F-18-2-Fluoro-2-Deoxyglucose Positron Emission Tomography Compared to Technetium-99m Hexakis-2-Methoxyisobutyl Isonitrile Single Photon Emission Chest Tomography in the Diagnosis of Indeterminate Lung Lesions

Mario Santini^a Alfonso Fiorelli^a Giovanni Vicidomini^a Paolo Laperuta^a
Luigi Busiello^a Pier Francesco Rambaldi^b Luigi Mansi^b Antonio Rotondo^b

^aThoracic Surgery Unit and ^bDepartment of Radiology and Nuclear Medicine, Second University of Naples, Naples, Italy

Key Words

¹⁸FDG-PET • Lung cancer • Lung mass • Positron emission tomography • Single photon emission chest tomography • Solitary pulmonary nodule • Technetium-99m hexakis-2-methoxyisobutyl isonitrile

Abstract

Background: ¹⁸FDG-PET plays a significant role in diagnosing malignancy of lung lesions but remains an expensive test available at a limited number of sites in Italy. **Objective:** We prospectively compare the diagnostic accuracy of ^{99m}Tc-MIBI-SPECT and ¹⁸FDG-PET in patients with indeterminate lung lesions to demonstrate that ^{99m}Tc-MIBI-SPECT may be considered as a valid alternative when ¹⁸FDG-PET is not available. **Methods:** 52 patients with indeterminate lung lesion were examined by ¹⁸FDG-PET and ^{99m}Tc-MIBI-SPECT before surgery. The scintigraphic findings were analyzed visually and semiquantitatively and then correlated to the definitive diagnosis. **Results:** 38 were malignant lesions while 14 were benign. At visual analysis, the sensitivities of ¹⁸FDG-PET and ^{99m}Tc-MIBI-SPECT were 92 and 84%, respectively (McNemar

test $p = 0.4$), whereas the specificities were 78.6 and of 93% ($p = 1.0$), respectively. At semiquantitative analysis, ¹⁸FDG-PET showed a sensitivity and specificity of 92 and 71.4%, respectively, while ^{99m}Tc-MIBI-SPECT produced a sensitivity and specificity of 86 and 100%, respectively ($p = 0.194$). For lymph node staging, ¹⁸FDG-PET and ^{99m}Tc-MIBI-SPECT have a sensitivity and specificity of 88 and 92 of 77 and 100%, respectively. **Conclusion:** ^{99m}Tc-MIBI-SPECT is similar to ¹⁸FDG-PET in the detection of lung malignancies and represents an alternative when PET is not available. Yet, the combination of both techniques may improve patient selection for surgery.

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AUC = Area under the ROC curve; BAC = bronchioloalveolar carcinoma; CI = confidence interval; CT = chest tomography; ¹⁸FDG-PET = F-18-2-fluoro-2-deoxyglucose positron emission tomography; GLUT = glucose transporter; NPV = negative predictive value; PPV = positive predictive value; ROC = receiver-operating curve; ROI = region of interest; SE = standard error; SPECT = single photon emission chest tomography; SUV = standardized uptake value; TB = tuberculosis; ^{99m}Tc-MIBI = technetium-99m hexakis-2-methoxyisobutyl isonitrile.

Introduction

Early detection and accurate staging of lung cancer often present a diagnostic challenge [1]; only one third of pulmonary lesions can be typified based on radiological criteria, while invasive techniques are required in the remaining two thirds [2]. However, after a diagnostic workup according to current international recommendations, up to 50% of surgery performed for indeterminate lung nodules results in resection of a benign nodule. Therefore, the accurate diagnosis is crucial not only for early detection of malignancy, but also to avoid unnecessary thoracotomies for benign lesions [3]. Molecular imaging techniques may play a significant role in optimizing the use of invasive procedures selecting those patients with a greater probability of malignancy. ^{18}F -FDG-PET is the gold standard for diagnosing lung malignancies but remains an expensive test available only at a limited number of sites in Italy. In addition, well-differentiated malignancies such as BAC and carcinoids potentially exhibit low-grade ^{18}F -FDG uptake, whereas uptake in pulmonary TB, fungal infections, and sarcoidosis is occasionally increased [4, 5]. These reasons have generated interest in applying radiopharmaceuticals such as ^{67}Ga , ^{201}Tl , $^{99\text{m}}\text{Tc}$ -depreotide, and $^{99\text{m}}\text{Tc}$ -MIBI in SPECT cameras as an alternative technique for ^{18}F -FDG-PET imaging [6, 7]. In the present study, we prospectively compare the diagnostic accuracy of $^{99\text{m}}\text{Tc}$ -MIBI-SPECT and ^{18}F -FDG-PET in patients with indeterminate lung lesions to demonstrate that $^{99\text{m}}\text{Tc}$ -MIBI-SPECT may be considered as a valid alternative when ^{18}F -FDG-PET is not available.

