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Assessment of Mediastinal Involvement in Lung Cancer with Technetium-99m-Sestamibi SPECT

Arturo Chiti, Lorenzo S. Maffioli, Maurizio Infante, Giacomo Grasselli, Matteo Incarbone, Massimo D. Gasparini, Giordano Savelli and Emilio Bombardieri

Divisions of Nuclear Medicine and Thoracic Surgery, National Institute of Cancer Research, Milan, Italy

This study evaluated the clinical role of SPECT with sestamibi versus CT in the presurgical staging of lung cancer. **Methods:** Forty-seven consecutive patients (44 men, 3 women; mean age 63.3 yr, range 49–82 yr) with clinical and radiological suspicion of lung cancer were enrolled in this study. Staging procedures included radiography, CT, fiberoptic bronchoscopy and sestamibi SPECT of the thorax. Radionuclide imaging was performed after intravenous injection of 740–925 MBq of sestamibi. In 36 patients a histological diagnosis was made, and these patients were evaluated for the study of mediastinal lymph node involvement. **Results:** Mediastinal lymph node involvement was demonstrated in 11 of the 36 patients evaluated. Sestamibi SPECT correctly staged 10 of 11 patients with and 21 of 25 without mediastinal nodes, showing a diagnostic sensitivity of 91% and a specificity of 84%. Computed tomography gave 8 true-positive and 15 true-negative results, with a sensitivity of 73% and a specificity of 60%. Sestamibi SPECT results were also better than those of CT with regard to positive and negative predictive values and accuracy. **Conclusion:** The clinical role of sestamibi SPECT can be fully appreciated when the technique is used in selected patients, combined with CT or MRI, or both, to assess mediastinal involvement and avoid any invasive staging procedures.

Key Words: lung cancer; mediastinal lymph nodes; technetium-99m-sestamibi

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Technetium-99m-hexakis-2-methoxy-isobutyl-isonitrile (sestamibi) is a lipophilic cation widely used in clinical practice as a myocardial perfusion imaging agent (*1,2*). Several studies have used sestamibi as an oncologic tracer for a variety of malignancies, such as tumors of the thyroid, brain, breast and bone (*3–10*). Several reports have also described the possible application of this radiopharmaceutical for bronchogenic carcinoma in clinical practice (*11–16*).

Nuclear medicine procedures using SPECT are currently being assessed with the aim of improving lesion detection (*17*). These techniques have proved to have a higher specificity than planar acquisition. Moreover, new instrumentation has made it possible to acquire and reconstruct SPECT images rapidly, making it a useful tool in clinical practice.

The most useful and commonly applied histopathological classification of lung cancer differentiates this frequent disease into four main types: epidermoid or squamous cell carcinoma, large-cell anaplastic carcinoma, adenocarcinoma and small-cell lung cancer (*18*).

In non–small-cell lung cancer, surgery offers the greatest chance of obtaining complete remissions if performed at the very early stages of the disease (UICC stages I and II). Unfortunately, less than 30% of patients are eligible for curative resection. Radiotherapy and chemotherapy can be used as palliative treatment in patients with advanced disease (UICC stages IIIb and IV) (*18,19*).

The therapeutic approach is completely different in patients with small-cell lung cancer. For this carcinoma, combination chemotherapy is the first-line therapy because the role of additional irradiation or surgery is still controversial (*20*).

The stage of the tumor at the time of surgery is the most important determinant for prognosis and therapeutic strategy. Accurate imaging of primary lung cancer can be obtained with transmission CT and MRI, whereas the preoperative assessment of mediastinal lymph nodes with radiological procedures is still a matter of debate. In fact, the disadvantage of these imaging techniques is that the only useful criterion for determining metastatic involvement of mediastinal lymph nodes is based on evaluation of their size (*21–23*). Recent studies have demonstrated that up to 40% of mediastinal lymph node metastases are not visualized by CT or MRI but use surgical staging as the standard (*24,25*).

