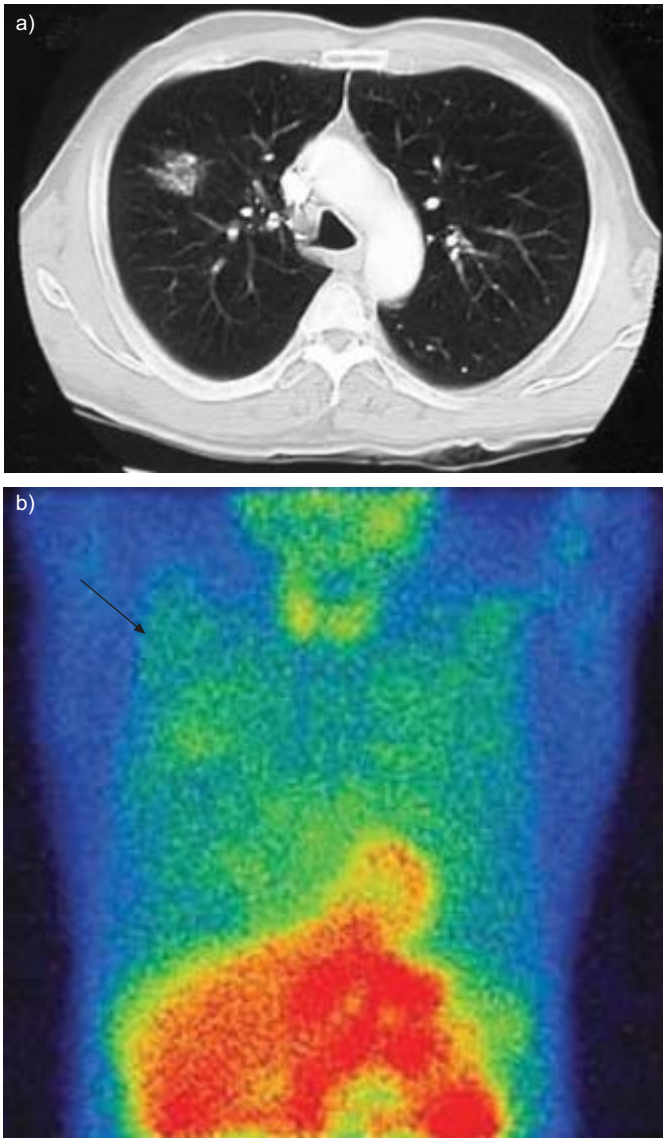

FIGURE 2. Computed tomography (CT) of a 61-yr-old male patient who presented with a solitary pulmonary nodule of the right lung. a) CT showed a 2.4-cm solitary pulmonary nodule in the right upper lobe. b) Both the planar views and single photon emission CT demonstrated increased uptake in a lesion in the right lung (score 2.5; arrow), corresponding to the lesion on the CT. Bronchoscopic evaluation yielded negative results. Surgical resection of the nodule histologically confirmed squamous cell carcinoma.

detection of metastatic lesions 18 months after initial evaluation. The clinical course of these four patients was suggestive of nonsmall cell lung cancer.

MIBI scans

In total, 15 (31%) positive and 34 (69%) negative MIBI scans were scored. There were three false-positive scans and one false-negative scan, which translated into 92.3% sensitivity, 91.7% specificity, 80.0% positive predictive value (PPV) and 97.1% negative predictive value (NPV) for the detection of malignancy (table 2). If the analysis is restricted to lesions $\leqslant$3 cm, which corresponds to the classical definition of SPN, the following results are obtained (n=42): 100% sensitivity, 93.9% specificity, 81.8% PPV and 100% NPV. A consensus reading was required in five scans, when initial assessment by the image readers led to a discordant assessment between positive (increased uptake) and negative (no uptake) results. False-positive results occurred in distinct situations: one case of TB with mild uptake and documentation of acid-fast bacilli and culture-positive result from bronchoscopic sample; one case of silicosis with mild uptake and the histological finding of granuloma negative for TB; and one case of aspergilloma with high MIBI uptake (table 3). The one false-negative lesion observed was a 4.4-cm poorly differentiated carcinoma with mild uptake, which was scored as negative during the consensus reading after one reader had classified it as positive (score 1) and the other as negative. *Post hoc* analysis using a MIBI score >1 to define a positive scan resulted in a 84.6% sensitivity, 97.2% specificity, 91.7% PPV and 94.6% NPV for the detection of malignancy.

