Lung ^{99m}Tc-MIBI scintigraphy: impact on diagnosis of solitary pulmonary nodule

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Abstract

Most of today available non-invasive procedures cannot clearly determinate between benign and malignant solitary pulmonary nodules (SPN). The purpose of the study was to assess the possibility of using ^{99m}Tc labeled hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-MIBI) to differentiate benign from malignant SPN. Sixty patients were included in the study if the CT scan showed indeterminate SPN. Prior to definitive diagnosis ^{99m}Tc-MIBI single photon emission computerized tomography (SPECT) was performed: early scan 10 minutes and delayed 60-120 minutes after the intravenous injection of 740 MBq ^{99m}Tc-MIBI using dual-headed Gamma camera. The results were considered positive if there was an increased accumulation of the radiopharmaceutical in the area of the lung corresponding to the location of the lesion.

The mean nodule size ± SD measured on CT scan was 2.96 cm. Lung cancer was diagnosed in 30/60 patients (14 squamocellular, 10 adenocarcinoma, 3 large-cell and 3 microcellular lung carcinomas). Of the 30 patients with malignant lesions, 27 patients (90%) had positive ^{99m}Tc-MIBI scan results by qualitative assessment. Among benign lesions, 23/30 (76.7%) were negative on ^{99m}Tc-MIBI scan. The size and PH report of SPN is statistically significantly influencing on ^{99m}Tc-MIBI accumulation in the SPN (p<0.01). The sensitivity, specificity, accuracy, positive and negative predictive value were 90%, 76.6%, 79.4%, 88.5% and 83.3% respectively.

^{99m}Tc-MIBI SPECT is an inexpensive non-invasive diagnostic procedure which might be useful diagnostic modality in the evaluation of SPN. Easy availability and low cost makes ^{99m}Tc-MIBI SPECT an attractive method in evaluating SPN.

KEY WORDS: ^{99m}Tc-Sestamibi, radionuclide imaging, solitary pulmonary nodule, diagnosis

INTRODUCTION

Lung cancer is one of the most aggressive malignancies and the leading cause of cancer death in man. For the 5-year period (2004-2008) lung cancer was the cause of death in 28.01 % of man who died from cancer in Vojvodina[1]. The 5-year survival rate is very low and early diagnosis is closely related to the survival. Surgery offers the major prospect of cure in lung cancer including squamocellular carcinoma, adenocarcinoma and large cell carcinoma. Microcellular carcinoma accounts about 20% of lung cancers, clinically is aggressive and 2-year survival is less than 10% [2]. About 30% of all cases of lung carcinoma will present as solitary pulmonary nodule (SPN). SPN frequently presents a diagnostic dilemma especially when is surrounded by normal tissue, not grater than 3 cm in diameter and with no radiographic evidence of hilar or mediastinal adenopathy. The only radiographic criteria accepted as suggestive of a benign nodule are stable nodule size for two year period or longer, presence of fat in the nodule and characteristic concentric, central or stippled calcification pattern. Patients with SPN are usually required to undergo one of invasive procedures (such as bronchoscopy, transthoracic needle biopsy, thoracoscopy) in order to gain specific tissue diagnosis. Most of today available non-invasive procedures cannot clearly determinate between benign and malignant SPN. Various radiolabelled pharmaceuticals have been used as non-invasive procedure for this purpose with different success. ^{67}Ga and ^{201}Tl achieved widespread clinical acceptance but poor emission characteristics, cyclotron production and lack of specificity due to uptake in sarcoidosis and granulomatous lung lesions are their serious disadvantages in clinical use [3,4]. Positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) has shown to be highly accurate in distinguishing benign from malignant lesions, evaluating solitary pulmonary nodule and mediastinal staging [5,6]. Limitations of PET scanners are the availability and high costs [7]. Technetium-99m labeled hexakis-2-methoxyisobutylisoni-

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trile (^{99m}Tc-MIBI) is a lipophilic cation widely used for myocardial perfusion imaging. Incidental noncardiac findings of ^{99m}Tc-MIBI are not uncommon [8,9]. Malignant tumors in the breast, thyroid, bones, central nervous system and lungs could be visualized with ^{99m}Tc-MIBI [10]. The purpose of the study was to assess the possibility of using ^{99m}Tc-MIBI to differentiate benign from malignant solitary pulmonary nodule.