Materials and Methods

Study Design

A prospective single-center study was performed at the Hospital of the Second University of Naples, Italy, with the aim of comparing the diagnostic role of ^{18}F -FDG-PET and $^{99\text{m}}\text{Tc}$ -MIBI-SPECT in patients with indeterminate lung lesion on CT scan.

Patient inclusion criteria were:

- lung lesion diagnosed based on a CT scan, rounded, ovoid or lobulated in shape, and not associated with visible satellite lesions, and
- subsequent pathological study indicated to establish diagnosis: surgical resection of lesion (thoracotomy or video-assisted thoracic surgery), fine needle aspiration biopsy, or bronchoscopy. Criteria of exclusion were:
- lesions with radiological characteristics of benign (calcifications: laminated, central, or popcorn type) or malignant (spiculated margin) disease,

- history of cancer or a recent pulmonary infection (<15 days), and
- contraindication for invasive procedures.

The clinical assessment included laboratory screening, bone scan, and CT of the total body with a contrast medium. Each lung lesion was measured in its greatest diameter on the transverse axis on CT and defined as solitary pulmonary nodule if ≤ 3 cm in size, completely surrounded by normal lung, and in the absence of lymphadenopathy, according to the standard definition [6]. A lesion >3 cm in size was referred to as mass. Mediastinal lymph nodes >1 cm in diameter were considered as suspicious for metastases [8]. Each patient underwent an ^{18}F -FDG-PET and $^{99\text{m}}\text{Tc}$ -MIBI-SPECT before the invasive procedure and completed within 10 days of each other. Scintigraphic findings were analyzed visually and semiquantitatively, and then correlated to the definitive diagnosis based on histopathological findings or clinical and radiological follow-up. Finally, patients with lung malignancy (stage I or II) underwent surgical resection and mediastinal lymph node dissection. The protocol of this study was approved by the Hospital Ethics Committee of the Second University of Naples, and written informed consent was obtained from all patients before inclusion in the study.

Study Population

Between January 2006 and September 2008, 52 consecutive patients (36 men, 16 women; median age: 65.5; range: 34–79 years) met the inclusion criteria. Of these, 30/52 (57.6%) had solitary pulmonary nodules (range 1–3 cm, mean $\pm$ SD: 2.4 ± 0.10) whereas 22/52 (42.3%) had lung mass (range: 3.5–6 cm, mean $\pm$ SD: 4.67 ± 0.82) according to our definition. Only 1 patient was excluded because unfit for interventional procedures.

^{18}F -FDG-PET

After a 6-hour fast, each patient received 18.5 MBq (0.5 mCi)/10 kg of body weight of ^{18}F -FDG intravenously. Serum glucose levels just before the injection of ^{18}F -FDG were ≤ 120 mg/dl in all patients. Imaging started 50–70 min after tracer injection using 3D dedicated PET (Siemens EXACT HR+ or ART) scanning from the base of the brain to the level of the proximal thighs. Transmission scans using a ^{68}Ge pin or ^{137}Cs source were also performed and allowed the calculation of attenuation correction factors that were used to correct the ^{18}F -FDG emission data. The attenuation-corrected and non-corrected emission data were reconstructed with an iterative reconstruction algorithm using an ordered subset expectation maximization method.

$^{99\text{m}}\text{Tc}$ -MIBI-SPECT

A commercial $^{99\text{m}}\text{Tc}$ -MIBI preparation (Cardiolite; Squib International) was used. SPECT data were acquired 5 min after injecting the tracer while using a large-field-of-view, double-head rectangular gamma camera (ECAM; Siemens) equipped with low-energy, high-resolution, parallel-hole collimators; a 20% symmetric window at 140 keV; a 128×128 word matrix, zoom 1.45; an elliptic orbit with step-and-shoot acquisition at 3° intervals over 360° (180° per head), and a 20-second dwell time per stop. After prefiltration with a count-optimized Metz filter, images were reconstructed with a ramp filter to produce 4-pixel-thick transaxial slices. Coronal and sagittal views were then obtained.

