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A Comparative Study of Lung Masses with ^{99m}Tc-Technetium Sestamibi and Pathology Results

Shahram Dabiri Oskoei and Babak Mahmoudian
Department of Nuclear Medicine, Tabriz University of Medical Sciences,
Imam Hospital, Tabriz, Islamic Republic of Iran

Abstract: Bronchial carcinoma is the leading cause of death from cancer in most countries. The aim of this prospective study was to assess the ability of ^{99m}Tc-Technetium Sestamibi (^{99m}Tc-MIBI) SPECT in differentiating benign from malignant pulmonary masses. 30 patients with lung mass, radiologically suspicious for malignancy were included. Planar scintigraphy was performed on all patients 10 and 120 min after intravenous injection of ^{99m}Tc-MIBI. Also SPECT was done after completion of first static image series. Images were evaluated qualitatively and quantitatively for abnormal accumulation of radiotracer corresponding to the location of the masses. Increased ^{99m}Tc-MIBI uptake was considered as positive scan result. Biopsy from lung mass was performed in all patients. Twenty patients (67%) had malignant lung lesions, which were confirmed pathologically [90% had primary lung cancer (PLC)]. ^{99m}Tc-MIBI scan had sensitivity, specificity, positive and negative predictive values of 80, 70, 84 and 64% in detection of lung malignancies, respectively. Quantitatively, malignant lesions revealed high mass/lung count ratio comparing to benign lesions (1.21±0.12 vs. 1.09±0.07, p<0.01). Small cell tumors had higher ^{99m}Tc-MIBI uptake than squamous cell tumors (p<0.05). ^{99m}Tc-MIBI scanning can be helpful in prediction of malignancy in suspicious pulmonary masses due to its high specificity and positive predictive value.

Key words: ^{99m}Tc-MIBI, lung cancer, malignancy, lung mass

INTRODUCTION

Bronchial carcinoma is one of the most prevalent and aggressive malignancies and is the leading cause of death from cancer in most countries (Landis *et al.*, 1998). Survival in bronchial carcinoma is closely related to the stage of the disease at the time of diagnosis. Invasive procedures are often undertaken to obtain a specific tissue diagnosis because none of the currently available non-invasive diagnostic modalities affords accurate differentiation between benign and malignant pulmonary nodules (Cummings *et al.*, 1986). Stable nodule size for more than two years, the presence of fat within the nodule and characteristic patterns of calcification (concentric, central or stippled) are the only radiographic criteria currently accepted as suggestive of a benign lesion (Minai *et al.*, 2000; Nosotti *et al.*, 2002). Computerized Tomography (CT) of the chest is the standard procedure for the diagnosis and staging of lung cancer. CT provides very good anatomic imaging but has limitations in the detection of nodal metastases (sensitivity, 61 to 73%; specificity, 62 to 86%). The

relatively poor performance of CT in the identification of nodal metastases has led to a search for new approaches (Gross *et al.*, 1988).

Various radionuclides, such as ⁶⁷Ga and ²⁰¹Tl, have been utilized in lung cancer for staging, follow-up and monitoring the response to therapy (Abdel-Dayem *et al.*, 1994). Several studies have reported the superior accuracy of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) over CT in the mediastinal staging of lung cancer (sensitivity, 62 to 97%; specificity, 79 to 99%). Unfortunately FDG-PET has some limitations: The increase in glucose metabolism is not specific to neoplastic diseases, the anatomic resolution of the images is limited, the availability of positron emission tomography scanners is still limited and their costs are high (Saunders *et al.*, 1999; Dwamena *et al.*, 1999; Lowe and Naun Heim, 1998).

