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Solitary pulmonary nodule evaluation with Technetium-99m MIBI in tuberculosis-endemic area

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Abstract

High prevalence of tuberculosis increases the odds for non-malignant solitary pulmonary nodules (SPN). Positron emission tomography (PET) using F-18 fluoro-deoxy-glucose is the method of choice to identify malignant SPNs requiring curative surgery but PET is not widely available. Technetium-99m-methoxy isobutyl isonitrile (MIBI) is inexpensive, widely available and shows increased uptake in malignant SPNs. The aim was to prospectively evaluate the diagnostic value of MIBI-Single Photon Emission Computed Tomography (SPECT) to distinguish between benign and malignant SPN in a tuberculosis-endemic area.

Forty-nine patients with radiologically indeterminate SPN (single lesion ≤ 6cm in diameter) were prospectively evaluated with MIBI. The final diagnosis was established with bronchoscopy, fine needle aspiration, surgical resection or clinical follow-up for at least 2 years.

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

In this tuberculosis-endemic area MIBI-SPECT evaluation of SPNs had a high negative predictive value. It therefore has the potential to prevent unnecessary surgical resections of benign nodules and serve as a low-cost alternative when PET is not available.

Introduction

Most solitary pulmonary nodules (SPN) 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 a solitary pulmonary nodule (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 health care system with limited financial resources. The Cape Town Metropole has a very high prevalence and incidence of tuberculosis (678 per 100 000 in the year 2003) as well as a high incidence of bronchial carcinoma with approximately 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”). On the other hand, 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 therefore “indeterminate” [2]. For such lesions additional evaluations are needed.

F-18 fluoro-deoxy-glucose positron emission tomography (FDG-PET) has become the method of choice to evaluate such SPNs but availability and cost still limit its widespread use [3, 4]. There are also several reports indicating false positive results of FDG-PET in patients with active TB [4-6]. Radiopharmaceuticals containing either Technetium-99m or Thallium 201 are more affordable than FDG because 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]. 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, 11, 12]. This study was conducted to evaluate MIBI for 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

This prospective single centre study was performed at Tygerberg Academic Hospital, a tertiary university hospital in Cape Town, South Africa, with a drainage area of approximately 1.5 million people. Patients referred to the Lung Unit with single pulmonary lesions ≤ 6 cm in diameter on CXR were included if the lesion was a solitary pulmonary nodule (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 of ≤3 cm we chose to investigate lesions of ≤6 cm because 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.

Clinical and radiological examinations

The primary procedure for establishing a diagnosis was fiberoptic 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 workup 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 at least 2 years.

Imaging Protocol

MIBI scanning was performed before any invasive diagnostic procedure. After intravenous administration of 740 MBq Tc-99m methoxy-isobutyl-isonitrile (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 computed tomography (SPECT) images of the chest were acquired. Image acquisition commenced 5-10 minutes 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 minutes each. The acquisition parameters for the SPECT studies included step-and-shoot mode over 30 minutes, with 120 projection angles over 360° rotation, 15 s per frame acquisition time and a 64 x 64 matrix. No attenuation correction was done.

SPECT data were reconstructed by filtered back projection using a Butterworth filter with a cut off frequency of 0.8. SPECT studies were viewed in the coronal, axial and sagittal planes and in reprojection 3-dimensional cine mode. Iterative reconstruction, currently the preferred method, only became available at our institution toward the

end of the study period. 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 at least 2 years of radiological follow-up. Tuberculous granuloma met the same criteria, but acid-fast bacilli were detected and mycobacterial cultures were negative. Active tuberculosis was diagnosed when mycobacterial cultures were positive of samples obtained from the lesion and/or lesion size diminished during antituberculosis treatment. Malignant tumours were diagnosed when two independent pathologists diagnosed malignancy in a specimen obtained from the SPN. In a few cases with non-diagnostic 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 (HB, AE) 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 the 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 chest radiograph 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 4

categories: 0 = negative scan, no uptake in region of interest; 1 = minimal uptake; 2 = intermediate uptake; and 3 = high uptake in region of interest. Categories 1 to 3 were considered positive. We graded positive scans 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 4 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 to the clinical diagnosis as the gold standard. In a post hoc analysis we also used a MIBI score of > 1 to define a positive result. Basic descriptive statistical tests were done with Excel (Microsoft Corp., Redmond, WA, USA).

Results

Patient Population

Between August 2000 and November 2003, 53 consecutive patients met inclusion criteria. Forty-nine of these had SPNs according to our definition. Thirteen patients had a past history of tuberculosis. Four patients were excluded after CT scanning for having multiple lesions (2 patients), pleural based lesions or lesions > 6 cm in diameter (1 patient each). The demographical data and lesion characteristics of these 49 patients are presented in Table 1. Seven nodules were larger than 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).