Table 1. Characteristics of the patients (n = 38) with malignant pulmonary lesions (means $\pm$ SD)

Diagnosis	n	Size	PET		SPECT	
			positive on visual analysis	SUV	positive on visual analysis	T/N
Squamous cell carcinoma	23	3.6 $\pm$ 1.4	23	11.1 $\pm$ 3.6	19	1.7 $\pm$ 0.3
Adenocarcinoma	7	2.9 $\pm$ 1.0	7	7.9 $\pm$ 3.2	6	1.7 $\pm$ 0.4
BAC	3	2.6 $\pm$ 1.3	1	4.5 $\pm$ 4.2	3	1.8 $\pm$ 0.5
Large cell carcinoma	3	2.5 $\pm$ 0.5	3	9.5 $\pm$ 2.2	2	1.6 $\pm$ 0.3
Carcinoid	1	4.0	0	2.1	1	2.1
Metastasis	1	2.3	1	0	1	1.6

Imaging Interpretation

The study results were independently assessed by two nuclear medicine specialists blinded to each other and the final results of the true lesion status.

Visual Analysis

The ^{18}F -FDG and $^{99\text{m}}\text{Tc}$ -MIBI-SPECT examinations were reconstructed in three orthogonal planes (transaxial, sagittal, and coronal). The images were visually compared with the chest CT scan at the same time to aid in locating focal lesions without avid uptake of tracer. Scans were qualitatively interpreted by the investigators as abnormal (positive) or normal (negative) in view of the presence or absence of an increased uptake of ^{18}F -FDG or $^{99\text{m}}\text{Tc}$ -MIBI in the area of the lesion compared with background. Disagreements were resolved by consensus, with a third observer as referee.

^{18}F -FDG Semiquantitative Analysis

ROIs were defined manually on the transaxial tomograms with the highest uptake in the middle of the tumor lesion. The ROIs placed on the lesion encompassed all the pixels that had uptake values $>90\%$ of the maximum uptake in that slice, and the average SUV, calculated as tumor concentration of tracer per injected tracer dose per body weight, was considered.

$^{99\text{m}}\text{Tc}$ -MIBI-SPECT Semiquantitative Analysis

It was based on the lesion count number on SPECT slices. Circular ROIs were manually defined on the lesion (T) in several transaxial sections and the highest tumor activity was selected. The same ROI in the contralateral normal lung (N) was considered as background activity, and the T/N ratio was calculated for each patient.

Evaluation of Lymphadenopathy

Qualitative analysis of nodal involvement was performed. Foci of FDG and MIBI uptake greater than the activity of mediastinal background were considered positive for nodal metastases. Semiquantitative analysis was not performed, because the small size of the nodal metastases resulted in underestimation due to partial volume effect.

Statistical Analysis

Sensitivity, specificity, PPV and NPV were computed in the standard manner. McNemar and χ^2 tests were used for differ-

Table 2. Comparison of visual analysis findings of FDG PET and MIBI SPECT in diagnosing lung malignancy (n = 38)

	FDG PET+	FDG PET–
MIBI SPECT+	29	3 ¹
MIBI SPECT–	6 ²	0

¹ Two BAC and 1 carcinoid tumor.

² Four squamous cell carcinomas, 1 large cell carcinoma, and 1 adenocarcinoma.

ences between the results of both methods. The Mann-Whitney test and ROC curves were assessed for the comparison of quantitative variables. $p < 0.05$ was considered statistically significant. MedCalc® statistical software was used for analysis.

Results

Thirty-eight (73%) patients had malignant lesions: 23 squamous cell carcinomas, 7 adenocarcinomas, 3 BACs, 3 large cell carcinomas, 1 carcinoid tumor, and 1 metastasis to the lung from another organ. Twenty-eight (73.6%) lesions were peripheral. The diagnosis was obtained via fine needle aspiration biopsy (n = 25) and bronchoscopy (n = 10), while 3 patients with a negative cytology were diagnosed postoperatively. In 28/38 patients the tumor was completely removed, in 8 it was potentially not suitable for resection (stage II/III); in 2 cases resection was contraindicated.