Encouraging results have also been obtained with Single Photon Emission Computerized Tomography (SPECT) scanning using ^{99m}Tc-MIBI (Piwnica-Worms and Holman, 1990). ^{99m}Tc-MIBI is a lipophilic cation widely used as a tracer for myocardial perfusion imaging but is

also taken up by various malignant tumors. Several reports also described the possible application of this radiopharmaceutical for lung cancer in clinical practice (Kao *et al.*, 1993; Chiti *et al.*, 1996). Increased uptake of ^{99m}Tc-MIBI in bronchogenic carcinoma on SPECT has been reported (Minai *et al.*, 2000; Nosotti *et al.*, 2002; Hassan *et al.*, 1989).

The purpose of this prospective study was to assess the ability of ^{99m}Tc-MIBI SPECT in differentiating benign from malignant pulmonary masses, which are detected on radiological images.

MATERIALS AND METHODS

This prospective study was performed between May 2004 and June 2005 in Tabriz nuclear medicine center. Thirty patients with pulmonary mass larger than 2 cm, suspicious for malignancy on chest X ray or CT scan in whom a procedure to obtain definitive tissue diagnosis was planned, were included in this study. Patients with previous malignancies or those who had already undergone neoadjuvant therapy were excluded. All of the patients gave their informed written consent for participation in the study. ^{99m}Tc-MIBI scan was performed on all patients before receiving any kind of treatment such as chemotherapy or radiation therapy. Ten and 120 min after intravenous injection of 555-740 MBq (15-20 mCi) of ^{99m}Tc-MIBI, static images from 8 standard views (Anterior, Right Anterior Oblique, Right Lateral, Right Posterior Oblique, Posterior, Left Posterior Oblique, Left Lateral and Left Anterior Oblique) were performed in supine position in a 256×256 matrix, obtaining 750,000 count, using a dual headed Vertex-ADAC gamma camera equipped with

low-energy high resolution collimators. Also SPECT was performed from 64 projections over 360 degrees, with 20 sec per projection, after completion of first static image series. Raw data were processed using routine back projection algorithms. Reconstructed images were evaluated qualitatively (subjective visual evaluation) for abnormal accumulation of ^{99m}Tc-MIBI corresponding to the location of the masses on the chest radiograph or CT scan. Increased ^{99m}Tc-MIBI uptakes were considered as positive scan result. Biopsy from lung mass was performed in all patients taken by bronchoscopy or transthoracic needle biopsy. ^{99m}Tc-MIBI scan results were compared with the pathology results to assess the sensitivity, specificity, positive and negative predictive values of ^{99m}Tc-MIBI in detection of lung malignancies and differentiating benign from malignant pulmonary lesions. An illustrative image of ^{99m}Tc-MIBI SPECT in a patient with true-positive results is shown in Fig. 1. A χ^2 -test was performed to determine the statistical differences.

Quantitative study: Regions Of Interest (ROI) were drawn over the lesions, the rest of the lung and the left ventricle in all patients (Fig. 2). By assigning ROIs to the images of the patients, the mean counts per pixel were calculated and the uptake ratios of the heart to the mass (H/M), the Heart to the Lung (H/L) and the Mass to the Lung (M/L) were calculated. These ratios were presented as average±SD.

The statistical significance between H/M and H/L was assessed by Mann-Whitney U-test. A Wilcoxon test was used to determine the statistical significance between early and late uptake ratios.

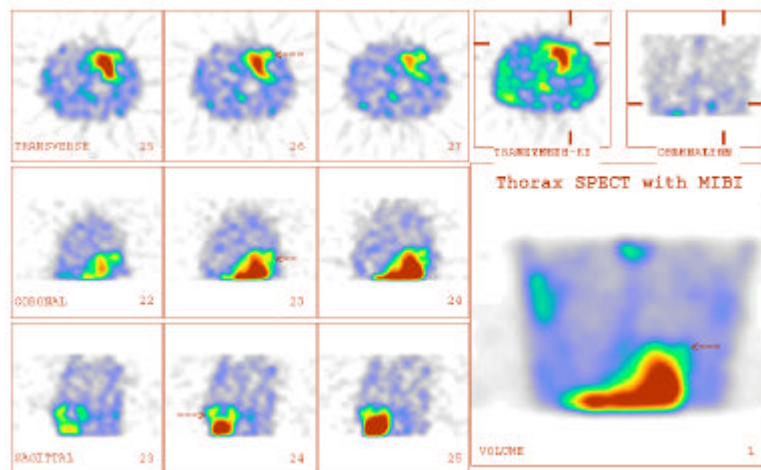


Fig. 1: An illustrative image of ^{99m}Tc-MIBI SPECT in a patient with squamous cell carcinoma in lingual superior segment of left lung (arrow)

