^{99m}Tc-tetrofosmin SPECT in solitary pulmonary nodule evaluation

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Abstract. A correct differential diagnosis between benign and malignant lesions is mandatory in patients with solitary pulmonary nodule (SPN). The aim of the present study was to investigate whether ^{99m}Tc-tetrofosmin SPECT may play a role in SPN evaluation. A consecutive series of 111 patients with an uncalcified ≤3 cm (range: 0.8-3 cm) SPN, without definite benign findings and indeterminate at CT, were studied. Within 1 week of CT scan, following 740 MBq of ^{99m}Tc-tetrofosmin i.v. injection, all patients underwent chest SPECT using a rectangular dual head gamma camera with HR collimators. The images were analysed both qualitatively and semiquantitatively by calculating tumor/normal tissue ratio (T/N). All nodules were referred to a definitive diagnosis after scintigraphy: 84/111 nodules resulted malignant (primary lung carcinomas in 59 cases and metastases in 25), whereas 27/111 were benign. SPECT was true positive in 77/84 malignant nodules (overall sensitivity: 91.7%), detecting 55/59 carcinomas (93.2%) and 22/25 metastases (88%), whereas it was false negative in 4 carcinomas (3 adenocarcinomas and 1 squamous cell carcinoma, the latter with necrotic areas; range size: 1.5-2.4 cm) and in 3 metastases (range size: 1.0-1.2 cm). SPECT was true negative in 24/27 benign lesions (specificity: 88.9%) and false positive in 2 hamartomas and in 1 aspecific inflammation (range size: 0.8-2 cm), each with a T/N value ≤1.4. Accuracy, positive predictive value and negative predictive value were 91, 96.2 and 77.4%, respectively. Mean T/N value was significantly higher in malignant than in benign nodules (2.1±0.6 vs. 1.3±0.1, $P<0.05$), whereas no significant differences were observed between primary lung carcinomas and metastases (2.1±0.6 vs. 1.9±0.6) or in the different histologic types of carcinomas. ^{99m}Tc-tetrofosmin SPECT proved a highly sensitive imaging method in both primary and secondary malignant ≤3 cm SPNs detection, with a high accuracy value in discriminating malignant from benign lesions, also by adding semiquantitative analysis. A larger clinical application of this non-invasive, simple and widely available procedure is thus suggested in SPN management, especially when FDG-PET is not available.

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Introduction

Solitary pulmonary nodule (SPN), defined as a spherical lesion ≤3 cm-well surrounded in the lung parenchyma without any associated atelectasis or lymphadenopathy (1), is a frequent and often incidental discovery on chest radiographs or conventional computed tomography (CT) (2,3).

An SPN may be due to benign or malignant lesions (1), the latter generally including primary lung carcinoma at an early presentation or single lung metastasis; however, larger nodules, from 3 to 6 cm, currently classified as masses, are almost always malignant (4).

The management of a patient with an SPN is generally based on the probability of malignancy frequently obtained following Bayesian analysis models (5) which take into account both certain standard clinical criteria (i.e. patient age, cigarette smoking history, previous malignancy, present symptoms) and conventional radiological features (i.e. nodule size, site, margins, growth rate, calcification pattern, edge characteristics), to which, more recently, have been added other findings by contrast-enhanced dynamic CT (dCT), based on the difference in density (degree of contrast enhancement) which occurs in a nodule after the intravenous injection of iodinated contrast material (6).

A watchful observation, including repeat CT aimed at excluding nodule growth, may be sufficient when the probability of malignancy of an SPN is low, while invasive biopsy techniques, such as percutaneous transthoracic needle biopsy

Table I. Definitive diagnosis of the 111 SPNs.

Diagnosis	No.
Primary lung carcinomas	59
Adenocarcinoma	34
Squamous cell carcinoma	19
Giant cell carcinoma	2
Unclassified NSCLC	2
Small cell lung cancer	2
Lung metastasis	25
Benign lesion	27
Hamartoma	7
Aspecific inflammatory lesion	5
Sclerohyaline nodule	4
Sarcoidosis	3
Infarction	2
Tuberculosis	3
Benign according to 3-year stability size criterion	3

Table II. Lesion size according to the definitive diagnosis.