Fourteen (27%) patients had benign disease: 5 sequelae of pneumonia, 2 active TBs, 3 tuberculomas, 1 chronic abscess, 2 hamartomas, and 1 fibrotic nodule. Twelve (85.7%) lesions were peripheral. In 4 patients, the diagnosis was established by means of surgical resection where-

Table 3. Characteristics of the patients (n = 14) with benign pulmonary lesions (means $\pm$ SD)

Diagnosis	n	Size	PET		SPECT	
			negative on visual analysis	SUV	negative on visual analysis	T/N
Pneumonia	5	2.8 $\pm$ 0.4	4	3.7 $\pm$ 1.7	5	1.1 $\pm$ 0.1
Tuberculoma	3	2.3 $\pm$ 0.5	2	4.3 $\pm$ 2.5	3	1.1 $\pm$ 0.7
Active TB	2	2.2 $\pm$ 0.1	1	2.5 $\pm$ 2.0	1	1.3 $\pm$ 0.3
Hamartoma	2	3	2	2.5 $\pm$ 1.3	2	1.2 $\pm$ 0.2
Abscess	1	2.3	1	5.7	1	1.1
Fibrotic nodule	1	5	1	4	1	1.1

Table 4. Comparison of visual analysis findings of FDG PET and MIBI SPECT in diagnosing benign lung lesions (n = 14)

	FDG PET+	FDG PET–
MIBI-SPECT+	1 ¹	0
MIBI-SPECT–	2 ²	11

¹ One active TB.² One patient with sequelae of pneumonia and 1 with tuberculoma.

as in the remaining 10 patients, the benign nature was confirmed by the absence of malignant cells in histological specimens obtained by invasive procedures and clinical follow-up after medical therapy.

The mean size $\pm$ SD of malignant and benign lesions was 3.48 $\pm$ 1.37 (range 1.0–6.0) and 2.96 $\pm$ 0.97 (range 1–5) cm, respectively.

Visual Analysis

Concordant positive results were seen in 29 of 38 (76%) lung malignancies (table 1). ^{99m}Tc-MIBI-SPECT identified 3 additional lung cancers that ¹⁸F-FDG-PET did not reveal whereas ¹⁸F-FDG-PET detected 6 additional lung cancers that ^{99m}Tc-MIBI-SPECT failed to visualize (table 2). The sensitivity and NPV of ¹⁸F-FDG-PET and ^{99m}Tc-MIBI-SPECT in the diagnosis of lung malignancies were 92 (35/38) and 78%, respectively, and 84 (32/38) and 68%, respectively, but the difference was not significant (McNemar test, p = 0.4, difference: 7.89, 95% CI: 7.64–16.76). ¹⁸F-FDG-PET was more sensitive than MIBI-SPECT in the detection of squamous cell carcinomas (23/23 = 100% vs. 19/23 = 82.6%, respectively) and of large cell carcinomas (3/3 = 100% vs. 2/3 = 66%, respectively)

whereas ^{99m}Tc-MIBI-SPECT provided higher sensitivity than ¹⁸F-FDG-PET in the detection of BAC (3/3 = 100% vs. 1/3 = 33%, respectively). Our series included only 1 case of carcinoid tumor positive at ^{99m}Tc-MIBI-SPECT but negative at ¹⁸F-FDG-PET.

Combining the results of both tests and interpreting a lesion as malignant when either scan result was positive yielded a sensitivity of 100% (38/38), which was not significantly different from the sensitivity of ¹⁸F-FDG-PET alone (McNemar test, p = 0.25, 95% CI: 3.08–7.09, difference: 7.89%) but significantly different from that of ^{99m}Tc-MIBI-SPECT alone (McNemar test, p = 0.03, 95% CI: 1.28–15.79, difference: 17.59%).

Regarding benign lesions (table 3), ¹⁸F-FDG-PET and ^{99m}Tc-MIBI-SPECT showed no uptake for the same benign lesion (active TB, size 4 cm) while two more false-positive results (sequelae of pneumonia, size 5 cm, and tuberculoma, size 2 cm) were seen on ¹⁸F-FDG-PET (table 4).

The specificity values and PPVs of ¹⁸F-FDG-PET and ^{99m}Tc-MIBI-SPECT were 78 (11/14) and 92%, respectively, and 92.8 (13/14) and 97%, respectively, but the difference was not significant (McNemar test, p = 0.5, difference: 14.29%, 95% CI: 8.77–14.29).

Combining the results of both tests and interpreting a lesion as benign when either scan results were negative yielded a specificity of 78.5% (11/14), which was similar to that of ¹⁸F-FDG PET alone but lower than that of ^{99m}Tc-MIBI-SPECT alone (McNemar test, p = 0.5, difference: 14.2%; 95% CI: 16.95–26.22).