At present, the most accurate technique is doubtless mediastinoscopy, which is a surgical, invasive procedure. Thus, the aim of the present study was to assess the diagnostic contribution of sestamibi SPECT to the presurgical staging of lung cancer, so that mediastinoscopy could be avoided, with no decrease in sensitivity.

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For correspondence or reprints contact: Emilio Bombardieri, MD, Divisione Medicina Nucleare, Istituto Nazionale Tumori, Via Venezian 1, I-20133, Milano, Italy.

MATERIALS AND METHODS

Patients

Forty-seven consecutive patients (44 men, 3 women; mean age 63.3 yr, range 49–82 yr) with clinical and radiological suspicion of lung cancer were enrolled in the study.

The staging procedures included plain film radiography and CT scanning of the thorax, fiberoptic bronchoscopy with biopsy, pulmonary function tests, preoperative cardiological examination, arterial blood analysis, routine laboratory tests and sestamibi SPECT. Of the 47 patients, 31 underwent thoracic surgery, 2 of whom received preoperative treatment (radiotherapy plus chemotherapy in 1 and radiotherapy alone in the other). Five patients underwent mediastinoscopy with sampling of mediastinal nodes. A total of 36 patients (34 men, 2 women; mean age 63.3 yr, range 49–82 yr) were finally evaluated for mediastinal involvement. The thoracic surgery techniques were lobectomy or pneumonectomy, depending on the locoregional extension of the disease. Nine patients did not undergo operation because of the extent of their disease, which precluded surgical treatment. Two patients did not undergo surgery after clinical and instrumental demonstration of the phlogistic nature of their disease.

Scintigraphic Technique

All patients gave written informed consent before entering the study, and all received an injection of 740–925 MBq of ^{99m}Tc-sestamibi. The radiopharmaceutical was prepared according to the manufacturer's instructions. Scintigraphic acquisition started 25 min after tracer administration. Data from the first 38 patients were acquired using a Toshiba GCA-901A single-head gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator. The remaining images were acquired using a Toshiba GCA-7200A dual-head gamma camera equipped with low-energy, high-resolution, parallel-hole collimators. For both gamma cameras the acquisition parameters were 60 frames over 360°, 30 sec/frame, 64 × 64 matrix, zoom 1.5. All images were processed on the Toshiba GCA-7200A console. Transaxial slices (2-pixel width, 1-pixel overlap) were reconstructed after prefiltering (Butterworth 9 × 9, order 8, cutoff 0.25) with a Ramp filter. Coronal and sagittal views of 2 pixels (1-pixel overlap) were then obtained. The data were visually evaluated by two experienced nuclear medicine physicians (CAC, LSM) with knowledge of the CT results and blinded to the pathological findings. For all patients studied, the coronal slices were evaluated first, followed by the transaxial and sagittal views. Maximum intensity projection images were also considered in the diagnostic evaluation.

Computed tomographic scanning of the thorax was performed after intravenous injection of non-ionic iodinated contrast medium with a window for the lung parenchyma and a window for the mediastinum. Transaxial slices of 8 mm without overlap were reconstructed and evaluated by experienced radiologists.

RESULTS

Histopathological results in the 36 patients evaluated are summarized in Table 1. Eleven patients who did not undergo operation because of extensive disease or the presence of distant metastases were excluded from the final evaluation. Seventeen patients had adenocarcinomas; 12 had squamous cell carcinomas; and 2 had small-cell lung cancer. One patient had a lung carcinoid; one had multiple lung amartochondromas; and one had a metastasis from gastric cancer. Five patients had non-neoplastic lung diseases (lung fibrosis in one, abscess bronchiolitis in one, pachypleuritis in one and phlogistic lesions in two). In this series, one patient had two tumors (adenocarcinoma and squamous cell carcinoma), one had bilateral adenocarcinomas and another had a bifocal squamous-cell carcinoma.