Lesion size	Lung carcinomas (n=59)	Lung metastases (n=25)	Benign lesions (n=27)
≤10 mm	5	7	6
11-15 mm	14	8	8
16-20 mm	13	6	5
21-25 mm	9	3	4
26-30 mm	18	1	4

or broncoscopic biopsy, should be considered for the broad spectrum of nodules with a high or intermediate probability of malignancy (7); however, exploratory surgery may also be necessary in these cases when biopsy techniques are inconclusive, although a high number of nodules often result benign at histology.

During the last few years, non-invasive radioisotopic imaging procedures have been proposed in the differential diagnosis of SPNs as a complementary tool to CT. Among these, positron emission tomography with 18F-fluorodesossiglucose (FDG-PET) has proved the most effective and at present represents the procedure of reference in the differential diagnosis of SPNs ≥0.8 cm (over the spatial resolution limit of PET scanner) indeterminate at thin section CT (8); its employment has been in particular suggested in nodules at intermediate/high degree of malignancy for a better selection of those to submit to biopsy or excision, a negative FDG-PET study generally excluding malignancy (8). Moreover, single photon emission computed tomography (SPECT) with the somostatin analogues ^{99m}Tc-Depreotide (9) and ^{99m}Tc-EDDA-HYNIC-TOC (10) and with the cationic lipophilic radiotracer ^{99m}Tc-sestaMIBI (11) have also been used. The results obtained have been encouraging, but they refer to a limited number of cases.

More recently, another cationic lipophilic radiotracer with tumor-seeking properties, ^{99m}Tc-tetrofosmin, has been employed in lung cancer patients proving an accurate imaging method in both detection of primary lung cancer and mediastinal lymph node staging, as well as in the follow-up of affected patients and in monitoring the response to chemotherapy (12-16). Moreover, ^{99m}Tc-tetrofosmin SPECT has also been shown as a reliable diagnostic tool in the detection of lung metastases from extrapulmonary tumors of different origin (17). This radiotracer clears rapidly from the lungs and liver, thereby permitting early high-quality images of the chest (18). Published data indicate that ^{99m}Tc-tetrofosmin clearance from the lung and the liver appears to be faster than the ^{99m}Tc-sestaMIBI clearance (18,19).

In the present study, we investigated a large group of patients with uncalcified ≤3 cm SPNs without definite benign findings and indeterminate at CT. We evaluated the usefulness of ^{99m}Tc-tetrofosmin SPECT, combining both qualitative and semiquantitative analysis of images, in the identification of the nodules, but in particular we focused on its capability in differentiating malignant from benign lesions.

Materials and methods

Patients. From January 1997 to April 2005, a consecutive series of 111 patients with an SPN, 69 males and 42 females, aged 36-82 years (mean age: 71.6 years), were studied. All patients had already undergone clinical examination, X-Ray and CT scan of the chest and were referred for further diagnostic evaluation to definitively assess the nature, malignant or benign, of each nodule.

At CT, all nodules were uncalcified and ≤3 cm in diameter, without definite benign radiological features or any associated atelectasis or lymphadenopathy and were classified as indeterminate by two trained radiologists (A. Arru and P. Pirina) independently. Nodule size ranged from 0.8 to 3 cm (mean: 1.92 cm).

In all cases ^{99m}Tc-tetrofosmin scintigraphy of the chest, routinely used in our Referral Nuclear Medicine Department since 1996, was performed within 1 week of the CT scan. Eighty of 111 patients had no history of previous malignancy, while 31 had been previously operated for an extrapulmonary primary carcinoma [breast (n=15), colon (n=5), kidney (n=3), endometrium (n=2), larynx (n=2), oral cavity (n=1), vulvar (n=1), prostate (n=1) and bladder (n=1)]. A definitive diagnosis was obtained in all cases after scintigraphy. Written informed consent was obtained in all cases before scintigraphy.

^{99m}Tc-tetrofosmin scintigraphy protocol. Radiolabelling and quality control procedures of the radiotracer were carried out according to the manufacturer's instructions. Labelling efficiency was always >95%.