Regarding lesion diameter (table 5), for lesions $\leq$ 3 cm ¹⁸F-FDG-PET had a higher sensitivity than ^{99m}Tc-MIBI-SPECT (88.8 vs. 83.3%, respectively), but the difference was not statistically significant (McNemar test, p = 1.0, difference: 5.56%, 95% CI: 3.72–5.56). In contrast, ^{99m}Tc-MIBI-SPECT had a higher specificity than ¹⁸F-FDG-PET (100 vs. 83.3%, respectively), but the difference was not

Fig. 1. **a** FDG uptake was significantly higher in malignant than benign lesions: 9.8 ± 3.77 vs. 4.3 ± 2.78 (z-test value: 4.33; $p < 0.0001$). **b** MIBI uptake was significantly higher in malignant than benign lesions: 4.3 ± 2.78 vs. 1.1 ± 0.14 (z-test value: 5.03; $p < 0.0001$), respectively.

Fig. 2. In malignant lesions, FDG uptake (**a**) and MIBI uptake (**b**) did not significantly differ between lesions >3 and ≤ 3 cm. **a** 11.0 ± 4.1 vs. 8.7 ± 3.0 (z-test value: 1.82; $p = 0.06$), respectively. **b** 1.8 ± 0.3 vs. 1.6 ± 0.3 (z-test value: 1.64; $p = 0.09$), respectively.

Table 5. Sensitivity and specificity of FDG-PET and MIBI-SPECT in diagnosing lung malignancy lesions (n = 52) according to lesion size

Size of lesion	Sensitivity		Specificity	
	FDG-PET	MIBI-SPECT	FDG-PET	MIBI-SPECT
≤ 3 cm	16/18 (88.8%) ¹	15/18 (83.3%) ¹	10/12 (83.3%) ²	12/12 (100%) ²
> 3 cm	19/20 (95%) ³	17/20 (85%) ³	1/2 (50%)	1/2 (50%)

¹ McNemar test, $p = 1.0$, difference: 5.56%, 95% CI: 3.72–5.56. ² McNemar test, $p = 0.5$, difference: 16.67%, 95% CI: 10.24–16.67. ³ McNemar test, $p = 0.5$, difference: 10%, 95% CI: 6.4–10.

statistically significant (McNemar test, $p = 0.5$, difference: 16.6%, 95% CI: 10.24–16.67). For lesions > 3 cm, both methods showed the same specificity (50%) but the sensitivity of ^{18}F -FDG-PET was higher than that of $^{99\text{m}}\text{Tc}$ -MIBI-SPECT (95 vs. 85%, respectively) with no statistically significant difference (McNemar test, $p = 0.5$, difference: 10%, 95% CI: 6.4–10).

In 11 of the 52 patients, discordant findings between the results of the two radionuclide examinations were observed. ^{18}F -FDG-PET was more right in 6/11 cases (54.5%) compared to 5/11 (45.4%) with $^{99\text{m}}\text{Tc}$ -MIBI-

SPECT. However, the difference was not significant (χ^2 test, $p = 0.9$, 95% CI: 32.5–50.71; difference: 9.10%).

Quantitative Analysis

FDG uptake (fig. 1a) and MIBI uptake (fig. 1b) were significantly higher in the malignant than in the benign lesions [9.8 ± 3.77 vs. 4.3 ± 2.78 (z-test value: 4.33; $p < 0.0001$) and 4.3 ± 2.78 vs. 1.1 ± 0.14 (z-test value: 5.03; $p < 0.0001$), respectively]. In malignant lesion, FDG uptake (fig. 2a) and MIBI (fig. 2b) uptake were not significantly higher in lesions > 3 versus ≤ 3 cm [11.0 ± 4.1 vs.

Fig. 3. a Considering the peak SUV at a cutoff point of 5.7, sensitivity, specificity, PPV, and NPV were 92, 71.4, 94.6, and 80%, respectively (AUC: 0.854, SE: 0.05, 95% CI: 0.729–0.937). **b** Considering the T/N ratio at a cutoff point of 1.36, sensitivity, specificity, PPV, and NPV were 86, 100, 100, and 73.7%, respectively (AUC: 0.959, SE: 0.026, 95% CI: 0.863–0.993).