MATERIALS AND METHODS

Patients

^{99m}Tc-MIBI single photon emission tomography (SPECT) of the chest was performed in 60 patients (45 males and 15 females aged 37-76 years, mean age ± SD: 56.70 ± 9.527). Patients were included in the study if the chest radiograph or CT scan showed SPN, which was considered indeterminate or suspect of malignancy. Only patients where a definitive diagnosis (pathohistology report or findings of sputum on TBC culture) was achieved were included in the study. Before the diagnosis, all patients were completely evaluated by their physicians (anamnesis, examination, chest X-ray, CT).

Procedures

Two phase ^{99m}Tc-MIBI SPECT of the chest (early and delayed scan) was performed prior to definitive diagnosis. Early ^{99m}Tc-MIBI SPECT of the chest was done 10 minutes after the intravenous injection of 740 MBq ^{99m}Tc-MIBI with dual-headed Gamma-camera equipped with low-energy, high-resolution collimator. Delayed ^{99m}Tc-MIBI SPECT of the chest was performed 60 to 120 minutes after the intravenous injection of radiopharmaceutical. ^{99m}Tc-MIBI was prepared according to the instructions of the manufacturer. Projection data were acquired for 25 minutes. Sixty images were acquired for 10 seconds each and stored in 64x64 matrixes. The images were reconstructed in coronal, transversal and sagital sections and were qualitatively evaluated. The results were considered positive if there was an increased accumulation of the radiopharmaceutical in the area of the lung corresponding to the location of the SPN. ^{99m}Tc-MIBI SPECT scan results were compared with definitive diagnoses of SPN.

Statistical analysis

Diagnostic efficacy of ^{99m}Tc-MIBI SPECT scan to differentiate benign from malignant SPN (by qualitative assessment) was evaluated by calculating sensitivity, specificity, positive and negative predictive value and accuracy. Statistical difference between ^{99m}Tc-MIBI results in malignant and benign SPN was evaluated by Fisher's test and p value. Individual influence of nodule size, nodule localisation and PH report on ^{99m}Tc-MIBI accumulation in SPN was analyzed with regression analysis.

RESULTS

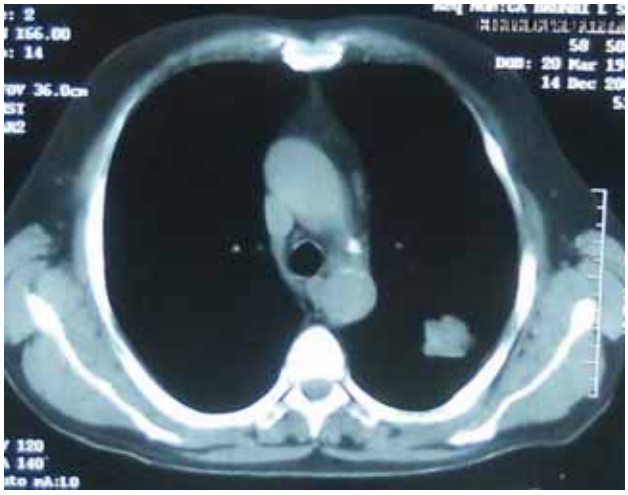
Between December 2003 and December 2008, 60 patients with lung lesions were investigated. The mean size ± SD of all SPN measured on CT scan was 2.96 ± 12.1 (range 1.1 – 5.8 cm) or 2.67 ± 11.5 among benign and 3.25 ± 13.8 among malignant SPN. Lung cancer was diagnosed in 30/60 (50%) patients. According to pathohistology report, there were 14/30 squamocellular carcinoma, 10/30 adenocarcinoma (including one bronchoalveolar carcinoma), 3/30 large cell carcinoma and 3/30 microcellular carcinoma. The characteristics of 60 patients with SPN are listed in Table 1.