In all patients, 740 MBq of ^{99m}Tc-tetrofosmin (Myoview, Amersham International, Amersham, UK) were injected intravenously into the arm contralateral to the affected lung. Twenty minutes later, SPECT was acquired using a rectangular, large

Table III. ^{99m}Tc-tetrofosmin SPECT results at qualitative analysis in the 111 SPNs; 84 malignant and 27 benign.

True positive	77
True negative	24
False positive	3
False negative	7
Sensitivity	91.7% (77/84)
Specificity	88.9% (24/27)
Accuracy	91% (101/111)
Positive predictive value	96.2% (77/80)
Negative predictive value	77.4% (24/31)

field of view, dual-head gamma camera (Helix, Elscint or Millennium VG, GE Medical System) equipped with low-energy, high-resolution, parallel-hole collimators. A ±10% window and a 140 KeV photopeak were selected.

SPECT images were acquired over 360˚ (180˚ per head) in a step-and-shoot mode with the patient in supine position, using a zoom factor which ranged from 1 to 1.2 according to individual patients, a 64x64 matrix size, a 3˚ angular step and an acquisition time of 30 sec/frame. The body contouring system was always used in order to ensure the minimum distance between the chest and the collimator. Before reconstruction, SPECT images were normalized to correct for misalignments and radiation time decay.

Reconstruction was performed with the Back Projection Filter Method (with a count-optimized Metz filter) without attenuation correction, to obtain transaxial, coronal and sagittal slices and 3D images.

SPECT images were always preceded by acquisition of anterior and posterior (600 sec) planar images starting 10 min after ^{99m}Tc-tetrofosmin injection. However, for the present study we have reported only the SPECT results.

Data analysis. SPECT images were independently evaluated by three experienced nuclear medicine physicians (A. Spanu, O. Schillaci, G. Madeddu) who were informed of the clinical reason pertinent to the scintigraphy; however, they were unaware of the results of the final true lesion status, which was achieved in all cases after scintigraphy.

The reconstructed SPECT images were related to CT images and considered positive at qualitative analysis (subjective visual evaluation), and thus suggestive of malignancy, in the presence of a focal area of ^{99m}Tc-tetrofosmin abnormal accumulation corresponding to the nodule ascertained at CT. Interobserver variability was extremely low, with disagreement in only 1 case in the analysis of SPECT images and was resolved by consensus.

The radiotracer uptake at SPECT was also analysed semi-quantitatively drawing regions of interest (ROIs) over the tumor uptake (T) and in the corresponding site of the contralateral normal lung (N) in the transaxial slice in which the lesion was more clearly evident. The mean ROI values were measured (total counts/total pixels) and the T/N ratio was then calculated. All imaging data were related to those obtained by the definitive diagnosis.

Definitive diagnosis. The definitive diagnosis was achieved in 108/111 SPNs at histology, by obtaining tissue from thoracotomy in 64 cases, by broncoscopic biopsy in 36 cases and by CT guided transthoracic needle biopsy in 8 cases. The remaining 3 SPNs, also indeterminate at broncoscopic biopsy, were considered benign according to stable size on chest CT for at least 3 years.

Statistical analysis. ^{99m}Tc-tetrofosmin SPECT images were classified as true-positive, true-negative, false-positive or false-negative considering the definitive lesion diagnosis, obtained with the above mentioned criteria, as a gold standard.

Per-patient sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were then calculated. χ^2 test or Fisher exact test, when appropriate, were used to assess the statistical differences in sensitivity in the two different groups of patients with malignant lesions (primary lung carcinomas vs. lung metastases).

Student's t-test for unpaired data was used to assess the statistical differences in T/N values between patients with malignant and those with benign nodules, and among the former between those with primary lung cancer and those with lung metastases. T/N values were also compared in the different histological types of primary lung carcinomas. The statistical results were considered significant when $P<0.05$.