DISCUSSION

The present study is the first to investigate the diagnostic performance of MIBI in the differentiation of SPNs in an area with a high prevalence (74% in the present study) of TB-associated benign lesions. Increased MIBI uptake indicative of malignant lesions had a sensitivity and specificity of 92%, respectively, and an NPV of 97%. In the absence of PET, the preferred method to assess SPNs, the results of MIBI uptake could have been used to select patients for surgical resection, with the drawback that three patients with benign lesions would have undergone unnecessary surgery and one malignant lesion would have been observed. This false-negative lesion with a diameter of 4.4 cm would have been surgically removed based on its size according to conventional rules. When analysing only lesions $\leqslant$3 cm in diameter (classical definition of SPN) the NPV of MIBI was 100%.

The high NPV of MIBI in the present study is in line with results from the only two previous studies from Turkey and Italy performed in settings with a relatively high prevalence of benign lesions, which resulted in NPVs of 83 and 92%, respectively [15, 16]. In the study from Turkey [15], 37 patients (51% benign lesions) were investigated with MIBI and positive scans indicated malignancy with a sensitivity, specificity, PPV and NPV of 79, 83, 79 and 83%, respectively. In the study from Italy [16], 23 SPNs were included, 56% of which were reported to be benign. MIBI positive scans identified all malignant lesions and only one false-positive scan occurred. Malignancy was detected with a sensitivity, specificity, PPV and NPV of 91, 92, 91 and 92%, respectively. However, these studies [15, 16] were relatively small and follow-up was short for some cases, thus casting doubts on the validity of the negative scans. The present study obtained a tissue diagnosis in a large proportion of participants and negative results were documented with close and complete radiological and clinical follow-up for $\geqslant$2 yrs.

PET studies evaluating indeterminate SPNs in settings with high prevalence of TB are lacking. Infection with *Histoplasma capsulatum* leads to similar diagnostic problems as TB, due to the granulomatous nature of pulmonary lesions. CROFT *et al.* [17] evaluated 90 patients with SPNs in a region where histoplasmosis is endemic. A total of 70 lesions proved to be malignant. PET detected malignancy with a sensitivity of 93%

TABLE 3 Characteristics and quantitative assessment of methoxy isobutyl isonitrile (MIBI)-positive lesions#

Patient n	Nodule location	Nodule diameter cm	Diagnosis	Mean MIBI score
2	LUL	1.0	Adenocarcinoma	3
11	RLL	1.0	Adenocarcinoma	1.75
12	RLL	2.0	SCLC	1.25
15	RUL	1.5	NSCLC	3
18	LLL	6.0	Aspergilloma	3
19	LUL	5.5	Adenocarcinoma	1.5
20	RUL	1.5	Granuloma/silicosis	1
25	RUL	2.4	Squamous cell carcinoma	2.5
27	LLL	3.0	Adenocarcinoma	1.5
29	LUL	2.0	NSCLC	1.75
35	RUL	1.8	Active tuberculosis	1
38	LLL	2.1	NSCLC	3
41	RUL	3.5	Adenocarcinoma	2.5
43	LLL	5.8	Adenocarcinoma	1
45	LLL	2.0	NSCLC	1.5

LUL: left upper lobe; RLL: right lower lobe; RUL: right upper lobe; LLL: left lower lobe; SCLC: small cell lung cancer; NSCLC: nonsmall cell lung cancer. The mean MIBI score is derived from assessments of planar and single photon emission computed tomography images by two independent image readers (score 0: no uptake, negative scan; score 1, 2 or 3: minimal, intermediate or high uptake, respectively, positive scan). #: n=15.

but a specificity of only 40%, which falls short of the sensitivity of 97% and the specificity of 78% expected from a meta-analysis [3]. This means that the usefulness of PET in avoiding invasive investigation of SPNs in such a setting is limited.