TABLE 1. Characteristics of 60 patients with solitary pulmonary nodule

Characteristics	Total value	+ MIBI scan	- MIBI scan
Total	60	34	26
Male/female	45/15	25/9	20/6
Average age (SD) year	56.70 (9.5)	57.60 (9.9)	56.45 (8.2)
Average size of SPN (SD)cm	2.96 (12.1)	3.25 (13.8)	2.67 (11.5)
Adenocarcinoma	10	9	1
Squamocellular carcinoma	14	13	1
Large-cell carcinoma	3	3	0
Microcellular carcinoma	3	2	1
Inflamatory pseudonodule	14	6	8
Tuberculosis	7	0	7
Hamarthoma	6	0	6
Botriomycosis	1	1	0
Primary NE cyst	1	0	1
Fibrotic nodule	1	0	1

Benign lesion were diagnosed in 30/60 patients (50%) and definitive diagnosis showed in most of the cases inflamatory pseudonodule (14/30), tuberculosis in 7/30, hamarthoma in 6/30, botriomycosis 1/30, primary neuroendocrine cyst 1/30 and fibrotic nodule 1/30. Pathohistology (PH) report was helpful in achieving the diagnosis in majority of patients either by operation (24/60) or bronchoscopy (18/60). Transthoracic needle biopsy was useful in 14/60 and the rest of the patients (4/30) were diagnosed for tuberculosis by having positive sputum on TBC culture. Of the 30 patients with malignant lesions, 27 patients (90%) had positive ^{99m}Tc-MIBI SPECT scan results by qualitative assessment (Figure 1, 2). Three patients with lung carcinoma were false negative on ^{99m}Tc-MIBI SPECT scan (1-adenocarcinoma, 1-undifferentiated squamocellular carcinoma and 1-microcellular carcinoma). Among benign lesions, 23/30 (76.7%) were negative on ^{99m}Tc-MIBI SPECT scan, and 7 (23.3%) were positive (Figure 3). The majority of false positive results (6/7) were found in inflammatory pseudonodule, while botryomycosis was diagnosed in one case (1/7). There was statistically significant difference (Fisher's test, $p<0.01$) regarding ^{99m}Tc-MIBI SPECT findings

A



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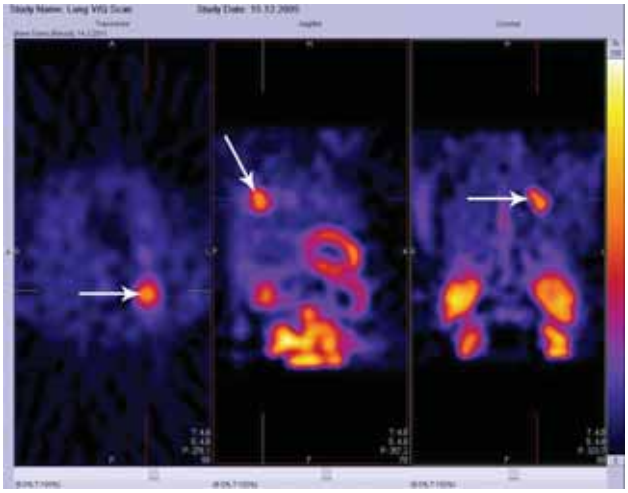

FIGURE 1. (A) CT scan of the chest of 59 year-old male patient revealing a 3 cm nodule in the left upper lobe (posterior segment) of the lung. (B) ^{99m}Tc-MIBI SPECT scan in the same patient showing very intense accumulation of ^{99m}Tc-MIBI in the lung region corresponding to the localisation of the nodule. At surgery the nodule was found to be adenocarcinoma.