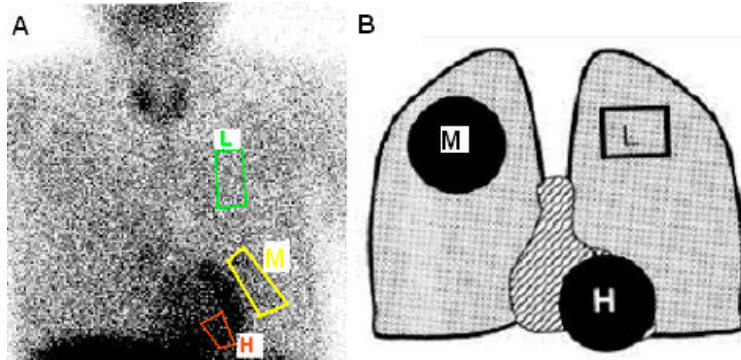


Fig. 2: Quantitative assessment of ^{99m}Tc-MIBI uptake in pulmonary mass. Anterior spot view of chest with regions of interest (A), schematic representation of regions of interest (B) (M: Mass, L: Lung, H: Heart)

RESULTS

Thirty patients (25 men and 5 women) with mean age (range) of 56±13 (26-76) years with a pulmonary mass were included in the study. Table 2 presents the characteristics and histopathological features of each case. Twenty patients (67%) had malignant and 10 patients (33%) had benign lung lesions. Ninety percent (18/20) of patients with lung malignancies had Primary Lung Cancer (PLC) and other ones (2/20) had metastatic lung cancer (one from gastric adenocarcinoma and one malignant lymphoma). Most of PLC's were squamous and small cell carcinomas, 60 and 30% respectively. Malignant lesions qualitatively had higher rate of positive scans comparing to benign lesions, [16/20 (80%) vs. 3/10 (30%), respectively ($p = 0.015$)]. It was shown that 75% (9/12) of patients with squamous cell carcinoma and 83% (5/6) of patients with small cell carcinoma had positive scans (Table 1). According to results of this study ^{99m}Tc-MIBI has sensitivity, specificity, positive and negative predictive values of 80, 70, 84 and 64% in the definition of malignancy in radiologically suspicious malignant lung masses, respectively. There is no statistically significant correlation between ^{99m}Tc MIBI uptake and chief complaint, sex, presence or absence of calcification in mass, size of mass (all masses were larger than 2 cm) and peripheral shape of tumors at this study.

Considering all patients, early and late M/L uptake ratios were 1.17±0.12 and 1.16±0.13, respectively. The difference was not significant ($p>0.05$). The early and late uptake ratios were 2.18±0.23 and 2.45±0.28 ($p<0.01$) in masses (H/M) and 2.55±0.28 and 2.79±0.42 ($p<0.01$) in the rest of the lung (H/L), respectively. While the differences

Table 1: Qualitative assessment of 99 m Tc-MIBI scans in pulmonary masses

Characteristics	MIBI positive	MIBI negative
Malignant (n = 20)	16	4
Benign (n = 10)	3	7

between mass and lung uptake ratios were significant ($p<0.01$), no significant differences were found between early and late uptake ratios in masses and lungs (Table 2).

Malignant lung lesions revealed high M/L ratio comparing to benign lesions (1.21±0.12 vs. 1.09±0.07, $p<0.01$). However, no significant difference was detected in H/M and H/L ratios between malignant and benign lesions and also between early and late M/L uptake ratios ($p>0.05$) (Table 2).