8.7 ± 3.0 (z-test value: 1.82; $p = 0.06$) and 1.8 ± 0.3 vs. 1.6 ± 0.3 (z-test value: 1.64; $p = 0.09$), respectively]. Considering $SUV \geq 5.7$, sensitivity, specificity, PPV, and NPV of 92, 71.4, 94.6 and 80%, respectively, were obtained (AUC: 0.854, SE: 0.05, 95% CI: 0.729–0.937; fig. 3a) while for $T/N \geq 1.36$ sensitivity, specificity, PPV, and NPV were 86, 100, 100, and 73.7%, respectively (AUC: 0.959, SE: 0.026, 95% CI: 0.863–0.993; fig. 3b). However, comparison of ROC curves revealed not statistically significant differences (difference between AUCs: 0.064, SE: 0.049, 95% CI: 0.033–0.160, $p = 0.194$; fig. 4).

Lymph Node Evaluation

In the patients with lung malignancy, 36 pathologic results of lymph node staging were obtained while in patients with benign lesion ($n = 14$) lymph nodes were classified as negative. Of the 9 patients with positive lymph node pathology, ^{18}F -FDG-PET and ^{99m}Tc -MIBI-SPECT detected 8/9 and 7/9, respectively, with sensitivities of 88 and 77%, respectively, and NPV of 97 and 94%, respectively. All benign lymph nodes were negative at ^{99m}Tc -MIBI-SPECT (specificity 100%, PPV: 100%) whereas only 1 of the benign lymph nodes showed uptake at ^{18}F -FDG-

Fig. 4. Comparison of ROC curves revealed nonsignificant differences between ^{18}F -FDG-PET and ^{99m}Tc -MIBI-SPECT for the evaluation of lung malignancy (difference between areas: 0.064, SE: 0.049, 95% CI: 0.033–0.160, $p = 0.194$).

Fig. 5. A 70-year-old woman with squamous cell carcinoma (T2N0M0). CT scan shows primary tumor of the right upper lobe surrounded by normal lung tissue, ≤ 3.5 cm in its largest diameter, without evidence of hilar or mediastinal adenopathy (a). ^{18}F -FDG-PET (b) and $^{99\text{m}}\text{Tc}$ -MIBI SPECT (c) in transaxial view demonstrate an area of increased abnormal uptake corresponding to lung cancer.

Table 6. Sensitivity, specificity, PPV and NPV of FDG-PET, MIBI-SPECT and CT, respectively, for the evaluation of lymph node metastasis

	FDG-PET	MIBI-SPECT	CT
Sensitivity	88% ^a	77% ^b	66% ^c
Specificity	92% ^d	100% ^e	92%
PPV	88%	100%	83%
NPV	97%	95%	91%

McNemar test, $p = 1.0$, difference: 11.1%, 95% CI: 7.43–11.1 (^a versus ^b); $p = 0.25$, difference: 33.3%, 95% CI: 13.01–33.1 (^a versus ^c); $p = 0.5$, difference: 22.2%, 95% CI: 13.65–22.22 (^b versus ^c), and $p = 1.0$, difference: 2.44%, 95% CI: 1.63–2.44 (^d versus ^e).

PET (specificity 92%, PPV: 88%). However, no significant difference was found in sensitivity (McNemar test, $p = 1.0$, difference: 11.1%, 95% CI: 7.43–11.1) and specificity (McNemar test, $p = 1.0$, difference: 2.44%, 95% CI: 1.63–2.44, $p = 1.0$) of ^{18}F -FDG-PET and $^{99\text{m}}\text{Tc}$ -MIBI. Using CT, 5/9 metastatic lymph nodes and 1/14 non-metastatic lymph nodes were >1 cm in size (sensitivity, specificity, PPV, and NPV value of 66, 92, 83.3, and 91%, respectively). No statistically significant differences were found of CT versus ^{18}F -FDG-PET and $^{99\text{m}}\text{Tc}$ -MIBI-SPECT, respectively (table 6). Representative cases of FDG and MIBI uptake of lung lesion are depicted in figures 5 and 6.