Table 1 Descriptive statistics of patients evaluated with MIBI SPECT (n=49)

Male patients	29 (59%)
Age, years	54.2 (14.4)
Solitary pulmonary nodule diameter, cm	2.24 (1.2)
Location of solitary pulmonary nodule	
R upper lobe/L upper lobe	12/11
Middle lobe	5
R lower lobe/L lower lobe	9/12

Data are presented as number or mean (+/- standard deviation) unless indicated otherwise. R, right; L, left.

Diagnosis and outcome

A histological, cytological or microbiological diagnosis was established at initial evaluation in 36 (73%) patients and 13 patients (27%) were observed. In total, 14 patients underwent surgery, 42 bronchoscopy, and 3 received a transthoracic CT-guided needle biopsy. Table 2 summarizes the diagnoses of the 49 patients investigated. Of these 13 (27%) had malignant tumours (Figure 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 detection of metastatic lesions 18 months after initial evaluation. The clinical course of these 4 patients was suggestive of non-small cell lung cancer.

Table 2 Distribution of solitary pulmonary nodules according to diagnosis and results from MIBI SPECT imaging

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

MIBI scans

In total, 15 positive (31%) and 34 negative (69%) MIBI scans were scored. There were three false positive and one false negative scans, 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 ≤ 3 cm (which corresponds to the classical definition of SPN) the following results are obtained (n=42): Sensitivity 100%, specificity 93.9%, PPV 81.8% and NPV 100%. A consensus reading was required in 5 scans when image readers' initial assessment lead to a discordant assessment between

positive (increased uptake) and negative (no uptake) results. False positive results occurred in distinct situations: one case of tuberculosis 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), the other as negative. Post hoc analysis with a MIBI score of >1 to define a positive scan resulted in a sensitivity of 84.6%, specificity 97.2%, PPV 91.7% and NPV 94.6% for the detection of malignancy.

Table 3 Characteristics and quantitative assessment of MIBI-positive lesions (N=15)

Patient Number	**Nodule Location**	**Nodule Diameter (cm)**	**Diagnosis**	**Mean MIBI score**
2	LUL	1.0	Adeno-Ca	3
11	RLL	1.0	Adeno-Ca	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	Adeno-Ca	1.5
20	RUL	1.5	Granuloma/Silicosis	1
25	RUL	2.4	Squamous cell Ca	2.5
27	LLL	3.0	Adeno-Ca	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	Adeno-CA	2.5
43	LLL	5.8	Adeno-CA	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, non small cell lung cancer. The mean MIBI score is derived from assessments of planar and SPECT images by two independent image readers (score 0= no uptake, negative scan; score 1, 2 or 3 = minimal, intermediate or high uptake, positive scan).

Discussion

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

The high negative predictive value 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 negative predictive values of 83% and 92%, respectively [15, 16]. In the study from Turkey 37 patients (51% benign lesions) were investigated with MIBI and positive scans indicated malignancy with a sensitivity, specificity, positive and negative predictive value of 79, 83, 79 and 83%, respectively [15]. The Italian study included 23 SPNs of which 56% 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, positive and negative predictive value of 91, 92, 91 and 92%, respectively [16]. However, these studies 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 at least 2 years.

PET studies evaluating indeterminate SPNs in settings with high prevalence of tuberculosis are lacking. Infection with *Histoplasma capsulatum* leads to similar diagnostic problems as TB due to the granulomatous nature of pulmonary lesions: Croft et al. evaluated 90 patients with SPNs in a region where histoplasmosis is endemic [17]. Seventy lesions proved to be malignant. PET detected malignancy with a sensitivity of 93% 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 to avoid 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. showed increased uptake in 19 out of 21 malignant lesions (sensitivity 85.7%), with all 4 benign lesions showing no uptake (specificity 100%) [11]. Nosotti et al. investigated 116 patients with potentially resectable lung lesions of which 99 were malignant and the sensitivity and specificity were 89% and 100%, respectively [9]. Again, none of the benign lesions had a positive SPECT result.

Other radiopharmaceuticals containing Tc-99m have also been used successfully for the evaluation of SPNs: A recent European multicentre study using Tc-99m 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]. This study included 118 patients of which 45 patients (38%) had benign lesions. Tc-Depreotide compared favourably with FDG-PET in a subset of patients.

In the present study one false negative result and 3 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 tuberculosis). High MIBI uptake in active tuberculosis is a known phenomenon. ONSEL et al. investigated MIBI uptake in patients with extensive and minimal radiological evidence of active pulmonary TB [20]. Patients with extensive pulmonary disease (> 50% with bilateral infiltrates) showed MIBI positive scans in 92%, 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 likely 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. Semiquantitative 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 here is a further shortcoming of this study. Multicentre trials with large numbers of patients are needed to confirm our findings and evaluate if semiquantitative 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 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 to evaluate indeterminate SPNs the access to PET facilities is limited in many parts of the world. In the absence of PET one may resort to MIBI SPECT, however, our preliminary data needs confirmation in larger prospective studies.