in benign and malignant group of patients - scan is significantly more often positive in patients with malignant SPN, and frequently negative in group of patients with benign SPN. Regression analysis was used to evaluate how is size, localisation and PH report of SPN influencing on ^{99m}Tc-MIBI accumulation in SPN (dependent variable - ^{99m}Tc-MIBI accumulation). The size of SPN is statistically significantly influencing on ^{99m}Tc-MIBI accumulation in the SPN (p<0.01). ^{99m}Tc-MIBI findings are explained with 13.3% (R2=0.133) change of SPN size, meaning that 13,3% of all ^{99m}Tc-MIBI findings are dependant on PH report (Figure 4). Localisation of SPN in left/right lung or lung segments was not statistically significantly influencing on ^{99m}Tc-MIBI accumulation in the SPN (p>0.01). PH report is statistically significantly influencing on ^{99m}Tc-MIBI accumulation in the SPN (p<0.01) with frequently positive ^{99m}Tc-MIBI finding in malignant SPN. ^{99m}Tc-MIBI findings are explained with 38.8% (R^2=0.388) change of PH report, meaning that 38.8% of all ^{99m}Tc-MIBI findings are dependant on PH report. Different histological type of lung carcinoma was not statistically significantly influencing on ^{99m}Tc-MIBI accumulation in the SPN (p>0.01). The sensitivity, specificity, accuracy, positive and negative predictive value were 90 %, 76.6 %, 79.4 %, 88.5 % and 83.3 % respectively.

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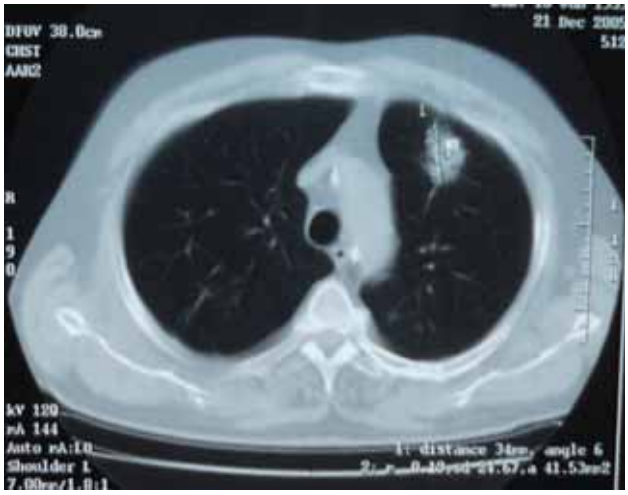

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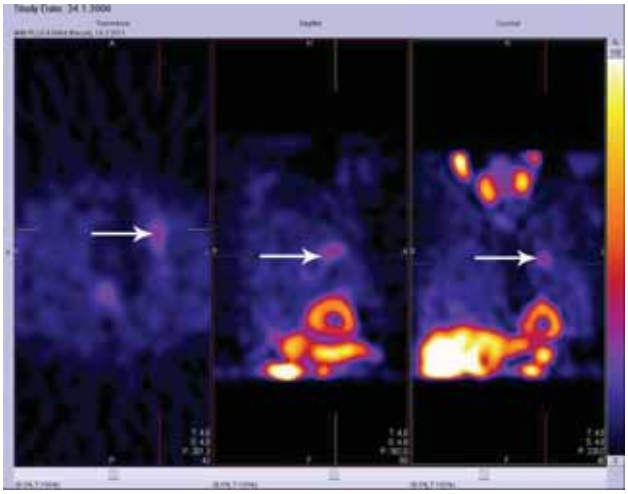

FIGURE 2. (A) CT scan of the chest of 67 year-old male patient revealing a 3.4 cm nodule in the left upper lobe (anterior segment) of the lung. (B) 99mTc-MIBI SPECT scan in the same patient showing moderatly increased accumulation of 99mTc-MIBI in the lung region corresponding to the localisation of the nodule. At surgery the nodule was found to be medium differentiated squamocellular carcinoma.

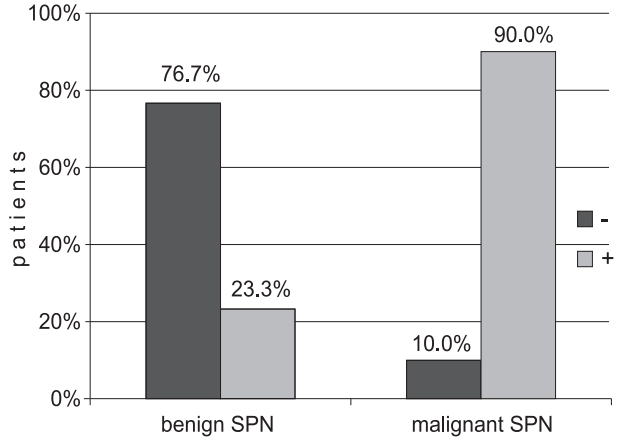

FIGURE 3. ^{99m}Tc-MIBI SPECT scan results in patients with benign and malignant solitary pulmonary nodule