Discussion

Our results show that both techniques have similar accuracy in diagnosing lung malignancy in agreement with a previous study by Wang et al. [9]. However, the important difference is that they report only patients with lung malignancy ($n = 19$) whereas in our study patients with malignant ($n = 38$) and benign lesions ($n = 14$) were investigated. At visual analysis, ^{18}F -FDG-PET shows a sensitivity and specificity of 92 and 78%, respectively, in agreement with a meta-analysis by Gould et al. [4] who obtained mean values of 96 and 74% for sensitivity and specificity, respectively, after assessment of 1,474 patients with indeterminate lung lesions. On the other hand, using $^{99\text{m}}\text{Tc}$ -MIBI-SPECT sensitivity and specificity were 84 and 92.8%, respectively, being lower than those observed by Minai et al. [10] and Nosotti et al. [11], who reported sensitivity and specificity values of 85 and 100, and 89 and 100%, respectively. In theory, the reduction in sensitivity and specificity seen in our group may be related to misinterpreted areas of radiotracer accumulation by visual evaluation, which depended on the experience of the readers. Consequently, 1 patient with active TB had a low MIBI increase (T/N value: 1.2) but the SPECT image was considered ‘positive’ while in 2 patients with squamous cell carcinoma (T/N value: 1.39 and 1.37, respectively), the tracer uptake is restricted to the periphery of the lesion with a central hypoactive focus, but SPECT images are considered as ‘negative’. Thus, semiquantitative analysis of SPECT results revealed higher sensitivity and of specificity values than those observed by visual analy-

Fig. 6. A 53-year-old man with adenocarcinoma of the left upper lobe and an enlarged mediastinal lymph node (T2N2M0). CT scan shows a large mass in the left upper lobe (size: 4.5 cm) and an enlarged (size: 1.5 cm) mediastinal lymph node (a). Transverse image of FDG-PET (b) and MIBI-SPECT (c) illustrate abnormal uptake in the areas corresponding to the lesion and mediastinal lymph node.

sis (84 vs. 86 and 92.8 vs. 100%, respectively). In contrast, ^{18}F FDG-PET semiquantitative analysis provides a similar sensitivity (92%) but lower specificity (71%) than that reported by visual evaluation, in agreement with the data of Lowe et al. [12] and Gould et al. [4], who observed no diagnostic advantage to using SUV over visual inspection.

Yet, the combination of ^{18}F FDG-PET and $^{99\text{m}}\text{Tc}$ -MIBI-SPECT provides strong sensitivity and NPV (100%) and more modest specificity and PPV (78 and 82%, respectively). The clinical implication is that if ^{18}F FDG-PET and $^{99\text{m}}\text{Tc}$ -MIBI-SPECT imaging findings are both negative in a patient with a lesion that is estimated to have a low likelihood of being malignant, lung cancer can be ruled out with a reasonable degree of reliability, and invasive diagnostic procedures like surgical resection may be avoided with significant cost savings. Conversely, in case of a pulmonary lesion with indeterminate nature after noninvasive evaluation, a positive ^{18}F FDG-PET and $^{99\text{m}}\text{Tc}$ -MIBI-SPECT may help to avoid unnecessary invasive diagnostic testing and allow the physician to proceed directly to surgical resection. In addition, it may be helpful in cases where noninvasive testing is suspicious for malignancy but the patients have impaired cardiopulmonary function such that the risks of surgical resection are judged to be too high.

Moreover, ^{18}F FDG-PET is superior in terms of diagnostic sensitivity for lymph node involvement compared with $^{99\text{m}}\text{Tc}$ -MIBI-SPECT. Hypothetically, it may be explained considering that a positive ^{18}F FDG-PET shows higher contrast imaging compared with the lower spa-

tial resolution and counting/sensitivity of $^{99\text{m}}\text{Tc}$ -MIBI-SPECT. Conversely, $^{99\text{m}}\text{Tc}$ -MIBI-SPECT provides better specificity and PPV than ^{18}F FDG-PET. If the specificity and PPV of 100% of $^{99\text{m}}\text{Tc}$ -MIBI-SPECT reported in our study are confirmed by other extensive clinical trials, for lymph nodes >1 cm at CT, and positive at $^{99\text{m}}\text{Tc}$ -MIBI-SPECT and ^{18}F FDG-PET, histological confirmation may not be necessary, especially in high-risk patients, considering that mediastinoscopy, actually the standard strategy of lymph node staging, remains an invasive method with acknowledged risk of morbidity [8].