A number of studies evaluated MIBI in settings with a low prevalence of benign lesions [9, 11]. MINAI *et al.* [11] showed increased uptake in 19 out of 21 malignant lesions (sensitivity 85.7%), with all four benign lesions showing no uptake (specificity 100%). NOSOTTI *et al.* [9] investigated 116 patients with potentially resectable lung lesions, of which 99 were malignant, and the sensitivity and specificity were 89% and 100%, respectively. Again, none of the benign lesions had a positive SPECT result.

Other radiopharmaceuticals containing ^{99m}Tc have also been used successfully for the evaluation of SPNs. A recent European multicentre study using ^{99m}Tc-depreotide SPECT for evaluation of indeterminate SPNs resulted in a sensitivity of 89%, a specificity of 67% and a diagnostic accuracy of 81% for detection of malignancy [18]. The study included 118 patients of which 45 (38%) patients had benign lesions. ^{99m}Tc-depreotide compared favourably with FDG-PET in a subset of patients.

In the present study, one false-negative result and three false-positive results occurred. Tissue factors, such as poor vascularisation or low content in mitochondria, could possibly account for poor MIBI uptake leading to false-negative results in malignant lesions. It is not surprising that the three false-positive scans occurred in conditions of chronic inflammation of variable degrees (aspergilloma, silicotic granuloma and active TB). High MIBI uptake in active TB is a known phenomenon. ONSEL *et al.* [19] investigated MIBI uptake in patients with extensive and minimal radiological evidence of active pulmonary TB. Patients with extensive pulmonary disease (>50% with bilateral infiltrates) showed MIBI-positive scans in 92% of cases, whereas patients with minimal radiological infiltration had positive MIBI scans only in 50% [19]. Therefore, active TB lesions limit the value of MIBI for the differentiation between benign and malignant lesions, and alternative methods to diagnose TB must complement MIBI in order to avoid unnecessary surgery in active TB sometimes presenting as SPN. Increased MIBI uptake in aspergilloma and granuloma due to silicosis has not yet been described. These false-positive results show similar limitations for MIBI as are known for PET [4, 6, 17].

Some limitations of the current study need to be considered. The qualitative visual evaluation of images is strongly dependent on the experience of the image readers and probably influenced the study outcome. As a single-centre study performed at a tertiary university hospital with experienced staff in nuclear medicine, the results may not easily be reproduced in other settings with a high prevalence of benign lesions. Semi-quantitative methods, such as region of interest analysis or the lesion-to-background ratio, may help standardise the image evaluation [11, 12]. Also, the limited number of patients studied is a further shortcoming of the present study. Multicentre trials with large numbers of patients are needed to confirm the present findings and evaluate whether semi-quantitative approaches of image evaluation are superior to the qualitative image analysis used in this setting. In addition, the use of combined SPECT-CT equipment is likely to enhance the efficiency of this approach, saving time and unnecessary invasive interventions in some patients who travel far to receive expert evaluation or who have not refrained from food intake prior to evaluation.

Although PET and PET-CT are certainly the preferred and recommended methods for the evaluation of indeterminate SPNs, access to PET facilities is limited in many parts of the

world. In the absence of PET, MIBI-SPECT could be used; however, the present preliminary data needs confirmation in larger prospective studies.

In conclusion, the present study is the first to demonstrate the usefulness of technetium-99m methoxy isobutyl isonitrile single photon emission computed tomography in separating malignant and benign solitary pulmonary nodules in an area with very high prevalence of tuberculosis where positron emission tomography scanning was not available.

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