Results

The definitive diagnosis of SPNs is reported in Table I. The pulmonary nodules were malignant in 84/111 cases (75.7%) and benign in 27/111 (24.3%); moreover, 59 of the 84 patients with malignant nodules, including 2 patients with a previous history of malignancy (prostate carcinoma in one case and bladder carcinoma in the other case), had a primary lung cancer, while the remaining 25, each with a previous history of malignancy, had a single pulmonary metastasis. An extra-pulmonary tumor (breast cancer in 2 cases and oral cavity spinocellular carcinoma in 1 case) had also been previously ascertained in 3 patients with benign SPNs.

Nodule size according to the definitive aetiology is reported in Table II. The mean nodule size was 2 cm (range: 0.8-3 cm) in malignant nodules and 1.7 cm (range: 0.8-2.8 cm) in benign. Among malignant nodules, the mean nodule size was 2.1 cm (range: 0.8-3 cm) in primary lung carcinomas and 1.6 cm (range: 0.8-3 cm) in lung metastases.

The results of ^{99m}Tc-tetrofosmin SPECT qualitative analysis are reported in Table III, which also includes per-lesion sensitivity, specificity, PPV, NPV and accuracy.

SPECT was true positive in 77/84 malignant nodules (overall sensitivity: 91.7%), detecting 55/59 primary lung carcinomas (sensitivity: 93.2%) and 22/25 single lung

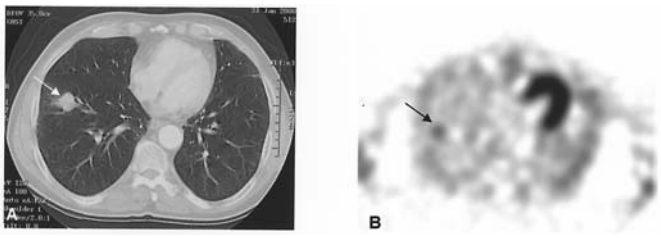

Figure 1. A 69-year-old male patient with a 20-mm unclassified NSCL in the lower lobe of the right lung which appeared as an SPN at CT (A, arrow). ^{99m}Tc-tetrofosmin SPECT was true positive showing a focal area of increased uptake corresponding to the carcinoma (B, arrow). T/N value was 2.2.

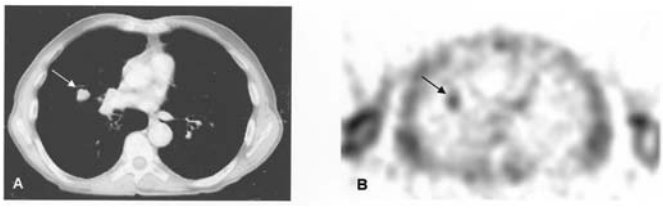

Figure 2. A 78-year-old male patient with a 12-mm single lung metastasis from colon carcinoma in the medium lobe of the right lung which appeared as an SPN at CT (A, arrow). ^{99m}Tc-tetrofosmin SPECT was true positive showing a focal area of increased uptake corresponding to the metastasis (B, arrow). T/N value was 2.1.

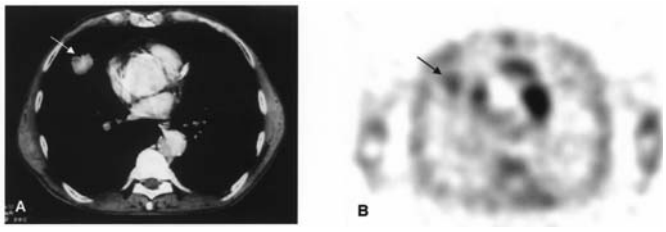

Figure 3. A 70-year-old male patient with a 25-mm squamous cell carcinoma in the lower lobe of the right lung which appeared as an SPN at CT (A, arrow). A focal area of increased ^{99m}Tc-tetrofosmin uptake, with a T/N value of 2.9, was evidenced at transaxial SPECT (B, arrow), corresponding to the carcinoma.