TABLE 1
Results of CT and Sestamibi SPECT Evaluation of Mediastinal Involvement in 36 Patients Undergoing Surgery

Patient No.	CT	Sestamibi SPECT	Pathology	Histology
1	Neg	Neg	Pos	Squamous cell cancer
2	Neg	Neg	Neg	Squamous cell cancer
3	Pos	Neg	Neg	Adenocarcinoma
5	Pos	Pos	Pos	Squamous cell cancer
7	Pos	Neg	Neg	Carcinoid
8	Pos	Neg	Neg	Small-cell cancer
9	Neg	Pos	Pos	Adenocarcinoma
10	Neg	Neg	Neg	Fibrosis
11	Pos	Neg	Neg	Adenocarcinoma
14	Pos	Pos	Pos	Bilateral adenocarcinoma
15	Pos	Neg	Neg	Amartochondroma
16	Neg	Neg	Neg	Squamous cell cancer
17	Neg	Neg	Neg	Adenocarcinoma
18	Neg	Neg	Neg	Adenocarcinoma
19	Pos	Neg	Neg	Adenocarcinoma and squamous cell cancer
20	Neg	Neg	Neg	Adenocarcinoma
21	Pos	Pos	Pos	Adenocarcinoma
22	Neg	Neg	Neg	Squamous cell cancer
23	Neg	Neg	Neg	Adenocarcinoma
24	Pos	Pos	Pos	Small-cell cancer
25	Neg	Neg	Neg	Squamous cell cancer
26	Pos	Pos	Neg	Bifocal squamous cell cancer
27	Pos	Neg	Neg	Abscess bronchiolitis
28	Neg	Neg	Neg	Metastatic gastric cancer
29	Neg	Neg	Neg	Squamous cell cancer
31	Neg	Pos	Neg	Adenocarcinoma
35	Neg	Neg	Neg	Adenocarcinoma
36	Neg	Pos	Neg	Squamous cell cancer
37	Pos	Pos	Pos	Squamous cell cancer
38	Pos	Pos	Pos	Adenocarcinoma
39	Pos	Pos	Pos	Adenocarcinoma
41	Pos	Neg	Neg	Pachypleuritis
42	Neg	Pos	Pos	Adenocarcinoma
44	Pos	Pos	Neg	Squamous cell cancer
45	Pos	Pos	Pos	Adenocarcinoma
47	Neg	Neg	Neg	Adenocarcinoma

We therefore studied 39 lung lesions in the 36 patients evaluated.

Mediastinal node involvement was pathologically demonstrated in 11 (31%) of the 36 patients studied. In addition, all five mediastinoscopic results were positive (Fig. 1 and 2).

Sestamibi SPECT correctly staged 10 of 11 patients with and 21 of 25 without mediastinal nodes, for a sensitivity of 91% and a specificity of 84%. Eight true-positive and 15 true-negative results were obtained with CT, for a sensitivity of 73% and a specificity of 60%. Positive and negative predictive values and accuracy were also better with sestamibi SPECT than with CT

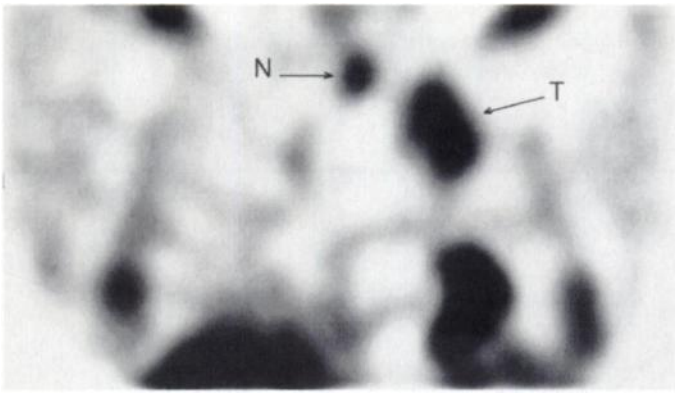

FIGURE 1. Coronal slice from Patient 39 showing a left upper lobe tumor (T) and a large adenopathy in the upper mediastinum (N). This finding was confirmed by mediastinoscopy, and histopathological findings demonstrated an adenocarcinoma.