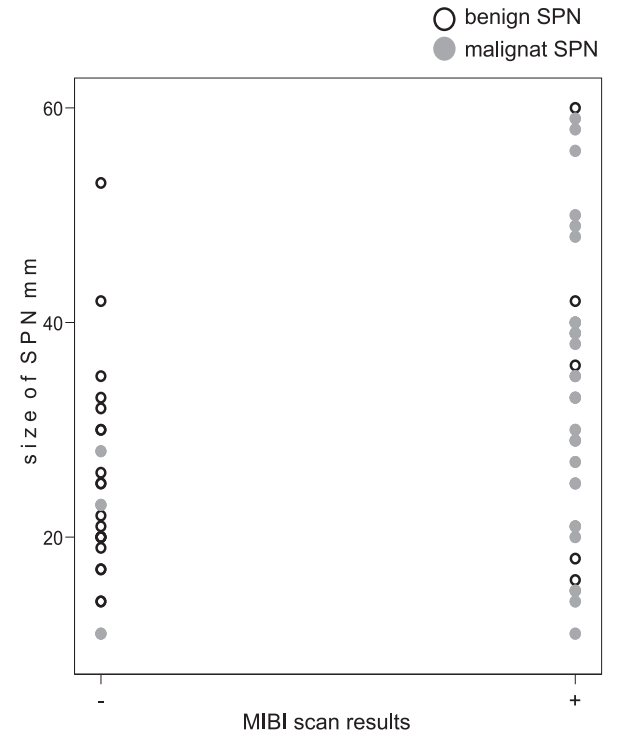

FIGURE 4. ^{99m}Tc-MIBI SPECT scan results and size of solitary pulmonary nodule in patients with benign and malignant SPN

DISCUSSION

Several papers described the possible application of ^{99m}Tc-MIBI for lung cancer in clinical practice [11,12]. The exact mechanism is not yet completely known but there are some studies showing that passive uptake of ^{99m}Tc-MIBI depends on the negative potential of the cytoplasmatic and mitochondrial membrane of neoplastic cell [13]. This uptake increases after oxygen inhalation and is related to increasing perfusion and positive acute cellular response of the tumor tissue to the rising tissue oxygen level in lung cancer [14, 15]. Hassan et al. [16] were one of the first who described increased uptake of ^{99m}Tc-MIBI in lung cancer. Because of the potential of this radiopharmaceutical uptake by various malignant tumors, observation of abnormal foci of activity may result in life-saving early cancer identification. Considering the importance of useful non-invasive method for the identification of malignant SPN in everyday surgical practice, high specificity for malignancy (100%) of ^{99m}Tc-MIBI SPECT result is desirable, as reported by Minai et al. [11] and Nosotti et al. [12]. Based on these results and high values of positive predictive value (100% in both studies), Minai et al. [11] recommends that positive ^{99m}Tc-MIBI scan allows physician to avoid unnecessary invasive diagnostic procedures and to proceed to thoracotomy. In our study the results of diagnostic significance of ^{99m}Tc-MIBI scan showed sensitivity, specificity, accuracy, positive and negative predictive value 90%, 76.6%, 79.4%, 88.5% and 83.3% respectively. Comparing to Minai et al. [11] and Nossoti et al. [12] in our study specificity was lower (76.6%), mostly due to false positive results in inflammatory pseudonodule (6/7), a group of benign SPN which were not included in previously reported studies. Sensitivity and specificity value in our patient population mostly correlates with the results of Santini et al. [17] who investigated group of 79 patients (60 malignant SPN and 19 benign) and gain sensitivity, specificity, positive and negative predictive value 91%, 73 %, 91 % and 73 % respectively. High negative predictive value (88.5%) could be explained with the high prevalence of benign SPN in our patient population. Several studies from Turkey, Italy and South Africa reported high negative predictive value of 83%, 92% and even 97% respectively and all of them had relatively high prevalence of benign SPN [18, 19, 20]. Studies from Turkey and Italy [18, 19] had similar results reporting 51% and 56% benign lesions of all SPN respectively, while the highest number of benign lesions was diagnosed in the study of Schuurmans et al. [20] – in 73% and was explained with the study being conducted in endemic area of tuberculosis. Positive predictive value is relatively low in our study (79.4 %) which could suggest that, according to our results, further work up is needed to establish the definitive diagnosis. Only few studies came out with the results which highly limit the use of ^{99m}Tc-MIBI in evaluation of SPN, such as Kao CH who studied 54 patients with SPN and reported 65% sensitivity, 57% specificity and 70% accuracy of this method [21]. Only three patients with malignant lesions had negative ^{99m}Tc-MIBI scan result (false negative), one of them was among the smallest SPN in our study (microcellular carcinoma 1.3 cm) which is under the resolution of Gamma-camera. One patient with undifferentiated squamocellular carcinoma was also negative on ^{99m}Tc-MIBI scan. Nishiyama et al. had previously reported that squamose cell carcinoma had lower early ratio (ER= ratio of tumor uptake to contralateral uptake) 2.5 ± 0.9 than microcellular carcinoma 3.0 ± 1.1 or adenocarcinoma 2.7 ± 1.4 [22]. Third patient with malignant SPN (ad-