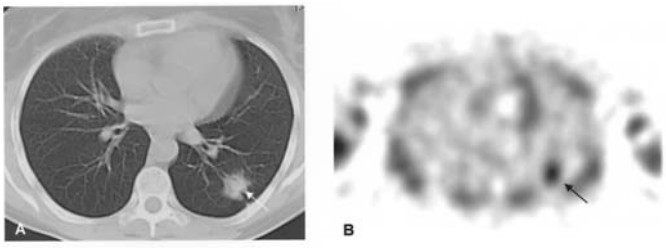

Figure 4. A 52-year-old female patient with a 20-mm adenocarcinoma in the lower lobe of the left lung which appeared as an SPN at CT (A, arrow). A focal area of increased ^{99m}Tc-tetrofosmin uptake, with a T/N value of 2.6, was evidenced at transaxial SPECT (B, arrow), corresponding to the carcinoma.

metastases (sensitivity: 88%). One case of primary lung carcinoma and one case of lung metastasis are reported in Figs. 1 and 2, respectively. The difference in sensitivity in the two groups of malignant SPNs was not statistically significant (P>0.05). The smallest carcinoma and lung metastasis detected at SPECT measured 0.8 cm.

The procedure was false negative in 7 malignant lesions, 4 primary lung carcinomas, which included 3 adenocarcinomas 1.5, 1.8 and 2.4 cm large, respectively, and 1 squamous cell carcinoma with necrotic areas 1.5 cm large, and 3 metastases from colon (n=1), endometrium (n=1) and kidney carcinoma (n=1), 0.8, 1.0 and 1.2 cm large, respectively; the smallest of these metastases was sited in the basal region of the left lung near the myocardium.

SPECT imaging was true negative in 24/27 patients with benign nodules (specificity: 88.9%) and false positive in 3, two of which were hamartomas 0.8 and 1.8 cm large, respectively, and one an aspecific inflammation of 2.0 cm. The overall accuracy of SPECT in differentiating malignant from benign nodules was 91%, whereas PPV and NPV were 96.2% and 77.4%, respectively.

At semiquantitative analysis, all malignant nodules positive at SPECT, both primary tumors and metastases with a pattern of focal homogeneous increased uptake at qualitative analysis, had a T/N ratio >1.4 in each case, while in all 3 false positive lesions T/N ratio was under this value.

The mean T/N ratio calculated in malignant SPNs was significantly higher than that obtained in benign nodules (2.1±0.6 vs. 1.3±0.1, P<0.05).

Mean T/N ratio was higher in primary lung carcinomas than in lung metastases (2.1±0.6 vs. 1.9±0.6), but the difference was not statistically significant. Moreover, no statistical differences in T/N ratios were found among the different histological types of primary lung carcinomas (2.1±0.4 in adenocarcinomas, 2.1±0.8 in squamous cell carcinomas and 2.6±1.1 in small cell lung carcinomas). Two different histologic types of primary lung carcinomas, a squamous cell carcinoma and an adenocarcinoma, are illustrated in Figs. 3 and 4, respectively.

Discussion

The accurate differential diagnosis between benign and malignant lesions represents the most important goal in the evaluation of SPN in order to discover malignancy when it is in an early and potentially more curative stage.

Radiography and CT are the imaging procedures commonly used to evaluate SPN, but many nodules remain indeterminate notwithstanding the different criteria employed for their characterization, and invasive and expensive diagnostic procedures, including surgical exploration, are often necessary, although these can also result in non-diagnostic findings.

Over the last few years FDG-PET, particularly when combined with standardized uptake value (SUV) calculation, has progressively become the diagnostic non-invasive radioisotopic procedure of choice in SPN, proving highly accurate in differentiating benign from malignant nodules seen on chest radiograph or CT (20-22). FDG-PET has shown an extremely high sensitivity value, 95% in mean (22-28), with a low risk of malignancy (<5%) when it is negative (22) and with a satisfactory specificity value of 80% (22-28), thus limiting the number of unnecessary biopsies or surgical

explorations for benign disease. Moreover, the addition of PET to CT has given more favourable results, also in terms of cost-effectiveness, than conventional approaches (29). It has been demonstrated that combined PET/CT imaging offers significant advantages than PET alone in solitary pulmonary nodule evaluation, including more accurate localization of focal uptake, distinction of pathology from physiological uptake, and improvement in evaluating therapy response (30).