The early M/L ratio for squamous cell tumors was 1.17±0.13 and 1.29±0.08 for small cell carcinomas. The late M/L ratio for squamous cell tumors was 1.17±0.10 and 1.26±0.16 for small cell tumors. In small cell tumors, early ^{99m}Tc-MIBI uptake were higher than squamous cell tumors and the differences were significant ($p<0.05$). The differences between early and late M/L ratios in each tumor type were not significant ($p>0.05$).

DISCUSSION

Accurate differentiation between malignant and benign lesions via a noninvasive procedure using radiopharmaceuticals is the pleasure aim of most studies, however to date no effective compound has been available. Despite the use of advanced CT techniques such as contrast enhancement, high resolution CT scanning, densitometry using reference phantoms and spiral CT scans, a significant number of single pulmonary nodules remain indeterminate (Cortese, 1982).

Table 2: ^{99m}Tc-MIBI uptake ratios and histological types of lung mass (H: Heart, L: Lung, M: Mass, Ca: cancer, SD: standard deviation)

No.	Histological type	Early			Delay		
		H/M	H/L	M/L	H/M	H/L	M/L
1	Squamous Cell Ca	2.11	2.82	1.32	2.68	3.18	1.18
2		2.28	2.77	1.21	2.45	2.87	1.17
3		2.1	2.68	1.27	2.51	3.07	1.22
4		2.19	2.33	1.06	2.34	2.76	1.18
5		2.3	2.9	1.26	2.85	3.12	1.09
6		2.42	3.56	1.47	2.75	3.67	1.33
7		2.4	2.71	1.13	2.58	2.85	1.1
8		2.29	2.65	1.15	2.59	2.95	1.39
9		2.24	2.46	1.1	2.45	2.78	1.13
10		2.47	2.57	1.05	2.69	2.8	1.04
11		2.08	2.23	1.07	2.34	2.63	1.12
12		2.3	2.43	1.05	2.51	2.77	1.1
	SCC Mean±SD	2.27±0.13	2.68±0.34	1.18±0.13	2.56±0.16	2.95±0.28	1.17±0.10
13	Small cell Ca	1.9	2.4	1.26	2.21	2.67	1.21
14		1.79	2.46	1.37	2.13	2.89	1.35
15		2.1	2.43	1.15	2.44	3.67	1.5
16		1.76	2.35	1.33	2.12	2.77	1.3
17		2.08	2.81	1.35	2.25	2.3	1.02
18		1.88	2.37	1.26	2.28	2.77	1.21
	Small cell Ca Mean±SD	1.92±0.14	2.47±0.17	1.29±0.08	2.24±0.12	2.85±0.45	1.27±0.16
19	Gastric adenocarcinoma	2.48	2.76	1.11	2.99	3.51	1.17
20	Lymphoma	1.84	2.29	1.24	1.46	2.18	1.49
	Malign Mean±SD	2.15±0.23	2.60±0.30	1.21±0.12	2.43±0.33	2.91±0.39	1.22±0.14
21	Hidatid Cyst	2.46	2.56	1.04	2.58	2.70	1.05
22	Hidatid Cyst	2.28	2.4	1.05	2.5	2.61	1.04
23	TB	1.76	2.13	1.21	2.38	2.69	1.13
24	TB	1.92	2.08	1.08	2.06	2.14	1.04
25	Lung abscess	2.58	2.64	1.02	2.75	2.81	1.02
26	Lung abscess	2.48	2.51	1.01	2.7	2.73	1.01
27	Wegner granulomatosis	2.24	2.65	1.18	2.57	2.81	1.09
28	Sarcoidosis	2.31	2.77	1.2	2.57	2.94	1.14
29	Giant cell granuloma	2.08	2.23	1.07	2.35	2.43	1.03
30	Hamartoma	2.42	2.57	1.06	2.55	2.71	1.06
	Benign Mean±SD	2.25±0.26	2.45±0.24	1.09±0.08	2.51±0.20	2.56±0.40	1.06±0.05
	Total Mean±SD	2.18±0.24	2.55±0.29	1.17±0.12	2.46±0.29	2.79±0.42	1.16±0.14