(Table 2). For mediastinal imaging, results were concordant with both sestamibi and CT in 24 cases (66%).

When the primary tumors were evaluated, 39 lesions (20 in the right lung and 19 in the left lung) were found in the 36 patients enrolled in the study. It must be emphasized that in the entire series, five false-positive results were obtained with CT. With histopathological results as a reference, sestamibi SPECT had a sensitivity of 85% and a specificity of 100%. The positive and negative predictive values were, respectively, 100% and 50%, and the accuracy was 87% (Table 3).

When the patients with mediastinal involvement were classified according to tumor histological analysis, sestamibi identified all seven adenocarcinomas, one of one small-cell lung cancer and two of three squamous cell carcinomas. Computed tomography correctly staged five of seven adenocarcinomas, one of one small-cell lung cancer and two of three squamous cell carcinomas. For primary lesions, sestamibi uptake was seen in 14 of 18 adenocarcinomas, 11 of 13 squamous cell carcinomas, 2 of 2 small-cell carcinomas, 1 carcinoid and 1 metastasis from gastric carcinoma. Sestamibi uptake was negative in the patient with multiple amartochondromas and in the three patients with non-neoplastic lesions. Computed tomography identified all lung lesions, including three non-neoplastic masses.

DISCUSSION

The usual diagnostic course in lung cancer staging can be divided into three steps. The first is diagnostic and includes plain film radiography, sputum cytology, fiberoptic bronchoscopy with biopsy and bronchoalveolar lavage or brushing. Occasionally, fine-needle aspiration biopsy of peripheral lesions is added. The second step is staging, that is, the evaluation of the locoregional extent of the disease with CT or MRI of the thorax and, sometimes, mediastinoscopy or thoracoscopy. This step includes the search for distant metastases. Techniques used include CT scan of the brain, CT or ultrasound scan of the abdomen, ^{99m}Tc-methyldiphosphonate bone scan and bone marrow biopsy. The third step concerns patient selection for surgery and requires a general assessment based on age and liver, kidney, heart and lung function.

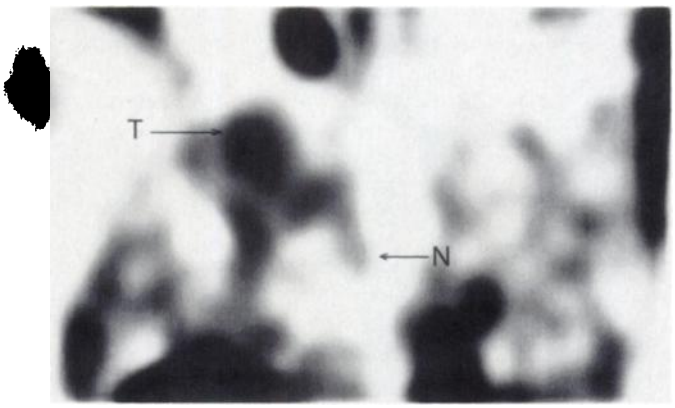

FIGURE 2. Coronal slice from Patient 42 showing a large right upper lobe tumor (T) and, in continuity with it, a lymph node enlargement in the right part of the mediastinum (N). This finding was confirmed by mediastinoscopy, and histopathological findings demonstrated an adenocarcinoma.

Computed tomography and MRI are currently superior to other diagnostic procedures for the detection of primary lung tumors. Although spiral CT represents the most advanced technique for imaging primary tumors (*23*), MRI may have the advantage in patients with superior sulcus tumors and in the assessment of mediastinal penetration and critical organ invasion. Moreover, MRI may have a slight advantage over CT in the assessment of chest wall invasion, but the accuracy of both methods has been disappointing in this regard (*24–30*)

Mediastinal involvement is a critical issue both for therapeutic decision making and prognosis assessment (*18,31*). Mediastinoscopy is the most accurate staging technique for the evaluation of nodal involvement. It is generally acknowledged that lymph node enlargement on CT requires histological confirmation by mediastinoscopy or an alternative technique, particularly if the demonstration of nodal metastases would preclude surgical resection (*29*). The need for mediastinoscopy in the presence of normal-sized lymph nodes is more controversial, and no definite agreement has yet been reached among surgeons (*32*). Radiological procedures, such as CT or MRI, are commonly used for this purpose but are flawed by their low sensitivity (*24,25,27*). State-of-the-art techniques are, as previously mentioned, spiral CT and dynamic contrast-enhanced MRI, but no data can demonstrate a definite advantage for these imaging methods (*26,33*).