In conclusion, this is the first study to demonstrate the usefulness of Technetium-99 MIBI SPECT in separating malignant and benign solitary pulmonary nodules in an area with very high prevalence of tuberculosis where PET scanning was not available.

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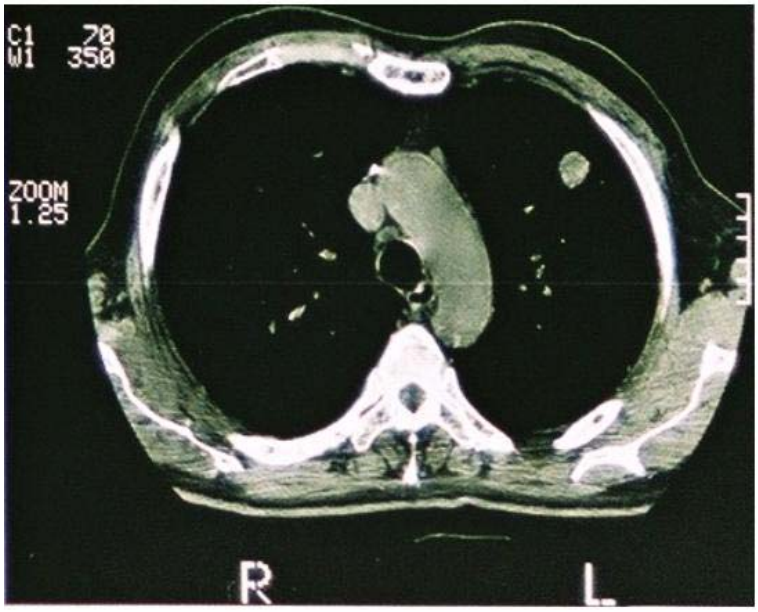
Figure Legends

Figure 1A and Figure 1B: Sixty-one year old male patient with a solitary pulmonary nodule in the left upper lobe. Chest CT-scan showed a 1 cm lesion without mediastinal or hilar lymphnode enlargement. Planar views and coronal slices showed increased uptake in the nodule (score 3, solid arrow) as well as uptake in ipsilateral mediastinal lymphnode (open arrow). Surgical resection showed adenocarcinoma in the nodule and in the N2 lymphnode.



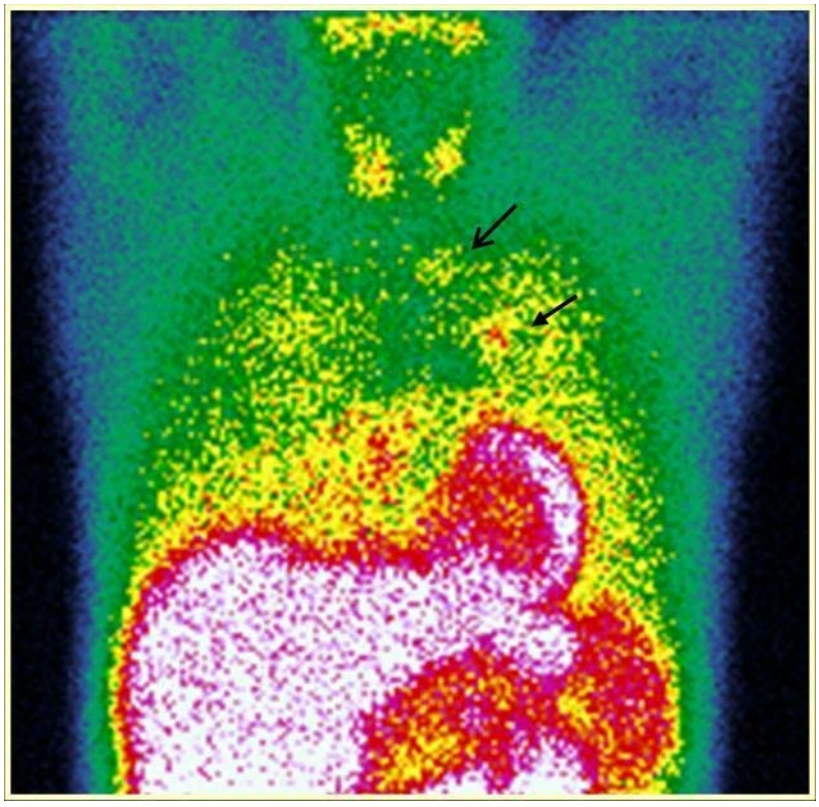


Figure 2A and Figure 2B: Sixty-six year old man presented with a solitary pulmonary nodule of the right lung. CT showed a 2.4 cm solitary pulmonary nodule in the right upper lobe. Both the planar views and SPECT demonstrated increased uptake in a lesion in the right lung (score 2.5, solid arrow), corresponding to the lesion on the CT.

Bronchoscopic evaluation yielded negative results. Surgical resection of the nodule histologically confirmed squamous cell carcinoma.