enocarcinoma) and negative ^{99m}Tc-MIBI scan had lesion with central necrotic area. Considering the theory of ^{99m}Tc-MIBI being accumulated inside the cell mitochondria, it is not surprising that MIBI could not accumulate in necrotic non-viable tissue which leads to absent uptake inside the nodule. Other factors such as tissue characteristics, poor vascularisation and low content of mitochondria could also contribute to poor ^{99m}Tc-MIBI uptake leading to false negative results. False positive results occurred in 7 out of 30 benign lesions, 6 in inflammatory pseudonodule and 1 in botriomycosis. It is well known that chronic inflammation and active pulmonary tuberculosis could lead to high MIBI uptake. Onsel et al investigated MIBI accumulation in extensive pulmonary disease with bilateral infiltrates and gain MIBI scan positive results in 92% of cases [23]. These results show that chronic inflammatory diseases, inflammatory pseudonodules and active tuberculosis are limiting the value of ^{99m}Tc-MIBI in differentiation benign from malignant SPN and have similar limitations as are known for PET [24]. Our data showed that the size of SPN is statistically significantly influencing on ^{99m}Tc-MIBI accumulation in the SPN meaning that larger nodules will be easier to identify on ^{99m}Tc-MIBI scans. These results are in concordance with the findings of Minai et al. [11] who also report a significant relationship between uptake of MIBI and nodule size. On the other hand, Nossoti et al. [12] and Santini et al. [17] report that no correlation is found between the size of a nodule and ^{99m}Tc-MIBI SPECT results. Our findings that different histological types of lung carcinoma are not statistically significantly influencing on ^{99m}Tc-MIBI accumulation in the SPN are confirmed with the several studies [12, 17].

CONCLUSION

^{99m}Tc-MIBI SPECT is an inexpensive, non-invasive and reliable diagnostic tool which might be useful diagnostic modality in the evaluation of SPN, particularly in the cases where radiological evaluation is indeterminate. Easy availability (readily available), safe and low cost (compared with PET) makes ^{99m}Tc-MIBI SPECT an attractive method in evaluating SPN. Although a positive ^{99m}Tc-MIBI SPECT scan in patients where standard diagnostic evaluation failed to determine the nature of SPN may help in decision making process for surgical intervention, relatively low positive predictive value in our study (79.4%) suggests that further work up is needed to establish the definitive diagnosis.

DECLARATION OF INTEREST

There was no financial support received for the work and the authors had no financial involvement or affiliation with any organization whose financial interests may be affected by material in the manuscript, or which might potentially bias it.

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