Given the still limited availability of PET centers, where FDG-PET was not practicable, the use of SPECT with gamma-emitter tumor seeking radiotracers has also been proposed in combination with CT in the differential diagnosis of SPN. Such a procedure is certainly more available and less expensive than FDG-PET and clinical results are very encouraging, although still limited.

The majority of SPECT studies refer to the employment of ^{99m}Tc-depreotide, at present the only gamma-emitting radiotracer approved by the U.S. FDA and also in Europe for SPN evaluation. In a multicenter trial, this procedure gave high sensitivity (96.6%) and accuracy (91.2%) values in the characterization of pulmonary nodules ranging in size from 0.8 to 6 cm, thus including both SPNs and masses, with mean size of malignant nodules of 3.0 cm, and with 73% specificity value (31); the sensitivity was 94.4% when only SPNs ≤3 cm were considered.

However, in a recent comparative study (32) carried out on 28 patients with ≤3 cm SPNs, ^{99m}Tc-depreotide SPECT proved less sensitive than FDG-PET (88.9 vs. 94.4%), and even more in ≤1.5 nodules (83.3 vs. 100%), but more specific in those >1.5 cm.

Other promising SPECT imaging procedures have employed ^{99m}Tc-EDDA-HYNIC-TOC (10) and ^{99m}Tc-sestaMIBI (11), as radiotracers, with sensitivity and specificity values of 90 and 71% for the former (nodule size: 1-5.5 cm, with mean size of malignant nodules of 2.9) and 85.7 and 100% (nodule size: 1.1-5 cm, with mean size of malignant nodules of 2.15 cm) for the latter which included only 4 benign lesions. In both these series, sensitivity decreased to 80% when only nodules ≤3 cm were considered.

In the present study, we have investigated the clinical usefulness of ^{99m}Tc-tetrofosmin SPECT, combining qualitative and semiquantitative analysis of images, focusing on the differential diagnosis of patients with uncalcified ≤3 cm SPNs without definite benign findings and indeterminate at CT; all the nodules underwent a definitive histological diagnosis after scintigraphy.

The prevalence of malignancy in our series was 75.7%; almost 70% of malignant SPNs were due to primary lung carcinomas and the remaining 30% to single lung metastases.

^{99m}Tc-tetrofosmin SPECT proved an extremely highly sensitive diagnostic tool, identifying almost 92% of malignant nodules globally considered and reaching a sensitivity value of 93.2% in the detection of primary lung carcinomas.

These sensitivity values are comparable to those obtained with both FDG-PET and ^{99m}Tc-Depreotide SPECT and higher than those observed with ^{99m}Tc- sestaMIBI-SPECT. Moreover, the results obtained with ^{99m}Tc-tetrofosmin SPECT appear even more favourable in respect of the other aforementioned gamma-emitter radiotracers since the size of nodules were smaller in the present study, only including SPNs ≤3 cm, with mean size of malignant nodules of 2.0 cm (2.1 cm for primary lung carcinomas and 1.6 for metastases), unlike the other casuistries which also included masses.

In our series, ^{99m}Tc-tetrofosmin SPECT failed to detect 7 malignant nodules. Four of these were due to primary lung carcinomas ranging from 1.5 to 2.4 cm, and the remaining 3 were related to metastases from extrapulmonary tumors of different origin, which were relatively small in size, ranging from 0.8 to 1.2 cm, one of these located near the myocardium.

Probably in the former 4 cases, rather than the small size of the nodule below SPECT spatial resolution given that some carcinomas with the same size and even smaller were positive, other factors inherent to the tumor may be involved, such as metabolic or histologic factors (3/4 false negative tumors were adenocarcinomas and one a squamous cell carcinoma but with necrotic areas); moreover, an overexpression of P-glycoprotein or other MDR-related proteins, not measured in these false negative cases, cannot be excluded, tetrofosmin being a substrate of these efflux-pump proteins (33).

The sensitivity of ^{99m}Tc-tetrofosmin SPECT was high also in the detection of small size metastases from extrapulmonary tumors, although it was slightly lower than that obtained in primary lung carcinomas (88 vs. 93.2%).