There have been many attempts to use nuclear medicine procedures to overcome the limitations of morphological imaging and the invasiveness of mediastinoscopy, so that unnecessary surgical procedures can be safely avoided. The first radiopharmaceutical used for this purpose was ^{67}Ga-citrate. The published data are controversial because some investigators have reported a high sensitivity and specificity for mediastinal evaluation (*34,35*), whereas others have obtained poorer results (*36*). No clinical role has yet been established for ^{67}Ga. Thallium-201-chloride has been used for the detection of many tumors, but it seems to have limited use in mediastinum imaging, although a recent communication suggests that ^{201}Tl SPECT could correctly diagnose mediastinal metastases (*37*). Several investigators have studied monoclonal antibodies labeled with ^{111}In, ^{131}I and ^{99m}Tc (*12,38,39*). The role of this type of radiopharmaceutical is still a matter of debate, and monoclonal antibodies are still an open issue in cancer imaging. Recently, patients with lung cancer have been studied with ^{111}In-pentetreotide. Because of its biologic characteristics, this radiopharmaceutical is most suitable for small-cell lung cancer staging and restaging (*40–42*). Moreover, visualization of non–small-cell lung cancer with ^{111}In-pentetreotide has been reported on the basis of a specific uptake of this radiopharmaceutical (*43*). These studies have reported good sensitivity in detecting mediastinal involvement from small-cell lung cancer, but data for patients with other histological types are disappointing. There is growing interest in the use of PET in bronchogenic carcinoma. Most studies have successfully used ^{18}F-fluoro-2-deoxy-D-glucose and ^{11}C-methionine (*12*). How-

TABLE 2
Comparison of CT and Sestamibi for Evaluation of Mediastinal Node Involvement from Lung Cancer in 36 Patients

	CT	Sestamibi SPECT
Sensitivity	(8/11) 73%	(10/11) 91%
Specificity	(15/25) 60%	(21/25) 84%
Positive predictive value	(8/18) 44%	(10/14) 71%
Negative predictive value	(15/18) 83%	(21/22) 95%
Accuracy	(23/36) 64%	(31/36) 86%

Results are expressed according to surgical evaluation of the mediastinum, either with mediastinoscopy or thoracotomy, as the reference.

ever, the high cost of PET remains the greatest obstacle to the clinical use of this technique.

The oncological application of ^{99m}Tc-sestamibi is gaining interest among clinicians. Many tumor cells have been proved to concentrate sestamibi in vivo (*3–10*), and this radiopharmaceutical is under investigation for its ability to demonstrate the presence of the multidrug resistance gene (*44*). The short half-life, the optimal energy for currently used gamma cameras and the availability of a technetium-labeled compound make sestamibi a suitable tracer for easy clinical use. Moreover, the short time between injection and imaging facilitates the test procedure.

Some investigators have reported data on sestamibi in bronchogenic carcinoma that seem very similar to results obtained with ^{201}Tl (*13–15*). When the primary lesion was investigated, the lack of specificity and the high myocardial uptake of both tracers led to discouraging results. Moreover, in our opinion, it is not necessary to evaluate the primary lesion with techniques other than CT or MRI. The only information one would expect to obtain from nuclear medicine procedures on the primary lesion is histological type, but no tracer to date is able to give such essential information with the required accuracy. This approach will only be of interest when new radiopharmaceuticals that are able to distinguish different tumor types become available.