Of the available radionuclides thallium-201 and gallium-67 are used for this purpose. Thallium- 201 suffers from a lack of specificity due to uptake in granulomatous inflammation such as tuberculosis and sarcoidosis (Abdel-Dayem *et al.*, 1994). ^{99m}Tc-MIBI has been reported to accumulate in tumors. Although the tumor uptake mechanism is not clearly defined, possible factors that affect ^{99m}Tc-MIBI uptake by tumors are its lipophilicity, cell membrane potential, mitochondrial content, increased tumor blood flow, capillary permeability and P-glycoprotein (Pgp) activity (Piwnica-Worms *et al.*, 1990; Chin *et al.*, 1990; Scopinaro *et al.*, 1994; Piwnica-Worms *et al.*, 1993). Muller *et al.* (1989) were the first to describe increased uptake of ^{99m}Tc-MIBI in bronchogenic carcinoma (Muller *et al.*, 1989). There have been several studies in the literature on the use of ^{99m}Tc-MIBI for differentiating benign from malignant lung tumors. In these studies, the sensitivity and specificity of ^{99m}Tc-MIBI for detecting primary lung cancer were various and were within 65-96% and 50-100%, respectively (Abdel-Dayem *et al.*, 1994; Hassan *et al.*, 1989; Yang *et al.*, 1999; Kao *et al.*, 1993; LeBouthiller *et al.*, 1993).

Minai *et al.* (2000) suggested that ^{99m}Tc-MIBI SPECT scanning has a high specificity for malignancy. The

clinical implication of the finding of a very high specificity and positive predictive value is that, in the case of a pulmonary mass whose nature is indeterminate after non-invasive evaluation, a positive ^{99m}Tc-MIBI scan may help to avoid unnecessary invasive diagnostic testing and allow the physician to proceed directly to thoracotomy. In addition, it may be helpful in cases where non-invasive testing is suspicious for malignancy but the patient has impaired cardiopulmonary function such that the risks of thoracotomy are judged to be high. A positive MIBI scan would increase the patient's and physician's level of comfort that surgical intervention is necessary and worth the risk (Minai *et al.*, 2000). Present study had a low negative predictive value which may be due in part to a low prevalence of benign lesions in our patient population.

It has previously been reported that undifferentiated squamous cell carcinomas can be negative by MIBI SPECT scanning (Hassan *et al.*, 1989). Nishiyama *et al.* (1997) found that squamous cell carcinomas had lower Tumor /Normal lung ratios [2.5 (0.9)] than adenocarcinomas [2.7 (1.4)] and small cell carcinomas [3.0 (1.1)]. The degree of ^{99m}Tc-MIBI accumulation in the malignant lung tumors differed in each histological type, where ^{99m}Tc-MIBI uptake in small cell carcinoma was

higher than in squamous cell tumors (Sahin *et al.*, 1999). In our study group 25% (3/12) of SCC patients had negative scan whereas 17% (1/6) of small cell carcinomas had negative scans.

Easy availability and lower cost of ^{99m}Tc-MIBI SPECT compared with positron emission tomography, coupled with its high specificity and positive predictive value, make it attractive as a diagnostic modality. On the other hand, there are some case reports of bronchioloalveolar cell carcinoma with a false negative finding in FDG imaging and a positive finding in MIBI imaging, which indicates that the FDG uptake and MIBI uptake might provide different information regarding characteristics of lung cancer (Higuchi *et al.*, 2003).

The low negative predictive value in this study suggests that, if the scan is negative, further work up is needed to establish the final diagnosis. We conclude that, Tc-99m MIBI SPECT imaging can be helpful in the evaluation of suspicious pulmonary masses due to its high specificity and positive predictive value in determination of malignancy.

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