These data are comparable to those with FDG-PET which has obtained sensitivity and accuracy values of 80 and 90% (34,35), respectively, in lung metastasis detection; however, ^{99m}Tc-tetrofosmin SPECT would seem more sensitive in respect of the somatostatin analogues when compared to the results obtained by some authors in the few cases studied in which a high rate of false negative findings have been reported, missing all metastases (10), the uptake of these radiotracers strictly depending on the expression of somatostatin receptors, not always consistent in the most frequent carcinomas which tend to develop metastases in the lungs (36).

The mechanism of tetrofosmin uptake in tumoral cells is less specific and is not yet well understood. Its uptake is essentially favoured by an increased blood flow and capillary permeability and by an elevated metabolic activity of tumoral cells; it also depends on both cell membrane and mitochondrial potentials and is partially related to Na+/K+ pump, tetrofosmin mainly accumulating in the cytosol and only a small fraction inside the mitochondria (37-40). Such a tumor aspecific uptake mechanism probably explains the absence of significant differences in tetrofosmin uptake between primary and secondary malignant lung lesions and in lung metastases of different origin.

In our series, ^{99m}Tc-tetrofosmin SPECT also showed a high specificity value (88.9%), with only 3 false positive results which refer to 2 hamartomas and one aspecific inflammation ranging from 0.8 to 2 cm, tetrofosmin accumulation in similar benign lesions having also been reported in other studies (12,16); these false positive results seem independent of size and histologic type, since other 5 hamartomas and 4 aspecific inflammations of the current series resulted true negative. Moreover, in our series, no significant differences in tetrofosmin T/N values were found among the different histogical types, unlike the results obtained with ^{99m}Tc-Depreotide by some authors (41) who reported a T/N ratio significantly higher in squamous cell carcinomas than in adenocarcinomas and giant cell carcinomas.

According to the high PPV (96.2%), SPNs positive at ^{99m}Tc-tetrofosmin SPECT should be referred to biopsy or exploratory surgery. However, in the present study 3.7% of positive cases resulted false positive and were submitted to unnecessary invasive procedures which, however, would have had to be avoided on the basis of semiquantitative analysis, these false positive nodules having showed a significantly lower T/N value in respect of malignant lesions.

On the contrary, NPV was 77.4%; thus, SPECT negative cases should be taken into account in order not to obviate further investigation, although in all benign lesions tracer accumulation was absent or very low. However, these results would seem to be affected, at least in part, by the limited number of benign lesions (27 cases) in the present study.

Further prospective studies are necessary to assign a definitive role to ^{99m}Tc-tetrofosmin SPECT as a complementary tool to conventional radiologic methods in the management of patients with an SPN; for this purpose, a comparative evaluation could be useful on a large number of cases of ^{99m}Tc-tetrofosmin SPECT and other radioisotopic procedures with gamma-emitter radiotracers such as ^{99m}Tc-Depreotide in respect of which, however, ^{99m}Tc-tetrofosmin SPECT might be more easily available and advantageous in terms of cost for those departments that also routinely use it for myocardial scintigraphy.

A comparison with FDG-PET, at present the radioisotopic procedure of choice, could be suggested; although, PET procedures present some intrinsic advantages over SPECT, such as a higher spatial resolution and the capability of giving simultaneously diagnostic and staging information, the alternative role of ^{99m}Tc-tetrofosmin SPECT should not be excluded, especially when FDG-PET is not available. Furthermore, fused images with hybrid SPECT/CT recently proposed in clinical practice might further aid in the correct characterization of SPNs near sites of physiological radiopharmaceutical uptake such as the myocardium and the liver (42).

In conclusion, the data of the present study proved that ^{99m}Tc-tetrofosmin SPECT is a highly sensitive imaging method in the detection of both primary and secondary malignant ≤3 cm SPNs. Moreover, SPECT also revealed high specificity and accuracy values in discriminating malignant from benign lesions indeterminate at CT, with semiquantitative analysis as an additional tool. Thus, we suggest a larger clinical application of this relatively simple and widely available diagnostic method in the management of patients with SPNs; in particular, the procedure could be useful as a complementary tool to CT for the characterization of the nodules and for a better selection of the cases to be referred to invasive diagnostic investigation, especially if FDG-PET is not available.

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