Two recent studies have used sestamibi to evaluate the extent of mediastinal involvement. LeBouthillier et al. (*11*) studied 26 patients. Both planar and SPECT images were acquired, and the data were compared with the pathological diagnosis. They found a 100% (4 of 4) sensitivity for mediastinal involvement and a 96% sensitivity for the primary tumor (22 of 23). LeBouthillier et al. reported no advantage of SPECT over planar imaging. The specificity for mediastinal and hilar lymph nodes with planar imaging was 100% (12 of 12), whereas that for a side-by-side comparison of planar and SPECT studies was 92% (11 of 12). They concluded that sestamibi SPECT could be a useful tool in the evaluation of negative hilar and mediastinal lymph node regions, so that mediastinoscopy could be safely avoided. Aktoloun et al. (*16*) reported data from 38 patients with lung cancer studied with CT scanning and planar sestamibi acquisition. Twenty-nine of these patients were also studied with SPECT. In that series, the results were compared with those of CT, which was used as the reference standard. With regard to the primary tumor, Aktoloun et al. reported a sensitivity of 89% and 93% for planar and SPECT studies, respectively. On a per-patient basis, the sensitivity for detection of hilar and mediastinal metastasis was 90% for planar imaging and 100% for SPECT, but when the number of nodes was considered these values were 62% and 100%, respectively. To differentiate between squamous cell carcinoma and adenocarcinoma, Aktoloun et al. performed semiquantitative analyses of tumor uptake, but no significant differences were found. They concluded that sestamibi SPECT can be used for the staging of patients with lung cancer, for the evaluation of mediastinal involvement and in follow-up, to distinguish residual or recurrent disease from postradiotherapy necrosis.

TABLE 3
Results of Sestamibi SPECT in 39 Primary Lung Lesions Evaluated in 36 Patients

Sensitivity	(29/34) 85%
Specificity	(5/5) 100%
Positive predictive value	(29/29) 100%
Negative predictive value	(5/10) 50%
Accuracy	(34/39) 87%

In our series, the data were matched with the final histological staging, which is crucial for correct evaluation of a new imaging technique. Our findings demonstrated that sestamibi-SPECT was superior to CT in evaluating mediastinal node metastases from lung cancer. We found a sensitivity and specificity for CT in our patients similar to that reported previously (*24*). It has been reported that SPECT provides no additional information with respect to planar imaging (*11*). This is a controversial statement because SPECT is generally considered to have superior resolution, which is why we preferred to acquire only SPECT images and thus avoid submitting patients to time-consuming acquisitions. The same investigators reported findings slightly superior to ours in terms of sensitivity and specificity, but this could perhaps be explained by the fact that they studied fewer patients. In any case, their data support our findings. From a nuclear physician's point of view, the method, although simple to perform, yields images that are not easy to interpret. In fact, the heart and many vascular structures can interfere with a correct interpretation of the images, even when only the mediastinum is being evaluated. It is also difficult to distinguish the exact number of involved nodes; however, this information is not crucial for the correct staging of the disease.

We had only one false-negative result, for which no clear explanation could be found. It was a squamous cell carcinoma, and the CT scan results were also negative. We also had four false-positive results, which we believe were due to incorrect image interpretation. In particular, it can be postulated that we interpreted some areas of physiological uptake in the posterior aspect of the thorax as pathological uptake in the mediastinum, which points out the difficulties encountered in correctly evaluating the images.

Another critical issue is the timing of the acquisition. In our previous experience, the optimal time proved to be between 20 and 30 min after injection. Later acquisitions result in noisy elevation of the low physiological uptake of the lungs and other structures that can be considered as background.

CONCLUSION

On the basis of the present results, we can conclude that sestamibi-SPECT is a sensitive, noninvasive method for assessing mediastinal involvement in the preoperative staging of lung cancer, and its diagnostic accuracy is better than that of CT. This technique, performed in combination with CT or MRI, or both, in selected patients can safely avoid invasive staging procedures such as mediastinoscopy.

Future prospects include the image fusion technique, which allows superimposition of a functional color scale on morphological, gray-scale images.

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