As reported in the Results, in 11 of our 52 patients findings were discordant between the two radionuclide examinations. First, a carcinoid tumor (size: 4 cm) and two BAC (size: 3 and 2.2 cm, respectively) revealed uptake of $^{99\text{m}}\text{Tc}$ -MIBI-SPECT whereas they were not visualized by ^{18}F FDG-PET. The low ^{18}F FDG accumulation in carcinoid tumors is well known and may be ascribed to its low growth rate [12]; Higuchi et al. [13] reported a case of BAC negative at ^{18}F FDG-PET but positive at $^{99\text{m}}\text{Tc}$ -MIBI uptake. This phenomenon may be due to different mechanisms of ^{18}F FDG and $^{99\text{m}}\text{Tc}$ -MIBI uptake in tumor cells. ^{18}F FDG is transported, phosphorylated and metabolically trapped in tumor cells as ^{18}F FDG-6-phosphate whose increased accumulation involves overexpression of GLUT 1 and GLUT 3 in the cell membrane compared with normal tissue [14]. However, GLUT 1 expression is correlated with the degree of cell differentiation and its expression is significantly lower in BAC than in non-BAC. In addition, ^{18}F FDG uptake is related to the proliferation potential of lung cancer, which is lower in BAC than in non-BAC

[15]. In contrast, MIBI accumulation depends on several factors as lesional blood flow, mitochondrial membrane potentials and P-glycoprotein expression [16, 17]. Although the precise mechanism is not clear, we hypothesize that blood flow might mainly contribute to the increased MIBI uptake in BAC. Tumor size ≤ 1 cm is another important factor for negative findings in ^{18}F FDG-PET imaging [18], but negative findings were also encountered in cases with lesions of 4, 3 and 2.2 cm in diameter, respectively. Second, 6 lung cancers were identified by ^{18}F FDG-PET but not by $^{99\text{m}}\text{Tc}$ -MIBI-SPECT. At surgery, 3/6 cases present tumor necrosis, which may explain the absence of MIBI uptake due to poor vascularization or low mitochondrial content [19]. Thus, $^{99\text{m}}\text{Tc}$ -MIBI is used as a sensitive indicator of myocardial cell viability because it does not accumulate in the ischemic myocardial tissue [20, 21]. Finally, in the remaining 3 cases other factors should also be considered, such as metabolic and/or biological factors not evaluated in these patients [22, 23].

Third, 1 TB (size: 2 cm) and 1 pneumonia (size: 3 cm) were correctly identified by $^{99\text{m}}\text{Tc}$ -MIBI-SPECT but not by ^{18}F FDG-PET, whereas 1 active TB (size: 4 cm) was missed by both methods. Inflammatory and infectious processes are known to result in false-positive results of ^{18}F FDG-PET, and $^{99\text{m}}\text{Tc}$ -MIBI uptake in active TB is a known phenomenon. In a study by Onsel et al. [24] patients with extensive radiological evidence of pulmonary TB disease ($>50\%$ with bilateral infiltrates) had positive $^{99\text{m}}\text{Tc}$ -MIBI-SPECT in 92% of cases, whereas patients with minimal radiological infiltration had positive $^{99\text{m}}\text{Tc}$ -MIBI-SPECT in only 50%. In the series of Schuurmans et al. [25], one third of the benign lesions not detected by $^{99\text{m}}\text{Tc}$ -MIBI-SPECT were active TB.

Limitations of the Study

First, a combined PET-CT unit and SPECT-CT unit are not available in this trial. It is certainly possible that tumor and lymph node characterizations would have been improved by the use of PET-CT or SPECT-CT. Second, in all of the patients the disease location has already been identified, thereby excluding the study of extrathoracic sites. Third, in primary malignant lesions, we found a higher incidence of squamous cell carcinomas (23/37, 62%) than that usually expected in a European population with peripheral lung nodules. Theoretically, the data observed may be explained considering that our study group includes 17 solitary pulmonary nodules and 20 lung mass lesions. Yet, 10/37 lesions are not peripheral. Finally, the small numbers of BAC ($n = 3$) and large cell carcinomas ($n = 3$), and the absence of small cell carcinoma preclude definitive conclusions regarding the sensitivity of ^{18}F FDG-PET and $^{99\text{m}}\text{Tc}$ -MIBI SPECT for the detection of these particular tumors.

Conclusion

The data of our study show that ^{18}F FDG-PET and $^{99\text{m}}\text{Tc}$ -MIBI-SPECT have similar accuracy in finding lung malignancies. Thus, $^{99\text{m}}\text{Tc}$ -MIBI-SPECT may be considered an alternative when ^{18}F FDG-PET is not available. Yet, the combination of both techniques may improve the selection of patients for invasive procedures, thus avoiding the morbidity and mortality associated with thoracotomy in those having benign disease. Finally, because of the small patient cohort, further studies are warranted to corroborate our preliminary results.

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